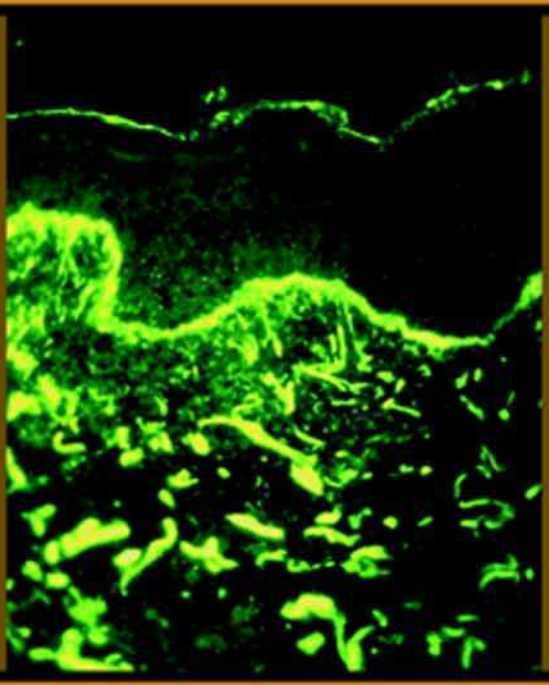
ELSEVIER

HANDBOOK OF SYSTEMIC AUTOIMMUNE DISEASES

Series Editor: Ronald A. Asherson
Volume 5



The Skin in Systemic Autoimmune Diseases

Edited by
Piercarlo Sarzi-Puttini, Andrea Doria,
Giampiero Girolomoni & Annegret Kuhn

Handbook of
Systemic Autoimmune Diseases

Volume 5

The Skin in Systemic Autoimmune Diseases

Handbook of
Systemic Autoimmune Diseases

Series Editor: Ronald A. Asherson

Volume 1	The Heart in Systemic Autoimmune Diseases *Edited by: Andrea Doria and Paolo Pauletto*
Volume 2	Pulmonary Involvement in Systemic Autoimmune Diseases *Edited by: Athol U. Wells and Christopher P. Denton*
Volume 3	Neurologic Involvement in Systemic Autoimmune Diseases *Edited by: Doruk Erkan and Steven R. Levine*
Volume 4	Reproductive and Hormonal Aspects of Systemic Autoimmune Diseases *Edited by: Michael Lockshin and Ware Branch*
Volume 5	The Skin in Systemic Autoimmune Diseases *Edited by: Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn*

Handbook of
Systemic Autoimmune Diseases

Volume 5

The Skin in Systemic Autoimmune Diseases

Edited by:

Piercarlo Sarzi-Puttini
Rheumatology Unit, I. Sacco University Hospital
Milan, Italy

Andrea Doria
Division of Rheumatology, University of Padova
Padova, Italy

Giampiero Girolomoni
Department of Dermatology, University of Verona
Verona, Italy

Annegret Kuhn
Department of Dermatology, University of Düsseldorf
Düsseldorf, Germany

Series Editor

Ronald A. Asherson

ELSEVIER

Amsterdam – Boston – Heidelberg – London – New York – Oxford
Paris – San Diego – San Francisco – Singapore – Sydney – Tokyo

ELSEVIER B.V.
Radarweg 29
P.O. Box 211, 1000 AE
Amsterdam. The Netherlands

ELSEVIER Inc.
525 B Street
Suite 1900. San Diego
CA 92101-4495, USA

ELSEVIER Ltd.
The Boulevard
Langford Lane, Kidlington,
Oxford OX5 1GB, UK

ELSEVIER Ltd.
84 Theobalds Road
London WC1X 8RR
UK

First edition 2006

Library of Congress Cataloging in Publication Data
A catalog record is available from the Library of Congress.

British Library Cataloguing in Publication Data
A catalogue record is available from the British Library.

ISBN-13: 978-0-444-52158-3
ISBN-10: 0-444-52158-5
ISSN: 1571-5078

® The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).
Printed in Italy.

Preface

The skin is a frequent site of immunopathological reactions, and is commonly involved in systemic autoimmune diseases. In many instances, the skin is affected together with the musculoskeletal system resulting in complex inflammatory disorders with concurrent cutaneous and rheumatic manifestations. These diseases may represent a real challenge from both a diagnostic and therapeutic point of view.

This volume of the ''Handbook of Systemic Autoimmune Disease'' provides up-to-date knowledge on skin immunology and the cellular and molecular players of the immune response. Most chapters are devoted to immune-mediated skin diseases and rheumatologic diseases with skin manifestations, including connective tissue diseases and vasculitides, and will help clinicians at a more comprehensive approach to diagnosis and treatment. The chapters are prepared by internationally recognized leading experts, and cover issues that have not been put together before.

This volume is subdivided into four parts. In the first part, the immune mechanisms involved in the cutaneous damage are considered. In the second part, the cutaneous manifestations observed in the major systemic autoimmune diseases are reviewed. In the third part, the focus is on the cutaneous manifestations observed in systemic vasculitis. Finally, in the fourth part, an extensive description of the new systemic and topical therapeutic options are reported.

We would like to thank the contributing authors for their expertise and efforts in preparing the chapters.

It is our hope that this volume could help to focus the attention on some pathogenetic, clinical and therapeutic aspects at the boundary between Rheumatology and Dermatology, and encourage the debate among clinicians and basic researchers with different backgrounds and experiences.

This page intentionally left blank

Series Editor

Ronald A. Asherson

Ronald A Asherson, MD, FACP, MD (Hon), FRCP (London), FCP (SA), FACR, is Honorary Consultant Physician at the Rheumatic Disease Unit, Department of Medicine, University of Cape Town Health Sciences Centre in Cape Town, as well as being Consultant Rheumatologist at the Rosebank Clinic in Johannesburg, South Africa. He is also a Visiting Professor at the Systemic Autoimmune Diseases Unit at the Hospital Clinic, Barcelona, Spain where he regularly visits and coordinates research projects.

From 1976 to 1981 he was Assistant Clinical Professor of Medicine at the New York Hospital – Cornell Medical Center in New York under the late Professor Henry Heineman. From 1981 to 1986 he was associated with the Rheumatology Department at the Royal Postgraduate Medical School of London where he developed his interests in connective tissue diseases and antiphospholipid antibodies.

In 1986 he moved to the Rayne Institute and St Thomas' Hospital in London, where he was appointed Honorary Consultant Physician and Senior Research Fellow and remained there until 1991.

In 1998 he was elected as Fellow of the American College of Physicians (FACP) as well as a Founding Fellow of the American College of Rheumatology (FACR). From 1988 to 1991 he served on the Council of the Royal Society of Medicine in London. In 1992 he was co-winner of the European League Against Rheumatism (EULAR) Prize and in 1993 was the co-recipient of the International League Against Rheumatism (ILAR) Prize, both for his research on antiphospholipid antibodies. In 1994 he was elected as a Fellow of the Royal College of Physicians (FRCP) of London. In 2002 he was awarded an Honorary Doctorate in Medicine from the University of Pleven in Bulgaria.

Dr Asherson has been an invited speaker at many universities and on the Scientific Committees of many international conferences both in the USA and Europe. He is the author of more than 280 papers on connective tissue diseases and has contributed to more than 30 textbooks of medicine, rheumatology and surgery as well as having co-edited "*Problems in the Rheumatic Diseases*", the "*Phospholipid Binding Antibodies*", two editions of "*The Antiphospholipid Syndrome*" and "*Vascular Manifestations of the Systemic Autoimmune Diseases*" He is on the Editorial Boards of many international and Internet Rheumatology journals. He is currently engaged in research on connective tissue diseases, particularly on the antiphospholipid syndrome .In 1999, he was the co-recipient of the Juan Vivancos Prize in Spain and in 2003 was the co-recipient of the Abbott Prize, awarded at the European League Against Rheumatism (EULAR) International Meeting, held in Lisbon, Portugal. In September 2003 was Co-Chairman of the First Latin American Congress on Autoimmunity, held in the Galapagos Islands, Ecuador. In 2005, he was honored by the South African Rheumatism and Arthritis Association and made a Life Member.

His original description of the "Catastrophic Antiphospholipid Syndrome" and the publishing of more than 40 papers on this new disease was rewarded by the attachment of the eponym "Asherson's Syndrome" to this condition at the November 2002 International Phospholipid Conference held in Sicily.

He is currently Series Editor of 12 volumes entitled "The Handbook of Systemic Autoimmune Disease" (Elsevier, Holland).

This page intentionally left blank

Volume Editors

Piercarlo Sarzi-Puttini

Piercarlo Sarzi-Puttini graduated in Medicine in 1981 from University of Parma. He became specialist in Rheumatology in 1985 at the Chair of Rheumatology Ospedale Pini, University of Milan. He is also a specialist in Physical therapy and Rehabilitation (1989) and in Internal Medicine (1994).

Since 1995 (when he was appointed as Lecturer in Rheumatology) he has been involved in undergraduate and postgraduate teaching. Actually, he is responsible for the training of junior doctors at L. Sacco Hospital.

He is a member of Italian Society of Rheumatology (SIR) and American College of Rheumatology (ACR). From 1999 to 2005 he has been a Council member of Italian College of Hospital Rheumatology (CROI).

Dr Sarzi-Puttini is co-author of nearly 100 original papers and more than 200 abstracts, mostly on the clinical aspects and treatment of rheumatic diseases, cardiovascular manifestations on autoimmune diseases, fibromyalgia, and autoimmune diseases. He is author or co-author of 5 books and 15 chapters.

He is also an ad hoc reviewer for numerous journals: Arthritis Rheumatism, Lupus, Clinical Experimental Rheumatology, Reumatismo, Rheumatology, and Progressi in Reumatologia (Official Journal of Italian College of Hospital Rheumatology). His research activity has been mainly addressed to the following topics: treatment of Rheumatoid Arthritis and Psoriatic Arthritis, Fibromyalgia and other dysfunctional syndromes, cardiovascular aspects of rheumatic diseases, and systemic autoimmune diseases.

Andrea Doria

Andrea Doria is Assistant Professor of Rheumatology at the University of Padova. His research is primarily involved in the clinical and immunological aspects of autoimmune diseases and he is author of many publications in this field. Recently he has focused his interest on the atherosclerosis in systemic lupus erythematosus.

Dr Doria graduated in Medicine in 1982 from University of Padova. He trained at the Division of Rheumatology at the same University, and in 1986 became Specialist in Rheumatology. From 1986 to 1990 he was a research fellow in Rheumatology at the University of Padova, and in 1990 he was appointed as Assistant Professor of Rheumatology. In 1991, he became Lecturer at the Postgraduate School of Rheumatology. Since 1995 he has collaborated in teaching Rheumatology at Padova University School of Medicine.

He is a member of Italian Society of Rheumatology (SIR) and American College of Rheumatology (ACR). From 1999 to 2005 he has been a Council member of Italian College of Hospital Rheumatology (CROI).

He has a long-standing experience in clinical management of connective tissue disease patients. The Unit in which he works is a 3rd referral rheumatological center, of prominence within Italy, for the diagnosis and management of patients affected with systemic connective diseases. In addition, he has expertise in the management and follow-up of pregnant patients with systemic rheumatic diseases. His research group is primarily involved in the clinical as well as immunological aspects of autoimmune diseases and he is author of many publications in this field.

Dr Doria is co-author of 120 original articles, 90 book chapters or Conference Proceedings, 2 books, and 200 abstracts. He is also an ad hoc reviewer for numerous journals: Annals of Rheumatic Diseases, Arthritis Research and Therapy, Arthritis Rheumatism, Lupus, New England Journal of Medicine, Clinical Experimental Rheumatology, Reumatismo, Rheumatology, Scandinavian Journal of Rheumatology, The Journal of Rheumatology, and member of the scientific board of Lupus, Autoimmunity Review, Reumatismo

(Official Journal of Italian Society of Rheumatology), Progressi in Reumatologia (Official Journal of Italian College of Hospital Rheumatology), and Artrite e Reumatismi.

Giampiero Girolomoni

Giampiero Girolomoni is professor of dermatology and head of the Dermatology Section at the University of Verona School of Medicine, Verona, Italy. Dr Girolomoni is member of the executive board of national and international scientific societies. He is the secretary of the Italian Society of Dermatology (SIDeMaST) where he also serves as secretary of the Gruppo Italiano di Ricerca Sperimentale in Dermatologia. Dr Girolomoni is member of the scientific board of various dermatological journals. He has published 150 original articles, 58 reviews, 53 book chapters, 4 books, and 354 abstracts.

Dr Girolomoni's scientific interests include immunodermatology, immunobiology of dendritic cells, immunologic functions of keratinocytes, immunology and immunopharmacology of allergic contact dermatitis, atopic dermatitis, and psoriasis.

Annegret Kuhn

Annegret Kuhn is currently a Heisenberg-Associate Professor of the German Research Society (DFG) and has a joint appointment at the German Cancer Research Center (DKFZ), Heidelberg, Germany, and the Department of Dermatology, University of Dusseldorf, Germany. She graduated from the Medical School of the University of Munich, Germany, and after completion of her residency program in dermatology and venereology at the University of Dusseldorf, Germany, she joined the faculty as a senior staff member. Furthermore, she was a research postdoctoral fellow at the Institute of Cell Biology, Center for Molecular Biology of Inflammation (ZMBE), and the Max-Planck-Institute of Molecular Biomedicine, Muenster, Germany, during her Lise-Meitner-Scholarship. She is also the leading attending of the outpatient clinic for patients with connective tissue diseases and is responsible for the Laboratory of Clinical Immunology.

Annegret Kuhn is president of the ''Interdisciplinary Study Group of Lupus Erythematosus (ISGLE)'', secretary of the ''European Society of Cutaneous Lupus Erythematosus (EuSCLE)'' and served as the organizer of the ''1st International Conference on Cutaneous Lupus Erythematosus'' in 2004, and is also member of the Organizing Scientific Committee for the conference ''Skin, Rheumatism and Autoimmunity'' in 2006. She is also member of the ''Study Group of Dermatological Research (ADF)'', ''German Dermatological Society (DDG)''''German-Hungarian Dermatological Society (DUDG)'', ''German-Japanese Society of Dermatology (DJGD)'', ''German Network of Systemic Scleroderma (DNSS)'', and the ''EULAR Scleroderma Trials and Research Group (EUSTAR)''.

The clinical interests of Annegret Kuhn include characterization and classification of the different cutaneous subtypes of lupus erythematosus. Since 1999 she is principal investigator and co-investigator in several clinical trials including multicenter and investigator-initiated studies for autoimmune skin diseases and photodermatoses. Her scientific focus is immunodermatology, photoimmunology, and immunopharmacology of lupus erythematosus, systemic scleroderma, and photodermatoses. Furthermore, she is involved in characterizing novel endothelial specific antigens and transgenic and knock-out mouse models.

Annegret Kuhn is co-author of 57 original articles, 16 reviews, 9 book chapters, and co-editor of 2 books. She is also a reviewer for numerous international journals.

List of Contributors

Joerg Albrecht
Department of Dermatology, University of Pennsylvania, USA

Jenny Apelt
Department of Dermatology, University of Münster, Münster, Germany

Ronald A. Asherson
Division of Rheumatology, University of Cape Town Health Sciences Centre, Cape Town, and the Rosebank Clinic, Johannesburg, South Africa.

Fabiola Atzeni
Rheumatology Unit, University Hospital L, Sacco, Via GB Grassi 74, 20157 Milan, Italy

Chaira Baldini
Rheumatology Unit, Department of Internal Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy

Stefania Bano
Division of Dermatology, University of Padova, Italy

Stefan Beissert
Department of Dermatology, University of Münster, Münster, Germany

Markus Böhm
Department of Dermatology, University of Münster, Von-Esmarch-Str. 58-48149 Münster, Germany

Stefano Bombardieri
Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

Raffaella Bonecchi
Institute of General Pathology, Medical Faculty, University of Milan, Milan, Italy and Istituto Clinico Humanitas, 20089 Rozzano (MI), Italy

Jan D. Bos
Department of Dermatology, Academic Medical Center, University of Amsterdam, The Netherlands

Mario Carrabba
Rheumatology Unit, University Hospital L, Sacco, Via GB Grassi 74, 20157 Milan, Italy

Ilaria Cavazzana
Servizio di Reumatologia e Immunologia Clinica, Spedali Civili di Brescia, Cattedra di Immunologia Clinica, University of Brescia, Brescia, Italy

M. Cem Mat
Department of Dermatology, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey

Maurizio Cutolo
Division of Rheumatology, Department of Internal Medicine, Universita degli Studi di Genova, Genova, Italy

Marinos C. Dalakas
Neuromuscular Diseases Section, National Institute of Neurological Diseases and Stroke, National Institutes of Health, USA

Jean-Claude Davin
Paediatric Nephrology Unit, Het EKZ/Kinder AMC, Amsterdam Z-O, The Netherlands

Cuyan Demirkesen
Department of Pathology, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey

Yeny Martinez de la Torre
Institute of General Pathology, Medical Faculty, University of Milan, 20133 Milan, Italy

Andrea Doria
Division of Rheumatology, Department of Medical and Surgical Sciences, University of Padova, Padova, Italy

Marie-Sylvie Doutre
Department of Dermatology, Hôpital Haut-Lévêque, Pessac Cedex, France

Clodoveo Ferri
Chair to Rheumatology, University of Modena Reggio Emilia, Policlinico di Modena, Modena, Italy

Rebecca Fischer-Betz
Rheumatology, University of Düsseldorf, Düsseldorf, Germany

Camille Francès
Department of Dermatology, Allergology Hopital Tenon, 4 zero de le chine 75020 Paris, France

Emanuela Galliera
Institute of General Pathology, Medical Faculty, University of Milan, Milan, Italy

Kulndina Gensch
Department of Dermatology, University of Düsseldorf, Düsseldorf, Germany

Giampiero Girolomoni
Department of Biomedical and Surgical Sciences, Section of Dermatology, University of Verona, Verona, Italy

Loïc Guillevin
Department of Internal Medicine, Université Paris 5, Hôpital Cochin, Paris, France

Nicolas Hunzelmann
Department of Dermatology, University of Cologne, Cologne, Germany

Luca Iaccarino
Division of Rheumatology, University of Padova, Italy

Christof Iking-Konert
Rheumatology, University of Düsseldorf, Düsseldorf, Germany

Joseph L. Jorizzo
Department of Dermatology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, N C 27157, USA

Tomisaku Kawasaki
Japan Kawasaki Disease Research Center, Tokyo, Japan

Thomas Krieg
Department of Dermatology, Cologne, Germany

Annegret Kuhn
Department of Dermatology, University of, Düesseldorf, 40225 Düesseldorf, Germany

Percy Lehmann
Department of Dermatology, Allergology and Environmental Medicine, Helios Klinikum Wuppertal, Universität Witten-Herdecke, Germany

Massimo Locati
Institute of General Pathology, Medical Faculty, University of Milan, Milan, Italy and Istituto Clinico Humanitas, 20089 Rozzano (MI), Italy

Karin Loser
Department of Dermatology, University of Münster, Münster, Germany

Thomas Luger
Department of Dermatology, University of Münster, Münster, Germany

Alberto Mantovani
Institute of General Pathology, Medical Faculty, University of Milan, 20133 Milan, Italy and Istituto Clinico Humanitas, 20089 Rozzano (MI), Italy

Maria Teresa Mascia
Chair of Rheumatology, Rheumatology Unit, University of Modena & Reggio Emilia, Policlinico di Modena, Via Del Pozzo 71, 41100, Modena, Italy

Melike Melikoğlu
Division of Rheumatology, Department of Medicine, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey

Pier Luigi Meroni
Allergy, Clinical Immunology & Rheumatology Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy

Thorsten M. Olski
Department of Dermatology, University of Cologne, 50931 Cologne, Germany

Christian Pagnoux
Department of Internal Medicine, Université Paris 5, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France

Manisha J. Patel
Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA

Jean-Charles Piette
Department of Internal Medicine, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital 75651, Paris Cedex 13, France

Carmen Pizzorni
Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, San Martino Hospital, Viale Benedetto xv 6, 16132 Genova, Italy

Pierfranco Riboldi
Allergy, Clinical Immunology & Rheumatology Unit, Department of Internal Medicine, IRCCS Istituto Auxologico Italiano, University of Milan, Italy

Riccardo Rondinone
Division of Rheumatology, Department of Medical and Surgical Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy

Piercarlo Sarzi-Puttini
Rheumatology Unit, University Hospital L, Sacco, Via GB Grassi 74, 20157 Milan, Italy

Matthias Schneider
Rheumatology, Heinrich-Heine-University, Duesseldorf, Moorenstr. 5–40225 Duesseldorf, Germany

Richard D. Sontheimer
Department of Dermatology, Fleischaker, Endowed Chair in Dermatology, University of Oklahoma Health Science Center, 619 N.E, 13th Street, Oklahoma City, Oklahoma 73104, USA

Alberto Sulli
Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, San Martino Hospital, Viale Benedetto xv 6, 16132 Genova, Italy

Gianpaolo Tessari
Department of Biomedical and Surgical Sciences, Section of Dermatology, University of Verona, Verona, Italy

Angela Tincani
Rheumatology Unit, Spedali Civili, Piazza Spedali Civili 1, Brescia, Italy

Gianluca Vago
Pathology Unit, L. Sacco Institute of Medical Science, University of Milan, 20157 Milan, Italy

Annunciata Vecchi
Istituto Clinico Humanitas, 20089 Rozzano, (MI) Italy

Victoria P. Werth
Department of Dermatology, University of Pennsylvania 2, Rhodes Pavilion - 3600 Spruce street and Philadelphia Veterans Administration Medical Centre, Philadelphia, PA 19104, USA

Hasan Yazici
Division of Rheumatology, Dept. of Medecine, Cerrahpasa Medical Faculty, University of Istanbul, Aksaray, Istanbul 34303, Turkey

Francesco Zulian
Pediatric Rheumatology Unit, Department of Pediatrics, University of Padua, Via Giustiniani, 3, 35128 Padua, Italy

Contents

PART I:

The Skin and the Immune System

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 1

The Skin as an Immunologic Organ

Giampiero Girolomoni[a], Gianpaolo Tessari[a], Jan D. Bos[b]

[a]*Department of Biomedical and Surgical Sciences, Section of Dermatology, University of Verona, Verona, Italy*

[b]*Department of Dermatology, Academic Medical Center University of Amsterdam, The Netherlands*

1. Introduction: the skin as an organ of defence

Human skin is the largest organ of the body that provides a protective barrier to ensure that exogenous 'noxious' agents do not affect the homeostasis of the organism. Being situated at the interface between external and internal milieus, a number of remarkable structural and functional characteristics of skin have been delineated that contribute to its effectiveness at maintaining homeostasis. The skin has two main systems of defence. The first is related to its physical and chemical properties, the other is the 'immunological' defence. The major physical properties of the skin are impermeability for water and water-soluble compounds, and mechanical resistance to exogenous traumas and optic properties making it relatively insensitive to ultraviolet (UV) radiation. The barrier function of the skin is provided by the stratum corneum (Elias, 2004) that is an effective barrier to the loss of endogenous water and to the penetration of exogenous potentially dangerous substances. Key constituents of the stratum corneum include corneocytes packed by lipids, among which are prominent ω-hydroxylated long-chain *N*-acyl fatty acids (ceramides) (Madison, 2003). During the normal process of keratinization, keratinocytes undergo a unique form of programmed cell death, which leads to their transformation into corneocytes. Corneocytes are anucleated cells where the plasma membrane is replaced by the cornified envelope, which consists of keratins that are enclosed within an insoluble amalgam of proteins, crosslinked by transglutaminases and surrounded by a lipid envelope (Candi et al., 2005). Multiple sheets of ceramides and sphingolipids are generated by keratinocytes and discharged into the extracellular space. For this reason, molecules larger than 500 Da cannot easily penetrate into the normal skin, penetration of larger molecules can occur if they are lipophylic or if the skin is damaged (e.g., chronic or acute eczema) (Bos and Meinardi, 2000). The stratum corneum acts also as a biosensor, and can transfer information to the underlying living epidermal cells.

The skin has many eccrine and sebaceous glands. While eccrine glands produce predominantly a watery type of sweat important for thermoregulation, sebaceous glands secrete a complex mixture of triglycerides, fatty acids, squalene and cholesterol, which forms a film on hair follicles and the epidermal surface. Sebum has several protective functions, including its ability to repel water and protect the surface of the skin from growth and invasion by bacteria and fungi (Nickoloff, 2001). In addition, after exposure to various microorganisms or inflammatory cytokines, keratinocytes secrete several antimicrobial peptides, including defensins and cathelecidins (Bardan et al., 2004). These antibiotics introduce pores in bacterial walls, which can directly kill the infectious microbe in the absence of a specific immune reaction. Moreover, they can attract and activate immature dendritic cells, thus providing an important link between innate and adaptive immunity.

DOI: 10.1016/S1571-5078(05)05001-4

UV radiation induces the formation of free radicals, but many defence mechanisms (free radical-trapping molecules, thiols, melanin and enzyme systems) can neutralize these DNA-damaging, potentially carcinogenous substances (Parrish, 1983; Agar and Young, 2005). Other relevant physiological functions of the skin are the maintenance of body temperature, production of hormones and bearing of peripheral nerve receptors and endings.

In addition, the skin has a complex and well organized immune system, with the normal resident skin cells displaying an impressive armamentarium of defence strategies and the ability of recruiting circulating cells that are present throughout the body to complement the initial tissue response (Bos, 2005).

2. Evolving concepts of the skin as an immunological organ

In the early 1970s, the skin was considered to be a first-level lymphoid organ, similar to the thymus (Fichtelius et al., 1970). The authors identified some lymphoepithelial micro-organs in the skin of new-borns and human foetuses, which can be detected at orifices of the body (preputial fornix, vagina, external ear canal) and in other skin sites (nail bed, pilosebaceous unit, scrotum, mammary gland). In these organs, lymphocytes are educated to discern self from non-self antigens. These lymphoid accumulations may recur in adult life and are then diagnosed as benign lymphoproliferative diseases (lymphadenosis cutis benigna). Also, it has been suggested, but not definitively confirmed, that the secondary classic type IV hypersensitivity reaction can occur entirely in the skin, without the involvement of regional lymph nodes. At the present time, a primary lymphoid function of the skin during the embryonal or foetal life cannot be excluded. But further studies are needed to better elucidate these mechanisms. In the following years, other models of the skin as an immunologic organ have been proposed. In 1978, Streilen proposed the Skin Associated Lymphoid Tissue (SALT), which included the professional (e.g., Langerhans cells) and non-professional (e.g., keratinocytes) antigen-presenting cells, epidermotropic T lymphocytes, endothelial cells and regional lymph nodes. Langerhans cells, process and carry antigens into the regional lymph nodes, where the immune response is induced (Streilein, 1978). In 1990, Streilen detected in the epidermis of mice a dendritic T cell expressing the T-cell receptor $\gamma\delta$ that is involved in the primary immune response (Streilein, 1990). Till now, a human equivalent of these cells has not been clearly identified. Seven years later, Bos introduced a new model denominated Skin Immune System (SIS) (Bos and Kapsenberg, 1986). A detailed description of this system is reported in Tables 1 and 2. In 1989, Sontheimer considered the dermis as the very center of immune reactivity in many immune-mediated dermatoses (Sontheimer, 1989). He observed that most of the T cells, monocytes and other cells involved in the immune reactions can be found in the papillary dermis. Accumulations of T cells, monocytes and macrophages, mast cells and dendritic cells are often detected around the post-capillary venules in the dermis. He proposed that the Dermal Microvascular Unit (DMU) should be a sub-unit of the SIS (Sontheimer and Tharp, 1991).

In 1993, Nicoloff introduced the definition of Dermal Immune System (DIS), as a humoral and cellular counterpart of SALT, including dermal fibroblasts in the immune skin system, because of their

Table 1
Normal human skin: overview of cell types present and differentiation between immune-response associated and non–immune response-associated cells

Immune response-associated	Non-immune response-associated
Keratinocytes	Merkel cells
Epidermal Langerhans cells	Melanocytes
Dermal dendritic cells	Fibroblasts/fibrocytes/ myofibroblasts
Monocytes	Pericytes
T lymphocytes	Eccrine glandular cells
Vascular/lymphatic endothelial cells	Apocrine glandular cells
Granulocytes	Sebocytes
Tissue macrophages	Schwann cells
Mast cells	Smooth muscle cells

Table 2
Cellular and humoral constituents of the skin immune system

Cellular constituents	Humoral constituents
Keratinocytes	Defensins, cathelicidins
Epidermal Langerhans cells	Complement and complement regulatory proteins
Dermal dendritic cells	Mannose binding lectins
Plasmocytoid dendritic cells	Immunoglobulins
T lymphocytes	Cytokines
Monocytes/macrophages	Chemokines
Granulocytes	Growth factors
Mast cells	Neuropeptides
Vascular endothelial cells	Eicosanoids and prostaglandins
Lymphatic endothelial cells	Free radicals

Table 3
A comparison of the proposed constituents of the skin associated lymphoid tissues (SALT), the dermal microvascular unit (DMU), the dermal immune system (DIS), and skin immune system (SIS)

	SALT	DMU	DIS	SIS
Keratinocytes	+	–	–	+
Langerhans cells	+	–	–	+
Epidermal T lymphocytes	+	–	–	+
Dermal T lymphocytes	–	+	+	+
Mast cells	–	+	+	+
Vascular endothelial cells	+	+	+	+
Lymphatic endothelial cells	+	–	–	+
Dermal dendritic cells	–	+	+	+
Monocytes/macrophages	–	+	+	+
Fibroblasts	–	–	+	–
Granulocytes	–	–	–	+
Free radicals	–	–	–	+
Secretory immunoglobulins	–	–	–	+
Complement factors	–	–	–	+
Eicosanoids	–	–	–	+
Cytokine/chemokine network	–	–	+	+
Coagulation/fibrinolysis system	–	–	–	+
Neuropeptides	–	–	+	+
Skin draining lymph nodes	+	–	–	–

strict relationships with the other skin components of the epidermis (Nickoloff, 1993). More details are reported in Table 3. Recently, Paus et al. (1998) proposed a hair follicle immune system scheme based largely on murine models of hair cycling and immune privilege (Paus et al., 2005).

Table 4
Innate and adaptive cells of the SIS, divided over resident, recruited and recirculating populations

	Resident	Recruited	Recirculating
Innate	Keratinocytes	Monocytes	Natural killer cells
	Endothelial cells	Granulocytes	
	- Vascular	- Eosinophilic	
	- Lymphatic	- Neutrophilic	
	Mast cells	Monocytes	
	Tissue macrophages	Epithelioid cells	
Adaptive	T lymphocytes	T lymphocytes	T lymphocytes
	Dendritic cells	Dendritic cells	
		B lymphocytes	

3. The skin immune system

Various cellular constituents of the skin contribute to innate immunity as well as adaptive immune responses of the skin (Bos, 2005). Immunocompetent cells of the skin may also be divided in cells of the innate SIS as well as cells of the adaptive SIS, each having recirculating, recruitable and resident subpopulations. In addition to the cellular constituents of the SIS, a wide variety of inflammatory and immune mediators are present within the normal integument (Bos and Kapsenberg, 1993). A part of them reach the skin by the circulatory route, whereas many are constitutively produced within the organ itself. A summary of all these constituents is reported in Table 4.

Keratinocytes can be directly activated by a high number of exogenous stimuli (UV rays, infectious agents, exogenous chemicals), then they take place in the generation, perpetuation and termination of the subsequent immune reactions (Barker et al., 1991). Also they may act as antigen-presenting cells. Activated keratinocytes express interleukins (IL-1α, IL-1β, IL-6, IL-15), tumour necrosis factor-α (TNFα), granulocyte–macrophage colony-stimulating factor (GM-CSF) and adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) (Albanesi et al., 2005). Moreover, keratinocytes can produce and secrete an array of chemokines that can recruit blood

immunocompetent cells into the epidermis (Pastore et al., 2004). Also, all these mediators activate the underlying dermal microvascular endothelial cells (Nickoloff and Naidu, 1994) that express adhesion molecules to facilitate recruitment of circulating cells into the local tissue (i.e. dermis). The most potent stimuli for activation of keratinocytes are cytokines produced by T cells, particularly interferon (IFN)-γ, TNF-α and IL-17. Therefore, keratinocytes appear very relevant in the amplification of immune responses. Keratinocytes can act as antigen-presenting cells for experienced T lymphocytes and become target of cytotoxic T cells, such as in allergic contact dermatitis and drug eruptions. Indeed, IFN-γ derived from activated T cells and natural killer (NK) cells induces the expression of both class I and class II major histocompatibility complex (MHC) molecules and the adhesion molecule ICAM-1 on the surface of keratinocytes, which facilitates their subsequent stimulation of recruited memory T cells bearing appropriate T-cell receptors. In addition to initiating and perpetuating T-cell-mediated immune responses, keratinocytes can also potentially terminate such reactions by expressing Fas ligand (CD95L) which can induce apoptosis in T cells bearing Fas (CD95) as well as other immunoregulatory surface receptors such as programmed cell death ligand-1 and RANK-L.

The major antigen-presenting cells that are critical to the skin immune system are the dendritic cells (Langerhans cells, dermal dendritic cells), which are the only ones capable of activating naive T lymphocytes (Girolomoni and la Sala, 2005). The epidermal Langerhans cell is a bone marrow-derived cell that is normally present in the suprabasal layer of the epidermis, where it extends its dendritic processes to the surface of the skin as well as interacting not only with adjacent keratinocytes, but also with nerve fibres emanating from and interconnecting with dermal mast cells. This anatomical configuration appears to provide a hard-wiring type of arrangement in which surface stimuli can be rapidly transmitted horizontally among the epidermal cells as well as vertically into the dermis (Rowden, 1981; Schuler, 1991). Plasmocytoid dendritic cells (the major source of IFN-α) occur rarely in normal, unperturbed skin, but accumalate during disease states (e.g., allergic contact dermatitis, lupus erythematosus) thanks to the expression of specific chemokines on the surface of dermal endothelial cells. Dendritic cells are not only involved in the initiation of protective or immunopathologic immune responses, but also in the induction of immune tolerance. A low-grade migration of immature dendritic cells from the skin to the regional lymph nodes may indeed favour the activation of these T regulatory cells (Cavani et al., 2005).

An integral cellular component for all of these models is the T lymphocyte (Cavani et al., 2005). A high number of T cells are normally present in healthy epidermis and dermis. The existence of skin-selective and skin-seeking T-cell subsets has been recently demonstrated. These T cells express a specific homing receptor, named the cutaneous lymphocyte-associated antigen (CLA). This surface molecule contains an oligosaccharide determinant that has an affinity for E-selectin (and also P-selectin) expressed by cutaneous postcapillary venules endothelial cells. Other receptors involved in the selective accumulation of T cells in the skin include the chemokine receptors CCR4 and CCR10 (Boehncke et al., 2005). In adult human skin, almost all T cells possess the CD3-associated T-cell receptor containing α and β chains rather than the $\gamma\delta$ heterodimers present on early foetal thymocytes. In general CD8+ T cells tend to predominate in the epidermis, whereas CD4+ T cells are more commonly seen in the dermis. There is a non-random distribution of certain T-cell subsets bearing specific Vβ T-cell receptors in normal human skin. While the majority of T cells in the skin belong to memory rather than naive populations, only a fraction of cutaneous T cells express activation markers such as the high-affinity IL-2 receptor (CD25) or CD69, or display evidence of cell cycle progression beyond G0/G1. Thus, it appears that the majority of skin-homing T cells are actively stimulated to proliferate and become activated extracutaneously (i.e. in peripheral lymph nodes), and they tend to accumulate not so much by local proliferation as by selective recruitment and retention (Cavani et al., 2005). Some specialized subsets of T lymphocytes exert suppressive functions on immune responses. In particular, T regulatory cells 1 producing high level of IL-10

suppress immune responses by blocking the functions of dendritic cells, whereas $CD4^+CD25^+$ regulatory T cells prevent immunopathological reactions and maintain peripheral tolerance by acting via a cell-to-cell contact mechanism (Cavani et al., 2003). These cells represent important targets for new therapies aimed at reinforcing naturally occurring immunoregulatory mechanisms.

Another important cell type in the skin capable of contributing to the skin immune system, besides the keratinocyte, dendritic cell and T cell, is the mast cell (Galli et al., 2005). Mast cells, like neutrophils and eosinophils, are haematopoietic cells that are confined primarily to the dermis near nerve axons where they participate in both inflammation and immune-based reactions. Dermal mast cells contain high-affinity receptors for IgE, and also produce and secrete vasoactive substances such as histamine, as well as primary cytokines such as TNF-α. Thus, mast cells can function in both innate and acquired-type immune responses in the skin. Mast cells are activated by many stimuli such as neuropeptides, complement components, physical stimuli (cold or hot temperatures, sunlight). The ability of mast cells to produce TNF-α can facilitate recruitment of circulating cells since the mast cells are adjacent to endothelial cells which respond to TNF-α by up regulating various adhesion molecules such as ELAM-1, VCAM-1 and ICAM-1. Given the diverse repertoire of mast cells, it should not be surprising that they are involved in both immediate type I 7hypersensitivity responses as well as in contact hypersensitivity and delayed-type hypersensitivity reactions. When specific IgE antibodies bound by Fc receptors on the surface of mast cells recognize their respective antigen, the mast cell is triggered to release potent pre-formed substances such as histamine. Besides participating in humoral reactions involving circulating IgE, mast cells also influence T cells as exemplified in T-cell-mediated skin reactions (e.g. allergic contact dermatitis). In these skin reactions, mast cells influence the local immunological microenvironment by producing immunomodulatory cytokines such as TNF-α, IL-1, as well as chemokines, histamine and eicosanoids.

4. Immune responses in skin

Since the skin is the largest organ of the body and thus is continuously exposed to a tremendous diversity of antigenic stimuli, there is a bewildering array of immune responses that occur in the dermal and/or the epidermal compartments. In general, the adaptive immune responses that occur in skin are beneficial to the host, but if they occur in response to an inappropriate and innocuous stimulus, or proceed in an exaggerated fashion, they produce various pathological conditions. These reactions are classically named hypersensitivity-type responses and have been classified by Coombs and Gell into four different types (Gell et al., 1974). It should be noted that the skin may not only be the site at which a hypersensitivity reaction begins, but it may also be the site where an immunological reaction that began elsewhere (i.e. extracutaneously) becomes clinically manifest.Type I hypersensitivity reactions (immediate hypersensitivity) are rapid (from minutes to hours) responses featuring the role of IgE which is initially produced upon first exposure to the allergen. Mast cell degranulation occurs when the allergen is reintroduced into the patient's environment and binds to surface IgE on the mast cell. On mast cell activation, many potent mediators of inflammation are released (histamine, proteolytic enzymes, chemotactic polypeptides, prostaglandins, leucotrienes and thromboxanes), all of which contribute to the clinical manifestations in the skin and the participation of other inflammatory cells (neutrophils, macrophages, eosinophils and lymphocytes).In this group are included the anaphylactic skin response to a bee or wasp sting, which manifest as an urticarial reaction. Type II hypersensitivity reactions are rare in the skin and are referred to in the context of antibody-dependent cytotoxicity. These reactions feature IgG and IgM antibodies which interact with the complement system. Once the complement system is activated, inflammation ensues producing membrane damage and keratinocyte cytopathic changes. In patients with pemphigoid, IgG and various complement components (including C3) are deposited at the dermoepidermal junction, and initiate inflammatory reactions with the accumulation of neutrophils, mast cells,

lymphocytes and eosinophils. This reaction is implicated in the disruption of the attachment mechanism resulting in blister formation (Schmidt and Zillikens, 2000). Type III hypersensitivity reactions involve immune complex deposits; a frequent site includes the postcapillary venules of the superficial vascular plexus in the skin. Patients who develop allergic or hypersensitivity reactions to various medications may present with palpable purpuric skin lesions or vasculitis caused by deposits of immunoglobulins and complement in the vessel walls. Such deposits provoke neutrophil- or lymphocyte-mediated inflammatory reactions; how these immune complexes form and why they become deposited in the skin, or persist in the circulation, remain unanswered questions. Type IV hypersensitivity reactions are also referred to as delayed-type reactions since they generally require several days to become clinically manifest. This immune response requires T lymphocytes. Two of the most common type IV immune hypersensitivity responses in the skin include allergic contact dermatitis from epicutaneous exposure to antigens, and tuberculin-type reactions in which intradermal antigens are deposited. In both types of reactions, Langerhans cells and dermal dendritic cells initiate a complex series of steps leading to T-cell activation. In eczematous skin reactions, T cells in turn induce tissue damage by exerting direct cytotoxicity (mostly $CD8^+$ T cells) against keratinocytes or other resident cell types, and by releasing cytokines, which amplify the inflammatory response by targeting resident skin cells.

In light of recent advances, it appears however, that the Gell and Coombs classification may represent an oversimplification, and other classifications that have been proposed to better describe the complexity of events occurring during immunopathological reactions, as proposed for drug-induced exanthems (Lerch and Pichler, 2004). The characteristics involvement of certain cell types (e.g., eosinophils or neutrophils) in some cell-mediated skin reactions underlies the expression of mediators specifically targeting these cells. Moreover, the diversity of the T-cell response with the prevalent recruitment and activation of different T-cell subsets (e.g., type 1 vs. type 2 T cells), and the involvement of distinct T regulatory cells in different skin diseases await a more complex classification of immunopathological reactions.

5. Conclusions

Knowledge of skin immunological defence mechanisms is advancing rapidly and provides new insights into the normal homeostasis of this vital organ, as well as improving our understanding of various disease processes. Structure–function correlations are being expanded to include detailed molecular dissection of the events that are principally responsible for the SIS, and which guide the coordinated intercellular interplay crucial for immune surveillance involving the skin. We believe that it is essential for our understanding of cutaneous immunology, to keep in mind what distinguishes the skin from other organs. From such a platform of specific immunophysiology of the skin, one might try to understand its dysregulations as we know them in the form of a surprisingly large number of inflammatory and immunodermatological diseases.

Key points

- The skin provides a complex microenvironment where several cell types actively participate in the initiation and regulation of inflammatory and immune responses.
- Cutaneous dendritic cells serve as dominant antigen-presenting cells in the induction of T-cell-mediated immune responses and subsequent reactivation of T cells. Under homeostatic conditions, however, dendritic cells are primarily involved in the maintenance of immune tolerance to self and innocuous non-self antigens.
- T lymphocytes with specificity for antigens entered through the skin acquire a propensity, based on the expression of specific homing receptors, to recirculate in the skin.
- Keratinocytes have the capacity to secrete an array of cytokines and chemokines very important for the regulation of T-cell and dendritic cell functions, and the recruitment and activation of inflammatory cells.

- Mast cells and peptidergic nerve endings form an integrated unit, which can readily release factors involved in the initiation of the vascular phase of acute inflammation, but, together with endothelial cells, they also regulate cell-mediated immune responses.

References

Agar, N., Young, A.R. 2005. Melanogenesis: a photoprotective response to DNA damage?. Mutat. Res. 571, 121.

Albanesi, C., Scarponi, C., Giustizieri, M.L., et al. 2005. Keratinocytes in skin inflammation. Curr. Drug Targets Inflamm. Allergy, 4, 329.

Bardan, A., Nizet, V., Gallo, R.L. 2004. Antimicrobial peptides and the skin. Expert Opin. Biol. Ther. 4, 543.

Barker, J.N.W.N., Mitra, R.S., Griffiths, C.E.M., et al. 1991. Keratinocytes as initiators of inflammation. Lancet 337, 211.

Boehncke, W.-H., Schön, M.P., Girolomoni, G., et al. 2005. Leukocyte extravasation as a target for antiinflammatory therapy—Which molecule to choose?. Exp. Dermatol. 14, 70.

J.D. Bos (Ed.), 2005. Skin Immune System. Cutaneous immunology and clinical immunodermatology, 3rd ed., CRC Press, Boca Raton, FL.

Bos, J.D., Kapsenberg, M.L. 1986. The skin immune system (SIS): its cellular constituents and their interactions. Immunol. Today 7, 235.
The original description of the organization of skin immune system with its cellular and humoral constituents.

Bos, J.D., Kapsenberg, M.L. 1993. The skin immune system: progress in cutaneous biology. Immunol. Today 14, 75.

Bos, J.D., Meinardi, M.M.H.M. 2000. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp. Dermatol. 9, 224.

Candi, E., Schmidt, R., Melino, G. 2005. The cornified envelope: a model of cell death in the skin. Nat. Rev. Mol. Cell. Biol. 6, 328.
A comprehensive review on the characteristics and the mechanisms governing the terminal differentiation of keratinocytes.

Cavani, A., Di Nuzzo, S., Girolomoni, G., et al. 2005. T lymphocytes of the skin. In: J.D. Bos (Ed.), Skin Immune System (SIS), 3rd ed CRC Press, Boca Raton, FL, p. 101.

Cavani, A., Nasorri, F., Ottaviani, C., et al. 2003. Human CD25+ regulatory T cells maintain immune tolerance to nickel in healthy, non allergic individuals. J. Immunol. 171, 5760.
A seminal paper suggesting that T regulatory cells play a key role in determining whether an immune reaction to innocuous non-self antigens will be clinically silent or pathological.

Elias, P.M. 2004. The epidermal permeability barrier: from the early days at Harvard to emerging concepts. J. Invest. Dermatol. 122, xxxvi.

Fichtelius, K.E., Groth, O., Liden, S. 1970. The skin, a first level lymphoid organ?. Int. Arch. Allergy 37, 607.

Galli, S.J., Kalesnikoff, J., Grimbaldeston, M.A., et al. 2005. Mast cells as tunable effector and immunoregulatory cells: recent advances. Annu. Rev. Immunol. 23, 749.

Gell, P.G.H., Coombs, R.R.A., Lachmann, P. (Eds.), 1974. Clinical Aspects of Immunology, 3rd ed, Blackwell Science, Oxford.

Girolomoni, G., la Sala, A. 2005. Dendritic cells (T-lymphocyte stimulating). In: Encyclopedia of Life Science. Wiley Interscience, Hoboken, NJ. www.els.net.

Lerch, M., Pichler, W.J. 2004. The immunological and clinical spectrum of delayed drug-induced exanthems. Curr. Opin. Allergy Clin. Immunol. 4, 411.

Madison, K.C. 2003. Barrier function of the skin: la raison detre of the epidermis. J. Invest. Dermatol. 121, 231.

B.J. Nickoloff (Ed.), 1993. Dermal Immune System. CRC Press, Boca Raton, FL.

Nickoloff, B.J., 2001. Skin immunological defense mechanisms. In: Encyclopedia of Life Science. Nature Publishing Group, London. www.els.net.

Nickoloff, B.J., Naidu, Y. 1994. Perturbation of epidermal barrier function correlates with initiation of cytokines cascade in human skin. J. Am. Acad. Dermatol. 30, 535.

J.A. Parrish (Ed.), 1983. The Effect of Ultraviolet Radiation on the Immune System. Johnson & Johnson Co., Skillman, NJ.

Pastore, S., Mascia, F., Dattilo, C., et al. 2004. Chemokine networks in inflammatory skin diseases. Eur. J. Dermatol. 14, 203.

Paus, R., Nickoloff, B.J., Ito, T. 2005. A 'hairy' privilege. Trends Immunol. 26, 32.

Paus, R., van der Veen, C., Eichmuller, S., et al. 1998. Generation and cyclic remodeling of the hair follicle immune system in mice. J. Invest. Dermatol. 111, 7.

Rowden, G. 1981. The Langerhans cell. CRC Crit. Rev. Immunol. 3, 95.

Schmidt, E., Zillikens, D. 2000. Autoimmune and inherited subepidermal blistering diseases: advances in the clinic and the laboratory. Adv. Dermatol. 16, 113.

G. Schuler (Ed.), 1991. Epidermal Langerhans cells. CRC Press, Boca Raton, FL.

Sontheimer, R.D. 1989. Perivascular dendritic macrophages as immunobiological constituents of the human dermal perivascular unit. J. Invest. Dermatol. 93, 96S.

Sontheimer, R.D., Tharp, M.D. 1991. Immunological repertoire of the dermal microvascular unit. In: B.J. Nickoloff (Ed.), Dermal Immune System. CRC Press, Boca Raton, FL, p. 117.

Streilein, J.W. 1978. Lymphocyte traffic, T cell malignancies and the skin. J. Invest. Dermatol. 71, 167.

Streilein, J.W. 1990. Skin-associated lymphoid tissues (SALT): the next generation. In: J.D. Bos (Ed.), Skin Immune System (SIS). CRC Press, Boca Raton, FL, p. 25.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 2

T Cells and Dendritic Cells in Immuno-Mediated Skin Pathology

Karin Loser, Jenny Apelt, Stefan Beissert*
Department of Dermatology, University of Münster, Münster, Germany

1. Introduction

Autoimmune diseases play an increasingly important role in public health systems of the First World since according to the American Autoimmune Related Diseases Association (AARDA) about 20% of the US population is affected by autoimmune symptoms (http://www.aarda.org/qa_frames.html). Within the most prevalent autoimmune diseases in dermatology are cutaneous as well as systemic lupus erythematosus, bullous autoimmune disorders, dermatomyositis, scleroderma, psoriasis, vitiligo, lichen planus, and many more some of which are described throughout this book. Also, autoimmune disorders of the skin can be paralleled by autoimmune symptoms in other organs such as the thyroid gland or the insulin-producing Langerhans' islets of the pancreas indicating that cutaneous lesions can mirror internal autoimmune processes. Cutaneous autoimmune diseases are rarely lethal, however, significant morbidity and disabilities can result. The underlying pathomechanism of loss of immunotolerance against the skin is largely unknown. The current hypothesis is that genetic predisposition and environmental factors participate in the multifaceted aspects of disease development and contribution of susceptibility to autoimmune reactions. Until now most studies on the early events of autoimmune development are restricted to processes after the outbreak of diseases. Of great help are several animal models, mostly of systemic lupus erythematosus, with spontaneous loss of immunotolerance and disease development (Theofilopoulos and Dixon, 1985; Stoll and Gavalchin, 2000). These models and the emerging new 'high thruput' technologies such as expression profiling of whole human and murine genomes will enable us in the future to study all stages of disease progression and to identify early genes or proteins that are already expressed without overt symptoms. In addition, these technologies will lead to the detection of new drug targets, which will hopefully result in the development of new treatment regimes that are specific, effective, and safe to use.

2. Self-reactive T cell subsets

Originally the immune system has evolved to combat infections. Accordingly, immunocompetent cells can be specifically activated by microbial antigens via Toll-like receptors (TLR). Furthermore, activation of immune responses needs to be controlled or 'switched off' after accomplishment of its effector functions. Based on experimental data several models have been proposed on how the immune system works: The so-called self/non-self model predicts that the immune system is based on its ability to discern between self and foreign constituents thus, allowing the subsequent destruction of foreign pathogens. The infectious non-self model (danger model) adds the aspect that activation

*Corresponding author.
Department of Dermatology, University of Münster, Von-Esmarch-Str. 58, D-48149 Münster, Germany.
Tel.: +49-251-835-8599; Fax: +49-251-835-8579.
E-mail address: beisser@uni-muenster.de (S. Beissert).

DOI: 10.1016/S1571-5078(05)05002-6

of antigen-presenting cells (APC), generally the first immunocytes to be involved in a primary immune response, via TLR's and costimulatory molecules is a necessary event in initiation of an immune response. APCs are not antigen-specific and present a variety of different antigens. The danger model proposes that these danger signals supplied by tissues or cells injured by trauma, pathogens, toxins, etc. activate the APCs possibly in a tissue-dependent manner (Matzinger, 1994). APCs activated in the vicinity of danger signals become mature, develop potent T cell stimulatory capacity such as the high expression of MHC as well as costimulatory molecules, and migrate from the site of danger to the draining lymph node. There they encounter naïve T cells, which can be activated in a MHC class I- or MHC class II-restricted fashion. Upon stimulation, these effector cells must be able to recognize the antigenic constituents along with the danger signals that mark the presence of an invading pathogen. Complex interactions of a vast array of cell-types and cell-signaling processes along with the specific ontological development of two of the major cell-types involved in the immune process, the T- and B cells, are necessary to achieve this goal.

During intrathymic development, somatic selection processes allow a fraction of T cells to differentiate, mature, and to emigrate into the circulation. It is the current belief that auto-antigens play an essential role in establishing the repertoire of mature T cells. In the first phase of T cell selection within the thymus termed 'positive selection', T cells with a sufficient affinity to self-antigens bind to these antigens, which are expressed on thymic epithelial cells, and become selected for survival whereas the remaining T cells die by neglect via apoptosis. In the second phase termed 'negative selection', T cells with an excessive affinity to self-epitopes are once again deleted from the system via the apoptotic pathway. These developmental processes have been described in the cortex and the medulla of the thymus. However, recent experimental evidence questions such a strict compartimentalization in the thymus (Derbinski et al., 2005). A gene that appears to play an important role in regulating antigen expression on thymic epithelial cells is AIRE (autoimmune regulator) since AIRE knockout mice suffer from a severe form of autoimmunity (Johnnidis et al., 2005; Kuroda et al., 2005; Villasenor et al., 2005). In certain forms of human autoimmune diseases mutations in the AIRE gene have been detected suggesting that, indeed, AIRE plays an important role in autoimmune development (Cavadini et al., 2005).

The remaining T cells then constitute the T cell population enabling the recognition and combat of foreign pathogens. Some are polyactive and can recognize self-antigens as well as foreign antigens (Joshi et al., 2001; Martin et al., 2001). A similar mechanism for the selection of self-reactive B cell precursors within the bone marrow has been postulated although this pathway has not been extensively investigated. Yet under the conditions prevailing in the thymus, not all auto-antigens are presented and T cells possessing high avidity to auto-antigens can 'slip' through the selection process. In contrast to the longstanding dogma that auto-reactive T cells are completely removed from the system via clonal deletion, new studies on T cell receptor rearrangements revealed that in fact auto-reactivity is perhaps necessary for immune functions as low grade exposure to auto-antigens within the periphery seem to be required for T cell maintanence (Anderton and Wraith, 2002). As these T cells are per definition auto-reactive it is essential to differentiate between autoimmunity and autoimmune disease in this context (Ermann and Fathman, 2001).

In dermatology, auto-reactive T cells have been also detected in the peripheral blood of patients suffering from pemphigus vulgaris or bullous pemphigoid, both disorders are acquired bullous autoimmune diseases (Budinger et al., 1998; Hertl and Veldman, 2003; Veldman et al., 2004b). In pemphigus vulgaris the auto-antigen is desmoglein 3 (Dsg 3) a hemidesmosomal protein, which is important for the firm adhesion of keratinocytes. Stimulation of PBMC with Dsg 3 revealed the presence of Dsg 3-reactive T cell clones. However, in pemphigus vulgaris auto-antibodies to Dsg 3 are crucial and pathogenic, because they induce loss of keratinocyte adherence as well as blister formation. How do, therefore, auto-reactive T cells participate in disease development? It might be possible that Dsg 3-reactive T cells could provide T cell help to B cells for the development of plasma cells and

subsequently anti-Dsg 3 auto-antibody production. Similarly, in patients suffering from bullous pemphigoid BP180-reactive T cell clones were identified in the PBMC fraction of the patient's blood samples. Interestingly, BP180-reactive T cells were also detectable in HLA-matched individuals without disease (Budinger et al., 1998). These findings suggest that auto-reactive (effector) T cells are present in the periphery of patients suffering from autoimmune skin disorders and that these cells are present without onset of overt disease.

An important cellular mechanism for the inhibition of autoimmunity is the active suppression of auto-reactive effector T cells by regulatory ('suppressor') T cells (Sakaguchi et al., 2001; Sakaguchi, 2003; Shevach, 2002; Shevach et al., 2001). Suppressor T cells have been described already several decades ago, however, the lack of molecular markers to further characterize these cells has drawn their existence into question for a long time (Gershon et al., 1972, 1974; Gershon and Kondo, 1970; Janeway, 1988). While studying colitis development in adoptively transferred SCID mice Sakaguchi et al. (1995) have detected $CD4^+CD25^+$ T cells with potent suppressor function (Sakaguchi et al., 1995). Since then the term regulatory T cells (Treg) has been coined although the main function of these cells is to suppress the activation and proliferation of auto-reactive effector T cells. $CD4^+CD25^+$ T cells represent one subset of regulatory T cells, which make up about 6–9% of the $CD4^+$ T cell population. This subset has been detected in humans and rodents with similar suppressor function (Sakaguchi et al., 1995; Jonuleit et al., 2001; Dieckmann et al., 2001). Treg have to be activated via the T cell receptor to exert their inhibitory function. This activation can be achieved by exposure to specific antigens or mitogenic antibodies. Once activated Treg suppress the activation of effector T cells in an antigen non-specific fashion (bystander suppression) (Thornton and Shevach, 2000; Thornton et al., 2004). In contrast to effector T cells, Treg are anergic upon activation. The molecular mechanisms that mediate suppression are incompletely understood. In vitro investigations indicate a cell contact-dependent form of suppression, which is mediated in part by the expression of granzyme B, modulation of tryptophan metabolism and perhaps killer C-type lectins expressed on the surface of Treg (Fallarino et al., 2003; Gondek et al., 2005). Coincubation of Treg and effector T cells results in the downregulation of IL-2 expression in the latter. IL-2 appears to be an important growth factor for Treg and perhaps the high expression of CD25 reflects this need for IL-2 (Malek et al., 2002). Besides CD25 a number of surface molecules, which are associated with Treg have been identified such as intracellular cytotoxic T lymphocyte activation antigen 4 (CTLA-4; CD152), neuropilin-1 (Nrp-1), $CD45RB^{low}$, glucocorticoid-induced TNF family related receptor (GITR), the chemokine receptors CCR4 and CCR8, CD62L (L-selectin), LAG-3, and integrin $\alpha_E\beta_7$ (CD103) (Read et al., 1998, 2000; McHugh et al., 2002; Lehmann et al., 2002; Huang et al., 2004; Iellem et al., 2001; Salomon et al., 2000; Takahashi et al., 2000; Bruder et al., 2004). Some of these molecules have been shown to be important for the suppressor function of Treg.

Treg develop in the thymus and the transcription factor that controls lineage commitment is *Foxp3* (Fontenot et al., 2003; Hori et al., 2003; Khattri et al., 2003). *Foxp3* is highly expressed in $CD4^+CD25^+$ T cells in humans and rodents. In mice, deletion of *Foxp3* results in loss of Treg and development of severe lymphoproliferation. In humans, the IPEX syndrome has been associated with a mutation in the *Foxp3* gene resulting in a multi-organ inflammatory disorder (Bennett et al., 2001; Wildin et al., 2001). Overexpression of *Foxp3* conveys suppressor function to naïve T cells, which can be used for immunotherapy of ongoing systemic autoimmunity in mice (Loser et al., 2005). Using a *Foxp3*-specific antibody, $Foxp3^+$ cells can be detected in situ in the T cell area of human lymph node tissue demonstrating their distribution pattern (Fig. 1).

Another subset of regulatory T cells is T regulatory type 1 cells (Tr1), which are characterized by the expression of high amounts of IL-10 (Foussat et al., 2003; Groux et al., 1997; Kemper et al., 2003). Tr1 cells appear to play a role in the inhibition of colitis in animal models. In humans, however, there is recent evidence that Tr1 cells play a role in controlling cutaneous autoimmune disorders. Dsg 3-specific Tr1 cells were identified in

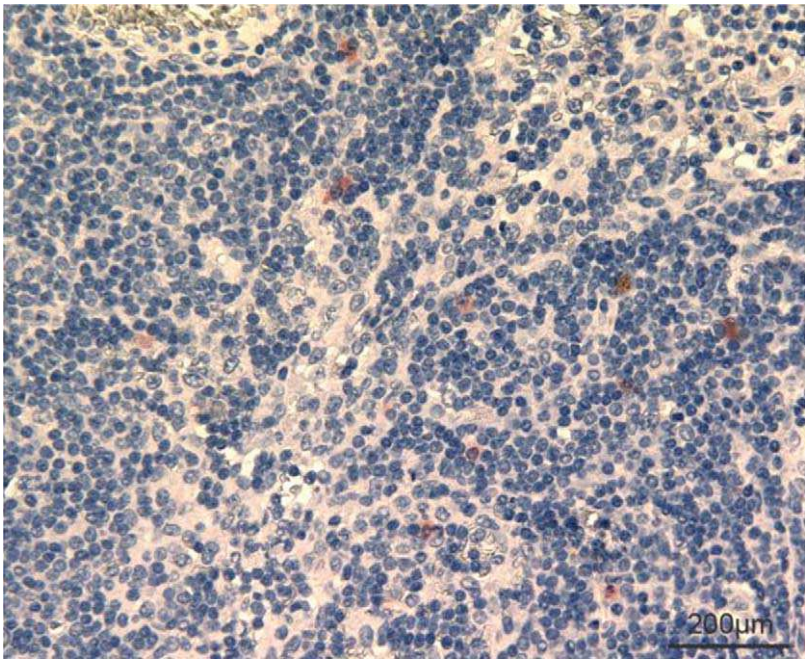


Figure 1. Detection of Foxp3$^+$ T cells in human skin draining lymph node tissue. (Foxp3 polyclonal goat antibody, Abcam, Cambridge, UK.)

humans, which may maintain and restore natural tolerance against Dsg 3 (Veldman et al., 2004a). Dsg 3-responsive IL-10-secreting Tr1 cells were isolated from healthy carriers of the pemphigus-associated HLA class II alleles, DRB1*0402 and DQB1*0503, but were only rarely detected in pemphigus patients. In addition, it was shown that growth of Dsg 3-responsive Tr1 cells requires the presence of IL-2, and that they exert their Dsg 3-dependent inhibitory function by the secretion of IL-10 and TGF-β. Thus, these Tr1 cells may be critically involved in the maintenance and restoration of tolerance against Dsg 3.

Besides CD4$^+$ T cells, CD8$^+$T cells with suppressor activity have also been described, which were able to inhibit the development of experimental allergic encephalomyelitis (EAE) (Jiang et al., 1992). CD8$^+$ suppressor T cells abrogated the activation of encephalitogenic CD4$^+$ Th1 cells. However, CD8$^+$ suppressor T cells required priming during the first episode of EAE to regulate CD4$^+$ T cells triggered by secondary MBP stimulation in vivo. Since the suppressor function of CD8$^+$T cells could be blocked by antibodies to the MHC class 1b Qa-1 molecule it was proposed that perhaps the non-classical MHC class 1b pathway plays a role in restricting the suppression mediated by CD8$^+$T cells. Indeed, Qa-1$^{-/-}$ mice display severe EAE, which is associated with the escape of Qa-1$^{-/-}$ CD4$^+$ T cells from CD8$^+$T cell suppression (Hu et al., 2004). Qa-1 is of limited polymorphism and is expressed on activated but not resting T cells. Qa-1 has the potential to present foreign and auto-antigens to CD8$^+$T cells, indicating that Qa-1 may serve as a target antigen for CD8$^+$T cells. Because Qa-1 auto-antigen complexes can bind to CD94-NKG2 receptors on CD8$^+$T cells, CD8$^+$ suppressor T cells may regulate T cell responses via CD94-NKG2 receptors.

Since several subsets of Treg have been described their function was recently determined in inflammatory skin diseases. In psoriasis, it was found that a CD4$^+$ T lymphocyte subpopulation in peripheral blood, phenotypically resembling Treg (CD25^{high}, CTLA-4$^+$, Foxp3^{high}) is deficient in its suppressor activity. This was associated with accelerated proliferation of CD4$^+$ responder T cells in psoriasis (Sugiyama et al., 2005). In addition, CD4$^+$CD25$^+$

T cells were found significantly increased in patients with atopic dermatitis compared with asthmatic patients or nonatopic healthy control subjects. These cells effectively suppressed proliferative responses of $CD4^+CD25^-$ cells after anti-CD3 stimulation. In contrast, after stimulation with staphylococcal enterotoxin B $CD4^+CD25^+$ cells were no longer anergic and had lost their suppressive function (Ou et al., 2004). This indicates that patients with atopy have significantly increased numbers of peripheral blood Treg cells with normal immunosuppressive activity. However, activation of innate response pathways induced after stimulation with staphylococcal antigens, resulted in loss of suppressor activity in these Treg. These data suggest a novel mechanism by which staphylococci may augment T cell activation in atopic patients. Besides their role in inflammatory skin disorders Treg appear to play a role in cutaneous malignancies. It was recently shown that cutaneous T cell lymphoma (CTCL) cells adopt a Treg phenotype expressing CD25/CTLA-4 and *Foxp3* and secreting IL-10 and TGF-β (Berger et al., 2005).

Taken together, effector as well as regulatory T cells can respond to self-antigens and are therefore per definition both auto-reactive. However, once activated these T cell populations exert completely different functions. Whereas effector T cells can induce pathology upon stimulation, activated Treg are able to suppress the proliferation of these effectors resulting in inhibition of autoimmunity. Thus, the presence and homeostasis of especially auto-reactive Treg is required for the maintenance of tolerance to self. In this context, a more semantic difficulty becomes apparent since actually both T cell subpopulations are per se effectors, which induce or suppress immune responses upon activation.

3. Dendritic cells—key regulators of immune responses

As described above auto-reactive effector T cells are present in both rodents and humans before the overt onset of disease (Anderson et al., 2001; Yan and Mamula, 2002). These auto-reactive effectors are normally not activated as effective checks and balances such as active suppression by Treg or antigen-presentation in the absence of costimulation prevent their stimulation and the subsequent induction of autoimmune responses. This raises the question by which mechanisms autoreactive effector T cells become activated resulting in the breakdown of immunological self-tolerance. Since APC are specialized in activating T cells, they can logically be implicated in the stimulation of autoreactive effector T (and B) cells. Among the different APC subsets, dendritic cells (DC) are the most potent professional APC known today (Banchereau and Steinman, 1998). In the periphery, DC built a network of sentinel cells that untiringly sample antigens. They are extremely adept in antigen uptake as they are equipped with the means to ingest antigens by a manifold of different mechanisms, e.g. via pinocytosis, macropinocytosis, mannose receptor-mediated endocytosis, and phagocytosis. The antigenic material is internalized, processed, and loaded onto the MHC class I or MHC class II molecules. DC play a key role in antigen translocation as antigen transport from periphery to lymph nodes is primarily achieved by DC. Intrinsic and extrinsic signals, such as trauma or infection, induce the release of various cytokines, like tumor necrosis factor (TNF) alpha, which constitute a 'danger' signal for DC (Matzinger, 1994). These danger signals induce profound morphological and physiological changes in DC as they begin to migrate from the periphery to the regional lymph nodes. They simultaneously mature and switch from an antigen uptake mode to an antigen presentation mode. The antigen presentation mode is characterized by upregulation of the various costimulatory and adhesion molecules required for effective T cell stimulation along with an intracellular redistribution of MHC molecules, which results in an increase of antigen-laden MHC on the cell surface. Upon contact with T cells, the very high density of MHC molecules on the cell surface at this stage makes DC extremely well equipped to present antigens to T cells via antigen-specific TCR engagement.

However, not only the TCR/MHC engagement (signal 1) is required for effective antigen

presentation, but also costimulatory molecules (signal 2) need to be present to elicit an immune response. Among these costimulatory molecules one receptor/ligand pair plays a prominent role in this context and that is the CD40 receptor on DC and its ligand CD154 (CD40L) on T cells. Ligation of this receptor pair leads to activation signals both in DC as well as in T cells (Brenner et al., 1997). Furthermore, ligation of CD40 provides one of the strongest activation signals for DC resulting in the production of IL-12 and tipping the T cell responses toward the Th1-type (Cella et al., 1996). As CD40/CD154 interaction is also crucial for B cell stimulation and immunoglobulin class switching, this suggests that CD40 engagement plays an essential role in the communication between DC, T and B cells. Therefore, it has been proposed that CD40/CD40L cross-linking contributes to the generation of autoimmune responses. DC can prime both $CD4^+$ or $CD8^+$ T cells and B cells independently of each other (Dubois et al., 1999; Ridge et al., 1998). They consequently not only play a role in initiating cytotoxic immune responses but also play a role in the regulation of humoral responses.

On the other hand, DC also play a contrasting and yet pivotal role in promoting tolerance. During T cell development, thymic DC are involved in processes for deleting autoreactive T cells (Anderson et al., 1996). In addition, it was shown that in particular DC of the immature phenotype are responsible for downregulating immune responses. Although mature DC do not seem to be affected by IL-10, the presence of IL-10, a Th2 promoting cytokine, during the initial stages of activation of DC causes a reduction in the maturation process of DC and can induce tolerance (Steinbrink et al., 1997, 2002; Enk et al., 1993). This includes the downregulation of inflammatory cytokines such as IL-6, IL-1β and TNFα along with a downregulation of MHC class II molecules and various costimulatory as well as adhesion factors. Jonuleit et al. (2000), reported that repeated stimulation of T cells with immature DC results in the generation of regulatory IL-10 producing $CD4^+$ $CD25^+$ T cells which in turn promote tolerogenicity. Interestingly, two reports in which hemaglutinin or ovalbumin function as model self-antigens of the periphery, revealed that presentation of auto-antigens via DC are a prerequisite for CD4 and CD8 mediated tolerance (Adler et al., 1998; Kurts et al., 1998). In mice, DC that were generated in the presence of TNF α and pulsed with auto-antigenic peptide ameliorated experimental autoimmune encephalomyelitis already upon the first injection (Menges et al., 2002). TNF α-treated DC expressed MHC class II as well as costimulatory molecules, but produced significantly higher concentrations of IL-10 compared to CD40L-treated DC. In two volunteers, injection of immature DC pulsed with influenza matrix peptide (MP) led to a specific inhibition of MP-specific $CD8^+$ T-cell effector function (Dhodapkar et al., 2001). Additionally, it was demonstrated by the same investigators that application of immature DC induced hapten-specific $CD8^+$ regulatory T cells in vivo (Dhodapkar and Steinman, 2002). More recently DC have been shown to be able to directly expand $CD4^+CD25^+$ Treg (Yamazaki et al., 2003). These data suggest that DC might be a useful tool under certain conditions for the therapeutic downregulation of antigen-specific immunity.

In the case of autoimmunity, players in the immune system go astray, the most well known being dysregulated T- and B cells. Normally, these cells are held in abeyance by the simple lack of the costimulatory molecules in the microenvironment necessary to stimulate them (Steinman and Nussenzweig, 2002). T cells and in particular $CD8^+$ but also $CD4^+$ T cells are the effector cells that attack or activate target cells and elicit tissue destruction in this scenario. B cells produce large quantities of antibodies and various mechanisms can lead to tissue injury, e.g. the formation of large deposits of immune complexes in the kidney often leading to nephritis and tissue damage. Furthermore, auto-antibodies can initiate cytolysis of these cells or opsonize them for elimination via phagocytosis. Activated B cells also play another role in the elicitation of autoimmune responses, namely they themselves can function as antigen presenting cells that present auto-antigens to the relevant T cells and contribute to epitope spreading. In the past few years, evidence has accumulated, that DC play a much larger role in autoimmune responses than originally thought.

DC are accomplices in the elicitation of autoimmunity in that they play a pivotal role in the activation of both T- and B cells and by delivering the auto-antigens with the appropriate factors necessary to elicit an immune response. Because DC cannot discriminate between the antigens they capture at the site of inflammation and will thus inadvertently present auto-antigens along with pathogen-specific antigens, a complex interplay of factors has evolved as a necessity for the prerequisite maturation of DC needed for the activation of naive T cells. DC react differently to dying cells as necrotic cells elicit other responses than apoptotic cells (Sauter et al., 2000). DC promote stimulatory responses from $CD4^+$ and $CD8^+$ T cells following exposure to necrotic cells (cell death due to trauma or infection), whereas DC that have had contact to apoptotic cells (physiologic cell death) do not.

An emerging factor in the induction of autoimmune disease is the uptake and processing of auto-antigens originating from apoptotic cells. This model has received increased attention as latest evidence seems to support the idea that the self-determinants involved in autoimmune responses are supplied by dying cells as the reservoir for auto-antigens. Physiologic apoptosis is generally considered to promote tolerogenicity and not autoimmunity. Apoptosis usually occurs sporadically and asynchronously within tissues with no proinflammatory cytokines present. Under steady state conditions, T cells presented with autoantigens by DC either become anergic or are deleted. Yet, during the apoptotic process, many proteins and other cell constituents are uniquely modified which can expose cryptic epitopes or even generate novel autoantigens (Rosen and Casciola-Rosen, 1999). Antiphospholipid antibodies are found in some patients afflicted with SLE. Phosphatidyl-serine is generally located on the inner surface of the plasma membrane yet it is exposed to the outside on the surface of apoptotic blebs thus making it accessible as an epitope (Casciola-Rosen et al., 1996). Other modifications are the apoptosis-specific proteolytic cleavage and/or phosphorylation of the substrate molecules. Defects in apoptotic cell clearance also seem to play a central role. Macrophages and DC scavenge apoptotic cells, ingest these cell components and present them to T cells via MHC complexes thus initiating the signaling cascade leading to autoimmune disease. Furthermore, increased or aberrant apoptotic rates have been reported in tissue-specific as well as systemic autoimmune disorders. At this point it is important to note that exposure to high numbers of apoptotic cells is able to mature DC even in the absence of further inflammatory signals and this may explain why the threshold for an autoimmune response is reached (Rovere et al., 1998a,b).

This is especially interesting when microbial insult leads to the generation of an immune response to such antigens. Emerging evidence also points to a role of pathogens in the modulation of DC function. The infectious agents associated with autoimmune disease are diverse and include the involvement of streptococci in rheumatic fever, Borrelia burgdorfii in Lyme arthritis, Coxsackie virus in myocarditis, Cytomegalie virus or rubella in type 1 diabetes, etc. (Benoist and Mathis, 2001). Although, only circumstantial evidence is yet available and the underlying mechanisms as to how they set off disease are unclear, it intriguingly incriminates APC in this context. One possibility is that APC present self-determinants, a simple bystander activation process takes place and non-specifically activates the cells of the immune system in the close vicinity or within the lymph node during the immune response to the microbes. The process of 'T cell epitope mimicry' has also been proposed to be a major factor in the proclivity of microbial infection to elicit processes leading to autoimmune diseases (Benoist and Mathis, 2001). In this case, as antigen recognition/specificity by T cells can be degenerated, T cells can recognize autoantigens that are similar to those of the pathogen. A report by Ludewig et al. (2001) revealed that stringent threshold levels not only of antigen load but also of the duration of (auto)antigen presentation determines whether stimulation of self-reactive CTLs with subsequent autoimmunity ensues or not in this context, the maturation status of the DC is of prime importance: immature DC have a high turnover rate of MHC/antigen complexes on their cell surface whereas mature DC downregulate turnover rates and stabilize the presence of the antigen/MHC complex on the surface of the DC (Cella et al., 1997).

3.1. Dendritic cells in mixed connective tissue disease

Mixed connective tissue disease (MCTD) is an autoimmune overlap syndrome that shows aspects of lupus erythematosus, scleroderma, and dermatomyositis. We were interested in investigating the role of epidermal APC, the Langerhans cells (LC), in regulating cutaneous immunity. In the skin LC express the CD40 receptor, the CD40L co-receptor can be detected on activated keratinocytes, to address the relevant role of CD40-CD40L(CD154)-signaling during the induction of immune responses, transgenic (tg) mice were generated that overexpress the CD40L on LC neighboring keratinocytes (Mehling et al., 2001). Interestingly, these CD40L tg mice show almost complete depletion of epidermal LC and increased numbers of activated DC in skin-draining lymph nodes. Additionally, CD40L tg mice spontaneously develop autoimmune dermatitis, lymphadenopathy, splenomegaly, lung fibrosis, and nephritis (Mehling et al., 2001). Anti-nuclear antibodies are detectable within the serum of these mice and indirect immunofluorescence studies show that these autoantibodies bind to the skin. CD40L tg mice lose weight as disease progresses and have a significantly reduced life expectancy. These results point to an inherent role of aberrantly activated LC in breaking self-tolerance resulting in the development not only of cutaneous but also of widespread systemic autoimmunity resembling MCTD.

3.2. Dendritic cells in Sjögren's syndrome

Sjörgen's syndrome is another autoimmune disorder affecting the skin and mucous membranes in which DC play an essential role in course of the illness. This disease is characterized by lymphocytic infiltrates in the salivary and lacrimal glands resulting in the loss of function. To this end, van Blokland et al. (2000a) used the NOD and MRL/lpr mouse models to particularly focus on APC in the pathogenic process. Increased numbers of DC were detected in the submandibular glands of NOD/SCID mice prior to lymphocytic infiltration and the outbreak of sialoadenitis in these mice. The same group found correlating results in the human counterparts (van Blokland et al., 2000b). A differentiation was made between patients suffering from Sjögren's syndrome and those with focal sialoadenitis without the clinical criteria of Sjögren's syndrome.

3.3. Dendritic cells induce psoriasis

Psoriasis in one of the most common autoimmune diseases affecting the human skin (Lebwohl, 2003). Similar to other forms of autoimmunity psoriasis results from a self-perpetuation of auto-reactive T cells (Lew et al., 2004). Recently, it was demonstrated in a xenograft model of human psoriasis that plasmacytoid predendritic cells (PDC) are able to initiate lesion formation via secretion of interferon(IFN)-α (Nestle et al., 2005). PDC are a rare cell population in the peripheral blood and secondary lymphoid organs characterized by plasma cell-like morphology and a unique surface phenotype (Liu, 2005). Blocking IFN α or inhibition of PDC to produce IFN α abrogated psoriasis development. PDC were also found in human psoriatic skin lesions. Interestingly, IFN α reconstitution experiments suggested that PDC-derived IFN α is necessary to induce psoriasis development in vivo. These data suggest an innate immune pathway for the initiation of cutaneous inflammatory autoimmune disorder.

Acknowledgments

Due to space restrictions many publications could not be referenced, we apologize to their authors. This work was supported by the German Research Association (DFG) grants BE 1580/6-2, BE 1580/7-1, SFB 293 B8, and a grant from the Interdisciplinary Clinical Research Center (IZKF) Münster, Germany.

References

Adler, A.J., Marsh, D.W., Yochum, G.S., et al. 1998. CD4+ T cell tolerance to parenchymal self-antigens requires presentation by bone marrow-derived antigen-presenting cells. J. Exp. Med. 187, 1555.

Anderson, A.C., Nicholson, L.B., Kuchroo, V.K. 2001. The origin and regulation of autopathogenic T cells. J. Clin. Immunol. 21, 74.

Anderson, G., Moore, N.C., Owen, J.J., et al. 1996. Cellular interactions in thymocyte development. Annu. Rev. Immunol. 14, 73.

Anderton, S.M., Wraith, D.C. 2002. Selection and fine-tuning of the autoimmune T-cell repertoire. Nat. Rev. Immunol. 2, 487.

Banchereau, J. and Steinman, R.M. 1998. Dendritic cells and the control of immunity. Nature 392, 245.
This is an excellent overview on the biology of dendritic cells.

Bennett, C.L., Christie, J., Ramsdell, F., et al. 2001. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat. Genet. 27, 20.

Benoist, C., Mathis, D. 2001. Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry?. Nat. Immunol. 2, 797.

Berger, C.L., Tigelaar, R., Cohen, J., et al. 2005. Cutaneous T-cell lymphoma: malignant proliferation of T-regulatory cells. Blood 105, 1640.

Brenner, B., Koppenhoefer, U., Grassme, H., et al. 1997. Evidence for a novel function of the CD40 ligand as a signalling molecule in T-lymphocytes. FEBS Lett. 417, 301.

Bruder, D., Probst-Kepper, M., Westendorf, A.M., et al. 2004. Neuropilin-1: a surface marker of regulatory T cells. Eur. J. Immunol. 34, 623.

Budinger, L., Borradori, L., Yee, C., et al. 1998. Identification and characterization of autoreactive T cell responses to bullous pemphigoid antigen 2 in patients and healthy controls. J. Clin. Invest. 102, 2082.

Casciola-Rosen, L., Rosen, A., Petri, M., et al. 1996. Surface blebs on apoptotic cells are sites of enhanced procoagulant activity: implications for coagulation events and antigenic spread in systemic lupus erythematosus. Proc. Natl. Acad. Sci. U S A 93, 1624.
This is a classical report on the development of autoimmunity to intracellular antigens.

Cavadini, P., Vermi, W., Facchetti, F., et al. 2005. AIRE deficiency in thymus of 2 patients with Omenn syndrome. J. Clin. Invest. 115, 728.

Cella, M., Engering, A., Pinet, V., et al. 1997. Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature 388, 782.

Cella, M., Scheidegger, D., Palmer-Lehmann, K., et al. 1996. Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation. J. Exp. Med. 184, 747.

Derbinski, J., Gabler, J., Brors, B., et al. 2005. Promiscuous gene expression in thymic epithelial cells is regulated at multiple levels. J. Exp. Med. 202, 33.

Dhodapkar, M.V., Steinman, R.M. 2002. Antigen-bearing immature dendritic cells induce peptide-specific CD8(+) regulatory T cells in vivo in humans. Blood 100, 174.

Dhodapkar, M.V., Steinman, R.M., Krasovsky, J., et al. 2001. Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. J. Exp. Med. 193, 233.

Dieckmann, D., Plottner, H., Berchtold, S., et al. 2001. Ex vivo isolation and characterization of CD4(+)CD25(+) T cells with regulatory properties from human blood. J. Exp. Med. 193, 1303.

Dubois, B., Bridon, J.M., Fayette, J., et al. 1999. Dendritic cells directly modulate B cell growth and differentiation. J. Leukoc. Biol. 66, 224.

Enk, A.H., Angeloni, V.L., Udey, M.C., et al. 1993. Inhibition of Langerhans cell antigen-presenting function by IL-10. A role for IL-10 in induction of tolerance. J. Immunol. 151, 2390.

Ermann, J., Fathman, C.G. 2001. Autoimmune diseases: genes, bugs and failed regulation. Nat. Immunol. 2, 759.

Fallarino, F., Grohmann, U., Hwang, K.W., et al. 2003. Modulation of tryptophan catabolism by regulatory T cells. Nat. Immunol. 4, 1206.

Fontenot, J.D., Gavin, M.A., Rudensky, A.Y. 2003. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat. Immunol. 4, 330.

Foussat, A., Cottrez, F., Brun, V., et al. 2003. A comparative study between T regulatory type 1 and CD4+CD25+ T cells in the control of inflammation. J. Immunol. 171, 5018.

Gershon, R.K., Cohen, P., Hencin, R., et al. 1972. Suppressor T cells. J. Immunol. 108, 586.

Gershon, R.K., Kondo, K. 1970. Cell interactions in the induction of tolerance: the role of thymic lymphocytes. Immunology 18, 723.

Gershon, R.K., Mokyr, M.B., Mitchell, M.S. 1974. Activation of suppressor T cells by tumour cells and specific antibody. Nature 250, 594.

Gondek, D.C., Lu, L.F., Quezada, S.A., et al. 2005. Cutting edge: contact-mediated suppression by CD4+CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. J. Immunol. 174, 1783.

Groux, H., O'Garra, A., Bigler, M., et al. 1997. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature 389, 737.

Hertl, M., Veldman, C. 2003. T-cellular autoimmunity against desmogleins in pemphigus, an autoantibody-mediated bullous disorder of the skin. Autoimmun. Rev. 2, 278.

Hori, S., Nomura, T., Sakaguchi, S. 2003. Control of regulatory T cell development by the transcription factor Foxp3. Science 299, 1057.

Hu, D., Ikizawa, K., Lu, L., et al. 2004. Analysis of regulatory CD8T cells in Qa-1-deficient mice. Nat. Immunol. 5, 516.

Huang, C.T., Workman, C.J., Flies, D., et al. 2004. Role of LAG-3 in regulatory T cells. Immunity 21, 503.

Iellem, A., Mariani, M., Lang, R., et al. 2001. Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. J. Exp. Med. 194, 847.

Janeway, C.A., Jr. 1988. Do suppressor T cells exist? A reply. Scand. J. Immunol. 27, 621.

Jiang, H., Zhang, S.I., Pernis, B. 1992. Role of CD8+ T cells in murine experimental allergic encephalomyelitis. Science 256, 1213.

Johnnidis, J.B., Venanzi, E.S., Taxman, D.J., et al. 2005. Chromosomal clustering of genes controlled by the aire transcription factor. Proc. Natl. Acad. Sci. USA. 102, 7233.

Jonuleit, H., Schmitt, E., Schuler, G., et al. 2000. Induction of interleukin 10-producing, nonproliferating CD4(+) T cells with regulatory properties by repetitive stimulation with allogeneic immature human dendritic cells. J. Exp. Med. 192, 1213.

Jonuleit, H., Schmitt, E., Stassen, M., et al. 2001. Identification and functional characterization of human CD4(+)CD25(+) T cells with regulatory properties isolated from peripheral blood. J. Exp. Med. 193, 1285.
This report describes the detection of CD4+CD25+ regulatory T cells in humans.

Joshi, S.K., Suresh, P.R., Chauhan, V.S. 2001. Flexibility in MHC and TCR recognition: degenerate specificity at the T cell level in the recognition of promiscuous Th epitopes exhibiting no primary sequence homology. J. Immunol. 166, 6693.

Kemper, C., Chan, A.C., Green, J.M., et al. 2003. Activation of human CD4+ cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype. Nature 421, 388.

Khattri, R., Cox, T., Yasayko, S.A., Ramsdell, F. 2003. An essential role for Scurfin in CD4+CD25+ T regulatory cells. Nat. Immunol. 4, 337.

Kuroda, N., Mitani, T., Takeda, N., et al. 2005. Development of autoimmunity against transcriptionally unrepressed target antigen in the thymus of Aire-deficient mice. J. Immunol. 174, 1862.

Kurts, C., Heath, W.R., Kosaka, H., et al. 1998. The peripheral deletion of autoreactive CD8+ T cells induced by cross-presentation of self-antigens involves signaling through CD95 (Fas, Apo-1). J. Exp. Med. 188, 415.

Lebwohl, M. 2003. Psoriasis. Lancet 361, 1197.

Lehmann, J., Huehn, J., de la Rosa, M., et al. 2002. Expression of the integrin alpha Ebeta 7 identifies unique subsets of CD25+ as well as CD25- regulatory T cells. Proc. Natl. Acad. Sci. USA. 99, 13031.

Lew, W., Bowcock, A.M., Krueger, J.G. 2004. Psoriasis vulgaris: cutaneous lymphoid tissue supports T-cell activation and "Type 1" inflammatory gene expression. Trends Immunol. 25, 295.

Liu, Y.J. 2005. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu. Rev. Immunol. 23, 275.

Loser, K., Hansen, W., Apelt, J., Balkow, S., Buer, J., Beissert, S. 2005. In vitro-generated regulatory T cells induced by Foxp3-retrovirus infection control murine contact allergy and systemic autoimmunity. Gene Ther. 12, 1294–1304.

Ludewig, B., McCoy, K., Pericin, M., et al. 2001. Rapid peptide turnover and inefficient presentation of exogenous antigen critically limit the activation of self-reactive CTL by dendritic cells. J. Immunol. 166, 3678.

Malek, T.R., Yu, A., Vincek, V., et al. 2002. CD4 regulatory T cells prevent lethal autoimmunity in IL-2Rbeta-deficient mice. Implications for the nonredundant function of IL-2. Immunity 17, 167.

Martin, R., Gran, B., Zhao, Y., et al. 2001. Molecular mimicry and antigen-specific T cell responses in multiple sclerosis and chronic CNS Lyme disease. J. Autoimmun. 16, 187.

Matzinger, P. 1994. Tolerance, danger, and the extended family. Annu. Rev. Immunol. 12, 991.

McHugh, R.S., Whitters, M.J., Piccirillo, C.A., et al. 2002. CD4(+)CD25(+) immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor. Immunity 16, 311.

Mehling, A., Loser, K., Varga, G., et al. 2001. Overexpression of CD40 ligand in murine epidermis results in chronic skin inflammation and systemic autoimmunity. J. Exp. Med. 194, 615.

Menges, M., Rossner, S., Voigtlander, C., et al. 2002. Repetitive injections of dendritic cells matured with tumor necrosis factor alpha induce antigen-specific protection of mice from autoimmunity. J. Exp. Med. 195, 15.

Nestle, F.O., Conrad, C., Tun-Kyi, A., et al. 2005. Plasmacytoid predendritic cells initiate psoriasis through interferon-{alpha} production. J. Exp. Med. 202, 135.

Ou, L.S., Goleva, E., Hall, C., et al. 2004. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. J. Allergy Clin. Immunol. 113, 756.

Read, S., Malmstrom, V., Powrie, F. 2000. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25(+)CD4(+) regulatory cells that control intestinal inflammation. J. Exp. Med. 192, 295.

Read, S., Mauze, S., Asseman, C., et al. 1998. CD38+ CD45RB(low) CD4+ T cells: a population of T cells with immune regulatory activities in vitro. Eur. J. Immunol. 28, 3435.

Ridge, J.P., Di Rosa, F., Matzinger, P. 1998. A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper and a T-killer cell. Nature 393, 474.

Rosen, A., Casciola-Rosen, L. 1999. Autoantigens as substrates for apoptotic proteases: implications for the pathogenesis of systemic autoimmune disease. Cell Death Differ 6, 6.

Rovere, P., Manfredi, A.A., Vallinoto, C., et al. 1998a. Dendritic cells preferentially internalize apoptotic cells opsonized by anti-beta2-glycoprotein I antibodies. J. Autoimmun. 11, 403.

Rovere, P., Vallinoto, C., Bondanza, A., et al. 1998b. Bystander apoptosis triggers dendritic cell maturation and antigen-presenting function. J. Immunol. 161, 4467.

Sakaguchi, S. 2003. The origin of FOXP3-expressing CD4+ regulatory T cells: thymus or periphery. J. Clin. Invest. 112, 1310.

Sakaguchi, S., Sakaguchi, N., Asano, M., et al. 1995. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J. Immunol. 155, 1151.

This manuscript reports the rediscovery of regulatory (CD4 + CD25 +) T cells.

Sakaguchi, S., Sakaguchi, N., Shimizu, J., et al. 2001. Immunologic tolerance maintained by CD25 + CD4 + regulatory T cells: their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. Immunol. Rev. 182, 18.

Salomon, B., Lenschow, D.J., Rhee, L., et al. 2000. B7/CD28 costimulation is essential for the homeostasis of the CD4 + CD25 + immunoregulatory T cells that control autoimmune diabetes. Immunity 12, 431.

Sauter, B., Albert, M.L., Francisco, L., et al. 2000. Consequences of cell death: exposure to necrotic tumor cells, but not primary tissue cells or apoptotic cells, induces the maturation of immunostimulatory dendritic cells. J. Exp. Med. 191, 423.

Shevach, E.M. 2002. CD4 + CD25 + suppressor T cells: more questions than answers. Nat. Rev. Immunol. 2, 389.

Shevach, E.M., McHugh, R.S., Piccirillo, C.A., et al. 2001. Control of T-cell activation by CD4 + CD25 + suppressor T cells. Immunol. Rev. 182, 58.

Steinbrink, K., Graulich, E., Kubsch, S., et al. 2002. CD4(+) and CD8(+) anergic T cells induced by interleukin-10-treated human dendritic cells display antigen-specific suppressor activity. Blood 99, 2468.

Steinbrink, K., Wolfl, M., Jonuleit, H., et al. 1997. Induction of tolerance by IL-10-treated dendritic cells. J. Immunol. 159, 4772.

Steinman, R.M., Nussenzweig, M.C. 2002. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. Proc. Natl. Acad. Sci. USA 99, 351.

Stoll, M.L., Gavalchin, J. 2000. Systemic lupus erythematosus-messages from experimental models. Rheumatology (Oxford) 39, 18.

Sugiyama, H., Gyulai, R., Toichi, E., et al. 2005. Dysfunctional blood and target tissue CD4 + CD25 high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. J. Immunol. 174, 164.

Takahashi, T., Tagami, T., Yamazaki, S., et al. 2000. Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-associated antigen 4. J. Exp. Med. 192, 303.

Theofilopoulos, A.N., Dixon, F.J. 1985. Murine models of systemic lupus erythematosus. Adv. Immunol. 37, 269.

Thornton, A.M., Piccirillo, C.A., Shevach, E.M. 2004. Activation requirements for the induction of CD4 + CD25 + T cell suppressor function. Eur. J. Immunol. 34, 366.

Thornton, A.M., Shevach, E.M. 2000. Suppressor effector function of CD4 + CD25 + immunoregulatory T cells is antigen nonspecific. J. Immunol. 164, 183.

van Blokland, S.C., van Helden-Meeuwsen, C.G., Wierenga-Wolf, A.F., et al. 2000a. Two different types of sialoadenitis in the NOD- and MRL/lpr mouse models for Sjogren's syndrome: a differential role for dendritic cells in the initiation of sialoadenitis?. Lab. Invest. 80, 575.

van Blokland, S.C., Wierenga-Wolf, A.F., van Helden-Meeuwsen, C.G., et al. 2000b. Professional antigen presenting cells in minor salivary glands in Sjogren's syndrome: potential contribution to the histopathological diagnosis?. Lab. Invest. 80, 1935.

Veldman, C., Hohne, A., Dieckmann, D., et al. 2004a. Type I regulatory T cells specific for desmoglein 3 are more frequently detected in healthy individuals than in patients with pemphigus vulgaris. J. Immunol. 172, 6468.

Veldman, C.M., Gebhard, K.L., Uter, W., et al. 2004b. T cell recognition of desmoglein 3 peptides in patients with pemphigus vulgaris and healthy individuals. J. Immunol. 172, 3883.

Villasenor, J., Benoist, C., Mathis, D. 2005. AIRE and APECED: molecular insights into an autoimmune disease. Immunol. Rev. 204, 156.

Wildin, R.S., Ramsdell, F., Peake, J., et al. 2001. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat. Genet. 27, 18.

Yamazaki, S., Iyoda, T., Tarbell, K., et al. 2003. Direct expansion of functional CD25 + CD4 + regulatory T cells by antigen-processing dendritic cells. J. Exp. Med. 198, 235.

Yan, J., Mamula, M.J. 2002. Autoreactive T cells revealed in the normal repertoire: escape from negative selection and peripheral tolerance. J. Immunol. 168, 3188.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 3

D6 as a Decoy and Scavenger Receptor for Inflammatory CC Chemokines in the Skin

Massimo Locati[a,b], Yeny Martinez de la Torre[a,b], Emanuela Galliera[a], Raffaella Bonecchi[a,b], Gianluca Vago[c], Annunciata Vecchi[b], Alberto Mantovani[a,b,*]

[a]*Institute of General Pathology, Medical Faculty, University of Milan, Milan, Italy*
[b]*Istituto Clinico Humanitas, Rozzano (MI), Italy*
[c]*Pathology Unit, L. Sacco Institute of Medical Science, University of Milan, Milan, Italy*

Abbreviations: DARC, Duffy antigen receptor for chemokines; CCL, CC chemokine ligand; CCR, CC chemokine receptor; TM, Transmembrane domain; GPCR, G protein-coupled receptor

1. Introduction

Chemokines are small secreted proteins with leukocyte chemoattractant and cytokine-like activities (Luster, 1998). This large family of related molecules is classified based on structural properties related to the number and position of conserved cysteine residues in two major (CXC and CC chemokines) and two minor (C and CX3C chemokines) subfamilies (Baggiolini, 1998; Rollins, 1997), and according to their production regulation in homeostatic (i.e. produced constitutively) and inflammatory (i.e. produced in response to inflammatory or immunological stimuli) molecules (Mantovani, 1999).

Chemokine biological activities are mediated by a distinct subfamily of the rhodopsin-like 7 transmembrane domain (TM) G protein-coupled receptor (GPCR) superfamily (Murphy, 1994). Chemokine receptors are single polypeptide chains with three extracellular and three intracellular loops, an acidic N-terminal extracellular domain involved in ligand binding, and a serine/threonine-rich intracellular C-terminal domain. The external interface contributes to the ligand recognition specificity, while the cytoplasmic loops and the C-terminal domain provide the interacting surfaces for signalling and internalization machinery. At present, 18 chemokine receptors have been molecularly defined, 10 for CC chemokines (CCR1–10), 6 for CXC chemokines (CXCR1–6), and 1 for C chemokines and CX3C chemokines (XCR1 and CX3CR1, respectively).

Chemokine binding molecules with high structural similarity to chemokine receptors have been described, namely the Duffy Antigen Receptor for Chemokines (DARC) (Horuk et al., 1993), D6 (Bonini et al., 1997; Nibbs et al., 1997b), and CCX CKR (Gosling et al., 2000). These molecules are characterized by distinct patterns of tissue distribution and different ligand specificities, but they share the ability to bind chemokines with high affinity in the absence of any demonstrable signalling function, and therefore are now indicated as 'silent' receptors. 'Silent' receptors have been suggested to favor transfer of chemokines across endothelial barriers and/or to act as decoy receptors which dampen inflammatory reactions (Mantovani et al., 2001). Here we will review recent studies, which have shed new light on the specificity, mode of action and actual function in the skin

*Corresponding author.
Istituto Clinico Humanitas, Via Manzoni 56, I-20089 Rozzano (MI), Italy.
Tel.: +39-02-82242444; Fax: +39-02-82245101.
E-mail address: alberto.mantovani@humanitas.it (A. Mantovani).

DOI: 10.1016/S1571-5078(05)05003-8

of one 'silent' receptor, the D6 molecule, which behaves as a decoy and scavenger receptor for inflammatory CC chemokines.

2. Expression and ligand recognition by the D6 chemokine decoy receptor

After the initial observation in the IL (interleukin)-1 system, decoy receptors have been identified for a large number of cytokines, in particular inflammatory cytokines (Mantovani et al., 2001). Decoy receptors have been identified in cytokine receptor families characterized by different structures and signalling properties, including the IL-1R family (IL-18 binding protein), the TNFR family (e.g. osteoprotegerin), the IL-10 family (IL-22 binding protein), the IL-4/IL-13R family (IL-13R2). In Drosophila, Argos was recently shown to act as a decoy for epithelial growth factor (Klein et al., 2004). The first evidence that a similar strategy could also exist in the chemokine system stemmed from the observation that under appropriate environmental conditions inflammatory chemokine receptors can be uncoupled from the signalling machinery retaining the ability to bind the ligand and targeting it to degradation. Under these conditions, chemokine receptors have been named 'functional' decoy receptors, in that they are structurally identical to signalling receptors but act as decoys (D'Amico et al., 2000). These observations prompted us and others to revisit chemokine silent receptors as candidate decoy receptors.

Originally identified as a CCL3-binding molecule expressed in murine hemopoietic stem cells (Nibbs et al., 1997a) and soon after in human cells (Bonini et al., 1997; Nibbs et al., 1997b), the D6 molecule is a typical chemokine receptor. The 7 TM domain organization is well conserved, the overall sequence identity to conventional chemokine receptors is in the 30–35% range, similar to the identity rate observed among conventional receptors, and the N-terminal domain presents several charged residues, most likely involved in ligand recognition as for other chemokine receptors. Radioligand binding experiments have demonstrated that D6 recognizes an unusual broad spectrum of ligands, being able to interact with most agonists at inflammatory CC chemokine receptors from CCR1 through CCR5 (Bonecchi et al., 2004; Nibbs et al., 1997b). Although D6 behaves as a highly promiscuous receptor for CC chemokines, it also expresses some selectivity in ligand recognition. Homeostatic CC chemokines, agonists at CCR6—CCR10, are not recognized, nor are chemokines belonging to other subfamilies. Even among CC inflammatory chemokines, D6 recognition is restricted to the biologically active form. In the case of CCL22 for example, the intact biologically active molecule is efficiently recognized by D6, while N-terminal CD26-processed CCL22 variants, which loosen their ability to trigger leukocyte recruitment by acting as CCR4 agonists, are not recognized by D6 (Bonecchi et al., 2004). Thus, D6 behaves as a broad spectrum receptor that selectively interacts with biologically active inflammatory CC chemokines. Unlike conventional chemokine receptors, D6 is not expressed at appreciable levels on any leukocyte population analyzed in vitro. While the ligand binding profile is unusually broad, receptor expression is fairly restricted, being D6 only detectable on endothelial cells of lymphatic afferent vessels in skin, gut, and lung, and in placenta (Bonini et al., 1997; Nibbs et al., 1997b, 2001).

3. In vitro properties

Conventional (i.e. signalling) chemokine receptors, like all other members of the GPCR family, mainly transduce intracellular signals through the activation of heterotrimeric G-proteins, and all chemokine receptors in particular mediate signalling through pertussis toxin-sensitive $G\alpha_i$ proteins (Arai et al., 1997; Neptune and Bourne, 1997; Wu et al., 1993). A significant body of evidence has been gathered demonstrating that neither the human nor murine D6 sustain signalling activities typically observed after chemokine receptor triggering, such as calcium fluxes and chemotaxis (Bonecchi et al., 1998; Martinez de la Torre et al., 2005; Nibbs et al., 1997a,b), and preliminary results indicate that D6 is in fact structurally unable to sustain G protein activation (ML, data not shown). Sequence motifs critical for G protein

coupling and signalling functions of chemokine receptors have been identified, and include the DRYLAR/IV in the second intracellular loop as well as the TXP motif in the second TM domain (Farzan et al., 1997; Govaerts et al., 2001). It is noteworthy that these motifs are not conserved in D6. Whether these modifications account for D6 loss of signalling function, while retaining high-affinity ligand binding, is presently under investigation.

After engagement, conventional chemokine receptors, as well as most GPCRs, undergo agonist-induced GRK-mediated receptor phosphorylation on serine/threonine residues located in the C-terminal tail, followed by β-arrestin recruitment and clathrin-coated pit-dependent internalization (Pierce et al., 2002; Thelen, 2001). At the endosomal level, β-arrestin is released, the receptor is dephosphorylated and recycled back to the cell membrane (Pierce et al., 2002). Several key elements of this central paradigm have been altered in D6, allowing it to internalize and recycle constitutively. Independently from the presence or not of ligands, after a time period as short as 3 min most D6 expressed on the cell membrane is found intracellularly and colocalizes with markers of early endosomes (Galliera et al., 2004; Weber et al., 2004). Concomitantly, a comparable number of receptors is recycled on the cell membrane, so that at any given time point the apparent number of receptors expressed on the cell membrane is constant. As for conventional chemokine receptors (Ferguson et al., 1996), D6 internalization requires association to β-arrestin, as demonstrated by the use of β-arrestin-deficient cells (Galliera et al., 2004). As mentioned, receptor association to β-arrestin is usually dependent on agonist-dependent receptor phosphorylation of serine/threonine residues located in the C-terminal domain. In the case of D6, colocalization experiments indicate that D6 is constitutively associated with β-arrestin (Galliera et al., 2004), and consistently with this two independent reports demonstrated that the phosphorylation status of the receptor is not influenced by ligand binding (Galliera et al., 2004; Weber et al., 2004). It is however unclear whether a ligand-independent basal level of phosphorylation is present (Weber et al., 2004), similarly to what previously described for the cytomegalovirus-encoded chemokine receptor US28 (Mokros et al., 2002), or whether D6 association occurs in the absence of receptor phosphorylation (Galliera et al., 2004). Moreover, distal to the putative phosphorylated residues, the C-terminal domain of D6 presents a stretch of acidic residues not detected in other chemokine receptors which is required for β-arrestin association and receptor cycling (Galliera et al., 2004). Whether negative charges substitute for phosphorylation requirements or are instead required for constitutive phosphorylation is presently under investigation.

The constitutive cycling properties, the peculiar expression profile, and the absence of signalling activity, prompted us to investigate whether D6 could mediate chemokine transfer through biological barriers, as previously demonstrated for DARC on vascular endothelium (Middleton et al., 1997). When D6 was expressed on a lymphatic endothelial cell line (Fra et al., 2003) no evidence for facilitated chemokine transfer through the cell monolayer was obtained. Conversely, the presence of D6 consistently resulted in the degradation of appropriate ligands. Similar results were obtained in different D6 cell transfectants (Bonecchi et al., 1998; Fra et al., 2003; Galliera et al., 2004; Weber et al., 2004). Analysis of the biochemical properties of D6 indicated that D6-internalized chemokines are readily released from the receptor during vescicle acidification, allowing subsequent ligand degradation and leaving D6 free to recycle to the cell surface (Weber et al., 2004). Consistently with this, prevention of vesicle acidification by pretreatment with ammonium chloride resulted in reduction of ligand degradation and accumulation of the receptor in intracellular compartments (Fra et al., 2003). Thus, in in vitro settings D6 does not mediate signalling activities or support chemokine transcytosis, but behaves as a decoy receptor that scavenges inflammatory CC chemokines acting as 'tapis roulant' that cycles continuously and independently from ligand engagement.

4. D6 as a decoy in the skin

To put into a test the potential role of D6 as a regulator of inflammatory chemokines in invivo

settings, D6-null mice have been investigated in two different models of local inflammation. By using a model of inflammation induced by phorbol ester skin painting, Jamieson et al. (2005) recently demonstrated that D6-null mice had an exacerbated inflammatory response, initiated by TNF and then sustained by inflammatory chemokines, with a prominent inflammatory infiltrate that included T lymphocytes, mast cells and polymorphonuclear neutrophils. Keratinocyte proliferation and neovascularization were also observed, leading to the development of psoriasiform lesions. In an independent study, D6 deletion resulted in an abnormal inflammatory response in a model of skin inflammation induced by subcutaneous injection of complete Freund adjuvant (Martinez de la Torre et al., 2005). In this model, inflammatory lesions were evident earlier and showed a more severe evolution in D6-deficient animals, which also developed prominent necrosis and neovascularization. At short times (e.g. day 7) inflammation evolved in macroscopic granuloma-like lesions in a significant percentage of D6−/− animals, and only in minority wild-type littermates. Interestingly, differences were not evident at later time points (e.g. day 21). Increased levels of inflammatory CC chemokines were detected locally in both models (Jamieson et al., 2005; Martinez de la Torre et al., 2005), and pretreatment with chemokine receptors blocking antibodies was able to prevent lesions' development, demonstrating that the increased inflammatory response is caused by an inefficient control of the chemokine system in the absence of D6 (Jamieson et al., 2005). Although the specific role of individual CC chemokines in the recruitment of different leukocyte populations has not been defined, both reports described an unbalance restricted to inflammatory CC chemokines, consistently with D6 binding profile. Interestingly, some features were observed in both experimental conditions, including the predicted derangement of CC chemokines and the unexpected effect on neovascularization, while others were apparently restricted to the specific model under investigation, such as keratinocyte proliferation and the prominent neutrophil infiltrate, possibly sustained by a synergistic effect of CC chemokines on CXC chemokines-dependent neutrophil recruitment (Struyf et al., 2005). In synthesis, the two models highlighted a non-redundant role of D6 in the control of local inflammation in skin, but molecular mechanisms involved are still ill-defined and deserve further investigation, as well as the evaluation of a similar role of D6 in other tissues.

The requirement of D6 to control skin inflammation and its restricted expression to afferent lymphatic vessels suggests that this compartment acts as an active disposal system for inflammatory chemokines (Gerard, 2005), and that this function is at least in part mediated by the expression of D6 on lymphatic endothelial cells. During the development of an inflammatory reaction, chemokines have been demonstrated to be transferred to draining lymph nodes where they sustain monocyte recruitment, a phenomenon called 'remote control'

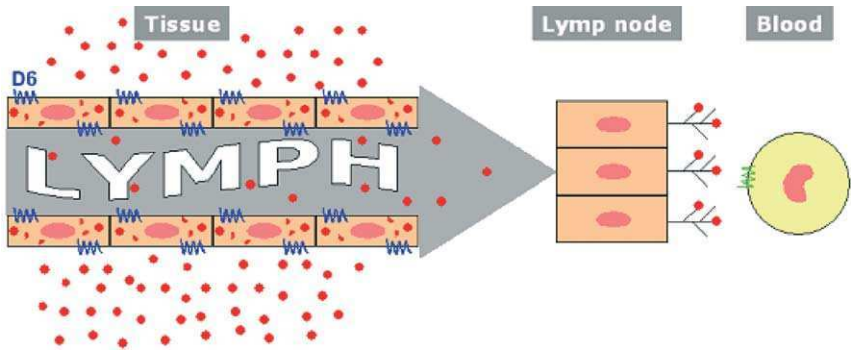


Figure 1. Proposed mode of action of the chemokine decoy receptor D6 in lymphatic vessels. D6 is expressed on lymphatic vessels plays a role in dampening concentrations of inflammatory chemokines in inflamed tissues and tune their access to draining lymph nodes.

(Janatpour et al., 2001; Palframan et al., 2001). In the absence of D6 the increased concentrations of CCL2 and increased cellularity was demonstrated in draining lymph nodes (Martinez de la Torre et al., 2005), demonstrating that D6 is strategically located on afferent lymphatic vessels to scavenge inflammatory chemokines during their drainage, and to tune the amount of chemokines that reach the lymph node. Thus, results obtained in *in vitro* and *in vivo* settings candidate the 'silent' chemokine receptor D6 as the first decoy receptor for inflammatory chemokines, with a non-redundant role in the control of inflammatory CC chemokines in inflamed tissues and in tuning their access to draining lymph nodes (Fig. 1).

5. Concluding remarks

The chemokine system includes at least three seemingly silent receptors, DARC, D6, and CCX CKR. These molecules are structurally characterized by the lack of a canonical residue in the second TM domain and of a canonical DRY motif in the second intracellular loop. There is strong evidence at least for DARC and D6 that these receptors do not activate conventional signalling responses. DARC has most likely a dual function, acting as mechanism that facilitates transfer of chemokines across vascular endothelium and as a chemokine buffering system under different circumstances. In contrast, in vitro and in vivo evidence, including gene targeted mice (Jamieson et al., 2005; Martinez de la Torre et al., 2005), is consistent with the view that D6 is a bona fide decoy receptor and scavenger for inflammatory CC chemokines (Fra et al., 2003; Mantovani et al., 2001). D6 is strategically located on lymphatic endothelial cells in the skin and other organs. Its ligand-independent shuttling from the plasma membrane to endocytic compartments where chemokines are targeted to degradation represents, an unicum for 7 TM receptors. Thus, D6 is a genuine decoy and scavenger for inflammatory CC chemokines, uniquely adapted and located to tame inflammation in the skin and draining lymph nodes.

Key points

D6 is a non-signalling chemokine receptor expressed at high levels in afferent lymphatic vessels in the skin. This 'silent' receptor binds most inflammatory, but not homeostatic, CC chemokines, and targets chemokines to degradation by means of constitutive receptor internalization and recycling. In vitro and in vivo evidence, including results with gene-targeted mice, is consistent with the view that D6 acts as a decoy and scavenger for inflammatory CC chemokines in the skin, dumpening the inflammatory response and tuning the transfer of inflammatory chemokines to the draining lymph nodes. Thus, D6 is ideally adapted to act as a chemokine decoy and scavenger receptor, strategically located on lymphatic endothelium to dampen inflammation in skin and draining lymph nodes.

References

Arai, H., Tsou, C.L., Charo, I.F. 1997. Chemotaxis in a lymphocyte cell line transfected with C-C chemokine receptor 2B: evidence that directed migration is mediated by betagamma dimers released by activation of Galphai-coupled receptors, Proc. Natl. Acad. Sci. USA 94, 14495.

Baggiolini, M. 1998. Chemokines and leukocyte traffic. Nature 392, 565.

Bonecchi, R., Bianchi, G., Bordignon, P.P., et al. 1998. Differential expression of chemokine receptors and chemotactic responsiveness of type 1T helper cells (Th1s) and Th2s. J. Exp. Med. 187, 129.

Bonecchi, R., Locati, M., Galliera, E., et al. 2004. Differential recognition and scavenging of native and truncated macrophage-derived chemokine (MDC/CCL22) by the D6 decoy receptor. J. Immunol. 172, 4972.

Bonini, J.A., Martin, S.K., Dralyuk, F., et al. 1997. Cloning, expression, and chromosomal mapping of a novel human CC-chemokine receptor (CCR10) that displays high-affinity binding for MCP-1 and MCP-3. DNA Cell. Biol. 16, 1249.

D'Amico, G., Frascaroli, G., Bianchi, G., et al. 2000. Uncoupling of inflammatory chemokine receptors by IL-10: generation of functional decoys. Nat. Immunol. 1, 387.

Farzan, M., Choe, H., Martin, K.A., et al. 1997. HIV-1 entry and macrophage inflammatory protein-1beta-mediated signaling are independent functions of the chemokine receptor CCR5. J. Biol. Chem. 272, 6854.

Ferguson, S.S., Downey, W.E., 3rd, Colapietro, A.M., et al. 1996. Role of beta-arrestin in mediating agonist-promoted G protein-coupled receptor internalization. Science 271, 363.

Fra, A.M., Locati, M., Otero, K., et al. 2003. Cutting edge: scavenging of inflammatory CC chemokines by the promiscuous putatively silent chemokine receptor D6. J. Immunol. 170, 2279.
Provides the first evidence of a role as inflammatory chemokine decoy and scavenger receptor of D6.

Galliera, E., Jala, V.R., Trent, J.O., et al. 2004. Beta-arrestin dependent constitutive internalization of the human chemokine decoy receptor D6. J. Biol. Chem. 279, 25590.
Provides a detailed structure–function analysis of D6, focusing on the mechanisms supporting receptor internalization and ligand scavenging.

Gerard, C. 2005. Inflammatory chemokines: tuned in, turned on, dropped out. Nat. Immunol. 6, 366.

Gosling, J., Dairaghi, D.J., Wang, Y., et al. 2000. Cutting edge: identification of a novel chemokine receptor that binds dendritic cell- and T cell-active chemokines including ELC, SLC, and TECK. J. Immunol. 164, 2851.

Govaerts, C., Blanpain, C., Deupi, X., et al. 2001. The TXP motif in the second transmembrane helix of CCR5. A structural determinant of chemokine-induced activation. J. Biol. Chem. 276, 13217.

Horuk, R., Chitnis, C.E., Darbonne, W.C., et al. 1993. A receptor for the malarial parasite Plasmodium vivax: the erythrocyte chemokine receptor. Science 261, 1182.

Jamieson, T., Cook, D.N., Nibbs, R.J., et al. 2005. The chemokine receptor D6 limits the inflammatory response in vivo. Nat. Immunol. 6, 403.
Provides evidence for a role of D6 in the control of inflammatory response in the skin in vivo.

Janatpour, M.J., Hudak, S., Sathe, M., et al. 2001. Tumor necrosis factor-dependent segmental control of MIG expression by high endothelial venules in inflamed lymph nodes regulates monocyte recruitment. J. Exp. Med. 194, 1375.

Klein, D.E., Nappi, V.M., Reeves, G.T., et al. 2004. Argos inhibits epidermal growth factor receptor signalling by ligand sequestration. Nature 430, 1040.

Luster, A.D. 1998. Chemokines–chemotactic cytokines that mediate inflammation. N. Engl. J. Med. 338, 436.

Mantovani, A. 1999. The chemokine system: redundancy for robust outputs. Immunol. Today, 20, 254.

Mantovani, A., Locati, M., Vecchi, A., et al. 2001. Decoy receptors: a strategy to regulate inflammatory cytokines and chemokines. Trends Immunol. 22, 328.
Provides an overview on cytokine decoy receptors, and first introduces the concept of chemokine decoy receptors.

Martinez de la Torre, Y.M., Locati, M., Buracchi, C., et al. 2005. Increased inflammation in mice deficient for the chemokine decoy receptor D6. Eur. J. Immunol. 35, 1342.
Provides evidence for a role of D6 in the control of inflammatory response in the skin in vivo.

Middleton, J., Neil, S., Wintle, J., et al. 1997. Transcytosis and surface presentation of IL-8 by venular endothelial cells. Cell 91, 385.

Mokros, T., Rehm, A., Droese, J., et al. 2002. Surface expression and endocytosis of the human cytomegalovirus-encoded chemokine receptor US28 is regulated by agonist-independent phosphorylation. J. Biol. Chem. 277, 45122.

Murphy, P.M. 1994. The molecular biology of leukocyte chemoattractant receptors. Annu. Rev. Immunol. 12, 593.

Neptune, E.R., Bourne, H.R. 1997. Receptors induce chemotaxis by releasing the betagamma subunit of Gi, not by activating Gq or Gs. Proc. Natl. Acad. Sci. USA 94, 14489.

Nibbs, R.J., Kriehuber, E., Ponath, P.D., et al. 2001. The beta-chemokine receptor D6 is expressed by lymphatic endothelium and a subset of vascular tumors. Am. J. Pathol. 158, 867.
Description of expression profile of the decoy receptor D6, with the first evidence of D6 expression in lymphatic vessels in the skin.

Nibbs, R.J., Wylie, S.M., Pragnell, I.B., et al. 1997a. Cloning and characterization of a novel murine beta chemokine receptor, D6. Comparison to three other related macrophage inflammatory protein-1alpha receptors, CCR-1, CCR-3, and CCR-5. J. Biol. Chem. 272, 12495.

Nibbs, R.J., Wylie, S.M., Yang, J., et al. 1997b. Cloning and characterization of a novel promiscuous human beta-chemokine receptor D6. J. Biol. Chem. 272, 32078.

Palframan, R.T., Jung, S., Cheng, G., et al. 2001. Inflammatory chemokine transport and presentation in HEV: a remote control mechanism for monocyte recruitment to lymph nodes in inflamed tissues. J. Exp. Med. 194, 1361.

Pierce, K.L., Premont, R.T., Lefkowitz, R.J. 2002. Seven-transmembrane receptors. Nat. Rev. Mol. Cell. Biol. 3, 639.

Rollins, B.J. 1997. Chemokines. Blood 90, 909.

Struyf, S., Gouwy, M., Dillen, C., et al. 2005. Chemokines synergize in the recruitment of circulating neutrophils into inflamed tissue. Eur. J. Immunol. 35, 1583.

Thelen, M. 2001. Dancing to the tune of chemokines. Nat. Immunol. 2, 129.

Weber, M., Blair, E., Simpson, C.V., et al. 2004. The chemokine receptor D6 constitutively traffics to and from the cell surface to internalize and degrade chemokines. Mol. Biol. Cell. 15, 2492.
Structure–function analysis of D6, focusing on the mechanisms supporting receptor constitutive cycling.

Wu, D., LaRosa, G.J., Simon, M.I. 1993. G protein-coupled signal transduction pathways for interleukin-8. Science 261, 101.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 4

Autoantibodies and Skin Involvement in Systemic Autoimmune Diseases

Ilaria Cavazzana[a,*], Angela Tincani[a], Pierfranco Riboldi[b], Pier Luigi Meroni[b]

[a]*Servizio di Reumatologia e Immunologia Clinica, Spedali Civili di Brescia, Cattedra di Immunologia Clinica, University of Brescia, Italy*

[b]*Allergy, Clinical Immunology & Rheumatology Unit, Department of Internal Medicine, IRCCS Istituto Auxologico Italiano, University of Milan, Italy*

1. Introduction

Systemic autoimmune disorders are characterized by the occurrence of autoantibodies; most of them display an association with a specific disease (i.e. anti-dsDNA and anti-Sm as specific markers of SLE) or with a subset of the same disease [i.e. anti-centromere in limited in systemic sclerosis (SSc) and anti-topoisomerase I in diffuse SSc] (Le Roy et al., 1988). Moreover, some others have been associated with specific features of a given autoimmune disease (i.e. anti-Ro antibodies in photosensitive skin rash of different forms of SLE).

In some circumstances, rather than being diagnostic markers only, autoantibodies play a direct pathogenic role by inducing specific tissue damage or by modifying the phenotype of specific key cells in a way that might explain the disease manifestations. Several mechanisms have been suggested in order to explain the autoantibody-mediated tissue damage:

1. *Direct autoantibody reaction with cell membranes*: antibody targets could be normal surface antigens, altered antigens or antigens migrated to the cell surface. Autoantibody binding induces the cellular lysis through complement activation, receptor-mediated phagocytosis by mononuclear phagocytes or cell death by natural killer (i.e. anti-lymphocyte antibodies, anti-Ro/La antibodies). In some cases, autoantibodies might trigger an apoptotic process both by itself or in conjunction with an effector cell (i.e. apoptosis activity of Lupus Anticoagulant and anti-endothelial cell antibodies) (Nakamura et al., 1994, 1998; Worda et al., 2003).
2. *Immune complex deposition*: autoantibodies might react with their own antigens in fluid phase and the resulting immune complexes are deposited in the vessel walls where they trigger a complement-mediated inflammation. Alternatively, self-antigens (proteins or nuclear acids) might be planted on the cell membranes or in the interstitial matrix and then be recognized by the specific circulating autoantibodies. The in situ formed immune complexes activate complement cascade and induce inflammation and tissue damage [i.e. antineutrophil cytoplasmic antibody (ANCA) and vasculitides or anti-DNA in lupus nephritis].
3. *Direct antibody penetration into the cells*: IgG autoantibodies could, in fact, be rapidly internalized with an energy-dependent and F(ab)2-mediated mechanism, interfering with signal

*Corresponding author.
Servizio di Reumatologia e Immunologia Clinica, Spedali Civili di Brescia, Piazza Spedali Civili, 1, 25125 Brescia (I), Italy.
Tel.: +39-030-3995-488; Fax: +39-030-3995-085.
E-mail address: ilariacava@virgilio.it (I. Cavazzana).

DOI: 10.1016/S1571-5078(05)05004-X

transduction pathways (Ronda et al., 2002; Cepeda and Reveille, 2004).

4. Autoantibodies can directly stimulate or inhibit target cells, acting as a signal-receptor system (Orlandini et al., 1999; Hayes and Cambridge, 2004). In fact, different authors suggested that autoantibody binding to endothelium might induce a pro-inflammatory cell phenotype (Carvalhor et al., 1996; Meroni et al., 2005). A model of a direct functional effect of anti-endothelial cell antibodies (AECA) on endothelial cells is consistent with the hypothesis that AECA might recognize a cell membrane structure and modulate gene expression (Meroni et al., 2005).

2. Autoantibodies in Systemic Sclerosis (SSc)

The SSc is a systemic autoimmune disease affecting the skin and several internal organs, characterized by small vessel vasculopathy causing severe ischaemia and progressive tissue fibrosis. Patients usually display frequent attacks of Raynaud's phenomenon, progressive skin thickening and a variable involvement of lungs, heart, kidneys and gastrointestinal tract (LeRoy et al., 1988).

Fibroblast activation has been suggested to be responsible for an excessive extracellular matrix deposition with fibrosis and vascular obliteration (LeRoy et al., 1988; Trojanowska et al., 1988; Korn, 1997; Strehlow and Korn, 1998; Mouthon et al., 2002).

Several autoantibodies have been described in SSc and associated to different disease subsets, but only a few of them have been proposed as having a direct role in inducing skin inflammation and fibrosis.

2.1. Pathogenic autoantibodies

2.1.1. Anti-fibroblast antibodies

Some authors reported a specific association between SSc and anti-fibroblast antibodies (AFA), detected in 46–100% of SSc sera (Brentnall et al., 1982; Hill et al., 1996; Chizzolini et al., 2002). Anti-fibroblast IgG antibodies react with cell membrane antigens of normal and SSc fibroblasts in vitro; they recognize constitutive antigens, and are actively internalized via an Fcγ receptor-independent way (Ronda et al., 2002). Anti-fibroblast antibodies are able to activate fibroblasts, up-regulating the expression of ICAM-1 and of pro-inflammatory cytokines and chemokines in a dose-dependent way. Such a pro-inflammatory phenotype was shown to enhance the adhesion of mononuclear cells to fibroblast monolayers in vitro (Chizzolini et al., 2002). Although the ability of AFA to induce collagen synthesis is still debated, the above-mentioned fibroblast activation might play a key role in triggering and/or maintaining skin inflammation. It has been suggested that skin inflammation might be the '*primum movens*' for the development of dermal fibrosis. Recent findings demonstrate a close association between AFA and anti-topoisomerase I antibodies in SSc sera; in fact, anti-topoisomerase-I antibodies seem to react with specific antigens on fibroblast surface, displaying an AFA activity (Henault et al., 2004).

This finding is in clash with previous reports that did not find any correlation between anti-nuclear antibodies and AFA (Ronda et al., 2002). Anyway, it is still unknown whether anti-topoisomerase-I antibody binding might have any role in activating the fibroblasts.

2.1.2. Anti-endothelial antibodies

AECA have been described in about 40% of SSc sera (Rosenbaum et al., 1988; Nylander Lundquist et al., 1992; Salojin et al., 1997; Falcini et al., 1998; Pignone et al., 1998). These autoantibodies react with endothelial cells and induce a pro-inflammatory and pro-adhesive phenotype (Carvalhor et al., 1996). In addition, several reports showed the capacity of SSc–AECA positive sera to mediate antibody-dependent cellular cytotoxicity (ADCC) on human endothelial cells in vitro (Penning et al., 1984; Marks et al., 1988; Holt et al., 1989). However, additional mechanisms have been described: (i) AECA might induce endothelial apoptosis by themselves or through natural killer cells (Bordron et al., 1998; Worda et al., 2003); (ii) AECA can induce tissue

damage through complement activation and cellular lysis (Meroni et al., 2005). As a whole these findings speak in favour of a direct AECA pathogenic role in inducing the endothelial dysfunction characteristic of the early phases of SSc. Endothelial perturbation, in fact, might trigger platelet and leukocytes activation/adhesion with dysregulation of the vascular tone that represents the hallmark of the scleroderma microvasculopathy.

2.1.3. Anti-matrix metalloproteinase (MMP) antibodies

The accumulation of extracellular matrix is dependent on a balance between its synthesis and degradation, the latter process being regulated mainly by MMP. Anti-MMP1 and anti-MMP3 IgG antibodies were recently described in sera of SSc patients, displaying a strong association with the extent of skin, lung and kidney fibrosis.

These new SSc autoantibodies selectively inhibit the activity of different human matrix metalloproteinase collagenases, actively contributing to the development of fibrosis (Sato et al., 2003; Nishijima et al., 2004).

2.2. Prognostic autoantibodies

Systemic Sclerosis is characterized by the presence of a wide variety of autoantibodies, usually reacting with nuclear proteins [antinuclear antibodies (ANA)]. Besides their possible pathogenic role in the disease, ANA have been clearly associated with different clinical manifestation and variable degree of SSc severity (Henault et al., 2004; Hasegawa et al., 2005). Regarding skin involvement, the main antinuclear specificities are represented by anti-DNA topoisomerase I, anti-centromere and anti-nucleolar antibodies. These autoantibody specificities are usually mutually exclusive.

Anti-topoisomerase I antibodies, previously named anti-Scl70 antibodies, are usually associated with diffuse cutaneous SSc (Leroy et al., 1988; Steen et al., 1988). They are directed to topoisomerase I, a 90 kDa nuclear protein localized both in the nucleoplasm and in the nucleoli of interphase cells. The enzyme converts the supercoiled DNA into a relaxed form, playing a key role in chromatin organization, mitosis, DNA replication and RNA transcription during the cell cycle (Verheijen, 1996b). Anti-topoisomerase I antibodies are also common in patients with kidney, pulmonary involvement and acral ischaemic ulcers (Catoggio et al., 1983; Steen et al., 1984; Kuwana et al., 1994), carrying an increased SSc-related mortality rate because of right heart failure and pulmonary fibrosis (Jacobsen et al., 2001).

Anticentromere (ACA) are primarily found in limited cutaneous SSc. They are usually associated with less extensive skin thickening, calcinosis and ischaemic fingertip ulcers (Rothfield, 1996). In these patients internal organ involvement is less frequent, even if ACA are associated with the development of pulmonary hypertension (Steen et al., 1988; Cepeda and Reveille, 2004). Anticentromere antibodies are directed to three proteins of the centromere complex: CENP-B (80 kDa), referred as the major antigen, CENP-A (17 kDa) and CENP-C (140 kDa). CENP-B protein displays a DNA-binding region and it is localized in the central domain of the kinetocore of the centromere. The three CENP antigens play an active role in packaging chromatine in interphase and during mitosis (Verheijen, 1996a).

Anti-nucleolar antibodies represent a large set of autoantibodies reacting with multiple complexes of proteins and small RNAs in the nucleoli. Anti-RNA polimerase I–III antibodies are detected in about 28% of SSc and are associated to extensive skin involvement (Rothfield, 1996) and right heart failure unrelated to pulmonary fibrosis (Jacobsen et al., 2001). More rarely, SSc sera might display a reactivity against other nucleolar antigens, such as fibrillarin, Nor90 or Th, generally in diffuse SSc. In particular, anti-fibrillarin antibodies recognize a 34 kDa nucleolar protein that binds small nucleolar RNA. It has been shown that fibrillarin plays a pivotal role in processing ribosomal RNA and assembling ribosomes (Verheijen, 1996c). Anti-fibrillarin antibodies are present in about 4% of SSc, depicting a peculiar subset of disease characterized by myositis, pulmonary hypertension and renal disease (Tormey et al., 2001; Ho and Reveille, 2003).

3. Pathogenic autoantibodies in systemic lupus erythematosus: the anti-Ro/SSA model

Anti-Ro/SSA and anti-La/SSB antibodies were originally described as the two precipitating immunoglobulins reacting with different tissue extracts of patients affected by Sjögren's syndrome (Jones, 1958; Anderson et al., 1961) and systemic lupus erythematosus (SLE) (Clark et al., 1969).

Ro antigen is a ribonuclear complex, constituted by two proteins of 52 kDa and 60 kDa, encoded by different and unrelated genes. Ro 60 binds to small cytoplasmic RNAs (namely hYRNA), while Ro 52 shows a direct binding to three peptides of 60 kDa Ro (Franceschini and Cavazzana, 2005). La antigen is a 48 kDa phosphorilated protein that binds many small RNAs in the nucleus, playing a key role in RNA polimerase III transcription process (van Venroij et al., 1993). RNA–Ro complex is associated to La/SSB protein, with a specific binding at the poliU tail of hYRNA (Franceschini and Cavazzana, 2005).

3.1. Clinical and pathogenic associations

Anti-Ro antibodies are the most prevalent ANA specificity detected in different autoimmune diseases, but they are frequently associated with specific subset of SLE or SS: subacute cutaneous LE (60–80%) (Mc Cauliffe, 1997), neonatal lupus (Buyon et al., 1993), SLE (40%) (Maddison et al., 1981), homozygous complement deficiency SLE (C2 and C4) (75%) (Tappainer et al., 1982; Provost et al., 1983), late onset SLE (92%) (Catoggio et al., 1984) and hypergammaglobulinuemic purpura (100%) (Senecal et al., 1995). Most of these cutaneous features are strictly correlated to photosensitivity, that is a decreased threshold of tolerance to natural or artificial light, inducing specific skin lesions after the UV exposure (Mc Cauliffe et al., 1997). Several reports, in fact, suggest an association between photosensitivity and anti-Ro antibodies, showing a direct role of this autoantibody in the pathogenesis of photosensitive skin lesions (Mond et al., 1989; Mc Cauliffe et al., 1996; Reichlin, 1998). In vitro experiments suggest that anti-Ro antibodies selectively bind human basal keratinocytes and this binding could be markedly increased by UB light exposure (Lee et al., 1989). In fact, UV irradiation can induce apoptosis in keratinocytes and the subsequent exposition of Ro antigen in apoptotic blebs on the cell surface.

This event leads to antigen presentation to the immune cells with the eventual production of anti-Ro autoantibodies (Casciola-Rosen et al., 1994). In addition, Ro antigen exposition might enhance the anti-Ro antibody binding on keratinocytes; these in situ-formed immune-complexes might activate complement and the inflammatory cascade, resulting in erythema and the other clinical manifestations of photodermatitis (Golan et al., 1992; Casciola-Rosen et al., 1994; Reichlin, 1998). However, skin tissue damage might be mediated also by other mechanisms. In vitro experiments demonstrate that anti-Ro antibodies could be internalized by UV exposed cells and interact with cytoplasmic structures (Golan et al., 1992). Moreover, keratinocytes sensitised by autoantibodies can be easily lysed by ADCC, when mixed with peripheral blood mononuclear cells (Norris et al., 1984, 1985; Furukawa et al., 1994).

There is a wide variation in the expression of Ro and La antigens in the skin of patients suffering from SLE and the expression of each antigen seems to be under separate control. Some patients behave as high or low expressor for one or both antigens, without apparent differences of age and sex (Niimi et al., 1995).

According to the above mentioned findings, it has been suggested that skin involvement in anti-Ro/La positive SLE patients might be the consequence of the following events (Bennion and Norris, 1997):

1. UV susceptibility would promote keratinocyte apoptosis and the expression of surface nucleoproteins (such as Ro).
2. UV susceptibility would induce the production of high levels of inflammatory cytokines and adhesion molecule expression on dermis and epidermis, without an effective counterbalance by anti-inflammatory cytokines (such as IL10).

3. The Ro expression on keratinocyte surface would facilitate the production of specific autoantibodies.
4. Keratinocyte toxicity and tissue damage would be eventually mediated by the in situ formation of antigen–antibody complexes, complement activation and cell lysis by ADCC.

4. Prognostic autoantibodies in other systemic autoimmune diseases

4.1. Dermatomyositis (DM)

Dermatomyositis is a rare autoimmune inflammatory myopathy, characterized by peculiar skin lesions: violaceous and scaling rash (i.e. heliotrope) at upper eyelids, malar areas and anterior areas of chest and neck, Gottron's papules over the dorsum of the hands. Juvenile and adult DM share the same pathogenic features, such as endothelial cells damage, peri-vascular infiltration of B lymphocytes with deposition of immunoglobulins and complement factors on intramusculature microvessels (Plotz et al., 1995).

Among the large group of myositis-specific autoantibodies, anti-Mi2 autoantibodies are considered exclusively associated to DM (Targoff and Reichlin, 1985; Targoff et al., 1997). Anti-Mi2 are globally detected in 5–10% of overall polymyositis (PM)/DM diseases (Targoff et al., 1997) and in up to 22% of the DM sera (Targoff and Reichlin, 1985). They are associated with the characteristic DM dermatological features and represent a good prognostic factor. In fact anti-Mi2 positive patients usually show a good response to therapy, with rare exacerbations after treatment's tapering (Targoff and Reichlin, 1985; Targoff et al., 1997). Anti-Mi2 antibodies are directed against a set of nuclear proteins, whose main antigen is represented by a 240 kDa protein, probably involved in transcriptional processes (Ge et al., 1995; Nilasena et al., 1995; Seelig et al., 1995).

Different authors reported a strict immunogenetic correlation between anti-Mi2 and DR7 and DR53 HLA complex (Love et al., 1991; Mierau et al., 1996).

4.2. Other myositis

The only skin manifestation of PM is represented by the so-called 'mechanic hands,' characterized by cracking and fissuring of distal digital pad skin (Medsger and Oddis, 1997). Such cutaneous feature, as well as muscular and pulmonary involvement, is associated with anti-t-RNA synthetase antibodies (Jo1, PL7, PL12, EJ, OJ) (Targoff et al., 1997).

Anti-Jo1, the most frequent autoantibody, binds a cytoplasmic enzyme (hystidine-t-RNA synthetase) that assembles hystidine amino acid to its cognate t-RNA during protein synthesis (Plotz and Targoff, 1996). Although t-RNA synthetases possess a crucial role in the cell cycle and the specific autoantibodies display an inhibitory activity, there is no evidence supporting a pathogenic role for anti-synthetase antibodies in inducing tissue damage.

Clinical features of PM and scleroderma, namely PM/SSc overlap syndrome, is associated with rare autoantibody specificity, called anti-PM/Scl antibody. These autoantibodies are directed to a nucleolar complex of 11 proteins, being two polypeptides (PM/Scl 75 and PM/Scl 100) the major antigens (Bautz and Blüthner, 1996).

4.3. Rheumatoid arthritis (RA)

Rheumatoid nodules are the most frequent cutaneous features occurring in patients affected by RA. Firm nodules commonly develop on pressure areas, such as elbows, finger joints, ischial or sacral prominences. They are histologically characterized by central fibrinoid necrosis and peripheral fibroblasts, as the result of small vessel vasculitis (Matteson et al., 1997). Rheumatoid nodules and skin vasculitis exclusively occur in patients with Rheumatoid factor positivity.

In fact, this serological marker is strictly associated with systemic complications and increased

mortality, and it represents a bad prognostic factor, depicting an aggressive systemic disease, not only confined at joints (Smolen, 1996). Otherwise, the positivity for anti-CCP antibodies, considered a marker of aggressive joint disease (Fosrlind et al., 2004), is not associated with the onset of rheumatoid nodules or skin vasculitis.

Key points

Autoantibodies are the hallmark of systemic autoimmune diseases. Few of them display a direct pathogenetic role in inducing skin manifestations:

- Antifibroblast antibodies (AFA) can activate fibroblasts, inducing a pro-inflammatory phenotype in Systemic Sclerosis.
- Antiendothelial cell antibodies (AECA) induce endothelial activation in early phase of Systemic Sclerosis.
- Anti-Ro/SSA antibodies show a direct role in the parhogenesis of photosensitive skin lesions in Systemic Lupus Erythematosus.

References

Anderson, J.R., Gray, K.G., Beck, J.S. 1961. Precipitating autoantibodies in Sjogren's disease. Lancet 2, 456.

Bautz, F.A., Blüthner, M. 1996. The PM/Scl antigens. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, B5.4, p. 1.

Bennion, S.D., Norris, D.A. 1997. Ultraviolet light modulation of autoantigens, epidermal cytokines and adhesion molecules as contributing factors of the pathogenesis of cutaneous LE. Lupus, 6, 181.
UV radiation induces keratinocyte apoptosis and Ro antigen expression on cell surface. Circulating anti-Ro and new anti-Ro antibodies interact with keratinocytes' surface. These immunocomplexes can display direct keratinocyte toxicity by ADCC and complement cascade.

Bordron, A., Dueymesm, M., Levy, Y., et al. 1998. The binding of some antiendothelial cell antibodies induces endothelial cell apoptosis. J. Clin. Invest. 101, 2029.

Brentnall, T.J., Kenneally, D., Barnett, A.J., et al. 1982. Autoantibodies to fibroblasts in scleroderma. J. Clin. Lab. Immunol. 8, 9.

Buyon, J.P., Winchester, R.J., Slade, S.G., et al. 1993. Identification of mothers at risk for congenital heart block and other neonatal lupus syndromes in their children. Arthritis Rheum. 36, 1263.

Carvalhor, D., Savage, C.O.S., Black, C.M., et al. 1996. IgG antiendothelial cell autoantibodies from patients with systemic sclerosis induce leukocyte adhesion to human vascular endothelial cells in vitro. Induction of adhesion molecule expression and involvement of endothelium derived cytokines. J. Clin. Invest. 97, 111.

Casciola-Rosen, L.A., Anhalt, G., Rosen, A. 1994. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J. Exp. Med. 179, 1317.

Catoggio, L.J., Skinner, R.P., Maddison, P.J. 1983. Frequency and clinical significance of anticentromere and anti-Scl 70 antibodies in an English connective tissue disease population. Rheumatol. Int. 3, 19.

Catoggio, L.R., Skinner, R.P., Smith, G., et al. 1984. Systemic lupus erythematosus in the elderly. Clinical and serological characteristics. J. Rheumatol. 11, 175.

Cepeda, E.J., Reveille, J.D. 2004. Autoantibodies in systemic sclerosis and fibrosing syndromes: clinical indications and relevance. Curr. Opin. Rheumatol. 16, 723.

Chizzolini, C., Raschi, E., Rezzonico, R., et al. 2002. Autoantibodies to fibroblasts induce a proadhesive and proinflammatory fibroblast phenotype in patients with systemic sclerosis, Arthritis Rheum., 46, 1602.
Antifibroblast antibodies, detected in systemic sclerosis sera, could activate fibroblast in vitro. They up-regulate the fibroblast expression of ICAM, pro-inflammatory cytokines and chemokines. Activated fibroblasts can induce adhesion of mononuclear cells in vitro.

Clark, G., Reichlin, M., Tomasi, T.B. 1969. Characterization of a soluble cytoplasmatic antigen reactive with sera from patients with systemic lupus erythematosus. J. Immunol. 102, 117.

Fosrlind, K., Ahlmen, M., Eberhardt, K., et al. 2004. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann. Rheum. Dis. 63, 1090.

Franceschini, F., Cavazzana, I. 2005. Anti-Ro/SSA and La/SSB antibodies. Autoimmunity 38, 55.

Furukawa, F., Kanauchi, H., Imamura, S. 1994. Susceptibility to uvb light in cultured keratinocytes of cutaneous lupus erythematosus. Dermatology 189 (Suppl. 19), 18.

Ge, Q., Nilasena, D.S., O'Brien, C.A., et al. 1995. Molecular analysis of a major antigenic region of the 240-kD protein of Mi2 autoantigen. J. Clin. Invest. 96, 1730.

Golan, T.D., Elkon, K.B., Gharavi, A.E., et al. 1992. Enhanced membrane binding of autoantibodies to cultured keratinocytes of systemic lupus erythematosus patients after ultraviolet B/ultraviolet A radiation. J. Clin. Invest. 90, 1067.

Hasegawa, M., Fujimoto, M., Takemara, K., et al. 2005. Pathogenesis of systemic sclerosis: altered B cell function is the key linking systemic autoimmunity and tissue fibrosis. J. Dermatol. Sci. 39, 1–7.

Hayes, M.J., Cambridge, G. 2004. An IgM class antineutrophil cytoplasm antibody inhibits adhesion and apoptosis via a Syk dependent signalling cascade. Mol. Immunol. 41, 457.

Henault, J., Tremblay, M., Clement, I., et al. 2004. Direct binding of anti-DNA topoisomerase I autoantibodies to the cell surface of fibroblasts in patients with systemic sclerosis. Arthritis Rheum 50, 3265.

Hill, M.B., Phipps, J.L., Cartwright, R.J., et al. 1996. Antibodies to membranes of endothelial cells and fibroblasts in scleroderma. Clin. Exp. Immunol. 106, 491.

Ho, K.T., Reveille, J.D. 2003. The clinical relevance of autoantibodies in scleroderma. Arthritis Res. Ther. 5, 80.

Holt, C.M., Lindsey, N., Moult, J., et al. 1989. Antibody dependent cellular cytotoxicity of vascular endothelium: characterization and pathogenic associations in systemic sclerosis. Clin. Exp. Immunol. 78, 359.

Jacobsen, S., Ullman, S., Shen, G.Q., et al. 2001. Influence of clinical features, serum antinuclear antibodies, and lung function on survival of patients with systemic sclerosis. J. Rheumatol. 28, 2454.

Jones, B. 1958. Lacrimal and salivary precipitating antibodies in Sjogren's syndrome. Lancet 195, 773.

Korn, J.H. 1997. Fibroblast function and fibrosis. In: W.N. Kelley, E.D. Harris, Jr, S. Ruddy, C.B. Sledge (Eds.), Textbook of Rheumatology. Philadelphia, WB Saunders, p. 199.

Kuwana, M., Kaburaki, J., Okono, Y., et al. 1994. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. Arthritis Rheum. 37, 75.

Lee, L.A., Gaither, K.K., Coulter, S.N., et al. 1989. Pattern of cutaneous immunoglobulin G deposits in subacute cutaneous lupus erythematosus is reproduced by infusing purified anti-Ro(SSA) autoantibodies into human skin-grafted mice. J. Clin. Invest. 83, 1556.

LeRoy, E.C., Black, C., Fleischmajer, R., et al. 1988. Scleroderma (systemic sclerosis): classification, subsets, and pathogenesis. J. Rheumatol. 15, 202.

Love, L.A., Leff, R.L., Fraser, D.D., et al. 1991. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine 70, 360.

Maddison, P., Provost, T.T., Reichlin, M. 1981. Serological findings in patients with ANA negative SLE. Medicine (Baltimore) 60, 87.

Marks, R.M., Czerniecki, M., Andrews, B.S., et al. 1988. The effects of scleroderma serum on human microvascular endothelial cells. Induction of antibody dependent cellular cytotoxicity. Arthritis Rheum. 31, 1524.

Matteson, E.L., Cohen, M.D., Conn, D.L. 1997. Rheumatoid arthritis. Clinical features and systemic involvement. In: J.H. Klippel, P.A. Dieppe (Eds.), Rheumatology, vol. 1. 2nd ed., Mosby, St. Louis, p. 5.4.1

Mc Cauliffe, D.P. 1997. Cutaneous diseases in adults associated with anti-Ro/SSA autoantibody production. Lupus 6, 158.

Mc Cauliffe, D.P., Faircloth, E., Wang, L., et al. 1996. Similar Ro/SSA autoantibody epitope and titer responses in annular erythema of Sjogren's syndrome and subacute cutaneous lupus erythematosus. Arch. Dermatol. 132, 528.

Medsger, T.A., Oddis, C.V. 1997. Inflammatory muscle disease. Clinical features. In: J.H. Klippel, P.A. Dieppe (Eds.), Rheumatology. 2nd ed., vol. 2. Mosby, St. Louis, p. 7.13.1.

Meroni, P.L., Ronda, N., Raschi, E., et al. 2005. Humoral autoimmunity against endothelium: theory or reality? Trends Immunol. 26, 275.

AECA display a direct role in causing endothelium dysfunction, characteristic of early systemic sclerosis. AECA induce a proinflammtory phenotype on endothelium, probably recognizing membrane structures and modulating gene expression. In addition, AECA display tissue damage through complement activation and cellular lysis.

Mierau, R., Dick, T., Bartz-Bazzanella, P., et al. 1996. Strong association of dermatomyositis-specific Mi1 autoantibodies with a tryptophane at position 9 of the HLA-DRβ chain. Arthritis Rheum 39, 868.

Mond, C.B., Peterson, M.G.E., Rothfield, N.F. 1989. Correlation of anti-Ro antibody with photosensitivity rash in systemic lupus erythematosus. Arthritis Rheum 32, 202.

Mouthon, I., Garcia De La Pena-Lefebvre, P., Chanseaud, Y., et al. 2002. Pathogenesis of systemic scleroderma: immunological aspects. Ann. Med. Intern. (Paris) 153, 167.

Nakamura, N., Ban, T., Yamaji, K., et al. 1998. Localization of the apoptosis-inducing activity of lupus anticoagulant in an annexin V-binding antibody subset. Clin. Invest. 101, 1951.

Nakamura, N., Shidara, Y., Kawaguchi, N., et al. 1994. Lupus anticoagulant autoantibody induces apoptosis in umbilical vein endothelial cells: involvement of annexin V. Biochem. Biophys. Res. Commun. 15, 1488.

Niimi, Y., Ioiannides, D., Buyon, J., et al. 1995. Heterogeneity in the expression of Ro and La antigens in human skin. Arthritis Rheum. 38, 1271.

Nilasena, D.S., Trieu, E.P., Targoff, I.N. 1995. Analysis of the Mi2 autoantigen of dermatomyositis. Arthritis Rheum. 38, 123.

Nishijima, C., Hayakawa, I., Matsushita, T., et al. 2004. Autoantibodies against matrix metalloproteinase-3 in patients with systemic sclerosis. Clin. Exp. Immunol. 138, 357.

Norris, D.A., Ryan, S.B., Kissinger, B.M., et al. 1985. Systematic comparison of antibody-mediated mechanisms of keratinocytes lysis in vitro. J. Immunol. 135, 1073.

Norris, D.A., Ryan, S.R., Fritz, K.A., et al. 1984. The role of RNP, Sm, and SSA/Ro specific antisera from patients with lupus erythematosus in inducing antibody-dependent cellular cytotoxicity (ADCC) of targets coated with nonhistone nuclear antigens. Clin. Immunol. Immunopathol. 31, 311.

Nylander Lundquist, E., Back, O., Nilsson, T.K., et al. 1992. Prevalence of anti-endothelial cell antibodies in patients with autoimmune diseases. Clin. Rheumatol. 11, 248.

Orlandini, G., Ronda, N., Gatti, R., et al. 1999. Receptor-ligand internalisation. Method Enzymol. 307, 340.

Penning, C.A., Cunningham, J., French, M.A.H., et al. 1984. Antibody-dependent cellular cytotoxicity of human vascular endothelium in systemic sclerosis. Clin. Exp. Immunol. 57, 548.

Pignone, A., Scaletti, C., Matucci-Cerinic, M., et al. 1998. Anti-endothelial cell antibodies in systemic sclerosis: significant association with vascular involvement and alveolo-capillary impairment. Clin. Exp. Rheum. 16, 527.

Plotz, P., Targoff, I.N. 1996. Myositis-associated antigens. Aminoacyl-tRNA synthetases Jo1, Pl-7, Pl-12, EJ, and OJ. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, B6.1, p. 1.

Plotz, P.H., Rider, L.G., Targoff, I.N., et al. 1995. NIH conference. Myositis: immunologic contributions to understanding cause, pathogenesis and therapy. Ann. Int. Med. 122, 715.

Provost, T.T., Arnett, F., Reichlin, M. 1983. C2 deficiency, lupus erythematosus, and anti-cytoplasmic Ro(SS-A) antibodies. Arthritis Rheum. 26, 1279.

Reichlin, M. 1998. Clinical manifestations associated with anti-Ro antibodies in adults. Sem. Clin. Immunol. 1, 21.

Ronda, N., Gatti, R., Giacosa, R., et al. 2002. Antifibroblast antibodies from systemic sclerosis patients are internalized by fibroblasts via a caveolin-linked pathway. Arthritis Rheum. 46, 1595.

Rosenbaum, J., Pottinger, B.E., Woo, P., et al. 1988. Measurement and characterisation of circulating anti-endothelial cell IgG in connective tissue diseases. Clin. Exp. Immunol. 72, 450.

Rothfield, N.F. 1996. Autoantibodies to scleroderma-associated antigens. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, C5.1, p. 1.

Salojin, K.V., Le Tonqueze, M., Saraux, A., et al. 1997. Anti-endothelial cell antibodies: useful markers of systemic sclerosis. Am. J. Med. 102, 178.

Sato, S., Hayakawa, I., Hasegawa, M., et al. 2003. Function blocking autoantibodies against matrix metalloproteinase-1 in patients with systemic sclerosis. J. Invest. Dermatol. 120, 542.

Seelig, H.P., Moosbrugger, I., Ehrfeld, H., et al. 1995. The major dermatomyositis specific Mi2 autoantigen is a presumed helicase involved in transcriptional activation. Arthritis Rheum. 38, 1389.

Senecal, J.L., Chartier, S., Rothfield, N. 1995. Hypergammaglobulinemic purpura in systemic autoimmune rheumatic diseases: predictive value of anti-Ro (SSA) and anti-La (SSB) antibodies and treatment with indomethacin and hydroxychloroquine. J. Rheum. 22, 868.

Smolen, J.S. 1996. Autoantibodies in rheumatoid arthritis. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, C1.1, p. 1.

Steen, V.D., Powell, D.L., Medsger, T.A., Jr. 1988. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum. 31, 196.

Steen, V.D., Ziegler, G.L., Rodnan, G.P., et al. 1984. Clinical and laboratory associations of anticentromere antibody in patients with progressive systemic sclerosis. Arthritis Rheum. 27, 125.

Strehlow, D., Korn, J.H. 1998. Biology of scleroderma fibroblast. Curr. Opin. Rheumatol. 10, 572.

Tappainer, G., Hintner, H., Scholz, S., et al. 1982. Systemic lupus erythematosus in hereditary deficiency of the fourth component of complement. J. Am. Acad. Dermatol. 7, 66.

Targoff, I.N., Miller, F.W., Medsger, T.A., Jr., et al. 1997. Classification criteria for the idiopathic inflammatory myopathies. Curr. Opin. Rheum. 9, 527.

Targoff, I.N., Reichlin, M. 1985. The association between Mi-2 antibodies and dermatomyositis. Arthritis Rheum. 28, 796.

Tormey, V.J., Bunn, C.C., Denton, C.P., et al. 2001. Anti-fibrillarin antibodies in systemic sclerosis. Rheumatology (Oxford) 40, 1157.

Trojanowska, M., Le Roy, E.C., Eckes, B., et al. 1988. Pathogenesis of fibrosis: type 1 collagen and the skin. J. Mol. Med. 76, 266.

van Venroij, W., Slobbe, R., Pruijn, G. 1993. Structure and function of La and RNPs. Mol. Biol. Rep. 18, 113.

Verheijen, R. 1996a. Centromere proteins. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of biological markers of disease. Kluwer Academic Publishers, Dordrechit, B5.2, p. 2.

Verheijen, R. 1996b. DNA topoisomerase I. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, B5.1, p. 3.

Verheijen, R. 1996c. Fibrillarin. In: W.J. van Venrooij, R.N. Maini (Eds.), Manual of Biological Markers of Disease. Kluwer Academic Publishers, Dordrechit, B5.3, p. 1.

Worda, M., Sgonc, R., Dietrich, H., et al. 2003. In vivo analysis of the apoptosis-inducing effect of anti-endothelial cell antibodies in systemic sclerosis by the chorioanallantoic membrane assay. Arthritis Rheum. 48, 2605.

PART II:

Skin Involvement in Systemic Autoimmune Diseases

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 5

Photosensitivity in Lupus Erythematosus

Percy Lehmann*

Department of Dermatology, Allergology and Environmental Medicine, HELIOS Klinikum Wuppertal, University of Witten-Herdecke, Germany

1. Introduction

Lupus erythematosus (LE) represents an autoimmune disease with great clinical variability in which photosensitivity is a common feature for all forms and subsets. Cutaneous LE lesions often arise in sun-exposed areas and it is well reported and recognized that sun exposure may also exacerbate or induce systemic manifestations of this disease (Dubois and Tuffanelli, 1964; Nived et al., 1993; White and Rosen, 2003). The original concept of photosensitivity in LE dates back to the first description by Cazenave (1851) and early observations since the beginning of the 19th century, where the role of environmental factors were related to disease activity and even induction of the disease. Of the different external factors that have detrimental effects on disease activity, the sun's radiation has been best studied. Hutchinson (1888) reported in his Harveian Lectures on Lupus, that patients with LE did not tolerate the sun.

Pusey (1915) described a young lady with LE in which the first lesions appeared after some days of extensive golfing in the summertime. The lesions disappeared after sun avoidance, just to reexacerbate the next summer after a golf tournament.

Freund (1929) reported between 1920 and 1929 the prevalence of LE admissions to his Department of Dermatology in Berlin. He could show a significant increase of LE admissions during the months of May to July and concluded that climatic factors were responsible for this climax of new LE patients.

Additionally to these observations on natural sunlight it also became clear that artificial light sources were also detrimental in LE. Jesionek (1916), a famous German pioneer of phototherapy warned not to apply phototherapy in patients with LE.

The term "Lupus erythematosus subacutus" was first described by Fuhs (1929) when he described a patient whose disease broke out after irradiation with an artificial light source. Possibly, this is the first description of the exquisitely light-sensitive subset of LE, nowadays well known as subacute cutaneous lupus erythematosus (Gilliam and Sontheimer, 1982).

Despite those reports, the incidence of photosensitivity remained unclear and, therefore, since 1965 (Epstein et al., 1965) phototesting procedures were developed in order to reproduce specific LE lesions by exposure to standardized UV radiation.

In the following years, photosensitivity became a well-established factor in the pathogenesis of LE in clinical and experimental settings and was included as a discriminating factor in the revised criteria of the American Rheumatism organization (ARA) for the classification of systemic LE (SLE).

*Corresponding author.
Tel.: +49-202-896-5400; Fax: +49-202-896-5332
E-mail address: plehmann@wuppertal.helios-kliniken.de (P. Lehmann).

DOI: 10.1016/S1571-5078(05)05005-1

2. Pathophysiology of photosensitivity in LE

LE represents an autoimmune disease characterized by UV-sensitivity, apoptosis of keratinocytes, and an inflammatory infiltrate in superficial and deep dermal compartments (Casciola–Rosen et al., 1994; Crowson and Margo, 2001; Farkas et al., 2001; McHugh, 2002; White and Rosen, 2003).

Since clinical data, phototesting procedures, and experimental evidence demonstrate the detrimental effects of sun irradiation on LE patients, research on pathogenetic mechanisms of UV-induced LE has become an increasingly dynamic field in the past years, which was additionally supported by the immense progress of the disciplines of photoimmunology and genetics. Initiation and perpetuation of autoimmune responses by UV irradiation have been subjects of extensive in vivo and in vitro studies (Norris and Lee, 1985; Furukawa et al., 1990, 1997; Kuhn et al., 1998a,b, 2005; Lehmann, 2005; Meller et al., 2005). UV irradiation is a well-known trigger of apoptosis in keratinocytes, and there is growing consensus that abnormalities in the generation and clearance of apoptotic material is an important source of antigens in autoimmune diseases (McHugh, 2002; White and Rosen, 2003). Casciola–Rosen et al. (1994) have experimentally demonstrated the clustering of autoantigens at the cell surface of cultured keratinocytes with apoptotic changes due to UV-irradiation. This localized concentration of autoantigens may be able to break self-tolerance, thus leading to autoimmunity.

Using a standardized photoprovocation protocol our group was able to detect increased numbers of apoptotic keratinocytes in cutaneous LE after UVA and UVB irradiation compared to control subjects (Kuhn et al., 1998). Since the cytokine inducible nitric oxide synthase (iNOS) is believed to play an important role in the course of autoimmunity and in the regulation of apoptosis (Kolb and Kolb–Bachofen, 1998), we have studied in further experiments the expression of iNOS at the mRNA and protein level in UV-induced LE. The results of this study (Kuhn et al., 1998) demonstrated a delayed iNOS-specific signal after UV irradiation in LE compared to normal controls. These data suggest that kinetics of iNOS and abnormalities in the apoptotic pathway play an important role in the pathogenesis of UV-induced LE.

Furthermore, UV irradiation may cause the formation of molecules by different epidermal and dermal cells. These molecules have the capacity to upregulate (PGE2, ROS, TNF-alfa, IL-1, ICAM1) or downregulate (IL-10, IL-1 receptor antagonist) inflammatory processes. Since genetic regulation is crucial for the induction of these molecules, a putative genetic polymorphism in LE may play an important role in the specific photosensitivity of LE (Von Schmiedeberg et al., 1996). The current genetic data suggest that increased amounts of TNF-alfa that induce apoptosis due to a UV sensitive TNF promoter polymorphism or to decreased clearance of apoptotic cells due to polymorphisms associated with decreased serum levels of collections such as C1q and mannose binding lectin (Bagglioni et al., 1998; Krutmann, 2000; Ronnblom et al., 2002, 2003).

Specific pathogenetic pathways in UV-induced autoreactivity have been demonstrated experimentally. Thus, Furukawa (1997) could demonstrate the cellular redistribution of the Ro antigen in absence of apoptosis upon UV radiation, which enables its presentation to the immune system as a possible first step in the autoimmune cascade. The four step model for the pathogenesis of UV-induced LE by Norris and Lee (1985) based on the translocation of the Ro antigen after UV injury has been widely referred to and agreed upon but, however, this model is limited to the Ro-positive forms of LE such as SCLE and neonatal LE (Kind et al., 1993; Lehmann, 1996, 2005).

The role of UV-irradiation in the induction of cytokine, mediator release and adhesion molecules in epidermis and dermal vessels have also been investigated. Adhesion molecules are not only induced secondary to cytokines, but also directly through transcriptional activation. This activation occurs by the formation of transcriptional factors like activator protein-2 in a singlet oxygen-dependent mechanism (Golan et al., 1994; Grether–Beck et al., 1996). Since there is a link between UVA sensitivity and free radical formation, free radical scavengers may be of special value in order to prevent UV-induced LE lesions (Tebbe et al., 1997; Lehmann and Ruzicka, 2001).

Although the relevant antigen in LE remains unknown, skin-infiltrating activated leukocytes are thought to play a crucial role in the induction and maintenance of this autoimmune disease (Bagglione M, 1998) Furthermore, skin-infiltrating memory T lymphocytes, which display the CD4 phenotype (Tebbe et al., 1995) dominate the inflammatory infiltrate in cutaneous LE.

Plasmocytoid dendritic cells (PDC) accumulate in cutaneous LE lesions, whereas they in systemic LE a decreased number of those cells are found in the peripheral blood. PDCs and their secreted products (interferon-alfa) play a crucial role in the pathogenesis of SLE (Ronnblom and Alm, 2002; Ronnblom et al., 2003). In a recent study our group (Meller et al., 2005) has studied the recruitment and activation pathways of skin infiltrating leukocytes in cutaneous LE. Meller et al. (2005) were able to show that UV irradiation induces the release and production of a distinct set of PDC- and T cell-attracting chemokines. In summary, these data show an amplification cycle in which UV light-induced injury induces apoptosis, necrosis, and chemokine production. These mechanisms, in turn, mediate recruitment and activation of autoimmune T cells and IFN-alfa-producing PDC's, which subsequently release more effector cytokines, thus amplifying chemokine production and leukocyte recruitment, finally leading to the development of LE lesions (Table 1).

Further elucidation of the various different factors which contribute to the UV initiation and perpetuation of LE autoimmunity may lead in future to the development of effective strategies in the prevention of LE induction by sunlight.

According to the present evidence it is conceivable that besides simple photoprotective measures, a further beneficial effect could be achieved by additional use of oxygen scavengers and, i.e., nitric oxide via chemical donors. Since DNA is a primary target for UV insults, a very interesting photoprotection concept includes the addition of DNA repair enzymes into sunscreens (Stege et al., 2000). However, clinical data on this hypothetical treatment strategies for the prevention of UV-induced LE are still lacking.

Table 1
Series of published systematic phototesting in LE

Epstein et al. (1965)	$n = 25$	UVB
Baer and Harber (1965)	$n = 29$	UVB
Freeman et al. (1969)	$n = 15$	UVB
Cripps et al. (1973)	$n = 11$	UVB
Wolska et al. (1989)	$n = 227$	UVB

3. Clinical photosensitivity and phototesting

Despite many anecdotal reports and the obvious clinical evidence showing the clear relationship between sunlight exposure and the manifestation of LE, no systematic studies existed on the photoreactivity in patients with this disease until the early 1960s.Epstein et al. (1965) were the first to introduce the repeated exposure technique, which made it possible to induce specific LE lesions in 5 of the 25 treated patients by UVB radiation (Table 2).

In the same year, Everett and Olson (1965) demonstrated that 1 minimal erythema dose (MED) of hot quartz UV light exposure produced an increase in the size of skin lesions in patients with DLE. Baer and Harber (1965) administered phototests to 29 patients with LE by applying one to six times the MED of UVB in single exposures to multiple test sites. An abnormal reaction was detected in only one patient with SCLE, and it consisted of a markedly decreased erythema threshold dose and persistence of the erythema for 4 weeks. Wavelengths longer than 315 nm were not evaluated in this study. Freeman et al. (1969) used monochromatic light to determine the wavelength dependency of phototest reactions in 15

Table 2
Series of published systematic phototesting in LE

Lehmann et al. (1986, 1990)	$n = 128$	UVB, UVA
Nived et al. (1993)	$n = 23$	UVA
Van Weelden et al. (1999)	$n = 16$	UVB, UVA
Leenutaphong et al. (1999)	$n = 15$	UVB, UVA
Sanders et al. (2003)	$n = 100$	UVB, UVA
From Lehmann (2005). prolonged test protocol		

patients with LE by also applying the repeated UV exposure technique, which became a valuable tool later on for photoprovocation tests in several photosensitive disorders, such as polymorphous light eruption (PLE) (Lehmann et al., 1986). However, the UVA doses used in only a few patients with LE were probably too low for positive photoprovocation reactions. Cripps and Rankin (1973) also used monochromatic light between 250 and 330 nm in an attempt to determine the erythema action spectrum; specific lesions of LE were reproduced in the UVB range by applying 8–13 times the MED. At 330 nm (UVA) only a persistent erythematous response but not LE lesions could be detected. Because of these studies, the action spectrum of LE was ascribed to the UVB range despite experimental evidence from in vitro and animal studies indicating that UVA irradiation also had specific detrimental effects in LE (Doria et al., 1996; Friou, 1957; Sontheimer, 1996; Zamansky et al., 1980). However, the clinical phototesting experiments had shortcomings in that either only a very limited number of patients had been tested or the UVA testing was insufficient (Cripps and Rankin, 1973; Epstein et al., 1965; Freeman et al., 1969; van Weelden et al., 1989).

The description by Gilliam and Sontheimer (1982) of SCLE as a very photosensitive subset marked a major step forward in the photobiology of this disease. Evidence of a role for UV irradiation in the pathogenesis of SCLE came from the observations of patients that sun exposure resulted in lesion formation, the limitation of SCLE lesions to sun-exposed skin, and the predilection for fair-skinned individuals with skin type I or II. The observation that certain photosensitizing drugs, such as thiazide diuretics and sulfonylureas, can induce SCLE is also an indication that sun exposure plays an important role in the pathogenesis of this disease. Further experiments evolving from these clinical results have led to the concept that keratinocytes damaged by antibody-dependent cellular cytotoxicity might be a mechanism in photosensitive LE (Norris and Lee, 1985).

In 1986, our group (Kind et al., 1993; Lehmann et al., 1986, 1990) was the first to demonstrate experimental reproduction of skin lesions by UVB and UVA irradiation using a standardized test protocol on a large number of patients with the disease (Tables 3 and 4). A total of 128 patients with different forms of LE underwent phototesting with polychromatic UVB and long-wave UVA irradiation, and characteristic skin lesions clinically and histologically resembling LE were induced in 43% of patients (Gif. 12.1). Subsequent investigations confirmed UVA reactivity in LE by phototesting (Nived et al., 1993; Wolska et al., 1989). In the following years, this testing regimen received much attention because the reproduction of skin lesions in patients with LE by UVB and UVA irradiation is an optimal model for clinical and experimental studies (Beutner et al., 1991; Hasan et al., 1997; Kind et al., 1993; Kuhn et al., 1998a, b; Leenutaphong and Boonchai, 1999; van Weelden et al., 1989; Walchner et al., 1997). Meanwhile, provocative phototesting in patients with LE has become routine at our department, and protocols for phototesting have become optimized by taking into account multiple factors. Nonlesional, non-sun-exposed areas of the upper back or extensor aspects of the arms were used for performance of the phototest reactions because other parts of the skin might not react to the same extent, probably

Table 3
Lupus erythematosus Photoprovocation procedure

Test site:	Back or forearms
Test area:	5 × 8 cm
Irradiation source:	UVASUN 3000 (Mutzhas) Philips TL 20W/12 (Waldmann)
Dose:	3 × 60–100 J/cm^2 UVA 3 × 1.5–fold MED UVB
Readings:	24, 48, 72 h and sometimes up to 3 weeks

From Lehmann (1990).

Table 4

Provocative phototesting
In lupus erythematosus
$n = 432$
43% of all lupus erythematosus patients showed a positive test result
15% via UVA
49% via UVB
36% via UVA and UVB
For optimal results it is very important to extend the reading up to 14 days and more from Lehmann (2005).

owing to some kind of local predisposion of unknown nature other than UV irradiation, such as thickness of the stratum corneum, vascularization, presence of antigens, or distribution of antigen-presenting cells (Walchner et al., 1997). Furthermore, it is important to use a defined test area, which should be sufficiently large to provide reactions. The initial observable response following exposure to UV irradiation is an erythema reaction that most commonly arises with the normal time course. Although the duration of the erythema was not studied in particular, a prolonged erythematous response was not a conspicuous feature. In contrast to other photodermatoses, such as PLE, the development of skin lesions in patients with LE is characterized by a latency of several days to 3 weeks or even longer, and it might persist in some cases for several months (Kuhn, 2001a; Lehmann, 1996) (Figs. 1a,b, and 2). In addition, phototesting has been crucial in further characterizing a highly photosensitive form of CLE, namely, LE tumidus (LET) (Kuhn et al., 2000; Kuhn et al., 2001b). LET was first described by Gougerot and Bournier (1930) and has since been somewhat 'forgotten' or rarely described and diagnosed. In 1990, Goerz et al. (1990) emphasized for the first

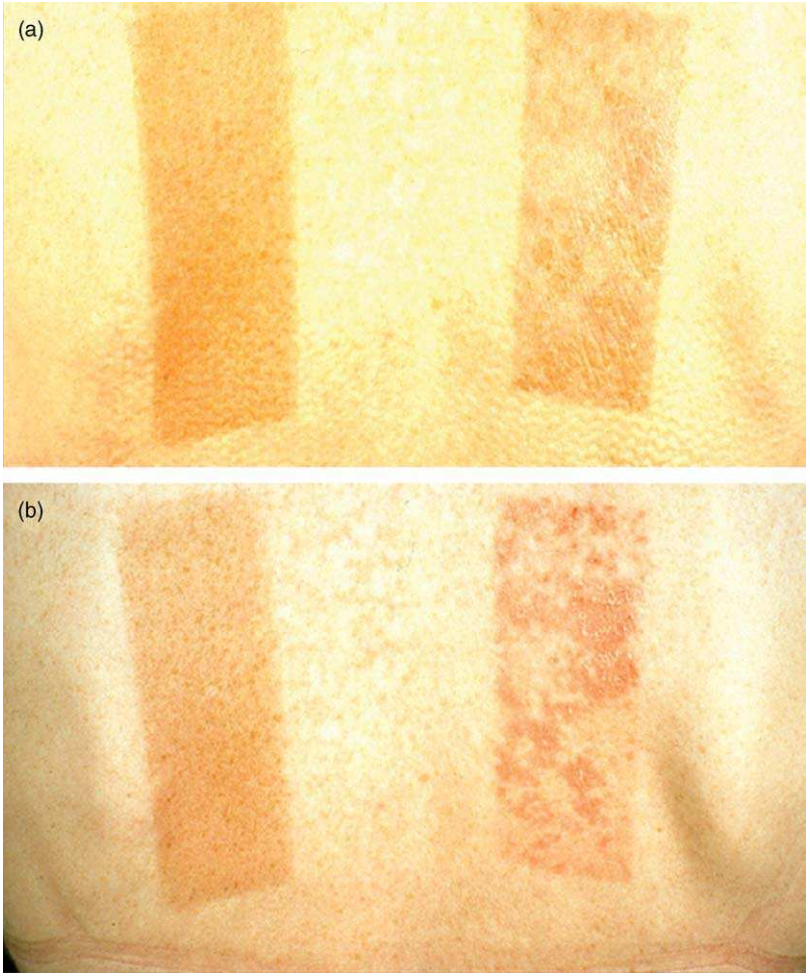


Figure 1. Photoprovocation tests in SCLE. (a) Left, normal UVA-response. Right: beginning pathological response, 48 h after last phototesting.(b) Right test field: Pathological test-reaction corresponding to photo-induced SCLE, 2 weeks after last phototesting procedure.

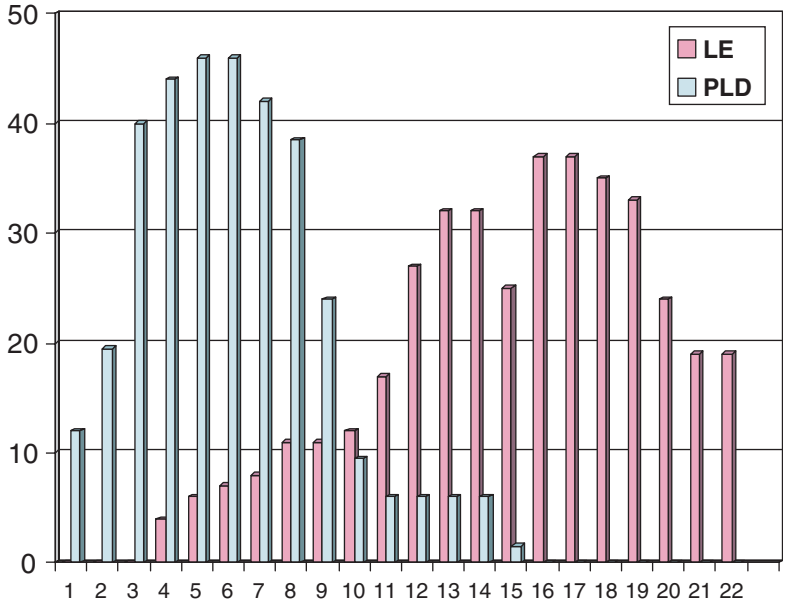


Figure 2. Time course of positive photoreactions of LE compared to polymorpic light eruption. (From Kuhn (2001)).

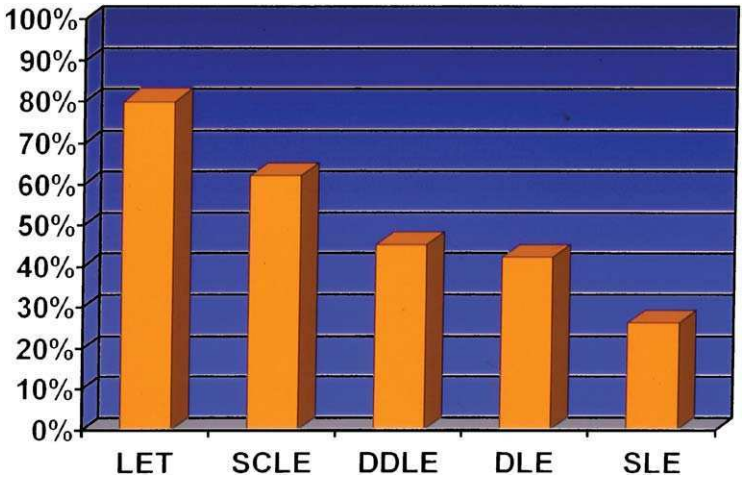


Figure 3. Lupus erythematosus subgroups Positive photoprovocations 2004. From Lehmann (2005).

time that extreme photosensitivity is a major characteristic of LET. According to our experience, we regard LET to be an unusual clinical variant of CLE, and skin lesions of LET consist of sharply demarcated, smooth, red-violet, infiltrated plaques with hardly any scaling and no scarring. The lesions usually disappear on therapy with antimalarials and sun avoidance. It could be shown that this form is even more UV sensitive than SCLE, which until recently, was believed to be the most photosensitive LE subset (Fig. 3). Using a standardized protocol, reproduction of characteristic skin lesions occurred in 76% of patients with LET, 63% with SCLE, 45% with DLE, and 41% with other forms of CLE, such as LE profundus and Chilblain LE (Kuhn et al., 2001).

Results of reported phototesting in patients with LE often differ between various groups because there are numerous technical differences between the studies that could explain the different findings (Beutner et al., 1991; Hasan et al., 1997; Kind et al., 1993; Kuhn et al., 2001; Lehmann et al., 1990; Nived et al., 1993; Van Weelden et al., 1989; Sanders et al., 2003; Walchner et al., 1997; Wolska et al., 1989). Varying factors are light source, energy dose, wavelength, time points of provocation and evaluation, and location and size of the test area. Most studies were conducted in white patients; however, there is one recent article on phototesting in 15 oriental patients with LE using exactly the same test protocol as our group (Leenutaphong and Boonchai, 1999). The incidence of positive phototest reactions in these patients seem to be similar to or a little lower than that in white patients, and there was no correlation between a positive history of UV sensitivity and phototest reactions. However, classification of positive test results might be difficult in some patients because persistent erythema can develop, which is even histologically hard to interpret. It is also unclear why skin lesions cannot always be reproduced under the same conditions several months after the initial phototest and why phototesting results are not positive in all patients with LE tested, providing indirect evidence for variant factors in the pathophysiology of this disease (Fig. 4).

Furthermore, a history of photosensitivity in patients with LE does not necessarily predict positive reactions on phototesting, and results of reported photosensitivity often differ between various groups (Kuhn et al., 2001; Lehmann et al., 2005). This might be because skin lesions after UV irradiation do not develop rapidly after sun exposure, and, therefore, a relationship between sun exposure and exacerbation of LE does not seem obvious to the patient. An additional factor might be age at onset of disease, as observed by Walchner et al. (1997), demonstrating that mainly patients younger than 40 years reported photosensitivity. Furthermore, the occurrence of photosensitivity varies among different types of LE, and some ethnic groups, such as African blacks, seem to be less photosensitive than others. Nevertheless, the term in ''photosensitivity'' (skin

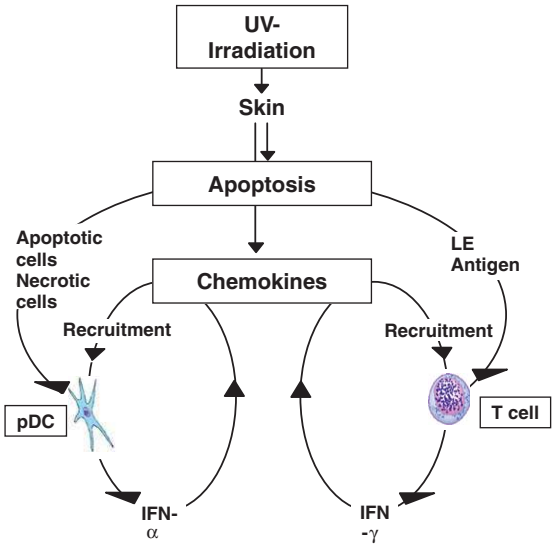


Figure 4. Amplification cycle demonstrating UV-injury, apoptosis, necrosis, and chemokine production. Mediation of recruitment and activation of autoimmune T-cells and INF-alfa producing PDCs. Release of more effector cytokines amplifying chemokine production and leukocyte recruitment leading to LE-lesion From Meller (2005).

rash as a result of unusual reaction to sunlight by patient history or physician observation) is poorly defined, although it is listed as one of the American Rheumatism Association (ARA) criteria for the classification of SLE. Therefore, a detailed clinical history is important to the diagnosis and assessment of photosensitivity in patients with LE. There are several key components to a history of photosensitivity, including the morphology of the rash, duration, distribution, and the relationship to sun exposure and specific symptoms (such as pain, pruritus, burning, blistering, and swelling). Each of these symptoms may provide clues to the nature of the photosensitive eruption and thus the diagnosis. Differentiating between the morphology and the time course of CLE and, for instance, PLE, according to the history alone can be difficult; clinically, PLE tends to consist of an acute eruption of tiny, pruritic plaques and vesicles that lasts several days, in contrast to SCLE, which usually involves larger, non-pruritic annular or psoriasiform lesions that persist for weeks to months after UV exposure. In contrast, LET may, in some cases, be clinically very similar to

PLE. A past medical history should also include a detailed drug history, particularly in temporal relation to a suspected phototoxic eruption.

Physical examination may reveal a distribution suggestive of a photosensitive condition in the absence of a history of photosensitivity. The most common areas for skin lesions in LE include sun-exposed areas such as the face, the V-area and posterior aspect of the neck, the ears, the dorsa of the hands, and the forearms. Equally helpful may be areas that are specifically spared from sun exposure, including the upper eyelids, submental areas, finger web spaces, and general creases within skin folds, where a photosensitive eruption is noticeably absent. Furthermore, investigation of patients with photosensitivity includes routine tests to establish the diagnosis and extent of disease activity, including hematology, biochemistry, serology, and complement studies. Skin biopsies and immunofluorescence may also be appropriate. Provocative phototesting is an objective means of demonstrating whether a patient has an abnormal response to UV exposure; however, phototesting does not play a role in the routine assessment or diagnosis of a patient with CLE. Indications for phototesting in patients with LE include (a) the objective demonstration of photosensitivity where there is doubt about the history and where such demonstration would support a diagnosis of LE; (b) the exclusion of other causes of photosensitivity, such as PLE, chronic dermatitis, solar urticaria, and drug-induced phototoxicity; and (c) use of the photoprovocation test as a useful research tool with which to study the immunopathology of evolving lesions of LE-specific skin disease.

Results of histopathologic and immunopathologic examination of UV-induced LE lesions are similar to the findings of spontaneously developing primary skin lesions but can give further insight into the earliest pathologic events of CLE lesions. Kind (1993) demonstrated that histopathologic examination of early UV-induced lesions (up to 10 days) in patients with CLE and SLE shows nonspecific changes such as superficial perivascular lymphocytic infiltration. On the other hand, late UV-induced lesions (more than 10 days) were characterized by parakeratosis, few necrotic basal keratinocytes, and vacuolar degeneration of the dermoepidermal zone. Furthermore, under experimental conditions, the appearance of immunoglobulins in UV-induced LE lesions has been reported as a late phenomenon, and in our study, direct immunofluorescence findings were negative in all skin lesions investigated up to 3 weeks after UV exposure. This is in accordance with Cripps and Rankin (1973), who detected the first immunoglobulin deposits 6 weeks after irradiation and mainly along the basement membrane.

In conclusion, extensive clinical and experimental evaluation of photosensitivity and phototesting in LE has lead to significant better understanding of the pathophysiology of LE, the clinical subgroups of this complex disease, verification of treatment effectiveness of photoprotective measures (Kuhn et al., 2002), and, finally, the elaboration of responsible action spectra, which lead to the induction and/or exacerbation of LE.

References

Baer, R.L., Harber, L.C. 1965. Photobiological of lupus erythematosus. Arch. Dermatol. 92, 124.

Baggiolini, M. 1998. Chemokines and leukocyte traffic. Nature 392, 565.

Beutner, E.H., Blaszyk, M., Jablonska, S., et al. 1991. Studies on criteria of the European Academy of Dermatology and venereology for the classification of cutaneous lupus erythematosus. J. Int. Dermatol. 30, 411–417.

Casciola-Rosen, L.A., Anhalt, G., Rosen, A. 1994. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. J. Exp. Med. 179, 1317.

Cazénave, P.L.A. 1851. Lupus erythémateux (érythéme centrifuge). Ann. Mal. Peau Syph. 3, 297.

Cripps, D.J., Rankin, J. 1973. Action spectra of lupus erythematosus and experimental immunofluorecence. Arch. Dermatol. 107, 563.

Crowson, A.N., Magro, C. 2001. The cutaneous pathology of lupus erythematosus: a review. J. Cutan. Pathol. 28, 1.

Doria, A., Biasinutto, C., Ghirardello, A., et al. 1996. Photosensitivity in systemic lupus erythematosus: laboratory testing of ARA/ACR definition. Lupus 5, 268–283.

Dubois, E.L., Tuffanelli, D.L. 1964. Clinical manifestations of systemic lupus erythematosus. JAMA 190, 104.

Epstein, J.H., Tufanelli, D.L., Dubois, E.L. 1965. Light sensitivity and lupus erythematosus. Arch. Dermatol. 91, 483.

Everett, M.A., Olson, R.L. 1965. Response of cutaneous lupus erythematosus to ultraviolet light. J. Invest. Dermatol. 44, 133.

Farkas, L., Beiske, K., Lund-Johansen, F., et al. 2001. Plasmacytoid dendritic cells (natural interferon-α/β-producing cells) accumulate in cutaneous lupus erythematosus lesions. Am. J. Pathol. 159, 237.

Freeman, R.G., Knox, J.M., Owens, D.W. 1969. Cutaneous lesions of lupus erythematosus induced by monochromatic light. Arch. Dermatol. 100, 677.

Freund, H. 1929. Inwieweit ist der Lupus erythematodes von allgemeinen Erbfaktoren abhängig?. Dermatol. Wochenschr. 89, 1939.

Friou, G.J. 1957. Clinical application of lupus serum: nucleoprotein reaction using fluorescentantibody technique. J. Clin. Invest. 36, 890–896.

Fuhs, E. 1929. Lupus erythematosus subacutus mit ausgesprochener Überempfindlichkeit gegen Quarzlicht. Z. Hautkr. 30, 308.

Furukawa, F., Kashihara-Sawami, M., Lyons, M.B., et al. 1990. Binding of antibodies to the extractable nuclear antigens SS-A/Ro and SS-B/La in induced on the surface of human keratinocytes by ultraviolet light (UVL): implications for the pathogenesis of photosensitive cutaneous lupus. J. Invest. Dermatol. 94, 77.

Furukawa, F. 1997. Animal models of cutaneous lupus erythematosus and lupus erythematosus photosensitivity. Lupus 6, 193.

Gilliam, J.N., Sontheimer, R.D. 1982. Subacute cutaneous lupus erythematosus. Clin. Rheum. Dis. 8, 343.

Goerz, G., Lehmann, P., Schuppe, H.C., et al. 1990. Lupus erythematodes (LE). Z. Hautkr. 65, 226.

Golan, T.D., Dan, S., Haim, H., et al. 1994. Solar ultraviolet radiation induces enhanced accumulation of oxygen radicals in murine SLE-derived splenocytes in vitro. Lupus 3, 103.

Gourgerot, H., Bournier, R. 1930. Lupus érythémateux tumidus. Bull. Soc. Fr. Dermatol. Syphil. 37, 1291.

Grether-Beck, S., Olaizola-Horn, S., Shmitt, H., et al. 1996. Activation of transcription factor AP-2 mediates UV radiation and singlet-oxygen-induced expression of the human intercellular adhesion molecule 1 gene. Proc. Natl. Acad. Sci. USA 93, 14586.

Hasan, T., Nyberg, F., Stephansson, E., et al. 1997. Photosensitivity in lupus erythematosus, UV photoprovocation results compared with history of photosensitivity and clinical findings. J. Br. Dermatol. 136, 699–705.

Hutchinson, J. 1888. Harveian lectures on lupus. Lecture III. On the various forms of lupus vulgaris and erythematosus. Br. Med. J. 1, 113.

Jesionek, A. 1916. Richtlinien der modernen Lichttherapie. Strahlentherapie 7, 41.

Kind, P., Lehmann, P., Plewig, G. 1993. Phototesting in lupus erythematosus. J. Invest. Dermatol. 100, 53S.

Kolb, H., Kolb-Bachofen, V. 1998. NO in autoimmune disease: cytotoxic or regulatory mediator?. Immunol. Today 1912, 556.

Krutmann, J. 2000. Ultraviolet A radiation-induces biological effects in human skin: relevance for photoaging and photodermatosis. J. Dermatol. Sci. 23, S22.

Kuhn, A., Fehsel, K., Lehmann, P., et al. 1998. Detection of apoptosis in human epidermis after ultraviolet irradiation in cutaneous lupus erythematosus. Arch. Dermatol. Res. 290, 82.

Kuhn, A., Fehsel, K., Lehmann, P., et al. 1998a. Detection of apoptosis in human epidermis after ultraviolet radiation in cutaneous lupus erythematosus. Arch. Dermatol. Res. 290, 82.

Kuhn, A., Fehsel, K., Lehmann, P., et al. 1998b. Aberrant timing in epidermal expression of inducible nitric oxide synthase after UV irradiation in cutaneous lupus erythematosus. J. Invest. Dermatol. 111, 149.

Kuhn, A., Richter-Hintz, D., Oslislo, C., et al. 2000. Lupus erythematosus tumidus, a neglected subset of cutaneous lupus erythematosus: report of 40 cases. Arch. Dermatol. 136, 1033.

Kuhn, A., Sonntag, M., Richter-Hintz, D., et al. 2001a. Phototesting in lupus erythematosus: a 15-year experience. J. Am. Acad. Dermatol. 45, 86.

Kuhn, A., Sonntag, M., Richter-Hintz, D., et al. 2001b. Phototesting in lupus erythematosus tumidus. Review of 60 patients. Photochem. Photobiol. 73, 532.

Kuhn, A., Sonntag, M., Boyer, F., et al. 2002. Evaluation of photoprotective effects of a broad spectrum highly protective sunscreen in photoinduced cutaneous lupus erythematosus. Ann. Dermatol. Venereol. 129, 1S726.

Kuhn, A., Lehmann, P., Ruzicka, T. 2005. Cutaneous Lupus Erythematosus. Springer, Berlin.

Leenutaphong, V., Boonchai, W. 1999. Phototesting in oriental patients with lupus erythematosus. Photodermatol. Photoimmunol. Photomed. 15, 7.

Lehmann, P., Hölzle, E., von Kries, R., et al. 1986. Lichtdiagnostische Verfahren bei Patienten mit Verdacht auf Photodermatosen. Z. Haut. Geschlechtskr. 152, 667.

Lehmann, P., Hölzle, E., Kind, P., et al. 1990. Experimental reproduction of skin lesions in lupus erythematosus by UVA and UVB radiation. J. Am. Acad. Dermatol. 22, 181.

Lehmann, P. 1996. Photosensitivität des Lupus erythematodes. Akt. Dermatol. 22, 52.

Lehmann, P., Ruzicka, T. 2001. Sunscreen and photoprotection in lupus erythematosus. Dermatol. Therapy 14, 167.

Lehmann, P. 2005. Historical background of cutaneous lupus erythematosus. In: Cutaneous Lupus Erythematosus. Springer, Berlin, p. 45.

Lehmann, P. 2005. Photosensitivity of lupus erythematosus. In: Cutaneous Lupus Erythematosus. Springer-Verlag Berlin Heidelberg, New York, p. 161.

McHugh, N.J. 2002. Systemic lupus erythematosus and dysregulated apoptosis: what is the evidence?. Rheumatology (Oxford) 41, 242.

Meller, S., Winterberg, F., Gilliet, M., et al. 2005. Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: an amplification cycle triggering cutaneous lupus erythematosus. Arthritis Rheum. 52, 1504.

Nived, O., Johansen, P.B., Sturfelt, G. 1993. Standardized ultraviolet-A exposure provokes skin reaction in systemic lupus erythematosus. Lupus 2, 247–250.

Norris, D.A., Lee, L.A. 1985. Antibody-dependent cellular cytotoxicity and skin disease. J. Invest. Dermatol. 85, 165S.

Pusey, W.A. 1915. Attacks of lupus erythematosus following exposure to sunlight or other weather factors. Arch. Dermatol. Syph. 34, 388.

Ronnblom, L., Alm, G.V. 2002. The natural interferon-α producing cells in systemic lupus erythematosus. Hum. Immunol. 63, 1181.

Ronnblom, L., Eloranta, M.L., Alm, G.V. 2003. Role of natural interferon-α producing cells (plasmacytoid dendritic cells) in autoimmunity. Autoimmunity 36, 463.

Sanders, C.J., Van Weelden, H., Kazzaz, G.A., et al. 2003. Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. J. Br. Dermatol. 149, 131.

Sontheimer, R.D. 1996. Photoimmunology of lupus erythematosus and dermatomyositis: a spculative review. Photochem. Photobiol. 63, 583–594.

Stege, H., Roza, L., Viink, A.A., et al. 2000. Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. Proc. Natl. Acad. Sci. USA 97, 1790.

Tebbe, B., Mazur, L., Stadler, R., et al. 1995. Immunohistochemical analysis of chronic discoid and subacute cutaneous lupus erythematosus: relation to immunopathological mechanisms. J. Br. Dermatol. 132, 25.

Tebbe, B., Wu, S., Geilen, C.C., et al. 1997. L-ascorbic acid inhibits UVA-induced lipid peroxidation and secretion of IL-1alpha and IL-6 in cultured human keratinocytes in vitro. J. Invest. Dermatol. 108, 302.

Van Weelden, H., Velthuis, P.J., Baart de la Faille, H. 1989. Light induced skin lesions in lupus erythematosus. Photobiological studies. Arch. Dermatol. Res. 281, 470.

Von Schmiedeberg, S., Fritsche, R., Rönnau, A.C., et al. 1996. Polymorphisms of drug-metabolizing enzymes in patients with idiopathic systemic autoimmune diseases. Exp. Toxic. Pathol. 48, 349.

Walchner, M., Messer, G., Kind, P. 1997. Phototesting and photoprotection in LE. Lupus. 6, 167.

White, S., Rosen, A. 2003. Apoptosis in systemic lupus erythematosus. Curr. Opin. Rheumatol. 15, 557.

Wolska, H., Blazczyk, M., Jablonska, S. 1989. Phototests in patients with various forms of lupus erythematosus. J. Int. Dermatol. 28, 98.

Zamansky, G.B., Kleinmann, L.F., Kaplan, J.C. 1980. Effect of UV light radiation on the survival of NZB mouse cells. Arthritis. Rheum. 23, 866–867.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 6

Cutaneous Manifestations of Lupus Erythematosus

Annegret Kuhn*
Department of Dermatology, University of Düsseldorf, Düsseldorf, Germany

1. Introduction

The clinical expression of skin involvement in lupus erythematosus (LE) is very common and extremely heterogeneous. Therefore, it has been difficult to develop a unifying concept of the various cutaneous manifestations of LE, and much attention has been paid to the issue of classifying this disease from the dermatological perspective in the past (Sontheimer, 1997; Kuhn et al., 2004). In 1977, Gilliam (1977) initially proposed, with several refinements soon thereafter (Gilliam and Sontheimer, 1981, 1982), a nomenclature and classification system for the extremely varied skin lesions that can be encountered in patients with LE. He divided the cutaneous manifestations of this disease into those that are histologically specific for LE (i.e., LE-specific skin disease) and those that are not histologically specific for this disease (i.e., LE-non-specific skin disease). The LE-specific skin manifestations included the classical cutaneous subtypes of LE, acute cutaneous LE (ACLE), subacute cutanoeus LE (SCLE), and chronic cutaneous LE (CCLE). However, this classification system was not meant to rigidly define subtypes of LE since there are certain patterns of systemic disease activity that can also be seen in conjunction with these subtypes (Sontheimer, 1997). Furthermore, overlapping features can occur with any arbitrary subdivision of a disease as heterogeneous as LE (Costner et al., 2003). In addition, the LE-non-specific skin manifestations, such as calcinosis cutis, Raynaud's phenomenon, and annular erythema, have histologic changes that are also seen in conditions other than LE and are thus not specific for this disease.

Since the initial formulation of the nomenclature system by Gilliam in 1977 (Gilliam, 1977), several attempts have been made to improve upon this system and to provide new approaches for the classification of the cutaneous manifestations of LE (Sontheimer, 1997). Consequently, this has led to the practice of identifying further subsets, which have been defined by constellations of clinical features, laboratory abnormalities, histologic findings, immunohistologic patterns, genetic associations, and, more recently, phototesting results. Most commonly, patients with LE complain of photosensitivity, which shows a strong association to disease manifestation suggesting that abnormal reactivity to ultraviolet (UV) light is one important factor in the pathogenesis of this disease (Kuhn and Beissert, 2005). Photoprovocation tests are an optimal procedure to evaluate photosensitivity in these patients and are even required for diagnosis in some cases (Kuhn et al., 2001a). Furthermore, the capacity of UVA and UVB irradiation to reproduce LE skin lesions is an ideal model for several experimental approaches, which allows the study of inflammatory and immunologic events that take place prior to and during lesion formation. In addition, phototesting has been crucial in further analyzing a highly photosensitive form of the disease, namely, LE tumidus (LET). The

*Corresponding author.
Annegret Kuhn, Department of Dermatology, University of Düsseldorf Moorenstrasse 5, 40225 Düsseldorf, Germany.
Tel.: + +49-211-8118798; Fax: + +49-211-8119175.
E-mail address: kuhnan@uni-duesseldorf.de (A. Kuhn).

DOI: 10.1016/S1571-5078(05)05006-3

Table 1
Düesseldorfer classification of cutaneous lupus erythematosus 2003

Acute cutaneous lupus erythematosus (ACLE)
Subacute cutaneous lupus erythematosus (SCLE)
Chronic cutaneous lupus erythematosus (CCLE)
Discoid lupus erythematosus (DLE)
Lupus erythematosus profundus (LEP)
Chilblain lupus erythematosus (CHLE)
Intermittent cutaneous lupus erythematosus (ICLE)
Lupus erythematosus tumidus (LET)

characteristic features of this subtype have been evaluated by our group (Kuhn et al. 2000a, 2001b, 2002a,b 2003) and confirmed by several other investigators (Dekle et al. 1999, Ruiz and Sanchez, 1999; Alexiades-Armenakas et al., 2003) demonstrating that LET can clinically and histologically be differentiated from ACLE, SCLE, and CCLE. Furthermore, patients with LET show a mild, intermittent course of their disease. Once a lesion has developed, it can also disappear spontaneously even if the disease recurs chronically in these patients. Therefore, LET is now considered as a separate entity and included in the classification system as an intermittent subtype of cutaneous LE (ICLE) (Kuhn and Ruzicka, 2004) (Table 1).

In the following part, the clinical features of the specific cutaneous manifestations of LE including ACLE, SCLE, CCLE, and ICLE are described. Furthermore, less common, LE-non-specific cutaneous manifestations, such as bullous skin lesions, urticarial vasculitis, papulonodular mucinosis, and annular erythema are depicted, which can also occur in the context of other diseases and, therefore, often lead to diagnostic difficulties.

2. Specific cutaneous manifestations of lupus erythematosus

2.1. Acute cutaneous lupus erythematosus

Acute cutaneous lupus erythematosus (ACLE) usually occurs in association with systemic manifestations preceding by weeks or months the onset of a multisystem disease (Watanabe and Tsuchida, 1995; Wysenbeek et al., 1992; Yung and Oakley, 2000). Sun exposure is a common exogenous factor to be capable of precipitating ACLE (Kuhn et al., 2001a; Wysenbeek et al., 1989), and some patients even report an exacerbation of their systemic symptoms after exposure to sunlight. Furthermore, infections, especially with subtle types of viruses, or certain drugs, e.g. hydralazine, isoniazide, and procainamide, have also been found to induce or aggravate this disease (Pramatarov, 1998; Rubin, 1999).

There are localized and generalized manifestations of ACLE (Costner et al., 2003; Fabbri et al., 2003). The localized form commonly presents as the classic ''malar rash'' or ''butterfly rash'' on the central portion of the face and may only affect the skin transiently. Therefore, at the onset of disease, the patient may mistake this rash for sunburn. It usually begins with small, discrete erythematous macules and papules, occasionally associated with fine scales and gradually becomes confluent and hyperkeratotic. Facial swelling may be severe in some patients with ACLE; however, it mostly disappears without scarring and pigmentation (Norden et al., 1993; Yell et al., 1996). Similar lesions have also been found to occur on the forehead, the V-area of the neck, the upper limbs, and the trunk. In addition, patients with ACLE may have diffused thinning or a receding frontal hairline with broken hair (lupus hair), and may further present with teleangiectasias and erythema of the proximal nail fold and cuticular abnormalities (Patel and Werth, 2002). Superficial ulcerations of the oral and/or nasal mucosa are also frequently accompanied with this subtype and may cause extreme discomfort in some patients.

The generalized form of ACLE is a less common variety and may be located anywhere on the body although the preferred sites are above the waistline (Fig. 1) (Costner et al., 2003; Yell et al., 1996). The onset of this form usually coincides with exacerbation of systemic manifestations developing a prolonged disease activity and may resemble a drug eruption or can simulate toxic epidermal necrolysis. The incidence of this generalized form is estimated to be approximately in 5–10% of patients with systemic lupus erythematosus (SLE) (Cardinali et al., 2000; Fabbri et al., 2003;

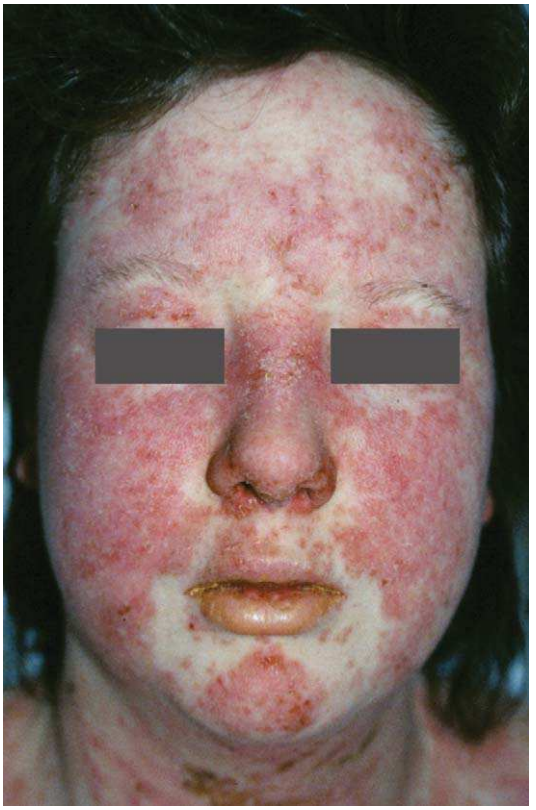


Figure 1. Acute cutaneous lupus erythematosus (ACLE). Confluent, erythematous, hyperkeratotic lesions on the face of a patient with a generalized form.

Sontheimer, 1997). It is characterized by a symmetrically distributed maculopapular or exanthematous eruption with a pruritic component. The colour of the lesions is usually red or, less frequently, dull red or livid, and there have been reports of patients presenting with severe involvement of the oral mucosa or the palms and phalanges (Braverman, 1981; McCauliffe, 2001).

2.2. Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) is a distinct entity with specific clinical and serologic features that was first described by Gilliam in 1977 (Gilliam, 1977), with expanded discussion in 1979 (Sontheimer et al., 1979) and 1982 (Gilliam and Sontheimer, 1982). Most patients with SCLE are sensitive to sunlight and have prominent cutaneous and musculoskeletal complaints but generally do not develop a severe systemic disease (Crowson and Magro, 2001; Cohen and Crosby, 1994; Tan et al., 1982). Furthermore, the majority of patients with this subtype produce anti-Ro/SSA antibodies, the presence of which supports, but is not necessary to make the diagnosis of SCLE.

Initially, SCLE patients show sharply demarcated, elevated, erythematous papules or small plaques covered with fine scales affecting shoulders, upper back, extensor aspects of the arms, and the V-area of the back or neck. The lesions expand and merge in some patients producing papulosquamous lesions that can mimic those of psoriasis vulgaris. In other patients, the primary lesions expand and clear centrally to produce annular lesions that may merge into polycyclic arrays (Fig. 2) (Sontheimer, 1989; Bangert et al., 1984). While few patients with SCLE simultaneously exhibit both papulosqaumous and annular lesions, most have predominantly one type. Some groups have observed a predominance of the papulosquamous lesions, whereas others have noted an abundance of the annular/polycyclic type (Herrero et al., 1988; Molad et al., 1987; Callen and Klein, 1988; Fabbri et al., 1990; David-Bajar, 1993; Chlebus et al., 1998; Cohen and Crosby, 1994). Both types of SCLE lesions heal without scarring but can leave long-lasting and permanent vitiligo-like pigmentary changes as a 'clue' for the clinical diagnosis (Milde and Goerz, 1994).

Occasionally, SCLE lesions may present with an appearance of erythema multiforme, which can simulate the appearance of Rowell's syndrome (erythema multiforme-like lesions occurring in patients with SLE in the presence of anti-La/SSB antibodies) (Sontheimer, 1985b; Rowell et al., 1963). In 1998, Lyon et al. (1998) reported two cases of delayed diagnosis of SCLE because of the clinical and histologic similarities between SCLE and erythema multiforme. Furthermore, several LE-non-specific skin manifestations have been described in patients with SCLE (Sontheimer, 1989; Parodi et al., 2000) including non-scarring alopecia, livedo reticularis, periungual teleangiectasias, and Raynaud's phenomenon (Sontheimer,

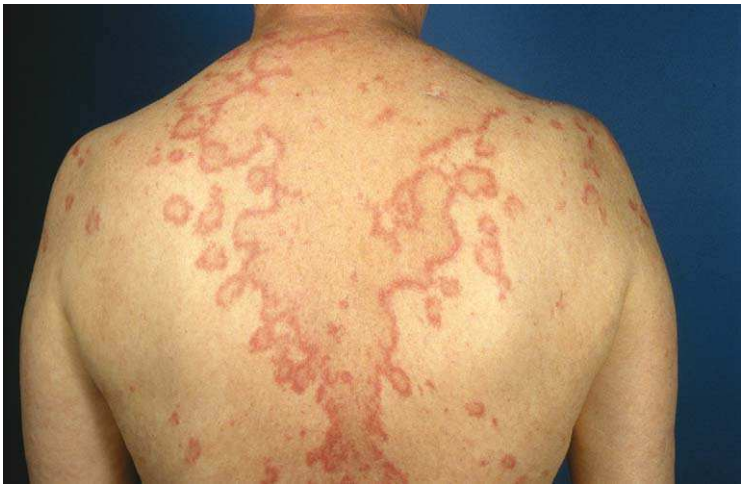


Figure 2. Subacute cutaneous lupus erythematosus (SCLE). Annular, polycyclic lesions with erythematous borders and central hypopigmentation on the back.

1985a; Herrero et al., 1988; Molad et al., 1987; Callen and Klein, 1988; Callen et al., 1986; David et al., 1984; Sanchez-Perez et al., 1993). Cutaneous vasculitis of the lower extremities is a further frequent finding in anti-Ro/SSA-positive patients with SCLE described under the rubric of Sjögren's syndrome/LE overlap syndrome (Provost et al., 1988b). Calcinosis cutin may be seen rarely in patients with SCLE, and HPV-11-associated squamous cell carcinoma of the skin was also noted in one patient with this subtype (Cohen et al., 1992). In one case, annular/polycyclic SCLE lesions were reported over time to progress to plaques of morphea (Rao et al., 1990). In a study by Herrero et al. (1988), vesiculobullous changes were present in 38% of the SCLE population, which coincided histologically with focal areas of necrosis. In 1988 (DeSpain and Clark, 1988), one patient with SCLE was reported to initially present exfoliative erythroderma which was also noted more recently by Mutasim (2003).

2.3. Chronic cutaneous lupus erythematosus

The group of chronic cutaneous lupus erythematosus (CCLE) includes several entities, such as discoid LE (DLE) and the more rare subtypes LE profundus (LEP) and chilblain LE (CHLE).

2.3.1. Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common subtype of the chronic cutaneous variants of LE and may present as a localized or disseminated form. The localized form, characterized by limited cutaneous involvement of the head and scalp, usually accounts for 70% of patients with DLE, and the disseminated form, characterized by the extension to areas below the neck for 30% of patients with DLE. Disseminated DLE, especially when involving the trunk, is in most cases associated with progression to SLE. Interestingly, approximately 30% of patients with SLE may develop DLE lesions during the course of their disease and, in about 5–10% of patients, DLE lesions may already be present at the onset of the disease (Cervera et al., 1993; Hymes and Jordon, 1989; Tebbe et al., 1997).

Clinically, the skin lesions of patients with DLE begin with flat or slightly elevated, demarcated, erythematous macules or papules with a scaly surface. Early lesions most commonly evolve into larger, coin-shaped (''discoid''), confluent, disfiguring plaques of varying size demonstrating a prominent adherent scale formation (Fig. 3) (Crowson and Magro, 2001). When the adherent scale is peeled back from more advanced lesions, follicle-sized keratotic spikes similar in appearance to carpet tacks can be seen projecting from the

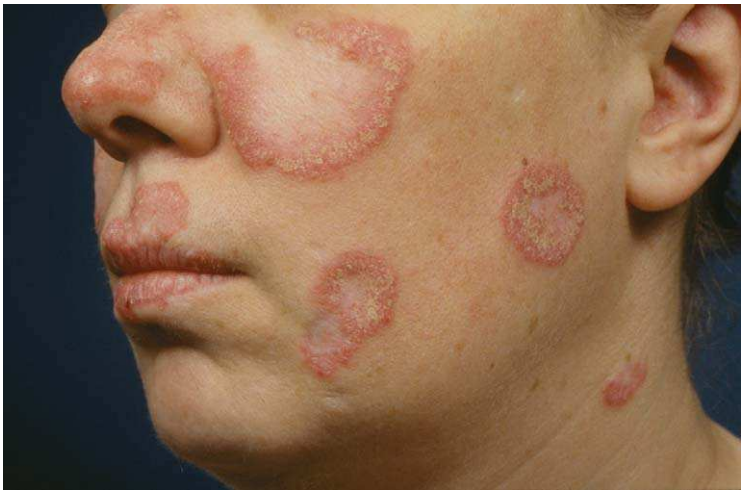


Figure 3. Discoid lupus erythematosus (DLE). Facial erythematous plaques with active inflammation at the periphery and central atrophic scarring.

undersurface of the scale ('the carpet tack sign'). Teleangiectasia and hyperpigmentation can replace the active inflammation, and the lesions may give a poikilodermatous appearance. The DLE plaques are generally progressive, and resolution of the lesions leaves more or less evident atrophy and scarring, depending on the duration and severity of the lesions during the active phase. This may result in considerable mutilations, particularly when present in acral regions on the face, such as the tip of the nose and the ears, or in irreversible scarring alopecia on the scalp. A characteristic pitted, acneiform scarring is also a common feature of the perioral area.

Approximately 2% of patients with DLE show a hyperkeratotic type of lesion (Mascaro et al., 1997; Costner et al., 2003; Kuhn et al., 2000c) consisting of dull, red, and indurated lesions. These verrucous, hyperkeratotic plaques can occur at any site of the body where classical DLE lesions develop, although the extensor aspects of the arms and limbs, the upper back, and the face are most frequently affected (Mascaro et al., 1997; Daldon et al., 2003). Recently, conjunctival hyperkeratotic lesions have been reported in a patient with a history of chronic blepharoconjunctivitis (Uy et al., 1999). When the palms and soles are involved, hyperkeratotic DLE produces localized or partially diffuse keratoderma, up to 1–3 mm thick, that makes mobility more difficult (Rothfield, 1993). Differential diagnosis of the hyperkeratotic type of DLE must take into consideration verrucous psoriasis, hyperkeratotic lichen planus, prurigo nodularis, keratoacanthoma, and squamous cell carcinoma (Romero et al., 1977; Perniciaro et al., 1995; Daldon et al., 2003; Vinciullo, 1986).

DLE lesions predominantly occur in sun-exposed areas of the skin and the appearance in unusual locations and on completely sun-protected areas may be evidence that these lesions can follow in the wake of any form of trauma to the skin (Koebner's phenomenon or isomorphic response) (Ueki, 2005). Mostly, the lesions appear on the face, particularly the cheeks and ears, the neck, and arms, but may also be found in inguinal folds, palmo-plantar, and the scalp (McCauliffe, 2001; Fabbri et al., 2003; Patel and Werth, 2002; Costner et al., 2003). At the latter location, DLE may even be the only cutaneous manifestation in 10% of cases and thus presents a classical differential diagnosis of scarring alopecia (Prystowsky and Gilliam, 1975). In some patients, DLE on the scalp progresses to the point of total, irreversible scarring alopecia and may be accompanied by secondary bacterial superinfection. Mucous membrane involvement can be found in 25% of patients with DLE, but does not necessarily reflect systemic manifestation or high disease activity (Burge et al.,

1989; Botella et al., 1999; Andreasen and Poulsen, 1964); however, it is included in the list of the 11 diagnostic Criteria of the American College of Rheumatology (ACR) for the diagnosis of SLE (Tan et al., 1982). The lesions usually begin as painful, erythematous patches, later maturing to a chronic plaque that has a sharply marginated, irregularly scalloped white border with radiating white striae. The centers of older lesions cause atrophy and may become depressed and, occasionally, undergo painful ulceration. Oral, mainly buccal, manifestations are most common, with the palate, alveolar processes, and tongue less frequently involved, but nasal, conjunctival, and anogenital mucous membranes may also be affected at times. Persistent erythema, epithelial thickening, fine keratosis, or erosions are also seen on the vermilion border of the lips and can present as a diffuse cheilitis, especially on the more sun-exposed lower lip, causing considerable discomfort and disfiguration. The nails can be involved as a very uncommon site of occurrence; however, periungual teleangiectasias and erythema of the proximal nail fold are significant features that can occur in patients with DLE prone to developing systemic disease. Furthermore, focal lesions of DLE occurring over the nail fold can produce nail plate dystrophy (Kanwar et al., 1993).

2.3.2. *Chilblain lupus erythematosus*

Chilblain lupus erythematosus (CHLE), distinguished by Hutchinson in 1888 (Hutchinson, 1888), is seen predominantly in females and strongly influenced by environmental factors (Breathnach and Wells, 1979; Rowell, 1987; Uter et al., 1988; Doutre et al., 1992; Helm and Jones, 2002). The pathogenesis of this rare subtype of CCLE is unknown, but microvascular injury secondary to exposure to cold, damp weather, or a drop in temperature and possible hyperviscosity from immunologic abnormalities may play a role (Yell et al., 1996; Mascaro et al., 1997). The risk of developing SLE is estimated to be approximately 20%, but only few studies of patients with CHLE have been reported (Viguier et al., 2001).

The lesions of CHLE are clinically characterized by symmetrically distributed, circumscribed, sometimes infiltrated, pruriginous or painful areas of livid and purple plaques. There is only a slight tendency to central regression, and the lesions, in their evolution, may ulcerate or present firmly adherent hyperkeratosis (Costner et al., 2003; Kuhn et al., 2000c). Mostly, the dorsal and lateral parts of the hands and feet, the ears, the nose, the elbows, the knees, or the calves are involved (Su et al., 1994; Helm and Jones, 2002). On toes and fingers, the lesions present on the back or on the pads (Fisher and Everett, 1996; Doutre et al., 1992), and fissuring of the knuckles as well as accompanying hyperhidrosis are common, producing a great deal of discomfort (Costner et al., 2003). Ulceration is frequent in digital pulp lesions, and they easily become necrotic on the soles (Mascaro et al., 1997). When located in the periungual zone, the nail plate may develop mild to severe dystrophy. A chronic form of CHLE occurs especially in older patients who have underlying vascular abnormalities, such as acrocyanosis, Raynaud's phenomenon, atherosclerosis, or erythrocyanosis. In such patients, this subtype of CCLE can last for several months and tends to recur annually, sometimes with hemorrhagic blisters, erosions, or ulcers.

2.3.3. *Lupus erythematosus profundus*

Historically referred to as Kaposi–Irgang disease (Kaposi, 1883; Irgang, 1940), lupus erythematosus profundus (LEP) is a rare variant of CCLE characterized by inflammatory lesions in the lower dermis and subcutaneous tissue. This subtype generally affects middle-aged women; however, in a recent study it has been shown that in Asian patients LEP is more frequent in a younger age group compared with the Caucasian population (Ng et al., 2002). Patients with LEP present most commonly without any or only mild signs of systemic manifestations and it can only be found in 2% of patients with SLE. The course of LEP is usually chronic and characterized by periods of remission and exacerbation, and the major morbidity is usually disfigurement and disability related to pain (Mascaro et al., 1997; Kuhn et al., 2000c).

The lesions of LEP typically appear as single or multiple sharply defined, persistent, asymptomatic

or sometimes painful subcutaneous plaques or nodules of varying sizes (Peters and Su, 1989; Costner et al., 2003). The overlying skin becomes attached to the firm lesions, producing a deep depression into the subcutis with a normal or erythematous, inflammatory surface. Dystrophic calcifications or ulcerations within older lesions of LEP, leaving atrophic scars or sometimes resembling lipatrophy, may occur and at times can be a prominent clinical feature of the disease requiring surgical excision. Trauma may often directly be related to the lesions of LEP (Tuffanelli, 1971). Most lesions of LEP are usually found on the trunk, buttocks, and proximal upper and lower extremities, but the shoulders and thighs are further sites of predominant involvement (Martens et al., 1999). This subtype may also develop on the scalp clinically simulating alopecia areata (Kossard, 2002) and in unusual areas on the face, such as the parotid region. Furthermore, periorbital edema as an initial symptom of LEP has also been described in several patients as the only clinical manifestation of the disease (Lodi et al., 1993; Magee et al., 1991; Franke et al., 1999).

2.4. Intermittent cutaneous lupus erythematosus

LET has recently been defined as a distinct entity of cutaneous lupus erythematosus (CLE) and is now inclued in the new classification as the intermittent subtype. The importance of re-evaluating this form lies in the characteristic clinical picture, the histologic pattern, the remarkable photosensitivity, and in the course of the disease (Kuhn et al., 2004). In several aspects, LET differs from other variants of CLE. Scarring, the hallmark of DLE, does not occur in LET, even in patients with recurrent skin lesions. Follicular plugging and adherent hyperkeratotic scaling, which are further features of DLE, have also not been seen in any of the patients with LET. Hypopigmentation, frequently evident in patients with SCLE after the active phase with erythema and scaling, has never been detected in LET (David-Bajar and Davis, 1997). Furthermore, association with systemic disease seems to be very rare in patients with LET, and has only been documented in very few cases (Jolly et al., 2004). Although joint symptoms occur temporarily, no signs of inflammatory joint disease or rheumatoid arthritis have been detected, and further systemic manifestations, such as renal, central nervous system, or lung involvement, have not yet been appreciated in any of the patients. Therefore, the prognosis in patients with LET is generally more favorable than in those with other forms of CLE (Kuhn et al., 2000a).

2.4.1. Lupus erythematosus tumidus

LET is clinically characterized by succulent, urticaria-like, single or multiple plaques with a bright reddish or violaceous smooth surface (Fig. 4). The swollen appearance of the lesions and the absence of clinically visible epidermal involvement are the most important features of this subtype. The borders are sharply limited, and, in some cases, there is a tendency for the lesions to coalesce in the periphery, producing a gyrate configuration, or to swell in the periphery and flatten in the center (Mascaro et al., 1997). LET lesions can coexist with DLE lesions (Ruiz and Sanchez, 1999) and have been reported to mimic alopecia areata when present on the scalp (Werth et al., 1992). Some patients develop erythematous, annular lesions on the cheeks and upper extremities imitating the annular type of SCLE, and, recently, a patient with LET following the lines of Blaschko has been reported (Pacheco et al., 2002). However, other LE-non-specific manifestations such as calcinosis cutis and livedo reticularis, have never been detected in any of the patients.

The skin lesions in LET are primarily found on sun-exposed areas, such as the face, the upper back, the V-area of the neck, the extensor aspects of the arms, and the shoulders (Kuhn et al., 2000a). Therefore, it has long been suggested that this subtype of CLE is characterized by a remarkable photosensitivity (Goerz et al., 1990). Provocative phototesting confirmed that patients with LET are more photosensitive than those with other forms of CLE. In a study by our group (Kuhn et al., 2001b), characteristic skin lesions

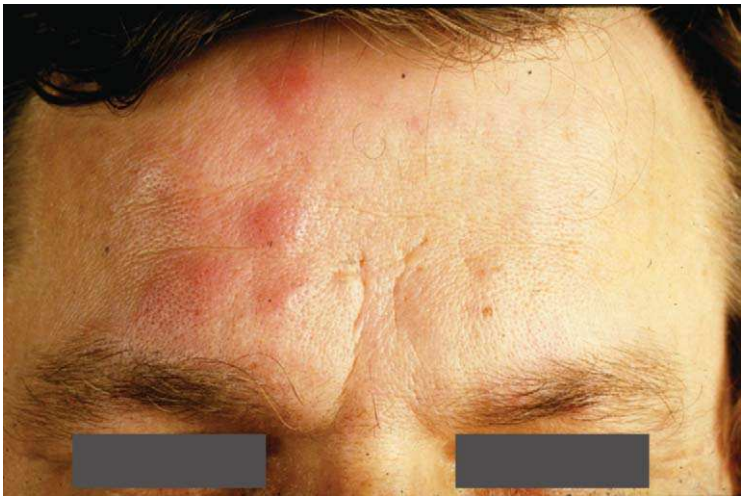


Figure 4. Lupus erythematosus tumidus (LET). Single. rythematous, succulent, urticaria-like plaques on the forehead.

were induced by UV irradiation in 72% of the patients. However, because of the latency period in developing positive phototest reactions, it may be difficult for patients to link sun exposure to their disease.

The most frequent histologic features in LET lesions are a fairly well-circumscribed lymphocytic dermal infiltrate in a perivascular and periadnexal pattern and abundant interstitial mucin deposition (Kuhn et al., 2003). In a few cases, the epidermis is acanthotic, and the dermis shows edema in its upper part; however, in contrast to other forms of CLE, epidermal changes such as atrophy and follicular plugging, and vacuolar degeneration of the dermoepidermal junction or basement membrane thickening are absent. Therefore, some authors have not considered LET as a subtype of CLE or as a separate entity different from other variants of CLE, and it is likely that skin lesions described under different designations, such as ''urticarial plaque lupus erythematosus,'' represent the same disease entity (Sontheimer and Provost, 1996). Further more, some skin conditions share a variety of similar features, demanding attention to rather subtle details and appreciation of the characteristic signs of LET as well as the course of the disease. In 2000, our group (Kuhn et al. 2000a) analyzed 40 patients with LET and defined diagnostic criteria for the classification of this disease, which have been confirmed by other investigators (Alexiades-Armenakas et al., 2003; Choonhakarn et al., 2004). Interestingly, most case reports of LET in the literature are published by European countries indicating that many more patients are seen in the Caucasian population (Sontheimer, 2000).

3. Non-specific cutaneous manifestations of lupus erythematosus

Skin lesions which are seen not only in patients with LE but are also found in association with other conditions are defined as non-specific cutaneous manifestations. These non-specific cutaneous manifestations are morphologically varied and include non-scarring alopecia, calcinosis cutis, rheumatoid nodules, and sclerodactyly (Table 2). Several skin diseases can also be found in the context of LE, such as acanthosis nigricans, anetoderma, cutaneous vascular diseases, e.g. Raynaud's phenomenon, erythema multiforme, lichen planus, and porphyria cutanea tarda (Costner et al., 2003; Provost, 2004). In addition, bullous skin lesions, and autoimmune disorders, urticaria vasculitis, papulonodular mucinosis, and annular erythema can be associated with various forms of LE and will be described in the following.

Table 2
Non-specific cutaneous manifestations of lupus erythematosus

Skin Lesions	Skin Diseases
Alopecia (non-scarring)	Acanthosis nigricans
Annular erythema	Anetoderma
Bullous skin lesions	Bullous autoimmune disorders
Calcinosis cutis	Cutaneous vascular diseases (e.g., urticaria vasculitis (Raynaud's phenomenon)
Papulonodular mucinosis	
Rheumatoid nodules	Erythema multiforme
Sclerodactyly	Lichen planus Porphyria cutanea tarda

3.1. Bullous skin lesions in lupus erythematosus

A variety of primarily blistering diseases have been reported to occur in patients with SLE, in particular, dermatitis herpetiformis (Davies et al., 1976) bullous pemphigoid (Miller et al., 1978), pemphigus erythematosus (Chorzelski et al., 1968), pemphigus foliaceus (Blanchet et al., 1981), epidermolysis bullosa acquisita (Dotson et al., 1981), and linear IgA dermatoses (Lau et al., 1991). In addition, further types of vesicular and bullous skin lesions can be associated with different subtypes of LE. In 1997, Sontheimer (1997) divided the various bullous skin lesions into those that have or do not have LE-specific pathology and proposed the following classification scheme: (i) The cutaneous lesions of patients with LE may blister because of severe vacuolar degeneration of the basement membrane zone. Skin cleavage occurs as a result of dissolution of the basal cell layer, resulting in subepidermal cleavage that may have the clinical appearance of toxic epidermal necrolysis. Documentation of CLE as the causal factor in this type of bullous skin lesion can be difficult because such patients are also frequently taking systemic medications, and toxic epidermal necrolysis, therefore, may also develop as a result of drug hypersensitivity reaction. In patients with SCLE, vesiculobullous changes may occur at the active edge of annular lesions (Sontheimer, 1985b; Grant, 1981; Wechsler and Stavrides, 1982), and have also been reported to be present in DLE lesions; however, these changes seem to be extremely rare (Nagy and Balogh, 1961). (ii) Bullous lesions may also arise on normal or erythematous skin of patients with SLE, tend to be tense, and may approach the size of blisters in bullous pemphigoid or may resemble the vesiculobullous lesions of dermatitis herpetiformis (Bacman et al., 2004; Olansky et al., 1982; Penneys and Wiley, 1979; Hall et al., 1982; Gammon et al., 1985; Camisa and Sharma, 1983). If the bullous lesions rupture, they leave erosions, crusts, and pigmentary changes, and when they regress, scars, milium cysts, or calcinosis cutis can remain (Eckman and Mutasim, 2002). In this form of bullous skin lesions, the activity of blistering may or may not coincide with the activity of the patient's disease, and occasionally, serious cases associated with organ-threatening manifestations have been reported (Sontheimer, 1997; Gammon and Briggaman, 1993). Histologically, the subepidermal blisters demonstrate neutrophilic microabscesses in dermal papillae along with a perivascular and periadnexal infiltration consisting of lymphocytes and neutrophils (Megahed, 2004). Direct immunofluorescence shows linear or granular deposits of IgG, IgA, and/or IgM and complement along the basement membrane zone, and immunoelectron microscopic studies demonstrate IgG deposits at or below the lamina densa (Gammon and Briggaman, 1993; Yell and Wojnarowska, 1997). Furthermore, indirect immunofluorescent studies are positive using a 1 M NaCl split skin demonstrating mostly dermal binding (Gammon et al., 1985), and Western blot analysis showed that these autoantibodies bind to the non-collagenous portion of type VII collagen (Shirahama et al., 1998). These data further demonstrated that the autoantibodies in this bullous form of LE bind to the same epitopes as described in epidermolysis bullosa (Lapiere et al., 1993; Barton et al., 1986). In more recent studies, Chan et al. (1999) concluded that patients with this type of blistering in LE may have autoantibodies to multiple basement membrane components, such as bullous pemphigoid antigen-1, laminin-5, laminin-6.

3.2. Urticarial Vasculitis

Urticarial vasculitis is usually an acquired idiopathic phenomenon but may also occur in association with other disorders, such as SLE or Sjögren's syndrome (Davis et al., 1998; Sanchez et al., 1982;

Mehregan et al., 1992; O'Loughlin et al., 1978;, Provost et al., 1980). All of the patients reported with urticarial vasculitis in association with SLE have shown varying combinations of multisystem disease, and two forms of urticarial vasculitis have been described (Provost, 2004). The most common form, occurring in approximately 10% of patients with SLE, is associated with various autoantibodies (anti-dsDNA, anti-Ro/SSA, and anti-U1RNP antibodies) and, furthermore, these patients show a systemic disease, including glomerulonephritis and arthritis. Most of these patients also demonstrate a leukocytoclastic angiitis and, in some cases, a mononuclear vasculopathy has been described. The second form of urticarial vasculitis seen in patients with SLE is characterized by the presence of anti-C1q antibodies and hypocomplementemia. This form of urticarial vasculitis can also occur in patients without SLE and is termed hypocomplementemic urticarial vasculitis (HUVS) (Uwatoko and Mannik, 1988). Clinically, these patients frequently demonstrate arthralgias, arthritis, glomerulonephritis, angioedema, ocular inflammation (conjunctivitis, episcleritis, uveitis, etc.), and obstructive lung disease.

Urticarial vasculitis has usually a chronic course lasting for years; however, complete resolution of the skin lesions has also been described. The urticarial skin lesions are characterized as transient, well-circumscribed, edematous, lightly erythematous wheals, often with central clearing or a peripheral halo. However, the individual lesions usually persist for 24 h or longer. Occasionally, these lesions resolve with secondary changes, e.g. pigmentation, scaling, or purpura. With regard to symptoms, some patients complain of burning or painful lesions as opposed to pruritic lesions of classic urticaria. The typical histologic feature is a fibrinoid necrotizing vasculitis in the upper dermis, with leukocytoclasis and erythrocyte diapedesis. Direct immunofluorescence of urticarial lesions demonstrates various combinations of immunoglobulins and complement components in the vessels walls.

3.3. Papulonodular mucinosis

Mucin deposition is generally restricted to primary mucinoses, such as lichen myxedematosus, and is rarely present in sufficient quantity to produce lesions that are clinically detectable in other diseases, such as LE (Kanda et al., 1997). Although recognized as early as 1954 by Gold (1954), only approximately 40 patients with papulonodular mucinosis associated with various forms of LE have been described in the literature (Sonntag et al., 2003; Hazan, 2004; Ortiz et al., 2004). In most cases, papulonodular mucinosis is associated with SLE, but can also be found in patients with DLE and SCLE. Interestingly, it has been indicated that papulonodular mucinosis tends to occur more frequently in males, indicating a possible role for sex-related factors, such as androgenic hormones, in the pathogenesis of this associated disease (Kanda et al., 1997). In addition, exposure to sunlight may be a further contributing factor in the pathogenesis of papulonodular mucinosis (Nagy et al., 1967; Moulin et al., 1980; Weidner and Djawari, 1982; Sonntag et al., 2003).

Clinically, papulonodular mucinosis presents with asymptomatic skin-colored papules and nodules that can be seen inside and outside of typical lesions of LE and involve mostly the trunk and upper extremities, but the face and other locations can also be affected. In some patients, papulonodular mucinosis predates LE, and in others it is associated with its activity, and it can even be the only cutaneous manifestation of LE during a period of time (Sonntag et al., 2003). The histologic picture of papulonodular mucinosis is dominated by abundant interstitial mucin deposition in the papillary and reticular dermis, which can be confirmed by colloidal iron staining, and there is also a mild superficial perivascular lymphocytic infiltrate. However, the characteristic alterations of LE, such as epidermal involvement and vacuolar degeneration of the dermoepidermal junction, are absent (Kanda et al., 1997; Weigand et al., 1981).

Several cutaneous mucinoses might lead to diagnostic confusion with papulonodular mucinosis, including lichen myxedematosus, reticular erythematosus mucinosis, and pretibial or generalized myxedema (Reed et al., 1973; Rongioletti and Rebora, 1991, 2001). Lichen myxedematosus most likely bears striking similarities to papulonodular mucinosis, but the clinical features differ in the form of the papules, which tend to be

smaller, and the localization is most common on the face and arms.

3.4. Annular erythema

Annular erythema has been recognized as a cutaneous manifestation of Sjögren's syndrome in Asian patients and, in only one case report, it has been described in a white female (Haimowitz et al., 2000; Watanabe et al., 1997; Teramoto et al., 1989). However, in certain cases it can also represent an unusual skin manifestation within the spectrum of LE (Kuhn et al., 2000b; Ruzicka et al., 1991). Since there are common pathophysiologic mechanisms, mainly the presence of anti-Ro/SSA or anti-La/SSB antibodies, it is in some cases difficult to separate annular erythema from SCLE. However, more recent studies demonstrated that annular erythema associated with Sjögren's syndrome can clinically and histologically be differentiated from SCLE and that HLA-DRw52/-Cw3 is closely related to patients with annular erythema (Hoshino et al., 1992; Katayama et al., 1991, 1994; Miyagawa, 1994; Provost et al., 1988a; Watanabe et al., 1997).

Clinically, annular erythema is characterized by erythematous papules and centrifugal extension leading to urticarial plaques with annular elevated borders and central hyperpigmentation. In majority of patients, the erythema appears symmetrically on the face, the trunk, or the extensor aspects of the extremities, but the entire integument may also be involved. Histologic investigation shows slight epidermal changes without dyskeratotic cells or follicular plugging and reveals no changes at the dermoepidermal junction. A lymphocyte infiltration around the blood vessels and a marked edema are seen in the papillary dermis. Additional studies demonstrated prominent mucin deposition in these lesions (Kuhn et al., 2000b; Nishikawa and Provost, 1991).

4. Conclusions

Cutaneous manifestations in patients with LE are very frequent, show a great variety and can occur at any stage of the disease. A classification system has been established dividing the skin lesions associated with LE in specific and non-specific manifestations. The non-specific manifestations such as urticaria vasculitis and annular erythema, are also seen in conditions other than LE and are thus not specific for this disease. Although the specific cutaneous manifestations of this disease are considered to have a less severe course and to carry a better prognosis than the systemic form, 67–70% of patients with SCLE and 14–27% of patients with DLE have extracutaneous signs (Tebbe and Orfanos, 1997). Patients who have a more generalized involvement of the skin tend to have more systemic symptoms than those with lesions localized to the face or neck. Nevertheless, all cutaneous manifestations of LE can result in limited patient quality of life and disability from work. It has also been found that 45% of patients with CLE experience some form of vocational handicap. However, recent epidemiological data of the cutaneous manifestations of LE are not available (Jimenez et al., 2004). Therefore, it has been a long standing need for a study group including experts of different medical specialities in order to better focus on all aspects related to LE. In 2004, the 'Interdisciplinary Study Group of Lupus Erythematosus (ISGLE)' was founded with the aims (i) to receive an overview of the spectrum of clinical and laboratory features and therapeutic strategies of this disease, (ii) to develop criteria for disease activity and diagnostic guidelines for patients with LE, and (iii) to implement evidence based management strategies and standards of care for patients with the various manifestations of this disease. Further aims of ISGLE are (i) continuous standardized evaluation of the different organ systems, (ii) continuous exchange between the involved specialists on problems of their patients (e.g., pregnancy); (iii) communication of early diagnosis and treatment as well as patient education improving the quality of life and the socioeconomic status of patients with LE (http://www.ISGLE.rheumanet.org).

5. Acknowledgements

This work was supported by Heisenberg professorship from the German Research Association (DFG) to A.K. (KU 1559/1-1).

Key points

- The clinical expression of skin involvement in lupus erythematosus (LE) is very frequent and shows a great variety.
- Gilliam (1977) initially proposed a classification system for the skin lesions that can be encountered in patients with LE and divided the cutaneous manifestations of this disease into those that are histologically specific for LE (i.e., LE-specific skin disease) and those that are not histologically specific for this disease (i.e., LE-non-specific skin disease).
- In 2003, a modified classification system of cutaneous LE (CLE) has been developed including acute CLE, subacute CLE, chronic CLE, and the intermittent subtype of CLE, ICLE.
- Non-specific cutaneous manifestations of LE which can also occur in association with other disorders include non-scarring alopecia, annular erythema, calcinosis cutis, papulonodular mucinosis, rheumatoid nodules, and sclerodactyly. Furthermore, several skin diseases can also be found in the context of LE such as acanthosis nigricans, anetoderma, cutaneous vascular diseases, e.g., Raynaud's phenomenon and urticaria vasculitis, erythema multiforme, bullous autoimmune diseases, lichen planus, and porphyria cutanea tarda.

References

Alexiades-Armenakas, M.R., Baldassano, M., Bince, B., et al. 2003. Tumid lupus erythematosus: criteria for classification with immunohistochemical analysis. Arthritis Rheum. 5, 494.

Andreasen, J.O., Poulsen, H.E. 1964. Oral discoid and sytemic lupus erythematosus. Acta Odont. Scand. 22, 289.

Bacman, D., Ostendorf, B., Megahed, M., et al. 2004. Bullous systemic lupus erythematosus. Hautarzt. 55, 392.

Bangert, J.L., Freemann, R.G., Sontheimer, R.D., et al. 1984. Subacute cutaneous lupus erythematosus and discoid lupus erythematosus. Comparative histopathologic findings. Arch. Dermatol. 120, 332.

Barton, D.D., Fine, J.D., Gammon, W.R., et al. 1986. Bullous systemic lupus erythematosus: an unusual clinical course and detectable circulating autoantibodies to the epidermolysis bullosa acquisita antigen. J. Am. Acad. Dermatol. 16, 369.

Blanchet, P., Auffret, N., Fouchard, J., et al. 1981. Association of thymoma, superficial pemphigus, nephrotic syndrome and lupus biology. Ann. Dermatol. Venereol. 108, 471.

Botella, R., Alfonso, R., Silvestre, J., et al. 1999. Discoid lupus erythematosus-like lesions and stomatitis. Arch. Dermatol. 135, 847.

Braverman, I.M. 1981. Connective tissue (rheumatic) diseases. In: I.M. Braverman (Ed.), Skin Signs of Systemic Diseases. WB Saunders company, Philadelphia, p. 255.

Breathnach, S.M., Wells, G.C. 1979. Chilblain lupus erythematosus with response to chemical sympathectomy. Br. J. Dermatol. 101, 49.

Burge, S.M., Frith, P.A., Juniper, R.P., Wojnarowska, F. 1989. Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. Br. J. Dermatol. 121, 727–741.

Callen, J.P., Klein, J. 1988. Subacute cutaneous lupus erythematosus. Clinical, serologic, immunogenetic, and therapeutic considerations in seventy-two patients. Arthritis Rheum. 31, 1007.

Callen, J.P., Kulick, K.B., Stelzer, G., et al. 1986. Subacute cutaneous lupus erythematosus. Clinical, serologic, and immunogenetic studies of forty-nine patients seen in a non-referral setting. J. Am. Acad. Dermatol. 15, 1227.

Camisa, C., Sharma, H.M. 1983. Vesicobullous systemic lupus erythematosus: report of two cases and a review of the literature. J. Am. Acad. Dermatol. 9, 924.

Cardinali, C., Caproni, M., Bernacchi, E., et al. 2000. The spectrum of cutaneous manifestations in lupus erythematosus—the Italian experience. Lupus 9, 417.

Cervera, R., Khamashta, M.A., Font, J., et al. 1993. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 72, 113.

Chan, L.S., Lapiere, J.C., Chen, M., et al. 1999. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Arch. Dermatol. 135, 569.

Chlebus, E., Wolska, H., Blaszczyk, M., et al. 1998. Subacute cutaneous lupus erythematosus versus systemic lupus erythematosus: diagnostic criteria and therapeutic implications. J. Am. Acad. Dermatol. 38, 405.

Choonhakarn, C., Poonsriaram, A., Chaivoramukul, J. 2004. Lupus erythematosus tumidus. Int. J. Dermatol. 43, 815.

Chorzelski, T., Jablonska, S., Blaszczyk, M. 1968. Immunopathological investigations in the Senear–Usher syndrome (coexistence of pemphigus and lupus erythematosus). Br. J. Dermatol. 80, 211.

Cohen, L.M., Tyring, S.K., Rady, P., et al. 1992. Human papillomavirus type 11 in multiple squamous cell carcinomas in a patient with subacute cutaneous lupus erythematosus. J. Am. Acad. Dermatol. 26, 840.

Cohen, M.R., Crosby, D. 1994. Systemic disease in subacute cutaneous lupus erythematosus: a controlled comparison with systemic lupus erythematosus. J. Rheumatol. 21, 1665.

Costner, M.I., Sontheimer, R.D., & Provost, T.T. 2003. Lupus erythematosus. In: R.D. Sontheimer, & T.T. Provost (Eds.), Cutaneous Manifestations of Rheumatic Diseases. Williams & Wilkins, Philadelphia, p. 15.
Cutaneous Manifestations of Rheumatic Diseases is a clinical reference for dermatologists and rheumatologists with colour representations and comprehensive discussions of the various clinical manifestations of rheumatic diseases.

Crowson, A.N., Magro, C. 2001. The cutaneous pathology of lupus erythematosus: a review. J. Cutan. Pathol. 28, 1.

Daldon, P.E., Macedo de Souza, E., Cintra, M.L. 2003. Hypertrophic lupus erythematosus: a clinicopathological study of 14 cases. J. Cutan. Pathol. 30, 443.

David, K.M., Thornton, J.C., Davis, B., et al. 1984. Morbidity and mortality in patients with subacute cutaneous lupus erythematosus (SCLE). J. Invest. Dermatol. 82, 408.

David-Bajar, K.M. 1993. What's new in cutaneous lupus syndromes: subacute cutaneous lupus erythematosus. J. Invest. Dermatol. 100, 2S.

David-Bajar, K.M., Davis, B.M. 1997. Pathology, immunopathology, and immunohistochemistry in cutaneous lupus erythematosus. Lupus 6, 145.

Davies, M.G., Marks, R., Waddington, E. 1976. Simultaneous systemic lupus erythematosus and dermatitis herpetiformis. Arch. Dermatol. 112, 1292.

Davis, M.D., Daoud, M.S., Kirby, B., et al. 1998. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J. Am. Acad. Dermatol. 38, 899.

Dekle, C.L., Mannes, K.D., Davis, L.S., et al. 1999. Lupus tumidus. J. Am. Acad. Dermatol. 41, 250.

DeSpain, J.D., Clark, D.P. 1988. Subacute cutaneous lupus erythematosus presenting as erythroderma. J. Am. Acad. Dermatol. 19, 388.

Dotson, A.D., Raimer, S.S., Pursley, T.V., et al. 1981. Systemic lupus erythematosus occurring in a patient with epidermolysis bullosa acquisita. Arch. Dermatol. 117, 422.

Doutre, M.S., Beylot, C., Beylot, J., et al. 1992. Chilblain lupus erythematosus: report of 15 cases. Dermatology 184, 26.

Eckman, J.A., Mutasim, D.F. 2002. Bullous systemic lupus erythematosus with milia and calcinosis. Cutis 70, 31.

Fabbri, P., Bernacchi, E., Neri, R. 1990. Subacute cutaneous lupus erythematosus. Review of the literature and immunological studies of 11 patients. G. Ital. Dermatol. Venereol. 125, 329.

Fabbri, P., Cardinali, C., Giomi, B., Caproni, M. 2003. Cutaneous lupus erythematosus: diagnosis and management. Am. J. Clin. Dermatol. 4, 449–465.

Fisher, D.A., Everett, M.A. 1996. Violaceous rash of dorsal fingers in a woman. Diagnosis: chilblain lupus erythematosus (perniosis). Arch. Dermatol. 132, 459.

Franke, W., Kuhn, A., Megahed, M., et al. 1999. Periorbital edema as the initial symptom of lupus erythematosus profundus. Case report and discussion of the literature. Hautarzt 50, 889.

Gammon, W.R., Briggaman, R.A. 1993. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. J. Invest. Dermatol. 100, 28S.

Gammon, W.R., Woodley, D.T., Dole, K.C., et al. 1985. Evidence that anti-basement membrane zone antibodies in bullous eruption of systemic lupus erythematosus recognize epidermolysis bullosa acquisita autoantigen. J. Invest. Dermatol. 84, 472.

Gilliam, J.N. 1977. The cutaneous signs of lupus erythematosus. Cont. Educ. Fam. Phys. 6, 34.

Gilliam, J.N., Sontheimer, R.D. 1981. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J. Am. Acad. Dermatol. 4, 471.

Gilliam, J.N., Sontheimer, R.D. 1982. Subacute cutaneous lupus erythematosus. Clin. Rheum. Dis. 8, 343.

Goerz, G., Lehmann, P., Schuppe, H.C., et al. 1990. Lupus erythematosus. Z. Hautkr. 65, 226.

Gold, S.C. 1954. An unusual papular eruption associated with lupus erythematodes. Br. J. Dermatol. 66, 429.

Grant, J.M. 1981. Annular vesicular lupus erythematosus. Cutis 28, 90.

Haimowitz, J.E., McCauliffe, D.P., Seykora, J., et al. 2000. Annular erythema of Sjogren's syndrome in a white woman. J. Am. Acad. Dermatol. 42, 1069.

Hall, R.P., Lawley, T.J., Smith, H.R., et al. 1982. Bullous eruption of systemic lupus erythematosus. Ann. Intern. Med. 97, 165.

Hazan, C. 2004. Papulonodular mucinosis with subacute cutaneous lupus erythematosus. Dermatol. Online J. 10, 6.

Helm, T.N., Jones, C.M. 2002. Chilblain lupus erythematosus lesions precipitated by the cold. Cutis 69, 183–184.

Herrero, C., Bielsa, I., Font, J., et al. 1988. Subacute cutaneous lupus erythematosus: clinicopathologic findings in thirteen cases. J. Am. Acad. Dermatol. 19, 1057.

Hoshino, Y., Hashimoto, T., Mimori, T., et al. 1992. Recurrent annular erythema associated with anti-SS-B/La antibodies: analysis of the disease-specific epitope. Br. J. Dermatol. 127, 608.

Hutchinson, J. 1888. Harveian lectures on lupus. Lecture III. On the various form of lupus vulgaris and erythematosus. Br. Med. J. 1, 113.

Hymes, S.R., Jordon, R.E. 1989. Chronic cutaneous lupus erythematosus. Med. Clin. North. Am. 73, 1055.

Irgang, S. 1940. Lupus erythematosus profundus. Arch. Dermatol. Syph. 42, 97.

Jimenez, S., Cervera, R., Ingelmo, M., et al. 2004. The epidemiology of lupus erythematosus. In: A. Kuhn, P. Lehmann, T. Ruzicka (Eds.), Cutaneous Lupus Erythematosus. Springer, Heidelberg, pp. 33–44.

Jolly, M., Laumann, A.E., Shea, C.R., et al. 2004. Lupus erythematosus tumidus in systemic lupus erythematosus: novel association and possible role of early treatment in prevention of discoid lupus erythematosus. Lupus 13, 64.

Kanda, N., Tsuchida, T., Watanabe, T., et al. 1997. Cutaneous lupus mucinosis: a review of our cases and the possible pathogenesis. J. Cutan. Pathol. 24, 553.

Kanwar, J., Dhar, S., Ghosh, S. 1993. Involvement of nails in discoid lupus erythematosus. J. Assoc. Phys. India 41, 543.

Kaposi, M.K. 1883. Pathologie und Therapie der Hautkrankheiten. Urban and Schwarzenberg, Wien, p. 642.

Katayama, I., Teramoto, N., Arai, H., Nishioka, K., Nishiyama, S. 1991. Annular erythema. A comparative study of Sjogren syndrome with subacute cutaneous lupus erythematosus. Int. J. Dermatol. 30, 635.

Katayama, I., Yamamoto, T., Otoyama, K., et al. 1994. Clinical and immunological analysis of annular erythema associated with Sjogren syndrome. Dermatology 189, 14.

Kossard, S. 2002. Lupus panniculitis clinically simulating alopecia areata. Australas. J. Dermatol. 43, 221.

Kuhn, A., Ruzicka, T. 2004. Classification of cutaneous lupus eyrthematosus. In: A. Kuhn, P. Lehmann, T. Ruzicka (Eds.), Cutaneous Lupus Erythematosus. Springer, Heidelberg, pp. 53–58.

Kuhn, A., Beissert, S. 2005. Photosensitivity in lupus erythematosus. Autoimmunity, *in press*.

Kuhn, A., Richter-Hintz, D., Oslislo, C., et al. 2000a. Lupus erythematosus tumidus—a neglected subset of cutaneous lupus erythematosus: report of 40 cases. Arch. Dermatol., 136, 1033.
Clinical, histologic, and laboratory features of 40 patients with LET were analyzed and diagnositic criteria were established to differentiate this subtype from other skin disorders.

Kuhn, A., Richter-Hintz, D., Schuppe, H.C., et al. 2000b. Annular erythema in Sjogren syndrome. A variant of cutaneous lupus erythematosus?. Hautarzt. 51, 270.

Kuhn, A., Schuppe, H.C., Ruzicka, T., et al. 2000c. Seltene kutane Manifestationsformen des Lupus erythematodes. Hautarzt. 51, 818.

Kuhn, A., Sonntag, M., Richter-Hintz, D., et al. 2001a. Phototesting in lupus erythematosus: a 15-year experience. J. Am. Acad. Dermatol. 45, 86.

Kuhn, A., Sonntag, M., Richter-Hintz, D., et al. 2001b. Phototesting in lupus erythematosus tumidus—review of 60 patients. Photochem. Photobiol. 73, 532.

Kuhn, A., Sonntag, M., Lehmann, P., et al. 2002a. Characterization of the inflammatory infiltrate and expression of endothelial cell adhesion molecules in lupus erythematosus tumidus. Arch. Dermatol. Res. 294, 6.

Kuhn, A., Sonntag, M., Sunderkotter, C., et al. 2002b. Upregulation of epidermal surface molecule expression in primary and ultraviolet-induced lesions of lupus erythematosus tumidus. Br. J. Dermatol. 146, 801.

Kuhn, A., Sonntag, M., Ruzicka, T., et al. 2003. Histopathologic findings in lupus erythematosus tumidus: review of 80 patients. J. Am. Acad. Dermatol. 48, 901.

Kuhn, A., Sontheimer, R.D., Ruzicka, T. 2004. Clinical manifestations of cutaneous lupus erythematosus. In: A. Kuhn, P. Lehmann, T. Ruzicka (Eds.), Cutaneous Lupus Erythematosus. Springer, Heidelberg, p. 59.
Cutaneous Lupus Erythematosus is based on multidisciplinary knowledge and is written by leading clinicians and scientists providing a comprehensive description of the classification and clinical aspects, pathogenesis, treatment and management of CLE.

Lapiere, J.C., Woodley, D.T., Parente, M.G., et al. 1993. Epitope mapping of type VII collagen. Identification of discrete peptide sequences recognized by sera from patients with acquired epidermolysis bullosa. J. Clin. Invest. 92, 1831.

Lau, M., Kaufmann-Grunzinger, I., Raghunath, M. 1991. A case report of a patient with features of systemic lupus erythematosus and linear IgA disease. Br. J. Dermatol. 124, 498.

Lodi, A., Pozzi, M., Agostoni, A., et al. 1993. Unusual onset of lupus erythematosus profundus. Br. J. Dermatol. 129, 96.

Lyon, C.C., Blewitt, R., Harrison, P.V. 1998. Subacute cutaneous lupus erythematosus: two cases of delayed diagnosis. Acta Derm. Venereol. 78, 57.

Magee, K.L., Hymes, S.R., Rapini, R.P., et al. 1991. Lupus erythematosus profundus with periorbital swelling and proptosis. J. Am. Acad. Dermatol. 24, 288.

Martens, P.B., Moder, K.G., Ahmed, I. 1999. Lupus panniculitis: clinical perspectives from a case series. J. Rheumatol. 26, 68.

Mascaro, J.M., Herrero, C., Hausmann, G. 1997. Uncommon cutaneous manifestations of lupus erythematosus. Lupus 6, 122.

McCauliffe, D.P. 2001. Cutaneous lupus erythematosus. Semin. Cutan. Med. Surg. 20, 14.

Megahed, M. 2004. Bullous systemic lupus erythematosus. In: M. Megahed (Ed.), Histopathology of Blistering Disaeses with Clinical, Electron Microscopic, Immunological, and Molecular Biological Correlations. Springer, Berlin, Heidelberg, New York, p. 236.

Mehregan, D.R., Hall, M.J., Gibson, L.E. 1992. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. J. Am. Acad. Dermatol. 26, 441.

Milde, P., Goerz, G. 1994. Depigmentierung bei Lupus erythematodes (LE)—Klinischer "Clue" zum subakut kutanen Lupus erythematodes (SCLE). Z. Hautkr. 69, 123.

Miller, J.F., Downham, T.F., Chapel, T.A. 1978. Coexistent bullous pemphigoid and systemic lupus erythematosus. Cutis 21, 368.

Miyagawa, S. 1994. Clinical, serological and immunogenetic features of Japanese anti-Ro/SS-A-positive patients with annular erythema. Dermatology 189, 11.

Molad, Y., Weinberger, A., David, M., et al. 1987. Clinical manifestations and laboratory data of subacute cutaneous lupus erythematosus. Isr. J. Med. Sci. 23, 278.

Moulin, G., Bouchet, B., Souteyrand, P., et al. 1980. Papulous photodependent mucinosis and disseminated lupus erythematosus. Ann. Dermatol. Venereol. 107, 1193.

Mutasim, D.F. 2003. Severe subacute cutaneous lupus erythematosus presenting with generalized erythroderma and bullae. J. Am. Acad. Dermatol. 48, 947.

Nagy, E., Balogh, E. 1961. Bullous form of chronic discoid lupus erythematodes accompanied by LE-cell symptoms. Dermatologica 122, 6.

Nagy, E., Meszaros, C., Daroczy, P. 1967. Mucinosis papulosa. Hautarzt. 18, 283.

Ng, P.P., Tan, S.H., Tan, T. 2002. Lupus erythematosus panniculitis: a clinicopathologic study. Int. J. Dermatol. 41, 488.

Nishikawa, T., Provost, T.T. 1991. Differences in clinical, serologic, and immunogenetic features of white versus Oriental anti-SS-A/Ro-positive patients. J. Am. Acad. Dermatol. 25, 563.

Norden, D., Weinberg, J.M., Schumacher, H.R., et al. 1993. Bilateral periorbital edema in systemic lupus erythematosus. J. Rheumatol. 20, 2158.

O'Loughlin, S., Schroeter, A.L., Jordon, R.E. 1978. Chronic urticaria-like lesions in systemic lupus erythematosus. A review of 12 cases. Arch. Dermatol. 114, 879.

Olansky, A.J., Briggaman, R.A., Gammon, W.R., et al. 1982. Bullous systemic lupus erythematosus. J. Am. Acad. Dermatol. 7, 511.

Ortiz, V.G., Krishnan, R.S., Chen, L.L., et al. 2004. Papulonodular mucinosis in systemic lupus erythematosus. Dermatol. Online J. 10, 16.

Pacheco, T.R., Spates, S.T., Lee, L.A. 2002. Unilateral tumid lupus erythematosus. Lupus 11, 388.

Parodi, A., Caproni, M., Cardinali, C., et al. 2000. Clinical, histological and immunopathological features of 58 patients with subacute cutaneous lupus erythematosus. A review by the Italian group of immunodermatology. Dermatology 200, 6.

Patel, P., Werth, V. 2002. Cutaneous lupus erythematosus: a review, Dermatol. Clin. 20, 373.
This article reviews information about the pathogenesis, clinical presentation, diagnosis, and treatment of CLE.

Penneys, N.S., Wiley, H.E. 1979. Herpetiform blisters in systemic lupus erythematosus. Arch. Dermatol. 115, 1427.

Perniciaro, C., Randle, H.W., Perry, H.O. 1995. Hypertrophic discoid lupus erythematosus resembling squamous cell carcinoma. J. Rheumatol. 21, 255.

Peters, M.S., Su, W.P. 1989. Lupus erythematosus panniculitis. Med. Clin. North Am. 73, 1113.

Pramatarov, K. 1998. Drug-induced lupus erythematosus. Clin. Dermatol. 16, 367.

Provost, T.T. 2004. Nonspecific cutaneous manifestations of systemic lupus erythematosus. In: A. Kuhn, P. Lehmann, T. Ruzicka (Eds.), Cutaneous Lupus Erythematosus. Springer, Heidelberg, p. 93.

Provost, T.T., Talal, N., Bias, W., et al. 1988a. Ro(SS-A) positive Sjogren's/lupus erythematosus (SC/LE) overlap patients are associated with the HLA-DR3 and/or DRw6 phenotypes. J. Invest. Dermatol. 91, 369.

Provost, T.T., Talal, N., Harley, J.B., et al. 1988b. The relationship between anti-Ro (SS-A) antibody-positive Sjogren's syndrome and anti-Ro (SS-A) antibody-positive lupus erythematosus. Arch. Dermatol. 124, 63.

Provost, T.T., Zone, J.J., Synkowski, D., et al. 1980. Unusual cutaneous manifestations of systemic lupus erythematosus: I. Urticaria-like lesions. Correlation with clinical and serological abnormalities. J. Invest. Dermatol. 75, 495.

Prystowsky, S.D., Gilliam, J.M. 1975. Discoid lupus erythematosus as part of a larger disease spectrum. Correlation of clinical features with laboratory findings in lupus erythematosus. Arch. Dermatol. 111, 1448.

Rao, B., Coldiron, B., Freemann, R.G., et al. 1990. Subacute cutaneous lupus erythematosus lesions progressing morphea. J. Am. Acad. Dermatol. 23, 1019.

Reed, R.J., Clark, W.H., Mihm, M.C. 1973. The cutaneous mucinoses. Hum. Pathol. 4, 201.

Romero, R.W., Nesbitt, L.T.J., Reed, R.J. 1977. Unusual variant of lupus erythematosus or lichen planus. Clinical, histopathologic, and immunofluorescent studies. Arch. Dermatol. 113, 741.

Rongioletti, F., Rebora, A. 1991. The new cutaneous mucinoses: a review with an up-to-date classification of cutaneous mucinoses. J. Am. Acad. Dermatol. 24, 265.

Rongioletti, F., Rebora, A. 2001. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. J. Am. Acad. Dermatol. 44, 273.

Rothfield, N.F. 1993. Lupus erythematosus. In: T.B. Fitzpatrick, A.Z. Eisen, K. Wolff, I.M. Freedberg, K.F. Austen (Eds.), Dermatology and General Medicine. McGraw, New York, p. 2138.

Rowell, N.R. 1987. Chilblain lupus erythematosus responding to etretinate. Br. J. Dermatol. 117, 100.

Rowell, N.R., Swanson-Beck, J., Anderson, J.P. 1963. Lupus erythematosus and erythema multifirme-like lesions. Arch. Dermatol. 88, 176.

Rubin, R.L. 1999. Etiology and mechanisms of drug-induced lupus. Curr. Opin. Rheumatol. 11, 357.

Ruiz, H., Sanchez, J.L. 1999. Tumid lupus erythematosus. Am. J. Dermatopathol. 21, 356.

Ruzicka, T., Faes, J., Bergner, T., et al. 1991. Annular erythema associated with Sjögren's syndrome: a variant of systemic lupus erythematosus. J. Am. Acad. Dermatol. 25, 557.

Sanchez, N.P., Winkelmann, R.K., Schroeter, A.L. 1982. The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. J. Am. Acad. Dermatol. 7, 599.

Sanchez-Perez, J., Fernandez-Herrera, J., Sols, M., et al. 1993. Leucocytoclastic vasculitis in subacute cutaneous lupus erythematosus. Br. J. Dermatol. 128, 469.

Shirahama, S., Furukawa, F., Yagi, H., et al. 1998. Bullous systemic lupus erythematosus: detection of antibodies against noncollagenous domain of type VII collagen. J. Am. Acad. Dermatol. 38, 844.

Sonntag, M., Lehmann, P., Megahed, M., et al. 2003. Papulonodular mucinosis associated with subacute cutaneous lupus erythematosus. Dermatology 206, 326.

Sontheimer, R.D. 1985a. Clinical significance of subacute cutaneous lupus erythematosus skin lesions. J. Dermatol. 12, 205.

Sontheimer, R.D. 1985b. Subacute cutaneous lupus erythematosus. Clin. Dermatol. 3, 58.

Sontheimer, R.D. 1989. Subacute cutaneous lupus erythematosus: a decade's perspective. Med. Clin. North Am. 73, 1073.

The clinical features of SCLE are summarized on its 10th anniversary and the results of published data are compared with unpublished experience in over 100 patients with this subtype.

Sontheimer, R.D. 1997. The lexicon of cutaneous lupus erythematosus—a review and personal perspective on the nomenclature and classification of the cutaneous manifestations of lupus erythematosus. Lupus 6, 84.

Sontheimer, R.D. 2000. Questions answered and a $1 million question raised concerning lupus erythematosus tumidus: is routine laboratory surveillance testing during treatment with hydroxychloroquine for skin disease really necessary. Arch. Dermatol. 136, 1044.

Sontheimer, R.D., Provost, T.T. 1996. Lupus erythematosus. In: R.D. Sontheimer, T.T. Provost (Eds.), Cutaneous Manifestatons of Rheumatic Diseases. Williams & Wilkins, Baltimore, p. 1.

Sontheimer, R.D., Thomas, J.R., Gilliam, J.N. 1979. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. Arch. Dermatol. 115, 1409.

Su, W.P., Perniciaro, C., Rogers, R.S.R., et al. 1994. Chilblain lupus erythematosus (lupus pernio): clinical review of the Mayo Clinic experience and proposal of diagnostic criteria. Cutis 54, 395.

Tan, E.M., Cohen, A.S., Fries, J.F., et al. 1982. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 25, 1271.

Tebbe, B., Orfanos, C.E. 1997. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus 6, 96.

Tebbe, B., Mansmann, U., Wollina, U., et al. 1997. Markers in cutaneous lupus erythematosus indicating systemic involvement. A multicenter study on 296 patients. Acta Derm. Venereol. 77, 305.

Teramoto, N., Katayama, I., Arai, H., et al. 1989. Annular erythema: a possible association with primary Sjogren's syndrome. J. Am. Acad. Dermatol. 20, 596.

Tuffanelli, D.L. 1971. Lupus erythematosus panniculitis (profundus). Arch. Dermatol. 103, 231.

Ueki, H. 2005. Koebner phenomenon in lupus erythematosus with special consideration of clinical findings. Autoimmunity 4, 219.

Uter, W., Proksch, E., Schauder, S. 1988. Chilblain lupus erythematosus. Hautarzt 39, 602.

Uwatoko, S., Mannik, M. 1988. Low-molecular weight C1q-binding immunoglobulin G in patients with systemic lupus erythematosus consists of autoantibodies to the collagen-like region of C1q. J. Clin. Invest. 82, 816.

Uy, H.S., Pineda, R., 2nd., Shore, J.W., et al. 1999. Hypertrophic discoid lupus erythematosus of the conjunctiva. Am. J. Ophthalmol. 127, 604.

Viguier, M., Pinquier, L., Cavelier-Balloy, B., et al. 2001. Clinical and histopathologic features and immunologic variables in patients with severe chilblains. A study of the relationship to lupus erythematosus. Medicine (Baltimore) 80, 180.

Vinciullo, C. 1986. Hypertrophic lupus erythematosus: differentiation from squamous cell carcinoma. Australas. J. Dermatol. 27, 76.

Watanabe, T., Tsuchida, T. 1995. Classification of lupus erythematosus based upon cutaneous manifestations. Dermatological, systemic and laboratory findings in 191 patients. Dermatology 190, 277.

Watanabe, T., Tsuchida, T., Ito, Y., et al. 1997. Annular erythema associated with lupus erythematosus/Sjogren's syndrome. J. Am. Acad. Dermatol. 36, 214.

Wechsler, H.L., Stavrides, A. 1982. Systemic lupus erythematosus with anti-Ro antibodies: clinical, histologic and immunologic findings. Report of three cases. J. Am. Acad. Dermatol. 6, 73.

Weidner, F., Djawari, D. 1982. Mucinosis papulosa bei Lupus erythematodes integumentalis. Hautarztn 33, 286.

Weigand, D.A., Burgdorf, W.H., Gregg, L.J. 1981. Dermal mucinosis in discoid lupus erythematosus. Report of two cases. Arch. Dermatol. 117, 735.

Werth, V.P., White, W.L., Sanchez, M.R., et al. 1992. Incidence of alopecia areata in lupus erythematosus. Arch. Dermatol. 128, 368.

Wysenbeek, A.J., Block, D.A., Fries, J.F. 1989. Prevalence and expression of photosensitivity in systemic lupus erythematosus. Ann. Rheum. Dis. 48, 461.

Wysenbeek, A.J., Guedj, D., Amit, M., et al. 1992. Rash in systemic lupus erythematosus: prevalence and relation to cutaneous and non-cutaneus disease manifestations. Ann. Rheum. Dis. 51, 717.

Yell, J.A., Mbuagbaw, J., Burge, S.M. 1996. Cutaneous manifestations of systemic lupus erythematosus. Br. J. Dermatol. 135, 355.

Yell, J.A., Wojnarowska, F. 1997. Bullous skin disease in lupus erythematosus. Lupus 6, 112.

A number of bullous and vesicular skin lesions that are encountered in patients with LE are described and classified in this article.

Yung, A., Oakley, A. 2000. Bullous systemic lupus erythematosus. Australas. J. Dermatol. 41, 234.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 7

Subacute Cutaneous Lupus Erythematosus: A Quarter Century's Perspective

Richard D. Sontheimer*

Department of Dermatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

1. Introduction and historical perspective

In the 1960–1970s, the study of human lupus erythematosus (LE) was undergoing a revolution resulting from the description and characterization of various autoantibody–autoantigen systems as disease markers (e.g., Ro/SS-A, La/SS-B, U1RNP, Sm).[1] That such autoantibody systems were found to be associated with specific clinical features of LE and associated rheumatic diseases led to the idea of subsetting LE patients on the basis of shared clinical, pathological, laboratory, and immunogenetic findings (Urowitz, 1977; Provost, 1979). Today, "sub-phenotyping" would be a more modern designation for the exercise of "subsetting" (Stewart, 2002).

One example would be the increased risk of lupus nephritis in LE patients found to have high levels of double-stranded DNA autoantibody and low levels of complement (C3, C4, CH-50). Another example would be mixed connective tissue disease (syn. Sharp's syndrome) that was defined as a characteristic set of overlapping features of several rheumatic disorders including systemic LE (SLE) that occurred in the context of U1RNP autoantibody production. It was hoped that the early identification of subsets of LE and related rheumatic diseases could provide a better understanding of these disorders and thereby lead to improved management and prognosis.

In the early 1970s, Dr. James N. Gilliam in the Divisions of Dermatology and Rheumatology at UT Southwestern Medical Center in Dallas, Texas and Dr. Thomas T. Provost in the Departments of Dermatology at the State University of New York at Buffalo and later at Johns Hopkins Medical Center in Baltimore, Maryland were focusing on the idea of subsetting LE patients based upon the presence of different forms of cutaneous LE and associated immunogenetic findings (Gilliam and Sontheimer, 1981; Provost, 1979). Dr. Provost chose to focus on the "ANA-negative SLE" clinical constellation in which there was an enrichment of clinical photosensitivity and Ro/SS-A assay antibody production. However, Dr. Gilliam chose to focus upon the clinical and immunogenetic significance of a widespread, symmetrical, photosensitive, non-scarring, form of cutaneous LE for which he coined the term "Subacute Cutaneous Lupus Erythematosus (SCLE)". In retrospect, it became clear that these two investigators had been predominately focusing on the same subgroup of patients having non-scarring, photosensitive cutaneous LE skin lesions that we now recognized as SCLE.

*Corresponding author.
Department of Dermatology,University of Oklahoma Health Sciences Center,619 N.E, 13th Street,Oklahoma City, OK 73104, USA.
Tel.: +1-405-271-4662;Fax: +1-405-271-7216.
E-mail address: richard-sontheimer@ouhsc.edu
(R.D. Sontheimer).

[1]Portions of this chapter have been excerpted from several other recent review publications in which the author has participated (Pellowski et al., 2005; Costner et al., 2004; Sontheimer, 2004a; Sontheimer, 2005; Sontheimer and Costner, 2002). The reader is referred to these sources for additional citations of the material discussed in the current presentation.

DOI: 10.1016/S1571-5078(05)05007-5

Dr. Gilliam initially hypothesized that patients who present with a widespread, non-scarring, photosensitive/photo-inducible SCLE skin lesions might share common clinical, pathological, laboratory, and immunogenetic features and thereby represent a distinctive subset of LE (Gilliam, 1977). It was not that Dr. Gilliam was the first to observe and describe SCLE skin lesions. Patients exhibiting such lesions appear to have previously been discussed under various designations in the historical literature including "lupus marginatus" (Hutchinson-1880), "symmetrical erythema centrifigum" (Brocq-1925), and "disseminated discoid LE" (O'Leary-1934). Other designations that have been used for annular SCLE include "autoimmune annular erythema" and "lupus erythematosus gyratus repens". Papulosquamous SCLE has also been referred to alternatively as "psoriasiform LE" and "pityriasiform LE". The designation "maculopapular photosensitive LE" has been used by some rheumatologists to describe what appears to be SCLE.

What Dr. Gilliam did do was to question whether SCLE skin lesions might represent a visible clue to a variant pattern of systemic autoimmune response and thereby have clinical relevance with respect to management and prognosis. Over the past 25 years, many investigators around the world have tested Dr. Gilliam's hypothesis. In May 2005, there were 303 PubMed citations that included the specific phrase "subacute cutaneous lupus erythematosus". This presentation will summarize the results of those efforts in an attempt to provide a succinct modern picture of the nature of clinical illness experienced by individuals whose disease presentation includes the expression of SCLE skin lesions. In addition, as space allows, a brief overview of the etiopathogenesis of SCLE skin disease will be presented. More in-depth discussions of these and related issues can be found elsewhere (Pellowski et al., 2005; Costner et al., 2004; Sontheimer, 1996; Orteu et al., 2001; Dutz and Sontheimer, 2002).

The initial description of the clinical and laboratory features shared by 27 patients presenting with SCLE skin lesions was presented by Dr. James Gilliam in 1979 (Sontheimer et al., 1979). The author had the privilege of working with Dr. Gilliam as a research fellow on that effort. Had it not been realized a short time later that SCLE lesions were associated with a distinctive immunogenetic background (i.e., Ro/SS-A and La/SS-B autoantibody production and the presence of the HLA A1, B8, DR3 haplotype) (Sontheimer et al., 1981, 1982), it is quite likely that the concept of SCLE as we know it today would not have been recognized and adopted by physicians and investigators around the world to the same degree.

Like "discoid LE", the term "SCLE" can be used in two different ways. "SCLE" can be used to describe a specific type of photosensitive, nonscarring LE-specific skin lesions described below. In addition, it can also be used to refer to a subset/subphenotype of LE patients having SCLE skin lesions as a major component of their disease presentation who also share other clinical and laboratory features. This latter context will be referred to here as the "SCLE subset/sub-phenotype".

2. Epidemiology

2.1. Incidence and prevalence

Unfortunately, there are no population-based data relating to the incidence/prevalence of SCLE or other forms of LE-specific skin disease including classic discoid LE (Tebbe and Orfanos, 1997). Virtually all published data relate the incidence of SCLE to that of unselected SLE. Such estimates have suggested that patients presenting with SCLE skin lesions as a clinical component of their illness represent approximately 10–15% of the total population of LE patients within a defined geographic locale. However, as with all other clinical forms of cutaneous LE, this might be an under representation since some workers have argued that patients having isolated forms of cutaneous LE such as chronic cutaneous LE (e.g., discoid LE) or SCLE might be 2–3 times more prevalent than patients with SLE (Tebbe and Orfanos, 1997).

2.2. Demographics

Patients who have SCLE skin lesions in North America are predominately Caucasian females

with a mean age in the 40s (Costner et al., 2004). However, the age range extends from as early as 18 months to the elderly. While other forms of cutaneous LE such as discoid LE are more common in African-Americans than Caucasians, SCLE is distinctly uncommon in African-Americans. In addition, SCLE has been found to be quite uncommon in Hispanics,Koreans and Chinese.

2.3. Environmental influences

Various environmental factors can induce or exacerbate SCLE skin lesions. Both natural (sunlight) and artificial forms of *ultraviolet radiation* routinely precipitate SCLE. However, it has been the author's personal experience that a small percentage of SCLE patients vehemently deny that their skin lesions are not photosensitive. Phototesting studies have indicated that the action spectrum includes both UVB and UVA wavelengths (Kuhn et al., 2001). Photo-induction studies have suggested that 100% of SCLE patients have abnormal patterns of reaction to UV light that is typically observed beginning about 1 week after delivery of the photo-challenge (Sanders et al., 2003).

In the initial description of SCLE lesions, there was no indication that they could be induced by *drugs*. However, Reed et al. (1985) reported that SCLE skin lesions and Ro/SS-A autoantibodies could be precipitated by hydrochlorothiazide. When the hydrochlorothiazide was discontinued, the SCLE skin lesions spontaneously involuted. As can be seen in Table 1 there is now a rather long list of drugs that have been reported to or suspected of triggering otherwise typical SCLE skin lesions and Ro/SS-A antibody production (Costner et al., 2004; Pellowski et al., 2005). Is interesting how many of these drugs have been reported to produce photosensitivity skin reactions in the absence of evidence of LE. A possible explanation might be that an individual who is immunogenetically predisposed might experience a Köebnerization of SCLE skin lesions as a result of a phototoxic or photoallergic drug reaction.

Drug-induced SCLE should be differentiated from classical drug-induced SLE. The former is associated with Ro/SS-A autoantibodies and is defined by a characteristic photo-distribution of SCLE lesions. The latter is dominated by histone autoantibodies and systemic symptoms such as fever, arthritis, myalgias, and serositis. LE-specific

Table 1
Drugs implicated in precipitating SCLE

Diuretics
Thiazides[a]
Spironolactone[a]
Calcium channel blockers
Diltiazem[a]
Nifedipine[a]
Nitrendipine
ACE inhibitors
Captopril[a]
Cilazapril
Acid blockers
Ranitidine[a, b]
Omeprazole[b]
Non-steroidal anti-inflammatory agents
Naproxen[a]
Piroxicam[a]
β Blockers
Oxprenolol
Lipid lowering
Pravastatin[a]
Simvastatin[a]
Antimicrobials
Griseofulvin[a]
Terbinafine[a]
Antihistamines
Cinnarazine/triethylperazine
Anti-convulsants
Phenytoin[a]
Antimalarials
Hydroxychloroquine[a]
Sulfonylureas
Glyburide[a]
Chemotherapy
Taxotere (Docetaxel)[a]
Tamoxifen
Others
Leflunomide[a]
Interferon-α[a]
Procainamide
D-penicillamine[b]
Etanercept/infliximab[a]
Insecticides
Tetracycline derivatives (CO1-3)[a]

[a] Drugs reported to be capable of producing photosensitivity skin reactions in individuals not having SCLE.
[b] Unpublished personal observation by author of SCLE induction with drug in question.

skin changes of any type are rarely present in the classical form of drug-induced SLE. With exceptions, the medications that typically trigger SCLE lesions are distinct from those that trigger classical drug-induced SLE (e.g., hydralazine, procainamide, isoniazid, minocycline, sulfasalazine), probably reflecting fundamentally different underlying disease mechanisms.

Cigarette smoking has been implicated as an eliciting/exacerbating factor for cutaneous and systemic LE (Costenbader et al., 2004). Curiously, several studies have also documented that cutaneous LE lesions, including SCLE, do not respond to antimalarials therapy in patients who smoke cigarettes compared to those who do not smoke (Rahman et al., 1998).

Experienced clinicians also recognize that *psychological stress* can precipitate/exacerbate cutaneous LE including SCLE skin lesions. However, this phenomenon has not been systematically studied. It has also been the author's personal experience long-term LE skin lesions, including SCLE, appear to be especially prone to clinical depression.

3. Etiology/pathogenesis

Observations relating to the etiopathogenesis of a clinically complex, multigenic, environmentally exacerbated autoimmune disorder such as LE can be organized using a sequential stage framework: (1) inheritance of susceptibility genes, (2) loss of tolerance/induction of autoimmunity, (3) expansion/maturation of autoimmune responses and (4) tissue injury/disease induction resulting from autoimmune effector mechanisms. While this paradigm can be useful in conceptualizing the etiopathogenesis of LE in general and its subsets, in this example, it is used to outline observations relating to the etiopathogenesis of SCLE skin lesions. Table 2 provides an outline of the key etiopathogenetic elements of SCLE as they are currently understood. This paradigm has been discussed in depth elsewhere (Costner et al., 2004).

During characterization of the initial cohort of SCLE patients it was recognized that they were markedly enriched for the HLA-A1, B8, DR3 haplotype that is shared by approximately 25% of the North American Caucasian population (Sontheimer et al., 1981). The HLA-A1, B8, DR3 haplotype has subsequently been markedly extended and is now referred to as the 8.1 ancestral haplotype, i.e., the common Caucasoid haplotype (HLA-A1, Cw7, B8, TNFAB* a2b3, TNFN*S, C2*C, Bf*s, C4A* Q0, C4B*1, DRB1*0301, DRB3*0101, DQA1*0501, DQB1*0201) carried by most people who type for HLA-B8, DR3 (Lio et al., 2001). In addition, some SCLE patients have been reported to be partially or completely deficient in C2 and C4, the genes of which are located in the HLA region on chromosome 6. More recently, SCLE skin lesions have been significantly associated with a single nucleotide polymorphism (SNP) in the TNF-α gene promoter (-308A) (Werth et al., 2000; Millard et al., 2001). (The TNF-α gene is also located within the HLA region.) This TNF-α promoter in the presence of IL-1 alpha has been associated with exaggerated TNF-α expression in human epidermal keratinocytes following UVB exposure (Werth et al., 2000).

It is also possible that polymorphism in other pro-inflammatory cytokine/cytokine receptor genes, adhesion molecule genes, and chemokine/chemokine receptor genes could play a predisposing role in SCLE. Meller et al. (2005) have recently suggested that the CXCR3 ligands, CXCL9 (interferon-γ [INFγ]-induced monokine), CXCL10 (INFγ-inducible protein 10), and CXCL11 (INF-inducible T-cell α chemoattractant) are the most abundantly expressed chemokine family members in cutaneous LE lesions, including SCLE. CXCL9, CXCL10, and CXCL11 were observed to be expressed in cutaneous LE lesions at much higher levels than in disease controls (atopic dermatitis, psoriasis) and normal skin. In addition, the inflammatory infiltrate in cutaneous LE lesions was reported to be rich in CXCR3-expressing cells, especially skin homing T-cells and plasmacytoid dendritic cells. These findings were interpreted to suggest an amplification cycle in which UV light-induced injury induces cutaneous cell apoptosis, necrosis, and chemokine production (Meller et al., 2005). These mechanisms, in turn, mediate the recruitment and activation of autoimmune T-cells and INFα-producing plasmacytoid dendritic cells

Table 2
Sequential etiopathogenetic stages of SCLE skin lesions

Susceptibility stage (*Genetic predisposition*)

1. 8.1 ancestral HLA haplotype (A*01, B*08, DRB1*0301, DQB1*0201, TNFAB* a2b3, C2*C, C4 null) (syn. HLA A1, B8, DR3, DQ1/DQ2 of earlier nomenclature)
   (a) C2, C4 deficiency
   (b) TNF-α -308A SNP
2. Partial C1q deficiency (C1qA gene SNP)
3. Sex hormone metabolism pathway polymorphism (?)

Induction phase (*Loss of immune tolerance*)

1 Environmental eliciting factors
   (a) Ultraviolet light (UVB and UVA)
   (b) Drugs/chemicals
      (i) Photosensitizing drugs (see Table 1)
      (ii) Cigarette smoking
      (iii) Exogenous estrogens/estrogen mimics (?)
   (c) Psychological stress (?)
   (d) Infection (?)

2 Loss of tolerance to cutaneous autoantigens
   (a) Ro/SS-A and La/SS-B
   (b) Keratinocyte-/melanocyte-specific antigens (?)

Possible mechanisms include: (i) dysregulation of UV light-induced keratinocyte apoptosis (ii) faulty disposal of autoantigen-bearing apoptotic keratinocytes, (iii) impaired induction of immune tolerance to cutaneous antigens following exposure to UV light

Expansion phase (*Expansion of autoimmune effector mechanisms*)

1. Autoantibodies (Ro/SS-A, La/SS-B) leading to immune complex formation, Partial C1q deficiency could exacerbate the biological impact of immune complex formation (C1q solubilizes and prevents immune precipitation of immune complexes)
2. Cutaneous autoantigen reactive T-cells (?) Currently, there is only indirect evidence supporting this possibility

Injury phase (*Tissue injury resulting in clinical disease*)

1. Autoantibody-mediated cutaneous injury (?)
2. Immune complex-mediated cutaneous injury (?)
   a. Complement activation, membrane attack complex formation, cellular injury
3. Autoreactive T-cell-mediated cutaneous injury (?)
   a. Direct T-cell-mediated cytotoxicity involving granzyme and perforin mechanisms
   b. Apoptosis resulting from local cytokine elaboration (e.g., TNF-α)
4. Mixed patterns of immunological cutaneous injury (?)
   a. Antibody-dependent cell-mediated cytotoxicity

?-indicates author's speculation.

that subsequently release more effector cytokines, thus amplify chemokine production and leukocyte recruitment, finally leading to the development of a cutaneous LE phenotype. It would be interesting to know whether these chemokine abnormalities are specific for cutaneous LE or might be seen in other interface dermatidities such as cutaneous dermatomyositis.

Based on observations indicating that complete congenital deficiency of C1q is very strongly

associated with photosensitive SLE (Botto and Walport, 2002), our lab has began to probe for more subtle forms of C1q deficiency as a predisposing factor for photosensitive cutaneous LE. Using a candidate gene approach, we recently identified what appears to be a association between the SCLE sub-phenotype and a newly described synonymous SNP in the second exon of the gene that encodes the A chain of C1q, the initial recognition molecule for the classical pathway of complement (Racila et al., 2003). In addition, SCLE patients who were found to be homozygous for this SNP were found to have lower serum levels of C1q antigen compared to SCLE patients not having this SNP. To date, this C1qA SNP is the only genetic association of SCLE that lies outside the HLA region.

4. Clinical manifestations

4.1. Clinical features

The original report of SCLE described it as a photosensitive, recurring, superficial, nonscarring type of cutaneous LE that occurred in a characteristic photo-related distribution including the V-area of the neck, upper trunk, and extensor aspects of the shoulders arms, forearms and the dorsal aspects of the hands and fingers relatively sparing the knuckles (Figs. 1–4). Curiously, it has been the author's experience that the central facial skin is less frequently affected by SCLE compared to other less photosensitive forms of cutaneous LE like discoid LE. It has always been curious that a photosensitive process like SCLE relatively spares a highly photoexposed area of skin – the central face. When SCLE does involve the face it typically is seen on the upper neck and mandibular areas of the lateral face, sparing the central aspects of the face. It is distinctly unusual to see SCLE lesions below the waist. It has been pointed out by others that the absence of induration in SCLE lesions can help to distinguish it clinically from discoid LE skin lesions (David-Bajar et al., 1992).

Because of the relatively strong association between the SCLE phenotype and production of Ro/SS-A autoantibody, some physicians have come to require the presence of Ro/SS-A antibody for the diagnosis of SCLE. However, it should be remembered that in virtually all studies reported to date a certain percentage (10–35%) of otherwise typical SCLE patients have been negative for Ro/SS-A antibody by various assay methods. This observation raises concerns about the hypothesis that Ro/SS-A antibody is directly involved in the pathogenesis of SCLE skin lesions.

There are two major morphological varieties of fully expressed SCLE lesions – annular and papulosquamous (Figs. 1–4). Both of these types of SCLE begin with the same primary lesion – a non-indurated papulosquamous papule or small plaque. In some patients, these primary lesions expand to produce multiple discrete papulosquamous plaques that can merge together to produce a retiform array (Figs. 1 and 2, panel B). In other patients, for unknown reasons, the primary lesions expand and

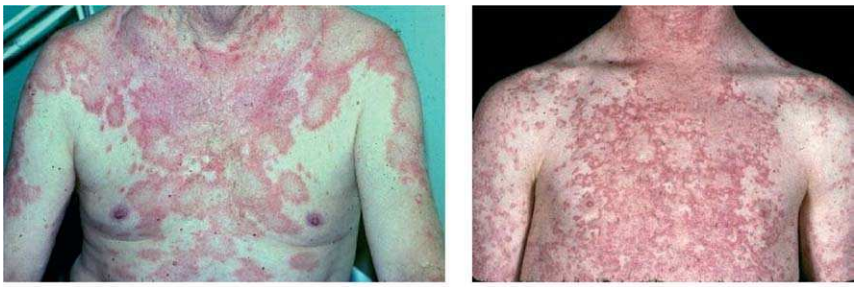


Figure 1. A fully developed flare of SCLE lesions on the chest, V-area of neck, and deltoid areas. (A) annular SCLE. Note the polycyclic array produced by merging of the individual lesions. (B) papulosquamous/psoriasiform SCLE. Note the reticulated, retiform array produced by merging of the individual lesions.

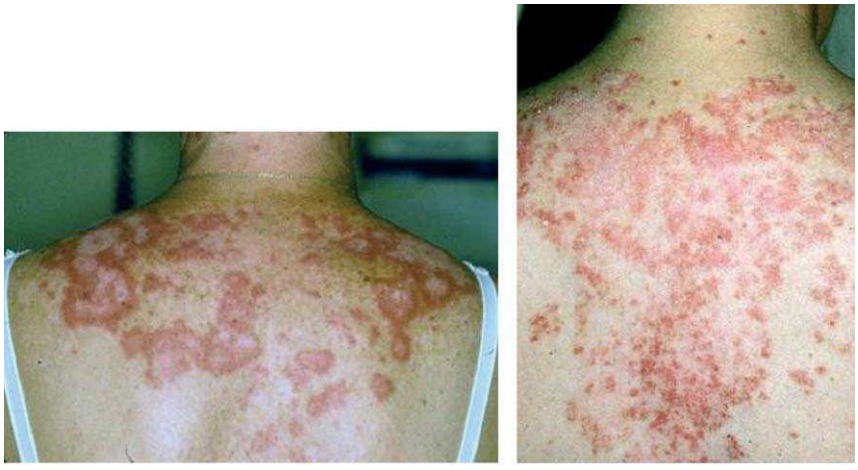


Figure 2. A fully developed flare of SCLE on the mid and upper back. (A) annular SCLE. (B) papulosquamous/psoriasiform SCLE.

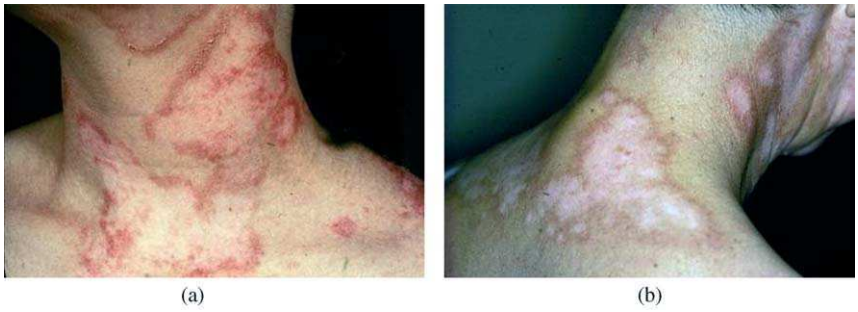


Figure 3. Annular SCLE on the chest, back, and neck. (A) Note the trailing scale at the borders of the annular lesions. Rarely, the active advancing edge of annular SCLE lesions will undergo a vesiculobullous change as a result of epidermal basal layer apoptotic disruption resulting from a highly intense form of interface dermatitis. (B) Note the marked postinflammatory hypopigmentation at the center of the annular lesions

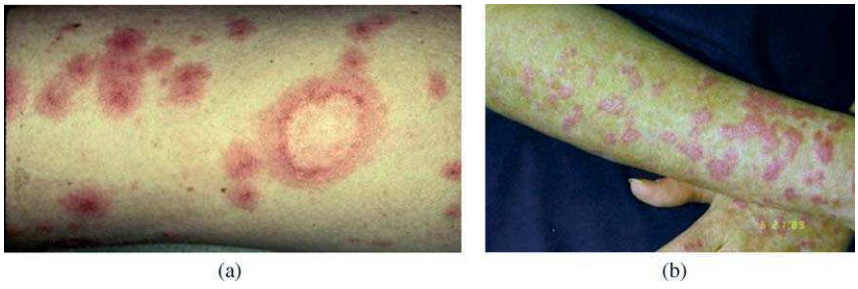


Figure 4. SCLE on the extensor aspect of the arms. (A) Note the erythema multiforme-like morphology of the smaller early lesions and the typical annular SCLE appearance of the single more advanced lesion. (B) Note the psoriasiform appearance of this example of papulosquamous SCLE.

clear in the center to produce annular lesions that can merge together to produce a polycyclic array (Figs. 1 and 2, panel A). Annular SCLE typically displays postinflammatory depigmentation at the center of lesions that distinguishes it from other types of annular erythema reactions that are not related to LE.

While most patients exhibit one or the other of these two major morphological variants of SCLE, some display both elements concurrently. To date, there has been no convincing significant differences reported in the clinical, genetic, immunologic, and other laboratory features of patients who display only annular or papulosquamous SCLE skin lesions. However, it has been suggested anecdotally by the author (Sontheimer, 1989; Costner et al., 2004) and others (Cohen and Crosby, 1994) that the papulosquamous variant of SCLE, especially in males, might carry a higher risk for features of more severe systemic LE (e.g., nephritis).

Since the original description of SCLE, a number of morphological variants have been described including pityriasisiform, exanthematous, erythrodermic, erythema multiforme-like, poikilodermatous, annular-vesiculopustular, and toxic epidermal necrolysis-like among others (Costner et al., 2004; Pellowski et al., 2005). However, it should be emphasized that each of these variants is quite rare.

The relationship between SCLE and erythema multiforme deserves separate consideration. Neville Rowell and coworkers (Rowell et al., 1963) described erythema multiformly like lesions occurring in LE patients who produced autoantibodies to the Sjögren's syndrome autoantigen Sj-T. The Sj-T autoantibody specificity is now thought to be immunologically identical to the La/SS-B autoantibody specificity. La/SS-B autoantibodies are closely linked to Ro/SS-A autoantibodies and are present in one-third to one-half of SCLE patients depending on the method of assay. Other features in the original description of Rowell's syndrome include the presence of antinuclear antibodies in a speckled pattern and a positive test for rheumatoid factor. There continues to be debate concerning the relationship between the skin lesions seen in Rowell's syndrome and erythema multiforme-like variant of annular SCLE with some workers suggesting that they are identical (Vassileva, 2004; Roustan et al., 2000). The author has recently presented his views on this subject within the framework of a conceptual discussion of all vesicular-bullous skin lesions that can be seen in the context of LE (Ting et al., 2004).

4.2. Association with other forms of cutaneous LE and LE nonspecific skin disease

SCLE lesions can occur in the same patient in association with other forms of LE-specific skin disease such as chronic cutaneous LE (discoid LE) or acute cutaneous LE. It has been suggested that approximately 20% of SCLE patients will develop typical chronic cutaneous LE lesions and (e.g., classical discoid LE) or acute cutaneous LE lesions (e.g., nonscarring malar butterfly erythema) at some point in the course of their illness. In addition, SCLE patients can also develop one or more types of LE-nonspecific skin disease (e.g., small vessel leukocytoclastic vascultis, Raynaud's phenomenon, finger nailfold telangiectasias, livedo reticularis) (Sontheimer, 1989). These LE-nonspecific skin disease findings have been reported in 10–20% of SCLE patient cohorts (Sontheimer, 1989). It has been the author's experience that grossly visible finger nailfold telangiectasia are seen much less commonly in SCLE patients compared to patients having either clinically amyopathic dermatomyositis or classic dermatomyositis.

It has been the author's personal experience that SCLE patients who develop either acute cutaneous LE or a form of LE-nonspecific skin disease might have a higher risk of developing clinically significant SLE. This is not surprising as both acute cutaneous LE and LE-nonspecific skin disease are known to be associated with a higher risk of clinically significant SLE compared to other forms of LE skin disease such as the various clinical varieties of chronic cutaneous LE.

4.3. Association with SLE

SCLE patients in the original cohort were observed to frequent display symptoms of a mild

systemic illness marked predominately by lethargy, easy fatigability, and musculoskeletal complaints (Sontheimer et al., 1979). While 48% had four or more of the American Rheumatism Association classification criteria for SLE, none had serious central nervous system or renal disease (the American Rheumatism Association is now known as the American College of Rheumatology). The American Rheumatism Association classification criteria for SLE that were fulfilled in these patients related predominately to cutaneous and musculoskeletal manifestations and mild serological and other laboratory changes. A review of published cases of SCLE in 1989 revealed that severe systemic manifestations of SLE (e.g., central nervous system disease, nephritis) appeared to occur only infrequently in patients presenting with SCLE skin lesions (Sontheimer, 1989). Subsequent longer-term all want studies have revealed that only about 10–15% of patients whose presenting illness includes SCLE skin lesions go on to develop severe clinical manifestation of SLE (Sontheimer, 1989; Chlebus et al., 1998; Costner et al., 2004; Pellowski et al., 2005). The clinical and/or laboratory features that might identify the small percentage of SCLE patients who at risk for developing more severe manifestations of SLE over time have yet been systematically examined.

4.4. Association with other autoimmune diseases

SCLE skin lesions can occur in other clinical settings in which Ro/SS-A autoantibody is seen such as Sjögren's syndrome and rheumatoid arthritis (Costner et al., 2004; Pellowski et al., 2005). The association with Sjögren's syndrome might be expected from the 8.1 ancestral haplotype immunogenetic background and Ro/SS-A autoantibody production that it shares. In some studies involving prolonged follow-up intervals, as many as 43% of SCLE patients have been observed to also develop features of Sjögren's syndrome (Black et al., 2002).

Indurated annular erythematosus plaques have been described predominately in Asian patients (especially Japanese) having Sjogren's syndrome in association with the presence of Ro/SS-A and La/SS-B antibodies (Miyagawa, 1994; Watanabe et al., 1997; Yamamoto and Nishioka, 2004). The histopathology of such lesions reveals prominent dermal mucin accumulation and perivascular mononuclear cell inflammation but no interface dermatitis that would be typical of SCLE. There has been some debate over the possibility that annular erythema of Sjogren's syndrome represents an ethnic variant of SCLE. However, several Caucasian patients with annular erythema of Sjogren's have recently been reported suggesting that these two clinical entities might be distinct (Haimowitz et al., 2000).

By virtue of their Ro/SS-A autoantibody production, women with SCLE lesions are at a small degree of risk for delivering an infant affected by neonatal LE. However, this risk ($<0.5\%$) appears to be no greater than for Ro/SS-A autoantibody-positive pregnancies occurring in other clinical settings (Sjogren's syndrome, rheumatoid arthritis, SLE). SCLE skin lesions have also been reported to occur in patients with autoimmune thyroiditis, hereditary angioedema, and autoimmune polyglandular syndrome Type II (Schmidt's syndrome).

4.5. SCLE as a paraneoplastic phenomenon

In addition, there has been the suggestion that SCLE skin lesions can occur as a paraneoplastic phenomenon. Approximately 10 cases have been reported to date in which SCLE skin lesions appeared to relate to the presence of various types of internal malignancy (lung and breast being the most common) (data reviewed in Dawn and Wainwright (2002)). The significance of this association is currently uncertain. It has not been the author's habit to evaluate all new SCLE patients for internal malignancy.

5. Diagnostic investigations

5.1. Serology/immunology

Sixty-three percent of the original cohort of SCLE patients tested had positive antinuclear antibody

assays using human tumor cell substrates (Sontheimer et al., 1979). In addition, 62% of the initial cohort of SCLE patients tested had Ro/SS-A autoantibodies by Ouchterlony double immunodiffusion analysis (Sontheimer et al., 1982). Other autoantibodies seen in SLE patients such as double-stranded DNA and Sm were seen much less commonly than Ro/SS-A autoantibodies in the original cohort of SCLE patients (Sontheimer et al., 1982). Subsequent studies by others employing the same assay techniques found similar results (Sontheimer, 1989). When more sensitive solid phase immunoassays such as ELISA have been employed, higher rates of Ro/SS-A autoantibody have been observed (up to 90%) (Lee et al., 1994). However, with such sensitive assays the clinical utility of Ro/SS-A autoantibody decreases since up to 10% of normal individuals have been found to have "abnormal" levels of anti-Ro/SS-A by solid phase immunoassays.

Twenty-five percent of the initial cohort of SCLE patients tested was positive for La/SS-B autoantibodies by Ouchterlony double immunodiffusion (Sontheimer et al., 1982). As with Ro/SS-A antibody, higher percentages of La/SS-B antibody have been observed in SCLE patient cohorts using solid phase immunoassays. Ro/SS-A and La/SS-B autoantibodies have been observed to be a linked set of autoantibodies. That is to say, they are frequently seen to be present in association with each other. This is due to the fact that the two separate proteins that bear Ro/SS-A and La/SS-B autoantigenic determinants are components of the same ribonucleoprotein particle that is identified by the presence of small uridine-rich hYRNA molecules that were initially thought to be restricted to the cytoplasm. Experimental work has shown that when an autoantibody response is generated against one component of a cellular ribonucleoprotein particle autoantibodies are subsequently produced against antigenic determinants on other molecular components of the same ribonucleoprotein particle via a mechanism of epitope spreading (Kinoshita et al., 1998).

As the molecular identity of the various components of the Ro/SS-A ribonucleoprotein particle became known there was hope that qualitative difference in the autoantibody response to these various components of the Ro/SS-A ribonucleoprotein particle might correlate with the various clinical phenotypes that have been associated with Ro/SS-A antibody production (i.e., SCLE, Sjogren's syndrome, SLE, rheumatoid arthritis, neonatal lupus). However, for the most part, this has not been found to be the case (McCauliffe et al., 1996).

A biologic false positive test for syphilis has been reported in 7–33% of SCLE cases (Sontheimer, 1989). Follow-up studies have revealed elevated levels of anti-cardiolipin antibody in 16% of SCLE patients (Fonseca et al., 1992). The author has personally observed several SCLE patients that developed deep-vein thrombosis who were subsequently found to be positive for high levels of IgG anti-cardiolipin antibodies.

5.2. Other laboratory features

Other laboratory abnormalities have been reported in SCLE patients at various rates in different studies (Sontheimer, 1989). Those include: elevated erythrocyte sedimentation rates (15–60%), elevated gamma globulin levels (30–50%), hypocomplementemia (15–25%), leukopenia (20–50%), anemia (5–50%) thrombocytopenia (0–40%) rheumatoid factor (35–50%), circulating immune complexes (40–60%) and positive LE cell prep (10–75%).

6. Differential diagnosis

During the early phase of lesions there can be difficulty in distinguishing SCLE from early classical discoid LE lesions before the typical follicular changes and atrophic scarring of discoid LE have appeared. Typically, the carpet tack sign that is a characteristic of discoid LE lesions is not seen and SCLE lesions. (The carpet tack sign is the presence of punctate spikes present on the underside of scale that has been physically removed from the surface of lesions. These small spikes represent the physical manifestations of the follicular hyperkeratosis characteristic of discoid LE lesions on biopsy.) In

addition, it has been noted that the presence of induration can serve to help distinguish early discoid LE lesions from SCLE lesions (David-Bajar et al., 1992). The greater depth of the dermal inflammatory infiltrate in discoid LE lesions that can extend even into the subcutaneous layer is thought to be responsible for this induration that is not seen with the more superficial pattern of dermal inflammatory infiltrate that is typical of SCLE.

Differential diagnostic considerations can be different for fully developed annular and papulosquamous SCLE lesions. These issues have been discussed elsewhere (Costner et al., 2004) and are summarized in Table 3.

Annular SCLE lesions in Caucasians have a tendency to become depigmented in their inactive centeral areas resulting from damage to the pigment cell compartment that occurs as a result of the interface dermatitis that is seen in this setting. However, other types of cutaneous annular erythema reactions show either postinflammatory hyperpigmentation at the inactive center of lesions or no pigmentary disturbance at all.

It has been the author's experience that cutaneous dermatomyositis is the skin disease that is most frequently confused by practitioners (including at times even experienced dermatologists) with non-scarring forms of cutaneous LE such as SCLE and acute cutaneous LE. Acute cutaneous LE is more easily distinguished from cutaneous dermatomyositis due to the frequent presence in acute cutaneous LE patients of overt clinical and laboratory features of systemic LE. The real challenge in distinguishing SCLE from cutaneous dermatomyositis is when the cutaneous dermatomyositis occurs for prolonged periods of time in the absence of muscle weakness (i.e., clinically amyopathic dermatomyositis).

Clinically amyopathic dermatomyositis is a subset of the idiopathic inflammatory myopathies disease spectrum in which the hallmark cutaneous manifestations of dermatomyositis are present for 6 months or longer in the absence of clinically significant muscle weakness (Sontheimer, 2002, 2004b; Sontheimer et al., 2004). The histopathological and immunopathological findings in the early course of SCLE and cutaneous dermatomyositis can be quite similar if not indistinguishable. Adding to the confusion with SCLE, in the majority of cases clinically amyopathic dermatomyositis is associated with cutaneous photosensitivity and the production of antinuclear antibodies.

However, when cutaneous LE and cutaneous dermatomyositis become fully expressed clinically there are morphological and regional anatomical differences that can make the distinction between these two entities quite straightforward:

- SCLE only rarely affects the upper eyelids and periorbital areas that are especially targeted by dermatomyositis (i.e., heliotrope erythema).
- SCLE only rarely affects the skin over the bony prominence such as knuckles, elbows, knees, and greater trochanteric area of the lateral proximal thighs that are typically affected in dermatomyositis.
- Göttron's papules and grossly visible finger nailfold telangiectasias do not occur in SCLE to the extent and prominence that they are seen in cutaneous dermatomyositis.
- SCLE typically does not itch while cutaneous dermatomyositis typically itches severely, sometimes with a burning quality. The pruritus of dermatomyositis can be especially severe in the scalp and at night, often to the point of disturbing sleep.

Table 3
Differential diagnosis of idiopathic SCLE

Annular SCLE
Tinea incognito
Granuloma annulare
Erythema multiforme/Rowell's syndrome
Erythema annular centrifugum
Erythema gyratum repans
Papulosquamous SCLE
Cutaneous dermatomyositis
Psoriasis
Polymorphous light eruption
Pityriasis rubra pilaris
Crusted scabies
Seborrheic dermatitis
Nummular eczema
Contact dermatitis
Cutaneous T-cell lymphoma

- Poik“ilodermatous skin changes result much more commonly from cutaneous dermatomyositis than cutaneous LE including SCLE.
- While anti-Ro/SS-A antibodies can occasionally be seen in dermatomyositis patients they are typically present in a large majority of SCLE patients.

Some might argue that drug-induced SCLE should be discussed when considering the differential diagnosis of SCLE. While it is quite important clinically to recognize when a drug is precipitating or exacerbating SCLE skin lesions, the author personally considers drug-exposure as another type of environmental stimulus, much like ultraviolet light, that can precipitate or exacerbate SCLE in an immunogenetically predisposed individual.

7. Treatment

The management of patients with new-onset SCLE lesions should include evaluation to rule out underlying systemic disease at the time of diagnosis, then again at 6–12 month intervals, unless the patient develops symptoms that dictate an earlier reassessment. The initial evaluation should include a history, including a careful medication history to rule out drug-induced SCLE (see above), and a review of systems and physical exam to elicit symptoms and signs of underlying systemic disease (i.e., arthritis, serositis, CNS disease, renal disease). Initial laboratory evaluation should include, at the minimum, a complete blood count, platelet count, erythrocyte sedimentation rate, urinalysis, and blood chemistry profile. Additional determinations that can be of help include complement levels (C3, C4, CH_{50}) as well as dsDNA and Sm autoantibodies.

The initial management of all SCLE patients should include education regarding protection from sunlight and artificial sources of ultraviolet light and the avoidance if possible of potentially provocative photosensitizing drugs such as those indicated in Table 1. With regard to specific medical therapy, local measures should be maximized first and then systemic agents used if significant disease activity continues.

7.1. Protection from ultraviolet light

Issues relating to photoprotection in LE patients have been discussed elsewhere in depth by the author (Ting and Sontheimer, 2001).

7.1.1. Physical protection

Patients should be advised to avoid direct sun exposure, particularly during the midday hours and during the summer months when the UV component of sunlight is least attenuated by the atmosphere. Tightly woven clothing and hats should be worn in conjunction with broad-spectrum sunscreens to achieve maximal shielding from sunlight. The use of broad-brimmed hats should be encouraged. Several clothing lines offering maximized protection from UV light are currently being marketed. UV light blocking films can be applied to home and automobile windows. Plastic/acrylic shields can be placed over fluorescent light tubes to block the small amount of UVB and UVA radiation that can leak from such sources.

7.1.2. Chemical sunscreens

Patients should select broad-spectrum sunscreens that contain agents that block UVB with a sun protection factor (SPF) of 30 or greater. Under everyday usage conditions, the actual SPF of the product is much less than the advertised SPF. This is due mainly to the fact that patients tend to use much less of the product on their skin than is used during the initial laboratory determination of the SPF value for the product. In the USA, preparations containing Parsol 1789/avobenzone and zinc oxide provide the broadest degree of UVA protection, and such products can have added value in SCLE patients. Sunscreen products available in other countries containing the most effective chemical UVA blocker, mexoryl SX, are not yet available in the US (mexoryl SX appears to be more resistant to photodegradation than Parsol 1789/avobenzone). Products should also be selected that are most resistant to being washed off by sweating or bathing. Sunscreens should be applied at least 30 min before sun exposure and reapplied after bathing or appreciable perspiration.

Opaque corrective camouflage cosmetic products (e.g., Dermablend, Covermark) are designed to optimally conceal pigmentary changes and scarring. These products offer the dual benefit of being highly effective physical sunscreens as well as aesthetically pleasing cosmetic masking agents for patients suffering psychologically from chronic, disfiguring skin disease as a result of cutaneous LE (Kaye et al., 1991). The proper use of such products can improve the quality of life of patients (Boehncke et al., 2002).

7.2. Local corticosteroids

Initial treatment usually includes daily application of a formulation containing a medium strength topical corticosteroid (e.g., triamcinolone acetonide 0.1%). If this does not provide adequate relief, a more potent topical corticosteroid such as clobetasol propionate 0.05%, betamethasone dipropionate 0.05%, diflorasone diacetate 0.05%, or amcinonide 0.1% can be tried. Daily application of these products to lesional skin for 2 weeks followed by a 2-week rest period of treatment can lessen the risk of local complications such as steroid-atrophy and telangiectasia. Cutaneous LE represents one the very few clinical situations where such potent topical fluorinated corticosteroids can be recommended for use on atrophy-prone areas such as the face, since the alternatives are disfiguring skin disease or risk of side effects from systemic therapy. Unfortunately, topical corticosteroids alone do not provide adequate improvement for the large majority of SCLE patients. Most SCLE patients' lesions are too numerous to be managed by intralesional corticosteroid injections and oral corticosteroids should be avoided as long as possible when treating isolated cutaneous LE lesions.

Several topical formulations of the calcineurin inhibitors, tacrolimus and pimecrolimus, have been examined in cutaneous LE including SCLE Yoshimasu et al., 2002; Walker et al., 2002; Kreuter et al., 2004). It has been the author's experience that LE skin lesions on facial skin can respond to these preparations better than LE skin lesions on other parts of the body. It is hoped that higher strength formulations of tacrolimus/pimecrolimus that are currently being developed will have greater clinical efficacy in cutaneous LE as has been observed anecdotally with compounded formulations (Walker et al., 2002).

7.3. Antimalarials

While a number of systemic medications have been reported to be of benefit to SCLE patients, by far those having the highest safety/benefit ratios are the aminoquinoline antimalarial agents. There is general agreement that 70–80% of SCLE patients will respond to single agent or combination antimalarial therapy. The three agents most frequently prescribed in the USA for SCLE patients are hydroxychloroquine sulfate (Plaquenil [Sanofi-Synthelabo]), chloroquine phosphate (Aralen [Sanofi-Synthelabo]), and quinacrine (currently available in the USA only as a compounded formulation of the dihydrochloride salt which must be encapsulated). In general, hydroxychloroquine is best tolerated with the least side effects.

Therapy with hydroxychloroquine alone should be tried initially starting at 6.5 mg/kg/day in two divided doses (approximately 400 mg/day for the average size person). Hydroxychloroquine reaches steady state levels in 6–8 weeks and its full clinical efficacy cannot be judged before then. Its full clinical effects can take even longer. If there is no significant improvement by 2–3 months, quinacrine 100 mg/day can be added to the hydroxychloroquine (Toubi et al., 2000; Chung and Hann, 1997; Lipsker et al., 1995; Feldmann et al., 1994). If the response is inadequate after 4–6 weeks of combined hydroxychloroquine and quinacrine therapy, chloroquine 250 mg/day can be substituted for the hydroxychloroquine in this combination as an occasional cutaneous LE patient will respond better to chloroquine than hydroxychloroquine. (Hydroxychloroquine and chloroquine should not be used concurrently because of enhanced risk of retinopathy.) Once disease activity is controlled, the hydroxychloroquine can be decreased to 200 mg/day for maintenance. Most authorities recommend a treatment period of 1–2 years to fully suppress cutaneous LE activity. As

noted previously there is evidence that cigarette smoking through a unknown mechanisms can interfere with efficacy of antimalarials in cutaneous LE.

It should also be realized that the aminoquinoline antimalarials, especially hydroxychloroquine, are being increasingly recognized to have a salutary effect on the extracutaneous manifestations of SLE (Canadian Hydroxychloroquine Study Group, 1991; Molad et al., 2002). Thus, the malaise, fatigue, and arthralgia that SCLE patients can experience can respond to antimalarials that have been given to control SCLE skin disease activity. As with the cutaneous LE disease activity, the musculoskeletal manifestations of SCLE patients will take several months to be fully impacted after starting antimalarials.

When using either hydroxychloroquine or chloroquine, ophthalmological moniotoring is required to minimize the risk of retinal toxicity (quinacrine is not retinopathic). A baseline ophthalmological evaluation should be obtained before starting antimalarial therapy to document any pre-existing changes that might subsequently attributed to the medication. The frequency with which patients are subsequently monitored has been debated. The most recent set of guidelines published by the American Academy of Ophthalmologists in April, 2002 suggests that this should be repeated at 6–12 month intervals while the patient is undergoing therapy (Marmor et al., 2002). This evaluation should, at minimum, include a funduscopic exam, visual field testing (including central fields with a red object), and visual acuity testing. Use of the self-administered Amsler Grid at home to detect the earliest evidence of visual field defects has become popular. Retinal changes can become irreversible if not detected early. It has been suggested that the risk of retinal toxicity is minimized when the total daily dose of hydroxychloroquine does not exceed 6.5 mg/kg/day (3.5 mg/kg/day for chloroquine). There does not appear to be an upper limit on the "safe" total lifetime dose of these drugs if these daily maximum dosing recommendations are not exceeded.

Periodic assessments of hematological and hepatic function are carried out by most dermatologists during the hydroxychloroquine and chloroquine therapy to identify the occasional patient who will suffer an idiosyncratic reaction. However, it should be noted that when using hydroxychloroquine for SLE, the American College of Rheumatology guidelines indicate that no such routine hematologic monitoring is necessary (American College of Rheumatology Ad Hoc Committee on Clinical Guidelines, 1996). It should be noted that full-dose hydroxychloroquine or chloroquine therapy in an individual having subclinical porphyria cutanea tarda can produce an acute hepatotoxic reaction that it can produce symptoms simulating an acute surgical abdomen. Quinacrine hydrochloride is more likely to induce hemolysis in glucose-6-phosphate dehydrogenase-deficient patients than is hydroxychloroquine or chloroquine and routine hematologic monitoring should be carried out with this agent. Neurotoxicity and muscular toxicity (including cardiotoxicity) can occur with the aminoquinoline antimalarials but was much more of a problem in the past when much higher daily doses of these drugs were used.

Antimalarial agents can induce a number of dermatological changes. All can cause a blue-black pigmentation of the skin (particularly in the sun exposed areas), palatal mucosa, nails, and pretibial surfaces. They can also rarely cause bleaching of lightly pigmented hair, although this is rare with currently recommended daily doses. Quinacrine frequently causes diffuse yellowing of the skin, sclera, and bodily secretions that is fully reversible on discontinuation of the drug. On occasion, quinacrine produces a lichenoid drug reaction that can be the harbinger of severe bone marrow toxicity if the drug is must not discontinued (Wallace, 1989). The lichenoid drug eruptions that can be produced by all of the aminoquinoline antimalarials can at time simulate the appearance of cutaneous LE lesions, including SCLE, resulting in a highly confusing clinical setting (Geraminejad et al., 2004).

7.4. Dapsone

Dapsone (diaminodiphenylsulfone) has been reported in small numbers of cases to be of benefit

to SCLE within a few weeks after starting therapy (Holtman et al., 1990; Fenton and Black, 1986; McCormack et al., 1984). Dose of 50–200 mg/day are typically required but even higher doses might be needed. Hematological, renal, and hepatic toxicity can occur with this drug and thus careful monitoring is required. Unfortunately, in SCLE patients personally treated by the author Dapsone has been of only moderate to marginal benefit.

7.5. Retinoids

Isotretinoin (Accutane) at approximately 1 mg/kg/day and acitretin (Soriatane) at 25–50 mg/day have been shown to significantly improve cutaneous LE including SCLE lesions (Furner, 1990). The great potential for teratogenic effects with the retinoids makes it imperative that fertile females use contraceptive techniques according to guidelines set forth specifically for patients on retinoids. A common dose-related side effect is mucocutaneous dryness. It is advisable to have patients use sunscreens judiciously while being treated with these agents to minimize their tendency to aggravate photosensitivity. Drug-induced hepatitis and hypertriglyceridemia can occur with these agents and requires periodic laboratory evaluation. Occasionally, these drugs can also induce bony changes consistent with the diffuse idiopathic skeletal hyperostosis (DISH) syndrome. Hair loss and peeling of the hands and feet are seen more often with acitretin. Cutaneous LE disease activity tends to recur quickly after discontinuing systemic retinoids. This plus their high rates of adverse reactions limit the clinical utility of systemic retinoids in the management of long-term skin disorders such as cutaneous LE.

7.6. Thalidomide

Thalidomide 50–200 mg/day can be very effective for active SCLE (Volc-Platzer and Wolff, 1983; Naafs et al., 1982) but due to its side effects is generally limited to use in difficult, refractory cutaneous LE patients. Its clinical benefit can be seen as early as 2 weeks, however cutaneous LE disease activity typically relapses 2–3 months after discontinuing the drug.

The severe teratogenicity of thalidomide is well known and has limited the frequency with which it is prescribed. Additionally, a predominately sensory peripheral neuropathy has been described to occur in 10–25% of treated cutaneous LE patients even with low doses as much as 50–100 mg/daily. Since thalidomide works quickly in SCLE, it is possible to treat recalcitrant patients with short courses of thalidomide (8–16 weeks) to minimize toxicity. To prevent flares after discontinuation of thalidomide, antimalarial therapy can be administered concomitantly with thalidomide and continued after thalidomide is withdrawn. Other side effects include secondary amenorrhea and induction of a hypercoagulable state, especially in the setting of antiphospholipid antibody production. Thalidomide's mechanism of action is unclear, however many have suggested TNF-α inhibition.

7.7. Gold

Oral gold (auranofin [Ridaura]) therapy has been successfully used in cutaneous LE patients whose disease is resistant to the less toxic forms of therapy (Dalziel et al., 1986). Generally, parenteral forms of gold (aurothiomalate and aurothioglucose) have been more efficacious for most indications than the oral form of gold. However, the parenteral forms of gold previously available in the US have been supplanted by other drugs having less mucocutaneous, hematological, renal, and pulmonary toxicity.

7.8. Clofazimine

Crovoto reported the successful use of clofazimine (Lamprene) in a patient with annular SCLE in 1981 (Mackey and Barnes, 1974). He used a dose of 100 mg/day and noted clearing of the lesions within a few weeks. At this dosage clofazimine is generally well tolerated, though gastrointestinal intolerance can be a problem. At higher doses,

clofazimine has rarely been reported to precipitate in mesenteric arteries, resulting in major abdominal catastrophes such as splenic infarction. A pink-brown-black skin pigmentation develops in most patients on long-term clofazimine therapy. This pigmentation resolves over months to years after discontinuing the drug. Similar discoloration of bodily secretions also frequently occurs. Clofazimine is currently not available in the USA.

7.9. Other agents

Several other agents have been suggested anecdotally to be of benefit in SCLE. Those include cefuroxime axetil (Rudnicka et al., 2000), statins (Namazi, 2004), pulsed by laser (Gupta and Roberts, 1999), and recombinant interferon-α 2a (Nicolas and Thivolet, 1989; Nicolas et al., 1990). However, interferon-α therapy has also been associated with the precipitation of SCLE. The author has no personal experience with any of these agents in SCLE.

7.10. Systemic corticosteroids and other immunosuppressive agents

Systemic corticosteroids and other immunosuppressive/cytotoxic agents (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, etc) are reserved for patients with more severe SCLE that have failed to respond to the less toxic forms of therapy discussed above. A patient may occasionally be encountered whose disease is so severe that these more potent agents may be used earlier in the disease course, even before the patient is given a complete trial of the less toxic agents, or before the less toxic agents (i.e., hydroxychloroquine) reach steady state levels. It should be remembered that long-term systemic corticosteroid usage in LE patients carries a high risk of complications such as avascular bone necrosis and premature atherosclerosis. Thus, when treating only or predominately the cutaneous manifestations of LE every effort should be made to avoid long-term use of systemic corticosteroids.

Methylprednisolone given in pulse doses (1 g intravenously slowly [approximately 4 h] daily for 3 consecutive days) has been reported to provide improvement in SCLE patients with systemic LE. Anecdotally, methotrexate, azathioprine, and cyclophosphamide have been suggested to be of benefit in refractory SCLE. Due to the potential for severe immunosuppression, bone marrow and mucous membrane toxicity, hepatotoxicity, and opportunistic malignancies, these agents should be reserved for patients with severe disease and used only as a last resort in patients with severe cutaneous LE alone.

7.11. Combination therapy

Although drug combinations have long been frowned upon by the USA Food and Drug Administration, various combinations of the above systemic anti-inflammatory and immunosuppressive agents have routinely been employed by rheumatologists in diseases such as rheumatoid arthritis. The rationale for such combined "chemotherapy-like" approaches to non-malignant inflammatory musculoskeletal disease has been to provide additive or synergistic clinical efficacy by employing combinations of drugs that act through different mechanisms while minimizing toxicity by limiting daily dosage maxima of individual drugs. The downside is that adverse reactions developing during combination therapy can be difficult to ascribed to a specific agent.

Except for the above comments concerning combination antimalarial therapy, USA dermatologists have traditionally not been very creative in employing combination of therapeutic agents for the management of rheumatic skin diseases such as SCLE. There is published data suggesting that the following drugs can be used concurrently with hydroxychloroquine safely and effectively in other rheumatic disease settings: sulfasalazine, methotrexate, gold, azathioprine. The author has personally observed this to be the case for dapsone as well. In addition, the following combinations of other anti-rheumatic drugs have safely been employed concurrently with hydroxychloroquine: sulfasalazine + methotrexate, sulfasalazine + gold,

and methotrexate + azathioprine. Perhaps dermatologists have missed opportunities by not more systematically examining such combinations for efficacy in difficult cutaneous LE patients including SCLE.

7.12. Experimental therapy

7.12.1. UVA-1 phototherapy

Preliminary animal work has suggested that UVA might dampen the autoimmune abnormalities in experimental murine models of SLE (McGrath, Jr. et al., 1987). In addition, small controlled trials from two groups of investigators have suggested that SCLE patients might actually benefit from very low doses of whole-body UVA-1 irradiation (340–400 nm) (McGrath, Jr. 1997; McGrath et al., 1996; Polderman et al., 2001). However, the true value of this somewhat controversial form of treatment remains to be confirmed by controlled studies in larger groups of patients. Caution should be taken in interpreting these data in view of the increasing evidence that UVA (190–200), including long-wave UVA-1, can play an exacerbating role in the cutaneous manifestations of SLE (Nived et al., 1993).

7.12.2. Recombinant biologic response modifiers

As previously discussed, variant TNF-α gene expression has been implicated as a predisposing genetic factor for SCLE. This plus the remarkable efficacy of thalidomide, a known inhibitor of TNF-α expression, has suggested the possibility that the new recombinant TNF-α inhibitors such as etanercept, infliximab, and adalimumab might potentially be of benefit to SCLE patients. However, a drug-induced form of cutaneous LE including SCLE has now been recognized as a potential complication of treatment with this class of biologics. Despite this, one report describes rapid improvement of SCLE in a patient with rheumatoid arthritis who was treated with etanercept (Fautrel et al., 2002).

In addition, other recombinant biologics that interfere with antigen presenting cell:T-cell interaction that have proven to be of benefit in psoriasis (Amevive [Alefecept], efalizumab [Raptiva]) theoretically could be of benefit in other T-cell-dependent autoimmune skin diseases such as cutaneous LE. The author is personally aware of one recent case of therapeutically refractory SCLE seen by others that was said to have responded quickly and remarkably well to efalizumab [Raptiva].

B-cell depleting recombinant biologics acting through CD-20 such as ritixumab (Rituxan) have been recently been reported in preliminary studies to be of possible benefit in humoral autoimmune diseases such as SLE and pemphigus (Saito et al., 2003; Cooper et al., 2003; Herrmann et al., 2003; Perrotta et al., 2002; Heizmann et al., 2001). It would be interesting to know what their impact might be on SCLE.

By way of summary, an algorithm of the author's personal approach to using the various treatment options discussed above is presented in Fig. 5.

8. Prognosis

Data from the original SCLE study cohort suggested that patients presenting with SCLE skin lesions might have an illness intermediate in severity between that of those presenting with isolated chronic cutaneous LE (discoid LE) skin lesions and those presenting with SLE not accompanied by SCLE or chronic cutaneous LE skin lesions (Sontheimer et al., 1979, 1981, 1982; Gilliam and Sontheimer, 1981). However, longer term follow-up studies including an informal one in which the author has participated have indicated that the large majority of SCLE patients enjoy a good prognosis over their disease course (Chlebus et al., 1998; Pellowski et al., 2005). The combined international experience of a quarter century now suggest that no more than 10–15% of SCLE patients are at risk for developing potentially life-threatening manifestations of the SLE (Sontheimer, 1989; Costner et al., 2004; Pellowski et al., 2005).

Unfortunately, prognostic indicators for those destined to have a more severe course have yet to be identified. As previously mentioned, it has been

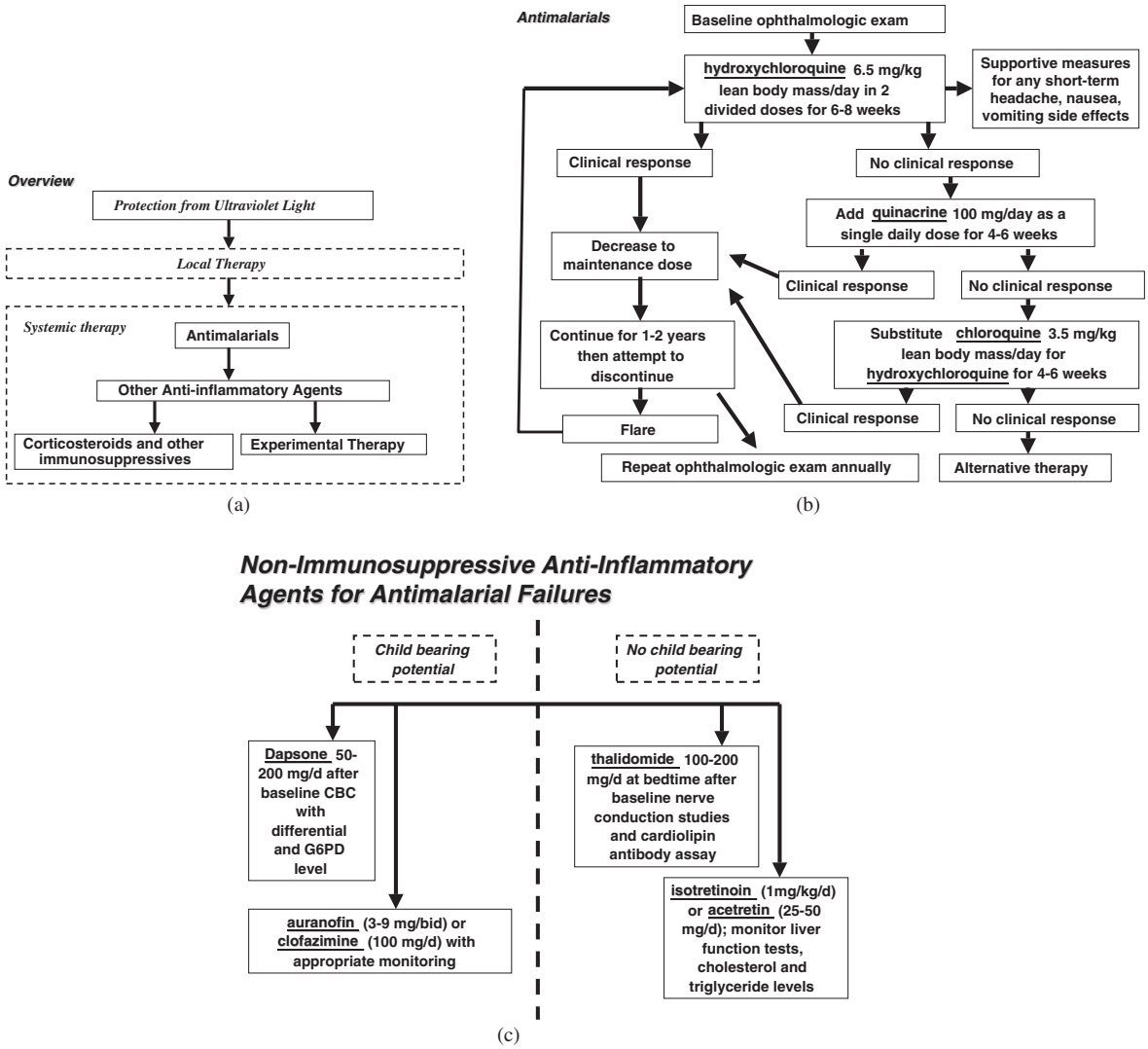


Figure 5. The author's approach to the management of SCLE presented in algorithm format. (A) Overview of management. (B) Approach to the use of systemic aminoquinoline antimalarials. (C) Approach to the use of non-immunosuppressive anti-inflammatory agents for antimalarial failures.

the author's impression that patients having the papulosquamous type of SCLE and a high titer ANA may be at greater risk for developing clinically significant SLE including nephritis (Sontheimer, 1985; Pellowski et al., 2005). Other investigators have subsequently had similar impressions especially in males with papulosquamous SCLE skin lesions (Cohen and Crosby, 1994). In addition, the author has the impression that the appearance of localized acute cutaneous LE (facial butterfly rash) in a SCLE patient also places them in a higher risk category for the development of clinically significant SLE. The presence of laboratory changes that are seen typically in active SLE (e.g., hypocomplementemia, elevated levels of double-stranded DNA antibody, high erythrocyte sedimentation rate) would also be reason for concern that an SCLE patient might be at greater risk for more aggressive manifestations of SLE.

Acknowledgements

All of the original work by the author pertaining to SCLE discussed in this chapter was supported either directly or indirectly by NIH (NIAMS) grant AR019101 (the contents of this chapter are solely the responsibility of the author and do not necessarily represent the official views of NIAMS). This NIH grant was initially funded in 1979, the same year that the description of the original cohort of SCLE patients was published. This grant will terminate in 2005. The author wishes to thank the US taxpayers and NIAMS Skin Disease Program staff for their long-term support of this work.

Key points

- ''Subacutecutaneous lupus erythematosus'' (SCLE) is the 25-year-old designation for a widespread, photosensitive, nonscarring, nonindurated form of LE-specific skin disease.
- SCLE skin lesions are associated with a distinctive immunogenetic background including the production of Ro/SS-A autoantibodies.
- Individuals who have SCLE skin lesions as a prominent component of their presenting illness represent a distinctive subset (sub-phenotype) of LE that enjoys a good prognosis with respect to life-threatening systemic manifestations of LE.
- SCLE skin lesions and Ro/SS-A autoantibody production can be triggered by UV light and a number of different drugs, the majority of which are capable of producing photosensitivity drug reactions in non-lupus patients.
- The etiopathogenesis of SCLE skin lesions is thought to result from four sequential stages: (1) inheritance of susceptibility genes, (2) loss of tolerance/induction of autoimmunity, (3) expansion/maturation of autoimmune responses, and (4) tissue injury/disease induction resulting from various autoimmune effector mechanisms.
- The majority of SCLE patients will require systemic therapy. Single agent or combination aminoquinoline antimalarial therapy will suffice for 75–80% of SCLE patients. The remaining 20–25% will require other forms of systemic anti-inflammatory therapy (e.g., diaminodipenylsulfone [Dapsone], retinoids, thalidomide) or conventional systemic immunosuppressive/immunomodulatory therapy. Several types of the new recombinant biologic response modifier drugs may provide future benefit to severely affected SCLE patients.

References

American College of Rheumatology Ad Hoc Committee on Clinical Guidelines 1996. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum. 39, 723.

Black, D.R., Hornung, C.A., Schneider, P.D., et al. 2002. Frequency and severity of systemic disease in patients with subacute cutaneous lupus erythematosus. Arch. Dermatol. 138, 1175.

Boehncke, W.H., Ochsendorf, F., Paeslack, I., et al. 2002. Decorative cosmetics improve the quality of life in patients with disfiguring skin diseases. Eur. J. Dermatol. 12, 577.

Botto, M., Walport, M.J. 2002. C1q, autoimmunity and apoptosis. Immunobiology 205, 395.

Canadian Hydroxychloroquine Study Group 1991. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. N. Engl. J. Med. 324, 150.

Chlebus, E., Wolska, H., Blaszczyk, M., et al. 1998. Subacute cutaneous lupus erythematosus versus systemic lupus erythematosus – Diagnostic criteria and therpeutic options. J. Am. Acad. Dermatol. 38, 405.

Chung, H.S., Hann, S.K. 1997. Lupus panniculitis treated with a combination therapy of hydroxychloroquine and quinacrine. J. Dermatol. 24, 569.

Cohen, M.R., Crosby, D. 1994. Systemic disease in subacute cutaneous lupus erythematosus: a controlled comparison with systemic lupus erythematosus. J. Rheumatol. 21, 1665.

Cooper, H.L., Healy, E., Theaker, J.M., Friedmann, P.S. 2003. Treatment of resistant pemphigus vulgaris with an anti-CD20 monoclonal antibody (Rituximab). Clin. Exp. Dermatol. 28, 366.

Costenbader, K.H., Kim, D.J., Peerzada, J., et al. 2004. Cigarette smoking and the risk of systemic lupus erythematosus – a meta-analysis. Arthritis Rheum 50, 849.

Costner, M.I., Provost, T.T., Sontheimer, R.D. 2004. Lupus erythematosus. In: R.D. Sontheimer, T.T. Provost (Eds.), Cutaneous Manifestations of Rheumatic Diseases, 2nd ed, Lippincott-Williams & Wilkins, Philadelphia.

Dalziel, K., Going, G., Cartwright, P.H., et al. 1986. Treatment of chronic discoid lupus erythematosus with an oral gold compound (Auranofin). Br. J. Dermatol. 115, 211.

David-Bajar, K.M., Bennion, S.D., DeSpain, J.D., et al. 1992. The clinical, histologic and immunofluorescent distinctions betwen subacute cutaneous lupus erythematosus and discoid lupus erythematosus. J. Invest. Dermatol. 99, 251.

Dawn, G., Wainwright, N.J. 2002. Association between subacute cutaneous lupus erythematosus and epidermoid carcinoma of the lung: a paraneoplastic phenomenon? Clin. Exp. Dermatol. 27, 717.

Dutz, J.P., Sontheimer, R.D. 2002. The pathogenesis of LE-specific skin disease. In: D.J. Wallace, B.H. Hahn (Eds.), Dubois' Lupus Erythematosus, 6th ed, Lippincott-Williams & Wilkins, Philadelphia, p. 549.

Fautrel, B., Foltz, V., Frances, C., et al. 2002. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: Comment on the article by Pisetsky and the letter from Aringer et al. Arthritis Rheum. 46, 1408.

Feldmann, R., Salomon, D., Saurat, J.-H. 1994. The association of the two antimalarials chloroquine and quinacrine for treatment-resistant chronic and subacute cutaneous lupus erythematosus. Dermatology 189, 425.

Fenton, D.A., Black, M.M. 1986. Low-dose dapsone in the treatment of subacute cutaneous lupus erythematosus. Clin. Exp. Dermatol. 11, 102.

Fonseca, E., Alvarez, R., Gonzalez, M.R., et al. 1992. Prevalence of anticardiolipin antibodies in subacute cutaneous lupus erythematosus. Lupus 1, 265.

Furner, B.B. 1990. Subacute cutaneous lupus erythematosus response to isotretinoin. Int. J. Dermatol. 29, 587.

Geraminejad, P., Stone, M.S., Sontheimer, R.D., et al. 2004. Antimalarial lichenoid tissue reactions in patients with pre-existing lupus erythematosus. Lupus 13, 473.

Gilliam, J.N. 1977. The cutaneous signs of lupus erythematosus. Cont. Educ. Fam. Phys. 6, 34.

Gilliam, J.N., Sontheimer, R.D. 1981. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J. Am. Acad. Dermatol. 4, 471.

Gupta, G., Roberts, D.T. 1999. Pulsed dye laser treatment of subacute cutaneous lupus erythematosus. Clin. Exp. Dermatol. 24, 498.

Haimowitz, J.E., McCauliffe, D.P., Seykora, J., et al. 2000. Annular erythema of Sjogren's syndrome in a white woman. J. Am. Acad. Dermatol. 42, 1069.

Heizmann, M., Itin, P., Wernli, M., et al. 2001. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am. J. Hematol. 66, 142.

Herrmann, G., Hunzelmann, N., Engert, A. 2003. Treatment of pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). Br. J. Dermatol. 148, 602.

Holtman, J.H., Neustadt, D.H., Klein, J., et al. 1990. Dapsone is an effective therapy for the skin lesions of subacute cutaneous lupus erythematosus and urticarial vasculitis in a patient with C2 deficiency. J. Rheumatol. 17, 1222.

Kaye, E.T., Levin, J.A., Blank, I.H., et al. 1991. Efficiency of opaque photoprotective agents in the visible light range. Arch. Dermatol. 127, 351.

Kinoshita, G., Keech, C.L., Sontheimer, R.D., et al. 1998. Spreading of the immune response from 52 kDA Ro and 60 kDA Ro to calreticulin in experimental autoimmunity. Lupus. 7, 7.

Kreuter, A., Gambichler, T., Breuckmann, F., et al. 2004. Pimecrolimus 1% cream for cutaneous lupus erythematosus. J. Am. Acad. Dermatol. 51, 407.

Kuhn, A., Sonntag, M., Richter-Hintz, D., et al. 2001. Phototesting in lupus erythematosus: a 15-year experience. J. Am. Acad. Dermatol. 45, 86.

Lee, L.A., Roberts, C.M., Frank, M.B., et al. 1994. The autoantibody response to Ro/SSA in cutaneous lupus erythematosus. Arch. Dermatol. 130, 1262.

Lio, D., Candore, G., Colombo, A., et al. 2001. A genetically determined high setting of TNF-alpha influences immunologic parameters of HLA-B8,DR3 positive subjects: implications for autoimmunity. Hum. Immunol. 62, 705.

Lipsker, D., Piette, J.-C., Cacoub, P., et al. 1995. Chloroquine-quinacrine association in resistant cutaneous lupus. Dermatology 190, 257.

Mackey, J.P., Barnes, J. 1974. Clofazimine in the treatment of discoid lupus erythematosus. Br. J. Dermatol. 91, 93.

Marmor, M.F., Carr, R.E., Easterbrook, M., et al. 2002. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: a report. Am. Acad. Ophthal. 109, 1377.

McCauliffe, D.P., Faircloth, E., Wang, L., et al. 1996. Similar Ro/SS-A autoantibody epitope and titer responses in annular erythema of Sjögren's syndrome and subacute cutaneous lupus erythematosus. Arch. Dermatol. 132, 528.

McCormack, L.S., Elgart, M.L., Turner, M.L. 1984. Annular subacute cutaneous lupus erythematosus responsive to Dapsone. J. Am. Acad. Dermatol. 11, 397.

McGrath, H., Jr. 1997. Prospects for UV-A1 therapy as a treatment modality in cutaneous and systemic LE. Lupus 6, 209.

McGrath, H., Jr., Bak, E., Michalski, J.P. 1987. Ultraviolet–A Light prolongs survival and improves immune function in (New Zealand Black X New Zealand White)F1 hybrid mice. Arthritis Rheum. 30, 557.

McGrath, H., Martinez-Osuna, P., Lee, F.A. 1996. Ultraviolet-A1 (340–400nm) irradiation therapy in systemic lupus erythematosus. Lupus 5, 269.

Meller, S., Winterberg, F., Gilliet, M., et al. 2005. Ultraviolet radiation-induced injury, chemokines, and leukocyte recruitment: an amplification cycle triggering cutaneous lupus erythematosus. Arthritis Rheum. 52, 1504.

Millard, T.P., Kondeatis, E., Cox, A., et al. 2001. A candidate gene analysis of three related photosensitivity disorders: cutaneous lupus erythematosus, polymorphic light eruption and actinic prurigo. Br. J. Dermatol. 145, 229.

Miyagawa, S. 1994. Clinical, serological and immunogenetic features of Japanese anti-Ro/SS-A-positive patients with annular erythema. Dermatology 189 (Suppl. 1), 11.

Molad, Y., Gorshtein, A., Wysenbeek, A.J., et al. 2002. Protective effect of hydroxychloroquine in systemic lupus erythematosus. Prospective long-term study of an Israeli cohort. Lupus 11, 356.

Naafs, B., Bakkers, E.J.M., Flinterman, J., et al. 1982. Thalidomide treatment of subacute cutaneous lupus erythematosus. Br. J. Dermatol. 107, 83.

Namazi, M.R. 2004. Statins: novel additions to the dermatologic arsenal? Exp. Dermatol. 13, 337.

Nicolas, J.-F., Thivolet, J. 1989. Interferon alfa therapy in severe unresponsive subacute cutaneous lupus erythematosus. N. Engl. J. Med. 321, 1550.

Nicolas, J.-F., Thivolet, J., Kanitakis, J., et al. 1990. Response of discoid and subacute cutaneous lupus erythematosus to recombinant interferon alpha 2a. J. Invest. Dermatol. 95 (Suppl.), 142S.

Nived, O., Johansen, P.B., Sturfelt, G. 1993. Standardized ultraviolet-A exposure provokes skin reaction in systemic lupus erythematosus. Lupus 2, 247.

Orteu, C.H., Sontheimer, R.D., Dutz, J.P. 2001. The pathophysiology of photosensitivity in lupus erythematosus. Photodermatol. Photoimmunol. Photomed. 17, 95.

Pellowski, D.M., Kihslinger, J.E., Sontheimer, R.D. 2005. Subacute cutaneous lupus erythematosus. In: Autoimmune Diseases of the Skin. 2nd ed., Springer, Wien/New York.

Perrotta, S., Locatelli, F., La Manna, A., et al. 2002. Anti-CD20 monoclonal antibody (Rituximab) for life-threatening autoimmune haemolytic anaemia in a patient with systemic lupus erythematosus. Br. J. Haematol. 116, 465.

Polderman, M.C., Huizinga, T.W., Le Cessie, S., et al. 2001. UVA-1 cold light treatment of SLE: a double blind, placebo controlled crossover trial. Ann. Rheum. Dis. 60, 112.

Provost, T.T. 1979. Subsets in systemic lupus erythematosus. J. Invest. Dermatol. 72, 110.

Racila, D.M., Sontheimer, C.J., Sheffield, A., et al. 2003. Homozygous single nucleotide polymorphism of the complement C1QA gene is associated with decreased levels of Clq in patients with subacute cutaneous lupus erythematosus. Lupus 12, 124.

Rahman, P., Gladman, D.D., Urowitz, M.B. 1998. Smoking interferes with efficacy of antimalarial therapy in cutaneous lupus. J. Rheumatol. 25, 1716.

Reed, B.R., Huff, J.C., Jones, S.K., et al. 1985. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. Ann. Intern. Med. 103, 49.

Roustan, G., Salas, C., Barbadillo, C., et al. 2000. Lupus erythematosus with an erythema multiforme-like eruption. Eur. J. Dermatol. 10, 459.

Rowell, N.R., Swanson-Beck, J., Andrson, J.R. 1963. Lupus erythematosus and erythema multiforme-like lesions. Arch. Dermatol. 88, 176.

Rudnicka, L., Szymanska, E., Walecka, I., et al. 2000. Long-term cefuroxime axetil in subacute cutaneous lupus erythematosus. A report of three cases. Dermatology 200, 129.

Saito, K., Nawata, M., Nakayamada, S., et al. 2003. Successful treatment with anti-CD20 monoclonal antibody (rituximab) of life-threatening refractory systemic lupus erythematosus with renal and central nervous system involvement. Lupus 12, 798.

Sanders, C.J., Van, W.H., Kazzaz, G.A., et al. 2003. Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. Br. J. Dermatol. 149, 131.

Sontheimer, R.D. 1985. Clinical significance of subacute cutaneous lupus erythematosus skin lesions. J. Dermatol. 12, 205.

Sontheimer, R.D. 1989. Subacute cutaneous lupus erythematosus: a decade's perspective. Med. Clin. North Am. 73, 1073.

Sontheimer, R.D. 1996. Photoimmunology of lupus erythematosus and dermatomyositis: a speculative review. Photochem. Photobiol. 63, 583.

Sontheimer, R.D. 2002. Dermatomyositis. An overview of recent progress with emphasis on dermatological aspects. Dermatol. Clin. 20, 387.

Sontheimer, R.D. 2004a. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. Best Pract. Res. Clin. Rheumatol. 18, 429.

Sontheimer, R.D. 2004b. The management of dermatomyositis: current treatment options. Expert Opin. Pharmacother. 5, 1083.

Sontheimer, R.D. 2005. Subacute cutaneous lupus erythematosus – a 25 year personal perspective. Autoimmun. Rev. 4 (5), 253–263.

Sontheimer, R.D., Costner, M.I. 2002. Dermatomyositis. 6th ed, McGraw-Hill, New York.

Sontheimer, R.D., Euwer, R.L., Costner, M.I., 2004. Dermatomyositis. In: Cutaneous Manifestations of Rheumatic Diseases. 2nd ed. Lippincott-Williams & Wilkins, Philadelphia.

Sontheimer, R.D., Maddison, P.J., Reichlin, M., Jordan, R.E., Stastny, P., Gilliam, J.N. 1982. Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. Ann. Intern. Med. 97, 644–671.

Sontheimer, R.D., Stastny, P., Gilliam, J.N. 1981. Human histocompatibility antigen associations in subacute cutaneous lupus erythematosus. J. Clin. Invest. 67, 312–316.

Sontheimer, R.D., Thomas, J.R., Gilliam, J.N. 1979. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. Arch. Dermatol. 115, 1409–1415.

Stewart, J. 2002. Towards the genetic analysis of mulfactorial diseases: the estimation of allele frequency and epistasis. Hum. Hered. 54, 118–131.

Tebbe, B., Orfanos, C.E. 1997. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus 6, 96–104.

Ting, W.W., Sontheimer, R.D. 2001. Local therapy for cutaneous and systemic lupus erythematosus: practical and theoretical considerations. Lupus 10, 171.

Ting, W., Stone, M.S., Racila, D.R., et al. 2004. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus and the spectrum of the acute syndrome of apoptotic panepidermolysis (ASAP): a case report, concept review and proposal for new classification of lupus erythematosus vesiculobullous skin lesions. Lupus 13, 941.

Toubi, E., Rosner, I., Rozenbaum, M., et al. 2000. The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. Lupus 9, 92.

Urowitz, M.B. 1977. SLE subsets–divide and conquer. J. Rheumatol. 4, 332.

Vassileva, S. 2004. Bullous systemic lupus erythematosus. Clin. Dermatol. 22, 129.

Volc-Platzer, B., Wolff, K. 1983. Treatment of subacute cutaneous lupus erythematosus with thalidomide. Der Hautarzt. 34, 175.

Walker, S.L., Kirby, B., Chalmers, R.J.G. 2002. The effect of topical tacrolimus on severe recalcitrant chronic discoid lupus erythematosus. Br. J. Dermatol. 147, 405.

Wallace, D.J. 1989. The use of quinacrine (Atabrine) in rheumatic diseases: a re-examination. Semin. Arthritis Rheum. 18, 282.

Watanabe, T., Tsuchida, T., Ito, Y., et al. 1997. Annular erythema associated with lupus erythematosus and Sjogrens syndrome. J. Am. Acad. Dermatol. 36, 214.

Werth, V.P., Zhang, W., Dortzbach, K., et al. 2000. Association of a promoter polymorphism of tumor necrosis factor-alpha with subacute cutaneous lupus erythematosus and distinct photoregulation of transcription. J. Invest. Dermatol. 115, 726.

Yamamoto, T., Nishioka, K. 2004. Coexistence of psoriasis vulgaris, systemic sclerosis, and annular erythema in association with Sjogren's syndrome. J. Dermatol. 31, 69.

Yoshimasu, T., Ohtani, T., Sakamoto, T., et al. 2002. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. Eur. J. Dermatol. 12, 50.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 8

Differential Diagnosis of LE-specific Skin Lesions

Riccardo Rondinone[a,*], Stefania Bano[b], Luca Iaccarino[a], Andrea Doria[a]
[a]*Division of Rheumatology, University of Padova, Padova, Italy*
[b]*Division of Dermatology, University of Padova, Padova, Italy*

1. Introduction

Lupus erythematosus (LE) is a multisystemic autoimmune disease that can occur with a wide spectrum of clinical manifestations. The skin is frequently involved, either as an isolated finding, i.e. when no other sign or symptom of systemic involvement can be disclosed, or as a part of a complex syndrome with multiple organ involvement.

Based on dermatologic and pathological criteria, the cutaneous manifestations of LE (CLE) have been classified as LE-specific and LE-nonspecific (Gilliam et al., 1981).

LE-specific skin lesions have been subdivided into three broad categories: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE). Although their clinical features are often very clear and the pathology is rather characteristic, many different diseases have to be considered in the differential diagnosis.

2. Acute cutaneous lupus erythematosus

2.1. Dermatologic features

ACLE consists of transient erythematous lesions, sometimes with a slight edema or a fine scaling, which are generally localized on the face (localized ACLE), with a peculiar (but not exclusive) involvement of the malar areas and the bridge of the nose, the so-called 'malar' or 'butterfly rash'. Sometimes the rash also involves the extensor surface of the arms, the hands, and the upper trunk with a widespread photodistributed maculopapular rash (generalized ACLE). The histology shows an interface dermatitis as in other LE-specific cutaneous manifestations but with more edema, vacuolar degeneration of the basal keratinocytes and epidermal atrophy, and with a less-pronounced inflammatory infiltrate and a minor degree of hyperkeratosis. Direct immunofluorescence (DIF) study of the ACLE lesions generally shows the deposition of immunoglobulins and complement components along the dermo-epidermal junction.

2.2. Clinical background

ACLE lesions are almost exclusively observed in systemic LE (SLE), during the active phases of the systemic disease.

2.3. Differential diagnosis of localized ACLE

The diseases, which we may consider in the differential diagnosis with localized ACLE, are acne rosacea, contact dermatitis and photodermatitis, seborrheic dermatitis, dermatomyositis, erysipelas, and delusion of lupus.

*Corresponding author.
Division of Rheumatology, University of Padova, Via Giustiniani, 2, 35128 Padova, Italy.
Tel.: +49-8212190; fax: +49-8212191.
E-mail address: riccardo.rondinone@unipd.it (R. Rondinone).

DOI: 10.1016/S1571-5078(05)05008-7

2.3.1. Acne rosacea vs ACLE

In its early stages, rosacea may present with a purely erythematous rash on the malar areas that can be very similar to ACLE. The rash may be triggered or aggravated by heat, cold, emotions, and by the ingestion of hot drinks, alcohol, and spicy foods.

Differentiating early rosacea from ACLE only on the basis of the dermatologic evaluation may be very difficult, and therefore the clinical background has to be evaluated because ACLE patients almost always have an active systemic disease.

Over time, a diffuse network of telangiectases may present on the erythematous background, which is characteristic of acne rosacea: nonetheless in patients with SLE who have long been treated with systemic steroids, the atrophy of the skin overlying the malar areas may lead to the appearance of a similar network of telangiectases, and therefore the clinical background remains an essential feature for the differential diagnosis.

In advanced stages of acne rosacea, papules and pustules appear, which are never observed in ACLE, and at this stage clinical differentiation is possible (Fig. 1).

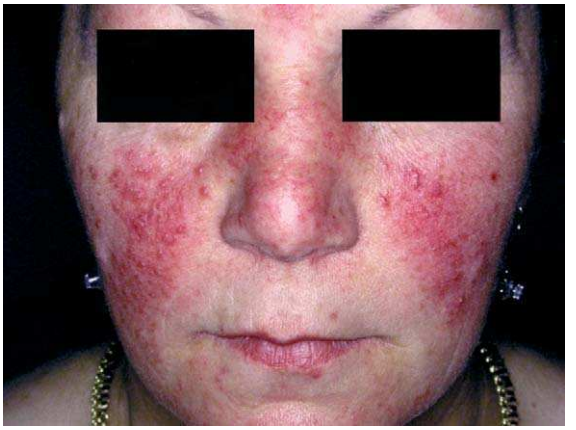


Figure 1. Rosacea: malar erythema with papules and pustules.

2.3.2. Contact dermatitis vs ACLE

A contact dermatitis of the face may be caused by cosmetics, chemical substances, or plants.

The rash has an acute onset, causes itching, and presents with erythema, vesciculation, oozing, and weeping. Any part of the face may be involved depending on the pattern of exposure to the sensitizer (Fig. 2). In severe acute cases, the differentiation with ACLE is easy, but mild subacute cases, in which vesiculation and itching are not relevant, may sometimes create some suspicion.

In such cases, the histology of spongiotic dermatitis and a negative DIF allow for clinical differentiation.

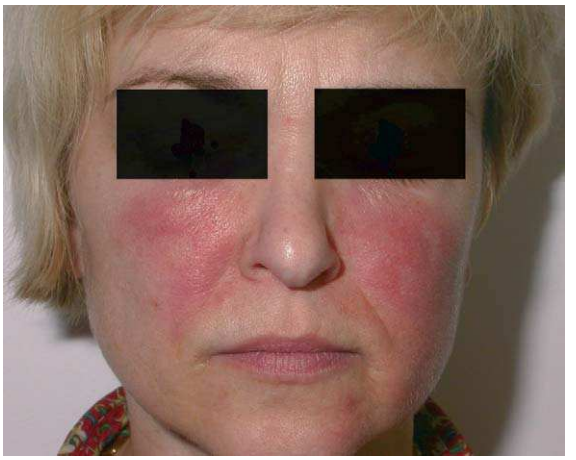


Figure 2. Contact dermatitis: acute eruption with a butterfly distribution caused by cosmetic application.

2.3.3. Photodermatitis vs ACLE

Drugs or other chemical substances may act as photosensitizers and induce a phototoxic or—in predisposed individuals—a photoallergic reaction resulting in a facial rash resembling ACLE.

The list of possible photosensitizers is very long, comprising many currently used drugs like sulfonamides, sulfonylureas, tetracyclines, nalidixic acid, thiazides, non-steroidal anti-inflammatory drugs like piroxicam and ketoprofen, chlorpromazine, and many others.

Some of these drugs may be frequently prescribed for the treatment of SLE, and considering that some of the patients are not compliant and do not adhere to a strict sun avoidance, the possibility of a photodermatitis has to be kept in mind.

The onset is generally acute, hours (phototoxic reaction) or few days (photoallergic reaction) after ultraviolet exposure, and besides the face, other photoexposed areas may be involved as well, like the dorsa of the hands and feet or the ears, which

are generally spared in ACLE, thus allowing for the differentiation. When necessary, histologic examination will reveal a spongiotic dermatitis in photoallergic drug eruptions or vacuolated keratinocytes (sunburn cells) and dyskeratosis in a phototoxic reaction (Gilchrest et al., 1981).

2.3.4. Seborrheic dermatitis vs ACLE

Seborrheic dermatitis is a very common cutaneous disease presenting as erythemato-squamous plaques, generally located on the face, scalp, presternal area, interscapular region, and occasionally the skin folds. The scales have a characteristic yellowish, non-adherent, greasy appearance. The distribution of the dermatosis and the peculiar scaling generally allow for an easy differentiation from ACLE.

Moreover, in the case of facial involvement, seborrheic dermatitis frequently affects the nasolabial folds that are—as a rule—spared in ACLE.

In rare instances, the localization on the malar areas and the paucity of scaling may induce some suspicion (Fig. 3), but in any case the plaques tend to have a rather rough and oily surface, which is never encountered in ACLE.

2.3.5. Dermatomyositis vs ACLE

The most frequent initial cutaneous manifestation of dermatomyositis consists of a photosensitive erythematous violaceous eruption (Parodi et al., 2002). When localized exclusively to the face, this rash can be very similar to ACLE (Fig. 4), sharing the same histologic features of an interface dermatitis.

In most of the cases, dermatomyositis patients do not have a sufficient number of clinical and immunological criteria for being classified as SLE, as we would expect in the presence of ACLE.

Differentiation is easier when dermatomyositis-specific cutaneous manifestations (Gottron' papules (Fig. 5), Gottron's sign or the upper eyelid heliotrope rash) are present, if the patient has any clinical evidence of myositis or has any dermatomyositis-specific autoantibodies (anti-Mi-2, anti-synthetases, anti-SRP) (Ghirardello et al., 2005).

2.3.6. Erysipelas vs ACLE

Streptococcal infection of the skin may manifest as a superficial cellulitis, appearing as a bright red, edematous plaque with sharply demarcated, elevated, advancing borders. The face is commonly involved with a predilection for the bridge of the nose and the extension to one or both cheeks. The onset is abrupt, with fever and chills. Erysipelas occurs most commonly in children or elderly patients, and has therefore a different age distribution than SLE.

Erysipelas can be considered in the differential diagnosis with ACLE in the case of a bilateral

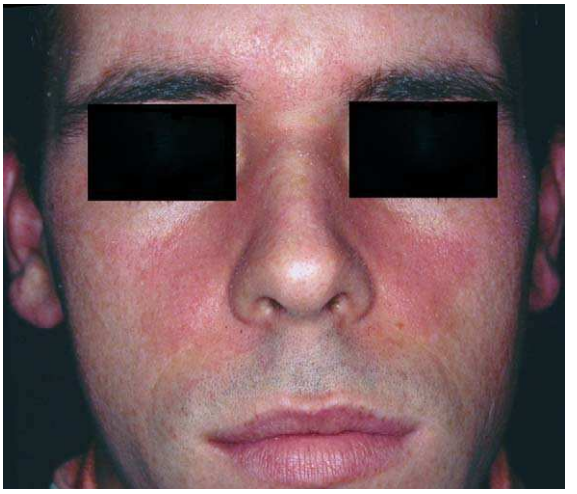


Figure 3. Seborrheic dermatitis: erythematous eruption with a fine yellowish scaling extending to the malar area, the glabella and the eyebrows.

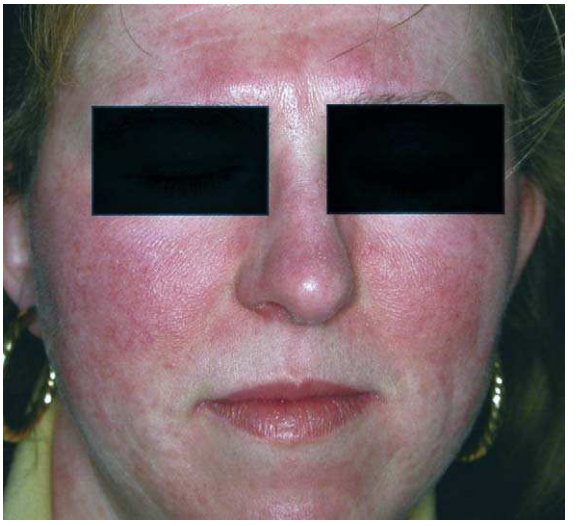


Figure 4. Dermatomyositis: violaceous erythema on the face resembling ACLE.

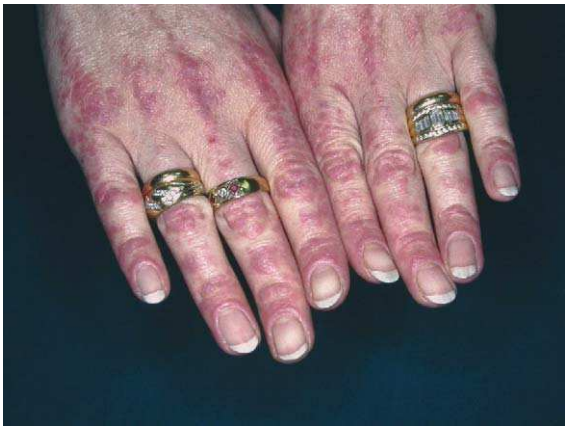


Figure 5. Dermatomyositis: Gottron's papules on the dorsal surface of the interphalangeal and metacarpophalangeal joints.

symmetrical involvement of the butterfly area, but the sharp margins, the rapid peripheral extension, the abrupt onset are differential criteria. In the case of erysipelas arising in a SLE patient, the finding of a leukocytosis might be another important element to consider in the differential diagnosis with ACLE.

2.3.7. Delusion of lupus vs ACLE

Delusional beliefs of having a butterfly rash occasionally induce some otherwise healthy subjects to ask for a rheumatological consultation (Fig. 6). In these cases, the differential diagnosis is easier than convincing the patient and sometimes the relatives that share the same delusional beliefs.

2.4. Differential diagnosis of generalized ACLE

The diseases, which we may consider in the differential diagnosis with generalized ACLE are morbilliform drug reactions and erythema multiforme.

2.4.1. Morbilliform drug reactions vs generalized ACLE

Drug reactions with cutaneous manifestations occur in approximately 2.2% of inpatients according to the Boston Collaborative Drug Surveillance Program (Bigby et al., 1986) and an estimate of the overall reaction rate per course of drug therapy is around 3/1000.

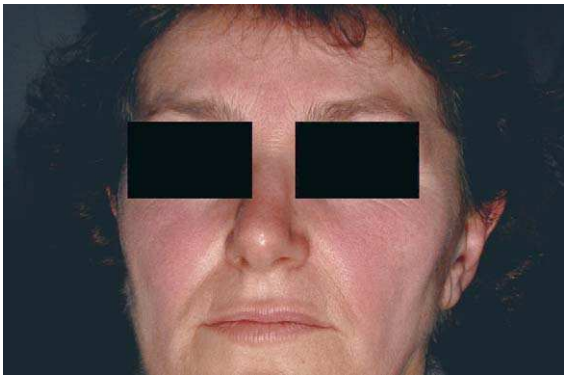


Figure 6. Delusion of lupus: slight erythema on the malar areas in a perfectly healthy subject with delusional beliefs.

Antibiotics are the most frequent culprit drug, with a reaction rate as high as 8% (Bigby, 2001) and an average latency of around 1 week from the drug administration. The exanthematous pattern is the most frequently observed.

The diagnostic problem arises in a SLE patient who develops a morbilliform drug reaction, which the clinician has to differentiate from generalized ACLE.

In the case of a drug reaction the malar rash is not necessarily present, the distribution is wider than in generalized ACLE with involvement on non-sun exposed areas, the palms and soles; the rash may be unrelated to SLE activity, and there is a history of a drug administration 1–2 weeks before the onset. The biopsy examination may reveal eosinophils in the inflammatory infiltrate as a distinctive feature.

2.4.2. Erythema multiforme vs generalized ACLE

Erythema multiforme is a reaction pattern induced by a variety of stimuli, mainly infections (Herpes simplex, *Mycoplasma pneumoniae*, and streptococcal infections) and drugs. Three form of erythema multiforme can be recognized according to the extent of cutaneous and mucosal involvement: of these, erythema multiforme minor can sometimes be considered in the differential diagnosis with generalized ACLE.

The initial manifestations are round erythematous papules, spreading over the extensor surface

of the limbs with a symmetrical distribution and can be differentiated from generalized ACLE because of the predominant involvement of the extremities (including palms and soles) and the subsequent spread in a centripetal manner (Fig. 7). Moreover, an isomorphic response may be observed, which is not the case of ACLE.

Over some hours or a few days, the cutaneous lesions enlarge with possible coalescence, and may evolve toward the formation of concentric zones of different colors, thus giving rise to the characteristic 'iris' or 'target lesion' that cannot be confused with generalized ACLE (Fig. 8).

Erythema multiforme may develop in SLE patients, and in these cases the rash is not necessarily related to disease activity. However, if asked, patients may recall an infection or drug administration 1–4 weeks before the onset.

The histopathology of early erythema multiforme lesions is characterized by a lymphocytic infiltrate around the upper dermal vessels, hydropic degeneration and necrosis of basal keratinocytes. The presence of dyskeratotic cells, the inflammatory infiltrate sparing the appendages, the absence of hyperkeratosis and epidermal atrophy may be some important differential features.

DIF: IgM and C3 around blood vessels in the superficial dermis and C3 along the dermo-epidermal junction can be present in erythema multiforme as compared to the lesional lupus band test observed in SLE. In those cases of erythema multiforme occurring in a SLE patient, the presence of a non-lesional lupus band test can be superimposed, and therefore DIF is not very helpful in differential diagnosis.

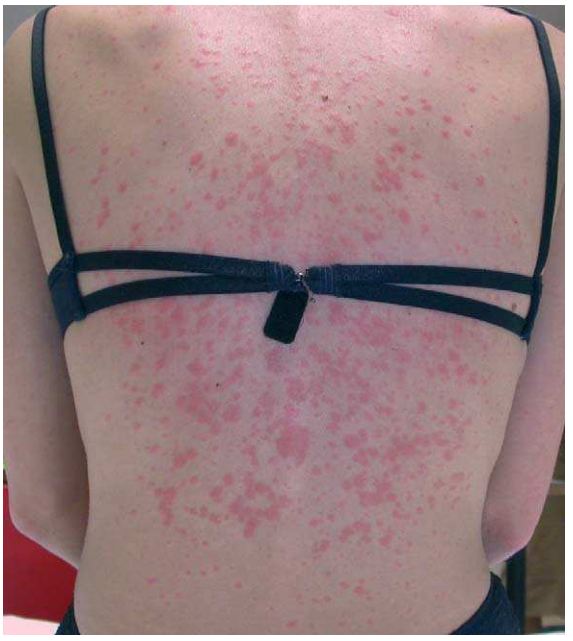


Figure 7. Erythema multiforme: SLE patient with a widespread, non-photodistributed, erythemato-maculo-papular eruption. The characteristic "iris" or "target" lesions are not evident in the early phases of the rash.

3. Subacute cutaneous lupus erythematosus

3.1. Dermatologic features

SCLE has been originally described as a recurring, superficial, non-scarring type of CLE, occurring in a characteristic distribution on the face, upper part of the trunk, and extensor surfaces of the arms with sparing the inner aspects of the arms and the lateral part of the trunk (Gilliam and Sontheimer, 1981).

Hyperkeratosis may be very prominent (psoriasiform SCLE) but scales are never as adherent or as thick as in CCLE; moreover SCLE lesions, though

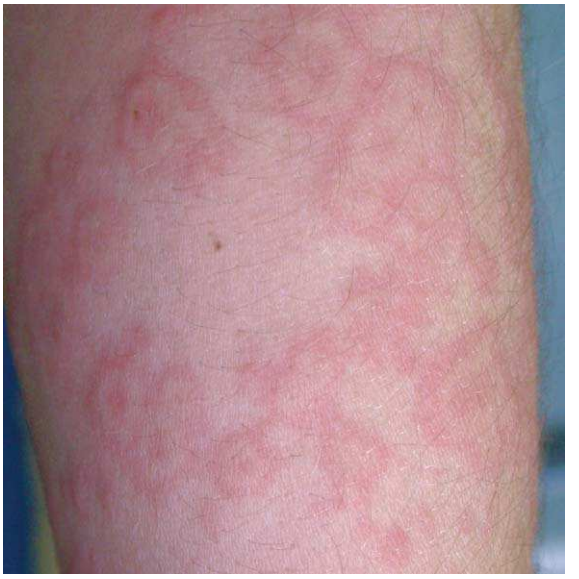


Figure 8. Erythema multiforme: characteristic "iris" or "target" lesion.

persistent for several months, are never as indurated as in CCLE, do not tend to develop scarring and heal with a grayish hypopigmentation and eventually some telangiectases.

Two possible SCLE patterns have been identified: a papulosquamous pattern with psoriasiform lesions that may merge to form wide plaques, and an annular-polycyclic pattern, in which lesions undergo central resolution while extending peripherally to form annular elements that may coalesce producing polycyclic, gyrate configurations. Photosensitivity occurs in the majority of SCLE patients.

The histology shows an interface dermatitis as in other LE-specific cutaneous manifestations, almost indistinguishable from CCLE: the most important difference is the inflammatory infiltrate, which is more sparse and superficial in SCLE and denser and deeper in CCLE (Bangert et al., 1984).

The DIF study of the SCLE lesions generally shows the deposition of immunoglobulins and complement components along the dermo-epidermal junction, and in some cases a granular IgG deposition within the epidermis, due to anti-SSA autoantibodies (Nieboer et al., 1988).

3.2. Clinical background

SCLE patients have four or more American College of Rheumatology (ACR) criteria for the classification of SLE in approximately 50% of cases (Sontheimer et al., 1979). Those SLE patients with SCLE generally have a mild systemic disease, with a low incidence of glomerulonephritis, arthritis, serositis, and with a mild neurological involvement (Callen and Klein, 1988).

Anti-SSA antibodies are very frequently observed (up to 90% of the cases) and their prevalence increases if repeated evaluations are made during follow-up.

3.3. Differential diagnosis of papulosquamous SCLE

The diseases, which we may consider in the differential diagnosis with the papulosquamous pattern of SCLE are psoriasis and polymorphic light eruption.

3.3.1. Psoriasis vs papulosquamous SCLE

Psoriasis is a chronic inflammatory disorder characterized by the presence of erythematous scaling plaques that in some cases can resemble SCLE. Differential features are a thicker scaling, with a silvery, micaceous appearance (Fig. 9) and a different distribution of psoriasis plaques that predominantly affect the elbows, knees, and the scalp, with no tendency to photodistribution.

In some cases skin folds and nails can be involved.

There is a genetical predisposition to develop psoriasis and therefore some of the relatives of affected patients may have the same disease.

Histology shows a characteristic hyperplasia (the so-called psoriasiform hyperplasia) with spongiform pustules and Munro microabscesses, that can be easily differentiated from SCLE.

3.3.2. Polymorphic light eruption vs papulosquamous SCLE

Polymorphic light eruption represents the most common form of idiopathic photosensitivity disorder. It presents with a pruritic eruption with a variety of dermatologic expressions (erythematous papules, vescicles, or plaques) appearing on sun-exposed areas, mainly the extensor surfaces of the forearms and chest, less frequently also on the legs

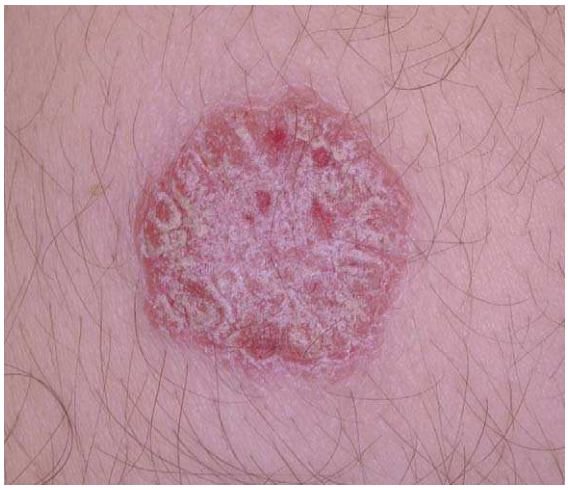


Figure 9. Psoriasis: typical erythematous plaque with silvery white scaling.

and the face. The rash generally appears within a few hours, sometimes even 1–2 days after sun exposure and subsides spontaneously within 1–7 days provided that no further exposure occurs.

When appearing as erythematous plaques (Fig. 10), polymorphic light eruption may sometimes resemble early SCLE lesions, but can be differentiated because of the severe itch and the very precise timing with sun exposure, as polymorphic light eruption lesions erupt a few hours later and spontaneously resolve within some days without scarring or hypopigmentation.

Histological examination may not show a prominent epidermal involvement as in interface dermatitis, and when present, spongiosis may be an important differentiating feature.

The inflammatory infiltrate is mainly composed of lymphocytes, with variable amounts of neutrophils and eosinophils, and does not surround the appendages. Moreover, dermal edema may be prominent (Stratigos et al., 2002; Tutrone et al., 2003).

3.4. Differential diagnosis of annular-polycyclic SCLE

The diseases, which we may consider in the differential diagnosis, are superficial gyrate erythema and tinea corporis.

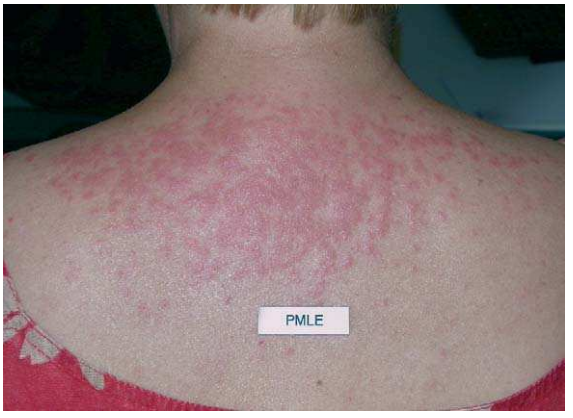


Figure 10. Polymorphic light eruption: such photodistributed erythematous plaques may resemble early SCLE lesions, in which scaling may be initially inconspicuous.

3.4.1. Superficial gyrate erythema vs annular-polycyclic SCLE

Superficial gyrate erythema is considered as a poliaetiological reaction-pattern with a typical expression and running a chronic course. It may present with elevated urticarial plaques with centrifugal spreading and central resolution that form arched, ring-shaped or polycyclic patches involving the trunk and the proximal limbs resembling SCLE.

Differential features are the asymmetric involvement of the trunk without photodistribution, the rapid extension of the rings, which may become larger than it can possibly be observed in SCLE, and the spontanous clearing without hypopigmentation or telangiectases. Moreover, a characteristic scaling at the trailing edge of the advancing border may be observed (Fig. 11).

Histological examination reveals spongiosis with microvesciculation, focal parakeratosis, and a mild perivascular lymphohistiocytic inflammatory infiltrate, with sparing of the appendages (Lever and Schaumburg-Lever, 1990).

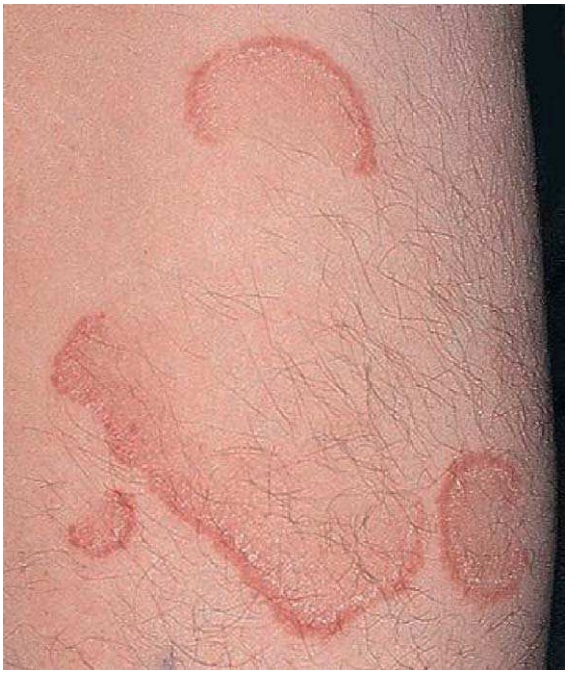


Figure 11. Superficial gyrate erythema: round and arcuate erythematous lesions with central clearing and scaling at the trailing edge of the advancing borders.

3.4.2. Tinea corporis vs annular-polycyclic SCLE

Dermatophytes are keratinophilic fungi that can produce different patterns of superficial infection of the glabrous skin. A non-inflammatory pattern, tinea circinata, presents with annular lesions with an active erythematous scaling border and central clearing. Contiguous annular lesions may merge to form polycyclic plaques that can be confused with SCLE, but tinea corporis is generally asymmetric and non-photodistributed.

Moreover, KOH examination of the scales obtained by scraping from the active border can show the presence of hyphae, and the culture on appropriate media can allow for the identification of the causative microorganism.

4. Chronic cutaneous lupus erythematosus

4.1. Dermatologic features

Among the cutaneous manifestations of LE, those comprised under the category of CCLE are the most frequently observed. The face and the scalp are the most commonly affected areas (localized CCLE) but any other part of the body below the neck can be involved as well (generalized CCLE).

At onset, CCLE appears as a sharply demarcated, slightly raised, erythematous lesion. Hyperkeratosis gradually develops and therefore the surface becomes rough at first, and then scaly.

Sometimes hyperkeratosis may be predominant at the follicular orifices, which appear dilated and filled with a keratin plug. The scales may then become thick, adherent, and when they are removed, the follicular plugs attached to the underside form characteristic horny spikes, the so-called 'carpet tack' appearance.

CCLE lesions gradually become infiltrated and extend peripherally with an active erythematosquamous border, while partially resolving in the central area, with the development of scleroatrophy, telangiectases, hypo- or hyperpigmentation and cicatricial alopecia.

In larger plaques, the peripheral extension may become irregular, with only isolated arciform segments of the active border.

With time, inflammation subsides leaving only scleroatrophic and dyschromic residues that cause permanent disfiguring results.

Various diseases have to be considered in differential diagnosis according to the different stages of the evolution of the CCLE. For this reason, we have separated early, fully developed, and late CCLE lesions, and within early lesions we have arbitrarily identified two clinical patterns: scaling and non-scaling early CCLE.

The non-scaling pattern of early CCLE lesion presents as an erythematous plaque, sharply demarcated, with minimal scaling. Lupus tumidus, in which the papular component is predominant, can be considered as an extreme of the spectrum of the non-scaling pattern of CCLE manifestations.

The scaling pattern of early CCLE lesion presents as an erythematous plaque with prominent follicular hyperkeratosis and scaling. A hypertrophic variant of CCLE may represent one extreme of the spectrum of the scaling pattern.

Fully developed CCLE lesion: annular lesion with an active border with erythema, infiltration and scaling and a central area with sclerosis, atrophy, and telangiectases.

Late CCLE lesions: scleroatrophic patches with telangiectases and only limited areas of residual inflammation within the patch and in the periphery, where they may form an incomplete active margin.

4.2. Clinical background

CCLE can be the isolated expression of a localized cutaneous disease but it can also occur in patients with SLE.

4.3. Differential diagnosis of early CCLE, non-scaling pattern

The diseases, which we may consider in differential diagnosis with the non-scaling pattern of early CCLE, are polymorphic light eruption, Jessner's benign lymphocytic infiltration of the skin, lymphocytoma cutis, granuloma faciale, pernio (chilblain), and lupus pernio (sarcoidosis). The same diseases may also be considered in the differential diagnosis with tumid LE.

4.3.1. Polymorphic light eruption vs early CCLE, non-scaling pattern

Polymorphic light eruption has already been mentioned in Section 3.3.2.

When it presents as an erythematous papular or plaque eruption involving the face, it should be considered in the differential diagnosis with CCLE, and above all, tumid LE.

Distinguishing clinical features are the presence of itching, which is often severe and the precise correlation with the sun exposure and the quick resolution within a few days, while CCLE and tumid LE do not itch and the latency before the eruption is longer, days or even weeks after sun exposure, and the lesions tend to be persistent.

Histology shows the following distinguishing features: there is no epidermal involvement in the papular variants of polymorphic light eruption, there is edema in the papillary dermis, the inflammatory infiltrate may contain variable amounts of neutrophils, and does not involve the appendages as in CCLE.

4.3.2. Jessner's benign lymphocytic infiltration of the skin vs early CCLE, non-scaling pattern

Jessner and Kanof (1953) first described this disease which is characterized by the occurrence of asymptomatic, erythematous papules and plaques, with a smooth surface, that tend to a peripheral extension and central resolution evolving to annular or horseshoe-like configuration, occurring mainly on the face (Fig. 12) and less often on the trunk. Jessner's lesions tend to be persistent or may have a relapsing course, may be induced or aggravated by sun exposure, but most of the patients have active lesions during wintertime and on non-exposed areas of the trunk.

Jessner's lymphocytic infiltration may closely resemble tumid LE, and in this respect, some authors suggest that it should not be considered as a separate entity but rather a variant of CCLE or, in some cases, of polymorphic light eruption.

Jessner's lymphocytic infiltration is characterized by a coat-sleeve perivascular lymphocytic infiltrate as the only histologic feature (Massi, 1995). CCLE may, therefore, be differentiated by the presence of epidermal involvement and patchy lymphocytic infiltrates in the superficial dermis below the dermoepidermal junction and around hair follicles while tumid LE may be distinguished by the presence of minimal signs of epidermal involvement and the abundant mucin deposition. DIF is negative in Jessner's lymphocytic infiltration and recently immunohistochemical analysis has revealed a predominance of CD8+ T lymphocytes in the inflammatory infiltrate (Poenitz et al., 2003).

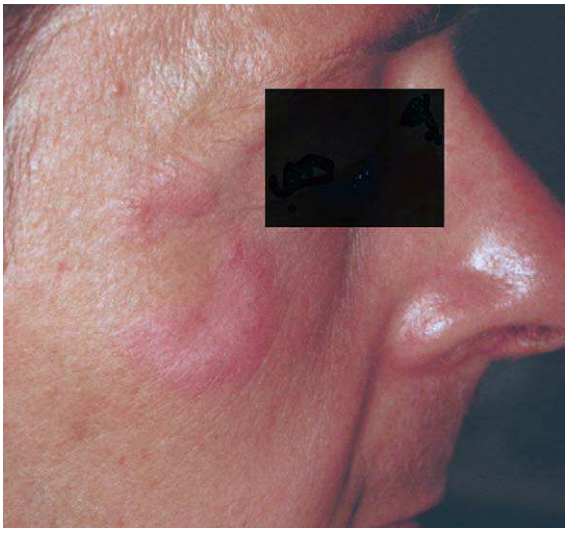


Figure 12. Jessner's benign lymphocytic infiltration of the skin: erythematous tumid lesion with an incomplete annular configuration.

4.3.3. Lymphocytoma cutis vs early CCLE, non-scaling pattern

Lymphocytoma cutis is the prototype of cutaneous B-cell pseudolymphomas. It appears as one or several erythematous papules or plaques, with a smooth surface (Fig. 13). The majority of lymphocytoma cutis involve exposed areas of the head and the neck, and in the earlier stages of development, when the papular or plaque component is not yet fully expressed, it can be considered in the differential diagnosis with early CCLE, while in later stages lymphocytoma cutis lesions can more closely resemble tumid LE.

Clinical diagnosis is impossible and therefore the differentiation requires the histologic examination

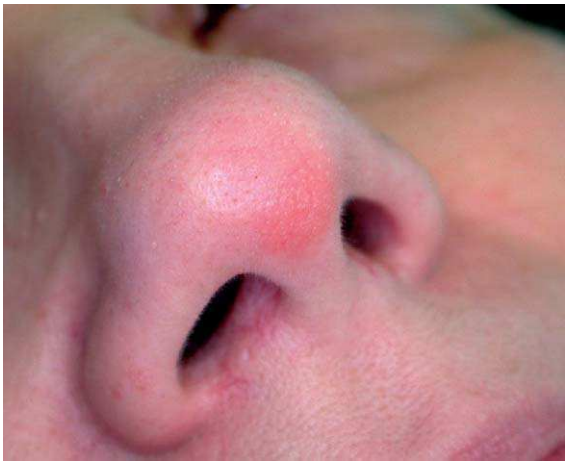


Figure 13. Lymphocytoma cutis: smooth, bright red papule on the tip of the nose.

of the lesions. Lymphocytoma cutis presents with a normal epidermis, a grenz-zone of uninvolved superficial dermis, and an underlying dense infiltrate extending throughout the reticular dermis in a 'top-heavy' pattern, composed of a mixed infiltrate with a majority of B-lymphocytes, and a variable amount of histocytes, plasma cells, and occasional eosinophils. Germinal centers are often present, surrounded by plasma cells (Massi, 1995).

4.3.4. Granuloma faciale vs early CCLE, non-scaling pattern

This is a rare form of localized chronic fibrosing vasculitis of the skin. It generally begins as a solitary, well-circumscribed erythematous papule (Fig. 14), and at this stage a biopsy is necessary for the differential diagnosis with early CCLE. Eventually, the initial purple color may shift to reddish-brown (due to hemosiderin deposition), and the slightly raised smooth surface develops characteristic prominent follicular orifices, but never hyperkeratosis or follicular plugging as in CCLE, therefore allowing for a high degree of clinical suspicion.

The main histologic features of granuloma faciale are the absence of epidermal involvement, a grenz-zone of uninvolved superficial dermis, a leukocytoclastic vasculitis with nuclear dust and a mixed dermal infiltrate with prominent neutrophils and eosinophils.

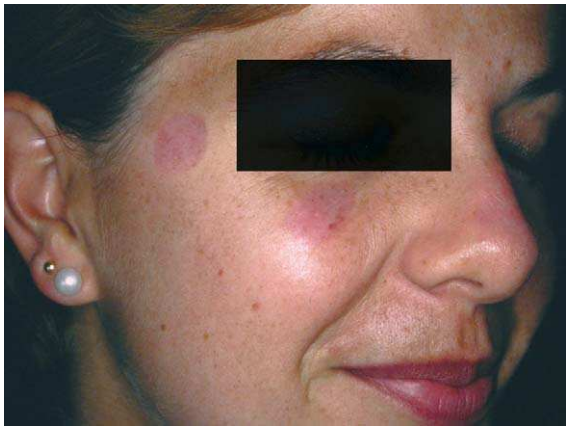


Figure 14. Granuloma faciale: round erythematous papules with sharply defined margins.

DIF studies (Zirwas et al., 2003) have given conflicting results as some authors have reported the presence of immunoglobulin deposits in the blood vessel walls, while others have not confirmed this finding. Moreover, the deposition of IgA, IgG, IgM, and C3 along the dermo-epidermal junction with a granular pattern and a negative fluorescence of the blood vessel walls, may closely mimic the DIF pattern found in LE.

4.3.5. Pernio vs early CCLE, non-scaling pattern

Pernio or chilblain is a reaction pattern to cold exposure in damp climates, presenting as vivid red to purple plaques, warm to the touch, accompanied by itching and at times also soreness and pain. They are most commonly localized on the dorsal surface of the fingers and in other acral areas, and tend to persist throughout the cold season.

The face may be affected, and when plaques are localized in the malar area (Fig. 15) and itching is not prominent, a suspicion of CCLE may arise. Generally other lesions may be present in areas unusual for CCLE, but in some cases a biopsy will be necessary for differential diagnosis.

Peculiar histologic features are the presence of spongiosis, necrotic keratinocytes, an intense papillary dermal edema, a mononuclear inflammatory infiltrate with a prevalence of T cell and with a perieccrine reinforcement, and sometimes thrombosis

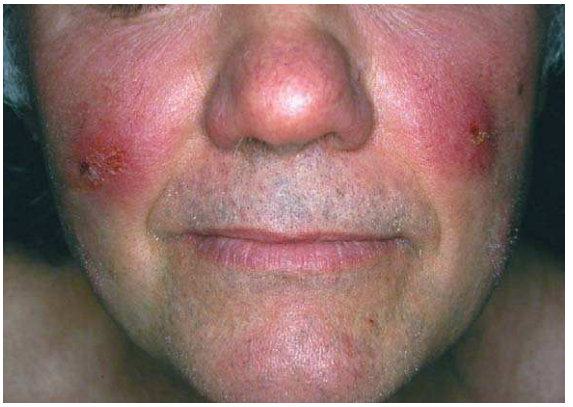


Figure 15. Chilblain: tumid papules on the cheeks, with crusting.

of dermal papillae capillaries (Crowson and Magro, 1997; Cribier et al., 2001).

Some CCLE patients may develop chilblain lesions on the extremities that evolve to form characteristic discoid LE (DLE) plaques, with a typical clinical appearance and a diagnostic pathology, for which the term 'chilblain lupus' or 'perniotic LE' has been proposed. This phenomenon might represent a peculiar form of a Koebner reaction triggered by the chilblains (Millard and Rowell, 1978).

4.3.6. Lupus pernio vs early CCLE, non-scaling pattern

Lupus pernio is a peculiar pattern of cutaneous involvement in patients with sarcoidosis with a chronic, fibrotic involvement of the lungs and other systems. It presents with persistent, violaceous plaques on the nose, cheeks, and ears that must be differentiated from CCLE (Fig. 16). On clinical groundlupus pernio tends to have a smooth, glistening surface without scaling, and follicular orifices may be prominent but without follicular plugging. Histology shows the absence of epidermal involvement but the most important differentiating feature is the presence of non-caseating epithelioid-cell granulomas. Eventually, some biological markers like elevated levels of serum-angiotensin converting enzyme, lysozyme, beta 2 microglobulin, and disturbed calcium metabolism (hypercalcemia and hypercalciuria) may be helpful for the diagnosis of sarcoidosis.

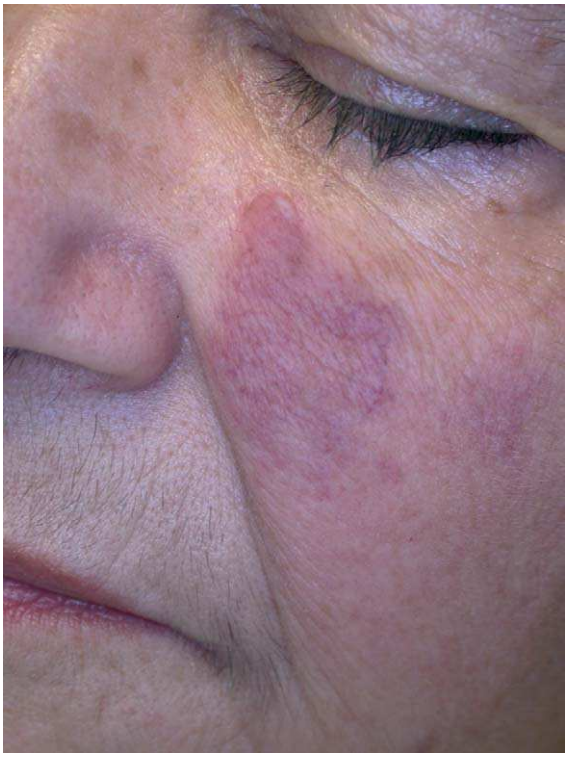


Figure 16. Lupus Pernio: smooth, dark red, sarcoidal plaque on the cheek.

4.4. Differential diagnosis of early CCLE, scaling pattern

The diseases, which we may consider in differential diagnosis with the scaling pattern of early CCLE are actinic keratoses, seborrheic dermatitis, tinea faciei, psoriasis, and lichen ruber planus.

4.4.1. Actinic keratoses vs early CCLE, scaling pattern

Actinic keratoses are the most frequent precancerous cutaneous lesions. They may be found on the exposed areas, most frequently on the face and the bald portion of the scalp, but also on the trunk and arms in fair-skinned individuals. They appear as areas of macular erythema with an overlying adherent scale. Scaling may be minimal, best appreciated by touch, while on the other hand, in some cases of hypertrophic actinic keratoses the formation of a cutaneous horn may be seen.

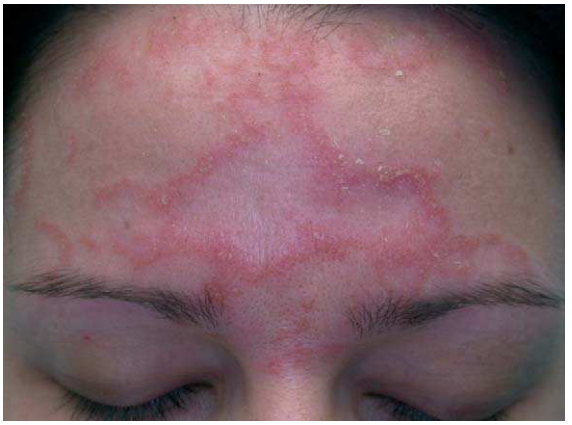


Figure 17. Seborrheic dermatitis: round, annular, and arcuate lesions on the forehead with an unusual polycyclic configuration.

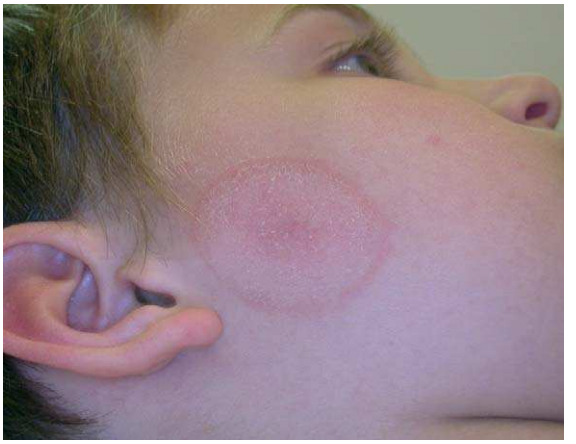


Figure 18. Tinea faciei: round, scaly plaque of dermatophyte infection on the face.

Actinic keratoses may be similar to early CCLE but are slower in their evolution, rougher to the touch, and the scales are very difficult to detach, with no follicular plugging.

Moreover, they are always observed within areas of photodamaged skin in individuals older than the average CCLE patient.

Histology shows dysplastic keratinocytes, dyskeratosis, loss of cell polarity, especially in the lower epidermis, with sparing of the adnexa.

4.4.2. Seborrheic dermatitis vs early CCLE, scaling pattern

Seborrheic dermatitis may be considered in differential diagnosis with early CCLE when it presents as erythematous scaling patches on the scalp or with atypical features (Fig. 17).

The scales in seborrheic dermatitis have a greasy appearance, a yellowish color, and may be easily detached by scraping while CCLE tends to develop dry, whitish, adherent scales with a tendency to follicular plugging, and therefore a clinical differentiation is generally possible.

4.4.3. Psoriasis vs early CCLE, scaling pattern

As in the case of seborrheic dermatitis, psoriasis can create some suspicion of CCLE when it presents with an isolated localization on the scalp. Psoriasis also frequently involves the peripheral areas of the scalp extending toward the forehead and the retroauricular folds. Moreover, the scales are silvery-white, easily detached by gentle scraping, and uniformly distributed over the plaque surface, where they may sometimes form a thick layer, and leaving only a peripheral erythematosus, raised border.

4.4.4. Tinea faciei vs early CCLE, scaling pattern

Dermatophytic infection of the face has been referred to as tinea faciei, and may take on unexpected forms, particularly in the adult or in immunocompromised patients, thus resembling other diseases, most frequently DLE (Alteras et al., 1988).

It may appear as non-symmetric erythematous plaques, with variable scaling (Fig. 18) and sometimes follicular plugging and a suspicion of DLE may arise when the nose or the malar areas are involved.

For the differential diagnosis, KOH examination of cutaneous scales may be employed, allowing for the detection of the hyphae. Moreover, a precise identification of the causative dermatophyte can be made on appropriate culture media.

4.4.5. Lichen ruber planus vs early CCLE, scaling pattern

Lichen ruber planus is characterized by the eruption of tiny, flat-topped, polygonal, violaceous papules, with variable hyperkeratosis going from delicate white lines (Wickham's striae) to a

verrucous appearance. The papules are generally symmetrically distributed over the flexor surfaces of the forearms and wrists but may be more widespread to involve the trunk, the genital and oral mucosa, and sometimes the scalp.

The distribution of the rash and the presence of itching are characteristic differentiating features from CCLE, but occasionally, isolated plaques of lichen ruber planus may induce a suspicion of LE.

Distinguishing histologic features of lichen ruber planus are the presence of a band-like inflammatory infiltrate below the dermo-epidermal junction, a 'saw-toothed contour' of the rete ridges, and colloid bodies, which are more numerous than in CCLE and may be aggregated.

DIF may show a fibrillar or band-like pattern of fibrin deposition along the dermo-epidermal junction, while colloid bodies demonstrate IgM staining and less frequently IgA, IgG and C3 staining (Nieboer, 1987).

Nonetheless, rare patients with intermediate features or with the simultanous occurrence of CCLE and lichen ruber planus have been described as lichen-lupus overlap syndrome.

4.5. Differential diagnosis of fully developed CCLE lesions

Fully developed CCLE lesions have a unique appearance and can hardly be confused with other diseases. According to Sontheimer and Provost (1995), ''Discoid-shaped skin lesions that have erythema and hyperpigmentation at their active borders, and depigmentation, telangieactasia, and atrophy at the centres are very unlikely to result from dermatologic disorders other than cutaneous LE''.

4.6. Differential diagnosis of late CCLE lesions

The diseases, which can be considered in differential diagnosis with late CCLE are lichen ruber planus, lupus vulgaris, and other granulomatous infectious diseases.

4.6.1. Lichen ruber planus vs late CCLE

The involvement of the scalp is very frequent in a variant of lichen ruber planus called lichen planopilaris, and leads to the development of a cicatricial alopecia that has to be differentiated from late CCLE of the scalp.

Initially small erythematous follicular papules may be observed, with little scaling stuffing the infundibula and progressing to form follicular horny plugs. Soon scarring takes place leaving a white, smooth alopecic area (Fig. 19), while follicular plugging and inflammatory papules remain visible only at the periphery (Fig. 20).

On clinical grounds it can be differentiated from late CCLE lesions because of the absence of telangiectases, hyperpigmentation, and of residual areas of inflammatory activity and scaling at the margins of the patch. During active phases, the hairs surrounding the alopecic area can be easily pulled out with a minimal traction, even if the underlying skin is apparently normal, while in CCLE this can happen only within the inflamed area.

Moreover, late CCLE lesions are generally completely devoid of hairs while in lichen planus sparse isolated hairs may still be observed within the area of alopecia.

Some peculiar histologic features allow for the differentiation from CCLE: the inflammatory infiltrate involves predominantly the hair follicles and the surrounding dermis in lichen planus, and in alopecic areas, a band-like fibrotic thickening of the papillary

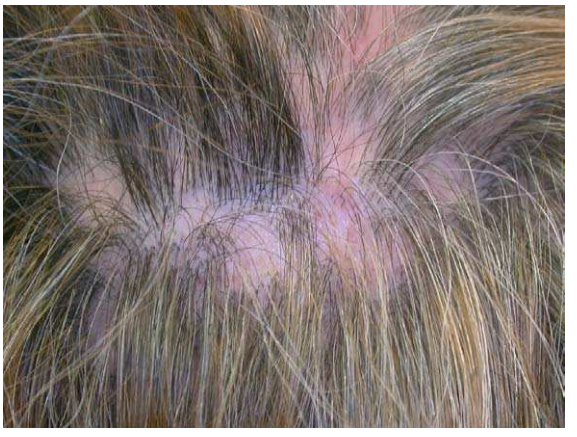


Figure 19. Lichen planopilaris: smooth areas of non-inflammatory cicatricial alopecia of the scalp.

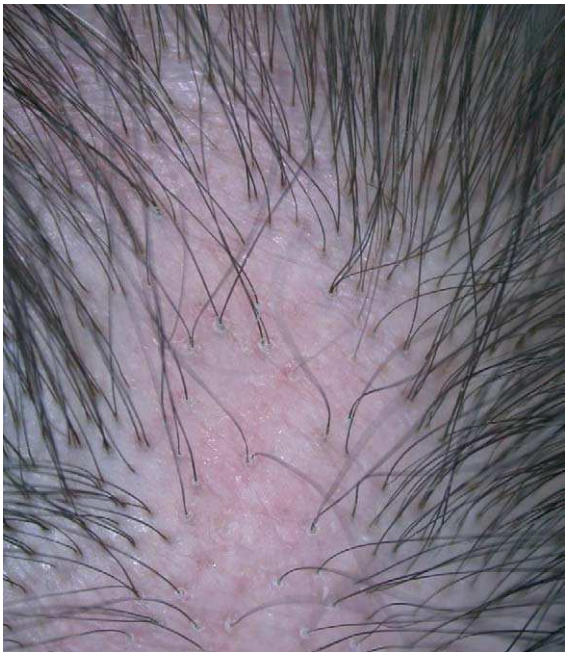


Figure 20. Lichen planopilaris: close-up view of early lesions showing slight erythema and follicular hyperkeratosis.

dermis may be observed, with fibrotic tracts at the sites of destroyed hair follicles (Annessi et al., 1999).

The lupus band test is positive in the majority of cases of late CCLE of the scalp (Fabbri et al., 2004) and therefore DIF is particularly helpful in the differentiation from alopecia of lichen planopilaris (see Section 4.4.5).

4.6.2. Lupus vulgaris vs late CCLE

Among the various forms of cutaneous tuberculosis, lupus vulgaris should be considered in differential diagnosis with late CCLE. It can be observed in patients with a considerable degree of immunity against mycobacteria, and runs a chronic, progressive course.

It begins as a small erythematous plaque of soft consistency, generally involving the head and neck, most frequently around the nose. The plaques slowly extend peripherally and may develop variable amounts of scaling and irregular scarring and ulcerations. At the edge of the plaque, small nodules may be observed, with a characteristic 'apple jelly' color; when gently probed, they result of a soft consistence, and the overlying skin can be easily torn-up.

In untreated cases, the involvement and the destruction of the cartilages of the nose and the ear may lead to deformity and mutilation, hence the term 'lupus'.

Differentiating clinical features are the development of ulcerations and crusts, which are rather unusual in CCLE, and the presence of the characteristic 'apple-jelly' nodules.

Histology shows the presence of epithelioid cell granulomas with Langhans giant cells and variable caseation, surrounded by an infiltrate of histiocytes and lymphocytes and variable amounts of fibrosis. Moreover, mycobacteria can be isolated from a biopsy specimen by culture or identified by polymerase chain reaction.

4.6.3. Other infectious granulomatous diseases vs late CCLE

Other rare infectious granulomatous diseases like cutaneous leishmanisis, late syphilis, and leprosy may display a lupoid-pattern and should be considered in differential diagnosis with late CCLE lesions.

Key points

- Lupus erythematosus is a complex disease with different cutaneous manifestations that can mimic a variety of diseases. During their clinical evolution, the cutaneous manifestations vary considerably, and therefore the diseases which should be considered in differential diagnosis are different, according to the stages of development.
- Sometimes clinical examination allows for the identification of peculiar differentiating features, which the clinicians must be aware of. When a clinical diagnosis is impossible or unreliable, histological examination of a cutaneous biopsy and further techniques like direct immunofluorescence, immunohistochemical studies, and the polymerase chain reaction are helpful.
- In other cases, differential diagnosis requires a more in-depth evaluation of the general conditions of the patients to assess the systemic nature of the disease and the identification of the autoantibodies.

References

Alteras, I., Sandbank, M., David, M., et al. 1988. 15-year survey of tinea faciei in the adult. Dermatologica 177, 65.
This interesting study focuses on the differential diagnosis of tinea faciei: 52 of the 100 patients included in the study group were at initial evaluation diagnosed as DLE.

Annessi, G., Lombardo, G., Gobello, T., et al. 1999. A clinicopathologic study of scarring alopecia due to lichen planus: a comparison with scarring alopecia in discoid lupus erythematosus and pseudopelade. Am. J. Dermatopathol. 21, 324.
This paper gives clear indications about the histologic features that can help in differential diagnosis between lichen planus and DLE of the scalp.

Bangert, J.L., Freeman, R.G., Sontheimer, R.D., et al. 1984. Subacute cutaneous lupus erythematosus and discoid lupus erythematosus. Comparative histopathologic findings. Arch. Dermatol. 120, 332.

Bigby, M. 2001. Rates of cutaneous reactions to drugs. Arch. Dermatol. 137, 765.
This paper analyzes nine studies that included primary data on cutaneous reaction rates to drugs. They were evaluated for their validity, magnitude, precision, and applicability.
The studies agree on the conclusions that antibiotics are the most common culprit of a cutaneous drug reaction, and morbilliform eruption and urticaria are the most commonly observed reaction patterns.

Bigby, M., Jick, S., Jick, H., et al. 1986. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 256, 3358.
This is an important study about the incidence of cutaneous adverse reactions to drugs, the different clinical patterns observed and the most frequent culprit drugs.

Callen, J.P., Klein, J. 1988. Subacute cutaneous lupus erythematosus. Clinical, serologic, immunogenetic, and therapeutic considerations in seventy-two patients. Arthritis Rheum. 31, 1007.

Cribier, B., Djeridi, N., Peltre, B., et al. 2001. A histologic and immunohistochemical study of chilblains. J. Am. Acad. Dermatol. 45, 924.
Chilblains have long been considered a trivial dermatologic problem. Nowadays they are less frequently observed and differential diagnosis may require the evaluation of a cutaneous biopsy. This paper provides a set of histologic features for differentiation from LE.

Crowson, A.N., Magro, C.M. 1997. Idiopathic perniosis and its mimics: a clinical and histological study of 38 cases. Hum. Pathol. 28, 478.

Fabbri, P., Amato, L., Chiarini, C., et al. 2004. Scarring alopecia in discoid lupus erythematosus: a clinical, histopathologic and immunopathologic study. Lupus 13, 455.

Ghirardello, A., Zampieri, S., Iaccarino, L., et al. 2005. Myositis specific and myositis associated autoantibodies in idiopathic inflammatory myopathies: a serologic study of 46 patients. Reumatismo 57, 22.

Gilchrest, B.A., Soter, N.A., Stoff, J.S., et al. 1981. The human sunburn reaction: histologic and biochemical studies. J. Am. Acad. Dermatol. 5, 411.

Gilliam, J.N., Sontheimer, R.D. 1981. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J. Am. Acad. Dermatol. 4, 471.

Jessner, M., Kanof, N.B. 1953. Lymphocytic infiltration of the skin. Arch. Dermatol. 68, 447.
This is the first description of benign lymphocytic infiltration of the skin.

Lever, W.F., Schaumburg-Lever, G. 1990. Histopathology of the Skin. J.B. Lippincott Company, Philadelphia, USA.

Massi, G. 1995. Atlante di Dermatopatologia. Masson, Milano, Italy.

Millard, L.G., Rowell, N.R. 1978. Chilblain lupus erythematosus (Hutchinson). Br. J. Dermatol. 98, 497.

Nieboer, C. 1987. The reliability of immunofluorescence and histopathology in the diagnosis of discoid lupus erythematosus and lichen planus. Br. J. Dermatol. 116, 189.
This is an old but an interesting paper showing that direct immunofluorescence is an important tool in the differentiation between DLE and lichen planus.

Nieboer, C., Tak-Diamand, Z., VanLeeuwen-Wallau, A.G. 1988. Dust-like particles: a specific direct immunofluorescence pattern in sub-acute cutaneous lupus erythematosus. Br. J. Dermatol. 118, 725.

Parodi, A., Caproni, M., Marzano, A.V., et al. 2002. Dermatomyositis in 132 patients with different clinical subtypes: cutaneous signs, constitutional symptoms and circulating antibodies. Acta Derm. Venereol. 82, 48.
This is a multicenter retrospective study aimed at defining the prevalence of the different clinical manifestations of dermatomyositis.

Poenitz, N., Dippel, E., Klemke C.D. 2003. Jessner's lymphocytic infiltration of the skin: a CD8+ polyclonal reactive skin condition. Dermatology 207, 276.
Differentiating Jessner's lymphocytic infiltration of the skin from other diseases like tumid lupus erythematosus is difficult: immunohistochemical evaluation might be a useful tool.

Sontheimer, R.D., Provost, T.T. 1995. Lupus erythematosus. In: R.D. Sontheimer, T.T. Provost (Eds.), Cutaneous Manifestations of Rheumatic Diseases. Williams & Wilkins, Baltimore, p. 36.

Sontheimer, R.D., Thomas, J.R., Gilliam, J.N. 1979. Subacute cutaneous lupus erythematosus. A cutaneous marker for a distinct lupus erythematosus subset. Arch. Dermatol. 115, 1409.
This paper is a milestone in the field of lupus erythematosus: SCLE is recognized as an individual entity that defines a subset of SLE patients with a milder disease.

Stratigos, A.J., Antoniou, C., Katsambas, A.D. 2002. Polymorphous light eruption. J. Eur. Acad. Dermatol. Venereol. 16, 193.

Tutrone, W.D., Spann, C.T., Scheinfeld, N., et al. 2003. Polymorphic light eruption. Dermatol. Ther. 16, 28.

Zirwas, M.J., Abell, E., Ruben, A., et al. 2003. Immunofluorescence findings in granuloma faciale: report of two cases. J. Cutan. Pathol. 30, 314.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 9

Dermatologic aspects of Antiphospholipid Antibody Syndrome

Camille Frances[a,*], Jean-Charles Piette[a], Ronald A. Asherson[b,c]

[a]*Department of Dermatology, Allergology, 4, rue de la Chine, Paris 75020, France*
[b]*Department of Autoimmune Diseases, Institut Clínic de Medicina i Dermatologia, Hospital, Clínic, Barcelona, Catalonia, Spain*
[c]*Division of Rheumatology, University of Cape Town Health Sciences Centre, Cape Town, and the Rosebank Clinic, Johannesburg, South Africa*

1. Introduction

The first definition of the *antiphospholipid antibody syndrome* (APS) described recurrent arterial and venous thrombosis and miscarriages in association with positive tests for the lupus anticoagulant, antibodies to negatively charged phospholipids (mainly cardiolipin) and to one of the bodies natural anticoagulants, a glycoprotein (B2GP1) (Harris et al., 1987). These remain the leading clinical features of this syndrome although its spectrum has broadened and has been expanded considerably over the last 15 years (Asherson and Cervera, 1992). Among these, a wide variety of dermatologic manifestations have been reported (Table 1) (Frances et al., 1996). Their clinical significance is highly variable and their management depends on their clinical aggressivity and the presence of other APS manifestations requiring therapeutic intervention.

2. Prevalence

The prevalence of dermatologic manifestations in APS is highly variable depending on the series. They have been reported to occur in 4–55% of patients (Asherson et al., 1989; Vianna et al., 1994; Cervera et al., 2002). In these previous series, there was no systematic examination of the skin. The dermatologic literature only contains reports of small series or isolated cases of these dermatological manifestations. In our series of 200 consecutive APS patients at the Hopital Pitie Salpetriere in Paris, the presence of dermatologic manifestations

Table 1
Dermatologic manifestations of the antiphospholipid syndrome

Livedo reticularis
Skin ulcerations
Post phlebitic skin ulcers
Livedoid vasculitis-like ulcers
Large ulceration ressembling pyoderma gangrenosum
Pseudo-vasculitis lesions
Purpura
Palmar or plantar erythema
Nodules
Pustules
Malignant atrophic papulosis-like lesions
Superficial skin necrosis
Digital gangrenes
Superficial phlebitis
Multiple subungual splinter hemorrhages
Anetoderma
Melanoderma

*Corresponding author.
Service de Dermatologie, Allergologie, Hopital Tenon 4, rue de la Chine 75020, France.
Tel.: 33156 01 64 62; Fax: 33156 01 64 58.
E-mail address: camille.frances@tnn.ap-hop-paris.fr (C. Frances).

DOI: 10.1016/S1571-5078(05)05009-9

was evaluated systematically by the attending physicians and confirmed by a senior dermatologist. Dermatologic manifestations were present in 49% of our patients, and a dermatologic manifestation was the presenting symptom in 30.5% of cases (Frances et al., 2005). Prevalence was similar in both the primary APS (45%) and systemic lupus erythematosus (SLE)-related APS (53%).

Livedo reticularis (LR) was the most frequently observed lesion, then, other lesions by order of frequency were ulcerations, digital gangrene, subungual splinter hemorrhages, superficial venous thrombosis, thrombocytopenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis and primary anetoderma (Frances et al., 2005).

3. Clinical manifestations

3.1. Livedo reticularis

LR is a mottled red or bluish discoloration of the skin with a netlike pattern. It is caused by stagnation of blood in dilated superficial capillaries and venules. Livedo may occur in normal subjects on cold exposure. The term *cutis marmorata* is given to this physiological livedo, which is very common, especially in children. It consists of a symmetrical, regular mottling localized mainly on the limbs.

LR is a skin manifestation of a large variety of pathological states.Different clinical features have to be considered in the differential diagnosis of a livedo including its localization, extension, possible infiltration, and regularity of the fishnet reticular pattern. This pattern may be either fine or large, or complete or irregular. In the last case, livedo is made of broken circular segments with branching extensions and is referred to as "*livedo racemosa*" in the European literature.

Although LR was considered for many years as a common manifestation of SLE (Golden, 1963), there was no description in the literature of the clinical features of LR associated with SLE. The association of LR with antiphospholipid (aPL) antibodies was first reported by Hughes (1983) in the Prosser White Oration and further confirmed by others soon after (Asherson et al., 1989; Mc Hugh et al., 1988; Weinstein et al., 1987). A high prevalence (62–81%) of anticardiolipin (aCL) antibodies was then observed in patients with both SLE and LR (Englert et al., 1989; Alarcon-Segovia et al., 1989). In one series, the relative odds of LR was found to be 23-fold greater in SLE patients with, as opposed to without, elevated aCL levels (Englert et al., 1989). In other reported series of patients, it was only 1.7 (Alarcon-Segovia et al., 1989). Conversely, the reported prevalence of LR in SLE-related APS ranges from 9 to 50% (Mc Hugh et al., 1988; Weinstein et al., 1987; Alarcon-Segovia et al., 1992). This discrepancy may reflect differences in patient population but also in the recognition of LR by physicians. In our experience, LR was the most frequently observed dermatologic manifestation (25.5%) with prevalence quite similar in primary APS (31%) and in SLE-related APS (20%) (Frances et al., 2005) .It was a *presenting manifestation in 17.5% of cases. In the European cohort of 1000 patients* (Cervera et al., 2002), its overall prevalence was found to be 24.1%, higher in patients with APS associated to SLE than in patients with primary APS (36% vs. 16%, $p<0.001$), and in females than in males (26% vs. 16%, $p<0.005$). LR was part of the presenting manifestations in 20.4% of cases (Cervera et al., 2002). LR is more noticeable and troublesome in women than in men. When associated with circumscribed skin necrosis, it is mainly localized on the lower limbs. When it is the sole cutaneous manifestation, its clinical features, although non-specific, is rather suggestive of APS. It is usually widespread, non-infiltrated, localized, not only on the limbs, but also on the trunk and/or buttocks (Fig. 1). In few patients, it may be initially restricted to the hands or feet (Grob et al., 1991). The *fishnet reticular pattern* is mainly irregular (livedo racemosa). On the trunk, the fishnet of the livedo is usually fine in contrast to the large fishnet observed in aPL negative patients with Sneddon's syndrome (Francès et al., 1999). This fine pattern may explain why it may be hidden by hair, especially in men.

3.2. Skin ulcerations

Skin ulcerations have been reported since 1963 (Bowie et al., 1963) in association with lupus

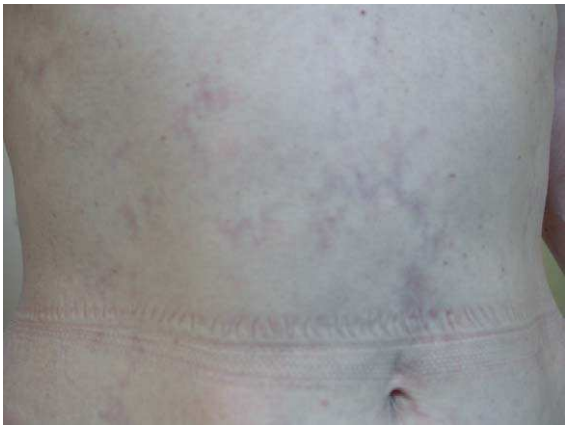


Figure 1. Livedo reticularis in SLE-related APS.

anticoagulant (LAC). A strong association between leg ulcers and aCL has been reported in SLE, the prevalence of aCL reaching 87% in such patients (Alarcon-Segovia et al., 1989). They were observed in 5.5% of the 1000 European patients with APS, as a presenting manifestation in 3.9% (Cervera et al., 2002). In our series of 100 patients with primary APS and 100 patients of SLE-related APS, *ulcers were detected in 8% of cases;* they were the *presenting feature of APS in 4%* of cases without difference of prevalence in both groups (Francès et al., 2005). However, they were not reported in some series (Vianna et al., 1994). In a series of 115 consecutive dermatology patients hospitalized for leg ulcers, aCL could be detected in 43% of cases (Marechal et al., 2000).

Different types of skin ulcerations may be encountered.

Post-phlebitic ulcers were observed in patients with recurrent phlebitis of the leg after many years of follow-up in 4.5% of 200 APS patients (Francès et al., 2005). Usually, a post-phlebitic syndrome was also present characterized by edema and cutaneous erythema of the lower limbs accompanied by inflammatory changes.

In contrast, ulcerations resulting from *circumscribed skin necrosis* are frequently a presenting feature of APS, occurring in 3.5% of cases (Francès et al., 2005). They consist of painful small (0.5–3 cm in diameter) ulcers with oval, star-like, or irregular borders surrounded by a purplish-brown halo and recurrent purpura (Fig. 2). They develop around the ankles, on the feet and in some cases on the calves. They are often preceded by necrotizing purpura and associated with LR of the legs. After healing, the ulcers leave white atrophic scars with a dark pigmented halo. In a series of 21 consecutive patients with "*atrophie blanche*"*-like ulcers* or *livedoid vasculitis*, aPL antibodies were detected in four patients (19%) of whom one had SLE-related APS and three primary APS (Tran et al., 2001). Other prothrombotic factors may also be present (Combemale et al., 2002).

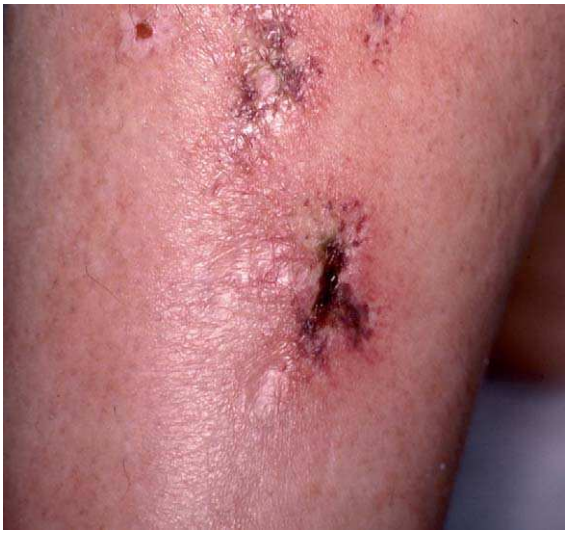


Figure 2. Typical pigmented and atrophic scars of livedoid vasculitis-like ulcers with purpuric necrotic lesions in primary APS.

About 10 cases of large *ulcers resembling pyoderma gangrenosum* have been reported in the literature in association with primary or SLE-related APS (Schmid et al., 1998; Chacek et al., 1998).

Contrary to pyoderma gangrenosum, these ulcers did not present undermined borders and were only found on the legs. We have not encountered these types of ulcerations.

3.3. Digital gangrene

Digital gangrene (Fig. 3) was present in 3.3%–7.5% of APS cases and the presenting feature in 2.5% of one series (Cervera et al., 2002; Francès et al.,

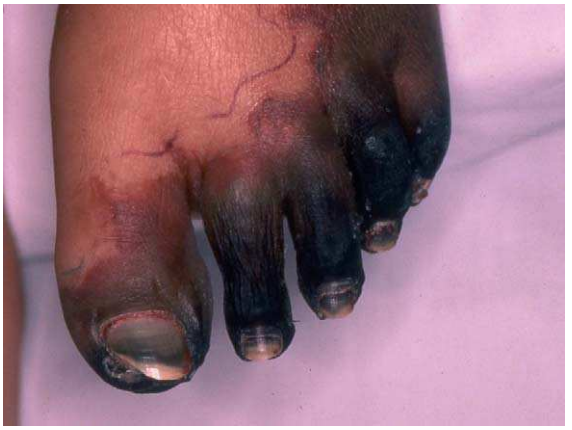


Figure 3. Digital gangrene.

2005). Gangrene may be preceded by *distal erythema* (Asherson et al., 1986), *cyanotic macules* (Grob et al., 1989) or *pseudo-cellulitis* (Jindal et al., 1983). Associated vascular risk factors such as smoking, oral contraceptives, or hypertension were present in some cases (Asherson et al., 1989; Jindal et al., 1983). Angiography visualized occlusion, or sometimes stenosis of large or medium-sized vessels.

3.4. Multiple subungual splinter hemorrhages

Subungual splinter hemorrhages appear as tiny linear longitudinally oriented, reddish-brown to black, distal subungual lesions that fail to blanch under pressure. They may result from nail dystrophy. When the nail shape is normal, subungual splinter hemorrhages were initially recognized as an important sign of *subacute bacterial endocarditis*. In fact they can be observed in various other conditions, such as Trichinella spiralis infection or hypereosinophilic syndrome, and even in healthy people. When multiple hemorrhages are seen on different fingers, the existence of an underlying disease is probable (Fig. 4). In 1966, they were reported in SLE prior to research on the antiphospholipid antibodies (Fraga and Mintz, 1966). *Multiple splinter hemorrhages* may be observed in APS regardless of the presence of SLE (Asherson, 1990; Ames et al., 1992; Frances et al., 1994; Mujic et al., 1995). Within the APS, their sudden onset on multiple fingers is frequently concomitant to other worrying thrombotic events, therefore leading to a probable underestimation, as illustrated by the 0.7% prevalence observed in 1000 APS patients (Cervera et al., 2002). A prevalence of 4–5% is likely as in other series (Mujic et al., 1995; Francès et al., 2005). Although their pathogenesis is not fully elucidated due to the rarity of histological examinations performed on this peculiar area, a thrombotic or an embolic process is possible.

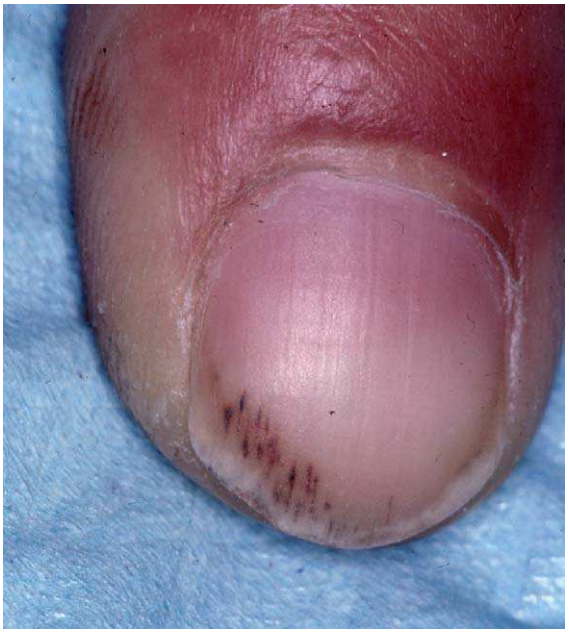


Figure 4. Multiple subungual splinter hemorrhages concomitant to pulmonary embolism in APS.

3.5. Superficial venous thrombosis

Superficial venous thromboses were present in 11.7% of the 1000 European patients with APS (Cervera et al., 2002), and in 5% of another series of 200 APS patients (Francès et al., 2005). They have been included in the classification criteria for definite APS (Table 2) (Wilson et al., 2001). The diagnosis of *superficial thrombophlebitis* usually is

clinically evident, but may sometimes require echo-Doppler examination or skin biopsy. In APS, they are mostly localized on the limbs. It should be kept in mind that repeated episodes of superficial thrombophlebitis, mainly affecting the trunk, may also reveal an occult cancer, at times accompanied by aPL production (Bessis et al., 1995).

3.6. Thrombocytopenic purpura

Purpura due to a platelet deficiency usually occurs with a count below 20×10^9/l. Bleeding occurs into the skin with crops of petechiae localized on the trunk or on the limbs. Mucosa bleeding is frequently associated. It is a rare manifestation of APS, not reported in many series (Cervera et al., 2002; Vianna et al., 1994), observed in 3.5% of cases in our experience (Francès et al., 2005). It may be the presenting feature of APS (1.5%).

3.7. Pseudovasculitis manifestations

These pseudovasculitic lesions may mimic cutaneous vasculitis and may be misdiagnosed if skin biopsies are not performed, especially in patients with SLE. They are the presenting manifestations in about 3% of cases and present during the course of the disease in 3–4% (Cervera et al., 2002; Francès et al., 2005). Different skin lesions have been reported i.e. purpura (Fig. 5a), small erythematous or cyanotic lesions on hands and feet, papules or nodules (Fig. 5b) of the limbs, ears, neck or thighs (Farrant et al., 1989; Grob et al., 1991; Asherson et al., 1992; Renfro et al., 1992; Ishikawa et al., 1999; Francès et al., 2005). The purpura is frequently necrotic and it may precede the livedoid vasculitis-like ulcers by several years. (Grob and Bonerandi, 1989; Francès et al., 2005).

Lesions *similar to those of malignant atrophic papulosis* may also be included in pseudovasculitis manifestations. They consist of multiple pink, gray, or yellow papules that become umbilicated and develop a porcelain-white central scar with a telangiectatic border (Fig. 5c). They have been reported in SLE-related APS and primary APS (Dublin and Stawiski, 1974; Black and Hudson, 1976; Doutre et al., 1987; Burton, 1988). Exceptionally, aPL were detected in patients with malignant atrophic papulosis (Farrell et al., 1988;

Table 2
Preliminary criteria for the classification of antiphospholipid syndrome according to Wilson et al. 1998

Clinical criteria

Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

Pregnancy morbidity

One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe pre-eclampsia or eclampsia, or severe placental insufficiency, or

Three more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic, or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titre, on two or more occasions, at least 6 weeks apart, measured by a standard enzyme linked immunosorbent assay for ß2-glycoprotein 1-dependent anticardiolipin antibodies.

Lupus anticoagulant present in plasma on two or more occasions at least 6 weeks apart, detected according to the guide lines of the International Society on Thrombosis and Hemostasis.

Definite APS is considered to be present if at least one of the clinical and one of the laboratory criteria are met.

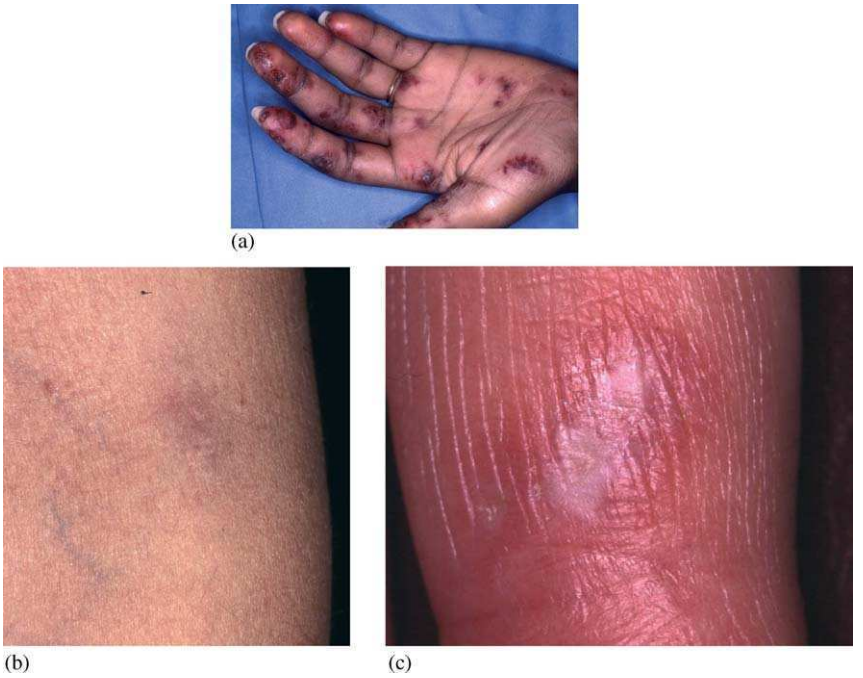


Figure 5. Pseudovasculitis manifestations (a) necrotic purpura in SLE-related APS; (b) nodule of the upper limb; (c) malignant atrophic papulosis-like lesion.

Assier et al., 1995). In our mind, APS and malignant atrophic papulosis should be regarded as distinct conditions (Assier et al., 1995).

3.8. Extensive cutaneous necrosis

Clinical features of *widespread superficial cutaneous necrosis* within APS (Fig. 6) are similar to those observed in other thrombophilic states such as protein C or protein S deficiencies, monoclonal cryoglobulinemia or cryofibrinogenemia. In some cases, these biological abnormalities, present in association with aPL, may contribute to the thrombotic process (Moreb and Kitchens, 1989; Dessein et al., 1989). APS may be primary or associated with other disorders such as SLE, rheumatoid arthritis, mycosis fungoides, or human immunodeficiency virus infection (Dodd et al., 1985; Francès et al., 1989; O' Neill et al., 1990; Creamer et al., 2000b). Widespread cutaneous necrosis occurs in about 2% of APS patients (Cervera et al., 2002; Francès et al., 2005). The onset is often acute with extensive painful purpura followed by a black necrotic plaque with an active purpuric border and bullous lesions. The necrosis is usually localized on the limbs, head (cheeks, nose, and ears), or buttocks.

3.9. Primary anetoderma

Anetoderma is a rare disorder characterized clinically by a circumscribed area of slack skin with macular depressions or outpouchings of skin. Skin lesions are numerous (>10), localized on the half upper part of chest and arms (Fig. 7). Histologically there is a *loss of dermal elastic tissue* (Disdier et al., 1994). Anetoderma may be primary or secondary to various dermatoses. When primary, it is frequently observed in patients with autoimmune diseases and especially related to antiphospholipid antibodies (Francès and Piette, 1997; Romani et al., 2000). A review of literature disclosed more than 20 such patients with aPL (Romani et al., 2000). Among nine patients with primary anetoderma referred to

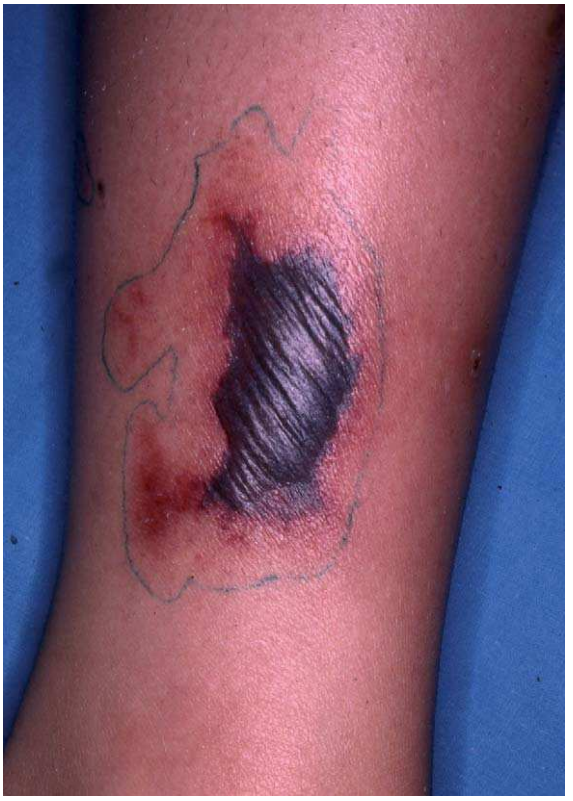


Figure 6. Widespread superficial skin necrosis in SLE-related APS.

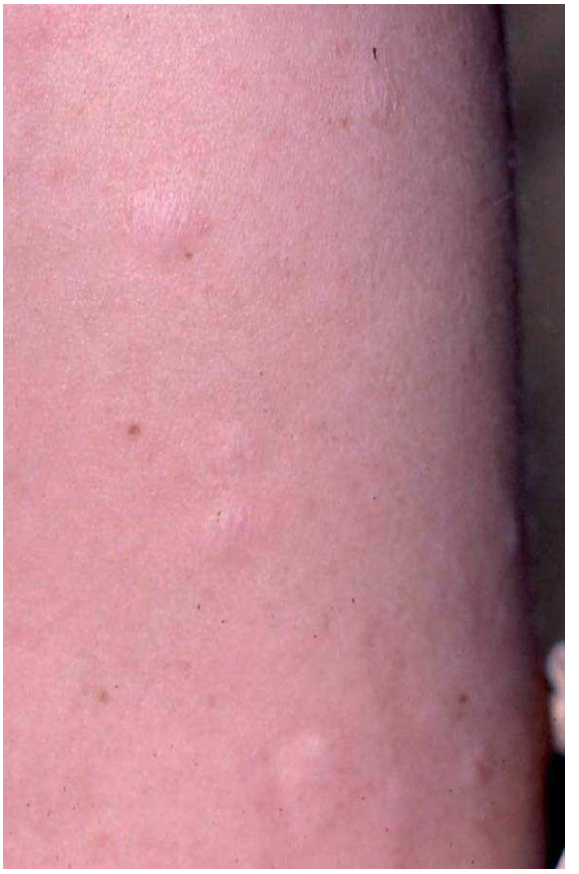


Figure 7. Diffuse anetoderma in SLE-related APS.

our Connective Tissue Disorders Clinic, aPL was detected in eight, of whom four had APS (Sparsa et al., 2003).

3.10. Melanoderma

Adrenal failure secondary to hemorrhagic infarction of the adrenal glands is usually a critical manifestation of APS. However, in about 10% of patients, it may manifest itself as melanoderma of recent onset (Asherson and Hughes, 1989). This rare manifestation was not noticed in the large series of the literature.

4. Histologic features

Non-inflammatory thrombosis in small arteries and/or veins throughout the dermis and the subcutaneous fat tissue are the main histological findings (Alegre and Winkelmann, 1988; Smith et al., 1990). Endarteritis obliterans, characterized by a narrowing of the vascular lumen with endothelial cell proliferation and fibro-hyalinization of the vessel wall, is sometimes associated with or may even be the sole pathological finding. Similarly, capillary proliferation, endarteritis obliterans may be induced by the thrombotic process (Alegre and Winkelmann, 1988). A lymphocytic or lymphoplasmocytic infiltrate is often encountered without any evidence of vasculitis or infiltration of the vessel walls. However, in some rare cases (Alegre and Winkelmann, 1988; Rocca et al., 1994), manifestations of vasculitis such as vessel wall necrosis and leukocytoclastic infiltration may be present. According to Lie (1994), the vasculitis is probably *coincidental*, especially in patients with SLE, and not causally related to APS. One of our patients

with SLE-related APS had simultaneous on the legs onset of palpable purpura related to cutaneous leukocytoclastic vasculitis and widespread cutaneous necrosis related to dermal vessels thrombosis.

The pathological features observed in APS are slighty different according to the clinical manifestations.

Thrombosis is rarely observed from biopsies of LR except in the catastrophic APS (Ingram et al., 1987). In our experience, no obvious pathological change has been detected despite careful examination of numerous serial sections of the two livedo biopsy specimens from 19 out of 26 (73%) patients. Vascular abnormalities were noted from one of the two livedo biopsy specimens in the 7 other patients (4 primary APS and 3 SLE-related APS). Abnormal specimens were obtained from the center of the livedo (4 cases) or from the violaceous fishnet (3 cases). Vascular changes involved one small to medium-sized artery with a distinct lamina elastica interna—localized at the dermis-subcutis boundary or in the subcutis. In three cases, arteriolar lesions consisted of a partial or complete occlusion of the arterial lumen by a cellular plug with numerous mononuclear cells. In three cases, arterioles were shrunken and occluded by a fibrotic, acellular plug. The lamina elastica interna was deteriorated. In only one case of primary APS, the thrombosis of an arteriole of the subcutis was evident (Francès et al., 2005). We no longer consider skin biopsies of LR to be useful in patients with APS and consequently no longer perform them in our Institution. Vascular proliferation (Nahass, 1997) or endarteritis obliterans of arterioles (Grattan et al., 1989) have been previously reported in some cases. These features do not exclude patchy previous thrombosis. An interaction of aPL with endothelium or other cellular elements of the vessels in a way that alters function and induces vasoconstriction is another possible mechanism of LR (Piette, 2000). When livedo is associated with other APS-related skin lesions, biopsies should be performed on these other lesions to show thrombosis.

In biopsy specimens from the edge of livedoid vasculitis-like ulcerations, skin thrombosis is either obvious or masked by a frank capillary proliferation with extravasated red blood cells and sparse inflammatory cell infiltrates (Alegre and Winkelmann, 1988). Nonspecific granulomatous tissue and epidermal hyperplasia have been reported in large ulcers resembling pyoderma gangrenosum (Schmid et al., 1998). In pseudovasculitic lesions, thrombosis of skin vessels is usually obvious on biopsies, even when a lymphocytic or lymphoplasmocytic infiltrate is encountered without evidence of true vasculitis (Lie, 1994). Histopathology from early purpuric lesions of widespread cutaneous necrosis shows diffuse thrombosis of skin vessels. In one case, both focal thrombosis and a reactive angioendotheliomatosis contributed to the angio-occlusive pathology (Creamer et al., 2000a).

The histological features of anetoderma associated with APS are not usually different from those of other cases of primary anetoderma (Romani et al., 2000; Sparsa et al., 2003). In rare cases, thrombosis of dermal vessels was however reported (Stephansson et al., 1991; Stephansson and Niemi, 1995). In other cases, biopsy is probably too late to show thrombosis. Hypoxia-reoxygenation may enhance expressions of some metalloproteinases in various tissues leading to the destruction of elastic tissue (Sparsa et al., 2003).

5. Relationship between skin lesions and other manifestations of aps

For more than 15 years, LR in SLE was found to be strongly associated with cerebrovascular events (Weinstein et al., 1987; Englert et al., 1989). In 1965, this association, i.e. LR and cerebrovascular events, had been first documented in otherwise healthy people (Sneddon, 1965) and was further individualized as *Sneddon's syndrome*. A relationship between APS and Sneddon's syndrome was first documented by Hughes (1984) and confirmed later on (Levine et al., 1988; Asherson and Khamashta, 1990; Kalashnikova et al., 1994). The prevalence of aPL in Sneddon's syndrome has been reported to range from 0 to 85% depending upon the series (Zelger et al., 1993; Kalashnikova et al., 1994). In our experience, it was 41% (Frances et al., 1999). The comparison of aPL-negative vs. aPL-positive patients devoid of any manifestation

suggestive of SLE showed significant differences (Frances et al., 1999). The fishnet of the livedo was clearly larger in aPL negative patients, who therefore frequently had obvious and sometimes troublesome skin involvement. This fact might explain the low prevalence of aPL in dermatological series of Sneddon's syndrome (Zelger et al., 1993). Seizures were more frequent in aPL-positive (37%) than in aPL-negative patients (11%, $p<0.05$). Onset of livedo occurred before neurologic ischemic events in a majority of patients, with a mean duration of 14 years (Frances et al., 1999).

In our recent study of 200 APS patients, we confirmed a significant association between *LR and cerebral or ocular ischemic arterial events* (OR: 10.8, IC 95% 5.2–22.5). A significant association was also demonstrated between *LR and seizures* (OR: 6.5, IC: 2.6–16), all arterial events (OR: 6, IC 95% 2.9–12.6), *heart valve abnormalities* detected on echocardiography (OR: 7.3, IC 95% 3.6–14.7), and *arterial systemic hypertension* ($\geq$160–90 mm Hg) (OR: 2.9, IC 95% 1.5–5.7). Conversely, LR was less frequently observed in patients with only venous thrombosis (OR: 0.22, IC 95% 0.1–0.5).

LR was observed in 7 of 16 patients who developed *intrarenal* vascular lesions associated with primary APS (Nochy et al., 1999). Finally, livedo appears as a good marker of the "arterial/arteriolar APS subset" currently under delineation (Table 3).

Livedoid vasculitis-like ulcers are frequently the sole manifestation of APS. Post phlebitic ulcers are associated with APS venous subset.

The onset of multiple subungual splinter hemorrhages is frequently coincidental to worrying thrombotic events of various sites (brain, digits, skin, and adrenal glands.) (Francès et al., 1994, Mujic et al., 1995).

The "catastrophic" APS (Asherson's Syndrome) (Piette et al., 2003), characterized by widespread vascular occlusions involving multiple organs simultaneously, also includes skin lesions in half of the patients (Asherson, 1992; Ruffati et al., 1994; Asherson et al., 1998, 2001). When present, they mainly consist of LR (57%), ischemic ulcers (28%) and digital gangrene (21%). Purpura, large cutaneous necrosis, splinter hemorrhages, digital ischemia, acrocyanosis, and palmar erythema, have also been reported in this condition (Asherson et al., 1998, 2001).

Table 3
Main clinical features of the "arterial/arteriolar APS subset"

Livedo
Strokes/TIA
Seizures
Heart valve lesions
Intrarenal thrombosis
Systemic hypertension

6. Detection of antiphospholipid antibodies (aPL) in dermatology

6.1. Skin manifestations

Theoretically, all the skin manifestations secondary to a non-inflammatory thrombosis whatever the size of cutaneous involved vessels should lead clinicians to look for aPL as for other causes of thrombophilic states. The presence of classical risk factors for thrombosis such as pregnancy, postpartum, smoking, or use of estrogen-containing oral contraceptive pill should not exclude this research as these classical risk factors can act as cofactors for thrombosis in APS (Asherson et al., 1989). Dermatologic manifestations with skin vessels thrombosis were included as a clinical criterion for classification of definite APS (Table 2) (Wilson et al., 1999).

However, others manifestations without obvious histological thrombosis should also lead the physicians to look for aPL, specially fine, widespread, irregular LR, but also multiple subungual splinter hemorrhages, and primary anetoderma. Due to the high prevalence of LR in APS, we think the clinical aspect of a widespread, irregular, nonpalpable LR might be included in future "minor criteria" for APS (Wilson et al., 2001).

6.2. Tests for detection of aPL

Although new tests have become available, determination of lupus anticoagulant LAC and measurement of anticardiolipin antibodies aCL by

enzyme-linked immunosorbent assay (ELISA) are still the first choice to be used in the diagnosis of APS (Table 2). The first aCL test was developed in 1983 and subsequently standardized (Pierangeli et al., 1998). Both IgG and IgM isotypes are usually determined. IgG aCL is however the most relevant isotype as isolated IgM aCL are present in only 5% of the cases. International guidelines and criteria for the detection of LA have been established (Brandt et al., 1995). The basic criteria for the presence of LA are as follows: (1) Prolongation of a phospholipid-dependent coagulation test. (2) Evidence of an inhibitor demonstrated by mixing studies. (3) Confirmation of the phospholipid-dependent nature of inhibitor.

Anti-ß2 glycoprotein I (ß2GPI) assays have several advantages compared to conventional aCL assays. The plasma protein ß2GPI is essential in controlling the assembly of endothelial cell surface procoagulant complexes responsible for enzymatic acceleration of clotting, and ß2GPI is regarded as the target of most of autoimmune aPL. The presence of anti-ß2GPI antibodies concomitantly to aCL suggests these aCL are pathogenic. In some studies, a strong association between IgG anti-ß2GPI antibodies and thrombosis was found, whereas in others, this association could not be demonstrated (Tubach et al., 2000; Reber and de Moerloose, 2004). It has been shown that in up to 10% of patients, IgG anti-ß2GPI antibodies are the sole antibodies present and therefore the diagnosis would be missed in these patients. In addition, some studies suggest that the severity of disease is dependent on the number of positive tests and on their titers (Reber and de Moerloose, 2004). However, the heterogeneity in the antigenic reactivity pattern of IgG anti-ß2GPI antibodies represents a crucial factor of variability in tests results and underlines the difficulty of getting standardization (Sanmarco et al., 2005). This standardization is required to ensure better comparability between the studies. The lack of standardization is still a serious drawback to the clinical evaluation of anti-ß2GPI measurements.

The existence of patients who seem to fit the clinical profile of APS but remain negative for all the preceding assays has led to develop newer tests. At present time, detection of antibodies directed to phosphatidylethanolamine or to a mixture of phospholipids are of possible interest (Balada et al., 2001). Other tests such as ELISA for prothrombin or annexin V antibodies are still under development and will require extensive evaluation (Galli and Barbui, 2005). In our experience very few APS patients only display chronic biologically false positive serology for syphilis.

Whatever the tests, transient aPL are sometimes encountered in the absence of thrombosis, particularly after diverse infections. It is therefore important to demonstrate the persistence of positivity, by further testing after at least 6 weeks. Infections may be associated with APS. In a recent analysis of 100 cases (Cervera et al., 2004), skin involvement was reported in 36 patients; 16 had LR, 9 had *purpura fulminans*, 8 had skin ulcers, and 3 had digital necrosis.

7. Treatment

Treatment of patients with skin lesions must be considered according to both the differing dermatological manifestations and the presenting clinical situation. Two questions should be answered:

(a) How to treat dermatological manifestations?
(b) Is any prophylactic long-term treatment required in such patients?

In the absence of randomized controlled trials, therapy of dermatological lesions remains empirical.

Widespread cutaneous necrosis and/or digital gangrene are major thrombotic events, which require full anticoagulation with heparin. If extension of these skin lesions persists despite anticoagulation, then other treatments may be added such as iloprost, intravenous tissue plasminogen activator, and/or plasma exchanges as they have been reported to be successful in isolated cases (Frances et al., 1989; Zahavi et al., 1993; Srinivasan et al., 2001). When plasma exchanges are used, steroids and/or cytotoxics should probably be added to prevent "aPL rebound" (Piette et al., 1995).

When these lesions appear concomitantly with multiple vascular occlusions (catastrophic APS/Asherson's Syndrome), the rationale of treatment is to control thrombosis by anticoagulation and to

prevent the circulation and the production of aPL and of mediators (such as cytokines) which generate the hypercoagulable state. So treatment may consist of *anticoagulation, immunosuppressives, such as corticosteroids or cytotoxics, plus repeated plasma exchanges, and high dose intravenous immunoglobulins*. The beneficial effect of this combination has been reported in a retrospective study. Indeed, patients treated with anticoagulation in addition to steroids plus a therapy which can achieve a prompt reduction of aPL titers (either plasma exchange or intravenous immunoglobulins) had the highest survival rate of almost 70% (Asherson et al., 1998). Favorable outcome has been recently reported in other patients treated with plasma exchanges (Neuwelt et al., 1997; Flamholz et al., 1999). Local treatment consists of the removal of necrotic eschars and local antiseptic therapy to reduce the risk of secondary infection.

No treatment has been proven to be effective for livedo reticularis, which in our experience may extend or appear despite anticoagulant or antiplatelet therapy. Livedo reticularis is less visible on sun-tanned skin; but sun exposure is not recommended in SLE-related APS, and we think it should be proposed only to aPL-negative patients desiring to mask a troublesome livedo.

In isolated other skin lesions such as livedoid vasculitis-like ulcers or pseudo-vasculitis lesions, low-dose –aspirin, and dipyridamole has been reported as effective in some patients (Grob and Bonerandi, 1989; Asherson et al., 1992). If these lesions recur or extend despite anti-platelet agents, anticoagulation is usually prescribed (Francès and Barete, 2004). Fibrinolytic agents and sildenafil have been successful in cases of recalcitrant nonhealing cutaneous ulcers (Gertner and Lie, 1994; Gertner, 2003).

Prevention of recurrence of skin lesions depends not only on their severity, but also on the other features of the disease. There are no data concerning the frequency of recurrence of skin vessel thrombosis. In the literature, only one patient had two separate episodes of widespread cutaneous necrosis; each was precipitated by surgical manipulation of the urinary tract in the presence of urinary tract infection (Del Castillo et al., 1997). As widespread cutaneous necrosis and/or digital gangrene are considered to be major thrombotic events, the current recommendations for the treatment of such cases is *long-term warfarin* in fact the same as in patients with large vessel thrombosis. The optimal intensity of oral anticoagulation for the prevention of these recurrent large vessel thrombosis is still controversial (Finazzi et al., 2005).

Prevention of recurrences of isolated "minor dermatological manifestations" (i.e. livedoid vasculitis-like ulcers, pseudo-vasculitis skin lesions, and superficial thrombophlebitis) is unclear. *Antiplatelet therapy* such as low-dose aspirin (75 mg/day) is usually chosen as first-line treatment. *Hydroxychloroquine* has also well-documented antiplatelet effects and has been shown to reduce the risk of thrombosis in both SLE patients and animal models of APS (Petri, 1996; Edwards et al., 1997). However, in our experience, these treatments are rarely effective and long-term anticoagulation is frequently required (Francès and Barete, 2004).

Of major concern is the problem of patients presenting with *isolated livedo reticularis* and aPL. Some of them are prone to develop *ischemic cerebral events* over years, as illustrated by our abovementioned experience of Sneddon's syndrome (Frances et al., 1999). Low-dose aspirin is frequently prescribed in such patients for prevention of strokes, but its effectiveness is doubtful. These patients require careful investigation in order to detect possible latent APS-related organ involvement such as silent brain infarcts on MRI, heart valve lesion, or even APS nephropathy (in cases where there is systemic hypertension and/or abnormal renal function tests). The results of these investigations may prompt the institution of warfarin therapy, eg. when a silent brain infarct is found, or lead to its empirical use (Khamashta, 2000).

The use of *Clopidrogel,* a potent anti-platelet agent, should also be evaluated in such circumstances. Whatever the type of skin involvement, it is important to remove or reduce other risk factors for thrombosis or arterial wall lesions (Piette and Piette, 1996). Among others, patients are advised to stop smoking and women are counseled against the use of estrogen-containing pills. The potential benefit of statins (Meroni et al., 2001) or angiotensin-conversing enzyme inhibitors (Progress, 2001) needs to be carefully determined.

8. Conclusions

The dermatological manifestations of the APS may be the presenting feature of the APS syndrome. They are extremely diverse and heterogeneous, ranging from minor signs to life-threatening conditions such as widespread cutaneous necrosis. LR is strongly associated with a ''subset'' of the APS. More scientific data are urgently required to determine the optimum management of these patients, who might certainly benefit from recently developed newer antithrombotic agents.

Key points

- Dermatologic manifestations are present in near half patients with antiphospholipid syndrome (APS). They are the presenting manifestation in about one-third of the patient.
- Livedo reticularis (LR) is the most frequent observed dermatologic lesion. Its clinical features, although non-specific, is rather suggestive of APS. It is usually fine, widespread, non-infiltrated, localized not only on the limbs but also on the trunk and/or buttock. Biopsy of LR is of poor interest. LR is strongly associated to the arterial subset of APS (arterial events, valvulopathy, and systemic arterial hypertension).
- Skin ulcerations may be secondary to venous thrombosis or to circumscribed skin necrosis. In the last case, thrombosis of dermal vessels is sometimes masked by a frank capillary proliferation. Pyoderma gangrenosum like ulcers are less frequent. Ischemic ulcers, widespread cutaneous necrosis, and digital gangrenes may be the sole manifestation of APS or associated with widespread vascular occlusions in the ''catastrophic'' APS.
- Scientific data are required to determine the optimum management of these patients, which might benefit from recently developed antithrombotic agents.

References

Alarcon-Segovia, D., Delezé, M., Oria, C.V., et al. 1989. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. Medicine 68, 353.

Alarcon-Segovia, D., Perez-Vazquez, M.E., Villa, A.R., et al. 1992. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. Semin. Arthritis Rheum. 21, 275.

Alegre, V.A., Winkelmann, R.K. 1988. Histopathologic and immunofluorescence study of skin lesions associated with circulating anticoagulant. J. Am. Acad. Dermatol. 19, 117.

Ames, D.E., Asherson, R.A., Ayres, B., et al. 1992. Bilateral adrenal infarction, hypoadrenalism and splinter haemorrhages in the primary antiphospholipid syndrome. Br. J. Rheumatol. 31, 117.

Asherson, R.A. 1990. Subungual splinter haemorrhages: a new sign of antiphospholipid coagulopathy?. Ann. Rheum. Dis. 49, 268.

Asherson, R.A. 1992. The catastrophic antiphospholipid syndrome. J. Rheumatol. 19, 508.

Asherson, R.A., Cervera, R. 1992. The antiphospholipid syndrome: a syndrome in evolution. Ann. Rheum. Dis. 51, 147.

Asherson, R.A., Cervera, R., Piette, J.C., et al. 1998. Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. Medicine (Baltimore) 77, 195.

Asherson, R.A., Cervera, R., Piette, J.C., et al. 2001. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 80, 355. Largest series on catastrophic APS.

Asherson, R.A., Derksen, R.H.W.M., Harris, E.N., et al. 1986. Large vessel occlusion and gangrene in systemic lupus erythematosus and lupus-like disease: a report of 6 cases. J. Rheumatol. 13, 740.

Asherson, R.A., Hughes, G.R.V. 1989. Recurrent deep vein thrombosis and Addison's disease in primary antiphospholipid syndrome. J. Rheumatol. 16, 378.

Asherson, R.A., Jacobelli, S., Rosenberg, H., et al. 1992. Skin nodules and macules resembling vasculitis in the antiphospholipid syndrome. Clin. Exp. Dermatol. 17, 266.

Asherson, R.A., Khamashta, M.A. 1990. Sneddon's syndrome and the primary antiphospholipid syndrome. Br. J. Dermatol. 122, 115.

Asherson, R.A., Khamashta, M.A., Ordi-Ros, J., et al. 1989. The primary antiphospholipid syndrome: major clinical and pathological features. Medicine 68, 366.

Asherson, R.A., Mayou, S.C., Merry, P., et al. 1989. The spectrum of livedo reticularis and anticardiolipin antibodies. Br. J. Dermatol. 120, 215.

Assier, H., Chosidow, O., Piette, J.C., et al. 1995. Absence of antiphospholipid antibodies and anti-endothelial cell antibodies in malignant atrophic papulosis. J. Am. Acad. Dermatol. 33, 831.

Balada, E., Ordi-Ros, J., Paredes, F., et al. 2001. Antiphosphatidylethanolamine antibodies contribute to the diagnosis of antiphospholipid syndrome in patients with

systemic lupus erythematosus. Scand. J. Rheumatol. 30, 235.

Bessis, D., Sotto, A., Viard, J.P., et al. 1995. Trousseau's syndrome with nonbacterial thrombotic endocarditis: pathogenic role of antiphospholipid syndrome. Am. J. Med. 98, 511.

Black, M.M., Hudson, P.M. 1976. Atrophie blanche lesions closely resembling malignant atrophic papulosis (Degos' disease) in systemic lupus erythematosus. Br. J. Dermatol. 95, 649.

Bowie, E.J.W., Thompson, J.H., Pascuzzi, C.A., et al. 1963. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. J. Lab. Clin. Med. 62, 416.

Brandt, J.T., Triplett, D.A., Alving, B., et al. 1995. Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the subcommittee for the standardization of lupus anticoagulants. Thromb. Haemost. 74, 1185.

Burton, J.L. 1988. Livedo reticularis, porcelain-white scars and cerebral thrombosis. Lancet I, 1263.

Cervera, R., Asherson, R.A., Acevedo, M.L., et al. 2004. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann. Rheum. Dis. 63, 1312.

Cervera, R., Piette, J.C., Font, J., et al. 2002. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 46, 1019.

Largest European series on APS

Chacek, S., Mac-Gregor-Gooch, J., Halabe-Cherem, J., et al. 1998. Pyoderma gangrenosum and extensive caval thrombosis associated with antiphospholipid syndrome—a case report. Angiology 49, 157.

Combemale, P., Amiral, J., Estival, J.L., et al. 2002. Cutaneous necrosis revealing the coexistence of an antiphospholipid syndrome with acquired protein S deficiency, factor V Leiden and hyperhomocysteinemia. Eur. J. Dermatol. 12, 278.

Creamer, D., Black, M.M., Calonje, E. 2000a. Reactive angioendotheliomatosis in association with the antiphospholipid syndrome. J. Am. Acad. Dermatol. 42, 903.

Creamer, D., Hunt, B.J., Black, M.M. 2000b. Widespread cutaneous necrosis occurring in association with the antiphospholipid syndrome: a report of two cases. Br. J. Dermatol. 142, 1199.

Del Castillo, L.E., Soria, C., Schoendorff, C., et al. 1997. Widespread cutaneous necrosis and antiphospholipid antibodies: two episodes related to surgical manipulation and urinary tract infection. J. Am. Acad. Dermatol. 36, 872.

Dessein, P.H., Lamparelli, R.D., Phillips, S.A., et al. 1989. Severe immune thrombocytopenia and the development of skin infarctions in a patient with an overlap syndrome. J. Rheumatol. 16, 1494.

Disdier, P., Harlé, J.R., Andrac, L., et al. 1994. Primary anetoderma associated with the antiphospholipid syndrome. J. Am. Acad. Dermatol. 30, 133.

Dodd, H.J., Sarkany, I., O'Shaugnessy, D. 1985. Widespread cutaneous necrosis associated with the lupus anticoagulant. Clin. Exp. Dermatol. 10, 581.

Doutre, M.S., Beylot, C., Bioulac, P., et al. 1987. Skin lesion resembling malignant atrophic papulosis in lupus erythematosus. Dermatologica 175, 45.

Dublin, H.V., Stawiski, M.A. 1974. Systemic lupus erythematosus resembling malignant atrophic papulosis. Arch. Int. Med. 134, 321.

Edwards, M.H., Pierangeli, S., Liu, X., et al. 1997. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. Circulation 96, 4380.

Englert, H.J., Loizou, S., Derue, G.G.M., et al. 1989. Clinical and immunologic features of livedo reticularis in lupus: a case–control study. Am. J. Med. 87, 408.

Farrant, J.M., Judje, M., Thompson, R.P.H. 1989. Thrombotic cutaneous nodules and hepatic vein thrombosis in the anticardiolipin syndrome. Clin. Exp. Dermatol. 14, 306.

Farrell, A.M., Moss, J., Costello, C., et al. 1998. Benign cutaneous degos' disease. Br. J. Dermatol. 139, 708.

Finazzi, G., Marchioli, R., Brancaccio, V., et al. 2005. A randomized trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J. Thromb. Haemost. 3, 848.

Flamholz, R., Tran, T., Grad, G.I., et al. 1999. Therapeutic plasma exchange for the acute management of the catastrophic antiphospholipid syndrome: beta(2)-glycoprotein I antibodies as a marker of response to therapy. J. Clin. Apheresis 14, 171.

Fraga, A., Mintz, G. 1966. Splinter haemorrhages in SLE. Arthritis Rheum 9, 648.

Francès, C., Barete, S. 2004. Difficult management of livedoid vasculopathy. Arch. Dermatol. 140, 2011.

Frances, C., Blétry, O., Piette, J.C. 1996. Dermatologic manifestations in the antiphospholipid syndrome. In: R.A. Asherson, R. Cervera, J.C. Piette, Y. Shoenfeld (Eds.), The Antiphospholipid Syndrome. CRC Press, Boca Raton, FL, p. 201.

Frances, C., Niang, S., Laffitte, E., et al. 2005. Dermatologic manifestations of antiphospholipid syndrome. Two hundred consecutive cases. Arthritis Rheum 52, 1785.

Largest dermatologic series.

Francès, C., Papo, T., Wechsler, B., et al. 1999. Sneddon syndrome with or without antiphospholipid antibodies: a comparative study in 46 patients. Medicine (Baltimore) 78, 209.

Francès, C., Piette, J.C. 1997. Cutaneous manifestations of Hughes syndrome occurring in the context of lupus erythematosus. Lupus 6, 139.

Francès, C., Piette, J.C., Saada, V., et al. 1994. Multiple subungual splinter hemorrhages in the antiphospholipid syndrome. A report of five cases and review of the literature. Lupus 3, 123.

Francès, C., Tribout, B., Boisnic, S., et al. 1989. Cutaneous necrosis associated with the lupus anticoagulant. Dermatologica 178, 194.

Galli, M., Barbui, T. 2005. Antiphospholipid syndrome: clinical and diagnostic utility of laboratory tests. Semin. Thromb. Hemost. 31, 17.

Gertner, E. 2003. Treatment with sildenafil for the healing of refractory skin ulcerations in the antiphospholipid syndrome. Lupus 12, 133.

Gertner, E., Lie, J.T. 1994. Systemic therapy with fibrinolytic agents and heparin for recalcitrant nonhealing cutaneous ulcer in the antiphospholipid syndrome. J. Rheumatol. 21, 2159.

Golden, A.L. 1963. Livedo reticularis in systemic lupus erythematosus. Arch. Dermatol. 87, 299.

Grattan, C.E.H., Burton, J.L., Boon, A.P. 1989. Sneddon's syndrome (livedo reticularis and cerebral thrombosis) with livedo vasculitis and anticardiolipin antibodies. Br. J. Dermatol. 120, 441.

Grob, J.J., Bonerandi, J.J. 1989. Thrombotic skin disease as a marker of the anticardiolipin syndrome. Livedo vasculitis and distal gangrene associated with abnormal serum antiphospholipid activity. J. Am. Acad. Dermatol. 20, 1063.

Grob, J.J., San Marco, M., Aillaud, M.F., et al. 1991. Unfading acral microlivedo: a discrete marker of thrombotic skin disease associated with antiphospholipid antibody syndrome. J. Am. Acad. Dermatol. 24, 53.

Harris, E.N., Baguley, E., Asherson, R.A., et al. 1987. Clinical and serological features of the antiphospholipid syndrome (abstract). Br. J. Rheumatol. 26, 19.

Hughes, G.R.V. 1984. Connective tissue disease and the skin. The prosser-white oration 1983. Clin. Exp. Dermatol. 9, 535.

Ingram, S.B., Goodnight, S.H., Bennett, R.M. 1987. An unusual syndrome of a devastating noninflammatory vasculopathy associated with anticardiolipin antibodies: report of two cases. Arthritis Rheum 30, 1167.

Ishikawa, O., Takahashi, A., Tamura, A., et al. 1999. Cutaneous papules and nodules in the diagnosis of antiphospholipid syndrome. Br. J. Dermatol. 140, 725.

Jindal, B.K., Martin, M.F.R., Gayner, A. 1983. Gangrene developing after minor surgery in a patient with undiagnosed systemic lupus and lupus anticoagulant. Ann. Rheum. Dis. 42, 347.

Kalashnikova, L.A., Nasonov, E.L., Stoyanovich, L.Z., et al. 1994. Sneddon's syndrome and the primary antiphospholipid syndrome. Cerebrovasc. Dis. 4, 76.

Khamashta, M.A. 2000. Primary prevention of thrombosis in subjects with positive antiphospholipid antibodies. J. Autoimmun. 15, 249.

Levine, S.R., Langer, S.L., Albers, J.W., et al. 1988. Sneddon'syndrome: an antiphospholipid antibodies syndrome. Neurology 38, 798.

Lie, J.T. 1994. Vasculitis in the antiphospholipid syndrome: culprit or consort?. J. Rheumatol. 21, 397.

Marechal, V., De Maistre, E., Barbaud, A., et al. 2000. Résistance à la protéine C activée et anticorps anticardiolipine dans les ulcères de jambes. Ann. Dermatol. Venereol. 127, 585.

Meroni, P.L., Raschi, E., Testoni, C., et al. 2001. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis Rheum 44, 2870.

Mc Hugh, M.J., Maymo, J., Skinner, R.P., et al. 1988. Anticardiolipin antibodies, livedo reticularis and major cerebrovascular and renal disease in systemic lupus erythematosus. Ann. Rheum. Dis. 47, 110.

Moreb, J., Kitchens, C.S. 1989. Acquired functional protein S deficiency, cerebral venous thrombosis, and coumarin skin necrosis in association with antiphospholipid syndrome. Report of two cases. Am. J. Med. 87, 207.

Mujic, F., Lloyd, M., Cuadrado, M.J., et al. 1995. Prevalence and clinical significance of subungual splinter hemorrhages in patients with the antiphospholipid syndrome. Clin. Exp. Rheumatol. 13, 327.

Nahass, G.T. 1997. Antiphospholipid antibodies and the antiphospholipid antibody syndrome. J. Am. Acad. Dermatol. 36, 149.
Review on antiphospholipid syndrome in a dermatologic journal.

Neuwelt, C.M., Daikh, D.I., Linfoot, J.A., et al. 1997. Catastrophic antiphospholipid syndrome: response to repeated plasmapheresis over three years. Arthritis Rheum 40, 1534.

Nochy, D., Daugas, E., Droz, D., et al. 1999. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J. Am. Soc. Nephrol. 10, 507.

O'Neill, A., Gatenby, P.A., McGaw, B., et al. 1990. Widespread cutaneous necrosis associated with cardiolipin antibodies. J. Am. Acad. Dermatol. 22, 356.

Petri, M. 1996. Hydroxychloroquine use in the Baltimore lupus cohort: effects on lipids, glucose and thrombosis. Lupus 5, S16.

Pierangeli, S.S., Stewart, M., Silva, L.K., et al. 1998. Report of an anticardiolipin wet workshop during the VIIth International Symposium on antiphospholipid antibodies. J. Rheumatol. 101, 616.

Piette, J.C., Cervera, R., Levy, R.A., et al. 2003. The catastrophic antiphospholipid syndrome—Asherson's syndrome. Ann. Med. Interne. 154, 195.

Piette, J.C., Karmochkine, M., Papo, T., et al. 1995. Treatment of the antiphospholipid syndrome. Clin. Rev. Allergy Immunol. 13, 73.

Piette, J.C., Piette, A.M. 1996. Management of the antiphospholipid syndrome: main trends, unsolved questions, practical and educational aspects. Ann. Med. Interne. 147 (Suppl. 1), 28.

Piette, W.W. 2000. Antiphospholipid syndrome: the problems and the promise. Br. J. Dermatol. 142, 1080.

PROGRESS Collaborative Group. 2001. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358, 1033.

Reber, G., de Moerloose, P. 2004. Anti-beta2-glycoprotein I antibodies—when and how should they be measured? Thomb. Res. 114, 527.

Renfro, L., Franks, A.G., Grodberg, M., et al. 1992. Painful nodules in a young female. Arch. Dermatol. 128, 847.

Rocca, P.V., Siegel, L.B., Cupps, T.R. 1994. The concomitant expression of vasculitis and coagulopathy: synergy for marked tissue ischemia. J. Rheumatol. 21, 556.

Romani, J., Perez, F., Llobet, M., et al. 2000. Anetoderma associated with antiphospholipid antibodies. Case report and review of the literature. J. Eur. Acad. Dermatol. Venereol. 15, 175.

Ruffati, A., De Silvestro, G., Ghirardello, A., et al. 1994. A catastrophic antiphospholipid syndrome: the importance of high levels of warfarin anticoagulation. J. Intern. Med. 235, 81.

Sanmarco, M., Bardin, N., Blank, M., et al. 2005. Heterogeneity of anti-beta2-glycoprotein I antibodies. A factor of variability in test results. Thromb. Haemost. 93, 80.

Schmid, M.H., Hary, C., Marstaller, B., et al. 1998. Pyoderma gangrenosum associated with the secondary antiphospholipid syndrome. Eur. J. Dermatol. 8, 45.

Smith, K.J., Skelton, H.G., James, W.D., et al. 1990. Cutaneous histopathologic findings in antiphospholipid syndrome. Arch. Dermatol. 126, 1176.

Sneddon, I.B. 1965. Cerebrovascular lesions and livedo reticularis. Br. J. Dermatol. 77, 180.

Sparsa, A., Piette, J.C., Wechsler, B., et al. 2003. Anetoderma and its prothrombotic abnormalities. J. Am. Acad. Dermatol. 49, 1008.

Srinivasan, S.K., Pittelkow, M.R., Cooper, L.T., Jr. 2001. Recombinant tissue plasminogen activator for the treatment of cutaneous infarctions in antiphospholipid antibody syndrome: a case report. Angiology 52, 635.

Stephansson, E.A., Niemi, K.M. 1995. Antiphospholipid antibodies and anetoderma; are they associated?. Dermatology 191, 204.

Stephansson, E.A., Niemi, K.M., Jouhikainen, T., et al. 1991. Lupus anticoagulant and the skin. A long term follow-up study of SLE patients with special reference to histopathological findings. Acta Derm. Venereol. (Stockholm) 71, 416.

Tran, M.D., Bécherel, P.A., Cordel, N., et al. 2001. Atrophie blanche idiopathique. Ann. Dermatol. Venereol. 128, 1003.

Tubach, F., Hayem, G., Marchand, J.L., et al. 2000. IgG anti-beta 2-glycoprotein I antibodies in adult patients with systemic lupus erythematosus: prevalence and diagnostic value for the antiphospholipid syndrome. J. Rheumatol. 27, 1437.

Vianna, J.L., Khamasta, M.A., Ordi-Ros, J., et al. 1994. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. Am. J. Med. 96, 3.

Weinstein, C., Miller, M.H., Axtens, R., et al. 1987. Livedo reticularis associated with increased titres of anticardiolipin antibodies in systemic lupus erythematosus. Arch. Dermatol. 123, 596.

Wilson, W.A., Gharavi, A.E., Koike, T., et al. 1999. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 42, 1309.
This study established the current classification criteria for definite antiphospholipid syndrome.

Wilson, W.A., Gharavi, A.E., Piette, J.C. 2001. International classification criteria for antiphospholipid syndrome: synopsis of a post-conference workshop held at the Ninth International (Tours) aPL Symposium. Lupus 10, 457.

Zahavi, J., Charach, G., Schafer, R., et al. 1993. Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost (letter). Lancet 342, 862.

Zelger, B., Sepp, N., Stockhammer, G., et al. 1993. Sneddon's syndrome. A long term follow up of 25 patients. Arch Dermatol 129, 437.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 10

The Skin in Systemic Scleroderma

Thorsten M. Olski, Nicolas Hunzelmann, Thomas Krieg
Department of Dermatology, University of Cologne, 50931 Cologne, Germany

1. Introduction

Systemic scleroderma (SSc) is a chronic progressing disease, which manifests clinically by the sequential appearance of three phases of skin changes: an initial edematous phase, a sclerotic or indurative phase and an atrophic phase. The diagnosis can be further confirmed by the presence of Raynaud's phenomenon, characteristic changes in the nailfold capillary pattern, teleangiectasias, internal organ involvement and scleroderma-specific autoantibodies. Thickening of skin is the result of excessive deposition of extracellular matrix proteins. Similar alterations are also observed in the patient's gastrointestinal tract, lungs, heart, and kidneys.

Two subtypes of the disease are usually distinguished (LeRoy et al., 1988). In *diffuse cutaneous scleroderma*, the patient rapidly develops a symmetric skin thickening of extremities, the face, and trunk. The risk for kidney damage and other visceral involvement is significantly increased during the course of the disease. In patients suffering from *limited cutaneous scleroderma* (lSSc), skin thickening is limited to distal extremities and the face. This form is preceded by the occurrence of Raynaud's phenomenon for many years. Progression is slow and involvement of internal organs is limited. However, these patients may develop pulmonary artery hypertension.

The American College of Rheumatology proposed classification criteria for systemic scleroderma. Either the major criterion or two or more minor criteria have to be fulfilled to assure the diagnosis. The major criterion is the presence of sclerodermatous skin changes of the fingers of both hands accompanied by scleroderma at any location proximal to the metacarpal phalangeal joints, entire extremity, face, neck, chest, and abdomen. The minor criteria are the presence of digital ulcers, sclerodactyly and pulmonary bibasilar fibrosis. These criteria result in 97% sensitivity and show a specificity of 98% (Tables 1, 2 and 3).

Other diseases have to be distinguished from SSc. There are localized forms of scleroderma, which show single or multiple plaques of skin induration but are not associated with organ complications. Other disorders, like graft-versus-host disease, may share many clinical features but can be identified after more detailed diagnosis, as they will differ in some critical characteristics like pattern of skin affection, autoantibodies or clinical history.

Skin sclerosis may also occur in other diseases as a paraneoplastic phenomenon, as a consequence of endocrinological disorders (diabetes mellitus) and after exposure to or ingestion of certain chemicals.

2. Prevalence/epidemiology

Systemic scleroderma appears worldwide and affects all races. Women overall are affected approximately three times as often as men and even more often during the late childbearing and early menopausal years. Although, no strong racial predilection has been reported, certain incidence data suggest, that blacks have a higher risk of developing the disease than whites. The annual incidence has been estimated to be between 0.6 and 19 cases

DOI: 10.1016/S1571-5078(05)05010-5

Table 1
Disease activity score from EUSTAR

Parameter	Score[a]	Evaluation
Modified Rodnan skin score > 14	1	Evaluation of skin thickness on a scale from 0 (normal) to 3 (very strong) in 17 anatomical areas resulting in overall scores between 0 and 51
Scleredema	0.5	Swelling and increase in connective tissue with loss of wrinkles and rete patterns
Skin	2	On being asked, whether the skin manifestations have changed during the last month, the patient confirms a worsening
Digital ulcers	0.5	Active digital ulcers are present
Vascular	0.5	The patient declares, that his/her perfusion problems have worsened during the last month
Arthritis[b]	0.5	Symmetric swelling and hyperesthesia of peripheral joints
DLCO[c]	0.5	DLCO <80% of the predicted value
Heart/lungs	2	The patient confirms, that his heart-/lung problems have worsened during the last month
ESR > 30	1.5	Westergren-method
Hypocomplementemia	1	Either low C3 or C4 according to any quantitation method

Note: Various parameters are determined including skin score, digital ulcers and parameters reflecting systemic affection. The disease is considered to be active, if the score equals or exceeds 3.

[a] The disease is considered to be active, if the total score equals or exceeds 3.

[b] Excluding articular or periarticular inflammation caused by subcutaneous crystals.

[c] CO_2-diffusion capacity.

Table 2
ACR criteria for systemic scleroderma

Major criterion	Minor criteria
Proximal scleroderma	Sclerodactyly Digital pitting scars Bibasilar pulmonary fibrosis

Note: Either one major or two minor criteria have to be fulfilled.

per million population. The reported prevalence of SSc is between 19 and 75 per 100,000 persons. The real numbers are probably underestimated, as many patients are diagnosed at very late stages of the disease. The incidence increases with age, peaking in the principal manifestation age, which is between 45 and 55 years (Ioannidis et al., 2005; Mayes et al., 2003; Medsger et al., 1971).

Although SSc is not considered to be an inheritable disorder, an exceptionally high prevalence of SSc (472 per 100,000 persons) has been noted in the Choctaw Native Americans in Oklahoma. An individual also appears to have a higher risk of developing SSc, if it has occurred in a first-degree relative. Attempts to prove associations between certain human leukocyte antigens and the susceptibility to SSc have not lead to strong correlations. Still, the occurrence of anticentromere antibodies has been shown to be associated with HLA-DRβ1*0101 and HLA- DQβ1*0501. Similar associations have been suggested for the other autoantibodies and antigens, as well.

It has long been discussed that infectious agents may play a role in SSc.

The environment could also have an effect, as gold miners have a higher incidence for SSc, suggesting that silica dust may be a predisposing factor. Other environmental agents involved may include polyvinylchloride, epoxy resins and aromatic hydrocarbons, such as benzine, toluene, and trichloroethylene. Pentazocine and bleomycin have also been considered as putative causes for SSc.

3. Etiology/pathogenesis of skin fibrosis

The etiology of SSc still remains obscure. Certain features like lymphocytic infiltration in the skin, antinuclear antibodies, and the occurrence of overlap syndromes with lupus erythematodes, dermatomyositis or Sjögren's syndrome point toward an autoimmune pathogenesis. Several disease models hypothesize, that genetically predisposed

Table 3
Characteristics of the dSSc lSSc subtypes of systemic scleroderma

Diffuse cutaneous SSc (dSSc)
Onset of Raynaud's syndrome less than one year before skin changes
Skin changes also affecting trunk and proximal extremities
Tendon friction rubs
Increased incidence of organ damages:
Interstitial pulmonary
Renal insufficiency
Diffuse gastro-intestinal affection
Myocardial complications
No anti-centromeric antibodies
Scl-70-autoantibodies
Capillaroscopy: dilatation and destruction of capillaries
Limited cutaneous SSc (lSSc)
Long history (10–15 years) of Raynaud's syndrome
Skin affection distal to elbows and knees only
Risk of pulmonary arterial hypertension and
Trigeminal neuralgias
Subcutaneous calcifications
Teleangiectasias
Often associated with anti-centromere antibodies
Capillaroscopy: dilated capillaries

From LeRoy et al. (1988).

individuals (with certain HLA characteristics) may develop an immune response on contact to external triggers like infectious agents, certain autoantigens, or cell components previously unencountered by the immune system.

The outstanding feature of SSc is overproduction and accumulation of collagen and other extracellular matrix proteins, including fibronectin, tenascin, and glycosaminoglycans, in skin and other organs. The disease process involves immunologic mechanisms, vascular endothelial cell activation and/or injury, and activation of fibroblasts resulting in production of excessive collagen.

Raynaud's phenomenon results from an abnormal regulation of blood flow. It can lead to and accompany vascular injury to endothelial cells and basal lamina involving small arteries, arterioles, and capillaries appearing early in SSc, which precedes fibrosis. Subsequently, the intima thickens, narrowing the lumen, and finally leading to the obliteration of blood vessels.

T cells play a role by secreting granzyme 1, which may stimulate an immune response to the basal lamina. Furthermore, autoantibodies against endothelial cells, AECA, are found to be elevated in a significant number of SSc-patients. They mediate cytotoxic reactions and apoptosis in endothelial cells. AECA also stimulates the expression of VCAM-1, ICAM-1, E- and P-selectin, and elevates IL-1 and IL-8 levels, which are all involved in cell adhesion or chemoattraction. They may facilitate the adhesion and diapedesis of monocytes, T- and B cells into the interstitium with consequences for the inflammatory process.

The damage to the vascular endothelium results in lower levels of prostacyclin. Vasoconstriction and platelet aggregation results in the release of PDGF. This in turn acts as a chemotactic factor and mitogen for fibroblasts and smooth-muscle cells. Transforming growth factor (TGF) leads to an elevation of collagen synthesis and acts together with the other cytokines in further promoting intimal fibrosis.

The vasodilator nitric oxide is diminished in some patients with SSc, suggesting an impairment of its synthesis on endothelial damage. The initial damages caused by tissue hypoxia can be aggravated by reperfusion, which can declench the release of oxygen free radicals. Laminin and type IV collagen have been proposed as possible targets for cell-mediated immunity in the early stages of SSc. The tissue surrounding small blood vessels in the dermis shows high contents of mononuclear and activated helper-inducer T cells.

Another factor possibly involved in the development of skin sclerosis is the vasoconstrictor ET-1. It is a potent pro-fibrotic signalling molecule, which stimulates the synthesis of extracellular matrix. It inhibits the production of matrix-degrading enzymes. ETA- and ETB-receptors transduce these signals. In vitro, ET-1 makes myoblasts differentiate and leads to production of intercellular adhesion molecule-1 by fibroblasts. ET-1 is a promising target for clinical trials as in addition to these biochemical properties its inhibition has been shown to be beneficial for exercise capacity in pulmonary arterial hypertension resulting from

SSc as well as beneficial for the treatment of scleroderma digital ulcers.

Following inflammation with an activation of T cells a number of different factors lead to the induction of fibroblasts in scleroderma. It is assumed that significant numbers of fibroblasts are permanently activated, due in part to autocrine and paracrine stimulation by TGF-β and connective tissue growth factor (CTGF) and these cells overproduce collagens I and III (Kawakami et al., 1998).

There is also increasing evidence for posttranslational modification of the deposited collagen indicating the development of ''bone-type'' collagen crosslinks in the fibrotic skin of scleroderma (Brinckmann et al., 2001; van der Slot et al., 2003). There, it has been hypothesized that altered collagen crosslinks may result in reduced susceptibility to proteolytic degradation.

TGF-β is considered to be the major factor in the induction of fibrosis (Denton and Abraham, 2001). Its intracellular signalling cascade involving different smad proteins has been elucidated in detail. The TGF-β, receptor and the regulation of smad proteins appear to be interesting target structures for developing novel therapeutic approaches (Simms and Korn, 2002).

4. Clinical manifestations

The first symptoms of SSc are usually puffy fingers and Raynaud's phenomenon, which can be detected in 95% of patients. It appears as recurrent vasoconstriction of small arteries at fingers and toes, sometimes also affecting the tip of the nose (Table 4).

Patients may experience Raynaud's phenomenon for months or even years before they develop skin sclerosis. It is estimated that 10 to 15% of patients experiencing isolated Raynaud's phenomenon will develop a connective tissue disorder, subsequently.

The intermittent hypoperfusion can aggravate and finally lead to the development of digital ulcers. In very severe cases, subsequent gangrene may necessitate amputation. The risk for the development of digital ulcers is especially high during the winter months.

Swelling of fingers and hands appearing early during the disease usually begins distally in the extremities and advances proximally extending to the forearms, feet, lower legs, and face usually not affecting the lower extremities. The edematous stage can last for months or even years. The edema may be accompanied by erythema. After these initial changes, the skin thickens and will show more induration. The speed of disease progression varies greatly between patients.

As mentioned above, two main subsets of clinical manifestations can be distinguished (Subcommitee for scleroderma criteria of the American Rheumatism Association). In limited SSc, skin sclerosis affects the extremities up to knees or elbows (Fig. 5). In diffuse cutaneous SSc, skin changes are more generalized, also involving proximal extremities, followed by the face and trunk. This process can take months up to years. A

Table 4
The main skin manifestations, how they are detected/quantitated and how they are treated

Symptom	Diagnosis	Treatment
Skin sclerosis	Modified Rodnan skin score (mRSS) durometer, elastometer 22 MHz dermal ultrasound	UV-therapy, physical exercise, antifibrotic, and immunosuppressive drugs
Raynaud's phenomenon, digital ischemia, digital ulcerations	Anamnesis, capillaroscopy, angiography, thermoimaging, thermoprovocation	Warm environment, vasodilators, Ca-inhibitiors, ACE inhibitors, prostaglandin derivatives (iloprost), ET-1-antagonists, vardenafil/sildenafil, paraffin bath exercise
Teleangiectasias		Laser
Calcinoses	Anamnesis, physical exam, X-ray	Surgery, CO_2- laser
Contractures	Mobility testing	Physical exercise, lymph drainage, paraffin bath exercise, surgery

rapid progression of these changes in less than 3 to 4 years poses a greater risk of developing visceral involvement, which can affect the lungs, heart, or kidneys. Interestingly, in diffuse cutaneous SSc, the skin fibrosis can improve after 3 to 5 years of progression, particularly affecting the trunk and proximal extremities. Patients with lSSc usually show a slower progression of skin induration (Fig. 1). Independent of the subset of SSc, distal extremities are affected more severely, in general. In later stages of the disease, the skin may become atrophic. Especially in the extremities, the tethered skin leads to impairment of extension and flexion, resulting in contractures (Fig. 2). A typical complication is ulcer of the fingertips, and the proximal inter-phalangeal joints, eventually with secondary infection. The affected skin may show hyperpigmentation, which may also occur over superficial blood vessels and tendons. Interspersed maculae of hypo-pigmented skin may become visible in a vitiligo-like appearance predominantly at the scalp and around the hair follicles resulting in a typical ''salt-and-pepper'' appearance.

The involvement of the face leads to a mask like appearance with loss of wrinkles, microstomia, diminished facial expression and perioral wrinkles perpendicular to the thinned lips.

Increased fibrosis of the skin resulting in itching and eczema may result in a loss of hair follicles and sweat, and sebaceous glands leading to dryness.

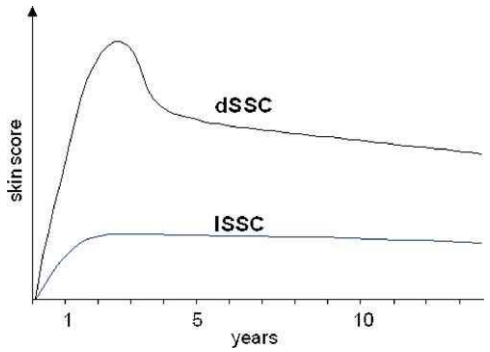


Figure 1. Approximate course of skin thickening in patients having diffuse cutaneous (dSSc) or limited cutaneous scleroderma (lSSc). During the initial 3 to 5 years in dSSc, skin sclerosis progresses most rapidly. Organ manifestations may develop. In later stages, many investigators report no further progression of skin thickness or even a decrease. Patients with lSSc show a much slower progression and a lower risk for developing systemic affections. Still, pulmonary arterial hypertension may develop in later stages.

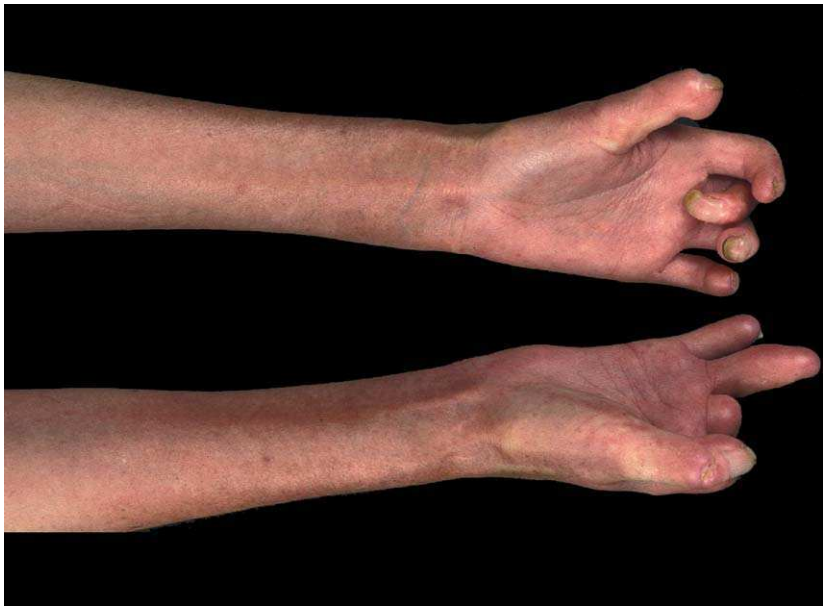


Figure 2. Skin sclerosis in the distal upper extremities. The fibrosis can result in joint contractures. Chronic digital ulcerations may necessitate amputations.

Especially patients with the limited cutaneous form of the disease can develop calcific deposits intra- and subcutaneously. They may appear as nodules of considerable size even with pseudotumorous appearance. They are tightly bound to the skin surface but mobile above the deeper dermal layers. These are present mainly at finger pads, and extensor surfaces of elbows and knees. They can cause complications, reveal their presence by causing local painful inflammations or resolve by drainage of the calcific material after skin damage.

Teleangiectasias, which are usually round-shaped, are frequently encountered over fingers, lips, face, and oral mucosa. Although, patients with limited cutaneous SSc may show these vascular changes more frequently, they can also be observed in diffuse cutaneous SSc-patients (Fig. 3).

Capillaroscopy shows typical changes. Capillaries are enlarged and dilated. Areas of complete loss of capillaries can be found (Cutolo et al., 2004). Patients suffering from Raynaud's phenomenon will not show these changes except for a slightly increased capillary diameter. If the patient complains of dry eyes or dry oral mucosa, this may be due to either periglandular fibrosis or due to an overlap with Sjögren's syndrome. In these Sjögren-patients, SS-A (Ro) or SS-B (La) autoantibodies are found.

The progression of the disease is highly variable and very difficult to predict. If the patient suffers from diffuse cutaneous disease, the first 1 to 3 years will belong to the inflammatory stage. Usually, this is the period, when the skin sclerosis progresses the most. In general, the time following this phase is characterized by a stabilization of the sclerosis or even subjective improvements, as physical therapy and regular exercise will help the patient to maintain or even regain motility. These first 3 years are the most critical for the development of visceral complications.

If in patients with limited SSc skin sclerosis only affects fingers and does not appear proximal to the elbows or knees (except for the face), then progression, most often, is much slower, resulting in a much better prognosis and patients will not experience any significant progression, once a certain level is reached. The probability of developing internal organ complications is by far lower than in dSSc.

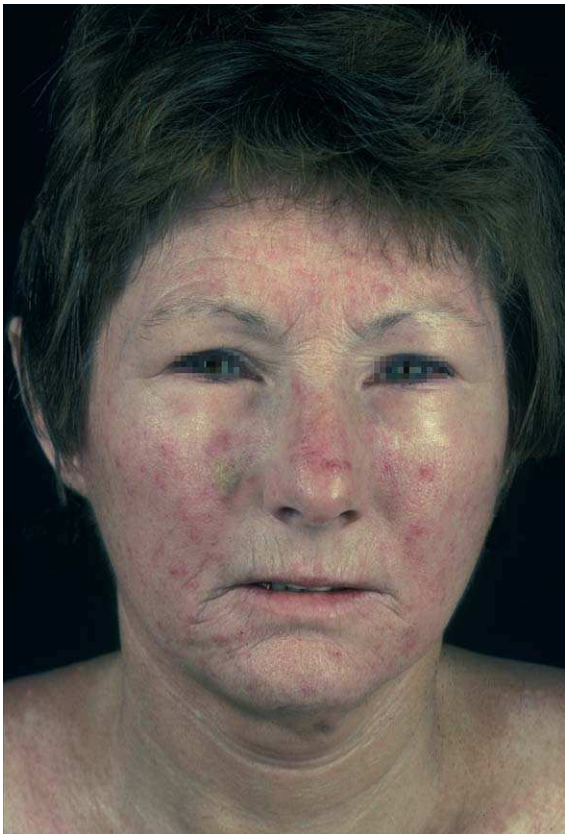


Figure 3. Teleangiectasias developing in the course of the disease are most often associated with lSSc.

Prognosis depends on the extent and progression of skin sclerosis. A recent study in the US estimated the average 5-year survival rate at 77%. The appearance of pulmonary, renal, or cardiac complications has a significant impact on both short-term (<5 years) and long-term (>10 years) survival (Mayes et al., 2003). The combination of several risk factors (high skin score, pulmonary affection, inflammatory symptoms, and anaemia) results in higher mortality, which ranges from 2% (no risk factors), 26% (2 risk factors) up to 75% (4 risk factors). If no organ involvement has appeared during the first 6 years after initial symptoms, the patient can be reassured, that the probability of still developing visceral complication is very low, as only 10% of all patients will show a worsening after this time point (Silman, 1991; Mayes, 2003).

5. Diagnostic investigations

The main and nearly universal symptom of SSc is skin sclerosis. Still, in some cases patients with characteristic serologic, visceral, and vascular changes lack skin thickening, which are then termed systemic scleroderma sine scleroderma. Several studies have suggested that the extent and progression of skin sclerosis is associated with mortality and internal organ involvement (Clements et al., 2000; Steen and Medsger, 2001).

The most widely used assessment method for skin involvement is the modified Rodnan skin score (Figs. 4 and 5). The initial approach (Rodnan et al., 1979) used a 5-degree scale measured at 20 areas leading to a maximum score of 100. In order to minimize inter-observer variability and increase reproducibility, this system has been subject to constant improvements. Areas that are involved less frequently (e.g. back) are not examined separately. The accuracy and sensitivity to change can be increased, when the investigator follows clear practical guidelines. There has been a recent tendency toward a focus on measuring skin thickness rather than mobility or tethering leading to lower scores, especially in the later stages of the disease, when the skin often becomes very thin and more difficult to lift from the subcutaneous tissue giving a hardened impression. The investigator has to make sure, that this score is not influenced by contributions from edema or inflammation, as they may alter the appearance of the skin without increasing its thickness, which is the crucial parameter to be examined. The body surface is subdivided into 17 areas. It is squeezed between two fingers and the degree of thickness is given scores from 0 (no detectable thickening), 1 (questionable alteration of skin thickness), 2 (clearly detectable skin thickness) to 3 (strong thickening). The total skin score then reflects the sum of all areas. If investigators compare their scoring method regularly at workshops, a variation below 15% can be achieved. When assessing the patient's anatomical areas, the following details should be considered:

In the face the area between the os zygomaticum and lower mandible is to be measured. The forehead should not be evaluated. When checking the fingers, hands, and feet, only the dorsum is

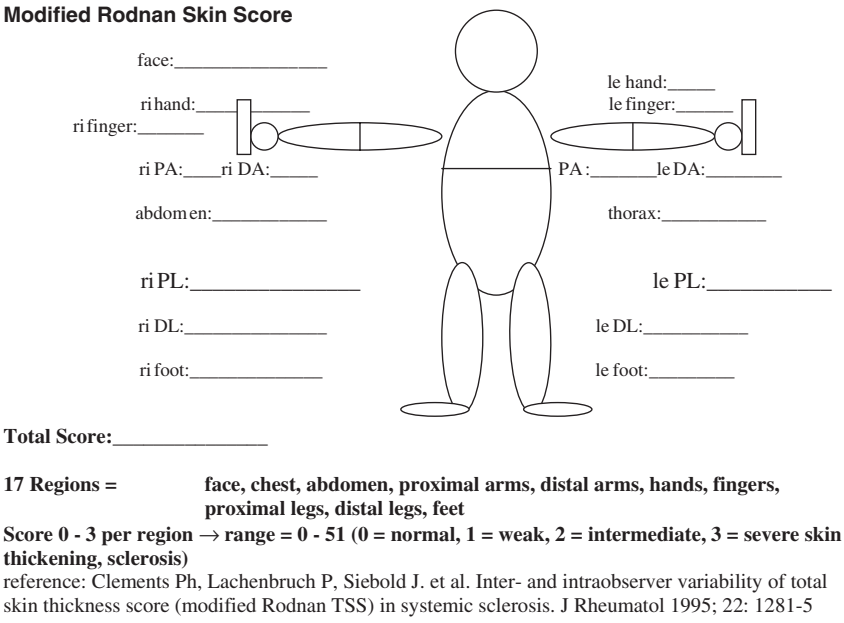


Figure 4. Skin scoring using the modified Rodnan skin score. The whole body surface is divided into 17 areas. In each area, the skin score ranging from 0 (no thickening) to 3 (very strong sclerosis) is determined. In large areas, the score is averaged to reflect the accurate skin state. The total score ranges from 0 to 51.

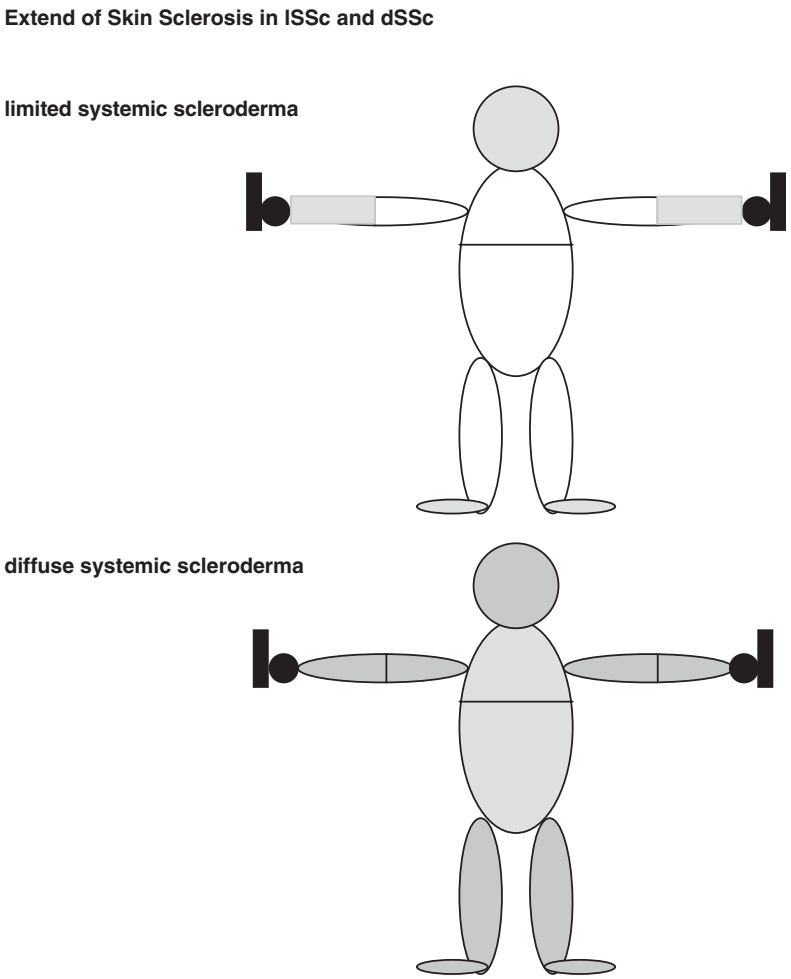


Figure 5. Differences in extent of skin affection in lSSc and dSSc. In lSSc is limited to the areas distal to the elbows and knees. In diffuse scleroderma (dSSc) no such limitation is observed.

examined. The palmar aspect of the fingers and the skin distal to the distal interphalangeal joint should not be measured. The extremities should be relaxed during examination and an average score is calculated over the whole area. During thorax and abdomen scoring, the patient sits upright (Akesson et al., 2003; Valentini et al., 2001).

It takes less than 10 min to acquire the data for the modified Rodnan skin score. It has been shown to be a reliable, accurate, and reproducible method of assessing the patient's skin and can be used for follow-up tests (Black, 1995; Seibold, 2001; Clements et al., 1995).

Still, clinical experience has shown, that some investigators tend to "maximize" scores. It turns out to be most appropriate to score an average over a certain area, which then reflects the area score most exactly.

Furthermore, some disadvantages have been discussed for the use of the Rodnan skin score (Herrick et al., 2001), as despite very thorough investigations, it may appear difficult to distinguish between inflammatory, edematous, and fibrotic processes. Still, the score was shown to correlate with the weight of biopsy specimen (Furst et al., 1998), indicating, that it reflects the underlying disease process.

Some data suggest a higher variability (Pope et al., 1995) than previously reported (Clements et al., 1993), which has made many scientists look for other more accurate methods.

Various approaches have been proposed, one of them using a skin durometer, which determines hardness and deformability of substances (Romanelli and Falanga, 1993; Aghassi et al., 1995; Seyger et al., 1997). Similar good results were obtained with an elastometer/cutometer (Balbir-Gurman et al., 2002; Enomoto et al., 1996; Ishikawa and Tamura, 1996; Ballou et al., 1990.), which applies a vacuum and measures deformation. Various other devices have been tried. Some measure torsional stiffness (Knight et al., 2001) or resistance to squeezing with a "plicometer" (Nives Parodi et al., 1997). Levels of intra- as well as interobserver variability were low enough to call these methods promising for trials to come.

Even more sophisticated devices (Takei et al., 2004) use a tactile skin sensor, which consists of a piezoelectric vibrator with vibration detector. It measures frequency when placed on the skin. All these proposals although appearing as good complements to the classical scoring, still await evaluation.

The use of 22 MHz dermal ultrasound at 17 predefined anatomical locations was proposed (Moore et al., 2003). Previous investigators have reported a correlation between echogenicity and protein composition in the examined areas (Hesselstrand et al., 2002). The ultrasound approach has been shown to provide reproducible data and appears to suit the prerequisites as a follow-up tool for clinical trials (Akesson et al., 2004).

The investigator should also check for the presence of tendon friction rubs, which appear as a "leathery crepitus" while the joint is moved.

As joint contractures may result from scleroderma, there have been attempts to quantitate the mobility impairment faced by the patient (Sandqvist and Eklund, 2000a and b).

For the correct diagnosis of Raynaud's phenomenon, a detailed history of the patient's symptoms is crucial. The rare occurrence of "cold fingers" is not reliable enough to confirm the diagnosis. A discoloration on mental, thermal (cold), or sometimes physical stress has to be observed (Fig. 7). Typically, the patient will tell about pain and a "whitening" of his/her distal phalanges immediately after exposure to cold temperatures. For further confirmation, a Raynaud's provocation test, can be performed. The use of thermography has also been described (Schuhfried et al., 2000), in particular, when alternative diagnoses as e.g. scleredema adultorum, scleromyxedema, nephrogenic fibrosing dermopathy are discussed.

5.1. Histology

A skin biopsy is often recommended and can be helpful in confirming the diagnosis. Compact parallel collagen bundles are visible beneath a thin epidermis. The collagen deposition is not limited to this layer as fiber projections are found in the subcutis and the underlying tissue. Fibrosis can be so extensive that the rete pattern is lost and hair follicles become atrophic. The small blood vessels are typically surrounded by mononuclear cells and the deeper dermal areas show increased numbers of plasma cells, T cells, mast cells, and monocytes.

Histology does not offer specific alterations distinguishing between lSSc or dSSc. However, it allows to detect the presence of inflammatory infiltrates and could therefore be helpful to identify patients, in which anti-inflammatory therapy may be started.

Biopsies over a longer period of time could also be used for a better quantification of the development of fibrosis and are helpful for following diverse cohorts in clinical trials.

6. Differential diagnosis

Diffuse fasciitis with eosinophilia, Shulman's syndrome or *eosinophilic fasciitis* consist of deeply indurated skin and subcutaneous tissue. It usually appears on the extremities and is associated with initial peripheral eosinophilia, hypergammaglobulinemia and elevated sedimentation rate. No Raynaud's phenomenon, autoantibodies or acral scleroderma are detected. Eosinophilic fasciitis lacks all other systemic complications present in SSc (Table 5). It is considered to be a

Table 5
Most important differential diagnoses of SSc and their main characteristics

Disease	Diagnosis
Overlap syndromes	Accompanying symptoms in addition to SSc
MCTD	U1-RNP-antibody
Graft-versus-host disease	Raynaud's symptom may be present, no anti-topoisomerase or anticentromere autoantibodies, patient's history
Paraneoplastic scleroderma	Typically mainly involving lower extremities
Morphea, linear scleroderma, en coup de sabre	Appearance of plaques, no autoantibodies, localized scleroderma only
Eosinophilic fasciitis	Initial eosinophilia, no Raynaud's, no ANA's, typical clinical symptoms
Scleromyxedema	Gylcosamionglycane deposits, affects the face and backside of hands, sometimes light chain gammopathy
Scleredema (scleredema adultorum Buschke)	Typical clinical symptoms, hands and feet are spared
Eosinophilia-myalgia syndrome (EMS)	Initial pruritus, associated with L-tryptophan ingestion, no sclerodactily
Other environmentally induced scleroderma (epoxy hydrocarbons, bleomycin, vinyl chloride, etc.)	Patient's history, typical pattern of affection
Scleroderma secondary to amyloidosis, diabetes, etc.	Typical pattern of skin affection, biopsy

subset of localized scleroderma and can be often treated successfully with systemic corticosteroids. In severe cases, joint contractures and immobilizations have been reported.

The *Eosinophilia-myalgia syndrome* (EMS) begins with pruritus, cutaneous lesions, scleroderma-like changes, arthralgias and edema. The eosinophilic blood count is elevated. As 96% of all cases have been associated with L-tryptophan consumption, this agent is considered to be the declenching factor. In contrast to SSc, skin sclerosis will not affect digits. The pruritus, the proximal muscle weakness and occasional urticaria are distinguishing features.

Scleromyxedema is a rare disorder characterized by the sclerodermiform and papulous skin changes appearing at the distal extremities, behind the hands and the face. It can be distinguished histologically by the presence of glycosamionoglycane deposits found in the specimen. The infiltrate consists mainly of fibroblasts. A monoclonal IgG light chain λ gammopathy may also be present.

Sclerodermiform changes have also been described in the course of amyloidoses, mastocytoses, Werner's syndrome or diabetes mellitus.

The clinical appearance of graft-versus-host disease especially after bone marrow transplantation can be similar, so that skin stiffening, Raynaud's phenomenon, a characteristic histology, antinuclear antibodies or an elevation of soluble IL-2-receptor can be detected.

Localized forms like linear scleroderma and morphea can usually be distinguished clinically. The most frequent ones are the plaque-type skin changes, which will normally begin with an erythematous macule extending excentrically. The center will eventually show depigmentation and become sclerotic. The periphery will still be present with a so-called ''lilac ring'', which will give evidence of the ongoing inflammatory process. After variable time spans, the plaque will stabilize or even show remission often leaving some residual atrophy or pigmentation. The number and extent of plaques varies greatly between individuals. In some cases they may extend significantly and lead to mobility impairments, although no organ affection will ever accompany this disorder (Fig. 6).

Scleredema (scleredema adultorum of Buschke) may be associated with the previous streptococcal infections and is usually self-limited, resolving in 6 to 12 months. Histology reveals accumulation of mucopolysaccharides in the dermis and skeletal muscles. Typically, a painless induration occurs in the face, neck, and proximal extremities. Hands and feet are spared.

Scleroderma can occur as a paraneoplastic phenomenon. It may sometimes be hard to distinguish from the ordinary SSc, as Raynaud's phenomenon and autoantibodies have been described. But, a more severe affection of the lower extremities, the sparing of fingers, the patient's history, progression

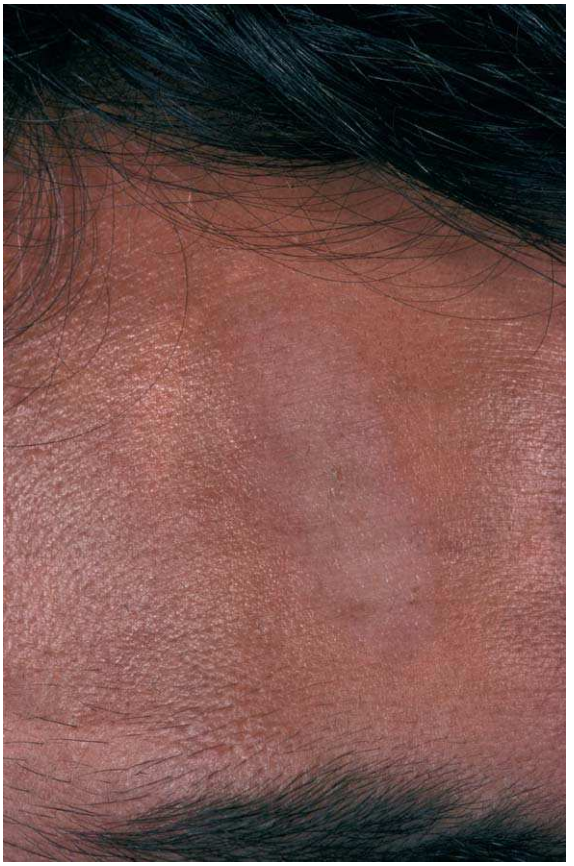


Figure 6. Localized scleroderma is a differential diagnosis of SSc. It can appear in a plaque or linear configuration (''en coup de sabre'' as shown). Usually, no autoantibodies are found and it can be distinguished from systemic scleroderma by its typical appearance.

speed, and accompanying symptoms may lead to the suspicion of an underlying tumor.

Patients with insulin-dependent diabetes mellitus may develop digital sclerosis and contractures (prayer hand deformity). Primary amyloidosis and amyloidosis associated with multiple myeloma may involve the skin of the extremities and face diffusely to give the appearance of scleroderma. Biopsy will clearly differentiate these entities. Chemically induced forms have to be considered as well. Vinyl chloride, pentazocine, bleomycin, and epoxy carbons may cause similar changes. The aberrant pattern of skin affection, serology will help finding the cause, in addition to the crucial history taking of the patient.

In patients with acute or chronic renal failure, the acute onset of induration involving the upper and lower limbs may herald a nephrogenic fibrosing dermopathy (Swartz et al., 2003). No effective treatment has been found, yet. No histocompatibility antigens or laboratory abnormalities were shown to be consistently associated with this condition. Histology detected the presence of smooth muscle actin-positive myofibroblasts.

7. Treatment

It appears almost impossible to cure the underlying disease process of SSc, however considerable progress has been made to provide symptomatic organ specific therapy (Genth, 2001).

As patients show major differences in the course of the disease, it appears extremely difficult to evaluate the effectiveness of pharmaceutical interventions in SSc. Although, various treatments have been tried in the treatment of scleroderma, none of them has shown proven clinical benefit. D-penicillamine has been, initially, observed to have a positive effect on skin thickness in uncontrolled studies. But the results of a double-blind randomized trial (Clements et al., 2004), which compared high-dose D-penicillamine (750 to 1000 mg/day) with low-dose D-penicillamine (125 mg/day) in patients with early diffuse SSc, have shown no significant difference for skin thickening, the occurrence of organ involvement or mortality between the two dosages. Patients in the early rapidly progressive inflammatory stage are still treated by a significant number of physicians with certain immunosuppressants like azathioprin (Dheda et al., 2004), methotrexate (Pope et al., 2001; van den Hoogen et al., 1996), cyclosporine A (Basso et al., 2001; Roch et al, 2004), cyclophosphamide (Airo et al., 2004) or others, although no controlled studies exist proving their effectiveness. Colchicine, *p*-aminobenzoic acid, vitamin E and human relaxin belong to the drugs, which despite initial optimism still lack the proof of their effectiveness. Prednisone has been used for reduction of edema appearing in the early phase. Otherwise, glucocorticoids are not indicated in the long-term treatment even less as high dose glucocorticoid

application has been suggested to play a role in precipitating renal crisis (Steen and Medgser, 1998; Pai et al., 1995; Sharada et al., 1994).

Promising new treatments like interferon or extracorporeal photochemotherapy have been used for some patients. So far, no therapy has shown a clear suppression or even reversal of the disease process in a controlled, prospective study.

High-dose immunosuppression followed by autologous stem cell transplantation is an innovative approach currently under examination in a Europe-wide trial, which aims mainly at patients with a rapid onset of cutaneous disease and show internal organ involvement very early (Binks et al., 2001).

To improve mobility and comfort in daily life, various physical therapies have been proven to be effective. Regular physical exercise training should focus on improving joint extension to prevent contractures. The positive influence of specific physical exercise has been shown even for individual joints resulting in gain of function and improved life-quality (Pizzo et al., 2003). Specialized massages improving lymph drainage can be helpful as well. Hand exercise against a resistant substance using a warm paraffin bath helps in increasing joint motility as well as peripheral blood flow. Clinical trial data supports its effectiveness (Sandqvist et al., 2004). Innovative approaches enlarge the spectrum of physical therapy by co-applying vibration (Klyscz et al., 1999).

Among the first and most effective measures to be taken are skin care as dryness of the skin should be reduced by avoiding detergent soaps and by application of bath oils. Fingertip ulcerations may heal faster with the use of hydrocolloid membranes. They should be kept clean, which may require intermittent debridement.

Besides all medical or physical approaches, it is indispensable, that the patient him/herself avoids harmful environmental influences. Cold places should be avoided and nicotine consumption is known to worsen digital perfusion even leading to digital ulcers in patients, who without smoking would have been spared from this complication.

The frequently used calcium channel blockers nifedipine and amlodipine have been proven very effective in alleviating Raynaud's symptoms but show side effects like light-headedness and palpitations. ACE inhibitors as well as angiotensin receptor blockers have been shown to be effective.

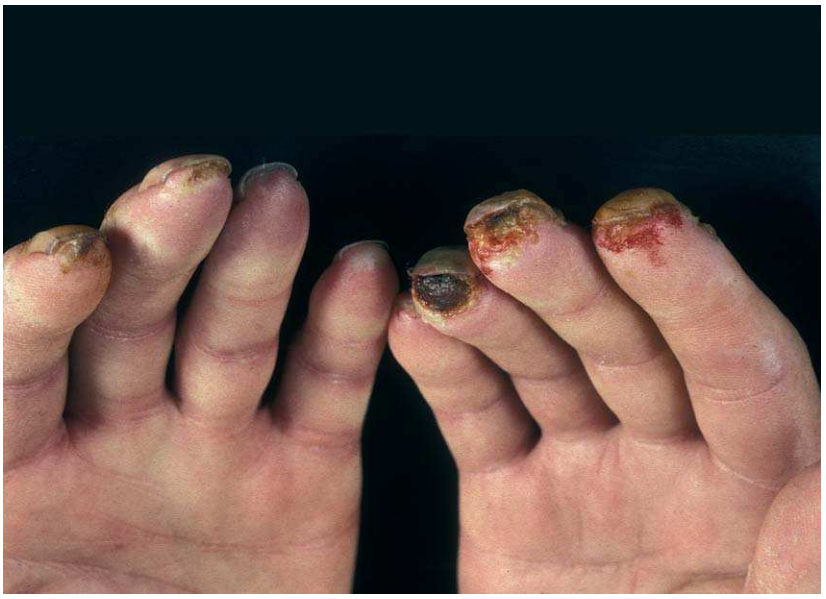


Figure 7. Severe Raynaud's symptoms and chronic digital ischemia can lead to the development of ulcerations. The use of vasodilators has been very effective in treatment of these complications.

The frequency and severity of Raynaud's attacks can be significantly reduced and the healing of digital ulcers is increased by using the prostacyclin analogue iloprost intravenously (Bettoni et al., 2002). A double-blind study on the use of the endothelin receptor antagonist bosentan is under way.

Any diagnosis of severe Raynaud's phenomenon should explicitly include the possibility of a primary vascular occlusion, which after having been revealed by angiography should be treated by revascularization or digital sympathectomy by vascular surgeons. Digital ulcers may become more and more severe, leading to gangrene and requiring surgical amputation (Fig. 7).

Surgical correction of contractures can bring substantial improvement in the ability to perform everyday tasks (Bogoch and Gross, 2005). Still, there is the risk of developing postoperative digital ulcers secondary to vascular changes and surgical wounds. Correction of severe microsurgical revascularization of the hand and digital arterial reconstruction may improve digital vascular perfusion, heal digital ulcers, and relieve pain. Peripheral sympathectomy may alleviate severe ischemic pain. Subcutaneous calcifications can be removed with a carbon dioxide laser or a high-speed burr (Chamberlain and Walker, 2003).

Teleangiectasias can be treated with different (585 nm, KTP) lasers (Ciatti et al., 1996), as well.

UV therapy is becoming more and more important, when dealing with skin fibrosis.

UVA irradiation can increase the expression, synthesis and activation of metalloproteinases enhancing turnover of the extracellular matrix.

It can be applied in different dosages ranging from 20 (300 J/cm^2 cumulative dose) up to 130 J/cm^2 (up to 1800 J/cm^2 cumulative dose).

The first hints for the benefit of UV therapy came from the treatment of localized scleroderma (Hunzelmann et al., 1998; Kerscher et al., 1994; El-Mofty et al., 2004).

In an uncontrolled study, low-dose UVA1 phototherapy has been reported to have a benefit in acrosclerosis (von Kobyletzki et al., 2000). The dosage used was 30 J/cm^2 UVA1 for a total of 50 sessions resulting in a cumulative dose of 1500 J/cm^2. Other studies were able to confirm a positive effect (Morita et al., 2000; El-Mofty et al., 2004).

As mentioned above, considerable progress has been made to improve organ specific therapy. This includes the management of pulmonary arterial hypertension, lung fibrosis, and renal crisis.

Organ specific therapy, however, also requires a continuous follow-up of the patient and an early diagnosis of organ involvment. The methods required for such early diagnostic procedures have been continuously improved and allow for a much better management of the disease (Sule and Wigley, 2003; Wigley and Sule, 2001).

Key points

- Systemic scleroderma (SSc) manifests clinically by initial edematous skin changes and Raynaud's phenomenon followed by a sclerotic or indurative phase and an atrophic phase. Further complications may include the appearance of digital ulcers, hyperpigmentation, microstomia, joint contractures, teleangiectasias, the development of calcific deposits intra- and subcutaneously and the affection of internal organs.
- Two subtypes of the disease are usually distinguished (LeRoy et al., 1988). In patients suffering from *limited cutaneous scleroderma*, skin thickening is limited to distal extremities and the face. In *diffuse cutaneous scleroderma*, the patient rapidly develops a symmetric skin thickening of extremities, the face and trunk.
- Several disorders have to be distinguished from systemic scleroderma as they may cause similar skin changes, like eosinophilic fasciitis, localized scleroderma, scleromyxedema, amyloidoses, mastocytoses, Werner's syndrome or diabetes mellitus, graft-versus-host disease, scleredema or forms chemically induced by vinyl chloride, pentazocine, bleomycin or epoxy carbons.
- The most widely used assessment method for skin involvement is the modified Rodnan skin score, but there have been attempts to obtain more reproducible measures using technical devices like skin durometers or 22 MHz dermal ultrasound.

References

Aghassi, D., Monoson, T., Braverman, I. 1995. Reproducible measurements to quantify cutaneous involvement in scleroderma. Arch. Dermatol. 131, 1160.

Airo, P., Danieli, E., Parrinello, G., et al. 2004. Intravenous cyclophosphamide therapy for systemic sclerosis. A single-center experience and review of the literature with pooled analysis of lung function test results. Clin. Exp. Rheumatol. 22, 573.

Akesson, A., Fiori, G., Krieg, T., et al. 2003. Assessment of skin, joint, tendon and muscle involvement. Clin. Exp. Rheumatol. 21 (3 Suppl. 29), S5.

Akesson, A., Hesselstrand, R., Scheja, A., et al. 2004. Longitudinal development of skin involvement and reliability of high frequency ultrasound in systemic sclerosis. Ann. Rheum. Dis. 63, 791.

Balbir-Gurman, A., Denton, C.P., Nichols, B., et al. 2002. Non-invasive measurement of biomechanical skin properties in systemic sclerosis. Ann. Rheum. Dis. 61, 237.

Ballou, S.P., Mackiewicz, A., Lysikiewicz, A., Neuman, M.R. 1990. Direct quantitation of skin elasticity in systemic sclerosis. J. Rheumatol. 17, 790.

Basso, M., Filaci, G., Cutolo, M., et al. 2001. Long-term treatment of patients affected by systemic sclerosis with cyclosporin A. Ann. Ital. Med. Int. 16, 233.

Bettoni, L., Geri, A., Airo, P., et al. 2002. Systemic sclerosis therapy with iloprost: a prospective observational study of 30 patients treated for a median of 3 years. Clin. Rheumatol. 21, 244.

Binks, M., Passweg, J.R., Furst, D., et al. 2001. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. Ann. Rheum. Dis. 60, 577.

Black, C.M. 1995. Measurement of skin involvement in scleroderma. J. Rheumatol. 22, 1217.

Bogoch, E.R., Gross, D.K. 2005. Surgery of the hand in patients with systemic sclerosis: outcomes and considerations. J. Rheumatol. 32, 642.

Brinckmann, J., Neess, C.M., Gaber, Y., et al. 2001. Different pattern of collagen cross-links in two sclerotic skin diseases: lipodermatosclerosis and circumscribed scleroderma. J. Invest. Dermatol. 117, 269.

Clements, P., Lachenbruch, P., Siebold, J., et al. 1995. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J. Rheumatol. 22, 1281.

Clements, P.J., Hurwitz, E.L., Wong, W.K., et al. 2000. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum. 43, 2445.

Clements, P.J., Lachenbruch, P.A., Seibold, J.R., et al. 1993. Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. J. Rheumatol. 20 (11), 1892–1896.

Clements, P.J., Seibold, J.R., Furst, D.E., et al. 2004. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial: lessons learned. Semin Arthritis Rheum. 33 (4), 249–263.

Chamberlain, A.J., Walker, N.P. 2003. Successful palliation and significant remission of cutaneous calcinosis in CREST syndrome with carbon dioxide laser. Dermatol. Surg. 29, 968.

Ciatti, S., Varga, J., Greenbaum, S.S. 1996. The 585nm flashlamp-pumped pulsed dye laser for the treatment of telangiectases in patients with scleroderma. J. Am. Acad. Dermatol. 35, 487.

Cutolo, M., Pizzorni, C., Tuccio, M., et al. 2004. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. Rheumatology (Oxford) 43, 719.

Denton, C.P., Abraham, D.J. 2001. Transforming growth factor-beta and connective tissue growth factor: key cytokines in scleroderma pathogenesis. Curr. Opin. Rheumatol. 13, 505.

Dheda, K., Lalloo, U.G., Cassim, B., et al. 2004. Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. Clin. Rheumatol. 23, 306.

El-Mofty, M., Mostafa, W., El-Darouty, M., et al. 2004. Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. Photodermatol. Photoimmunol. Photomed. 20, 148.

Enomoto, D.N., Mekkes, J.R., Bossuyt, P.M., et al. 1996. Quantification of cutaneous sclerosis with a skin elasticity meter in patients with generalized scleroderma. J. Am. Acad. Dermatol. 35, 381.

Furst, D.E., Clements, P.J., Steen, V.D., et al. 1998. The modified Rodnan skin score is an accurate reflection of skin biopsythickness in systemic sclerosis. J. Rheumatol. 25, 84.

Genth, E. 2001. Evidence-based therapy of systemic sclerosis. J. Rheumatol. 60, 464.

Herrick, A., Rooney, B., Finn, J., et al. 2001. Lack of relationship between functional ability and skin score in patients with systemic sclerosis. J. Rheumatol. 28, 292.

Hesselstrand, R., Westergren-Thorsson, G., Scheja, A., et al. 2002. The association between changes in skin echogenicity and the fibroblast production of biglycan and versican in systemic sclerosis. Clin. Exp. Rheumatol. 20, 301.

Hunzelmann, N., Scharffetter Kochanek, K., Hager, C., et al. 1998. Management of localized scleroderma. Semin. Cutan. Med. Surg. 17, 34.

Ioannidis, J.P., Vlachoyiannopoulos, P.G., Haidich, A.B., et al. 2005. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am. J. Med. 118, 2.

Ishikawa, T., Tamura, T. 1996. Measurement of skin elastic properties with a new suction device (II): systemic sclerosis. J. Dermatol. 23, 165.

Kawakami, T., Ihn, H., Xu, W., et al. 1998. Increased expression of TGF-beta receptors by scleroderma fibroblasts: evidence for contribution of autocrine TGF-beta signaling to scleroderma phenotype. J. Invest. Dermatol. 110, 47.

Kerscher, M., Volkenandt, M., Meurer, M., et al. 1994. Treatment of localised scleroderma with PUVA bath photochemotherapy. Lancet 343, 1233.

Klyscz, T., Rassner, G., Guckenberger, G., et al. 1999. Biomechanical stimulation therapy. A novel physiotherapy method for systemic sclerosis. Adv. Exp. Med. Biol. 455, 309.

Knight, L.R., Smeathers, J.E., Isdale, A.H., et al. 2001. Evaluating the cutaneous involvement in scleroderma: torsional stiffness revisited. Rheumatology (Oxford) 40, 128.

LeRoy, E.C., Black, C., Fleischmajer, R., et al. 1988. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J. Rheumatol. 15, 202.

Mayes, M.D., Lacey, J.V., Jr., Beebe-Dimmer, J., et al. 2003. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 48, 2246.

Mayes, M.D. 2003. Scleroderma epidemiology. Rheum. Dis. Clin. North. Am. 29, 239.

Medsger, T.A., Jr., Masi, AT., Rodnan, G.P., et al. 1971. Survival with systemic sclerosis (scleroderma). A life-table analysis of clinical and demographic factors in 309 patients. Ann. Intern. Med. 75, 369.

Moore, T.L., Lunt, M., McManus, B., et al. 2003. Seventeen-point dermal ultrasound scoring system–a reliable measure of skin thickness in patients with systemic sclerosis. Rheumatology (Oxford) 42, 1559.

Morita, A., Kobayashi, K., Isomura, I., Tsuji, T., Krutmann, J. 2000. Ultraviolet A1 (340–400nm) phototherapy for scleroderma in systemic sclerosis. J. Am. Acad. Dermatol. 43 (4), 670–674.

Nives Parodi, M., Castagneto, C., Filaci, G., et al. 1997. Plicometer skin test: a new technique for the evaluation of cutaneous involvement in systemic sclerosis. Br. J. Rheumatol. 36, 244.

Pai, B.S., Srinivas, C.R., Sabitha, L., et al. 1995. Efficacy of dexamethasone pulse therapy in progressive systemic sclerosis. Int. J. Dermatol. 34, 726.

Pizzo, G., Scardina, G.A., Messina, P. 2003. Effects of a non-surgical exercise program on the decreased mouth opening in patients with systemic scleroderma. Clin. Oral Investig. 7, 175.

Pope, J.E., Baron, M., Bellamy, N., et al. 1995. Variability of skin scores and clinical measurements in scleroderma. J. Rheumatol. 22, 1271.

Pope, J.E., Bellamy, N., Seibold, J.R., et al. 2001. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum. 44, 1351.

Roch, B., Wollina, U., Schroeder, H.E. 2004. Long-term cyclosporin A in systemic sclerosis. J. Eur. Acad. Dermatol. Venereol. 18, 235.

Rodnan, G.P., Lipinski, E., Luksick, J. 1979. Skin thickness and collagen content in progressive systemic sclerosis and localized scleroderma. Arthritis Rheum. 22, 130.

Romanelli, M., Falanga, V. 1993. Use of a durometer to measure the degree of skin induration in lipodermatosclerosis. J. Am. Acad. Dermatol. 29, 47.

Sandqvist, G., Eklund, M. 2000a. Hand Mobility in Scleroderma (HAMIS) test: the reliability of a novel hand function test. Arthritis Care Res. 13, 369.

Sandqvist, G., Eklund, M. 2000b. Validity of HAMIS: a test of hand mobility in scleroderma. Arthritis Care Res. 13, 382.

Sandqvist, G., Akesson, A., Eklund, M. 2004. Evaluation of paraffin bath treatment in patients with systemic sclerosis. Disabil. Rehabil. 26, 981.

Schuhfried, O., Vacariu, G., Lang, T., et al. 2000. Thermographic parameters in the diagnosis of secondary Raynaud's phenomenon. Arch. Phys. Med. Rehabil. 81, 495.

Seibold, J.R. 2001. Clinical trials: types, design, and end-points. Curr. Opin. Rheumatol. 13 (6), 512–515.

Seyger, M.M., van den Hoogen, F.H., de Boo, T., et al. 1997. Reliability of two methods to assess morphea: skin scoring and the use of a durometer. J. Am. Acad. Dermatol. 37, 793.

Sharada, B., Kumar, A., Kakker, R., et al. 1994. Intravenous dexamethasone pulse therapy in diffuse systemic sclerosis. A randomized placebo-controlled study. Rheumatol. Int. 14, 91.

Silman, A.J. 1991. Scleroderma and survival. Ann. Rheum. Dis. 50, 267.

Simms, R.W., Korn, J.H. 2002. Cytokine directed therapy in scleroderma: rationale, current status, and the future. Curr. Opin. Rheumatol. 14, 717.

Steen, V.D., Medgser, T.A. 1998. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum. 41, 1613.

Steen, V.D., Medsger, T.A., Jr. 2001. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum. 44, 2828.

Sule, S.D., Wigley, F.M. 2003. Treatment of scleroderma: an update. Expert Opin. Investig. Drugs 12, 471.

Swartz, R.D., Crofford, L.J., Phan, S.H., et al. 2003. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. Am. J. Med. 114, 563.

Takei, M., Shiraiwa, H., Omata, S., et al. 2004. A new tactile skin sensor for measuring skin hardness in patients with systemic sclerosis and autoimmune Raynaud's phenomenon. J. Int. Med. Res. 32, 222.

Valentini, G., D'Angelo, S., Della Rossa, A., et al. 2001. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. IV. Assessment of skin thickening by modified Rodnan skin score. Ann. Rheum. Dis. 60, 592.

van den Hoogen, F.H., Boerbooms, A.M., Swaak, A.J., et al. 1996. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. Br. J. Rheumatol. 35, 364.

van der Slot, A.J., Zuurmond, A.M., Bardoel, A.F., et al. 2003. Identification of PLOD2 as telopeptide lysyl hydroxylase, an important enzyme in fibrosis. Biol. Chem. 278, 40967.

von Kobyletzki, G., Uhle, A., Pieck, C., et al. 2000. Acrosclerosis in patients with systemic sclerosis responds to low-dose UV-A1 phototherapy. Arch. Dermatol. 136, 275.

Wigley, F.M., Sule, S.D. 2001. Novel therapy in the treatment of scleroderma. Expert Opin. Investig. Drugs 10, 31.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 11

Dermatomyositis

Marinos C. Dalakas*

Neuromuscular Diseases Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA

1. Introduction

Dermatomyositis (DM) is one of the three main inflammatory myopathies, the other two being polymyositis and inclusion-body myositis (Dalakas, 1991; Dalakas, 2003). Although, it may have been recognized earlier by Wagner (1863), the first definitive description of DM was reported by Unverricht (1891). Before the extensive use of immunosuppressive drugs, DM was the cause of considerable disability and mortality, especially in children. During the last 30 years, the extensive use of these drugs and the better understanding of the immunopathology of the disease have significantly improved the prognosis. DM, a disease affecting skin and muscle, is cared for not only by neurologists but also by rheumatologists and dermatologists. The role of the physician is essential to exclude other diseases associated with skin and muscle pathologies, to establish the cause of the symptoms, to confirm the immune-basis of the disease, and supervise the immunotherapeutic interventions.

2. Epidemiology/Prevalence

The exact incidence of DM is unknown. Along with the other two forms of inflammatory myopathies (polymyositis and inclusion-body myositis), they occur in approximately 1 in 100,000 adults.

3. Etiology

3.1. Overlap syndromes

"Overlap syndrome" defines a disorder that shares the characteristics of two usually distinct disorders. As such, DM truly overlaps with two connective tissue disorders, scleroderma and mixed connective tissue disease. Specific signs of systemic sclerosis or mixed connective tissue disease such as sclerotic thickening of the dermis, contractures, esophageal dysmotility, microangiopathy, and calcium deposits are present only in DM but not in other inflammatory myopathies. Conversely, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjögren syndrome are very rare in DM. Patients with the overlap syndrome of DM/systemic sclerosis may have an antinuclear autoantibody, the anti-polymyositis/Scl, directed against a nucleolar protein complex.

3.2. Viruses

Coxsackie viruses, influenza, vaccinations, or even retroviruses have been proposed as possible causes of DM. However, there are no signs to indicate that they play a pathogenic role in the disease, and their association has been peripheral and circumstantial. All attempts to isolate viruses, including

*Corresponding author.
Neuromuscular Diseases Section, NINDS, NIH, Building 10, Room 4N248, 10 Center Dr. MSC 1382, Bethesda, MD, 20892-1382, USA.
Tel.: +1-301-496-9979; Fax: +1-301-402-0672.
E-mail address: dalakasm@ninds.nih.gov (M.C. Dalakas).

DOI: 10.1016/S1571-5078(05)05011-7

retroviruses, from the patients' muscle or amplify viral products by polymerase chain reaction have been unsuccessful.

3.3. Cancer

The incidence of malignancies is increased in patients with DM (Buckbinder et al., 2001; Hill et al., 2001). Ovarian cancer is most frequent, followed by intestinal, breast, lung, and liver cancer. In Asian populations, nasopharyngeal cancer is more common. In general, however, the cancer sites correspond to those occurring more frequently at the patient's age (Callen, 2002). Because tumors are often uncovered at autopsy or on the basis of abnormal findings on medical history and physical examination, blind radiologic searches are rarely fruitful. A complete annual physical examination with breast, pelvic, and rectal examinations (including colonoscopy in high-risk patients), urinalysis, complete blood-cell count, blood chemistry tests, and chest X-ray, is usually sufficient and is highly recommended especially during the first 3 years.

3.4. Myotoxic drugs

There are anecdotal reports that some cholesterol lowering drugs may cause disease resembling DM. Three cases, one with pravastatin, another with simvastatin, and a third with atorvastatin (Schalke et al., 1992; Khattak et al., 1994; Noel et al., 2001) suggest that these agents are not only myotoxic but they can also affect the skin in a DM-like pattern and induce an inflammatory response in susceptible individuals.

4. Pathogenesis

4.1. Presence of autoantibodies

Various autoantibodies against nuclear (antinuclear antibodies) and cytoplasmic antigens are found in up to 20% of the patients with all the inflammatory myopathies (Dalakas, 1990, 1991, 1995, 1997, 2001c; Engel and Emslie-Smith, 1989; Karpati and Carpenter, 1993; Engel et al., 1994; Dalakas and Karpati, 2001). The antibodies to cytoplasmic antigens are directed against ribonucleoproteins that are involved in translation and protein synthesis and include various synthetases and translation factors. The antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the anti-synthetases and is clinically useful because up to 80% of DM patients with anti-Jo-1 antibodies develop interstitial lung disease. However, these antibodies may not be muscle-specific, because (a) they are directed against ubiquitous targets and may represent epiphenomena of no pathogenic significance; (b) they also occur in polymyositis and inclusion-body myositis despite the clinical and immunopathologic differences of these disorders from DM; and (c) they also occur in patients with interstitial lung disease even without myositis (Friedman et al., 1996; Hengstman et al., 2001; Dalakas and Hohlfeld, 2003), indicating that they can be equally specific markers for interstitial lung disease as they are for DM. Patients with the overlap syndrome of DM and systemic sclerosis may have autoantibodies of unclear significance, including the anti-polymyositis/Scl, directed against a nucleolar protein complex, anti-Ku, anti-U2RNP and others (Kubo et al., 2001; Jury et al., 2001).

4.2. Immunopathology of muscle and skin

4.2.1. Muscle

The primary antigenic targets in DM are components of the endothelium of the blood vessels in the endomysium and probably the skin. Signs of an ongoing angiopathy in DM were first shown by light and electron-microscopic observations (Banker and Victor, 1966; Banker, 1975). The earliest pathological alterations are changes in the endothelial cells consisting of pale and swollen cytoplasm with microvacuoles (Jerusalem et al., 1974). The endothelial cells have multiple pinocytotic vesicles in their cytoplasm, a wide lumen filled with plasma, and distinct intercellular junctions. The swollen endothelial cytoplasm may also contain tubuloreticular aggregates consisting of

small aggregates of dark-staining granular material. The capillaries undergo active focal destruction with undulating tubules in the smooth endoplasmic reticulum of the endothelial cells, leading to vascular necrosis and thrombi (Carpenter et al., 1976). Such alterations in the microvasculature are caused by an immune-mediated process as evidenced by the presence of immune complexes immunolocalized in the endomysial blood vessels (Whitaker and Engel, 1972), along with the C5b-9 membranolytic attack complex, the lytic component of the complement pathway (Kissel et al., 1986). The membranolytic attack complex and the early complement components C3b and C4b are deposited on the capillaries early in the disease, and precede the signs of inflammation or structural changes in the muscle fibers (Emslie-Smith and Engel, 1990; Dalakas, 1991, 1995), are detected in the serum, and correlate with disease activity (Basta and Dalakas, 1994). The neoantigen C3bNEO, which is complex-specific because it gets exposed when the C3b is incorporated into an immune complex, is also deposited on the muscle capillaries along with the membranolytic attack complex (Basta and Dalakas, 1994).

The disease begins when putative antibodies or other factors activate complement C3, C3b, and C4b fragments, that lead to the formation of C3bNEO and membranolytic attack complex, both of which are deposited in the endomysial microvasculature (Dalakas, 1995b, 2001a, 2001b; Dalakas and Hohlfeld, 2003). The membranolytic attack complex deposition on the intramuscular capillaries leads to osmotic lysis of the endothelial cells and necrosis of the capillaries. This results in marked reduction in the number of capillaries per muscle fiber and dilatation of the remaining capillaries in an effort to compensate for impaired perfusion. Larger intramuscular blood vessels are also affected in the same pattern, leading to muscle fiber destruction (often resembling microinfarcts) and inflammation. The perifascicular atrophy often seen in more chronic stages is probably a reflection of the endofascicular hypoperfusion that is prominent distally (Fig. 1). Specific pathogenic autoantibodies against the endothelial cells have not yet been identified in spite of some early efforts (Cervera et al., 1991; Stein et al., 1993). The activation of complement induces the release of cytokines and chemokines, which, in turn, upregulate the expression VCAM-I and ICAM-I on the endothelial cells (Stein and Dalakas, 1993). These molecules serve as ligands for the integrins VLA-4, LFA-I, and Mac-I expressed on T cells and facilitate their exit through the blood vessel wall to the perimysial and endomysial spaces. Various chemokines have been upregulated at the protein and mRNA level (De Bleecker et al., 2002; Raju et al., 2003; Confalonieri et al., 2000). Immunophenotypic analysis of the lymphocytic infiltrates demonstrates B cells, CD4+ cells and plasmacytoid and dendritic cells in the perimysial and perivascular regions, supporting the view that a humoral-mediated mechanism plays the major role in the disease. Other molecules upregulated in DM include TGF-beta (Amemiya et al., 2000) and (in the perifascicular regions) the cathepsins and STAT-I, probably triggered by interferon-gamma (Gallardo et al., 2001). After successful therapy, repeat biopsies fail to demonstrate such abnormalities, as described later. Using gene arrays, a number of adhesion molecules, cytokine and chemokine genes are upregulated in the muscles of DM patients. Most notable among those genes are the KAL-1 adhesion molecule, which is upregulated by TGF-β and may have a role in inducing fibrosis (Raju and Dalakas, 2005), and genes induced by α/β interferon (Greenberg et al., 2005). One of the proteins induced by α/β interferon is the Myxovirus Resistance MxA protein, which is found in abundance predominantly in the perifascicular regions. The cellular source of the abundant interferon α/β in DM is probably the large number of plasmacytoid dendritic cells suggesting that in DM the innate immune response is also involved in a pattern similar to systemic lupus erythematosus (Greenberg et al., 2005).

4.2.2. Skin

The histological picture of skin lesions in DM is characterized by dermal perivascular infiltrates consisting mainly of CD4+ cells, followed by macrophages (Hausmann et al., 1991). B lymphocytes are sparse and CD1α+ Langerhans cells are diminished in the epidermis but increased in dermal

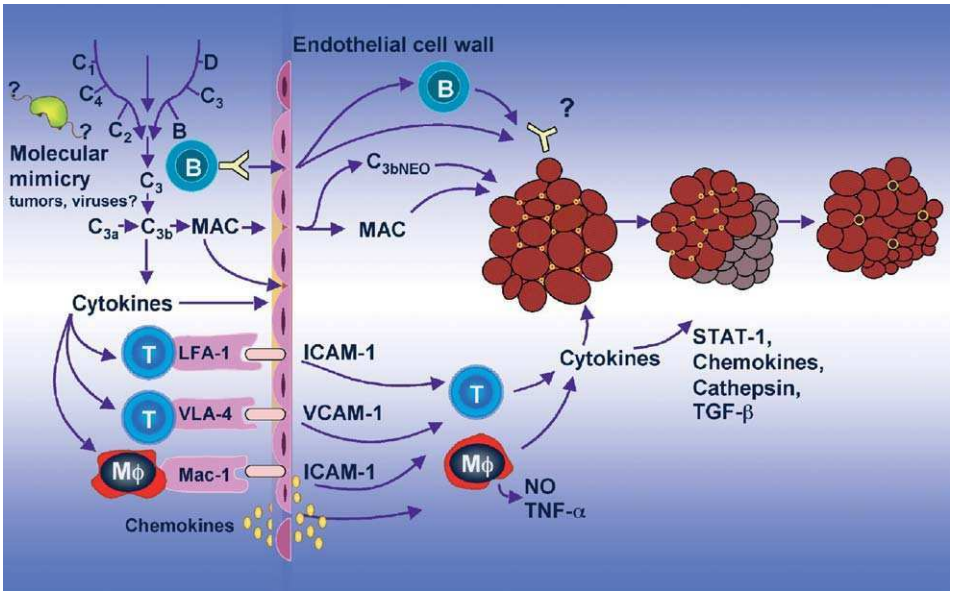


Figure 1. Sequence of immunopathologic changes in dermatomyositis beginning with activation of complement and formation of C3 through the classic or alternative pathway by antibodies (Y) against endothelial cells. Activated C3 leads to formation of C3b, C3bNEO, and membranolytic attack complex that transverse across the endothelial cell wall to the endomysial capillaries (A). Deposition of membranolytic attack complex leads to destruction and reduced number of capillaries, with ischemia or microinfarcts most prominent in the periphery of the fascicle (B). Finally, a smaller than normal number of capillaries with dilated diameter remain and perivascular atrophy ensues (C). Not only the complement-fixing antibodies (Y) but also B cells, CD8+ T cells, and macrophages traffic to the muscle. The migration of cells from the circulation is facilitated by the VCAM and ICAM molecules whose expression on the endothelial cells is upregulated by the released cytokines. T cells and macrophages through their integrins VLA-4, LFA-I, and Mac-I bind to the VCAM and ICAM and traffic to the muscle through the endothelial cell wall.

papillae. Skin biopsies of the Gottron's papules demonstrate cellular infiltrates consisting of activated CD4+ lymphocytes (expressing HLA-DR and CD40L molecules) located in the perivascular areas of the upper dermis and subepidermally (Caproni et al., 2004). The CD8+ T cells are few. This finding is consistent with the humoral-mediated process seen in the muscle of DM patients, as described earlier. Because CD40 molecule was present on the basal keratinocytes while the neighboring CD4+ T cells expressed CD40L, the CD40-CD40-L system appears to be involved in the cutaneous manifestation of DM, probably via the upregulation of cytokines and chemokines, in a pattern similar to the one described for the muscle (Sugiura et al., 2000). Upregulation of cytokines, chemokines and deposits of C5b-9 have been also observed in the skin lesions of DM patients (Magro and Crowson, 1997). Although the immunopathology of the skin has not been studied as thoroughly as the muscle, it appears to be based on these limited studies that in DM a complement-mediated endotheliopathy is a common final pathway for both the skin and the muscle. For the immunopathology of the skin, it remains to be established what is the role of dendritic cells or plasmacytoid cells, the APC function of keratinocytes or Langerhans cells and the immunomodulatory genes involved in the manifestation of skin lesions. Considering the accessibility of the skin, these studies are not difficult to pursue.

The cause of calcifications, which are more prominent in juvenile DM (Dalakas, 1995a) remains unclear. In two cases, the milk of calcium extracted from the subcutaneous collections was found to contain macrophages, IL6, IL1, and TNF-α suggesting activation of macrophages. These cases have also responded to alendronate (Mukamel et al., 2001).

5. Clinical manifestations

Dermatomyositis occurs in both children and adults. It is a distinct clinical entity identified by a characteristic rash accompanying or, more often, preceding the muscle weakness. The skin manifestations include a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron rash) (Dalakas 1990, 1991; Karpati and Carpenter, 1993; Engel et al., 1994; Dalakas and Hohlfeld, 2003). The initial erythematous lesions may result in scaling of the skin accompanied by pigmentation and depigmentation, giving at times a shiny appearance. In contrast to systemic lupus erythematosus, in which the phalanges are involved and the knuckles are spared, the erythema of DM spares the phalanges. The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck, and anterior chest (often in a V sign), or back and shoulders (shawl sign), and may be exacerbated after exposure to the sun. Dilated capillary loops at the base of the fingernails are also characteristic of DM. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, ''dirty'' horizontal lines, resembling a mechanic's hand. DM in children resembles the adult disease, except for more frequent extramuscular manifestations, as discussed later. A tiptoe gait due to flexion contracture of the ankles is a common early abnormality in children. A common early abnormality in children is ''misery,'' defined as an irritable child that feels uncomfortable, has a red flush on the face, is fatigued, does not feel like socializing, and has a varying degree of muscle weakness (Dalakas 1991, 2001c; Dalakas and Karpati, 2001; Dalakas and Hohlfeld, 2003). When the weakness develops, it takes the form of a myopathy, with proximal more than distal involvement. The degree of weakness can be mild, moderate, or severe, leading to quadriparesis. Some patients with the classic skin lesions appear to have clinically normal strength even up to 3–5 years after onset. This form, referred to as ''dermatomyositis sine myositis'' or ''amyopathic dermatomyositis'' (Sontheimer, 2002), has a better overall prognosis. Although in these cases the disease appears limited to the skin, the muscle biopsy shows significant perivascular and perimysial inflammation and immunopathological features identical to those seen in classic DM (Otero and Dalakas, 1992) suggesting that amyopathic and myopathic forms are part of the range of DM affecting skin and muscle to a varying degree.

Dermatomyositis usually occurs alone, but it may overlap with systemic sclerosis and mixed connective tissue disease. Fasciitis and skin changes similar to those found in DM have occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated L-tryptophan (Medsger, 1990; Dalakas, 1991); and with eosinophilic fasciitis or macrophagic myofasciitis (Gherardi et al., 1998).

5.1. Extramuscular manifestations

In addition to the primary disturbance of the skeletal muscles and skin, extramuscular manifestations may be prominent in some patients with DM. These include (a) dysphagia, similar to that of patients with scleroderma; (b) cardiac abnormalities consisting of atrioventricular conduction defects, tachyarrhythmia, low ejection fraction, and dilated cardiomyopathy (either due to the disease itself or, more often, to hypertension or fluid retention associated with long-term steroid use); (c) pulmonary involvement, resulting from primary weakness of the thoracic muscles, drug-induced pneumonitis (eg. from methotrexate), or interstitial lung disease. Interstitial lung disease may precede the myopathy or occur early in the course of the disease, especially in patients who have anti-Jo-1 antibodies, as discussed later; (d) subcutaneous calcifications, sometimes opening onto the skin and causing ulcerations and infections, especially in children (Dalakas, 1995; Dalakas and Hohlfeld, 2003); (e) gastrointestinal ulcerations, seen more often in the childhood form, due to vasculitis and infections; (f) contractures of the joints, especially in the childhood form; and (g) general systemic disturbances,

such as fever, malaise, weight loss, arthralgia, and Raynaud phenomenon, especially when DM is associated with a connective tissue disorder.

6. Diagnostic investigations

The clinical diagnosis of DM is confirmed by assessing the level of serum muscle enzymes, the electromyographic findings, and the muscle biopsy. In classic cases, however, the typical skin manifestations in combination with muscle weakness are almost sure indicators of DM, even on clinical grounds alone.

6.1. Serum muscle enzymes

The most sensitive enzyme is creatine kinase, which in the presence of active disease can be elevated up to 50 times the normal level. Although creatine kinase activity usually parallels disease severity, it can be normal in some patients with untreated DM and in others with DM and connective tissue disease, probably reflecting the predominant involvement of the intramuscular vessels and the perimysium. Along with creatine kinase, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase, and aldolase may also be elevated.

6.2. Electromyography

Needle electromyography shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed myopathic and neurogenic potentials (polyphasic units of short- and long-duration) can occasionally be seen in DM as a consequence of muscle fiber regeneration and indicate chronicity of the disease.

6.3. Muscle biopsy

Muscle biopsy is the definitive test to exclude other neuromuscular diseases and assess severity of involvement. The following unique histological features are characteristic of DM (Dalakas and Hohlfeld, 2003) (a) endomysial inflammation, predominantly perivascular or in the interfascicular septa and around rather than within the fascicles; (b) endothelial hyperplasia with tubuloreticular profiles in the intramuscular blood vessels along with fibrin thrombi (especially in children) and obliteration of capillaries; (c) necrosis, degeneration, and phagocytosis affecting often groups of fibers within a muscle fascicle in a wedge-like shape or at the periphery of the fascicle due to microinfarcts within the muscle; and (d) perifascicular atrophy. The presence of perifascicular atrophy is diagnostic of DM, even in the absence of inflammation. The skin biopsy also shows the abnormalities mentioned earlier but taking routine skin biopsy samples is not helpful (Callen, 2000).

7. Differential diagnosis

The rash and the calcifications are so characteristic that the diagnosis of DM is very rarely in doubt. Sometimes muscle strength is normal (DM sine myositis), in spite of clear evidence of subclinical muscle involvement in the muscle biopsy. At times, the rash may be barely detectable (especially in dark-skinned people), and the diagnosis can be made only in retrospect on the basis of subcutaneous calcifications found accidentally. The skin changes in the phalanges may be distinguished from those due to systemic lupus erythematosus because in the latter the phalanges are involved and the knuckles are spared while in DM the reverse is true.

Calcinosis universalis (the subcutaneous calcifications seen in DM) should not be confused with myositis ossificans, a rare disease associated with skeletal deformities, such as short great toe or curved fingers. This disease begins in the second year of life and involves bone and subcutaneous tissue rather than muscle. The bone is deposited beneath the skin or within the muscle in the limbs or paraspinal regions, and this is often preceded by soft localized swellings.

Another disease that shares features with DM is the eosinophilia myalgia syndrome caused by the

ingestion of contaminated L-tryptophan (Medsger, 1990). In the eosinophilia myalgia syndrome, the skin can be very tight and shiny but is not erythematous. Joint contractures are common. Although the inflammatory process is mostly confined to the subcutaneous tissue, inflammation can spread to the muscle and cause myopathic muscle weakness (Illa et al., 1993). The eosinophilia myalgia syndrome resembles the Spanish toxic oil syndrome, but it has not yet been seen with other contaminants.

Dermatomyositis may rarely have some overlapping similarities with Shulman syndrome (eosinophilic fasciitis), especially joint contractures and thickening of the skin and subcutaneous tissue (Shulman, 1975).

Another disorder recently recognized that may have some apparent similarities with DM is the macrophagic myofasciitis identified in French patients at the areas of local intramuscular injection with aluminum-containing vaccines. This entity can cause systemic symptoms of fatigue, myalgia, and mild muscle weakness years after the vaccinations. Although it has no skin manifestations, the pathology is in the perimysial and perifascicular regions as in DM. In contrast to DM, however, the inflammatory cells are exclusively macrophages, and the capillaries are normal (Gherardi et al., 2001).

8. Prognosis and complications

The natural history of DM is unknown, as most patients nowadays are treated with steroids. The mortality rates reported 20–30 years ago are outdated. Clinical experience indicates that DM responds to therapy more readily than polymyositis. In children, DM may at times be a monophasic disease with infrequent flares once the disease is under control. We have seen, however, late progression in some patients, including the development of inclusion-body myositis in two patients (Dalakas, unpublished observations). Patients with interstitial lung disease may have a high mortality rate, requiring aggressive treatment with cyclophosphamide or Tacrolimus. Overall, there are still a number of patients who do not respond adequately to therapies and remain disabled. The rare patients with acute fulminating disease seem to be more difficult to treat and more resistant to therapies. A major problem with DM is the subcutaneous calcifications that, once formed, are not easily dissolved and are resistant to all therapies. When they protrude to the skin, they result is ulcerations, infections, and permanent disfiguring scars. The pathogenic mechanism of these calcium deposits is obscure. Other complications are related to gastrointestinal ulcerations, melena, hematemesis, or even infarctions affecting long stretches of the bowel. Before the use of steroids and other immunosuppressants, these complications were serious, leading to death. Although rare now, they still occur, especially in children.

9. Management

The evidence that immunopathologic mechanisms are primarily involved in the pathogenesis of DM justifies treating the disease with immunosuppressive therapies. Most of the treatment trials, however, have been empirical, because large-scale control therapeutic studies in childhood or adult DM have not been conducted (Dalakas 1989, 1991, 1994a, 2001c; Dalakas and Karpati, 2001). As the specific target antigens are also unknown, these therapies are not selectively directed to the autoreactive T cells or to the complement-mediated process in the intramuscular blood vessels; rather, they induce nonselective immunosuppression or immunomodulation (Dalakas, 1995).

The goal of therapy in DM is to improve function in activities of daily living as the result of improvement in muscle strength, and improve the skin alterations. Although improvement in strength is usually accompanied by a fall in serum creatine kinase, decreases of serum creatine kinase have to be interpreted with caution because most immunosuppressive therapies result in a decrease in serum muscle enzymes without necessarily improving muscle strength (Dalakas, 1992a, 1997). For patients with disease limited to the skin, our preference is to use low doses of steroids or hydroxychloroquine sulfate and avoid immunosuppressants until weakness develops.

9.1. Corticosteroids

Prednisone is the first-line drug of this empirical treatment. Its mechanism of action is unclear, but it may involve inhibiting recruitment and migration of lymphocytes to the areas of muscle inflammation and interfering with the production of lymphokines. Because response to prednisone, an effective and relatively safe drug for short-term use, determines whether or not stronger immunosuppressive drugs will be needed, I prefer an aggressive approach with high-dose prednisone beginning early in the disease (Dalakas, 1997). A high dose of 80–100 mg/day as a single daily morning dose for an initial period of 3–4 weeks is my preference. In patients with aggressive disease, methylprednisolone 1 gm i.v. every day for 3 days may be considered first, followed by the oral steroid dose. Prednisone is then tapered over a 10-week period to an 80–100 mg single dose every other day by gradually reducing an alternate "off-day" dose by 10 mg per week, or faster if necessitated by side effects (though this carries a greater risk of breakthrough of disease). If there is evidence of efficacy and no serious side effects, the dosage is reduced gradually by 5–10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. If by the time the dosage has been reduced to 80–100 mg every other day (approximately 14 weeks after initiating therapy) there is no objective benefit (defined as increased muscle strength and not as decreased serum creatine kinase or subjective feeling of increased energy), the patient may be considered unresponsive to prednisone and tapering is accelerated while another immunosuppressive drug is started (Dalakas, 1988, 1989, 1994a).

9.2. Prednisone failures and nonsteroidal immunosuppressive therapies

Although it is my view that almost all patients with DM respond to steroids to some degree and for some period of time, some patients fail to respond or become steroid-resistant. The rationale for starting another immunosuppressive drug in DM patients is based on the following factors: (a) need for a "steroid-sparing" drug when, despite steroid responsiveness, the patient has developed significant complications; (b) repeated relapses after attempts to lower a high steroid dosage; (c) ineffectiveness of an adequate dose of prednisone for at least a 2–3 month period; and (d) rapidly progressive disease with evolving severe weakness and respiratory failure. The preference for selecting the next-in-line immunosuppressive therapy is, however, empirical. The choice is usually based on a physician's own bias, personal experience with each drug, and assessment of the relative efficacy/safety ratio. The following therapies are used in the treatment of patients with DM:

Azathioprine a derivative of 6-mercaptopurine, is given orally. Although lower doses (1.5–2 mg/kg) are commonly used, I prefer higher doses up to 3 mg/kg for effective immunosuppression. This drug is well tolerated, has fewer side effects, and empirically appears to be as effective for long-term therapy as other drugs. Because azathioprine is usually effective after 6–9 months of treatment, patience is required before concluding that the drug is ineffective.

Methotrexate an antagonist of folate metabolism, is also used and preferred among some practitioners because it acts faster than azathioprine. It can be given orally starting at 7.5 mg weekly for the first 3 weeks (given in a total of 3 doses, 2.5 mg every 12 h), increasing it gradually by 2.5 mg/week up to a total of 25 mg weekly. An important side effect is methotrexate-pneumonitis, which can be difficult to distinguish from the interstitial lung disease accompanying DM and often associated with Jo-1 antibodies, as described above.

Cyclophosphamide an alkylating agent, is preferably given intravenously at doses of 0.5–1 gm/m^2. Cyclophosphamide has shown promising results in some patients (Bombardieri et al., 1989). Although in our hands it was ineffective in patients with severe disease, the drug may be helpful in a subset of patients with interstitial lung disease.

Cyclosporine has been used with limited success. Although, the toxicity of the drug can be monitored by measuring optimal trough serum levels (which vary between 100 and 250 ng/mL), its effectiveness in DM is uncertain. Low doses of cyclosporine can

benefit children with DM (Heckmatt et al., 1989). Cyclosporine has been tried as a first-line therapy in DM patients with promising results (Grau et al., 1994). The advantage of cyclosporine is that it acts faster than azathioprine, so the results (positive or negative) may be apparently early.

Mycophenolate is another agent that appears promising, even for the skin lesions in some cases (Gelber et al., 2000), but control studies have not yet began.

Tacrolimus acting as calcineurin inhibitor, has shown promise in the treatment of difficult cases (Yamada et al., 2004). The experience with this drug is however limited.

Rituximab is an anti-CD20 monoclonal antibody that causes depletion of B cells. This drug seems to be a promising new agent in some DM patients (Levine, 2005).

Rapamycin a new immunosuppressant that binds to FKB protein, inhibits the IL2 synthesis by autoreactive T cells. It was shown to improve skin lesions in a patient with DM unresponsive to available agents (Nadiminti and Arbiser, 2005).

Plasmapheresis was not helpful in a double-blind, placebo-controlled study that we conducted (Miller et al., 1992). However, occasional patients with active DM can improve if plasmapheresis is combined with immunosuppressive drugs.

Intravenous immunoglobulin taken from human serum pools, has been shown to be very effective, although very expensive, therapy. In uncontrolled studies, intravenous immunoglobulin was reported to be effective (Cherin et al., 1991; Lang et al., 1991), but efficacy was confirmed with a controlled trial. In the first double-blind study, intravenous immunoglobulin was shown to be effective in patients with refractory DM, not only improving the strength and the skin rash but also clearing the underlying immunopathology (Dalakas et al., 1993; Dalakas, 1999). The improvement begins after the first intravenous immunoglobulin infusion and is clearly evident by the second monthly infusion, often showing first in the skin. The benefit is short-lived (not more than 8 weeks), requiring repeated infusions every 6–8 weeks to maintain improvement.

The mechanism of action of intravenous immunoglobulin in DM is by inhibiting the deposition of activated complement fragment in the capillaries (Basta and Dalakas, 1994), by suppressing cytokines (especially ICAM-I), or by saturating Fc receptors and interfering with the action of macrophages (Dalakas et al., 1993).

According to the efficacy of the aforementioned agents and our experience, our step-by-step approach in the treatment of DM is as follows:

Step 1: High-dose prednisone (oral or intermittent intravenously in acute cases)
Step 2: Add mild immunosuppressants, such as azathioprine, methotrexate or mycophenolate, for steroid sparing effect
Step 3: If Step 1 fails, try high-dose intravenous immunoglobulin
Step 4: If the above fail, consider a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug and the patient's general health: cyclosporin, cyclophosphamide, tacrolimus or rituximab.

Treatment for calcinosis remains difficult. Attempts with alendronate (Mukamel et al., 2001), probenecid (Harel et al., 2001), or diltiazem thought to be promising, offer limited help.

References

Amemiya, K., Semino-Mora, C., Granger, R.P., et al. 2000. Downregulation of TGF-β1 mRNA and protein in the muscles of patients with inflammatory myopathies after treatment with high-dose intravenous immunoglobulin. Clin. Immunol. 94, 99.

Banker, B.Q. 1975. Dermatomyositis of childhood. Ultrastructural alterations of muscle and intramuscular blood vessels. J. Neuropathol. Exp. Neurol. 35, 46.

Banker, B.Q., Victor, M. 1966. Dermatomyositis (systemic angiopathy) of childhood. Medicine 45, 261.

Basta, M., Dalakas, M.C. 1994. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J. Clin. Invest. 94, 1729.

Bombardieri, S., Hughes, G.R., Neri, R., et al. 1989. Cyclophosphamide in severe polymyositis. Lancet 1, 1138.

Buckbinder, R., Forbes, A., Hall, S., et al. 2001. Incidence of malignant disease in biopsy-proven inflammatory myopathy. A population-based cohort study. Ann. Intern. Med. 134, 1087.

Callen, J.P. 2000. Dermatomyositis. Lancet 355, 53.

Caproni, M., Torchia, D., Cardinali, C., et al. 2004. Infiltrating cells, related cytokines and chemokine receptors in lesional skin of patients with dermatomyositis. Br. J. Dermatol. 151, 784.

Carpenter, S., Karpati, G., Rothman, S., et al. 1976. The childhood type of dermatomyositis. Neurology 26, 952.

Cervera, R., Ramires, G., Fernandez-Sola, J., et al. 1991. Antibodies to endothelial cells in dermatomyositis: association with interstitial lung diseases. Br. Med. J. 302, 880.

Cherin, P., Herson, S., Wechsler, B., et al. 1991. Efficacy of intravenous immunoglobulin therapy in chronic refractory polymyositis and dermatomyositis. An open study with 20 adult patients. Am. J. Med. 91, 162.

Confalonieri, P., Bernasconi, P., Megna, P., et al. 2000. Increased expression of beta-chemokines in muscle of patients with inflammatory myopathies. J. Neuropathol. Exp. Neurol. 59, 164.

Dalakas, M.C. 1989. Treatment of polymyositis and dermatomyositis. Curr. Opin. Rheumatol. 1, 443.

Dalakas, M.C. 1990. Inflammatory myopathies. Curr. Opin. Neurol. Neurosurg. 3, 689.

Dalakas, M.C. 1991. Polymyositis, dermatomyositis, and inclusion-body myositis. N. Engl. J. Med. 325, 1487.

Dalakas, M.C. 1994a. Current treatment of the inflammatory myopathies. Curr. Opin. Rheumatol. 6, 595.

Dalakas, M.C. 1995a. Calcifications in dermatomyositis. N. Engl. J. Med. 333, 978.

Dalakas, M.C. 1995b. Immunopathogenesis of inflammatory myopathies. Ann. Neurol. 37, 74.

Dalakas, M.C. 1997. Polymyositis. In: S. Gilman, G.W. Goldstein, S.G. Waxman (Eds.), MedLink Neurology. Arbor Publ, San Diego, CA.

Dalakas, M.C. 1999. Intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: present status and practical therapeutic guidelines. Muscle Nerve 22, 1479.

Dalakas, M.C. 2001a. Progress in inflammatory myopathies: good but not good enough. Editorial. J. Neurol. Neurosurg. Psychiatry 70, 569.

Dalakas, M.C. 2001b. The molecular and cellular pathology of inflammatory muscle diseases. Curr. Opin. Pharmacology 1, 300.

Dalakas, M.C. 2001c. Polymyositis, dermatomyositis and inclusion body myositis. In: E. Braunwald, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J.L. Jameson (Eds.), Harrison's Principles of Internal Medicine, 15th ed., McGraw-Hill, New York, p. 2524.

Dalakas, M.C. 2003. Therapeutic approaches in patients with inflammatory myopathies. Semin. Neurol. 23, 121.

Dalakas, M.C., Hohlfeld, R. 2003. Polymyositis and dermatomyositis. Lancet 362, 971.

Dalakas, M.C., Karpati, G. 2001. The inflammatory myopathies. In: G. Karpati, D. Hilton-Jones, R.C. Griggs (Eds.), Disorders of Voluntary Muscle, 7th ed., Cambridge University Press, London, p. 636.

Dalakas, M.C., Illa, I., Dambrosia, J.M., et al. 1993. A controlled trial of high-dose intravenous immunoglobulin infusions as treatment for dermatomyositis. N. Engl. J. Med. 329, 1993.

De Bleecker, J.L., De Paepe, B., Vanwalleghem, I.E., et al. 2002. Differential expression of chemokines in inflammatory myopathies. Neurology 58, 1779.

Emslie-Smith, A.M., Engel, A.G. 1990. Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann. Neurol. 27, 343.

Engel, A.G., Emslie-Smith, A.M. 1989. Inflammatory myopathies. Curr. Opin. Neurol. Neurosurg. 2, 695.

Engel, A.G., Hohlfeld, R., Banker, B.Q. 1994. The polymyositis and dermatomyositis syndrome. In: A.G. Engel, C. Franzini-Armstrong (Eds.), Myology. McGraw-Hill, New York, p. 1335.

Friedman, A.W., Targoff, I.N., Arnett, F.C. 1996. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. Semin. Arthritis Rheum. 26, 459.

Gallardo, E., De Andres, I., Illa, I. 2001. Cathepsins are upregulated by IFN-gamma/STAT1 in human muscle culture: a possible active factor in dermatomyositis. J. Neuropath. Exp. Neurol. 60, 847.

Gelber, A.C., Nousari, H.C., Wigley, F.M. 2000. Mycophenolate mofetil in the treatment of severe skin manifestations of dermatomyositis: a series of 4 cases. J. Rheumatol. 27, 1542.

Gherardi, R.K., Coquet, M., Cherin, P., et al. 1998. Macrophagic myofasciitis: an emerging entity. Lancet 352, 347.

Gherardi, R.K., Coquet, M., Cherin, P., et al. 2001. Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. Brain 124, 1821.

Grau, J.M., Herrero, C., Casademont, J., et al. 1994. Cyclosporine A as first choice for dermatomyositis. J. Rheumatol. 21, 381.

Greenberg, S.A., Pinkus, J.L., Pinkus, G.S., et al. 2005. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann. Neurol. 57, 664.

Harel, L., Harel, G., Korenreich, L., et al. 2001. Treatment of calcinosis in juvenile dermatomyositis with probenecid: the role of phosphorus metabolism in the development of calcifications. J. Rheumatol. 28, 1129.

Hausmann, G., Herrero, C., Cid, M.C., et al. 1991. Immunopathologic study of skin lesions in dermatomyositis. J. Am. Acad. Dermatol. 25, 225.

Heckmatt, J., Hasson, N., Saunders, C., et al. 1989. Cyclosporin in juvenile dermatomyositis. Lancet 1, 1063.

Hengstman, G.J.D., van Engelen, B.G.M., Egberts, W.T.M.V., et al. 2001. Myositis-specific autoantibodies: overview and recent developments. Curr. Opin. Rheumatol. 13, 476.

Hill, C.L., Zhang, Y., Sigurgeirsson, B., et al. 2001. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 357, 96.

Illa, I., Dinsmore, S., Dalakas, M.C. 1993. Immune-mediated mechanisms and immune activation of fibroblasts in the pathogenesis of eosinophilia-myalgia syndrome induced by L-tryptophan. Hum. Pathol. 24, 702.

Jerusalem, F., Rakusa, M., Engel, A.G., et al. 1974. Morphometric analysis of skeletal muscle capillary ultrastructure in inflammatory myopathies. J. Neurol. Sci. 23, 391.

Jury, E.C., D'Cruz, D., Morrow, W.J. 2001. Autoantibodies and overlap syndromes in autoimmune rheumatic disease. J. Clin. Pathol. 54, 340.

Karpati, G., Carpenter, S. 1993. Pathology of the inflammatory myopathies. In: F.L. Mastaglia (Ed.), Bailliere's Clinical Neurology. WB Saunders, London, p. 527.

Khattak, F.H., Morris, I.M., Branford, W.A. 1994. Simvastatin-associated dermatomyositis. Br. J. Rheumatol. 33, 199.

Kissel, J.T., Mendell, J.R., Rammohan, K.W. 1986. Microvascular deposition of complement membrane attack complex in dermatomyositis. N. Engl. J. Med. 314, 329.

Kubo, M., Ihn, H., Kuwana, M., et al. 2001. Prevalence in myositis of antibodies recognizing anti-U3 RNA probably in a novel complex with 22/25 kD protein and not fibrillarin. Clin. Exp. Immunol. 126, 339.

Lang, B., Laxer, R.M., Murphy, G., et al. 1991. Treatment of dermatomyositis with intravenous immunoglobulin. Am. J. Med. 91, 169.

Levine, T.D. 2005. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 52, 601.

Magro, C.M., Crowson, A.N. 1997. The immunofluorescent profile of dermatomyositis: a comparative study with lupus erythematosus. J. Cutan. Pathol. 24, 543.

Medsger, T.A. 1990. Tryptophan induced eosinophilia myalgia syndrome. N. Engl. J. Med. 322, 926.

Miller, F.W., Leitman, S.F., Cronin, M.E., et al. 1992. A randomized double-blind controlled trial of plasma exchange and leukapheresis in patients with polymyositis/dermatomyositis. N. Engl. J. Med. 326, 1380.

Mukamel, M., Horey, G., Mimouni, M. 2001. New insight into calcinosis of juvenile dermatomyositis: a study of composition and treatment. J. Pediatr. 138, 763.

Nadiminti, U., Arbiser, J.L. 2005. Rapamycin (sirolimus) as a steroid-sparing agent in dermatomyositis. J. Am. Acad. Dermatol. 52, 517.

Noel, B., Cerottini, J.P., Panizzon, R.G. 2001. Atorvastatin-induced dermatomyositis. Am. J. Med. 1, 670.

Otero, C., Dalakas, M.C. 1992. Onset of polymyositis (PM) and dermatomyositis (DM) during pregnancy: report of 4 cases. Ann. Neurol. 32, 282.

Raju, R., Dalakas, M.C. 2005. Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIg and biological validation of clinically relevant genes. Brain 128, 1887–1896.

Raju, R., Vasconcelos, O.M., Semino-Mora, C., et al. 2003. Expression of interferon-gamma inducible chemokines in the muscles of patients with inclusion body myositis. J. Neuroimmunol. 141, 125.

Schalke, B.B., Schmidt, B., Toyka, K., et al. 1992. Pravastatin-associated inflammatory myopathy. N. Engl. J. Med. 327, 649.

Shulman, L.E. 1975. Diffuse fasciitis with eosinophilia: a new syndrome. Trans. Assoc. Am. Physicians 88, 70.

Sontheimer, R.D. 2002. Dermatomyositis: an overview of recent progress with emphasis on dermatologic aspects. Dermatol. Clin. 20, 387.

Stein, D.P., Dalakas, M.C. 1993. Intercellular adhesion molecule-I expression is upregulated in patients with dermatomyositis (DM). Ann. Neurol. 34, 268.

Stein, D.P., Jordan, S.C., Toyoda, M., et al. 1993. Anti-endothelial cell antibodies (AECA) in dermatomyositis (DM). Neurology 43, 356.

Sugiura, T., Kawaguchi, Y., Harigai, M., et al. 2000. Increased CD40 expression on muscle cells of polymyositis and dermatomyositis: role of CD40-CD40 ligand interaction in IL-6, IL-8, IL-15, and monocyte chemoattractant protein-1 production. J. Immunol. 164, 6593.

Unverricht, H. 1891. Dermatomyositis acuta. Dtsch. Med. Wochenschr. 17, 41.

Wagner, E. 1863. Fall liner selt nen. Muskelkrankhet Arch. Heilkd. 4, 288.

Whitaker, J.N., Engel, W.K. 1972. Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. N. Engl. J. Med. 286, 333.

Yamada, A., Ohshima, Y., Omata, N., et al. 2004. Steroid-sparing effect of tacrolimus in a patient with juvenile dermatomyositis presenting poor bioavailability of cyclosporine A. Eur. J. Pediatr. 163, 561.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 12

Mucocutaneous Manifestations of Sjogren's Syndrome

Stefano Bombardieri*, Chiara Baldini

Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy

1. Introduction

Sjogren's syndrome is a chronic autoimmune disorder of unknown aetiology characterized by the dysfunction and destruction of exocrine glands (Ramos-Casals et al., 2005). Sjogren's syndrome is one of the most common systemic autoimmune diseases and it may occur alone, as a primary condition (primary Sjogren's syndrome—pSS), or in association with other connective tissue diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), as secondary variants (secondary Sjogren's syndrome). In both cases salivary and lachrymal glands are the major target organs, typically associated with focal lymphocytic infiltrates, leading to dry mouth (xerostomia) and dry eyes (xerophthalmia) (Skopouli and Moutsopoulos, 1994). Although the sicca symptoms are the hallmarks of the syndrome, during disease progression any organ or mucosal surface may be involved. Thus, pSS presents as a heterogeneous non-organ-specific autoimmune entity, encompassing a wide spectrum of clinical manifestations, serological abnormalities and scattered complications (Roguedas et al., 2004). The most common extra-glandular symptoms are fatigue, arthralgias/myalgias and Raynaud's phenomenon. Moreover, systemic manifestations include chronic atrophic gastritis, renal tubular acidosis of the distal type, lung and skin involvement (Konttinen et al., 2000). Cutaneous manifestations are considered one of the most typical extraglandular features of pSS, although underestimated, owing both to their aspecificity and to the severe disability due to the exocrine glands involvement (Konttinen et al., 2000; Roguedas et al., 2004; Belenguer et al., 2005; Ramos-Casals et al., 2005). In particular, due to the involvement of the sweat and/or sebaceous glands, the dryness of the skin, a condition referred to as xerosis is frequently described (Konttinen et al., 2000). Quite commonly, in about two-thirds of the patients with pSS, epidermal IgG deposits have also been detected in the intracellular areas of the epidermidis using a direct immunofluorence technique, and they have been related to hypergammaglobulinaemia (Oxholm et al., 1984; Oxholm et al., 1987; Velthius et al., 1989). Moreover, a wide spectrum of vasculitis and non-vasculitic lesions, including leucocytoclastic vasculitis, mononuclear vasculitis, urticarial vasculitis, alopecia, non specific photosensitive cutaneous lesions, vitiligo, cutaneous amyloidosis and annular granuloma, have been described among the cutaneous manifestations of pSS (Roguedas et al., 2004; Ramos-Casals et al., 2005). In addition, cutaneous B and T cell lymphoma have also been reported to be associated with pSS (Jubert et al., 1993; Stroehmann et al., 2002; Selva -O' Callaghan et al., 2003). Although pSS often remains a relatively benign condition, lymphomas are traditionally considered as the main complication in the natural history of the disease (Ramos-Casals et al., 2005). Lymphomagenesis might be induced by

*Corresponding author.
Tel.: +39-050-40124; Fax: +39-050-502299.
E-mail address: s.bombardieri@int.med.unipi.it
(S. Bombardieri).

DOI: 10.1016/S1571-5078(05)05012-9

chronic stimulation of polyclonal B cells, and the transition from polyclonal lymphoproliferation to monoclonal lymphoproliferation to low-grade lymphoma and finally to high-grade lymphoma is considered a multi-step process involving B cells secreting rheumatoid factors and oncogenic proteins (Masaki and Sugai, 2004). Cutaneous lymphomas are quite rare and certainly they appear far less frequent than the more common B cell mucosa associated lymphoid tissue (MALT) lymphomas of the salivary glands or of other extra-nodal sites. Nevertheless, a recent multicentre European concerted action, describing malignant lymphomas characteristics, their clinical course and evolution in 33 patients followed in nine centres, reported two cases of cutaneous B-cell lymphoma (Voulgarelis et al., 1999).

2. Prevalence

The prevalence of pSS in the general population varies widely from 0.05% to 4.8% due to the different 'classification criteria' used (Drosos et al., 1988; Jacobsson et al., 1989; Zhang et al., 1995; Thomas et al., 1998). In fact, various classification criteria sets for pSS have been proposed in the last 30 years, from the "Copenhagen Criteria" (1976) (Manthorpe et al., 1986) to the "San Diego Criteria" (1986) (Fox et al., 1986) to the Preliminary European Classification Criteria (1993) (Vitali et al., 1993). None of them was universally accepted till the recent elaboration of the "Revised International Classification Criteria (2002) by an American and European Consensus Group (Vitali et al., 2002). It was thus difficult until recently to establish the real prevalence of pSS, since according to some criteria, the diagnosis of pSS can be made in the absence of objective evidence of inflammation and autoimmunity, while other criteria restrictively require both the presence of biopsy proven inflammation and autoimmunity (Gran 2002). Discordant data were thus available. Studies on geriatric populations revealed a prevalence of 1.9–4.83% (Drosos et al., 1988). In an epidemiological study performed in Sweden, the calculated prevalence of pSS according to the Copenhagen Criteria in 705 randomly selected adults, aged 52–72 years, was 2.7% (Manthorpe et al., 1986). In another epidemiological study in a Beijing suburban village, the prevalence of pSS was 0.77% according to the Copenhagen Criteria, and 0.33% according to the modified San Diego criteria (Zhang et al., 1995). Moreover, in Slovenia in an epidemiological study performed on 889 randomly selected adults, according to the Preliminary European Classification Criteria the estimated prevalence of definite SS is 0.60% (Tomsic et al., 1999). Nowadays the prevalence of pSS is estimated around 3% in the general population and in the US it is calculated that pSS is the second most common rheumatologic disorder. Moreover, internationally comparative studies between different ethnic groups have suggested that pSS is a homogeneous disease that occurs worldwide with similar prevalence and affects 1–2 million people (Phelan, 2001; Sanchez-Guerrero et al., 2005).

3. Epidemiology

pSS can occur in patients of all ages, but it affects primarily females during the fourth and fifth decade of life. The female/male ratio is about 9:1 (Rehman, 2003), thus, making pSS in men an uncommon condition with clinical and serological characteristics similar to those observed in women (Anaya et al., 1995; Cervera et al., 2000). Studies evaluating clinical or serological differences between male and female patients with pSS reveal that women may have more positive serological findings than men and a higher prevalence of fatigue, fibromyalgia, thyroidal manifestations and carpal tunnel syndrome. No sex differences could be established with other extraglandular manifestations of pSS, such as the presence of Raynaud's phenomenon, arthritis, erosive osteoarthritis, liver disease or other visceral manifestations (Brennan and Fox, 1999; Diaz-Lopez et al., 2004).

Paediatric presentation of pSS is very rare even though sporadic cases of the disease are reported in children from the age of 3 to the mid-teens (Siamopoulou-Mavridou et al., 1989). Data on 40 cases of pSS with onset before the 16th birthday have been recently published. Almost all patients (35/40) were females, age at onset varied from 9.3 to 12.4 years (mean 10.7 years), signs and

symptoms at disease onset were mainly recurrent parotid swelling followed by sicca symptoms and abnormal laboratory tests were found in the majority of cases (Cimaz et al., 2003).

Finally, elderly onset pSS disease seems to have milder clinical symptoms with fewer immunological manifestations than younger onset disease and the elevation of salivary interleukin (IL)-6 in the younger group of SS patients supports in part the differences in the inflammatory process between the two groups (Tishler et al., 2001).

4. Aetiology/Pathogenesis

Sjogren's syndrome is a systemic autoimmune disease characterized by dryness of the eye and mouth resulting from the lymphocytic infiltrates of the exocrine glands. The etiopathogenesis of the disease is generally thought as multifactorial involving a genetic predisposition, ambiental factors and disimmunity but, at present, remains broadly unknown (Delaleu et al., 2005). Table 1 summarizes the pSS etiopathogenetic process.

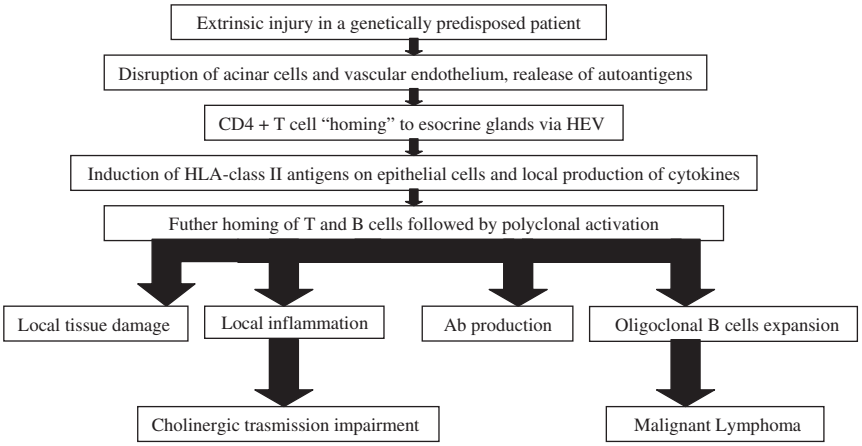
4.1. Aetiology: genetic predisposition

The hypothesis of a genetic predisposition to pSS lies in familial aggregation studies since cases of two or more individuals with pSS per family and pSS in twins have been described (Delaleu et al., 2005). Candidate genes for this genetic background are human leukocyte antigen (HLA) gene segments and, in particular in Caucasians, a correlation between pSS and haplotypes DR3 (DRB1*0101) and Drw52 has been demonstrated (Delaleu et al., 2005). Studies in Japanese patients have suggested that DRB4 allele DRw53 was the strongest risk factor in that population (Reveille and Arnett, 1992). Furthermore, Fas and Fas L, IL-10, TNF-alpha, IL-4 receptor and IL-1 RA gene polymorphisms have been analysed but no clear–cut relationship between these gene polymorphisms and pSS have been identified (Reveille and Arnett, 1992; Ramos-Casals et al., 2004; Tobon et al., 2005).

4.2. Aetiology: hormones

Sex hormones appear to play an important role as modulators of autoimmune disease onset/perpetuation. Steroid hormones are implicated in the immune response, with estrogens as enhancers at least of humoral immunity, and androgens and progesterone (and glucocorticoids) as natural immune suppressors (Cutolo et al., 2003). It is not a case then, if, as other autoimmune disease, pSS occurs more frequently in female than in male. Concerning the role of estrogens in autoimmunity, animal models showed controversial results. From

Table 1
Primary Sjogren's syndrome pathogenesis



one side it has been described that estrogens have the ability to promote naïve B-cell development in mice and to rescue B cells from B-cell receptor–mediated apoptosis while androgens may reduce glandular inflammation on the other side, it appears that estrogens deficiency may accelerate autoimmune exocrinopathy in murine Sjogren's syndrome through fas-mediated apoptosis (Parke, 2000; Ishimaru et al., 1999). The last results indicate that dysfunction of regulatory T cells by estrogens deficiency may play a crucial role on acceleration of organ-specific autoimmune lesions, and estrogenic action further influences target epithelial cells through Fas-mediated apoptosis in a murine model for SS (Ishimaru et al., 1999). Moreover, if it is widely accepted that estrogens promote the expression of autoimmune disease, it is at the same time true that pSS arises more typically in postmenopausal women; one explanation may be that sicca complaints, and not the glandular lesion process itself, may be worsened by lack of estrogens (Parke, 2000).

4.3. Aetiology: exogenous agents

The most discussed infectious agents in human pSS are Epstein-Barr virus (EBV), Coxsackievirus and human T-cell leukaemia virus-1 (HTLV-1) (Delaleu et al., 2005). The EBV genomic sequences were amplified in 88% of lachrymal glands obtained from patients with SS compared with 36% in control individuals. In contrast, several studies demonstrated normal serological response to EBV in pSS (Delaleu et al., 2005). As far as HTLV-1 is concerned, a possible association between HTLV and pSS was proposed in 1994 since mice transgenic for HTLV-1 tax gene developed an exocrinopathy similar to pSS (Green et al., 1989). Following studies aiming at detecting the tax gene of HTLV-I by polymerase chain reaction (PCR) in labial salivary glands from patients with Sjogren's syndrome, confirmed that HTLV-1 tax gene may play a role as a co-factor in the development of pSS (Mariette et al., 2000). However, additional studies in regions endemic for HTLV-1 revealed no association between HTLV-1 and pSS (Georges-Gobinet et al., 1998; Delaleu et al., 2005).

Finally, concerning Coxsackievirus infection, Triantafyllopoulou et al. (2004), using reverse transcriptase–polymerase chain reaction on minor salivary gland RNA samples, have recently provided evidence that pSS may be associated with this virus, and proposed a model suggesting that, in early preclinical stages of the disease, lymphocytes may carry the virus in the epithelial cells of the exocrine glands, which become persistently infected. During the course of the disease, the virus would be cleared from the systemic circulation, while it continues to replicate in epithelial cells that become highly specialized antigen-presenting cells. This initiates T- and B-cells recruitment in exocrine glands, which lead to the hallmark glandular infiltration (Triantafyllopoulou et al., 2004).

Many other viruses have been evaluated in the etipathogenesis of pSS and, among them, HCV virus has yielded a considerable interest due to the histological similarities between pSS sialoadenitis and sialoadenitis observed in HCV-infected patients (Delaleu et al., 2005). However, HCV patients present certain features that may allow to clinically differentiating them from pSS, including hepatic involvement and a different immunologic pattern, characterized by a higher prevalence of cryoglobulins and hypocomplementemia, and a lower prevalence of anti-Ro/SSA and anti-La/SSB (Ramos-Casals et al., 2002). These facts received attention in the newly proposed American-European consensus criteria, where HCV is listed as an illegibility criterion in clinical studies investigating pSS (Vitali et al., 2002).

4.4. Aetiology: microchimerism

Microchimerism of fetal cells has been involved in the etiopathogenesis of a wide spectrum of systemic autoimmune diseases (Mosca et al., 2003; Giacomelli et al., 2004). A possible role of maternal–fetal microchimerism in the etiopathogenesis of pSS has been suggested too, due to the presence of microchimeric cells in the salivary glands and lungs of female affected by pSS and to the histological similarity between pSS, systemic sclerosis and the chronic graft-vs-host disease, but the exact mechanisms by which microchimerism may contribute

to pSS etiopathogenesis needs to be further elucidated (Kuroki et al., 2002; Endo et al., 2002).

4.5. Pathogenesis: autoimmune epithelitis

The main histopathological feature of pSS is a persistent mononuclear cell infiltrate of exocrine glands consisting of T cells, B cells, dendritic cells and macrophages. These events may be accompanied by parenchymal atrophy and replacement of glandular structures by fibrotic scar tissue (Skopouli and Moutsopoulos, 1994). These histological observations suggest that inflamed ductal epithelial cells are the focus of the inflammatory reaction in pSS, expressing elevated levels of HLA-DR and secreting high levels of proinflammatory cytokines (Skopouli and Moutsopoulos, 1994). The general mechanisms involved in the recruitment of inflammatory cells into sites of chronic inflammation assumes that, at an early stage of the disease, lymphocytes begin to accumulate in the lachrymal and salivary glands, most likely as a result of a homing process due to their adhesion to high endothelial venules (HEV) in the gland (Delaleu et al., 2005). The process is mediated by adhesion molecules as ICAM and VCAM-1 (Delaleu et al., 2005). Once recruited, lymphocytes within the salivary glands survive, consequent to reduced levels of apoptosis and induce epithelial cells activation secerning a wide spectrum of cytokines including INF-γ and TNF-α (Amft and Bowman, 2001). INF-γ, produced by infiltrating lymphocytes, plays a major role in the development of cell infiltrates by inducing the production of chemokines such as IP-10 and Mig in the ductal epithelium and the expression of CXCR3 on T cells (Ogawa et al., 2002). Moreover, production of the chemokines contribute to B cell-homing and ectopic germinal-like structure formation (Amft and Bowman, 2001). Finally, epithelial cells express Fas together with Bax, suggesting increased apoptosis as a major mechanism responsible for acinar cell destruction (Bolstad et al., 2003). Besides the interactions Fas/Fas ligand between epithelial cells and T-cytotoxic lymphocytes, apoptosis of the acinar and ductal epithelial cells may be induced by cytotoxic T cells through the release of proteases, such as perforin and granzyme B (Manganelli and Fietta, 2003). The increased rate of apoptosis of epithelial cells in pSS may result from either the imbalance between the downregulated apoptosis-inhibitor Bcl-2 and the upregulated apoptosis-inducer Bax, or the autocrine and/or paracrine Fas/FasL interaction (Manganelli and Fietta, 2003). Apoptotic salivary epithelial cells produce and present various autoantigens and autoreactive T cells in association with B cell, which may initiate the umoral autoimmune response (Ogawa et al., 2002). Polyclonal chronic B stimulation, then, could explain the presence in pSS of high titres of serum autoantibodies. Moreover, polyclonal B-cell activation can develop into an oligoclonal or monoclonal B-cell expansion, which may be the basis for the arising of a malignant lymphoproliferative disease (Delaleu et al., 2005).

4.6. Pathogenesis: interaction of immune and neurosecretory functions

Infiltrating lymphocytes play a major role in cell-mediated glandular destruction. Nevertheless, the sicca symptoms derive from a combination of destruction of glandular elements and dysfunction of the residual glands (Anaya and Talal, 1999). The inflammation in the microenvironment of a pSS-affected gland, and in particular inflammatory cytokines, including IL-1, interferon-γ and TNF-α can interfere with the ability of cholinergic nerves to release acetylcholine or with the cholinergic signal transmission impairing the acinar secretion. The glandular secretion, in fact, is mediated by cholinergic nerves that interact with muscarinic acetylcholine receptors predominantly of M1 and M3 subtypes. These cholinergic nerves release acetylcholine and vasoactive intestinal peptide mediating glandular function; inflammatory cytokines and Fas/Fas ligand interactions may then respectively, inhibit release of acetylcholine and interrupt the generation of second signals by G-coupled proteins of acetylcholine receptors, contributing to the development of sicca syndrome (Fox and Stern, 2002). A further mechanism that could be involved in the inhibition of secretory response in pSS, is the production of antibodies directed

against M3 muscarinic acetylcholine receptors (anti-M3R Abs) (Naito et al., 2005). The presence of anti-M3R Abs has been reported, and studies in animal model demonstrated that anti-M3R Abs reduce the secretory function in nonobese diabetic mouse (NOD) mice however, the ability of pSS sera to react with human M3 muscarinic acetylcholine receptors has not yet been proved (Robinson et al., 1998; Fox and Stern, 2002; Naito et al., 2005). An additional hypothesis that might contribute to the glandular dysfunction is a disorder of fluid transport. With regard to this aspect, it is worth noting that, in pSS, an abnormal distribution of aquaporin channels in salivary glands has been described (Fox and Stern, 2002). Aquaporin channels are water-specific and they regulate water movement across biological membranes; their hypoexpression may play a role in the deficiency of fluid secretion (Fox and Stern, 2002). However, studies aimed to analyse aquaporin channels distribution and density in labial salivary glands have thus far presented contrasting results.

In conclusion, the etiopathogenesis of pSS is a complex multifactorial process, which largely needs to be elucidated, and that causes an anatomical damage and a functional impairment of exocrine glands, progressively leading to many symptoms, the hallmark of which are the dryness of the eyes and of the mouth. A deeper comprehension of the pSS molecular mechanisms may allow to improve therapeutic strategies and disease control.

5. Clinical manifestations

5.1. Mucosal involvement: dry eyes

The tear film plays an essential role in promoting ocular surface integrity, defending against microbial challenge and preventing visual acuity. These functions, in turn, are extremely dependent upon the composition and stability of the tear-film structure. This includes an underlying mucin foundation (derived from globet cells and conjunctival- and corneal epithelial cells), a middle aqueous component (secreted primarily by lachrymal gland acinar and ductal epithelial cells) and an overlying lipid layer (originating from the meibomian glands). In pSS, due to the lymphocyte infiltration of lachrymal glands, a progressive decrease of the tear film, and especially of its aqueous component, develop and lead to a keratocongiuntivits sicca (KCS). The ocular surface disorder is then associated with a serious corneal disease affecting the lubrification and the homeostasis of the corneal surface (Rolando, 2001). Ocular irritation, burning, foreign body sensation and the need to keep the eye closed are the most common symptoms in patients with dry eye. Photophobia, pain, heavy eye and blurred vision may also be commonly described. Moreover, the cornea becomes irregular on the surface and the barrier activity of the epithelium may be impaired. Because of the failure of this barrier, frequent complications may arise, including ocular infections, keratitis and sometimes melting of the cornea or perforations (Rolando, 2001). Dry eyes disease is accompanied by an increase in the presence of inflammatory cytokines such as IL-1 β, which may play a key role in the pathogenesis and in perpetuation of KCS (Solomon et al., 2001). An interesting hypothesis is that IL-1β might contribute to a loss of corneal sensitivity, causing an interruption of the nerve impulse stimulation to the lachrymal gland, which in turn produces less fluid tears and an amount of tears rich of proinflammatory cytokines. As a consequence, the secretion of the lachrymal gland will inflame the ocular surface, keeping the vicious cycle going on (Rolando, 2001). This hypothesis of the diseased ocular surface that could further depress tear secretion, may justify the steady state situation of the tear gland function in pSS KCS during a long-term follow-up, compared with better prognosis in other forms of KCS (Kruize et al., 1997).

5.2. Mucosal involvement: dry mouth

Saliva, with its proteins and mineral salts, carries out many essential functions from the lubrification of the oral mucosa, to the contribution in initiating the digestive process, to soft tissue repair and the teeth remineralization. Moreover, saliva contains different antibacterial, antiviral and antimycotic agents, which are implicated in innate immunity and defence. These agents balance oral flora and inhibit bacterial colonization of teeth and soft

tissue, by modulating the adherence of microorganisms (Soto-Rojas and Kraus, 2002). The main consequence of hyposalivation is the constant feeling of dry mouth (xerostomia), with a wide spectrum of subjective symptoms, varying from burning mouth to difficulties while swallowing and chewing dry foods, sensitivity to spicy foods, altered taste, speech difficulties and increased liquid intake. Dryness of the mouth is the most common complaint in pSS patients, reported by 98% and assessed as moderate to severe in 90% of the cases (Lundstrom and Lundstrom, 1995). Dental decay, in the border of teeth as well as in radicular sites, and oral infections are also commonly observed and oral mucosa may appear affected by recurrent mucositis, and ulcers (Soto-Rojas and Kraus, 2002). Mucosal changes may also include dry, cracked lips and alterations of the tongue surface, which may become furrowed and deep fissured (Soto-Rojas and Kraus, 2002). Chronic erythematous candidiasis has been described in 70–75% of patients (Daniels and Fox, 1992). The oral symptoms of pSS usually have an insidious onset and progress gradually, and nutrition may be compromised either by the hyposalivation itself or by the related dysphagia, and by an impaired clearance of esophageal acid leading to chronic esophagitis. Finally, a further complication associated with hyposalivation is sleep disturbance caused by nicturia, due to an increase in fluid intake (Daniels and Fox, 1992).

5.3. Cutaneous involvement

Cutaneous manifestations of pSS seem to be frequent and various, and are generally distinguished in vasculitic and non vasculitic lesions (Roguedas et al., 2004; Ramos-Casals et al., 2005). Table 2 summarizes the broad spectrum of cutaneous lesions. The number of literature studies specifically dedicated to skin involvement, nonetheless, is quite limited and skin lesions are minimized, overwhelmed by the most subjective painful lachrymal and salivary glands impairment (Roguedas et al., 2004). So far, only few studies on large numbers of patients have been published and this appears quite surprising, considering the clinical significance of cutaneous vasculitis and its correlations with lymphoma development (Bloch et al., 1965; Whaley et al., 1973; Veki et al., 1991; Bernacchi et al., 2004).

5.3.1. Cutaneous involvement: xerosis

Skin dryness has been shown to be very common in Sjogren's syndrome with a frequency varying from 23 to 68% (Bloch et al., 1965; Whaley et al., 1973; Provost and Watson. 1992; Roguedas et al., 2004). The level of xerosis is significantly higher in the

Table 2
Primary Sjogren's syndrome cutaneous manifestations

Cutaneous vascular manifestation	Hypothesized explanation mechanism
Raynaud's phenomenon	Vasospastic phenomenon
Purpura	Leukocytoclastic /Mononuclear vasculitis
Urticarial vasculitis	Leukocytoclastic vasculitis
Erythematous nodules	Cutaneous vasculitis
Erythema multiforme—like lesion/ erythema perstants	dermal perivascular lymphohistiocytic infiltrate
Annular erythema	Dermal perivascular coat-sleeve-like lymphocytes infiltration
Non vascular cutaneous manifestations	**Hypothesized explanation mechanism**
Xerosis	Sweat glands number reduction and dysfunction
Angular cheilitis	Erythemato-squamous lesion predisposed by xerostomia
Eyelid dermatitis	Erythematous lesion predisposed by xerophthalmia (rubbing)
Alopecia areata	Lymphocitic infiltration of the sebaceous glands
Vitiligo	Loss of skin pigment due to autoimmune mechanism
Cutaneous B cell Lymphomas	Malignant B cells proliferation

primary than in the secondary form of the disease (Bernacchi et al., 2004). The most classical subjective symptoms of xerosis are non-specific pruritus, sensation of dryness, and a 'pin prick-like' feeling, which are associated with various objective signs such as rough, inelastic, hypotrophyc or fine scaling skin (Bernacchi et al., 2004). Scratching in response to the pruritus can lead to hyperpigmentation due to the repeated stimulation of the local melanocytes (Provost and Watson, 1992). The mechanism responsible for the skin xerosis in pSS patients has not been adequately elucidated (Provost and Watson, 1992). Cutaneous lubrification is provided basically by sebaceous glands, but sweat glands and apocrine glands may also contribute (Roguedas et al., 2004). An impairment of sweat glands is widely thought to be involved in pSS xerosis, since a decreased sweating has been reported in pSS patients (Whaley et al., 1973; Roguedas et al., 2004). A study by Katayama et al. (1995), aimed to assess the capacity of sweating in 49 patients affected by pSS, showed a statistically significant reduction in sweat volume of pSS in comparison with normal controls and patients affected by other dermatitis; sweating was induced by mental stimulation through hand grasping, measured with perspirometer and continuously recorded. Patients affected by other dermatitis displayed a decrease of sweating too, but their flow was not statistically lower than that of normal controls (Katayama et al., 1995). Other reports support the hypothesis of an impairment of eccrine sweat glands in pSS (Provost and Watson, 1992). Mitchell et al. (1987) performed a punch biopsy of the skin in a pSS patient with difficulty in perspiring and demonstrated a reduction of eccrine glands and ductal structures within reticular dermis and lymphocytes infiltration of all the remaining epithelial structures Studies of cholinergic-stimulated flow showed discordant results: some of them revealed a decreased sweating, while others presented no difference in the sweating response to pilocarpine between pSS patients and normal controls (Whaley et al., 1973; Katayama et al., 1995). The sweat secretion rate stimulated by iontophoresis was also studied in 22 pSS patients and 22 age- and sex-matched normal controls and no significant difference was found (Rees and Pal, 1989). Other possible explanations of the cutaneous dryness involve both sebaceous glands and apocrine glands abnormality. The hypothesis of an abnormal sebum production due to an absence of sebaceous glands may at least explain dryness of the hair (Provost and Watson, 1992). Apocrine glands dysfunction has also been mentioned to explain a deficient production of cerumen, associated with pruritus, scaling and crusting of the external ear canal in PSS patients (Henkin et al., 1972). Nonetheless, the function of apocrine glands is still poorly understood (Roguedas et al., 2004).

5.3.2. *Cutaneous involvement: vascular lesions*

Vascular lesions are quite frequent in pSS and their clinical manifestations are extremely various. Raynaud's phenomenon is probably the most common vascular feature seen in pSS with a prevalence varying from 15 to 35% (Provost and Watson, 1992; Bernacchi et al., 2004; Ramos-Casals et al., 2005). Moreover, it can be one of the earlier manifestations of the disease, preceding sicca symptoms by many years (Ramos-Casals et al., 2005). Unlike scleroderma patients, pSS patients with Raynaud's phenomenon present a mild vasospastic phenomenon and do not develop teleangiectasias or digital ulcers. Non-erosive arthritis has also been shown to be significantly more common in patients with Raynaud's phenomenon than in those without (Skopouli et al., 1990).

Cutaneous vasculitis includes a variety of lesions depending on the level of blood vessel involvement in the skin and the intensity of inflammatory response. The most common vasculitis lesions are flat and palpable purpura (Provost and Watson, 1992). Flat purpura is usually seen in patients with hypergammaglobulinemia, while palpable purpura is a manifestation of dermal vasculitis (Provost and Watson, 1992). Bloch et al. (1965) described purpura in 17% of their pSS patients. Pavlidis et al. (1982) found purpura, at disease onset, in 28% of the 47 patients described and Garcia-Carrasco et al. (2002) in 15% of their 253 patients analyzed. Finally, of the 62 pSS patients included in the study by Bernacchi et al. (2004), 19 presented with cutaneous vasculitis, while there were only nine in the group of 31 secondary Sjogren's syndrome patients. Palpable purpura was the most common

clinical feature identified (Bernacchi et al., 2004). Purpura appears as recurrent crops of round, pink, separated or confluent lesions turning dull purple and brown in a few days and finally resolving or leaving a pale brown stain (Roguedas et al., 2004); in contrast with simple purpura, palpable purpura does not blanch when pressure is applied to the skin. Moreover, due to the increased hydrostatic pressure, it typically involves lower extremity and buttocks (Gonzalez-Gay et al., 2003). Cutaneous purpura has been associated with lymphoma development and mortality, cutaneous vasculitis thus becoming significant in the prognosis and outcome of patients with pSS (Voulgarelis et al., 1999; Ramos-Casals et al., 2005). Two different types of vasculits have been histopathologically described in pSS: the neutrophilic inflammatory vascular disease, indistinguishable from a leukocytoclastic vasculitis, and the mononuclear inflammatory vascular disease (Provost and Watson, 1992; Roguedas, et al., 2004). The first pattern is characterized by an inflammatory infiltrate composed predominantly by neutrophils, many of which are fragmented. Moreover, the lesions typically display fibrinoid necrosis, lumen occlusion and extravasation of red blood cells. The mononuclear inflammatory vascular disease is characterized by a mononuclear inflammatory infiltrate with invasion of the blood vessel walls. Fibrinoid necrosis is present, but less prominent than the neutrophilic inflammatory infiltrate (Provost and Watson, 1992; Roguedas et al., 2004). Despite the evidence of these two forms of vasculitis, their clinical expression is very similar, so that is not predictable, the histopathologic pattern of vascular insult, in examining the skin (Provost and Watson, 1992). Nonetheless, neutrophilic inflammatory vascular disease, in contrast with mononuclear inflammatory vascular disease is statistically associated with antinuclear antibodies, high titres of anti-Ro/SSA and anti-La/SSB antibodies, hypergammaglobulinemia, rheumatoid factor and hypocomplementemia (Oxholm et al., 1984; Provost and Watson, 1992 Roguedas et al., 2004).

The second most common form of inflammatory vascular disease is urticarial vasculitis, which is a manifestation of inflammatory injury of capillaries and postcapillary venules in the skin (Wisnieski, 2000). From a clinical point of view, urtical vasculitis differs from true urticaria for the following reasons: (i) urticarial vasculitis lesions can be pruritic, like in true urticaria, but are more likely to be stinging or burning; (ii) urticarial vasculitis lesions are typically 0.5–5 cm in diameter, while true urticaria may coalesce into larger lesions; (iii) urticarial vasculitis lesions typically persist for 24 h and often resolve with hyperpigmentation, indicating red blood cell extravasation. In contrast, true urticaria persists for 2–8 h and leaves no trace (Wisnieski, 2000; Gonzalez-Gay et al., 2003). The histology of the urticarial vasculitis includes the features of a leukocytoclastic vasculitis with the neutrophilic infiltrate (or a mixed infiltrate of neutrophils and lymphocytes), the extravasion of red blood cells and injury of the endothelial cells with disruption of the vessel wall. Fibrinoid change or necrosis are less common in urticarial vasculitis lesions than in the fully developed lesions of palpable purpura (Wisnieski, 2000).

In addition to these common manifestations of inflammatory vascular disease, pSS patients may rarely demonstrate erythematous nodules on the lower extremities, persistent plaque-like lesions (erythema multiforme-like lesions) as well as superficial ill-defined patches (erythema perstans) (Roguedas et al., 2004). Provost and Watson (1992) reported persistent plaque-like lesion in 9% of their patients with pSS and ill-defined superficial patches in 4% of them.

Sweet's syndrome, which is characterized by erythematosus -oedematous plaques and reflects inflammatory infiltration of the dermis with neutrophils, has been occasionally reported in pSS (Vatan et al., 1997) In Japanese pSS patients annular erythema is often reported, while in Caucasian patients only anecdotic reports have been published (Katayama et al., 1991; Watanabe et al., 1997; Bernacchi et al., 2004). Annular erythema lesions have been described as recurrent, non photosensitive, erythematous-indurated plaque-like lesion with central clearing without pigmentation or atrophy. Lesions typically involve the face (especially the cheek and preauricular region), the upper extremities and the trunk and a correlation with anti-Ro/SSA and anti-La/SSB antibodies has been reported in as many as 78–100% of pSS cases

(Katayama et al., 1991; Watanabe et al., 1997). Histological examination revealed marked oedema of the upper dermis and a coat-sleeve-like infiltration of lymphocytes around the blood vessels throughout the dermis (Kawakami and Saito, 1999). Thus, Asian patients appear to have lesions that might be considered similar to Caucasian subacute cutaneous lupus erythematosus, although, the latter are not photosensitive and display a distinct histological profile (Watanabe et al., 1997; Bernacchi et al., 2004).

5.3.3. Cutaneous involvement: miscellaneous

A broad spectrum of other cutaneous manifestations has been described in pSS including angular cheilitis, eyelid dermatitis, vitiligo and alopecia (Bernacchi et al., 2004). Angular cheilitis has been described as recurrent, symmetrical erythematosquamous infiltrated lesion, often itching and fissuring and it is more common in primary than in secondary variants. Xerostomia may be a predisposing factor for the development of angular cheilitis (Bernacchi et al., 2004). Eyelid dermatitis is defined by the presence of erythematous, infiltrated and lichenificated lesions of the upper and/or lower eyelids and it is associated with itching and foreign body sensation. It has been hypothesized that ocular dermatosis may not be a simple consequence of contact sensitization, but also the result of continuous rubbing of the periorbital area due to xerophthalmia (Bernacchi et al., 2004). Alopecia areata has also been described in pSS as well as in other autoimmune diseases, and it has been explained by a possible lymphocytic infiltration of the sebaceous glands (Provost and Watson, 1992). Moreover, vitiligo consisting in localized areas of hypopigmentation has been associated with pSS too (Roguedas et al., 2004). Finally, a true complication of pSS is represented by malignant lymphomas (Voulgarelis et al., 1999; Roguedas et al., 2004). Skin lymphomas are quite rare and data on their real incidence in pSS are lacking (Bernacchi et al., 2004). Nonetheless, many case reports have been published describing cutaneous B-cell lymphomas, or most infrequently T-cell lymphomas, and all these cases have to be considered as part of the increase risk of pSS proliferative disorders (Jubert et al., 1993; Voulgarelis et al., 1999; Stroehmann et al., 2002; Selva-O' Callaghan et al., 2003; Masaki and Sugai, 2004; Ramos-Casals et al., 2005a).

6. Diagnostic investigations

6.1. Laboratory tests

pSS is associated with a broad spectrum of autoantibodies including Rheumatoid factors (90%), antinuclear antibodies (80%), and antibodies anti-Ro/SSA and anti-La/SSB (50–90%) (Ramos-Casals et al., 2005). Routine laboratory tests reveal, in addition, hypergammaglobulinemia (80%) and may also display mild anemia of chronic disease (25%), leukopenia (10%) and elevated erythrocyte sedimentation rate (ESR) despite normal levels of C-reactive protein (PCR) (Ramos-Casals et al., 2005).

6.2. Tests used for the evaluation of xerophthalmia

According to the International Classification Criteria, tear secretion may be evaluated either by Schirmer's tear test and Rosa Bengala staining (or other vital staining) (Vitali et al., 2002). Schirmer's test defines abnormal tear secretion as 5 mm or less of wetting of a standard strip of filter paper slipped in the inferior lid after 5 min.Rose Bengala is an aniline dye, which stains the devitalized or damage epithelium of the cornea and the conjunctiva and may be scored according to the van Bijsterveld system (Kruize et al., 1997; Rolando, 2001; Vitali et al., 2002).

6.3. Tests used for the evaluation of xerostomia

Many tests are included in the International Criteria for the evaluation of the oral symptoms of pSS: the sialometry measures saliva flow function, with or without stimulation, for the single parotid, submandibolar or sublingual glands or for total saliva production. Differences on sensitivity and

specificity may be found, because salivary secretion depends on many factors, including age, sex, drugs taken and that time of the day. Sialography is a radiographic method of assessing architecture and configuration of glandular ducts by the retrograde instillation of a contrast medium through the excretory duct. Scintigraphy evaluates function of salivary glands by observing the rate and density of sodium pertechnate of ^{99m}Tc uptake and time of appearance in the mouth after intravenous injection. Finally, lip biopsy allows to demonstrate and to quantify the typical mononuclear infiltrate through the histopathologic examination of salivary gland and up to now it is considered the most reliable oral diagnostic test (Danielsand Fox, 1992; Lundstrom and Lundstrom, 1995; Soto-Rojas and Kruas, 2002; Vitali et al., 2002).

7. Differential diagnosis

Differential diagnosis of pSS basically includes all those diseases, which may potentially cause dryness of the eyes and of the mouth. Most of them have been included in the recent Exclusion Criteria including past history of head and neck radiation therapy, hepatitis C infection, acquired immunodeficiency disease (AIDS), pre-existing lymphoma, sarcoidosis, graft-vs-host disease and use of anticholinergic drugs (within four half-lives of the drug) (Vitali et al., 2002).

As far as pSS cutaneous involvement is concerned, cutaneous xerosis is an extraordinarily common problem, especially in the elderly, affecting at least 75% of the population aged 64 and older. Moreover, besides from elderly xerosis, pSS xerosis has also to be differentiated from dry skin secondary to underlying malignancy, renal insufficiency, obstructive biliary disease, hypothyroidism and idiopathic conditions (Vivino, 2001). Cutaneous vasculitis differential diagnosis includes both secondary vasculitis, due to infective agents, drugs or malignancies, and primary systemic vasculitis (mainly Mixed Crioglobulinaemia) (Gonzalez-Gay et al., 2003). Finally, annular erythema has to be differentiated from sub acute cutaneous lupus erythematosus (Katayama et al., 1991).

8. Treatment

8.1. Treatment of ocular- and oral involvement

Artificial tears drops represent the most widely accepted treatment for dry eyes. When the benefit of lachrymal substitutes is insufficient, viscous solutions may be used; there is also growing evidence to suggest that topical corticosteroids, cyclosporine and intraocular androgens may be beneficial in the treatment of keratoconjunctivitis sicca. In refractory cases, punctual plugs may be inserted (Kruize et al., 1997). Oral dryness may be ameliorating by the recurrent use of artificial saliva and lubricants; daily topical fluoride use and antimicrobial may also help in preventing caries (Daniels and Fox, 1992). New therapeutic agents include muscarinic agonists (pilocarpine and cevimeline) that have been recently approved for the treatment of the sicca symptoms in pSS (Ramos-Casals et al., 2005). These agents stimulate muscarinic receptors present on salivary glands, leading to increased secretory function (Ramos-Casals et al., 2005). Clinical studies with pilocarpine in the USA have demonstrated significant subjective and objective benefit for xerostomia at doses of 20 mg/day or more (Vivino, 2001). Similar results have been reached with cevimeline 30 mg three times daily (Petrone et al., 2002).

8.2. Treatment of extraglandular manifestations

Cutaneous involvement and most of the other extraglandular manifestations of pSS are generally mild and merely controlled by low doses of corticosteroids and antimalarial drugs (200–400 mg/day) (Ramos-Casals et al., 2005). Cutaneous dryness is treated with decreased frequency of bathing and increased use of lubricants (Ramos-Casals et al., 2005). Other immunosuppressive agents, including azathioprine, methotrexate or cyclosporine have a limited employment in pSS (Ramos-Casals et al., 2005). Recent studies have analysed the role of biological agents for the treatment of pSS concluding that antitumor necrosis factor agents should not be considered as the first line option

for the treatment of pSS, but merely used for the treatment of specific severe extraglandular features (Mariette et al., 2004). A promising treatment for pSS is rituximab, monoclonal autoantibodies against a specific marker of B cells (CD20). The specific target of rituximab might suggest a role in modifying the aetiopathogenetic events of pSS, a disease specifically characterized by B-cell hyperactivity (Ramos Casals et al., 2005).

Key points

- Primary Sjogren's syndrome (pSS) is a chronic autoimmune disorder of unknown aetiology characterized by dryness of the eyes and mouth resulting from the lymphocytic infiltrates of the exocrine glands.
- The etiopathogenesis of pSS is thought as multifactorial involving a genetic predisposition, ambiental factors and disimmunity but, at present, remains broadly unknown
- Cutaneous manifestations are considered one of the most typical extraglandular features of primary Sjogren's syndrome, although underestimated due to both their aspecificity and to the severe disability derived from glands involvement.
- Generally cutaneous manifestations of pSS are distinguished in vasculitic and non-vasculitic lesions. Among non vasculitc lesions, skin dryness (xerosis) has been shown to be very common in pSS while vasculitis lesions include typically flat and palpable purpura and urticarial vasculits.
- A broad spectrum of other cutaneous manifestations has been described, including Raynaud's phenomenon, angular cheilitis, eyelid dermatitis, vitiligo, alopecia, erythemarous nodules, erythema multiforme-like lesions, erythema perstans, Sweet's syndrome and annular erythema (the last often reported in Asiatic patients).
- Finally, B-cell cutaneous lymphoma, and most infrequently T-cell lymphoma, may represent a complication of pSS.

References

Amft, N., Bowman, S.J. 2001. Chemokines and cell trafficking in Sjogren's syndrome. Scand. J. Immunol. 54, 62.

Anaya, J.M., Liu, G.T., D'Souza, E., et al. 1995. Primary Sjogren's syndrome in men. Ann. Rheum. Dis. 54, 748.

Anaya, J.M., Talal, N. 1999. Sjogren's syndrome comes of age. Semin. Arth. Rheum. 28, 355.

Belenguer, R., Ramos-Casals, M., Brito-Zeron, P., et al. 2005. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjogren's syndrome. Clin. Exp. Rheumatol. 23, 351.

Bernacchi, E., Amato, L., Parodi, A., et al. 2004. Sjogren's syndrome: a retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology. Clin. Exp. Rheumatol. 22, 55.
It provides a good overview of pSS cutaneous manifestations.

Bloch, K.J., Buchanan, W.W., Whohl, M.J. 1965. Sjogren's syndrome: a clinical, pathological and serological study of 62 cases. Medicine 44, 187.

Bolstad, A.I., Eiken, H.G., Rosenlund, B., et al. 2003. Increased salivary gland tissue expression of Fas, Fas ligand, cytotoxic T lymphocyte-associated antigen 4 and programmed cell death in primary Sjogren's syndrome. Arth. Rheum. 48, 174.

Brennan, M.T., Fox, P.C. 1999. Sex differences in primary Sjogren's syndrome. J. Rheumatol. 26, 2373.

Cervera, R., Font, J., Ramos-Casals, M., et al. 2000. Primary Sjogren's syndrome in men: clinical and immunological characteristics. Lupus 9, 61.

Cimaz, R., Casadei, A., Rose, C., et al. 2003. Primary Sjogren's syndrome in the paediatric age: a multicenter survey. Eur. J. Pediatr. 162, 661.

Cutolo, M., Capellino, S., Montagna, P., et al. 2003. New roles for estrogens in rheumatoid arthritis. Clin. Exp. Rheumatol. 21, 687.

Daniels, T.E., Fox, C.P. 1992. Salivary and oral components of Sjogren's syndrome. Rheum. Dis. Clin. N. Am. 18, 571.
It critically reviews the most relevant aspects of mucosal involvement in pSS.

Delaleu, N., Jonsson, R., Koller, M.M. 2005. Sjogren's syndrome. Eur. J. Oral Sci. 113, 113.

Diaz-Lopez, C., Geli, C., Corominas, H., et al. 2004. Are there clinical or serological differences between male and female patients with primary Sjogren's syndrome?. J. Rheumatol. 31, 1352.

Drosos, A.A., Andonopoulos, A.P., Costopoulos, J.S., et al. 1988. Prevalence of primary Sjogren's syndrome in an elderly population. Br. J. Rheumatol. 27, 123.

Endo, Y., Negishi, I., Ishikawa, O. 2002. Possibile contribution of microchimerism to the pathogenesis of Sjogren's syndrome. Rheumatology 41, 490.

Fox, R.I., Robinson, C.A., Curd, J.G., et al. 1986. Sjogren's syndrome proposed criteria for classification. Arth. Rheum. 29, 577.

Fox, R., Stern, M. 2002. Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. Scand. J. Rheumatol. 31, 3.

Garcia-Carrasco, M., Ramos, Casals, M., Rosas, J. 2002. Primary Sjogren's syndrome. clinical and immunological disease patterns in a cohort of 400 patients. Medicine 81, 270.

Georges-Gobinet, A., Moynet, D., Hajjar, C., et al. 1998. HTLV—associated sicca syndrome in Guadalupe: lack of relation with a peculiar encoding sequence of surface envelope glycoprotein. Virus Genes 16, 195.

Giacomelli, R., Cipriani, P., Fulminis, A., et al. 2004. Gamma/delta T cells in placenta and skin: their different functions may support the paradigm of microchimerism in systemic sclerosis. Clin. Exp. Rheumatol. 22 (Suppl. 33), S28.

Gonzalez-Gay, M.A., Garcia-Porrua, C., Salvarani, C., et al. 2003. Cutaneous vasculitis: a diagnostic approach. Clin. Exp. Rheumatol. 21, S85.

Gran, J.T. 2002. Diagnosis and definition of primary Sjogren's syndrome. Scand. J. Rheumatol. 31, 57.

Green, J.E., Hinrich, S.H., Vogel, J., et al. 1989. Exocrinopathy resembling Sjogren's syndrome in HTLV-1 tax transgenic mice. Nature 341, 72.

Henkin, R.I., Talal, N., Larson, A.L., et al. 1972. Abnormalities of taste and smell in Sjogren's syndrome. Ann. Intern. Med. 76, 375.

Ishimaru, N., Saegusa, K., Yanagi, K., et al. 1999. Estrogen deficiency accelerates autoimmune exocrinopathy in murine Sjogren's syndrome through fas-mediated apoptosis. Am. J. Pathol. 155, 173.

Jacobsson, L.T., Axell, T.E., Hansen, B.U., et al. 1989. Dry eyes or mouth—an epidemiological study in Swedish adults, with special reference to primary Sjogren's syndrome. J. Autoimmun. 2, 521.

Jubert, C., Cosnes, A., Clerici, T., et al. 1993. Sjogren's syndrome and cutaneous B cell lymphoma revealed by anetoderma. Arth. Rheum. 36, 133.

Katayama, I., Teramoto, N., Arai, H., et al. 1991. Annular erythema. a comparative study of Sjogren's syndrome with sub acute cutaneous lupus erythematosus. Int. J. Dermatol. 30, 635.

Katayama, I., Yokozeki, H., Nishioks, K. 1995. Impaired sweating as an exocrine manifestation in Sjogren's syndrome. Br. J. Dermatol. 133, 716.

Kawakami, T., Saito, R. 1999. The relationship between facial annular erythema and anti-SS-A/Ro antibodies in three East Asian women. Br. J. Dermatol. 140, 136.

Konttinen, Y.T., Ramsay, H., Hietanen, J., et al. 2000. Otitis externa sicca/fibrotising external otitis (FEO) as a complication of Sjogren's syndrome. Clin. Exp. Rheumatol. 18, 746.

Kruize, A.A., van Bijsterveld, O.P., Hene, R.J., et al. 1997. Long term course of tear gland function in patients with keratoconjunctivitis sicca and Sjogren's syndrome. Br. J. Ophthalmol. 81, 435.

Kuroki, M., Okayama, A., Nakamura, S., et al. 2002. Detection of maternal–fetal microchimerism in the inflammatory lesions of patients with Sjogren's syndrome. Ann. Rheum. Dis. 61, 1041.

Lundstrom, I.M.C., Lundstrom, F.D. 1995. Subjective and clinical oral symptoms in patients with primary Sjogren's syndrome. Clin. Exp. Rheumatol. 13, 725.

Manganelli, P., Fietta, P. 2003. Apoptosis and Sjogren's syndrome. Semin. Arth. Rheum. 33, 49.

Manthorpe, R., Oxholm, P., Prause, J.U., et al. 1986. The Copenhagen criteria for Sjogren's Syndrome. Scand. J. Rheumatol. 15, 19.

Mariette, X., Agbalika, F., Zucker-Franklin, D., et al. 2000. Detection of the tax gene of HTLV-I in labial salivary glands from patients with Sjogren's syndrome and other diseases of the oral cavity. Clin. Exp. Rheumatol. 18, 341.

Mariette, X., Ravaud, P., Steinfeld, S., et al. 2004. Inefficacy of Infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's syndrome (TRIPSS). Arth. Rheum. 50, 1270.

Masaki, Y., Sugai, S. 2004. Linphoproliferative disorders in Sjogren's syndrome. Autoimmun. Rev. 3, 175.

Mitchell, J., Greenspan, J., Daniels, T., et al. 1987. Anhidrosis in Sjogren's syndrome. J. Am. Acad. Dermatol. 16, 233.

Mosca, M., Curcio, M., Lapi, S., et al. 2003. Correlations of Y chromosome microchimerism with disease activity in patients with SLE: analysis of preliminary data. Ann. Rheum. Dis. 62, 651.

Naito, Y., Matsumoto, I., Wakamatsu, E., et al. 2005. Muscarinic acetylcholine receptor autoantibodies in patients with Sjogren's syndrome. Ann. Rheum. Dis. 64, 510.

Ogawa, N., Ping, L., Zhenjun, L., et al. 2002. Involvement of Interferon-gamma—induced T cell-attracting chemokines, Interferon-gamma—inducible 10-Kd Protein (CXCL10) and Monokine Induced by Interferon-gamma (CXCL9), in the salivary gland lesions of patients with Sjogren's syndrome. Arth. Rheum. 46, 2730.

Oxholm, A., Manthorpe, R., Oxholm, P. 1984. Immunoglobulin deposits in the epidermidis of patients with primary Sjogren's syndrome. Rheumatol. Int. 4, 9.

Oxholm, P., Oxholm, A., Manthorpe, R. 1987. Epidermal IgG deposits in patients with chronic inflammatory connective tissue diseases: diagnostic value and correlation to clinical and immunological parameters in patients with primary Sjogren's syndrome. Clin. Exp. Rheumatol. 5, 5.

Parke, A.L. 2000. Sjogren's syndrome: a women's health problem. J. Rheumatol. 61, 4.

Pavlidis, N.A., Karsh, J., Moutsopoulos, H.M. 1982. The clinical picture of primary Sjogren's syndrome: a retrospective study. J. Rheumatol. 9, 685.

Petrone, D., Candemi, J.J., Fife, R., et al. 2002. A double blind, randomized, placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum. 46, 748.

Phelan, D. 2001. Sjogren's syndrome. eMedicine J 2, 10.

Provost, T.T., Watson, R. 1992. Cutaneous manifestations of Sjogren's syndrome. Rheum. Dis. Clin. N. Am. 18, 609.
It provides an exhaustive analysis of pSS cutaneous principal manifestations and of their pathogenetical aspects.

Ramos-Casals, M., De Vita, S., Tzioufas, A.T. 2005a. Hepatitis C virus, Sjogren's syndrome and B-cell lymphoma: linking infection, autoimmunity and cancer. Autoimmun. Rev. 4, 8.

A complete analysis of the relationships between Hepatitis C and Sjogren's syndrome with a special focus on lymphoproliferative disorders.

Ramos-Casals, M., Font, J., Brito-Zeron, P., et al. 2004. Interleukin-4 receptor alpha polymorphisms in primary Sjogren's syndrome. Clin. Exp. Rheumatol. 22, 374.

Ramos-Casals, M., Garcia-Carrasco, M., Pilar Brito Zeron, M., et al. 2002. Viral etiopathogenesis of Sjogren's syndrome: role of the hepatitis C virus. Autoimmun. Rev. 1, 238.

Ramos-Casals, M., Tzioufas, A.G., Font, J. 2005. Primary Sjogren's syndrome: new clinical and therapeutic concepts. Ann. Rheum. Dis. 64, 347.

Rees, J., Pal, B. 1989. Stimulated eccrine gland function in primary Sjogren's syndrome. Clin. Exp. Dermatol. 14, 191.

Rehman, H. 2003. Sjogren's syndrome. Yonsei Med. J. 44, 947.

Reveille, J.D., Arnett, F.C. 1992. The immunogenetics of Sjogren's Syndrome. Rheum. Dis. Clin. N. Am. 18, 539.

Robinson, C.P., Brayer, J., Yamachika, S., et al. 1998. Transfer of human serum IgG to nonobese diabetic Igμnull mice reveals a role for autoantibodies in the loss of secretori function of exocrine tissues in Sjogren's syndrome. Proc. Natl. Acad. Sci. USA 95, 7538.

Roguedas, A.M., Misery, L., Sassolas, B., et al. 2004. Cutaneous manifestations of primary Sjogren's syndrome are underestimated. Clin. Exp. Rheumatol. 22, 632.

It provides a good overview of pSS cutaneous manifestations.

Rolando, M. 2001. Sjogren's syndrome as seen by an ophthalmologist. Scand. J. Rheumatol. 115, 27.

Sanchez-Guerrero, J., Perez-Dosal, M.R., Cardenas-Velazquez, F., et al. 2005. Prevalence of Sjogren's syndrome in ambulatory patients according to the American-European Consensus Group criteria. Rheumatology 44, 235.

Selva-O' Callaghan, A., Perez-Lopez, J., Solans-Laque, R., et al. 2003. Primary cutaneous large B-cell lymphoma of the legs in a patient with primary Sjogren's syndrome. Clin. Exp. Rheumatol. 21, 672.

Siamopoulou-Mavridou, A., Drosos, A.A., Andonopoulos, A.P. 1989. Sjogren's syndrome in childhood: report of two cases. Eur. J. Paediatr. 18, 523.

Skopouli, F.N., Moutsopoulos, H.M. 1994. Autoimmune epitheliitis: Sjogren's syndrome. Clin. Exp. Rheumatol. 12 (Suppl.11), S9.

Skopouli, F.N., Talal, A., Galanopoulou, V. 1990. Raynaud's phenomenon in primary Sjogren's syndrome. J. Rheumatol. 17, 618.

Solomon, A., Dursun, D., Liu, Z., et al. 2001. Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry eyes disease. Invest. Ophtalmol. Vis. Sci. 42, 2283.

Soto-Rojas, A.E., Kraus, A. 2002. The oral side of Sjogren's syndrome. Diagnosis and treatment. A review. Arch. Med. Res. 33, 95.

Stroehmann, A., Dorner, T., Lukowsky, A., et al. 2002. Cutaneous T cell lymphoma in a patient with primary biliary cirrhosis and secondary Sjogren's syndrome. J. Rheumatol. 29, 1326.

Thomas, E., Hay, E.M., Hajeer, A., et al. 1998. Sjogren's syndrome: a community-based study of prevalence and impact. Br. J. Rheumatol. 37, 1069.

Tishler, M., Yaron, I., Shirazi, I., et al. 2001. Clinical and immunological characteristics of elderly onset Sjogren's syndrome: a comparison with younger onset disease. J. Rheumatol. 28, 795.

Tobon, G.J., Correa, P.A., Gomez, L.M., et al. 2005. Lack of association between TNF-308 polymorphism and the clinical and immunological characteristics of systemic lupus erythematosus and primary Sjogren's syndrome. Clin. Exp. Rheumatol. 23, 339.

Tomsic, M., Logar, D., Grmek, M., et al. 1999. Prevalence of Sjogren's syndrome in Slovenia. Rheumatology 38, 164.

Vatan, R., Sire, S., Constans, J., Ragnaud, J.M. 1997. Association syndrome de Gourgerot-Sjogren primitif et syndrome de Sweet: a propos d'un cas. Rev. Med. Intern. 18, 734.

Veki, H., Inagaki, Y., Hamasaki, Y., et al. 1991. Dermatologische manifestationem des Sjogren's syndrome. Hautarz 42, 741.

Velthius, P.J., Niebor, C., Kater, L., et al. 1989. A prospective immunofluorescence study of immune deposits in the skin of primary Sjogren's syndrome. Acta Dermatol. Venereol. 69, 487.

Vitali, C., Bombardieri, S., Jonsson, R., et al. 2002. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann. Rheum. Dis. 61, 554.

It represents a mile stone in the history of the disease.

Vitali, C., Bombardieri, S., Moutsopoulos, H.M., et al. 1993. Preliminary criteria for the classification of Sjogren's syndrome. Results of a prospective concerted action supported by the European Community. Arth. Rheum. 36, 340.

Vivino, F.B. 2001. The treatment of Sjogren's syndrome patients with pilocarpine tablets. Scand. J. Rheumatol. Suppl. 115, 1.

Voulgarelis, M., Dafni, U.G., Isenberg, D.A., et al. 1999. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European concerted action on Sjogren's syndrome. Arthritis Rheum. 42, 1765.

Watanabe, T., Tsuchida, T., Ito, Y., et al. 1997. Annular erythema associated with lupus erythematosus/Sjogren's syndrome. J. Am. Acad. Dermatol. 36, 214.

Whaley, K., Williamson, J., Chisolm, D.M. 1973. Sjogren's syndrome sicca components. Q. J. Med. 166, 279.

Wisnieski, J.J. 2000. Urticarial vasculitis. Curr. Opin. Rheumatol. 12, 24.

Zhang, N.Z., Shi, C.S., Yao, Q.P., et al. 1995. Prevalence of primary Sjogren's syndrome in China. J. Rheumatol. 22, 659.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 13

Rheumatoid Arthritis and the Skin

Piercarlo Sarzi-Puttini*, Fabiola Atzeni, Mario Carrabba
Rheumatology Unit, L. Sacco University Hospital, Milan, Italy

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disorder of unknown aetiology. This disease affects about 0.5–1% of the population worldwide, most commonly middle-aged women. The hallmark of the disease is a synovial inflammation and pannus formation involving small and large joints, often symmetrical in distribution, resulting in pain, stiffness, and loss of function. In fact, in many cases, ongoing synovitis of diarthrodial joints leads to destruction of articular cartilage and juxtaarticular bone (Harris Jr., 1994).

Numerous extra-articular manifestations occur, particularly in male patients who are anti-nuclear antibodies (ANA) and rheumatoid factor (RF) positive. Extra-articular manifestations can be detected in almost any organ system, causing considerable disease-related morbidity and interference with quality of life (Cimmino et al., 2000).

The most widely recognized skin lesion is the rheumatoid nodule. A variety of skin manifestations can be observed either non-specific or related to the disease itself and/or to the commonly used drugs (Sayah and English, 2005).

2. Epidemiology/Prevalence

The prevalence of RA is approximately 0.5–1% in diverse populations worldwide (Alamanos and Drosos, 2005). However, an unusually high prevalence of the disease has been reported in certain North American Indian tribes, while the disease is rare in rural Africans and rural and urban Chinese. RA affects women more often than men. The annual incidence is approximately 0.2–0.4 per 1000 in females and 0.1–0.2 per 1000 in males (Alamanos and Drosos, 2005).

3. Aetiology

The aetiology of RA remains elusive, although it appears that genetic, infectious, environmental, and hormonal factors are all involved in complex, interrelated ways.

3.1. Genetic factors

Genetic factors were implicated by population studies that showed a slight increase in the frequency of RA in first-degree relatives of patients with RA (Lawrence, 1970). The major histocompatibility complex (MHC) genes encode the α and β chain of heterodimer HLA-DR molecule that presents antigenic peptide to T-lymphocyte receptor (TCR) (Spies et al., 1985). In white population, RA is essentially associated with the HLA-DRB1*01, DRB1*10, and DRB1*04 genes (Nepom et al., 1989). The presence of one of these susceptibility alleles influences the course and the severity of RA because patients with these alleles have extra-articular features and higher frequencies of joint damage (Weyand et al., 1992)

*Corresponding author.
Piercarlo Sarzi-Puttini, MD Rheumatology Unit, - University Hospital L. Sacco Via GB Grassi, 74 20157 Milan - Italy
E-mail address: sarzi@tiscali.it (P. Sarzi-Puttini).

DOI: 10.1016/S1571-5078(05)05013-0

3.2. Environmental factors

Population and twin studies strongly suggest that non-inherited, presumably environmental, factors such as smoking and infections may play a part in the aetiology of RA, although rearrangement of the $\alpha\beta$ genes on T-cell receptors may also contribute to the non-inherited component.

3.3. Viruses

Increased antibody titres to Epstein–Barr virus (EBV) antigens and an induced RA nuclear antigen have suggested that this ubiquitous virus, known to infect the majority of people by the late teens, may be of aetiological importance (Venables et al., 1981) However, only a small proportion of individuals infected with EBV might develop RA, and conversely, that there are well-documented patients with RA who have not been infected with EBV (Venables et al., 1981).

Parvovirus B19 has also been proposed by several groups over the years to be possibly involved, but the consensus is that while parvovirus causes different types of arthritis, which in it chronic form may resemble clinical features of RA, it is not a cause of RA (Moore, 2000).

3.4. Bacteria

Three bacteria have attracted attention in recent years as candidate agents in the aetiology of RA. The first, *Mycobacterium tuberculosis*, gained current interest following the studies of on an animal model of RA (Cohen et al., 1985). The second, *Escherichia coli*, were reported to elicit T-cell responses only in patients with RA (Albani et al., 1995). The third bacterium proposed as a candidate aetiological agent is *Proteus mirabilis*.

3.5. Sex hormones

Epidemiologic evidence indicates that during the fertile period women are affected by RA, more often than men (Bijlsma et al., 2002). The pre- or postmenopausal sex hormone status and the protective effect of the contraceptive pill, presumably because of its progesterone content, have suggested that sex hormones may accelerate or retard its onset (Cutolo et al., 2003).

4. Pathogenesis

RA is a disorder characterized by persistent inflammatory synovitis, predominantly affecting the peripheral joints. This is associated with pannus formation, cartilage destruction, bone erosions, and joint destruction (Lipsky, 2000). The synovial membrane in patients with RA is characterized by hyperplasia, increased vascularity, and an infiltrate of inflammatory cells that are predominantly CD4+ T cells. RA has been linked to some MHC Class II antigens (HLA-DRB1FN*010404, DRB1FN*010401, DRB1FN*010405, DRB1FN*010101 and DRB1FNx011402). The β chains of all the above HLA-DR molecules contain the same amino acids at positions 67 through 74, a concept known as 'shared epitope'. The main function of MHC Class II molecules is to present antigenic peptides to CD4+ T cells, which suggests that RA is caused by an unidentified arthritogenic antigen (Gregersen et al., 1987). The antigen could be either an exogenous antigen, such as a viral or bacterial protein, or an endogenous protein such as citrullinated protein, human cartilage glycoprotein 39, or heavy-chain-binding protein (Blass et al., 1999).

A self-perpetuating series of inflammatory reactions in concert with the predisposing genetic background of the patient lead to degenerative and proliferative responses in target cell populations responsible for the disease phenotype. Antigen-activated CD4+ T cells stimulate monocytes, macrophages, and synovial fibroblasts to produce various cytokines. TNF-α, IL-1, and IL-6 are the key cytokines that drive inflammation in RA and cause joint damage (Fig. 1). They are potent stimulators of synovial fibroblasts, osteoclasts, and chondrocytes that release tissue-destroying matrix metalloproteinases (MMP), which contribute to joint damage (Shingu et al., 1993). The serum and synovial concentrations of IL-1 and TNF-α are high in patients with active RA (Chikanza et al.,

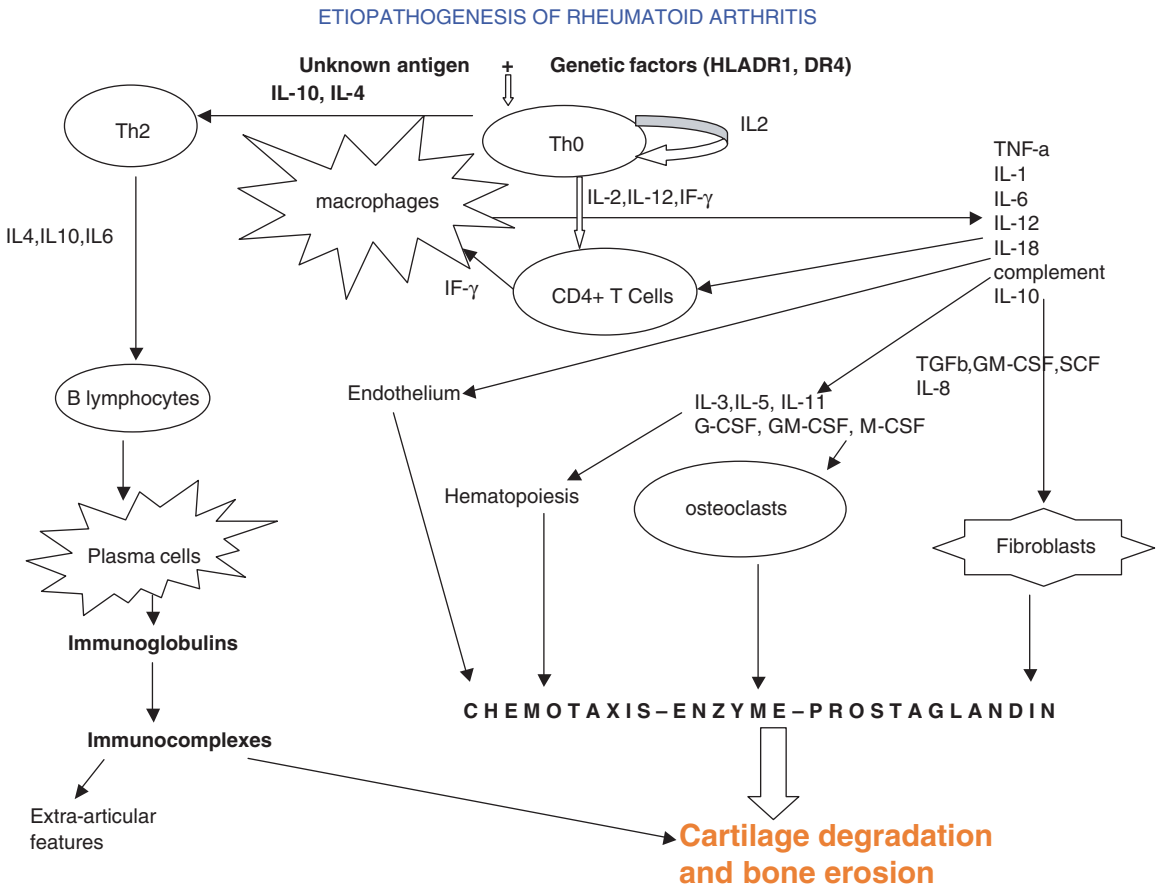


Figure 1. Pathogenesis of rheumatoid arthritis.

1995; Saxne et al., 1988). Activated CD4+ T cells also stimulate B cells to produce immunoglobulins, including RF. RF may involve the activation of complement through the formation of immune complexes.

The products of activated macrophages, lymphocytes, and fibroblasts stimulate angiogenesis (Choy and Panayi, 2001). Inflammatory cells are recruited into the joint by expression of adhesion molecules in endothelial cells in the synovium. This leads to the formation of hyperplastic, proliferating, inflammed synovium, also called 'pannus' (Choy and Panayi, 2001; Hayashida et al., 2001). Activated macrophages and synovial fibroblasts are present in the interface between the pannus and cartilage and cause damage to the joint (Lee and Weinblatt, 2001; Nanki and Lipsky, 2000).

The release of enzymes like elastases and proteases leads to the degradation of proteoglycans in the superficial layer of cartilage. Activated CD4+ T cells along with the macrophages express the receptor activator of nuclear factor-kB ligand (RANK-L) that stimulates osteoclastogenesis and arthritic bone erosion (Walsh and Gravellese, 2004). As a final step, ongoing synovitis of diarthrodial joints leads to destruction of articular cartilage and juxtaarticular bone (Harris Jr., 1994) (Fig. 1).

5. Diagnosis and clinical features

The classic clinical picture of RA usually emerges within a few months of disease onset. The natural

history of the disease in most patients involves chronic low-grade inflammation, eventually involving many joints, with periodic flares in the intensity of inflammation. In clinical practice, synovitis is initially classified on the basis of the extent, location, and symmetry of the joint involvement. The etiopathogenic mechanisms determining these patterns of joint involvement are unknown, and therefore the clinical and therapeutic implications are empirical. For these purposes, the classification criteria of the American Rheumatism Association (ARA) were developed, which in 1987 were replaced by the criteria of the American College of Rheumatology (ACR) (Arnett et al., 1988) (Table 1). RA is diagnosed if at least four out of seven criteria are present. The 1987 ACR criteria are good and sensitive for diagnosis of established RA while they have important limitations when used for case recognition of early disease. There are, however, no accepted criteria for early RA, although recent data from early arthritis clinics may be helpful in this respect (Visser et al., 2002).

The onset of the disease may be either abrupt/acute or gradual/insidious or anywhere between these extremes. A gradual onset is present in 50% of the cases and usually starts with systemic features, such as fatigue, generalized weakness, loss of weight, and fever, followed by synovitis and evolving to chronic disease. An abrupt onset of the disease is less common (10–25%) and functional outcome in these patients is contradictory (Harris Jr., 1994). In a minority of patients, there is a 'malignant' onset and a relentless disease course cannot be controlled by any anti-rheumatic drug regimen.

Symmetrical involvement of the wrists and small joints of the hands and feet is highly characteristic of established RA and, when present at the onset of the synovitis, suggests that the patient's symptoms will probably evolve into the typical RA phenotype, particularly if RF is present. Severe disease is frequently associated with involvement of large joints, such as the shoulders, elbows, and knees (Grassi et al., 1998).

Numerous extra-articular manifestations occur in RA patients, particularly in male patients who are ANA and RF positive (Cimmino et al., 2000). Some features occur early in the disease, like general fatigue, low-grade fever, and weight loss and can predominate the clinical picture, thus causing diagnostic problems. Extra-articular manifestations can be detected in almost any organ system, causing considerable disease-related morbidity and interference with quality of life (Turesson et al., 2003) (Table 2).

Table 1
American College of Rheumatology revised criteria for classification of rheumatoid arthritis[a]

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around joints lasting at least 1 h before maximal improvement
2. Arthritis of three or more joint areas	At least three joint areas simultaneously affected by soft-tissue swelling or fluid accumulation (not bony overgrowth alone); the 14 possible areas are right and left PIP, MCP, MTP, wrist, elbow, knee, and ankle joints
3. Arthritis of hand joints	At least one area swollen (as previously defined) in wrist, MCP, or PIP joint
4. Symmetrical arthritis	Simultaneous involvement of previously defined joint areas on both sides of body (bilateral involvement of PIPs, MCPs, or MTPs acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences, extensor surfaces, or in juxtaarticular regions
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which result has been positive in $<5\%$ of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs; findings must include erosions or unequivocal bony decalcification localized in or most marked adjacent to involved joints (osteoarthritis changes alone do not qualify)

Note: MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

[a] For diagnosis of RA, a patient must meet at least four of these seven criteria. The first four criteria listed must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Adapted from Arnett et al. (1988).

Table 2
Main extra-articular disease manifestations in RA

General	Fever, Linfoadenopathy, Fatigue, Anemia	Onset of the disease Flare of arthritis Infections
Heart	Dyspnoea, Heart failure, Angina and myocardial infarction	Constrictive pericarditis Myocarditis Coronary arteritis Valve lesions
Lung	Dyspnoea, Dry cough	Pleuritis Interstitial lung BOOP methotrexate Lung fibrosis
Eye	Dry eye, Blurred vision, Red eye	Sjogren's syndrome Keratitis Scleritis, episcleritis,
Nervous system	Paresthesias, Muscle weakness, Stroke	Entrapment neuropathy Cervical mielopathy Disuse atrophy Steroid miopathy CNS vasculitis
Skin	Nodules, Ulcerations, Urticaria, purpura, Nailfold lesions, Digital infarcts, gangrene	Cutaneous vasculitis Nodulosis Felty's syndrome
Kidney	Haematuria, Proteinuria	Amyloidosis Glomerulonephritis
Gastrointestinal tract	Nausea, Epigastric pain, Bowel infarcts and ulcers	Vasculitis Amyloidosis Drug toxicity
Bone	Bone pain, Fractures	Osteoporosis

Note: BOOP = bronchiolitis obliterans-organizing pneumonia.

The natural course of RA is not fully known, because patients are always treated with non-steroidal anti-inflammatory agents (NSAIDs) and often with disease-modifying anti-rheumatic drugs (DMARDs) (Ollier et al., 2001). In controlled studies, remissions were observed in 10% of patients, chronic progressive disease in 40–70%, and a course showing remissions and exacerbations in 20–40% (Makinen et al., 2005). The rate of remission in RA depends on the criteria used (Paulus, 2004). No gold standard exists for defining remission in RA. A set of criteria including no sign of inflammatory activity and no radiographic progression might be a basis for development of clinically relevant remission criteria for RA. Published data from early arthritis cohorts indicate that a large percentage of patients can only be labelled as having 'unclassified' or 'undifferentiated' arthritis. In different studies, approximately 30–50% of the patients who were evaluated within 1 year of symptom onset fell into this category (El-Gabalawy, 1999). A major future goal will be to identify properly the subgroup of patients with early RA (Caruso et al., 1990) at risk for progression to severe RA (Combe, 2004). This should enable patients with highly progressive disease to receive aggressive treatment (e.g. a combination of DMARDs or biological therapy) very early on with the goal of minimizing joint destruction and subsequent functional impairments (Quinn et al., 2005).

6. Imaging

Radiographic imaging of articular and periarticular structures may contribute information that defines specific anatomic damage more precisely (Babyn and Doria, 2005). However, many of the findings such as soft tissue swelling, periarticular bone loss, new bone formation, and bone erosion may be non-specific. Moreover, the radiographic findings in patients with early synovitis are often subtle, confounding diagnostic categorization. In particular, establishing the unequivocal presence of erosions is notoriously difficult within the first year of synovitis. The insensitivity of plain radiography in detecting early erosions is evident when these techniques are compared to magnetic resonance imaging (MRI). Furthermore, in addition to detecting early erosions with a high degree of sensitivity, MRI is currently the only modality that clearly images the synovium, allowing the generation of quantitative data regarding synovial volume and perfusion (Ejbjerg et al., 2005).

7. Laboratory abnormalities

7.1. Rheumatoid factor

The so-called RF was first described about 75 years ago; since then a vast amount of work has

been performed on the incidence, nature, and specificity of RF (Renaudineau et al., 2005). The RF antibody is present in about 75% of RA patients, but its specificity is limited since RF is also found in patients with other autoimmune diseases (e.g. Sjögren's syndrome), infectious diseases (e.g. hepatitis, tuberculosis), and to a certain extent in the healthy population (3–5%) and healthy elderly individuals (10–30%). Despite its relatively low specificity, the presence of RF is widely used as a diagnostic marker for RA.

RFs are antibodies directed to the crystallizable fragment of IgG molecules. They are found in every immunoglobulin subclass (IgE, IgM, IgA, and IgG). IgG RF has a self-binding capacity that can result in the formation of very large immune complexes, which are able to (further) activate the immune system. It is not clear whether RF is directly related to the symptoms of RA, although RF is found significantly more often in cases of aggressive joint inflammation. In those cases, RF titers are linearly related with the severity of inflammation. Since the presence of RF is one of the ACR criteria for RA (Arnett et al., 1988), the test is performed on a routine basis in most clinical laboratories.

7.2. Other autoantibodies in RA

Anti-keratinized epithelium antibody (AKA), anti-perinuclear factor (APF), anti-cyclic citrulline-containing peptide antibodies (anti-CCP), and antibodies to citrullinated human fibrinogen (ACF) (Nielen et al., 2005) may be useful diagnostic markers in RA and be also positive in RF-negative RA patients. They are also present early in the disease and may indicate a more severe disease. Data from several investigators indicated that anti-citrullinated peptide autoantibodies (ACPAs), including anti-CCP antibodies, are specifically present in the sera of patients with RA; increased specificity is the major advantage of this test (Van Venrooij et al., 2004). There is good evidence for an association of anti-CCP with radiological joint changes in RA. Anti-CCP is an independent predictor of radiological damage and progression (Forslind et al., 2004). A significant decrease of anti-CCP titer has been observed during treatment (Aotsuka et al., 2005), in particular with anti-TNF agents (Atzeni et al., 2005c).

7.3. Acute phase reactants

The acute-phase response can be assessed by measuring different phase reactants. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are most frequently used for disease activity measurement (Dawes et al., 1986). Both measures correlate with disease activity, especially joint swelling, but not with pain. ESR is the cheapest, but can be easily influenced by anaemia and hyperglobulinaemia frequently present. CRP is more sensitive. Persistent elevated acute-phase response is associated with an increased rate of radiographic progression and also predicts radiographic progression (van Leeuwen et al., 1994).

7.4. Synovial fluid analysis

Synovial fluid analysis plays an important role in the differential diagnosis of inflammatory versus non-inflammatory arthropathies, infections, and crystal-induced arthropathies (Punzi et al., 2002).

8. Assessment

8.1. Disease activity measures

The core set is a set of standardized measures covering the variable presentation of the disease, and thus assessing disease activity (Sarzi-Puttini et al., 2002). The core set includes several components and does not give a single value for disease activity. Joint scores usually evaluate the number of total tender and swollen joints. Pain and global disease activity (assessed by both physicians and patients) can be measured by using a visual analog scale (VAS) or a Likert scale. ESR and CRP are the most frequently used laboratory variables (Creemers and van de Putte, 2004).

8.2. Functional disability

The Stanford Health Assessment Questionnaire (HAQ) (Fries et al., 1980; Wolfe, 2004), the

Arthritis Impact Measurement Scale (AIMS) (Meenan et al., 1980), and the Medical Outcomes Survey Short-Form (SF-36) (Ware et al., 1992) are the three most frequently used questionnaires in RA.

8.3. Radiographic assessment

Radiographic damage is considered to be the 'gold standard' for assessment of outcome and is used in clinical trials as primary outcome or end point. In general, radiographs of hands and/or feet are used since they include the joints affected earliest and may be a good measure of general joint damage. The two most commonly used radiographic scores are the Sharp score (Sharp et al., 1971) and the Larsen score (Larsen et al., 1977). A number of modifications of these methods have been published (van der Heijde et al., 1992; Larsen 1995; Genant, 1983). Recently, an MRI imaging score (Bird et al., 2005) and an ultrasonographic (US) synovitis scoring system (Scheel et al., 2005) have been proposed especially to score early synovitis.

8.4. Indices

Indices of disease activity such as the disease activity score (DAS) are being developed to combine disease activity measures into a single expression of disease activity (van der Heijde et al., 1990). Also available are the mathematical modifications to the DAS, namely the DAS28 (based on 28-joint counts) and the DAS28-CRP (i.e. the DAS28 using CRP instead of ESR) (Prevoo et al., 1995), and the recently introduced Simplified Disease Activity Index (SDAI) (Smolen et al., 2003). Other indices evaluate efficacy of treatment in clinical trials (ACR-20 and EULAR response criteria) (Felson, 1995: van Gestel et al., 1996).

9. Treatment

The management of RA has changed substantially in the last 10–15 years as a result of new insights into the course of the disease and proliferation of the number of therapeutic agents for its treatment (Bingham et al., 2004). Drugs used in the treatment of RA have been traditionally divided into the so-called first- and second-line drugs. First-line drugs include NSAIDs, which have a rapid suppressive effect on signs of inflammation, including pain and stiffness. Second-line drugs, also called DMARDs, influence the disease process more fundamentally by decreasing disease activity, slowing down the progression of joint damage, and preserving functional capacity (Bingham et al., 2004). Glucocorticosteroids are usually considered a separate category and can be used in different ways and are still indispensable to treat a certain number of patients affected by RA. A better understanding of the pathophysiology of RA has enabled scientists to develop a new class of drugs, termed 'biologicals' that tackle the key inflammatory cytokines like TNF-α. These include monoclonal antibodies, soluble cytokine receptors, and natural antagonists. The first two biologicals developed for the treatment of RA were the TNF-α inhibiting agents, namely etanercept and infliximab. Thereafter, newer agents were developed, including anakinra, a recombinant form of the naturally occurring IL-1 (Ra), and adalimumab, a fully human monoclonal antibody against TNF-α.

9.1. Management of early and established active inflammatory disease

Probably the greatest advance in recent DMARDs treatment has been the early aggressive management of active RA disease, be it as monotherapy or in combination (Bingham et al., 2004). Previously, a therapeutic pyramid consisted of initial conservative therapy with NSAIDs until erosions were observed, at which point treatment was switched to DMARDs added in slow succession as disease progressed (American College of Rheumatology Subcommitee on Rheumatoid Arthritis Guidelines, 2002). Nowadays, early DMARD therapy is becoming standard in those with potential for disease progress; several studies have demonstrated that early treatment decreases disease progression, slows radiographic progression, and reduces the severity of the disease affecting the overall morbidity and mortality. Conventional DMARDs, however, have several limitations like slow onset of action, induction of partial remission, and modest 5-year

retention rates. The quest for an ideal DMARD thus continues (Chen and Wie, 2005).

A variety of recent studies showed an increased efficacy of a combination therapy with DMARDs in patients with disease that does not respond adequately to monotherapy.

Combination therapy may be applied according to different designs (step-up, step-down, parallel, and bridging designs). In clinical practice, the step-up and bridging variants are most frequently used. Interestingly, several studies have shown that combination of DMARDs does not lead to more toxicity.

The recently developed biologic agents (anti-TNF and anti-IL-1 targeted therapies) have shown impressive clinical results. TNF-blocking agents already show effects within days of administration. These agents have to be administered at regular intervals, and, therefore, suppress inflammation, rather than cure the disease (Subramanian and Handa, 2004). These drugs may determine increased susceptibility to infections, development of antibodies against the agents, and seldom development of autoimmune syndromes. Early treatment with these drugs seems to reduce disease progression substantially and to increase the remission rates.

However, these agents are very expensive and they are currently reserved for people who have failed at least one DMARD including methotrexate (MTX).

9.2. Management of end-stage disease

End-stage disease is dominated by joint destruction and the extensive drug therapy may be somewhat less important, whereas a multidisciplinary approach (including surgical and rehabilitative approaches) may help the patients to face severe joint damage and the loss of function and the disability.

Assessment of these patients should consider the distinction between destructive lesions and active synovitis, and the latter should be treated appropriately.

However, primary goals include preservation and maximization of function and prevention of disability. In case of severe disability, handicaps should be overcome by adapting the environment (Bingham et al., 2004).

9.3. Non-steroidal anti-inflammatory drugs

NSAIDs are widely used for relief of pain and stiffness in RA (Pham and Hirschberg, 2005). These are usually the first drugs commenced following disease onset and often prior to assessment by a rheumatologist.

9.4. Corticosteroids

In most patients, steroids rapidly reduce the level of inflammation, but are associated with significant toxicity when a high cumulative dose is given (Bijlsma et al., 2005). Short-term steroids and low dosage (5–10 mg/day) can be useful as bridge therapy waiting for DMARDs to start working. Calcium, vitamin D, hormone replacement therapy, and biphosphonates have all been used to prevent steroid-induced bone loss.

9.5. Disease-modifying anti-rheumatics drugs

Antimalarials hydroxychloroquine (*HCQ*) *and chloroquine* (*CQ*) has low efficacy when used as monotherapy, but is sometimes used as first-line therapy in mild disease (Tutor-Ureta and Yebra-Bango, 2005). Recently, its use in severe disease has increased following studies showing additional efficacy of combination therapy in patients with refractory disease.

Sulfasalazine (SSA) is used in many centres as the first-line DMARD. SSA reduces the rate of bone erosions in early (van der Heijde et al., 1989) and established disease (Pullar et al., 1987).

MTX, an antagonist of folate metabolism, is used commonly (increasingly first line) both alone and in combination with other DMARDs (commonly SSA and/or hydroxychloroquine) (Prodawich et al., 2005; Strand et al., 2005). It is normally given with folic acid to reduce the incidence of toxicity. MTX has been shown to reduce the progression of erosions when used first line. MTX is normally given orally once a week (range dose 7.5–25 mg), but can also be given parenterally if there is concern regarding bioavailabity or in order to prevent gastric toxicity.

Leflunomide (*LEF*) is currently licensed only as monotherapy, although studies are underway with combination therapy with SSA or MTX. In clinical studies, LEF reduces disease activity and radiological progression (Smolen et al., 1999).

Cyclosporine (*CsA*) monotherapy has been shown to be efficacious in the treatment of RA (Tugwell, 1992) and to reduce radiographic progression. It is often used in combination therapy with MTX (Sarzi-Puttini et al., 2005a, b).

Injectable gold (*sodium aureothiomalate*) *and oral gold* (*auranofin*) are no longer first-line therapies and tend to be used in patients who have failed treatment with MTX and SSA.

9.6. Biological agents

9.6.1. anti-TNF-α monoclonal antibody therapy

The introduction of TNF blockade such as infliximab, etanercept, and adalimumab has been a breakthrough in the management of severe refractory RA.

Infliximab, a recombinant chimeric antibody produced by mouse myeloma cells, contains sequences from human IgG1 constant and mouse variable regions, is specific for the membrane-bound or secreted or extracellular space TNF-α of humans and chimpanzees, and prevents TNF from binding to its membranous and soluble receptors. Infliximab is registered by the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) as therapy for treatment-resistant RA, treatment-resistant moderate to severe Crohn's disease (CD), and CD with fistulas (Elliott et al., 1994; Present et al., 1999). It is now approved for the treatment of ankylosing spondylitis (AS), psoriasis and psoriatic arthritis. (Braun et al., 2002).

Etanercept, a fusion protein (decoy receptor) secreted by Chinese ovary (CHO) cells, combines the ligand-binding portion of human TNF receptor 2(TNFR2 = p75 = CD120b) with sequences of human IgG1. Unlike TNFR1 (p55 = CD120a), TNFR2 is a constitutive membrane receptor that is inducible upon stimulation and can be found on the surface of almost all cells except red blood cells and resting lymphocytes. Etanercept is approved by the FDA and the EMEA for use in treatment-resistant RA as well as for severe active and progressive RA and treatment-resistant polyarticular juvenile chronic arthritis. It is also approved by the FDA for treatment-resistant psoriatic arthritis, and it has a beneficial effect in AS (Moreland et al., 1996; Genovese et al., 2002; Kietz et al., 2001; Mease et al., 2000; Brandt et al., 2004).

Adalimumab is a recombinant human immunoglobulin G1 monoclonal antibody that is specific for human TNF. It specifically binds to circulating and cell surface TNF-α and blocks its interaction with p55 and p75 cell surface TNF receptors. The first fully human anti-TNF-α monoclonal antibody was approved for the treatment of moderate to severe RA by the FDA in 2002 and by the EMEA in September 2003 (Keystone and Haraqui, 2004; Furst et al., 2002; Scheinfeld, 2005).

9.6.2. Anakinra

Anakinra is the first biologic drug that has been developed specifically as an interleukin (IL)-1 Ra and is derived from an endogenous IL-1Ra. The drug blocks the activity of IL-1 in synovial joints, reducing the inflammatory and joint destructive processes associated with RA (Waugh and Perry, 2005). In randomized, placebo-controlled trials of up to 52-weeks duration, anakinra has shown efficacy both as monotherapy and in combination with other DMARDs in adults with RA (Furst, 2004). It is subcutaneously administered (dosage 150 mg/day) and is generally well tolerated.

9.7. Anti-B-cell therapy

Rituximab is an anti-CD20 monoclonal antibody that causes depletion of B cells. It is a novel targeted therapy for the treatment of RA and it appears to be highly effective and safe (Kimby, 2005).

10. Cutaneous manifestations

Non-specific skin changes may be observed in patients with RA. The skin can become atrophic and lead to fragility and easy bruisability (Sayah and English, 2005) (Table 3). Skin overlying the digits

Table 3
Skin manifestations in Rheumatoid arthritis

1.	Nailfold lesions
2.	Digital infarcts
3.	Urticaria
4.	Gangrene
5.	Ulcers
6.	Nodules
7.	Purpura

may become pale or even translucent. Nail changes may occur in RA patients. Michel et al. (1997) evaluated the frequency and the specificity of nail changes associated with RA in a case-controlled study including 50 patients suffering from RA and 50 controls. The only nail abnormalities significantly associated with RA were longitudinal ridging (onychorrhexis) and clubbing of the fingers. Nails of the RA patients also manifest periungual erythema with teleangectasia, onycholysis, red lunula, or pterygium inversum (Jorizzo et al., 1983; Daniel et al., 1985).

Specific cutaneous manifestations of RA are varied and encompass a number of entities, some of which define the dominant clinical features, such as the rheumatoid papule or subcutaneous cords, while others allude to the histopathology, i.e. rheumatoid neutrophilic dermatosis (RND) (Chen et al., 2002). Magro and Crowson (2003) proposed a more simplified classification scheme using the adjectival modifiers of 'rheumatoid-associated' and then further categorizing the lesions according to the dominant reaction pattern. Three principal reaction patterns are recognized, namely (i) extravascular palisading granulomatous inflammation; (ii) interstitial and/or subcuticular neutrophilia; and (iii) active vasculopathy encompassing lymphocyte-dominant, neutrophil-rich, and granulomatous vasculitis. In most cases, an overlap of the three reaction patterns is seen.

10.1. Rheumatoid nodules

Rheumatoid nodules are the classic cutaneous manifestation of RA (Fig. 2). They are not diagnostic for this disease and can be seen in other processes, especially other connective tissue diseases. Rheumatoid nodules occur in about 25% of patients with RA, and reflect high levels of disease activity and severity (Ziff, 1990). Clinically, rheumatoid nodules are extremely relevant as they correlate with more severe arthritis, higher levels of RF, and with an increased incidence of rheumatoid vasculitis (RV). The presence of RF within rheumatoid nodules suggests the possibility of immune complex-mediated vasculitis as the initiating event in rheumatoid nodule development (Chu et al., 1994). Clinically, they are firm, dome-shaped, skin-coloured papules within the subcutaneous tissue. They are mobile and non-tender. Typically, they are present at pressure areas throughout the skin, like extensor areas of the forearm, finger joints, ischial and sacral prominences, occipital scalp, and Achilles tendon (Jorizzo et al., 1983; Chu et al., 1994; Harris Jr. et al., 1994). Rheumatoid nodules are firm and frequently adherent to the underlining periosteum. Rarely, they are the first presenting symptom of the disease and occasionally are present in internal organs, i.e. lungs, gallbladder, and heart (Abbas and Byrd, 2000; Kitamura et al., 2004). Histopathologically, the rheumatoid nodules manifest three characteristic zones (i) an inner central necrotic zone; (ii) a surrounding zone of palisading granulomas (predominantly macrophages); and (iii) an outer zone with perivascular infiltration of chronic inflammatory cells (Ziff, 1990). The granulomas are surrounded by third zone of fibrotic tissue reaction containing fibroblasts, plasma cells, and lymphocytes. The lesion is assumed to be the result of small-vessel vasculitis with fibrinoid necrosis (Fig. 3). Local collagenase and proteinase production may explain the central necrosis (Palmer et al., 1987). Nodules may regress during effective treatment with DMARDs as disease activity reduces (Harris Jr., 1994). However, MTX has been reported to induce or aggravate nodulosis, especially over finger tendons, despite reduction of disease activity (Duong et al., 1999; Agarwal et al., 2004). Braun et al. (2004) recently reported three cases of nodulosis during LEF therapy. Progression and acceleration of nodulosis during MTX therapy in RA patients is caused by adenosine A1 receptor promotion of multinucleated giant cell formation by human monocytes. LEF has no known influence on adenosine metabolism, so different pathogenetic mechanisms must be assumed for the induction of nodulosis by LEF.

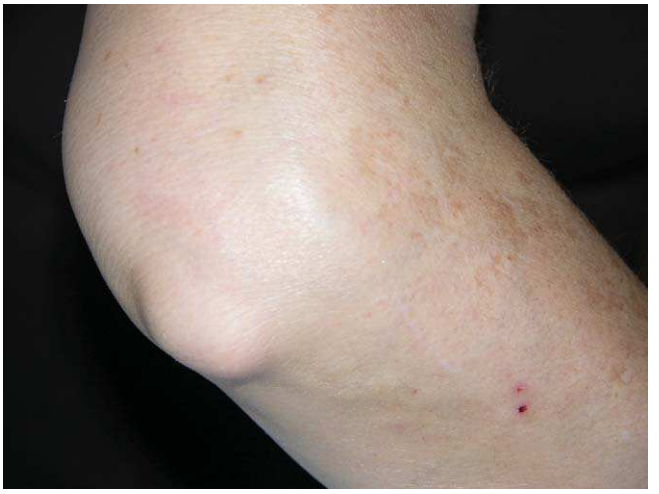


Figure 2. Rheumatoid nodule. Such nodules are seen in patients with severe rheumatoid arthritis and appear beneath the skin over bony prominences such as the elbow. They can occasionally appear in visceral organs.

10.2. Cutaneous vasculitis

Cutaneous vasculitis (CV), a complication seen in approximately 5–15% of patients with RA, is associated with positive, often high-titer, RF, anti-endothelial antibodies of IgA class, anti-Ro and anti-cardiolipin antibodies, advanced erosive disease, and increased patient morbidity and mortality (Quismorio et al., 1983; Ziff, 1990; Coremans et al., 1992). CV should be suspected in advanced disease associated with fever, weight loss, and fatigue (Fig. 4). CV can be present without active joint disease. Frequently, other extra-articular features are present like episcleritis, pleural, and pericardial effusions, a raised ESR, a low serum albumin, and sometimes liver enzymes disturbances (Harris Jr., 1994). The most frequently observed features are chronic deep-skin ulcers and nailfold lesions. The latter occur in about 5% of patients and are not associated with a worse prognosis. The clinical implication is that the primary joint inflammatory process is poorly controlled. Manifestations are often precipitated by abrupt discontinuation of systemic therapy with rebound circulating immune complex disease. CV can be classified by the size of the largest vessel involved and by the presence or absence of systemic involvement. The severity of the vasculitis cannot be defined by the cutaneous examination alone; a thorough evaluation searching for systemic involvement is essential. Jorizzo and Daniels (1983) divided the RV spectrum of disease in cutaneous vessels, ranging from severe with multisystem larger-vessel vasculitis, to moderate with cutaneous small vessel and possibly systemic small-vessel vasculitis, and mild with Bywaters lesions only.

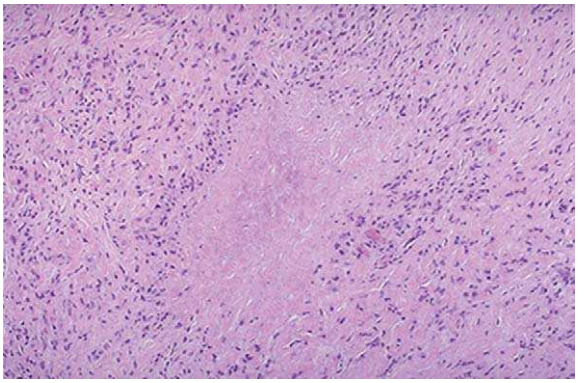


Figure 3. Rheumatoid nodule. There is a central area of fibrinoid necrosis surrounded by palisading epithelioid macrophages and other mononuclear cells.

As described in many studies, immune complexes are assumed to be responsible for pathogenesis of RV. IgM and C3 were identified in many patients. The presence of circulating immune complexes and hypocomplementaemia during the development of the vasculitis strongly suggest a

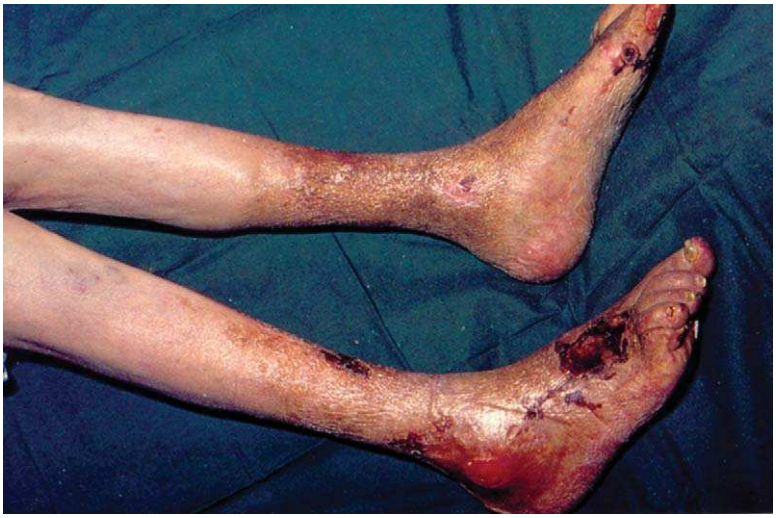


Figure 4. Severe rheumatoid cutaneous vasculitis (Dieppe, 1984).

pathogenesis of immune complex-mediated vasculitis occurring in patients with RA (Scott et al., 1981). To establish the diagnosis, a full thickness skin and muscle biopsy must be performed (Harris Jr., 1994). Serological tests are of limited value for the diagnosis of RV. In the past several autoantibodies have been suggested to be present, more frequently in patients with RV compared to patients without. However, none of them is pathognomonic. Some reports are contradictory. ANA are present in a large proportion of CV patients (Scott, 1981; Quismorio et al., 1983; Jorizzo, 1983).

10.2.1. Histological characteristics

1. Severe RV results from a systemic arteritis of small to medium arteries. Histologically, this is a leukocytoclastic vasculitis with endothelial swelling, polymorphonuclear leukocyte invasion of vessel walls with necrosis, leukocytoclasis, and extravasation of red blood cells. Peripheral neuropathy presenting as mononeuritis, mononeuritis multiplex, or distal symmetric neuropathy may be the first sign. Neuropathy is assumed to result from vasculitis of the vasa nervorum. Gangrene of the digits, nailfold thromboses and infarcts, and deep cutaneous ulcers can also be seen. Less common manifestations of this larger vessel vasculitis include ischemic bowel disease, cerebral vasculitis, pulmonary vasculitis, and vasculitic glomerulonephritis.
2. Moderate RV results from limited small vessel vasculitis involving the postcapillary venules. Histopathologically, it is also a leukocytoclastic vasculitis. Patients most often present with cutaneous lesions, most characteristically, palpable purpura, on dependent sites. Cutaneous small-vessel vasculitis can be seen in many disease states and can be caused by infection, drugs, foreign protein, or immune complexes (autoimmune diseases). Moderate RV is believed to be an immune complex-mediated vasculitis in patients with high-titer RF that represents IgM (or IgA)/IgG immune complexes.
3. Mild RV describes cutaneous manifestations of RA that occur in the absence of systemic vasculitis, and includes nailfold teleangiectasias with thromboses, minute digital ulcerations (Fig. 5), digital petechiae, livedo reticularis, and digital pulp papules also known as Bywaters lesions. Bywaters lesions are purpuric papules that primarily affect the pulp of the distal digits. Histopathologic examinations of these lesions again reveals leukocytoclastic vasculitis. Bywaters lesions

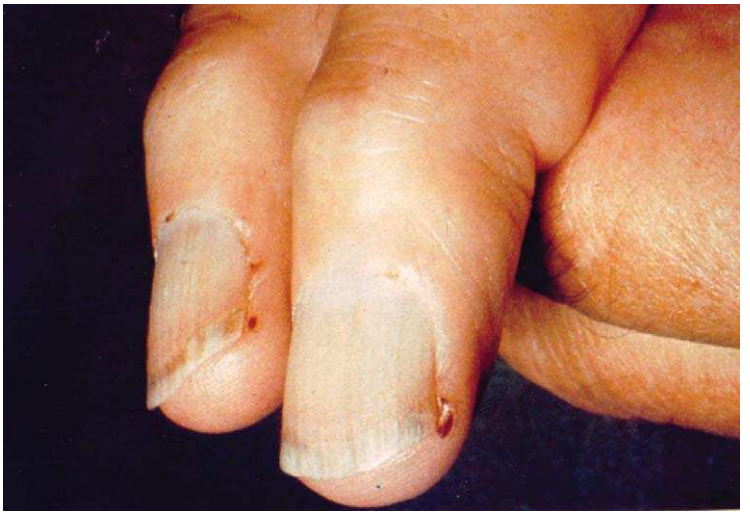


Figure 5. Digital infarcts in a patient with rheumatoid vasculitis (Dieppe, 1984).

differ from rheumatoid nodules in that no palisading granulomatous response is found in histologic specimens.

Features of cutaneous RV overlapping both the characteristics of cutaneous necrotizing venulitis and cutaneous polyarteritis nodosa together with coexistence of these different type of vasculitis in the same or different lesional skin account for the associated diverse cutaneous vasculitic manifestations. Although dermal venulitis (leucocytoclastic vasculitis) was the most common presentation, the presence of leucocytoclastic vasculitis in rheumatoid patients did not necessarily indicate a favourable prognosis (Voskuyl et al., 1996a; Crowson et al., 2003). Associations with mononeuritis multiplex and bowel involvement had a fatal prognosis, while patients with superficial dermal venulitis without other extra-articular involvement may follow a favourable prognosis (Voskuyl et al., 1996b).

10.2.2. Leg ulcers

Cutaneous ulceration, primarily of the lower extremities, is frequently found in patients with chronic, debilitating disease (Oien et al., 2000; Margolis et al., 2004). Lower extremity ulceration in patients with RA may be due to an associated disease process such as RV or pyoderma gangrenosum (PG). If in CV the large vessels are affected, skin ulceration develops, often on lower extremities, or where skin is exposed to pressure, for example, in interphalangeal joints of the toes, over bunions, ankles, elbows and, in bedridden patients, the buttocks. These ulcerations may be very painful, come in crops, and tend to grow and become chronic. Superinfection frequently occurs, particularly being a great risk for patients with joints prostheses. In severe cases, ulcerations may form over subcutaneous nodules. CV or leucocytoclastic vasculitis, seen as palpable purpura, heals as a rule and responds to conventional DMARDs (Heurkens et al., 1991). Large-vessel vasculitis requires prompt treatment with corticosteroids and cytotoxic drugs. In addition to drug treatment, pressure ulcers should be treated by eliminating pressure, frequent bathing in soda or betadine water, and careful local bandage therapy (Dowsett, 2005). It is difficult to determine whether pressure is the only cause of such ulcers, and vasculitis should be regarded in case of any irregularly shaped purpuric lesions and non-healing ulcers.

Symmetric lower extremity ulcerations in patients with RA, resembling necrobiosis lipoidica diabeticorum, have been called superficial ulcerating rheumatoid necrobiosis. More common causes of lower extremity ulceration should also be considered,

such as venous stasis ulcers, granulocytopenia, and splenomegaly in patients with RA is diagnostic for Felty syndrome (Goldberg and Pinals, 1980; Balint and Balint, 2004).

10.2.3. Felty's syndrome

Felty's syndrome is defined as RA in combination with splenomegaly and leucopaenia. It is seen in less than 1% of hospital RA patients and occurs in the same frequency in males and females (Goldberg and Pinals, 1980; Balint and Balint, 2004). Clinically, it is characterized by severe joint destruction contrasting with moderate or absent joint inflammation and severe extra-articular disease, including a high frequency of rheumatoid nodules, lymphadenopathy, hepatopathy, vasculitis, leg ulcers, skin pigmentation, etc. The management of Felty's syndrome is still under investigation. In a review, MTX haematopoietic growth factors, and splenectomy appeared to be the most efficacious in increasing granulocyte count and improving clinical outcome (Rashba et al., 1996; Wassenberg et al., 1998; Hellmich et al., 1999). Treatment with DMARDs might improve cytopaenia and reduce the susceptibility to infection (Breedveld et al., 1987).

10.3. Neutrophilic dermatoses

The neutrophilic dermatoses are a group of related cutaneous disorders that frequently have systemic manifestations or associations (Callen, 2002; Wallach, 2005). Several neutrophilic dermatoses occur in patients with RA (Wallach, 2005). These include PG, RND, acute febrile neutrophilic dermatosis (Sweet's syndrome), erythema elevatum diutinum, subcorneal pustular dermatitis (Sneddon-Wilkinson's disease), and neutrophilic lobular panniculitis. Sweet syndrome is a reactive dermatological disease characterized by fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques, which show dense neutrophilic infiltrates and papillary dermal edema (Joe, 2003). It may occur in the absence of other diseases but is often associated with other systemic autoimmune diseases, infections, and myelodysplastic malignancies (Gouliaris et al., 2003; Theng et al., 2003). Its association with RA has been well described (Wallach, 2005). Clinical overlap between these disorders led to the concept of 'the neutrophilic dermatosis'. In addition, patients with a neutrophilic skin disorder may also suffer from extra-cutaneous aseptic neutrophilic infiltrates. The mechanisms underlying the inappropriate activation of polymorphonuclears are poorly understood (Wallach, 2005). Hematopoietic growth factors and adhesion molecules are believed to play a role in the pathophysiology of the neutrophilic dermatoses.

10.3.1. Pyoderma gangrenosum

PG is a condition characterized by acute, necrotizing, rapidly expanding cutaneous ulcers (Mani, 2002; Groves, 2004). These ulcers may occur on cutaneous site, yet they most commonly occur on the lower extremities and abdomen. Lesions begin as erythematous papulopustules. They quickly expand to become fluctuant, painful ulcerations with dusky, undermined borders. When the lesions heal, they demonstrate a characteristic atrophic 'papyraceous' scar. PG can be seen in association with multiple systemic diseases such as CD, ulcerative colitis, RA, and malignancies, especially hematologic malignancies (Brown et al., 2001; Tavarela Veloso, 2004; Harati et al., 2005). The ulcers of patients with PG seem more refractory to treatment than the ulcers of patients with PG alone. Those with PG ulcers represent a refractory subset of patients, and the ulcers are possibly secondary to unique pathophysiological features. In patients with RA, the lesions have often been confused with venous stasis ulcers, necrobiosis lipoidica diabeticorum, and bacterial pyoderma. No histologic pattern is pathognomonic for PG and it is ultimately a clinical diagnosis of exclusion. However, histopatologic examination often reveals neutrophils in the dermis with signs of endothelial swelling and deposits of immunoglobulins and complement factors in the dermal blood (Jorizzo et al., 1988; Magro and Crowson, 2003).

10.3.2. Rheumatoid neutrophilic dermatosis

RND is a rare cutaneous manifestation seen in patients with severe RA (Brown et al., 2001; Defaria and Kroumpouzos, 2004). All have had severe disease and a RF positive, but recently the literature reports RND as presenting sign of

seronegative arthritis. This presents as chronic, erythematosus, 'urticaria-like' plaques and papules over the extensor surfaces on the extremities and the trunk. The lesions are usually non-tender, non-scaling, and nomigratory. They may persist for weeks to months, and ulceration may occur. Histopathologiacally, a dense neutrophilic infiltrate is seen throughout the dermis without an associated vasculitis (Magro and Crowson, 2003). It may be difficult to distinguish RND from acute febrile neutrophilic dermatosis, which also occurs in patients with RA.

10.3.3. Cutaneous atrophy with stellate scarring

Patients with RA occasionally present with livedo reticularis, a reticulated vasodilatatory response that occurs predominantly on the trunk and on entire extremities (Cimmino et al., 2000). The lesions are non-palpaple and often quite subtle. The reticulated pattern results from the occlusion of distal vessels that supply the upper skin leading to a compensatory vasodilation of surrounding vessels. Ulceration and scarring are common. Patients with RA may also have livedoid vasculopathy. Also known as atrophie blanche, a chronic dermatological disorder associated with petechiae and recurrent, unusually shaped ulcers that heal to form hyperpigmentated areas and atrophie blanche (Schroeter and Harris, 1984; Cimmino et al., 2000).

11. Adverse skin reactions to drugs

11.1. Non-steroid anti-inflammatory drugs

The wide usage of NSAIDs in RA patients raises the significance of their side effects. Among cutaneous symptoms, intolerance was present at a relatively low frequency (Rethy and Balo-Banga, 2004). The most frequent cutaneous side effects are caused by pyrazolon derivates. Urticaria and angioedema were the most frequently observed symptoms. Pseudoporphyria is a photosensitive bullous skin disease that is distinguished from porphyria cutanea tarda (PCT) by its normal porphyrin profile. NSAIDs, especially naproxen and other propionic acid derivatives, appear to be the most common offenders (Al-Khenaizan et al., 1999).

11.2. Disease-modifying anti-rheumatics drugs

Intramuscular gold is a well-documented treatment in RA, but its mechanism of action is still poorly understood. Patients given gold salts have a high risk of cutaneous reactions. The mechanisms of cutaneous reactions are unknown and vary according to the molecules (Hofmann et al., 1986; Bonnetblanc, 1996). Smokers, HLA Bw35 patients, and perhaps atopic states are more prone to gold drug reaction. Inflammation at the site of injections is frequent but with no consequence. (Hofmann et al., 1986). Pruritus is frequently observed, more often with oral salts. Exanthemas are common and may disclose an associated visceral disease. Drug hypersensitivity is rare, but severe. Accumulation (chrysiasis) may be observed with long-term treatment (Smith et al., 1995). Chrysiasis is a distinctive and permanent pigmentation of light-exposed skin resulting from the administration of parenteral gold salts (Fig. 6). Focal aggregates of particulate gold are deposited in the reticular and papillary dermis in amounts that correlate with the degree of pigmentation (Bonet et al., 1990; Smith et al., 1995). Characteristically, initially the periorbital region is affected by a mauve discoloration, which intensifies and deepens into a blue/slate-grey colour, while extending to involve the face, neck and upper limbs. Prevention is difficult, but measures to reduce sunlight exposure may be helpful. All these types necessitate drug interruption (Bonet et al., 1990). Lichenoid eruptions require withdrawal, but the skin disease may continue.

Antimalarials are generally well tolerated when compared with other disease-modifying drugs. In terms of cutaneous reactions, antimalarials can induce urticaria, pruritus (Holme et al., 1999), alopecia, hair bleaching, dry skin, pigment changes, rashes, flares of psoriasis, and exfoliating lesions (Vine et al., 1996), as well as a Stevens-Johnson-like syndrome (Kutz and Bridges, 1995). Most patients continue HCQ therapy in the long term, but ~3% discontinue HCQ because of adverse cutaneous reactions (Salido et al., 2002).

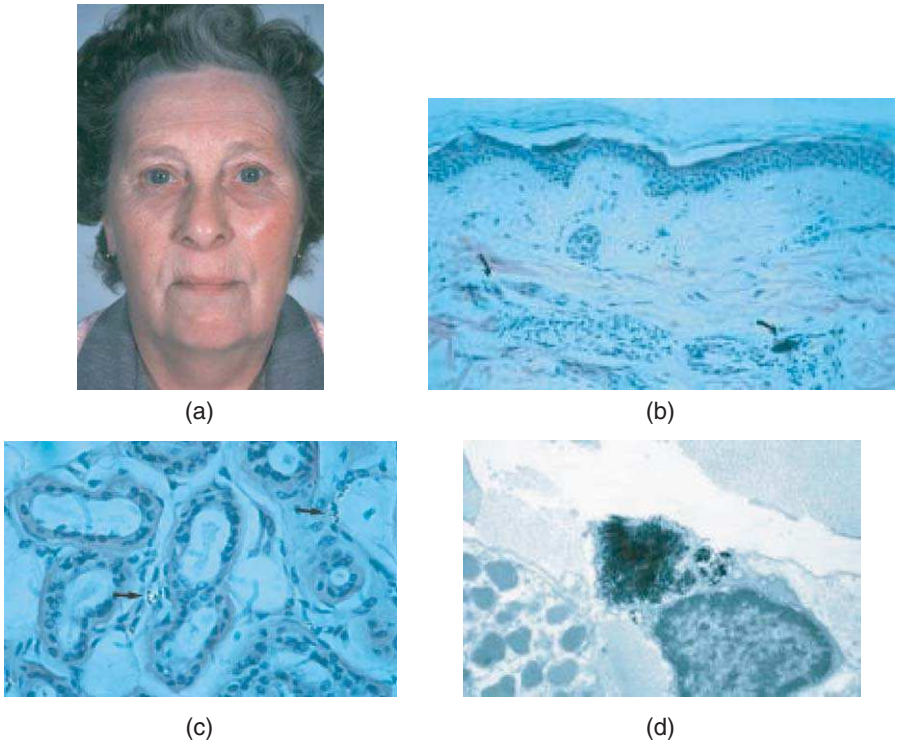


Figure 6. a) Severe chrysiasis: marked blue/slate grey discoloration affects the entire face, most obviously involving the eyelids and forehead.
b) Lateral forehead biopsy (H + E × 50) shows focal aggregates of dark pigment (curved arrows) in the reticular and papillary dermis.
c) At high power (H + E 312 ×) perivascular deposits (straight arrows) are seen concentrated around blood vessels in the reticular dermis and around vessels within sweat glands.
d) Electron microscopy (× 12,000) demonstrates aggregates of filamentous electron! dense material within a macrophage aurosome.
(With permission from Blackwell Science Ltd and were first published in the *British Journal of Dermatology* 1995; 133, 671–678).

Skin adverse reactions to SSA are seen in 10% patients with RA and are usually mild. However, severe skin reactions including Stevens-Johnson reactions, erythema multiforme, bullous dermatitis, toxic pustuloderma and epidermal necrolysis, and exfoliative dermatitis may occur. Serious skin reactions were also reported more commonly in patients receiving SSA for RA rather than inflammatory bowel syndromes (IBD) (Gran and Myklebust, 1993). However, serious skin side effects with SSA are rare (8.6 per million prescriptions) (Ransford et al., 2002)

D-penicillamine therapy can produce an unusual variety of skin lesions; some are acute sensitivity reactions; some are caused by metabolic effects of the drug; and some are due to autoimmune phenomena or to unknown mechanisms (Sternlieb et al., 1981). The type and incidence of side effects depend on the original disease, on penicillamine dosage, and on duration of treatment.

LEF is an anti-rheumatic agent of the type of a 'disease-modifying anti-rheumatic drug'. In rare cases, severe skin reactions up to the extreme expression of toxic epidermal necrolysis have been observed (Fisher et al., 2003).

MTX inhibits DNA synthesis by competition with dihydrofolate reductase. Adverse cutaneous reactions to MTX are usually dose-related and have been mainly reported in patients receiving extremely large doses of chemotherapy (Del Pozo, 2001). Rheumatoid nodulosis is characterized by multiple small-subcutaneous granulomatous nodules

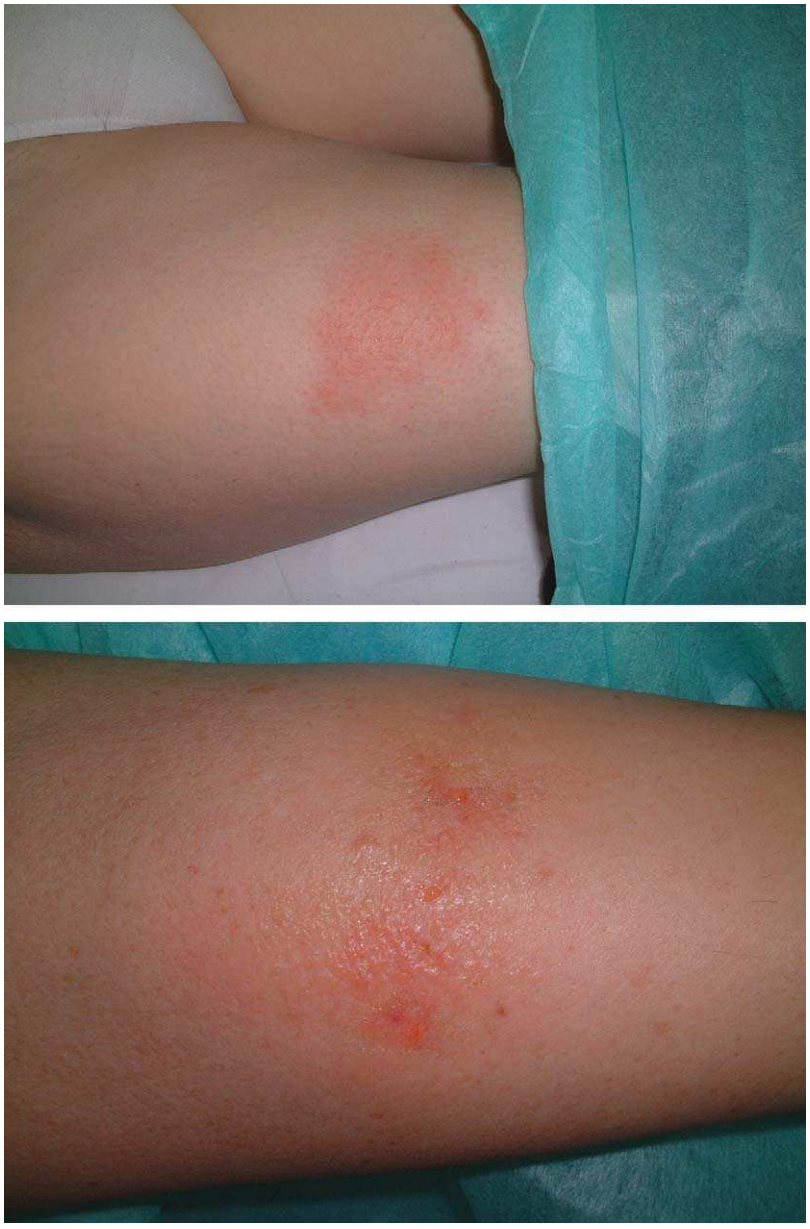


Figure 7. Adverse skin reactions with anakinra. The onset of reactions was within the first month of treatment and appeared as well-defined erythema and oedema involving the injection sites.

typically located on the elbows in approximately 20% of patients with RA. Accelerated rheumatoid nodulosis, especially involving the hands and feet, has recently been reported in patients receiving MTX therapy for RA (Williams et al., 1998) and some cases have been reported for LEF.

11.3. Biologic agents

11.3.1. Anti-TNF-α monoclonal antibody therapy

Various adverse cutaneous reactions to anti-TNF-α agents have been reported (Livermore and Murray,

2002; Roux et al., 2004). In clinical studies with infliximab adverse drug reactions were most frequently reported in the respiratory system and in the skin and appendages. Devos et al. (2003) described here six patients receiving anti-TNF-α therapy for CD or RA who consulted our out-patient department for adverse cutaneous reactions: leukocytoclastic vasculitis, lichenoid drug reaction, perniosis-like eruption, superficial granuloma annulare and acute folliculitis. Mohan et al. (2004) reported 35 cases of LCV, 20 following etanercept administration and 15 following infliximab administration. Seventeen of the 35 (48.5%) were biopsy-proven cases and the others had skin lesions that were clinically typical for LCV. Twenty-two of 35 (62.8%) patients had complete or marked improvement of skin lesions upon stopping the TNF-α blocker. In a recent prospective study (Flendrie et al., 2005) 128 dermatological events were recorded in 72 patients (25%) during 911 patient-years of follow-up. TNF-α-blocking therapy was stopped in 19 (26%) of these 72 patients because of the dermatological event. The events recorded most frequently were skin infections, eczema, and drug-related eruptions. Other events with a possible relation to TNF-α-blocking therapy included vasculitis, psoriasis, drug-induced systemic lupus erythematosus, dermatomyositis, and a lymphomatoid-papulosis-like eruption (Fliendre, 2005). An association between the use of TNF-α-blocking therapy and the induction of systemic lupus erythematosus and discoid lupus erythematosus is suggested by the number of cases that have been published (Sarzi-Puttini et al., 2003; Atzeni et al., 2005a, c). Moreover, reports of CV induced by biologic agents are described in the literature, although it is a known extra-articular manifestation of RA (McCain et al., 2002; Jarrett et al., 2003).

11.3.2. Anakinra

Anakinra, a recombinant-methionyl human IL-1Ra, has been shown to reduce joint inflammation and swelling, cartilage destruction, and bone resorption in several animal models of RA (Lebsack et al., 1991; Bendele et al., 1999).

The only side effects that appeared to be closely linked with administration of anakinra were skin reactions at the injection site (Bendele et al., 1999) (Fig. 7). Such reactions were the most frequent adverse events, and their frequency and severity increased with increasing doses of anakinra. Following adjustment for drug exposure time, the frequency of injection site reactions (ISRs) was 0.82 per patient-year of exposure in the placebo group (first 24 weeks) and 1.01, 2.43, and 3.73 for the 30 mg, 75 mg, and 150 mg doses of anakinra, respectively (long-term rates) (Riente, 2004). The most common symptoms and signs at the injection site were erythema, pruritus, and rash. The most relevant histopathological findings include dermal oedema and a lichenoid, perivascular predominantly lymphomononuclear infiltrate, with many eosinophils and the presence of enlarged CD68+ macrophages (Vila et al., 2005).

12. Conclusion

Extra-articular manifestations can be detected in almost any organ system, causing considerable disease-related morbidity and interference with quality of life. Cutaneous manifestations of RA include three principal reaction patterns: (i) extravascular palisading granulomatous inflammation; (ii) interstitial and/or subcuticular neutrophilia; and (iii) active vasculopathy encompassing lymphocyte-dominant, neutrophil-rich, and granulomatous vasculitis. The most widely recognized skin lesion is the rheumatoid nodule, but various cutaneous lesions can be observed either related to the disease itself or to the commonly used drugs.

Key points

- Cutaneous manifestations of RA include three principal reaction patterns: (i) extravascular palisading granulomatous inflammation; (ii) interstitial and/or subcuticular neutrophilia; and (iii) active vasculopathy encompassing lymphocyte-dominant, neutrophil-rich, and granulomatous vasculitis.
- The most widely recognized skin lesion is the rheumatoid nodule. Rheumatoid

nodules correlate with more severe arthritis, higher levels of RF, and with an increased incidence of RV.
- CV can be classified by the size of the largest vessel involved and by the presence or absence of systemic involvement. The immune complexes are assumed to be responsible for pathogenesis of RV.
- Several neutrophilic dermatoses occur in patients with RA. RND is a rare cutaneous manifestation seen in patients with severe RA, and a RF positive.
- Adverse skin reactions to drugs in RA patients may occur.

References

Abbas, A., Byrd, B.F., II. 2000. Right-sided heart failure due to right ventricular cavity obliteration by rheumatoid nodules. Am. J. Cardiol. 86, 711.

Agarwal, V., Aggarwal, A., Misra, R. 2004. Methotrexate induced accelerated nodulosis. J. Assoc. Physicians India 52, 538.

Alamanos, Y., Drosos, A.A. 2005. Epidemiology of adult rheumatoid arthritis. Autoimmun. Rev. 4, 130.

Albani, S., Keystone, E.C., Nedson, J.L., et al. 1995. Positive selection in autoimmunity: abnormal immune responses to a bacterial dnaJ antigenic determinant in patients with early rheumatoid arthritis. Nat. Med. 1, 448.

Al-Khenaizan, S., Schechter, J.F., Sasseville, D. 1999. Pseudoporphyria induced by propionic acid derivatives. J. Cutan. Med. Surg. 3, 162.

American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines 2002. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum. 46, 328.

Aotsuka, S., Okawa-Takatsuji, M., Nagatani, K., et al. 2005. A retrospective study of the fluctuation in serum levels of anticyclic citrullinated peptide antibody in patients with rheumatoid arthritis. Clin. Exp. Rheumatol. 23, 475.

Arnett, F.C., Edworthy, S.M., Bloch, D.A., et al. 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 31, 315.

Atzeni, F., Ardizzone, S., Sarzi-Puttini, P., et al. 2005a. Autoantibody profile during short-term infliximab treatment for Crohn's disease: a prospective cohort study. Aliment. Pharm. Therap. 22, 453.

Atzeni, F., Sarzi-Puttini, P., Doria, A., et al. 2005b. Potential off-label use of infliximab in autoimmune and non-autoimmune diseases: a review. Autoimmun. Rev. 4, 144.

Atzeni, F., Turiel, M., Capsoni, F., et al. 2005c. Autoimmunity and anti-TNF-α agents. Ann. NY Acad. Sci. 1051, 559.

Babyn, P., Doria, A.S. 2005. Radiologic investigation of rheumatic diseases. Pediatr. Clin. North Am. 52, 373.

Balint, G.P., Balint, P.V. 2004. Felty's syndrome. Best Pract. Res. Clin. Rheumatol. 18, 631.

Bendele, A., McAbee, T., Sennello, G., et al. 1999. Efficacy of sustained blood levels of interleukin-1 receptor antagonist in animal models of arthritis: comparison of efficacy in animal models with human clinical data. Arthritis Rheum. 42, 498.

Bijlsma, J.W., Saag, K.G., Buttgereit, F., et al. 2005. Developments in glucocorticoid therapy. Rheum. Dis. Clin. North Am. 31, 1.

Bijlsma, J.W., Straub, R.H., Masi, A.T., et al. 2002. Neuroendocrine immune mechanisms in rheumatic diseases. Trends Immunol. 23, 59.

Bingham, S.L., Quinn, M.A., Emery, P. 2004. Rheumatoid arthritis-management. In: D.A. Isenberg, P.J. Maddison, P. Woo, F.C. Breedveld (Eds.), Oxford Textbook of Rheumatology. Oxford University Press, New York, p. 719.

Bird, P., Conaghan, P., Ejbjerg, B., et al. 2005. The development of the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann. Rheum. Dis. 64 (Suppl.), 18.

Blass, S., Engel, J.M., Burmester, G.R. 1999. The immunologic homunculus in rheumatoid arthritis. Arthritis Rheum. 42, 2499.

Bonet, M., Olive, A., Maymo, J., Cucurull, J. 1990. Chrysiasis in rheumatoid arthritis. Clin. Rheumatol. 9, 254.

Bonnetblanc, J.M. 1996. Cutaneous reactions to gold salts. Presse. Med. 25, 1555.

Brandt, J.J., Listing, J., Sieper, J., et al. 2004. Development and presentation of criteria for short term improvement after TNF alpha treatment in ankylosing spondylitis. Ann. Rheum. Dis. 63, 1438.

Braun, J., Brandt, J., Listing, J., et al. 2002. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 359, 1187.

Braun, M.G., Van Rhee, R., Becker-Capeller, D. 2004. Development and/or increase of rheumatoid nodules in RA patients following leflunomide therapy. Z. Rheumatol. 63, 84.

Breedveld, F.C., Fibbe, W.E., Hermans, J. 1987. Factors influencing the incidence of infections in Felty's syndrome. Archiv. Intern. Med. 147, 915.

Brown, T.S., Fearneyhough, P.K., Burruss, J.B., et al. 2001. Rheumatoid neutrophilic dermatitis in a woman with seronegative rheumatoid arthritis. J. Am. Acad. Dermatol. 5, 596.

Callen, J.P. 2002. Neutrophilic dermatoses. Dermatol. Clin. 2, 409.

Caruso, I., Santandrea, S., Sarzi-Puttini, P., et al. 1990. Clinical, laboratory and radiographic features in early rheumatoid arthritis. J. Rheumatol. 17, 1263.

Chen, K.R., Toyohara, A., Suzuki, A., et al. 2002. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. Br. J. Dermatol. 147, 905.

Chen, E.H., Wie, W. 2005. New therapeutic approaches for rheumatoid arthritis. Assay Drug Dev. Technol. 3, 329. Relevant review on the different therapies in rheumatoid arthritis.

Chikanza, I.C., Kingsley, G., Panayi, G.S. 1995. Peripheral blood and synovial fluid monocyte expression of interleukin 1α and 1α during active rheumatoid arthritis. J. Rheumatol. 22, 600.

Choy, E.H., Panayi, G.S. 2001. Cytokine pathways and joint inflammation in rheumatoid arthritis. N. Engl. J. Med. 344, 907.

Chu, P., Connolly, M.K., LeBoit, P.E. 1994. The histopathologic spectrum of palisaded neutrophilic granulomatous dermatitis in patients with collagen vascular disease. Arch. Dermatol. 130, 1278.

Cimmino, M.A., Salvarani, C., Macchioni, P., et al. 2000. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. Rheumatol. Int. 19, 213.
Relevant study on epidemiological and clinical features of largest rheumatoid arthritis Italian cohort.

Cohen, I.R., Mihn, M.C., van Eden, W., et al. 1985. T lymphocyte clones illuminate pathogenesis and affect therapy of experimental arthritis. Arthritis Rheum. 28, 841.

Combe, B. 2004. Should patients with recent-onset polyarthritis receive aggressive treatment?. Joint Bone Spine 71, 475.

Coremans, I.E., Hagen, E.C., Daha, M.R., et al. 1992. Anti-lactoferrin antibodies in patients with rheumatoid arthritis associated with vasculitis. Arthritis Rheum. 35, 1466.

Creemers, M.C.W., van de Putte, L.B.A. 2004. Rheumatoid arthritis-the clinical picture. In: D.A. Isenberg, P.J. Maddison, P. Woo, F.C. Breedveld (Eds.), Oxford Textbook of Rheumatology. Oxford University Press, New York, p. 697.

Crowson, A.N., Mihm, M.C., Jr., Magro, C.M. 2003. Cutaneous vasculitis: a review. J. Cutan. Pathol. 30, 161.
Excellent review on the different aspects of cutaneous vasculitis.

Cutolo, M., Capellino, S., Montagna, P., et al. 2003. New roles for estrogens in rheumatoid arthritis. Clin. Exp. Rheumatol. 21, 687.

Daniel, C.R., Sams, W.M., Jr., Scher, R.K. 1985. Nails in systemic disease. Dermatol. Clin. 3, 465.

Dawes, P.T., Fowler, P.D., Clarke, S., et al. 1986. Rheumatoid arthritis: treatment which controls the C-reactive protein and erythrocyte sedimentation rate reduces radiological progression. Br. J. Rheumatol. 25, 44.

Defaria, D., Kroumpouzos, G. 2004. Rheumatoid neutrophilic dermatitis as presenting sign of seronegative arthritis. Acta Derm. Venereol. 84, 236.

Del Pozo, J., Martinez, W., Garcia-Silva, J., et al. 2001. Cutaneous ulceration as a sign of methotrexate toxicity. Eur. J. Dermatol. 11, 450.

Devos, S.A., Van Den Bossche, N., De Vos, M., et al. 2003. Adverse skin reactions to anti-TNF-alpha monoclonal antibody therapy. Dermatology 206, 388.

Dieppe, P.A., Bacon, P.A., Bamji, A.N., et al. 1984. Slide atlas of rheumatology. Gower Medical, London.

Dowsett, C. 2005. Assessment and management of patients with leg ulcers. Nurs. Stand. 19, 65.

Duong, T.N., Blume-Peytavi, U., Krengel, S., et al. 1999. Rheumatoid nodules developing under methotrexate treatment for rheumatoid arthritis. Acta Derm. Venereol. 79, 397.

Ejbjerg, B.J., Vastergaard, A., Jacobsen, S., et al. 2005. The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the Sharp/van der Heijde radiographic score. Arthritis Rheum. 52, 2300.

El-Gabalawy, H. 1999. The challenge of early synovitis: multiple pathways to a common clinical syndrome. Arthritis Res. 1, 31.

Elliott, M.J., Maini, R.N., Feldmann, M. 1994. Randomized double-blind comparison of chimeric monoclonal antibody tumor necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 344, 1105.

Felson, D.T., Anderson, J.J., Boers, M., et al. 1995. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 38, 727.

Fisher, T.W., Bauer, H.I., Graefe, T., Barta, U., Elsner, P. 2003. Erythema multiforme-like drug eruption with oral involvement after intake of leflunomide. Dermatology 207, 386.

Flendrie, M., Vissers, H.P.M., Creemers, M., de Jong, E., van de Kerkhof, P., van Riel, P. 2005. Dermatological conditions during TNF-α-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res. Ther. 7, 666.

Forslind, K., Ahlmén, M., Eberhardt, K., et al. 2004. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann. Rheum. Dis. 63, 1090.

Fries, J.F., Spitz, P., Kraines, R.G., Holman, H.R. 1980. Measurement of patient outcome in arthritis. Arthritis Rheum. 23, 137.

Furst, D.E. 2004. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin. Ther. 26, 1960.

Furst, D.E., Schiff, E., Fleischman, R., et al. 2002. Safety and efficacy of adalimumab, a fully human anti-TNF-monoclonal antibody, given in combination with stardard antirheumatic therapy: safety trial of adalimumab in rheumatoid arthritis (STAR). Arthritis Rheum. 46, S572.

Genant, H.K. 1983. Methods of assessing radiographic change in rheumatoid arthritis. Am. J. Med. 30, 35.

Genovese, M.C., Bathon, J.M., Martin, R.W., et al. 2002. Etanercept vs methotrexate in patients with early rheumatoid arthritis: two-year radiography and clinical outcomes. Arthritis Rheum. 46, 1443.

Goldberg, J., Pinals, R.S. 1980. Felty's syndrome. Semin. Arthritis Rheum. 10, 52.

Gouliaris, A., Papadakis, P., Kranias, D. 2003. Sweet's syndrome with arthritis and vasculitis. Clin. Rheumatol. 22, 244.

Gran, J.T., Myklebust, G. 1993. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. Scand. J. Rheumatol. 22, 229.

Grassi, W., De Angelis, R., Lamanna, G., et al. 1998. The clinical features of rheumatoid arthritis. Eur. J. Radiol. 27, S18.

Gregersen, P.K., Silver, J., Winchester, R.J. 1987. The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 30, 1205.

Groves, R. 2004. Polyderma gangrenosum. J. Dermatolog. Treat. 15, 135.

Harati, A., Brockmeyer, N.H., Altmeyer, P., et al. 2005. Skin disorders in association with monoclonal gammopathies. Eur. J. Med. Res. 10, 93.

Harris, E.D., Jr. 1994. Rheumatoid arthritis. Curr. Opin. Rheumatol. 6, 287.

Hayashida, K., Nanki, T., Girschick, H., et al. 2001. Synovial stromal cells from rheumatoid arthritis patients attract monocytes by producing MCP and IL8. Arthritis Res. 3, 118.

Hellmich, B., Schnabel, A., Gross, W.L. 1999. Treatment of severe neutropenia due to Felty's syndrome or systemic lupus erythematosus with granulocyte colony-stimulating factor. Semin. Arthritis Rheum. 29, 82.

Heurkens, A.H., Westedt, M.L., Breedveld, F.C. 1991. Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. Arch. Intern. Med. 151, 2249.

Hofmann, C., Burg, G., Jung, C. 1986. Cutaneous side effects of gold therapy. Clinical and histologic results. Z. Rheumatol. 45, 100.

Holme, S.A., Holmes, S.C. 1999. Hydroxychloroquine-induced pruritus. Acta Derm. Venereol. 79, 333.

Jarrett, S.J., Cunnane, G., Conaghan, P.G., et al. 2003. Anti-tumor necrosis factor-alpha therapy induced vasculitis: case series. J. Rheumatol. 30, 2287.

Joe, E.K. 2003. Sweet syndrome. Dermatol. Online J. 9, 28.

Jorizzo, J.L., Daniels, J.D. 1983. Dermatological conditions reported in patients with rheumatoid arthritis. J. Am. Acad. Dermatol. 8, 439.
Excellent review and good description of dermatological lesions in rheumatoid arthritis patients.

Jorizzo, J.L., Gonzales, E.B., Daniels, J.C., et al. 1983. Red lunulae in a patient with rheumatoid arthritis. J. Am. Acad. Dermatol. 8, 711.

Jorizzo, J.L., Solomon, A.R., Zanolli, M.D., et al. 1988. Neutrophilic vascular reactions. J. Am. Acad. Dermatol. 19, 983.

Keystone, E., Haraqui, B. 2004. Adalimumab therapy in rheumatoid arthritis. Rheum. Dis. Clin. North. Am. 30, 349.

Kietz, D.A., Pepmueller, P.H., Moore, T.L. 2001. Clinical response to etanercept in polyarticular course juvenil arthritis. J. Rheumatol. 28, 360.

Kimby, E. 2005. Tolerability and safety of rituximab (MabThera(R)). Cancer Treat. Rev. 3, 456.

Kitamura, A., Matsuno, T., Narita, M., et al. 2004. Rheumatoid arthritis with diffuse pulmonary rheumatoid nodules. Pathol. Int. 54, 798.

Kutz, D.C., Bridges, A.J. 1995. Bullous rash and brown urine in a systemic lupus erythematosus patient treated with hydroxychloroquine. Arthritis Rheum. 38, 440.

Larsen, A. 1995. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J. Rheumatol. 22, 1974.

Larsen, A., Dale, K., Eek, M. 1977. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol. Diagn. (Stockh) 18, 481.

Lawrence, J.S. 1970. Heberden Oration, 1969. Rheumatoid arthritis—nature or nurture? Ann. Rheum. Dis. 29, 357.

Lebsack, M.E., Paul, C.C., Bloedow, D.C., et al. 1991. Subcutaneous IL-1 receptor antagonist in patients with rheumatoid arthritis. Arthritis Rheum. 34 (Suppl. 9), S45.

Lee, D.M., Weinblatt, M.E. 2001. Rheumatoid arthritis—Review. Lancet 358, 903.

Lipsky, P.E. 2000. Rheumatoid arthritis. In: E. Braunwald, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J.L. Jameson (Eds.), Harrison's Principles of Internal Medicine, 15th ed., McGraw-Hill, New York, p. 1928.

Livermore, P.A., Murray, K.J. 2002. Anti-tumour necrosis factor therapy associated with cutaneous vasculitis. Rheumatology (Oxford) 41, 1450.
First description of anti-TNF therapy and cutaneous vasculitis.

Magro, C.M., Crowson, A.N. 2003. The spectrum of cutaneous lesions in rheumatoid arthritis: a clinical and pathological study of 43 patients. J. Cutan. Pathol. 30, 1.
Important study on clinical and pathological alterations demonstrating a new simplified classification of cutaneous manifestations.

Makinen, H., Kautiainen, H., Hannonen, P., et al. 2005. Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. A 5-year followup study. J. Rheumatol. 32, 796.

Mani, V. 2002. Pyoderma gangrenosum. Int. J. Low Extrem. Wounds 1, 43.

Margolis, D.J., Knauss, J., Bilker, W. 2004. Medical conditions associated with venous leg ulcers. Br. J. Dermatol. 150, 267.

McCain, M.E., Quinet, R.J., Davis, W.E. 2002. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology 41, 116.

Mease, P.J., Ease, P.J., Goffe, B.S., et al. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 356, 385.

Meenan, R.F., Gertman, P.M., Mason, J.H. 1980. Measuring health status in arthritis. The arthritis impact measurement scales. Arthritis Rheum. 23, 146.

Michel C., CribierB., Sibilia, J., et al. 1997. Nail abnormalities in rheumatoid arthritis. Br. J. Dermatol. 137, 958.

Mohan, N., Edwards, E.T., Cupps, T.R., et al. 2004. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. J. Rheumatol. 31, 1955.

Moore, T.L. 2000. Parvovirus-associated arthritis. Curr. Opin. Rheumatol. 12, 289.

Moreland, L.W., Margolies, G., Heck, L.W., et al. 1996. Recombinant soluble tumor necrosis factor receptor (p80) fusion protein: toxicity and dose finding trial in refractory rheumatoid arthritis. J. Rheumatol. 23, 1849.

Nanki, T., Lipsky, P.E. 2000. Cytokine, activation marker, and chemokine receptor expression by individual CD4+ memory T cells in rheumatoid arthritis synovium. Arthritis Res. 2, 415.

Nepom, G.T., Byers, P., Sevfried, C., et al. 1989. HLA genes associated with rheumatoid arthritis. Identification of susceptibility alleles using specific oligonucleotide probes. Arthritis Rheum. 32, 15.

Nielen, M.M.J., van der Horst, A.R., van Schaardenburg, D., et al. 2005. Antibodies to citrullinated human fibrinogen (ACF) have diagnostic and prognostic value in early arthritis. Ann. Rheum. Dis. 64, 1199.

Oien, R.F., Hakansson, A., Hansen, B.U. 2000. Leg ulcers in patients with rheumatoid arthritis—a prospective study of aetiology, wound healing and pain reduction after pinch grafting. Rheumatology 40, 816.

Ollier, W.E., Harrison, B., Symmons, D. 2001. What is the natural history of rheumatoid arthritis?. Best Pract. Res. Clin. Rheumatol. 15, 27.

Palmer, D.G., Hogg, N., Higton, J., et al. 1987. Macrophage migration and maturation within rheumatoid nodules. Arthritis Rheum. 30, 729.

Paulus, H.E. 2004. Defining remission in rheumatoid arthritis: what is it? Does it matter?. J. Rheumatol. 31, 1.

Pham, K., Hirschberg, R. 2005. Global safety of coxibs and NSAIDs. Curr. Top. Med. Chem. 5, 465.

Present, D.H., Rutgeerts, P., Targan, S., et al. 1999. Infliximab for the treatment of fistulas in patients with Crohn's disease. N. Engl. J. Med. 340, 1398.

Prevoo, M.L., van't Hof, M.A., Kuper, H.H., et al. 1995. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 38, 44.

Prodawich, S., Ma, F., Taylor, J.R., et al. 2005. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J. Am. Acad. Dermatol. 52, 262.

Pullar, T., Hunter, J.A., Capell, H.A. 1987. Effect of sulphasalazine on the radiological progression of rheumatoid arthritis. Ann. Rheum. Dis. 46, 398.

Punzi, L., Calo, L., Plebani, M. 2002. Clinical significance of cytokine determination in synovial fluid. Crit. Rev. Clin. Lab. Sci. 39, 63.

Quinn, M.A., Conaghan, P.G., O'Connor, P.J., et al. 2005. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 52, 27.

Quismorio, F.P., Beardmore, T., Kaufman, R.L., et al. 1983. IgG rheumatoid factors and anti-nuclear antibodies in rheumatoid vasculitis. Clin. Exp. Immunol. 53, 333.

Ransford, R.A., Langman, M.J. 2002. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the committee on safety of Medicines. Gut. 51, 536.

Rashba, E.J., Rowe, J.M., Packman, C.H. 1996. Treatment of the neutropenia of Felty syndrome. Blood 10, 177.

Renaudineau, Y., Jamin, C., Saraux, A., et al. 2005. Rheumatoid factor on a daily basis. Autoimmunity 38, 1.

Rethy, L.A., Balo-Banga, J.M. 2004. The allergic and other side effects of non-steroid antiinflammatory drugs and gold salts. Orv. Hetil. 145, 1943.

Riente, L. 2004. The safety of interleukin-1 receptor antagonist (anakinra) in the treatment of rheumatoid arthritis. Reumatismo 56 (Suppl. 1), 74.

Roux, C.H., Brocq, O., Albert, C., et al. 2004. Cutaneous vasculitis and glomerulonephritis in a patient taking the anti-TNF alpha agent etanercept for rheumatoid arthritis. Joint Bone Spine 71, 444.

Salido, M., Joven, B., D'Cruz, D.P., et al. 2002. Increased cutaneous reactions to hydroxychloroquine (Plaquenil) possibly associated with formulation change: comment on the letter by Alarcon. Arthritis Rheum. 46, 3392.

Sarzi-Puttini, P., Ardizzone, S., Manzionna, G., et al. 2003. Infliximab-induced lupus in Crohn's disease: a case report. Dig. Liver Dis. 35, 814.

Sarzi-Puttini, P., Atzeni, F., Schoenfeld, Y., et al. 2005a. TNF-alpha, rheumatoid arthritis, and heart failure: a rheumatological dilemma. Autoimmun. Rev. 4, 153.

Sarzi-Puttini, P., D'Ingianna, D., Fumagalli, M., et al. 2005b. An open, randomized comparison study of cyclosporine A, cyclosporine A + methotrexate and cyclosporine A + hydroxychloroquine in the treatment of early severe rheumatoid arthritis. Rheumatol. Int. 25, 15.

Sarzi-Puttini, P., Fiorini, T., Panni, B., et al. 2002. Correlation of the score for subjective pain with physical disability, clinical and radiographic scores in recent onset rheumatoid arthritis. BMC Musculoskelet Disord. 3, 18.

Saxne, T., Palladino, M.A., Jr., Heinegard, D., et al. 1988. Detection of tumor necrosis factor α but not tumor necrosis factor α in rheumatoid arthritis synovial fluid and serum. Arthritis Rheum. 31, 1041.

Sayah, A., English, J.C. 2005. Rheumatoid arthritis: a review of the cutaneous manifestations. J. Am. Acad. Dermatol. 53, 191.

Scheel, A.K., Hermann, K.G., Khaler, E., et al. 2005. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis Rheum. 52, 733.

Scheinfeld, N. 2005. Adalimumab: a review of side effects. Expert Opin. Drug Saf. 4, 637.

Schroeter, A.L., Harris, R.B. 1984. The vasculitis of atrophie blanche (livedoid vasculitis) and abdominal aortic pathology. Cutis 34, 298.

Scott, D.G.I., Bacon, P.A., Tribe, C.R. 1981. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. Medicine (Baltimore) 60, 288.

Sharp, J.T., Lidsky, M.D., Collins, L.C., et al. 1971. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum. 14, 706.

Shingu, M., Nagai, Y., Isayama, T., et al. 1993. The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. Clin. Exp. Immunol. 94, 145.

Smith, R.W., Leppard, B., Barnett, N.L., et al. 1995. Chrysiasis revisited: a clinical and pathological study. Br. J. Dermatol. 133, 671.
Important study on the gold's adverse events.

Smolen, J.S., Breedveld, F.C., Schiff, M.H., et al. 2003. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 42, 244.

Smolen, J.S., Kalden, J.R., Scott, D.L., et al. 1999. Efficacy and safely of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double blind, randomised, multi-centre trial. Lancet 353, 259.

Spies, T., Sorrentino, R., Boss, J.M., et al. 1985. Structural organization of the DR subregion of the human major histocompatibility complex. Proc. Natl. Acad. Sci. USA. 82, 5165.

Sternlieb, I., Fisher, M., Scheinberg, I.C.H. 1981. Penicillamine-induced skin lesions. J. Rheumatol. Suppl. 7, 149.

Strand, V., Scott, D.L., Emery, P., et al. 2005. Leflunomide rheumatoid artrhitis investigators group, physical function and health related quality of life: analysis of 2-year data from randomized, controlled studies of leflunomide, sulfasalazine, or methotrexate in patients with active rheumatoid arthritis. J. Rheumatol. 32, 590.

Subramanian, S., Handa, R. 2004. Biological agents in rheumatoid arthritis. J. Postgrad. Med. 50, 293.

Tavarela Veloso, F. 2004. Review article: skin complications associated with inflammatory bowel disease Aliment. Pharmacol. Ther. 20, 50.
Excellent review on skin complications in patients with inflammatory bowel disease.

Theng, T.S., Chan, Y.C., Leow, Y.H., et al. 2003. Sweet's syndrome associated with Mycobacterium chelonae and herpes simplex virus infections: a case report. Ann. Acad. Med. Singapore 32, 411.

Tugwell, P. 1992. Cyclosporine in rheumatoid arthritis: documented efficacy and safety. Semin. Arthritis Rheum. 21, 30.

Turesson, C., O'Fallon, W.M., Crowson, C.S. 2003. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann. Rheum. Dis. 62, 722.

Tutor-Ureta, P., Yebra-Bango, M. 2005. Antimalarials in systemic diseases. Rev. Clin. Esp. 205, 230.

van der Heijde, D.M., van Riel, P.L., Nuver-Zwart, I.H., et al. 1989. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1, 1036.

van der Heijde, D.M., van't Hof, M.A., van Riel, P.L., et al. 1990. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann. Rheum. Dis. 49, 916.

van der Heijde, D.M., van Leeween, M.A., van Riel, P.L., et al. 1992. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 35, 26.

Van Gestel, A.M., Prevoo, M.L., van't Hof, M.A., et al. 1996. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 39, 34.

Van Leeuwen, M.A., van der Heijde, D.M., van Rijswijk, M.H., et al. 1994. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J. Rheumatol. 21, 425.

Van Venrooij, W.J., Vossenaar, E.R., Zendman, A.J. 2004. Anti-CCP antibodies: the new rheumatoid factor in the serology of rheumatoid arthritis. Autoimmun. Rev. 3 (Suppl. 1), S17.

Venables, P.J., Roffe, L.M., Erhardt, C.C., et al. 1981. Titers of antibodies to RANA in rheumatoid arthritis and normal sera. Relationship to Epstein–Barr virus infection. Arthritis Rheum. 4, 1459.

Vila, A.T., Puig, L., Fernandez-Figueras, M.T., et al. 2005. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. Br. J. Dermatol. 153, 417.

Vine, J.E., Hymes, S.R., Warner, N.B., et al. 1996. Pustular psoriasis induced by hydroxychloroquine: a case report and review of the literature. J. Dermatol. 23, 357.

Visser, H., le Cassie, S., Vos, K., et al. 2002. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum. 46, 357.

Voskuyl, A.E., Zwinderman, A.H., Westedt, M.L., et al. 1996a. The mortality of rheumatoid vasculitis compared to rheumatoid arthritis. Arthritis Rheum. 39, 266.

Voskuyl, A.E., Zwinderman, A.H., Westedt, M.L., et al. 1996b. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. Ann. Rheum. Dis. 55, 190.

Wallach, D. 2005. Neutrophilic dermatoses. Rev. Med. Interne. 26, 41.
Important review on the main neutrophilic dermatoses and point on their multisystemic dimension.

Walsh, N.C., Gravellese, E.M. 2004. Bone loss in inflammatory arthritis: mechanisms and treatment strategies. Curr. Opin. Rheumatol. 16, 419.

Ware, J.E., Sherbourne, C.D. 1992. The MOS 36-item short form health survey (SF-36): conceptual framework and item selection. Med. Care 30, 473.

Wassenberg, S., Herborn, G., Rau, R. 1998. Methotrexate treatment in Felty's syndrome. Br. J. Rheumatol. 37, 908.

Waugh, J., Perry, C.M. 2005. Anakinra: a review of its use in the management of rheumatoid arthritis. Biodrugs 19, 189.

Weyand, C.M., Hicok, K.C., Conn, D.L., et al. 1992. The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. Ann. Intern. Med. 117, 801.

Williams, F.M., Cohen, P.R., Arnett, F.C. 1998. Accelerated cutaneous nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. J. Am. Acad. Dermatol. 39, 359.

Wolfe, F., Michaud, K., Pincus, T. 2004. Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. Arthritis Rheum. 50, 3296.

Ziff, M. 1990. The rheumatoid nodule. Arthritis Rheum 33, 761.
Excellent review of rheumatoid nodule and clinical aspects.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 14

Behçet's Syndrome

M. Cem Mat[a], Cuyan Demirkesen[b], Melike Melikoğlu[c], Hasan Yazıcı[c,*]

[a]*Department of Dermatology, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey*
[b]*Department of Pathology, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey*
[c]*Division of Rheumatology, Department of Medicine, Cerrahpaşa School of Medicine, University of Istanbul, Istanbul, Turkey*

1. Introduction

As one of us (HY) had already pointed out in the introduction to the Behçet's syndrome chapter in a similar volume of this series, that time on its neurological manifestations (Siva and Yazici, 2004), "the skeptic would challenge the inclusion of Behcet's syndrome (BS) in a textbook of systemic autoimmune disease". In BS not only the phenotype is clearly different, many of the telltale features of autoimmune diseases like serosal disease, Raynaud's phenomenon are absent and there is the singular absence of association with Sjögren's syndrome (Yazici, 1997). There are usually no antibodies, and no immune specificity has been demonstrated in any of the many immunological aberrations thus far reported. On the other hand, some of the clinical manifestations, especially features like genital ulceration, the pathergy phenomenon, the nature of the central nervous system (CNS) and pulmonary disease are not in the spectrum of classical autoimmune diseases. More recently there has been a recent interest calling BS an autoinflammatory condition (Gul, 2005), perhaps acknowledging that it does not easily fit into the autoimmune model.

Assuming a need for a generalization and an umbrella for classification, one can perhaps say that BS is a complex disease with a genetic component. There is a propensity for inflammation in many organs, which goes in parallel, or is part of a systemic vasculitis which manifests itself more on the venous side. The most common phenotypic manifestations are in the dermatological realm—the oral and genital ulceration—and it is thus no surprise that it has initially been described by a dermatologist (Behçet, 1937). Uveitis threatening vision is BS' most serious morbidity while pulmonary artery aneurysms are the most common reason of mortality.

The diagnosis is clinical. The course is one of exacerbations and remissions and majority of the patients eventually go into a remission (Kural-Seyahi et al., 2003).

2. Prevalence

The only true population studies have been conducted in Turkey. In a survey in the Northwestern Turkey, prevalence was $38/10^4$ among people aged 10 or over (Yurdakul et al., 1988). In another survey involving 24,000 individuals in Istanbul a similar prevalence was found ($42/10^4$) (Azizlerli et al., 2003). Case registries show frequencies of 1/10,000 in Japan (Shimizu et al., 1979). The prevalence is

*Corresponding author.
Division of Rheumatology, Department of Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Aksaray, Istanbul 34303, Turkey

DOI: 10.1016/S1571-5078(05)05014-2

definitely lower in the West (Gonzalez-Gay et al., 2000).

In one survey searching for rheumatological diseases no cases were identified among 450,000 children (Ozen et al., 1998). This study provided formal proof that BS is indeed rare among children. No observations among 45,000 surveyed puts the 95% the upper limits of the estimated frequency to 1/15,000 (Rumke, 1975; Yazici et al., 2001). There is however, an increased awareness of the pediatric cases (Kone Paut et al., 1998).

3. Epidemiology

BS shows a distinct distribution around the globe. The frequency of disease is high in the Mediterranean (Turkey, Israel, Tunisia, Morocco, Egypt, Greece) and Middle-Eastern countries (Iraq, Iran, Jordan) and Japan, Korea, China. It is rare in Northern Europe (Chamberlain, 1977), North Asia, Africa, Australia and the Americas. This distribution seems to follow the ancient Silk Road. A parallel variation in the frequency of human leukocyte antigen HLA B51, strongly associated with the condition, in the general population supports this concept (Ohno et al., 1982; Verity et al., 1999).

BS affects all age groups. Formal studies are lacking but there is the general impression that it is rare in African Blacks.

It is rare before puberty and after the sixth decade. BS equally affects both genders however male patients have more severe disease, with mortality being significantly increased only among the males (Kural-Seyahi et al., 2003).

4. Etiology/Pathogenesis

BS appears to be a disorder of complex etiology in which the interaction of unknown environmental triggers and genetic susceptibility jointly influences the course and clinical expression of disease (Sakane et al., 1999). The unifying feature of the inflammation observed in BS is a nonspecific inflammatory hyperreactivity with vasculitis as its main clinical consequence (Gul, 2001a). Conceptually, BS may result from an inappropriate and exaggerated inflammatory response to an unknown antigen that is, in part, genetically determined.

The family studies have provided evidence of a genetic predisposition to BS. The sibling recurrence risk ratio (λs) in Turkey has been estimated to be between 11 and 53, implying a strong genetic influence on disease expression (Gul et al., 2000). Although multicase familial studies have suggested a multifactorial mode of inheritance, an autosomal recessive pattern of inheritance has been implicated in childhood BS (Molinari et al., 2003).

HLA B51 has been the most consistently reported HLA-association in BS (Ohno et al., 1982), however, the mechanism whereby HLA B51 confers susceptibility to BS is not known. A HLA B51-related peptide might function as a cross-reactive antigen, such as in the proposed role played by the retinal S antigen and HLA B27 in the pathogenesis of ankylosing spondylitis (Kurhan-Yavuz et al., 2000). A neutrophil hyperreactivity reported in BS has been tied up with HLA B51 as determined by the detection of excessive neutrophil responses to f-Met-Leu-Phe (fMLP) stimulation in HLA B51 transgenic mice as well as in HLA B51-positive healthy individuals (Takeno et al., 1995). The specificity of the neutrophil hyperreactivity, however has been challenged (Tuzun et al., 1999).

HLA B51 may account for no more than 20% of the sibling relative risk (Gul et al., 2001b), which supports the view that, in addition to potential environmental triggers for disease onset, susceptibility is dependent on other genetic loci. Among these, suggestive evidence of linkage was detected on chromosomes 6p22-23 (Gul et al., 2001c). A preliminary whole-genome screening also provided evidence of non-major histocompatibility complex (MHC) genetic-susceptibility loci in BS (Karasneh et al., 2005).

Histologically, (CD4+) T lymphocytes seem to be major cell-type in inflammatory infiltrates (Lakhanpal et al., 1985; Ben Ahmed et al., 2004) and peripheral T cells have a predominant Th1-type cytokine pattern (Frassanito et al., 1999). These suggest T-cell-mediated immune response in

pathogenesis. However, heterogenity is evident by different histologic. Features of various lesions, the presence of neutrophil-predominating inflammatory infiltrates which, are also capable of causing identically appearing skin lesions, suggest immune complex-dependent inflammation responsible for tissue damage (Mangelsdorf et al., 1996). It is not clear whether these reflect different pathophysiologic mechanisms operating in tissue damage of BS. The nature of infiltrate may obviously depend on the timing of the biopsy in relation to the age of the lesions.

A unifying feature of the inflammation observed in BS is the presence of pathergy phenomenon where traumatic insult or various types of inflammatory stimuli to the tissue is followed by an enhanced inflammatory response. In clinical practice, skin pathergy reaction (SPR), is induced by needle prick leading to the development of papule or pustule at 48 h. Pathogenetically, SPR shows features in common with T-cell-mediated immune response (Gul et al., 1995) and the results of recent, study suggested that injury to the skin of BS patients elicits a T helper 1 (T_H1)-cell response owing to interleukin (IL)-12-mediated production of interferon (IFN)-γ by CD4+ T cells (Melikoglu et al., 2002). It has been suggested that pathergy phenomenon might provide insights into the dysregulated immunity underlying other affected organ systems in BS. Not only nonspecific trauma may elicit an important disease but there is evidence at the cellular level as demonstrated by spontaneous or induced over-production of proinflammatory cytokines from T cells (Gul et al., 2001a), monocytes and neutrophils (Mege et al., 1993) which might prime the immune system for an enhanced T-cell response observed in BS.

Present evidence suggests that BS is an immunologically mediated disease, however, little is known about the cellular and molecular mechanisms responsible for tissue damage at related tissue sites. Increasing evidence led to the current view that Th1-type T cells are the main cell type responsible for tissue destruction; however, the possibility that it is caused by specific or nonspecific T-cell activation is still a matter of debate. The former possibility is indicated by the evidence for the presence of the increased susceptibility to infectious triggers (Kaneko et al., 2003), the upregulation of heat-shock protein (hsp60) expression in mucosal lesions of BS (Ergun et al., 2001), a strong oligoclonal T-cell response to human hsp60 or other antigens from different strains of streptoccocci or other microbial agents (Esin et al., 1997; Pervin et al., 1993) suggesting the participation of potential antigenic stimuli in disease process. In this context, one attractive hypothesis is the involvement of HSP in disease pathogenesis which can mediate Th1-type immune response without requiring specific TCR engagement, and therefore link the innate immune system to T-cell immunity (Direskeneli and Saruhan-Direskeneli, 2003). The other possibility that T cells expand in response to nonspecific mechanisms is exemplified by a model that essential proinflammatory cytokines are overproduced by innate immune cells of BS (Mege et al., 1993; Zierhut et al., 2003) that would, in turn, overstimulate mononuclear cells, thereby amplifying the inflammatory T-cell response in BS.

Another potential connection between the innate and adaptive immune system involves the interaction of MHC class I molecules with the killer-cell immunoglobulin-like receptors (KIRs), which are expressed by natural killer cells and T cells. A particular association between HLA B51 and KIR3DL1 or KIR3DS1 receptors on inflammatory cells has been reported in BS (Gul et al., 2002), however, the evidence for the significance of this interaction has been limited.

Increased B-cell reactivity a autoantibodies, is not part of BS. This is also true for ANCA (Tunc et al., 2001) and anticardiolipin antibodies (Tokay et al., 2001). However antibodies to Saccharomyces cerevisiae, usually seen in Crohn's disease have also been reported in BS (Krause et al., 2002; Fresko et al., in print). Antibodies to alpha-tropomysin with an animal model for uveitis has also been described (Mahesh et al., 2005). Finally, the target antigen for the endothelial antibodies found in some patients has been described as alpha-enolase (Lee et al., 2003).

The thrombophlebitis of deep veins is the most frequent manifestation of large vessel involvement in BS (Kural-Seyahi et al., 2003). Several studies have been reported on inherited and acquired

cause of thrombophilia that may contribute to the development of thrombosis complicating large vessel inflammation in BS. No single coagulation abnormality has been described apart from a decrease in fibrinolysis (Espinosa et al., 2002; Leiba et al., 2004). We have recently observed that a deficiency of tissue Plasminogen Activator (tPA) production in acute thrombosis of BS was associated with this decrease in fibriolysis (Yurdakul et al., in print). Coupled with the decreased nitric oxide (NO) production-related endothelial dysfunction (Chambers et al., 2001) these findings suggest that the primary pathology in thrombophilia of BS is in the vessel wall.

Premature atherosclerosis is part of many diseases that are associated with vasculitis. Our preliminary observations suggest that this probably is not the case for BS (Seyahi et al., 2004).

5. Clinical manifestations

Behçet's disease affects oral and genital integument, eye, joints, vascular and CNS.

5.1. Oral ulcers

The most frequent finding is the aphthous stomatitis which cannot be differentiated from idiopatic reccurrent aphthous stomatitis on clinical grounds. Some patients have oral ulcers for 6–8 years before other clinical findings appear (Gürler et al., 1997; Verpilleux et al., 1999; Bang et al., 1993). The ulcers are usually localized at the lips, buccal mucosa, gums, tongue, as well as the posterior parts of the mouth such as uvula and pharynx. The presence of posteriorly located oral ulcers occurring in crops of 5 or less, with a healing time of more than a week appear to be associated with BS (Ifeacho et al., 2004).

Oral ulceration of BS can be minor, major or herpetiform. Ulcers in minor form are round or oval, rather shallow and, less than 10 mm in diameter, with yellow-tan pseudomembrane which is surrounded by an erythematous halo (Fig. 1). They usually heal within 7–10 days without scarring.

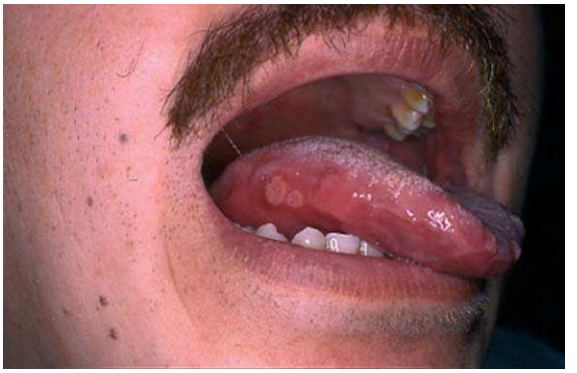


Figure 1. Minor aphtous ulcers.

Major aphthous ulcers are seen less often. These ulcers are painful, larger (range from 1 to 3 cm in diameter), deeper and heal more slowly (15–30 days) and often with scarring. They can be localized in any part of the mouth and may cause pharyngeal stenosis, resulting in malnutrition. The herpetiform ulcers are rather uncommon and these ulcers present as multiple clusters of small ulcers, 2–3 mm in diameter, distrubuted throughout the oral cavity. In a recent study the frequency of oral ulcer type was studied (Cosgun et al., 2004). Minor aphthous ulcers were the most common presentation of BS (85%). The frequency of major aphthae was found to be 14% and it was more frequent among the females. Major and minor aphthae were equally distrubuted among both genders in recurrent apthous stomatitis group. Herpetiform aphthae were not observed.

In histologic specimens the oral aphthae of BS, the squamous epithelium is replaced by a necrotic and fibrinopurulent exudate. Inflammatory cells and regenerative changes in keratinocytes can be detected in the epithelium adjacent to the ulcer. Underlying mucosa is heavily infiltrated with neutrophils, lymphocytes, histiocytes and plasma cells. There is a prominent vascular proliferation, together with endothelial swelling. Partial occlusion of the lumen (Nazzaro, 1966) and rarely leukocytoclastic vasculitis (Chun et al., 1990) have also been reported in the aphthous lesions of BS. These findings are similar to other aphthous lesions, seen in idiopathic recurrent aphthous stomatitis (RAS).

It is interesting to note that in both BS and RAS, activated gammadelta T cells are present in peripheral blood. In BS, they are capable of producing IFN-gamma and tumor necrosis factor (TNF)-alpha, while in RAS they produce IFN-gamma, but not TNF-alpha (Freysdottir et al., 1999).

5.2. Genital ulcerations

Genital ulcers are one of the cardinal signs of BS with a frequency of about 85%. They are oval or round with punched-out appearence. They usually begin as a papule, pustule or necrotic crust that ulcerate within a short period (Fig. 2). Genital ulcers of BS can be painful. Their borders are regular and oedematous and their base are covered with a yellow fibrin.

We have recently formally studied the fate of these genital ulcers in a sizeable group of patients (Mat et al., in print). If they are not secondarily infected they usually heal in 10–30 days. In males, genital ulcers occur mostly on scrotum (88.9%), penis, femoral and perianal regions. Large ulcers usually end up with scarring (89.4%). Scarring rate of small ulcers was 48.9%. In females, ulcers are commonly found on both major and minor labiae (Fig. 3). Vaginal and cervical lesions are less frequent. Similarly large ulcers heal with scar, while only 54% of small ulcers do so in females. The ulcers, located at the labia minor, do not result in scar while healing, rather similar to the situation in oral ulcers. It is also possible that mucosal scarring cannot be discerned by the naked eye.

The histopathology is similar to that seen in oral aphthous lesions. Neutrophil-predominating infiltrate is a feature of early lesions. In older lesions, the inflammatory cells are mostly lymphocytes, mixed with histiocytes and plasma cells. Presence of lymphocytic vasculitis has been reported in almost half of the cases, while leukocytoclastic vasculitis was rare (Chun et al., 1990). Other vascular changes such as thickening of the walls, endothelial swelling, tendency to obliteration have also been reported particularly in small arteries and capillaries (Nazzaro, 1966).

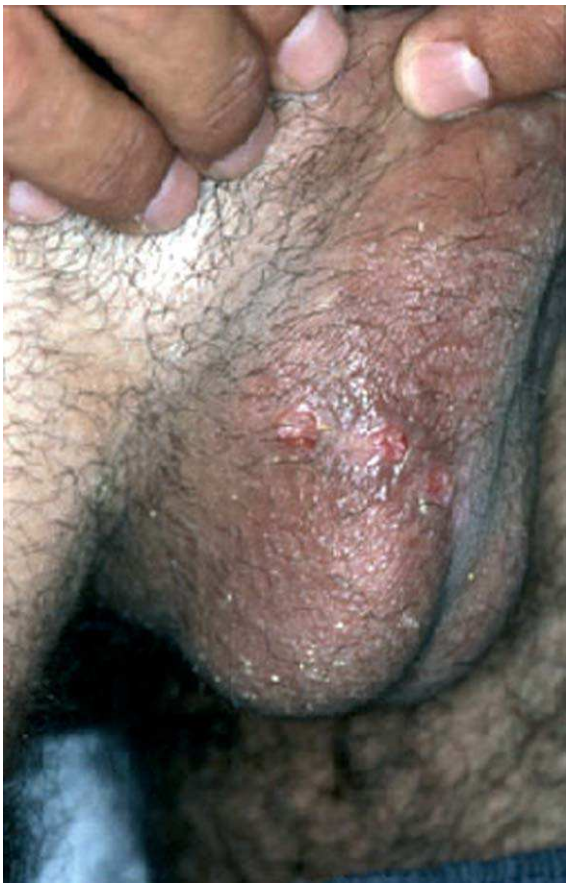


Figure 2. Scrotal ulcers.

Figure 3. Multiple genital ulcers.

5.3. Acneiform and papulopustular lesions

Pustular lesions may be found in various parts of the skin. Face, back, chest, shoulders, femoral regions, pubis and buttocks are the common sites. Acne and/or folliculitis (when the lesion is around a hair follicle). And acne-like lesions, located at the back, face or the upper torso—the common acne vulgaris sites—cannot be clinically differentiated from acne vulgaris even by experienced dermatologists. Sebum secretion in BS is as high as acne vulgaris (Yazici et al., 1987). Pustules, more commonly formed in the follicular lesions, are surrounded by an erythematous halo. They usually heal within 2–3 days. Contrary to the conventional wisdom these lesions are not sterile (Hatemi et al., 2004). Bacteriologic examination of the pustular lesions of BS showed that *Staphylococcus aureus* and *Provotella* spp. were significantly more common in pustules from BS, however coagulase-negative *S. aureus* was present in acne patients. The microbiology is somewhat different from acne vulgaris while it remains to be seen whether this infection is secondary or has a role in pathogenesis. It is also worth noting here that these lesions are more frequent in BS patients with arthritis suggesting a reactive form of arthritis in BS (Diri et al., 2001; Tunc et al., 2002).

The histopathology of papulopustular lesions are similar to those of deep supurative folliculitis or acne vulgaris (Fig. 4). There is a neutrophil-pre-dominating infiltrate around the hair follicle, with or without destruction of the follicular epithelium and sebaceous gland. There may be intrafollicular abscess formation. By the release of the follicular content, perifollicular abscess, localized cellulitis and foreign body granulomatous reaction can be seen. Some of these lesions contain dilation of the infundibular portion of the follicle, with a lumen containing a plug of keratin and sebaceous material. By the development of such comedones, they resemble acne vulgaris both clinically and histopathologically (Ergun et al., 1998a). The small vessels display some thickening, fibrin deposition in the vessel wall and within the lumen, at times. These vascular changes are more likely to be secondary to acute inflammation or less likely can be seen as a manifestation of neutrophilic vascular reaction in BS.

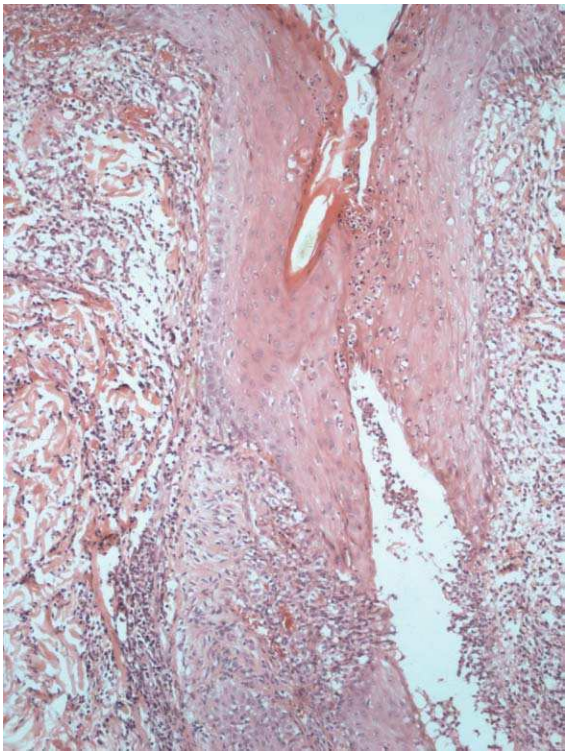


Figure 4. Supurative folliculitis in BS (HE ×40).

In brief it can be said that it is difficult to differentiate, both clinically and by histology, the acne-like lesions of BS from ordinary acne. Clinically, the most important differentiating feature is the presence, in BS, of these lesions at the arms and legs, unusual for ordinary acne.

5.4. Nodular lesions

Nodular lesions seen in BS may be due to panniculitis (erythema nodosum-like lesions) or superficial thrombophlebitis.

Erythema nodosum (EN)-like lesions are observed in 50% of the patients. They are most frequently detected in the shins, thighs and rarely in the upper extremities. They are characterized by painful erythematous-purple nodules (Fig. 5).

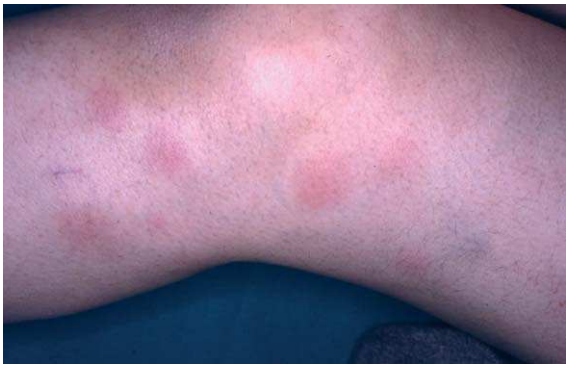


Figure 5. Erythema nodosum-like lesions.

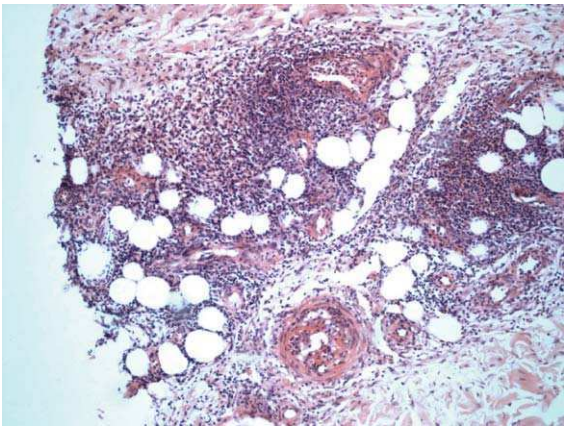


Figure 6. Neutrophil predominating infiltrate mainly in the lobules, together with vasculitis (HE ×40).

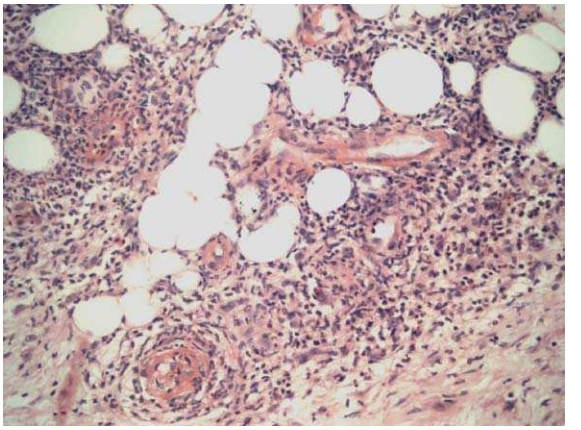


Figure 7. Neutrophil predominating infiltrate mainly in the lobules, together with vasculitis (HE ×40) and (HE ×100).

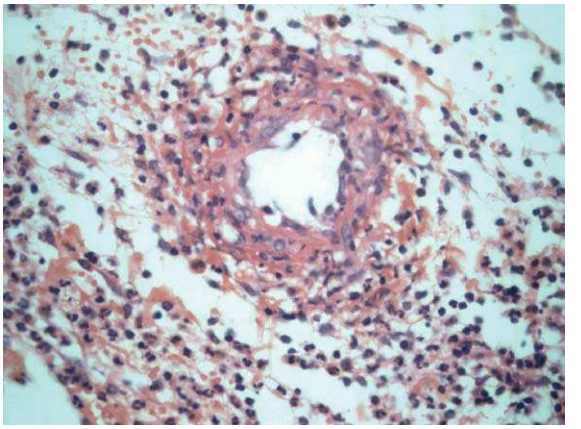


Figure 8. Neutrophilic vasculitis in a small vessel (HE ×200).

They can be few or many. Some may ulcerate. As they heal, hyperpigmentation is seen. They are more common in women (Tursen et al., 2003).

The histopathological features of nodular lesions of BS, are characterized by neutrophil-predominating infiltrate both in lobules and septum of the subcutis (Figs. 6 and 7). Rarely, the inflammatory cell infiltrate is dominated by lymphocytes. Neutrophilic vasculitis, involving mostly arterioles and venules, can be detected in almost half of the cases (Kim and Le Boit, 1998; Demirkesen et al., 2001) (Fig. 8). Involvement of veins and sometimes, even small arteries can be seen in a limited number of cases (Fig. 9). Chun et al. (1989) also reported the presence of lymphocytic vasculitis in 40% of their cases, however, they indicated that it may be a secondary phenomenon rather than a primary vasculitis. Necrobiosis and leukocytoklasia are other common features of nodular lesions of BS. Granuloma formation is less frequent. By these features, nodular lesions of BS can be distinguished from EN associated with other diseases—where as a rule vasculitis is not found—but resemble nodular vasculitis (NV), another common type of panniculitis.

Superficial thrombophlebitis affects large and small veins of the lower extremities and is more common among men. Nodules are usually seen as unilateral, painful nodules or sting-like lesions following the vein tracts (Fig. 10). Great saphenous vein is the most affected site. The presence of

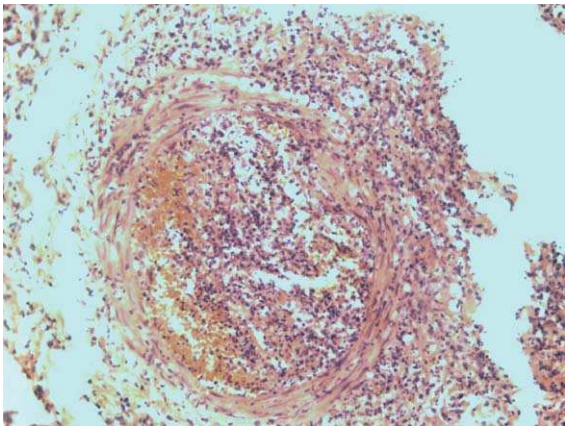


Figure 9. Neutrophilic vasculitis in a small- to medium-sized artery (HE ×100).

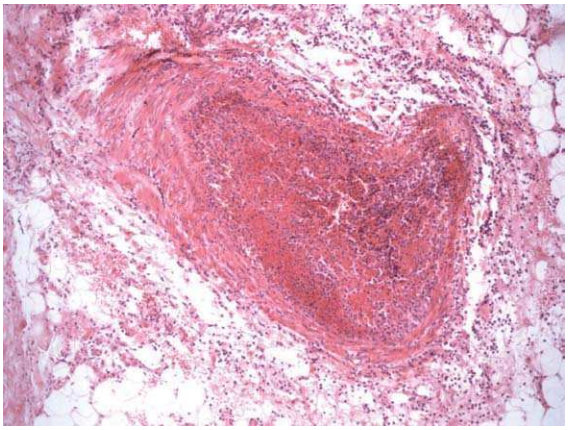


Figure 11. Superficial thrombophlebitis: Obliteration of the vein with partially organizing thrombus (HE ×40).

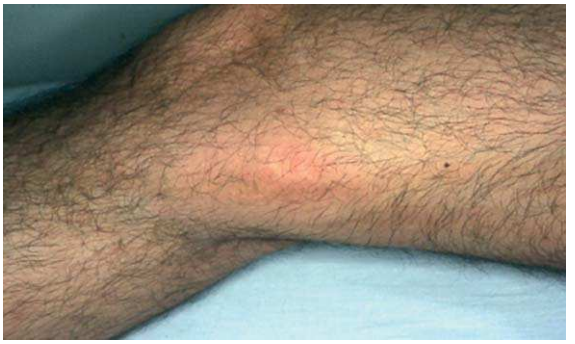


Figure 10. Superficial thrombophlebitis migrans at the medial aspect of leg.

superficial thrombophlebitis clusters thrombosis in the big veins (Tunc et al., 2002).

In histology the involved veins are obliterated by organizing thrombi (Fig. 11). The walls show fibrous thickening, sometimes accompanied by mononuclear cell infiltrate. In early lesions, neutrophils may be present at the vessel wall.

5.5. Sweet syndrome

The manifestations of Sweet syndrome are sometimes observed in BS. They are usually located on the face and extremities and consist of painful inflammatory nodules and plaques (Fig. 12) (Oguz

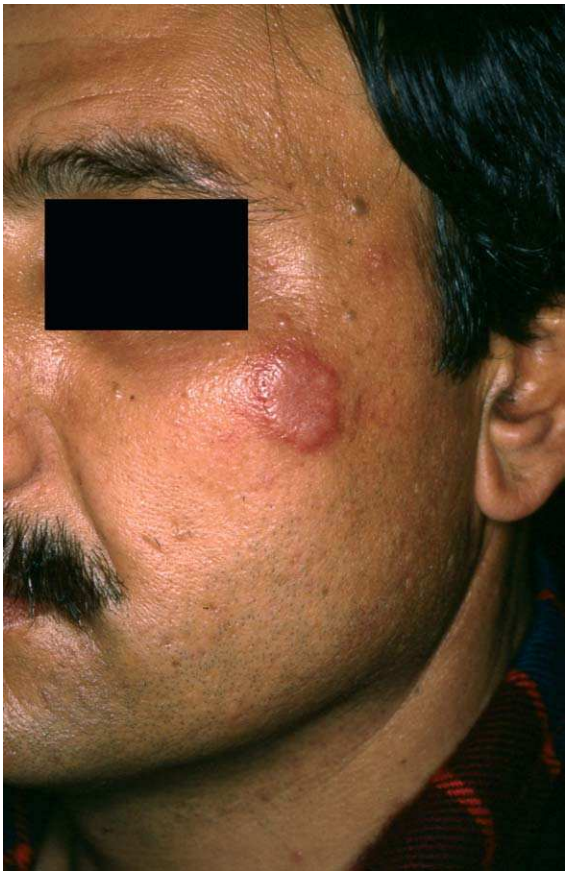


Figure 12. Sweet-like nodules on the face.

et al., 1992). Their frequency ranged from 2.1 to 4% in one series (Shi Hui-Li and Huang-Zheng-ji, 1993).

The histopathological examination reveals dense, diffuse or patchy neutrophilic infiltration within the dermis, sometimes extending to the subcutis. Leukocytoclasia and extravasated erytrocytes are frequent. Prominent edema in the upper dermis, which may result in blister formation, is commonly found. Within the dermal infiltrate, vascular proliferation and swelling of the endothelial cells are detected. There is no fibrin deposition. The epidermis may be slightly acanthotic or normal. In later stages, neutrophilic infiltration can be replaced by lymphohistiocytic infiltration.

Since some features of BS—like arthritis and oral ulcers—can also accompany the so-called idiopathic Sweet syndrome (Magro and Crowson, 1995), sometimes it becomes only an exercise in semantics whether a patient manifesting these lesions has primary or secondary Sweet's syndrome.

5.6. The pathergy reaction

Pathergy reaction, one of the characteristic features of BS, is diagnostically useful. A 20-gauge needle insertion in the flexural site of the forearm skin causes a nonspecific inflammatory reaction after 48 h. Presence of 1–2 mm papule or pustule usually surrounded by an erythematous halo is interpreted as a positive reaction (Fig. 13). Only erythema without induration is considered as negative. This reaction usually subsides in 4–5 days. Pathergy reaction is rarely observed in controls or in the other diseases (Tüzün et al., 1980). Pathergy test is usually positive at the active phase of disease and male patients have stronger pathergy reactions (Yazici et al., 1985).

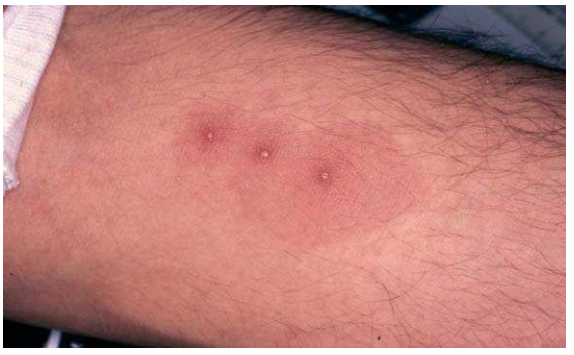


Figure 13. Pathergy reaction. Non-specific papule or pustule formation at the site of needle prick at the 48th hour.

A positive pathergy test is an important parameter in the diagnosis of BS in the Middle East and Mediterranean countries. The frequency of positive reaction is very low among the British (Yazici et al., 1984a) and the Korean patients (Bang et al., 2001). The specificity of the pathergy test is very high whereas the sensitivity of the reaction varies in different studies. The use of the disposable needles induces lesser amount of trauma and seems to account for the decrease (Ozarmagan et al., 1991). The application of the needles after blunting their surfaces and sterilization increase the rate of positivity (Dilsen et al., 1993). The surgical cleaning of the forearm of the patients with povidone iodine reduced the positivity rate of the reaction from 48 to 27% compared to cleaning the arm with alcohol alone. This showed that trauma alone was not sufficient to explain the phenomenon (Fresko et al., 1993).

It has been claimed that surgical procedures, similar to what is observed in pathergy, might also lead to nonspecific inflammatory reaction as in pathergy reaction. There is only anecdotal evidence that surgical intervention in BS patients causes a nonspecific, heightened inflammation as in pathergy reaction while in a formal study we demonstrated wound healing was normal (Mat et al., 1998).

The intensity of pathergy reaction is not the same in every case, besides, there is considerable intra and interobserver variation (Altaç et al., 1982).

In response to a needle-prick, a dermal inflammation composed of lymphocytes, neutrophils, eosinophils, mainly localized around the vessels are detected starting after 12 h, becoming denser at 24 h (Ergun et al., 1998b). Edema and leukocytoclasia are seen in most cases. Intraepidermal pustules develop, correlated with the clinical pathergy response. Epithelial necrosis can be observed in some cases (Nazarro, 1966). Vascular changes such as endothelial swelling, thickening and

homogenization of the wall of the small blood vessels, vascular obliteration, even leukocytoclastic vasculitis were reported by some authors (Nazzaro, 1966; Bang et al., 2001; Jorizzo et al., 1985). However, some authors maintain that the histopathology of pathergy lesions demonstrate mixed inflammatory infiltrate without vasculitis (Ergun et al., 1998b; Haim et al., 1976).

Haim et al. (1976) and Gilhar et al. (1989) reported an increase in the number of mast cells, however, this finding was not confirmed by the others (Ergun et al., 1998b).

Later at 48 h, mononuclear inflammatory cells predominate, mostly T lymphocytes (Gül et al., 1996). Small clusters of neutrophils and plasma cells may also be detected. The majority of the T cells express CD4. The endothelial cells express ICAM-1 strongly, and E-selectin moderately, while VCAM-1 is not expressed (Gül et al., 1995). According to the expression patterns of these adhesion molecules, Gül et al. (1995) suggested that the direct epidermal injury was the cause of cutaneous inflammation in pathergy in BS. We have recently suggested that injury to the skin of BS patients elicits a T helper 1 (T_H1)-cell response owing to IL-12-mediated production of IFN-γ by CD4+ T cells. Consistently, the concentrations of chemokines that are active on monocytes/macrophages and T_H1-cells, such as MCP-1 and IFN-γ-inducible chemokines, IP-10, Mig, and iTac, are increased during the pathergy reaction and the increases are correlated with the extent of mononuclear-cell infiltration at the site of inflammation (Melikoglu et al., 2002). An increased release of cyokines from the keratinocytes, such as IL-6 and IL-1β, as a result of skin injury and overproduction of various cytokines by T cells and monocytes have also been reported by others (Fujii et al., 1983; Hamzaoui et al., 1990; Sakane, 1991; Mege et al., 1993; Ben Ahmed et al., 2004). It seems that the initial reaction to needle-prick is nonspecific, but later on an increase in cytokine release may play the major role in pathergy.

The propensity to sustained inflammation in BS can be shown simply by the intradermal injection of monosodium urate (MSU) crystals. This causes an erythema and induration at the injection site in BS patients (Cakir et al., 1991) that does not go away at 48 h when compared to controls. It was interesting to note that this reaction could not be suppressed by etanercept (Melikoglu et al., 2005).

5.7. Other cutaneous manifestations

Rare cutaneous manifestations of BS include pyoderma gangrenosum-like lesions, erythema multiforme, pernio-like lesions, neutrophilic eccrine hidradenitis, bullous lesions due to necrotizing vasculitis, and Kaposi sarcoma (Lee et al., 1997; Cantini et al., 1998; Biliç and Mutasim, 2001; Nijsten et al., 2002; Mercader-Garcia et al., 2003; Lee et al., 1989; Louthrenoo et al., 2003; Kotter et al., 2001).

In histology the central areas of pyoderma gangrenosum display a necrotizing, neutrophil-rich infiltration usually with ulceration. In the adjacent areas, lymphocyte predominating infiltrate is detected mainly around and within the vessel walls. Luminal fibrin deposition, mural necrosis of the vessels or leukocytoclastic vasculitis are rare findings due to maximal tissue reaction, but do not reflect a primary vasculitis.

In a well-developed lesion of erythema multiforme, the most prominent feature is the hydropic degeneration of the basal keratinocytes in epidermis. Many apoptotic cells, called Civatte bodies are present, together with the lymphocytes at the dermoepidermal junction. Papillary dermis is usually edematous. Perivascular lymphohistiocytic infiltration is seen in the upper dermis. Rarely, eosinophils may also be present. In severe cases, epidermal necrosis may result in blister formation.

Cantini et al. (1998) described a BS patient with recurrent, multiple, papulonodular cutaneous lesions on the palm and fingers of both hands. The lesions were roundish, erythematous, painful, bluish-red nodules, 0.5–1 cm in diameter, with a ''pernio-like'' aspect. Histologic examination revealed a perivascular neutrophilic infiltrate.

Neutrophilic eccrine hidradenitis, another neutrophil-mediated disorder, has recently been reported in some BS patients (Biliç and Mutasim, 2001; Nijsten et al., 2002; Mercader-Garcia et al., 2003). Neutrophilic eccrine hidradenitis is a rare

entity that usually presents as asymptomatic erythematous papules that disappear spontaneously in 1–3 weeks. However, it may be polymorphic, pruritic, recurrent or even chronic. The histopathology of neutrophilic eccrine hidradenitis reveals a dense neutrophilic infiltration around and within the eccrine secretory coil, sometimes together with necrosis of the eccrine secretory gland epithelium. Degenerative changes may include the whole secretory epithelium or can be seen as individual cells with increased cytoplasmic eosinophilia. It typically occurs in patients receiving chemotherapeutic drugs for malignancies, but other associations have also been reported (Nijsten et al., 2002).

5.8. Extragenital ulcers

Recurrent aphthous lesions, located extragenitally, mostly in the intertriginous areas such as inframammary, axillary regions, interdigital areas of the foot, have also been reported in BS (Azizlerli et al., 1992).Their clinical appearance resemble those seen in genital areas and they heal with scar tissue formation. In the skin biopsies, vasculitis was reported as the most prominent feature (Azizlerli et al., 1992).

5.9. Dermographism and atopy

The prevalence of Th-2 cell-mediated diseases, such as atopy and atopic diseases, in Behcet's disease, a Th-1 cell-mediated disease, has been looked at by several authors. As expected in a Th-1 disease the prevalence of atopy and atopic diseases were significantly lower in BS patients than in controls (Chang et al., 2003). On the other hand, dermographism was found to be common (Dinç et al., 2000).

5.10. Eye involvement

Eye involvement is the most serious manifestation of BS. The overall frequency is about 50%, with a higher frequency in young males and a much lower frequency in older females. It runs a course of exacerbations and remissions, which may lead to blindness in some patients. Ocular involvement is usually bilateral but unilateral involvement may be seen. Panuveitis is the most common form of uveitis (Tugal-Tutkun et al., 2004; Kural-Seyahi et al., 2003). Late-onset eye disease has a better prognosis. Loss of useful vision mostly occurs in the first 7 years of the disease. It is quite rare for patients to develop eye disease after the initial 4–5 years of the disease course (Kural-Seyahi et al., 2003).

Patients usually complain of ocular pain, ocular discomfort and visual blurring. The primary lesion in eye involvement is retinal vasculitis, mainly involving the veins (Kim, 1997). Fundoscopic examination reveals choroidal and retinal exudates, hemorrhages, cytoid bodies or white patches, venous thrombosis, papilledema and macular disease. Hypopyon, a hallmark of BS, is seen much less commonly than retinal lesions. Retinal lesions, which are sight threatening, are distinctly more common among the male (Tugal-Tutkun et al., 2004). Hypopyon occurs in about 10% of the BS patients with eye involvement and always indicates accompanying severe retinal disease. Recurrent inflammatory activity may lead to anterior and posterior synechia, secondary glaucoma, optic atrophy and macular degeneration. Conjunctivitis and episcleritis are rare in BS. Conjunctival ulcerations revealed intraepithelial and perivascular infiltration with neutrophils and lymphocytes (Matsuo et al., 2002).

5.11. Musculoskeletal involvement

Arthritis and arthralgia are seen in about 50% of BS patients. Mono or oligoarticular involvement is common. The most frequently involved joints are knees, ankles, hands and elbow joints. Axial or hip involvement is rare (Yurdakul et al., 1983). An association of arthritis and acneiform lesions was noted (Diri et al., 2001; Tunç et al., 2002).

Local myositis is occasionally seen in BS, but serum levels of muscle enzyme are not increased (Arkin et al., 1980; Yazici et al., 1981). The prevalence of fibromyalgia in BS is around 10%,

mostly in female patients with mild-to-moderate activity (Yavuz et al., 1998).

5.12. Vascular involvement

BS is a systemic vasculitis, affecting both arteries and veins of any diameter (Lie, 1992; Koc et al., 1992). Venous involvement is more frequent and may result in superficial thrombophlebitis, deep-vein thrombosis of the extremities, caput medusa, superior vena cava or Budd–Chiari syndrome (Plotkin et al., 1985). Thrombophlebitis occurs in one-third of all patients and it is more common in man. It is more frequently observed in leg veins, in decreasing order in vena cava inferior and superior, dural sinuses, axillary vein, brachial vein and the portal vein. Thrombi strictly adhere to the vein wall and for this reason the risk of embolization is low. Recurrent deep-vein thrombophlebitis of legs may lead to stasis dermatitis and leg ulcers around the ankle. Occlusion of the vena cava superior or inferior may lead to the vena cava syndrome, whereas obliteration of the hepatic vein may cause Budd–Chiari syndrome. Budd–Chiari syndrome is a rare complication of BS, however, it has a mortality rate of 60% (Saatci et al., 1993).

Pulmonary artery aneurysms are seen in 1–2% of mainly the male patients. (Hamuryudan et al., 2004). It frequently (>80%) coexists with thrombophlebitis of the big veins. Haemoptysis is the most common symptom.

Involvement of great vessels sometimes is referred to as vasculo-Behçet's disease. It mainly affects the aorta, showing irregular fibrous thickening in all layers and focal aneurysmal dilatation (Fukuda et al., 1980). There is loss or interruption of medial elastic fibers, perivascular lymphocytic infiltration, and proliferation of vasa vasorum. In active aortitis, the cellular infiltrate was predominantly neutrophils, lymphocytes and plasma cells, admixed with histiocytes and eosinophils (Matsumoto et al., 1991).

Sometimes, granulomatous inflammation with giant cells in the media can be detected. Accumulation of mucopolysaccharidase within the media, as a degenerative change was reported (Balic, 1995). The pathogenesis of arterial aneurysms are thought to be obliterative endarteritis of vaso vasorum, resulting in dilatation and aneurysm or pseudoaneurysm formation (Rosenthal et al., 1982; Gruber and Weisman, 1983). Luminal obstruction by organized thrombi in venous occlusions is the main pathological feature.

5.13. Neurologic manifestations of Behçet's syndrome

Two main types of CNS lesions are seen (Siva et al., 2001; Akman-Demir et al., 1999). The more common is the parenchymal lesion (80%). Dural sinus thrombi, on the other hand, account for 20% of the cases. A prevalence of neurological involvement was found as 5.3% in a prospective study among the Turkish patients (Serdaroğlu, 1998). The CNS disease is more severe among the males as is true for most of the other lesions of BS. The dural sinus thrombi have a much more favorable course and it is rare to see both parenchymal and dural sinus thrombi at the same time.

The common presenting features are headache and pyramidal signs—with or without cerebellar findings. Isolated cerebellar involvement is uncommon and so is peripheral neuropathy, a feature helpful in differentiating BS from other vasculitides (Siva and Yazici, 2004).

Cerebrospinal fluid findings are nonspecific. These findings are mild pleocytosis and slight elevation in protein concentration, normal or low glucose level.

In imaging, the lesions are more commonly located in the basal areas. Small vessel vasculitis, a mild inflammatory cell infiltration, demyelinization and degenerative changes can all be seen on microscopy (Yuh et al., 1994; Hirohita, 2004).

5.14. Gastrointestinal involvement

Gastrointestinal involvement shows geographical variation in different populations. It is common among patients from Japan and Korea (Lee, 1986), but rare in Turkish patients (Yurdakul

et al., 1996). The main complaints are abdominal pain, diarrhea and melena/hematochezia. The pathologic hallmark of intestinal BS is known to be the presence of a few punched-out ulcers of variable size. There may be deep ulcers resulting in perforation. These ulcers usually appear in the iliocecal region but they may be present at any site, throughout the digestive system (Lee et al., 2001). Ano-rectal involvement is very rare in BS but common in inflammatory bowel disease. Multiple, small shallow ulcers have also been reported in esophagus, stomach and duedonum in some cases of BS (Mori et al., 1983; Good et al., 1982).

5.15. Behçet's syndrome in children

BS in childhood is rare (Kone-Paut et al., 1998) It affects both sexes equally. When compared to the frequency of clinical manifestations with adults, no difference was observed in the frequency of oral and genital ulcerations, but erythema nodosum and folliculitis are more common in Juvenile BS (Azizlerli, 2002). Family history is more common in JBS cases (Kone-Paut et al., 1999).

6. Diagnosis

There is no specific laboratory test for BS, and the diagnosis is based upon clinical criteria. In 1990, International study group for BS published a set of classification criteria (International study Group for Behçet's disease, 1990) with oral ulcers constituting the cardinal feature of the set. In the absence of additional organ involvement a single one organ involvement plus a positive pathergy test are required for the diagnosis of BS, as shown below:

1. Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in 12-month period; and two of the following
2. Recurrent genital ulceration
3. Eye lesions; anterior uveitis, posterior uveitis, cells in the vitreous by slit lamp examination, or retinal vasculitis observed by an ophthalmologist
4. Skin lesions, erythema nodosum, pseudofolliculitis, papulo-pustular lesions, or acneiform nodules in postadolescent patients not on corticosteroids
5. Pathergy, read by a physician at 24–48 h.

A detailed clinical history is essential to exclude other conditions and reveal subtle features of this complex disease.

Oral ulcers occur in virtually every BS patient. Genital aphthae and cutaneous lesions occur in three-fourth of BS patients.

7. Differential diagnosis

7.1. Differential diagnosis of oral and mucocutaneous disease

Complex aphthosis
HSV infection
Inflammatory Bowel disease

- Crohn's disease
- Chronic ulcerative colitis

Reiter's syndrome
Erythema multiforme
Lichen planus
Autoimmune bullous disorders

- Pemphigus vulgaris
- Mucous membrane pemphigoid
- Linear IgA dermatosis.

7.2. Differential diagnosis of oral genital and ocular mucocutaneous disease

- HSV infection
- Reiter syndrome
- Erythema multiforme (EM)
- Mucous membrane pemphigoid.

The overlap of inflammatory bowel disease, such as Crohn's disease and chronic ulcerative colitis and BS is well recognized, particularly when extra colonic manifestations of inflammatory bowel disease

such as aphthosis, iritis, erythema nodosum and nonerosive arthropathy are also present.

Mucocutaneous disease presents a similar diagnostic dilemma. In this context patients with complex aphthosis, erythema multiforme, mucosal pemphigoid and vulvovaginal form of erosive lichen planus are particularly problematic (Rogers, 2003). Virtually all patients with BS have RAS classified as simple or complex aphtosis. Simple aphtosis is common, episodic short-lived variant of canker sores affecting 20–50% of the population in their youth.

Complex aphthosis may be associated secondarily with inflammatory bowel disease, HIV disease, cyclic neutropenia, FAPA (fever, aphtous stomatitis, pharyngitis, adenitis), various vitamin deficiencies (iron, zinc, folat, vitamins, B1, B2, B6, B12), gluten-sensitive enteropathies (Letsinger et al., 2005).

Some EM patients have recurrent disease. When recurrent disease is present with mucocutaneous manifestations, BS is included in differential diagnosis. Other EM patients have a recurrent or chronic mucosal disease, which is centered on oral lesions.

Patients with oral EM have labial lesions involving the vermillon. Such lesions would be quite unusual for BS. In addition they are not discrete aphthae, but tend toward diffuse vesiculoerosive lesions.

About one-fourth oral EM patients have target lesions of the skin and or genital lesions. The clinical pattern may be confused with BS. Ocular involvement in oral EM is rare.

In mucous membrane pemphigoid erythema, edema, desquamative gingivitis, erosions and blisters are seen. Individual lesions are discrete vesiculoerosive patches, which do not resemble aphthae. Many patients present with diffuse, desquamative gingivitis. In addition, the genital lesions are vesiculoerosive. Ocular lesions include conjunctivitis with foreshortening of the fornices leading to symplepharon and ectropion formation. Cutaneous lesions are blistering in nature. The blistering and mucosal erosions separates MMP from BS.

Vulvovaginal–gingival variant of erosive oral lichen planus (LP) also enters into differential diagnosis. The vulvovaginal gingival variant of erosive oral LP is immunologically mediated mucocutaneous disease with oral, genital and cutaneous manifestation. Lesions result from inflammatory destruction of epithelial basal cell keratinocytes resulting in an interface inflammatory reaction pattern.

Clinically, the cutaneous lesions of LP are papulosquamous. The scaly papules are purple, polygonal and pruritic and thus do not look like any of the common skin lesions of BS. Mucosal lesions are discrete, they may be thickened, white, hyperkeratotic papules and plaques or thinned, red erosions or superficial ulcers. Gingival involvement may be diffuse. Genital lesions are also discrete or desquamative. Ocular lesions are rare. The papulosquamous cutaneous and erosive mucosal lesions are distinct. Neither the oral lesions nor the cutaneous lesions resemble the mucocutaneous manifestation.

RAS also associate with inflammatory bowel disease, but genital ulceration or scars are not a feature of these condition. Pathergy test is usually negative in inflammatory bowel disease.

Sarcoidosis can also present with erythema nodosum, uveitis and arthralgia, but genital ulcers are not a feature. Chest radiography may be helpful.

Other causes of periodic fevers, such as familial Mediterranean fever, hyper IgD syndrome or periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome (Thomas et al., 1999) should be considered in children as recurrent febrile episodes may characterize the onset of BS.

Patients with significant neurological involvement may occasionally be misdiagnosed as having multiple sclerosis (Marshall, 2004). True plaque formation is not a feature of BS.

8. Prognosis and treatment

We recently surveyed the two decade mortality and morbidity of BS (Kural-Seyahi et al., 2003) and saw that the disease activity was usually confined to the early years of its course. This was particularly true for skin-mucosa disease where if one took those patients with mainly skin-mucosa disease at the onset and reexamined them 20 years

later (Kural-Seyahi et al., 2003) many would not fulfill any one of the classification criteria proposed. Similarly the burden of eye disease and the overall mortality are usually more pronounced in the early years. The onset of major vessel disease and especially the CNS disease, on the other hand, usually have their onset later in the disease course.

As had been repeatedly demonstrated before (Yazici et al., 1984b, 1996, 1985, 2002) this survey also showed that male and young patients had a much more unfavorable course when compared to the females and older patients.

Although formal studies are lacking, of the skin-mucosa manifestations the superficial thrombophlebitis might turn out to be a somewhat poor prognostic indicator, in that it was formally shown (Tunc et al., 2004) to be associated with deep-vein thrombosis.

Currently, treatment of BS is directed at suppression of inflammation with an aim of preventing the occurrence of irreversible organ damage. Young and male patients usually have to be treated more aggresively because of the less favorable prognosis in this group, as outlined above. *Female* patients with mild disease can be followed up with reassurance and topical treatment is usually sufficient for oral and genital ulcers.

8.1. Treatment of mucocutaneous manifestations

Topical application of triamcinolon acetonide in oral paste usually shortens aphthous ulcer duration. Topical anesthetics such as lidocaine are usually helpful in controlling pain.

Over the years colchicine has widely been used in treating particularly the skin-mucosa manifestations. A 2-year controlled trial showed that colchicine (1.5 mg daily) was more effective than placebo in the treatment especially of arthritis in either sex. The only other significant effects were on genital ulcers and erythema nodosum only among women (Yurdakul et al., 2001).

Thalidomide at the dosage of 100 mg daily can induce prompt and sustained relief from oral and genital ulcers but they recur after the cessation of treatment (Hamuryudan et al., 1998). There is usually an increase in the nodular lesions during the first 8 weeks of treatment which is probably due to an increase in superficial thrombophlebitis, perhaps induced by thalidomide. Side effects, such as teratogenesis and polyneuropathy prevent its routine use. Low dose of thalidomide treatment may not prevent sensorial damage (de Wazieres et al., 1999).

Dapsone is a useful drug, particularly for the management of the mucocutaneous symptoms of Behcet's disease. In a double-blind, placebo-controlled, cross-over clinical trial, dapsone as a dosage of 100 mg daily was associated with a significant improvement in oral and genital ulceration, as well as in cutaneous lesions (Sharquie et al., 2002). Side effects include hemolysis, methemoglobinemia and agranulocytosis; regular monitoring for possible adverse events is required.

Topical sucralphate suspension has also been found to be effective in oral ulcers in a blind study (Alpsoy et al., 1999).

Recently, we have conducted a placebo-controlled double-blind study to determine the efficacy of the tumor necrosis factor-alpha blocker etanercept for pathergy and MSU-induced inflammation and on the mucocutaneous and articular manifestations in BS patients. This trial showed that Etenercept at 25 mg twice a day for 4 weeks was more effective than placebo in the treatment of mucocutaneous manifestations, especially the oral ulcers, however, etanercept did not suppress the pathergy reaction and the cutaneous response to MSU crystals (Melikoglu et al., 2005).

Various antibiotics have been found effective in suppressing the mucocutaneous manifestations and arthritis in BS. In a prospective study, a combination of benzathine penicillin with colchicine has been reported superior to colchicine alone in managing mucocutaneous and arthritic episodes of BS (Calguneri et al., 1996). In an open study, azithromycin was found to be effective in decreasing folliculitis and shortening the healing time of oral ulcers in BS (Mumcu et al., 2005).

Interferon alpha 2a was used in the treatment of mucocutaneous manifestations of BS patients (Azizlerli et al., 1996; O'Duffy et al., 1998; Georgiou et al., 1998; Zouboulis and Orfanos,

1998). A double-blind, placebo-controlled trial tested the efficacy of IFN on the mucocutaneous manifestations of BS. IFN-alpha reduced the duration and pain of oral ulcers, the frequency of genital ulcers and papulopustular and articular symptoms. When the treatment was stopped, all lesions came back as in pretreatment period (Alpsoy et al., 2002).

A double-masked trial topical application of an oral paste containing interferon alfa (Hamuryudan et al., 1991), and a placebo-controlled double-blind study using topical cyclosporin A (Ergun et al., 1997) showed that these topical agents were ineffective in the treatment of oral ulcers. Similarly, in double-blind controlled study 4% cromolyn gel was found ineffective in the treatment of genital ulcers (Mat et al., 2000).

A lactobacillus strain has been recently characterized which is endowed with a high activity of arginine deaminase. This enzyme acts on arginine, converts it into ammonia and citrulline and thus downregulates its conversion into nitric oxide, a major endogenous proinflammatory mediator. In an open study, the efficacy of *Lactobacillus brevis* lozenges in oral ulcer was studied among 25 consecutive patients with BS in a pilot protocol. A significant reduction in the numbers of oral ulcer (OU) at the end of 1 week treatment was found. In this pilot and open study *Lactobacillus brevis* lozenges seemed to be rather effective in controlling the oral ulcer of BS (Taslı et al., 2004).

The efficacy of Depot steroids (40 mg methyl prednisolon acetate) intramuscular injection was evaluated for the treatment of mucocutaneous manifestation of 86 BS patients in double-blind placebo-controlled study. Low dose depot-steroids used in BS are useful in controlling erythema nodosum lesions among females; however, it is ineffective for oral ulcearations, genital ulcers, folliculitis and arthritis during the trial (Mat et al., 2004).

8.2. Treatment of systemic manifestations

Especially in the young male, where the prognosis, is the worst, it is important to start treatment as early as possible. Efficacy of this approach has formally been shown for eye disease (Hamuryudan et al., 1997) and in the management of pulmonary artery aneurysms (Hamuryudan et al., 2004).

Azathioprine has been formally shown that to be effective in controlling eye disease and some of the extraocular manifestations including skin-mucosa disease, in a double-blind placebo controlled study. Recommended dose of azathioprine is 2.5 mg/kg/day (Yazici et al., 1990).

Cyclosporin-A, a noncytotoxic immunosupressant agent is probably still the most rapidly effective agent in controlling eye inflammation. It is found superior to monthly pulses of cyclophosphamide in a single-blind study (Ozyazgan et al., 1992). It induces anti-inflammatory effect at the dosage of 2–5 mg/kg/day. The long-term use of cyclosporin is limited by the development of side effects, particularly hypertension and renal impairment. It has also been reported to have a favorable effect on mucocutaneous disease, thrombophebilitis and systemic symptoms. It was reported in a retrospective survey that the incidence of neurological disease was significantly higher in patients receiving cyclosporin and cyclosporine-associated side effects could not be differentiated from CNS involvement (Kotake et al., 1999).

We commonly treat severe eye disease with a combination of azathioprin and cyclosporin A mainly using the latter as a remisson inducing agent and the former as the maintenance drug (Yazici et al., 1999).

Interferon alpha is widely used for the uveitis of BS (Kotter et al., 2003). It is also beneficial for the extraocular manifestations of the disease, although less so for oral aphthous ulcers (Kotter et al., 2004).

Infliximab, in uncontrolled studies, has been shown to have a beneficial effect in BS not only in eye disease (Sfikakis, 2002; Ohno et al., 2004; Lindstedt et al., 2005) but on the extraocular manifestations as well (Haugeberg et al., 2004; Sarwar et al., 2005).

Oral and intravenous cyclophosphamide either as single agent or combination with high-dose corticosteroids has been used in patients with systemic vasculitis (pulmonary arterial involvement) and parenchymal CNS involvement (Yazici et al., 2002; Kantarci and Siva, 2003; Hamuryudan et al., 2004).

In brief within the last decades substantial progress has been made in managing BS. Patients with eye disease, pulmonary artery aneurysms and skin-mucosa disease are with little doubt doing better when compared to 20 years ago.

On the other hand, the management of thrombophilia and that of CNS disease are the two main problem areas due to the lack of reported formal clinical trial data.

Key points

- Epidemiology: Prevalence of BS 38–42/10^4 in Turkey. 1/10^4 in Japan, lower in the West. Distrubution seems to follow the ancient Silk Road.
- Demographics: It is rare before puberty and after the sixth decade. It affects both genders equally but young male patients have more severe disease.
- Etiopathogenesis: BS is a complex multisystem inflammatory disorder of unknown etiology. HLA B51 has been the most consistently reported HLA-association in the disease. The unifying feature of the inflammation observed in BS is a nonspecific inflammatory hyperreactivity—a phenomenon known as 'pathergy'—with vasculitis as its main clinical consequence. Th1-mediated immune response seems to be responsible for tissue damage.
- Clinical symptoms: Typically manifests with recurrent oral and genital ulcerations and uveitis, variably accompanied by symptoms affecting skin, the large vessels, gastrointestinal and CNS, or other organs.
- Pathology: BS is a systemic vascular disease, affecting blood vessels of all size. A nonspecific inflammatory hyperreactivity, mainly neutrophilic, with or without vasculitis is its main consequence.
- Prognosis and treatment: In many patients disease abates with the passage of time. Mucocutaneous lesions can often be managed symptomatically. However, if they become severe enough to interfere with quality of life, then systemic therapy is required. Certain manifestations, including ocular, neurological and large vessel involvement are indications for aggressive therapy, especially in the young males in whom the mortality and morbidity are raised especially in early disease. Preliminary experience indicates TNF inhibition might be helpful in disease control.

References

Akman-Demir, G., Serdaroğlu, P., Taşcı, B. 1999. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. Brain 122, 2171.

Alpsoy, E., Er, H., Durusoy, C., Yilmaz, E. 1999. The use of sucralfate suspension in the treatment of oral and genital ulceration of Behcet disease: a randomized, placebo-controlled, double-blind study. Arch. Dermatol. 135, 529.

Alpsoy, E., Durusoy, C., Yilmaz, E., et al. 2002. Interferon alfa-2a in the treatment of Behcet disease: a randomized placebo-controlled and double-blind study. Arch. Dermatol. 138, 467.

Altac, M., Tuzun, Y., Yurdakul, S., et al. 1982. The validity of pathergy test (non-specific skin hyperreactivity) in Behcet's disease: a double-blind study by independent observers. Acta Derm. Venereol. (Stockh) 62, 158.

Arkin, C.R., Rothschild, B.M., Florendo, N.T., et al. 1980. Behçet's syndrome and myositis. A case report with pathologic findings. Arthritis Rheum. 23, 600.

Azizlerli, G., Ozarmagan, G., Ovul, C., et al. 1992. A new kind of skin lesion in Behcet's disease: extragenital ulcerations. Acta Derm. Venereol. 72, 286.

Azizlerli, G., Sarica, R., Kose, A., et al. 1996. Interferon alfa-2a in the treatment of Behcet's disease. Dermatology 192, 239.

Azizlerli, G. 2002. Juvenil Behçet's syndrome. In: G.V. Ball, L. Bridges (Eds.), Vasculitis. Oxford University Press, Oxford, p. 441.

Azizlerli, G., Kose, A.A., Sarica, R., et al. 2003. Prevalence of Behcet's disease in Istanbul, Turkey. Int. J. Dermatol. 42, 803.

Baliç, A., 1995. Behçet Hastalığında Damar Lezyonlarının Morfolojik Değerlendirmesi (Uzmanlık Tezi). İstanbul.

Bang, D., Hur, W., Lee, E.S., et al. 1993. Prognosis and clinical elevance of recurrent oral ulceration in Behçet's disease. J. Dermatol. 22, 926.

Bang, D., Lee, J.H., Lee, E.S., et al. 2001. Epidemiologic and clinical survey of Behcet's disease in Korea: the first multicenter study. J. Korean Med. Sci. 16, 615.

Behçet, H. 1937. Ueber rezidivierende aphtose durch ein virus verursachte geschwuere am mund, am auge und an den genitalien. Dermatol. Wochensch. 105, 1152.

Ben Ahmed, M., Houman, H., Miled, M., et al. 2004. Involvement of chemokines and Th1 cytokines in the pathogenesis

of mucocutaneous lesions of Behcet's disease. Arthritis Rheum. 50, 2291.
Bilic, M., Mutasim, D.F. 2001. Neutrophilic eccrine hidradenitis in a patient with Behcet's disease. Cutis 68, 107.
Cakir, N., Yazici, H., Chamberlain, M.A., et al. 1991. Response to intradermal injection of monosodium urate crystals in Behcet's syndrome. Ann. Rheum. Dis. 50, 634.
Calguneri, M., Kiraz, S., Ertenli, I., et al. 1996. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behcet's disease. A randomized clinical trial. Arthritis Rheum. 39, 2062.
Cantini, F., Salvarani, C., Niccoli, L., et al. 1998. Behcet's disease with unusual cutaneous lesions. J. Rheumatol. 25, 2469.
Chamberlain, M.A. 1977. Behcet's syndrome in 32 patients in Yorkshire. Ann. Rheum. Dis. 36, 491.
Chambers, J.C., Haskard, D.O., Kooner, J.S. 2001. Vascular endothelial function and oxidative stress mechanisms in patients with Behcet's syndrome. J. Am. Coll. Cardiol. 37, 517.
Chang, H.K., Lee, S.S., Kim, J.W., et al. 2003. The prevalence of atopy and atopic diseases in Behcet's disease. Clin. Exp. Rheumatol. 21 (4Suppl 30), S31.
Chun, S.I., Su, W.P., Lee, S., et al. 1989. Erythema nodosum-like lesions in Behcet's syndrome: a histopathologic study of 30 cases. J. Cutan. Pathol. 16, 259.
Chun, S.I., Su, W.P., Lee, S. 1990. Histopathologic study of cutaneous lesions in Behcet's syndrome. J. Dermatol. 17, 333.
Cosgun, S., Seyahi, E., Mat, C., et al. 2004. Female Behcet's syndrome patients have more severe oral ulceration. XI International Congress on BD. Clin. Exp. Rheumatol. 22, S86.
Dilsen, N., Konice, M., Aral, O., et al. 1993. Comparative study of the skin pathergy test with blunt and sharp needles in Behcet's disease: confirmed specificity but decreased sensitivity with sharp needles. Ann. Rheum. Dis. 52, 823.
Dinc, A., Karaayvaz, M., Caliskaner, A.Z., et al. 2000. Dermographism and atopy in patients with Behcet's disease. J. Invest. Allergol. Clin. Immunol. 10, 368.
Diri, E., Mat, C., Hamuryudan, V., et al. 2001. Papulopustular skin lesions are seen more frequently in patients with Behcet's syndrome who have arthritis: a controlled and masked study. Ann. Rheum. Dis. 60, 1074.
Direskeneli, H., Saruhan-Direskeneli, G. 2003. The role of heat shock proteins in Behcet's disease. Clin. Exp. Rheumatol. 21, S44.
Demirkesen, C., Tuzuner, N., Mat, C., et al. 2001. Clinicopathologic evaluation of nodular cutaneous lesions of Behcet syndrome. Am. J. Clin. Pathol. 116, 341.
Ergun, T., Gurbuz, O., Yurdakul, S., et al. 1997. Topical cyclosporine-A for treatment of oral ulcers of Behcet's syndrome. Int. J. Dermatol. 36, 720.
Ergun, T., Gurbuz, O., Dogusoy, G., et al. 1998a. Histopathologic features of the spontaneous pustular lesions of Behcet's syndrome. Int. J. Dermatol. 37, 194.
Ergun, T., Gurbuz, O., Harvell, J., et al. 1998b. The histopathology of pathergy: a chronologic study of skin hyperreactivity in Behcet's disease. Int. J. Dermatol. 37, 929.
Ergun, T., Ince, U., Eksioglu-Demiralp, E., et al. 2001. HSP 60 expression in mucocutaneous lesions of Behcet's disease. J. Am. Acad. Dermatol. 45, 904.
Esin, S., Gül, A., Hodara, V., et al. 1997. Peripheral blood T cell expansions in patients with Behcet's disease. Clin. Exp. Immunol. 107, 520.
Espinosa, G., Font, J., Tassies, D., et al. 2002. Vascular involvement in Behcet's disease: relation with thrombophilic factors, coagulation activation, and thrombomodulin. Am. J. Med. 112, 37.
Frassanito, M.A., Dammacco, R., Cafforio, P., et al. 1999. Th1 polarization of the immune response in Behcet's disease: a putative pathogenetic role of interleukin-12. Arthritis. Rheum. 42, 1967.
Fresko, I., Ugurlu, S., Ozbakir, F., et al. (2005). Anti saccharomyces cerevisiae (ASCA) antibodies in Behcet's syndrome. Clin. Exp. Rheum. 23, S38, 67–70.
Fresko, I., Yazici, H., Bayramicli, M., et al. 1993. Effect of surgical cleaning of the skin on the pathergy phenomenon in Behcet's syndrome. Ann. Rheum. Dis. 52, 619.
Freysdottir, J., Lau, S., Fortune, F. 1999. Gammadelta T cells in Behcet's disease (BD) and recurrent aphthous stomatitis (RAS). Clin. Exp. Immunol. 118, 451.
Fujii, N., Minagawa, T., Nakane, A., et al. 1983. Spontaneous production of gamma-interferon in cultures of T lymphocytes obtained from patients with Behcet's disease. J. Immunol. 130, 1683.
Fukuda, Y., Uekusa, T., Watanabe, I., et al. 1980. Pathological studies of Behçet's disease. Ryumachi 20, 268.
Georgiou, S., Monastirli, A., Pasmatzi, E., et al. 1998. Efficacy and safety of systemic recombinant interferon-alpha in Behcet's disease. J. Intern. Med. 243, 367.
Gonzalez-Gay, M.A., Garcia-Porrua, C., Branas, F., et al. 2000. Epidemiologic and clinical aspects of Behcet's disease in a defined area of Northwestern Spain, 1988–1997. J. Rheumatol. 27, 703.
Good, A.E., Mutchnick, M.G., Weatherbee, L. 1982. Duodenal ulcer, hepatic abscess and fatal hemobilia with Behçet's syndrome: a case report. Am. J. Gastroenterol. 77, 905.
Gruber, H.E., Weisman, M.H. 1983. Aortic thrombosis during sigmoidoscopy in Behcet's syndrome. Arch. Intern. Med. 143, 343.
Gül, A. 2001a. Behcet's disease: an update on the pathogenesis. Clin. Exp. Rheumatol. 19, S6.
Gul, A. 2005. Behcet's disease as an autoinflammatory disorder. Curr. Drug Targets Inflamm. Allergy 4, 81.
Gul, A., Esin, S., Dilsen, N., et al. 1995. Immunohistology of skin pathergy reaction in Behcet's disease. Br. J. Dermatol. 132, 901.
Gül, A., Hajeer, A.H., Worthington, J., et al. 2001b. Evidence for linkage of the HLA-B locus in Behcet's disease, obtained using the transmission disequilibrium test. Arthritis Rheum. 44, 239.
Gül, A., Hajeer, A.H., Worthington, J., et al. 2001c. Linkage mapping of a novel susceptibility locus for Behcet's disease to chromosome 6p22-23. Arthritis Rheum. 44, 2693.

Gül, A., Inanc, M., Ocal, L., et al. 2000. Familial aggregation of Behcet's disease in Turkey. Ann. Rheum. Dis. 59, 622.

Gül, A., Özbek, U., Öztürk, C., et al. 1996. Coagulation factor V gene mutation increase the risk of venous thrombosis in Behçet's disease. Br. J. Rheumatol. 35, 1178.

Gul, A., Uyar, F.A., Inanc, M., et al. 2002. A weak association of HLA-B*2702 with Behcet's disease. Genes Immun. 3, 368.

Gürler, A., Boyvat, A., Tursen, U. 1997. Clinical manifestations of Behçet's disease. An analysis of 2147 patients. Yonsei Med. J. 38, 423.

Haim, S., Sobel, J.D., Friedman-Birnbaum, R., et al. 1976. Histological and direct immunofluorescence study of cutaneous hyperreactivity in Behcet's disease. Br. J. Dermatol. 95, 631.

Hamuryudan, V., Mat, C., Saip, S., et al. 1998. Thalidomide in the treatment of the mucocutaneous lesions of the Behcet syndrome. A randomized, double-blind, placebo-controlled trial. Ann. Intern. Med. 128, 443.

Hamuryudan, V., Oz, B., Tuzun, H., et al. 2004. The menacing pulmonary artery aneurysms of Behcet's syndrome. Clin. Exp. Rheumatol. 22, S1.

Hamuryudan, V., Ozyazgan, Y., Hizli, N., et al. 1997. Azathioprine in Behcet's syndrome: effects on long-term prognosis. Arthritis Rheum. 40, 769.

Hamuryudan, V., Yurdakul, S., Rosenkeimer, F., et al. 1991. Inefficacy of topical alpha interferon in the treatment of oral ulcers in Behçet's syndrome. A randomized double-blind trial. Br. J. Rheumatol. 30, 395.

Hamzaoui, K., Ayed, K., Slim, A., et al. 1990. Natural killer cell activity, interferon-gamma and antibodies to herpes viruses in patients with Behcet's disease. Clin. Exp. Immunol. 79, 28.

Hatemi, G., Bahar, H., Uysal, S., et al. 2004. The pustular skin lesions in Behcet's syndrome are not sterile. Ann. Rheum. Dis. 63, 1450.

Haugeberg, G., Velken, M., Johnsen, V. 2004. Successful treatment of genital ulcers with infliximab in Behcet's disease. Ann. Rheum. Dis. 63, 744.

Hirohata, S. 2004. Histopathology of central nervous system lesions of Behcet's disease. XI International Congress on Behçet's disease. Clin. Exp. Rheumatol. 22, S 131.

Ifeacho, S.N., Malhi, G., Hamburger, M. 2004. Recurrent aphtous stomatitis and Behçet's disease:is there a link? XI International Congress on BD. Clin. Exp. Rheumatol. 22, S 101.

International study Group for Behçet's disease 1990. Criteria for diagnosis of Behçet's disease. Lancet 335, 1078.

Jorizzo, J.L., Solomon, A.R., Cavallo, T. 1985. Behcet's syndrome. Immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow-up. Arch. Pathol. Lab. Med. 109, 747.

Kaneko, F., Tojo, M., Sato, M., et al. 2003. The role of infectious agents in the pathogenesis of Behcet's disease. Adv. Exp. Med. Biol. 528, 181.

Kantarci, O., Siva, A. 2003. Behçet's disease. Diagnosis and management. In: J. Norewosty (Ed.), Neurological Therapies. Principles and Practice. Martin Dunitz Publishers, London, p. 1084.

Karasneh, J., Gül, A., Ollier, W.E.R., et al. 2005. Whole-genome screening for susceptibility genes in multicase families with Behcet's disease. Arthritis Rheum. 52, 1836.

Kim, B.S., LeBoit, P.E. 1998. Erythema nodosum-like lesions in Behçet's disease: Is vasculitis the main pathological feature (abstract)?. J. Cutan. Pathol. 25, 500.

Kim, H.B. 1997. Ophthalmologic manifestation of Behcet's disease. Yonsei Med. J. 38, 390.

Koc, Y., Gullu, I., Atakpek, G., et al. 1992. Vascular involvement in Behcet's disease. J. Rheumatol. 19, 402.

Kone-Paut, I., Geisler, I., Wechsler, B., et al. 1999. Familial aggregation in Behcet's disease: high frequency in siblings and parents of pediatric probands. J. Pediatr. 135, 89.

Kone-Paut, I., Yurdakul, S., Bahabri, S.A., et al. 1998. Clinical features of Behcet's disease in children: an international collaborative study of 86 cases. J. Pediatr. 132, 721.

Kotake, S., Higashi, K., Yoshikawa, K., et al. 1999. Central nervous system symptoms in patients with Behcet disease receiving cyclosporine therapy. Ophthalmology 106, 586.

Kotter, I., Aepinus, C., Graepler, F., et al. 2001. HHV8 associated Kaposi's sarcoma during triple immunosuppressive treatment with cyclosporin A, azathioprine, and prednisolone for ocular Behcet's disease and complete remission of both disorders with interferon alpha. Ann. Rheum. Dis. 60, 83.

Kotter, I., Vonthein, R., Zierhut, M., et al. 2004. Differential efficacy of human recombinant interferon-alpha2a on ocular and extraocular manifestations of Behcet's disease: results of an open 4-center trial. Semin. Arthritis Rheum. 33, 311.

Kotter, I., Zierhut, M., Eckstein, A.K., et al. 2003. Human recombinant interferon alfa-2a for the treatment of Behcet's disease with sight threatening posterior or panuveitis. Br. J. Ophthalmol. 87, 423.

Krause, I., Monselise, Y., Milo, G., et al. 2002. Anti-*Saccharomyces cerevisiae* antibodies—a novel serologic marker for Behcet's disease. Clin. Exp. Rheumatol. 20, S21.

Kural-Seyahi, E., Fresko, I., Seyahi, N., et al. 2003. The long-term mortality and morbidity of Behçet syndrome. A 2-decade outcome survey of 387 patients follows at a dedicated center. Medicine 82, 60.

Kurhan-Yavuz, S., Direskeneli, H., Bozkurt, N., et al. 2000. Anti-MHC autoimmunity in Behcet's disease: T cell responses to an HLA-B-derived peptide cross-reactive with retinal-S antigen in patients with uveitis. Clin. Exp. Immunol. 120, 162.

Lakhanpal, S., Tani, K., Lie, J.T., et al. 1985. Pathologic features of Behcet's syndrome: a review of Japanese autopsy registry data. Hum. Pathol. 16, 790.

Lee, R.G. 1986. The colitis of Behçet's syndrome. Am. J. Surg. Pathol. 10, 888.

Lee, E.S., Bang, D., Lee, S. 1997. Dermatologic manifestations of Behçet's disease. Yonsei Med. J. 38, 380.

Lee, K.H., Chung, H.S., Kim, H.S., et al. 2003. Human alpha-enolase from endothelial cells as a target antigen of

anti-endothelial cell antibody in Behcet's disease. Arthritis Rheum. 48, 2025.
Lee, S.H., Chung, K.Y., Lee, W.S., et al. 1989. Behcet's syndrome associated with bullous necrotizing vasculitis. J. Am. Acad. Dermatol. 21, 327.
Lee, C.R., Kim, W.H., Cho, Y.S., et al. 2001. Colonoscopic findings in intestinal Behçet's disease. Inflamm. Bowel Dis. 7, 243.
Leiba, M., Slingshot, U., Sidi, Y., et al. 2004. Thrombophilic factors are not the leading cause of thrombosis in Behcet's disease. Ann. Rheum. Dis. 63, 9.
Letsinger, J.A., McCarty, M.A., Jorizzo, J.L. 2005. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. J. Am. Acad. Dermatol. 52, 500.
Lie, J.T. 1992. Vascular involvement in Behçet's disease: arterial and venous and vessels of all sizes. J. Rheumatol. 19, 341.
Lindstedt, E.W., Baarsma, G.S., Kuijpers, R.W., et al. 2005. Anti-TNF-alpha therapy for sight threatening uveitis. Br. J. Ophthalmol. 89, 533.
Louthrenoo, W., Kasitanon, N., Mahanuphab, P., et al. 2003. Kaposi's sarcoma in rheumatic diseases. Semin. Arthritis Rheum. 32, 326.
Magro, C.M., Crowson, A.N. 1995. Cutaneous manifestations of Behcet's disease. Int. J. Dermatol. 34, 159.
Mahesh, S.P., Li, Z., Buggage, R., et al. 2005. Alpha tropomyosin as a self-antigen in patients with Behcet's disease. Clin. Exp. Immunol. 140, 368.
Mangelsdorf, H.C., White, W.L., Jorizzo, J.L. 1996. Behcet's disease. Report of twenty-five patients from the United States with prominent mucocutaneous involvement. J. Am. Acad. Dermatol. 34, 745.
Marshall, S.E. 2004. Behçet's disease. Best Pract. Res. Clin. Rheumatol. 18, 291.
Mat, C., Goksugur, N., Ergin, B., et al. (in print). The frequency of scarring after genital ulcers in Behcet's syndrome: a prospective study. Int. J. Dermatol.
Mat, M.C., Nazarbaghi, M., Tuzun, Y., et al. 1998. Wound healing in Behcet's syndrome. Int. J. Dermatol. 37, 120.
Mat, C., Tuzun, T., Ozsoy, Y., et al. 2000. Cromolyn gel 4% in the treatment of genital ulcers of Behcet's disease. In: D. Bang, E. S. Lee, S.S. Lee (Eds.), Proceeding of the International Conference on Behçet's disease, Seul-Korea, p. 907.
Mat, C., Yurdakul, S., Ozyazgan, Y., et al. 2004. A double blind trial of depot corticosteroids in Behcet's syndrome (abstract). XI International Congress on Behcet's disease. Clin. Exp. Rheumatol. 22, S116.
Matsumoto, T., Uekusa, T., Fukuda, Y. 1991. Vasculo-Behcet's disease: a pathologic study of eight cases. Hum. Pathol. 22, 45.
Matsuo, T., Itami, M., Nakagawa, H., et al. 2002. The incidence and pathology of conjunctival ulceration in Behcet's syndrome. Br. J. Ophthalmol. 86, 140.
Mege, J.L., Dilsen, N., Sanguedolce, V., et al. 1993. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behcet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J. Rheumatol. 20, 1544.
Melikoglu, M., Fresko, I., Mat, C., et al. 2005. Short-term trial of etanercept in Behcet's disease: a double blind, placebo-controlled study. J. Rheumatol. 32, 98.
Melikoglu, M., Uysal, S., Kaplan, G., et al. 2002. Leukocyte phenotype and cytokine expression at the skin pathergy reaction in Behcet's disease: evidence for a type I immune response (abstract). Arthritis Rheum. 46, S191.
Mercader-Garcia, P., Vilata-Corell, J.J., Pardo-Sanchez, J., et al. 2003. Neutrophilic eccrine hidradenitis in a patient with Behcet's disease. Acta Derm. Venereol. 83, 395.
Molinari, N., Paut, I.K., Manna, R., et al. 2003. Identification of an autosomal recessive mode of inheritance in paediatric Behcet's families by segregation analysis. Am. J. Med. Genet. 122A, 115.
Mori, S., Yoshihira, A., Kawamura, H., et al. 1983. Esophageal involvement in Behçet's disease. Am. J. Gastroenterol. 78, 548.
Mumcu, G., Ergun, T., Elbir, Y., et al. 2005. Clinical and immunological effects of azithromycin in Behcet's disease. J. Oral Pathol. Med. 34, 13.
Nazarro, P. 1966. Cutaneous manifestations of Behçet's disease. International Symposium on Behçet's Disease, Rome, p. 15.
Nijsten, T.E., Meuleman, L., Lambert, J. 2002. Chronic pruritic neutrophilic eccrine hidradenitis in a patient with Behcet's disease. Br. J. Dermatol. 147, 797.
O'Duffy, J.D., Calamia, K., Cohen, S., et al. 1998. Interferon-alpha treatment of Behcet's disease. J. Rheumatol. 25, 1938.
Oguz, O., Serdaroglu, S., Tuzun, Y., et al. 1992. Acute febrile neutrophilic dermatosis (Sweet's syndrome) associated with Behcet's disease. Int. J. Dermatol. 31, 645.
Ohno, S., Nakamura, S., Hori, S., et al. 2004. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behcet's disease with refractory uveoretinitis. J. Rheumatol. 31, 1362.
Ohno, S., Ohguchi, M., Hirose, S., et al. 1982. Close association of HLA-Bw51 with Behcet's disease. Arch. Ophthalmol. 100, 1445.
Ozarmagan, G., Saylan, T., Azizlerli, G., et al. 1991. Re-evaluation of the pathergy test in Behçet's disease. Acta Derm. Venereol. (Stockh) 71, 75.
Ozen, S., Karaaslan, Y., Ozdemir, O., et al. 1998. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. J. Rheumatol. 25, 2445.
Ozyazgan, Y., Yurdakul, S., Yazici, H., et al. 1992. Low dose cyclosporin A versus pulsed cyclophosphamide in Behcet's syndrome: a single masked trial. Br. J. Ophthalmol. 76, 241.
Pervin, K., Childerstone, A., Shinnick, T., et al. 1993. T cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behcet's disease. J. Immunol. 151, 2273.
Plotkin, G.R., Patel, B.R., Shah, V.N. 1985. Behçet's syndrome complicated by cutaneous leukocytoclastic vasculitis.

Response to prednisone and chlorambucil. Arch. Intern. Med. 145, 1913.
Rogers, R., III. 2003. Pseudo-Behcet's disease. Dermatol. Clin. 21, 49.
Rosenthal, T., Rubenstein, Z., Adar, R., et al. 1982. Major vessel arteritis with aortic aneurysm in Behcet's disease. Vasa. 11, 124.
Rumke, C.L. 1975. Implications of the statement: no side effects were observed. N. Engl. J. Med. 292, 372.
Saatci, I., Ozmen, M., Balkanci, F., et al. 1993. Behcet's disease in the etiology of Budd-Chiari disease. Angiology 44, 392.
Sakane, T. 1991. Role of immunological abnormalities in the pathoetiology of Behçet's disease. In: J.D. O'Duffy, E. Kokmen (Eds.), Behçet's Disease: Basic and Clinical Aspects. Marcel Dekker Inc., New York, p. 475.
Sakane, T., Takeno, M., Suzuki, N., et al. 1999. Behcet's disease. N. Engl. J. Med. 341, 1284.
Sarwar, H., McGrath, H., Jr., Espinoza, L.R. 2005. Successful treatment of long-standing neuro-Behcet's disease with infliximab. J. Rheumatol. 32, 181.
Serdaroğlu, P. 1998. Behçet's disease and nervous system. J. Neurology 245, 197.
Seyahi, E., Memisoglu, E., Hamuryudan, V., et al. 2004. Coronary atherosclerosis in Behcet's syndrome: a pilot study using electron-beam computed tomography. Rheumatology (Oxford) 43, 1448.
Sfikakis, P.P. 2002. Behcet's disease: a new target for anti-tumour necrosis factor treatment. Ann. Rheum. Dis. 61 (Suppl. 2), ii51.
Sharquie, K.E., Najim, R.A., Abu-Raghif, A.R. 2002. Dapsone in Behcet's disease: a double-blind, placebo-controlled, cross-over study. J. Dermatol. 29, 267.
Shi Hui-li, Huang-Zheng-ji, 1993. Study on cutaneous lesions in Behcet's disease and meanings of relative laboratory parameters. In: F. Godeau, B. Weschler (Eds.), Behcet's Disease. Proceedings of the 6th International Conference on Behcet's Disease. Excerpta Medica, Amsterdam, p. 325.
Shimizu, T., Ehrlich, G.E., Inaba, G., et al. 1979. Behcet disease (Behcet syndrome). Semin. Arthritis Rheum. 8, 223.
Siva, A., Kantarcı, O.H., Saip, S., et al. 2001. Behçet's disease diagnostic and prognostic aspects of neurological involvement. J. Neurol. 248, 95.
Siva, A., Yazici, H. 2004. Behcet's syndrome. Neurologic involvement in systemic autoimmune disease. In: D. Erkan, S.R. Levine (Eds.), Handbook of Systemic Autoimmune Diseases 3. Elsevier, Amsterdam, p. 193.
Takeno, M., Kariyone, A., Yamashita, N., et al. 1995. Excessive function of peripheral blood neutrophils from patients with Behcet's disease and from HLA-B51 transgenic mice. Arthritis Rheum. 38, 426.
Taslı, L., Mat, C., De Simone, C., et al. 2004. Lactobacilli lozenges in the management of oral ulcers of Behçet's syndrome. XI International Congress on BD. Clin. Exp. Rheumatol. 22, S119.
Thomas, K.T., Feder, H.M., Jr., Lawton, A.R., et al. 1999. Periodic fever syndrome in children. J. Pediatr. 135, 15.
Tokay, S., Direskeneli, H., Yurdakul, S., et al. 2001. Anticardiolipin antibodies in Behcet's disease: a reassessment. Rheumatology (Oxford). 40, 192.
Tugal-Tutkun, İ., Onal, S., Altan-Yaylacıoğlu, R., et al. 2004. Uveitis in Behçet Disease: an analysis of 880 patients. Am. J. Ophthalmol. 138, 373.
Tunç, R., Keyman, E., Melikoğlu, M., et al. 2002. Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. J. Rheumatol. 29, 2393.
Tunc, R., Ozbakir, F., Caglayan, A. 2001. Absence of ANCA in Behçet syndrome with large vessel involvement. Angiology 10, 260.
Tunc, R., Saip, S., Siva, A., et al. 2004. Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome. Ann. Rheum. Dis. 63, 1693.
Tursen, U., Gürler, A., Boyvat, A. 2003. Evaluation of clinical findings according to sex in 2313 Turkish patients with Behçet's disease. Int. J. Dermatol. 42, 346.
Tuzun, Y., Altac, M., Yazici, H. 1980. Nonspecific hyperreactivity in Behcet's Disease. Haematologica 65, 395.
Tuzun, B., Tuzun, Y., Yurdakul, S., et al. 1999. Neutrophil chemotaxis in Behcet's syndrome. Ann. Rheum. Dis. 58, 658.
Verity, D.H., Marr, J.E., Ohno, S., et al. 1999. Behcet's disease, the Silk Road and HLA-B51: historical and geographical perspectives. Tissue Antigens 54, 213.
Verpilleux, M.P., Bastuji-Garin, S., Revuz, J. 1999. Comparative analysis of severe aphthosis and Behcet's disease:104 cases. Dermatology 198, 247.
de Wazieres, B., Gil, H., Magy, N., et al. 1999. Treatment of recurrent ulceration with low doses of thalidomide. Pilot study in 17 patients. Rev. Med. Interne. 20, 567.
Yavuz, S., Fresko, İ., Hamuryudan, V., et al. 1998. Fibromyalgia in Behçet's syndrome. J. Rheumatol. 25, 2219.
Yazici, H. 1997. The place of Behcet's syndrome among the autoimmune diseases. Int. Rev. Immunol. 14, 1.
Yazici, H. 2002. Behcet's syndrome: where do we stand?. Am. J. Med. 112, 75.
Yazici, H., Basaran, G., Hamuryudan, V., et al. 1996. The ten-year mortality in Behçet's syndrome. Br. J. Rheumatol. 35, 139.
Yazici, H., Biyikli, M., van der Linden, S., et al. 2001. The 'zero patient' design to compare the prevalences of rare diseases. Rheumatology (Oxford). 40, 121.
Yazici, H., Chamberlain, M.A., Tuzun, Y., et al. 1984a. A comparative study of the pathergy among Turkish and British Behcet's disease. Ann. Rheum. Dis. 43, 74.
Yazıcı, H., Fresko, I., Tunç, R., et al. 2002. Behçet's syndrome: pathogenesis, clinical manifestations and treatment. In: G.V. Ball, L. Bridges (Eds.), Vasculitis. Oxford University Press, Oxford, p. 406.
Yazici, H., Mat, C., Deniz, S., et al. 1987. Sebum production is increased in Behcet's syndrome and even more so in rheumatoid arthritis. Clin. Exp. Rheumatol. 5, 371.

Yazici, H., Pazarli, H., Barnes, C.G., et al. 1990. A controlled trial of azathioprine in Behcet's syndrome. N. Engl. J. Med. 322, 281.

Yazici, H., Tuzun, Y., Pazarli, H., et al. 1984b. Influence of age of onset and patient's sex on the prevalence and severity of manifestations of Behcet's syndrome. Ann. Rheum. Dis. 43, 783.

Yazici, H., Tuzun, Y., Tanman, A.B., et al. 1985. Male patients with Behcet's syndrome have stronger pathergy reactions. Clin. Exp. Rheumatol. 3, 137.

Yazici, H., Tüzüner, N., Tüzün, Y., et al. 1981. Localized myositis in Behçet's disease. Arthritis Rheum. 24, 636.

Yazici, H., Yurdakul, S., Hamuryudan, V. 1999. The management of Behçet's syndrome. How are we doing?. Clin. Exp. Rheumatol. 17, 145.

Yuh, W.T.C., Simonson, M.T., Wang, A. 1994. Venous sinus occlusive disease: MRI findings. Am. J. Neuroradiol. 15, 309.

Yurdakul, S., Gunaydin, I., Tuzun, Y., et al. 1988. The prevalence of Behcet's syndrome in a rural area in northern Turkey. J. Rheumatol. 15, 820.

Yurdakul, S., Hekim, N., Soysal, T., et al. 2005. Fibrinolytic activity and d-dimer levels in Behcet's syndrome. Clin. Exp. Rheum. 23 (S38), 53–58.

Yurdakul, S., Mat, C., Tuzun, Y., et al. 2001. A double-blind trial of colchicine in Behcet's syndrome. Arthritis Rheum. 44, 2686.

Yurdakul, S., Tüzüner, N., Yurdakul, I., et al. 1996. Gastrointestinal involvement in Behçet's syndrome: a controlled study. Ann. Rheum. Dis. 55, 208.

Yurdakul, S., Yazıcı, H., Tüzün, Y., et al. 1983. The arthritis of Behçet's disease:a prospective study. Ann. Rheum. Dis. 42, 505.

Zierhut, M., Mizuki, N., Ohno, S., et al. 2003. Immunology and functional genomics of Behcet's disease. Cell. Mol. Life Sci. 60, 1903.

Zouboulis, C.C., Orfanos, C.E. 1998. Treatment of Adamantiades-Behcet disease with systemic interferon alfa. Arch. Dermatol. 134, 1010.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 15

Outcome Measures in Cutaneous Autoimmune Disease: Dermatomyositis and Lupus Erythematosus

Joerg Albrecht, Victoria P. Werth*
Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA

1. Introduction to outcome measures in cutaneous autoimmune disease

The ability to measure, to describe, to classify and to diagnose diseases is the prerequisite for successful clinical research. Diagnosis and classification of cutaneous autoimmune diseases have made enormous progress during the latter half of the last century. In general, we now have a solid frame of reference for clinical research even though some of the diagnostic criteria are still being refined, and we are likely to see new and important markers of autoimmune diseases that will be introduced into clinical practice. However, comparative trials depend on outcome instruments that measure the extent and severity of a disease and can be used to compare the baseline status with the condition of the disease after treatment has been initiated. These are largely missing for the skin.

The success of any therapy for the skin can always be assessed by comparing the proportion of patients in each treatment group who have completely cleared their skin disease. While this basic comparison is readily available and likely to be reliable, this approach is not suitable for all diseases. It works only for diseases for which undisputed cure can be achieved, such as acute cutaneous bacterial infections, or for those diseases for which the study's baseline comparisons are likely to focus on secondary patient characteristics. The extent and activity of the disease in question cannot be measured without appropriate instruments.

The assessment of treatment success or the natural history of chronic skin diseases, particularly autoimmune diseases, has to allow measurement of subtle, gradual changes that are still clinically significant. Total permanent clearance is rarely achieved and patients who have been successfully treated may still have some lesional activity or suffer permanent damage from the disease. In addition, studies using binary outcome of total clearance and failure are likely to be prohibitively large for diseases that are as rare as many autoimmune diseases. Therefore, sensitive and clinically meaningful outcome instruments are a critical prerequisite for clinical research. Unfortunately, to date, the number of outcome instruments available to study autoimmune diseases is quite limited.

In this chapter, we will first describe some general experiences with outcome instruments in dermatology and then describe in detail the development of outcome instruments based on the experience in cutaneous lupus erythematosus (CLE) and dermatomyositis (DM).

2. Disease activity measurements for skin disease

During the last three or four decades there have been numerous attempts to develop instruments to

*Corresponding author.
Department of Dermatology, University of Pennsylvania, 2, Rhodes Pavillion, 3600 Spruce Street, Philadelphia, PA 19119, USA.
Tel.: +1-215-823-4439; Fax.: +1-215-823-5994
E-mail address: werth@mail.med.upenn.edu (V.P. Werth).

DOI: 10.1016/S1571-5078(05)05015-4

measure skin disease. Unfortunately, several of these instruments are not reliable and therefore lack the precision that is necessary to conduct trials in rare diseases (Charman and Williams, 2000). As a good approximation of the available scores, the medical algorithm project lists 111 medical algorithms in dermatology (www.medal.com, accessed 06/02/2005). Roughly, 30 of these can be used to grade the severity of diseases or were designed to be used as outcome instruments in clinical trials.

There have been attempts to develop general scores for dermatology, e.g. the dermatology index of disease severity (DIDS) (Faust et al., 1997), but the validation of general scores is challenging. The DIDS was validated in psoriasis patients and was helpful in the population studied. However, while it may work well in psoriasis, this score is not the solution for autoimmune diseases for various reasons. An accompanying editorial by Williams (1997) pointed out that the measure of extent of body surface area (BSA) involved was inappropriately crude for other diseases like acne—or indeed CLE or DM. These disease have a different distribution and involvement of BSA than psoriasis (Williams, 1997) and may hugely affect patients' lives while they only affect a small percentage of BSA. Also, the score tries to assess dermatological disease severity in terms of functional disability. This is helpful if the functional disability is the consequence of the skin disease alone. However, autoimmune diseases, particularly systemic LE and DM, can lead to functional disability due to systemic involvement or muscle disease, even though the skin lesions are improving on treatment, thus blurring or obstructing the treatment effect.

The desirable qualities of an outcome instrument for clinical trials have been summarized very succinctly by Finlay (1996):

1. The method should be simple enough to use in a busy clinical setting.
2. The method should clearly separate scores derived from the observer and from the patient.
3. The signs chosen to be recorded should be amenable to change and should be unambiguous in their meaning and proven to be so. If the presence of two signs is highly correlated only one needs to be recorded.
4. Recording of area of involvement should be based on an assessment of the site of involvement rather than the virtually impossible task of determining an accurate total percentage involvement.
5. Validity testing, including repeatability testing by the same and different observers, must be carried out.

Unfortunately, most of the developed scores in dermatology are disease specific and many have not been properly evaluated. Often they were developed for specific clinical trials, which can skew the instrument to fit the therapeutic mechanism of the treatment rather than the needs of the patient population. For skin diseases with a large population burden like psoriasis, atopic dermatitis and acne there are a number of scoring systems, some of which have been validated and are used frequently by a number of researchers. The number of instruments varies widely, e.g. there are 10 scores for atopic eczema but only 3 for psoriasis on the medal.org website. Even though it is likely that not all psoriasis instruments were captured on the website, this difference reflects the dominance of the PASI (Psoriasis Activity and Severity Index) for psoriasis research. For atopic dermatitis even the more elaborately evaluated instruments like the scoring atopic dermatitis (SCORAD) have not reached this level of dominance, which can make the comparison of trial results very difficult and certainly hinders the conduction of meta-analysis (Kunz et al., 1997).

3. The validation process

The design of an instrument is often a reflection of biometric necessities as well as of clinical judgement and knowledge. The design process of an instrument can be creative, but the validation process is well established and needs to be documented in detail. Many instruments used in dermatology are poorly validated. This lack of validation may mean that the results of studies may be hard to interpret and that it is unclear if

Table 1
Attributes that should be assessed for a new measurement scale

Validity (does the scale measure what is purports to measure?)	
Content	Does the scale include the things that are deemed to be important features for the disease?
Construct	Does the scale agree with other measures of the same disease chosen (if available)?
Criterion	Does the scale correlated with a widely used reference (if available)?
Reliability (how similar are measurements of the same patient?)	
Within observer	How well do two measurements performed by the same observer agree?
Between observer	How well do two measurements performed on the same person when recorded by different observers?
Internal consistency	Do the different items of a scale correlate with each other and with the total scale so that they measure the same attribute?
Sensitivity to change	How good is the scale in picking up minor changes in disease activity over time?
Acceptability/ convenience	How acceptable in terms of time or convenience or comfort is the instrument to those using it and to those being measured?

measurements coming from different observers can be compared. Table 1 describes attributes that should be tested in new measurement scales. It was adopted from an editorial by H Williams (2003), which readily acknowledges that the complete validation of an instrument means that one published study is never enough to fully test and launch a new instrument. Guidance on how to develop and validate a new instrument is readily available, e.g. by Streiner and Norman (1995).

4. What does the score mean? What is its clinical utility?

For cutaneous LE (CLE) and DM patients the score has to measure solely the cutaneous activity or damage if the intent is to assess treatment of the skin. Otherwise systemic disease may distort the results and a study can fail because of disease flares of extracutaneous manifestations that are unrelated to the treatment of the skin. For systemic disease a number of instruments are available. For SLE about 60 instruments measure the totality of systemic involvement (Parodi et al., 2000) and for myositis there is an extensive body of available instruments to measure the disease, as discussed below. For both diseases, development of the cutaneous outcome instruments is a fairly recent development and experience with these instruments is limited. However, in addition to these instruments, associated symptoms like itch, pain or fatigue should be measured as well. This should be done in a separate score because a combined score that reflects patient and physician assessment may be quite hard to interpret and it is unclear how the different aspects of the disease should be weighed. Attempts to combine patient-reported symptoms and physician-measured signs in one score have been attempted in atopic dermatitis but were abandoned subsequently (Anon, 1993; Berth-Jones et al., 1995).

As a consequence of repeated usage and evaluation, a body of experience has developed with the major instruments, thus facilitating the interpretation of study outcomes. However, the translation of improvements into clinical meaningful outcomes is often difficult. Is a score of 50 of the OSAAD (objective severity assessment of atopic dermatitis) twice as bad as a score of 25 (i.e. is the score linear)? What does a 75% reduction of the PASI, the PASI 75, mean for the patient? Depending on the severity and location of the lesions, patients may feel cured while others think that little has changed because they are still disfigured by a visually prominent lesion. This can only be assessed by correlating the score with simple patient-generated markers of disease severity.

Often the general criticism is voiced that outcome instruments do not adequately reflect the improvement of the patients. This is correct, but misleading because it assumes that the disease process as a conceptual entity is measurable and can be expressed as a clinical summary score. It is important to realize that instruments can only measure the aspect of the disease they were designed for. A thermometer measures body temperature, but cannot measure what it feels like

to have a fever, or whether the fever is dangerous. Similarly, an instrument like the PASI reflects the extent of the disease in terms of skin area, but it cannot score the psychological or, even necessarily, the physiological effect of the disease. A disease experience is a not a linear process that can be summarized in any score, e.g. a very small PASI score can be severely disabling if psoriasis affects the hands of a surgeon. One solution to this problem in therapeutic research is to measure a differential effect, i.e. the relative reduction of the score, but again this may not correlate well with the patient experience. The same PASI 75 can give the impression that patients with large confluent lesions have dramatically improved, while others feel little has changed because the most prominent lesions, e.g. on the hands or on the face proved treatment-resistant. Thus, dramatic improvement in quality of life instruments may be associated with changes in the disease activity based on the location of the lesions. Since health-related quality of life (HRQL) depends on personal perceptions and other facets of role functions, it often does not parallel clinical disease severity as assessed by the clinician (Carr and Higginson, 2001).

5. Assessors

Who can use a validated instrument? The validation of the instrument has to reflect the setting and the raters who will use the instrument in clinical trials, and cannot be extrapolated to related but unvalidated populations of raters. There are a variety of possibilities: raters can be trained dermatologists only (Carrol et al., in press), trained dermatologists and residents (Albrecht et al., 2005) or dermatologists, residents as well as nurses (Lucky et al., 1996). For autoimmune diseases it may be desirable to enable rheumatologists to score the patients so that it could be used for collaborative studies. However, it has been demonstrated that even for a more common and less complex disease like atopic dermatitis, scores by dermatologists were significantly better than those of nondermatologists (Oranje et al., 1997). Therefore, even a well-validated instrument would need to be revalidated with rheumatologists. While nurses have been involved in the validation of acne-lesion counting (Lucky et al., 1996), patient assessment in many dermatological trials is routinely done by physicians only. This should be especially true for diseases as serious and clinically heterogeneous as cutaneous LE or DM. Additionally, we believe that relevant comorbidity in cutaneous LE or DM may escape untrained observers. Examples are male or female pattern hair loss or fungal infections that can be easily mistaken for LE- or DM-specific skin lesions.

For all instruments, the assessors have to be trained in the use of the instrument to assure a common understanding of the scoring process. For every use of the instrument the training session must have at least the quality of the training that preceded the initial validation. Otherwise the validity of the results is not assured.

6. Dermatomyositis

As traditionally defined by the Bohan classification criteria (Bohan and Peter, 1975), all DM patients display a hallmark set of specific inflammatory skin lesions (Sontheimer, 2002).

Virtually, 100% of juvenile onset DM patients have inflammatory DM skin changes at the time of disease presentation. In approximately 60% of patients with adult-onset classical DM, the skin and muscle changes appear concurrently, while approximately 30% of adult classical DM patients have skin manifestations that precede the muscle symptoms by a period of several weeks to several months (data reviewed in Sontheimer and Provost, 2003). Ten per cent of classical DM patients first experience muscle weakness, followed in a short period of time by the appearance of the hallmark cutaneous manifestations of DM.

However, as in LE there is a subset of patients that experience only skin disease throughout. In approximately 10–20% of the population of DM patients seen in academic dermatology departments in the USA, the hallmark skin changes of DM have been present for 6 months or longer without the appearance of clinically significant muscle weakness or elevated muscle enzymes. Depending on these findings, the patients may be

referred to as amyopathic DM (Euwer and Sontheimer, 1993). Other patients may have mild electromyographic, biopsy or radiological evidence of muscle inflammation, but no clinical manifestations often over years or decades (Cohen, 2002; el Azhary and Pakzad, 2002; Sontheimer, 1999). Such individuals can be referred to as having "hypomyopathic DM". Together, these groups can be referred to as clinically amyopathic DM (i.e. their only clinical problem is the presence of DM skin lesions) (Sontheimer, 1999).

As a frequently photosensitive disorder, cutaneous DM typically affects exposed areas of skin on the face and upper extremities. Cutaneous symptoms including pruritus and dysesthesia are frequent. They can be disabling in their own right and are often worse at night, causing sleep disturbances. In addition, secondary skin changes occurring after the acute skin lesions can also produce permanent morbidity and disability (e.g. poikiloderma, cutaneous calcinosis).

Skin and muscle disease activity tends to respond to therapy in a parallel fashion during the initial treatment phase of most classical DM patients. Thus, the availability of validated outcome measures of DM skin disease activity could be of considerable benefit in clinical trials of new therapeutic agents.

6.1. Disease activity measurement for cutaneous DM

In this section, we will describe the outcome instruments that have been developed for dermato- and polymyositis and assess their usefulness as outcome measures for clinical trials designed to measure the response of the skin to interventions. We will introduce the dermatomyositis skin severity index (DSSI), which has not been published to date (June 2005). However, the instrument has been well validated and the publication (Carrol et al., in press) is forthcoming.

Rider et al. developed a cutaneous assessment tool (CAT) for DM, which was validated by 20 rheumatologists for inter-rater reliability. Yet, this instrument is only meant to determine the presence or absence of cutaneous manifestations of DM and has not been designed for therapeutic clinical trials. The purpose of the design is to educate physicians about cutaneous manifestations of DM and to help define new subsets of DM patients based upon the presence or absence of selected skin findings (Rider et al., 1995). For juvenile idiopathic inflammatory myopathies, Rider et al. developed and validated global disease assessment tools for physicians, parents and children (Lovell et al., 1999; Rider et al., 1997). These instruments were useful to assess disease activity as well as extent and proved reliable and valid. The global assessment of physicians and parents correlated and was clinically reactive enough to be a useful tool for clinical trials, while the children's assessment was deemed not reactive enough to be helpful. It helped to understand rating of this complicated multifaceted disease, which the authors also described as the relative influence that different symptoms had on the assessment of disease activity and global disease damage. They found that the global disease activity measure as assessed by the physician depends primarily on gastrointestinal symptoms and muscle strength, but that cutaneous ulceration was still of primary importance for treating physicians; this was true even though the patient population was primarily defined by myositis and many patients lacked skin involvement by definition. Physicians rated calcinosis as the most relevant symptom that influenced the global assessment of damage (Rider et al., 1997). This survey highlights the importance of cutaneous symptoms, and it illustrates how important the development of organ-specific activity scores is to assess skin-specific treatment. Therefore, skin-specific treatment cannot be assessed if global outcome measures are to a significant extent influenced by non-dermatological symptoms, which may be absent in a large number of clinically amyopathic patients.

Currently, the International Myositis Assessment and Clinical Studies (IMACS) group at the National Institute of Health (NIH) is validating outcome measures for myositis that include measuring the activity of the skin. The concept for the myositis disease activity assessment tool (MDAAT) has been published (Isenberg et al., 2004), but the MDAAT is currently being revised

and the validation has not been published. In its current form, the instrument measures the degree of disease activity of extra-muscular organ systems and muscle. It is a combined tool that includes the myositis disease activity assessment visual analogue scales (MYOACT) and the myositis intention to treat activity index (MITAX). The MYOACT is modified from the vasculitis activity index (VAI) (Whiting-O'Keefe et al., 1999). The VAI grades nine presentations of vasculitis on a visual analogue scale, while the MYOACT grades the activity of a variety of signs and symptoms of myositis, among them the skin, on a 10-cm visual analogue scale. The other component of the assessment of each element of activity in the MDAAT is the MITAX. The MITAX is modified from the British Isle Lupus Assessment Group (BILAG) approach to assess disease activity in lupus (Hay et al., 1993). The MITAX is composed of a series of organ-specific questions relating to the presence or absence of the clinical feature and the degree of treatment needed for it (intention to treat). By using the combination of a visual analogue scale and an assessment of treatment needed for component of the clinical activity, the score can assess the activity of the disease and changes of the activity fairly well. However, the instrument has not been fully validated and is currently only available to members of the IMACS group. While the publication of the validation is forthcoming, the authors' general impression is that the instrument was not designed to measure the disease activity of the skin in DM as a primary outcome of a therapeutic trial.

Recently, Isenberg et al. (2004) began to validate the MDI (myositis damage index), which is a composite index to assess myositis damage in paediatric and adult myositis patients. The index clearly has not been developed for clinical trials and does not monitor activity, which would most likely be of interest for most short- to medium-term clinical trials. It consists of 11 assessments of different aspects of damage, e.g. cardiovascular, skeletal or cutaneous damage, but also infections and malignancies. The damage is assessed in terms of a 10-cm overall visual analogue scale for all categories. In addition, presence or absence of signs of cutaneous damage, which have to be present for at least 6 months, are documented. The signs of damage listed are calcinosis, scarring alopecia, cutaneous scarring or atrophy, poikiloderma or lipodystrophy. In conclusion, due to its limitation to damage and the 6-month time horizon the index is not useful as an outcome instrument for clinical research but may well be used for baseline comparison.

Due to its primary focus on myositis, the group has gone on to develop outcome measures for myositis (Miller et al., 2001) and developed an international consensus on definitions of improvement in myositis (Rider et al., 2004), which do not explicitly involve the skin.

6.2. The Dermatomyositis Skin Severity Index (DSSI)

The DSSI (Carrol et al., in press) has been closely modelled on the PASI, which to date is the most successful and the dominant outcome instrument for psoriasis. The basis for the practically identical design of the DSSI and the PASI is the clinical observation that the skin lesions of both diseases share characteristics that are measured by the PASI. In exceptional cases the two diseases can present serious differential diagnostic challenges. However, the experience is that psoriasis is only very rarely a difficult differential diagnosis for DM and that DM has a number of skin signs that cannot be found in psoriasis. The PASI also has the advantage of being easy and quick to administer and there is a large amount of literature that describes its uses and characteristics, some of which may be applicable to DM or guide similar research into the properties of the DSSI.

The PASI is a clinical scoring system based on the visual inspection of four main body areas, which are the head, the trunk, the upper extremities and the lower extremities. The observer estimates the percentage of skin that is affected by the disease in each area and assigns scores based on the following 0–6 scale: 0 = no involvement; 1 = 10%; 2 = 10–30%; 3 = 31–50%; 4 = 51–70%, 5 = 71—90% and 6 = 91–100%. The PASI and the DSSI then score each affected area according to the average redness, induration

and scaliness of the lesions in the respective areas. Each of these three characteristics is then scored on a 0–4 scale, the sum of these 3 scores (maximum of 12) are multiplied by the area score (maximum of 6) for each body area. These totals are normalized, i.e. the scores are weighted in relation to the percentage of the total skin surface that constitutes the skin of each area (10% for the head, 20% for the upper extremities, 30% for the trunk and 40% for the lower extremities) and summed. The total DSSI or PASI score can range from 0 to 72.

Through a very thorough evaluation process, the DSSI has demonstrated content validity, construct and criterion validity as well as inter-rater and intra-rater reliability in two academic centres. After its publication it will be a useful instrument for clinical research of the skin manifestations of DM.

7. Lupus

In epidemiological studies, skin involvement has been found to be the second or most common manifestation and second most frequent presenting manifestation of SLE (Vlachoyiannopoulos et al., 1993).

Some types of CLE lesions such as classical discoid LE (DLE) and subacute cutaneous LE (SCLE) can occur in individuals who develop only minor manifestations of SLE or never develop any degree of SLE at all. The annual incidence and prevalence of patients having DLE or SCLE lesions in the absence of SLE has never been systematically determined. However, it has been estimated that individuals having isolated CLE lesions could be two to three times as common as individuals having SLE (Tebbe and Orfanos, 1997). Thus, in addition to being an integral component of SLE, CLE also impacts the lives of many other individuals suffering from isolated LE skin lesions.

Unchecked LE skin disease activity can produce considerable physical disfigurement in publicly visible areas such as the face, scalp, neck and hands (e.g. pigmentary change, alopecia, atrophic scarring, ulceration). As such, LE skin disease by itself has the potential to produce major psychological stress, occupational disability, and a lowered HRQL (Tebbe and Orfanos, 1997). It has been estimated that CLE is the third most common cause of industrial disability from dermatological disease, with 45% of CLE patients experiencing some degree of vocational handicap (O'Quinn et al., 1972).

In the remainder of this chapter we describe the design and validation process of the cutaneous LE activity and severity index (CLASI). First, we describe the instruments used to measure SLE and how they relate to the skin. Then we describe in detail the design and development of the CLASI.

7.1. Disease activity measurement for CLE

Recently, the Food and Drug Administration (FDA) (Anon, 2003) published the thoughtful draft of a background paper on lupus erythematosus and outlined some of the current standards for indices useful for clinical research in SLE. According to the FDA paper, the following measures are critical to delineate important clinical responses to therapy in all situations:

1. measure of disease activity,
2. measure of disease-induced damage,
3. measure of response as determined by the patient, ''a patient global response'',
4. measure of HRQL.

According to the FDA background paper, these measures are currently lacking or their validation is so low-level that their suitability for clinical trials is doubtful. The FDA assessment of the available scores to measure SLE was that while they acknowledge skin involvement as one aspect of the global score, these instruments are not sufficient to allow meaningful assessment of therapeutic effectiveness.

In a recent retrospective study (Parodi et al., 2000) the authors noted that 60 measures of SLE were available but only three of these appeared useful for dermatologists. One of these, the SLE disease activity index (SLEDAI) (Bombardier et al., 1992) scores the presence of rash, alopecia or mucosal ulcers independent of extent and allocates a maximum of 6 points to these manifestations. The

total maximum score is 105. The score involves little in terms of computation and the assessment as to whether symptoms are present or absent is quite straightforward; therefore the score is thought to be reliable. However, due to its coarse assessment, the score is not sensitive to change. It is even unsuitable for baseline assessment of patients with CLE. The second potentially suitable score for dermatologists is BILAG system. This score is highly sensitive but difficult to complete because the essential definitions or operational criteria are missing.

Other systems like the lupus activity criteria count (LACC) (Urowitz et al., 1984) count only the number of organ systems involved and the skin is one of potentially seven. Therefore, the clinical reactivity of the score is practically absent and it is certainly not useful for skin assessment. Similarly, the SLICC/ACR damage index for SLE (Gladman et al., 1996) allocates 1 point each to scarring alopecia, extensive scarring other than the scalp or pulp space and skin ulceration (excluding thrombosis) for more than 6 months. The total maximum score is 48. This coarse assessment is not useful in comparing the outcome after therapy of skin lesions, where relatively subtle differences in damage can make a tremendous difference for the patients.

Parodi et al. selected the systemic lupus activity measure (SLAM) (Liang et al., 1989) as the best available tool. It proved to have good inter-rater and inter-visit reliability (Liang et al., 1989). This tool is fairly complex with 24 clinical parameters, four of which are related to the skin: (1) Alopecia, (2) Vasculitis, (3) Erythematous maculopapular rash or DLE or lupus profundus or bullae and (4). Oral/nasal ulcer, periungal erythema, malar rash, photosensitivity or nail-fold infarct. Vasculitis and rash are scored based on the involvement of BSA from 0 to 4, alopecia based on the cause: spontaneous or traumatic as either 1 or 2 without any consideration to scarring or extent of the alopecia. Ulcers, periungal erythema, malar rash or photosensitivity are only scored as present or absent. The maximum score for skin involvement is 13, the maximum score for patients with SLE is 85; however, the mean activity score in SLE patients is between 9 and 12 points (Liang et al., 1989). Based on their experience with 176 patients with CLE, the authors found the score inadequate for dermatologists and called for a revision. The lack of distinction between scarring and non-scarring alopecia was particularly unhelpful. However, in spite of its limitations, they found that it provided useful information for follow-up (Parodi et al., 2000). Based on the author's results and the score we have a more negative conclusion. In our opinion the score lacks the precision that is necessary to be useful for therapeutic trials. The extent scores only differentiate between less than 20%, 20–50% and more than 50% surface areas. This rough estimation of skin surface area has little face validity for a disease that involves primarily photosensitive areas and for which the total extent of skin involvement is usually low, much like guttate psoriasis (Ramsay and Lawrence, 1991). The score, like many quality of life instruments, covers the symptoms of the previous month rather than the acute condition of the patient. Most importantly though, Parodi et al.'s assessment of the scores' usefulness is based on the authors' desire to monitor systemic involvement during early and aggressive SLE treatment. Therefore, the non-dermatological parts of the score were used as well.

7.2. Choice of CLE measures

7.2.1. Erythema

The CLASI, the PASI, the DSSI and many other clinical instruments depend heavily on the assessment of erythema when activity of the diseases is measured. This is quite reasonable since erythema is a prominent symptom that is easily recognized by patients and physicians alike; other symptoms like minor scaling and non-scarring diffuse alopecia may escape notice more easily. Physiologically, erythema is one of the most clear-cut symptoms of disease activity because it is a direct reflection of the hyperemia, which accompanies inflammation, and it can be assessed on black skin. Lahti et al. (1993) correlated the clinical assessment of erythema by the trained eye to assessment determined by a laser Doppler flowmeter, an erythema meter and a chromameter. Their findings indicate that visual assessments correspond well

with those determined by these objective techniques. Other studies using laser Doppler techniques and visual assessments of erythema have yielded similar results (Quinn et al., 1993).

7.2.2. Area

The area of skin involvement is an obvious reflection of the disease activity and the extent of the disease. Most often successful treatment will reduce the area involved as well as the erythema. Therefore, area measurements are frequently part of outcome instruments in dermatology. However, for the CLASI we have chosen to describe the extent of disease in terms of areas instead of percentage of BSA or number of lesions. This choice was based on the experiences with other scores like the SCORAD that heavily depend on assessment of the diseased skin area. Repeatedly, this assessment has been shown to be hard to reproduce (Charman and Williams, 2000; Charman et al., 1999; Tiling-Grosse and Rees, 1993). Area assessment is all the more difficult in LE, since as in guttate psoriasis, often only small areas of the skin are involved, making assessment of the proportion of skin involved even more difficult (Ramsay and Lawrence, 1991). An alternative to percentage assessment of BSA is lesion counting, which is most commonly used for acne. This approach is not suitable for two reasons. One, reliability of the lesion counting is not necessarily better than for surface area assessment (Lucky et al., 1996). Second, the nature of LE skin disease makes this approach difficult because the lesions have widely varying size and improvement of the skin condition may lead to large confluent lesions dividing into a number of smaller lesions, which would lead to a paradoxical score increase.

LE affects certain areas of the body more than others, since the disease develops primarily in photosensitive and thus visible areas. Discoid LE, for example, quite often only affects the head, but can be severely disfiguring and arguably more serious than SCLE, which may fade without scarring. The detailed description of the face and the scalp leads to an increase in weight assigned to the head. While this may be anatomically misleading, we feel that this detailed documentation of the lesions on the face reflects the patients' experience. For example, previous studies have shown that the extent and severity of inflammatory skin disease over the arms, legs and head seem to have a greater impact on patient experience than the extent and severity of disease over the trunk (Vardy et al., 2002). Thus, it seems that involvement of visible areas of the body causes greater impairment and therapeutic attention than that of hidden areas (Vardy et al., 2002; Williams, 1997). These results are in accordance with previous studies showing that social visibility of psoriasis is associated with higher impact on HRQL, while %BSA involvement is a poor indicator of psychological morbidity associated with skin disease (Krueger et al., 2001; Nichol et al., 1996). The weight placed on visible areas in the CLASI takes this disease-specific shift into account. Table 2 compares the results for our scores with the PASI and the rule of 9 s to estimate surface areas in relation to total BSA. The rule of 9 s is an established estimation of BSA. It is commonly used to determine either the extent of burns (Miller et al., 1991), or for calculating the dosage of therapy in dermatology (Long et al., 1998) or indeed to assess measures of extent in psoriasis (Ramsay and Lawrence, 1991). Table 2 was based on a theoretical maximum score and illustrates the proportion that different anatomical areas contribute to this score.

7.2.3. Separate measurements of disease activity and damage

The differentiation between activity and damage in our scores is unusual for dermatological scores,

Table 2
Contribution of body areas to the total score in different cutaneous outcome instruments

Area	CLASI (activity) (%)	CLASI (damage) (%)	PASI/ DSSI (%)	Rule of 9 (%)
Head	29	36	10	9
Breast	13	12	5	9
Abdomen	7	6	5	9
Back	13	12	10	18
Legs	13	12	40	36
Arms/ hands	13	12	30	18
Mucous membrane	7	6		

however, this distinction is established for scores of SLE, where these aspects are commonly separated. This separation leads to two separate scores results for each patient. We have chosen to calculate the score for activity and damage separately. Activity and damage are distinct aspects of the disease and the damage depends largely on the form of CLE present. Separating damage and activity makes both aspects easily quantifiable and assures that the CLASI is more reactive to therapy-induced changes of activity. In contrast, using one summary score may lead to paradoxically stable scores as the activity decreases and the damage becomes apparent. Thus, the score may remain the same, while the clinical picture changes completely.

7.2.4. Associated symptoms

Itch, pain and fatigue have been recorded separately on a visual 1–10 analogue scale by the patients. While itch and pain are relatively easy to associate with skin disease, it is hard to distinguish between fatigue caused by systemic disease and skin disease. Thus, there can be justified debate as to whether it is appropriate to measure it in this context. However, fatigue is a prominent symptom of patients who may have no other symptoms of systemic disease. Fatigue has also been specifically mentioned in the FDA background paper, and therefore we have recorded the level of fatigue for CLE evaluations. Also, fatigue has been shown to be a critical factor in determining HRQL among SLE patients (Hanly, 1997; Hochbert et al., 1990). Integration of these results is not easy though. The attempt to combine subjective patient outcomes and physician's assessment, as for the SCORAD, has been plagued with difficulties. Therefore, the SCORAD has abandoned the use of subjective patient outcomes in drug trials (Anon, 1993; Charman and Williams, 2000). Similarly, the Leicester score for atopic dermatitis distinguishes between recording of pruritus and the physician-administered skin score (Berth-Jones et al., 1995). Based on these precedents we have measured the results of the associated symptoms in terms of percentage change, as the most appropriate description (Farrar et al., 2003).

7.2.5. The Cutaneous LE Activity and Severity Index (CLASI)

As described above, the CLASI has two scores. It is designed as a table where the rows denote anatomical areas, while the columns score major clinical symptoms (see Fig. 1). The left side of the instrument describes the activity of the disease, while the right side describes the damage done by the disease. Activity is scored as a summary score of erythema, scale/hypertrophy, mucous-membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. Patients are asked whether dyspigmentation due to CLE lesions usually remains visible for more than 12 months, which is taken to be permanent. If so, the dyspigmentation score is doubled. The scores are calculated by simple addition based on the extent of the symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom. The subjective symptoms documented by the patient like itch, pain and fatigue are recorded separately on visual 1–10 analogue scales. These symptoms can be important for the assessment of therapeutic success because they can be more reactive than the visual skin to therapeutic improvement.

7.2.6. Validation of the CLASI

The validation of the CLASI is described in detail elsewhere (Albrecht et al., 2005). This process has confirmed content validity. Construct validity is assessed by comparing the instrument to the other outcome instruments for cutaneous lupus. These do not exist, but the measures used in the SLE instruments available correlate with the CLASI. We did not assess criterion validity because the reason for the development of the instrument was that there was no measurement available. Reliability studies demonstrated an intraclass correlation coefficient (ICC) for inter-rater reliability of 0.86 for the activity score [95% confidence interval (CI) 0.73–0.99] and of 0.92 for the damage score (95% CI 0.85–1.00). The Spearman's Rho for intra-rater reliability for the activity score was 0.96

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity **damage**

Extent

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

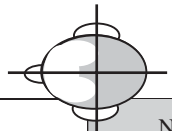
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Figure 1. Cutaneous LE Disease Area and Severity Index (CLASI).

(95% CI 0.89–1.00) and for the damage score Spearman's Rho was 0.99 (95% CI 0.97–1.00). Currently, we are conducting a clinical study to demonstrate clinical responsiveness of the CLASI on 10 patients who are started on a new treatment. During this observational study we correlate treatment response as measured with the CLASI with a 0–10 visual analogue scale measurements of pain, itch and fatigue by the patients, and assessment of skin health by the patients and the physician. In addition, the patients are photographed and the skin is assessed by an independent observer. Preliminary analysis of the first half of the patients shows that the CLASI reflects treatment success and demonstrates clinical responsiveness, but remains unchanged if the treatment fails.

Conclusion

This chapter is part of a book on autoimmune diseases and the skin. The development of two skin-specific outcome instruments for autoimmune diseases within 1 year is an important step forward. However, this small step only makes painfully clear that these instruments are lacking for all the other diseases discussed in this book. We hope that this discussion and the workshop will motivate others to extend the range of instruments available to more of cutaneous autoimmune diseases and that these instruments will be used frequently. It is important to note that from the beginning the development of a new outcome instrument for a disease must be an interactive process in as broad a disease community as possible. The experience with SLE illustrates that a large community can develop a variety of instruments. This abundance makes the comparison of clinical trials more difficult and limits the experience with each instrument. To avoid this, an open and interactive development process is needed.

Key points

- Without adequate outcome instruments, clinical research and therapeutic advances cannot be achieved.
- Cutaneous autoimmune diseases need outcome instruments that are skin specific.
- There is a body of experience on which the design and validation of cutaneous outcome instruments can be based.
- New outcome instruments need to be thoroughly evaluated in multiple stages to define their usefulness and biometric properties.
- Ideally, one outcome instrument is used as the basis for clinical research in any disease to allow standardization and comparability of clinical research.
- There are few outcome instruments for cutaneous autoimmune diseases, except the CLASI for CLE and the DSSI for DM and even these two instruments have not been fully evaluated.
- More instruments should be developed for cutaneous autoimmune diseases.
- Their development should be an open and interactive process within the disease community in order to avoid the development of scores that do not reach broad acceptance and the parallel development of more than one instrument.

Acknowledgement

This research was supported by NIH K24-AR 02207 (VPW) and a research training grant in dermatology NIH 2T32-AR-007465 (JA).

References

Albrecht, J., Taylor, L., Berlin, J., et al. 2005. The CLASI (Cutaneous LE Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus Erythematosus. J. Invest Dermatol. 125, 889.

Anon. 1993. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European task force on atopic dermatitis. Dermatology 186, 23.

Anon. 2003, Concept Paper Systemic Lupus Erythematosus.

Berth-Jones, J., Thompson, J., Graham-Brown, R.A. 1995. Evening primrose oil and atopic eczema. Lancet 345, 520.

Bohan, A., Peter, J.B. 1975. Polymyositis and dermatomyositis (first of two parts). New Engl. J. Med. 292, 344.

Bombardier, C., Gladman, D.D., Urowitz, M.B.etal. 1992. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum. 35, 630.

Carr, A.J., Higginson, I.J. 2001. Are quality of life measures patient centred?. BMJ 322, 1357.

Carrol, C.L., Lang, W., Snively, B. et al. Development and Validation of the Dermatomyositis Skin Severity Index (DSSI). In press.

Charman, C., Williams, H. 2000. Outcome measures of disease severity in atopic eczema. Arch. Dermatol. 136, 763.

Charman, C.R., Venn, A.J., Williams, H.C. 1999. Measurement of body surface area involvement in atopic eczema: an impossible task? Br. J. Dermatol. 140, 109.

Cohen, J.B. 2002. Cutaneous involvement of dermatomyositis can respond to Dapsone therapy. Int. J. Dermatol. 41, 182.

el Azhary, R.A., Pakzad, S.Y. 2002. Amyopathic dermatomyositis: retrospective review of 37 cases. J. Am. Acad. Dermatol. 46, 560.

Euwer, R.L., Sontheimer, R.D. 1993. Amyopathic dermatomyositis:a review. J. Invest Dermatol. 100, 124S.

Farrar, J.T., Berlin, J.A., Strom, B.L. 2003. Clinically important changes in acute pain outcome measures: a validation study. J. Pain Symptom Manage. 25, 406.

Faust, H.B., Gonin, R., Chuang, T.Y., et al. 1997. Reliability testing of the dermatology index of disease severity (DIDS). An index for staging the severity of cutaneous inflammatory disease. Arch. Dermatol. 133, 1443.

Finlay, A.Y. 1996. Measurement of disease activity and outcome in atopic dermatitis. Br. J. Dermatol. 135, 509.

Gladman, D.D., Urowitz, M.B., Ong, A., et al. 1996. A comparison of five health status instruments in patients with systemic lupus erythematosus (SLE). Lupus 5, 190.

Hanly, J.G. 1997. Disease activity, cumulative damage and quality of life in systematic lupus erythematosus: results of a cross-sectional study. Lupus 6, 243.

Hay, E.M., Bacon, P.A., Gordon, C., et al. 1993. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q. J. Med. 86, 447.

Hochbert, M.C., Engel, E.W., Pruitt, A., et al. 1990. Correlations of disease activity with physical disability in SLE. Arthritis Rheum. 222, S33.

Isenberg, D.A., Allen, E., Farewell, V., et al. 2004. International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease. Rheumatology (Oxford) 43, 49.

Krueger, G., Koo, J., Lebwohl, M., et al. 2001. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch. Dermatol. 137, 280.

Kunz, B., Oranje, A.P., Labreze, L., et al. 1997. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 195, 10.

Lahti, A., Kopola, H., Harila, A., et al. 1993. Assessment of skin erythema by eye, laser Doppler flowmeter, spectroradiometer, two-channel erythema meter and Minolta chromameter. Arch. Dermatol. Res. 285, 278.

Liang, M.H., Socher, S.A., Larson, M.G., et al. 1989. Reliability and validity of six systems for the clinical assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum. 32, 1107.

Long, C.C., Mills, C.M., Finlay, A.Y. 1998. A practical guide to topical therapy in children. Br. J. Dermatol. 138, 293.

Lovell, D.J., Lindsley, C.B., Rennebohm, R.M., et al. 1999. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies. II. The Childhood Myositis Assessment Scale (CMAS): a quantitative tool for the evaluation of muscle function. The Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Arthritis Rheum. 42, 2213.

Lucky, A.W., Barber, B.L., Girman, C.J., et al. 1996. A multirater validation study to assess the reliability of acne lesion counting. J. Am. Acad. Dermatol. 35, 559.

Miller, F.W., Rider, L.G., Chung, Y.L., et al. 2001. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatology (Oxford) 40, 1262.

Miller, S.F., Finley, R.K., Waltman, M., et al. 1991. Burn size estimate reliability: a study. J. Burn Care Rehabil. 12, 546.

Nichol, M.B., Margolies, J.E., Lippa, E., et al. 1996. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. Pharmacoeconomics 10, 644.

O'Quinn, S.E., Cole, J., Many, H. 1972. Problems of disability and rehabilitation in patients with chronic skin diseases. Arch. Dermatol. 105, 35.

Oranje, A.P., Stalder, J.F., Taieb, A., et al. 1997. Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. ETAC Study Group. Early Treatment of the Atopic Child. Pediatr. Allergy Immunol. 8, 28.

Parodi, A., Massone, C., Cacciapuoti, M., et al. 2000. Measuring the activity of the disease in patients with cutaneous lupus erythematosus. Br. J. Dermatol. 142, 457.

Quinn, A.G., McLelland, J., Essex, T., et al. 1993. Quantification of contact allergic inflammation: a comparison of existing methods with a scanning laser Doppler velocimeter. Acta Derm.Venereol. 73, 21.

Ramsay, B., Lawrence, C.M. 1991. Measurement of involved surface area in patients with psoriasis. Br. J. Dermatol. 124, 565.

Rider, L., Lachenbruch, P.A., Rennebohm, R.M., et al. 1995. Identifying skin lesions in dermatomyositis (DM): Inter-rater reliability of a new cutaneous assessment tool (CAT). Arthritis. Rheum. 38 (Suppl.), S168.

Rider, L.G., Feldman, B.M., Perez, M.D., et al. 1997. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: I. Physician, parent, and patient global assessments. Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Arthritis Rheum. 40, 1976.

Rider, L.G., Giannini, E.H., Brunner, H.I., et al. 2004. International consensus on preliminary definitions of improvement in adult and juvenile myositis. Arthritis Rheum. 50, 2281.

Sontheimer, R.D. 1999. Cutaneous features of classic dermatomyositis and amyopathic dermatomyositis. Curr. Opin. Rheumatol. 11, 475.

Sontheimer, R.D. 2002. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J. Am. Acad. Dermatol. 46, 626.

Sontheimer, R.D., Provost, T.T. 2003. In: R.L. Euwer, R.D. Sontheimer (Eds.), Cutaneous Manifestation of Rheumatic Diseases. Lippincott Williams & Wilkins, Philadelphia.

Streiner, D.L., Norman, G.R. 1995. Health Measurement Scales. a Practical Guide to their Development and Use. Oxford University Press, Oxford.

Tebbe, B., Orfanos, C.E. 1997. Epidemiology and socioeconomic impact of skin disease in lupus erythematosus. Lupus 6, 96.

Tiling-Grosse, S., Rees, J. 1993. Assessment of area of involvement in skin disease: a study using schematic figure outlines. Br. J. Dermatol. 128, 69.

Urowitz, M.B., Gladman, D.D., Tozman, E.C., et al. 1984. The lupus activity criteria count (LACC). J. Rheumatol. 11, 783.

Vardy, D., Besser, A., Amir, M., et al. 2002. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. Br. J. Dermatol. 147, 736.

Vlachoyiannopoulos, P.G., Karassa, F.B., Karakostas, K.X., et al. 1993. Systemic lupus erythematosus in Greece. Clinical features, evolution and outcome: a descriptive analysis of 292 patients. Lupus 2, 303.

Whiting-O'Keefe, Q.E., Stone, J.H., Hellmann, D.B. 1999. Validity of a vasculitis activity index for systemic necrotizing vasculitis. Arthritis Rheum. 42, 2365.

Williams, H. 2003. "Objective" measures of atopic dermatitis severity: in search of the holy Grail. Arch. Dermatol. 139, 1490.

Williams, H.C. 1997. Is a simple generic index of dermatologic disease severity an attainable goal? Arch. Dermatol. 133, 1451.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 16

Capillaroscopy: Which is Its Role in the Diagnosis of Connective Tissue Diseases?

Maurizio Cutolo[a,*], Carmen Pizzorni[a], Maria Elena Secchi[a], Alessandro Calvia[a], Alberto Sulli[a], Marco Matucci Cerinic[b]

[a]*Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, San Martino Hospital, Genova, Italy*
[b]*Division of Rheumatology, University of Florence, Italy*

1. Microvascular involvement

Diffuse endothelial cell dysfunction (ECD) documented by several techniques occurs commonly in adult and childhood systemic vasculitis (Bacon, 2005). Similar ECD is also seen in connective tissue diseases (CTDs). The mechanisms probably relate to inflammatory cytokines such as tumour necrosis factor (TNF). The particular role of vasculitic, as opposed to synovial or internal organ inflammation, may be release of secondary mediators directly into the blood stream—where they can reach distant endothelial beds to induce this diffuse ECD.

CTDs are the most important organic causes of Raynaud's phenomenon (RP), and systemic sclerosis is the most frequent one. Careful history taking and clinical examination eventually lead to further investigations where capillaroscopy and specific autoantibodies tests have the best performances to reach diagnosis (Guilmot et al., 1998).

Our understanding of local regulation of blood flow has been improved by the discovery of new neuromediators and local substances derived from endothelium. These compounds have direct implications for medical therapy and represent new hopes for the treatment of RP which, however, remains difficult and incomplete for most patients. Visualization of the skin capillary bed, i.e. capillaroscopy, was recently improved by the emergence of flexible videomicroscopes (videocapillaroscopy) easily allowing the exploration of the whole body skin surface and not only the classical site of the nailfold (Cutolo et al., 2003) (Fig. 1). 'In vivo' morphologic evaluation of skin capillaries is generally performed at the nailfold because that area is easily accessible for examination and here the major axis of the capillaries is parallel to the skin surface, while in other areas it appears in a perpendicular state (Cutolo et al., 2005).

2. Raynaud's phenomenon

Microvascular involvement represents a key feature of RP and several rheumatic diseases are characteized by the presence of the RP (Fig. 2). Generally, according to population-based surveys of various ethnic groups, the prevalence of primary RP is approximately 3–5% and geographic

*Corresponding author.
Research Laboratory and Division of Rheumatology, Department of Internal Medicine, University of Genova, San Martino Hospital, Viale Benedetto xv, 6, 16132 Genova, Italy.
Tel.: +39-010-353-7994; Fax: +39-010-353-8885.
E-mail address: mcutolo@unige.it (M. Cutolo).

DOI: 10.1016/S1571-5078(05)05016-6

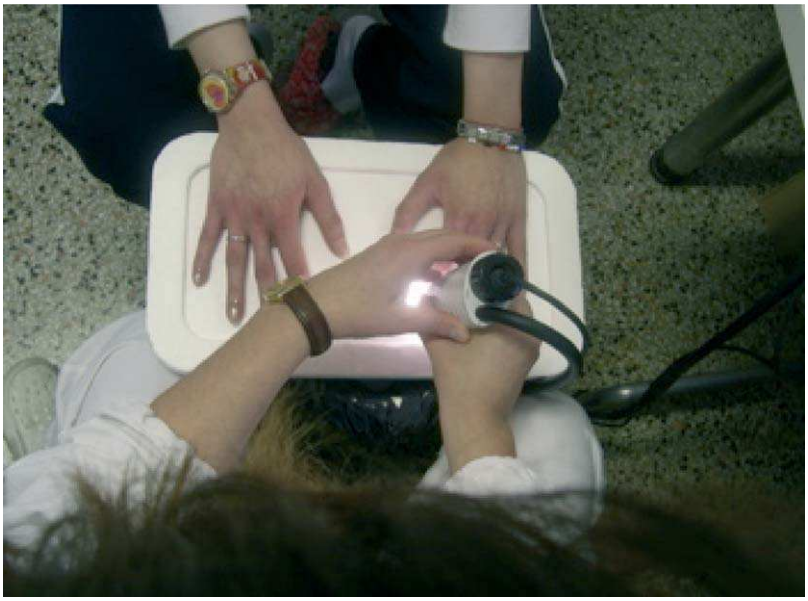


Figure 1. The videocapillaroscopic analysis.

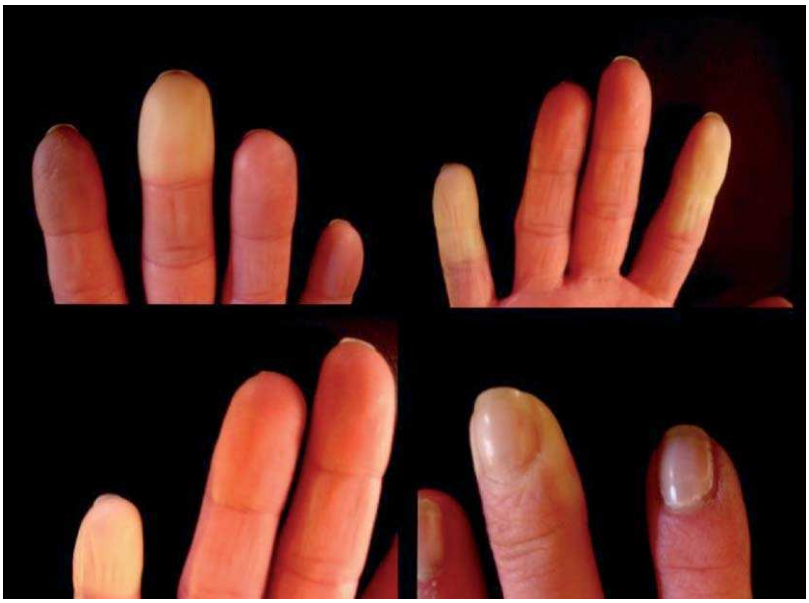


Figure 2. The Raynaud's phenomenon.

variations in prevalence reflect differences in climate (Silman et al., 1990; Maricq, 1997).

RP is the earliest and most common clinical manifestation of scleroderma (systemic sclerosis) as well is frequent in other CTDs such as systemic lupus erythematosus (SLE). Therefore, RP offers one of the best windows into the investigation of the early steps in the pathogenesis of systemic

sclerosis and generally CTD. The best technique currently available to study such an involvement is the: nailfold capillaroscopy. Clinical criteria have been suggested to distinguish between patients with uncomplicated, or primary RP, from those with secondary, CTD-associated RP.

The suggested criteria for primary RP include (Le Roy and Medsger, 1992) symmetric attacks

- the absence of tissue necrosis, ulceration or gangrene,
- the absence of a secondary cause (based on medical history and physical examination of the patient),
- a negative test for antinuclear antibodies,
- a normal erythrocyte sedimentation rate, and
- the presence of normal nailfold capillaries.

The mean age at the onset of primary RP is 14 years, with 27% of cases beginning at the age of 40 years or later (Planchon et al., 1994) On the contrary, a secondary cause of RP is suggested by different findings including (Kallenberg, 1990)

- age at onset of more than 30 years,
- episodes that appear intense, symmetric, painful and/or associated with ischemic skin lesions,
- clinical aspects suggestive of a CTD,
- presence of specific autoantibodies, and
- evidence of microvascular alterations as assessed by microscopy of nailfold capillaries.

Meta-analytic studies have shown that in patients with presumed primary RP, a secondary disorder developed in 12.6% , all but one of whom had a CTD (Spencer-Green, 1998).

On the contrary, nearly 15–20% of patients with RP who show autoantibodies, abnormalities of nailfold capillaries, or both, and who do not initially meet the criteria for a well-defined CTD ultimately will develop such disease within 2 years (Zuffery et al., 1992). It is now clear that subversion of the vascular tone, clinically evident as RP, is related to modification of the function of the endothelium. Recently, new advances on the mechanisms involved in the loss of vascular tone in RP have been identified.

3. The role of capillaroscopy in the early diagnosis of secondary RP

It is suggested that usually all fingers should be evaluated during the capillaroscopic analysis, however, the most accurate morphologic assessments are commonly performed at the 4th and 5th fingers, because of the greater transparency of the skin at these levels.

In normal conditions or in primary RP (excluding during the cold-exposure test) the normal nailfold capillaroscopic pattern shows a regular disposition of the capillary loops along with the nailbed (Grassi et al., 2001).On the contrary, in subjects suffering from secondary RP, one or more of peculiar capillaroscopic findings should alert the physician to the possibility of a CTD not yet detected. At this stage, the early detection of the following microvascular alterations allows the differential diagnosis between primary and secondary RP.

3.1. Giant capillaries

The presence of homogeneously and/or irregularly enlarged microvascular loops represents one of the earliest and striking features of the secondary RP (Fig. 3). These ectasias show a characteristic shape, which make them different with respect to those observed in other pathological conditions, such as diabetes mellitus and acrocyanosis. Capillaries with normal shape and diameter might coexist in most instances, together with enlarged or giant loops. Even the detection of a single loop with a circumscribed or homogeneous diameter $>50\,\mu m$ should be considered as a potential marker of microangiopathy related to an early scleroderma-spectrum disorder. It has been suggested that microvascular dilatation (enlarged/giant capillaries) represents a local autoregulatory response to tissue hypoxia (Colwell et al., 1979). In a recent study, enlarged capillaries have been found in 100% of SSc patients, 86% of patients affected by dermatomyositis (DM) and 56% of patients affected by undifferentiated connective tissue disease (UCTD).

3.2. Angiogenesis

A large range of different morphologic features of capillary neoformation may be observed in

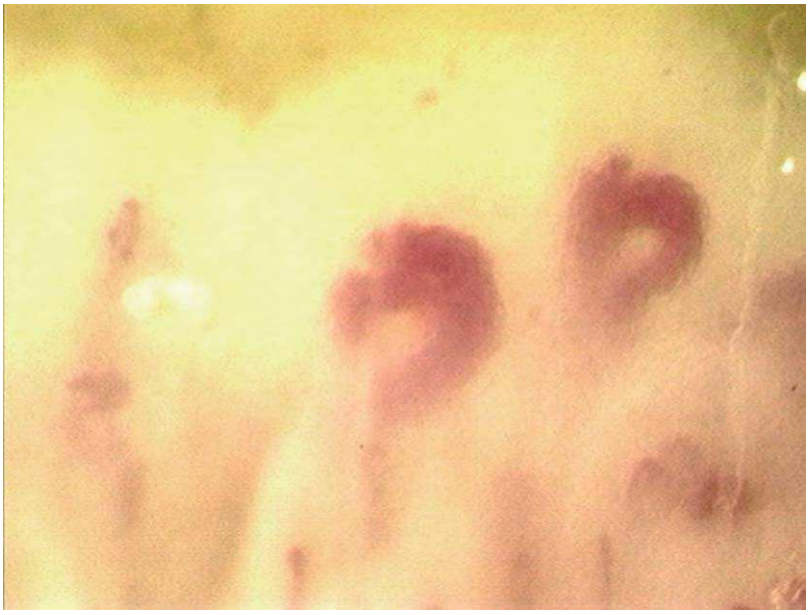


Figure 3. The giant (mega) capillaries.

patients with the secondary RP (Maricq et al., 1983). Highly tortuous and arborized capillary loop clusters, often surrounded by dropout of normal capillary loops are a characteristic feature of angiogenesis (Fig. 4). The main morphologic hallmark of angiogenesis is the clustering of tortuous capillaries with a pronounced shape heterogeneity, including thin or large meandering and bushy capillaries ramified capillaries. In addition coiled capillaries are the morphologic hallmark of angiogenesis in the elongated papillae of psoriatic plaque (Cutolo et al., 2005). These aspects are also frequently observed in the classical pattern of DM.

3.3. Architectural derangement of the nailfold microvascular network

As previously stated, the general architectural arrangement of skin microvascular bed is remarkably regular in healthy subjects. Nailfold capillaries at the level of the last row are characterized by uniform distribution, shape and diameter. Most capillaries show hairpin or U-shaped aspect. A striking modification of the normal architectural arrangement represents the early morphological feature in SSc. In addition, in patients with recent onset of RP, these changes may result in patchy, unilateral or limited in a single finger making important the early diagnosis.

3.4. Loss of capillaries and/or avascular areas

A decreased number of loops (<30 over 5 mm in the distal row of the nailfold) should be considered highly specific for secondary RP (Houtman et al., 1986). Loss of capillaries may result in critical tissue hypoxia. It has been estimated that the number of normal capillaries might be reduced to perhaps only 20 percent in Ssc patients (Jayson, 1984). The extensive disappearance of capillaries may generate large avascular areas with 'desert-like' appearance of the nailbed. In patients with even recent onset of the RP, the appearance of rapidly progressive capillary loss might represent the first dramatic capillaroscopic evidence of severe and progressive SSc. In fact, progressive loss of capillaries has been associated with more extensive skin involvement and with a poor prognosis (Chen et al., 1984).

Local microhaemorrhages (Fig. 5) are also associated with the early vascular damage and are characterized by a wide range of different morphological

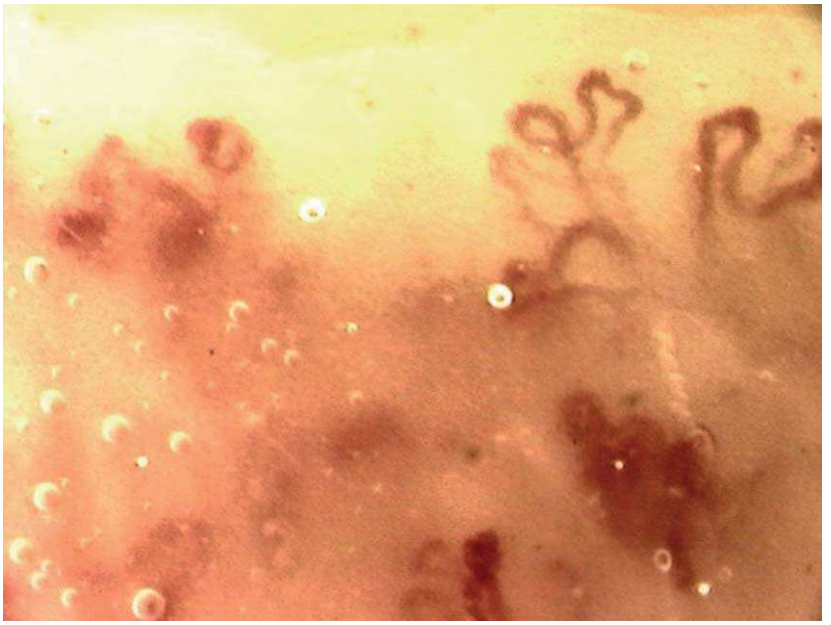


Figure 4. The angiogenesis.

presentation. Finally, enlarged loops, architectural disorganization, loss of capillaries, haemorrhages, angiogenesis and avascular areas characterize more than 95% of patients with overt SSc (Fig. 6). Therefore, the term 'scleroderma pattern' includes all together these sequential capillaroscopic changes typical of the microvascular involvement in SSc and represent an important diagnostic criterium (Bombardieri et al., 2003). The capillaroscopic aspects observed in DM and UCTD are generally reported as 'scleroderma-like pattern'.

In conclusion, the presence of even a single of the above microvascular alterations indicate the presence of a secondary RP and a CTD must be diagnosed.

4. The most common capillaroscopic patterns and the connective tissue diseases

4.1. Scleroderma and scleroderma-like

The presence of megacapillaries (giant capillaries) and a decreased capillary density are the hallmarks of the scleroderma capillary pattern, and have been detected by nailfold capillaroscopy. In a large recent study, 166 patients with RP, 65 cases with UCTD, 47 patients with SLE, 26 patients with dermato/polymyositis, 14 with rheumatoid arthritis, seven cases with primary Sjogren's syndrome and 102 patients with systemic sclerosis were investigated (Nagy and Czirjak, 2004).

Of the 16 patients with diffuse cutaneous SSc and the 86 limited cutaneous SSc cases, 87.5% and 61.6% showed the scleroderma capillary pattern, respectively. Nine of the 65 (13.8%) cases with UCTD and 24 of the 186 (12.9%) cases with RP also exhibited the same pattern. Four of the 47 (8.5%) with SLE and seven of the 26 (26.9%) with DM, and no patients with rheumatoid arthritis or Sjogren's syndrome, exhibited the scleroderma capillary pattern. The conclusion is that the scleroderma capillary pattern is often present in systemic sclerosis and DM. Furthermore, patients with RP and UCTD may also occasionally exhibit this pattern. Therefore, capillaroscopy seems to be an useful tool for the early selection of those patients who are potential candidates for developing scleroderma spectrum disorders.

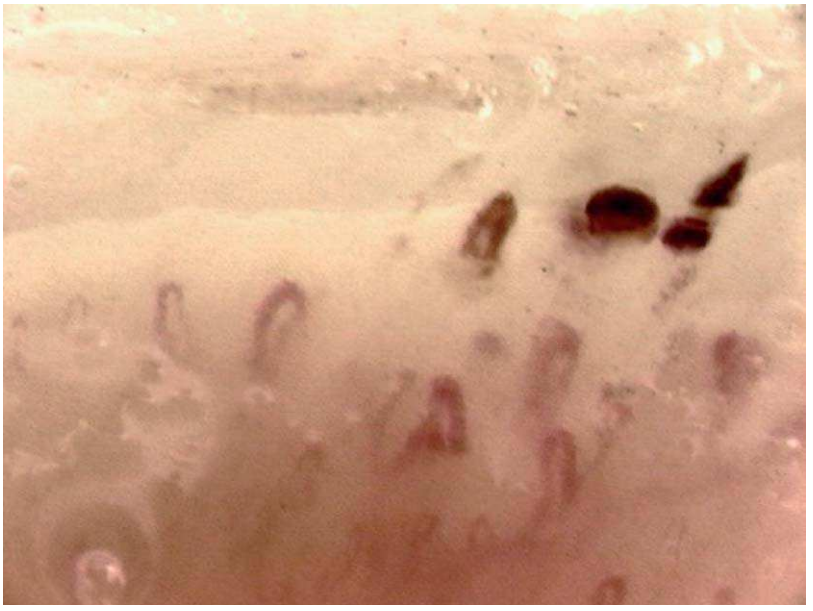


Figure 5. The microhaemorrhages.

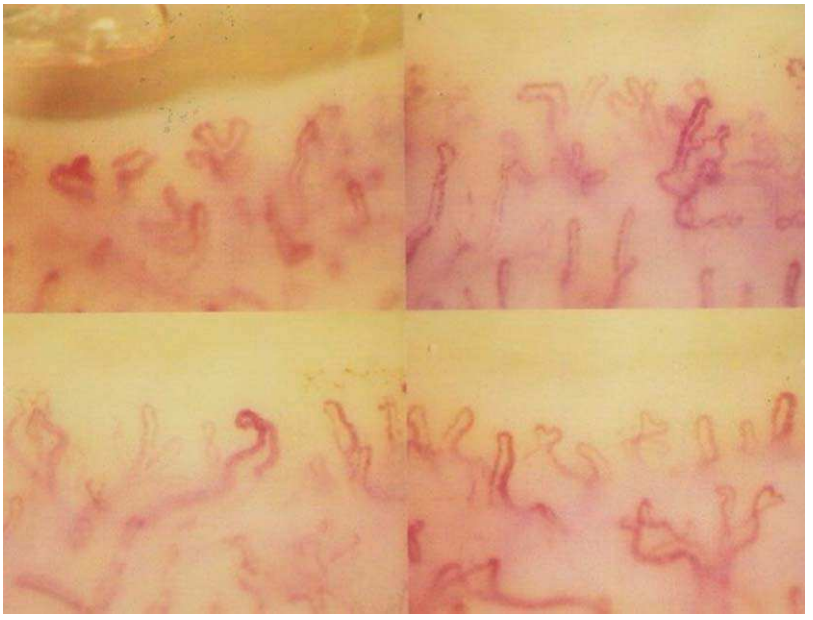


Figure 6. Avascular areas and architectural derangement.

In particular, a well-defined pattern has been reported in patients affected by DM (Klyscz et al., 1996). This pattern, often associated with classical aspects of the scleroderma pattern, includes the presence of two or more of the following findings in at least two nailfolds: enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, 'budding'

('bushy') capillaries, twisted enlarged capillaries and capillary haemorrhages (microbleeding). Typical SLE pattern includes morphological alterations of capillary loops, venular visibility and studying of blood with variability of capillary loop length (Candela et al., 1998).

A recent interesting study on scleroderma patients, investigated the relationship between some specific serum autoantibodies and the expression of the nailfolf video capillaroscopy (NVC) patterns in relation to the different subsets of skin involvement (limited and diffuse scleroderma) of the disease (Cutolo et al., 2004). The Scl70 positivity was found lower in patients showing the 'early' than in those with the 'active' and the 'late' NVC patterns, whereas no significant correlation was found between the Scl70 presence and both RP and SSc duration. The anticentromeric (ACA) positivity was found higher in patients showing the 'early' NVC pattern as well as in patients with longer disease duration. Therefore, the presence of the Scl70 antibodies seems related to a more rapid progression of the sclerodermic microangiopathy. On the contrary, the presence of ACA seems to be related to a slower progression of the SS microvascular damage. The sclerodermic peripheral microangiopathy is similar as in patients with limited systemic sclerosis, as in those affected by diffuse systemic sclerosis.

4.2. Systemic lupus erythematosus

In a recent study, 100 SLE patients were evaluated (Furtado et al., 2002). Widefield nailfold capillaroscopy was considered abnormal according to five criteria. Intercapillary distance, capillary width and capillary length were registered by videomorphometry in two fingers in 100 patients and in four fingers in 40 of these patients. Both, the presence of alterated capillaroscopy and the presence of scleroderma-pattern (SD-pattern), characterized by the presence of avascular areas and enlarged or giant loops, were associated with the isolated presence of RP ($P<0.001$) or anti-U1-RNP antibodies ($P<0.01$) as well as with the simultaneous presence of RP and anti-U1RNP antibodies ($P<0.001$). There was a negative association between the presence of ACL antibodies and SD-pattern ($P<0.05$). Higher figures for the videomorphometric parameters: capillary width, intercapillary distance and capillary length were observed in patients with RP. Patients presenting both RP and anti-U1-RNP antibodies showed higher figures for intercapillary distance and capillary width. This study demonstrated significant association between nailfold capillaroscopic abnormalities and either RP or anti-U1-RNP antibodies in SLE patients. The association of RP, anti-U1-RNP antibodies and 'scleroderma-like' findings on nailfold capillaroscopy (SD-pattern) in patients with SLE may suggest a new SLE subset with subclinical features of systemic sclerosis.

4.3. Antiphospholipid syndrome

Interesting microvascular alterations have been observed in patients affected by the antiphospholipid syndrome (APS). Studies in antiphospholipid patients evaluated the relationship between anti cardiolipin antibodies ACL (found in about 40–50% of patients suffering from SLE) and skin microcirculatory changes or vascular symptoms in 51 consecutive SLE patients (Bongard et al., 1995).

Twenty-two patients (43.1%) showed positive ACL (IgG 22 (5–60) GPL; IgM 5 (3–16.5) MPL; median titre and range) and 12 (54.5%) of them had abnormal capillaroscopic findings. On the contrary, among the 29 patients without ACL, only six (20.7%) showed an abnormal capillaroscopy ($P = 0.027$). There was no correlation between either ACL or capillaroscopy and RP. These results supported a relationship between ACL and nailfold capillary changes in patients with SLE, suggesting a direct damage of the vascular endothelium by ACL.

Another study, reported symmetrical microhaemorrhages at the nailfold analysis that were found particularly significant in patients showing the presence of both serum IgG and IgM ACL (Vaz et al., 2004). A marked microcirculatory damage was found related with the occurrence of thrombotic manifestations in the APS patients in other studies, confirming the pattern. A more

recent study confirmed that nailfold capillary morphology is altered in patients with APS, but these changes could not be correlated to the impairment of functional parameters (Sulli et al., 2000).

5. The most common capillaroscopic patterns for the diagnosis of secondary Raynaud: the scleroderma pattern

Previous investigations have partially characterized the morphological aspects of the vascular damage in patients with systemic sclerosis, as assessed by nailfold capillaroscopy, and two major patterns within the term of 'scleroderma pattern' have been recognized from the beginning: namely the 'active' and the 'slow' patterns (Maricq et al., 1980). However, more recently, attempts have been made in order to rate the capillary abnormalities in relation to selected characteristics of the disease progression, in order to improve the diagnostic and prognostic power of the capillaroscopic analysis (Cutolo et al., 2003).

In a more recent study, microvascular alterations as detected by capillaroscopy in patients with systemic sclerosis have been reclassified in three different patterns (Cutolo et al., 2000).

The patterns identified within the 'scleroderma pattern' include:

(1) '*Early*' pattern: few enlarged/giant capillaries, few capillary haemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries (Fig. 7).
(2) '*Active*' pattern: frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries, mild disorganization of the capillary architecture, absent or mild ramified capillaries (Fig. 8).
(3) '*Late*' pattern: irregular enlargement of the capillaries, few or absent giant capillaries and haemorrhages, severe loss of capillaries with extensive avascular areas, disorganization of the normal capillary array, ramified/bushy capillaries (Fig. 9).

These parameters, confirmed previous observations, indicating enlarged and giant capillaries, together with microhaemorrhages as the earliest capillaroscopic finding in scleroderma (Maricq et al., 1980; Jayson, 1984). In the late stage of the disease these abnormalities become rare.

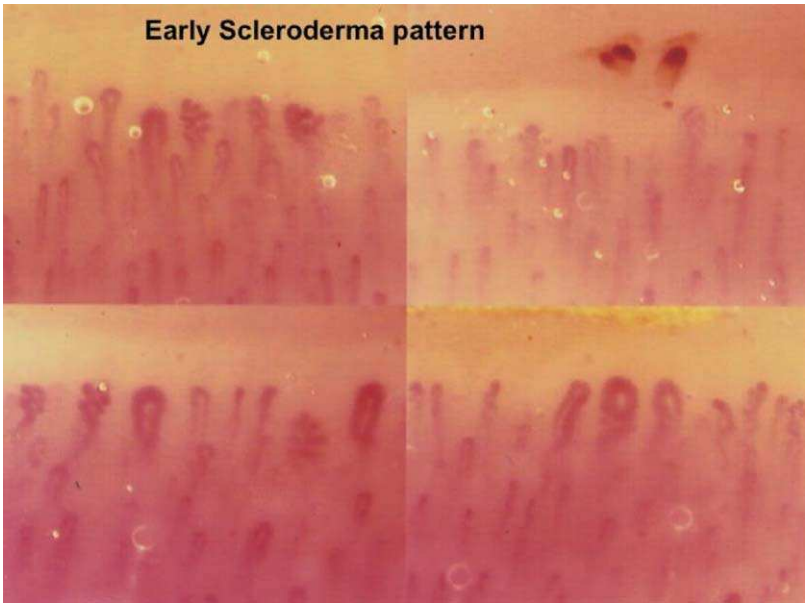


Figure 7. The early scleroderma pattern.

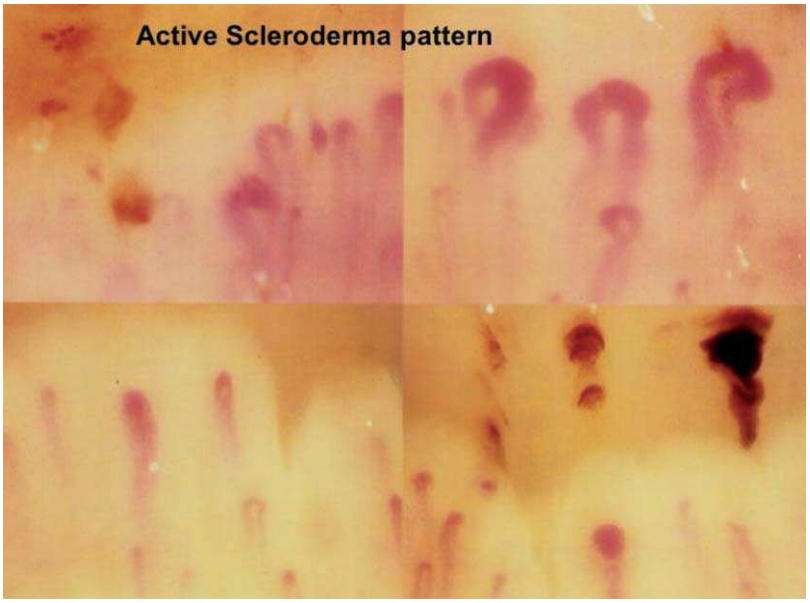


Figure 8. The active scleroderma pattern.

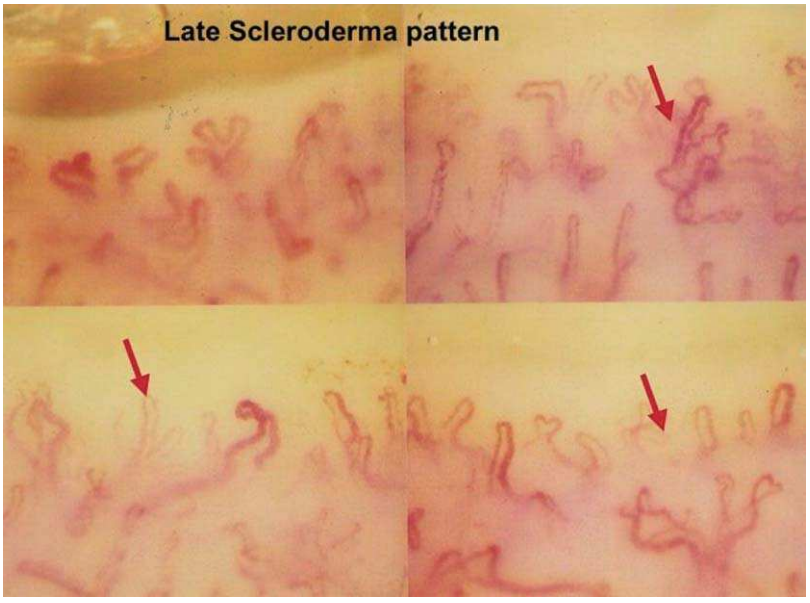


Figure 9. The late scleroderma pattern.

However, as already reported by other authors, the early stage is also characterized by microvessels with normal diameter coexisting with few enlarged capillaries that must be carefully investigated on all the fingers, by considering the limited number of these nailfold changes during early phases of the disease (Bollinger and Fagrell, 1990). Conversely, these changes are strongly increased in scleroderma patients with an 'active' pattern. Loss of capillaries, together with vascular architectural

disorganization and ramified capillaries were found to be rare in the early stages of systemic sclerosis, whereas they seem to increase with the progression of the fibrotic phase of the disease ('active' and 'late' patterns).

A significant and gradual increase of these latter vascular abnormalities is observed during the scleroderma progression and the three capillaroscopic patterns have been found to correlate with both RP and systemic sclerosis duration, reflecting at least the possible evolution of the disease process (Cutolo et al., 2000).

Key points

- RP is the most common and significant clinical condition suggesting as soon as possible a capillaroscopic analysis. The capillaroscopic patterns allow the early differential diagnosis between primary and secondary RP. Architectural disorganization, haemorrhages, enlarged loops, loss of capillaries, angiogenesis and avascular areas characterize classical capillaroscopic alterations.
- The presence even of a single of the above microvascular alterations indicate the presence of a secondary RP and a connective tissue disease must be searched.
- Systemic sclerosis capillaroscopic alterations have been reclassified into three different 'scleroderma' patterns (early, active, late).
- The capillaroscopic aspects observed in dermatomyositis and in the undifferentiated connective tissue disease are generally reported as 'scleroderma-like pattern'.

References

Bacon, P.A. 2005. Endothelial cell dysfunction in systemic vasculitis: new developments and therapeutic prospects. Curr. Opin. Rheumatol. 17, 49.

Bollinger, A., Fagrell Zurich, B. 1990. Collagen vascular disease and related disorders. In: Clinical Capillaroscopy. Hogrefe & Huber Publ., p. 121.

Bombardieri, S., Medsger, T.A., Jr., Silman, A.J., et al. 2003. The assessment of the patient with systemic sclerosis. Introduction. Clin. Exp. Rheumatol. 21 (Suppl. 22), S2.

Bongard, O., Bounameaux, H., Miescher, P.A., et al. 1995. Association of anticardiolipin antibodies and abnormal nailfold capillaroscopy in patients with systemic lupus erythematosus. Lupus 4, 142.

Candela, M., Pansoni, A., De Carolis, S.T., et al. 1998. Nailfold capillary microscopy in patients with antiphospholipid syndrome. Recent. Prog. Med. 89, 444.

Chen, Z.Y., Silver, R.M., Ainsworth, S.K., et al. 1984. Association between fluorescent antinuclear antibodies, capillary patterns, and clinical features in scleroderma spectrum disorders. Am. J. Med. 77, 812.

Colwell, J.A., Halusshka, P.V., Sarji, K.E., et al. 1979. Vascular disease in diabetes. Pathophysiological mechanisms and therapy. Arch. Intern. Med. 139, 225.

Cutolo, M., Grassi, W., Matucci Cerinic, M. 2003. Raynaud's phenomenon and the role of capillaroscopy. Arthritis. Rheum. 48, 3023–3030.

Cutolo, M., Sulli, A., Pizzorni, C., et al. 2000. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J. Rheumatol. 27, 155.

Cutolo, M., Pizzorni, C., Tuccio, M., et al. 2004. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. Rheumatology (Oxford) 43, 719.

Cutolo, M., Pizzorni, C., Sulli, A. 2005. Capillaroscopy. Best Pract. Res. Clin. Rheumatol. 19, 437.

Furtado, R.N., Pucinelli, M.L., Cristo, V.V., et al. 2002. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud's phenomenon in SLE patients. Lupus 11, 35.

Grassi, W., Medico, P.D., Izzo, F., Cerrini, C. 2001. Microvasucualr involvement in systemic sclerosis: capillaroscopic findings. Semin. Arthritis. Rheum. 30, 397–402.

Guilmot, J.L., Diot, E., Lasfargues, G., et al. 1998. Raynaud's phenomenon and connective tissue diseases. Rev. Prat. 48, 1647.

Houtman, P.M., Kallenberg, C.G.M., Fidler, V., et al. 1986. Diagnostic significance of nailfold capillary patterns in patients with RP: an analysis of patterns discriminating patients with and without connective tissue disease. J. Rheumatol. 13, 556.

Kallenberg, C.G. 1990. Early detection of connective tissue disease in patients with Raynaud's phenomenon. Rheum. Dis. Clin. North. Am. 16, 11.

Klyscz, T., Bogenschutz, O., Junger, M., et al. 1996. Microangiopathic changes and functional disorders of nail fold capillaries in dermatomyositis. Hautarzt 47, 289.

Le Roy, E.C., Medsger, T.A., Jr. 1992. Raynaud's phenomenon: a proposal for classification. Clin. Exp. Rheumatol. 10, 485.

Jayson, M.V. 1984. The microcirculation in systemic sclerosis. Clin. Exp. Rheumatol. 2, 85–91.

Maricq, H.R., Le Roy, E.C., D'Angelo, W.A., et al. 1980. Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis. Rheum. 23, 183.

Maricq, H.R., Harper, F.E., Khan, M.M., Tan, E.M., LeRoy, E.C. 1983. Microvascular abnormalities as possible predictors of disease subset in Raynaud's phenomenon and early connective tissue disease. Clin. Exp. Rheumatol. 1, 195–205.

Maricq, H.R., Carpentier, P.H., Weinrich, M.C., et al. 1997. Geographic variation in prevalence of Raynaud's phenomenon: a 5 region comparison. J. Rheumatol. 24, 879.

Nagy, Z., Czirjak, L. 2004. Nailfold digital capillaroscopy in 447 patients with connective tissue disease and Raynaud's disease. J. Eur. Acad. Dermatol. Venereol. 18, 62.

Planchon, B., Pistorius, M.A., Beurrier, P., et al. 1994. Primary Raynaud's phenomenon: age of onset and pathogenesis in a prospective study of 424 patients. Angiology 45, 677.

Silman, A., Holligan, S., Brennan, P., et al. 1990. Prevalence of symptoms of Raynaud's phenomenon in general practice. BMJ 301, 590.

Spencer-Green, G. 1998. Outcomes in primary Raynaud's phenomenon a meta-analysis and the frequency, rates, and predictors of transition to secondary disease. Arch. Intern. Med 158, 595.

Sulli, A., Pizzorni, C., Cutolo, M. 2000. Nailfold videocapillaroscopy abnormalities in patients with antiphospholipid antibodies. J. Rheumatol. 27, 1574.

Vaz, J.L., Dancour, M.A., Bottino, D.A., et al. 2004. Nailfold videocapillaroscopy in primary antiphospholipid syndrome (PAPS). Rheumatology (Oxford) 43, 1025.

Zuffery, P., Depairon, M., Chamot, A.M., et al. 1992. Prognostic significance of nailfold capillary microscopy in patients with Raynaud's phenomenon and scleroderma-pattern abnormalities: a six-year follow-up study. Clin. Rheumatol. 11, 536.

This page intentionally left blank

PART III:

Skin Manifestations in Vasculitides

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 17

Cutaneous Small Vessel Vasculitis including Urticarial Vasculitis

Manisha J. Patel*, Joseph L. Jorizzo
Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, USA

1. Cutaneous small vessel vasculitis

1.1. Introduction

Vasculitis refers to inflammation and necrosis of blood vessels, whether they are arteries, veins or both. It can be local or systemic, and may be primary or secondary to another disease process. The classic cutaneous manifestation of vasculitis is palpable purpura, however, the clinical manifestation greatly depends on the size of the vessel affected. Leukocytoclastic vasculitis is a pathologic description used to describe inflammation of post-capillary venules and is clinically more correctly termed cutaneous small vessel vasculitis (CSVV). The histopathologic pattern is that of a leukocytoclastic vasculitis — angiocentric, segmental inflammation with nuclear dust, endothelial cell swelling, and fibrinoid necrosis of blood vessel walls (Soter and Austen, 1978; Ekenstam and Callen, 1984; Lotti et al., 1996; Comacchi et al., 1998b).

1.2. Epidemiology

CSVV occurs equally in both sexes and at all ages (Lotti et al., 1996; Comacchi et al., 1998b). It is estimated that 10% of affected patients are children (Resnick and Esterly, 1985; Lynch, 1988). Prevalence numbers remain uncertain, however, given the lack of consensus on a classification schema. In 1990, the American College of Rheumatology (ACR) proposed criteria for the diagnosis of hypersensitivity vasculitis, which corresponds to CSVV, highlighted in Table 1. However, obvious problems in the schema exist. According to Lotti et al. (1998), these include the attempt to set an age limit, identify the causative drug, and codify the histologic findings. Given these limitations, a working classification has been proposed which attempts to address clinical and laboratory features in addition to underlying causes that is useful across various specialties. This schema is outlined in Table 2 (Jorizzo, 1993; Ghersetich et al., 1995). Despite this working classification, much of the epidemiologic data on vasculitis is limited by lack of a clear definition and diagnosis.

Table 1
American College of Rheumatology criteria for hypersensitivity vasculitis (1990) (Hunder et al., 1990)

1. Age at disease onset >16 years
2. Medication at disease onset
3. Palpable purpura
4. Maculopapular rash
5. Biopsy including arteriole and venule with histologic changes showing granulocytes in a perivascular or extravascular location

Note: At least three of five criteria must be present yielding a specificity of 83.9% and sensitivity of 71%.

*Corresponding author.
Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.
Tel.: +1-336-716-4735; Fax: +1-336-716-9258.
E-mail address: mapatel@wfubmc.edu (M.J. Patel).

DOI: 10.1016/S1571-5078(05)05017-8

Table 2
Proposed working classification of vasculitis (Ghersetich et al., 1995)

I. Cutaneous small-vessel vasculitis
- A. Idiopathic CSVV
- B. Henoch-Schönlein purpura
- C. Essential mixed cryoglobulinemia
- D. Waldenström's hypergammaglobulinemic purpura
- E. Associated with collagen vascular disease
- F. Urticarial vasculitis
- G. Erythema elevatum diutinum
- H. Rheumatoid nodules
- I. Reactive leprosy
- J. Septic vasculitis

II. Large-vessel necrotizing vasculitis
- A. Polyarteritis nodosa
  1. Benign cutaneous form
  2. Systemic form
- B. Granulomatous vasculitis
  1. Wegener's granulomatosis
  2. Allergic granulomatosis
  3. Lymphomatoid granulomatosis
- C. Giant cell arteritis
  1. Temporal arteritis
  2. Takayasu's disease
- D. Large-vessel vasculitis with collagen vascular disease
- E. Nodular vasculitis

1.3. Etiology

Most of the etiologic factors identified have been incriminated by association rather than by direct demonstration (Lotti et al., 1998). Table 3 reviews the major agents considered as precipitators of CSVV (Soter and Wolff, 1987; Lynch, 1988; Schifferli et al., 1989; Braun-Falco et al., 1991; Ryan, 1992; Lotti et al., 1996; Comacchi et al., 1998b). Lynch (1988) proposed that the frequency of viral or bacterial infections is probably underestimated. In up to 50–60% of patients no cause is identifiable (Lotti et al., 1998). Only three infectious agents have been found in the same pattern and in the same affected vessels as the corresponding antibodies, including streptococcal M protein, *Mycobacterium tuberculosis*, and hepatitis B surface antigen (Parish, 1971; Thorne et al., 1977; Gower et al., 1978). This information supports a causal relationship rather than a simple association.

CSVV has been reported in association with numerous coexistent diseases. These include

Table 3
Precipitating agents of CSVV (Lotti et al., 1998)

A. Infections
1. Bacterial
   - Group A β hemolytic *Streptococcus*
   - *Staphylococcus aureus*
   - *Mycobacterium leprae*
2. Viral
   - Hepatitis A, B, and C
   - Herpes simplex virus
   - Influenza virus
   - HIV/AIDS
3. Fungal
   - *Candida albicans*
4. Protozoan
   - *Plasmodium malariae*
5. Helminthic
   - *Schistosoma haematobium*
   - *Schistosoma mansoni*
   - *Onchocerca volvulus*

B. Drugs

Insulin	Penicillin
Hydantoins	Streptomycin
Aspirin	Sulfonamides
Thiazides	Phenothiazines
Vitamins	Phenylbutazone
Quinine	Streptokinase
Tamoxifen	Anti-influenza vaccine
Serum	Oral contraceptives

C. Chemical
- Insecticides
- Petroleum products

D. Foodstuff allergens
- Milk proteins
- Gluten

E. Idiopathic (50–60%)

Table 4
CSVV: association with coexistent diseases (Lotti et al., 1998)

Chronic disease
Systemic lupus erythematosus
Sjögren's syndrome
Rheumatoid arthritis
Behçet's disease
Hyperglobulinemic states
Cryoglobulinemia
Bowel bypass syndrome
Ulcerative colitis
Cystic fibrosis
Primary biliary cirrhosis
HIV seropositivity and AIDS
Malignant neoplasms
Lymphoproliferative disorders
Hodgkin's disease
Mycosis fungoides
Lymphosarcoma
Adult T-cell leukemia
Multiple myeloma
Solid tumors
Lung cancer
Colon carcinoma
Renal cancer
Prostate cancer
Head and neck cancer
Breast cancer

collagen vascular disease, inflammatory bowel disease, HIV/AIDS, and malignancy (Soter and Wolff, 1987; Jorizzo et al., 1988; Lynch, 1988; Braun-Falco et al., 1991; Ryan, 1992; Campanile and Lotti, 1995; Lotti et al., 1996; Comacchi et al., 1998a). Table 4 reviews the associated coexistent diseases.

The collagen vascular diseases most frequently associated with CSVV include: systemic lupus erythematosus (SLE), (Estes and Christian, 1971; Christian and Sergent, 1976; O'Loughlin et al., 1978; Dubois and Wallace, 1987; Chevalier et al., 1990; Belmont et al., 1996) Sjögren's syndrome (Lawley et al., 1979; Moutsopoulos et al., 1980; Talal et al., 1987), rheumatoid arthritis (Gray and Poppo, 1983; Nishikawa, 1983; Jorizzo and Daniels, 1983; Smith et al., 1989), and Behçet's disease (Levinsky and Lehner, 1978; Valesini et al., 1981; Jorizzo, 1986).

Sjögren's syndrome may be associated with CSVV in 20–30% of patients. Typically characterized by the triad of keratoconjunctivitis sicca, xerostomia, and positive rheumatoid factors, these patients may also be present with clinical lesions ranging from petechiae to widespread ecchymoses (Lawley et al., 1979; Moutsopoulos et al., 1980; Soter and Wolff, 1987; Talal et al., 1987; Lotti et al., 1996; Comacchi et al., 1998a).

Vasculitis associated with rheumatoid arthritis is more often seen in patients who are HLA-DR4 positive. In addition, patients with severe disease, high titer rheumatoid factor and nodules often have small to medium sized vessel involvement. Cutaneous lesions may include, petechiae, palpable purpura, nailfold infarcts/telangiectases, cutaneous ulceration, digital gangrene, and digital pulp papules (Bywater's lesions) (Gray and Poppo, 1983; Nishikawa, 1983; Jorizzo and Daniels, 1983; Soter and Wolff, 1987; Smith et al., 1989; Campanile and Lotti, 1995; Lotti et al., 1996; Comacchi et al., 1998a).

Behçet's disease is a multisystem polysymptomatic disease with unpredictable exacerbations and remissions (Arbesfeld and Kurban, 1988; Kaklamani et al., 1998; Sakane et al., 1999; Schirmer et al., 2001). Cutaneous findings range from sterile papulopustules and palpable purpura to erythema nodosum. Moschella (2003) showed, histologically, cutaneous lesion including oral and genital aphthosis show a leukocytoclastic (early) or lymphocytic (late) vasculitis. Confirmation of CSVV however is not included in the international study group criteria (1990) for the diagnosis of Behçet's disease.

1.4. Pathogenesis

The pathogenesis of vasculitis is a complex subject, not least because there are likely to be many different pathogeneses reflecting the many different causes. Mackel (1979, 1982) described circulating immune complexes in a large percentage of patients with CSVV. Factors that play a part in the pathogenesis of vasculitis include antigen—antibody-related mechanisms (including autoantibodies and immune complex disease), inflammatory cells,

Table 5
Theory of pathogenesis of CSVV (Modified from Klippel and Dieppe P.A., 1998)

Immune complexes interact with the complement system to generate C3a and C5a anaphylatoxins, which stimulate • Production of chemotactic factors which initiate chemotaxis of neutrophils • Release of vasoactive amines (such as histamine), which cause endothelial cell retraction • Release of proinflammatory cytokines (e.g., IL-1, TNF-α), which induce the expression of adhesion molecules (P- and E-selectin) in endothelial cells
Immune complexes deposit in vascular walls after histamine-induced endothelial retraction which increases selectin expression in endothelial cells Attracted neutrophils produce lysosomal enzymes in an attempt to engulf deposited immune complexes • Neutrophils are activated through Fc binding and degranulate, and also produce reactive oxygen species • Ultimate inflammation and 'bystander' fibrinoid necrosis of blood vessel walls

complement, cytokines, genetic influences, and the fibrinolytic system (Barham et al., 2004). Klippel and Dieppe (1998) proposed a theory about the pathogenesis of CSVV, which is depicted in Table 5.

1.5. Clinical manifestations

The typical primary skin lesion of CSVV is palpable purpura with lesions ranging in size from 1 mm to several centimeters (Figs. 1 and 2). The lesions arise as a simultaneous 'crop', resulting from the exposure to an inciting stimulus. Usually macular in the early stages, they may progress to wide array of lesions including, papules, nodules, vesicles, plaques, bullae, or pustules. Secondary finding include ulceration, necrosis, and post-inflammatory hyperpigmentation (Fig. 3). Other cutaneous findings include livedo reticularis, edema, and urticaria. Lesions most commonly occur on dependent areas, such as ankles and lower legs, or other areas prone to stasis (Ekenstam and Callen, 1984; Martinez-Taboada et al., 1997; Sais et al., 1998; Blanco et al., 1998).

Although normally asymptomatic, local symptoms may include pruritus, pain, or burning. Complaints of systemic symptoms, including fever, arthralgias, myalgias, anorexia, or gastrointestinal pain should raise the suspicion that a cutaneous vasculitis may be associated with a systemic vasculitis. In a study conducted by Ioannidou (2002) renal involvement in patients with CSVV led to the reclassification as Henoch-Schönlein purpura, microscopic polyangiitis, or Wegener's granulomatosus in 29–90 patients.

Cryoglobulinemia and chronic hepatitis C infection have been associated with chronic relapsing CSVV (Martinez-Taboada et al., 1997). The prognosis of isolated CSVV is generally quite good. A case series performed in a private practice by Ekenstam and Callen (1984) reported on 82 patients with CSVV, 51% of which had systemic

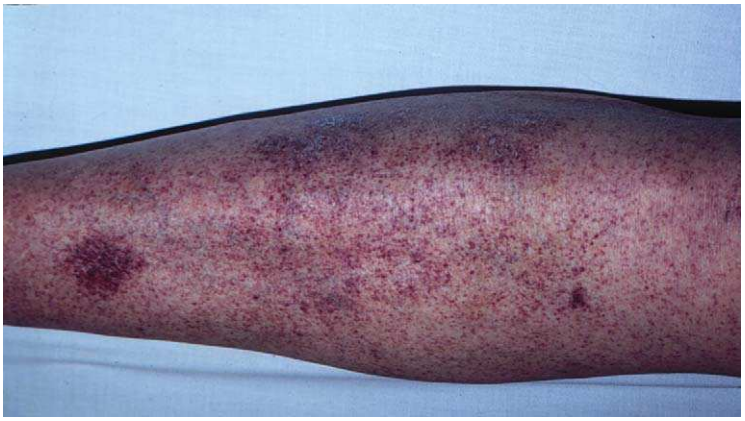


Figure 1. Cutaneous small vessel vasculitis. Note the purpura on the anterior aspect of the leg.

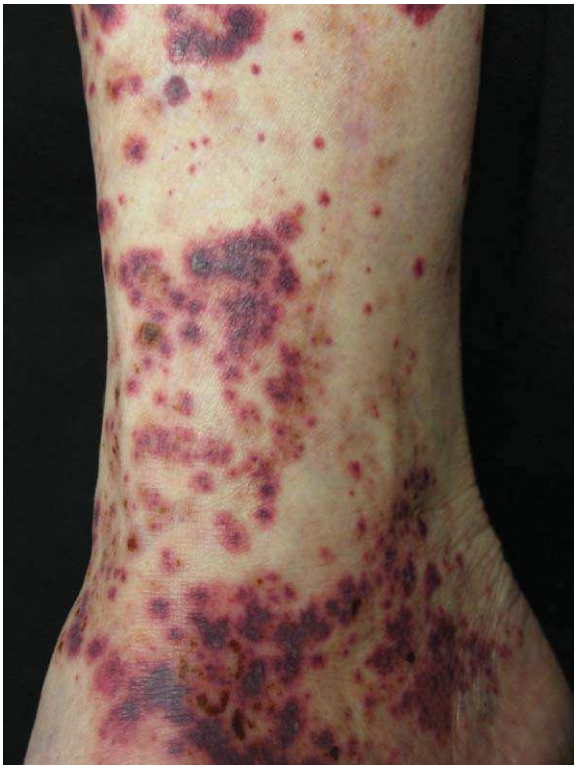


Figure 2. Cutaneous small vessel vasculitis. Palpable purpura and early central necrosis on the distal lower extremity. (Courtesy of Dr. Kelly Barham, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

involvement of one or more systems. Fifty-six percent had acute, 28% had chronic, and 16% had relapsing disease. Two point four percent of patients died which represented only patients with acute extensive systemic disease involvement. More recent studies performed in a referral center confirmed the benign nature of CSVV, however, 10% of patients were found to have systemic vasculitis (Martinez-Taboada et al., 1997).

1.6. Diagnostic investigations

A thorough history and physical examination is required for the correct diagnosis of CSVV. This should include screening tests for infections, connective tissue disease, medication usage, and cancer. Laboratory screening test are always required both to confirm the diagnosis and to determine the

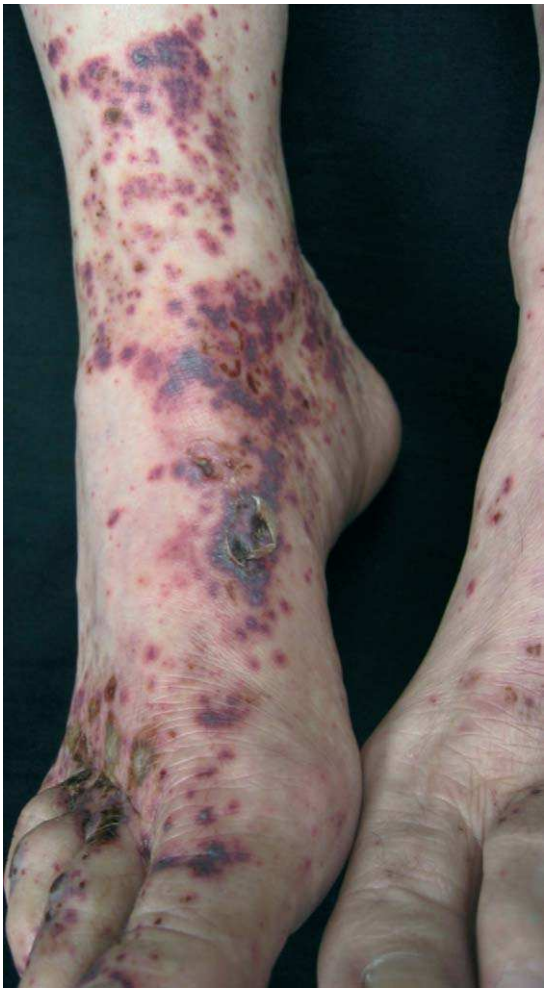


Figure 3. Cutaneous small vessel vasculitis. Central necrosis on the distal lower extremity. (Courtesy of Dr. Kelly Barham, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

etiology and possible extent of systemic disease. Vasculitides with systemic manifestations must be ruled out, as CSVV is diagnosed by exclusion. The necessary laboratory evaluations include histopathologic and occasionally immunofluorescent microscopic studies, blood tests, and urinalysis (Soter and Wolff 1987; Jorizzo et al., 1988; Lynch, 1988; Schifferli et al., 1989; Braun-Falco et al., 1991; Lotti et al., 1996, 1998; Comacchi et al., 1998a). Table 6 describes the evaluation of a patient with a suspected CSVV, highlighting the need to (1) make the clinical pathological correlation,

Table 6
Evaluation of patient with suspected CSVV (Barham et al., 2004; Lotti et al., 1998)

I. Confirm histopathological correlation
  A. Punch biopsy early lesion
  B. Incisional biopsy for suspected larger-vessel vasculitis

II. Assess the extent of the disease
  A. General
    1. Myalgia
    2. Arthralgia
    3. Fever
  B. Renal involvement (acute and chronic renal failure)
    1. Proteinuria
    2. Hematuria
  C. Nervous system
    1. Central or peripheral
    2. Diffuse or local findings
  D. Musculoskeletal involvement
    1. Non-erosive polyarthritis
  E. Gastrointestinal system
    1. Abdominal pain (colicky, nausea, vomiting, diarrhea)
    2. Gastrointestinal bleeding (melena or hematemesis)
  F. Pulmonary involvement
    1. Pleural effusion
    2. Pleuritis
    3. Hemoptysis
  G. Pericardial involvement (myocardial angiitis or pericarditis)
    1. Pericardial effusion
  H. Ocular involvement (retinal vasculitis)
    1. Conjunctivitis
    2. Keratitis

III. Attempt to establish etiology
  A. Infection
  B. Drugs
  C. Diseases associated with immune complexes
    1. Connective tissue/autoimmune disease (see Table 7)
    2. Malignancy
    3. Inflammatory bowel disease
  D. Idiopathic (50%)

(2) assess the extent of the disease, and (3) attempt to establish the etiology. Table 7 reviews screening laboratory abnormalities associated with autoimmune diseases in the work up for CSVV.

In attempting to determine etiology, specifically streptococcal infection as a cause, one should keep in mind that antistreptolysin (ASO) antibodies show a rapid rise in titers during acute infection followed by a peak within 2–3 weeks. If clinical suspicion remains high, one should consider checking anti-deoxyribonuclease B that remains positive longer.

The hallmark histopathologic pattern of CSVV is leukocytoclastic vasculitis. Their histology shows infiltration of neutrophils within and around blood vessel walls; leukocytoclasia (degranulation and fragmentation of neutrophils leading to the production of nuclear dust); fibrinoid necrosis of the damaged vessel walls; and necrosis, swelling, and proliferation of the endothelial cells (Figs. 4 and 5). However, the presence of leukocytoclasia is merely an expression of a significant neutrophilic infiltrate, which may also be found in nonvasculitic conditions involving the skin, such as in cutaneous infections or in Sweet syndrome (Gonzalez-Gay et al., 2005). Erythrocyte extravasation is another key feature. Old lesions of CSVV may no longer show leukocytoclastic vasculitis and may contain mainly lymphocytes and monocytes around blood vessels.

1.7. Differential diagnosis

It is important in the differential diagnosis of vasculitis to be aware of disorders that may present with livedo or infracted lesions secondary to occlusion disorders. These include cryoglobulinemic vasculitis, cholesterol embolization, Sneddon's disease, and malignant atrophic papulosis (Degos' disease). The major pathology in these is either initially occlusive or mediated by antiphospholipid antibodies and therefore falls into the category of microvascular occlusion.

Given the wide array of systemic diseases which can be associated with CSVV, it is important to carefully evaluate each patient for coexistent disease; keeping in mind that the first manifestation of large vessel vasculitis is often small vessel disease.

Table 7
Screening laboratory abnormalities associated with autoimmune diseases in the work up for CSVV

Laboratory test	Disease association	Findings
Direct immunofluorescence microscopy	Collagen vascular disease	IgG > IgM
	Henoch-Schönlein purpura	IgA
Complement level	Rheumatoid arthritis	Decreased C1, C4, C2
	Systemic lupus erythematosus	Decreased C1q, C4, C2, C3, factor B and C9
	Hypocomplementemic urticarial vasculitis	Anti-C1q precipitin and/or decreased C1
Anticardiolipin antibody lupus anticoagulant	Antiphospholipid antibody syndrome	IgG and/or IgM (measured by a standardized ELISA) for β2-glycoprotein I-dependent anticardiolipin antibodies and/or lupus anticoagulant activity the antibodies and/or activity should be found on two or more occasions, at least 6 weeks apart
Antineutrophil cytoplasm antibodies	Wegener's granulomatosis	c-ANCA

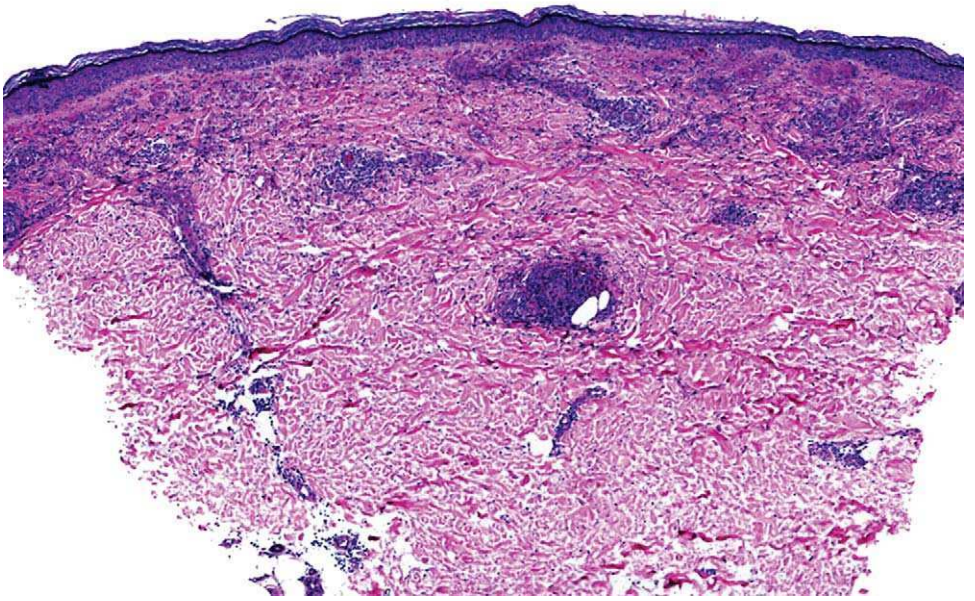


Figure 4. Leukocytoclastic vasculitis. Low-power photomicrograph showing perivascular infiltrates and fibrinoid deposits within the vessels of the upper dermis. (Courtesy of Dr. Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

1.8. Treatment

Treatment of CSVV is sometimes unnecessary as the disease is usually self-limiting. When possible, identification and removal of causative agents (e.g., infection, drug, chemicals, food) should be accomplished. Removal of an inciting agent is occasionally followed by rapid resolution of the lesions and no other treatment is indicated; otherwise local and systemic therapies are recommended (Sams, 1980; Soter and Wolff, 1987; Jorizzo et al., 1988; Lynch, 1988; Schifferli et al.,

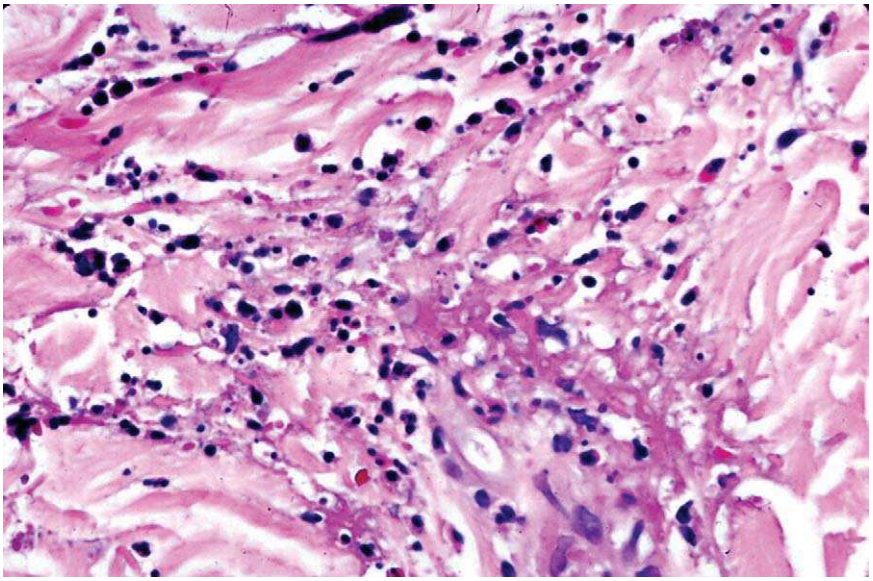


Figure 5. Leukocytoclastic vasculitis. Higher magnification demonstrates nuclear dust, fibrinoid deposits, vascular alteration, and collagen degeneration. (Courtesy of Dr. Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

1989; Chan et al., 1990; Habif, 1990; Braun-Falco et al., 1991; Ryan, 1992; Campanile and Lotti, 1995; Lotti et al., 1996; Comacchi et al., 1998a).

Local therapies are aimed at improving lower extremity circulation and relieve symptomatic complaints. Topical treatment (corticosteroid creams, calcineurin inhibitors, and antibiotic ointments) may be helpful in some patients however, there is no data to support their use (Barham et al., 2004). Gradient support stockings may also be useful as stasis changes often times compound the issue (Braun-Falco et al., 1991; Burge, 1991; Lotti et al., 1996; Comacchi et al., 1998a).

Systemic treatment is advised for patients with CSVV with significant systemic manifestations or those with significant cutaneous ulceration however almost no double-blind, placebo-controlled prospective trials exist (Lotti et al., 1998). Table 8 describes a therapeutic ladder for patients with CSVV (Barham et al., 2004).

Oral corticosteroids, prednisone at a dosage of 30–80 mg/day, tapered over 3–6 weeks often give effective symptom control. No controlled trials have been carried out to support the use in isolated CSVV, however, case series have shown benefit in cases with painful progressive cutaneous lesion.

Table 8
Therapeutic ladder for patients with CSVV (Modified from Lotti et al., 1998; Barham K.L. et al., 2004)

Skin lesions alone
Supportive therapy[a]
Antihistamines[a]
Non-steroidal anti-inflammatory drugs[b]
Pentoxiphylline[a]
Colchicine[c]
Dapsone[b]
Ulcerative skin lesions alone
Thalidomide[a]
Low-dose weekly methotrexate[a]
Prednisone[b]
Systemic disease
Prednisone[b]
Azathioprine[b]
Cyclophosphamide[b]
Mycophenolate mofetil[a]
Cyclosporine[a]
Interferon-α (if hepatitis C-associated)[c]
Intravenous gammaglobulin[a]
Extracorporeal immunomodulation[a]
Biologic agents – infliximab, etanercept (TNF-α inhibitors)[a]

[a] Case reports.
[b] Case series.
[c] Double-blind studies.

Rebound is a serious problem with rapid reduction of dose; therefore, a slow taper should be instituted. The risks of prednisone are well known and long-term use is rarely warranted (Lotti et al., 1998).

The neutrophil chemotaxis inhibitor colchicine failed to show benefit in a randomized controlled trial (Sais et al., 1995). Despite this recent study anecdotal evidence and open label studies have demonstrated effectiveness. The recommended dose is 0.6 mg tid. Gastrointestinal symptoms are the usual limiting factor. Benefits may be seen as early as 2 weeks after initiating therapy (Hazen and Michel, 1979; Callen, 1985; Plotnick et al., 1989; Lotti et al., 1998).

Similarly, dapsone in doses of 50–200 mg/day has anecdotally been reported to be effective in isolated cases of CSVV. Response may take several weeks and may be more advantageous when used in combination with colchicine (Lotti et al., 1998).

Nonsteroidal anti-inflammatory drugs such as acetylsalicylic acid and indomethacin in addition to antihistamines can be used to alleviate symptoms more than improving the actual lesions (Lotti et al., 1998).

Immunosuppressive agents, such as azathioprine (50–200 mg/day), cyclophosphamide (2 mg/kg/day or as monthly intravenous pulse), methotrexate (10–25 mg/week), and cyclosporine (3–5 mg/kg/day) have anecdotal evidence showing effectiveness in patients with a rapidly progressing course and systemic involvement that is controlled with corticosteroids (Jorizzo et al., 1988; Lynch, 1988; Habif, 1990; Lotti, 1991; Stadler and Ruszczak, 1995; Lotti et al., 1996; Comacchi et al., 1998a).

The mode of action of immunoglobulin is complex involving modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine network, provision of anti-idiotypic antibodies, and effects on the activation, differentiation, and effector functions of T- cells and B- cells. Currently only case reports are available to support its use in severe and refractory cases of CSVV (Mathieson et al., 1990; Ong and Benson, 2000).

The potential use of TNF-α inhibitors in systemic vasculitides is currently at the forefront of new treatment options available. TNF-α is known to play a crucial role in the establishment and maintenance of inflammation in multiple autoimmune and nonautoimmune disorders. A number of large placebo-controlled trials have shown TNF-α blockers as effective and well-tolerated treatment options in patients with Crohn's disease, rheumatoid and psoriatic arthritis, and psoriasis. So far, most case reports and case series have suggested favorable results with TNF-α inhibitor therapy in systemic lupus erythematosus (SLE), dermato- and polymyositis, giant cell arteritis, Churg–Strauss syndrome, Wegener's granulomatosis, and microscopic polyangiitis (Lamprecht, 2005). Results of randomized, placebo-controlled trials are eagerly awaited for several connective tissue diseases and systemic vasculitides.

2. Urticarial vasculitis

2.1. Introduction

Urticarial vasculitis (UV) is a chronic disorder consisting of episodic urticarial lesions lasting greater than 24 h that histologically manifest features of leukocytoclastic vasculitis. UV can be thought of as a subtype of CSVV. Two types of UV have been described: UV associated with hypocomplementemia and normocomplementemic UV.

2.2. Prevalence

Incidence and prevalence of UV is unknown. Of patients with urticarial lesions, roughly 5–10% have UV (Black, 1999; Wisnieski, 2000).

2.3. Epidemiology

In the hypocomplementemic type, UV is almost exclusively in women, while normocomplementemic UV has only a slight female predominance.

2.4. Etiology/pathogenesis

The mechanism of UV may be similar to that of CSVV with pronounced C5a-mediated mast cell

degeneration (Hannon and Swerlick, 2003). UV is strongly associated with connective tissue disease, infection, neoplastic processes, and drugs. Specifically these associations include:

- Autoimmune connective tissue disease: prevalence of 20% in SLE, and 32% in Sjögren's syndrome (Black, 1999)
- Infection: hepatitis B, hepatitis C, and Epstein-Barr virus
- Neoplasms: IgA multiple myeloma, IgM gammapathies, and colon carcinoma
- Drugs: potassium iodide, fluoxetine, and NSAIDs.

UV is thought to represent a type-III hypersensitivity reaction, as circulating immune complexes may be demonstrated in up to 75% of patients (Berg et al., 1988).

2.5. Clinical manifestations

The skin lesions in both the types of UV are similar, consisting of erythematous indurated wheals, angioedema, or macular erythema lasting more than 24 h (Fig. 6). Lesions often last for 3–5 days and heal with post-inflammatory hyperpigmentation. The wheals may contain purpuric foci. Patients may also present with livedo reticularis, nodules, and bullae.

Patients with the hypocomplementemic form may have extracutaneous manifestations such as fever, malaise, and myalgia as well as lymphadenopathy, hepatosplenomegaly, GI symptoms (abdominal pain with or without nausea and/or diarrhea), respiratory symptoms (laryngeal edema, dyspnea, chronic obstructive pulmonary disease (COPD)), and/or ocular involvement (conjunctivitis, episcleritis, and/or uveitis).

Although hypocomplementemic UV has features similar to SLE, signs such as ocular inflammation, angioedema, and COPD distinguish the two processes. Despite these distinguishing factors, clinicians must maintain a high index of suspicion for SLE, evaluating for a positive antinuclear antibody (ANA), positive lupus band test, and other clinical features supporting a diagnosis of SLE (Davis et al., 1998).

2.6. Diagnostic investigations

Hypocomplementemic UV is defined by the presence of anti-C1q precipitin and/or a decrease in the

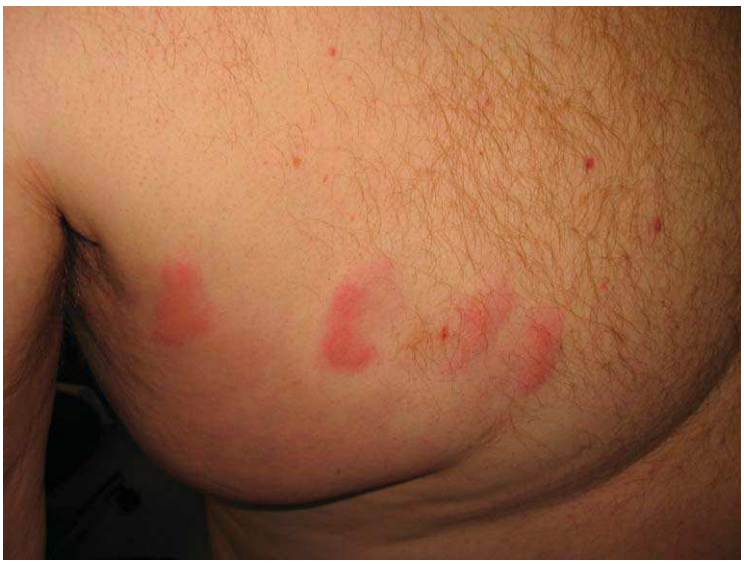


Figure 6. Urticarial vasculitis. Several erythematous urticarial plaques on the anterior chest.

level of C1 (Wisnieski et al., 1995; Wisnieski, 2000). Laboratory studies including C3, C4, ANA, and hepatitis C antibody help to establish extent of disease, exclude underlying disease and evaluate for SLE.

If urticarial lesions last for longer than 24 h then by definition they are not ordinary urticaria and a skin biopsy should be performed. Patients may complain of pain rather than itch and purpura may be visible.

Histologically, all UV lesions demonstrate leukocytoclastic vasculitis; however hypocomplementemic UV shows a larger number of interstitial neutrophils rather than eosinophils distinguishing it from normocomplementemic UV (Sanchez et al., 1982; Davis et al., 1998).

2.7. Differential diagnosis

Although all patients with hypocomplementemic UV have anti-C1q precipitin and/or a decrease in the level of C1, this process must be distinguished from SLE, which can show similar laboratory findings (Wener et al., 1989; Wisnieski and Jones, 1992). In addition, a biopsy will distinguish it from an atypical form of erythema multiforme.

2.8. Treatment

No single treatment is effective for all cases of UV, however, the majority of patients respond to systemic corticosteroids. Hydroxychloroquine sulfate, colchicine, dapsone, NSAIDs, or pentoxifylline may be useful as steroids sparing agents (Wisnieski et al., 1995; Nurnberg et al., 1995; Davis et al., 1998). For control of angioedema and urticaria like lesions, patients may also benefit from antihistamines.

Key points for CSVV

- Clinical: large spectrum of lesions ranging from purpura to palpable purpura, urticaria, or ulcers. Concentrated on dependent areas.
- Involves small vessels, post-capillary venules only.
- Histologically: leukocytoclastic vasculitis with a presumed immune complex-mediated pathogenesis.
- Extracutaneous involvement can occur; however it is unusual.

Key points for UV

- Clinical: Recurrent episodes of erythematous indurated wheals, angioedema, or macular erythema lasting more than 24 h.
- Two distinct groups of patients have been described with UV: those with or without associated hypocomplementemia.
- Histologically: leukocytoclastic vasculitis with a presumed immune complex-mediated pathogenesis.
- Extracutaneous involvement can include constitutional symptoms, arthritis, gastrointestinal, respiratory, or ocular involvement. Patient with hypocomplementemic type are more likely to have systemic involvement.
- Association disorders include autoimmune connective tissue diseases and viral infections.

References

Arbesfeld, S.J., Kurban, A.K. 1988. Behcet's disease. New perspectives on an enigmatic syndrome. J. Am. Acad. Dermatol. 19, 767.

Barham, K.L., Jorizzo, J.L., Grattan, B., Cox, N.H. 2004. Vasculitis and neutrophilic vascular reactions. In: T. Burns, et al. (Ed.), Rook's Textbook of Dermatology. Blackwell Publishing, Oxford, pp. 49.1–49.46.

Belmont, H.M., Abramson, S.B., Lie, J.T. 1996. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. Interactions of inflammatory cells and activated endothelium. Arthritis Rheum. 39, 9.

Berg, R.E., Kantor, G.R., Bergfeld, W.F. 1988. Urticarial vasculitis. Int. J. Dermatol. 27, 468.

Black, A.K. 1999. Urticarial vasculitis. Clin. Dermatol. 17, 565.

Blanco, R., Martinez-Taboada, V.M., Rodriguez-Valverde, V., et al. 1998. Cutaneous vasculitis in children and adults. Associated diseases and etiologic factors in 303 patients. Medicine (Baltimore) 77, 403.

Braun-Falco, O., Plewing, G., Wolff, H.H., et al. 1991. Dermatology. Springer, Berlin.

Burge, S. 1991. The management of cutaneous vasculitis. In: E. Panconesi (Ed.), Dermatology in Europe. Blackwell, Oxford, p. 328.

Callen, J.P. 1985. Colchicine is effective in controlling chronic cutaneous leukocytoclastic vasculitis. J. Am. Acad. Dermatol. 13, 193.

Campanile, G., Lotti, T. 1995. Clinical aspects of cutaneous necrotizing vasculitis. Int. Angiol. 14, 151.

Chan, L.S., Cooper, K.D., Rasmussen, J.E. 1990. Koebnerization as a cutaneous manifestation of immune complex-mediated vasculitis. J. Am. Acad. Dermatol. 22, 775.

Chevalier, X., Belmatoug, N., Kahn, M.F. 1990. Seronegative leukocytoclastic vasculitis preceding the onset of disseminated systemic lupus erythematosus. Rev. Rheum. Mal. Osteoartic. 57, 779.

Christian, C.L., Sergent, J.S. 1976. Vasculitis syndromes: clinical and experimental models. Am. J. Med. 61, 385.

Comacchi, C., Ghersetich, I., Lotti, T. 1998a. Vasculite necrotizzante cutanea. G. Ital. Dermatol. Venereol. 133, 23.

Comacchi, C., Ghersetich, I., Lotti, T. 1998b. Vasculite necrotizzante cutanea. G. Ital. Dermatol. Venereol. 133, 23.

Davis, M.D., Daoud, M.S., Kirby, B., et al. 1998. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. J. Am. Acad. Dermatol. 38, 899.

Dubois, E.L., Wallace, D.J. 1987. Clinical and laboratory manifestations of systemic lupus erythematosus. In: D.J. Wallace, E.J. Dubois (Eds.), Lupus Erythematosus. Lea & Febiger, Philadelphia, p. 317.

Ekenstam, E., Callen, J.P. 1984. Cutaneous leukocytoclastic vasculitis. Clinical and laboratory features of 82 patients seen in private practice. Arch. Dermatol. 120, 484.

Estes, D., Christian, C.L. 1971. The natural history of systemic lupus erythematosus by prospective analysis. Medicine (Baltimore) 50, 85.

Ghersetich, I., Jorizzo, J.L., Lotti, T. 1995. Working classification of vasculitis. Int. Angiol. 14, 101.

Gonzalez-Gay, M.A., Garcia-Porrua, C., Pujol, R.M. 2005. Clinical approach to cutaneous vasculitis. Curr. Opin. Rheumatol. 17, 56.

Gower, R.G., Sausker, W.F., Kohler, P.F., et al. 1978. Small vessel vasculitis caused by hepatitis B virus immune complexes. Small vessel vasculitis and HBsAG. J. Allergy Clin. Immunol. 62, 222.

Gray, R.G., Poppo, M.J. 1983. Necrotizing vasculitis as the initial manifestation of rheumatoid arthritis. J. Rheumatol. 10, 326.

Habif, T.P. 1990. Clinical Dermatology. Mosby, St. Louis.

Hannon, C., Swerlick, R.A. 2003. Vasculitis. In: J.L. Bolognia, J.L. Jorizzo, R.P. Rapini (Eds.), Dermatology. Mosby, London, p. 381.

Hazen, P.G., Michel, B. 1979. Management of necrotizing vasculitis with colchicine. Improvement in patients with cutaneous lesions and Behcet's syndrome. Arch. Dermatol. 115, 1303.

Hunder, G.G., Arend, W.P., Bloch, D.A., Calabrese, L.H., Fauci, A.S., Fries, J.F., Leavitt, R.Y., Lie, J.T., Lightfoot, R.W., Jr., Masi, A.T. 1990. The American College of Rheumatology, Criteria for the classification of vasculitis. Introduction. Arthritis Rheum. 33, 1065–1067.

Ioannidou, D.J., Krasagakis, K., Daphnis, E.K., Perakis, K.E., Sotsiou, F., Tosca, A.D. 2002. Cutaneous small vessel vasculitis. An entity with frequent renal involvement. Arch. Dermatol. 138, 412–414.

Jorizzo, J.L. 1986. Behcet's disease. An update based on the 1985 International Conference in London. Arch. Dermatol. 122, 556.

Jorizzo, J.L. 1993. Classification of vasculitis. J. Invest. Dermatol. 100, 106S.

Jorizzo, J.L., Daniels, J.C. 1983. Dermatologic conditions reported in patients with rheumatoid arthritis. J. Am. Acad. Dermatol. 8, 439.

Jorizzo, J.L., Solomon, A.R., Zanolli, M.D., et al. 1988. Neutrophilic vascular reactions. J. Am. Acad. Dermatol. 19, 983.

Kaklamani, V.G., Vaiopoulos, G., Kaklamanis, P.G. 1998. Behcet's Disease. Semin. Arthritis Rheum. 27, 197.

Klippel, J. H., Dieppe, P. A., 1998. Rheumatology, 2nd edn. Mosby, London.

Lamprecht, P. 2005. TNF-alpha inhibitors in systemic vasculitides and connective tissue diseases. Autoimmun. Rev. 4, 28.

Lawley, T.J., Moutsopoulos, H.M., Katz, S.I., et al. 1979. Demonstration of circulating immune complexes in Sjogren's syndrome. J. Immunol. 123, 1382.

Levinsky, R.J., Lehner, T. 1978. Circulating soluble immune complexes in recurrent oral ulceration and Behcet's syndrome. Clin. Exp. Immunol. 32, 193–687.

Lotti, T. 1991. The management of systemic complications of vasculitis. In: E. Panconesi (Ed.), Dermatology in Europe. Blackwell, Oxford, p. 330.

Lotti, T., Comacchi, C., Ghersetich, I. 1996. Cutaneous necrotizing vasculitis. Int. J. Dermatol. 35, 457.

Lotti, T., Ghersetich, I., Comacchi, C., Jorizzo, J.L. 1998. Cutaneous small-vessel vasculitis. J. Am. Acad. Dermatol. 39, 667–687.

Lynch, P.J. 1988. Vascular reactions. In: L.A. Schachner, R.C. Hansen (Eds.), Pediatric Dermatology. Churchill Livingstone, New York, p. 959.

Mackel, S.E., Jordon, R.E. 1982. Leukocytoclastic vasculitis. A cutaneous expression of immune complex disease. Arch. Dermatol. 118, 296–301.

Mackel, S.E., Tappeiner, G., Brumfield, H., Jordan, R.E. 1979. Circulating immune complexes in cutaneous vasculitis. Detection with C1q and monoclonal rheumatoid factor. J.Clin.Invest. 64, 1652–1660.

Martinez-Taboada, V.M., Blanco, R., Garcia-Fuentes, M., et al. 1997. Clinical features and outcome of 95 patients with hypersensitivity vasculitis. Am. J. Med. 102, 186.

Mathieson, P.W., Cobbold, S.P., Hale, G., et al. 1990. Monoclonal-antibody therapy in systemic vasculitis. N. Engl. J. Med. 323, 250.

Moschella, S.L. 2003. Neutrophilic Dermatoses. In: J.L. Bolognia, J.L. Jorizzo, R.P. Rapini (Eds.), Dermatology. Mosby, London, pp. 411–423.

Moutsopoulos, H.M., Chused, T.M., Mann, D.L., et al. 1980. Sjogren's syndrome (Sicca syndrome): current issues. Ann. Intern. Med. 92, 212.

Nishikawa, J.A. 1983. Are leg ulcers in rheumatoid arthritis due to vasculitis?. Eur. J. Rheumatol. Inflamm. 6, 288.

Nurnberg, W., Grabbe, J., Czarnetzki, B.M. 1995. Urticarial vasculitis syndrome effectively treated with dapsone and pentoxifylline. Acta Derm. Venereol. 75, 54.

O'Loughlin, S., Schroeter, A.L., Jordon, R.E. 1978. Chronic urticaria-like lesions in systemic lupus erythematosus. A review of 12 cases. Arch. Dermatol. 114, 879.

Ong, C.S., Benson, E.M. 2000. Successful treatment of chronic leucocytoclastic vasculitis and persistent ulceration with intravenous immunoglobulin. Br. J. Dermatol. 143, 447.

Parish, W.E. 1971. Studies on vasculitis I. Immunoglobulins, 1C, C-reactive protein, and bacterial antigens in cutaneous vasculitis lesions. Clin. Allergy, 1, 97.

Plotnick, S., Huppert, A.S., Kantor, G. 1989. Colchicine and leukocytoclastic vasculitis. Arthritis Rheum. 32, 1489.

Resnick, A.H., Esterly, N.B. 1985. Vasculitis in children. Int. J. Dermatol. 24, 139.

Ryan, T.J. 1992. Cutaneous vasculitis. In: A. Rook, D.S. Wilkinson, F.J.G. Ebling (Eds.), Textbook of Dermatology. Blackwell, Oxford, p. 1893.

Sais, G., Vidaller, A., Jucgla, A., et al. 1995. Colchicine in the treatment of cutaneous leukocytoclastic vasculitis. Results of a prospective, randomized controlled trial. Arch. Dermatol. 131, 1399.

Sais, G., Vidaller, A., Jucgla, A., et al. 1998. Prognostic factors in leukocytoclastic vasculitis: a clinicopathologic study of 160 patients. Arch. Dermatol. 134, 309.

Sakane, T., Takeno, M., Suzuki, N., et al. 1999. Behcet's disease. N. Engl. J. Med. 341, 1284.

Sams, W.M., Jr. 1980. Necrotizing vasculitis. J. Am. Acad. Dermatol. 3, 1.

Sanchez, N.P., Winkelmann, R.K., Schroeter, A.L., et al. 1982. The clinical and histopathologic spectrums of urticarial vasculitis: study of forty cases. J. Am. Acad. Dermatol. 7, 599.

Schifferli, J.A., Saurat, J.-H., Woodley, D.T. 1989. Cutaneous vasculitis. In: R. Ruiz-Maldonado, L.C. Parish, J.M. Beare (Eds.), Textbook of Pediatric Dermatology. Grune & Stratton, Philadelphia, p. 654.

Schirmer, M., Calamia, K.T., Direskeneli, H. 2001. Ninth International Conference on Behcet's Disease, Seoul, Korea, May 27–29, 2000. J. Rheumatol. 28, 636.

Smith, M.L., Jorizzo, J.L., Semble, E., et al. 1989. Rheumatoid papules: lesions showing features of vasculitis and palisading granuloma. J. Am. Acad. Dermatol. 20, 348.

Soter, N.A., Austen, K.F. 1978. Cutaneous necrotizing angiitis. In: M. Samter (Ed.), Immunological Diseases. Little, Brown, Boston, p. 993.

Soter, N.A., Wolff, S.M. 1987. Necrotizing vasculitis. In: T.B. Fitzpatrick, et al. (Ed.), Dermatology in General Medicine. McGraw-Hill, New York, p. 1300.

Stadler, R., Ruszczak, Z. 1995. Therapeutic guidelines in vasculitis. Int. Angiol. 14, 188.

Talal, N., Moutsopoulos, H.M., Kassan, S.S. 1987. Sjogren syndrome: clinical and immunological aspects. Springer-Verlag, Berlin.

Thorne, E.G., Gower, R.G., Claman, H.N. 1977. Hepatitis B surface antigen and leukocytoclastic vasculitis. J. Invest. Dermatol. 68, 243.

Valesini, G., Picardo, M., Pastore, R., et al. 1981. Circulating immune complexes in Behcet's syndrome: purification, characterization and cross-reactivity studies. Clin. Exp. Immunol. 44, 522.

Wener, M.H., Uwatoko, S., Mannik, M. 1989. Antibodies to the collagen-like region of C1q in sera of patients with autoimmune rheumatic diseases. Arthritis Rheum. 32, 544.

Wisnieski, J.J. 2000. Urticarial vasculitis. Curr. Opin. Rheumatol. 12, 24.

Wisnieski, J.J., Baer, A.N., Christensen, J., et al. 1995. Hypocomplementemic urticarial vasculitis syndrome. Clinical and serologic findings in 18 patients. Medicine (Baltimore) 74, 24.

Wisnieski, J.J., Jones, S.M. 1992. IgG autoantibody to the collagen-like region of Clq in hypocomplementemic urticarial vasculitis syndrome, systemic lupus erythematosus, and 6 other musculoskeletal or rheumatic diseases. J. Rheumatol. 19, 884.

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 18

Henoch–Schönlein Purpura

Jean-Claude Davin*

Emma Children's Hospital/Academic Medical Center, University of Amsterdam, The Netherlands

1. Introduction

Heberden (1802) was the first to describe the association of macroscopic heamaturia with a purpuric rash, colicky pain, bloody stools and arthralgia. Erythematous or purpuric rash, and joint pain was reported again by Schönlein (1847). Schönlein's former pupil, Henoch (1874), described four children with the combination of rash, colic, bloody diarrhoea and joint pain and in a later report added heamorrhagic nephritis to the list of components of the syndrome, thus completing the modern definition of the disease. The latter has been formulated by The International Consensus Conference on Nomenclature of Systemic Vasculitides as "a vasculitis with IgA-dominant immune deposits affecting small vessels and typically involving skin, gut and glomeruli and associated with arthralgias or arthritis" (Jennette et al., 1994).

Berger and Hinglais (1968) reported for the first time a form of glomerulonephritis characterized by mesangial accumulation of IgA, which led later on to the denomination of IgA nephropathy (IgAN). At the same time, Urizar and co-workers (1968) showed similar IgA deposits in renal biopsies of patients with Henoch–Schönlein purpura nephritis (HSPN).

HSPN and IgAN are considered nowadays as related diseases since both can be encountered consecutively in the same patient (Ravelli et al., 1969), have been described in identical twins (Meadow and Scott, 1985) and bear identical pathological and biological abnormalities (for a review: Davin et al., 2001; Knight, 1990).

2. Prevalence, Distribution, Age and Sex

Watts and co-workers (1995) report an annual incidence of 1 to 2/million in an ethnically homogeneous, stable adult population. In children, it varies between 10 and 20/100,000 children (Gardner-Medwin et al., 2002; Dolezalova et al., 2004; Yang et al., 2005). It must be stressed that not a single pediatric study is based on biopsy proven diagnosis. This is of importance since the latter is the gold standard to distinguish HSP from other vasculitides (Jennette et al., 1994) and that the clinical criteria of the American College of Rheumatism (ACR) used in most studies for diagnosis have been shown to be unreliable (Rao et al., 1998). It is probably one of the reasons why the reported annual incidence and the percentage of gastro-intestinal, renal and joint involvement vary so much from a study to another. It is generally agreed that the incidence of HSP decreases with age (Haycock, 1992).

3. Etiology/Pathogenesis

3.1. Histological findings

3.1.1. Skin

Histologically, cutaneous HSP is a leukocytoclastic form of vasculitis, with vessel wall necrosis and

*Corresponding author.
Pediatric Nephrology Unit, Het EKZ/Kinder AMC, 9, Meibergdreef, 1105 AZ Amsterdam Z-O, The Netherlands.

DOI: 10.1016/S1571-5078(05)05018-X

perivascular accumulation of inflammatory cells, mostly polymorphonuclear leucocytes and mononuclear cells, surrounding the capillaries and post-capillary venules of the dermis (Emancipator, 1994; Vernier et al., 1961). Immunofluorescence staining reveals the presence of IgA, C3c, a complex of C4 + C3c + C3d, fibrin/fibrinogen and rarely C4 in vessels and connective tissue of clinically involved skin (Baart De La Faille-Kuyper et al., 1976), which suggests an activation of the complement system by the alternative pathway. The incidence of vascular fluorescence with IgA does not differ between involved (75%) and uninvolved (67%) skin. Direct immunofluorescence using anti-IgA1 and anti-IgA2-specific monoclonal antibodies have shown that IgA1 is the dominant IgA subclass in the skin of patients with HSP (Egan et al., 1999) similarly to what is found in glomeruli (for a review: Emancipator, 1993).

3.1.2. Kidney

The classification of pathologic glomerular changes in HSPN is based on endo- and extracapillary inflammation of the glomerulus (Emancipator, 1993) and bears strong similarity to glomerular lesions observed in systemic vasculitis. Glomeruli show crescents in more than 50% of patients (Emancipator, 1993). There is an obvious correlation between neutrophil glomerular infiltration, endocapillary proliferation and crescent formation (Emancipator, 1993, 1994; Kincaid-Smith et al., 1989).

Predominant glomerular IgA deposists are a constant finding and IgA1 is the predominant subclass (Tomino et al., 1982; Emancipator, 1993). A mesangial localization of IgA is also constant (Urizar et al., 1968). Capillary wall staining for IgA may be found and even predominate on mesangial IgA, which might be absent in some rare cases (for a review: Emancipator, 1993). Polymeric IgA1 mesangial deposits have been demonstrated. Extensive capillary deposits are associated with more severe diffuse endocapillary proliferation and/or extensive crescent formation (for a review: Emancipator, 1993).

Glomerular deposits of IgG and IgM are also found in variable proportions (Urizar et al., 1968; Emancipator, 1993). C3 and alternative complement pathway components are also frequently found but complement factors of the classical pathway are rarely demonstrated (Urizar et al., 1968; Emancipator, 1993). Recently, Hisano and co-workers (2005) have shown that components of the lectin complement pathway are also present in glomeruli of some patients, mainly when IgA1 deposition is associated with IgA2. Glomerular fibrin deposits are frequently found (Emancipator, 1993).

By ultrastructural microscopy, the finding of electron-dense deposits in the mesangium is the rule and confirms the accumulation of IgA and C3 (Urizar et al., 1968; Emancipator, 1993).

Subepithelial and subendothelial). The latters are frequently associated with crescents and synechia, especially in case of large subepithelial deposits (Kincaid-Smith et al., 1989).

3.1.3. Digestive tract

In the digestive tract also a leucokytoclastic vasculitis accompanying IgA deposits has been reported in HSP (Gunasekaran, 1997).

3.2. IgA immunological abnormalities

3.2.1. Plasma IgA

Increased IgA plasma concentrations have been found in various percentages of patients in HSPN (Knight, 1990). This increase mainly involves polymeric IgA1. Qualitative abnormalities of IgA molecules such as IgA with rheumatoid factor activity and IgA anti-alpha galactosyl, which might favour IgA-containing complexes (IgA-CC) formation have also been found in HSPN (Davin et al., 2001). Early reports of plasma anti-neutrophil cytoplasm antibodies (ANCA) antibodies in HSPN could not be confirmed and have been attributed to technical artefacts and to aspecific binding based on lectin-like or electrostatic interactions (Ronda et al., 1994; Saulsbury et al., 1991; Sinico et al., 1994).

Increased binding of IgA to fibronectin (FN) leads to IgA-FN complexes formation (Cederholm et al., 1991; Davin et al., 1991), whereas incomplete glycosylation of IgA1 (Saulsbury, 1997; Allen et al., 1998) might favour the formation of IgA-lectin complexes, IgA1-IgG or IgA1-IgA1 aggregates (Davin et al., 1989; Kokubo et al., 1997;

Tomana et al., 1997). Abnormally glycosylated IgA1 was demonstrated in HSPN (Saulsbury, 1997; Allen et al., 1998).

3.2.2. IgA synthesis

Increased synthesis of IgA has been demonstrated in HSPN (for a review: Knight, 1990). It is not known whether this abnormality is due to a dysregulation of B cells by T lymphocytes.

3.2.3. IgA complexes

Glomerular deposition of circulating IgA-CC is thought to play a crucial role in the development of mesangial proliferation and extracellular matrix production leading to glomerular sclerosis in HSPN. This hypothesis results partly from the analysis of glomeruli and serum of patients. Besides, the pathogenic role of IgA-CC is also suggested in various experimental models of IgAN resulting from glomerular deposition of circulating IgA-CC either preformed and injected intravenously or endogenously synthesized (Scivittaro et al., 1993). Glomerular IgA is at least partly polymeric (pIgA) and belongs to the IgA1 isotype (Egido et al., 1980; Emancipator, 1993; Kaufman et al., 1980). High levels of circulating IgA-CC have been demonstrated in HSPN (for a review: Knight, 1990). These complexes contain IgA1 and also IgA2, IgG and fibronectin. They are generally found during acute phases of HSPN and are correlated with hematuric episodes (Kauffman et al., 1980; Levinsky and Barratt, 1979).

3.2.4. IgA complexes clearance

The formation of circulating IgA-CC is a normal process involved in the clearance of mucosal antigens that escape the mucosal barrier protective mechanisms and enter the organism. IgA1-CC are mainly cleared by the liver after IgA1 binding to hepatocyte receptors for asialoglycoproteins (Stockert et al. 1982). Hepatic clearance of IgA1-CC prevents thus accumulation in the circulation and deposition in other organs such as the kidney. High plasma levels of IgA-CC may theoretically result from an increased production or a reduced clearance or both.

IgA-CC clearance depends on their immune content and on the mononuclear phagocyte system function. Apart from IgA, IgA-CC may also contain IgG, IgM, fibronectin and complement components (for a review: Davin et al., 2001). Abnormally glycosylated IgA1 found in HSPN (Saulsbury, 1997; Allen et al., 1998) is possibly less cleared by the hepatocyte receptor for asialoglycoproteins than normal IgA1. We have reported a reduction of the fibronectin receptor function of mononuclear phagocytes in HSPN, which might affect the clearance of IgA-CC containing fibronectin (Davin et al., 1985). The latter abnormality was mostly not correlated with clinical signs, was transient and therefore more probably secondary to saturation of receptors rather than a primary event.

3.3. Complement

The plasma concentrations of the different components of the complement system are generally normal in HSPN (Davin et al., 1985). However, an activation of the complement cascade does occur since degradation of products in plasma and glomeruli have been shown (Julian et al., 1983; Davin et al., 1985; Smith et al., 1997). The role of this activation, however remains unclear. Results of studies trying to correlate the level of complement split products in the blood with clinical signs (Julian et al., 1983; Davin et al., 1985; Smith et al., 1997) or the glomerular deposition of various complement factors and histological lesions are contradictory (Emancipator, 1993). The almost constant finding of alternative complement pathway components in glomeruli contrasts with the rarity of components of the classical pathway and strongly suggests the pathophysiological role of IgA (for a review: Emancipator, 1993). It is of interest that aberrantly glycosylated IgA1 can activate complement more efficiently than normal IgA1 (Nikolova et al., 1994).

3.4. Immunogenetic factors

Immunogenetic studies in HSPN have demonstrated a strong link with homozygous C4A or C4B null phenotype (Mc Lean et al., 1984).

3.5. Coagulation

The coagulation system is possibly involved in the pathogenesis of HSPN as suggested by the finding in one study, presence of a circulating factor able to inhibit PGI2 synthesis (Turi et al., 1989), the depletion of fibrin-stabilizing factor (factor XIII) in acute HSP, the increased von Willebrand factor plasma levels (De Mattia et al., 1995; Soylemezoglu et al., 1996), and the intact cross-linked fibrin (XFb) intraglomerular deposits (Ono et al., 1996). As already mentioned, glomerular fibrin deposits may be abundant in HSPN. Although most of those coagulation abnormalities are probably secondary to a previous damage of the endothelium, they may contribute to further deterioration of glomerular structures and particularly to the formation of glomerular crescents.

3.6. Mucosal permeability

Increased formation of circulating IgA-CC in HSPN can be the consequence of transmucosal penetration of exogenous antigens. The intestinal permeability to 51Cr EDTA is increased in HSPN (Davin and Mahieu, 1992). This increase is correlated with circulating IgA-CC plasma levels and with haematuria as well as with systemic symptoms in HSPN. Transiently increased lung transfer for carbon monoxide (TCLO) has been reported in acute phases (Chaussain et al., 1992). The reason for this increased mucosal permeability remains unknown. Its reversibility suggests secondary alterations of the mucosal capillaries due to IgA-CC. Increased penetration of antigens inside the human organism may also result from a lack of specific mucosal IgA production as suggested by De Fijter and co-workers (1996) in IgAN. The latter authors have indeed shown an impairment of the specific IgA1 response in mucosae and blood after intranasal immunization with cholera toxin subunit B as a novel antigen in adult patients with IgAN. Such a mechanism should explain the high prevalence of anti-*Helicobacter pylori* antibodies found in adult patients with HSP (Novak et al., 2003) and of Group A streptococcal antigen in the glomeruli of children with HSPN (Masuda et al., 2003).

3.7. Allergy

Several studies have documented the association of HSP with hypersensitivity type 1. Early studies reported high IgE plasma levels in HSP (Davin et al., 1985). We have found that the incidence of increased plasma IgE levels according to age-matched normal values were significantly higher in HSPN (Davin et al., 1994). Moreover, IgE deposits were demonstrated on cutaneous langerhans and mast cells in four out of six patients with HSPN. Namgoong and co-workers (1997) have shown that serum eosinophil cationic protein levels were elevated in HSP as compared to normal controls. Furthermore, these levels were higher in HSP with renal involvement.

3.8. Pathophysiological hypothesis

The clinical association of respiratory tract infections with acute episodes of HSP suggests the triggering role of infectious agents. Secretory IgA in the mucosal lining plays a major role in the defence against exogenous antigens. A defect in the specific IgA1 antibody response at the mucosal level similar to the one reported in IgAN (De Fijter et al., 1996) could favour the antigen penetration and stimulate the systemic immune system. In the circulation, the antigens can be captured by circulating IgA1. On the contrary to IgA2, IgA1 is well provided with oligosaccharic chains in its hinge region. The latter plays a major role in the IgA1 hepatic clearance by binding to the asialoglycoprotein receptor of hepatocytes. The defect in IgA1 glycosylation shown in patients with HSPN might impede IgA1 clearance and determine an accumulation of IgA1 and IgA1-CC in plasma. The clearance of IgA1-CC containing other immunoglobulins, fibronectin and complement products, should therefore preferentially take place through other clearance mechanisms involving the recognition of non-IgA1 components of IgA1-CC (for a review: Davin et al., 2001). Saturation of the latter mechanisms might be responsible for further IgA-CC plasma accumulation and tissue deposition. Physico-chemical and biological properties of IgA and IgA-CC (as molecular weight, isoelectric point, ability to

bind to and stimulate glomerular cells …) should be important determinants of their site of deposition and of their abilities to provoke the inflammatory process leading to tissue lesions. The deposition of IgA1-CC in glomeruli is favoured by their high plasma concentration in HSPN. Their preferential accumulation in the mesangial area and under the endothelial cells is at least partly related to their relative large size (Germuth and Rodriquez, 1973; Batsford et al., 1985; Monteiro et al., 1985). Once in the mesangium, different components of IgA-CC (Fc-alpha and Fc-gamma fragments, fibronectin, C3b, lectins …) can bind to their specific receptors on the surface of mesangial cells and induce the latter to produce pro-inflammatory mediators and mesangial matrix components (for a review: Davies, 1994). The possible intervention of cytokines in the physiopathology of renal lesions is suggested by the relation between high serum TNF-alpha levels and proteinuria (Ha, 2005).

The leucocytoclastic vasculitis results from an invasion of leucocytes involving a three-step process of rolling, sticking and firm adhesion to endothelial cells followed by leucocyte migration in tissues. This process is regulated by a network of cytokines and chemokines leading to expression of adhesion molecules on endothelial and inflammatory cells. Interestingly, an increased expression of IL-1, IL-6 and TNF-alpha has been shown in skin biopsies of patients with HSP (Besbas et al., 1997). The primary event is probably a damage of endothelial cells, which can be induced by subendothelial immune-complex deposition (e.g. in serum sickness), binding of cytotoxic antibodies (e.g. in Kawasaki disease) or interaction with activated circulating cells (possibly in Wegener's disease) (Cohen and Kallenberg, 1991). The involvement of the first of those mechanisms in HSP is suggested by the presence of IgA-CC in plasma and tissues and by the stimulation of IL-8 production by human umbilical venous endothelial cells in presence of patients' serum (Yang et al., 2004).

It is not clear why extrarenal vasculitis is present in HSPN and not in IgAN, although both diseases share so many similitudes. Immunofluorescence studies show that immune complexes are more often found in a subendothelial localization in HSPN. This site of deposition favours primary endothelial lesions leading to glomerular endo- and extracapillary proliferation and fibrin formation. The higher size of IgA-CC in HSPN should favour a predominant subendothelial deposition. The association of HSP with hypersensitivity as well as a higher incidence of increased plasma IgE levels in HSPN as compared to IgAN (Davin et al., 1994) suggest the possible pathogenic role of hypersensitivity in the development of HSP vasculitis. IgE deposits were demonstrated by a peroxidase/anti-peroxidase method on cutaneous langerhans and mast cells in four out of six patients with HSPN (Davin et al., 1994). As mast cells are also present in intestine and lung, but not in kidney, immunoallergy might account, in some cases, for the cutaneous, intestinal and pulmonary signs observed in HSP and also for the lack of correlation between the intensity of the rash and of gastro-intestinal signs since mast cells are not usually found in the kidney.

4. Clinical Features

A history of a recent or simultaneous infection is common in HSP. Indeed, the latter is reported in 1/3 to 2/3 according to the studies (Haycock, 1992). Although any of the four major components of the syndrome (rash, joint pain, abdominal symptoms and renal disease) may be present before the other, it is rare for the renal disease to do so (Haycock, 1992).

4.1. Skin involvement

Skin involvement is present per definition. The characteristic sites of the rash are the external aspects of the limbs, the buttocks and occasionally the face. The eruption begins as a crop of erythematous macules, some of which may resolve in the early stages but most of which become papular, urticarial and purpuric. Generally, lesions resolve in a few days but relapses are possible.

4.2. Renal involvement

The lack of using appropriate diagnostic criteria possibly explains why the proportion of patients

presenting with renal involvement varies considerably among the different reports (20–100%) (for a review: White and Yoshikawa, 1993). Another explanation might reside in the use of different criteria for diagnosing HSPN since in many of the earlier studies, serial routine urinanalysis was not used and transient microscopic haematuria was probably missed (White and Yoshikawa, 1993). Finally, an underestimation should result from the existence of renal lesions without any clinical signs and the delay that can occur between the initial signs and renal symptoms. Indeed, the incidence of renal involvement increases with time after HSP diagnosis in children (Kaku et al., 1998). Kaku and co-workers (1998) have shown that the latter increased progressively to reach 35.4% after 1 year and continued to increase thereafter. On the contrary to studies in children, the incidence of renal involvement in HSP in adults has been more precisely assessed in one study using a cohort of patients in whom the diagnosis was made by showing the characteristic leucocytoclastic skin vasculitis accompanied by IgA deposits (Trancrede-Bohin et al., 1997). This study demonstrated that 49% of patients presented with abnormal urinary signs. The sex ratio (M/F: 1:5) shows an increased frequency in males (Habib and Cameron, 1982).

According to a single series from a tertiary centre (Goldstein et al., 1992), initial signs of HSPN are haematuria and proteinuria in 50% of patients, acute nephritic syndrome in 8%, nephrotic syndrome in 13% and an association of nephritic and nephrotic syndrome in 29% of patients. As expected, the incidence of mild symptoms is higher in unselected series (Koskimies et al., 1974; Nielsen, 1988). Unfortunately, none of the latter used cutaneous IgA deposits as a diagnostic criteria. Therefore, their results must be considered with caution.

The proportion of HSPN as cause of ESRF in adults is minimal (Haycock, 1992) whereas it can reach up to 5.1% in children (Broyer, 1983). In selected series, HSPN leads to chronic renal failure in up to 20% of children, 20 years after the diagnosis (Goldstein et al., 1992). The risk of chronic renal failure is related to the initial clinical presentation (Goldstein et al., 1992). Chronic renal failure will be encountered in less than 5% when clinical signs at presentation are haematuria and/or minimal proteinuria, 15% when proteinuria is heavy but not nephrotic or in case of acute nephritic syndrome, 40% in case of nephrotic syndrome and more than 50% when nephritic and nephrotic syndromes are associated. Of interest, even minimal urinary abnormalities can lead to chronic renal failure after decades (Goldstein et al., 1992). The general opinion is that HSP has a worse prognosis in adults than in children (for a review: Lahita, 1997). However, Coppo and co-workers (1997) showed that among patients with a clinical presentation which warrants renal biopsy, HSP nephritis has a similar prognosis in children and adults. Several risk factors for renal involvement have been reported in children: older age, abdominal symptoms, low factor XIII activity and persisting purpura (Kaku et al., 1998). In adults unlike children, the patients with renal involvement do not seem to differ from those without, according to any clinical parameter such as sex, prevalence of bullous or necrotic lesions of the skin, or gastro-intestinal and joints involvement (Trancrede-Bohin et al., 1997).

Interestingly, remissions of Henoch–Schönlein purpura in adults have been reported during pregnancy or sex-hormone therapy (Merril and Lahita, 1994). The latter observation as well as the mean sex ratio (M/F: 1:5) is in favour of a pathogenic role of male hormones. Recurrence can affect the transplanted kidney and lead to graft loss in 11–35% of patients 5 years after transplantation (Meulders et al., 1994). In a retrospective cohort study analysed 24 years after childhood HSPN, pregnancy was complicated by hypertension, proteinuria or both, in 70% of patients (Ronkainen et al., 2002). Complications occurred more often in case of severe initial symptoms but could also be observed in case of mild initial presentation.

4.3. Gastro-intestinal involvement

Gastro-intestinal symptoms occur in 50–90% of patients (Meadow et al., 1972; Chang et al., 2004; Haycock, 1992). Abdominal pain is the most common symptom. Gastro-intestinal bleeding or positive blood occult is reported in up to 40% of patients in some series (Meadow et al., 1972).

Intussusception, bowel perforation and hypovolemic shock have been exceptionally reported.

4.4. Joints involvement

Joints pain occurs in two-thirds of cases, and is the presenting symptom in one-quarter (Haycock, 1992). The arthralgia varies from mild to moderately severe. Swelling usually accompanies the pain but not always. The large joints, especially the ankles and knees, are principally affected. Diffuse swelling of the dorsum of the hand and foot is often observed. Affected joints are never permanently damaged.

4.5. Involvement of other organs

Cardiac and pulmonary involvements have been described in a few patients (Haycock, 1992). Testicular involvement mimicking testicular torsion is exceptional (Singer et al. 1992). Intracerebral heamorrhage has also been described (Misra et al., 2004).

4.6. Secondary forms of HSP

Henoch–Schönlein purpura nephritis (HSPN) has been described in association with hypersensitivity. Indeed, several drugs such as ciprofloxacin, acetylsalicylic acid, vancomycin, carbidopa/levodopa, cocaine, ACE inhibitors, carbamazepine and streptokinase have been implicated in HSP induction (Disdier et al., 1992; Moots et al., 1992; Kaneko et al., 1993; Drago et al., 1994; Chevalier et al., 1995; Niedermaier and Briner, 1997; Prajapati and Casson, 1997; Sola et al., 1997; Michail et al., 1998).

HSPN has also been occassionally reported in association with cancer (Cairns et al., 1978), blunt trauma (Talbot et al., 1988), monoclonal IgA gammopathy (Dosa et al., 1980), Wiskott–Aldrich syndrome carriers (Lasseur et al., 1997), chronic alcoholic liver disease (Feriozzi et al., 1995) and with alpha 1-antitrypsin deficiency (Elzouki et al., 1995).

5. Diagnosis

Localization and features of cutaneous lesions associated with joints and gastro-intestinal symptoms are very suggestive of HSP diagnosis. However, several other forms of leucocytoclastic vasculitis such as acute infantile haemorragic oedema (AIHE), hypersensitivity vasculitis, lupus erythematosus (LE), Wegener's disease and microscopic polyangiitis (MPA) can have a similar clinical presentation. None of the circulating IgA abnormalities described above are specific or constant. If specific immunological serological parameters can be used to differentiate HSP from LE, Wegener's disease and MPA, this is not the case for hypersensitivity vasculitis and AIHE. The AIHE is a rare cutaneous leucocytoclastic vasculitis generally without IgA deposits, clinically characterized by a symptom triad of fever, large purpuric skin lesions and oedema of hands, feet and face and taking place before the age of two (Caksen et al., 2002). It is a benign condition, which is confined to the skin and resolves without sequellae. Hypersensitivity vasculitis has been described in association with numerous drugs comprising commonly used antibiotics and antipyretics. It is estimated that 10–20% of dermal reactions to drugs are vasculitic (ten Holder et al., 2002). The histological picture of the latter is a leucocytoclastic vasculitis that can also damage end organs as the kidney. To differentiate HSP from the other types of vasculitis, most of the clinicans still use the clinical criteria proposed by the ACR that are not based on studies taking into account IgA deposits as a gold standard diagnostic tool (Mills et al., 1990). A prospective study designed to determine the value of the 1990 ACR criteria concluded that they function poorly in the diagnosis of vasculitides if they are used without additional information provided by complementary investigations (Rao et al., 1998). According to the ACR, the presence of palpable purpura in a patient younger than 20 years old was sufficient to assess the diagnosis. In a recent epidemiological study performed in the Netherlands on patients reported as having HSP, half of the skin biopsies performed did not display IgA deposits (personal observation). Therefore, it might be that a significant number of patients considered

as having HSP presents in fact with other types of vasculitis. A rash appearing during or after a respiratory infection (as reported in many patients with HSP) could be due to a hypersensitivity reaction to antibiotics or antipyretics given for infection. Another possibility is that some of those patients present with an infectious leucocytoclastic vasculitis as reported in association with infections by streptococcus, staphylococcus, hepatitis B or C, influenza, cytomegalovirus, parvovirus B *19* and *Mycobacterium* sp. (Crowson et al., 2003). That is the reason why the histological analysis of a biopsy (skin or kidney) remains the only way to diagnose HSP with certainty. Although glomerular IgA deposits can be observed rather frequently in various types of glomerulonephritis (lupus nephritis, acute post-infectious, membranoproliferative, mixed connective tissue disease) they are predominant on other deposits only in HSPN and IgAN (Emancipator, 1993). The leucocytoclastic vasculitis of small vessels with predominant IgA deposits is typical of HSP (Jennette and Falk, 1997). Even if IgA deposits are shown by immunofluorescence, light microscopy studies remain necessary to demonstrate the leucocytoclastic aspect since an IgA-associated lymphocytic vasculopathy has been recently described in various clinical conditions including a symptomatology compatible with HSP (Crowson et al., 2002).

IgA deposits can be absent in necrotic or old lesions. The choice of the lesion to analyse is therefore important. Renal biopsy is only recommended for therapeutic indication and prognosis purpose in case of nephrotic and/or nephritic syndrome or of persisting proteinuria (Davin and Weening, 2003).

6. Treatment

The usefulness of a therapy for HSPN is not easy to assess because of several reasons. Even if the severity of clinical signs and histological lesions are often related with the development of chronic renal failure, it is not a constant finding. Moreover, even an apparent complete healing may be followed by chronic renal insufficiency after decades. Finally, the small number of patients with bad prognosis (those with nephrotic syndrome, or a combination of nephrotic and nephritic syndrome) do not allow prospective randomized studies in which some patients should not be treated. Therefore, it is not astonishing that there is no strong evidence that any form of treatment alters the course of HSPN. Older studies report no beneficial effects of prednisone in patients with already established nephritis (Meadow et al., 1972; Levy et al., 1979; White et al., 1966). Likewise, no or few preventing effects of prednisone on the development of nephritis have been found (Saulsbury, 1993; Mollica et al., 1992). More recent studies are however more encouraging. Öner et al. (1995) have shown that an association of methylprednisolone pulse (3 days) with oral cyclophosphamide (6 months), oral dipyridamole (6 months) and oral prednisolone (3 months) allowed a return to normal GFR values in 11 out of 12 patients with rapidly progressive glomerulonephritis secondary to HSPN. Niaudet and Habib (1998) have compared a series of patients presenting with nephrotic syndrome and/or more than 50% crescentic glomeruli on initial biopsy treated with methylprednisolone with a similar historical series not treated. In the patients treated, only 4 out of 38 (10%) progressed to end stage renal failure instead of 11 out of 29 patients (38%) in the historical non-treated series. In a Japanese study, none of 14 children with HSPN and severe glomerular changes treated with a multiple combined therapy with prednisolone, cyclophosphamide, heparin/warfarin and dipyridamole did develop chronic renal insufficiency after a mean period of 7.5 years (Iijima et al., 1998). Foster and co-workers (2000) have shown that an association of oral prednisone (1–2 mg/kg/day) and azathioprine (2 mg/kg/day) for 4 weeks prevent progression of chronic histological glomerular changes and improved outcome. Cyclosporin A or a combination of methylprednisolone and urokinase pulse therapy should also be of value (Ronkainen et al., 2003; Kawasaki et al., 2003). Success has also been reported with plasmapheresis in combination with oral prednisone, cyclophosphamide, dipyridamole and oral warfarin (Kawasaki et al., 2004). The pitfall of all the above-mentionned studies resides in the relative short-term follow-up since chronic

renal insufficiency can develop decades after apparent complete healing. In his decision to treat, the pediatric nephrologist must overweight the possible beneficial effect of treatment versus possible complications of immunosuppression.

Key points

- IgAN and HSP are two different manifestations of the same pathophysiological process.
- Prevalence and distribution of HSP are difficult to assess because of diagnostic pitfalls.
- The ACR criteria for HSP diagnosis are not adequate.
- IgA1 is the main IgA subclass present in IgA-CC and in IgA tissue deposits.
- Aberrant IgA1 glycosylation is responsible for reduced hepatic clearance and IgA1 accumulation in blood and deposition in tissue.
- HSPN may lead to chronic renal failure mainly in case of initial clinical presentation as nephrotic syndrome or/and in presence of extensive glomerular extracapillary proliferation.
- Predominant IgA deposits in glomerular lesions or accompanying a leucocytoclastic vasculitis in a skin biopsy are the gold standard diagnostic features. Immunosuppressive treatment seems to be beneficial but strong evidence is lacking.

References

Allen, A.C., Willis, F.R., Beattie, J., et al. 1998. Abnormal IgA glycosylation in Henoch–Schönlein purpura restricted to patients with clinical nephritis. Nephrol. Dial. Transpl. 13, 930. First report of abnormally glycosylated IgA in HSP.

Baart De La Faille-Kuyper, E.H., Kater, L., Kuijten, R.H., et al. 1976. Occurrence of vascular IgA deposits in clinically normal skin of patients with renal disease. Kidney Int. 9, 424.

Batsford, S.R., Weghaupt, R., Takamiya, H., et al. 1985. Studies on the mesangial handling of protein antigens; influence of size, charge and biologic activity. Nephron 41, 146.

Berger, J., Hinglais, N. 1968. Les depots intercapillaires d'IgA-IgG. J. Urol. Nephrol. 74, 694. First report of IgA deposits in glomeruli and of IgA N.

Besbas, N., Saatci, U., Ruacan, S., et al. 1997. The role of cytokines in Henoch–Schönlein purpura. Scand. J. Rheumatol. 26, 456.

Broyer, M. 1983. Fréquence et cause de l'insuffisance rénale chez l'enfant. In: P. Royer, R. Habib, H. Matthieu, M. Broyer (Eds.), Néphrologie Pédiatrique. Flammarion Médecine-Sciences, Paris, p. 425.

Cairns, S.A., Mallick, N.P., Lawler, W., et al. 1978. Squamous cell carcinoma of bronchus presenting with Henoch–Schönlein purpura. BMJ 2, 474.

Caksen, H., Dursun, O., Kosem, M., et al. 2002. Report of eight infants with acute infantile hemorrhagic edema and review of the literature. J. Dermatol. 29, 290.

Cederholm, B., Linne, T., Wieslander, J., et al. 1991. Fibronectin-immunoglobulin complexes in the early course of IgA and Henoch–Schönlein nephritis. Pediatr. Nephrol. 5, 200.

Chang, W.L., Yang, Y.H., Lin, Y.T., CRiang, B.L. 2004. Gastrointestinal manifestations in Henoch-Schönlein purpura: a review of 261 patients. Acta Paediatr. 93, 1427–1431.

Chaussain, M., de Boissieu, D., Kalifa, G., et al. 1992. Impairment of lung diffusion capacity in Schönlein–Henoch purpura. J. Pediatr. 121, 12.

Chevalier, X., Rostoker, G., Larget-Piet, B., et al. 1995. Schönlein–Henoch purpura with necrotizing vasculitis after cocaine snorting. Clin. Nephrol. 43, 348.

Cohen Tervaert, J.W., Kallenberg, C.G.M. 1991. Vasculitis. In: T.H. The, C.G.M. Kallenberg, L. de Leij (Eds.), Klinische Immunologie. Bohn Stafleu van Loghum, Houten/Antwerpen, p. 216.

Coppo, R., Mazzuco, G., Cagnoli, L., et al. 1997. Long-term prognosis of Henoch–Schönlein nephritis in adults and children for the Italian group of renal immunopathology collaborative study on Henoch–Schönlein purpura. Nephrol. Dial. Transplant. 12, 2277.

Crowson, A.N., Magro, C.M., Usmani, A., et al. 2002. Immunoglobulin A-associated lymphocytic vasculopathy: a clinicopathologic study of eight patients. J. Cutan. Pathol. 29, 596.

Crowson, A.N., Mihm, M.C., Jr., Magro, C.M. 2003. Cutaneous vasculitis: a review. J. Cutan. Pathol. 30, 161.

Davies, M. 1994. The mesangial cell: a tissue culture view. Kidney Int. 45, 320.

Davin, J.C., Dechenne, C., Lombet, J., et al. 1989. Acute experimental glomerulonephritis induced by the glomerular deposition of circulating polymeric IgA-concanavalin A complexes. Virchows Archiv A Pathol. Anat. Histopathol. 415, 7.

Davin, J.C., Li Vecchi, M., Nagy, J., et al. 1991. Evidence that the interaction between circulating IgA and fibronectin is a normal process enhanced in IgA nephropathy. J. Clin. Immunol. 11, 78.

Davin, J.C., Mahieu, P.R. 1992. Sequential measurements of intestinal permeability to 51Cr EDTA in children with Henoch–Schönlein purpura nephritis. Nephron 60, 498.

Davin, J.C., Pierard, G., Dechenne, C., et al. 1994. Possible pathogenic role of IgE in Henoch–Schönlein purpura. Pediatr. Nephrol. 8, 169.

Davin, J.C., ten Berghe, I., Weening, J.J. 2001. Henoch–Schönlein purpura nephritis and IgA nephropathy: what makes the difference?. Kidney Int. 59, 823.

Davin, J.C., Vandenbroeck, M.C., Foidart, J.B., et al. 1985. Sequential measurements of the reticuloendothelial system function in Henoch–Schönlein disease in childhood. Correlation with various immunological parameters. Acta Paediatr. Scand. 74, 201.

Davin, J.C., Weening, J.J. 2003. Diagnosis of Henoch–Schönlein purpura: renal or skin biopsy. Pediatr. Nephrol. 18, 1201.

De Fijter, J.W., Eijgeraam, J.W., Braam, C.A., et al. 1996. Deficient IgA1 immune response to nasal cholera toxin subunit B in primary IgA nephropathy. Kidney Int. 50, 952.
Report of a defect in mucosal IgA1 specific response that could play a role for continuous stimulation of the systemic immune system in IgAN and may be also in HSP.

De Mattia, D., Penze, R., Giordano, P., et al. 1995. Von Willebrand factor and factor XIII in children with Henoch–Schönlein purpura. Pediatr. Nephrol. 9, 603.

Disdier, P., Harle, J.R., Verrot, D., et al. 1992. Adult Schönlein–Henoch purpura after lisinopril. Lancet 340, 304.

Dolezalova, P., Telekesova, P., Nemcova, D., et al. 2004. Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. J. Rheumatol. 31, 2295.

Dosa, S., Cairns, S.A., Mallick, M.P., et al. 1980. Relapsing Henoch–Schönlein syndrome with renal involvement in a patient with an IgA monoclonal gammapathy. Nephron 26, 145.

Drago, F., Arditi, M.R., Rebora, R. 1994. Henoch–Schönlein purpura induced by fluorquinolones. Br. J. Dermatol. 131, 448.

Egan, C.A., Taylor, T.B., Meyer, L.J., et al. 1999. IgA1 is the major IgA subclass in cutaneous blood vessels in Henoch–Schönlein purpura. Br. J. Dermatol. 141, 859.

Egido, J., Rancho, J., Mampaso, F., et al. 1980. A possible common pathogenesis of the mesangial IgA glomerulonephritis in patients with Berger's disease and Schönlein–Henoch syndrome. Proc. Eur. Dial. Transplant. Assoc. 17, 660.

Elzouki, A.N., Sterner, G., Erikson, S. 1995. Henoch–Schönlein purpura and α1-antitrypsin deficiency. Nephrol. Dial. Transplant. 10, 1454.

Emancipator, S.N. 1993. Primary and secondary forms of IgA nephritis and Schönlein–Henoch syndrome. In: R.H. Heptinshall (Ed.), Pathology of the Kidney. Little, Brown, Toronto London, p. 389.

Emancipator, S.N. 1994. IgA nephropathy: morphologic expression and pathogenesis. Am. J. Kidney Dis. 23, 451.

Feriozzi, S., Onetti Muda, A., Faraggiana, T., et al. 1995. Henoch–Schönlein disease with IgA nephropathy associated with chronic alcoholic liver disease. Nephrol. Dial. Transplant. 10, 1231.

Foster, B.J., Bernard, C., Drummond, K.N., et al. 2000. Effective therapy for severe Henoch–Schönlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. J. Pediatr. 136, 370.

Gardner-Medwin, J.M.M., Dolezalova, P., Cummins, C., et al. 2002. Incidence of Henoch–Schönlein purpura, kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 360, 1197.

Germuth, F.G., Rodriquez, E. 1973. Immunopathology of the renal glomerulus. Little, Brown, Boston, p. 15.

Goldstein, A.R., White, R.H.R., Akuse, R., et al. 1992. Long-term follow-up of childhood Henoch–Schönlein nephritis. Lancet 339, 280.

Gunasekaran, T.S. 1997. Henoch–Schönlein purpura: what does the "rash" look like in the gastrointestinal mucosa. Pediatr. Dermatol. 6, 437.

Ha, T.S. 2005. The role of tumor necrosis factor-alpha in Henoch–Schönlein purpura. Pediatr. Nephrol. 20, 149.

Habib, R., Cameron, J.S. 1982. Schönlein–Henoch purpura. In: P.A. Bacon, N.M. Hadler (Eds.), The Kidney and Rheumatic Disease. Butterworth, London, p. 178.

Haycock, G.B. 1992. The nephritits of Henoch–Schönlein purpura. In: S. Camerson, A.M. Davison, J.-P. Grünfeld, D. Kerr, E. Ritz (Eds.), Oxford Textbook of Clinical Nephrology. Oxford University Press, Oxford, p. 595.

Heberden, W. 1802. Commentaries on the history and cure of diseases. Payne T, London, chapter 78, p. 395.
First report of HSP.

Henoch, E. 1874. Über eine eigenthümliche Form von Purpura. Berliner Klin. Wochenschr. 11, 641.

Hisano, S., Matsuhita, M., Fujita, T., et al. 2005. Activation of the lectin complement pathway in Henoch–Schönlein purpura nephritis. Am. J. Kidney Dis. 45, 295.

Iijima, K., Ito-Kariya, S., Nakamura, H., et al. 1998. Multiple combined therapy for severe Henoch–Schönlein nephritis in children. Pediatr. Nephrol. 12, 44.

Jennette, J.C., Falk, R.J. 1997. Small-vessel vasculitis. N. Engl. J. Med. 337, 1512.

Jennette, J.C., Falk, R.J., Andrassy, K., et al. 1994. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 37, 187.

Julian, B.A., Wyatt, R.J., Mc Morrow, R.G., et al. 1983. Serum complement proteins in IgA nephropathy. Clin. Nephrol. 20, 251.

Kaku, Y., Nohara, K., Honda, S. 1998. Renal involvement in Henoch–Schönlein purpura: a multivariate analysis of prognostic factors. Kidney Int. 53, 1755.

Kaneko, K., Igarashi, J., Suzuki, Y., et al. 1993. Carbamazepine-induced thrombocytopenia and leucopenia complicated by Henoch–Schönlein purpura symptoms. Eur. J. Pediatr. 152, 769.

Kauffman, R.H., Herrman, W., Meyer, C.J.L.M., et al. 1980. Circulating IgA-immune complexes in Henoch–Schönlein purpura: a longitudinal study of their relationship to disease activity and vascular deposition of IgA. Am. J. Med. 69, 859.

Kawasaki, Y., Suzuki, J., Murai, M., et al. 2004. Plasmapheresis therapy for rapidly progressive Henoch–Schönlein nephritis. Pediatr. Nephrol. 19, 920.

Kawasaki, Y., Suzuki, J., Nozawa, R., et al. 2003. Efficacy of methylprednisolone and urokinase pulse therapy for severe Henoch–Schönlein nephritis. Pediatrics 111, 785.

Kincaid-Smith, P., Nichills, K., Birchall, I. 1989. Polymorphs-infiltrate glomeruli in mesangial IgA glomerulonephritis. Kidney Int. 36, 1108.

Knight, J.F. 1990. The rheumatic poison: a survey of some published investigations of the immunopathogenesis of Henoch–Schönlein purpura. Pediatr. Nephrol. 4, 533.

Kokubo, T., Hiki, Y., Iwase, H., et al. 1997. Evidence for involvement of IgA1 hinge glycopeptide in the IgA1–IgA1 interaction in IgA nephropathy. J. Am. Soc. Nephrol. 8, 915.

Koskimies, O., Rapola, J., Savilahti, E., et al. 1974. Renal involvement in Schönlein–Henoch purpura. Acta Paediatr. Scand. 63, 357.

Lahita, R.G. 1997. Influence of age on Henoch–Schönlein purpura. Lancet 350, 1116.

Lasseur, K., Allen, A.C., Deminière, C., et al. 1997. Henoch–Schönlein purpura with IgA nephropathy and abnormalities of IgA in a Wiskott–Aldrich syndrome carrier. Am. J. Kidney Dis. 2, 285.

Levinsky, R.J., Barratt, T.M. 1979. IgA immune complexes in Henoch–Schönlein purpura. Lancet 24, 1100.
First report of IgA-CC in HSP.

Levy, M., Broyer, M., Arsan, A., et al. 1979. Anaphylactoid purpura nephritis in childhood. Natural history and immunopathology. Adv. Nephrol. 6, 183.

Masuda, M., Nakashini, K., Yoshizawa, N., et al. 2003. Group A streptococcal antigen in the glomeruli of children with Henoch–Schönlein nephritis. Am. J. Kidney Dis. 41, 366.

McLean, R.H., Wyatt, R.J., Julian, B.A. 1984. Complement phenotypes in glomerulonephritis: increased frequency of homozygous null C4 phenotypes in IgA nephropathy and Henoch–Schönlein purpura. Kidney Int. 26, 885.

Meadow, S.R., Glasgow, E.F., White, R.H.R., et al. 1972. Henoch–Schönlein nephritis. QJM 41, 241.

Meadow, S.R., Scott, D.G. 1985. Berger disease: Henoch–Schönlein without the rash. J. Pediatr. 106, 27.
Best evidence that HSP and IgAN are two different manifestations of the same pathophysiological process.

Merril, J., Lahita, R.G. 1994. Henoch–Schönlein purpura remitting in pregnancy and during sex steroid therapy. Br. J. Rheumatol. 33, 586.

Meulders, Q., Pirson, Y., Cosyns, J.P., et al. 1994. Course of Henoch–Schönlein nephritis after renal transplantation. Report on ten patients and review of the literature. Transplantation 58, 1179.

Michail, S., Vaiopoulos, G., Nakopoulou, L., et al. 1998. Henoch–Schönlein purpura and acute interstitial nephritis after intravenous vancomycin administration in a patient with a staphylococcal infection. Scand. J. Rheumatol. 27, 233.

Mills, J.A., Michel, B.A., Bloch, D.A., et al. 1990. The American college of rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. Arthritis Rheum. 33, 1114.

Misra, A.K., Biswas, A., Das, S.K., et al. 2004. Henoch–Schönlein with intracerebral haemorrhage. J. Assoc. Phys. India 52, 833.

Mollica, F., Li Volti, S., Garzo, R., et al. 1992. Effectiveness of early prednisolone treatment in preventing the development of nephropathy in anaphylactoid purpura. Eur. J. Pediatr. 151, 140.

Monteiro, R.C., Albwachs-Mecarelli, L., Roque-Barreira, M.C., et al. 1985. Charge and size of mesangial IgA in IgA nephropathy. Kidney Int. 28, 666.

Moots, R.J., Keeling, P.J., Morgan, S.H. 1992. Adult Schönlein–Henoch purpura after enalapril. Lancet 340, 304.

Namgoong, M.K., Lim, B.K., Kim, J.S. 1997. Eosinophil cationic protein in Henoch–Schönlein purpura and in IgA nephropathy. Pediatr. Nephrol. 11, 703.

Niaudet, P., Habib, R. 1998. Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein–Henoch purpura. Acta Paediatr. Scand. 77, 125.
Best evidence that a treatment is usefull in HSP.

Niedermaier, G., Briner, V. 1997. Henoch–Schönlein syndrome induced by carbidopa/levodopa. Lancet 349, 1071.

Nielsen, H.E. 1988. Epidemiology of Schönlein–Henoch purpura. Acta Paediatr. Scand. 77, 125.

Nikolova, E.B., Tomana, M., Russell, M.W. 1994. The role of carbohydrate chains in complement (C3) fixation by solid-phase-bound human IgA. Immunology 82, 321.

Novak, J., Szekanecz, Z., Sebesi, J., et al. 2003. Elevated levels of anti-*Helicobacter pylori* antibodies in Henoch–Schönlein purpura. Autoimmunity 36, 307.

Öner, A., Tinaztepe, K., Erdogan, Ö. 1995. The effect of triple therapy on rapidly progressive type of Henoch–Schönlein nephritis. Pediatr. Nephrol. 9, 6.

Ono, T., Muso, E., Suyama, K., et al. 1996. Intraglomerular deposition of intact cross-linked fibrin in IgA nephropathy and Henoch–Schönlein nephritis. Nephron 74, 522.

Prajapati, C., Casson, I.F. 1997. Henoch–Schönlein purpura associated with ranitidine. Int. J. Clin. Pract. 51, 251.

Rao, J.K., Allen, N.B., Pincus, T. 1998. Limitations of the 1990 American college of rheumatology classification criteria in the diagnosis of vasculitis. Ann. Intern. Med. 129, 345.
Demonstration that the ACR criteria are not adequate for diagnosis purpose.

Ravelli, A., Carnevale-Maffe, G., Ruperto, N., et al. 1969. IgA nephropathy and Henoch–Schönlein syndrome occurring in the same patient. Nephron 72, 111.

Ronda, N., Esnault, V.L.M., Layward, L., et al. 1994. Anti neutrophil cytoplasm antibodies (ANCA) of IgA isotype in adult Henoch–Schönlein purpura. Clin. Exp. Immunol. 95, 49.

Ronkainen, J., Nuutinen, M., Koskimies, O. 2002. The adult kidney 24 years after childhood Henoch–Schönlein purpura: a retrospective cohort study. Lancet 360, 666.

Saulsbury, F.T. 1993. Corticosteroid therapy does not prevent nephritis in Schönlein–Henoch purpura. Pediatr. Nephrol. 7, 69.

Saulsbury, F.T. 1997. Alteration in the O-linked glycosylation of IgA1 in children with Henoch–Schönlein purpura. J. Rheumatol. 24, 2246.

Saulsbury, F.T., Kirkpatrick, P.R., Bolton, W.K. 1991. IgA antineutrophil cytoplasmic antibody in Henoch–Schönlein purpura. Am. J. Nephrol. 11, 295.

Schönlein, J.L., 1847. Allgemeine und spezielle pathologie und Therapie. Vol. 1. 3rd ed., p. 48.

Scivittaro, V., Amore, A., Emancipator, S.N. 1993. Animal models as a mean to study IgA nephropathy. Contrib. Nephrol. 104, 65.

Singer, J.I., Kissoon, N., Gloor, J. 1992. Acute testicular pain: Henoch–Schönlein purpura versus testicular torsion. Pediatr. Emerg. Care 8, 51.

Sinico, R.A., Tadros, M., Radice, A., et al. 1994. Lack of IgA antineutrophil cytoplasmic antibodies in Henoch–Schönlein purpura and IgA nephropathy. Clin. Immunol. Immunopathol. 73, 19.

Smith, G.C., Joyce, E.D., Hughes, D.A., et al. 1997. Complement activation in Henoch–Schönlein purpura. Pediatr. Nephrol. 11, 477.

Sola Alberich, R., Jammoul, A., Masana, L. 1997. Henoch–Schönlein purpura associated with acetylsalicylic acid. Ann. Intern. Med. 126, 665.

Soylemezoglu, O., Sultan, N., Gursel, T., et al. 1996. Circulating adhesion molecules ICAM-1, E-selection and von Willebrand factor in Henoch–Schönlein purpura. Arch. Dis. Child. 75, 507.

Stockert, R.J., Kressner, M.S., Collins, J.C., et al. 1982. IgA interaction with the asialoglycoprotein receptor. Proc. Natl. Acad. Sci. USA 79, 6229.

Talbot, D., Craig, R., Falconer, S., et al. 1988. Henoch–Schönlein purpura secondary to trauma. Arch. Dis. Child. 63, 1114.

Ten Holder, S.M., Joy, M.S., Falk, R.J. 2002. Cutaneous and systemic manifestations of drug-induced vasculitis. Ann. Pharmacothar. 36, 130.

Tomino, Y., Endoh, M., Suga, T., et al. 1982. Tokai J. Exp. Clin. Med. 7, 527.

Tomana, M., Matousovic, K., Julian, B.A., et al. 1997. Galactose-deficient IgA1 in sera of IgA nephropathy patients is present in complexes with IgG. Kidney Int. 52, 509.

Trancrede-Bohin, E., Ochonisky, S., Vignon-Pennamen, M.D., et al. 1997. Schönlein–Henoch purpura in adult patients. Predictive factors for IgA glomerulonephiritis in a retrospective of 57 cases. Arch. Dermatol. 133, 438.

Turi, S., Nagy, J., Haszon, I., et al. 1989. Plasma factors influencing PG12-like activity in patients with IgA nephropathy and Henoch–Schönlein purpura. Pediatr. Nephrol. 3, 61.

Urizar, R.E., Michael, A., Sisson, S., et al. 1968. Anaphylactoid purpura II. Immunoflurescent and electron microscopy studies of the glomerular lesions. Lab. Invest. 19, 437.
First demonstration of glomerular IgA deposits in HSP.

Vernier, R.L., Farquhar, M.G., Brunson, J.G., et al. 1961. Anaphylactoid purpura I. Pathology of the skin and kidney and frequency of streptococcal infections. Pediatrics 27, 181.

Watts, R.A., Carruthers, D.M., Scott, D.G. 1995. Epidemiology of systemic vasculitis: changing incidence or definition. Semin. Arthritis Rheum. 25, 28.

White, R.H.R., Cameron, J.S., Trounce, J.R. 1966. Immunosuppressive therapy in steroid-resistant proliferative glomerulonephritis accompanied by the nephrotic syndrome. BMJ 2, 853.

White, R.H.R., Yoshikawa, N. 1993. Henoch–Schönlein nephritis. In: T.M. Barrat, M. Holiday (Eds.), Pediatric Nephrology. Williams & Wilkins, Baltimore, p. 729.

Yang, Y.H., Hung, C.F., Hsu, C.R., et al. 2005. A nationwide survey on epidemiological characteristics of childhood Henoch–Schonlein purpura in Taiwan. Rheumatology 44, 618.

Yang, Y.H., Lai, H.J., Huang, C.M., et al. 2004. Sera from children with active Henoch–Schönlein purpura enhance the production of interleukin 8 by human umbilical venous endothelial cells. Ann. Rheum. Dis. 63, 1511.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 19

Mixed Cryoglobulinemia

Clodoveo Ferri*, Maria Teresa Mascia

Chair of Rheumatology, Unit of Rheumatology, Department of Internal Medicine, University of Modena & Reggio Emilia, Medical School, Modena, Italy

1. Introduction

The term cryoglobulinemia refers to the presence in the serum of one (monoclonal cryoimmunoglobulinemia) or more immunoglobulins (mixed cryoglobulinemia), which precipitate at temperatures below 37°C and redissolve on rewarming (Lospalluto et al., 1962; Gorevic et al., 1980; Gorevic and Frangione, 1991; Brouet et al., 1974; Meltzer et al., 1966; Ferri et al., 2002a; Fig. 1). The mechanism(s) responsible for cryoprecipitation still remains obscure; possibly it is secondary to intrinsic characteristics of different immunoglobulin (Ig) components and/or it can be due to the interaction among single cryoprecipitable Ig components (Ferri et al., 2002a).

Cryoglobulinemia is classified according to Ig composition into three main subgroups (Brouet et al., 1974); cryoglobulinemia type I is composed by a single monoclonal Ig; type II and III mixed cryoglobulinemia (MC) are immune complexes including polyclonal IgGs, the autoantigens, and mono- or poly clonal IgMs, respectively. The IgMs are the corresponding autoantibodies with rheumatoid factor (RF) activity. Cryoglobulinemia type I, usually a paraprotein, is mainly found in patients with overt lymphoid tumours, i.e. immunocytoma/Waldenstrom's macroglobulinemia, multiple myeloma, etc. (Gorevic et al., 1980; Gorevic and Frangione, 1991; Brouet et al., 1966; Ferri et al., 2002a) usually, it is

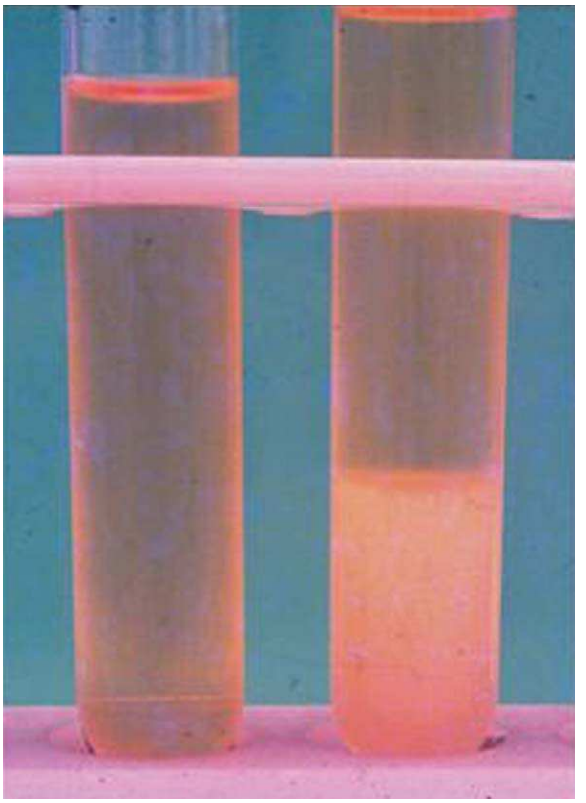


Figure 1. Cryoprecipitate of mixed cryoglobulins after 7 day storage at +4°C in a serum sample from a patient with cryoglobulinemic syndrome (right) compared to a normal serum.

*Corresponding author.
Cattedra di Reumatologia, Università di Modena e Reggio Emilia, Policlinico di Modena, Via del Pozzo, 71, 41100 Modena, Italy.
Tel.: +39-059-422-4199; Fax: +39-059-422-4178.
E-mail address: clferri@unimo.it (C. Ferri).

DOI: 10.1016/S1571-5078(05)05019-1

asymptomatic, in only few cases it can be complicated by hyperviscosity syndrome. Type II and III MC can be associated with well-known infectious, immunological, or neoplastic diseases (Gorevic et al., 1980; Gorevic and Frangione, 1991; Brouet et al., 1966; Ferri et al., 2002a). The composition of cryoprecipitates is usually evaluated by means of immunoelectrophoresis or immunofixation. Using more sensitive methodologies (immunoblotting or two-dimensional polyacrylamide gel electrophoresis) type II MC may show a microheterogeneous composition. In particular, oligoclonal IgMs or a mixture of polyclonal and monoclonal IgMs can be detected (Tissot et al., 1994). This serological subset, termed type II–III MC, could represent an intermediate state, suggesting the possible evolution from type III to type II MC. The composition of type II–III MC could reflect the most recent molecular studies showing the presence of oligoclonal B-lymphocyte proliferation in liver and bone marrow biopsies in the majority of patients with type II MC (Magalini et al., 1998; De Vita et al., 2000).

Variable amounts of circulating mixed cryoglobulins are often detected in a great number of infectious, immunological or neoplastic disorders (Gorevic et al., 1980; Gorevic and Frangione, 1991; Brouet et al., 1966; Ferri et al., 2002a); while the so-called 'essential' MC, first described in 1966, represents a distinct clinical syndrome, which can be classified among systemic vasculitides (Meltzer et al., 1966). Besides the presence of serum mixed cryoglobulins, the 'essential' MC is characterized by a typical clinical triad—purpura, arthralgias, and weakness and frequent multiple organ involvement (Table 1) (Gorevic et al., 1980; Gorevic and Frangione, 1991; Brouet et al., 1966; Ferri et al., 2002a).

Table 1
Demographic, clinical and serological features of 210 MC patients

Female/Male ratio	3.7:1
Mean age disease onset (yrs)	5311.6
Mean age at diagnosis (yrs)	56.4±11.2
Mean disease duration (yrs)	10.5±7.3
Purpura	98%
Weakness	100%
Arthralgias	98%
Arthritis	7%
Raynaud's phenomenon	48%
Sicca syndrome	53%
Skin ulcers	22%
Peripheral neuropathy	80%
Liver involvement	77%
Renal involvement	30%
Lung involvement	2%
Diffuse vasculitis	6.2%
Hyperviscosity syndrome	0.5%
B-cell lymphoma	10%
Hepatocellular carcinoma	3.3%
Thyroid cancer	1%
MC type II/type III ratio	2
Cryocrit %	4.4±11.7
Rheumatoid factor	98%
C4 mg% (nv 20–60)	11±7.7
C3 mg% (nv 90–180)	100±28
Autoantibodies[a]	56%
Anti-HCV Ab±HCV RNA	92%
Anti-HBV Ab	42%
HBsAg	9%

[a] Autoantibodies: anti-nuclear and/or anti-mithocondrial, and/or anti-smooth muscle antibodies.

2. Prevalence

The disease is considered to be a relatively rare disorder; however, as yet there are no adequate epidemiological studies regarding its overall prevalence. The prevalence of MC presents great geographic heterogeneity, being more common in Southern Europe than in Northern Europe or Northern America (Gorevic et al., 1980; Ferri et al., 2002a, 2004).

3. Epidemiology

The clinical MC syndrome affects prevalently the female gender (FM = 3.7:1; Table 1), while the disease onset varies between 4th and 6th decades (Ferri et al., 2004).

4. Etiopathogenesis

A possible role for hepatotropic viruses in the pathogenesis of the MC has long been hypothesized

on the basis of the frequent liver involvement observed during the clinical course of the disease (Gorevic et al., 1980; Gorevic and Frangione, 1991; Ferri et al., 2002a; Levo et al., 1977; Bombardieri et al., 1979). First, a role for hepatitis B virus (HBV) even in MC was investigated during the 1970s, following the example of polyarteritis nodosa, another systemic vasculitis, frequently associated with this virus (Levo et al., 1977; Bombardieri et al., 1979; Gocke et al., 1970). Since HBV antigenemia was rarely recorded, it can be estimated that HBV can represent a causative factor of MC in less than 5% of individuals (Ferri et al., 2004). With the discovery of hepatitis C virus (HCV) as the major etiologic agent of non-A-non-B chronic hepatitis (Choo et al., 1989), an increasing number of epidemiological studies suggested an important role for HCV in the pathogenesis of MC (Choo et al., 1989; Ferri et al., 1991, 1993a; Abel et al., 1993; Dammacco et al., 2001). HCV seropositivity in MC varies from 70% to 100% of individuals in different patient populations (Ferri et al., 1993a) and it is almost constantly associated to HCV viremia (Ferri et al., 1991). In addition, HCV RNA is often markedly concentrated (1000-fold) in the cryoprecipitates compared to supernatants (Abel et al., 1993). The pathogenic role of HCV infection in MC syndrome has been definitely demonstrated by a large body of clinico-epidemiological and laboratory investigations (Ferri et al., 1993a, 2002a, 2004; Abel et al., 1993; Dammacco et al., 2001). A direct involvement of HCV antigens in immune-complex-mediated cryoglobulinemic (MC) vasculitis has also been suggested, on the basis of immunohistochemical and molecular biological studies, including HCV RNA detection by in situ hybridization (Ferri et al., 2002a; Sansonno et al., 1996, Agnello and Abel, 1997). Therefore, the term 'essential' no longer seems to be appropriate for the majority of MC patients (Ferri et al., 2002a, 2004).

Low levels of circulating mixed cryoglobulins can be detected in over 50% HCV-infected individuals; however, overt MC syndrome develops in only a minority of cases (Lunel et al., 1994; Pawlotsky et al., 1994). On the other hand, the large diffusion of HCV infection worldwide contrasts with the geographical heterogeneity observed in the prevalence of HCV-related MC (Ferri et al., 1993a, 2002a), suggesting a role for particular HCV genotypes, unknown environmental and/or genetic co-factors. However, the actual role of the above co-factors still remains to be demonstrated (Ferri et al., 2000, 2002a).

The histopathological hallmark of MC is the leukocytoclastic vasculitis (Fig. 2) of small-sized vessels, including arterioles, capillaries, and venules (Gorevic et al., 1980; Gorevic and Frangione, 1991; Ferri et al., 2002a; Dammacco et al., 2001; Agnello and Abel, 1997). Leukocytoclastic vasculitis is secondary to the vessel deposition of circulating immune-complexes, mainly the cryoglobulins, and complement. This is a necrotizing vasculitis characterized by extensive fibrinoid necrosis of the vessel wall with permeation of the wall by disintegrating neutrophils (Fig. 2). The consequence of vasculitis is the ischemic organ damage responsible for typical clinical manifestations of MC syndrome: skin purpura and ulcers (Figs. 3 and 4), peripheral neuropathy, glomerulonephritis, lung alveolitis, endocrine disorders, and diffuse vasculitis (Gorevic et al., 1980; Gorevic and Frangione, 1991; Ferri et al., 2002a; Table 1).

Both epidemiological and clinico-pathological observations suggest that MC is the result of a multifactorial and multistep pathogenetic process (Ferri et al., 2002a). The immune-complex-mediated vasculitis is the result of this complex process, while B-lymphocyte expansion (Gorevic and Frangione, 1991) may represent the remote disorder responsible for autoantibodies and immune-complex production and in some instances for malignant lymphomas complicating the MC syndrome.

A direct role of HCV, both hepato- and lymphotropic virus (Ferri et al., 2000, 2002a; Zignego et al., 1992, 1995; Ferri et al., 1993b), in the B-cell expansion has been initially hypothesized on the basis of the high frequency of HCV-RNA positive lymphocytes in peripheral blood and bone marrow of cryoglobulinemic patients (Zignego et al., 1992, 1995; Ferri et al., 1993b), as well as the significant percentage of individuals developing malignant lymphomas (Ferri et al., 2000, 2002a). In patients with type II MC, the B-cell infection precedes tumoral transformation, possibly playing a major

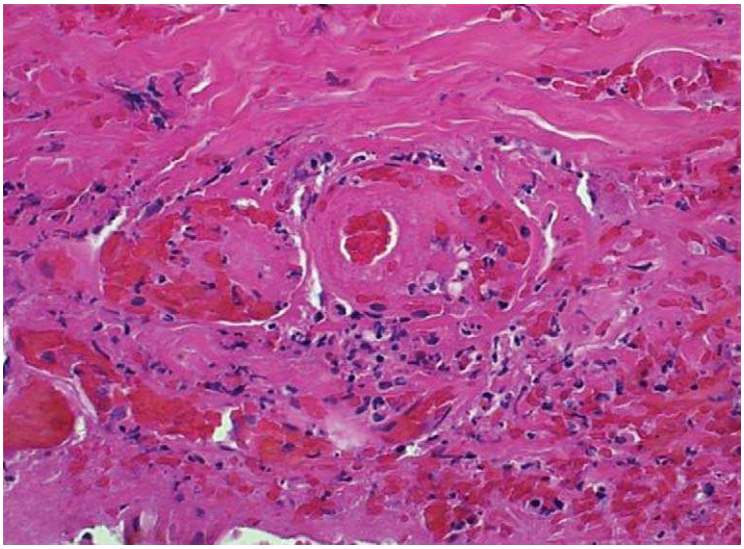


Figure 2. Severe necrotizing leukocytoclastic vasculitis: extensive fibrinoid necrosis of the vessel wall with permeation of the wall by disintegrating neutrophils. Leukocytoclastic vasculitis is secondary to the vessel deposition of circulating immune-complexes, mainly the cryoglobulins, and complement.

role in the lymphomagenesis, while anaplastic cells are no longer completely permissive to HCV replication (Sansonno et al., 1996).

Being HCV an RNA virus without reverse trascriptase activity, viral genome cannot integrate in the host genome. Probably, HCV may exert its oncogenic potential, indirectly, through viral proteins, particularly the core protein (Koike, 2002); even if the expression of core protein did not appear to significantly modify the main intracellular signalling transduction pathways (Giannini et al., 2002). The chronic stimulation of the lymphatic system might be exerted through viral epitopes, autoantigen production, and/or molecular mimicry mechanism (Ferri et al., 2000, 2002a).

Alternatively, HCV in association with very low-density lipoprotein (VLDL) would induce a T-independent primordial B-cell population producing monoclonal Ig with WA idiotype (Abel et al., 1993; Agnello, 1997). The RF activity of WA clones would be a consequence of somatic mutations induced after the stimulation by HCV–VLDL complexes. In this context, the possible evolution to B-NHL might be the consequence of the accumulation of stochastic genetic aberrations (Abel et al., 1993; Agnello, 1997).

A chronic stimulation of the B-cell by HCV epitopes may lead to the expansion of some B-cell subpopulations with favourable and/or dominant genetic characteristics (Ferri et al., 2000, 2002a; Zignego et al., 1997). The in vitro observation that HCV E2 protein is able to bind to CD81 molecule on the surface of B-cell (Pileri et al., 1998) suggested that this interaction may be responsible for the strong and sustained polyclonal stimulation of B lymphocytes (Zignego et al., 1997).

The significantly high frequency of t (14; 18) translocation or bcl-2 rearrangement observed in B cells may represent an important step of HCV-related lymphoproliferation (Zignego et al., 2000, 2002). The consequence is the abnormally elevated expression of Bcl-2 protein with consequent inhibition of apoptosis and abnormal B-cell survival (Zignego et al., 2002; Giannelli et al., 2003). In conclusion, it is possible to hypothesize that during chronic HCV infection, several factors, including the interaction between HCV E2 protein and CD81 molecule, the high viral variability, and the persistent infection of both hepatic and lymphatic cells, may favour a sustained and strong B-cell activation. The latter may in turn favour the apparition of t (14; 18) translocation with Bcl-2

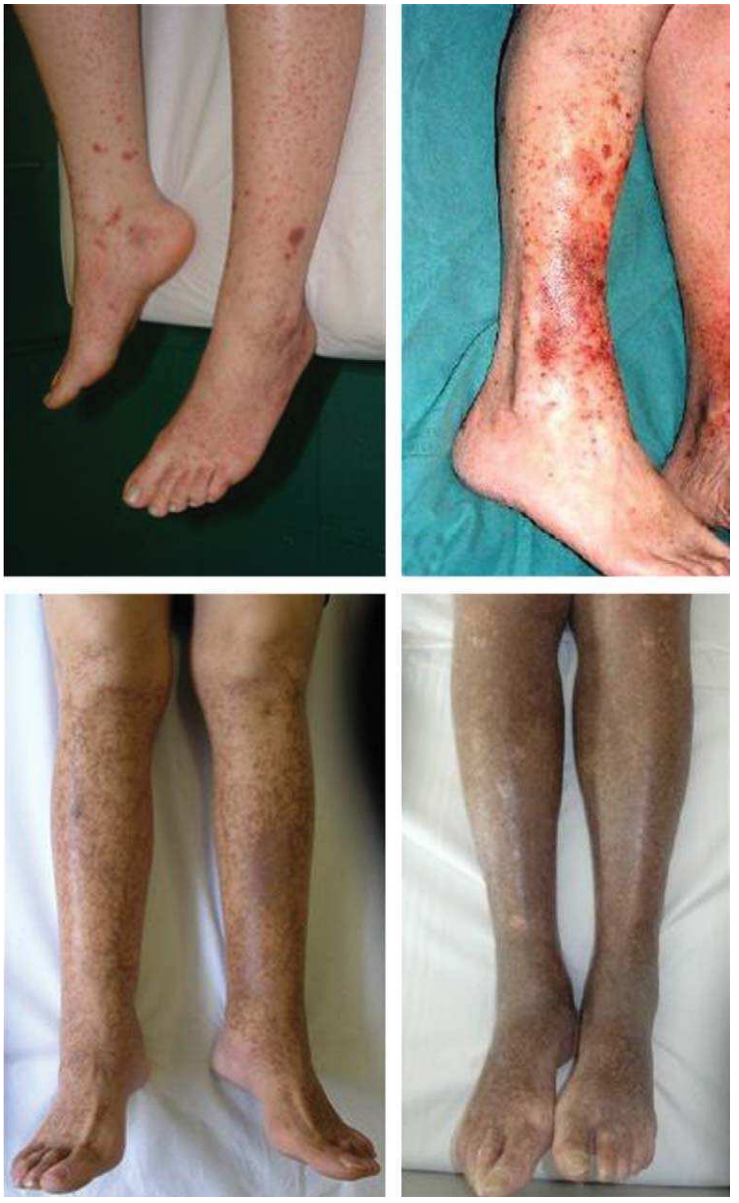


Figure 3. Cutaneous cryoglobulinemic vasculitis: recent onset, palpable purpura on the legs with both isolated and confluent purpuric lesions (above); ochreous coloration of the skin with sock-like distribution due to chronic hemosiderin deposits in two patient with long-lasting mixed cryoglobulinemia syndrome (below).

protein overexpression responsible for abnormally prolonged B-cell survival, which ultimately may favour the development of MC syndrome. Similarly, the prolonged B-cell survival may represent a predisposing condition for further genetic aberrations responsible for frank B-cell malignancy (Ferri et al., 2000, 2002a, 2004). This later may develop in patients with type II MC, usually after a long-term follow-up (Ferri et al., 2000, 2002a). It can vary from diffuse large B-cell lymphoma (observed in 40–50% of cases) to marginal-zone lymphoma (extranodal, nodal, or splenic) or, more

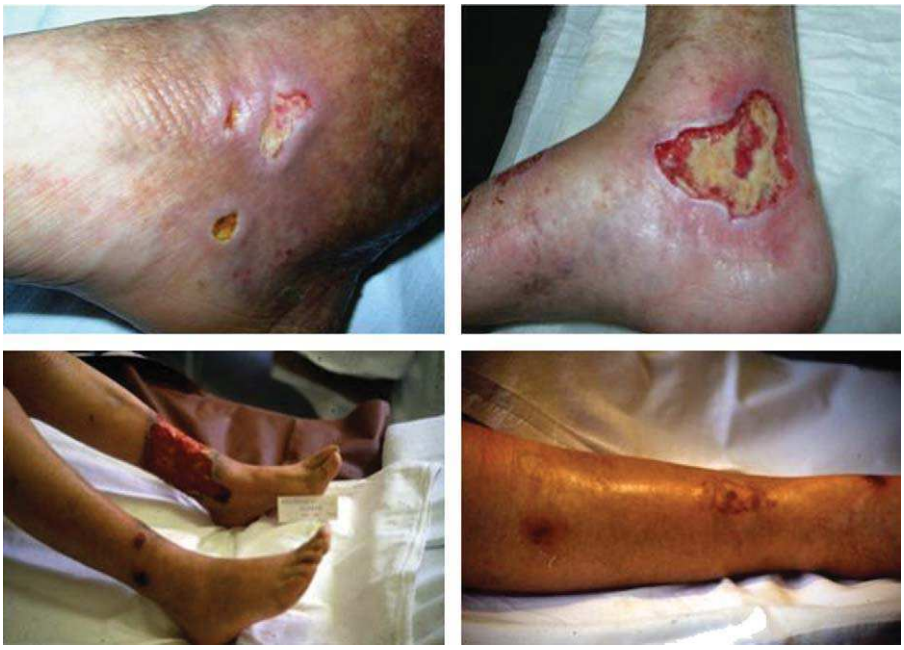


Figure 4. Perimalleolar torpid ulcers with diffuse hyperpigmentation of the surrounding skin (above, left); large and torpid ulcer (above, right); severe skin ulcers in a patient with cryoglobulinemic vasculitis before (bottom, left) and after (bottom, right) prolonged plasma exchange treatment.

rarely, B-cell chronic lymphocytic leukaemia (B-CLL) and lymphoplasmacytic lymphoma/immunocytoma (LPL/Ic) (Trejo et al., 2003; Ramos-Casals et al., 2004). The malignancy may be related to peripheral B-cell expansion (Ferri et al., 2000, 2002a) and to lymphoid infiltrates observed in the liver and bone marrow of MC patients (38). These infiltrates have been regarded as 'early lymphomas', since they are sustained by lymphoid components indistinguishable from those of B-CLL and LPL/Ic (Monteverde et al., 1997). However, unlike frank malignant lymphomas, they tend to remain unmodified for years or even decades and are followed by overt lymphoid tumours in about 10% of cases (Monteverde et al., 1997; Ferri et al., 2000). These characteristics justify the proposed term of 'monotypic lymphoproliferative disorder of undetermined significance (MLDUS)' (Monteverde et al., 1997; Ferri et al., 2000). Of interest, type II MC-related MLDUS has its highest incidence in the same geographic areas where about 30% of 'idiopathic' BCL patients also display HCV-positivity, and where an increased prevalence of HCV genotype 2a/c has been observed in both MC and BCL (Ferri et al., 2000; Zignego et al., 1996).

Type II MC-associated MLDUS presents two main pathological patterns; namely B-CLL-like and LPL/Ic-like, often detectable as lymphoid infiltrates in the liver and bone marrow (Ferri et al., 2000; Harris et al., 1994). In serial biopsies, these infiltrates tend to remain unmodified in the bone marrow and may undergo spontaneous re gression in the liver in case of cirrhotic evolution (Monteverde et al., 1997).

5. Clinical manifestations

Skin manifestations are the most frequent and typical symptoms of the MC (Table 1, Figs. 3 and 4). Orthostatic purpura is usually intermittent, the dimension and diffusion of skin lesions largely vary, from sporadic, isolated petechias to severe vasculitic lesions, often complicated by torpid ulcers

of the legs and malleolar areas (Figs. 3 and 4). After repeated episodes of purpura two-third of patients showed characteristic, often confluent areas of ochreous coloration on the legs. Besides the vasculitic mechanism, various co-factors, in particular chronic venous insufficiency, physical stress, such as prolonged standing, and/or muggy weather may trigger orthostatic purpura.

Arthralgias represent another frequent symptom of MC, while clinically overt arthritis is quite rare. Some patients show mild, non-erosive oligoarthritis, which is often sensitive to low doses of steroids with or without hydroxychloroquine. (Ferri et al., 2002a, 2004; Fadda et al., 2002; Ramos-Casals et al., 2001).

MC patients may complain of xerostomia and xerophthalmia; however, only a few cases meet the current criteria for the classification of primary Sjogren's syndrome (Ferri et al., 2002a, 2004).

Peripheral neuropathy, more often presenting as mild sensory neuritis, is a frequent complication of the MC (Ferri et al., 1992, 2002a, 2004), it is secondary to vasculitis of vasa nervorum and/or direct autoimmune nerve injury (Ferri et al., 1992, 2002a, 2004; Olivieri et al., 2003; Invernizzi et al., 1983). Usually, MC patients complained of paresthesias with painful and/or burning sensations in the lower limbs, often with nocturnal exacerbation. The chronicity of these symptoms along with their lack of response to common treatments may severely affect the quality of life of these patients. Peripheral motor neuropathy usually appeared abruptly, often as asymmetric mononeuritis and it may complicate the alpha-interferon treatment in some patients (Ferri et al., 2002a, 2004). The central nervous system involvement with dysarthria and hemiplegia is rare and often difficult to distinguish from the most common atherosclerotic manifestations (Ferri et al., 2002a, 2004).

Overt chronic hepatitis, generally with mild-moderate clinical course, can be observed at any time during the natural history of the disease. Liver involvement may evolve to cirrhosis in about 25% of cases, while only few patients develop hepatocellular carcinoma. However, in some individuals chronic hepatitis became a life-threatening complication, particularly in combination with renal involvement (Ferri et al., 2004). Membranoproliferative glomerulonephritis type I is one of the most important organ involvement, which may severely affect the prognosis and survival of the MC (Ferri et al., 2002a, 2004).

Widespread vasculitis involving medium-small sized arteries is observed in a minority of patients (2) (Ferri et al., 2002a, 2004; Agnello and Abel, 1997). This is an extremely severe complication, which may involve the skin, kidney, lungs, central nervous system, and/or gastrointestinal tract. Abdominal pain, simulating an acute abdomen, is the present symptom of intestinal vasculitis. A timely diagnosis and high-dosage steroid treatment are necessary for this life-threatening complication (Ferri et al., 2002a, 2004).

Interstitial lung involvement has been anecdotally observed in HCV-positive patients with or without MC syndrome (Ferri et al., 1997, 2002a, 2004). This complication is characterized by subclinical alveolitis, as demonstrated by means of bronco-alveolar lavage in unselected MC patient series (Salaffi et al., 1996). In rare cases, this generally mild manifestation may lead to clinically evident interstitial lung fibrosis (Ferri et al., 1997).

Some endocrine gland dysfunction can be observed in a significantly higher number of MC patients compared with age- and sex-matched controls; in particular, diabetes mellitus type II, thyroid, and gonadal dysfunction (Ferri et al., 2002a, 2004; Antonelli et al., 1999, 2004).

Hyperviscosity syndrome due to high levels of serum cryoglobulins is rare (Ferri et al., 1990). In general, there is no relationship between the severity of MC manifestations, such as glomerulonephritis, skin ulcers, or diffuse vasculitis and the serum levels of complement or cryoglobulins. Hemolytic complement activity is almost invariably depressed, showing the typical pattern of low or undetectable C4 and normal or relatively normal C3 serum levels. The level of circulating cryoglobulins rarely correlates with the MC features. This observation might be explained on the basis of different hypotheses: the pathogenic role of other non-cryoprecipitable immune-complexes, their intrinsic capacity to activate the complement, and/or the in situ formation of pathogenic immune-complexes, with a relative concentration of HCV virions (Ferri et al., 2002a, 2004; Abel et al., 1993).

The B-cell lymphomas represent the most frequent neoplastic complication of MC (Ferri et al., 2000, 2002a, 2004). Other neoplastic complications of MC, i.e. hepatocellular carcinoma and papillary thyroid cancer, are less frequently observed, often as late manifestations of the MC syndrome (Ferri et al., 1996, 2000, 2002a, 2004; Antonelli et al., 1999). In this light, the MC can be regarded as a pre-neoplastic disorder (Ferri et al., 2000, 2002a, 2004).

One or more serum autoantibodies can be detected in over half patients, more frequently low titer anti-nuclear (ANA, diffuse pattern) and/or anti-mitocondrial (AMA), and/or anti-smooth muscle (ASMA), without any relationship with other clinico-serological parameters. Serum anti-HCV antibodies, almost invariably associated to HCV RNA, are detectable in the large majority of MC patients (Ferri et al., 1991, 2002a, 2004). Conversely, markers of HBV infection can be detected in over one-third of patients often associated with HCV infection, while isolated ongoing HBV infection is rare (Ferri et al. 1991, 2002a, 2004).

6. Diagnostic investigations

A careful recording of anamnestic data along with a wide physical examination of MC patients is recommended at the first visit and at regular time intervals during the follow-up. A correct approach and monitoring of the patient is crucial for the diagnosis, as well as to timely detect some severe, life-threatening complications of MC. Usually, the presence of typical palpable purpura or areas of ochreous coloration on the legs (Fig. 3) is sufficient to suspect the disease, which needs to be confirmed by the detection of serum mixed cryoglobulins. The neurologic evaluation is necessary to early evidence the frequent peripheral sensory neuropathy or the less common motor involvement (Ferri et al., 1992). Peripheral edema, asciitis, and/or arterial hypertension are important symptoms of liver and/or kidney involvement. Besides, the enlargement of spleen and lymph nodes as well as constitutional symptoms (fever, fatigue, etc) are important to suspect the presence of malignant lymphomas (Ferri et al., 2004). Similarly, physical and ultrasonographic examination of the liver and thyroid, at least once a year, are mandatory to detect early the possible organ alterations, including the malignancies (Ferri et al., 2004).

Diagnosis of MC syndrome is based on both clinical and laboratory findings. Given its clinical polymorphism, a single manifestation (skin vasculitis, hepatitis, nephritis, peripheral neuropathy, etc.) is often the only apparent or clinically predominant feature, so that a correct diagnosis might be delayed or overlooked entirely (Ferri et al., 2002a, 2004).

The detection of circulating mixed cryoglobulins is essential for a definite diagnosis of MC syndrome. In this respect, repeated cryoglobulin determinations is often necessary in some subjects with very low amounts or transient absence of cryoglobulins, the latter due to the wide variability of cryoprecipitable immune-complex levels (Ferri et al., 2002a). On the other hand, it is necessary to avoid false-negative results due to Ig cold precipitation at room temperature also (Ferri et al., 2002a). Thus, the first steps to evaluate serum cryoglobulins (blood sampling, clotting, and serum separation by centrifugation) should be always carried out at 37°C and the cryocrit determination and cryoglobulin characterisation at 4°C, after 7 days. Moreover, cryocrit determinations should be done on blood samples without anticoagulation to avoid false-positive results due to cryofibrinogen. Theye are not universally accepted methodologies for cryoglobulin measurements; however, simple standardized indications are often sufficient for testing cryoglobulinemia (Ferri et al., 2002a; Kallemuchikkal and Gorevic, 1999). Generally, the analysis of cryoprecipitate is carried out by means of immunoelectrophoresis or immunofixation, or by more sensitive methodologies such as iimmunoblotting or two-dimensional polyacrylamide gel electrophoresis (Ferri et al., 2002a; Tissot et al., 1994).

There are not available diagnostic criteria for MC. Preliminary criteria for MC classification have been proposed: skin purpura, circulating mixed cryoglobulins, low C4, and leukocytoclastic vasculitis represent the major clinico-serological and pathological hallmarks of the disease, while

other minor features can be used to classify those patients with 'incomplete' MC syndrome (Ferri et al., 2002a). Finally, MC can be classified as 'essential' or 'secondary' with regard to the presence/absence of well-known triggering factor(s); following the striking association between MC and HCV infection, the term 'essential' can be referred to only a minority of patients (<5%).

On the basis of its clinical and histopathological features, MC is classified among systemic vasculitides, in the subgroup of small vessel vasculitides, which also includes cutaneous leukocytoclastic vasculitis and Schonlein–Henoch purpura (Ferri et al., 2004).

7. Differential diagnosis

Because of its clinical polymorphism MC syndrome may overlap with a variety of immunological and neoplastic diseases; namely, other systemic vasculitides, Sjogren's syndrome, autoimmune hepatitis, and B-cell lymphoproliferative disorders.

Differential diagnosis with other systemic vasculitides is quite easy if serological markers (cryoglobulinemia, specific autoantibodies, and complement profile) and histopathological patterns (different alterations and size of involved vessels) are correctly evaluated. MC and Sjogren's syndrome may share various symptoms: xerostomia, xerophthalmia, arthralgias, purpura, serum cryoglobulins and rheumatoid factor, as well as the possible development of B-cell lymphomas (Vitali et al., 2002; Ramos-Casals et al., 2001). A correct diagnosis can be done in the majority of cases by considering the following findings: typical histopathological alterations of salivary glands and specific autoantibodies (anti-RoSSA/LaSSB) of Sjogren's syndrome (Vitali et al., 2002) are rarely found in MC patients; conversely, HCV infection, cutaneous leukocytoclastic vasculitis, and renal and/or liver involvement are seldom recorded in primary Sjogren's syndrome. However, in some patients the differential diagnosis may result very difficult; thereafter, it might be correct to classify these cases as MC/Sjogren's overlap syndrome.

Patients with autoimmune hepatitis may present low amounts of serum cryoglobulins, HCV-positivity, and some extrahepatic manifestations, such as thyroiditis, sicca syndrome, and arthritis (Lenzi et al., 1991; Ferri et al., 1994). In these instances, searching some patognomonic findings can do a correct classification of the disease; in particular, high titre autoantibodies (ANA, ASMA, and anti-LKM1) are more often detectable in autoimmune hepatitis, while leukocytoclastic vasculitis and complications such as membranoproliferative glomerulonephritis are typically found in MC patients (Ferri et al., 2004).

Finally, B-NHL complicating HCV-related MC can be confused with some 'idiopathic' B-NHL showing clinico-serological findings of MC. The differential diagnosis of these two entities may be important especially for its therapeutic implications: the treatment of B-cell NHL complicating the MC may need some precautions due the concomitance of HCV infection and the possible liver and/or renal failure. These complications should also be taken into account in HCV-related B-NHL without MC syndrome (Ferri et al., 2000).

8. Treatment

Since the severity, activity, and the overall outcome of MC largely vary among patients, the disease behaviour is often unpredictable during the clinical follow-up (Ferri et al., 2002a, 2004).

In the majority of cases, MC can affect, directly and/or indirectly, the outcome of the patients. The cumulative 10th year survival of MC patients is significantly lower compared to age- and sex-matched general population (Ferri et al., 2004). A fatal outcome is the result of two or more concomitant clinical manifestations, including renal involvement, severe hepatitis possibly complicated by cirrhosis, diffuse vasculitis, and malignancies (Ferri et al., 2004). Other worse prognostic factors are the patient's age at the time of diagnosis (>60 years) and male gender (Ferri et al., 2004).

The clinical course and prognosis of type I cryoglobulinemia mainly depend on the underlying disease, varying from benign monoclonal

gammopathy to malignant B-cell neoplasias; consequently, the treatment is mainly directed to these disorders (Ferri et al., 2004). It is per se often asymptomatic with the exception of the hyperviscosity syndrome correlated to the high levels of cryocrit; this complication, especially in the presence of clinically severe hemorheological alterations, may be usefully treated with plasma exchange.

The treatment of MC syndrome is particularly challenging because of its complex etiopathogenesis. A correct therapeutic approach to HCV-related MC must deal with three conflicting conditions: HCV infection, autoimmune, and lymphoproliferative alterations. Considering the cascade of events leading from HCV infection to overt MC syndrome we can treat the disease at three different levels by means of etiological, pathogenetic, and/or symptomatic therapies (Ferri et al., 2000, 2002a, 2003; Gumber and Chopra, 1995; Monti et al., 1995; Lamprecht et al., 1999).

Given the causative role of HCV, an attempt at HCV eradication should be done in all cases of HCV-associated cryoglobulinemic vasculitis (Ferri et al., 2003). In patients with MC, the interferon treatment seems to lead to clinical improvement, along with viral clearance and regression of indolent lymphoid infiltrates in repeated bone marrow biopsies (Mazzaro et al., 1996). Moreover, combined alpha-interferon/ribavirin therapy can induce the regression of T (14; 18) bearing B-cell clones in HCV-positive patients (Giannelli et al., 2003). These observations suggest that antiviral therapy may improve or treat the immune-lymphoproliferative disorder underlying the MC. Unfortunately, HCV eradication is usually achieved in only a minority of treated patients; while the clinical response to antiviral treatment is often transient and not rarely associated with important immune-mediated complications (Ferri et al., 2003). In particular, interferon may trigger or severely worsen the peripheral sensory-motor neuropathy (Ferri et al., 2002a, 2003, 2004); moreover, polyarthritis, thyroid disorders, and erectile dysfunction may complicate alpha-interferon therapy in patients with type C hepatitis and/or MC (Ferri et al., 2002b, 2003, 2004). Possibly, the use of alpha-interferon, both antiviral and immunomodulating agent, may trigger or exacerbate some pre-existing, often subclinical, symptoms in predisposed subjects (Ferri et al., 2002a, 2003, 2004). The combination interferon/ribavirin might achieve the eradication of HCV infection in a significantly higher number of patients (McHutchison et al., 1998; Misiani et al., 1999; Zuckerman et al., 2000).

In the near future, a vaccine against HCV could represent a decisive advance in this field (Abrignani and Rosa, 1998). It could be able to prevent the evolution from HCV infection to both hepatic and extra-hepatic manifestations, including MC syndrome by interrupting the self-perpetuating autoimmune mechanism of the disease.

The most severe, life-threatening complications of MC may be responsive to immunosuppressive treatment with cyclophosphamide: a short-time course (2–3 months) of cyclophosphamide, in association with high dosage of steroids and/or plasma exchange, may be able to treat active or rapidly progressive glomerulonephritis, recent onset sensory-motor neuropathy, or widespread vasculitis (Gorevic et al., 1980; Ferri et al., 2002a, 2003, 2004). Interestingly, the treatment with cytotoxic drugs seems do not affect the progression of HCV infection, including liver involvement.

More recently, a pathogenetic treatment with rituximab, a monoclonal chimeric antibody that binds to the B-cell surface antigen CD20, has been proposed in HCV-positive MC patients (Zaja et al., 2003; Blood. 2003; Sansonno et al., 2003). Following the selective B-cell blockade, a clinico-serological improvement of MC was observed, along with a paradoxical increase of viral load in the responders (Sansonno et al., 2003). If confirmed, these preliminary observations suggest the possible use of combined or sequential therapy with rituximab and antiviral agents (Lamprecht et al., 2003).

The treatment with corticosteroids or plasma exchange may also work as immunomodulating or immunosuppressive treatments. Corticosteroids, alone or in association with plasma exchange and/or immunosuppressors, may represent the first-line intervention in the few cases of 'essential' CM. While in HCV-related MC an attempt with high dosage of steroids and plasma exchange (Fig. 4)

should be considered particularly in those patients who have failed to respond to alpha-interferon, or when this drug is contraindicated, or in the presence of severe rapidly progressive complications, especially active cryoglobulinemic nephropathy. The beneficial effect of such 'symptomatic' treatments can be reinforced by means of oral cyclophosphamide during the slow tapering and after the discontinuation of apheretic sessions (50–100 mg/day for 4–8 weeks). This sequential treatment can prevent the rebound phenomena that may be observed after the apheresis discontinuation. Low-antigen-content diet (LAC-diet) has been employed in some immune-complex-mediated disorders (Ferri et al., 1989, 1993c, 2002a, 2004). In MC patients, this particular dietetic treatment can improve the serum clearance of immune-complexes by restoring the activity of the reticulo-endothelial system overloaded by large amounts of circulating cryoglobulins (Ferri et al., 1989). Low dosage of steroids and/or LAC-diet may be sufficient to improve mild-moderate manifestations of cryoglobulinemic vasculitis, namely purpura, arthralgias, peripheral sensory neuropathy, and etc. (Ferri et al., 2002a, 2003, 2004).

Cryoglobulinemia may be responsible for hemorheological alterations, which may favour the appearance of vasculitic ulcers on the lower limbs (Ferri et al., 1990). Venous insufficiency and hot-muggy weather are important predisposing cofactors. Vascular manifestations, often associated with paresthesias due to peripheral sensory neuropathy, may severely affect the patient's quality of life. The treatment of venous insufficiency and/or climatotherapy, especially during the summer, may be of some usefulness.

In MC patients, the therapeutic approach should take into account the following guidelines: the treatment have to be tailored for the single patient, according to the severity of clinical symptoms (Ferri et al., 2002a, 2004) (58); during the asymptomatic phases of the disease, patients usually do not need any treatment, even in the presence of high levels of cryocrit; some symptoms such as arthralgias and palpable purpura are particularly sensitive to the smallest variations of daily steroid dosage (1–2 mg); combined peg-interferon/ribavirin may represent the choice treatment in patients with moderate-severe MC manifestations, especially those with active hepatitis; finally, severe, life-threatening vasculitic manifestations must be promptly treated with a combined therapy with plasma exchange, high dosage of steroids, and immunosuppressors. A careful clinical monitoring of the disease is mandatory in all cases, with particular attention to neoplastic complications.

Key points

- Mixed cryoglobulinemia (MC) includes: MC type II, composed by polyclonal IgG-monoclonal IgM, and MC type III, composed by polyclonal IgG-polyclonal IgM immune-complexes.
- MC may be secondary to various immunological, hematological, and infectious diseases, or it can represent a distinct disorder, the 'essential' MC. Following the discovery of a causative role of HCV, the term 'essential' is now referred to only a small percentage of patients.
- MC classification criteria include: serum mixed cryoglobulins, hypocomplementemia (low C4), leukocytoclastic vasculitis, typical clinical triad -purpura, weakness, arthralgias-, and multiple organ involvement.
- MC may share various clinico-serological features with different immunological/neoplastic diseases; differential diagnosis should take in account other systemic vasculitides, Sjogren's syndrome, autoimmune hepatitis, and B-cell lymphomas.
- MC syndrome is an immune-complex mediated systemic vasculitis (leukocytoclastic vasculitis) involving the small vessels, clinically characterized by cutaneous manifestations (orthostatic purpura, and ulcers), liver, renal, peripheral nerves, widespread vasculitis, and possible development of neoplastic disorders, mainly B-cell lymphomas.
- MC cumulative survival is significantly lower if compared to general population.

- Treatment of MC syndrome is particularly challenging because of its complex etiopathogenesis, including HCV infection, autoimmune, and lymphoproliferative alterations; it may include etiological, pathogenetic, and/or symptomatic therapies.

An attempt to eradicate the HCV (interferon ± ribavirin) should be done in all HCV-related MC, particularly in those with active hepatitis. The immunosuppressors (cyclophosphamide or rituximab), alone or in combination with high dosage steroids and/or plasma exchange, can be usefully employed in MC patients with severe/active complications (glomerulonephritis, widespread vasculitis, sensory-motor neuropathy).

References

Abel, G., Zhang, Q.X., Agnello, V. 1993. Hepatitis C virus infection in type II mixed cryoglobulinemia (review). Arthritis Rheum. 36, 1341.
Excellent review on mixed cryoglobulinemia and its relationship with HCV infection.

Abrignani, S., Rosa, D. 1998. Perspectives for a hepatitis C virus vaccine. Clin. Diagn. Virol. 10, 181.

Agnello, V. 1997. Hepatitis C virus infection and type II cryoglobulinemia: an immunological perspective. Hepatology 26, 1375.

Agnello, V., Abel, G. 1997. Localization of hepatitis C virus in cutaneous vasculitic lesions in patients with type II cryoglobulinemia. Arthritis Rheum. 40, 2007.
Nice study on the possible direct involvement of HCV in cryoglobulinemic vasculitis.

Antonelli, A., Ferri, C., Fallahi, P. 1999. Thyroid cancer in patients with hepatitis C infection. JAMA 281, 1588.
First report on the possible role of HCV in thyroid cancer.

Antonelli, A., Ferri, C., Fallahi, P., et al. 2004. Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. Rheumatology (Oxford) 43, 238.
Important study on the possible role of HCV in type 2 diabetes.

Bombardieri, S., Ferri, C., Di Munno, O., et al. 1979. Liver involvement in essential mixed cryoglobulinemia. La Ricerca Clin. Lab. 9, 361.

Brouet, J.C., Clouvel, J.P., Danon, F., et al. 1974. Biologic and clinical significance of cryoglobulins. Am. J. Med. 57, 775.

Choo, G.L., Kuo, G., Weiner, A.J., et al. 1989. Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome. Science 244, 359.

Dammacco, F., Sansonno, D., Piccoli, C., et al. 2001. The cryoglobulins: an overview. Eur. J. Clin. Invest. 31, 628.
Exhaustive review on mixed cryoglobulinemia syndrome.

De Vita, S., De Re, V., Gasparotto, D., et al. 2000. Type II mixed cryoglobulinemia is a non-malignant B-cell disorder. Clinical and molecular findings do not support bone marrow pathologic diagnosis of low grade B-cell lymphoma. Arthritis Rheum. 43, 94.
Excellent review of the biological bases and relationship between autoimmune-rheumatic disorders and limphoproliferation.

Fadda, P., La Civita, P., Zignego, A.L., et al. 2002. Hepatitis C virus infection and arthritis. A clinico-serological investigation of arthritis in patients with or without cryoglobulinemic syndrome. Reumatismo. 54, 316.

Ferri, C., Bertozzi, M.A., Zignego, A.L. 2002a. Erectile dysfunction and HCV infection. JAMA 14, 698.
First report on the possible role of HCV in gonadal dysfunction.

Ferri, C., Zignego, A.L., Pileri, S.A. 2002b. Cryoglobulins. J. Clin. Pathol. 55, 4.
Comprehensive review of mixed cryoglobulinemia and its relationship with other autoimmune and lymphoproliferative disorders.

Ferri, C., Giuggioli, D., Cazzato, M., et al. 2003. HCV-related cryoglobulinemic vasculitis: an update on its etiopathogenesis and therapeutic strategies. Clin. Exp. Rheumatol. 21 (Suppl. 32), S78.
Update on the therapeutic strategies in cryoglobulinemic vasculitis.

Ferri, C., Greco, F., Longobardo, G., et al. 1991. Association between hepatitis C virus and mixed cryoglobulinaemia. Clin. Exp. Rheumatol. 9, 621.
First report on the high prevalence of HCV viremia in a large series of mixed cryoglobulinemia patients.

Ferri, C., La Civita, L., Cirafisi, C., et al. 1992. Peripheral neuropathy in mixed cryoglobulinemia: clinical and electrophysiologic investigations. J. Rheumatol. 19, 889.

Ferri, C., La Civita, L., Fazzi, P., et al. 1997. Interstitial lung fibrosis and rheumatic disorders in patients with hepatitis C virus infection. Br. J. Rheumatol. 36, 360.

Ferri, C., La Civita, L., Longobardo, G., et al. 1993a. Hepatitis C virus and mixed cryoglobulinemia (review). Eur. J. Clin. Invest. 23, 399.

Ferri, C., La Civita, L., Zignego, A.L., et al. 1996. Hepatocellular carcinoma in mixed cryoglobulinemia patients. Clin. Exp. Rheumatol. 14, 111.

Ferri, C., Longobardo, G., La Civita, L., et al. 1994. Hepatitis C virus as common cause of mixed cryoglobulinemia and chronic liver disease. J. Intern. Med. 236, 31.

Ferri, C., Mannini, L., Batoli, V., et al. 1990. Blood viscosity and filtration abnormalities in mixed cryoglobulinemia patients. Clin. Exp. Rheumatol. 8, 271.

Ferri, C., Monti, M., La Civita, L., et al. 1993b. Infection of peripheral blood mononuclear cells by hepatitis C virus in mixed cryoglobulinemia. Blood 82, 3701.
First suggestion of the possible involvement of HCV in malignant lymphomas.

Ferri, C., Pietrogrande, M., Cecchetti, C., et al. 1989. Low-antigen-content diet in the treatment of mixed cryoglobulinemia patients. Am. J. Med. 87, 519.

Ferri, C., Pileri, S., Zignego, A.L. 2000. Hepatitis C virus, B-cell disorders, and non-Hodgkin's lymphoma chapter 19. In: J.J. Goedert (Ed.), Infectious Causes of Cancer. Targets for Intervention. National Cancer Institute (NIH). The Humana Press Inc. Totowa, New Jersey, p. 349.
Important update on the possible role of HCV in the lymphomagenesis.

Ferri, C., Puccini, R., Longobardo, G., et al. 1993c. Low-antigen-content diet in the treatment of patients with IgA nephropathy. Nephrol. Dial. Transpl. 8, 1193.

Ferri, C., Sebastiani, M., Giuggioli, D., et al. 2004. Mixed cryoglobulinemia: demographic, clinical, and serological features, and survival in 231 patients. Semin. Arthritis Rheum. 33, 355.
First prognostic and survival study on large series of patients with cryoglobulinemic vasculitis.

Giannelli, F., Moscarella, S., Giannini, C., et al. 2003. Effect of antiviral treatment in patients with chronic HCV infection and t (14; 18) translocation. Blood 102, 1196.
Excellent study on the possible therapeutic mechanism of antiviral treatment in cryoglobulinemic vasculitis.

Giannini, C., Caini, P., Giannelli, F., et al. 2002. Hepatitis C virus core protein expression in human B-cell lines does not significantly modify main proliferative and apoptosis pathways. J. Gen. Virol. 83, 1665.

Gocke, D.J., Hsu, K., Morgan, C., et al. 1970. Association between polyarteritis and Australia antigen. Lancet 2, 1149.

Gorevic, P.D., Frangione, B. 1991. Mixed cryoglobulinemia cross-reactive idiotypes: implication for relationship of MC to rheumatic and lymphoproliferative diseases. Semin. Hematol. 28, 79.
Excellent review of mixed cryoglobulinemia and its relationship with B-cell lymphoproliferiferation.

Gorevic, P.D., Kassab, H.J., Levo, Y., et al. 1980. Mixed cryoglobulinemia: clinical aspects and long-term follow-up of 40 patients. Am. J. Med. 69, 287.

Gumber, S., Chopra, S. 1995. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. Ann. Intern. Med. 123, 615.

Harris, N., Jaffe, E., Stein, H., et al. 1994. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood 84, 1361.

Invernizzi, F., Galli, M., Serino, G., et al. 1983. Secondary and essential cryoglobulinemias. Frequency, nosological classification, and long-term follow-up. Acta Haematol. 70, 73.

Kallemuchikkal, U., Gorevic, P.D. 1999. Evaluation of cryoglobulins. Arch. Pathol. Lab. Med. 123, 119.

Koike, K. 2002. Hepatocarcinogenesis in hepatitis viral infection: lessons from transgenic mouse studies. J. Gastroenterol. 37 (Suppl. 13), 55.

Lamprecht, P., Gause, A., Gross, W.L. 1999. Cryoglobulinemic vasculitis (review). Arthritis Rheum. 42, 2507.

Lamprecht, P., Lerin-Lozano, C., Merz, H., et al. 2003. Rituximab induces remission in refractory HCV associated cryoglobulinaemic vasculitis. Ann. Rheum. Dis. 62, 1230.

Lenzi, M., Johnson, P.J., McFarlane, I.G., et al. 1991. Antibodies to hepatitis C virus in autoimmune liver disease: evidence for geographical heterogeneity. Lancet 338, 277.

Levo, Y., Gorevic, P.D., Kassab, H.J., et al. 1977. Association between hepatitis B virus and essential mixed cryoglobulinemia. N. Engl. J. Med. 296, 1501.

Lospalluto, J., Dorward, B., Miller, W., Jr., et al. 1962. Cryoglobulinemia based on interaction between a gamma macroglobulin and 7S gamma globulin. Am. J. Med. 32, 142.

Lunel, F., Musset, L., Cacoub, P., et al. 1994. Cryoglobulinemia in chronic liver diseases: role of hepatitis C virus and liver damage. Gastroenterology 106, 1291.

Magalini, A.R., Facchetti, F., Salvi, L., et al. 1998. Clonality of B-cells in portal lymphoid infiltrates of HCV-infected livers. J. Pathol. 185, 86.

Mazzaro, C., Franzin, F., Tulissi, P., et al. 1996. Regression of monoclonal B-cell expansion in patients affected by mixed cryoglobulinemia responsive to a-interferon therapy. Cancer 77, 2604.

McHutchison, J.G., Gordon, S.C., Schiff, E.R., et al. 1998. Interferon alpha-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N. Engl. J. Med. 339, 1485.

Meltzer, M., Franklin, E.C., Elias, K., et al. 1966. Cryoglobulinemia. A clinical and laboratory study II. Cryoglobulins with rheumatoid factor activity. Am. J. Med. 40, 837.

Misiani, R., Bellavista, P., Baio, P., et al. 1999. Successful treatment of HCV-associated cryoglobulinaemic glomerulonephritis with a combination of interferon-alpha and ribavirin. Nephrol. Dial. Transplant. 14, 1558.

Monteverde, A., Ballarè, M., Pileri, S. 1997. Hepatic lymphoid aggregates in chronic hepatitis C and mixed cryoglobulinemia. Springer Semin. Immunopathology 19, 99.
Important study on the pathological alterations underlying clinical manifestation of mixed cryoglobulinemia.

Monti, G., Galli, M., Invernizzi, F., et al. 1995. Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. QJM 88, 115.
Relevant collaborative study on epidemiological and clinical features of largest mixed cryoglobulinemia series.

Olivieri, I., Palazzi, C., Padula, A. 2003. Hepatitis C virus and arthritis. Rheum. Dis. Clin. N. Am. 29, 111.

Pawlotsky, J., Mustapha, B., Andre, C., et al. 1994. Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. Hepatology 19, 841.

Pileri, P., Uematsu, Y., Campagnoli, S., et al. 1998. Binding of hepatitis C virus to CD81. Science 282, 938.

Excellent molecular biology study demonstrating the role of CD81 molecules in the binding of HCV to both hepatocytes and lymphocytes.

Ramos-Casals, M., Garcia-Carrasco, M., Cervera, R., et al. 2001. Hepatitis C virus infection mimicking primary Sjogren's syndrome. A clinical and immunologic description of 35 cases. Medicine (Baltimore) 80, 1.

Ramos-Casals, M., Trejo, O., Garcia-Carraasco, M., et al. 2004. Triple association between hepatitic C virus infection, systemic autoimmune diseases, and B cell lymphoma. J. Rheumatol. 31, 495.

Salaffi, F., Manganelli, P., Carotti, M., et al. 1996. Mixed cryoglobulinemia: effect of alpha-interferon on subclinical lymphocytes alveolitis. Clin. Exp. Rheumatol. 14, 219.

Sansonno, D., De Re, V., Lauletta, G., et al. 2003. Monoclonal antibody treatment of mixed cryoglobulinemia resistant to interferon alpha with an anti-CD20. Blood 101, 3818.
Important study on the possible therapeutic role of rituximab in cryoglobulinemic vasculitis.

Sansonno, D., De Vita, S., Cornacchiulo, V., et al. 1996. Detection and distribution of hepatitis C-related proteins in lymph nodes of patients with type II cryoglobulinemia and neoplastic or non-neoplastic lymphoproliferation. Blood 88, 4638.
Original study on the possible direct involvement of HCV in lymphoproliferation.

Sansonno, D., Iacobelli, A.R., Cornacchiulo, V., et al. 1996. Detection of hepatitis C virus (HCV) proteins by immunofluorescence and HCV RNA genomic sequences by non-isotopic in situ hybridization in bone marrow and peripheral blood mononuclear cells of chronically HCV- infected patients. Clin. Exp. Immunol. 103, 414.

Tissot, J.D., Schifferli, J.A., Hochstrasser, D.F., et al. 1994. Two-dimensional polyacrylamide gel electrophoresis analysis of cryoglobulins and identification of an IgM-associated peptide. J. Immunol. Methods, 173, 63.

Trejo, O., Ramos-Casals, M., Lopez-Guillermo, A., et al. 2003. Haematologic malignancies in patients with cryoglobulinemia: association with autoimmune and chronic viral diseases. Semin. Arthritis Rheum. 33, 19.

Vitali, C., Bombardieri, S., Jonsson, R., et al. 2002. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann. Rheum. Dis. 61, 554.

Zaja, F., De Vita, S., Mazzaro, C., et al. 2003. Efficacy and safety of rituximab in type II mixed cryoglobulinemia. Blood 101, 3827.
Important study on the possible therapeutic role of rituximab in cryoglobulinemic vasculitis.

Zignego, A.L., De Carli, M., Monti, M., et al. 1995. Hepatitis C virus infection of mononuclear cells from peripheral blood and liver infiltrates in chronically infected patients. J. Med. Virol. 47, 58.

Zignego, A.L., Ferri, C., Giannini, C., et al. 1996. Hepatitis C virus genotype analysis in patients with type II mixed cryoglobulinemia. Ann. Intern. Med. 124, 31.

Zignego, A.L., Ferri, C., Giannini, C., et al. 1997. Hepatitis C virus infection in mixed cryoglobulinemia and B-cell non-Hodgkin's lymphoma: evidence for a pathogenetic role. Arch. Virol. 142, 545.

Zignego, A.L., Ferri, C., Giannelli, F., et al. 2002. Prevalence of bcl-2 rearrangement in patients with hepatitis C virus-related mixed cryoglobulinemia with or without B-cell lymphomas. Ann. Intern. Med. 137, 571.
Excellent study suggesting the role of Bcl-2 in the HCV-related lymphomagenesis.

Zignego, A.L., Giannelli, F., Marrocchi, M.E., et al. 2000. T (14; 18) translocation in chronic hepatitis C virus infection. Hepatology 31, 474.

Zignego, A.L., Macchia, D., Monti, M., et al. 1992. Infection of peripheral mononuclear blood cells by hepatitis C virus. J. Hepatol. 15, 382.
First demonstration of HCV lymphotropism in HCV-related chronic hepatitis.

Zuckerman, E., Keren, D., Slobodin, G., et al. 2000. Treatment of refractory, symptomatic, hepatitis C virus related mixed cryoglobulinemia with ribavirin and interferon-alpha. J. Rheumatol. 27, 2172.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 20

Skin Involvement in Small, Medium-sized Vessel and Granulomatous Vasculitides

Christian Pagnoux[a], Camille Francès[b], Marie-Sylvie Doutre[c], Loïc Guillevin[a,*]

[a]*Department of Internal Medicine, Université Paris 5, Hôpital Cochin, 27, rue du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France*

[b]*Department of Internal Medicine, Groupe Hospitalier Pitié Salpêtrière, 47–83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France*

[c]*Department of Dermatology, Hôpital Haut-Lévêque, Avenue de Magellan, 33604 Pessac Cedex, France*

1. Introduction

Vasculitides are multiple organ and/or system diseases characterized by inflammation of blood vessel walls with resulting vascular obstruction, subsequent ischemia and injury of the involved tissues. They are classified according to the type of vessels affected, running the gamut from the aorta to capillaries to veins, and to the different target end-organs. Medium-sized vessel vasculitides include Kawasaki disease, detailed in Chapter 21 (Part III), and polyarteritis nodosa (PAN). Among small vessel vasculitides, Wegener's granulomatosis (WG) and Churg–Strauss syndrome (CSS) are the two predominant entities, characterized histologically by the association of necrosis and granulomatous inflammation within vessel walls, but other more rare and non-classified granulomatous vasculitides are known. Other small vessel vasculitides, according to the Chapel Hill Nomenclature, are cutaneous leukocytoclastic angiitis and microscopic polyangiitis (MPA), which are not histologically associated with granulomatous inflammation; Henoch–Schönlein purpura and mixed essential cryoglobulinemic vasculitis, detailed in Chapters 18 and 19 (Part III), respectively.

Dermatologic manifestations are frequent in patients with systemic vasculitides, and may correspond to a skin localization of the disease, result from an associated process or be induced by drugs or a coincidental and transient viral infection. Skin-lesion biopsies are easy to obtain and their histologic examination can often confirm the diagnosis of vasculitis, but cannot always determine the exact type of vasculitis. After a brief review of the classification of vasculitides, the pathogenic mechanisms and clinical specificities of cutaneous involvement in small and medium-sized vasculitides are described, with special attention accorded to granulomatous vasculitides and their therapies.

2. Definitions and classification of systemic vasculitides

Primary vasculitides can be classified according to the 1990 American College of Rheumatology classification criteria (Arend et al., 1990; Bloch et al., 1990; Fries et al., 1990; Hunder et al., 1990; Leavitt et al., 1990; Lightfoot et al., 1990; Masi et al., 1990; Mills et al., 1990) or to the more accurate and complete Nomenclature of Systemic Vasculitides,

*Corresponding author.
Tel.:
+33-1-58-41-14-41; Fax: +33-1-58-41-14-60.
E-mail address: loic.guillevin@cch.aphp.fr (L. Guillevin).

DOI: 10.1016/S1571-5078(05)05020-8

established at the Chapel Hill Consensus Conference (Jennette et al., 1994), reproduced in Table 1.

Vasculitides are defined based on their histologic features. Vasculitic lesions (fibrinoid necrosis of vessel walls, perivascular inflammatory infiltrates, fibrotic scar replacement, thromboses) have a segmental distribution pattern, with a predilection for arterial bifurcations, and can cause tissue ischemia and consequential damage. On the other hand, granulomatous inflammation is one of the characteristic features of WG and CSS.

However, because tissues easily accessible to biopsy may show only non-specific inflammation or may even be normal, diagnosis sometimes relies on a combination of clinical findings, and results of biologic, immunologic and radiologic investigations. Anti-neutrophil cytoplasmic antibodies (ANCA) and angiography are useful tools to help diagnose systemic necrotizing vasculitides. In immunofluorescence assays, C-ANCA give a cytoplasmic-labeling pattern in ethanol-fixed neutrophils and are detected in 60–90% of the patients with systemic WG, and in 50–75% of those with localized forms of WG (Kallenberg et al., 1992; van der Woude et al., 1985). P-ANCA, which give a perinuclear immunofluorescent labeling pattern, are more closely linked to pauci-immune glomerulonephritis (80% of the patients), microscopic polyangiitis (MPA; 50–75%) and CSS

Table 1
Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides[a]

Large vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. *Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.*
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. *Usually occurs in patients younger than 50.*
Medium-sized vessel vasculitis	
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. *Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.*
Small vessel vasculitis	
Wegener's granulomatosis[b]	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles and arteries). *Necrotizing glomerulonephritis is common.*
Churg—Strauss syndrome[b]	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.
Microscopic polyangiitis[b]	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Henoch–Schönlein purpura	Vasculitis with IgA-dominant immune deposits, affecting small vessels (i.e., capillaries, venules or arterioles). *Typically involves skin, gut and glomeruli, and is associated with arthralgias or arthritis.*
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with cryoglobulins in serum. *Skin and glomeruli are often involved.*
Cutaneous leukocytoclastic angiitis	Isolated leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Source: Reproduced with permission from Jennette et al. (1994)

[a] Large vessel refers to the aorta and the largest branches directed toward major body regions (e.g., to the extremities and the head and neck); medium-sized vessel refers to the main visceral arteries (e.g., renal, hepatic, coronary and mesenteric arteries); small vessel refers to venules, capillaries, arterioles and the intraparenchymal distal arterial radicals that connect with arterioles. Some small and large vessel vasculitides may involve medium-sized arteries, but large and medium-sized vessel vasculitides do not involve vessels smaller than arteries. Essential components are represented by normal type; italicized type represents usual, but not essential, components.

[b] Strongly associated with antineutrophil cytoplasmic autoantibodies.

(47%) (Hagen et al., 1998). Celiomesenteric and renal angiographic findings, such as multiple 1–5-mm diameter aneurysms or irregular stenoses are present in approximately 80% of PAN patients (D'Izarn et al., 1976; Guillevin et al., 1995a). Although highly suggestive, these findings are not absolutely specific and, to date, no diagnostic criteria for vasculitides have been established.

3. Pathogenesis

Pathogenic mechanisms implicated in the development of vasculitides are only partly understood and some are probably still unknown. Deposition of circulating immune complexes in the vessel walls seems to be relevant in hepatitis B virus (HBV)-related PAN, Henoch–Schönlein purpura, mixed cryoglobulinemic vasculitis and the necrotizing vasculitis of rheumatoid arthritis (Gower et al., 1978).

More specific antibody-mediated immunity is implied in some vasculitides, mainly by ANCA, but perhaps also by other autoantibodies, like anti-endothelial cell autoantibodies. ANCA were first detected in patients with pauci-immune glomerulonephritis (Davies et al., 1982). They are specific to peptides in neutrophil granules and monocyte lysosomes (Falk and Jennette, 1988). Target antigens, recognized and identified by antigen-specific enzyme-linked immunosorbent assays (ELISA), are proteinase 3 (PR3) for C-ANCA, myeloperoxidase (MPO) for 90% of the P-ANCA, and elastase, cathepsin G, lactoferrin and lysozyme for the remaining P-ANCA (Specks et al., 1993). The pathogenic role of ANCA is supported by the development of necrotizing glomerulonephritis in recombinase-activating gene-2-deficient ($rag2^{-/-}$) mice, but also in wild-type C57BL/6J mice, after injection of purified anti-MPO IgG (Heeringa et al., 1998; Xiao et al., 2002); and by the enhancement, after injection of anti-mouse PR3 antibodies, of the subcutaneous panniculitis induced by intradermal injection of tumor necrosis factor-alpha (TNFα) into wild-type mice (Pfister et al., 2004). Moreover, ANCA titers seem to fluctuate with the disease activity, at least in WG but, at present, must not be used as a tool to initiate or modify therapy because this relationship is not constant (Girard et al., 2001; Tervaert et al., 1990).

Conversely, T-cell-mediated immunity may contribute to the development of granulomatous vasculitides, i.e. WG and CSS. Infiltration by T helper 1 (Th1) lymphocytes secreting pro-inflammatory cytokines, essentially interferon (IFN)γ, has been observed in granulomatous lesions of the nasal mucose of WG patients. Thus, in WG, an imbalance between Th1 and Th2 lymphocyte-regulated pathways may be involved, with Th1 lymphocytes playing a major role in localized and granulomatous upper respiratory tract involvement, whereas a shift toward Th2 lymphocyte involvement would tend to be more predominant in systemic forms (Balding et al., 2001; Csernok et al., 1999), which are thought to have a poorer prognosis (Bligny et al., 2004).

Cytokine (Sundy and Haynes, 2000; Tesar et al., 1998) and adhesion-molecule (Sundy and Haynes, 2000) cascades may be perturbed, with, e.g., high levels of soluble endothelial cell receptors for neutrophils (intercellular adhesion molecule (ICAM)-1, E-selectin and vascular cell-adhesion molecule (VCAM)-1) in patients with active WG or MPA (Ara et al., 2001; Ohta et al., 2001).

Finally, viral agents such as HBV for PAN, genetic susceptibility and exposure to some drugs or environmental factors (especially silica and livestock) may also be involved in the development of various vasculitides (Lane et al., 2003; Watts et al., 1995).

4. Dermatologic manifestations of small, medium-sized vessel and granulomatous vasculitides

4.1. Main clinical cutaneous manifestations

The spectrum of clinical vasculitis-related lesions is wide and includes erythema, purpura, papules, pustules, nodules, livedo, necrosis, ulcerations and/or bullae. These different lesions are often associated, giving rise to a pleomorphic clinical picture, that is not specific to any of the systemic vasculitides, granulomatous or otherwise.

Palpable purpura and petechiae are unquestionably the most frequent manifestations (Figs. 1 and 2). Lesions usually begin as tiny red macules that later become papules and plaques ranging from few millimeters to several centimeters in diameter. The larger lesions are more often ecchymotic than purpuric. They are predominantly localized on legs, ankles and feet but may occur on any part of the body, especially areas subjected to local mechanical pressure.

Cutaneous nodules due to vasculitis are typically warm, tender, red and small; they may be surrounded by livedo reticularis. Like livedo, they are mainly localized on the lower limbs (legs, soles) but are also frequently seen in other sites, such as the dorsal face of the arms or more rarely on the trunk. They may occur in clusters along the superficial arteries.

Livedo reticularis is a reddish blue mottling of the skin in a 'fishnet' reticular pattern, typically

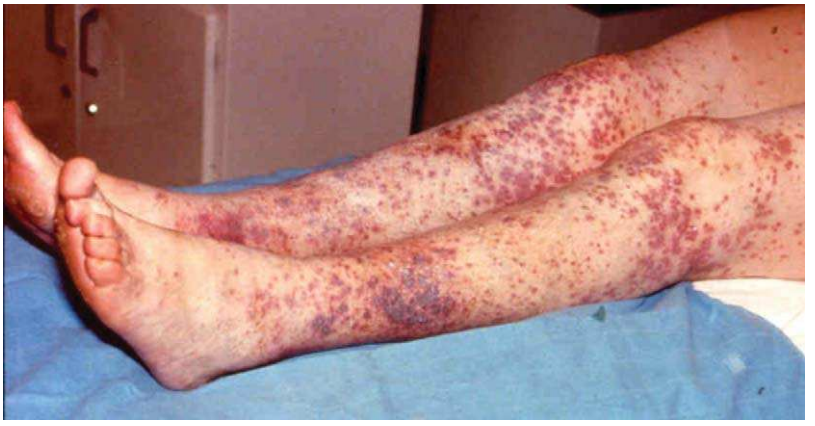


Figure 1. Lower leg necrotic purpura in a patient with polyarteritis nodosa.

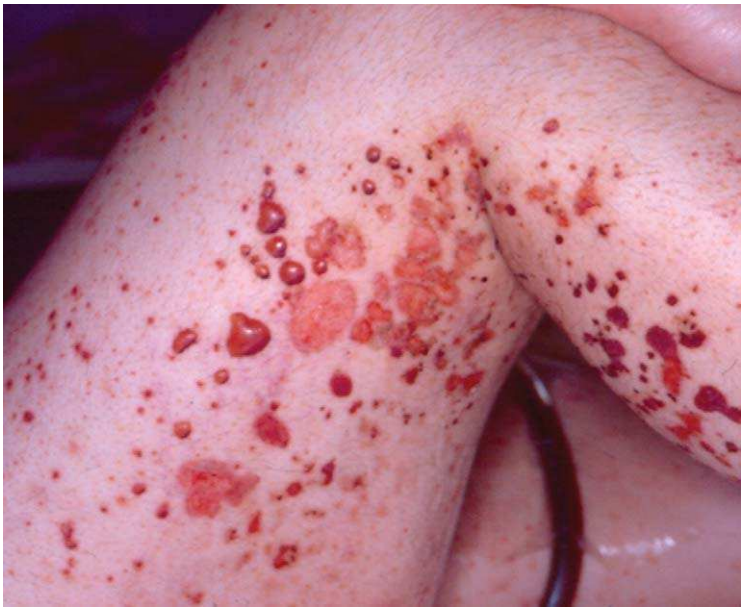


Figure 2. Necrotic and pustular hemorrhagic purpura in a patient with polyarteritis nodosa.

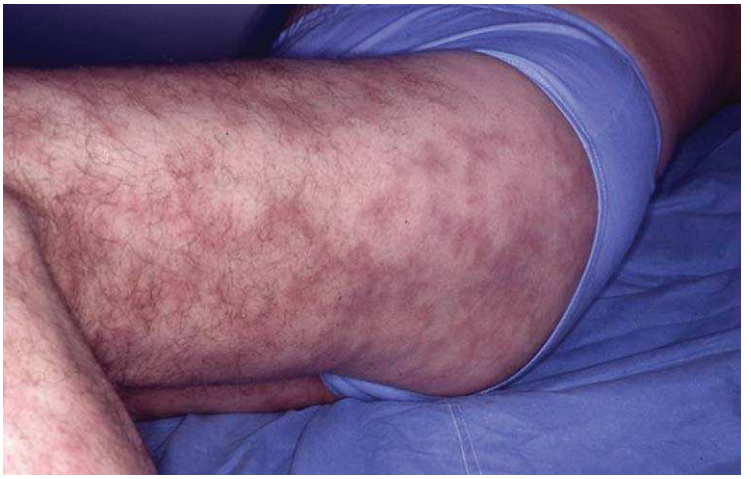


Figure 3. Livedo reticularis in a patient with Churg–Strauss syndrome.

irregular with broken circles (Fig. 3). When associated with vasculitis, it is persistent, although some fluctuations in intensity and extent may be observed, especially with variations of temperature. On careful examination, some infiltrated areas may often be detected.

Urticarial vasculitis is characterized by the presence of wheals, which persist for 2–3 days, unlike ordinary urticaria that disappear within 24 h. Pruritus is less intense. Urticaria may evolve into purpuric lesions. They are mainly localized on the trunk and the limbs. Some of them may have a chronic evolution, resembling erythema elevatum diutinum.

Skin purpuric necrosis might occur as the consequence of dermal vessel obstruction (Fig. 4). Its extension and depth are highly variable depending on the type, size and location of affected vessels. Localized purpuric and necrotic lesions may evolve into vesicles and then into pustules, due to superinfection. When necrosis is extensive, painful purpura is followed by black necrotic plaque formation with active purpuric edges and bullous lesions. After removal of necrotic tissue, ulcerations of various sizes are usually present and may take a long time to heal, often leaving large scars.

Pustular vasculitis is another possibility but less frequent, non-follicular, with underlying erythema and usually results from secondary infection of necrotic lesions.

4.2. Histopathology

Palpable purpura and papular lesions such as urticaria, usually correspond to leukocytoclastic or lymphocytic vasculitis of the small vessels of the dermis, while nodules are preferentially associated with vasculitis of arterioles or small vessels at the junction of dermis and the subcutis or in the subcutis. Necrosis and livedo develop when either small or larger vessels or both are involved.

The hallmark histopathologic feature of purpuric lesions is leukocytoclastic vasculitis of the small dermal vessels. Postcapillary venules are preferentially involved. This leukocytoclastic vasculitis is characterized by vascular anomalies and dermal cell infiltrates. Vascular abnormalities consist of endothelial cell swelling, nuclear activation, wrinkling of nuclear membranes, necrosis with the deposition of fibrinoid material and sometimes thrombosis (Fig. 5). The fibrinoid deposit contains predominantly fibrin but also necrotic endothelial cells and some immunoreactants, like immunoglobulins (Ig) and/or complement proteins, which may cause focal edema with resultant urticaria. Dermal infiltrates vary in intensity and are usually perivascular in location but may be widely dispersed. They are mainly composed of neutrophils with fragmented nuclei (karyorrhexis or leukocytoclasis). In some cases or older lesions, lymphocytes and monocytes may predominate.

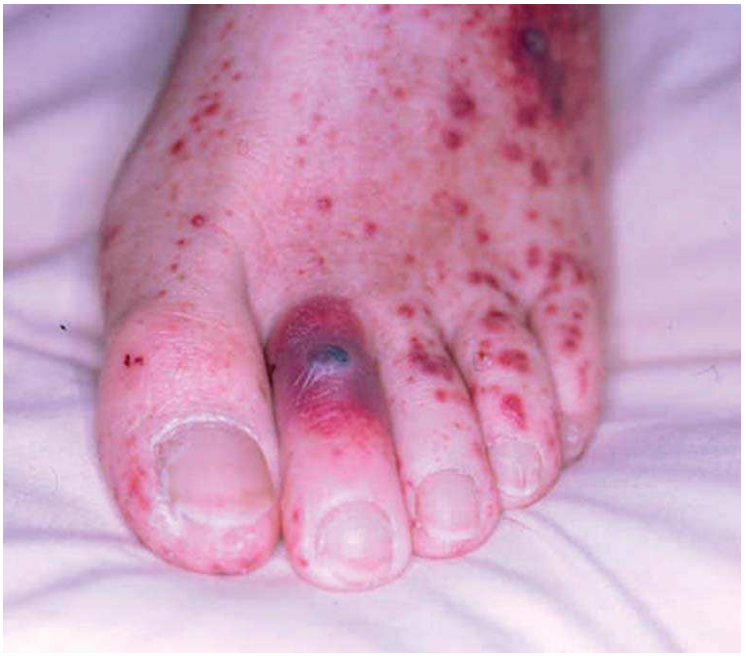


Figure 4. Necrotic purpuric toe lesion in a patient with polyarteritis nodosa.

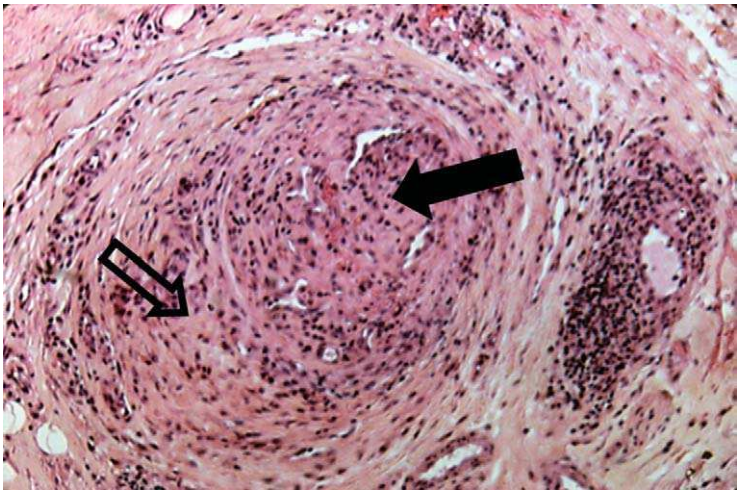


Figure 5. Skin biopsy: typical histologic aspect of vasculitis, with lymphocytes infiltrating the vessel wall and fibrinoid necrosis (outlined arrow), and partly repermeabilized thrombosis (solid arrow).

Nodular forms of vasculitis result from vessel-wall inflammation at the junction of the dermis and subcutis, or in the subcutis. Subcutaneous arteriole involvement is suggestive, but not absolutely specific, of PAN lesions. However, nodules are rarely seen in small vessel vasculitides. Neutrophil infiltration of the vessel wall is usual during the acute phase. Leukocytoclasis is less frequent, but a granulomatous infiltrate may be seen early during the course of the disease. Endothelial swelling and fibrinoid necrosis of the media may be severe and lead to thrombosis. During the healing stage,

vessel walls are invaded by granulation tissue and replaced by fibrous scarring, and capillary proliferation may persist.

4.3. Polyarteritis Nodosa

PAN affects men and women equally at all ages, with a predominance between 40 and 60 years. Its etiology remains unknown for most of the patients, with HBV-related PAN accounting for less than 10% of all currently diagnosed cases (Guillevin et al., 2004). It is a necrotizing angiitis, whose main manifestations are: weight loss; fever; asthenia; cutaneous lesions; peripheral neuropathy (mononeuritis multiplex); renal, musculoskeletal and/or gastrointestinal tract involvement; hypertension and/or congestive heart failure.

Theoretically, nodules are the cutaneous hallmarks of PAN. These cutaneous or subcutaneous nodules occur in clusters along the trajectories of superficial arteries. They measure 5–15 mm in diameter and are mainly located in the lower legs, especially the knees and feet. Livedo reticularis may precede, follow, or occur concomitantly with the onset of nodules. Livedo reticularis in PAN is typically localized on the lower limbs, the dorsal face of the arms and occasionally on the trunk. The fishnet reticular pattern is irregular with discontinuous circles, and often with some infiltrated areas. Local rupture of superficial arteries may lead to cutaneous hematoma or ecchymosis. Painful ulcerations may develop, frequently associated with indurated plaques resulting from the coalescence of nodules. Peripheral embolization of thrombi may cause infarction of the extremities (toes, fingers) or some skin areas.

Skin lesions have been reported in approximately 25–60% of patients with systemic PAN as reported in Table 2, but less frequently in those older than 65 years (Cohen et al., 1995; Fortin et al., 1995; Guillevin et al., 1985, 1995b; Leib et al., 1979; Puisieux et al., 1997). Indeed, a common cutaneous finding is palpable purpura corresponding to subcutaneous small vessel vasculitis, in association with medium-sized vessel involvement. Nodules (8–27%), ulcerations and livedo are less frequent (Leib et al., 1979). Although the Chapel Hill Nomenclature distinguishes large, medium-sized and small vessel vasculitides, it also recognizes some overlap forms, e.g., PAN with some, but not predominant, involvement of small vessels, especially in skin biopsies (ANCA Workshop, Birmingham, UK, 1998, unpublished revised version of the Nomenclature). Convenient threshold defining small vessel vasculitis has been set for nerve biopsies, around 50–70 μm in diameter for affected epineurial arteries and vasa nervorum (Gherardi et al., 1993; Moore, 1995). Other manifestations have been reported, such as urticaria, transient erythema, superficial phlebitis, Raynaud's phenomenon and splinter hemorrhages. Localized edema is usually associated with underlying muscle involvement.

Cutaneous signs are usually associated with other PAN-related symptoms, like arthralgias, hypertension, gastrointestinal manifestations and/or peripheral neuropathy. Notably, systemic PAN may develop later in a few patients, after a variable period ranging from 1 to 20 years after the first cutaneous signs (Diaz-Perez and Winkelmann,

Table 2
Cutaneous manifestations of polyarteritis nodosa

Reference	No. of patients	No. with skin involvement (%)	Cutaneous manifestations, when detailed
Fortin et al., 1995	45	20(44)	–
Puisieux et al., 1997	47	13(28)	Nodules = 7; purpura = 6
Cohen et al., 1995	53	31(58)	–
Guillevin et al., 1995b	62	25(40)	–
Leib et al., 1979	64	18(28)	Nodules = 5; purpura = 3; livedo = 2; vasculitis = 4; non-specific lesions = 4
Guillevin et al., 1985	126	65(52)	Nodules = 35; purpura = 30; distal gangrene = 20; Raynaud's syndrome = 15

1974). Thus, the spectrum of PAN can range from chronic cutaneous to acute systemic PAN.

4.4. Churg–Strauss syndrome

CSS is characterized by pulmonary and systemic small vessel vasculitis, extravascular necrotizing granulomas and hypereosinophilia occurring in patients with asthma and allergic rhinitis (Guillevin et al., 1999a; Lanham et al., 1984).

Cutaneous lesions have been observed in 40–75% of CSS patients, as listed in Table 3 (Abu-Shakra et al., 1994; Chumbley et al., 1977; Crotty et al., 1981; Davis et al., 1997; Guillevin et al., 1999a; Haas et al., 2001; Lanham et al., 1984; Sehgal et al., 1995; Solans et al., 2001). They are rarely (6%) the presenting manifestations (Davis et al., 1997). Palpable purpura, often necrotic, on the lower extremities is the most frequent cutaneous manifestation, seen in half the patients with dermatologic involvement. Cutaneous nodules (1/3 of the patients with skin manifestations) or papules, sometimes with an urticarial appearance, are also very common, localized on the lower limbs or on the extensor side of the elbows, fingers, scalp and/or breast. Lesions on the digits are usually multiple, often symmetrical and most commonly overlying the distal interphalangeal joints. These nodules or papules on the upper limbs frequently have central crusting or ulceration. They are usually firm. A pustular or vesicular component is rarely noted. Various other skin lesions have been reported: maculopapules resembling erythema multiforme, ulcerations, livedo reticularis, patchy and migratory urticarial rashes, nail-fold infarctions with splinter hemorrhages, deep pannicular vasculitis and facial edema (Davis et al., 1997; Schwartz and Churg, 1992).

Histologically, purpuric lesions usually correspond to leukocytoclastic or necrotizing vasculitis. Vasculitis affects small as well as medium-sized arteries and veins which explains the frequency of skin necrosis. The inflammatory infiltrate may be rich in eosinophils (Guillevin et al., 1999a). Nodules correspond to granulomatous vasculitis, necrotizing vasculitis of arterioles in the deep dermis or the subcutis (similar to those observed in PAN), or to extravascular granulomas. In majority of patients, papules and nodules on the extensor surfaces of the elbows correspond to extravascular granulomas. Non-specific granulomata without necrosis in the dermis or the subcutis may also be encountered. Noteworthy, histology of cutaneous lesions is often disappointing, since typical granuloma and eosinophilic granuloma are detected in less than half of the patients with skin lesions.

4.5. Wegener's granulomatosis

WG is characterized by necrotizing inflammatory lesions of the respiratory tract, usually accompanied by glomerulonephritis and/or systemic vasculitis. Klinger (1931) was the first to describe the disease, followed 5 years later by Wegener (1936). Detection

Table 3
Cutaneous manifestations of Churg–Strauss syndrome

References	No. of patients	No. with skin involvement (%)	Cutaneous manifestations, when detailed
Abu-Shakra et al., 1994	12	8(67)	—
Lanham et al., 1984	16	11(69)	Nodules = 2; purpura = 9; urticarial macules = 9
Haas et al., 2001	20	15(75)	Nodules = 6; purpura = 5; urticarial lesions = 3; other(s) = 6
Chumbley et al., 1977	30	20(67)	Nodules = 8, necrosis = 4
Solans et al., 2001	32	26(81)	Purpura = 16; maculopapular rash = 10; digit necroses = 3; nodules = 2
Davis et al., 1997	90	36(40)	Skin lesions as presenting sign = 5
Guillevin et al., 1999a	96	49(51)	Purpura = 30; nodules = 19; urticarial lesions = 8; livedo = 6; infiltrated papules = 2

of C-ANCA, with anti-PR3 specificity is an important clue to the diagnosis, as is paranasal sinus biopsy, which is diagnostic for over 50% of the cases, whereas the yield from nasal or laryngeal mucosa biopsy is less than 20% (Devaney et al., 1990).

Skin lesions occur in 10–50% of the patients (see Table 4), at some time during the course of the disease (Anderson et al., 1992; Brandwein et al., 1983; Daoud et al., 1994; de Groot et al., 2001a; Fauci et al., 1983; Guillevin et al., 1997; Hoffman et al., 1992; Koldingsnes and Nossent, 2003; Lie, 1997; Reinhold-Keller et al., 2000; Stone, 2003; Walton, 1958). They may be present at disease onset in about 10% of the patients and, exceptionally as the presenting symptom (Francès et al., 1994; Hoffman et al., 1992). Palpable purpura of the lower extremities is undoubtedly the most frequent cutaneous manifestation. Necrotic papules on the extensor surfaces of the limbs are less frequent but more suggestive of WG. Occasionally, they can resemble erythema elevatum diutinum and may be associated with IgA paraproteinemia. Nodules are frequent, mainly on the limbs. Extensive and painful cutaneous ulcerations may precede by several weeks to several years other systemic manifestations. Ulcers are sometimes described as 'pyoderma gangrenosum-like lesions', especially when occurring after even minor trauma to painful nodules or pustules. However, they usually lack the typical raised, tender, outlined border of pyoderma gangrenosum. Sometimes multiple, they are localized on the limbs, trunk, face (preauricular area), breasts and perineum. Lesions on the breasts may mimic adenocarcinoma with possible nipple retraction and galactorrhea (Trueb et al., 1999). Digital gangrene has occasionally been reported (Handa and Wali, 1996). Florid xanthelasma is associated with longstanding granulomatous orbital and periorbital infiltration (Francès et al., 1994; Tullo et al., 1995). In contrast to PAN, livedo reticularis is unusual in WG.

Mucosal manifestations might also be suggestive of WG. Buccal lesions are undoubtedly frequent, often reported as one of the ear, nose and throat manifestations of WG, present in 10–50% of the patients (D'Cruz et al., 1989; Francès et al., 1994). Their numbers and localizations vary widely, and, unlike recurrent aphthae, they are persistent. Hyperplastic gingivitis and gums are rare, but with some well-documented case reports (Patten and Tomecki, 1993). The gingiva is generally described as granular and red to purple with many petechiae. The entire gingiva and periodontium may be involved resulting in tooth mobility and loss. Major but incomplete regression can be obtained with empiric antimicrobial therapy. Genital ulcers are

Table 4
Cutaneous manifestations of Wegener's granulomatosis

Reference	No. of patients	No. with skin involvement (%)	Cutaneous manifestations, when detailed
Guillevin et al., 1997	50	15(30)	—
Walton, 1958	56	26(47)	—
Koldingsnes and Nossent, 2003	56	19(34)	—
Frances et al., 1994	75	35(47)	Purpura = 26; nodules = 6; ulcers = 5; necrotic papules = 5; pustules = 2; palpebral xanthoma = 2; digital necrosis = 1; livedo reticularis = 1
Fauci et al., 1983	85	38(45)	Present at diagnosis = 11
de Groot et al., 2001b	128	15(12)	—
Reinhold-Keller et al., 2000	155	51(33)	Present at diagnosis = 32; during the whole course of the disease = 51
Hoffman et al., 1992	158	73(46)	Present at diagnosis = 20; during the whole course of the disease = 73
Stone et al., 2003	180	36(20)	Purpura = 31; nodules = 18; ulcers = 6; gangrene = 1
Lie, 1997	216	26(12)	—
Anderson et al., 1992	265	66(25)	—

uncommon although penile necrosis has previously been described (Matsuda et al., 1976).

Histologically, purpuric papules correspond to leukocytoclastic vasculitis of small vessels; necrotic and purpuric lesions can be a consequence of necrotizing vasculitis of superficial and/or deep dermal and subcutaneous vessels. Other lesions are more frequently associated with granulomatous inflammation. Papules or papulonecrotic lesions are the histologic counterparts of leukocytoclastic or granulomatous vasculitis of small vessels, or to extravascular granuloma. Nodules coincide with necrotizing or granulomatous vasculitis of medium-sized arterioles, or to extravascular granuloma (Barksdale et al., 1995). All these lesions may evolve to ulceration with a secondary mixed inflammatory pattern. Histopathologic findings of oral ulcerations are often non-specific, showing mixed areas of acute and chronic inflammation, or granulomatous infiltration in some cases (Francès et al., 1994; Patten and Tomecki, 1993). Chronic histiocytic inflammation with inconstant vasculitis, necrosis and giant cells may be seen in gingival hyperplasia. Pseudoepitheliomatous hyperplasia and microabscesses with neutrophils and eosinophils are sometimes encountered (Handlers et al., 1985).

Regardless of the type of clinical and histological skin lesions, all of them, except xanthelasma, are usually associated with active systemic disease. They disappear in a few weeks or months after the onset of treatment, but reappear in about 50% of relapses. Skin lesions were significantly associated with articular and/or renal involvement in one series of dermatologic patients (Francès et al., 1994), and with peripheral neuropathy in another (de Groot et al., 2001b). Subacute forms of WG, limited to the skin have been individualized (Carrington and Liebow, 1966; D'Cruz et al., 1989). In our experience, the most frequent lesions in skin-limited WG are nodules, with granulomatous infiltration or granulomatous vasculitis found during histologic examination.

4.6. Microscopic polyangiitis

MPA, previously considered the microscopic form of PAN, is now defined as a systemic necrotizing vasculitis that clinically and histologically affects small-sized vessels (i.e. capillaries, venules or arterioles) without granulomata. MPA is associated with segmental necrotizing glomerulonephritis and anti-MPO ANCA. In practice, MPA is difficult to distinguish from PAN (see above, Section 4.3) and in most early populations studied, MPA was not identified as a separate entity. Hence, skin lesions in MPA have mainly been described in dermatology case reports, and their real frequency has probably been underestimated.

Skin manifestations occur in 30–60% of patients (Lhote et al., 1998; Penas et al., 1996). Maculopapular purpuric lesions of the lower limbs are the most frequent skin manifestations. However, other lesions have been described, such as mouth ulcers, vesicles, necrosis, ulcerations, nodules, splinter hemorrhages, livedo, hand and/or finger erythema, and facial edema (Homas et al., 1992; Seishima et al., 2004). Leukocytoclastic vasculitis of the small vessels of the dermis is usually observed. Sometimes, arterioles or smaller vessels of the deep dermis and subcutis are also involved, thereby explaining the nodular appearance of some skin lesions. In one patient, vasculitis was associated with eosinophilic panniculitis (Penas et al., 1996). Usually, all these cutaneous lesions disappear rapidly under treatment, but relapses are frequent.

4.7. Other dermatologic manifestations associated with systemic vasculitides

4.7.1. Extravascular necrotizing granuloma (Winkelmann's granuloma)

Initially described by Churg and Strauss (1951) as a manifestation of allergic angiitis, the extravascular granuloma has since been reported in other systemic vasculitides and connective tissue diseases (Crotty et al., 1981; Dicken and Winkelmann, 1978; Finan and Winkelmann, 1983; Gibson and Winkelmann, 1986). Clinically papular or nodular, the lesions vary in size from 2 mm to 2 cm, or more, in diameter. They also vary in color from red to violaceous. They are localized on the extensor surface of the elbows, the digits where they are usually multiple and often symmetrical, and

less frequently on the buttocks, scalp, extensor surface of the knees, hands, dorsum of feet, neck, forehead, ear, etc. Central crusting, ulceration or both are frequent. Rarely, other clinical aspects can be observed, such as vesicles, pustules, arciform plaques or indurated mass.

Histologic features include endothelial necrosis and edema, fibrinoid necrosis of collagen, and granulomas containing eosinophils, histiocytes and lymphocytes. The center of the granuloma consists of basophilic fibrillar necrosis, in which bands of destroyed tissue are interspersed with neutrophils and leukocytoclastic debris. This necrotic area is surrounded by a granulomatous mass of predominantly histiocytes, often arranged in palisading cascades. Elastic fibers are sparse in foci of degenerated collagen fibers or absent. No relationship has been established among the clinical appearance of the lesions, the histologic features and the systemic symptoms of the disease.

4.7.2. Panniculitis

Cutaneous eruptions are comprised of recurrent crops of erythematous, edematous and tender subcutaneous nodules, usually 1–2 cm in diameter, or sometimes larger. In lobular panniculitis, lesions are usually symmetrically distributed and occur most often on the thighs and lower legs. They usually regress spontaneously, but are replaced by hypopigmented and atrophic scars due to fat necrosis. Occasionally, they may become suppurative. In septal panniculitis, nodular lesions are located primarily over the extensor surfaces of the lower limbs, and they regress spontaneously without atrophic scar formation.

Lobular infiltrates of lymphocytes, plasma cells and histiocytes with fat necrosis are observed in lobular panniculitis, while infiltrates of septal panniculitis are perivascular in the septa.

4.7.3. Pyoderma gangrenosum

Pyoderma gangrenosum lesions usually start as deep-seated, painful nodules or as superficial hemorrhagic pustules, either de novo or after minor trauma. They then become ulcerated and discharge a purulent and hemorrhagic exudate (Fig. 6). Ulcers

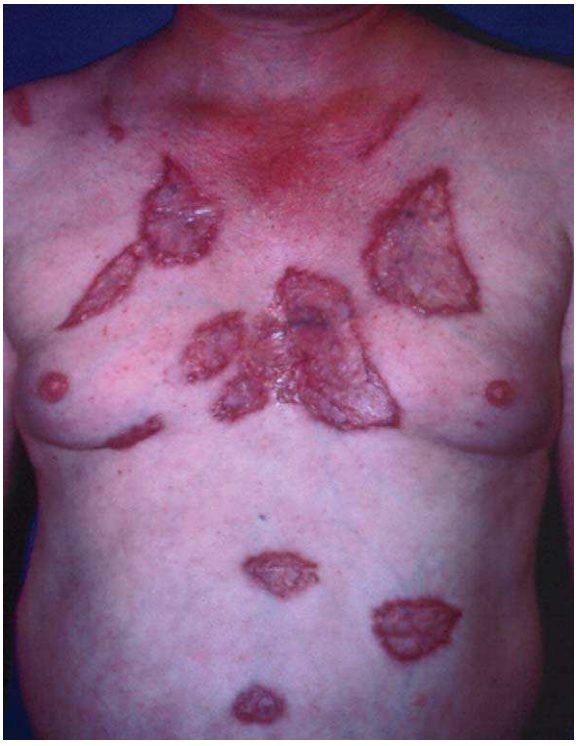


Figure 6. Pyoderma gangrenosum on the trunk of a patient with systemic Wegener's granulomatosis.

can then increase in size, up to 10 cm or more, partially recede or remain indolent for long periods. The irregular edges are raised, red or purplish, outlined, soggy and often perforated. The lower limbs, buttocks and abdomen are the sites of predilection, but any area of the body may be affected. Lesions are usually solitary but may arise in clusters, which then coalesce to form polycyclic irregular ulcerations. When healing occurs, it leaves an atrophic and often cribriform scar.

The histopathologic features consist of large, sterile abscesses containing thrombosed small and medium-sized vessels, hemorrhages and necrosis. Neutrophils are numerous but epithelioid, giant and/or mononuclear cells may also be seen, especially in chronic forms. Leukocytoclastic or lymphocytic vasculitis may be observed at the borders of the lesions. These changes are not pathognomonic and the diagnosis is essentially based on the clinical aspects of the lesions.

4.7.4. Granuloma

Granulomatous lesions without vasculitis or central necrosis may be observed in systemic vasculitis, mainly in WG. Their clinical aspects are highly variable, ranging from papules, nodules, subcutaneous infiltration or pseudotumor to chronic ulcers. Any site of the body may be involved: breasts, scrotum, face, gingivae, etc. Other granulomatous diseases have to be considered in the differential diagnosis including sarcoidosis, Crohn's disease, mycobacterial infections and foreign body granulomas.

4.7.5. Superficial thrombophlebitis

Sometimes, the clinical aspect of thrombophlebitis of superficial veins is non-specific and diagnosis can only be confirmed by histological examination of a deep skin biopsy. However, such lesions are more often found in thromboangiitis obliterans, Behçet's disease, Crohn's disease and relapsing polychondritis.

4.7.6. Gangrene

Gangrene resulting from arterial occlusion may develop in all vasculitides involving medium-sized or large arteries. Initially, gangrene is characterized by a blue-black color of the extremities, with sharply demarcated borders. The main differential diagnosis is arterial thrombosis associated with atherosclerosis and/or emboli. Angiography can only visualize occlusion or stenosis of arteries and is usually not helpful in distinguishing between these different pathogenic processes. The presence of other skin lesions with histologically proven vasculitis support the diagnosis of vasculitis, even though thrombosis, vasculitis and emboli may be associated.

4.7.7. Raynaud's phenomenon

Bilateral Raynaud's phenomenon is very common in all vasculitides. However, its prevalence in each of them is unknown and its diagnostic value is very low. In contrast, unilateral Raynaud's phenomenon suggests an obstructive arterial disease and is mainly observed in Takayasu's arteritis.

5. Diagnostic investigations and differential diagnoses

When cutaneous signs are associated with general symptoms and/or other organ or system involvement of vasculitis, differential diagnoses are primarily other systemic diseases, like systemic lupus erythematosus, and secondary vasculitides, attributed to infections, neoplasia, hematologic malignancies or drugs. Indeed, many drugs have been reported to be potential causative agents of vasculitis (Table 5). Differential diagnoses of isolated purpuric lesions are numerous and relatively easy to make (thrombotic and/or thrombocytopenic purpuras: idiopathic thrombocytopenic purpura, disseminated intravascular coagulopathy, thrombopathies; vascular purpuras, with exclusion of vasculitides: Ehlers–Danlos disease, scorbut, amyloidosis, Bateman's purpura, etc.). Embolic or atheromatous thromboses should also be ruled out when confronted with isolated distal necrosis or necrotic purpura. McDuffie's hypocomplementemic urticarial vasculitis is a rare systemic disease, characterized by the presence of circulating anti-C1q autoantibodies, mainly IgG, and hypocomplementemia. It preferentially affects women, in their 30 s, and is a vasculitis that involves postcapillary venules. Subacute and recurrent urticarial eruptions, each lasting about 12 h, with usually little pruritus, combined with systemic symptoms and, most characteristically, subacute obstructive pulmonary disease, in 25–65% of the patients, is suggestive of the affection. Histologically, lung manifestations are a consequence of emphysema that is far from usual in other primary vasculitides and in non-smokers. Quincke's edema, arthralgias, pericarditis and proliferative kidney disease that may require immunosuppressive therapy have been reported on several occasions (Schwartz et al., 1982). Schnitzler's syndrome is another chronic urticarial vasculitis, without pruritus and with no complement abnormalities. It is usually associated with bone osteocondensation, IgM paraproteinemia, leukocytoclastic vasculitis and vascular Ig deposits, detected during histologic examination of skin biopsies. Most of the reported cases followed benign courses, but some progressed to Waldenström's macroglobulinemia

Table 5
Drugs that have been reported to induce vasculitis

Antibiotics	*Antiviral agents*	*Antifungal*
Chloramphenicol	Acyclovir	Griseofulvin
Clindamycin	Efavirenz	
Gentamicin	Indinavir	
Isoniazid	Zidovudine	
Macrolides		
Penicillin		
β lactams		
Fluoroquinolones[a]		
Rifampicin		
Sulfamides		
Cyclines		
Minocycline[a]		
Vancomycin		
Vaccines	*Interferons (IFN)*	*Diuretics*
Influenzae	IFN-α, -β, -γ	Chlorthalidone
Hepatitis A, B		Furosemide
Pneumococcus		Hydrochlorothiazide
Measles		Spironolactone
Rubeola		
Antithyroid drugs	*Antiepileptic drugs*	*Cardiovascular drugs*
Carbimazole[a]	Valproic acid	Acebutolol
Methimazole	Carbamazepine	Amiodarone
Propylthiouracil[a]	Phenytoin[a]	Atenolol
	Trimethadione	Captopril
		Diltiazem
		Guanethidine Hydralazine[a]
		Methyl-dopa
		Nifedipine
		Losartan
		Procainamide
		Ramipril
		Quinidine
Psychotropic medications	*Anticoagulants*	*Sympathomimetics*
Amitriptyline	Heparin	Ephedrine
Clozapine[a]	Streptokinase	Methamphetamine
Cocaine	Warfarin	Phenylpropanolamine
Diazepam		
Ectasia		
Fluoxetine		
Heroine	*Growth factors*	
Maprotiline	G-CSF	
Paroxetine	GM-CSF	
Trazodone		
Leukotriene antagonists[a]	*Anti-cancer agents and immunosuppressants*	*Non-steroidal anti-inflammatory drugs*
Montelukast[a]	Azathioprine	Aspirin
Pranlukast[a]	Busulphan	Celecoxib
Zafirlukast[a]	Chlorambucil	Mefenamate
	Cyclophosphamide	Diclofenac

Table 5 (*continued*)

	Cytosine arabinoside	Flurbiprofen
	Melphalan	Ibuprofen
	Methotrexate	Indomethacin
	Retinoids	Phenylbutazone
	Tamoxifen	Piroxicam
	Aromatase inhibitors (anastrozole)	
Miscellanous		
Allopurinol[a]	Cyclosporin A	Potassium iodine
Additives	Dextran	Metformin
Bosentan	Diphenhydramine	Mefloquine
Bromide	D-Penicillamine[a]	Omeprazole
Cimetidine	Etanercept	Phenacetine
Chlorpropamide	Rituximab	Iodinated contrast agents
Colchicine	Infliximab	Gold therapy for rheumatoid arthritis
Cromolyn	Levamisole	Sirolimus
Sulfasalazine[a]	Quinine	Tacrolimus

[a] Drugs that may be associated with the presence of ANCA, predominantly anti-MPO P-ANCA.

or non-Hodgkin's lymphoma (Lipsker et al., 2001).

Investigational procedures must therefore be undertaken to confirm or refute the diagnosis of vasculitis, then rule out infections (or identify HBV- or HIV-related PAN, or HCV-mixed cryoglobulinemic vasculitides, which require specific therapeutic approaches), cancers, hemopathies or drug-induced vasculitis. Medical history and physical examination are essential to making the diagnosis of systemic vasculitis. Assessment of renal, heart and lung functions, and searching for any neurologic manifestation are mandatory. Some laboratory tests and examinations should be performed systematically: differential blood cell counts; coagulation tests; measurement of C-reactive protein, liver enzymes; serum protein electrophoresis; HBV, HCV and HIV serologies; testing for ANCA, cryoglobulinemia, antinuclear antibodies, rheumatoid factor; determinations of complement fractions (C3, C4, HC50); urinary sediment analysis and 24 h-proteinuria evaluation; ECG; and chest X-ray. Other investigations depend on the initial clinical conclusions and the first biological results, like blood hemocultures, other serologic tests (syphilis, streptococcus, cytomegalovirus, parvovirus B19, etc.), echocardiography, thoracoabdominal or sinus computed tomography scan, brain imaging, lumbar puncture, renal and celiomesenteric angiography, etc. Ideally, histologic confirmation of vasculitis should be obtained in a biopsy of the affected organ or tissue, with indirect immunofluorescence assay. As mentioned above, skin biopsies often show some abnormalities, especially leukocytoclastic vasculitis, which is unfortunately not specific to any of the primary systemic necrotizing vasculitides. However, skin biopsies are important to exclude some other diagnoses. Cutaneous lesions with histologically proven granulomatous inflammation may also be seen in inflammatory bowel diseases, sarcoidosis, systemic lupus erythematosus or lymphoma. Pertinently, old, scarred and healing skin lesions, especially when they are superinfected, should never be biopsied.

6. Prognosis

Patient outcome differs from one vasculitis to another and the relapse rate also varies, from 5% for HBV-related PAN (Guillevin et al., 1992a, 2001) to about 25% for CSS (Guillevin et al., 1991, 1999a), 33% for MPA (Guillevin et al., 1999b) and 50% for WG (de Groot et al., 1996; Hoffman et al., 1992). In contrast to specific kidney, heart,

gastrointestinal and central nervous system involvement, all of which being associated with increased mortality (five-factor score; FFS); skin manifestations do not appear to have any prognostic value in vasculitides (Guillevin et al., 1996).

Cutaneous manifestations have been included in the Birmingham vasculitis activity score (BVAS; Luqmani et al., 1994), which includes symptoms and signs of nine separate organ systems and is intended to assess the activity of systemic necrotizing vasculitides at any time during the course of the disease. The dermatologic items assessed in the BVAS are: infarct, purpura, other skin vasculitis, ulcer, gangrene and multiple digital gangrene. The revised BVAS version for WG (the so-called BVAS/WG) includes: purpura, ulcer and gangrene, with the latter being considered a major item (Stone et al., 2001).

7. Treatment

Before the introduction of corticosteroids (CS) in the 1970s, only 10% of untreated PAN patients survived (Frohnert and Sheps, 1967). Since then, survival has increased to 55% with the use of CS alone, and to 82% at 5 years with combined CS and immunosuppressants (Guillevin et al., 1992b; Leib et al., 1979). However, therapeutic decisions to treat and with which agents should rely on the severity of the disease, i.e. isolated and non-life-threatening skin manifestations should not always be considered an indication for systemic CS and/or immunosuppressants.

7.1. Principles of treatment for primary systemic vasculitides

The combination of CS and immunosuppressants should be prescribed only to patients with very severe forms of classical (non-HBV-related) PAN, MPA or CSS. When factors of poor prognosis are absent (FFS = 0), CS can be given alone. Conversely, for systemic WG, the combination of CS and oral or pulse cyclophosphamide (CYC) should be prescribed, followed by maintenance therapy with azathioprine, methotrexate or mycophenolate mofetil. Induction therapy for WG with drugs less toxic than CYC (i.e. methotrexate or cotrimoxazole) should be reserved for very limited forms, like isolated nasal crusting or cutaneous purpura (Hoffman, 1996). Alternative treatments, using other immunosuppressants or immunomodulating agents, can be administered for relapses or patients whose disease does not respond to conventional regimens.

7.1.1. Corticosteroids

First-line therapy for all systemic necrotizing vasculitides must include oral high dose prednisone (at least 1 mg/kg/d), usually preceded by a daily methylprednisolone pulse(s) for 1–3 days (15 mg/kg/d) to rapidly control the more disabling or life-threatening symptoms. The full oral dose should be maintained until clinical and biological improvement is achieved, usually within 1 month, and then gradually tapered over 12–18 months.

7.1.2. Immunosuppressants

Pulse IV CYC should be combined with CS for patients with poor prognostic factor(s), i.e. FFS $\geqslant$ 1. Pulse therapy acts more rapidly and engenders fewer side effects (hemorrhagic cystitis, leukopenia) than oral administration. Briefly, each CYC pulse (0.5–0.7 g/m^2) is administered every 15 days for the first 3 boluses, then every 3 weeks (WG and MPA) or monthly (PAN and CSS). When preferred (WG) or required (e.g., after failure of pulse CYC), oral CYC (2 mg/kg/d) should be prescribed. CYC should be sustained at least until remission is achieved, between 3 for pulse CYC and 18 months for oral CYC, then maintained for a total of 12 months for severe systemic PAN or CSS, whereas, for WG and MPA, it can be switched for maintenance therapy with methotrexate, azathioprine or mycophenolate mofetil, for an additional 1 or 2 years.

7.1.3. Other therapies

First reports of the use of intravenous immunoglobulins in patients with refractory systemic vasculitides yielded encouraging, then mixed, results. Forty to 92% of the patients with refractory disease (Jayne et al., 2000) responded, at least partially, but complete remission rates and their long-term

maintenance will have to be more closely analyzed as data from ongoing trials become available. Plasma exchanges may be useful as second-line therapy for refractory PAN or MPA, essentially those with rapidly progressive glomerulonephritis (Pusey et al., 1991) or in vasculitides associated with immune-complex deposits, like HBV-related PAN or cryoglobulinemia. Cotrimoxazole may be beneficial as adjuvant therapy for WG patients (Israel, 1988) or limited nasal and oral forms of WG (Lê Thi Huong et al., 1990; Reinhold-Keller et al., 1996). Treatment with anti-CD20 monoclonal antibodies (Specks et al., 2001) or anti-TNFα antibodies may be promising for patients with intractable vasculitides (Bartolucci et al., 2002).

7.2. Treatment of dermatologic manifestations

General measures, like rest and wearing elastic compression stockings, combined with local treatments of ulcers and/or gangrene, like disinfection, scraping, and, sometimes surgical debridation, do not differ from those applied for non-vasculitic skin ulcerations. Dapsone and colchicine can also occasionally help control some relapsing cutaneous manifestations (Thomas-Golbanov and Sridharan, 2001), and antihistamines may be useful for urticarial vasculitic manifestations. When associated with systemic manifestations or extensive skin necrosis, CS alone or in combination with an immunosuppressant, as recommended above, usually achieves rapid regression of the lesions, but relapses may occur or intractable skin manifestations may persist. Prevention of superinfection, especially in these latter patients receiving CS (and immunosuppressants), should always be kept in mind. Adjunction of alternative treatments (e.g., anti-CD20 monoclonal antibodies) may be effective in these cases, like in other refractory forms of vasculitis.

Key points

- Dermatologic lesions are frequent in small, medium-sized vessel and granulomatous systemic vasculitides.
- They usually do not affect the prognosis but relapsing or intractable forms have been described.
- The most frequent cutaneous manifestation is palpable purpura. Histologic examination of such lesions often provides confirmation of vasculitis, mainly by detection of small vessel leukocytoclastic vasculitis, but rarely contributes to determining the type of vasculitis.
- Histologic examination of other skin lesions (nodules, papules, pustules, livedo or necrotic ulcerations) is also necessary, and may show some more suggestive features, like granulomatous necrotizing vasculitis in Wegener's granulomatosis or Churg–Strauss syndrome.
- When skin manifestations are only one of the multiple clinical signs of vasculitis, the diagnosis is quite easy to make. Treatment with corticosteroids and, when indicated, an immunosuppressant, usually leads to the rapid disappearance of cutaneous lesions.
- Conversely, when skin lesions are isolated, making the diagnosis may be more challenging. In these cases, treatment may first be less aggressive, using dapsone or colchicine, and reserving corticosteroids only for those patients in whom the former are ineffective or when cutaneous necrosis is extensive.

References

Abu-Shakra, M., Smythe, H., Lewtas, J., et al. 1994. Outcome of polyarteritis nodosa and Churg–Strauss syndrome. An analysis of twenty-five patients. Arthritis Rheum. 37, 1798.

Anderson, G., Coles, E.T., Crane, M., et al. 1992. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q. J. Med. 83, 427.

Ara, J., Mirapeix, E., Arrizabalaga, P., et al. 2001. Circulating soluble adhesion molecules in ANCA-associated vasculitis. Nephrol. Dial. Transplant. 16, 276.

Arend, W.P., Michel, B.A., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 33, 1129.

Balding, C.E., Howie, A.J., Drake-Lee, A.B., et al. 2001. Th2 dominance in nasal mucosa in patients with Wegener's granulomatosis. Clin. Exp. Immunol. 125, 332.

Barksdale, S.K., Hallahan, C.W., Kerr, G.S., et al. 1995. Cutaneous pathology in Wegener's granulomatosis. A clinicopathologic study of 75 biopsies in 46 patients. Am. J. Surg. Pathol. 19, 161.

Bartolucci, P., Ramanoelina, J., Cohen, P., et al. 2002. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology (Oxford) 41, 1126.

Bligny, D., Mahr, A., Le Toumelin, P., et al. 2004. Predicting mortality in systemic Wegener's granulomatosis: a survival analysis based on 93 patients. Arthritis Rheum. 51, 83.

Bloch, D.A., Michel, B.A., Hunder, G.G., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum. 33, 1068.

Brandwein, S., Esdaile, J., Danoff, D., et al. 1983. Wegener's granulomatosis. Clinical features and outcome in 13 patients. Arch. Intern. Med. 143, 476.

Carrington, C.B., Liebow, A. 1966. Limited forms of angiitis and granulomatosis of Wegener's type. Am. J. Med. 41, 497.

Chumbley, L.C., Harrison, E.G., Jr., DeRemee, R.A. 1977. Allergic granulomatosis and angiitis (Churg–Strauss syndrome). Report and analysis of 30 cases. Mayo Clin. Proc. 52, 477.

Churg, J., Strauss, L. 1951. Allergic angiitis and periarteritis nodosa. Am. J. Pathol. 27, 277.

Cohen, P., Guillevin, L., Baril, L., et al. 1995. Persistence of antineutrophil cytoplasmic antibodies (ANCA) in asymptomatic patients with systemic polyarteritis nodosa or Churg–Strauss syndrome: follow-up of 53 patients. Clin. Exp. Rheumatol. 13, 193.

Crotty, C.P., DeRemee, R.A., Winkelmann, R.K. 1981. Cutaneous clinicopathologic correlation of allergic granulomatosis. J. Am. Acad. Dermatol. 5, 571.

CSS cutaneous lesions can be divided into 3 histologic categories: extravascular granulomas (50%), leukocytoclastic vasculitis (33%) and cutaneous 'polyarteritis nodosa' (17%).

Csernok, E., Trabandt, A., Muller, A., et al. 1999. Cytokine profiles in Wegener's granulomatosis: predominance of type 1 (Th1) in the granulomatous inflammation. Arthritis Rheum. 42, 742.

Daoud, M.S., Gibson, L.E., DeRemee, R.A., et al. 1994. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. J. Am. Acad. Dermatol. 31, 605.

In this study, 14% of 244 WG patients had skin lesions, usually at presentation. Leukocytoclastic vasculitis was the most common cutaneous pathologic pattern. Cutaneous involvement appeared to be premonitory sign of renal disease.

Davies, D.J., Moran, J.E., Niall, J.F., et al. 1982. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology?. Br. Med. J. (Clin. Res. Ed.) 285, 606.

Davis, M.D., Daoud, M.S., McEvoy, M.T., et al. 1997. Cutaneous manifestations of Churg–Strauss syndrome: a clinicopathologic correlation. J. Am. Acad. Dermatol. 37, 199.

Thirty-six (40%) of 90 CSS patients had cutaneous signs, as the initial manifestation in 5 of them. The most common clinical presentations were purpura and petechiae on lower extremities, and cutaneous nodules and papules on elbows. The most common histologic findings in skin biopsies (37 specimens) were extravascular necrotizing granuloma (15 specimens) and leukocytoclastic vasculitis (16 specimens).

D'Cruz, D.P., Baguley, E., Asherson, R.A., et al. 1989. Ear, nose, and throat symptoms in subacute Wegener's granulomatosis. BMJ 299, 419.

de Groot, K., Reinhold-Keller, E., Tatsis, E., et al. 1996. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. Arthritis Rheum. 39, 2052.

de Groot, K., Gross, W.L., Herlyn, K., et al. 2001a. Development and validation of a disease extent index for Wegener's granulomatosis. Clin. Nephrol. 55, 31.

de Groot, K., Schmidt, D.K., Arlt, A.C., et al. 2001b. Standardized neurologic evaluations of 128 patients with Wegener's granulomatosis. Arch. Neurol. 58, 1215.

Devaney, K.O., Travis, W.D., Hoffman, G., et al. 1990. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. Am. J. Surg. Pathol. 14, 555.

Diaz-Perez, J.L., Winkelmann, R.K. 1974. Cutaneous periarteritis nodosa. Arch. Dermatol. 110, 407.

Dicken, C.H., Winkelmann, R.K. 1978. The Churg–Strauss granuloma: cutaneous, necrotizing, palisading granuloma in vasculitis syndromes. Arch. Pathol. Lab. Med. 102, 576.

D'Izarn, J.J., Boulet, C.P., Convard, J.P., et al. 1976. Arteriography in polyarteritis nodosa. 15 cases [in French]. J. Radiol. Electrol. Méd. Nucl. 57, 505.

Falk, R.J., Jennette, J.C. 1988. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. New Engl. J. Med. 318, 1651.

Fauci, A.S., Haynes, B.F., Katz, P., et al. 1983. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann. Intern. Med. 98, 76.

Finan, M.C., Winkelmann, R.K. 1983. The cutaneous extravascular necrotizing granuloma (Churg–Strauss granuloma) and systemic disease: a review of 27 cases. Medicine (Baltimore) 62, 142.

Fortin, P.R., Larson, M.G., Watters, A.K., et al. 1995. Prognostic factors in systemic necrotizing vasculitis of the polyarteritis nodosa group–a review of 45 cases. J. Rheumatol. 22, 78.

Francès, C., Lê Thi Huong, D., Piette, J.C., et al. 1994. Wegener's granulomatosis. Dermatological manifestations in 75 cases with clinicopathologic correlation. Arch. Dermatol. 130, 861.

In this study, 35 of 75 WG patients had skin and/or mucosa involvement, mainly palpable purpura (26 patients), oral ulcers (15), skin nodules (6), ulcers (5), necrotic papules (5), gingival hyperplasia (3), pustules (2), palpebral xanthoma

(2), genital ulcer (1), digital necrosis (1) or livedo reticularis (1). At histology, nongranulomatous vasculitis was associated with purpuric lesions, whereas granulomatous inflammation was associated with nonpurpuric lesions. Skin manifestations were associated with a higher frequency of articular and renal involvement (68% vs. 25%; 80% vs. 47%, respectively). These manifestations responded well to steroids and cyclophosphamide, in most of the cases.

Fries, J.F., Hunder, G.G., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum. 33, 1135.

Frohnert, P., Sheps, S. 1967. Long term follow-up study of periarteritis nodosa. Am. J. Med. 43, 8.

Gherardi, R., Belec, L., Mhiri, C., et al. 1993. The spectrum of vasculitis in human immunodeficiency virus-infected patients. A clinicopathologic evaluation. Arthritis Rheum. 36, 1164.

Gibson, L.E., Winkelmann, R.K. 1986. Cutaneous granulomatous vasculitis: its relationship to systemic disease. J. Am. Acad. Dermatol. 14, 492.

Girard, T., Mahr, A., Noël, L.H., et al. 2001. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. Rheumatology (Oxford) 40, 147.

Gower, R.G., Sausker, W.F., Kohler, P.F., et al. 1978. Small vessel vasculitis caused by hepatitis B virus immune complexes. Small vessel vasculitis and HBsAG. J. Allergy Clin. Immunol. 62, 222.

Guillevin, L., Fechner, J., Godeau, P., et al. 1985. Periarteritis nodosa: clinical and therapeutic study of 126 patients followed-up during 23 years [in French]. Ann. Méd. Interne (Paris) 136, 6.

Guillevin, L., Jarrousse, B., Lok, C., et al. 1991. Long term follow-up after treatment of polyarteritis nodosa and Churg–Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange. A prospective randomized trial of 71 patients. The Cooperative Study Group for Polyarteritis Nodosa. J. Rheumatol. 18, 567.

Guillevin, L., Lhote, F., Jarrousse, B., et al. 1992a. Polyarteritis nodosa related to hepatitis B virus. A retrospective study of 66 patients. Ann. Méd. Interne (Paris) 143 (Suppl. 1), 63.

Guillevin, L., Lhote, F., Jarrousse, B., et al. 1992b. Treatment of polyarteritis nodosa and Churg–Strauss syndrome. A meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. Ann. Méd. Interne (Paris) 143, 405.

Guillevin, L., Lhote, F., Brauner, M., et al. 1995a. Antineutrophil cytoplasmic antibodies (ANCA) and abnormal angiograms in polyarteritis nodosa and Churg–Strauss syndrome: indications for the diagnosis of microscopic polyangiitis. Ann. Méd. Interne (Paris) 146, 548.

Guillevin, L., Lhote, F., Cohen, P., et al. 1995b. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg–Strauss syndrome patients with factors predicting poor prognosis. A prospective, randomized trial in sixty-two patients. Arthritis Rheum. 38, 1638.

Guillevin, L., Lhote, F., Gayraud, M., et al. 1996. Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 75, 17.

Follow-up and multivariate outcome analysis of 260 patients with PAN and 82 with CSS showed that serum creatinine > 1.58mg/dl, proteinuria (due to vascular or glomerular disease), GI tract involvement, specific cardiomyopathy and CNS involvement were independent prognostic factors. The five-factors score (FFS) considers these 5 parameters at initial assessment, and is a good predictor of death. Furthermore, FFS can be used to help the clinician choose the most adequate treatment.

Guillevin, L., Cordier, J.F., Lhote, F., et al. 1997. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum. 40, 2187.

Guillevin, L., Cohen, P., Gayraud, M., et al. 1999a. Churg–Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 78, 26.

Guillevin, L., Durand-Gasselin, B., Cevallos, R., et al. 1999b. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum. 42, 421.

Guillevin, L., Cohen, P., Larroche, C., et al. 2001. Treatment of HBV-related polyarteritis nodosa (PAN) with lamivudine and plasma exchanges: a prospective, multicenter, pilot trial in 10 patients. Arthrits Rheum. 44, S271.

Guillevin, L., Mahr, A., Cohen, P., et al. 2004. Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa. Arthritis Rheum. 51, 482.

Haas, C., Le Jeunne, C., Choubrac, P., et al. 2001. Churg Strauss syndrome. Retrospective study of 20 cases [in French]. Bull. Acad. Natl. Méd. 185, 1113.

Hagen, E.C., Daha, M.R., Hermans, J., et al. 1998. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR project for ANCA assay standardization. Kidney Int. 53, 743.

Handa, R., Wali, J.P. 1996. Wegener's granulomatosis with gangrene of toes. Scand. J. Rheumatol. 25, 103.

Handlers, J.P., Waterman, J., Abrams, A.M., et al. 1985. Oral features of Wegener's granulomatosis. Arch. Otolaryngol. 111, 267.

Heeringa, P., Brouwer, E., Tervaert, J.W., et al. 1998. Animal models of anti-neutrophil cytoplasmic antibody associated vasculitis. Kidney Int. 53, 253.

Hoffman, G.S., Kerr, G.S., Leavitt, R.Y., et al. 1992. Wegener granulomatosis: an analysis of 158 patients. Ann. Intern. Med. 116, 488.

Hoffman, G.S. 1996. Immunosuppressive therapy is always required for the treatment of limited Wegener's granulomatosis. Sarcoidosis Vasc. Diffuse Lung. Dis. 13, 249.

Homas, P.B., David-Bajar, K.M., Fitzpatrick, J.E., et al. 1992. Microscopic polyarteritis. Report of a case with cutaneous

involvement and antimyeloperoxidase antibodies. Arch. Dermatol. 128, 1223.

Hunder, G.G., Arend, W.P., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum. 33, 1065.

Israel, H.L. 1988. Sulfamethoxazole–trimethoprim therapy for Wegener's granulomatosis. Arch. Intern. Med. 148, 2293.

Jayne, D.R., Chapel, H., Adu, D., et al. 2000. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. Q. J. Med. 93, 433.

Jennette, J.C., Falk, R.J., Andrassy, K., et al. 1994. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 37, 187.

Kallenberg, C.G., Mulder, A.H., Tervaert, J.W. 1992. Antineutrophil cytoplasmic antibodies: a still-growing class of autoantibodies in inflammatory disorders. Am. J. Med. 93, 675.

Klinger, H. 1931. Grenzformen der periarteritis nodosa. Frankfur. Zeit. Pathol. 42, 455.

Koldingsnes, W., Nossent, J.C. 2003. Baseline features and initial treatment as predictors of remission and relapse in Wegener's granulomatosis. J. Rheumatol. 30, 80.

Lane, S.E., Watts, R.A., Bentham, G., et al. 2003. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 48, 814.

Lanham, J.G., Elkon, K.B., Pusey, C.D., et al. 1984. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg–Strauss syndrome. Medicine (Baltimore) 63, 65.

Lê Thi Huong, D., Wechsler, B., De Gennes, C., et al. 1990. Treatment of Wegener's granulomatosis with cotrimoxazole (7 cases) [in French]. Rev. Méd. Interne 11, 87.

Leavitt, R.Y., Fauci, A.S., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 33, 1101.

Leib, E.S., Restivo, C., Paulus, H.E. 1979. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. Am. J. Med. 67, 941.

Lhote, F., Cohen, P., Guillevin, L. 1998. Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. Lupus 7, 238.

Lie, J.T. 1997. Wegener's granulomatosis: histological documentation of common and uncommon manifestations in 216 patients. Vasa 26, 261.

Lightfoot, R.W., Jr., Michel, B.A., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum. 33, 1088.

Lipsker, D., Veran, Y., Grunenberger, F., et al. 2001. The Schnitzler syndrome. Four new cases and review of the literature. Medicine (Baltimore) 80, 37.

Luqmani, R.A., Bacon, P.A., Moots, R.J., et al. 1994. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. Q. J. Med. 87, 671.

Masi, A.T., Hunder, G.G., Lie, J.T., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 33, 1094.

Matsuda, S., Mitsukawa, S., Ishii, N., et al. 1976. A case of Wegener's granulomatosis with necrosis of the penis. Tohoku J. Exp. Med. 118, 145.

Mills, J.A., Michel, B.A., Bloch, D.A., et al. 1990. The American College of Rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. Arthritis Rheum. 33, 1114.

Moore, P.M. 1995. Neurological manifestation of vasculitis: update on immunopathogenic mechanisms and clinical features. Ann. Neurol. 37 (Suppl. 1), S131.

Ohta, N., Fukase, S., Aoyagi, M. 2001. Serum levels of soluble adhesion molecules ICAM-1, VCAM-1 and E-selectin in patients with Wegener's granulomatosis. Auris Nasus Larynx 28, 311.

Patten, S.F., Tomecki, K.J. 1993. Wegener's granulomatosis: cutaneous and oral mucosal disease. J. Am. Acad. Dermatol. 28, 710.

Penas, P.F., Porras, J.I., Fraga, J., et al. 1996. Microscopic polyangiitis. A systemic vasculitis with a positive P-ANCA. Br. J. Dermatol. 134, 542.

Pfister, H., Ollert, M., Frohlich, L.F., et al. 2004. Antineutrophil cytoplasmic autoantibodies against the murine homolog of proteinase 3 (Wegener autoantigen) are pathogenic in vivo. Blood 104, 1411.

This in vivo study provides the first evidence for a pathogenic effect of anti-PR3 C-ANCA. Indeed, local inflammation with subcutaneous panniculitis induced by intradermal injection of TNFα, was stronger when anti-PR3 C-ANCA were passively transferred into PR3/neutrophil elastase-deficient mice than in the presence of mock immune serum.

Puisieux, F., Woesteland, H., Hachulla, E., et al. 1997. Clinical symptomatology and prognosis of periarteritis nodosa in the elderly. Retrospective study of 25 periarteritis nodosa cases in young adults and 22 cases in aged patients [in French]. Rev. Méd. Interne 18, 195.

Pusey, C.D., Rees, A.J., Evans, D.J., et al. 1991. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int 40, 757.

Reinhold-Keller, E., de Groot, K., Rudert, H., et al. 1996. Response to trimethoprim/sulfamethoxazole in Wegener's granulomatosis depends on the phase of disease. Q. J. Med. 89, 15.

Reinhold-Keller, E., Beuge, N., Latza, U., et al. 2000. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum. 43, 1021.

Schwartz, H.R., McDuffie, F.C., Black, L.F., et al. 1982. Hypocomplementemic urticarial vasculitis: association with chronic obstructive pulmonary disease. Mayo Clin. Proc. 57, 231.

Schwartz, R.A., Churg, J. 1992. Churg–Strauss syndrome. Br. J. Dermatol. 127, 199.

Sehgal, M., Swanson, J.W., DeRemee, R.A., et al. 1995. Neurologic manifestations of Churg–Strauss syndrome. Mayo Clin. Proc. 70, 337.

Seishima, M., Oyama, Z., Oda, M. 2004. Skin eruptions associated with microscopic polyangiitis. Eur. J. Dermatol. 14, 255. In this study of 10 MPA patients with cutaneous involvement, predominant skin lesions were purpura and petechiae (6 patients), livedo (2) and erythema (7), especially on the hands and\or fingers (4). Histological findings were perivascular lymphocyte infiltration in the upper dermis (4), infiltration of lymphocytes and a few neutrophils around small arteries in the middle to deep dermis (2) and diffuse infiltration of histiocytes and lymphocytes in the middle dermis (1).

Solans, R., Bosch, J.A., Perez-Bocanegra, C., et al. 2001. Churg–Strauss syndrome: outcome and long-term follow-up of 32 patients. Rheumatology (Oxford) 40, 763.

Specks, U., Homburger, H.A., DeRemee, R.A. 1993. Implications of c-ANCA testing for the classification of Wegener's granulomatosis: performance of different detection systems. Adv. Exp. Med. Biol. 336, 65.

Specks, U., Fervenza, F.C., McDonald, T.J., et al. 2001. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis Rheum. 44, 2836.

Stone, J.H., Hoffman, G.S., Merkel, P.A., et al. 2001. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham vasculitis activity score. International network for the study of the systemic vasculitides (INSSYS). Arthritis Rheum. 44, 912.

Stone, J.H. 2003. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum. 48, 2299.

Sundy, J.S., Haynes, B.F. 2000. Cytokines and adhesion molecules in the pathogenesis of vasculitis. Curr. Rheumatol. Rep. 2, 402.

Tervaert, J.W., Huitema, M.G., Hene, R.J., et al. 1990. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. Lancet 336, 709.

Tesar, V., Jelinkova, E., Masek, Z., et al. 1998. Influence of plasma exchange on serum levels of cytokines and adhesion molecules in ANCA-positive renal vasculitis. Blood Purif 16, 72.

Thomas-Golbanov, C., Sridharan, S. 2001. Novel therapies in vasculitis. Expert Opin. Investig. Drugs 10, 1279.

Trueb, R.M., Scheidegger, E.P., Pericin, M., et al. 1999. Periarteritis nodosa presenting as a breast lesion: report of a case and review of the literature. Br. J. Dermatol. 141, 1117.

Tullo, A.B., Durrington, P., Graham, E., et al. 1995. Florid xanthelasmata (yellow lids) in orbital Wegener's granulomatosis. Br. J. Ophthalmol. 79, 453.

van der Woude, F.J., Rasmussen, N., Lobatto, S., et al. 1985. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1, 4259.

Walton, E.W. 1958. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br. Med. J. 2, 265.

Watts, R.A., Carruthers, D.M., Scott, D.G. 1995. Epidemiology of systemic vasculitis: changing incidence or definition? Semin. Arthritis Rheum. 25, 28.

Wegener, F. 1936. Uber generalisierte, septische Gefasserkrankungen. Verh. Dtsch. Ges. Pathol. 29, 202.

Xiao, H., Heeringa, P., Hu, P., et al. 2002. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J. Clin. Invest. 110, 955.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 21

Kawasaki Disease

Francesco Zulian[a,*], Tomisaku Kawasaki[b]

[a]*Rheumatology Unit, Department of Pediatrics, University of Padova, Italy*
[b]*Japan Kawasaki Disease Research Center, Tokyo, Japan*

1. Introduction

Kawasaki disease (KD) is an acute vasculitis of unknown etiology first described in Japan in l967 (Kawasaki, 1967). It occurs predominantly in infants and young children and is the second more frequent systemic vasculitis in children after Henoch-Schönlein Purpura.

Since it is complicated by coronary and peripheral arterial aneurysms in 20–35% of untreated patients, KD represents the commonest cause of acquired heart disease in children in developed countries.

A prompt diagnosis is critical as the early administration of intravenous gammaglobulin (IVIG) dramatically reduces the rate of coronary artery abnormalities (CAA) to less than 5%. Despite many efforts, there are no diagnostic tests available for KD, and the diagnosis is essentially based on clinical criteria. Since several conditions may mimic KD, the syndrome is under recognized, with high risk of developing CAA.

2. Prevalence

KD is markedly more prevalent in Japan and in children of Japanese ancestry, with an annual incidence of 112 cases per 100,000 children <5 years of age (Yanagawa et al., 2001).

In the United States, the incidence is 17.1/100,000 children <5 years, with a median age of 2 years. KD is most common among Asian and Pacific Islander children, intermediate in Blacks and Hispanics and more rare in Caucasians (Holman et al., 2003).

In Europe the annual reported incidence ranges from 3 to 8 per 100,000 children under 5 years and has increased between 1991 and 2000 (Harden et al., 2002; Rowley et al., 1999). It is possible, however, that this reflects an increase in recognition rather than incidence. In Italy the epidemiology of KD is not fully known, since only few data from single Pediatric Units are available (Falcini et al., 2002).

3. Epidemiology

Figure 1 summarizes the distribution of the age at onset of the disease in a cohort of 171 children followed at the Department of Pediatrics of Padua. As shown, the disease is more frequent in early infancy, very rare in children over 8 years of age, exceptional in adults.

The recurrence rate of KD has been reported to be around 3% (Yanagawa et al., 1998). The proportion of cases with a positive family history is around 1% (Yanagawa et al., 1998; Hirata et al., 2001) and the disease has been also reported in children of parents who themselves had the illness in childhood (Bruckheimer et al., 1998; Kaneko et al., 1999; Uehara et al., 2003).

*Corresponding author.
Pediatric Rheumatology Unit, Department of Pediatrics, Via Giustiniani 3, 35128 Padova, Italy.
Tel.: +39049-8213583; Fax: +39049-8218088.
E-mail address: zulian@pediatria.unipd.it (F. Zulian).

DOI: 10.1016/S1571-5078(05)05021-X

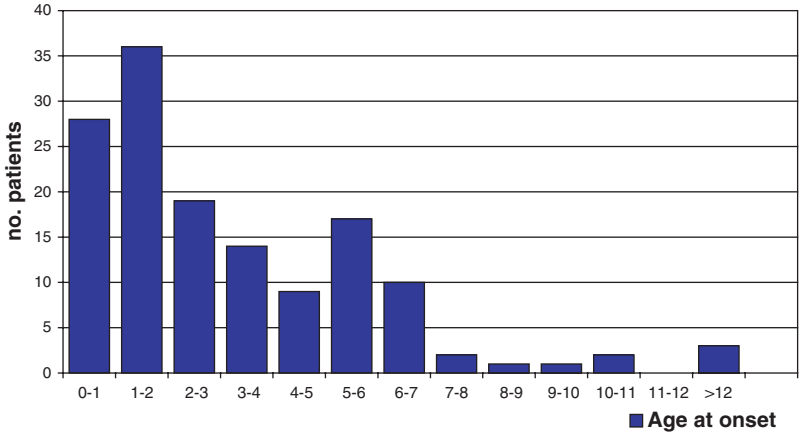


Figure 1. Age at onset of Kawasaki disease.

These data suggest a possible role for genetic predisposition that interacts with exposure to environmental agents.

KD is more common during the winter and early spring months, boys outnumber girls by 1.5–1.7:1 and 76% of children are <5-years old (Holman et al., 2003).

The case fatality rate in KD in Japan is 0.08% (Yanagawa et al., 1998). The standardized mortality ratio (the observed number of deaths divided by the expected number of deaths based on vital statistics in Japan) in patients diagnosed between 1982 and 1992 was 1.25 (95% CI, 0.84–1.85) overall and 2.35 (95% CI, 0.96–5.19) for boys with cardiac sequelae (Nakamura et al., 2002).

4. Etiopathogenesis

Despite the huge number of studies in this field, the cause of KD remains unclear. The role of an infectious trigger, inducing the disease in a genetically susceptible host, is still strongly suggested by the epidemiology of the disease in Japanese and North American epidemics that resembles the spread of viral or bacterial infections. However, efforts to identify an infectious agent in KD with conventional bacterial and viral cultures and serological methods, as well as with animal inoculation, have failed to identify an infectious cause. Also the genetic basis of susceptibility is currently unknown.

The hypothesis that KD is related to a bacterial superantigenic toxin has been suggested by the selective expansion of Vß2 and Vß8 T-cell receptor families, but this theory remains controversial (Abe et al., 1992; Leung et al., 1995, 2002; Yamashiro et al., 1996).

The key steps leading to coronary arteritis have not been fully clarified, although endothelial cell activation, CD68+ monocyte/macrophages, CD8+ (cytotoxic) lymphocytes, and oligoclonal IgA plasma cells appear to be involved (Brown et al., 2001; Rowley et al., 2000, 2001).

Enzymes including matrix metalloproteinases that are capable of damaging arterial wall integrity may be important in the development of aneurysmal dilatation (Takeshita et al., 2001). Eventually, vascular endothelial growth factor (VEGF), monocyte chemotactic and activating factor (MCAF or MCP-1), tumor necrosis factor α (TNFα), and various interleukins also appear to play important roles in the vasculitic process (Asano and Ogava, 2000; Eberhard et al., 1995; Yasukawa et al., 2002).

5. Clinical manifestations

5.1. Diagnostic criteria

In the absence of a specific diagnostic test, the diagnosis of KD is based on clinical criteria (Table 1). The presence of ≥5 days of otherwise unexplained

fever and four or more of the five following clinical features are needed for the diagnosis of complete KD (Centers for Disease Control, 1990):

1. bilateral conjunctival hyperemia
2. polymorphous rash
3. bilateral, non-suppurative cervical lymphadenopathy (at least one lymph node larger than 1.5 cm)
4. mucous membrane changes (i.e. injected or fissured lips, diffuse erythema of oropharyngeal mucosa)
5. extremity changes (e.g. erythema of palms and soles, edema of the hands and feet, and periungueal digital peeling).

The relative prevalence of the clinical manifestations at onset of KD are summarized in Fig. 2.

Table 1
Diagnostic criteria of Kawasaki disease

The diagnosis of KD is assessed by the presence of fever for at least five days and four out of five of the criteria below

- bilateral conjunctival injection
- polymorphous rash
- cervical adenopathy (>1.5 cm diameter)
- changes of mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue
- changes of the extremities: peripheral edema and erythema, periungueal desquamation

Fever typically is high spiking and remittent, with peak temperature generally over 39°C and in many cases over 40°C. In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3–4 weeks and, rarely, even longer. With appropriate therapy, the fever usually resolves within 2 days.

Bilateral conjunctival injection usually begins shortly after the onset of fever. It typically involves the bulbar conjunctivae much more often than the palpebral or tarsal conjunctivae (Fig. 3). It is not associated with an exudate, conjunctival edema or corneal ulceration and is usually painless. Mild acute anterior uveitis may be noted by slit lamp examination.

An erythematous rash usually appears within 5 days from the onset of fever. It may take various forms; the most common is a non-specific, diffuse maculopapular eruption. Occasionally are urticarial exanthema, scarlet-like rash, and even erythroderma. The rash usually is extensive, with involvement of the trunk and extremities and accentuation in the perineal region, where early desquamation may occur (Fig. 4).

Cervical lymphadenopathy is the least common of the principal clinical features. It is usually unilateral and its classic criteria include at least 1 lymph node that is >1.5 cm in diameter.

Changes in Lips and Oral Mucosa include the bright red, swollen lips with vertical cracking and

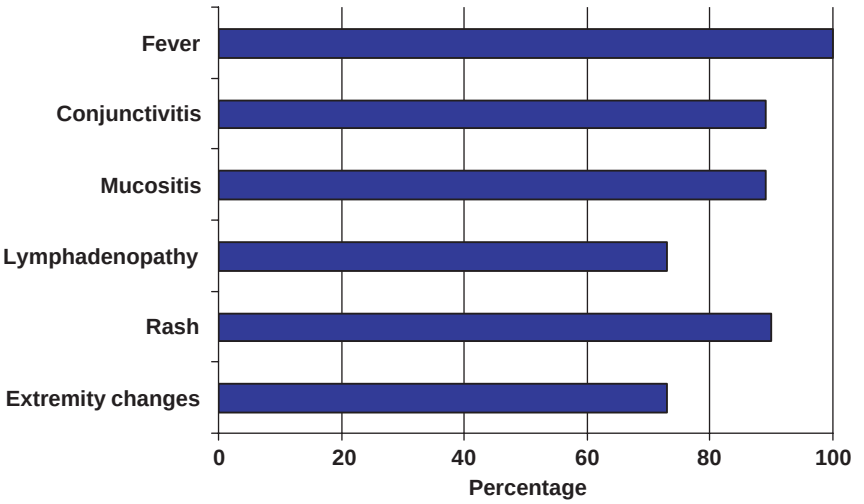


Figure 2. Presenting clinical manifestations of Kawasaki disease.

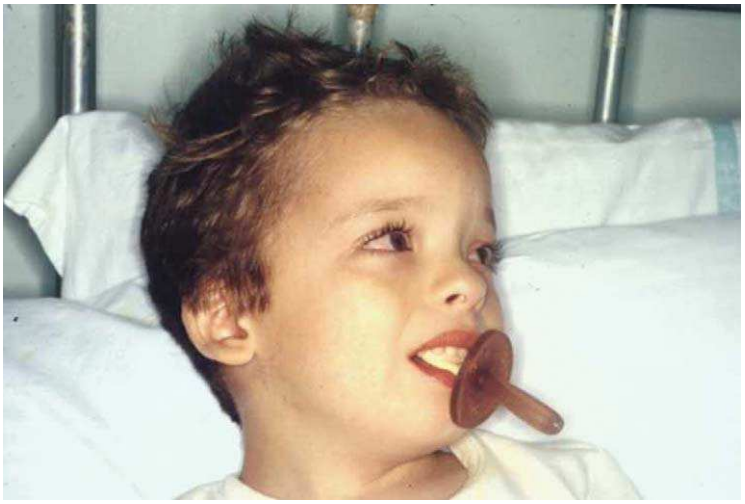


Figure 3. Bilateral conjunctival injection and hyperemia and swelling of the lips in a 3-year old boy with Kawasaki disease.

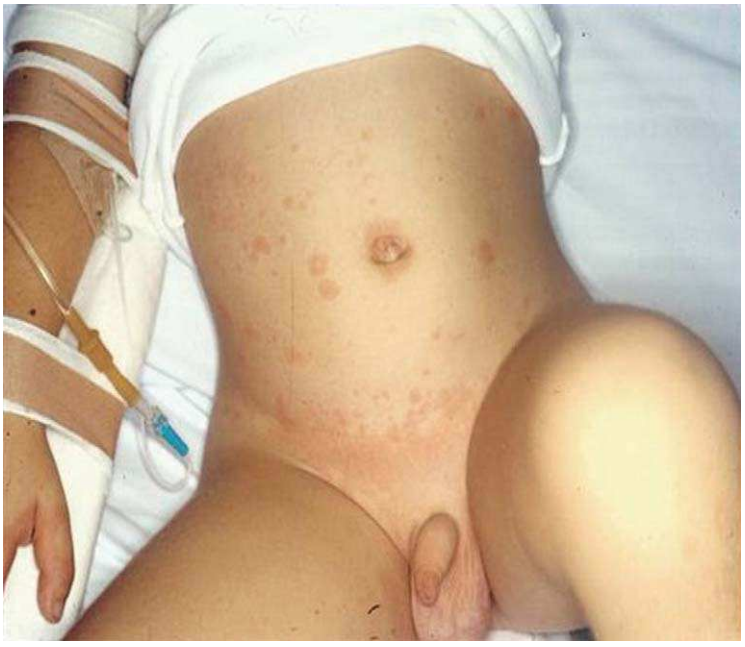


Figure 4. Erythematous rash of the abdomen with accentuation in the perineal region.

bleeding (Fig. 3). The mucosa of the oropharynx may be bright red, and the tongue may have a typical "strawberry" appearance.

Peripheral Extremity changes include reddish erythema of the palms and soles that is often accompanied by painful, brawny edema of the dorsa of the hands and feet. These changes usually last for 1–3 days. After the acute febrile phase, the fingertips begin to peel. This may involve the entire finger and, sometimes, the entire palm (Fig. 5). Toes are less commonly affected.

5.2. Atypical-incomplete kawasaki disease

Patients with fever for <5 days and <4 principal features are labeled as "incomplete-atypical" cases,

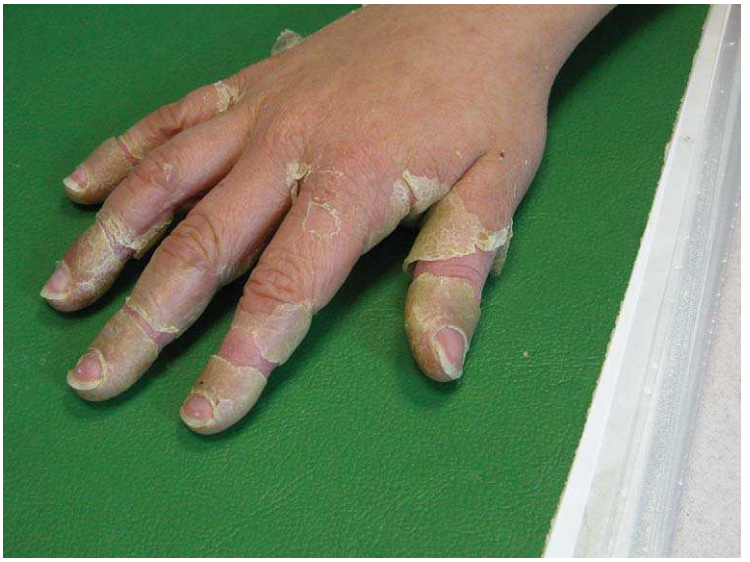


Figure 5. Peeling of the fingertips involving the entire finger and palm.

a diagnosis that often is based on echocardiographic findings of CAA (Rowley et al., 1987). The term ''incomplete'' may be preferable to ''atypical'' because these patients lack sufficient clinical signs of the disease to fulfill the classic criteria; they do not demonstrate atypical clinical features. The phrase ''atypical Kawasaki disease'' should be reserved for patients who have a problem, such as renal impairment, that generally is not seen in Kawasaki disease. Incomplete KD is more common in young infants than in older children, making accurate diagnosis and timely treatment especially important in these young patients who are at substantial risk of developing coronary abnormalities. Children with high persistent fever and incomplete onset represent a challenge for the pediatrician. In fact, associated to the classical clinical picture we can observe adjunctive clinical features that sometimes can lead to inappropriate diagnoses (Sundel et al., 1992). Fig. 6 summarizes the presence of these associated clinical features observed in 171 patients followed at the Pediatric Department, University of Padua. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain due to acute distension of the gallbladder (hydrops), identified by abdominal US, occur in ~50% of patients during the first 2 weeks of the illness (Sunddleson et al., 1987). Hepatic enlargement and jaundice can occur. One third of patients can start with respiratory symptoms while around 40% can show early cardiac involvement such as pericarditis, myocarditis, and EKG abnormalities. Osteoarticular involvement such as arthritis or arthralgia can occur in almost one third of the patients. Signs of lower urinary tract inflammation such as sterile pyuria or uretritis may be observed in some patients while acute surgical abdomen can be a rare but threatening presentation of KD (Zulian et al., 2003).

Transient unilateral peripheral facial nerve palsy and high-frequency sensorineural hearing loss can occur during acute Kawasaki disease (Knott et al., 2001).

5.3. Acute cardiac complications

The major sequelae of KD are related to the cardiovascular and, more specifically, the coronary arterial system. Depending on their size, the coronary artery aneurysms (CAA) can be classified as: small (<5 mm internal diameter), medium (5–8 mm internal diameter), giant (>8 mm internal diameter) (Dajani et al., 1993, 1994). The Japanese Ministry of Health criteria classify coronary arteries as abnormal if the internal lumen diameter is >3 mm in children <5-years old, >4 mm in children >5-years old, if it measures >1.5 times

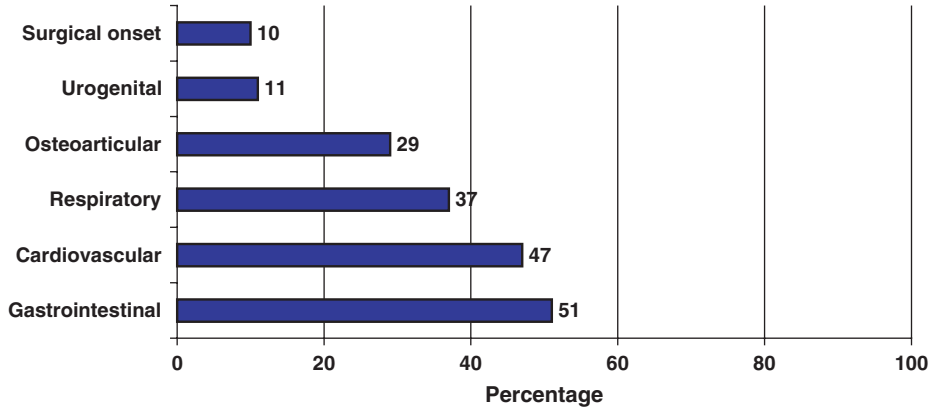


Figure 6. Associated symptoms in Kawasaki disease.

that of an adjacent segment or if the coronary lumen is clearly irregular (Research Committee on Kawasaki Disease, 1984).

Since the coronary artery dimensions in healthy children have been shown to increase with the body surface area (BSA) or body length, more recently, some authors have proposed to use these BSA–adjusted coronary standardized curves, available for the left main coronary artery (LMCA), proximal left anterior descending (LAD), and proximal right coronary artery (RCA), to assess KD patients both at diagnosis and during the follow-up (Kaneko et al., 1999; de Zorzi et al., 1998).

Most of CAA occurring during the acute phase of the disease regresses within several years; however, recent studies show that abnormal vascular wall morphology and vascular dysfunction may persist at the site of regressed alterations despite normal angiographic findings (Bruckheimer et al., 1998; Dhillon et al., 1996). In adult life premature atherosclerosis may develop in these patients, with high risk for myocardial infarction. Smoking, dietary fat, and additional risk factors for atherosclerosis should be avoided, and a long-term follow-up into adult life is advisable.

Several scoring systems have been developed to identify children at highest risk for CAA but duration of fever, presumably reflecting the severity of ongoing vasculitis, has been shown to be the more powerful predictor in various studies (Ichida et al., 1987; Koren et al., 1986).

Myocarditis has been shown to be a common feature of early KD. Its severity, however, is not associated with the risk of CAA (Hiraishi et al., 1981; Matsuura et al., 1987; Yutani et al., 1980).

Mitral and aortic valve regurgitation were shown in about 1% and 5% of patients, respectively, as a result of transient papillary muscle dysfunction or valvulitis (Kato et al., 1996; Nakano et al., 1985). Pericarditis associated with valvulitis and myocarditis is also easily found in some patients.

5.4. Long term cardiac complications

As stated previously, 20–35% of untreated and 5–10% of treated KD patients develop CAA (Falcini et al., 2002; Harden et al., 2002; Holman et al., 2003; Rowley et al., 1999; Yanagawa et al., 1998; Yanagawa, 2002). Approximately 50% of the vascular segments with CAA in KD show angiographic regression of aneurysms by the first year from the onset. This regression usually occurs by myointimal proliferation, more rarely by organization and recanalization of a thrombus (Sasaguri and Kato, 1982; Tanaka et al., 1986).

Factors that are positively associated with the regression of CAA include the smaller initial size, the age at onset of <1 year, fusiform rather than saccular morphology and aneurysm location in distal coronary segments (Takahashi et al., 1987).

Sometimes coronary lesions progress to stenosis, especially when giant aneurysms are present. In these aneurysms, thrombosis is promoted by the combination of sluggish blood flow within the massively dilated vascular space and the frequent occurrence of stenotic lesions at the proximal or

distal end of the aneurysms (Fujiwara et al., 1987; Tatara and Kusakawa, 1987).

Myocardial infarction (MI) caused by the thrombotic occlusion of an aneurismal or stenotic coronary artery is the principal cause of death from KD (Kato et al., 1986; Nakano et al., 1986).

Other cardiac alterations such as myocardial fibrosis, depressed left ventricular function or aortic root dilatation may persist for several years after the acute phase of the disease (Tanaka et al., 1986; Yutani et al., 1980).

A case control study, analyzing body mass index, cholesterol and triglyceride levels, and systolic and diastolic blood pressure, found that patients with previous KD have a more adverse cardiovascular risk profile than control subjects and an increased predisposition to premature atherosclerotic changes (Silva et al., 2001; Cheung et al., 2004).

6. Diagnostic investigations

6.1. Laboratory

Laboratory findings in KD are not specific and are shared by other acute inflammatory febrile diseases. Early in the course of illness all the usual inflammatory parameters are increased, namely erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell (WBC), and neutrophil counts. Anemia may develop, particularly with more prolonged duration of active inflammation. Platelet (PTL) count is normal in the acute phase and markedly increases at the end of the second week reaching a value as high as 1,000,000/mm^3. Occasionally, a low platelet count may be detected in the acute phase as well as neutropenia. A moderate-high increase of serum concentration of liver enzymes may occur in the early stage in $<40\%$ of patients and mild hyperbilirubinemia in 10% (Knott et al., 2001).

Hypoalbuminemia is associated with more severe and prolonged acute disease. Urinalysis may show leukocytes and erythrocytes but no bacteria. Cerebrospinal fluid contains increased numbers of WBC, mainly lymphocytes, as expression of aseptic meningitis. Lipid profile alterations occur in the early phase including decreased levels of high-density lipoprotein (HDL) and cholesterol, and increased levels of triglycerides (Silva et al., 2001).

6.2. Cardiac imaging

6.2.1. Echocardiography

Echocardiography is the ideal imaging modality for cardiac assessment in KD because it is not invasive and has high sensitivity and specificity for the detection of abnormalities of the proximal coronary segments. It allows to measure coronary artery dimensions, to reveal abnormal perivascular echogenicity or ''brightness'', pericardial effusion and valvular regurgitation (Scott et al., 1999).

For uncomplicated cases, echocardiographic evaluation should be performed at the time of diagnosis, at 2, 6, and 8 weeks thereafter. More frequent echocardiographic evaluation is needed for children at higher risk (e.g. those who are persistently febrile or who exhibit CAA, ventricular dysfunction, pericardial effusion, or valvular regurgitation). Repeated echocardiography performed 1 year after the onset of the illness is unlikely to reveal coronary artery enlargement in patients whose echocardiographic findings were normal at 4–8 weeks (McMorrow et al., 2001).

6.2.2. Cardiac stress testing

Cardiac stress testing is indicated to assess the presence of reversible ischemia in children with CAA. These functional procedures include nuclear perfusion scans under standard exercise, exercise echocardiography, and drug-induced stress echocardiography with agents such as dobutamine, dipyridamole, or adenosine (Jan et al., 2000; Kimball et al., 1997; Kondo et al., 1989; Noto et al., 1996; Pahl et al., 1995).

Used appropriately, stress test results represent a useful tool for clinicians' decision making in view to perform invasive procedures such as cardiac catheterization and surgical intervention.

6.2.3. Coronary angiography

Coronary angiography allows a more detailed definition of coronary artery anatomy than does cardiac ultrasound. It can show coronary artery stenosis or thrombotic occlusion and determine

the extent of collateral artery formation (Suzuki et al., 1986). Patients with complex lesions benefit from coronary angiography after the acute inflammatory process has resolved and is recommended 6–12 months after the onset of illness or sooner if clinically indicated (Dajani et al., 1994; Newburger et al., 2004). Afterwards, in the long-term follow-up, the decision to perform further angiographies should be guided by the appearance of ventricular regional wall motion abnormalities on echocardiography and/or by the presence of clinical signs or non-invasive studies (EKG, nuclear perfusion scans) indicating myocardial ischemia. Indeed, angiography is useful to evaluate the efficacy of surgical revascularization, or catheter intervention, and to guide the appropriate use of antithrombotic agents in patients in whom large proximal CAA have regressed and echocardiography fails to clearly assess distal coronary arteries (Dajani et al., 1994).

6.2.4. Magnetic resonance angiography (MRA)

Recently, MRA has been shown to be as accurate as standard angiography in detecting CAA, coronary occlusions, and stenoses (Greil et al., 2002). It provides a non-invasive alternative when transthoracic echocardiography image quality is insufficient, thereby reducing the need for coronary angiography in this patient group. Further studies are in progress to establish the real role of MRA as an alternative procedure in defining CAA in proximal coronary artery segments.

7. Differential diagnosis

Since the diagnosis of KD is essentially clinical, some conditions should be taken into consideration in the differential diagnosis. These include scarlet fever, staphylococcal toxic shock syndrome, polymorph erythema, viral infections, systemic-onset juvenile idiopathic arthritis, and polyarteritis nodosa. The main differential clinical features of these conditions can be summarized as follows:

Scarlet fever: throat swab positive for group A beta hemolytic Streptococcus, good response to antibiotic treatment.

Staphylococcal toxic shock syndrome: more frequent in the second infancy, compromized general conditions, shock, early coagulation abnormalities.

Polymorph erythema: no conjunctivitis, polycyclic lesions of the oral mucosa, typical skin marginated lesions.

Viral infections (Adenovirus, Rubeola, Parvovirus, Epstein-Barr virus, Cytomegalovirus): good general conditions, epidemic presentation, positive serology.

Systemic-onset juvenile idiopathic arthritis: intermittent fever, arthritis more prevalent, morning stiffness.

Polyarteritis nodosa: painful skin nodules, internal organ involvement, specific pathology.

Children may present with only fever and a unilateral enlarged cervical lymph node. The rash and mucosal changes that follow often are mistaken for a reaction to antibiotics that are administered for presumed bacterial lymphadenitis. Sterile pyuria may be mistaken for a partially treated urinary tract infection with sterile urine cultures. The young infant may present with fever, rash, and cerebrospinal fluid pleocytosis and be misdiagnozed with viral meningitis. Occasionally, a child may present with an acute abdomen and be admitted to a surgical service (Zulian et al., 2003). KD should be considered in the differential diagnosis of every child with fever of at least several days' duration, rash, and non-purulent conjunctivitis, especially in children <1-year old and in adolescents, in whom the diagnosis is frequently missed.

8. Treatment

8.1. Initial treatment

8.1.1. Aspirin

The current treatment of a patient with definite or suspected KD includes acetyl salicylic acid (ASA) and intravenous immunoglobulins (IVIG).

Despite it does not lower the frequency of development of CAA, ASA was the first medication to be used for treatment of KD because of its combined anti-inflammatory and anti-thrombotic effects (Durongpisitkul et al., 1995; Kuwasawa and Tatara, 1987). During the acute phase of

illness, ASA is administered at the dosage of 40–80 mg/kg/day in four doses. Once fever resolves, ASA is generally lowered to an anti-thrombotic dosage of 3–5 mg/kg once a day. Unless echocardiogram detects CAA, ASA is discontinued after 6–8 weeks from the onset of the illness. In children who develop CAA, ASA should be continued indefinitely (Newburger et al., 2004).

8.1.2. Intravenous immunoglobulins

IVIG administered in the acute phase of KD are very effective in preventing CAA (Furushho et al., 1984; Newburger et al., 1986; Terai and Shulman, 1997).

IVIG can be administered either at a dose of 2 g/kg given as a single infusion over 10–12 h or split into two daily doses of 1 g/kg over 6 h (Furusho et al., 1984; Newburger et al., 1986; Newburger et al., 1991).

IVIG should be administered as soon as the disease is suspected and however within the first 10–15 days from the onset of fever. In patients diagnozed later but with persistent signs of inflammation, IVIG should be given anyway. In most children the fever drops either during IVIG infusion or soon after. Before the introduction of IVIG treatment 20–35% of children with KD developed CAA. With an early IVIG treatment, the incidence of CAA dropped down to 5–10% and giant aneurysms to 1% (Dajani et al., 1994; Furusho et al., 1984; Newburger et al., 1986; Terai Shulman, 1997).

Their mechanism of action is still unknown although they seem to exert a generalized anti-inflammatory effect by the induction of immune inhibitory receptors, blocking of interaction between endothelial cells and natural killer cells, selective induction of interleukin-1-receptor antagonist and IL-8 and provision of specific antibody to the causative agent or a toxin (Finberg et al., 1992; Ravetch and Laneir, 2000; Ruiz de Souza et al., 1995). In vitro findings suggest that IVIG blocks endothelial-cell proliferation and synthesis of adhesion molecules, chemokines and cytokines (Xu et al., 1998).

8.1.3. Management of refractory Kawasaki disease

Despite the early IVIG treatment <15% of patients with KD fails to defervesce (Burns et al., 1998; Durongpisitkul et al., 2003; Fukunishi et al., 2000; Han et al., 2000; Hashino et al., 2001; Imagawa et al., 2004; Wallace et al., 2000). Failure to respond usually is defined as persistent or recrudescent fever <Object Deletion Spot> 36 h after completion of the initial IVIG infusion. It is not possible to predict which KD patient will not respond to the initial therapy. Some authors have identified laboratory predictors of IVIG non-responsiveness, such as degree of anemia or CRP and lactate dehidrogenase (LDH) elevation (Han et al., 2000). Others failed to confirm these findings (Han et al., 2000; Wallace et al., 2000).

Although specific guidelines for the management of patients with refractory KD do not exist, most experts recommend retreatment with IVIG (Burns et al., 1998; Durongpisitkul et al., 2003; Newburger et al., 2004; Wallace et al., 2000). Unfortunately, this intervention is ineffective in almost half of the patients and very often does not prevent the development of CAA (Fukunishi et al., 2000; Han et al., 2000; Hashino et al., 2001; Imagawa et al., 2004; Wallace et al., 2000).

Corticosteroids (CS) have also been used in KD. Several small case series have shown that in children with refractory KD steroid therapy was associated with an improvement in symptoms and rapid decrease of fever. These studies show that CS are effective in the majority of the patients with refractory KD although their efficacy in preventing the development of CAA is still uncertain (Dale et al., 2000; Hashino et al., 2001; Wallace et al., 2000; Wright et al., 1996). The most commonly used CS regimen is intravenous pulse methylprednisolone, 20–30 mg/kg/day, administered in 3 h once daily for 1–3 days. Although most authors recommend the use of CS only in children in whom two or more IVIG infusions have been ineffective (Dale et al., 2000; Hashino et al., 2001; Imagawa et al., 2004; Wright et al., 1996), others suggest they may have a role as initial treatment of KD in addition to traditional IVIG therapy as well (Sundel et al., 2003).

Among possible alternative therapies plasma exchange (PE) has been reported to be effective in refractory KD patients both by controlling fever and by lowering the incidence of CAA (Imagawa et al., 2004). However, being an invasive procedure that requires the placement of large bore central

venous catheter in very young children, PE is not generally recommended.

Some immunosuppressive agents, such as cyclophosphamide (CPM) or cyclosporine A (CyA), that are used to treat other vasculitides, have been suggested also for the treatment of refractory KD patients (Wallace et al., 2000). Unfortunately, the side effects of these cytotoxic agents exceed the benefits for the vast majority of the patients (Kuijpers et al., 2003; Wallace et al., 2000).

8.2. Experimental treatments

Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, has been used to treat patients in the acute or subacute phase of KD with large CAA. This treatment resulted in a greater regression in maximum aneurysm diameter, suggesting an important role in promoting the vascular remodeling (Williams et al., 2002).

Because TNF-α as other cytokines appears to be important in the inflammatory cascade of KD, infliximab, a humanized monoclonal antibody against TNF-α, has been successfully used for the treatment of a child with refractory KD (Weiss et al., 2004). More recently the efficacy of infliximab has been confirmed by a retrospective study of 17 patients (Burns et al., 2005). Response to therapy with cessation of fever occurred in 82% of the patients with no major effects.

Ulinastatin, an elastase inhibitor purified from human urine has been proposed for the treatment of IVIG-refractory KD patients (Zaitsu et al., 2000). Its mechanism of action consists essentially in the inhibition of arachidonate prostaglandin H_2 synthase (PHS) metabolism in peripheral blood mononuclear cells (PBMNC), so reducing their activity in the vasculitic process. However, its efficacy is still unproven and additional experience is needed before its wider use.

In summary, because controlled data are lacking, the role of repeated doses of IVIG, CS, TNF-α inhibitors and other immunosuppressive treatment in refractory KD patients remains uncertain.

On the other hand, since no diagnostic test for KD is available, in patients with refractory KD, clinicians should always consider other alternative conditions.

8.3. Medical treatment of coronary artery abnormalities

The management of CAA in patients with KD depends on the severity and extent of coronary involvement. No prospective data exist to guide clinicians in choosing the optimal regimen, so recommendations are based on known physiopathology, retrospective case series, and extrapolations from the experience in adults with coronary artery disease.

A long-term low dose ASA treatment is required in children with CAA or simple coronary alterations. The therapy should be continued until normalization of aneurysms is noted. In children with ASA intolerance, other anti-platelet agents such as dypiridamole (2–3 mg/kg) may be used (Dajani et al., 1994).

In patients with giant aneurysms the addition of warfarin (maintaining INR range of 2.0–2.5) to ASA has been suggested although there is no general agreement on this. As the early phase of warfarin administration is sometimes associated with a paradoxical prothrombotic state, intravenous heparin is advisable for a short period (Weiss et al., 1987).

Aims of acute coronary occlusion therapy in patients with KD consist essentially in re-establishing coronary patency, salvaging the myocardium and improving survival (Lange and Hillis, 2002). The treatment should target multiple steps in the coagulation cascade. Because no randomized controlled trials have been performed in children with KD, the treatment of coronary thrombosis is derived from studies in adults with acute coronary syndromes. In single case reports, streptokinase, urokinase, and tissue plasminogen activator (TPA) have been used with variable success rates (Burtt et al., 1986; Cheatham et al., 1987; Horigome et al., 1997; Katayama et al., 1997; Lange et al., 2002; Levy et al., 1991).

8.4. Surgical and catheter coronary interventions

8.4.1. Catheter coronary interventions

Catheter coronary interventions including balloon angioplasty, rotational ablation, and stent placement

have been performed in a relatively small number of children with KD, mostly in Japan.

In general, balloon angioplasty has not been successful even with high-pressure balloons because of dense fibrosis and calcification in the arterial wall (Muzik et al., 1996).

Stent placement has been useful in older children with mild calcification and in children with giant aneurysms. Rotational ablation and stent placement have met with a success rate >80% according to a multicenter survey in Japan (Ishii et al., 2002). Catheter intervention should be considered in patients with cardiac ischemic symptoms, asymptomatic but with reversible ischemia on stress test or with <75% stenosis in the LAD coronary artery. Catheter intervention is contraindicated in patients with multiple, ostial, or long-segment lesions (Ishii et al., 2001).

8.4.2. Coronary surgery

Bypass surgery is advisable for patients with severe left ventricular dysfunction and reversible ischemia on stress-imaging test results on condition that the myocardium to be perfused through the graft is still viable and no appreciable lesions are present in the artery distal to the planned graft site. In a recent retrospective study, the patency rates of arterial grafts (primarily internal mammary arteries) were 94%, 82%, and 78% at 1, 5, and 10 years, respectively, whereas patency rates for venous grafts were 82%, 63%, and 36%, respectively (Tsuda and kitamura, 2004).

Key points

- Kawasaki disease is an acute vasculitis that occurs in children of all ages. Since there are no diagnostic laboratory tests, the recognition of the typical mucocutaneous features is essential for the early diagnosis.
- KD can be complicated by coronary artery aneurysms in 20–35% of untreated patients and represents the commonest cause of acquired heart disease in children in developed countries. Much progress has been done in the management of KD during the last few years. However, while we have reached good results in the therapeutic approach to the acute phase of the disease (IVIG, CS, biologic agents, etc.), more effective treatments are needed to arrest the progression of coronary alteration.
- Future steps of the international research in this field are actually addressed to the comprehension of the pathogenetic mechanisms of this vasculitis and to the standardization of appropriate instruments for the long-term monitoring of the disease.

References

Abe, J., Kotzin, B.L., Jujo, K., et al. 1992. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. Proc. Natl. Acad. Sci. USA 89, 4066.

Asano, T., Ogawa, S. 2000. Expression of monocyte chemoattractant proytein-1 in Kawasaki disease: the anti-inflammatory effect of gamma globulin therapy. Scand. J. Immunol 51, 98.

Brown, T.J., Crawford, S.E., Cornwall, M.L., et al. 2001. CD8T lymphocytes and macrophages infiltrate coronary artery aneurysms in acute Kawasaki disease. J. Infect. Dis. 184, 940.

Bruckheimer, E., Bulbul, Z., McCarthy, P., et al. 1998. Images in cardiovascular medicine: Kawasaki disease: coronary aneurysms in mother and son. Circulation 97, 410.

Burns, J.C., Capparelli, E.V., Brown, J.A., et al. 1998. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. Pediatr. Infect. Dis. J, 17, 1144.
This study underlines the efficacy of IVIG re-treatment in refractory KD.

Burns, J.C., Mason, W.H., Hauger, S.B., et al. 2005. Infliximab treatment for refractory Kawasaki syndrome. J. Pediatr. 146, 662.
First retrospective study on the efficacy of a TNF-antagonist infliximab for the treatment of refractory KD.

Burtt, D.M., Pollack, P., Bianco, J.A. 1986. Intravenous streptokinase in an infant with Kawasaki's disease complicated by acute myocardial infarction. Pediatr. Cardiol. 6, 307.

Centers for Disease Control. 1990. Revised diagnostic criteria for Kawasaki disease. MMWR 39, 27.

Cheatham, J.P., Kugler, J.D., Gumbiner, C.H., et al. 1987. Intracoronary streptokinase in Kawasaki disease: acute and thrombolysis. Prog. Clin. Biol. Res. 250, 517.

Cheung, Y.F., Yung, T.C., Tam, S.C., et al. 2004. Novel and traditional cardiovascular risk factors in children after Kawasaki disease: implication for premature atherosclerosis. J. Am. Coll. Cardiol. 43, 120.
Case control study, analysing body mass index, cholesterol and triglyceride levels, systolic and diastolic blood pressure, showed that patients with previous KD have an increased predisposition to premature atherosclerotic changes than control subjects.

Dajani, A.S., Taubert, K.A., Gerber, M.A., et al. 1993. Diagnosis and therapy of Kawasaki disease in children. Circulation 87, 1776.

Dajani, A.S., Taubert, K.A., Takahashi, M., et al. 1994. Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 89, 916.

Dale, R.C., Saleem, M.A., Daw, S., et al. 2000. Treatment of severe complicated Kawasaki disease with oral prednisolone and aspirin. J. Pediatr. 137, 723.

de Zorzi, A., Colan, S.D., Gauvreau, K., et al. 1998. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J. Pediatr. 133, 254.
Interesting study showing that coronary artery dimensions, adjusted for body surface area, provide a more accurate assessment of the size of the proximal right coronary artery (RCA) or left anterior descending coronary artery (LAD) as compared with expected population norms.

Dhillon, R., Clarkson, P., Donald, A.E., et al. 1996. Endothelial dysfunction late after Kawasaki disease. Circulation 94, 2103.

Durongpisitkul, K., Gururaj, V.J., Park, J.M., et al. 1995. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics 96, 1057.

Durongpisitkul, K., Soongswang, J., Laohaprasitiporn, D., et al. 2003. Immunoglobulin failure and retreatment in Kawasaki disease. Pediatr. Cardiol. 24, 145.

Eberhard, B.A., Andersson, U., Laxer, R.M., et al. 1995. Evaluation of the cytokine response in Kawasaki disease. Pediatr. Infect. Dis. J. 14, 199.

Falcini, F., Cimaz, R., Calabri, G.B., et al. 2002. Kawasaki disease in Northern Italy: a multicenter data collection of 250 patients. Clin. Exp. Rheumatol. 20, 421.

Finberg, R.W., Newburger, J.W., Mikati, M.A., et al. 1992. High dose intravenous gammaglobulin treatment enhances natural killer cells activity in Kawasaki disease. J. Pediatr. 120, 376.

Fujiwara, T., Fujiwara, H., Hamashima, Y. 1987. Frequency and size of coronary arterial aneurysm at necropsy in Kawasaki disease. Am. J. Cardiol. 59, 808.

Fukunishi, M., et al. 2000. Prediction of non-responsiveness to intravenous high dose. J. Pediatr. 137, 172.

Furusho, K., Kamiya, T., Nakano, H., et al. 1984. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 2, 1055.

Greil, G.F., Stuber, M., Botnar, R.M., et al. 2002. Coronary magnetic resonance angiography in adolescents and young adults with Kawasaki disease. Circulation 105, 908.
Free-breathing 3D coronary MRA accurately defines CAA in patients with KD and provide a non-invasive alternative when transthoracic echocardiography image quality is insufficient, thereby reducing the need for coronary angiography in this patient group.

Han, R.K., Silverman, E.D., Newman, A., et al. 2000. Management and outcome of persistent or recurrent fever after initial intravenous gamma globulin therapy in acute Kawasaki disease. Arch. Pediatr. Adolesc. Med. 154, 694.

Harden, A., Laves, B., Sheikh, A. 2002. Rising incidence of Kawasaki disease in England: analysis of hospital admission data. BMJ 324, 1424.

Hashino, K., Ishii, M., Iemura, M., et al. 2001. Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. Pediatr. Int. 43, 211.

Hiraishi, S., Yashiro, K., Oguchi, K., et al. 1981. Clinical course of cardiovascular involvement in the mucocutaneous lymph node syndrome. Relation between clinical signs of carditis and development of coronary arterial aneurysm. Am. J. Cardiol. 47, 323.

Hirata, S., Nakamura, Y., Yanagawa, H. 2001. Incidence rate of recurrent Kawasaki disease and related risk factors: from the results of nationwide surveys of Kawasaki disease in Japan. Acta Paediatr. 90, 40.

Holman, R.C., Curns, A.T., Belay, E.D., et al. 2003. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 112, 495.

Horigome, H., Sekijima, T., Miyamoto, T. 1997. Successful thrombolysis with intracoronary administration of tissue plasminogen activator in an infant with Kawasaki disease. Heart 78, 517.

Ichida, F., Fatica, N.S., Engle, M.A., et al. 1987. Coronary artery involvement in Kawasaki syndrome in Manhattan, New York: risk factors and role of aspirin. Pediatrics 80, 828.

Imagawa, T., Mori, M., Miyamae, T., et al. 2004. Plasma exchange for refractory Kawasaki disease. Eur. J. Pediatr. 163, 263.

Ishii, M., Ueno, T., Akagi, T., et al. 2001. Guidelines for catheter intervention in coronary artery lesion in Kawasaki disease. Pediatr. Int. 43, 558.

Ishii, M., Ueno, T., Ikeda, H., et al. 2002. Sequential follow-up results of catheter intervention for coronary artery lesions after KD: quantitative coronary artery angiography and intravascular ultrasound imaging study. Circulation 105, 3004.

Jan, S.L., Hwang, B., Fu, Y.C., et al. 2000. Usefulness of pharmacologic stress 201Tl myocardial tomography. Comparison of 201Tl SPET and treadmill exercise testing in patients with Kawasaki disease. Nucl. Med. Commun. 21, 431.

Kaneko, K., Obinata, K., Katsumata, K., et al. 1999. Kawasaki disease in a father and daughter. Acta Paediatr 88, 791.

Katayama, F., Hiraishi, S., Takeda, N., et al. 1997. Intracoronary urokinase and post-thrombolytic regimen in an infant with Kawasaki disease and acute myocardial infarction. Heart 78, 621.

Kato, H., Ichinose, E., Kawasaki, T. 1986. Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases. J. Pediatr. 108, 923.

Kato, H., Sugimura, T., Akagi, T., et al.1996. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 94, 1379.
Study on the long term consequences of KD in the pre-IVIG era showing an incidence of CAA in 25% of the patients, ischemic heart disease developed 4.7%, myocardial infarction in 1.9% and death in 0.8%.

Kawasaki, T. 1967. [Pediatric acute mucocutaneous lymph node syndrome: clinical observation of 50 cases]. Arerugi (Jpn. J. Allergy) 16, 178.
This is the first historical description of Kawasaki disease in Japanese language. All the scientific community is grateful to Dr. Tomisaku Kawasaki for having so well defined a new clinical entity become soon after the first cause of acquired heart diseases in the developed countries.

Kimball, T.R., Witt, S.A., Daniels, S.R. 1997. Dobutamine stress echocardiography in the assessment of suspected myocardial ischemia in children and young adults. Am. J. Cardiol. 79, 380.

Knott, P.D., Orloff, L.A., Harris, J.P., et al. 2001. Kawasaki Disease Multicenter Hearing Loss Study Group. Sensorineural hearing loss and Kawasaki disease: a prospective study. Am. J. Otolaryngol. 22, 343.

Kondo, C., Hiroe, M., Nakanishi, T., et al. 1989. Detection of coronary artery stenosis in children with Kawasaki disease. Circulation 80, 615.

Koren, G., Lavi, S., Rose, V., et al. 1986. Kawasaki disease: review of risk factors for coronary aneurysms. J. Pediatr. 108, 388.

Kuijpers, T.W., Biezeveld, M., Achterhuis, A., et al. 2003. Longstanding obliterative panarteritis in Kawasaki disease: lack of cyclosporine A effect. Pediatrics 112, 986.

Kuwasawa, S., Tatara, K. 1987. Efficacy and risks of aspirin in the treatment of the Kawasaki disease. Prog. Clin. Biol. Res. 250, 401.

Lange, R.A., Hillis, L.D. 2002. Reperfusion therapy in acute myocardial infarction. N. Engl. J. Med. 346, 954.

Leung, D.Y., Giorno, R.C., Kazemi, L.V., et al. 1995. Evidence for superantigen involvement in cardiovascular injury due to Kawasaki syndrome. J. Immunol. 155, 5018.

Leung, D.Y., Meissner, H.C., Shulman, S.T., et al. 2002. Prevalence of superantigen-secreting bacteria in patients with Kawasaki disease. J. Pediatr. 140, 742.

Levy, M., Benson, L.N., Burrows, P.E., et al. 1991. Tissue plasminogen activator for the treatment of thromboembolism in infants and children. J. Pediatr. 118, 467.

Matsuura, H., Ishikita, T., Yamamoto, S., et al. 1987. Gallium-67 myocardial imaging for the detection of myocarditis in the acute phase of Kawasaki disease (mucocutaneous lymph node syndrome): the usefulness of single photon emission computed tomography. Br. Heart J. 58, 385.

McMorrow Tuohy, A.M., Tani, L.Y., Cetta, F., et al. 2001. How many echocardiograms are necessary for follow-up evaluation of patients with Kawasaki disease?. Am. J. Cardiol. 88, 328.

Muzik, O., Paridon, S.M., Singh, T.P., et al. 1996. Quantification of myocardial blood flow and flow reserve in children with a history of Kawasaki disease and normal coronary arteries using positron emission tomography. J. Am. Coll. Cardiol. 28, 757.

Nakamura, Y., Yanagawa, H., Harada, K., et al. 2002. Mortality among persons with a history of Kawasaki disease in Japan: the fifth look. Arch. Pediatr. Adolesc. Med. 156, 162.
The latest in an ongoing series of analyses of long-term outcomes among Japanese children diagnosed with KD. Unlike other iterations, however, this one suggests that coronary artery involvement may have prognostic implications.

Nakano, H., Nojima, K., Saito, A., et al. 1985. High incidence of aortic regurgitation following Kawasaki disease. J. Pediatr. 107, 59.

Nakano, H., Saito, A., Ueda, K., et al. 1986. Clinical characteristics of myocardial infarction following Kawasaki disease: report of 11 cases. J. Pediatr. 108, 198.

Newburger, J.W., Takahashi, M., Burns, J.C., et al. 1986. The treatment of Kawasaki syndrome with intravenous gamma globulin. N. Engl. J. Med. 315, 341.
Historical paper showing the efficacy of IVIG in both stopping the acute phase of the disease and reducing the frequence of CAA in KD.

Newburger, J.W., Takahashi, M., Burns, J.C., et al. 1991. A single infusion of gammaglobulin compared with four infusions in the treatment of acute Kawasaki. N. Engl. J. Med. 324, 1633.

Newburger, J.W., Takahashi, M., Gerber, M.A., et al. 2004. Diagnosis, treatment and long-term management of Kawasaki disease. Circulation 110, 2747.

Noto, N., Ayusawa, M., Karasawa, K., et al. 1996. Dobutamine stress echocardiography for detection of coronary artery stenosis in children with Kawasaki disease. J. Am. Coll. Cardiol. 27, 1251.

Pahl, E., Sehgal, R., Chrystof, D., et al. 1995. Feasibility of exercise stress echocardiography for the follow-up of children with coronary involvement secondary to Kawasaki disease. Circulation 91, 122.

Ravetch, J.V., Laneir, L.L. 2000. Immune inhibitory receptors. Science 290, 84.

Research Committee on Kawasaki Disease. 1984. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo, Japan: Ministry of Health and Welfare.

Rowley, A., Taubert, K., Myones, B.L., et al. 1999. Report of National Institutes of Health Workshop on Kawasaki disease. J. Rheumatol. 26, 170.

Rowley, A.H., Gonzalez-Crussi, F., Gidding, S.S., et al. 1987. Incomplete Kawasaki disease with coronary involvement. J. Pediatr. 110, 409.

Rowley, A.H., Shulman, S.T., Mask, C.A., et al. 2000. IgA plasma cell infiltration of proximal respiratory tract, pancreas,

kidney, and coronary artery in acute Kawasaki disease. J. Infect. Dis. 182, 1183.
Interesting study showing that IgA-secreting plasma cells (IgA-PCs) are significantly increased in the trachea of patients who died of acute KD. IgA-PCs also infiltrate coronary artery, pancreas, and kidney in all KD patients. These findings strongly support entry of the KD etiologic agent through the upper respiratory tract, resulting in an IgA immune response, with systemic spread to vascular tissue, pancreas, and kidney.

Rowley, A.H., Shulman, S.T., Spike, B.T., et al. 2001. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J. Immunol. 166, 1334.

Ruiz de Souza, V., Carreno, M.P., Kaver, S.V., et al. 1995. Selective induction of IL-1 receptor antagonist and IL-8 in human monocytes by normal polyspecific IgG. Eur. J. Immunol. 25, 1267.

Sasaguri, Y., Kato, H. 1982. Regression of aneurysms in Kawasaki disease: a pathological study. J. Pediatr. 100, 225.

Scott, J.S., Ettedgui, J.A., Neches, W.H. 1999. Cost-effective use of echocardiography in children with Kawasaki disease. Pediatrics 104, e57.

Silva, A.A., Maeno, Y., Hashmi, A., et al. 2001. Cardiovascular risk factors after Kawasaki disease: a case control study. J. Pediatr. 138, 400.

Suddleson, E.A., Reid, B., Woolley, M.M., et al. 1987. Hydrops of the gallbladder associated with Kawasaki syndrome. J. Pediatr. Surg. 22, 956.

Sundel, R.P., Baker, A.L., Fulton, D.R., et al. 2003. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. J. Pediatr. 142, 611.
Interesting prospective trial evaluating the effects of pulse intravenous methylprednisolone as adjunct therapy for treatment of acute Kawasaki disease.

Sundel, R.P., Cleveland, S.S., Beiser, A.S., et al. 1992. Audiologic profiles of children with Kawasaki disease. Am. J. Otol. 13, 512.

Suzuki, A., Kamiya, T., Kuwahara, N., et al. 1986. Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1100 cases. Pediatr. Cardiol. 7, 3.

Takahashi, M., Mason, W., Lewis, A.B. 1987. Regression of coronary aneurysms in patients with Kawasaki syndrome. Circulation 75, 387.

Takeshita, S., Tokutomi, T., Kawase, H., et al. 2001. Elevated serum levels of matrix metalloproteinase-9 (MMP-9) in Kawasaki disease. Clin. Exp. Immunol. 125, 340.

Tanaka, N., Naoe, S., Masuda, H., et al. 1986. Pathological study of sequelae of Kawasaki disease (MCLS) with special reference to the heart and coronary arterial lesions. Acta Pathol. Jpn. 36, 1513.

Tatara, K., Kusakawa, S. 1987. Long-term prognosis of giant coronary aneurysm in Kawasaki disease: an angiographic study. J. Pediatr. 111, 705.

Terai, M., Shulman, S.T. 1997. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gammaglobulin dose but independent of salicylate dose. J. Pediatr. 131, 888.
Study showing that the prevalence of CAA is inversely related to the total dose of IVGG and independent of the aspirin dose. The Authors conclude that 2gm/kg IVGG combined with at least 30–50mg/kg per day aspirin provides maximum protection against development of CAA after KD.

Tsuda, E., Kitamura, S., Cooperative Study Group of Japan. 2004. National survey of coronary artery bypass grafting for coronary stenosis caused by Kawasaki disease in Japan. Circulation 110, II61.
Recent report on a large collection of data regarding the long term patency of coronary artery bypass grafting for coronary stenosis caused by KD. Death occurred in 15 patients (6%). Internal thoracic artery grafts in children aged 12 years or older are favourable at 1, 5, and 15 years with 95%, 91%, and 91% patency, respectively. When the age at operation was younger than 12 years, the corresponding values were significantly lower. Low left ventricular ejection fraction (<40%) at operation influenced prognosis.

Uehara, R., Yashiro, M., Nakamura, Y., et al. 2003. Kawasaki disease in parents and children. Acta Paediatr 92, 694.

Wallace, C.A., French, J.W., Kahn, S.J., et al. 2000. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. Pediatrics 105, E78.

Weiss, J.E., Eberhard, B.A., Chowdhury, D., et al. 2004. Infliximab as a novel therapy for refractory Kawasaki disease. J. Rheumatol. 31, 808.

Weiss, P., Soff, G.A., Halkin, H., et al. 1987. Decline of proteins C and S and factors II, VII, IX and X during the initiation of warfarin therapy. Thromb. Res. 45, 783.

Williams, R.V., Wilke, V.M., Tani, L.Y., et al. 2002. Does abciximab enhance regression of coronary aneurysms resulting from Kawasaki disease?. Pediatrics 109, E4.

Wright, D.A., Newburger, J.W., Baker, A., et al. 1996. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. J. Pediatr. 128, 146.
The authors in this case series showed the efficacy of pulse iv methylprednisolone therapy for patients with KD who do not respond to IVIG or who have recrudescent disease after adequate therapy.

Xu, C., Poirier, B., Duong Van Huyen, J.P., et al. 1998. Modulation of endothelial cell function by normal polyspecific human intravenous immunoglobulins. Am. J. Pathol. 153, 1257.

Yamashiro, Y., Nagata, S., Oguchi, S., et al. 1996. Selective increase of V beta 2+ T cells in the small intestinal mucosa in Kawasaki disease. Pediatr. Res. 39, 264.

Yanagawa, H., Nakamura, Y., Yashiro, M., et al. 1998. Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. Pediatrics 102, E65.

Yanagawa, H., Nakamura, Y., Yashiro, M., et al. 2001. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. Pediatrics 107, E33.

Yasukawa, K., Terai, M., Shulman, S.T., et al. 2002. Systemic production of vascular endothelial growth factor and fms-like tyrosine kinase-1 receptor in acute Kawasaki disease. Circulation 105, 766.

Yutani, C., Okano, K., Kamiya, T., et al. 1980. Histopathological study on right endomyocardial biopsy of Kawasaki disease. Br. Heart J. 43, 589.

Zaitsu, M., Hamasaki, Y., Tashiro, K., et al. 2000. Ulinastatin, an elastase inhibitor, inhibits the increased mRNA expression of prostaglandin H2 synthase-type 2 in Kawasaki disease. J. Infect. Dis. 181, 1101.

Zulian, F., Falcini, F., Zancan, L., et al. 2003. Acute surgical abdomen as presenting manifestation of Kawasaki disease. J. Pediatr. 142, 731.

The authors aware the physicians that in older children with fever, rash, and acute surgical abdomen or hematemesis, KD should be considered in the differential diagnosis.

This page intentionally left blank

PART IV:

New Insight in the Treatment of the Skin Manifestations in Systemic Autoimmune Diseases

This page intentionally left blank

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 22

Skin Targets for New Biological Agents in Systemic Autoimmune Diseases

Thomas A. Luger*, Markus Böhm

Department of Dermatology, University of Münster, Münster, Germany

1. Introduction

Protocols for the treatment of autoimmune diseases of the skin are complex and involve topical as well as systemic immunosuppressive interventions. Although most of these strategies offer an effective disease control, they are frequently associated with side effects. Therefore, there is a need to search for novel efficient therapies with a favourable safety profile. The recent improvement in our understanding of the underlying pathomechanisms and the major advances in biotechnology resulted in the development of several novel compounds and strategies for the treatment of autoimmune diseases such as specific therapeutic approaches targeting mechanisms responsible for immune dysfunction and break of tolerance. Current approaches focus on autoantigen recognition and autoantibody production, cytokine function and production, tolerance induction, and gene transcription (Feldmann and Steinman, 2005; Gottlieb, 2005).

Among several new drugs and cellular and gene-therapeutic approaches, the development of biologic agents (biologics) for the treatment of inflammatory and autoimmune diseases has gained major attention. A major progress in the treatment of autoimmune mediated diseases such as rheumatoid arthritis (RA), Crohn's disease, and psoriasis has been achieved. Biologics are agents with specific cellular targets such as cell surface molecules, (adhesion molecules and receptors) or intracellular molecules (transcription factors), which are designed to imitate or inhibit the actions of naturally occurring proteins. They are derived from living sources such as humans, animals, plants, and microorganisms and currently include: recombinant proteins (cytokines), monoclonal antibodies, fusion proteins, and toxin-labelled proteins. Strategies for biologic therapy are multiple and may consist of mediators that promote immune deviation, agents that inhibit the effects of proinflammatory cytokines, compounds that target pathogenic T-cells, and agents that disrupt the antigen presentation/T-cell activation (Smolen and Steiner, 2003; Saripalli and Gaspari, 2005; Finucane and Archer, 2005; Kourbeti and Boumpas, 2005).

The present chapter reviews recent developments and available clinical experience with biological agents in the treatment of autoimmune diseases with a focus on their efficiency in skin lesions.

2. Nonspecific biological agents

2.1. High-dose intravenous immunoglobulins

Intravenous immunoglobulins (IVIgs) are derived from a purified human plasma pool of healthy blood donors and contain IgG as well as traces of

*Corresponding author.
Department of Dermatology, University of Münster, Von-Esmarch-Street 58, D–48149 Münster, Germany.

DOI: 10.1016/S1571-5078(05)05022-1

other immunoglobulins or aggregates. They exert a variety of immunomodulating activities and are currently used for the treatment of primary and secondary immunodeficiency diseases, autoimmune disorders, and certain infectious diseases (Rütter and Luger, 2002; Shoenfeld and Krause, 2004; Wetter et al., 2005). The complex mechanisms of action of IVIgs are still not fully understood. There is evidence of a suppression in autoantibody production, neutralization of complement-mediated effects, blocking of Fc receptors on macrophages and downregulation of costimulatory molecules. Moreover, IVIg preparations contain amounts of soluble CD4, CD8, and MHC-I and -II molecules, which may have the ability to inhibit autoreactive T lymphocytes. IVIgs also contain anti-Fas-receptor antibodies, which are able to block molecular Fas ligand/Fas receptor interactions and consequently cause keratinocyte apoptosis. This seems to play a vital role in the therapy of toxic epidermal necrolysis with IVIgs. IVIgs were also found to increase glucocorticoid receptor sensitivity and thereby in combination with glucocorticoids, they synergistically suppress lymphocyte activation (Viard et al., 1998; Spahn et al., 1999; Rütter and Luger, 2002; Ibanez and Montoro-Ronsano, 2003).

There is evidence from many case reports and clinical trials for the high efficacy of IVIg as an adjunctive treatment of otherwise refractory autoimmune diseases with skin involvement. Accordingly, IVIgs have been used successfully for the treatment of dermatomyositis, scleroderma, systemic lupus erythematosus (SLE), pemphigus vulgaris and pemphigus foliaceus, bullous pemphigoid, cicatrical pemphigoid, epidermolysis bullosa aquisita, pemphigoid gestationis, linear IgA bullous dermatoses, and toxic epidermal necrolysis. Other skin diseases with some evidence for a favourable response to IVIg are chronic autoimmune urticaria, atopic dermatitis, graft-versus-host disease, psoriasis, pyoderma gangrenosum, lichen ruber, livedoid vasculitis, scleromyxedema, pretibial myxedema, and acquired von Willebrand disease. Further potential advances in the treatment with IVIg require careful patient selection and appropriately designed placebo-controlled, randomized studies (Rütter and Luger, 2002; Emmi and Chiarini, 2002; Wetter et al., 2005).

3. Specific biological agents

3.1. Agents targeting T-cells

In a preliminary clinical trial, an antibody binding to CD2 (siplizumab), which was expressed on memory effector T-lymphocytes, was successfully evaluated in psoriasis (Bayes et al., 2003). An antibody directed against CD3 (visilizumab), a component of the T-cell receptor complex, which is expressed on all T-lymphocytes, is currently investigated for its efficacy in graft-versus-host disease and previously has been reported to have some therapeutic activity in psoriasis but may not be further developed for this indication (Carpenter et al., 2005). Several antibodies have been constructed against CD4 expressed on T-cells. According to the first clinical trials, HuMax-CD4 and OKT(R)cdr4a appear to be effective in the treatment of psoriasis (Bachelez et al., 1998; Gniadecki et al., 2002; Skov et al., 2003; Barry and Kirby, 2004).

Since T-helper cells may contribute directly to cutaneous tissue damage in LE by stimulating both macrophages and cytotoxic, specific inhibition of the T-helper cells using anti-CD4 was considered as a suitable approach to suppress disease activity (Owen and Harrison, 2000). Therefore, a recombinant chimeric CD4 monoclonal antibody (cM-T412) was investigated in clinical trials for its efficacy in the treatment of LE (Prinz et al., 1996). Treatment of five patients with chronic discoid LE including two patients with systemic involvement resulted in an immediate improvement in the skin lesions. Moreover, proteinuria as an index of lupus nephropathy was fully resolved and the antibody was well tolerated. Further controlled clinical trials are required to prove these very promising though preliminary results.

Antibodies against the interleukin (IL)-2Rα chain (daclizumab, basiliximab, and inolimomab), antibodies against T-cell markers and IL-2/toxin fusion proteins are currently investigated in many T-cell mediated diseases. According to clinical

studies, there is some evidence of the efficacy of anti-IL-2 in the treatment of psoriasis (Owen and Harrison, 2000; Mrowietz et al., 2000; Krueger et al., 2000). Recently, in a patient with severe chronic atopic dermatitis, the successful use of basiliximab, a chimeric anti-IL-2 receptor monoclonal antibody, has been reported (Kägi & Heyer, 2001). DAB_{389}IL-2 is an IL-2 receptor specific fusion protein in which the receptor-binding domain of the diphtheria toxin has been replaced by human IL-2 and the membrane translocating and cytotoxic domains have been retained. Clinical and laboratory investigations have demonstrated a selective destruction of IL-2 receptor expressing T-lymphocytes and DAB_{389}IL-2 has been successfully used in clinical trials for the treatment of cutaneous T-cell lymphomas and psoriasis. The most common side effects observed were flu-like symptoms with severity increasing at higher doses (Bagel et al., 1998; Martin et al., 2001; Eklund and Kuzel, 2005). Experimental approaches with immuno-cytokines being fusion proteins of IL-2 with tumour antigens have yielded promising results in the treatment of melanoma and lymphoma (Davis and Gillies, 2003; Gillies et al., 2005).

3.2. Agents targeting B-cells

The CD20 B-cell surface antigen is expressed only on pre-B as well as mature B cells and is lost before differentiation of B-cells into plasma cells. A murine monoclonal antiCD20 antibody (tositumomab) as well as a chimeric antiCD20 monoclonal antibody (rituximab), both of which cause a selective transient depletion of the $CD20^+$ B-cells, have been introduced for the treatment of $CD20^+$ low grade or follicular non-Hodgkin's lymphoma (Boye et al., 2003; Zelenetz, 2003; Stern and Herrmann, 2005). Similarly, epratuzumab, an antibody to CD22, a marker of mature B-lymphocytes, which also induces the targeted deletion of B-cells, is currently investigated in clinical trials in patients with non-Hodgkin's lymphoma (Leonard et al., 2004). In addition, targeting B-lymphocytes appears to be a promising approach for the treatment of autoimmune diseases. There is increasing evidence from several case reports and two recent small open-label trials for the efficacy of rituximab in the treatment of patients with SLE (Leandro et al., 2002; Looney et al., 2005; Gottenberg et al., 2005). Although the patients displayed some heterogeneity in disease severity and organ involvement, these studies indicate that a high dose rituximab provides significant benefits in most of these SLE patients.

The precise role of B-lymphocytes in the pathogenesis of RA is not fully understood. However, strong evidence of a crucial role of B-cells in RA came from a small open-label study and a recent randomized, double-blind, controlled study (Edwards et al., 2004). Accordingly, in patients with active RA, a single course of two infusions of rituximab, alone or in combination with either cyclophosphamide or continued methotrexate, provided significant improvement in the disease symptoms. Response rates were assessed according to the criteria of the American College of Rheumatology (ACR) and were maintained over a prolonged observation period of 24 wk. The treatment was well tolerated and the overall safety profile was consistent with that reported previously with rituximab in patients with lymphoma (Edwards et al., 2004).

Targeting B-cells may offer a novel therapeutic avenue for autoimmune blistering disorders some of which are characterized by aberrant production of pathogenetically relevant autoantibodies. Accordingly, rituximab was successfully used for the treatment of a patient with pemphigus vulgaris refractory to conventional disease. Four injections of rituximab at weekly intervals (375 mg/m^2) stopped blister formation and systemic steroids could subsequently be reduced to 5 mg daily (Herrmann et al., 2003). Future studies will have to confirm these promising findings.

3.3. Agents targeting proinflammatory or immunomodulatory cytokines

3.3.1. Anti-tumour necrosis factor-α

Tumour necrosis factor-α (TNF-α) is a homotrimeric protein, which exists in both transmembrane and soluble forms, the latter resulting from

proteolytic cleavage and release (Schottelius et al., 2004). It has been recognized as a key molecule mediating inflammation in immunologically mediated diseases such as RA, Crohn's disease, and psoriasis. Several different agents that neutralize the proinflammatory cytokine TNF-α such as a humanized antibody (infliximab), a fully human antibody (adalimumab), a protein containing the TNF-α receptor (p75) TNF-αRII fused with a humanized immunoglobulin fragment (etanercept), a fully human (p55) TNF-αRI (onercept), and pegylated anti-TNF's (CDP870, certolizumab) are available or are currently being developed for the treatment of inflammatory diseases (Smolen and Steiner, 2003; Braun and Sieper, 2003b; Schottelius et al., 2004; Feldmann and Steinman, 2005). In addition to approved indications such as RA, psoriatic arthritis ankylosing spondylitis, and Crohn's disease, anti-TNF-α strategies proved to be extremely effective for the treatment of psoriasis (Mease et al., 2000; Mahadevan and Sandborn, 2001; Iyer et al., 2002; Gottlieb et al., 2003; Braun and Sieper, 2003b; Imperato et al., 2004; Numerof et al., 2005; Tobin and Kirby, 2005). Accordingly, etanercept recently has been approved for the treatment of psoriasis and approval for infliximab will follow in the near future.

Etanercept (Enbrel) is a fusion protein consisting of two TNF receptors fused to the Fc portion of human IgG antibody, which binds to TNF-α resulting in a decrease of active soluble TNF-α (Goffe and Cather, 2003). Etanercept has been used in more than 210,000 patients over the past 6 years for the treatment of psoriatic arthritis, ankylosing spondylitis, juvenile and adult RA, and psoriasis (Saini et al., 2005). According to clinical trials, etanercept also was highly efficacious in plaque type psoriasis resulting in 59% improvement in the psoriasis activity and severity index (PASI) score. Adverse events and infections were comparable to placebo. Discontinuation of etanercept was not associated with rebound (Papp et al., 2005; Papp, 2004; Gottlieb, 2004; Mease, 2004). There is also preliminary evidence that patients with dermatomyositis/polymyositis may profit from therapy with etanercept. In a pilot study of four patients with polymyositis refractory to conventional therapy, etanercept reduced the serum levels of creatinine phosphokinase and markedly improved clinical signs (Saadeyh, 2000). In a recent case report, etanercept also significantly reduced disease activity of a patient with pemphigus vulgaris during a 16 wk treatment (Lin et al., 2005). In contrast, etanercept (50 mg/wk) was not effective in an open-label study of 17 patients with moderate to severe alopecia areata (Strober et al., 2005) confirming an anectodal report of a patient with RA receiving etanercept and in whom alopecia areata recurred (Posten and Swan, 2005). Moreover, a pilot study with etanercept in 15 patients with primary Sjögren's syndrome failed to demonstrate any effects on sicc symptoms, glandular functions, and histologic findings (Zandbelt et al., 2004).

Infliximab (Remicade) is a humanized murine antibody targeting TNF-α which is indicated for the treatment of RA, psoriatic arthritis, and Crohn's disease, with more than 500,000 patients having been treated worldwide (Schottelius et al., 2004; Braun and Sieper, 2003a). Treatment of psoriasis with infliximab (5 mg/kg) resulted in a rapid (2–4 wk) and significant improvement of plaque type psoriasis. Up to 80% of the patients with severe psoriasis experienced a 75% improvement in the PASI score. However, relapses often occur in 6–8 wk after the last infusion. Infliximab may only need to be administered intravenously once in every 2–3 months for maintenance after induction. Nail psoriasis also responded to infliximab as shown by a study of 25 plaque-type and arthropathic patients with a nail psoriasis severity index (NAPSI) of >14. After 22 weeks, complete clinical remission was achieved in all patients, which lasted for the subsequent follow-up time of 12 wk (Bianchi et al., 2005). In patients with psoriasis, infliximab monotherapy so far did not cause severe side effects. Due to the lack of adverse effects on liver function tests, infliximab may also be suitable in special clinical conditions, i.e. in patients with psoriasis and liver cirrhosis (Lehnen et al., 2005). However, adverse events such as mycobacterial infections, anaphylactic reactions, and autoimmune diseases have to be considered. Therefore, therapy guidelines developed for patients with RA have to be observed strictly (Gottlieb et al., 2002, 2003, 2004a; Winterfield and

Menter, 2004; Antoni et al., 2005). Similarly to etanercept, infiximab lacked any effect in a multicentre randomized double-blinded study on 103 patients with primary Sjögren's syndrome (Mariette et al., 2004). Further studies will have to confirm the observed beneficial effect of infliximab on dermatomyositis/polymyositis as reported in two case reports (Hengstman et al., 2003; Labioche et al., 2004) as well as on severe pemphigus vulgaris as reported in one case (Pardo et al., 2005).

Adalimumab (Humira1) is a fully human monoclonal antibody, which specifically binds to TNF-α, blocking its interaction with the p55 and p75 cell surface TNF receptors (Bain and Brazil, 2003; Schottelius et al., 2004). Adalimumab was shown to be an effective treatment in RA either as monotherapy or in combination with other disease-modifying antirheumatic drugs (Furst et al., 2003; Keystone and Haraoui, 2004). Adalimumab was further reported to be effective in treating refractory RA associated leg ulceration (Hirche et al., 2005). In a recent phase II clinical trial adalimumab was also effective in the treatment of moderate to severe psoriasis. At week 12, PASI 75 was achieved in 53% of patients in the low dose group, 80% in the high dose group, and 4% in the placebo group (Scheinfeld, 2004a; Chew et al., 2004). Adalimumab was well tolerated in this group of patients, and there were no new safety concerns identified in psoriasis patients when compared to the RA population (Scheinfeld, 2004a; Patel and Gordon, 2004). Although rare overall, it should be noted that under therapy with all the above anti-TNF strategies, side effects have been reported. In some cases, the development of lymphomas, mostly of the non-Hodgkin type with sometimes aggressive behaviour, have been associated with the use of anti-TNF-α therapy (Scheinfeld, 2004b).

The experience of using anti-TNF strategies for the treatment of LE are limited and have to be considered very carefully because of their potential to induce autoantibodies, which may cause exacerbation of the disease (Debandt et al., 2003; Eriksson et al., 2005; De Bandt et al., 2005). Of note, 10–16% of patients treated with infliximab developed de novo anti-ds DNA antibodies (Charles et al., 2000) and infliximab-induced cutaneous LE has been reported (High et al., 2005). However, one patient with RA and with subacute cutaneous LE was reported to be treated with etanercept, which resulted in a significant improvement of the previous therapy-resistant skin lesions within 15 days. After 6 months, the RA remained improved, there were no signs of active lupus, antinuclear antibodies were stable and no anti-ds DNA antibodies were present (Fautrel et al., 2002). Recently, in an open-label study, 6 patients with SLE (four with nephritis and three with arthritis refractory to other therapies) were treated with infliximab in addition to other immunosuppressive drugs (azathioprine or methotrexate). Levels of antibodies to ds DNA and cardiolipin increased in four patients. However, the disease activity decreased and all the three patients with joint involvement experienced remission of arthritis. In the four patients with lupus nephritis, proteinuria decreased significantly (Aringer et al., 2004). Further controlled clinical trials ultimately will reveal the role of anti-TNF-α strategies in the treatment of LE.

3.3.2. *Interleukin-1 receptor antagonist*

Targeting IL-1 represents a further promising approach for the treatment of inflammatory diseases. Accordingly, a recombinant human IL-1 receptor antagonist (anakinra) is currently being investigated for its efficacy in patients with RA (Schiff, 2000; Dinarello, 2004). Recently, the efficacy of anakinra in patients with SLE with joint involvement was reported. Treatment with anakinra resulted in a clinical as well as serological improvement and was safe and well tolerated (Moosig et al., 2004; Ostendorf et al., 2005).

3.4. *Cytokines causing immunodeviation*

The efficacy of immunomodulating cytokines shifting the immune response from Th1 towards Th2 is currently being investigated for the treatment of psoriasis. IL-10 , which is able to inhibit the expression of Th1 type cytokines was considered as a promising candidate. In first clinical trials, subcutaneous application of IL-10 resulted

in a significant drop of the PASI score. Although IL-10 was well tolerated, more clinical studies are required to evaluate the efficacy and possible long-term side effects of this treatment (Asadullah et al., 2004). According to preliminary clinical trials, IL-11, which exerts thrombopoietic activity and also downregulates a Th1 immune response, appears to be a promising approach for the treatment of psoriasis (Trepicchio et al., 1999). In animal experiments, it has been shown that IL-4 shifts the differentiation of naïve and probably also memory T-cells towards a Th2 phenotype in an antigen specific fashion. A recently published clinical study indicates that the treatment of psoriasis with rhIL-4 results in a significant improvement of the PASI score (up to 80%) within 6 wk and seems to be well tolerated (Ghoreschi et al., 2003). Thus IL-4 appears to have a considerable potential for the treatment of Th1 mediated diseases.

In patients with SLE an increased production of IL-10 by peripheral blood mononuclear cells was found to be associated with overproduction of pathogenic autoantibodies. Therefore, it seemed reasonable to investigate whether blocking IL-10 may provide a useful approach to treat autoimmune diseases such as LE. Accordingly, six steroid-dependent patients with SLE were treated for 21 consecutive days with intravenous infusion of anti-IL-10 (20 mg/day). The patients experienced a significant decrease in disease activity and were able to reduce concomitant steroid medication. In addition, a significant improvement of vasculitis and skin lesions was observed. Clinical scores remained stable through a follow-up of 6 months and no significant adverse events have been reported (Llorente et al., 2000).

3.5. Agents targeting T-cell/antigen-presenting cell interaction

Another promising approach to treat T-cell mediated diseases is to develop agents that disrupt antigen presentation and thus T-cell activation. Accordingly, antibodies against costimulatory molecules or fusion molecules consisting of costimulatory molecules and Fc portions of human IgG have been developed. Interestingly, in contrast to other biologics, many of these molecules have been investigated primarily for their efficacy in the treatment of psoriasis (Tutrone et al., 2004). Efalizumab is a humanized antibody that binds to the α chain of lymphocyte functioning antigen-1 (LFA-1, CD11a), blocks T-cell trafficking to the dermis and epidermis, and inhibits secondary activation of T-cells (Marecki and Kirkpatrick, 2004). Clinical trials in patients with psoriasis have shown a rapid response and a significant reduction in the PASI score (PASI 75: 29% of patients at 12 wk). Side effects consisted in an increased incidence of flu-like symptoms but no organ toxicity. Continuous treatment over a period of 3 years was shown to maintain or improve response rates with no evidence for new adverse events (Cather and Menter, 2005; Leonardi et al., 2005; Gottlieb et al., 2004b). Although the incidence of malignancy in the above clinical trials with efalizumab was 1.8 per 100 patient years and 1.6 per 100 patient years for placebo, caution should be advised in patients with long-term treatment. In one patient with a 27-year history of moderate-to-severe plaque psoriasis and treatment with efalizumab for 2 years development of cervical cancer was reported (Morse et al., 2005).

Alefacept is a human fusion protein where the CD2 binding domain of LFA_3 has been linked to the Fc portion of human IgG_1, leading to functional blockade of the LFA_3/CD2 pathway. Thus alefacept by binding to CD2 inhibits the function of CD4+ and CD8+ T-cells and selectively reduces memory-effector CD45RO+ T cells (Ormerod, 2003). Treatment with alefacept (12 wk) significantly improved psoriasis in comparison to placebo and a second course of alefacept after 12 wk was found to provide additional benefit. Alefacept has been shown to provide long-lasting periods of remission. It was well tolerated without any serious short-term side effects (Krueger and Ellis, 2003; Lebwohl et al., 2003). The safety and tolerability of alefacept was corroborated in two patients with psoriasis and hepatitis C. In these patients liver enzymes remained stable during the 12 wk therapy with alefacept (Thaci et al., 2005). An open-label single-centre study of 20 patients with chronic plague psoriasis in which alefacept

was given for 16 wk confirmed a similar safety profile as the 12 wk trial and also suggested further benefit to some patients with improvement in disease (Gribetz et al., 2005). However, monitoring of CD4+ cells may be required (Leone et al., 2003; Gordon and Valentine, 2004). In addition, as with anti-TNF-α strategies, treatment with alefacept bears the potential risk of reducing tumour immunosurveillance possibly promoting the development of lymphoma from preexistent subclinical tumour (Krueger and Callis, 2003; Schmidt et al., 2005). More recent studies further suggest that alefacept is helpful in nail and palmoplantar psoriasis (Cassetty et al., 2005; Myers et al., 2005).

4. Other biological compounds

Cytokines of the IL-12 (IL-12) family including IL-12, IL-23, and IL-27 are known to regulate Th1-cell responses. In addition, it recently turned out that IL-23 via stimulating T-cell IL-17 production plays an important role in autoimmune inflammation (Hunter, 2005). Accordingly, a monoclonal antibody to the human IL-12 p40 subunit (anti-IL-12p40), which is shared with IL-23 has been developed for the treatment of autoimmune diseases. In a first clinical trial, this antibody was evaluated for its efficacy and safety in the treatment of moderate-to-severe psoriasis. Anti-IL-12p40 was well tolerated and 67% of the patients achieved at least a 75% improvement in PASI between 8 and 16 week after a single application of the medication (Kauffman et al., 2004). These very promising results need to be confirmed by the ongoing long-term trials.

Targeting directly molecules of the B7 family which are crucial for providing costimulatory signals required for T-cell activation may be another effective strategy for the treatment of autoimmune diseases (Nathan, 1987; Christou et al., 1987). Studies in NZB/NZW mice have shown that the combined application of monoclonal antibodies directed against both B7-1 and B7-2 decreases anti-dsDNA and prolongs survival. Treatment with either mAb alone did not have a similar strong efficacy (Daikh and Wofsy, 1999). Antibodies against costimulatory molecules such as CD80 (IDEC-114 and galiximab) are being investigated and in some, the first clinical trial was found to be promising, safe, and well tolerated for the treatment of psoriasis (Gottlieb et al., 2002, 2004c). Moreover, antibodies against CD40-ligand (anti-CD154, IDEC-131, and ruplizumab) are investigated for the treatment of SLE (Davis et al., 2001; Kalunian et al., 2002).

CTLA-4 is expressed on the surface of a subpopulation of activated T-lymphocytes and binds with high affinity to molecules of the B7 family that are present on B-cells and antigen-presenting cells. CTLA-4Ig is a fusion protein of the extracellular domain of CTLA-4 with the Fc portion of IgG1, which serves as a soluble receptor. Therefore, this molecule prevents CTLA-4/B7 interaction by blocking T-cell activation and T-cell-dependent B-cell functions in vivo. In animal studies, treatment of NZB/W mice resulted in an improved survival rate as well as regression of nephritis (Finck et al., 1994). Clinical studies with CTLA-4Ig in patients with lupus nephritis are being initiated and one compound (BMS-188667) currently is investigated in clinical trials for patients with RA and psoriasis. Preliminary data indicate that treatment with CTLA-4 Ig appears to be an effective therapy for psoriasis and atopic eczema (Abrams et al., 1999; Najafian and Sayegh, 2000; Davenport et al., 2002; Davidson et al., 2005).

Decreased levels of complement components, including C3, C4, and/or CH50, are one of the characteristic laboratory parameters of SLE, which also correlate with disease activity. C3b, derived from C3 by either the classic or alternative pathway of complement activation, provides a binding site for C5, making it susceptible to the action of C5 convertase. This activity triggers the terminal sequence of complement activation that leads to membrane damage (Moxley and Ruddy, 1997). A monoclonal antibody designed to interfere with C5 activity decreased proteinuria and improved survival in treated NZB/NZW mice (Wang et al., 1996; Nassar et al., 1994). Moreover, in first clinical trials patients with SLE have been treated successfully with a humanized anti-C5 mAb (pexelizumab) (Rother et al., 2004).

5. Conclusion and outlook

The enormous progress in biotechnology as well as in the improved understanding of the underlying pathomechanisms of several autoimmune diseases has paved the road for the development of novel, more specific, and hopefully more efficient therapeutics strategies. In many cases, biologics have already given the physician novel, highly potent, and often patient-friendly drugs at hand in additional to the already existing armamentarium for autoimmune disorders. At present, the number of drugs being evaluated for their efficacy and safety in the treatment of various autoimmune disorders are rapidly increasing. It is clear that even in the current era of biologics autoimmune diseases cannot be cured until the precise cascade of pathogenetic events and the ultimate molecular mechanisms of such diseases are unravelled. However, in addition to offering novel alternative treatment strategies biologics will undoubtedly contribute to our current pathogenetic understanding of autoimmune disorders by providing novel clues to the putative role and relevance of a specific molecule being targeted by the administered substance. Whether biologics or conventional chemotherapeutics will end up as the most efficient therapy with a minimal profile of adverse events in autoimmune diseases of the skin remains to be seen in future and may also vary depending on the course, activity, and organ involvement of the disease. Finally, combination of biologics and other immunomodulating strategies may allow to increase efficacy and to minimize adverse events.

Key points

- Recent progress in understanding of the complex pathomechanisms underlying immune-mediated and inflammatory skin diseases has facilitated the development of novel therapeutic avenues.
- Among several systemic drugs being investigated for dermatological use, specific systemic immunomodulating strategies are aimed to target the function of antigen-presenting cells as well as T-cells including adhesion molecule expression and cytokine production. These approaches include several ''biologics'' such as immunodeviating cytokines (IL-4, IL-10, and IL-11), humanized antibodies (efalizumab dacalizumab, infliximab, and adalimumab), and fusion proteins (etanercept, alefacept, and denileukin).
- Alefacept recently has been approved for the treatment of psoriasis in the United States and several other substances are currently under investigation for the treatment of inflammatory skin diseases. These novel therapeutic tools not only will help to improve the current treatment of inflammatory skin diseases, but also will lead to identification of key-targets, which ultimately will allow the design of new and improved antiinflammatory and immunotherapeutic options.

References

Abrams, J.R., Lebwohl, M.G., Guzzo, C.A. 1999. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. J. Clin. Invest 103, 1243.

Antoni, C., Krueger, G.G., De, V.K., Birbara, C., et al. 2005. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann. Rheum. Dis. 64, 1150.

Aringer, M., Graninger, W.B., Steiner, G., et al. 2004. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus: an open-label study. Arthritis Rheum. 50, 3161.

Asadullah, K., Sabat, R., Friedrich, M., et al. 2004. Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. Curr. Drug Targets Inflamm. Allergy 3, 185.

Bachelez, H., Flageul, B., Dubertret, L., et al. 1998. Treatment of recalcitrant plaque psoriasis with a humanized non-depleting antibody to CD4. J. Autoimmun. 11, 53.

Bagel, J., Garland, W.T., Breneman, D., et al. 1998. Administration of DAB389IL-2 to patients with recalcitrant psoriasis: a double-blind, phase II multicenter trial. J. Am. Acad. Dermatol. 38, 938.

Bain, B., Brazil, M. 2003. Adalimumab. Nat. Rev. Drug Discov. 2, 693.

Barry, J., Kirby, B. 2004. Novel biologic therapies for psoriasis. Expert Opin. Biol. Ther. 4, 975.

Bayes, M., Rabasseda, X., Prous, J.R. 2003. Gateways to clinical trials. Methods Find. Exp. Clin. Pharmacol. 25, 483.

Bianchi, L., Bergamin, A., de Felice, C., et al. 2005. Remission and time of resolution of nail psoriasis during infliximab therapy. J. Am. Acad. Dermatol. 52, 736.

Boye, J., Elter, T., Engert, A. 2003. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Ann. Oncol. 14, 520.

Braun, J., Sieper, J. 2003a. Overview of the use of the anti-TNF agent infliximab in chronic inflammatory diseases. Expert Opin. Biol. Ther. 3, 141.

Braun, J., Sieper, J. 2003b. Role of novel biological therapies in psoriatic arthritis: effects on joints and skin. Bio. Drugs 17, 187.

Carpenter, P.A., Lowder, J., Johnston, L., et al. 2005. A phase II multicenter study of visilizumab, humanized anti-CD3 antibody, to treat steroid-refractory acute graft-versus-host disease. Biol. Blood Marrow Transplant. 11, 465.

Cassetty, C.T., Alexis, A.F., Shupack, J.L., et al. 2005. Alefacept in the treatment of psoriatic nail disease: a small case series. J. Am. Acad. Dermatol. 52, 1101.

Cather, J.C., Menter, A. 2005. Efalizumab: continuous therapy for chronic psoriasis. Expert Opin. Biol. Ther. 5, 393.

Charles, P.J., Smeenk, R.J., De Jong, J., et al. 2000. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum. 43, 2383.

Chew, A.L., Bennett, A., Smith, C.H., et al. 2004. Successful treatment of severe psoriasis and psoriatic arthritis with adalimumab. Br. J. Dermatol. 151, 492.

Christou, N.V., Mannick, J.A., West, M.A., et al. 1987. Lymphocyte macrophage interactions in the response to surgical infections. Arch. Surg. 122, 239.

Daikh, D.I., Wofsy, D. 1999. Effects of anti-B7 monoclonal antibodies on humoral immune responses. J. Autoimmun. 12, 101.

Davenport, C.M., McAdams, H.A., Kou, J. 2002. Inhibition of pro-inflammatory cytokine generation by CTLA4-Ig in the skin and colon of mice adoptively transplanted with CD45RBhi CD4+ T cells correlates with suppression of psoriasis and colitis. Int. Immunopharmacol. 2, 653.

Davidson, A., Diamond, B., Wofsy, D., et al. 2005. Block and tackle: CTLA4Ig takes on lupus. Lupus 14, 197.

Davis, C.B., Gillies, S.D. 2003. Immunocytokines: amplification of anti-cancer immunity. Cancer Immunol. Immun. 52, 297.

Davis, J.C., Jr., Totoritis, M.C., Rosenberg, J., et al. 2001. Phase I clinical trial of a monoclonal antibody against CD40-ligand (IDEC-131) in patients with systemic lupus erythematosus. J. Rheumatol. 28, 95.

De Bandt, M., Sibilia, J., Le Loet, X., et al. 2005. Club Rhumatismes et Inflammation, Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res. Ther. 7, R545.

Debandt, M., Vittecoq, O., Descamps, V., et al. 2003. Anti-TNF-alpha-induced systemic lupus syndrome. Clin. Rheumatol. 22, 56.

Dinarello, C.A. 2004. Blocking IL-1 in systemic inflammation. J. Exp. Med. 201, 1355.
This paper highlights the central role of IL-1 in systemic autoimmune diseases with emphasis on systemic onset juvenile idiopathic arthritis and the therapeutic perspective of IL-1 blocking.

Edwards, J.C., Szczepanski, L., Szechinski, J. 2004. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N. Engl. J. Med. 350, 2572.

Eklund, J.W., Kuzel, T.M. 2005. Denileukin diftitox: a concise clinical review. Expert Rev. Anticancer Ther. 5, 33.

Emmi, L., Chiarini, F. 2002. The role of intravenous immunoglobulin therapy in autoimmune and inflammatory disorders. Neurol. Sci. 23 (Suppl. 1), S1.

Eriksson, C., Engstrand, S., Sundqvist, K.G., et al. 2005. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann. Rheum. Dis. 64, 403.

Fautrel, B., Foltz, V., Frances, C., et al. 2002. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumor necrosis factor alpha-blocking agent: comment on the article by Pisetsky and the letter from Aringer et al. Arthritis Rheum. 46, 1408.

Feldmann, M., Steinman, L. 2005. Design of effective immunotherapy for human autoimmunity. Nature 435, 612.
This comprehensive review describes the current status of immunotherapeutics for human autoimmune diseases.

Finck, B.K., Linsley, P.S., Wofsy, D. 1994. Treatment of murine lupus with CTLA4Ig. Science 265, 1225.

Finucane, K.A., Archer, C.B. 2005. Recent advances in rheumatology: biological agents for the treatment of rheumatoid arthritis, the progression of psoriatic arthritis, autoantibodies in systemic lupus erythematosus. Clin. Exp. Dermatol. 30, 201.

Furst, D.E., Schiff, M.H., Fleischmann, R.M., et al. 2003. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J. Rheumatol. 30, 2563.

Ghoreschi, K., Thomas, P., Breit, S., et al. 2003. Interleukin-4 therapy of psoriasis induces Th2 responses and improves human autoimmune disease. Nat. Med. 9, 40.

Gillies, S.D., Lan, Y., Williams, S., et al. 2005. An anti-CD20-IL-2 immunocytokine is highly efficacious in a SCID mouse model of established human B lymphoma. Blood 105, 3972.

Gniadecki, R., Zachariae, C., Calverley, M. 2002. Trends and developments in the pharmacological treatment of psoriasis. Acta Derm. Venereol. 82, 401.

Goffe, B., Cather, J.C. 2003. Etanercept: an overview. J. Am. Acad. Dermatol. 49, S105.

This review summarizes the structure and mechanism of action of etanercept as well as therapeutic results derived from clinical trials with etanercept involving patients with psoriasis.

Gordon, K.B., Valentine, J. 2004. The efficacy of alefacept in the treatment of chronic plaque psoriasis. J. Cutan. Med. Surg. 8 (Suppl. 2), 3.

Gottenberg, J.E., Guillevin, L., Lambotte, O., et al. 2005. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann. Rheum. Dis. 64, 913.

Gottlieb, A.B. 2004. Etanercept for the treatment of psoriasis and psoriatic arthritis. Dermatol. Ther. 17, 401.

Gottlieb, A.B. 2005. Psoriasis: emerging therapeutic strategies. Nat. Rev. Drug Discov. 4, 19.

Gottlieb, A.B., Chaudhari, U., Mulcahy, L.D., et al. 2003. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. J. Am. Acad. Dermatol. 48, 829.

Gottlieb, A.B., Evans, R., Li, S., et al. 2004a. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J. Am. Acad. Dermatol. 51, 534.

Gottlieb, A.B., Gordon, K.B., Lebwohl, M.G., et al. 2004b. Extended efalizumab therapy sustains efficacy without increasing toxicity in patients with moderate to severe chronic plaque psoriasis. J. Drugs Dermatol. 3, 614.

Gottlieb, A.B., Kang, S., Linden, K.G., et al. 2004c. Evaluation of safety and clinical activity of multiple doses of the anti-CD80 monoclonal antibody, galiximab, in patients with moderate to severe plaque psoriasis. Clin. Immunol. 111, 28.

Gottlieb, A.B., Lebwohl, M., Totoritis, M.C., et al. 2002. Clinical and histologic response to single-dose treatment of moderate to severe psoriasis with an anti-CD80 monoclonal antibody. J. Am. Acad. Dermatol. 47, 692.

Gribetz, C.H., Blum, R., Brady, C., et al. 2005. An extended 16-week course of alefacept in the treatment of chronic plaque psoriasis. J. Am. Acad. Dermatol. 53, 73.

Hengstman, G.J., van den Hoogen, F.H., Barrera, P., et al. 2003. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations. Eur. Neurol. 50, 10.

Herrmann, G., Hunzelmann, N., Engert, A. 2003. Treatment of pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). Br. J. Dermatol. 148, 602.

High, W.A., Muldrow, M.E., Fitzpatrick, J.E. 2005. Cutaneous lupus erythematosus induced by infliximab. J. Am. Acad. Dermatol. 52, E5.

Hirche, D., Rubbert, A., Lunau, L., et al. 2005. Successful treatment of refractory rheumatoid arthritis-associated leg ulcerations with adalimumab. Br. J. Dermatol. 152, 1062.

Hunter, C.A. 2005. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. Nat. Rev. Immunol. 5, 521.

Ibanez, C., Montoro-Ronsano, J.B. 2003. Intravenous immunoglobulin preparations and autoimmune disorders: mechanisms of action. Curr Pharm Biotechnol 4, 239.

This paper is a review on the variety of molecular actions of intravenous immunoglubulins with focus on autoimmune disorders.

Imperato, A.K., Bingham III, C.O., Abramson, S.B. 2004. Overview of benefit/risk of biological agents. Clin. Exp. Rheumatol. 22, S108.

Iyer, S., Yamauchi, P., Lowe, N.J. 2002. Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. Br. J. Dermatol. 146, 118.

Kägi, M.K., Heyer, G. 2001. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. Brit. J. Dermatol. 145, 350.

Kalunian, K.C., Davis, J.C., Jr., Merrill, J.T., et al. 2002. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 46, 3251.

Kauffman, C.L., Aria, N., Toichi, E., et al. 2004. A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. J. Invest. Dermatol. 123, 1037.

Keystone, E., Haraoui, B. 2004. Adalimumab therapy in rheumatoid arthritis. Rheum. Dis. Clin. North Am. 30, 349.

Kourbeti, I.S., Boumpas, D.T. 2005. Biological therapies of autoimmune diseases. Curr. Drug Targets Inflamm. Allergy 4, 41.

Krueger, G.G., Callis, K.P. 2003. Development and use of alefacept to treat psoriasis. J. Am. Acad. Dermatol. 49, S87.

Krueger, G.G., Ellis, C.N. 2003. Alefacept therapy produces remission for patients with chronic plaque psoriasis. Brit. J. Dermatol. 148, 784.

Krueger, J.G., Walters, I.B., Miyazawa, M., et al. 2000. Successful in vivo blockade of CD25 (high-affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. J. Am. Acad. Dermatol. 43, 448.

Labioche, I., Liozon, E., Weschler, B., et al. 2004. Refractory polymyositis responding to infliximab: extended follow-up. Rheumatology (Oxford) 43, 531.

Leandro, M.J., Edwards, J.C., Cambridge, G., et al. 2002. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 46, 2673.

Lebwohl, M., Christophers, E., Langley, R., et al. 2003. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. Arch. Dermatol. 139, 719.

Lehnen, M., Franckson, T., Knab, J., et al. 2005. Successful infliximab therapy of psoriasis vulgaris and psoriatic arthritis in a patient with cirrhosis. Br. J. Dermatol. 153, 212.

Leonard, J.P., Coleman, M., Ketas, J.C., et al. 2004. Epratuzumab, a humanized anti-CD22 antibody, in aggressive non-Hodgkin's lymphoma: phase I/II clinical trial results. Clin. Cancer Res. 10, 5327.

Leonardi, C.L., Papp, K.A., Gordon, K.B., et al. 2005. Extended efalizumab therapy improves chronic plaque

psoriasis: results from a randomized phase III trial. J. Am. Acad. Dermatol. 52, 425.

Leone, G., Rolston, K., Spaulding, G. 2003. Alefacept for chronic plaque psoriasis: a selective therapy with long-lasting disease remissions and an encouraging safety profile. Dermatol. Nurs. 15, 216.

Lin, M.H., Hsu, C.K., Lee, J.Y. 2005. Successful treatment of recalcitrant pemphigus vulgaris and pemphigus vegetans with etanercept and carbon dioxide laser. Arch. Dermatol. 141, 680.

Llorente, L., Richaud-Patin, Y., Garcia-Padilla, C., et al. 2000. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis Rheum. 43, 1790.

Looney, R.J., Anolik, J., Sanz, I. 2005. Treatment of SLE with anti-CD20 monoclonal antibody. Curr. Dir. Autoimmun. 8, 193.

Mahadevan, U., Sandborn, W.J. 2001. Infliximab for the treatment of orofacial Crohn's disease. Inflamm. Bowel Dis. 7, 38.

Marecki, S., Kirkpatrick, P. 2004. Efalizumab. Nat. Rev. Drug. Discov. 3, 473.

Mariette, X., Ravaud, P., Steinfeld, S., et al. 2004. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum. 50, 1270.

Martin, A., Gutierrez, E., Muglia, J., et al. 2001. A multicenter dose-escalation trial with denileukin diftitox ONTAK, DAB(389)IL-2 in patients with severe psoriasis. J. Am. Acad. Dermatol. 45, 871.

Mease, P. 2004. TNFalpha therapy in psoriatic arthritis and psoriasis. Ann. Rheum. Dis. 63, 755.

Mease, P.J., Goffe, B.S., Metz, J., et al. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 356, 385.

Moosig, F., Zeuner, R., Renk, C., et al. 2004. IL-1RA in refractory systemic lupus erythematosus. Lupus 13, 605.

Morse, L.G., Yarbrough, L., Hogan, D.J. 2005. Cervical cancer in a woman associated with long-term efalizumab therapy. J. Am. Acad. Dermatol. 53, 354.

Moxley, G., Ruddy, S. 1997. Immune complexes and complement. In: W.N. Kelley (Ed.), Textbook of Rheumatology. Saunders, Philadelphia.

Mrowietz, U., Zhu, K., Christophers, E. 2000. Treatment of severe psoriasis with anti-CD25 monoclonal antibodies. Arch. Dermatol. 136, 675.

Myers, W., Christiansen, L., Gottlieb, A.B. 2005. Treatment of palmoplantar psoriasis with intramuscular alefacept. J. Am. Acad. Dermatol. 53, S127.

Najafian, N., Sayegh, M.H. 2000. CTLA4-Ig: a novel immunosuppressive agent. Expert Opin. Invest. Drugs 9, 2147.
This paper describes the mechanism of action of CTLA4-Ig and its efficacy in various disease models.

Nassar, G.M., Morrow, J.D., Roberts, L.J. 1994. Induction of 15-lipoxygenase by interleukin-13 in human blood monocytes. J. Biol. Chem. 269, 27631.

Nathan, C.F. 1987. Secretory products of macrophages. J. Clin. Invest. 79, 319.

Numerof, R.P., Dinarello, C.A., Asadullah, K. 2005. Cytokines as potential therapeutic targets for inflammatory skin diseases. Eur. Cytokine Netw. 16, 101.

Ormerod, A.D. 2003. Alefacept. Biogen. Curr. Opin. Invest. Drugs 4, 608.
This review summarizes the development, biochemistry and pharmacology of alefacept and its use as a biologic in patients with psoriasis.

Ostendorf, B., Iking-Konert, C., Kurz, K., et al. 2005. Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis. Ann. Rheum. Dis. 64, 630.

Owen, C.M., Harrison, P.V. 2000. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. Clin. Exp. Dermatol. 25, 195.

Papp, K.A. 2004. Etanercept in psoriasis. Expert Opin. Pharmacother. 5, 2139.

Papp, K.A., Tyring, S., Lahfa, M., et al. 2005. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br. J. Dermatol. 152, 1304.

Pardo, J., Mercader, P., Mahiques, L., et al. 2005. Infliximab in the management of severe pemphigus vulgaris. Br. J. Dermatol. 153, 222.

Patel, T., Gordon, K.B. 2004. Adalimumab: efficacy and safety in psoriasis and rheumatoid arthritis. Dermatol. Ther. 17, 427.

Posten, W., Swan, J. 2005. Recurrence of alopecia areata in a patient receiving etanercept injections. Arch. Dermatol. 141, 759.

Prinz, J.C., Meurer, M., Reiter, C., et al. 1996. Treatment of severe cutaneous lupus erythematosus with a chimeric CD4 monoclonal antibody, cM-T412. J. Am. Acad. Dermatol. 34, 244.

Rother, R.P., Mojcik, C.F., McCroskery, E.W. 2004. Inhibition of terminal complement: a novel therapeutic approach for the treatment of systemic lupus erythematosus. Lupus 13, 328.

Rütter, A., Luger, T.A. 2002. Immunoglobulin: an emerging treatment for immune-mediated skin diseases. J. Am. Acad, Dermatol. Curr. Opin. Invest. Drugs 3, 713.

Saadeyh, C. 2000. Etanercept is effective in the treatment of polymyositis/dermatomyositis which is refractory to conventional therapy. Arthritis Rheum. 43, S193.

Saini, R., Tutrone, W.D., Weinberg, J.M. 2005. Advances in therapy for psoriasis: an overview of infliximab, etanercept, efalizumab, alefacept, adalimumab, tazarotene, and pimecrolimus. Curr. Pharm. Des. 11, 273.

Saripalli, Y.V., Gaspari, A.A. 2005. Focus on: biologics that affect therapeutic agents in dermatology. J. Drugs Dermatol. 4, 233.

Scheinfeld, N. 2004a. Adalimumab (Humira): a brief review for dermatologists. J. Dermatol. Treat. 15, 348.

Scheinfeld, N. 2004b. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers

etanercept, infliximab and adalimumab. J. Dermatol. Treat. 15, 280.
This paper analyses the spectrum of adverse effects associated with use of anti-TNF-α therapy based on reports published in Medline for over 5 years.

Schiff, M.H. 2000. Role of interleukin 1 and interleukin 1 receptor antagonist in the mediation of rheumatoid arthritis. Ann. Rheum. Dis. 59 (Suppl. 1), i103.

Schmidt, A., Robbins, J., Zic, J. 2005. Transformed mycosis fungoides developing after treatment with alefacept. J. Am. Acad. Dermatol. 53, 355.

Schottelius, A.J., Moldawer, L.L., Dinarello, C.A. 2004. Biology of tumor necrosis factor-alpha- implications for psoriasis. Exp. Dermatol. 13, 193.

Shoenfeld, Y., Krause, I. 2004. ivIg for autoimmune, fibrosis, and malignant conditions: our experience with 200 patients. J. Clin. Immunol. 24, 107.

Skov, L., Kragballe, K., Zachariae, C., et al. 2003. HuMax-CD4: a fully human monoclonal anti-CD4 antibody for the treatment of psoriasis vulgaris. Arch. Dermatol. 139, 1433.

Smolen, J.S., Steiner, G. 2003. Therapeutic strategies for rheumatoid arthritis. Nat. Rev. 2, 473.

Spahn, J.D., Leung, D.Y., Chan, M.T., et al. 1999. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. J. Allergy Clin. Immunol. 103, 421.

Stern, M., Herrmann, R. 2005. Overview of monoclonal antibodies in cancer therapy: present and promise. Crit. Rev. Oncol. Hematol. 54, 11.

Strober, B.E., Siu, K., Alexis, A.F., et al. 2005. Etanercept does not effectively treat moderate to severe alopecia areata: an open-label study. J. Am. Acad. Dermatol. 52, 1082.

Thaci, D., Patzold, S., KauFmann, R., Boehncke, W. 2005. Treatment of psoriasis with alefacept in patients with hepatitis C infection: a report of two cases. Br. J. Dermatol. 152, 1048.

Tobin, A.M., Kirby, B. 2005. TNF alpha inhibitors in the treatment of psoriasis and psoriatic arthritis. BioDrugs 19, 47.

Trepicchio, W.L., Ozawa, M., Walters, I.B., et al. 1999. Interleukin-11 therapy selectively downregulates type I cytokine proinflammatory pathways in psoriasis lesions. J. Clin. Invest. 104, 1527.

Tutrone, W.D., Saini, R., Weinberg, J.M. 2004. Biological therapy for psoriasis: an overview of infliximab, etanercept, efalizumab and alefacept. Drugs 7, 45.
This paper reviews the progress of the above biologics in the treatment of psoriasis.

Viard, I., Wehrli, P., Bullani, R., et al. 1998. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science 282, 490.

Wang, Y., Hu, Q., Madri, J.A., et al. 1996. Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. Proc. Natl. Acad. Sci. USA. 93, 8563.

Wetter, D.A., Davis, M.D., Yiannias, J.A., et al. 2005. Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. Mayo Clin. Proc. 80, 41.

Winterfield, L., Menter, A., 2004. Psoriasis and its treatment with infliximab-mediated tumor necrosis factor alpha blockade, Dermatol. Clin., 22, 437, ix.

Zandbelt, M.M., de Wilde, P., van Damme, P., et al. 2004. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. J. Rheumatol. 1, 96.

Zelenetz, A.D. 2003. A clinical and scientific overview of tositumomab and iodine I 131 tositumomab. Semin. Oncol. 30, 22.

Handbook of Systemic Autoimmune Diseases, Volume 5
The Skin in Systemic Autoimmune Diseases
Piercarlo Sarzi-Puttini, Andrea Doria, Giampiero Girolomoni and Annegret Kuhn, editors

CHAPTER 23

New Trends in Topical and Systemic Immunosuppressive Treatment

Matthias Schneider[a,*], Rebecca Fischer-Betz[a], Kristina Gensch[b], Christof Iking-Konert[a], Annegret Kuhn[b]

[a]*Rheumatology, University of Düsseldorf, Düsseldorf, Germany*
[b]*Department of Dermatology, University of Düsseldorf, Düsseldorf, Germany*

Immunosuppressive treatment is a central element in managing patients with systemic autoimmune diseases. Up to now, mostly unspecific immunosuppressive agents are available, which helped to improve the survival and prognosis of e.g. systemic lupus erythematosus (SLE) continuously over the past decades. This is also caused by more sensitive detection of the diseases and their manifestations, diagnosis of milder cases, optimized use of known immunosuppressive drugs, and consequent treatment of disease consequences, such as hypertension. However, side effects of general immunosuppression limit their application and, therefore, nowadays infections are a major cause of death in severely ill patients suffering from autoimmune diseases. There is an urgent need for specific immunointervention and further therapeutic options, especially for patients in life-threatening situations and for non-responders to standard immunosuppression. However, until now, randomized controlled trials evaluating new drugs are missing and difficult to perform because autoimmune diseases are rare and heterogeneous.

A further important step in the future will be the identification of target organ specific therapy requiring an extremely careful evaluation of new drugs mandatory. It is well known, that, e.g. antimalarials, are effective in patients with joint and skin manifestations, but not with major organ involvements, whereas immunosuppressive agents, e.g. azathioprine and cyclophosphamide, are more helpful in treating nephritis and cerebritis. Furthermore, there is still need for alternative topical anti-inflammatory therapeutic modalities although newly developed immunomodulators have been shown to be active also in a topical formulation with enormous potential to change the way that skin lesions are treated and managed (Khandpur et al., 2004). Especially, calcineurin inhibitors, such as tacrolimus and pimecrolimus, are now emerging as the therapy of choice for several immune-mediated dermatoses and are currently under evaluation in patients with connective tissue diseases. In cases with extensive skin involvement, topical treatments offer an important addition to systemic therapy and concerning the side effects, topical agents show a clear advantage over systemic drugs because of their comparable efficacy, simpleness of application, and greater safety than their systemic counterparts.

1. Immunosuppressive agents licensed for other indications

Because there is desperate need for alternatives, traditional therapeutic concepts are expanding

*Corresponding author.
Matthias Schneider, Rheumatology, University of Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany.
Tel.: +49-211-8117817; Fax: +49-211-8116455.
E-mail address: schneider@rheumanet.org (M. Schneider).

DOI: 10.1016/S1571-5078(05)05023-3

mostly based on data received from case reports and small trials using systemic agents licensed for other indications, such as ciclosporin A, methotrexate, mycophenolate mofetil, and leflunomide.

1.1. Ciclosporin A

One of the first new immunosuppressive agents was ciclosporin (CSA), which is licensed and mostly used in organ transplantation. Although CSA has shown promising results in various diseases with disturbed immunoregulation, controlled studies in SLE are limited after nearly 20 years of experience. In open labelled trials, CSA is mostly well tolerated and reasons for discontinuation are side effects, such as hypertension, tremor, and nephrotoxicity. However, in lupus nephritis the antiprotein uric effect of CSA seems to be favourable, especially in type V nephritis. The largest and longest experience in lupus nephritis is documented by Dostal et al. (1998) reporting a clear reduction in proteinuria and disease activity with a complete remission in 5 of 11 patients of a group suffering mostly from nephrotic syndrome. The same authors presented data of response to CSA in patients with lupus nephritis refractory to cyclophosphamide and showed similar renal outcome comparing both drugs in an observational trial over 2 years.

In comparison with other immunosuppressive drugs used in SLE, CSA exhibits nearly no myelosuppressive effects, which may be a great advantage in special cases, e.g. leukopenia. However, the multiple interferences of CSA with further therapeutic agents have to be taken in mind before its application.

1.2. Calcineurin inhibitors

1.2.1. Tacrolimus (FK506)

Previously known under its experimental name, FK506, tacrolimus is a hydrophobic macrolide, which was extracted from the fermentation broth of *Streptomyces tsukuba*, a soil microbe found in Tsukuba, Japan. Initially, tacrolimus was administered to prevent graft rejection in a liver-transplant patient and is currently used both intravenously and orally as an immunosuppressive agent in many kinds of organ transplantations (Starzl et al., 1989; Wong et al., 2005). However, the experience with the systemic use of tacrolimus in autoimmune diseases is limited to some severe cases in which 'all other medications' have been tried unsuccessfully. In the 1990s, tacrolimus was also introduced as a topical agent producing favourable results in various skin disorders (Ruzicka et al., 1999). Meanwhile, safety and efficacy data of the topical formulation are available for more than 10 years from at least 20,000 cases worldwide (Assmann et al., 2001; Gupta et al., 2002). Tacrolimus ointment is generally well tolerated and all studies have shown a very good safety profile. The most common side effects are the sensation of skin burning and pruritus at the site of application, which are mostly of short duration and of mild or moderate severity. Sometimes, its application also leads to local erythema, skin infections, and, in rare cases, to flu-like symptoms and headache. In contrast to topical steroids, tacrolimus does not cause skin atrophy despite prolonged application (Cheer and Plosker, 2001). The cutaneous absorption of tacrolimus depends on the extent of the treated body surface and the skin barrier damage. Due to the low or even not detectable blood levels, there is only a very low risk of systemic toxicity. In Febuary 2005, the American Food and Drug Administration (FDA) advised physicians urging caution in prescribing tacrolimus and pimecrolimus because few cases of lymphoma have been reported in adults and children who were treated with one of these topical immunosuppressive agents (Luger and Gollnick, 2005). However, there were no recommendations from the FDA Advisory Committee that the appropriate use of topical calcineurin inhibitors should be discontinued.

Topical tacrolimus is licensed for the treatment of moderate and severe atopic eczema in children (0.03%) and adults (0.1%) and, more recently, it has also been applied to other inflammatory dermatoses such as contact dermatitis, erosive lichen ruber planus, steroid-induced rosacea, pyoderma gangrenosum, vitiligo, and psoriasis (Assmann and Ruzicka, 2002; Gupta et al., 2002; Nasr, 2000). In single case reports, topical tacrolimus has also been shown to be effective in treating cutaneous lupus erythematosus (CLE). According to

Lampropoulos et al. (2004) more than 50% of the 12 investigated patients mainly suffering from resistant lesions showed improvement after 6 weeks of treatment with tacrolimus 0.1% as monotherapy twice daily. Similar results for various subtypes of CLE have been reported by several other groups showing marked improvement especially for initial skin lesions within 4–8 weeks of application (Yoshimasu et al., 2002; Walker et al., 2002; Bacman et al., 2003; Böhm et al., 2003; Druke et al., 2004). Further studies also described that tacrolimus may be useful for treating the malar rash of patients with SLE (Kanekura et al., 2003). Actually, a phase II multicentre clinical trial is ongoing to analyse the efficacy of topical tacrolimus in patients with various cutaneous manifestations of this disease.

Treatment with topical tacrolimus of other connective tissue diseases is rarely mentioned in the literature. Recently, Hollar and Jorizzo (2004) reported some degree of improvement in all six investigated patients with dermatomyositis following 6–8 weeks of treatment with tacrolimus 0.1%. Yoshimasu et al. (2002) further demonstrated a therapeutic effect in three of four patients with facial lesions of dermatomyositis. In two patients with localized scleroderma, Mancuso and Berdondini (2003) described significant improvement of the skin lesions after using tacrolimus 0.1% under occlusion twice daily.

1.2.2. Pimecrolimus (ASM-981)

Pimecrolimus is an ascomycin macrolactam derivate and its clinical effects closely resemble those of tacrolimus differing in structure-related limitations of formulation (Bornhovd et al., 2001; Gisondi et al., 2005). In randomized controlled trials, topical pimecrolimus has shown to be effective, well tolerated and safe in both adults and children. Adverse effects include burning or stinging sensation at the site of application, which disappears after several days of application (Khandpur et al., 2004). Long-term risks of pimecrolimus still remain unclear; however, it does not produce skin atrophy or dermal thinning. Interestingly, in a long-term study, no clinical differences have been evaluated between the group receiving pimecrolimus and the group receiving placebo with respect to the incidence of common adverse events and skin infections (Kapp et al., 2002). As the foremost concern, pimecrolimus might also raise the risk of developing cancer, and, therefore, patients using topical pimecrolimus should limit their exposure to sunlight (Luger and Gollnick, 2005).

Pimecrolimus, 1% ointment, is licensed for mild to moderate atopic dermatitis (Van Leent et al., 1998; Luger et al., 2001) and has also shown efficacy in treating allergic contact dermatitis, seborrheic dermatitis, intertriginous psoriasis, and lichen planus (Queille-Roussel et al., 2000; Mrowietz et al., 1998; Gisondi et al., 2005). In patients with CLE, pimecrolimus seems to be an efficacious and safe option, although only few cases have been reported in the literature. Using a clinical score, Kreuter et al. (2004) measured skin lesions during a 3-week semiocclusive treatment with pimecrolimus and, in all 11 patients with CLE, a significant regression of the lesions was observed.

1.3. Methotrexate

Methotrexate is the most often used medication in patients with rheumatoid arthritis (RA). Because of its well-documented efficacy in joint symptoms, methotrexate is also applied to patients with non-organ threatening disease activity. The value of methotrexate in SLE was recently reviewed by Wong and Esdaile (2005) indicating some benefit in treating active skin and joint disease. Three controlled trials showed a reduction in steroid requirements, but only two studies could also document an improvement in the overall disease activity. One further study found some evidence that methotrexate is more efficacious in patients with no severe activity. However, a conclusive profile for an indication in patients with SLE is not obvious and the risk of accumulation in impaired kidney function and the associated risk of overdose have to be taken into consideration.

1.4. Leflunomide

Leflunomide, a pyrimidine synthesis inhibitor, is licensed for the treatment of RA. Because of its effects on T lymphocytes leflunomide might also succeed in SLE, but until now there are limited

data to support its effectiveness. In an open label trial, 9 of 14 patients with mild to moderate disease activity showed some improvement with the chance to reduce the dosage of steroids (Remer et al., 2001). The effect became obvious after 2–3 months and similar results were reported in other small pilot studies, e.g. from Erlangen, Vienna and Germany. Interestingly, Petri (2001) reported a complete response in 12 of 40 patients with SLE, but not any benefit in the rest of the group. In all studies, leflunomide was well tolerated without severe adverse events; however, there is one report on drug-induced SLE in a patient with Sjögren's syndrome (Gensburger et al., 2005).

1.5. Mycophenolate mofetil

Mycophenolate mofetil (MMF) was initially evaluated in RA and several years later also licensed for the treatment of organ transplantation. Because MMF inhibits specifically T- and B-lymphocyte proliferation by interfering with the inosine monophosphate dehydrogenase, it has emerged as an alternative in SLE mainly for patients refractory to other treatments. The growing interest on MMF in SLE is reflected by a supplement of the journal 'Lupus' to this drug (Hughes and D'Cruz, 2005).

In recent years, MMF is mostly described for the treatment of lupus nephritis. Chan et al. (2004) reported a comparable response to oral cyclophosphamide; however, long-term follow-up of the small number of patients indicated a high number of relapses. The still not fully published study comparing MMF with the protocol of the National Institute of Health by Ginzler et al. (2003) indicates a higher remission rate using MMF in type III–V lupus nephritis over 6 months. Unfortunately, follow-up data of this promising trial have not been taken into consideration, but such information would have been important to evaluate the long-term effect of MMF on the preservation of kidney function.

In a maintenance protocol, Contreras et al. (2004) showed in patients with type III and IV lupus nephritis that MMF is superior to cyclophosphamide in preventing renal relapses. These findings are supported by some other uncontrolled small trials; however, in comparison to azathioprine no superiority of MMF was observed. In a variety of other SLE manifestations, such as thrombocytopenia, autoimmune haemolytic anaemia, skin lesions, and uncontrolled disease activity, MMF has also been reported to be successful. Recently, the St. Thomas' group summarized the experiences in 86 patients with SLE using MMF in various indications (Pisoni et al., 2005) observing an overall reduction of disease activity, an increase in complement values, and a decrease in antibody titres. The limitations of MMF are the side effects, such as gastrointestinal intolerance accompanied by a haemorrhagic colitis in severe cases and, most frequently, infections, which occurred in nearly half of the patients. Actually, a phase III clinical trial is ongoing to analyse the efficacy of MMF in induction and maintenance therapy of lupus nephritis.

1.6. 15-deoxyspergualin

Deoxyspergualin (DSG) is a synthetic derivate of spergualin, originally isolated from Bacillus laterosporus, and licensed for reverse graft rejection in some countries. It is proven to be effective in animal models, such as experimental autoimmune encephalomyelitis and murine lupus. The precise mode of action is not known, but in vitro-studies indicate blocking of cell cycle progression in effector T cells following antigen stimulation and inhibition in the production of interferon gamma. Experiences in humans are limited and, in a few patients with primary vasculitis, DSG exhibited promising results. Actually, DSG is tested in a phase II/III trial in moderate SLE.

2. Anti-B cell therapy

Specific autoantibodies are the serological hallmark of SLE. Therefore, it is quite logic to address B lymphocytes, the precursors of immunoglobulin-producing plasma cells, in therapeutic intervention. In systemic autoimmune diseases, B cells are thought to play a major role, and animal models indicate that such diseases are blocked in mice deficient in B lymphocytes. Furthermore, B cells may

also be important in e.g. presenting autoantigens and promoting the breakdown of peripheral T-cell tolerance.

2.1. CD20

Numerous observations from single cases or small trials supporting the pathophysiologic idea by clinical successful applications have to be evaluated before therapeutic agents that are favourable in e.g. rheumatic diseases will be licensed for other indications. This is actually the situation with rituximab. Rituximab, a chimaeric anti-CD20 antibody, is approved in B-cell lymphomas and was documented to be safe in more than 300,000 treatments. CD20 is expressed on some B-cell types, both resting and activated mature B lymphocytes, but it is not expressed on plasma cells, which are thought to be the source of the possibly pathogenic autoantibodies. New data indicate that short-living plasmablasts bearing CD20 on their surface are responsible for increased antibody production in SLE flares. However, the role of this membrane-associated glycoprotein is unknown.

There are several case reports indicating the efficacy of rituximab in refractory autoimmune haemolytic anaemia, antiphospholipid-syndrome, and thrombocytopenia and central nervous system (CNS) involvement in SLE, nephrotic syndrome, and polymyositis. A first phase I/II by Looney et al. (2004) showed evidence that B-cell depletion is necessary for clinical efficacy of rituximab. Interestingly, immunoglobuline values and autoantibody titers remained in general unaffected and a reduction was observed in a few cases following the clinical response. Five out of 6 SLE patients with various disease manifestations responded in another open trial to treatment with steroids, cyclophosphamide, and rituximab (Leandro et al., 2002). The follow-up of the patients indicated that the clinical improvement was not limited to the period of B-lymphocyte depletion.

Further small studies showed remarkable response rates in about 70–80% of patients that were mostly selected because of a therapy-refractory disease activity. The safety profile was attractive in all reports. In a recent published trial, Sfikakis et al. (2005) focused the evaluation of anti-CD20 therapy to patients with type III and IV lupus nephritis. Using rituximab in combination with steroids, 8 out of 10 patients responded at least partially after 2 months (median). Analysis of lymphocyte subsets in these patients revealed a prompt and clear reduction of T-lymphocyte activation, reflected by a decrease of surface expression of CD40L, CD69, and HLA-DR on $CD4^+$ lymphocytes. These data suggest that B cells promote autoimmunity in humans by directly influencing T cells and are important in further understanding the pathophysiological process in SLE. The downregulation of CD40 and CD80 on B cells during treatment of SLE patients support this hypothesis (Tokunaga et al., 2005). Interestingly, Anolik et al. (2004) described that a specific B-cell depletion therapy with rituximab persistently improved abnormalities in B-cell homeostasis and tolerance. However, randomized controlled trials are urgently needed to confirm the excellent efficacy and safety profile of rituximab and to get the chance to offer this medication to the more severely ill patients with SLE.

2.2. CD22

Epratuzumab (hLL2) is a humanized monoclonal antibody that specifically binds to CD22 on B lymphocytes and leads to B-cell depletion. CD22 is an inhibitory coreceptor of the B-cell receptor, and there is some evidence that its ligation may regulate hyperactive B cells. Most experiences with epratuzumab evolved from treatment of B-cell non-Hodgkin lymphoma confirming that it is safe and well tolerated across a wide range of doses. Actually, a phase II/III clinical trial in SLE is ongoing.

2.3. B lymphocyte stimulator

B lymphocyte stimulator (BLyS) is a 285-amino acid member of the tumor necrosis factor (TNF) ligand superfamily, which stimulates B cells to develop in mature plasma B lymphocytes (Stohl, 2002). Studies indicate that increased levels of BLyS may contribute to the pathogenesis of autoimmune diseases, such as SLE, and a significant

correlation between BLyS levels and SLE activity has been observed. The therapeutic potential of LymphoStat-B^{TM}, a human monoclonal antibody that specifically inhibits the biological activity of BLyS, is currently evaluated in RA and SLE.

3. Costimulation

Isotype switching in antibody response and affinity maturation indicate a T-cell driven B-cell activation in SLE. Therefore, T-cell activation and interactions seem to be promising therapeutic targets in this disease. Unfortunately, the first attempt interfering with CD40L was disappointing: One antibody was without obvious efficacy and the clinical trials with the other antibody were stopped due to thrombo-embolic side effects in patients with SLE. However, at least the process of designing a further trial was an important step in the development of multicenter clinical trials for SLE in the future.

3.1. CTL4-Ig

Complete activation of T cells requires a CD28-mediated costimulatory signal. This signal is inhibited by abatacept, a fully human, recombinant, soluble fusion protein, which binds to B7-1 and B7-2 on antigen-presenting cells. This prevents downstream effects on B cells, macrophages, and synoviocytes. Abatacept was already used in some thousand patients exhibiting a good safety profile. In RA, phase II and III trials show an efficacy in clinical signs and symptoms and also in preventing structural damage. In summary, abatacept is well-tolerated and actually approved in this indication (Ruderman and Pope, 2005).

Furthermore, abatacept was successfully applied to various lupus mouse models resulting in an improvement of survival and proteinuria; however, data of patients with SLE are missing. A phase II trail is ongoing.

Another costimulatory molecule, CD137, was successfully blocked in murine lupus models, and anti-CD80 (anti-B7) showed a moderate effect in treating patients with psoriasis.

4. (Anti-) Cytokines

4.1. Tumor necrosis factor alpha

Tumor necrosis factor (TNF) alpha inhibitors are very successfully introduced as a therapy of RA, ankylosing spondylitis, and psoriatic arthritis. From these applications, it is well known that TNF alpha inhibition may lead to the formation of antinuclear and also anti-dsDNA antibodies, a finding that prevented the early use of these substances in SLE. Recently, in a retrospective national study few cases of disease induction were also published by De Bandt et al. (2005). However, after discontinuation of treatment systemic clinical manifestations abated within a few weeks in all patients except one with longer-lasting evolution (6 months).

Murine models indicate that TNF alpha might play a role in the release of immature B cells from bone marrow, in the decrease of regulatory T cells and might also participate in the inflammation of nephritis. Antagonizing these effects could be beneficial in SLE. Up to now, there is one pilot study published investigating the safety of therapeutic TNF alpha blockade in patients with SLE by Aringer et al. (2004). 4 doses of infliximab (300 mg) were given to 6 patients in addition to standard immunosuppression. The arthritis in three patients came to remission and the lupus nephritis in 4 patients improved by a reduced proteinuria, already after 1 week of treatment. Overall, infliximab did not lead to adverse events concerning disease activity, although autoantibody titers increased as expected. Controlled trials are needed to further evaluate the benefits and risks of TNF alpha blockade in SLE.

4.2. Interleukin 10

Interleukin 10 (IL-10) and interferon alpha are further candidates of therapeutic intervention in SLE. Whereas in MRL/MpJ-Tnfrsf6^{lpr} mice IL-10 can downregulate the disease through the inhibition of pathogenic Th1 cytokine responses (Yin et al., 2002), in humans the inhibition of IL-10 reverses the impaired antigen-presenting cell functions (Lauwers et al., 2000). This regime was already successfully applied to 6 patients using a murine

monoclonal antibody (B-N10) (Llorente et al., 2000). Joint and skin symptoms resolved, the overall disease activity decreased despite steroid dosage reduction, and antibody titers remained unchanged. Although no major side effects were reported, no follow-up study is published until now.

4.3. Interferon alpha

A link between interferon alpha (IFN alpha) and SLE was first evaluated by the induction of the disease during an IFN alpha therapy and the finding that many patients with SLE have increased serum concentrations of type I interferons. The main producers are plasmacytoid dendritic cells that are diminished in the circulation of SLE patients, but found in large numbers stimulated in e.g. skin lesions. The high concentrations of IFN alpha in the sera of patients with SLE were found to activate dendritic cells to trigger T cell-mediated autoimmunity and promote the differentiation of B cells into antibody-producing plasma cells (rev. by Colonna et al., 2004).

4.4. Interleukin 6

Interleukin 6 (IL-6) levels are elevated in human SLE and in murine models, and, blocking of IL-6 ameliorates the disease. From RA studies it is known that the inhibition of IL-6 with a humanized monoclonal antibody (MRA) is safe. Actually, IL-6 blockade is evaluated in moderately active SLE and a protocol with specific emphasis to the various subtypes of CLE is in the pipeline.

5. Hormone therapy

The immune system has been shown to be influenced by sex hormones. SLE predominantly occurs in women, tends to flare during pregnancy, and may be activated by hormone replacement in some cases. However, a recent randomized controlled trial could not confirm a general stimulation by oestrogen/gestagen intake (Buyon et al., 2005).

Several studies have noted alterations in oestrogen and androgen metabolism in SLE, e.g. in lupus mice, oestrogen antagonism showed a remarkable effect.

5.1. Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is an abundant adrenal hormone with only mild intrinsic androgenic activity, and supplementation in humans suggest overall good tolerance. Pilot studies indicated some benefit in moderate active SLE (Van Vollenhoven et al., 1994, 1995; Chang et al., 2002). Prasterone, oral DHEA, that suppresses IL-10 (Chang et al., 2004), was intensively evaluated in double-blind, randomized controlled trials. In patients with active SLE, administration of prasterone at a dosage of 200 mg/day improved or stabilized signs and symptoms of disease and was generally well tolerated (Petri et al., 2002, 2004). Mild acne and hirsutism and an increase in bone density were the expected side effects. However, the results were not sufficient for approving prasterone for the therapy of SLE by the FDA.

Another hormonal intervention that is already discussed for several years could be the blockade of prolactin, which is increased in 20% of the patients with SLE. The treatment with bromocriptine was recently reviewed by Walker (2001): Smaller studies indicate some benefit comparable to hydroxychloroquine in one trial, but the efficacy has to be evaluated in controlled trials with larger number of patients. The use in daily practice is mostly prohibited by side effects, such as nausea and headaches.

6. LE-specific immunomodulation

SLE is a disease of unknown etiology characterized by a number of immune abnormalities including the formation of diverse antibodies to a number of nuclear and other cellular antigens. The presence of anti-double-stranded (ds) DNA antibodies is virtually diagnostic of this disease and rarely occurs in other conditions (Emlen et al., 1990). High-avidity IgG autoantibodies to anti-dsDNA are seen mostly in patients with nephritis and may correspond with, or predict changes in, disease activity (Aarden et al., 1976; Swaak et al., 1979; Linnik et al., 2005).

These antibodies are believed to play a major role in the pathogenesis of SLE through the formation of immune complexes, which are not

handled properly and, instead, localize to organs such as the kidneys. This results in various degrees of cellular proliferation, inflammation, and fibrosis leading in some patients to renal failure. Numerous clinical studies have investigated anti-dsDNA antibodies and their relationship to flare and lupus nephritis.

Experiments in mice have confirmed the association between anti-DNA antibodies and lupus nephritis: Administration of these antibodies to non-autoimmune mice has been shown to produce nephritis, and transgenic mice expressing a secreted form of an anti-DNA antibody develop lupus nephritis.

6.1. LJP394

A further promising agent is LJP 394, a molecule shown to have high affinity to anti-DNA antibodies and to decrease anti-oligonucleotide antibody formation in mice through induction of B-cell tolerance. LJP 394 is composed of four deoxynucleotide sequences bound to a triethylene glycol backbone. Preliminary studies in humans demonstrated that i.v.-administration of LJP 394 was safe and a reduction of antibody titer was achieved (Furie et al., 2001).

Multicenter clinical trials with LJP 394 exhibited an efficacy on the rate of renal relapses in patients with high-affinity antibodies to its DNA epitope (Alarcón-Segovia et al., 2003). However, this hypothesis could not be confirmed in the following trial. The most significant finding with LJP 394 treatment was the improvement in health-related quality of life in patients with SLE.

6.2. Heteropolymer ETI-104

A heteropolymer (HP) system was developed to allow efficient removal of pathogens from the bloodstream through an immune adherence like mechanism (Lindorfer et al., 2001). Immune adherence is a physiological mechanism for the removal of immune complexes. When a foreign substance, an antigen, enters the bloodstream, the immune system develops antibodies that bind to it specifically. The resulting antigen–antibody complex activates the complement system resulting in the formation of the complement activation product C3b, which binds to the antibody–antigen complex. The resulting immune complex further binds to the complement receptor CR1 (C3b C4b receptor, CD35) on primate erythrocytes. The immune complex is then presented to fixed tissue macrophages in the liver, where it is destroyed, and the erythrocyte is returned to the circulation.

In order for heteropolymer technology to be successful in removing a target pathogen (in this case, autoantibodies to dsDNA), several steps have to be observed. ETI-104, an antigen-based heteropolymer, is a bi-specific molecule, one portion of the molecule binds to the CR1 receptor on RBCs and another portion of the immunoconjugate binds to the anti-dsDNA antibodies in patients. In a phase I/II trial, it could be shown that this agent rapidly binds to CR1 on RBCs of normal healthy volunteers and SLE patients, and at the same time, our group has demonstrated the rapid binding of the other portion of the molecule to dsDNA autoantibodies in SLE patients (Iking-Konert et al., 2004). Moreover, this binding results in a rapid substantial reduction in the level of Farr activity and total anti-dsDNA antibodies in the blood of the patients. However, the initial reduction (15 min) in Farr titer and total anti-dsDNA antibody was transient, with some patients having rebounds during the first 4 h after ETI-104 administration.

6.3. Anti id16/6-Peptides

A further form of specific immunomodulation in SLE is based on the finding that several pathogenic human anti-DNA antibodies bear the 16/6 idiotype (Id). The application of synthetic peptides of the complementary-determining regions of 16/6 Id in animal models was followed by reduced anti-DNA antibody titres and a less severe nephritis. Clinical trials evaluating the therapeutic value of tolerance induction by such peptides are in the pipeline.

7. Complement-inhibition

A hallmark of active SLE is complement activation and consumption. Whereas complement deficiency

in C1, C2, and C4 is known as a disposition to SLE, the activation of the complement cascade could participate in local inflammatory reactions in immune complex mediated disease, such as SLE. Therefore, the blocking of the inflammatory complement cascade might be a causal intervention. A fully humanized antibody against C5 was shown to be effective and safe in RA and paroxysmal nocturnal haemoglobinuria (Hillmen et al., 2004); however, it has not yet been approved in SLE.

8. Conclusion

The above-mentioned substances are just examples of new topical and systemic therapeutic options in the therapy of SLE and other systemic autoimmune diseases, which indicate the enormous development in this area. However, one important future step will be the initiation of optimized clinical trials, which need to take into account the heterogeneous expression of SLE and the lack of proven standardized therapy for specific organ manifestations, such as CNS and skin. Recently, the American College of Rheumatism (ACR) developed standardized response criteria to measure the overall disease activity in SLE (Liang et al., 2004) providing a common basis for comparing treatment options, permitting more diverse patients to be studied and to be compared statistically, and facilitating qualitative and quantitative (meta-analysis) synthesis of different clinical trials. Similar instruments have to be developed for other systemic autoimmune disease to answer the important question, does a substance work or not?

Key points

- There are several new substances in the pipeline, which target various steps in immunostimulation that may be pathophysiologically important in systemic autoimmune diseases. Some of the new, more unspecific immunosuppressive drugs, such as mycophenolate mofetile and deoxy-spergualine, are actually evaluated in clinical trials. Further agents, such as ciclosporin A or tacrolimus could also be of some important value in patients with SLE; however, adequate trials are missing.
- Antibodies against cell surface receptors of B and T lymphocytes and adhesion and activation molecules, which interfere with cellular activation in immune response, are increasingly tested in studies with SLE patients, some with advantage proven to be safe in further indications, such as psoriasis or malignancies. Future developments that try to correct the altered programmed cell death (apoptosis) in SLE are still tested in animals. As in rheumatoid arthritis, other new drugs, e.g. IL-10 antibodies, are focused on the re-balancing of the cytokine network, which is important for cell–cell communication and inflammatory response. The inhibition of activated complement factors that are important of local inflammation might be another target in the future.

Acknowledgements

This work was supported by a Heisenberg professorship from the German Research Association (DFG) to A.K. (KU 1559/1-1).

References

Aarden, L.A., Lakmaker, F., Feltkamp, T.E.W. 1976. Immunology of DNA. II. The effect of size and structure of the antigen on the Farr assay. J. Immunol. Meth. 10, 39.

Alarcón-Segovia, D., Tumlin, J.A., Furie, R.A., et al. 2003. The LJP Investigator Consortium. LJP 394 for the prevention of renal flares in patients with systemic lupus erythematosus. Results from a randomised, double-blind, placebo-controlled study. Arthritis Rheum. 48, 442.

Anolik, J.H., Barnard, J., Cappione, A., et al. 2004. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. Arthritis Rheum. 50, 3580.

Aringer, M., Graninger, W., Steiner, G., et al. 2004. Safety and efficacy of tumor necrosis factor alpha blockade in systemic lupus erythematosus. Arthritis Rheum. 50, 3161.

Assmann, T., Homey, B., Ruzicka, T. 2001. Topical tacrolimus for the treatment of inflammatory skin diseases. Expert Opin. Pharmacother. 2, 1167.

Assmann, T., Ruzicka, T. 2002. New immunosuppressive drugs in dermatology (Mycophenolate Mofetil, Tacrolimus): unapproved uses dosages, or indication. Clin. Derm. 20, 505.

Bacman, D., Tanbajewa, A., Megahed, M., et al. 2003. Topical treatment with tacrolimus in lupus erythematosus tumidus. Hautarzt. 54, 977.

Böhm, M., Gaubitz, M., Luger, T.A., et al. 2003. Topical tacrolimus as a therapeutic adjunct in patients with cutaneous lupus erythematosus. Dermatology 207, 381.

Bornhovd, E., Burgdorf, W.H., Wollenberg, A. 2001. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. J. Am. Acad. Dermatol. 45, 736.

Buyon, J.P., Petri, M.A., Kim, M.Y., et al. 2005. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomised trial. Ann. Intern. Med. 142, 953.

Chan, T.M., Li, F.K., Tang, C.S., et al. 2004. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N. Engl. J. Med. 350, 971.

Chang, D.M., Chu, S.J., Chen, H.C., et al. 2004. Dehydroepiandrosterone suppresses interleukin 10 synthesis in women with systemic lupus erythematosus. Ann. Rheum. Dis. 63, 1623.

Chang, D.M., Lan, J.-L., Lin, H.-Y., Luo, S.-F. 2002. Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus. Arthritis Rheum. 46, 2924.

Cheer, S.M., Plosker, G.L. 2001. Tacrolimus Ointment: a review of its therapeutic potential as a topical therapy in atopic dermatitis. Am. J. Clin. Dermatol. 2, 1.

Colonna, M., Trinchieri, G., Liu, Y.-J. 2004. Plasmacytoid dendritic cells in immunity. Nat. Immunol. 5, 1219.

Contreras, G., Pardo, V., Leclercq, B., et al. 2004. Sequential therapies for proliferative lupus nephritis. N. Engl. J. Med. 350, 971.

De Bandt, M., Sibilia, J., Le Loet, X., et al. 2005. Systemic lupus erythematosus induced by anti-tumor necrosis factor alpha therapy, a French national survey. Arthritis Res. Ther. 7, R545.

Dostal, C., Tesal, V., Rychlik, I., et al. 1998. Effect of 1 year ciclosporine A treatment on the activity and renal involvement of systemic lupus erythematosus, a pilot study. Lupus 7, 29.

Druke, A., Gambichler, T., Altmeyer, P., et al. 2004. 1% Tacrolimus ointment in a patient with subacute cutaneous lupus erythematosus. J. Dermatol. Treat. 15, 63.

Emlen, W., Jarusiripipat, P., Burdick, G. 1990. A new ELISA for the detection of double-stranded DNA antibodies. J. Immunol. Meth. 132, 91.

Furie, R.A., Cash, J.M., Cronin, M.E., et al. 2001. Treatment of systemic lupus erythematosus with LJP 394. J. Rheumatol. 28, 257.

Gensburger, D., Kawashima, M., Marotte, H., et al. 2005. Lupus erythematosus with leflunomide, induction or reactivation?. Ann. Rheum. Dis. 64, 153.

Ginzler, E.M., Buyon, J., Dooley, M.A., et al. 2003. A multicenter study of mycophenolate mofetil vs. intravenous cyclophosphamide as induction therapy for severe lupus nephritis, preliminary results. Arthritis Rheum. 49, S647.

Gisondi, P., Ellis, N.C., Girolomoni, G. 2005. Pimecrolimus in dermatology: atopic dermatitis and beyond. Int. J. Clin. Pract. 59, 969.

Gupta, A.K., Adamiak, A., Chow, M. 2002. Tacrolimus: a review of its use for the management of dermatoses. JEADV 16, 100.

Hillmen, P., Hall, C., Marsh, J.C.W., et al. 2004. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med. 350, 552.

Hollar, C.B., Jorizzo, J.L. 2004. Topical tacrolimus 0. 1% ointment for refractory skin disease in dermatomyositis: a pilot study. J. Dermatol. Treat. 15, 35.

Hughes, G.R.V., D'Cruz, D. (Eds.), 2005. Supplement issue mycophenolate mofetil, an advance in the therapy of autoimmune disease. Lupus 14, S1.
The recent advance of mycophenolate mofetil in autoimmune disease is reflected in this review.

Iking-Konert, C., Stocks, S., Weinsberg, F., et al. 2004. First clinical trials of a new heteropolymer technology agent in healthy volunteers and patients with systemic lupus erythematosus: safety and proof of principle of the antigen-heteropolymer ETI-104. Ann. Rheum. Dis. 63, 1104.

Kanekura, T., Yoshii, N., Terasaki, K., et al. 2003. Efficacy of topical tacrolimus for treating the malar rash of systemic lupus erythematosus. Br. J. Dermatol. 148, 353.

Kapp, A., Papp, K., Bingham, A., et al. 2002. Flare Reduction in Eczema with Elidel (infants) multicenter investigator study group. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J. Allergy Clin. Immunol. 110, 277.

Khandpur, S., Sharma, V.K., Sumanth, K. 2004. Topical immunomodulators in dermatology. J. Postgrad. Med. 50, 131.
In this article, the mechanism of action, common indications and most common side effects of topical immunomodulators are summarized.

Kreuter, A., Gambichler, T., Breuckmann, F., et al. 2004. Pimecrolimus 1% cream for cutaneous lupus erythematosus. J. Am. Acad. Dermatol. 51, 407.

Lampropoulos, C.E., Sangle, S., Harrison, P., et al. 2004. Topical tacrolimus therapy of resistant cutaneous lesions in Lupus erythematosus: a possible alternative. Rheumatology 43, 1383.

Lauwers, B.R., Garot, N., Renauld, J.-C., et al. 2000. Interleukin-10 blockade corrects impaired in vitro cellular immune responses of systemic lupus erythematosus patient. Arthritis Rheum. 43, 1976.

Leandro, M.J., Edwards, J.C., Canbridge, G., et al. 2002. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 46, 2673.

Leent, E.J., Graber, M., Thurston, M., et al. 1998. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. Arch. Dermatol. 134, 805.

Liang, M.H., Fortin, P., Schneider, M., et al. 2004. The American College of Rheumatology response criteria for systemic lupus erythematosus. Arthritis Rheum. 50, 3418.

ACR developed standardized response criteria are reported and evaluated for the measurement of overall disease activity in SLE.

Lindorfer, M.A., Hahn, C.S., Foley, P.L., et al. 2001. Heteropolymer-mediated clearance of immune complexes via erythrocyte CR1, mechanisms and applications. Immunol. Rev. 183, 10.

Linnik, M.D., Hu, J.Z., Heilbrunn, K.R., et al. 2005. Relationship between anti-double-stranded DNA antibodies and exacerbation of renal disease in patients with systemic lupus erythematosus. Arthritis Rheum. 52, 1129.

Llorente, L., Richaud-Patin, Y., Garcia-Padilla, C., et al. 2000. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis Rheum. 43, 1790.

Looney, R.J., Anolik, J.H., Campbell, D., et al. 2004. B cell depletion as a novel treatment for systemic lupus erythematosus, a phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 50, 2580.

Luger, T.A., Gollnick, H. 2005. Viewpoint of the German Dermatologic Society (DDG) concerning the decision of the American Food and Drug Administration (FDA) on the use of pimecrolimus cream and tacrolimus ointment in the treatment of atopic dermatitis (neurodermatitis). J. Dtsch. Dermatol. Ges. 3, 415.

Luger, T.A., Van Leent, E.J., Graeber, M., et al. 2001. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. Br. J. Dermatol. 144, 788.

Mancuso, G., Berdondini, R.M. 2003. Topical tacrolimus in the treatment of localized scleroderma. Eur. J. Dermatol. 13, 590.

Mrowietz, U., Graeber, M., Bräutigam, M., et al. 1998. The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. Br. J. Dermatol. 139, 992.

Nasr, I.S. 2000. Topical tacrolimus in dermatology. Clin. Exp. Dermatol. 25, 250.

Petri, M. 2001. High dose Arava in lupus. Arthritis Rheum. 44, S280.

Petri, M.A., Lahita, R.G., van Vollenhoven, R.F., et al. 2002. Effects of prasterone on corticoid requirements of women with systemic lupus erythematosus. Arthritis Rheum. 46, 1820.

Petri, M.A., Mease, P.J., Merrill, J.T., et al. 2004. Effects of prasterone on disease activity and symptoms in women with systemic lupus erythematosus. Arthritis Rheum. 50, 2858.

Pisoni, C.N., Sanchez, F.J., Karim, Y., et al. 2005. Mycophenolate mofetil in systemic lupus erythematosus, efficacy and tolerability in 86 patients. J. Rheum. 32, 1047.

Queille-Roussel, C., Graeber, M., Thursten, M., et al. 2000. SDZ ASM 981 is the first non-steroid that suppresses established nickel contact dermatitis elicited by allergen challenge. Contact Dermatitis. 42, 349.

Remer, C.F., Weisman, M.H., Wallace, D.J. 2001. Benefits of leflunomide in systemic lupus erythematosus, a pilot observational study. Lupus 10, 480.

Ruderman, E.M., Pope, R.M. 2005. The evolving clinical profile of abatacept (CTLA4-19) a novel costimulatory modulator for the treatment of rheumatoid arthritis. Arthritis Res. Ther. 7, 521.

Ruzicka, T., Assmann, T., Homey, B. 1999. Tacrolimus: the drug for the turn of the millennium?. Arch. Dermatol. 135, 574.

Sfikakis, P.P., Boletis, J.N., Lionaki, S., et al. 2005. Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the costimulatory molecule CD40 ligand. Arthritis Rheum. 52, 501.

Starzl, T.E., Todo, S., Fung, J., et al. 1989. FK 506 for liver, kidney, and pancreas transplantation. Lancet 28, 1000.

Stohl, W. 2002. Systemic lupus erythematosus, a blissless disease of too much BlyS protein. Curr. Opin. Rheum. 14, 522.

Swaak, A.J.G., Aarden, L.A., Statius, VanEps, L.W., et al. 1979. Anti-dsDNA and complement profiles as prognostic guides in systemic lupus erythematosus. Arthritis Rheum. 22, 226.

Tokunaga, M., Fujii, K., Saito, K., et al. 2005. Down-regulation of CD40 and CD80 on B cells in patients with life-threatening systemic lupus erythematosus after successful treatment with rituximab. Rheumatology 44, 176.

Van Vollenhoven, R.F., Engleman, E.G., McGuire, J.L. 1994. An open study dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum. 37, 1305.

Van Vollenhoven, R.F., Engleman, E.G., McGuire, J.L. 1995. Dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum. 38, 1826.

Walker, S.E. 2001. Bromocriptine treatment of systemic lupus erythematosus. Lupus 10, 762.

Walker, S.L., Kirby, B., Chalmers, R.J. 2002. The effect of topical tacrolimus on severe recalcitrant chronic disoid lupus erythematosus. Br. J. Dermatol. 147, 405.

Wong, J.M., Esdaile, J.M. 2005. Methotrexate in systemic lupus erythematosus. Lupus 14, 101.

Wong, W., Venetz, J.P., Tolkoff-Rubin, N., et al. 2005. Immunosuppressive strategies in kidney transplantation: which role for the calcineurin inhibitors?. Transplantation 80, 289.

Yin, Z., Bahtiyar, G., Zhang, N., et al. 2002. IL-10 regulates murine lupus. J. Immunol. 169, 2148.

Yoshimasu, T., Ohtani, T., Sakamoto, T., et al. 2002. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. Eur. J. Dermatol. 12, 50.

This page intentionally left blank

Index