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Radhika Tandon
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Manotosh Ray *Editors*

Peripheral Ulcerative Keratitis

A Comprehensive Guide

Springer

Essentials in Ophthalmology

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ISSN 1612-3212 ISSN 2196-890X (electronic)
Essentials in Ophthalmology
ISBN 978-3-319-50402-5 ISBN 978-3-319-50404-9 (eBook)
DOI 10.1007/978-3-319-50404-9

Library of Congress Control Number: 2016960309

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This textbook, Peripheral Ulcerative Keratitis, came about in 2014, when the topic was covered in the Cornea Subspecialty Day at the AAO meeting in Chicago and we realized that this was a clinical area that required an updated textbook of its own. Though not that common, the disease is of sufficient importance to merit special attention by virtue of it being sight threatening and a complex disorder with an interplay of systemic and local pathologies and advances in therapeutic strategies that should be highlighted.

The book has a galaxy of contributing authors who are all clinical luminaries in the field and were kind enough to join the journey of reposing their knowledge in the form of a book. The book has been designed to serve as a simple practical guide to understanding the disease in a basic and clinical sense with a view to help both general ophthalmologists and cornea specialists have a ready reference at hand to guide their clinical practice in dealing with such patients. In addition, ophthalmology residents and cornea fellows would find it useful to read as valuable study material to build their basic knowledge and enhance clinical skills.

The chapters deal with different aspects of the illness and all facets of diagnosis and management are well represented in the different sections. The text has been supplemented with useful references and the appendices provide a useful guide by simple step-by-step algorithms which are easy to comprehend and follow. Both medical and surgical treatment options are mentioned and the approach to management is covered in a style which is comprehensive and easy to understand.

The erudite authors are from different corners of the globe and we are most grateful that they were very forthcoming in their contributions and helpful with adherence to timelines. We are indeed indebted to them for the excellent contributions they have made in providing their expertise for this venture. The textbook is supported by illustrative examples and figures to enable the reader to apply the information gained in a practical and effective manner.

It has been an honor and privilege to work on this project with all the contributors and the team from Springer. We would like to acknowledge the aid provided by Rebecca and Tracy from Springer in coordinating the editorial efforts and that of Dr. Arun D. Singh in overall conception and design of the book.

We trust that libraries will take this volume to be a valuable asset on their bookshelves and the readers will find this compendium a useful addition to their personal collection and carry useful take home messages every time they go through it. We hope you enjoy absorbing the contents provided as much as we did in compiling all the information within the confines of the covers and wish you success in handling patients you may encounter from time to time.

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Part I
Basics

Anatomical Considerations

1

Saranya Devi, Anin Sethi, Noopur Gupta, Seema Sen and M. Vanathi

Introduction

Cornea is a transparent area which makes one-sixth of the outer circumference of the eye. **At the periphery is a transition zone 1–1.5 mm**, **limbus where corneal stroma is bonded to the sclera**. The adult cornea is 10.5 mm vertically and 11.5 mm horizontally. The anterior and posterior surfaces are parallel to each other in the central 4 mm spherical-shaped "optical zone" where the cornea averages 0.52 mm in thickness. **The peripheral cornea is slightly flattened**, **anterior and posterior surfaces are no longer parallel and corneal thickness increases to 0.65 mm**. Even though central cornea is responsible for the formation of sharp retinal image as it lies in the visual axis, studies have proven that peripheral cornea also has significant role in affecting the optical quality of the image formed [1].

Anatomy

The central cornea is divided into five distinct layers proceeding from without inwards: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The peripheral cornea requires specific mention as its anatomy and microscopic appearance differ from the remaining cornea.

The corneal epithelium is stratified squamous consisting of five or six layers of cells. **Towards the periphery**, epithelial cells are concentrated where these cells undergo proliferation [2, 3] **and the number of cells increases to 8–10** in the periphery. This explains the role of limbal vasculature in healing after surgery. The deepest or basal layer rests directly on the Bowman's membrane as a single layer of polygonal cells with flat bases and round heads. These cells are considerably large with pale-staining cytoplasm and oval nucleus lying perpendicular to the corneal surface. The thin basement membrane (480 Å) is seen on periodic acid-Schiff (PAS) stain. The basement membrane is composed of type IV collagen, proteoglycans, fibronectin, and laminin. Ultrastructurally hemidesmosomes are seen to lie along the attachment of the basal cell layer to its basement

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_1

membrane. The posterior portion of the basement membrane blends with the Bowman's layer. Various membrane associated mucins, which are important components of the tear film, as MUC 1 and 16, are found to be dispersed throughout the peripheral cornea. Also MUC 4 is found in higher levels at the peripheral region [4] which is associated with the serum albumin in the surrounding capillaries. This differential expression of the mucins affects the clinical manifestations of those with dry eye disease.

The Bowman's layer is 8–14 μm acellular structure that merges with the superficial stromal lamellae to which it is firmly attached. Bowman's layer is composed of type V collagen. Numerous pores in the inner portion provide passage for terminal branches of the corneal nerve. The peripheral margins of the Bowman's layer demarcate the anterior boundary of the limbus.

The stroma forms 90% of the corneal thickness. It is avascular and consists of collagenous lamellae interspersed with keratocytes and ground substance. The collagen fibrils are parallel to one another and to the surface. Majority of the stroma has type I collagen. The keratocytes in between the lamellae are like flattened and compressed fibroblasts. Stroma in the peripheral cornea forms a transition zone between cornea and sclera. Collagen fibers are loosely arranged in this area [5, 6]. The nutritional supply to this area is derived from the capillaries at the periphery of cornea [7]. Diffusion of various molecules occurs from these capillaries to the peripheral cornea resulting in higher concentration of serum albumin in the periphery which later diffuses to the central cornea [8]. This limited diffusion results in higher concentration of Langerhans cells, IgM and complement factor C1 [9]. Because of its proximity to the conjunctival tissue; peripheral cornea has access to the lymphatics and to both afferent and efferent arms of the immune system [10, 11].

The Descemet's membrane lies on the posterior aspect of the stroma. It is a true basement membrane formed by corneal endothelial cells. It contains type IV collagen. At the periphery Descemet's membrane terminates at the junction between trabecular and corneal endothelium. Descemet's membrane is acellular, faintly eosinophilic, and PAS positive. It is 3–4 μm at birth and 10–124 μm at 50 years.

The endothelium is a single layer of polygonal cells extending over the inner surface of Descemet's membrane. The cells appear rectangular with pale-staining granular cytoplasm and centrally located nucleus. This layer is derived from the neural crest. Unlike the epithelium it hardly undergoes mitotic division in normal eye. Corneal endothelial cells have maximum mitogenic activity in the peripheral area [3]. These cells might migrate towards the center to facilitate the healing after any damage [12].

These anatomical and physiological characteristics of the peripheral cornea make it vulnerable to various diseases such as:

(i) local infectious diseases or hypersensitivity reactions
(ii) systemic reactions such as vasculitides, autoimmune diseases, and metabolic disorders or
(iii) noninflammatory peripheral degenerations [11, 13, 14].

Limbus proper

Limbus is the peripheral area, 1 mm wide which forms a transition between the transparent cornea and conjunctiva/opaque sclera. Although it is transparent like the cornea, it is rich in blood vessels and nerve endings like the conjunctiva. It is further divided into anatomical, histological, and surgical limbus [15]. **Anatomical limbus** is formed by the junction of the conjunctival and corneal epithelia where multipotential limbal stem cells undergo differentiation [16]. Histologic limbus is defined as the junction of cornea and sclera documented in histological cross-sectional views. The microscopic anatomy of the limbus is depicted in Fig. 1.1.

The limbus is composed of only two layers namely the epithelium and the stroma, because

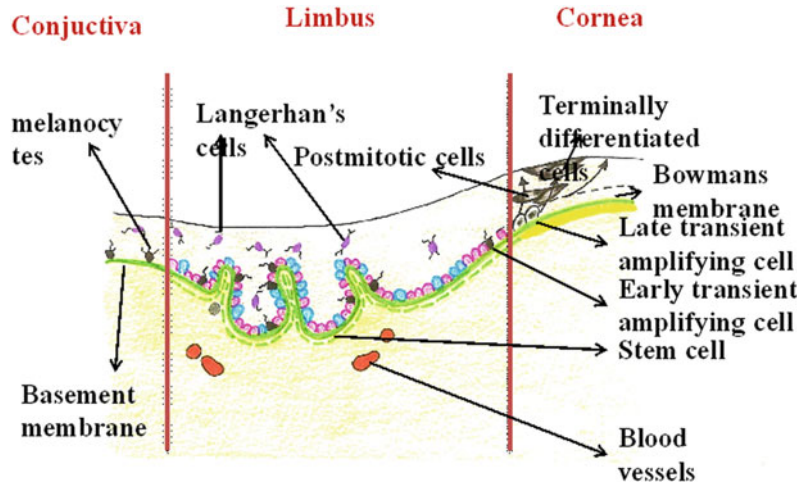

Fig. 1.1 Anatomy of the limbus

the Bowman's membrane stops abruptly and Descemet's membrane merges into the meshwork at the angle. **The epithelium is still stratified squamous but has 10 or more layers with the basal layer cells being smaller**, **more closely packed with scant cytoplasm**. The stroma loses its regular arrangement and becomes normal connective tissue with numerous blood vessels which are anastomosing branches of the anterior ciliary artery that terminate in the loops of the marginal plexus and then drain back into conjunctival venules. The limbus consists of stem cells which undergo slow cycling and are capable to undergo proliferation and differentiation. Each stem cell divides into a daughter stem cell and transient amplifying cell. These transient amplifying cells lie in the basal layer where they further divide to produce post-mitotic cells. These post-mitotic cells undergo further differentiation to produce terminally differentiated cells. These cells reach the superficial layers where continuous sloughing of the epithelium occurs.

Although both cornea and sclera consist of collagen fibers, corneal collagen is relatively less eosinophilic and is regularly arranged contributing to its transparency. These corneal collagen fibers are 600 Å in diameter whereas scleral fibers are 700–1000 Å in diameter. Scleral fibers are more branched and extend anteriorly on the external surface further than on the internal surface of the corneoscleral junction. This diagonal arrangement of the interface relates to the appearance of surgical limbus and is associated with the structures of the anterior chamber angle.

Clinically, the **surgical limbus** (Fig. 1.2) is appreciated as the blue-gray transition zone appearing after reflecting the conjunctiva away from the limbus. The classical blue-gray appearance of this zone results from the scattering of light through the oblique interface between the cornea and sclera. Surgical limbus is approximately

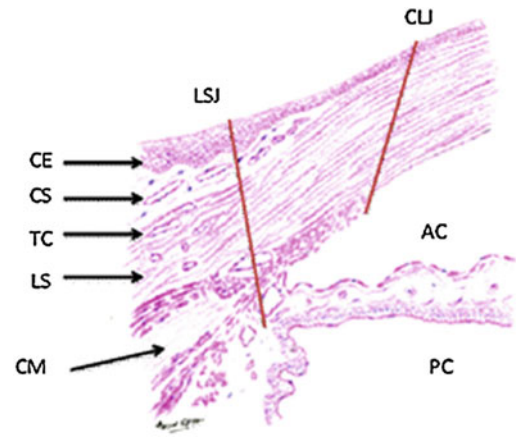

Fig. 1.2 Histological section showing the limbus. *CE* Conjunctival Epiethelium; *CS* Conjunctival Stroma; *TC* Tenons Capsule; *LS* Limbal Stroma; *CM* Ciliary Muscle; *LSJ* Limoscleral Junction; *CLJ* Corneolimbal Junction; *AC* Anterior Chamber; *PC* Posterior Chamber

1.2 mm wide but is narrower in the horizontal meridian owing to less obliquity of this diagonal interface in the horizontal meridian. The posterior border of this blue zone corresponds to the location of trabecular well. The posterior border of this blue zone corresponds to the location of trabecular meshwork internally. Thus surgical incisions located anterior to this blue zone would enter well away from the trabecular meshwork [17].

On advancing towards the cornea, another well-delineated white line is noticed which corresponds to the location of scleral spur internally. After crossing this region, tissue appears grayish corresponding to the location of Schwalbe's line. The limbus contains the aqueous outflow pathway system consisting of:

(i) trabecular meshwork,
(ii) Schlemm's canal and
(iii) aqueous collector channels.

The ***trabecular meshwork*** consists of three components (Fig. 1.3). The *uveal meshwork* is the innermost part extending from uveal tissue to trabeculum and the contribution of this part of the meshwork to the outflow resistance is very minimal. Next is the *middle trabecular component* which consists of fenestrated collagen bundles. This part of the extracellular matrix undergoes phagocytic activity under the influence of appropriate stimulus [18, 19]. The *juxtacanalicular meshwork* lies adjacent to the Schlemm's canal and consists of loosely arranged connective tissue.

The ***canal of Schlemm*** is single layer of endothelial-lined channel which plays a major role in the collection of aqueous humor. It is located in the groove formed by internal sclera sulcus which is sandwiched between the scleral spur posteriorly and by the sclera collagen fibers superiorly. Aqueous from the Schlemm's canal is drained externally by the aqueous collector channels. These collector channels in turn join the intrascleral and episcleral veins [20].

Vascular supply

Limbal vessels supply peripheral cornea, conjunctiva, episclera, limbal sclera, and peripheral uvea. The limbal vessels receive arterial supply from the anterior ciliary arteries [21]. Arterioles from these arteries supply the peripheral cornea and some of the terminal arterioles reach the Palisades of Vogt. The venules from the peripheral cornea drain into the orbital veins along with the venules from episclera. The deep scleral plexus and the intrascleral plexus drain into the episcleral veins. The aqueous collector channels may drain directly into the deep scleral vein or alternatively pass through the sclera into the aqueous vein [22].

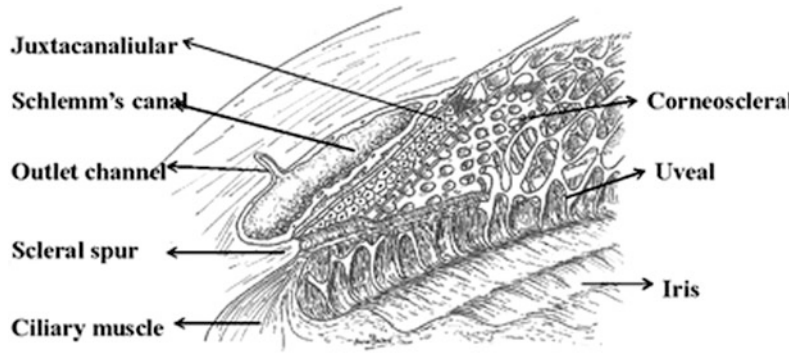

Fig. 1.3 Anatomy of the trabecular meshwork components

Nerve supply

Cornea possesses rich innervation by both sensory and autonomic nerve fibers [5, 23]. The sensory supply is from the ophthalmic division of the trigeminal nerve [24–30] while autonomic supply is derived from sympathetic fibers from superior cervical ganglion [31] and the parasympathetic fibers from the ciliary ganglion [32–34].

The ophthalmic division of the trigeminal nerve divides into nasociliary nerve and ciliary nerves which are its terminal branches. These ciliary nerves enter the peripheral cornea as radially arranged bundles forming the limbal plexus which supplies the peripheral cornea [35]. Nerve trunks from the limbal plexus enter the corneal stroma forming the anterior stromal nerves which are approximately 60–80 in number [2]. Then, they repeatedly branch to form the anterior stromal plexus. The superficial layer of the anterior stromal plexus is located just beneath the Bowman's membrane and it forms the sub-epithelial plexus (Fig. 1.4) by repeated arborization of the nerve fibers. There are a few more fibers which pass over these stromal bundles to supply the peripheral cornea. The sub-basal plexus is formed by about 5000–7000 fascicles [36]. The fibers from this plexus repeatedly branch to end up in a spiral pattern. The center of this pattern is called "vortex" which is about 2–3 mm inferior and nasal to the apex of the cornea. Most of the sub-basal nerves ascend vertically to reach the epithelium forming the intraepithelial nerve terminals.

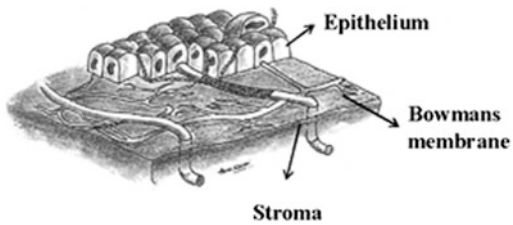

Fig. 1.4 Sub-basal nerve plexus

Palisades of Vogt

The limbal palisades were first described in 1914 [37] and Vogt gave the term "palisades" to this anatomical entity in 1921 [37, 38]. These are fibrovascular ridges located commonly in the superior and inferior corneoscleral limbus. The palisades harbor the limbal stem cells and thus can be identified as an indicator of health of the stem cells in normal population [39–43].

The palisades may be of (i) standard pattern, (ii) exaggerated pattern, or (iii) attenuated pattern [44]. In standard pattern, the palisades appear as thin cylindrical ridges with fairly uniform spacing and with little or no pigmentation. In the exaggerated pattern, the ridges are broader, highly pigmented, and show evidence of trabeculations whereas in the attenuated pattern, the ridges would be thinner and finer. Between the connective tissue of the palisades, there are zones of thickened epithelium called inter-palisades. Visualization of palisades has been studied extensively by various methods such as in vivo confocal microscopy [45] and even with optical coherence tomography [46].

Conclusions

The anatomy of the peripheral cornea owing to its special anatomical and physiological characteristics makes it more prone to local infectious diseases, hypersensitivity reactions, autoimmune processes, metabolic disorders, and noninflammatory peripheral degenerations.

Table 1.1 summarizes the major anatomical and physiological differences between the central and the peripheral cornea.

Compliance with Ethical Requirements Saranya Devi, Anin Sethi, Noopur Gupta, Seema Sen, and M. Vanathi declare that they have no conflict of interest. No human or animal studies were performed by the authors for this chapter.

Table 1.1 Differences between central and peripheral cornea

Central cornea	Peripheral cornea
• 0.5 mm thick	• 1 mm thick
• Epithelium is less tightly adherent to the basement membrane and stroma [12]	• Epithelium is tightly adherent to the underlying basement membrane and stroma [12]
• The epithelial stem cells are less in number in central cornea [2, 3]	• The epithelial stem cells are highly concentrated in the peripheral cornea [2, 3]
• Proliferation rate of epithelial cells is less in the central cornea [3]	• Proliferation rate of epithelial cells is highest in the peripheral cornea [3]
• Collagen fibers are arranged in a well-organized manner [5, 6]	• Collagen fibers are loosely arranged here [5, 6]
• Endothelial cells are non-mitogenic in the central cornea [3]	• Endothelial cells have maximum mitogenic activity in the peripheral cornea [3]
• Nutrition of the central cornea is derived from tear film and aqueous [7]	• Nutrition of the peripheral cornea is derived from the peri-limbal capillaries [7]
• MUC 1 and MUC 16 are diffusely distributed throughout the central cornea	• MUC 1 and MUC 16 are diffusely distributed throughout the peripheral cornea also
• Level of MUC 4 is lower in the central cornea [4]	• Levels of MUC 4 are considerably higher in the peripheral cornea [4]
• Central cornea has almost no access to blood and lymphatic supply [10, 11]	• Peripheral cornea has access to blood and lymphatic supply [10, 11]
• Central cornea is highly innervated and sensitivity is higher in this region [2]	• Peripheral cornea has less innervations and sensitivity is lower in this region [2]

References

1. Miller D, Atebara N, Stegmann R. The optical quality of the peripheral cornea. Acta Ophthalmol. 1989;67:165–70.
2. Muller L, Vrensen GF, Pels L, Cardozo BN, Willekens B. Architecture of human corneal nerves. Invest Ophthalmol Vis Sci. 1997;38(5):985–94.
3. Muller L, Pels E, Schurmans LR, Vrensen GF. A new three-dimensional model of the organization of proteoglycans and collagen fibrils in the human corneal stroma. Exp Eye Res. 2004;78:493–501.
4. Gipson IK, Hori Y, Argueso P. Character of ocular surface mucins and their alteration in dry eye disease. The Ocular Surface. 2004;2(2):131–45.
5. Lavker R, Dong G, Cheng SZ, Kudoh K, Cotarelis G, et al. Relative proliferation rates of limbal and corneal epithelia. Invest Ophthalmol Vis Sci. 1991;32(6):1864–75.
6. Cotsarelis G, Cheng S, Dong G, Sun TT, Lavker RM. Existence of slow-cycling limbal epithelial basal cells that can be preferentially stimulated to proliferate: implications on epithelial stem cells. Cell. 1989;57:201–9.
7. Freeman RD. Oxygen consumption by the component layers of the cornea. J Physiol Opt. 1972;225:15–32.
8. Maurice DM, Watson PG. The distribution and movement of serum albumin in the cornea. Exp Eye Res. 1965;4:355–63.
9. Allansmith M, Hutchison D. Immunoglobulins in the conjunctiva. Immunology. 1967;12(2):225–9.
10. Hogan MJ, Alvarado JA, Weddell JE. Histology of the human eye. Philadelphia. WB Saunders; 1971. p. 119.
11. Robin JB, et al. Peripheral corneal disorders. Surv Ophthalmol. 1986;31(1):1–36.
12. Gipson IK. Anatomy of the conjunctiva, cornea and limbus. In: Smolin G, Thoft RA, editors. The Cornea, 3rd ed., vol 3. Boston: Little, Brown; 1994.
13. Hyndiuk RA, Nassif KF, Burd E. Infectious diseases. In: Smolin G, Thoft A, eds. The Cornea. Boston: Little, Brown and Co., 1983; p. 147–209.
14. Mondino BJ. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95:463–72.
15. Van Buskirk EM. The anatomy of the limbus. Eye (Lond). 1989;3(Pt 2):101–8.
16. Schermer A, et al. Differentiation related expression of a major 64K corneal keratin in vivo and in culture suggests limbal location of corneal epithelial stem cells. Cell Bio. 1986;103:49–62.
17. Minckler: Anatomy in Glaucoma-Related Surgery. In: Waltman SR, Keates RH, Hoyt CS, Frueh BR, Herschler J, Carroll OM, editors. Surgery of the EYE, New York, NY: Churchill Livingstone Inc.; 1987. p. 311–22.

18. Polansky JR, Wood IS, Maglio MT, et al. Trabecular meshwork cell culture in glaucoma research: evaluation of biological activity and structural properties of human trabecular cells in vitro. Ophthalmology. 1984;91:580–95.
19. Acott TS, Kingsley PO, Samples JR, Van Buskirk EM. Human trabecular meshwork organ culture: morphology and glycosaminoglycan synthesis. Invest Ophthalmol Vis Sci. 1988;29: 90–100.
20. Ashton N, Smith R. Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. III. Arterial relations of Schlemm's canal. Br J Ophthalmol. 1953;37:577–86.
21. Morrison JC, Van Buskirk EM. Anterior collateral circulation in the primate eye. Am Acad Ophthalmol. 1983;90:707–15.
22. Ascher KW. Aqueous veins. Am J Ophthalmol. 1942;25:31–8.
23. Muller LJ, Marfurt CF, Kruse F, et al. Corneal nerves: structure, contents and function. Exp Eye Res. 2003;76:521–42.
24. Arvidson B. Retrograde axonal transport of horseradish peroxidase from cornea to trigeminal ganglion. Acta Neuropathol. 1977;38:49–52.
25. Morgan CW, Nadelhaft I, de Groat WC. Anatomical localization of corneal afferent cells in the trigeminal ganglion. Neurosurgery 1978;2:252–8.
26. Marfurt CF. The somatotopic organization of the cat trigeminal ganglion as determined by the horseradish peroxidase technique. Anat Rec. 1981;201: 105–18.
27. Marfurt CF, Del Toro DR. Corneal sensory pathway in the rat: a horseradish peroxidase tracing study. J Comp Neurol. 1987;261:450–9.
28. Morgan C, Jannetta PJ, deGroat WC. Organization of corneal afferent axons in the trigeminal nerve root entry zone in the cat. Exp Brain Res. 1987;68:411–16.
29. Ten Tusscher MP, Klooster J, Vrensen GF. The innervation of the rabbit's anterior eye segment: a retrograde tracing study. Exp Eye Res. 1988;46: 717–30.
30. Marfurt CF, Kingsley RE, Echtenkamp SE. Sensory and sympathetic innervation of the mammalian cornea. A retrograde tracing study. Invest Ophthalmol Vis Sci. 1989;30:461–72.
31. Marfurt CF, Ellis LC. Immunohistochemical localization of tyrosine hydroxylase in corneal nerves. J Comp Neurol. 1993;336:517–31.
32. Tervo T, Joo F, Huikuri KT, et al. Fine structure of sensory nerves in the rat cornea: an experimental nerve degeneration study. Pain. 1979;6:57–70.
33. Morgan C, DeGroat WC, Jannetta PJ. Sympathetic innervation of the cornea from the superior cervical ganglion. An HRP study in the cat. J Auton Nerv Syst. 1987;20:179–83.
34. Marfurt CF, Jones MA, Thrasher K. Parasympathetic innervation of the rat cornea. Exp Eye Res. 1998;66:437–48.
35. Al-Aqaba MA, Fares U, Suleman H, et al. Architecture and distribution of human corneal nerves. Br J Ophthalmol. 2010;94:784–9.
36. Belmonte C, Garcia-Hirschfeld J, Gallar J. Neurobiology of ocular pain. Prog Retinal Eye Res. 1997;16 (1):117–56.
37. Bron AJ, Goldberg MF. Clinical features of the human limbus. In: Trevor-Roper P, editor. The cornea in health and disease: proceedings of the vith congress of the european society of ophthalmology. London: Academic Press Inc; 1981.
38. Aurell G, Kornerup T. On glandular structures at the corneo-scleral junction in man and swine: the so-called "Manz glands". Acta Ophthalmol. 1949;27:19.
39. Goldberg MF, Bron AJ. Limbal palisades of Vogt. Trans Am Soc. 1982;80:155–171.
40. Echevarria TJ, Di Girolamo N. Tissue-regenerating, vision-restoring corneal epithelial stem cells. Stem Cell Rev. 2011;7:256–268.
41. Kinoshita S, Adachi W, Sotozono C. Characteristics of the human ocular surface epithelium. Prog Retin Eye Res. 2001;20:639–73.
42. Wolosin JM, Budak MT, Akinci MA. Ocular surface epithelial and stem cell development. Int J Dev Biol. 2004;48:981–91.
43. Budak MT, Alpdogan OS, Zhou M, Lavker RM, Akinci MA, et al. Ocular surface epithelia contain ABCG2-dependent side population cells exhibiting features associated with stem cells. J Cell Sci. 2005;118(pt 8):1715–24.
44. Townsend WM. The limbal palisades of Vogt. Trans Am Ophthalmol Soc. 1991;89(721–56):721–56.
45. Zheng T, Xu J. Age-related changes of human limbus on in vivo confocal microscopy. Cornea. 2008;27: 782–6.
46. Kira L. Lathrop et al. Optical coherence tomography as a rapid, accurate, noncontact method of visualizing the palisades of Vogt. Invest Ophthalmol Vis Sci. 2012;53:1381–1387.

Etiopathogenesis

2

Manotosh Ray and Hwei Wuen Chan

Introduction

Peripheral ulcerative keratitis (PUK) is a destructive inflammatory disease of the juxtalimbal corneal stroma that is associated with an epithelial defect, the presence of inflammatory cells in the stroma and progressive stromal melting [1]. It could be associated with various ocular and systemic infectious and noninfectious diseases [2]. The exact pathophysiologic mechanism of PUK is not known. Although different etiologies are suspected, the overall mechanisms are thought to be identical in all forms of PUK. A number of systemic conditions are known to be associated with PUK. These include collagen vascular diseases such as rheumatoid arthritis, Wegener's granulomatosis, systemic lupus erythromatosus, relapasing polychondritis, polyarteritis nodosa, and infectious conditions such as syphilis and hepatitis C [1]. Some noninfectious local conditions such as Mooren's ulcer can also cause PUK.

The peripheral cornea is unique in both its morphological as well as immunological characteristics that predisposes it to inflammatory reactions. The central cornea derives oxygen from ambient air, through the tear film and aqueous humor. In contrast, the peripheral cornea receives additional oxygen and nutrients from the perilimbal capillary arcades. The perilimbal vascular and lymphatic arcades primarily act as a reservoir for immunocompetent cells such as macrophages, lymphocytes, Langerhans, and plasma cells. The proximity of corneal tissue to these arcades readily exposes the peripheral cornea to inflammatory cells and mediators [1], which can result in peripheral ulcerative keratitis.

Morphologically, the corneal extracellular matrix comprises highly organized lamellae of collagen fibrils embedded in the framework of glycosaminoglycans. The predominant cells that lie in between these lamellae are flattened fibroblasts, although there are occasional presence of polymorphonuclear leucocytes, macrophages and lymphocytes as well. Corneal fibroblasts (keratocytes) play a crucial role in the maintenance and turnover of the corneal matrix. The principal mechanism involved in the rate of matrix turnover is the optimal balance between collagenases and their tissue inhibitors [2]. Collagenases are primarily produced by fibroblasts and invading mononuclear cells [3]. It is postulated that there is a local imbalance between levels of a specific collagenase (MMP-1) and its tissue inhibitor (TIMP-1) in PUK. This imbalance could be responsible for rapid keratolysis, a hallmark feature in this condition [4]. However,

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_2

it remains uncertain whether these factors could possibly initiate PUK. Research tends to suggest that both humoral-mediated and cell-mediated autoimmune processes are involved.

Predisposition to Immune Reaction

The peripheral cornea has distinct morphologic and immunologic characteristics that predispose it to immune reaction. The limbal vasculature is known to accumulate IgM, immune complexes, C1 (first component of the complement cascade) as well as other high molecular weight molecules [5]. Immune complex deposition activates the classical pathway of the complement system. This process, in turn results in chemotaxis of inflammatory cells including neutrophils and macrophages to the peripheral cornea. These inflammatory cells release the enzymes collagenases and proteases that can potentially disrupt the cornea stroma [6–8]. Stromal destruction can further be accelerated by the release of cytokines such as interleukin-1 from these inflammatory cells that enables stromal keratocytes to produce matrix metalloproteinase-1 & 2 [9].

PUK may occur in patients with some autoimmune diseases, especially rheumatoid arthritis, which is often associated with severe necrotizing scleritis. These lesions have a vasculitic pathogenesis whereby immune complexes are situated in the peripheral cornea as well as in the limbal vessels. There is also chemotaxis of inflammatory cells, particularly neutrophils and histiocytes in addition to enzyme liberation from inflammatory cells. As a result there is collagen and proteoglycan destruction.

Pathogenesis

Exposure to a foreign antigen activates an adaptive immune response that leads to the production of antigen-specific antibodies. The antigen-antibody combination creates immune complexes that neutralize the foreign antigen and allow it to be cleared safely by the reticuloendothelial system. This complex system, however, has the potential to fail. If the antibody response is just adequate, these immune complexes may escape early detection and become deposited in the vascular endothelium. These immune complexes can then activate compliments leading to severe local inflammation. The immune complexes within the blood vessels result in vasculitic reactions. Vasculitis frequently leads to cellular destruction, resulting in damage to the vascular structures and compromising blood flow to the organ supplied. Immune complexes are not necessarily pathogenic. Their immunogenicity is determined by several factors including antigen load, antibody response, the efficiency of reticuloendothelial system in clearance of immune complexes, preexisting damage of vascular endothelium and the solubility of the immune complexes themselves.

Immune complex solubility is determined by the antibody-antigen ratio. When they are present in equal proportion, large immune complexes are formed, which are identified easily and removed by reticuloendothelial system. When there is an excess of antibody, small immune complexes are formed, which remain in solution and do not elicit any immune response. When there is slight excess of antigen, however, the immune complexes precipitate from the solution and become trapped in the capillary beds or in the previously damaged vascular endothelium. Once immune complexes precipitate in the tissue, they fix the complement, leading to intense immune reaction. Complement fixation and local inflammation recruit neutrophils, which make an attempt to engulf the immune complexes. During this process, the neutrophils degranulate, releasing lysosomal enzymes and oxygen-free radicals that cause tissue necrosis [10].

Complement is a group of serum proteins, majority of which are produced by liver. Complement can be activated (fixed) by antigen-antibody complexes or other substances which may result in variety of biological effects including cytolysis, anaphylatoxin activity, chemotaxis, opsonization, and tissue damage. The consequences of complement activation can be broadly categorized in two groups:

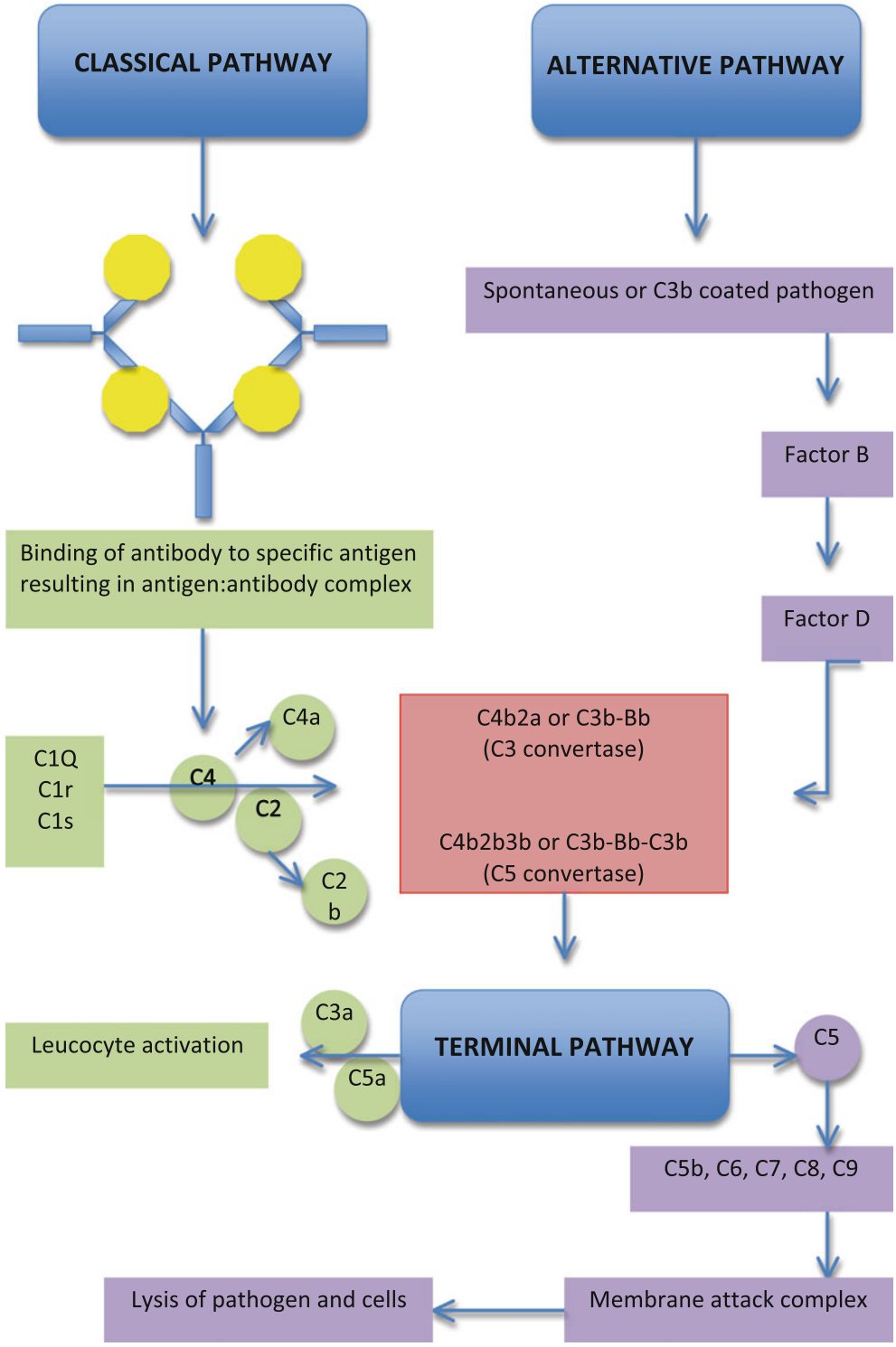

Fig. 2.1 Both classical and alternate pathways of the complement system are activated resulting in the production of "membrane attack complex" in the terminal pathway. Membrane attack complexes create pores in the cell wall leading to cellular lysis

(A) Facilitating antibody function (destruction and removal of foreign material): This is done by either lysis of the target cells or by immune clearance. Both classical and alternate pathways of complement fixation produce "membrane attack complex (MAC)" which in its final state creates pores in the cell wall leading to cellular lysis (Fig. 2.1). Immune clearance, on the other hand, is a critical function facilitated by the presence of receptors on the surface of leucocytes and erythrocytes. This is a special process by which the soluble immune complexes are removed from the serum.

(B) Development of inflammation: Complement components that are activated in plasma and body fluids are engaged in the regulation of virtually all phases of an acute inflammatory reaction, including changes in the vascular flow and caliber, the increase in vascular permeability, extravasation of leucocytes and chemotaxis. Several regulatory functions of complement affect other inflammatory mediators, whereas other compliment activities are associated with the direct action of complement proteins on target cells. Because of its variety of activating mechanisms, complement can independently participate in the regulation of inflammation, in either presence or absence of an infection.

Mooren's ulcer, a relatively uncommon painful peripheral corneal ulceration without associated scleral involvement deserves a special mention in this regard. Although there are sufficient evidences to suggest the autoimmune nature of the disease, the precise pathophysiological mechanism remains unclear. High levels of proteolytic enzymes have been demonstrated in the affected conjunctiva [11]. Foster and colleagues had established the presence of numerous activated neutrophils in the affected cornea and eventually proposed that these neutrophils were the source of proteolytic enzymes [12]. Researchers also noted that systemically, helper T cells outnumbered supressor T cells in patients with Mooren's ulcer. It was proposed that unregulated helper T cells could induce production of autoantibodies, resulting in deposition of immune complexes, complement activation followed by inflammatory cell infiltration and release of proteolytic enzymes [13, 14].

However, it is important to remember that inflammatory involvement of adjacent conjunctiva, episclera, and sclera is not a feature of all types of PUK. A simple hypersensitivity reaction to exogenous antigens may induce marginal keratitis and phlyctenular keratitis in the peripheral cornea that has an excellent prognosis when compared to immune diseases-related PUK.

Conclusions

Any inflammatory stimulus in the peripheral cornea, be it a microbial invasion, immune complex deposition as in systemic immune diseases, malignancy, or trauma, all result in neutrophil recruitment and activation of both classical and alternative pathways of complement in tissues and vessels. Activated components increase the vascular permeability and produces chemotactic factors for neutrophils such as C3a and C5a. These neutrophils infiltrate in peripheral cornea to release collagenolytic and proteolytic enzymes as well as many other proinflammatory substances. An inflamed limbal conjunctiva itself has the capability to generate collagenase enzymes. Therefore, the final result is disruption, dissolution, and tissue necrosis of corneal stroma followed by progressive thinning, a typical feature of PUK.

Compliance With Ethical Requirements

Conflict of Interest
Manotosh Ray and Hwei Wuen Chan declare that they no conflict of interest.

Informed Consent
No human studies were carried out by the authors for this article.

Animal Studies
No animal studies were carried out by the authors for this article.

References

1. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv ophthalmol. 1999;43:379–96.
2. Bron AJ, Tripath R, Tripath B, editors. The cornea. Wolff's anatomy of the eye and orbit. London: Chapman and Hall; 1997. p. 247–51.
3. Kervick GN, Pflugfelder SC, Haimovici R, et al. Paracentral rheumatoid corneal ulceration. Clinical features and cyclosporin therapy. Ophthalmology. 1992;99:80–8.
4. Riley GP, Harral GP, Watson PG, et al. Collagenase (MMP-1) and TIMP-1 in destructive corneal disease associated with rheumatoid arthritis. Eye. 1995;9:703–18.
5. Allansmith MR, Mc Clellan BH. Immunoglobulins in human cornea. Am J Ophthalmol. 1975;80 (1):123–32.
6. Mondino BJ. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95(4):463–72.
7. Shiuey Y, Foster CS. Peripheral ulcerative keratitis in collagen vascular disease. Int Ophthalmol Clin. 1998;38(1):21–32.
8. Gregory JK, Foster CS. Peripheral ulcerative keratitis in collagen vascular diseases. Int Ophthalmol Clin. 1996;36:21–30.
9. Dana MR, Qian Y, Hamrah P. Twenty-five year panorama of corneal immunology. Cornea. 2000; 19:625–43.
10. Philip S. Immune complex-mediated vasculitis, Chapter 21. In: John H, Kippel J, et al. editors. Primer in rheumatic diseases, Berlin: Springer; 2008. p. 427–34.
11. Brown S. Mooren's ulcer: histopathology and proteolytic enzymes of adjacent conjunctiva. Br J Ophthalmol. 1975;59:670–4.
12. Foster CS, Kenyon K, Greiner G, at al. The immunopathology of Mooren's ulcer. Am J Ophthalmol. 1979;88:149–59.
13. Murray P, Rahi A. Pathogenesis of Mooren's ulcer: some new concepts. Br J Ophthalmol. 1984;68: 182–6.
14. Eiferman RA, Carothers DJ, Yankeelov JA Jr. Peripheral rheumatoid ulceration and evidence of conjunctival collagenase production. Am J Ophthalmol. 1979;87(5):703–9.

Clinical Evaluation

3

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Introduction

Peripheral ulcerative keratitis (PUK) is a disorder of the juxtalimbal cornea characterized by a crescent-shaped destructive inflammation of corneal stroma associated with an epithelial defect, the presence of stromal inflammatory cells and progressive stromal degradation and thinning [1–3]. PUK can be associated with various ocular and systemic infectious and noninfectious diseases. Various systemic autoimmune vasculitic diseases that can prove potentially fatal may present as PUK. Because of its association with a large number of disease, it is very important to diagnose the etiology of the PUK. The clinical evaluation is often successful in identifying the cause. However, in certain cases a battery of investigations may be required [1, 2]. PUK often has involvement of adjacent structures like conjunctiva, episclera, and sclera inflammation. Potentially serious complications of PUK include corneal perforation and severe corneal scarring with thinning and vascularization. PUK-associated complications can be prevented with timely diagnosis, detection of the underlying systemic inflammatory disease, and proper treatment. A careful clinical evaluation often helps in timely diagnosis and prevention of complications.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*,
Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_3

Clinical Evaluation

History

A careful history is absolutely vital for making a diagnosis of PUK. The onset and progression of symptoms in a case of PUK are characteristic. The most common form of PUK, that is, Mooren's ulcer is classified into three different categories depending upon the onset, age of the patient, progression, and investigation findings. These three categories are summarized in Table 3.1. The onset can be especially acute in cases of Mooren's ulcer. The disease can be unilateral or bilateral. Most cases associated with systemic diseases can have bilateral presentation.

Symptoms

The various presenting complains in a case of PUK includes following:

Table 3.1 Systemic features and systemic diseases associated with peripheral ulcerative keratitis

Clinical features	Systemic disease
Skin and hair	
Rash/ulcers	All vascular syndromes, SLE
Sunburn easily	SLE, PSS
Depigmentation	SLE
Loss of hair	PSS, SLE, GCA
Painfully cold fingers	PSS
Puffy hands and feet	Sjog, CS, WG, RP
Respiratory	
Constant coughing	WG, SLE
Coughing blood	SLE, CS, WG, PSS, RP
Asthma attacks	CS
Shortness of breath	WG, SLE, PAN, CS, RP
Pneumonia	CS, WG, Sjorg, RP
Genitourinary	
Blood in urine	WG, SLE, PAN, CS, RP
Testicular pain	PAN
Rheumatologic	All vasculitic
Painful joints	PAN, GCA, PSS, Sjog
Muscle aches	PAN, GCA, PSS, Sjog
Gastrointestinal	
Abdominal pain	PAN, SLE, CS
Nausea, vomiting	SLE
Regurgitation	PSS
Jaundice	SLE
Blood in stool	PAN
Neurological	
Headaches	SLE, GCA, RP
Numbness/tingling	All vasculitic syndromes
Paralysis	SLE, WG, RP
Seizures	SLE, RP
Psychiatric	SLE, CS
Ear	
Deafness	RP, WG, GCA, Sjog
Swollen ear lobes	RP
Ear infections	WG, RP
Nose/sinus	
Nasal mucosal ulcers	WG, SLE
Rhinitis/nosebleeds	WG
Swollen nasal bridge	RP
Sinus trouble	WG

(continued)

Table 3.1 (continued)

Clinical features	Systemic disease
Mouth/throat	
Oral mucosal ulcers	SLE, Sjog
Dryness	Sjog
Persistent hoarseness	SLE, RP

SLE systemic lupus erythematosis, *RA* rheumatoid arthritis, *RP* relapsing polychondritis, *PSS* progressive systemic sclerosis, *PAN* polyarteritis nodosa, *Sjog* Sjogren's disease, *WG* Wegener's granulomatosis, *CS* Churg-Strauss, *GCA* giant cell arteritis

Ocular redness, Pain, Watering, and Photophobia: Pain is prominent and may be severe. Excruciating Pain out of proportion to the severity of ulcer is often a characteristic feature of Mooren's ulcer. During the healing stage of the ulcer, patients may get the relief from the excruciating pain that has been present throughout the course of the disease.

Decreased vision: In acute cases visual acuity may be normal or mild reduction can be there. Very rarely, a case can present with acute loss of vision when it is associated with corneal perforation. In long-standing cases visual acuity may be reduced secondary to induced astigmatism or corneal opacity.

Systemic features: The PUK can be a manifestation of an occult systemic disease. Thus, a thorough systemic history is very important and should include chief complaint, characteristics of present illness, past medical history, family history, and a meticulous review of systems [3–5]. Systemic diseases such as; Rheumatoid arthritis (RA), Wegener's granulomatosis (WG), Relapsing polychondritis (RP), Systemic lupus erythematosus (SLE), Polyarteritis nodosa (PAN), Microscopic polyangiitis, Sjogren syndrome, Giant cell arteritis (GCA), and Churg-Strauss syndrome may present with the following symptoms (Table 3.1):

- General—Constitutional symptoms such as chills, fever, evening rise of temperature, malaise, poor appetite, recent weight loss, and fatigue.
- Musculoskeletal—Myalgia, joint pain, arthritis, back pain, and limitation of motion.
- Skin—Rashes, pigmentations, nodules, vesicles, ulcer, nail changes, and periungual infarcts.
- Gastrointestinal—Abdominal pain, nausea, vomiting, difficulty in deglutition, and diarrhea.
- Respiratory—Coughing, chest pain, wheezing, pneumonia, and shortness of breath.
- Cardiac—Chest pain mimicking angina, and dyspnea
- Neurologic—Headaches, seizures, psychiatric, paralysis, and symptoms of peripheral neuropathy such as numbness/tingling/burning sensation.

Recurrent symptoms: Recurrences are common. Hence, a previous history of similar complaints can be found. Past history of trauma or recent surgery may precede an acute attack of PUK [6].

Signs

Ocular Examination

A careful slit-lamp examination can reveal following signs.

- **Peripheral crescentic ulceration** with an epithelial defect, thinning and stromal infiltration at the limbus (Fig. 3.1). It begins as a crescent-shaped gray-white infiltrate

in the peripheral cornea later followed by epithelial defect and stromal thinning. The ulcer typically involves the superficial one-third of the stroma initially. The ulcer is concentric to the limbus; the leading edges are undermined, infiltrated, and de-epithelialized. The spread is circumferential and occasionally central with variable epithelial loss and stromal thinning. As it progresses, it creates an overhanging edge at its central border. An undermined and infiltrated leading edge is characteristic. Probing of this edge may reveal a greater degree of stromal destruction in contrast to what it appears clinically [1–3]. In the severe cases stromal thinning may progress to corneal perforation. The perforated area is often plugged by the iris (Fig. 3.2) sealing the gap.

- Several distinct foci may be present and subsequently coalesce.
- Limbitis may be present.
- Scleritis, when present aids in distinguishing from systemic disease-associated PUK.
- Vascularization involving the bed of the ulcer up to its leading edge but not beyond.
- As the disease progresses, behind the advancing edge of the ulcer, healing may take place. The healing stage is characterized by thinning, vascularization, and scarring (Fig. 3.1). The healed area remains clouded.
- In an advanced case of Mooren's ulcer most of the cornea is lost, leaving behind a central island surrounded by area of grossly thinned, scarred, and vascularized tissue.
- Iritis and anterior chamber cells, flares are not uncommon.
- The adjacent conjunctiva and sclera are usually inflamed and hyperemic.
- PUK associated with systemic autoimmune disease presents with certain specific features that are often helpful in differentiating from Mooren's ulcer [3–5].
  - Pain is not as severe as Mooren's ulcer
  - In contrast to Mooren's ulcer, extension into the sclera may occur.
  - There is no separation between the ulcerative process and the limbus.

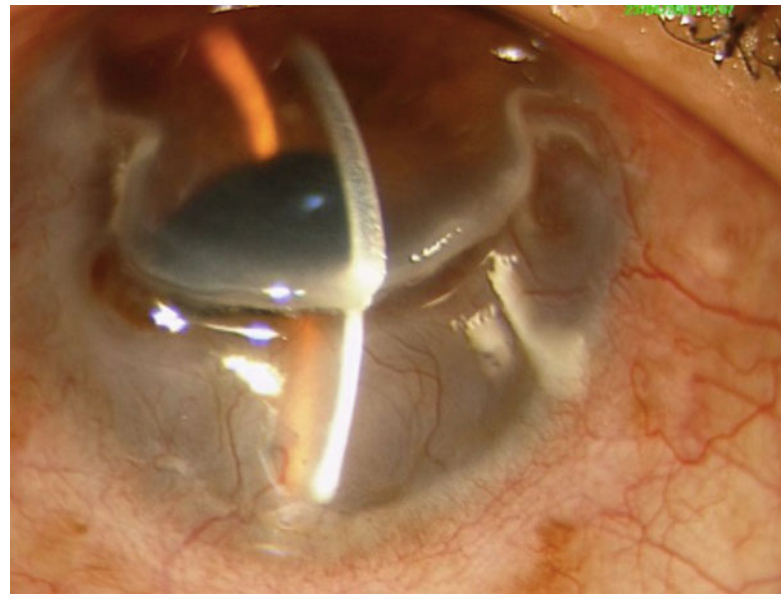

Fig. 3.1 Clinical photograph of peripheral ulcerative keratitis showing characteristic overhanging edge, stromal loss with thinning and adjacent stromal infiltrates with corneal edema. While the ulcer is progressing centripetally, healing can be seen in the periphery characterized by scarring and vascularization

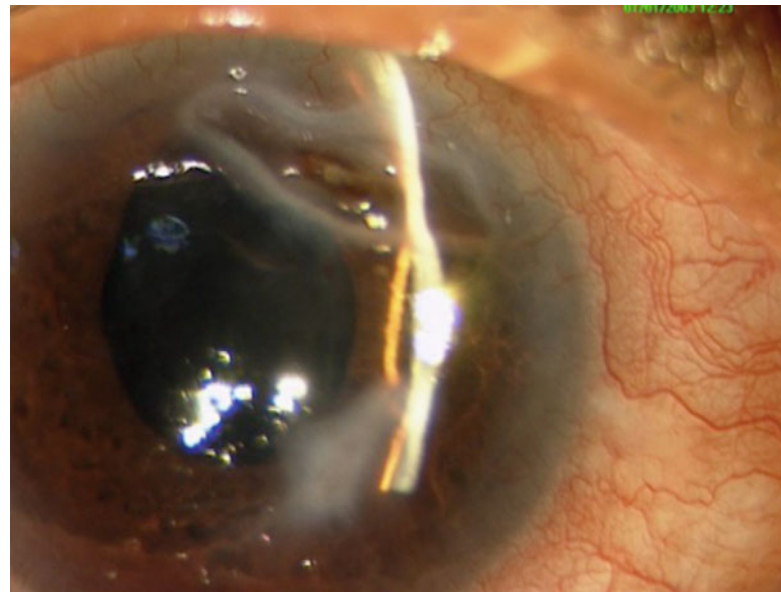

Fig. 3.2 Clinical photograph of peripheral ulcerative keratitis showing stromal loss with thinning and perforation with iris plugging at the site of perforation

Table 3.2 Clinical signs and systemic diseases in peripheral ulcerative keratitis

Clinical signs	Systemic disease
Saddle nose deformity	RP, WG
Auricular pinnae deformity	RP
Nasal mucosal ulcers	WG
Oral/lip/tongue mucosal ulcers	SLE, Sjog
Facial "butterfly" rash	SLE
Alopecia	SLE
Hypo/hyperpigmentation (scalp, face)	SLE, PSS, RP
Loss of facial expression	PSS
Facial telangiectasia	Rosacea, PSS
Rhinophyma	Rosacea
Facial/arms/legs rashes, ulcers	All vasculitic syndromes
Facial/arms/legs taught skin	PSS
Temporal artery erythema/tenderness	GCA
Raynaud's phenomenon (fingers)	PSS, SLE, G-C, Sjog
Ulcers in fingertips	All vasulitic syndromes
Subcutaneous nodules in arms and legs	RA, SLE, WG, CS, PAN
Arthritis in arms and legs	All vasculitic syndromes

SLE systemic lupus erythematosis, *RA* rheumatoid arthritis, *RP* relapsing polychondritis, *PSS* progressive systemic sclerosis, *PAN* polyarteritis nodosa, *Sjog* Sjogren's disease, *WG* Wegener's granulomatosis, *CS* Churg-Strauss, *GCA* giant cell arteritis

Systemic Examination

A complete systemic examination can provide a clue about the underlying systemic disease. The different clinical signs and the systemic diseases associated are summarized in Table 3.2 [1–5, 7–16].

Specific Diseases

Mooren's Ulcer

The most important differential diagnosis for PUK is Mooren's ulcer. It is a diagnosis of exclusion, made in cases of PUK without any systemic association and without scleritis. A typical case of Mooren's ulcer takes around 4–18 months of time for complete healing resulting in a scarred, vascularized cornea [1–3]. Complications like iritis, hypopyon, glaucoma, and cataract can be seen. Corneal perforation may occur in 35–40% of cases, often associated with minor trauma to the weakened cornea [1, 5]. Watson has classified the disease based on the clinical presentation and the low dose anterior segment fluorescein findings into; (1) Unilateral Mooren's ulcer (2) Bilateral aggressive Mooren's ulcer, and (3) Bilateral indolent Mooren's ulcer [9]. The various characteristics are outlined in Table 3.3.

Unilateral Mooren's ulcer: It is a rare type that mainly affects patients aged above 60 years. The onset is rapid with redness and severe pain in the affected eye. On examination, the cornea will reveal the typical features of Mooren's ulcer, which may progress slowly or extremely rapidly from a single focal point. Over the period the central corneal stroma is removed completely and a thin layer of scar tissue covering an intact endothelium and covered by epithelium derived from conjunctiva remains.

Bilateral aggressive Mooren's ulcer: Bilateral Mooren's ulcer is found commonly in the Indian subcontinent and in communities of Indian origin and in parts of West Africa. The age group affected is usually between 14 and 40 years. Usual presentation includes unilateral typical lesion in one eye followed by the development of the lesion in the other eye. Angiography reveals; changes in the architecture of episcleral vessels with some areas of closure,

Table 3.3 Watson's classification of Mooren's ulcer

Characteristics	Unilateral Mooren's ulcer	Bilateral aggressive Mooren's ulcer	Bilateral indolent Mooren's ulcer
Age	Old	Young	Middle-aged or old
Gender	Usually female	Male	Male and female
Race	Usually white	Usually African/Indian/Chinese	Usually Indian
Triggering factor	Minor trauma/infection	Trauma/infection	Chronic systemic infection Minor ocular trauma or infection
Laterality	Unilateral	Bilateral	Bilateral
Pain	Excruciating	Painful	Less
Progression	Rapid	Slow	Slow
Anterior segment angiography	Vaso-obliteration of superficial vascular networks with leakage from large vessels. Intense deep leakage. Vascularization of ulcer, from superficial and deep vessels	Conjunctival and episcleral networks normal. Intense deep leakage. Ulcer vascularized from deep vessels	Superficial networks normal Vasodilation of deep network Ulcer vascularized from deep vessels
Treatment	Unsatisfactory	Immunosuppression	Local immunosuppressive therapy + supportive general treatment
Keratoplasty	Recurrence common	Recurrence common	Recurrence rare
Perforation	Very rare	Can occur	Rare

break-up of the limbal arcade, leakage from the tips of these vessels, and extension of the vessels into the bed of the ulcer.

Bilateral indolent Mooren's ulcer: It usually affects patients in their fifth decade or older. It presents as bilateral indolent ulcers that progress slowly. Some may heal spontaneously.

PUK Associated with Systemic Disease

PUK may be associated with systemic conditions and can be an early manifestation of an underlying vasculitis. Most instances of the systemic conditions are already known at the time of diagnosis, however, approximately in 25% cases PUK precedes the systemic manifestation [1, 5]. Thus, a careful medical history, comprehensive review of systems, and appropriate laboratory testing are necessary in a case of PUK [5, 10].

Rheumatoid Arthritis

Rheumatoid arthritis is the most common systemic disease associated with the PUK. RA is observed in 34–42% of PUK cases [5, 10]. The prevalence of the PUK in patients with RA is around 3% [5]. PUK can arise as a complication of scleritis or independently of this condition. Rheumatoid PUK frequently occurs in patients with destructive, often nodular, RA of long duration, often after 20 years of disease progression, and in patients with high titers of RF and anti-CCP antibodies. The largest published series of patients with scleritis, comprising 500 patients, associated PUK was observed in 7.4% of scleritis cases, but in 35% of necrotizing scleritis cases [11]. It is hypothesized that the presentation of PUK may signify the transformation of RA into the systemic vasculitic phase [4, 11–13]. The presentation of PUK in a patient with RA suggests a life-threatening stage of the disease and should be treated as an emergency with immunosuppressant and cytotoxic therapy [4, 11–13]. The 5-year mortality rate for untreated RA with either PUK or scleritis is approximately 50%. The patient's clinical profile and positive serologic studies help in establishing the diagnosis.

Wegener's Granulomatosis

Wegener's granulomatosis (WG) is a rare disease, of unknown etiology, that is characterized by vasculitis of the upper and lower respiratory tracts, often in combination with glomerulonephritis [1, 2, 14]. The WG may affect multiple organs, including the skin, eye, heart, nervous system, and gastrointestinal tract and may cause a variety of ocular complications such as scleritis, proptosis, PUK, and conjunctivitis. Peripheral ulcerative keratitis experienced in a patient with WG is a nonspecific disease causing conjunctival and scleral inflammation that eventually leads to corneal thinning if systemic therapy is not initiated. In contrast to RA, PUK often manifests at the onset of WG, leading to the diagnosis of the systemic condition. Ocular involvement occurs in up to 50–60% [2, 14]. The patients may present with conjunctivitis and scleritis that may progress to PUK or PUK may be present as an isolated finding. The sclera is usually involved in these cases and this differentiates it from Mooren's ulcer in which sclera is generally not involved [2]. A laboratory test, like serum anti-neutrophil cytoplasmic antibody (ANCA) test helps to establish the diagnosis, ANCA titers correlate with the severity and extent of the disease and tend to decrease in remission of the disease. Two patterns of staining are associated with this test—the C-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) and the P-ANCA (perinuclear anti-neutrophil cytoplasmic antibody). The C-ANCA test has 99% specificity and 96% sensitivity [14]. This test also helps to follow the clinical response to therapy and the chances of recurrence of PUK are more if these values have not normalized, despite apparent clinical remission when therapy has been tapered or discontinued. When the disease is limited, the sensitivity drops and fluctuation in the c-ANCA titer may correlate with the disease state [2, 14].

Polyarteritis Nodosa

PAN is a rare multi-system disease with necrotizing vasculitis of the small- and medium-sized arteries [15, 16]. The etiology is unknown, and the diagnosis rests on the histopathology identification of typical vascular changes. Scleritis,

PUK, and retinal vasculitis are the predominant ocular inflammatory manifestations of this disease. PAN is a life-threatening disease with a death rate of 85% if untreated, a death rate of 50% if treated with corticosteroids only, and a death rate of only 5% if treated with cyclophosphamide and systemic corticosteroids with tapering of the corticosteroids [16]. The clinical characteristics of PUK in this disease are similar to those of Mooren's ulcer. The hepatitis B surface antigen is positive in about 50 percent patients with PAN. Systemic immunosuppressive therapy is the key to retard the progression of PUK [2, 16]. A development of peripheral ulcerative keratitis or scleritis or retinal vasculitis in a patient with already diagnosed polyarteritis nodosa, on therapy, is indicative of a need for more vigorous therapy [16].

Ocular and Systemic Infections

Ocular and systemic infections may also cause or be associated with the PUK. Microbial pathogens implicated in the etiology of PUK include bacteria (*Staphylococcus* and *Streptococcus* species), spirochetes (*Treponema pallidum*), Mycobacteria (tuberculosis), viruses (hepatitis C, herpes simplex virus, varicella zoster virus), acanthameoba, and fungi [2, 5].

Peripheral Corneal Diseases

Few peripheral corneal disorders can mimic PUK. Marginal keratitis and phlyctenular ulcers can present with a clinical appearance similar to PUK. The differentiation is often difficult during the active stage of ulceration. However, the signs are less severe and self-limited. ***Herpetic infections*** begin with an epithelial defect, followed by an infiltrate, which is the reverse order of that observed in marginal keratitis [1, 2]. ***Marginal keratitis*** responds rapidly to topical steroids, whereas PUK might worsen due to the lack of targeted systemic treatment. A clear intervening zone between the infiltrate and limbus, and the associated blepharitis can be seen in the case of Staphylococcal marginal keratitis. Patients generally do not complain of severe pain as seen in cases with Mooren's ulcer [1, 2]. ***Terrien's marginal degeneration*** (TMD) can be confused with PUK due to associated progressive peripheral corneal thinning and superficial vascularization. However, unlike PUK and Mooren's ulcer, inflammation and epithelial defects are not hallmarks of TMD, TMD is typically painless, does not ulcerate. Demarcation from the central cornea with a gray line is characteristic of TMD. TMD begins superiorly as fine punctate stromal opacities and a clear zone exists between the limbus and the infiltrate. Superficial vascularization is present in almost all cases. The peripheral thinned zone is determined by a white lipid line at its central edge slowly progressive thinning spreads circumferentially and causes irregular astigmatism [1, 2]. ***Senile furrow degeneration*** is characterized by thinning in the lucid interval between an arcus and limbus may occur in the elderly [2]. However, the epithelium is intact and there is no infiltrate or inflammation. The furrow is shallow and not vascularized, with sloping central and peripheral edges. Progression is extremely slow, and has no risk of perforation [1, 2].

Conclusions

Careful clinical evaluation often helps in the initiation of treatment, when reports of other investigations are still awaited. In addition, such approach tapers the differential diagnosis to a minimum, thereby avoiding unnecessary investigation and increased cost of the management of such cases.

Compliance with Ethical Requirements

Conflict of Interest
Prafulla K. Maharana, Rajesh Pattebahadur, and Namrata Sharma declare that they have no conflict of interest.

Informed Consent
No human studies were carried out by the authors for this article.

Animal Studies
No animal studies were carried out by the authors for this article.

References

1. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol. 2012;6:747–54.
2. Garg P, Sangwan VS. Mooren's ulcer. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: Fundamentals, diagnostic, management. 3rd ed. St Louis, MO: Elsevier; 2011.
3. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, Tandon R, Vajpayee RB. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: A prospective study. Br J Ophthalmol. 2015;99:1503–8.
4. Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:108–16.
5. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007;33:835–54.
6. Akpek EK, Demetriades AM, Gottsch JD. Peripheral ulcerative keratitis after clear corneal cataract extraction. J Cataract Refract Surg. 2000;26:1424–7.
7. Knox Cartwright NE, Tole DM, Georgoudis P, Cook SD. Peripheral ulcerative keratitis and corneal melt: A 10-year single center review with historical comparison. Cornea. 2014;33:27–31.
8. Zelefsky JR, Srinivasan M, Cunningham ET Jr. Mooren's ulcer. Expert Rev Ophthalmol. 2011; 6:461–7.
9. Watson PG. Management of Mooren's ulceration. Eye (Lond). 1997;11:349–56.
10. Sainz de la Maza M, Foster CS, Jabbur NS, Baltatzis S. Ocular characteristics and disease associations in scleritis-associated peripheral keratopathy. Arch Ophthalmol. 2002;120:15–9.
11. Sainz de la Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119:43–50.
12. Moreland LW, Curtis JR. Systemic nonarticular manifestations of rheumatoid arthritis: focus on inflammatory mechanisms. Semin Arthritis Rheum. 2009;39:132–43.
13. Zlatanović G, Veselinović D, Cekić S, Zivković M, Dorđević-Jocić J, Zlatanović M. Ocular manifestation of rheumatoid arthritis-different forms and frequency. Bosn J Basic Med Sci. 2010;10:323–7.
14. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:430–44.
15. Akova YA, Jabbur NS, Foster CS. Ocular presentation of polyarteritis nodosa. Clinical course and management with steroid and cytotoxic therapy. Ophthalmology. 1993;100:1775–81.
16. Foster CS. Ocular manifestations of the potentially lethal rheumatologic and vasculitic disorders. J Fr Ophtalmol. 2013;36:526–32.

Investigative Modalities

4

Divya Singh, Anat Galor and Radhika Tandon

Introduction

A wide variety of investigative modalities are called into play in managing a case of peripheral ulcerative keratitis [1]. The very nature of the disease entails a host of local and systemic effects either as cause or effect of the pathogenesis and consequently the investigations would also follow a path according to the need of the specific clinical situation. A bewildering array of tests with complex possibilities for interpretation can actually be fruitfully utilized in the best interest of the patient if applied well using a systematic logical approach while keeping abreast with the latest knowledge in the field [2].

One must keep in mind that all possible tools and technology may not be available or accessible, may not be affordable and in many circumstances may in fact even not be required [3]. For ease of understanding, the investigations can be considered as classified in different categories in terms of the type of test, what information is expected, the level at which it should be considered, how the results should be handled, and the situations when a higher level of expertize and machinery should be considered.

Evaluation of Patients with Peripheral Ulcerative Keratitis

Evaluation should include a careful history, physical examination and the systematic review. A holistic approach should be directed towards the symptoms of systemic conditions associated with peripheral ulcerative keratitis and scleritis [4]. These conditions include rheumatoid arthritis (RA), granulomatosis with polyangiitis (Wegener Granulomatosis), polyarteritis nodosa, relapsing polychondritis, systemic lupus erythematosus, Churg–Strauss syndrome, and inflammatory bowel disease. Infections should also be considered as a possibility and a careful history of any surgical insult or trauma should be extracted. The various investigative modalities are aimed at finding the underlying disease entity.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_4

Classification of Investigative Modalities

1. Standard screening tests
2. Tests required in specific situations
3. Establishing the etiology at a local ocular level
4. Establishing the etiology at a systemic level
5. Watching out for side effects of medications
6. Role of each of these investigations.

Standard Tests

Standard testing in all patients with peripheral ulcerative keratitis and scleritis includes hematological investigations with estimation of hemoglobin and the complete blood count, the renal and liver function tests, and a urinalysis with microscopy. In addition, immunological testing for markers of vasculitis is recommended [antineutrophil cytoplasmic antibodies (ANCA)]. Other markers to consider based on clinical history and examination include antinuclear antibodies (ANA), rheumatoid factor, and antibodies to cyclic citrullinated peptides (anti-CCP antibodies) [4, 5]. In addition, all patients should undergo testing for syphilis. Typically, both a nonspecific test [rapid plasma reagin (RPR)] and a treponema specific test [fluorescent treponemal antibody (FTA-ABS)] are used to evaluate for a spirochetal infection. In addition, a chest X-ray should be obtained to evaluate for pulmonary disease which may be seen in several systemic conditions associated with peripheral ulcerative keratitis and scleritis (e.g., sarcoidosis, vasculitis, tuberculosis).

In addition, a local microbiologic infection must be considered in all patients, especially those living in hot-humid climates where eye infections are more common. In eyes with features suspicious of local infection (necrosis, abscess formation), microbiological evaluation using cultures is needed to establish the diagnosis.

Tests that May Be Required in Specific Situations

Based on clinical history and examination, other tests should be considered including an evaluation for other infections (e.g., serologic testing for Lyme disease, skin test for tuberculosis). In those with pulmonary symptoms, a computed tomographic (CT) scan can be ordered which has greater sensitivity compared to standard X-ray. Additional serologic and radiographic tests may be required to exclude inflammatory and infectious conditions if mandated by specific clinical features or by the results of initial serological testing. For example, in patients with axial arthritis, sacroiliac joint radiographs (for spondyloarthropathies) can be performed; in those with sinus complaints, a CT scan of the sinuses can be ordered; and in those with liver function abnormalities, serologies for hepatitis B and C should be evaluated [5–7].

If there is a suspicion of posterior scleritis, ultrasonography is useful to evaluate for scleral thickening and fluid in Tenon's capsule. When there is fluid in Tenon's capsule, the finding is called the "T-sign". CT scan of the orbits can also demonstrate thickening of the sclera or inflammation of the orbit in posterior scleritis.

Establishing the Etiology at the Ocular Level

Ocular infections are the important cause of PUK. Microorganisms responsible for causing the peripheral ulcerative keratitis include bacteria (*Staphylococcus* and *Streptococcus species*), spirochetes (*Treponema pallidum*), Mycobacteria (tuberculosis), herpes simplex and varicella zoster virus, acanthameoba, and fungi. Laboratory procedures for the diagnosis of keratitis are directed towards the detection of the causative microorganism [5–8]. The samples should be collected at the initial visit prior to the commencement of the therapy. These should then be sent for smear examination and inoculated on the

culture media. These tests in unison with the serological testing help in establishing the etiological diagnosis of the peripheral ulcerative keratitis and impact management. The role of various imaging modalities such as SD-OCT and fluorescein angiography is important in confirming the clinical diagnosis, documenting the extent of involvement, and monitoring the course of the disease.

Establishing the Etiology at the Systemic Level

As described above, the combination of various hematological and serological testing along with the imaging such as chest radiographs and CT scanning may be required in establishing the etiological diagnosis at a systemic level [6, 7].

Monitoring for Any Potential Complications and Side Effects of Medications

Many individuals with immune mediated PUK or scleritis require immunosuppressive medications to control the disease process. In these patients, it is imperative to monitor for potential medication associated complications. In general, patients receiving an anti-metabolite (methotrexate, mycophenolate) and/or *T* cell inhibitor (cyclosporine, tacrolimus) require complete blood counts and comprehensive metabolic panel every 2–3 months. Patients on cyclophosphamide should have a complete blood count every one to two weeks in the initial phase of therapy with less frequent testing as proper dosage is established. In addition, urine analysis is mandated to monitor for the presence of any hematuria [7, 8]. Evaluation for glucocorticoid-induced bone weakening with a bone density scan must also be considered on a yearly basis and prophylaxis should be provided for osteoporosis in those requiring chronic corticosteroid therapy.

Role of each of the Investigations: Hematological Investigations

Hemoglobin

The commonest manifestation of the connective tissue disease is moderate to severe amount of anemia depending on the disease activity [4]. Hypochromic microcytic type of anemia is usually seen as a result of iron deficiency or the inability of the reticuloendothelial system to release sequestered iron. Autoimmune hemolytic anemia is also seen in up to 10% of the patients with systemic lupus erythematosus [5]. Pernicious anemia is also associated with rheumatoid arthritis and macrocytosis occurs as a complication of the therapeutic use of drugs such as methotrexate or azathioprine in such cases [6].

Total Leucocyte Count

An increased white cell count may be a feature of polyarteritis nodosa [7]. While leucopenia occurs in systemic lupus erythematosus, neutropenia is often seen in association with rheumatoid arthritis. Eosinophilia can occur as a result of gold sensitivity in rheumatoid arthritis and in strongly seropositive disease.

Platelet Count

Thrombocytopenia occurs with the use of antirheumatoid drugs such as gold, penicillamine, and other cytotoxic agents and also in approximately 20% of the patients with systemic lupus erythematosus and patients with primary antiphospholipid antibody syndrome. Raised thrombocyte levels are seen in approximately one-third of patients with rheumatoid arthritis [5–7].

Erythrocyte Sedimentation Rate and Viscosity

ESR is a nonspecific indicator of inflammation but it can be used to measure activity in rheumatoid arthritis and to follow the course of the disease. Raised ESR of over 50 mm/h in the first hour is usual in polymyalgia rheumatica and

temporal arteritis [6–9] Plasma viscosity is mainly dependent on the changes in the fibrinogen and globulin ratio and is not influenced by the age, sex, or the hematocrit values of the patient unlike ESR values.

Acute Phase Proteins

These include the C-reactive protein, ceruloplasmin, haptoglobin, fibrinogen, and alpha-1 antitrypsin which usually rise in the connective tissue disorders [10, 11]. The changes in these components may occur both in the acute and chronic inflammation. Measuring both CRP and ESR may be more helpful in the assessment of the disease activity rather than measuring either one alone. However, the increment in these components is quite variable and can be absent in 40% of patients with recent onset of rheumatoid arthritis [7, 8].

Other Serological Investigations

Angiotensin converting enzyme (ACE) can be elevated in sarcoidosis. Hepatitis B surface antigen is sent in suspected cases of polyarteritis nodosa. For the diagnosis of syphilis, fluorescent treponemal antibody (FTA) test against the treponemal antigen is helpful in earlier stages of the disease whereas non treponemal tests such as VDRL are useful in monitoring the progression of the disease as these become negative after the therapy [12, 13]. A variety of DNA probe assays are available for the direct detection of the microorganisms. Target amplification systems such as PCR (polymerase chain reaction) have the advantage of greater speed than the conventional culture methods in case of Herpes simplex virus (HSV) infection [8].

Immunological tests

Antirheumatoid Antibodies

Rheumatoid factors are produced in the synovium of rheumatoid arthritis patients. These are autoantibodies directed against the Fc fragment of the IgG [13, 14]. It is found in 80% of the patients with rheumatoid arthritis, chronic infections, other immunological diseases, and also in the general population in up to 4% cases. Rheumatoid factors can be detected with the use of enzyme-linked immunosorbent assay (ELISA) which is widely available [2, 8].

Anti-cyclic Citrullinated Peptide (anti-CCP) Antibodies

It is used in patients when rheumatoid arthritis is suspected but rheumatoid factor is negative as this is more specific than rheumatoid factor. The titres are directly related to the disease severity. However, because of the low sensitivity this test alone cannot be relied upon to detect rheumatoid arthritis [14, 15].

Antinuclear Antibodies

This is found in about 95% of the patients with systemic lupus erythematosus and it is perhaps the most widely used screening test for the disease. The positive ANA test supports the diagnosis but the negative ANA test makes the diagnosis of SLE unlikely [16, 17].

Antineutrophil Cytoplasmic Antibodies

This test is based on identification of antibodies to cytoplasmic targets in monocytes and neutrophils. This is done by indirect immunofluorescence by using normal neutrophils where different antibody specificities are indicated by different patterns [17, 18]. The two patterns are assigned as cANCA (classic perinuclear fluorescence pattern) and pANCA (atypical ANCA; more diffuse staining pattern). cANCA is produced by proteinase 3 (PR3) autoantibodies and is highly sensitive and specific granulomatosis with polyangiitis. pANCA is directed against myeloperoxidase and is associated with microscopic polyangiitis. This test is highly specific but less sensitive. Hence, this test is found to be valuable in the early diagnosis of the renal/pulmonary vasculitis syndromes [1, 2, 8].

Antiphospholipid Antibodies

These antibodies are responsible for false positive VDRL test in lupus. A wide variety of antibodies exist such as anticardiolipin antibodies. Anticardiolipin antibodies occur in up to 40% of the SLE patients [8, 18].

Lupus Erythematosus Cells

It is an antibody to the histone particle of the DNA molecule. This test is positive in up to 75% of SLE patients. However, it can also be found positive in other conditions such as Sjogren's syndrome, rheumatoid arthritis, chronic liver disease, and connective tissue diseases [1, 2, 18].

Microbiological Workup

Laboratory procedures for the diagnosis of keratitis are directed towards the detection of the causative microorganism. The samples should be collected at the initial visit prior to the commencement of the therapy [9]. These should then be sent for smear examination and inoculated on the culture media. The treatment can be initiated based on the result of smear examination and, if required can be modified in accordance with the culture and sensitivity results.

Corneal scraping is done under topical anesthesia with the help of Kimura's spatula. Other instruments which could be used for the same purpose are 26-gauge needle, Bard Parker blade #57 (Becton Dickinson, Franklin Lakes, New Jersey), surgical blade, hypodermic needle, and calcium alginate swab. The leading edges and the base of the ulcer are scraped. Multiple scrapings could be obtained to enhance the yield of the organism and proper care should be taken to avoid the contamination [1, 2, 9]. This material is then transferred onto the glass slide and the smear is prepared, one for gram staining, and the other for KOH wet mount. Additional smears can be prepared for special stains such as Giemsa, Ziehl–Neelsen, calcofluor white, periodic acid schiff, and Gomori Methenamine stain. The corneal scrapings are also inoculated onto the blood agar plate, chocolate agar plate, Sabouraud's dextrose agar, and anaerobic media (if anaerobes are suspected). This is done by streaking the platinum spatula lightly over the surface of the selective media plate in a C-shaped configuration and growth on the C streak is considered significant. Most aerobic bacteria grow on standard culture media within 48 h. Anaerobic and fungal cultures can take a longer time [9].

Imaging modalities

Low Dose Fluorescein Angiography

Fluorescein angiography has been described to be a helpful modality in monitoring the scleritis. The area of interest is first photographed at 10×, and 16× magnification. Fluorescein angiography is then performed after injecting 5 ml of 10% sodium fluorescein into the antecubital vein and the images are captured using the same camera at one second intervals, starting ten seconds after the injection of the dye. Low dose fluorescein angiography is preferred over the conventional fluorescein angiography as it utilizes lesser dose of the fluorescein dye and use of the more sensitive photographic film. This results in less leakage and better picture quality [19, 20].

Sclerokeratitis

Low dose anterior segment fluorescein angiography can be helpful in making the diagnosis and assessing the response to treatment in patients with peripheral ulcerative keratitis or scleroker-atitis. It determines the leakage into the cornea from the limbal capillaries and the newly formed vessels which are associated with ongoing inflammation and the response to therapy [21].

Stromal Keratitis

There is an area of poor perfusion adjacent to the limbus with new vessels extending from the surrounding vascular loops into the cornea. These can be derived from either deep or superficial vascular plexus. Leakage is seen on either side of the advancing tip in the active inflammatory phase. The leakage stops as soon as the treatment becomes effective [19–21].

Destructive Keratitis

In the mildest form, there is poor perfusion of vessels surrounding the limbus with disruption of the normal limbal arcade which in turn is replaced by the new vessels stretching into the superficial stroma.

In the peripheral ulcerative keratitis, there is a complete non-perfusion of the vessels sometimes

extending till the insertion of the rectus muscles. The arteries fill normally but there is poor perfusion of the limbal and episcleral venular arcades [20]. Leakage is not prominently seen. New vessels are usually seen to spread into the superficial part of the peripheral ectatic area which may form. This is most commonly seen in rheumatoid arthritis [19, 21].

Anterior Segment Optical Coherence Tomography

AS-OCT is an important tool to confirm the clinical diagnosis of scleritis. The differences in the type of collagen and their distribution between the cornea and sclera result in the different optical properties. This is the reason why we are able to differentiate between the corneal layers and the sclera based on AS-OCT [22]. The scleral image is seen as a highly reflective structure while cornea is a weakly scattering structure. The images are very useful in showing the full extent of the inflammatory process.

Diffuse Anterior Scleritis

There is a localized area of inflammation adjacent to the dilated vessels. The edema extends throughout the area of inflammation up to the limbus including the episclera and about half to two-thirds depth of the sclera. There is the gross separation of collagen fibers (Fig. 4.1) [22].

Necrotizing Anterior Scleritis

This condition is characterized by the destruction of the collagen fibers and the thinning of the sclera. The posterior scleral surface is easily observed with irregularly arranged and dense reflective collagen fibers [22].

Nodular Anterior Scleritis

This condition is marked by the hyporeflective nodule surrounded by the hyperreflective sclera. AS-OCT clearly illustrates the swollen tissue mixed with the blood vessels and the inflammatory cells (Fig. 4.2) [22].

The advent of SD-OCT has proved to be of significant improvement in increasing the sensitivity of diagnosis. It also helps in monitoring the disease progression in scleral disease and to monitor changes postoperatively (Fig. 4.3).

Ultrasonography

The B mode ultrasonography is helpful in imaging both anterior and posterior scleritis. However, its main role is in monitoring the posterior

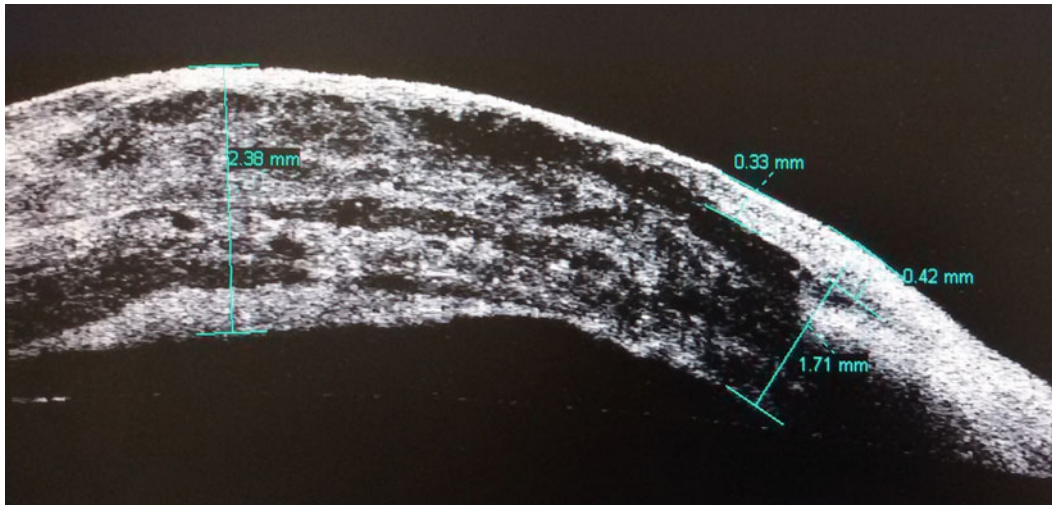

Fig. 4.1 AS-OCT shows area of inflammation with edema and gross separation of the collagen fibers

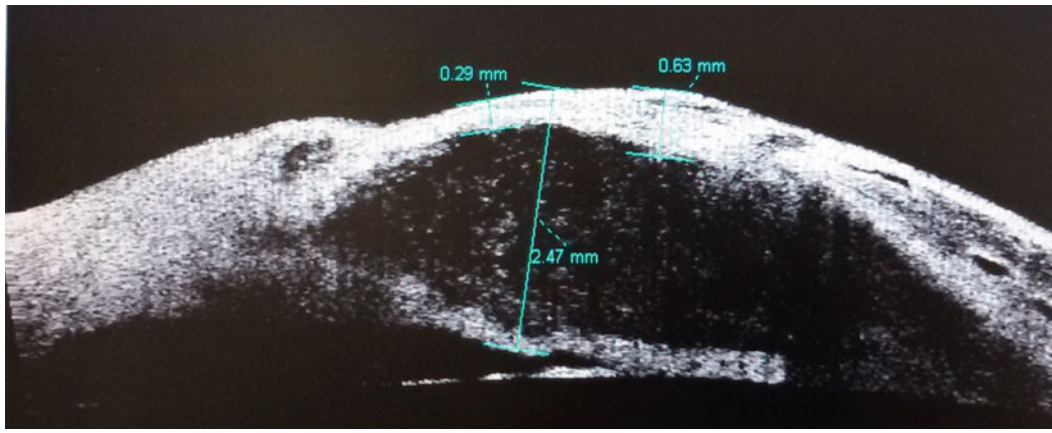

Fig. 4.2 AS-OCT demonstrating hyporeflective nodule surrounded by hyperreflective sclera

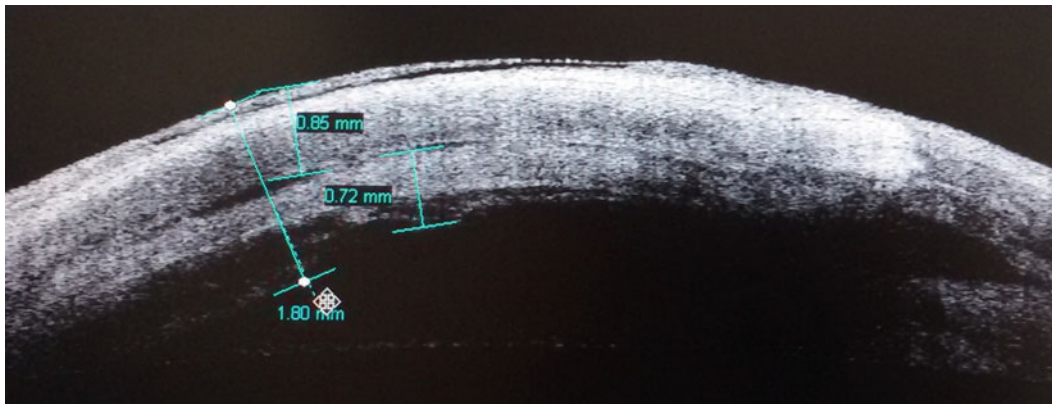

Fig. 4.3 AS-OCT showing resolution of edema and inflammation post patch graft

scleritis. The retinal, choroidal, and scleral complex is seen as the heterogenous layer surrounded by the echogenic orbital fat and the echolucent vitreous. In posterior scleritis, there is reduction in echogenecity of the posterior coats of the eyeball. The fluid in Tenon's capsule and the optic nerve sheath gives rise to the "T-sign". The vertical bar of the 'T' being formed by the dilated optic nerve which is echolucent and the horizontal bar formed by the echolucent tenon's fluid.

Computerized Tomography Scan

CT scanning utilizes the X-rays to generate the cross-sectional scans of the eye and the orbit [23]. It is particularly useful in the presence of granulomatous scleritis where there is destruction of the bone or the sinus infiltration. It is however, unsuitable for monitoring the course of the disease as it employs the X-rays [23].

Conclusions

Use of investigations could be classified into various categories based on the type of test, the level at which it needs to be considered, what information is expected, and how the results should be interpreted.

Compliance with Ethical Requirements Divya Singh, Anat Galor and Radhika Tandon declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

References

1. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol. 2012;6:747–54.
2. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin N Am. 2007;33:835–54.
3. Bartly J, Mondino BJ. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95:463–72.
4. ter Borg EJ, Houtman PM, Kallenberg CG, van Leeuwen MA, van Rÿswÿk MH. Thrombocytopenia and hemolytic anemia in a patient with mixed connective tissue disease due to thrombotic thrombocytopenic purpura. J Rheumatol. 1988;15:1174–7.
5. Giannouli S, Voulgarelis M, Ziakas PD, Tzioufas AG. Anaemia in systemic lupus erythematosus: from pathophysiology to clinical assessment. Ann Rheum Dis. 2006;65:144–8.
6. Ghazi HA. Pernicious anaemia and rheumatoid arthritis. Br Med J. 1972;1:144–5.
7. Sainz de la Maza M, Foster CS. The diagnosis and treatment of peripheral ulcerative keratitis. Semin Ophthamol. 1991;3:133.
8. Akpek EK, Thorne JE, Qazi FA, Do DV, Jabs DA. Evaluation of patients with scleritis for systemic disease. Ophthalmology. 2004;111:501–6.
9. Levey, Stephanie B, Katz, Harold R, Abrams, Donald A, Hirschbein, Marc J, Marsh, Marta J. The role of cultures in the management of ulcerative keratitis. Cornea. 1997;16:383–6.
10. Watson PG, Hayreh SS. Scleritis and episcleritis. Br J Ophthalmol. 1976;60(3):163–91.
11. Scleritis Schwam B. In: Krachmer J, Mannis M, Holland E, editors. Cornea and external disease: clinical diagnosis and management. 1. II. Saint Louis: Mosby; 1997. p. 1479–91.
12. Mondino B. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95:463–72.
13. Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. Curr Opin Ophthalmol. 2000;11(6):468–71.
14. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43(5):379–96.
15. Messmer EM, Foster CS. Destructive corneal and scleral disease associated with rheumatoid arthritis. Med Surg Manage Cornea. 1995;14(4):408–17.
16. McKibbin M, Isaacs JD, Morrell AJ. Incidence of corneal melting in association with systemic disease in the Yorkshire Region, 1995-7. Br J Ophthalmol. 1999;83(8):941–3.
17. Sainz de la Maza M, Foster CS, Jabbur NS, Baltatzis S. Ocular characteristics and disease associations in scleritis-associated peripheral keratopathy. Arch Ophthalmol. 2002;120(1):15–9.
18. Dana M, Qian Y, Hamrah P. Twenty-five-year panorama of corneal immunology: emerging concepts in the immunopathogenesis of microbial keratitis, peripheral ulcerative keratitis, and corneal transplant rejection. Cornea. 2000;19(5):625–43.
19. Saari KM. Anterior segment fluorescein angiography in inflammatory diseases of the cornea. Acta Ophthalmol (Copenh). 1979;57(5):781–93.
20. Watson PG, Bovey E. Anterior segment fluorescein angiography in the diagnosis of scleral inflammation. Ophthalmology. 1985;92(1):1–11.
21. Aydin P, Akova YA, Kadayifçila S. Anterior segment indocyanine green angiography in scleral inflammation. Eye. 2000;14:211–5.
22. Watson P, Romano A. The impact of new methods of investigation and treatment on the understanding of the pathology of scleral inflammation. Eye (Lond). 2014;28(8):915–30.
23. Biswas J, Mittal S, Ganesh SK, Shetty NS, Gopal L. Posterior scleritis: clinical profile and imaging characteristics. Indian J Ophthalmol. 1998;46(4):195–202.

General Principles of Medical Therapy

5

Radhika Tandon, Archita Singh
and Virender Singh Sangwan

Introduction

Peripheral ulcerative keratitis, a debilitating and potentially blinding ophthalmic disorder counts as a rare disease in general ophthalmic practice and falls within the purview of cornea specialists for detailed evaluation and treatment. Needless to say, as with all higher specialty care, the contribution of the primary care provider in early diagnosis and prompt referral is crucial in the ultimate outcome. A basic understanding of the etiopathogenesis and underlying pathophysiologic mechanisms leading to the various manifestations and stages of the illness is the key to a sound management plan incorporating the right combination of investigations and interpretation of results to reach a successful outcome. Notwithstanding our best efforts, it is important to be aware that sometimes the disease progression is relentless irrespective of all interventions, hence indicating there are still gaps in knowledge about the exact disease-causing agents and processes in some cases perhaps due to a complex interplay with other systemic predispositions and susceptibilities.

Salient Features

The key to medical therapy is a systematic and logical approach based on a sound understanding of the underlying disease process. Preliminary work up and investigations would guide whether primarily an anti-infective or anti-inflammatory approach should be taken, though often they may both be required *pari passu.* Empirical treatment should be initiated based on clinical acumen and basic investigations while more detailed work up and further tests are in progress. Review of response to medication and the results of the investigations would help determine further course of action. As one would expect, a tailored approach specific for each patient is required on the broad foundation of general principles of the treatment guidelines. This section attempts to help streamline thought processes by serving as a simple practical guide to follow in treating patients following best evidence based models.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*,
Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_5

Basic Principles

Broadly speaking, the main goals of medical treatment are to ensure quick healing of the ulcer with minimal sequelae and avoid recurrences. [1–7] This requires an understanding of the etiology or etiopathogenesis of the ulcerative process, effective measures to control the underlying disease or pathogen responsible, avoid secondary infection or other complications such as extreme melting or perforation or relentless progression and minimize the chances of recurrence. All these are required to be tackled simultaneously, though one or other may take the forefront if predominating the clinical picture.

In case of peripheral ulcerative keratitis, special consideration is due to the inherent unique nature of the peripheral cornea with its close proximity to the limbal vasculature and adjacent sclera and conjunctiva. This is of particular relevance to the immunological reactions that this part of the cornea is subjected to owing largely to the physical location adjacent to the conjunctiva which has full-fledged immunological mechanisms leading to important implications for treatment. The abundance of Langerhans cells and IgM [3] and C1 [4] the unit that recognizes the classic complement pathway makes the peripheral cornea prone to rapid immunological onslaught as activation of the complement pathway by antigen–antibody complexes is more efficient. The lymphatic drainage and the presence of unique T-cell subpopulations are other contributory elements.

Moreover, the peripheral cornea can be affected by antigen–antibody complexes which may be formed not only within the cornea itself, but also derived from the tears or aqueous humor or even accessible to circulating immune complexes via the limbal vessels.

Exogenous antigens such as in infected ulcers, phlyctenules, or catarrhal infiltrates in the peripheral cornea can also lead to a hypersensitivity reaction consequent to the inherent proneness to rapid inflammatory response.

All these factors play a role in pathogenesis of diseases and their manifestations and need to be considered when undertaking the task of planning a suitable therapeutic plan. Important considerations include of course the underlying disease process and predisposing factors, keeping in view the choice of medications and modes of delivery. A balance between medical therapy local and systemic and surgical interventions must be judiciously sought as demanded by the situation at hand.

Needless to say, an active infection, be it etiologically directly responsible or secondarily infected, requires to be addressed first with antimicrobial agents. As the infection comes under control, healing occurs and any additional measures to control residual or recalcitrant inflammation have to be taken so that the disease is tackled suitably. A graded stepwise approach should be followed, introducing various medications sequentially while monitoring the effect and judiciously modifying therapy ensuring one uses as little as possible to maximize benefits and minimize side effects as the key to a good outcome.

Management

Management includes the investigations and appropriate treatment of the disease [1, 8]. A systematic, logical approach must be followed using clinical acumen based on history and examination and investigations tailored according to the clinically derived differential diagnosis. A battery of immunological tests is warranted if the preliminary investigations suggest that a more detailed work up is necessary to arrive at the basic cause.

For all practical purposes, the treatment is started empirically in the clinic guided by one's clinical judgement and then modified or changed according to the response of the patient and the study of test results. While considering the course of action at the point of first contact, one should prudently follow the dictum to '*do no harm*'. This implies that one would consider an infectious etiology is ruled out before starting topical steroids and confirm safety of systemic status before instituting any potentially hazardous systemic therapy. In case of doubt, the

treatment can be started cautiously taking care to carefully monitor the response and look out for any serious side effects.

In considering treatment protocols, peripheral ulcerative keratitis can be handled considering them as clinical syndromes for convenience. The major categories would therefore be as follows [9–11]:

- PUK with suspected infectious etiology or active secondary infection bacterial/viral/fungal/protozoal/parasitic
- PUK with suspected inflammatory etiology secondary to a local infection controlled with treatment with no evidence of active infection present
- PUK with suspected inflammatory etiology secondary to a systemic infection (Tuberculosis, Varicella zoster virus, Dengue fever, Leishmaniasis, Gonococcal arthritis, Syphilis)
- PUK with inflammatory etiology of an autoimmune nature related to systemic collagen vascular disease
- PUK with inflammatory etiology of an autoimmune nature with no proven local or systemic etiological cause diagnosed as Mooren's ulcer by exclusion consistent with clinical manifestations.

In addition, evidence-based information suggests that there may be different expected responses to treatment and also differing likelihood of response to any particular treatment strategy based on laterality of involvement and chronology. One can streamline one's decision-making process by considering the presentation in the following sub-categories:

1. Unilateral PUK
2. Bilateral PUK
    a. Non-simultaneous involvement of both eyes
    b. Simultaneous involvement of both eyes.

Further, patients with recurrences must be dealt with keeping in view the type of presentation, whether similar or different from previous attacks and whether the recurrence occurred in quiescent stage or while patient was on maintenance immunosuppressive therapy or had acquired any other new risk factor.

The broad principles that govern the therapeutic approach to treatment of peripheral ulcerative keratitis can be individually elaborated under the following management goals:

1. Investigate to identify the underlying cause including risk factors and associated diseases so that specific targeted treatment can be planned
2. Evaluate and assess the extent of involvement to determine the urgency of the situation and plan suitable intervention
3. Look for any local comorbidities that require due attention
4. Give due attention to any active systemic disease by referring to a physician
5. If systemic medication is required to be prescribed particularly medicines with considerable systemic side effects, consult a physician for shared care.

Notwithstanding the broad principles and guidelines outlined above, a customized approach to each individual patient is required and evidence-based best practices serve as a guide to follow. Albeit, there is a lot of literature on the subject and numerous studies, and review articles discussing various aspects of treatment, high levels of evidence is lacking in support of any particular line of therapy. The nature of the disease is such, being rare and varied in expression and manifestation with a variety of contributory and exacerbatory factors and a wide individual variation in response, that it is counterproductive to plan any kind of therapeutic intervention trial with reasonable level of reliability and reproducibility to stand the test of science and time. Information gathered from various case series, retrospective and few prospective studies and a compilation of peer knowledge has provided some practical tips that can be followed and are reproduced below.

Non-Infectious Immuno-Inflammatory Peripheral Ulcers

Associated with systemic autoimmune or collagen vascular diseases [12–14]

In PUK with related systemic disease, systemic steroid therapy is considered more useful than topical drops which may in fact inhibit the formation of new collagen and increase the chance of perforation. In addition to usual measures, a rheumatology consult for active systemic immunosuppression and control of active systemic disease is warranted [12].

As high as 25% cases may present with ocular involvement alone and coincident systemic disease is detectable on careful medical history.

Not associated with systemic autoimmune or collagen vascular diseases (Mooren's ulcer) [15–22] (Table 5.1)

Likelihood of response to intensive topical steroids is related to the laterality of involvement. Nevertheless not all ulcers respond to topical steroid therapy and as opposed to other types of PUK, Mooren's ulcers are more likely to respond to conjunctival resection if not healing with topical steroids, hence surgical intervention is worth considering in the wake of active local inflammation before progressing to systemic medications.

If unilateral, 56% are reported to heal with intensive topical steroids,

If bilateral with non-simultaneous involvement, 50% have shown healing with intensive topical steroids, and

If bilateral ulcers occur simultaneously in both eyes, only 18% have healed with topical steroids alone [15]. Hence, intervention with systemic steroids and immunosuppressive agents may be considered early on in the course of management of such cases. In 86% cases with bilateral PUK, resolution was seen with oral steroids. Role of intravenous pulse steroids has been proven in controlling inflammation in active stage [23].

The presence of active vasculitis demonstrated by biopsy of adjacent conjunctival tissue taken at the time of conjunctival resection would indicate the need for systemic immunosuppression.

Though uncommon in the pediatric population, Mooren's ulcer requires intensive management [24]. Steroids are the first line of therapy but long-term use of steroids is associated with side effects which need a due consideration from the treating ophthalmologist. Long-term therapy with low potency steroids can be considered in children. Methotrexate is an important immunomodulator that is relatively safe in children and is used as a steroid-sparing agent in those at high risk for steroid associated side effects or for maintenance therapy.

Table 5.1 Points suggestive of infectious etiology

• History of trauma/injury with vegetative matter
• History of contact lens use
• Past history of viral keratitis
Slit lamp evaluation suggestive of poor ocular surface, presence of corneal infiltrates and hypopyon

Infectious Ulcerative Keratitis Affecting the Peripheral Cornea [25]

Primarily infective etiology

Targeted anti-microbial treatment based on clinical judgement and culture results following the local protocols for presumed microbial keratitis. Bacterial infections are treated with either combination therapy with fortified antibiotics following local protocols or monotherapy with fourth-generation fluoroquinolones or even second-generation fluoroquinolones such as ciprofloxacin or ofloxacin depending on local preferred practice patterns. Tuberculosis is managed with standard anti-tubercular treatment, any attendant inflammatory sequelae must be dealt with steroids based on clinical assessment to differentiate the stage of active infection which may worsen with steroids (Fig. 5.1). Syphilis is quite rare, but awareness of its likelihood can help provide early cure (Fig. 5.2). It is usually treated with parenteral penicillin, though

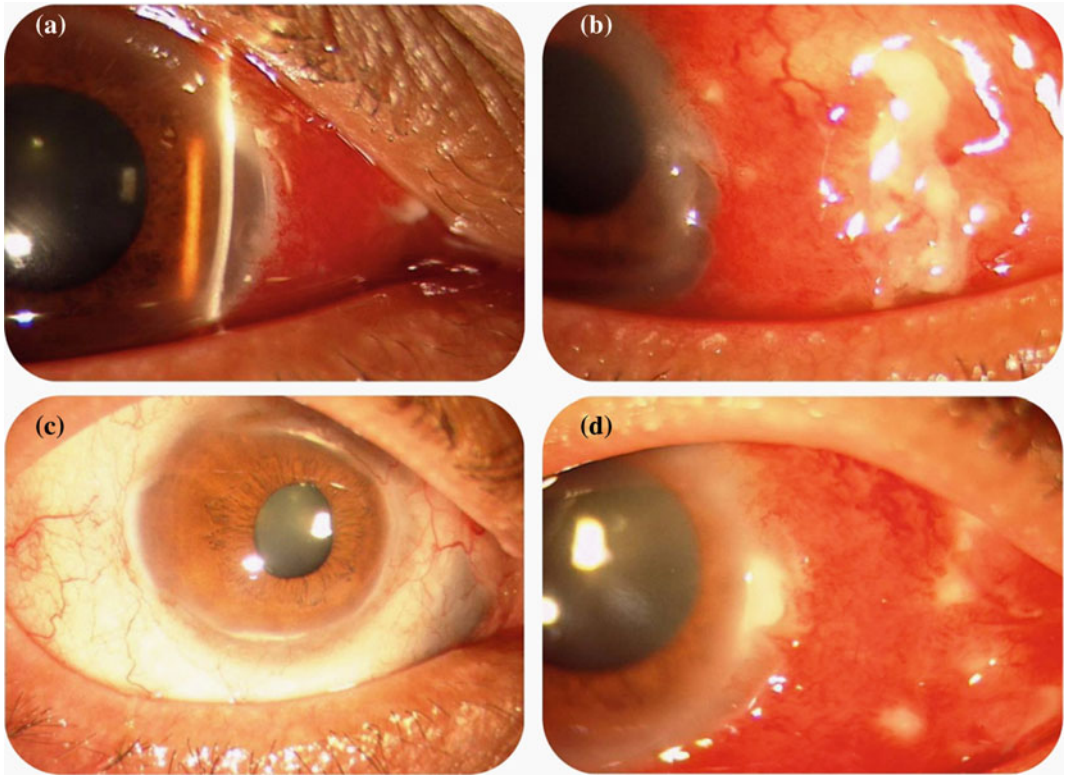

Fig. 5.1 **a**, **b** Slitlamp microscope (10×) clinical photograph of the *Left eye* suggestive of sclerokeratouveitis; **c** Worsening of keratitis with necrotising scleritis seen post steroid use; **d** Healing noted after treatment for tuberculosis was started in view of underlying Sweet's syndrome and primary ocular tuberculosis

erythromycin and doxycycline are also effective against Treponema pallidum. Viral infections could be due to HSV or HVZ and are treated with topical and systemic antivirals such as acyclovir valacyclovir.

Chlamydial infection is treated with oral tetracycline or erythromycin.

Primarily inflammatory etiology with secondary infection

In such situations, one can begin with topical medications to control the infection withholding topical steroids while relying on systemic medications to control the inflammation. Once the local active infection is conquered, one can add topical mild steroids in reduced frequency to reduce the inflammation and promote healing.

General Guidelines for Medical Therapy

Treating Active Disease [26, 27]

The main goal is to control inflammation, halt progression, promote healing of the epithelial defect and repair of damaged stroma, avoid secondary complications, minimize scarring and save or restore vision.

Follow a systematic evidence-based approach.

Institute targeted specific treatment if etiologic agent is known, especially if active infection is present (Table 5.1; Figs. 5.3, 5.4 and 5.5).

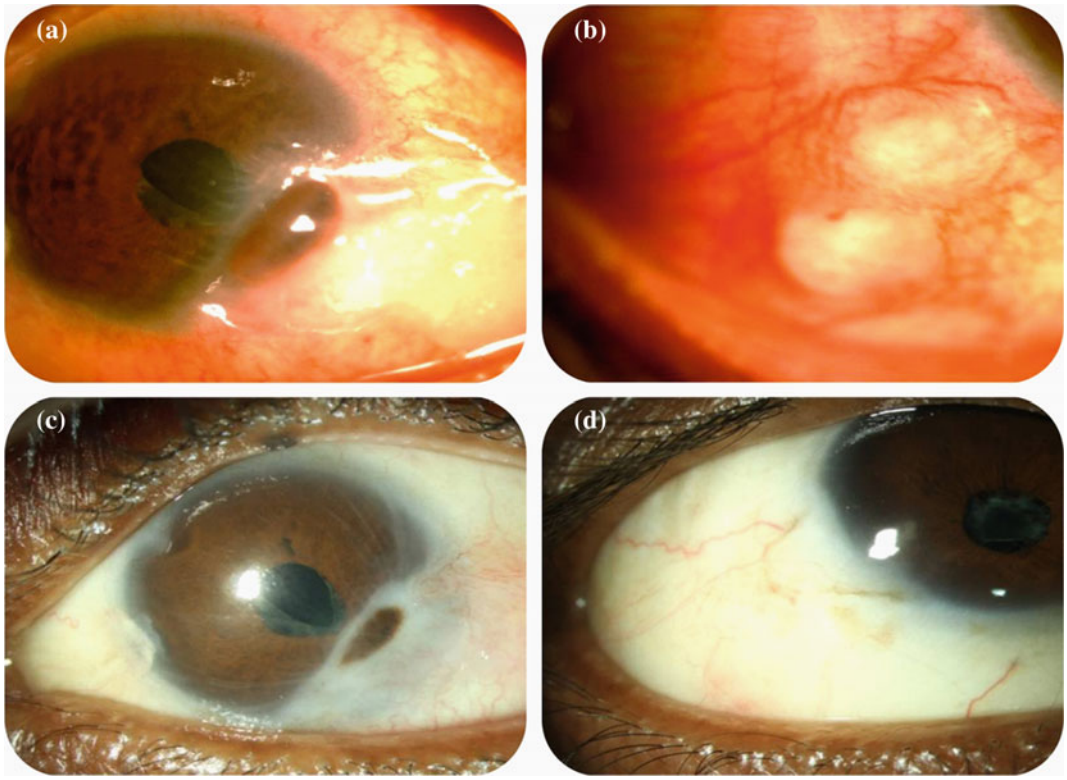

Fig. 5.2 **a** Slitlamp microscope (10×) clinical photograph OD suggestive of Peripheral ulcerative keratitis; **b** Slitlamp microscope (16×) clinical photograph OS suggestive of necrotising scleritis; **c** OD Healed PUK noted after treatment for underlying treponemal infection was started; **d** OS Healing noted. Patient was diagnosed to have genital ulcers and a diagnosis of syphilis was confirmed on laboratory tests

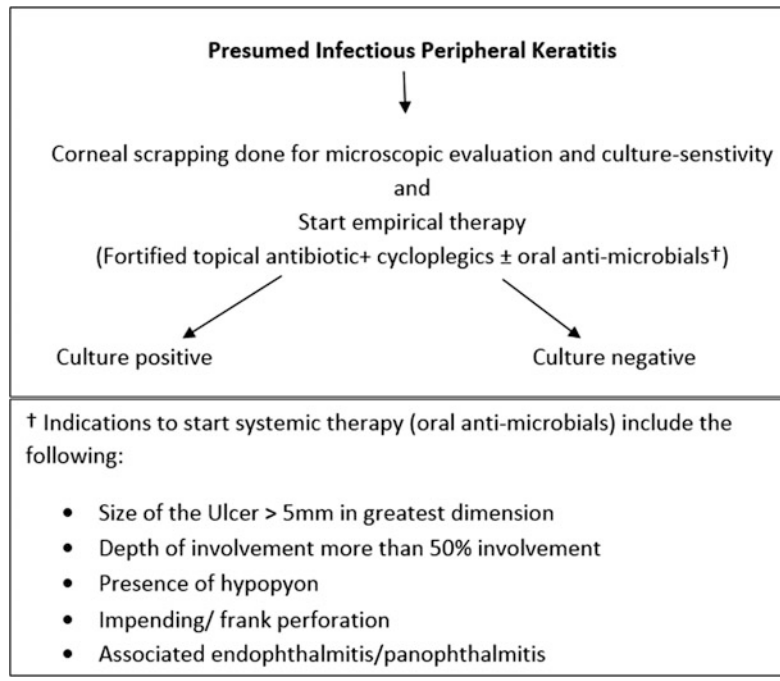

Fig. 5.3 Treatment algorithm for presumed infectious Peripheral ulcerative keratitis

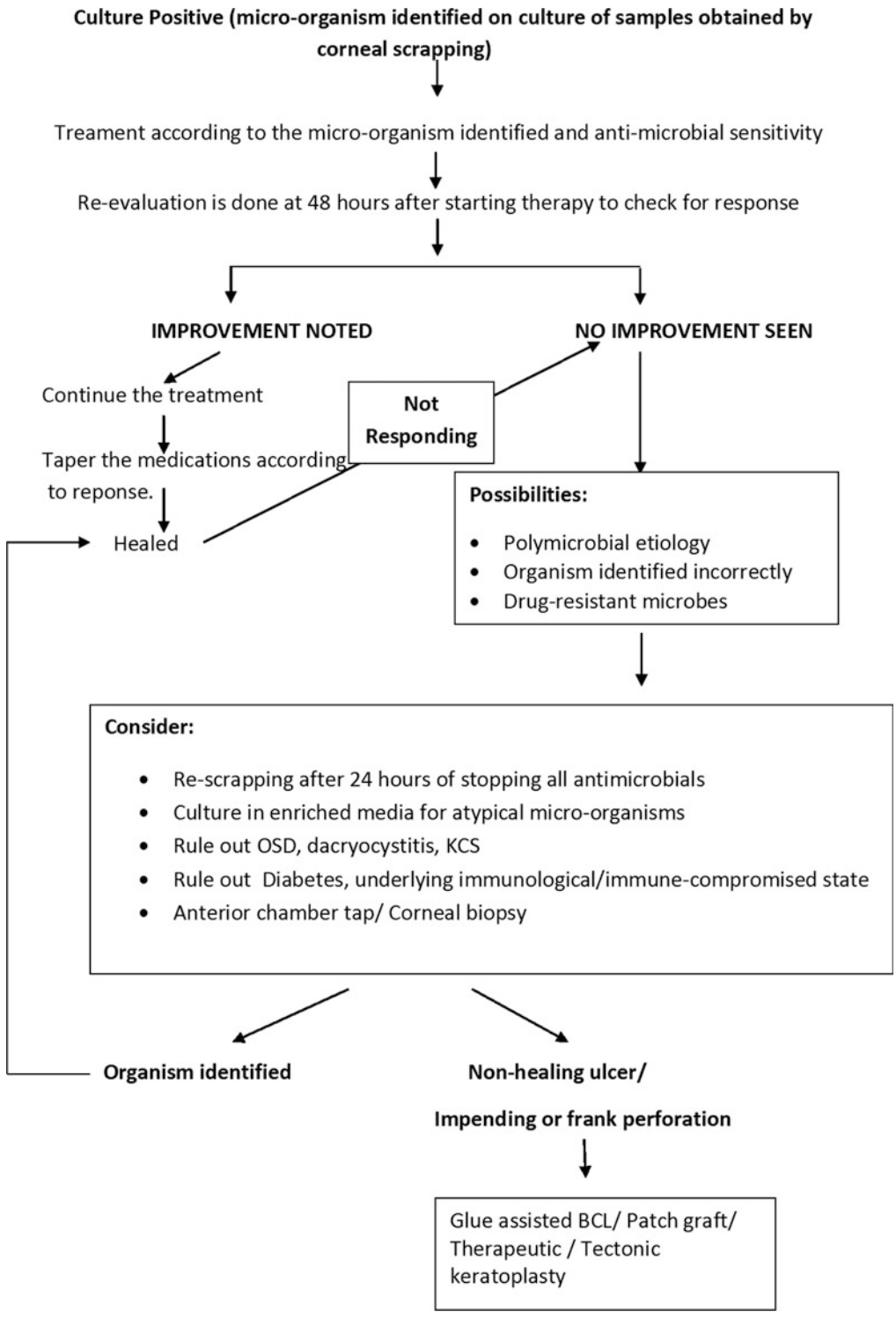

Fig. 5.4 Treatment Algorithm in cases of Infectious Peripheral ulcerative keratitis

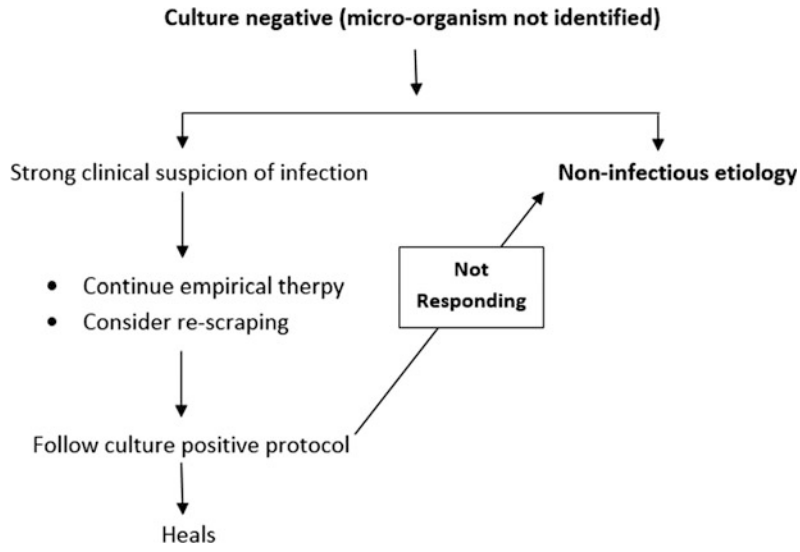

Fig. 5.5 Treatment Algorithm in cases of suspected infectious etiology (culture negative)

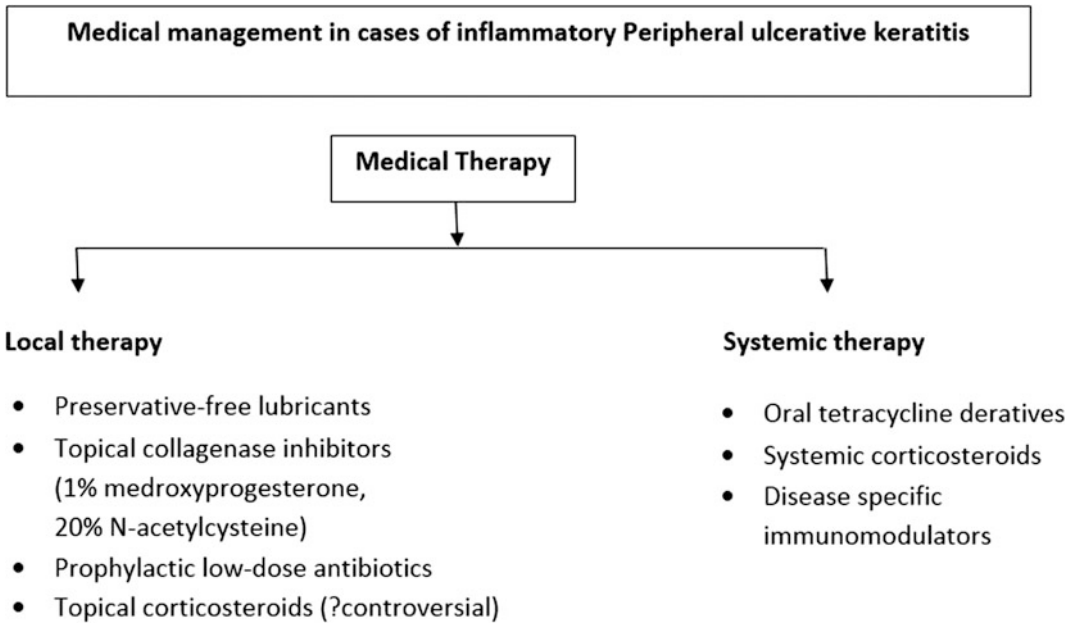

Fig. 5.6 Medical management in cases of inflammatory Peripheral ulcerative keratitis

Plan stepwise treatment beginning with topical steroids for inflammatory ulcers combined with surgical measures depending on the response to therapy or extent of disease (Figs. 5.6 and 5.7).

Be aware of indications for early institution of systemic immunosuppression with chemotherapeutic agents which could include the following [27–31]: (Fig. 5.8).

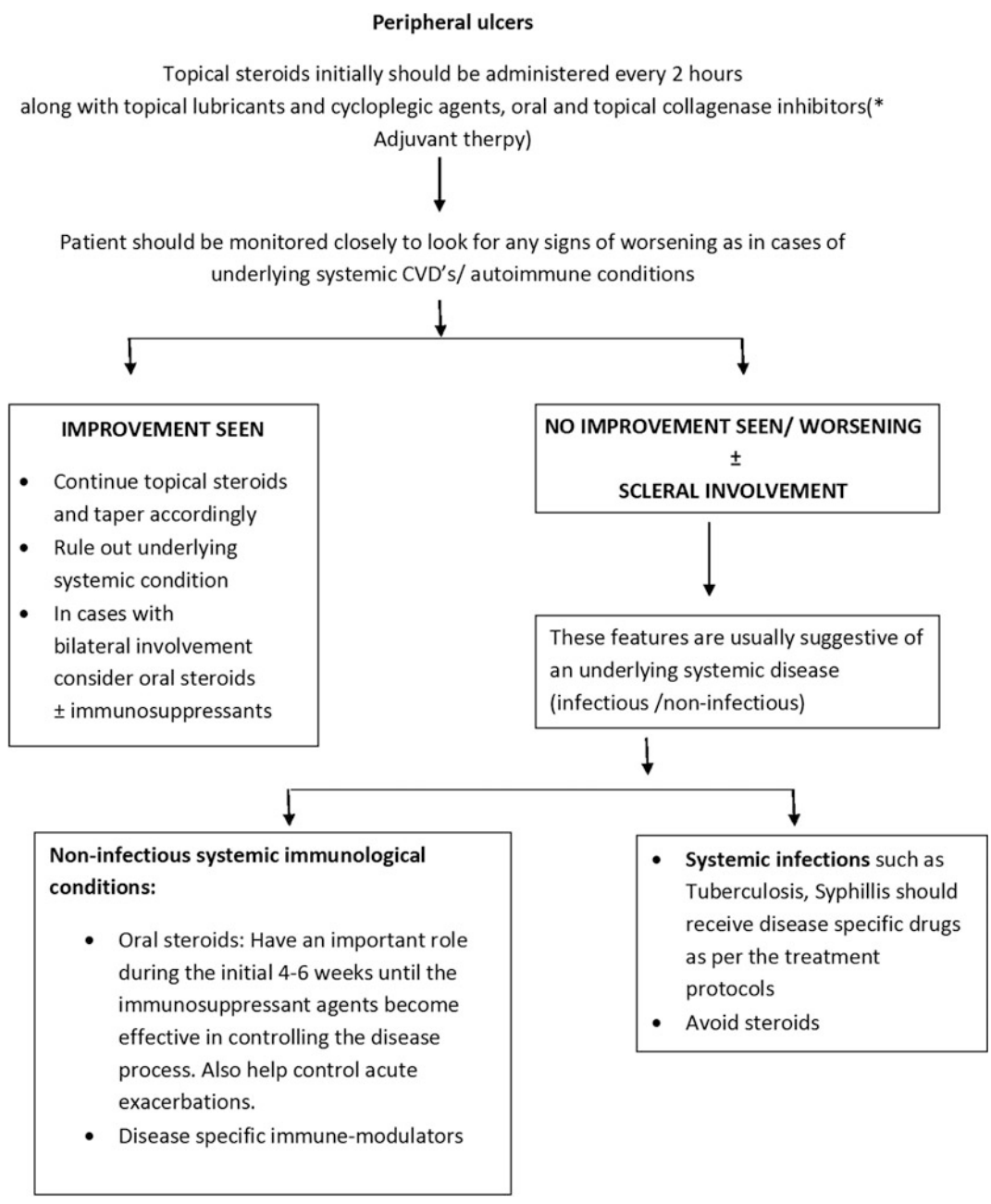

Fig. 5.7 Treatment algorithm for non-infectious immune-inflammatory peripheral ulcers

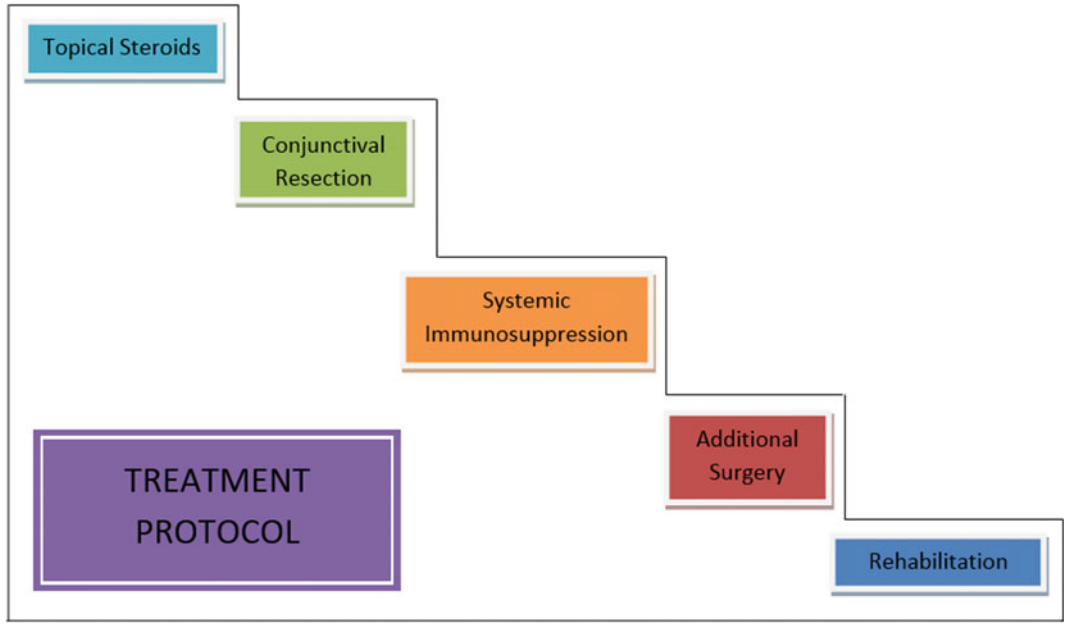

Fig. 5.8 Step-ladder pattern of treatment for Mooren's Ulcer [15]

- PUK with active systemic autoimmune disease particularly potentially lethal vasculitis associated with rheumatoid arthritis, polyarteritis nodosa, Wegener's granulomatosis, and relapsing polychondritis
- PUK with scleritis
- PUK with ocular vasculitis detected by conjunctival biopsy
- PUK with bilateral simultaneous involvement
- PUK with progressive worsening despite aggressive conventional medical and surgical therapy.

Primary Anti-inflammatory Agents as Mainstay of Treatment [10, 27, 29, 32–41]

A step-ladder pattern of approach is important when considering treatment with immunosuppressive agents. The drugs are tapered based on the response seen after 6 months of intensive therapy. Shifting to a less toxic agent is considered in cases when the condition is responding to the treatment and there is adequate control of inflammation [41].

Cyclophosphamide is an important drug used in cases of ulcerative keratitis associated with Rheumatoid and Wegner's. The commonly used medications with their dosage, frequency, duration, and side effects are summarized in Table 5.2.

Adjunctive Therapy [33, 42–47]

Sometimes, a combination of different classes of drugs is required to complement and supplement their role in curing the disease. In such situations the added drug plays an adjuvant role. Cyclosporine A prescribed topically (0.05–2% QID) or orally (3–4 mg/kg/day) has been reported to successfully treat cases by virtue of its action as an immunomodulator by suppressing helper T-cells and stimulating depressed populations of cytotoxic T-cells with the added benefit of acting as a steroid sparing agent in cases developing steroid-induced side effects [44–46].

Additional adjuvant medications include preservative-free tear substitutes or lubricating eye drops to take care of coincident ocular surface disease which is often present in patients with

Table 5.2 Commonly used medications in the treatment of Peripheral ulcerative keratitis

S. No.	Medications	Mechanism of action	Dose	Frequency	Duration	Side effects
1	Prednisolone	Blocks transcription of anti-inflammatory genes	1 mg/kg/day	Single dose	Taper over 8–12 weeks [65]	Hyperglycemia, hypertension, osteoporosis, gastric ulcers
2	Methotrexate	Antimetabolite which inhibits formation of THFR* thus decreasing DNA synthesis It induces apoptosis of T-Helper cells	5–25 mg/week	Once a week	Taper as required	Hepatotoxity, low WBC count, ulcerative stomatitis, nausea, fatigue, renal failure
3	Cyclophosphamide	Alkylating agent Decreases replication of T-cells	2 mg/kg/day	Single dose	Taper as required	Bone marrow suppression, nausea, vomiting, stomach aches, haemorrhagic cystitis, diarrhea
4	Azathioprine	Purine synthesis inhibitor. It inhibits enzyme required for DNA synthesis, thus affecting proliferating cells	1–2.5 mg/kg/day	Single/two divided doses	Taper as required	Hypersenstivity reaction, skin rashes, predisposition to neoplasias, nausea, vomiting, hepatic and renal damage
5	Cyclosporine	Calcineurin inhibitor Inhibits the T-cell activity	2.5–5 mg/kg/day	Divided doses	Taper as required	Gum hyperplasia, hypertension, hyperkalemia, hirsuitism, fever, vomiting, dyspnea, convulsions
6	Mycophenolate mofetil	Inhibits purine synthesis pathway inhibits replication of T and B cells	1–3 gm/day	Two divided doses	Taper as required	Gastrointestinal upset, elevated liver enzymes, bone marrow suppression, malaise, fatigue
Recent advances						
1	Infliximab	Anti-TNF-α chimeric monoclonal antibody	3 mg/kg(I.V.)	0,2 and 6 weeks, and then 2 monthly	18 months	Infections, drug induced lupus, psoriatic lesions, demyelinating diseases, new onset vitiligo
2	Etanercept	TNF inhibitor (decoy receptor)			Taper as required	Serious infections, reactivation of tuberculosis and hepatitis B
3	Rituximab	Anti-CD20 chimeric monoclonal antibody			Taper as required	Infusion reaction, cardiac arrest, reactivation of infections

peripheral ulcerative keratitis and also help wash off, remove, and dilute the effect of harmful inflammatory mediators on the ocular surface; topical antibiotics to minimize secondary infection; oral Vitamin C to enhance collagen synthesis and facilitate the process for stromal repair and oral Doxycycline, both as a medium to inhibit collagenolysis by inhibiting matrix metalloproteinase and as a means to also specifically take care of active blepharitis when present. Topical agents to reduce collagenolysis and promote healing which are often used include 1% medroxyprogesterone eye drops and 20% acetylcysteine by virtue of their effects as collagenase inhibitors or inhibitors of collagenase synthetase.

Recent Advances [8, 9, 39, 40, 48–64]

Recently there has been a surge of articles in the literature-sharing experience of successful usage of biologic agents such as infliximab, etanercept, and rituximab which have a direct biologic blocking effect on inflammatory mediators. Infliximab was approved for clinical use by US FDA in 1999 and was first reported for controlling ophthalmic inflammation in 2001 for patients with panuveitis and rheumatoid arthritis with scleritis. Subsequent reports have extended their usage to control inflammation in patients with PUK associated with systemic vasculitic autoimmune diseases like rheumatoid arthritis, Crohn's disease, and Wegener's granulomatosis.

Infliximab is a monoclonal antibody against the pro-inflammatory cytokine tumor necrosis factor alpha or TNF-α. The latter is known to stimulate the production of matrix metalloproteinases responsible for stromal lysis in the cornea in patients with PUK. Infliximab binds to soluble TNF-α, and also by blocking its receptor binds transmembrane TNF-α. Inflammatory cells which express transmembrane TNF-α bind to infliximab and are thus susceptible to complement mediated lysis, enhancing its anti-inflammatory effect. Etanercept is a human recombinant dimeric fusion protein mimicking the effect of soluble TNF-α receptors in binding the free-floating mediator of inflammation, but unlike infliximab has no effect on membrane-bound TNF-α. Hence, though reported for treatment of necrotizing scleritis and keratitis [9], etanercept has a lesser anti-inflammatory effect than infliximab. Another agent rituximab, which is a chimeric antibody against CD 20–α and depletes B lymphocytes has been used for treatment of PUK associated with Wegener's granulomatosis [54] and recalcitrant scleritis.

It is important to be aware of the potential of these new medications, but bear in mind that they are to be used selectively in extreme situations. One has to screen for underlying risk for precipitating congestive cardiac failure and un-harnessing latent infections like tuberculosis and be prepared to watch out for harmful effects due to opportunistic colonization and other rare complications.

Conclusions

PUK is a potentially blinding disease, sometimes proving to be recalcitrant to all modes of therapy and often associated with lethal potentially life-threatening systemic vasculitic autoimmune diseases needs to be treated with a systematic approach in conjunction with a physician and specialist in treating complex rheumatological disorders [65]. It is increasingly being recognized that systemic immunosuppressive measure is required to halt progression in consonance with local topical, both remedial and salvage surgical therapy and other ameliorative measures. New-emerging drug therapies proving to be successful in controlling inflammation by newer mechanisms indicate that there may be hope for recalcitrant cases with relentless progression.

Compliance With Ethical Requirements Radhika Tandon, Archita singh, and Virender Sangwan declare that they have no conflict of interest.

No human or animal studies were carried out by the authors for this article.

References

1. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol. 2012;6:747–54.
2. Bartly J, Mondino BJ. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95:463–72.
3. Allansmith MR, McClellan B. Immunoglobulins in the human cornea. Am J Ophthalmol. 1975;80: 123–32.
4. Mondino BJ, Brady KJ. Distribution of hemolytic complement activity in normal human donor cornea. Arch Ophthalmol. 1981;99:1430–43.
5. Dana MR, Qian Y, Hamrah P. Twenty five year panorama of corneal immunology. Cornea. 2000;19: 625–43.
6. Hogan MJ, Alvarado JA. The limbus. In: Hogan MJ, editor. Histology of the human eye: an Atlas and textbook. Philadelphia, PA: WB Saunders; 1971.
7. Mondino BJ. Experimental aspects and models of peripheral corneal disease. Int Ophthalmol Clin. 1986;26:5–14.
8. Thomas J, Pflugfelder S. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea. 2005;24:742–4.
9. Hernandez-Illas M, Tozman E, Fulcher S, et al. Recombinant human tumor necrosis factor receptor Fc fusion protein (Etanercept): experience as a therapy for sight-threatening scleritis and sterile corneal ulceration. Eye Contact Lens. 2004;30:2–5.
10. Virasch VV, Brasington RD, Lubniewski AJ. Corneal disease in rheumatoid arthritis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis, MO: Elsevier; 2011.
11. Sainz de la Maza M, Molina N, Gonzales LA, Doctor PP, Tauber J, Foster CS. Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119:43–50.
12. Tauber J, Sainz de la Maza M, HoangXuan T, Foster CS. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea. 1990;9:66–73.
13. Shiuey Y, Foster CS. Peripheral ulcerative keratitis and collagen vascular disease. Int Ophthalmol Clin. 1998;38:21–32.
14. Squirrel DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology. 1999;38: 1245–8.
15. Brown SI, Mondino BJ. Therapy of Mooren's ulcer. Am J Ophthalmol. 1984;98:1–6.
16. Brown SI. What is Mooren's ulcer? Trans Ophthalmol Soc UK. 1978;98:390–92.
17. Chow YC, Foster CS. Mooren's ulcer. Int Ophthalmol Clin. 1996;36:1–13.
18. Brown SI, Mondino BJ, Rabin BS. Autoimmune phenomenon in Mooren's ulcer. Am J Ophthalmol. 1976;82:835–40.
19. Kafkala C, Choi J, Zafirakis P, et al. Mooren ulcer: an immunopathologic study. Cornea. 2006;25:667–73.
20. Foster CS, Kenyon KR, Greiner J. The immunopathology of Mooren's ulcer. Am J Ophthalmol. 1979;88:149–59.
21. Gottsch JD, Liu SH, Minkovitz JB, Goodman DF, Srinivasan M, Stark WJ. Autoimmunity to a cornea associated stromal antigen in patients with Mooren's ulcer. Invest Ophthalmol Vis Sci. 1995;36:1541–7.
22. Garg P, Sangwan VS. Mooren's ulcer. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis, MO: Elsevier; 2011.
23. Ashar JN, Mathur A, Sangwan VS. Immunosuppression for Mooren's ulcer: evaluation of the stepladder approach—topical, oral and intravenous immunosuppressive agents. Br J Ophthalmol 2013;97:1391–4.
24. Mathur A, Ashar J, Sangwan VS. Mooren's ulcer in children. Br J Ophthalmol. 2011. doi:10.1136/bjophthalmol-2011-300985.
25. Chung G. Phlyctenular keratoconjunctivitis and marginal staphylococcal keratitis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis, MO: Elsevier; 2011.
26. Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. Curr Opin Ophthalmol. 2000;11:468–71.
27. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Ophthalmology. 1984;91:1253–63.
28. Akpek EK, Thorne JE, Qazi FA, Do DV, Jabs DA. Evaluation of patients with scleritis for systemic disease. Ophthalmology. 2004;111:501–6.
29. Messmer E, Foster S. Destructive corneal and scleral disease associated with rheumatoid arthritis: medical and surgical management. Cornea. 1995;14:408–17.
30. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:430–44.
31. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43: 379–96.
32. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin N Am. 2007;33:835–54.
33. Gregory JK, Foster CS. Peripheral ulcerative keratitis in the collagen vascular diseases. Int Ophthalmol Clin. 1996;36:21–30.
34. McCarthy JM, Dubord PJ, Chalmers A, Kassen BO, Rangno KK. Cyclosporin A for the treatment of necrotising scleritis and corneal melting in patients with rheumatoid arthritis. J Rheumatol. 1992;19: 1358–61.
35. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients

with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130:492–513.
36. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid sparing therapy for noninfectious ocular inflammation. Ophthalmology. 2008;115:1826–32.
37. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology. 2005;112:1472–7.
38. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology. 2008;115:1416–21.
39. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. AntiTNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies. Systematic review and metaanalysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275–85.
40. Chung ES, Packer M, Lo KH, et al. Randomized, doubleblind, placebo controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor alpha, in patients with moderate to severe heart failure. Results of the antiTNF therapy against congestive heart failure (ATTACH) trial. Circulation. 2003;107:3133–40.
41. Saw VPJ. Immunotherapy for corneal inflammatory disorders: stepping up and down the ladder. Br J Ophthalmol. 2013;97:1364–7. doi:10.1136/bjophthalmol-2013-303359.
42. Perry HD, Golub LM. Systemic tetracyclines in the treatment of noninfected corneal ulcers: a case report and proposed new mechanism of action. Ann Ophthalmol. 1985;17:742–4.
43. Golub LM, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. Crit Rev Oral Biol Med. 1991;2:297–321.
44. Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer: current concepts in management. Indian J Ophthalmol. 1997;45:7–17.
45. Jhao J, Jin X. Immunological analysis and treatment of Mooren's ulcer with cyclosporine A applied topically. Cornea. 1993;12:481–8.
46. Tandon R, Chawla B, Verma K, Sharma N, Titiyal JS. Outcome of treatment of Mooren ulcer with topical cyclosporine A 2%. Cornea. 2008;27:859–61.
47. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea. 2000;19:274–7.
48. Odorcic S, Keystone EC, Ma JJ. Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up. Cornea. 2009;28:89–92.
49. Oh YJ, Kim MK, Wee WR. Infliximab for progressive peripheral ulcerative keratitis in a patient with juvenile rheumatoid arthiritis. Jpn J Ophthalmol. 2011;55:70–1.
50. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behcet's disease. Lancet. 2001;358:295–6.
51. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Care Res. 2001;45:252–7.
52. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn's disease. Am J Ophthalmol. 2011;152:183–8.
53. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight threatening panuveitis in Behcet's disease. Lancet. 2001;358:295–6.
54. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:430–44.
55. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Care Res. 2001;45:252–7.
56. Oh YJ, Kim MK, Wee WR. Infliximab for progressive peripheral ulcerative keratitis in a patient with juvenile rheumatoid arthiritis. Jpn J Ophthalmol. 2011;55:70–1.
57. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn's disease. Am J Ophthalmol. 2011;152:183–8.
58. Thomas J, Pflugfelder S. Therapy of progressive rheumatoid arthritis associated corneal ulceration with infliximab. Cornea. 2005;24:742–4.
59. TugalTutkun I, Ayranci O, Kasapcopur O, Kir N. Retrospective analysis of children with uveitis treated with infliximab. J AAPOS. 2008;12:611–3.
60. Murphy CC, Ayliffe WH, Booth A, Makanjuola D, Andrews PA, Jayne D. Tumor necrosis factor a blockade with infliximab for refractory uveitis and scleritis. Ophthalmology. 2004;111:352–6.
61. Goff BL, Vabres B, Cochereau I, et al. Eye loss by exogenous endophthalmitis following antitumor necrosis factor therapy: a report of 4 cases. J Rheumatol. 2009;36:2202–3.
62. Puli SR, Benage DD. Retinal vein thrombosis after infliximab (Remicade) treatment for Crohn's disease. Am J Gastroenterol. 2003;98:939–40.
63. Theodossiadis PG, Markomichelakis NN, Sfikakis PP. Tumor necrosis factor antagonists. Preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina. 2007;27:399–413.

64. HernandezIllas M, Tozman E, Fulcher S, et al. Recombinant human tumor necrosis factor receptor Fc fusion protein (Etanercept): experience as a therapy for sight threatening scleritis and sterile corneal ulceration. Eye Contact Lens. 2004;30:2–5.

65. Maneo A, Naor J, Lee HM, Hunter WS, Rootman DS. Three decades of corneal transplantation: indications and patient characteristics. Cornea. 2000;19:7–11.

General Principles of Surgery

6

Hazel Anne Lin, Hui Chen Charmaine Chai and Donald Tan

Introduction

Peripheral Ulcerative Keratitis (PUK) consists of a group of diseases, which eventually lead to peripheral corneal thinning with potentially devastating consequences. These include inflammatory disorders, infections and a variety of ocular and systemic disorders, which can result in ocular surface instability. In addition, cornea ectatic conditions like Pellucid Marginal Degeneration can behave very similarly to PUK as it results in peripheral thinning, which affects visual quality. Table 6.1 illustrates a list of causes of PUK.

Treatment is individualized and frequently involves co-management with internal physicians. In most instances, medical treatment may suffice to halt disease progression and prevent future ulceration. However, in some patients, surgical intervention is undertaken either as an adjunct to medical therapy, when medical therapy proves inadequate to halt disease progression, or when complications arise with the primary aim of restoring tectonic integrity (Table 6.2). This chapter aims to explore why and when surgery should be considered, and what surgery to perform.

Previous studies have shown many different surgical approaches to management of PUK, depending on the cause and extent of disease. Penetrating keratoplasty (PK) was preferred to restore tectonic integrity prior to advancements in surgical techniques [1, 2]. However, graft survival was poor, and compared to optical grafts with survival rates of 72.0%, that of tectonic and therapeutic grafts were 41.7 and 58.3%, respectively, at 3 years [3]. Sequential cryopreserved PK followed by optical PK was found to have a 72.9% one-year graft survival [4], compared to 68.3% for tectonic grafts during the same period [3]. In PUK with peripheral melts, larger, decentred, circular grafts were used. As these were peripheral and possibly eccentrically shaped, it increased the chances of vascularisation, peripheral anterior synechiae, and anterior chamber angle and graft failure. In addition, areas of healthy, unaffected cornea were replaced, and these grafts frequently involved the visual axis. In view of these poor rates of graft survival, standard full thickness large keratoplasties should be avoided if other less aggressive or more successful procedures are possible.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_6

Table 6.1 Conditions that result in PUK

Causes of PUK
1. Inflammatory disorders
– Systemic vasculitides
• Rheumatoid arthritis
• Wegener's granulomatosis
• Polyarteritis nodosa
• Relapsing polychondritis
– Ocular conditions
• Mooren's Ulcer
• Marginal keratitis
2. Infections
– Viruses
– Bacteria
– Protozoa
– Fungi
3. Ocular surface instability
– Limbal stem cell deficiency
– Previous ocular surface surgery
– Severe chemical injury
– Inflammatory conditions
• Stevens Johnson syndrome
• Ocular cicatricial pemphigoid
4. Ectasia
– Pellucid marginal degeneration

Table 6.2 Complications of PUK

Complications of PUK
1. Disease progression—the area of corneal melt can extend circumferentially, centripetally and centrifugally to involve the central cornea, limbus and sclera
2. Perforation—this serious complication requires urgent therapy to restore integrity of the globe
3. Secondary infection—during the active phase of PUK, epithelial defects overlying the area of melt predisposes to secondary microbial infections in both infective and non-infective causes of PUK
4. Ectasia and astigmatism—irregular astigmatism results in a decrease in visual acuity and needs to be addressed together with treatment of the underlying disease

Lamellar keratoplasty (LK) is frequently performed for corneal disorders, including surgical treatment of PUK. This can be performed even in infective conditions and was found to have reduced the rates of endothelial failure, graft rejection, graft failure, and secondary endophthalmitis. The 5-year survival rate was shown to be higher at 66.8% versus 56.2% in PK [5–8].

Vanathi et al. described the use of PK, LK and mushroom grafts for a variety of corneal perforations with various aetiologies. Mushroom

grafts were performed for perforations with or without iris incarceration with a circumferential flange of corneal thinning at the edges of the perforation [9] with good tectonic outcomes. However, only 70.7% of all patients achieved visual acuity of 6/24 or better for all graft types, for reasons such as cataract formation, graft-host interface issues and astigmatism.

In addition to tectonic support, surgical intervention has a role in optical rehabilitation in PUK. This is sometimes necessary as corneal ectasia may develop post-keratoplasty. Vajpayee et al. described using "Tuck in" LK with successful improvement in visual acuities and significant reduction in astigmatism [10].

Although there exists a variety of surgical grafts, which can be used in PUKs, many involve larger than needed grafts, with "wastage" of healthy adjacent cornea and limbal tissues. We will now discuss our management principles in dealing with PUK, our indications for surgery therapy, and describe our latest surgical technique.

Management, Timing and Indications for Surgery

In patients with PUK, management can be broadly divided into medical, adjunctive therapy and/or surgical interventions. This may occur in the form of keratoplasty with a minimalist approach.

It is prudent to adopt a stepwise approach to escalation of therapy depending on the stage and severity of PUK (Fig. 6.1). Medical therapy is the mainstay of treatment for PUKs to treat the underlying primary condition and in so doing to prevent worsening and even halt the disease process at its early stages. In addition to systemic therapy, topical therapy reduces inflammation, thereby curbing cornea melting, promotes healing of epithelial defects, and prevents or treats any infections. Long-term medical therapy, usually in the form of systemic immunosuppression, is also indicated to maintain a disease-free state, or in cases of recurrent or relapsing disease and in patients who have undergone keratoplasty.

If disease progression occurs despite full medical therapy, adjunctive procedures can be undertaken. This may help to curb the progression of disease while avoiding the complexities of keratoplasty and its subsequent management.

Examples of adjunctive procedures include corneal gluing [11] (with or without grafts), Amniotic Membrane Transplantation [12, 13] and Conjunctival Resection [14] (in Mooren's Ulcer). However, although these techniques serve to restore and protect tectonic integrity of the cornea, it is insufficient for improvement of optical function.

Finally, more invasive surgical interventions should be undertaken in disease progression with severe melting which could lead to descemetocele formation or perforation, or if the patient already presents with advanced disease. The indications and surgical principles are listed in Table 6.3.

In our patients with PUK, when conservative measures are insufficient to control the disease process and the patient is at high risk of worsening morbidity, surgical intervention is necessary. We aim to concurrently achieve tectonic, therapeutic and optical goals, regardless of aetiology.

Our surgical method of choice is to perform ***tectonic, compressive, C-shaped lamellar corneal grafts*** [15], which uses undersized donor tissue to not only treat the peripheral melt, correct ectasia and reduce astigmatism, but also to reduce the risks of graft rejection and failure. This is similar to a technique described by Schanzlin et al. [16], with the addition of compressive effect of the graft to reduce ectasia and negate its effect of tissue protrusion. Although some patients had recurrence of disease, and required repeated grafts and in addition to cataract surgery, they achieved good visual outcomes. Figure 6.2a shows a patient who had significant inferior corneal thinning from Terrien's Marginal Degeneration and a preoperative cylinder of 8 dioptres. After undergoing compressive C-shaped LK (Fig. 6.2b), there was a good tectonic outcome and stable refraction with good visual acuity.

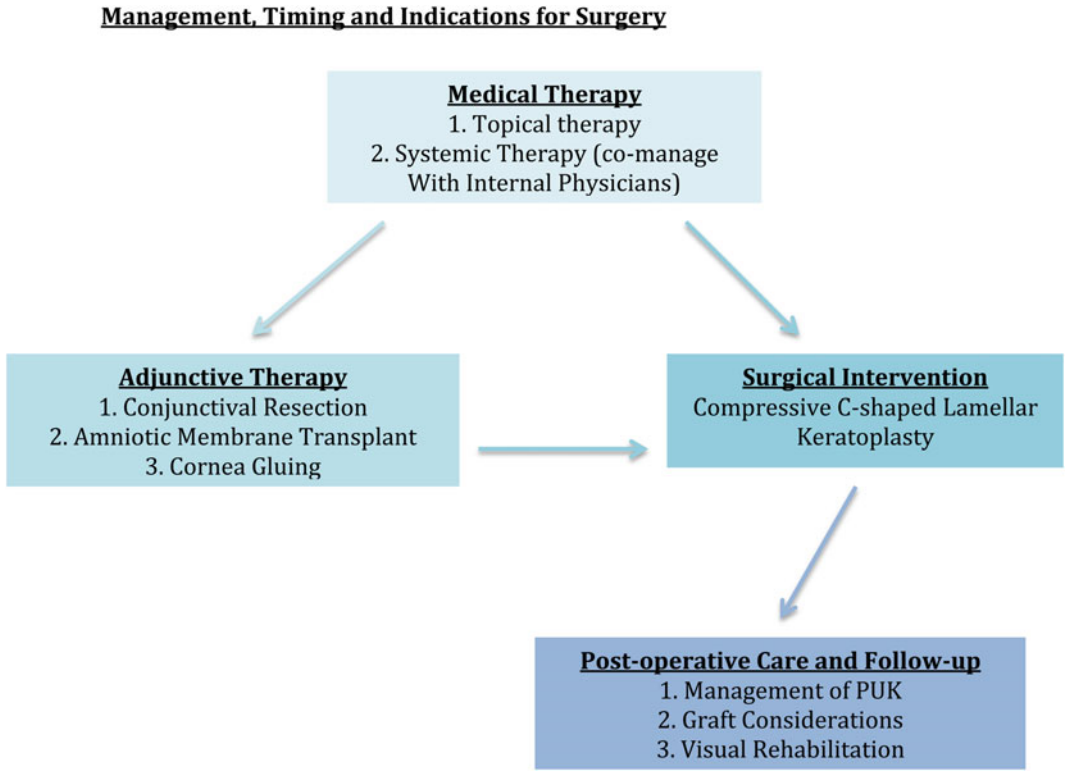

Fig. 6.1 Treatment algorithm for PUK

Table 6.3 Surgical Indications and Principles

Surgical indications
1. Tectonic/therapeutic: increasing depth of melt leading to descemetocele formation or impending perforation
2. Tectonic/therapeutic: advancing extension of melt circumferentially and/or centrally
3. Optical: after the active disease process has been treated—for visual rehabilitation of ectasia and induced astigmatism, and for structural stability of the residual thinning
Surgical principles
1. Restore structural integrity of the peripheral cornea in severe or progressive disease with tectonic keratoplasty
2. Adopt a minimalist approach—performing anterior lamellar surgery when possible, avoiding unnecessary replacement of unaffected central cornea, and minimizing limbal stem cell damage
3. Restore and retain visual function—to reduce ectasia, address topographic changes and correct irregular astigmatism

We managed a 60-year-old Burmese male, who first presented in June 1999 with a background history of Mooren's ulcer. He had undergone right eye Gunderson conjunctival flap (August 1998) and PK (December 1998), in addition to left eye conjunctival resection (May 1999) in Burma. At presentation, he had a sealed perforation of his right cornea, and left eye corneal melt. His right eye experienced multiple episodes of corneal melting and required repeated surgeries. This was complicated by graft rejection and fungal infections, eventually resulting in evisceration as a result of endophthalmitis. Similarly, his left eye also experienced multiple

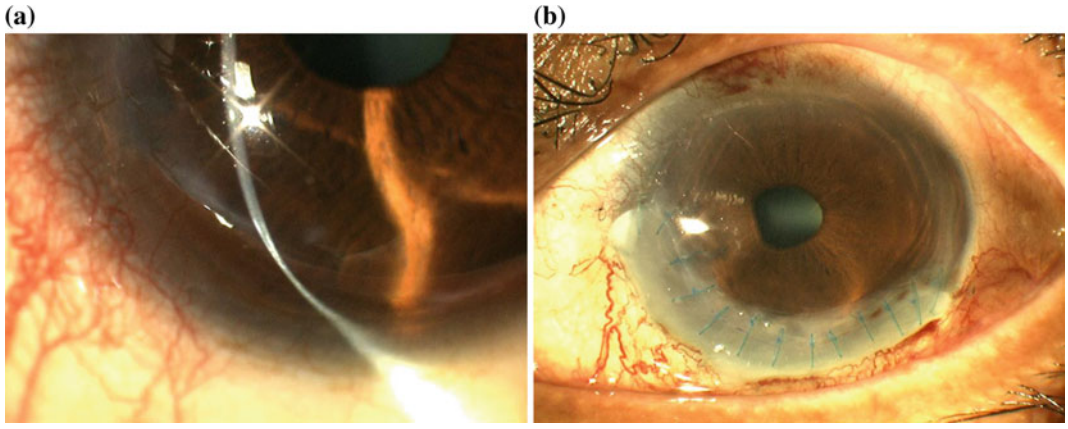

Fig. 6.2 **a** Preoperative photo showing inferior corneal thinning and ectasia. **b** Postoperative refraction was +1.00/−1.5 × 120. The patient had a vision of 6/9

episodes of corneal melting (Fig. 6.3a–h) and has been successfully treated with repeated C-shaped LK. He was treated with topical corticosteroids, and multiple cycles of systemic immunosuppressive agents managed by the rheumatologist.

The cases described demonstrate how this procedure can be repeated, while achieving good

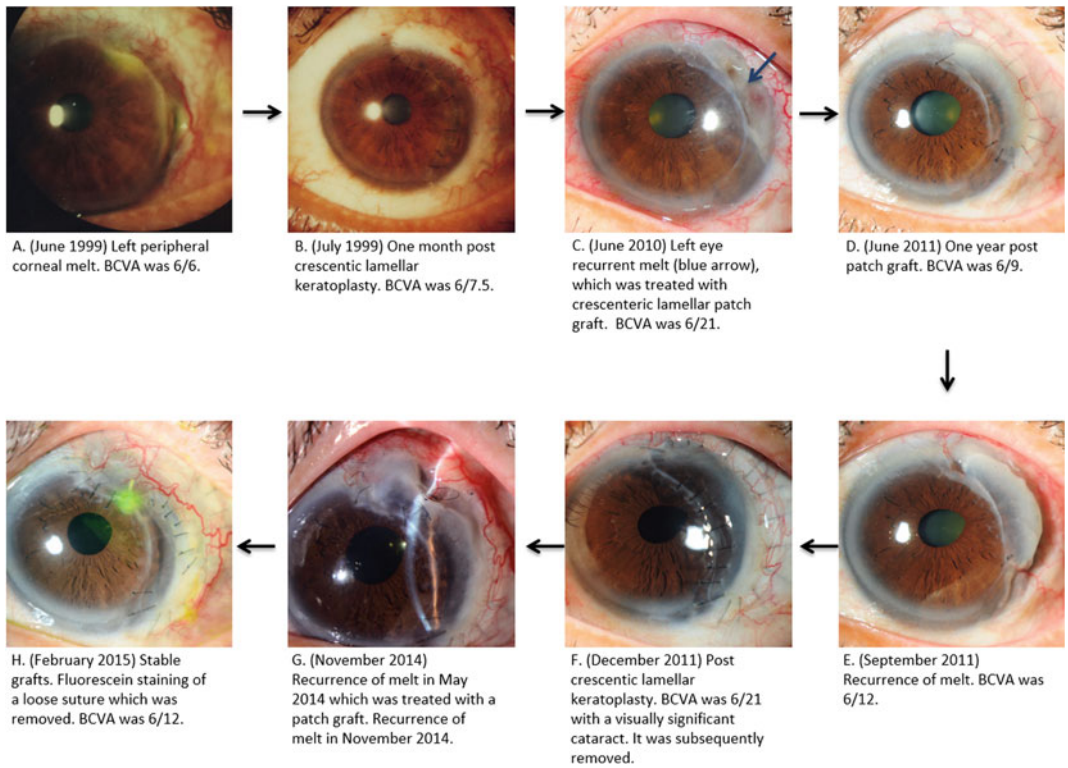

Fig. 6.3 **a**–**h** Progression of left eye recurrent corneal melt, with multiple patch grafts

Table 6.4 Postoperative Considerations

Postoperative care and considerations
1. Continue treatment of the underlying disease
– Anti-microbial therapy for infections
– Co-management with internal physicians for systemic and topical anti-inflammatory or immunosuppressive therapy for the primary condition
2. Management of the graft
– Reduce inflammation (both systemically and locally)
• Prevention of graft rejection and failure
– Antibiotic prophylaxis to prevent recurrent or secondary infections in view of immunosuppressive therapy and use of bandage contact lenses
– Other associated ocular complications and considerations
• Chronic steroid therapy—predisposes to glaucoma and cataract formation
• Limbal stem cell deficiency—potentially lead to persistent epithelial defects, ulceration and melting
3. Management of the ocular surface
– Promote re-epithelisation of the peripheral donor graft surface with the use of bandage contact lenses, and preservative-free medications
– Appropriate treatment of localized limbal stem cell deficiency
4. Visual Rehabilitation with appropriate and timely suture removal, astigmatic correction and secondary surgeries if necessary

visual acuity outcomes. The importance of postoperative care and compliance has to be emphasized and will be touched on later.

We will describe in detail our surgical technique of performing C-shaped LK in Chap. 10, which essentially describes using various trephines to mark out the area of "C-shaped" tissue, manual cutting of the recipient edges and lamellar bed according to the premarked areas, and duplication of the same "C-shape" in the donor tissue, with a deliberate under sizing of the width of the circumferential graft tissue to induce peripheral flattening and reduction of the ectasia.

Postoperative Care

After keratoplasty has been performed, meticulous postoperative care is essential to ensure success of intervention. Concurrent continuous treatment of the underlying disease and commencement of long-term postoperative graft management is crucial for disease eradication and graft survival. Close and timely postoperative surveillance is important to identify complications of disease and treatment, which have to be promptly addressed (Table 6.4).

Conclusions

Peripheral melting disorders require surgical intervention when medical treatment is insufficient and there is continual tissue destruction and the impending risk of perforation. The key is to identify and treat the primary condition, and when necessary, to select and perform the appropriate surgical intervention.

Peripheral lamellar "C" shaped grafts can effectively restore tectonic integrity, while maintaining a reasonable corneal contour to enhance visual acuity. In addition, this method also preserves healthy, unaffected cornea, unlike previous methods of keratoplasty.

Finally, postoperative continuity of care and surveillance is essential to ensure success of the keratoplasty and to manage other complications that may arise.

Conflict of Interest Hazel Anne Lin, Hui Chen Charmaine Chai and Donald Tan declare that we have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

The authors for this article did not carry out animal studies for this article.

References

1. Tan MH, Chen SD, Rubinstein A, Bron AJ. Corneal perforation due to severe peripheral ulcerative keratitis in Crohn disease. Cornea. 2006;25(5):628–30.
2. Raizman MB, de la Maza MS, Foster CS. Tectonic keratoplasty for peripheral ulcerative keratitis. Cornea. 1991; 10(4):312–6.
3. Tan DT, Janardhanan P, Zhou H, Chan YH, Htoon HM, Ang LP, Lim LS. Penetrating keratoplasty in Asian eyes: the Singapore corneal transplant study. Ophthalmology. 2008;115(6):975–82.
4. Lim LS, Arundhati A, Tan DT. Sequential therapeutic penetrating keratoplasty with cryopreserved and fresh corneal tissue for severe infectious keratitis: a case-control study. Cornea. 2011;30(7):739–43.
5. Ang M, Mehta JS, Sng CC, Htoon HM, Tan DT. Indications, outcomes, and risk factors for failure in tectonic keratoplasty. Ophthalmology. 2012;119 (7):1311–9.
6. Anshu A, Parthasarathy A, Mehta JS, Htoon HM, Tan DT. Outcomes of therapeutic deep lamellar keratoplasty and penetrating keratoplasty for advanced infectious keratitis: a comparative study. Ophthalmology. 2009;116(4):615–23.
7. Susiyanti M, Mehta JS, Tan DT. Bilateral deep anterior lamellar keratoplasty for the management of bilateral post-LASIK mycobacterial keratitis. J Cataract Refract Surg. 2007;33(9):1641–3.
8. Parthasarathy A, Tan DT. Deep lamellar keratoplasty for acanthamoeba keratitis. Cornea. 2007;26 (8):1021–3.
9. Vanathi M, Sharma N, Titiyal JS, Tandon R, Vajpayee RB. Tectonic grafts for corneal thinning and perforations. Cornea. 2002;21(8):792–7.
10. Vajpayee RB, Jhanji V, Beltz J, Moorthy S. "Tuck in" lamellar keratoplasty for tectonic management of postkeratoplasty corneal ectasia with peripheral corneal involvement. Cornea. 2011;30(2):171–4.
11. Gupta N, Sachdev R, Tandon R. Sutureless patch graft for sterile corneal melts. Cornea. 2010;29 (8):921–3.
12. Ngan ND, Chau HT. Amniotic membrane transplantation for Mooren's ulcer. Clin Exp Ophthalmol. 2011;39(5):386–92.
13. Jia Y, Gao H, Li S, Shi W. Combined anterior chamber washout, amniotic membrane transplantation, and topical use of corticosteroids for severe peripheral ulcerative keratitis. Cornea. 2014;33 (6):559–64.
14. Agrawal V, Kumar A, Sangwan V, Rao GN. Cyanoacrylate adhesive with conjunctival resection and superficial keratectomy in Mooren's ulcer. Indian J Ophthalmol. 1996;44(1):23–7.
15. Cheng CL, Theng JT, Tan DT. Compressive C-shaped lamellar keratoplasty: a surgical alternative for the management of severe astigmatism from peripheral corneal degeneration. Ophthalmology. 2005;112(3):425–30.
16. Schanzlin DJ, Sarno EM, Robin JB. Crescentic lamellar keratoplasty for pellucid marginal degeneration. Am J Ophthalmol. 1983;96(2):253–4.

Part II
Clinical Overview

Clinical Syndromes, Classifications, and Differential Diagnosis

7

Swapnali Sabhapandit and Somasheila I. Murthy

Introduction

Peripheral ulcerative keratitis (PUK) is an inflammatory condition characterized by presence of a crescentic area of epithelial defect with stromal necrosis in the peripheral part of the cornea. There might be a subepithelial infiltrate at the edge of the necrotic area. It may be unilateral or bilateral [1]. The condition is usually associated with contiguous involvement of conjunctiva, episclera, and sclera or with an anterior chamber reaction.

PUK may be due to local or systemic causes. Systemic association of collagen vascular disease may be present is as high as 50% of the cases of PUK [2]. The ocular manifestation may be the initial presentation of the systemic disease, thereby alerting the clinician about the underlying disease entity [1, 2]. The systemic diseases have a high rate of morbidity and mortality if left untreated [3]. It is therefore imperative on the part of the ophthalmologist to identify this association and refer the patient for prompt management of the systemic condition.

In addition, PUK associated with systemic diseases may have a rapidly progressive course leading to corneal perforation and its complications [4]. The underlying disease usually contributes to this aggressive behavior. Hence it is necessary to control the systemic condition for early ocular rehabilitation.

Salient Features

There are a host of systemic diseases, which are associated with PUK (Table 7.1). The autoimmune diseases are the commonest entities, with the highest association reported with rheumatoid arthritis [1, 2]. Rare instances of systemic malignancies and immunosuppressive diseases are reported in literature (Figs. 7.1 and 7.2).

A. Pathogenesis

The pathophysiology of perilimbal corneal involvement in PUK with systemic disease is multifactorial.

1. Role of immune complexes: The unique anatomical feature of the limbal area makes it an easy target for antigen–antibody reactions [1, 5]. There are vascular arcades which originate from capillaries up to 0.5 mm into the cornea. Moreover, subconjunctival lymphatics are also accessible to the peripheral corneal stroma. Both of these factors bring in

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_7

Table 7.1 Systemic diseases associated with peripheral ulcerative keratitis

Systemic diseases
1. Rheumatoid arthritis
2. Wegener's granulomatosis
3. Systemic lupus erythematosus
4. Polyarteritis nodosa
5. Relapsing polychondritis
6. Progressive systemic sclerosis
7. Giant cell arteritis
8. Churg-Strauss syndrome
9. Inflammatory bowel disease
10. Behcet's disease
11. Sarcoidosis
12. Malignancy
13. Immune deficiency disorders

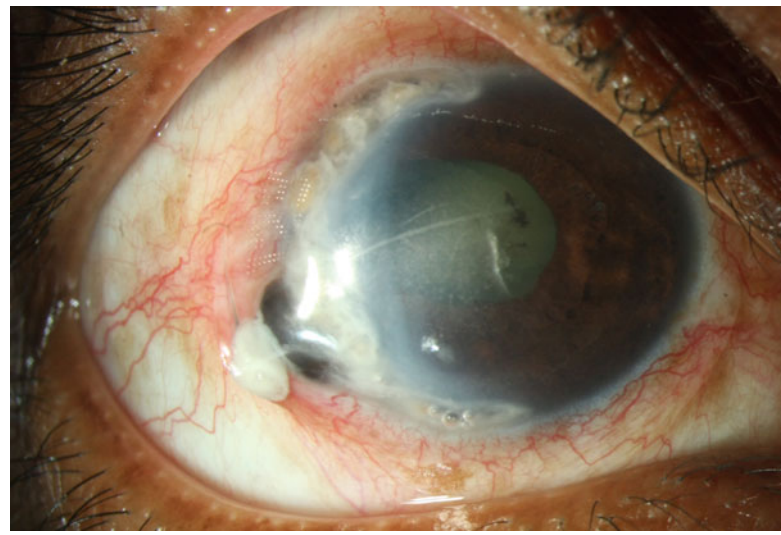

Fig. 7.1 Peripheral ulcerative keratits in a case of rheumatoid arthritis with sterile corneal melt and iris tissue prolapse

antigens which enable immune complexes to get deposited in the perilimbal cornea [6–8]. Immunoglobulin M (IgM) deposition triggers the classical pathway of the complement cascade leading to chemotaxis of neutrophils and macrophages to the stroma with increased phagocytic activity and release of proteolytic enzymes [6, 7]. There is increased release of cytokines from basophils and mast cells. These chemicals cause collagen degradation leading to corneal stromal ulceration.

A 66 KDalton protein autoantigen called cytokeratin 3 has been reported to be overexpressed in rheumatoid arthritis and Wegener granulomatosis. This cytokeratin is present in corneal epithelium and can lead to increased autoantibody formation in the peripheral cornea [9].

2. Role of matrix metalloproteinases (MMP): The release of cytokines such as tumor necrosis factor alpha (TNF alpha) in the complement cascade causes activation of conjunctival goblet cells, lymphoid tissues, and corneal keratocytes to release MMPs [10]. These enzymes digest extracellular matrix leading to corneal tissue degradation.

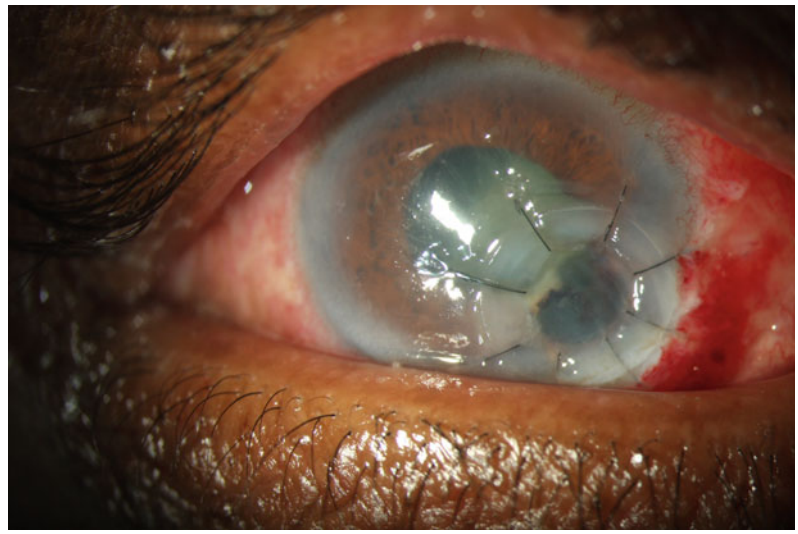

Fig. 7.2 Same case with patch graft done for corneal melt with perforation

MMPs are found in higher concentration in active stromal melts compared to healed ulcers [11].

The above-mentioned factors lead to progressive thinning of the peripheral cornea with a perilimbal spread of the area of involvement. Cytokines and MMPs present in tears also contribute to the disease process [11].

B. Clinical features

Nearly all of the systemic diseases show a similar manifestation of PUK that initially begins as a breakdown of the corneal epithelium in the perilimbal area. The concomitant keratoconjunctivitis sicca in these patients aid in this epithelial breakdown. Without adequate disease control, the underlying corneal stroma undergoes lysis with whitish, sterile infiltrates at the edges of the necrosed tissue. The ulcer may progress in a ring-like juxtalimbal pattern or move toward the central cornea. Inflammation of the adjoining conjunctiva, episclera, and sclera is common. The patient mainly complains of severe pain, redness, and watering of the eyes. Associated scleritis can aggravate the symptoms [2]. In Wegener granulomatosis, a granulomatous inflammation is noted distinctively in the cornea and sclera [12, 13].

1. ***PUK in rheumatoid arthritis***: The incidence of PUK in rheumatoid arthritis is reported to be 30–40% in different studies [2, 6, 7]. There is bilateral involvement in more than one-third of cases [2, 6]. Although PUK manifests in the later part of the disease process, the mortality rate is as high as 50% at a 10-year period [3]. The onset of PUK may in fact be a marker of worsening of the rheumatoid process [2, 3]. Most cases also show associated inflammation of conjunctiva, episclera, and sclera [14].
   Systemic features of rheumatoid arthritis manifests as a chronic, symmetrical, inflammatory polyarthritis of peripheral joints [15]. The incidence is nearly 3% of the general population and middle aged women are affected three times more often than men [16]. Extra-articular involvement in rheumatoid arthritis occurs in approximately 25% of patients [15]. This includes the heart, lung, skin, and the central nervous system [17]. The diagnostic criteria of rheumatoid arthritis are as follows [18]:

a. JOINT DISTRIBUTION (0–5)

   i. 1 large joint—0
   ii. 2–10 large joints—1
   iii. 1–3 small joints (large joints not counted)—2
   iv. 4–10 small joints (large joints not counted)—3
   v. >10 joints (at least one small joint)—5

b. SEROLOGY (0–3)

   i. Negative rheumatoid factor (RF) and negative anti-citrullinated protein antibody (ACPA)—0
   ii. Low positive RF or low positive ACPA—2
   iii. High positive RF or high positive ACPA—3

c. SYMPTOM DURATION (0–1)

   i. Less than 6 weeks—0
   ii. Greater or equal to 6 weeks—1

d. ACUTE PHASE REACTANTS (0–1)

   i. Normal C reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)—0
   ii. Abnormal CRP or abnormal ESR—1

Histopathology shows early deposition of IgM-RF IgG complexes in synovial vessels with endothelial swelling, perivascular cellular infiltration, thrombosis, and interstitial edema of the joint synovium [19, 20]. Common ocular involvements are keratoconjunctivitis sicca, episcleritis, anterior scleritis, marginal ulcerative keratitis, cataracts, optic nerve swelling, and choroidal or retinal vasculitis secondary to posterior scleritis [21]. Scleral involvement includes nodular and diffuse anterior scleritis, necrotizing scleritis, scleromalacia perforans, and posterior scleritis [22]. Nearly 50–70% of patients with scleral involvement have corneal changes [13, 23].

Severe keratoconjunctivitis sicca or secondary Sjögren syndrome is seen in up to 34% of patients with rheumatoid arthritis. This dryness causes epithelial breakdown of cornea and inadequate epithelial healing, thus contributing to the PUK mechanism. [24, 25] Patients of rheumatoid arthritis undergoing cataract surgery should be strictly monitored preoperatively and postoperatively for corneal melts [14, 26, 27]. Histopathology of conjunctival and scleral tissues in rheumatoid patients show microangiopathy with fibrinoid necrosis, neutrophil invasion of the vessels, and deposits of vascular immune complexes with IgA, IgG, IgM, C3, and C4 [14]. Unless aggressive immunosuppression is done, rheumatoid arthritis with PUK has a high mortality rate [3, 16].

2. ***PUK with granulomatosis with polyangitis or Wegeners granulomatosis***: Wegeners granulomatosis is a multisystem autoimmune disorder with majority of cases presenting in the fifth to sixth decade [28, 29]. It is broadly divided into two types. Ocular involvement has equal representation in both types of the disease.

   a. *Classic or generalized Wegeners granulomatosis*: In this form, there is necrotizing granulomatous vasculitis of entire respiratory tract including nasal septal collapse with saddle nose deformity, pulmonary nodules and cavitations [30, 31]. There is focal necrotizing glomerulonephritis which is usually seen late in the disease course [32].
   b. *Limited Wegeners granulomatosis*: In this form, there may be sparing of kidney involvement with lesser mortality [33, 34]. However, if left untreated, the limited form may progress to generalized form and cause death.

The diagnosis of Wegeners granulomatosis is based on clinical and laboratory investigations. Chest X-ray shows lung infiltrates and cavitations. Urine may show haematuria. Serum antineutrophil cytoplasmic antibody (ANCA) toward proteinase 3 with cytoplasmic immunofluorescence staining has nearly 100% sensitivity in classical form of the disease, while the sensitivity is around 70% in the limited form [34, 35]. The limited form shows greater sensitivity to the perinuclear immunofluorescent staining pattern (pANCA) [36]. Confirmatory diagnosis is established with nasal biopsy which shows necrotizing giant cell granulomas with occlusive small arteries vasculitis [37].

Ocular involvement in Wegeners granulomatosis ranges from 30 to 58% [38, 39]. The commonest involvement is seen in the orbit due to contiguous spread from the nasal tract leading to orbital inflammation, orbital myopathy, nasolacrimal duct obstruction or optic nerve compression due to granulomatous reaction of orbital tissues [40, 41]. The necrotizing scleritis and PUK seen in the disease are due to small vessel vasculitis of the intrascleral part of anterior ciliary arteries and perilimbal arteries [42, 43]. In Wegeners granulomatosis, PUK may be the initial manifestation of the systemic disease [39]. It presents as a granulomatous inflammation in the peripheral cornea and adjoining sclera with progressive ulceration and thinning. Histopathology of scleral and corneal tissue shows occlusive necrotizing vasculitis of anterior ciliary and perilimbal arteris with vascular and extravascular multinucleated giant cell granulomas along with rich infiltration of polymorphous cells such as lymphocytes, eosinophils, and epithelioid histiocytes [42, 43].

Wegeners granulomatosis is reported to coexist with rheumatoid arthritis, primarily in female patients [44–47]. The rheumatoid arthritis involvement precedes Wegeners granulomatosis. All cases reported till date had good outcome with immunosuppressive therapy. However, the predominant feature in rheumatoid arthritis is vascular occlusion whereas it is neovascularization in Wegeners granulomatosis. Corneal involvement in rheumatoid arthritis is confined to the limbus whereas there is continuous scleral involvement also in Wegeners granulomatosis. Corneal melt occurs early in Wegeners granulomatosis as compared to late occurrence in rheumatoid arthritis.

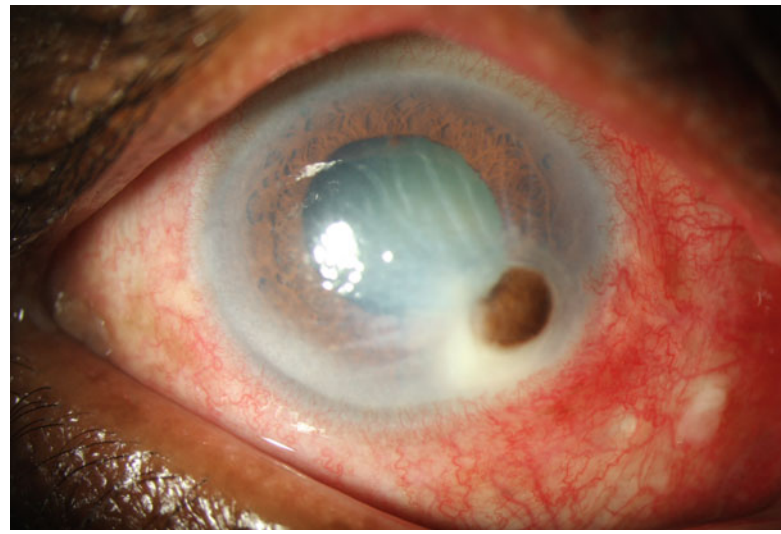

Fig. 7.3 Limbal corneal melt with peripheral ulcerative keratitis in a case of Wegeners granulomatosis

Figure 7.3 shows imbal corneal melt with peripheral ulcerative keratitis in a case of Wegeners granulomatosis.

3. ***Systemic lupus erythematosus* (*SLE*)**: This is a multisystem disorder involving the skin, kidneys, lungs, cardiovascular system, joints, blood, and the central nervous system [48]. Ocular involvement is seen in nearly a third of these patients [8]. The disease primarily affects females of child-bearing age [49]. Skin involvement includes the typical "butterfly rash" in the malar area and the nose along with discoid lesions, photosensitivity, and alopecia. Some patients develop Raynaud's phenomenon of the extremities. There can be associated arthritis, proteinuria, pleural effusion, arthritis, pericarditis, pancytopenia, and convulsions with psychosis [48]. The disease follows a protracted course with frequent exacerbations.

   The commonest ocular symptom is dryness, seen in 34–40% of patients. Superficial punctate keratitis can be as high as 88%, thereby suggesting immune mechanism along with dry eye for the corneal involvement [50]. Isolated case reports of unilateral or bilateral PUK with adjoining scleritis and cicatrizing conjunctivitis have been reported. The cases responded well to immunosuppressive therapy [51].

   Cataract (20–40%) and glaucoma (4–8%) occur secondary to chronic steroid use [52]. Lupus retinopathy occurs in 20–29% of patients in the later part of the disease [51, 53, 54]. This includes cotton-wool spots, hemorrhage, and vascular occlusion with neovascularization. The underlying pathogenesis involves microvascular occlusion by circulating immune complexes causing retinal nerve fiber layer infarction. A rare but severe form of occlusive ocular vascular disease can occur comprising of diffuse arteriolar occlusion with extensive capillary nonperfusion. This can lead to chronic retinal vein or artery occlusion and optic neuropathy. Incidence of maculopathy due to hydroxychloroquine cumulative toxicity has also been reported [55].

   The pathogenesis of SLE involves loss of the regulatory capacity of a subset of T cells over B lymphocytes, allowing constant polyclonal B-cell production with formation of different antibodies such as anti-DNA, antinuclear, antiphospholipid (lupus anticoagulant and anticardiolipin), antithyroid, and antilymphocyte antibodies [56–59]. There is also dysfunction of B-cell apoptosis. Acquired complement deficiency is common in SLE patients, leading to poor neutralization of immune complexes.

   SLE diagnosis is based on clinical features, histopathology of skin and other tissues with laboratory investigations. Biopsy shows subepithelial and perivascular cellular infiltration, granulomatous reaction, and immune complex deposition on vessel wall and epithelial basement membrane [60]. Blood anti-DNA and antinuclear antibody levels are strong markers for disease positivity. Antiphospholipid antibodies such as anticardiolipin and lupus anticoagulant can also be used for disease identification [61]. Management of dry eyes is of utmost importance in SLE cases as it usually precedes PUK and can delay healing with subsequent corneal perforation.

4. ***Polyarterits nodosa* (*PAN*)**: This a necrotizing vasculitis involving small and medium-sized vessels throughout the body. The reaction is nongranulomatous and has minimal respiratory involvement [62]. PAN has an incidence of 2.4/million [63]. It is seen in middle-aged males more commonly than females [62]. Childhood PAN has also been reported [64]. The diagnosis of PAN needs fulfillment of any 3 of the following 10 criteria [65]

   - Weight loss ≥ 4 kg
   - Livedo reticularis
   - Testicular pain or tenderness
   - Myalgias, weakness, or leg tenderness
   - Mononeuropathy or polyneuropathy
   - Diastolic blood pressure >90 mmHg

- Elevated urea or creatinine
- Positivity for hepatitis B virus (HBV) infection
- Arteriographic abnormality
- Biopsy of small- or medium-sized artery containing polymorphonuclear leukocytes.

Ocular involvement in PAN is about 10–20% [62, 66]. Necrotizing vasculitis of anterior ciliary arteries lead to conjunctival, scleral, and corneal lesions. Posterior segment is affected due to similar vessel infiltration and necrosis. Orbital pseudotumour with myopathy and papillitis are seen [67]. PUK presents in a similar way as Mooren's ulcer. Biopsy of resected conjunctival tissue shows fibrinoid necrosis and endothelial swelling with immune complex deposits and rich neutrophilic invasion of vessels and extravascular tissues [8]. Biopsies of nodular lesions, sural nerve, or affected muscle show similar picture.

The exact etiology of PAN is unknown, though strong association is seen with Hepatitis B or C infection [8]. Nearly 30–50% of hepatitis B and around 20% of Hepatitis C cases have been associated with occurrence of PAN. Viral antigen and antibody induced immune mechanism by molecular mimicry process is proposed as the probable cause of immune reaction in these hepatitis patients.

The 5-year mortality rate without immunosuppressive therapy in PAN is 12% [68]. Cardiac, central nervous system, and gastrointestinal involvement are poor prognostic markers. Antiviral therapy for Hepatitis B and C need to be concomitantly given as required.

5. ***Churg-Strauss syndrome and microscopic polyangitis***: These are pauci immune, ANCA positive or negative small vessel vasculitis. Churg-Strauss syndrome is characterized by multiorgan necrotizing vasculitis along with eosinophilia. Allergic rhinitis and asthma, lung infiltrates, myocarditis, and mononeuritis multiplex are seen. The diagnostic criteria are fulfilled if four of the following six criteria are present in a patient:

- Asthma
- Eosinophils greater than 10% of a differential white blood cell count
- Presence of mononeuropathy or polyneuropathy
- Unfixed pulmonary infiltrates
- Presence of paranasal sinus abnormalities
- Histological evidence of extravascular eosinophils.

Only 30–50% of patients of Churg-Strauss syndrome show positive pANCA values [69]. Pathogenesis of pANCA negative cases is hypothesized to be due to cytotoxic products of eosinophils.

Microscopic polyangitis involves granulomatous inflammation in kidneys, respiratory tract, and other organs. The positive pANCA cases can be as high as 70% in this disease entity [63].

Ocular involvement in Churg-Strauss syndrome may be in the form of conjunctival granuloma, scleritis, PUK, uveitis, ischemic optic neuropathy, multifocal choroidal ischemia, and muscle palsies [70–75]. Ocular involvement in microscopic polyangitis is rarely reported. PUK resembling Mooren's ulcer is seen in both disease entities [62]. Scleral involvement is however present along with PUK.

6. ***Relapsing polychondritis***: This is a rare immune disorder involving cartilaginous tissue in the body. It occurs in the middle ages equally in both sexes [8]. The ear and nose are commonly affected. McAdam laid diagnostic criteria for the disease and three out of six of the criteria need to be fulfilled [76]

- Bilateral auricular chondritis
- Nonerosive seronegative inflammatory polyarthritis
- Nasal chondritis

- Ocular inflammation
- Respiratory tract chondritis
- Audiovestibular damage.

The patient usually presents with saddle nose, drooping ears, vertigo, and tinnitus with deafness. Cardiac valve or aortic involvement can lead to mortality. Laryngotracheal collapse has also been reported [8].

Ocular involvement is common in this disease and can be an initial presenting feature in up to 30% of cases [77]. The commonly involved tissues are the episclera and sclera, followed by uveal tract, orbital tissue and muscles, retina, and optic nerve. PUK is seen in only 4–11% of cases, mostly in conjunction with scleritis. Biopsy of conjunctiva shows immune complex deposits on vessel wall in these patients [8].

The pathogenic mechanism is hypothesized to be autoimmune reaction to type II, IX, and XI collagen along with vasculitis of medium and large vessels [8, 77]. The disease may coexist with other immune disorders such as rheumatoid arthritis, Behcet's disease, Wegeners granulomatosis, and Sjogren's syndrome.

7. ***Behcet's disease***: This disease involves skin lesions, genital and oral aphthous ulcers with anterior or posterior uveitis. PUK is rare, having being reported till date in three cases [78–81]. One of the cases progressed to corneal perforation. Tear film abnormality along with the autoimmune reaction may contribute to the corneal ulceration. The association of this disease with HLA B51 has been established [82]. Increased cytokine production and an antigen driven immune response leads to inflammatory reaction in the blood vessels and T-cell mediated damage to perivascular and other tissues.
8. ***Inflammatory bowel disease (IBD)***: Crohn's disease and ulcerative colitis are two immune mediated disorders of the gastrointestinal tract. The ocular involvement in these disease entities includes iritis, scleritis, PUK, and retinal vascular disease. However, only 0.3–5% of IBD patients develop ocular complications [83].
9. ***Malignancies***: PUK has been reported in patients with multiple myeloma, sebaceous cell carcinoma, chronic myeloid leukemia, and acute lymphocytic leukemia [84–86]. The malignant cells infiltrate the perilimbal capillaries along with neutrophils and lymphocytes and incite an inflammatory reaction. Similar vascular spread may target the choroid and retina. Local immunosuppression is needed along with therapy for malignancy.
10. ***Sarcoidosis***: This granulomatous inflammatory disease usually manifests as interstitial keratitis in the cornea. Only two cases of PUK have been reported till date [87, 88]. The commonest ocular involvement is of the uveal tract, retina, and choroid. Panuveitis with choroiditis and optic neuritis is frequently encountered. The extraocular manifestations are commonly seen in the respiratory tract. Almost every organ of the body can be affected by these granulomatous nodules. There is a strong genetic predilection, with helper T-cell overproduction leading to inflammatory cascade [89, 90]. Management of this disease is similar to other autoimmune disorders.
11. ***Immune deficiency disorder***: PUK has been reported in patients of human immunodeficiency virus (HIV) infection either as an isolated finding or in association with central retinal vein occlusion or herpes zoster ophthalmicus [91–93]. The PUK resolved with localized immunosuppression in all cases. Antiretroviral therapy was initiated in the patients with good response. The patients with concomitant zoster infection were prescribed topical acyclovir along with oral acyclovir therapy.

    Although cellular immunity is low in HIV patients, the humoral immunity leading to complement cascade can induce inflammation in these eyes. Moreover, viral particles can directly cause vascular occlusion and ulceration of tissues.

Differential Diagnosis

1. **Mooren's ulcer**: This is an idiopathic peripheral ulcer with no scleral involvement which differentiates it from PUK [94, 95]. The disease may be unilateral or bilateral. Majority of the cases occur after the fourth decade. The patient usually is more symptomatic with severe pain. There is an overhanging edge of the ulcer toward the central cornea. Systemic investigations are negative for specific disease and surgical management with conjunctival resection and trimming of the overhanging edge is the preferred treatment. Cyanocrylate glue with bandage contact lens is used to prevent corneal perforation. Postoperative management with topical steroids and lubricants lead to adequate control. However, recurrences are seen in bilateral disease [95]. There may be need for systemic immunosuppression in such cases.

   Figure 7.4 shows Mooren's ulcer with central corneal edema and peripheral circumscribed thinning.
2. **Infective PUK**: Peripheral herpetic lesions may resemble noninfective PUK. However, presence of an infiltrate with minimal pain and low corneal sensitivity are hallmarks of herpetic diseases. Other organisms will also demonstrate infiltrates in corneal stroma prior to corneal melting. Microbiology workup is mandatory to rule out infective etiology before starting immunosuppressive therapy for PUK.
3. **Terrien's marginal degeneration**: This is a bilateral, noninflammatory degeneration of the peripheral cornea. The disease starts usually from the superior cornea. The overlying epithelium is intact while the juxtalimbal corneal stroma undergoes progressive thinning. There is a clear gray line of demarcation between the normal cornea and the involved area. Patients with this degeneration are mostly asymptomatic except for high oblique astigmatism [96, 97]. Superficial vascularisation of affected area with lipid deposits at ends of vessels is seen in late stage.

   Figure 7.5 shows inflammatory Terrien's marginal degeneration.
4. **Catarrhal ulcers**: These are commonly seen in patients with blepharitis and meibomianitis. The inciting agent is reported to be *Staphylococcus aureus* toxin [98]. Immune reaction to the toxin causes circumscribed infiltrates to deposit at the points of contact of the eyelids to the peripheral cornea, i.e., 2, 4, 7, and 11 o'clock [99]. There is a lucid interval of clear cornea between the infiltrate and the limbus

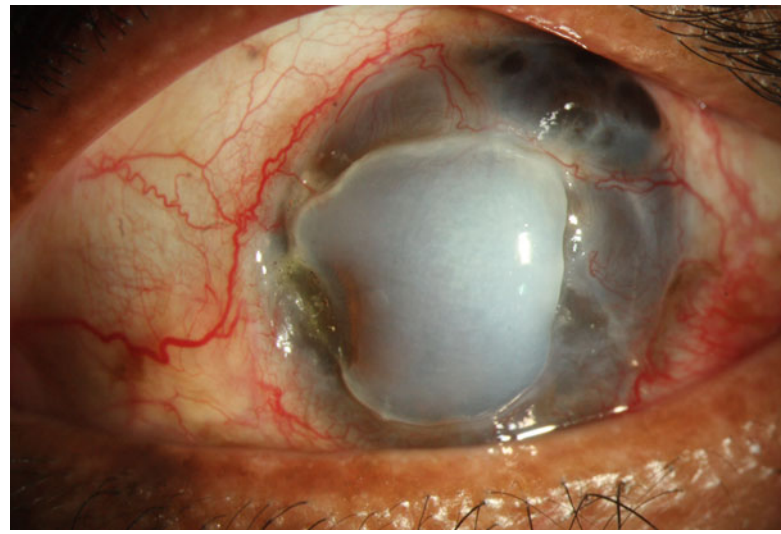

Fig. 7.4 Mooren's ulcer with central corneal edema and peripheral circumscribed thinning

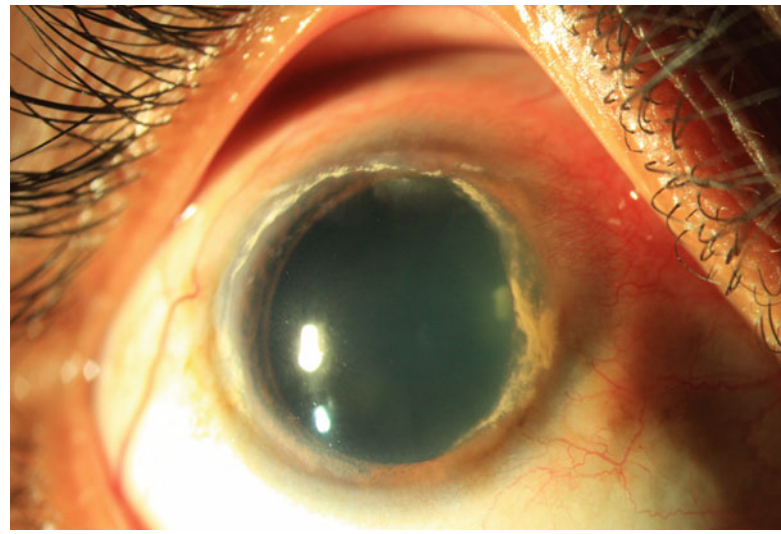

Fig. 7.5 Inflammatory Terrien's marginal degeneration

with intact epithelium. Without treatment, the epithelium may break down with spread of the infiltrate. Superficial vascuarisation is a common sequela. The management of this condition comprises of lid scrubs with warm compresses, macrolide antibiotics such as oral doxycyline and broad spectrum antibiotics eyedrops. Once infection is controlled, topical steroids are needed to control the immune reaction.

5. **Phlyctenular keratitis**: Phlyctens are circumscribed, gelatinous, elevated lesions of the conjunctiva and limbus [100]. Occasionally the peripheral cornea is involved as a whitish infiltrate with a tuft of superficial vessels. Later a wedge-shaped marginal ulcer may form. Patients have ocular pain with watering. The etiology is believed to be immune reaction to different antigens such as tuberculoprotein, Staphylococcal antigens, helminthiasis, and herpes simplex virus particles. Corneal perforation is rare and most patients respond to antibiotic and steroid topical therapy.
6. **Ocular rosacea**: This condition is seen in patients who have acne rosacea characterized by pustule formation on face and neck due to blockage of sebaceous glands [101]. The glands undergo hyperplasia, leading to secondary infection, rhinophyma of nose, skin erythema, and telangiectasia. The condition spreads from lower eyelids to the ocular surface causing blepharoconjunctivitis, PUK, and pannus formation. Nearly half of acne rosacea cases show such ocular involvement. The condition is easily differentiated from other forms of PUK due to the significant skin and eyelid changes. Such cases respond well to oral antibiotics such as tetracycline or doxycycline.

Management

Treatment of PUK associated with systemic diseases becomes a multidisciplinary approach. The mainstay of treatment is control of systemic inflammation after consultation with a physician or rheumatologist. Local management of the ulcer should happen concurrently. This can be done medically or surgically.

Investigations for systemic disease: There is a wide array of laboratory and radiological investigations associated with diagnosis of autoimmune diseases. However, the clinician has to correlate the disease history, symptoms, and signs to arrive at a differential diagnosis and advise investigations accordingly. The commonly done tests are complete haemogram (total

leucocyte count, differential leucocyte count, hemoglobin, erythrocyte sedimentation rate), C reactive protein, antinuclear antibody titre, and chest X-ray. Disease specific tests are given in Table 7.2.

Management of systemic disease: The principle behind treatment of the systemic conditions is immunosuppression and control of inflammation. Most patients require long-term therapy for disease control as objective markers for disease activity are not available. Table 7.3 shows the major groups of drugs used in medical control of the systemic diseases.

A. ***Corticosteroids***: These remain the mainstay for management of the acute phase of the systemic disease. The drug works via suppression of cytokine production and vasoactive substance release [2–4]. Moreover, the drug binds to glucocorticoid receptors in cytoplasm and this complex causes upregulation or downregulation of target gene production in the nucleus. Thus there is increased production of anti-inflammatory proteins and decreased production of proinflammatory proteins. However, they are unable to control the

Table 7.2 Laboratory and radiological investigations done in autoimmune diseases

Sl. no.	Systemic disease	Hematological investigations	Radiological investigations	Other investigations
1	Rheumatoid arthritis	Rheumatoid factor, anti-citrullinated protein antibody	X-ray of joints of digits	Muscle biopsy
2	Wegeners granulomatosis	cANCA, pANCA	Chest X-ray	Renal and lung biopsies, urine examination
3	Systemic lupus erythematosus	Anti-Smith antibody, anti-double stranded DNA antibody, anti-histone antibody		Skin biopsy
4	Polyarteritis nodosa	pANCA		Sural nerve or skin biopsy, renal function test, arteriogram
5	Relapsing polychondritis		X-ray or CT scan of cartilaginous tissue	Nasal or auricular cartilage biopsy, pulmonary function test
6	Churg-Strauss disease, microscopic polyangitis	pANCA		Nasal and skin biopsy, renal function test
7	Behcet's disease			Pathergy test
8	Inflammatory bowel disease			Biopsy on colonoscopy
9	Sarcoidosis	Angiotensin-converting enzyme, serum amyloid A	Chest X-ray or CT scan	Biopsy on bronchoscopy, FNAC of lymph nodes
10	Malignancies		CT or PET scan, MRI	Biopsy, FNAC of involved tissue
11	Immunosuppressive disease	ELISA and Western blot or immunofluorescence test for HIV, CD 4 cell count		

Table 7.3 Drugs used in medical therapy of systemic diseases associated with PUK

Name of drug	Dosage
1. Corticosteroids a. Intravenous: Methyl prednisolone b. Oral: Prednisolone	1 g/day for 3 consecutive days 1 mg/kg body weight (maximum 60 mg/day)
2. Cytotoxic agents a. Antimetabolites: Methotraxate Azathioprine Mycophenolate mofetil Leflunomide b. Alkylating agents: Cyclophosphamide c. T-cell inhibitors: Cyclosporin Hydroxychloroquine	7.5–25 mg/week 1.0–2.5 g/kg/day 1 g/twice daily 100 mg once daily for 3 days, then 20 mg once daily 1.5–2.5 mg/kg/day 5 mg/kg/day to 5 mg/kg/day 200–400 mg/kg/day
3. Biological agents a. Tumor necrosis factor alpha antibody: Infliximab b. CD 20 alpha antibody: Rituximab c. TNF alpha receptor antibody: Etanarcept d. Interleukin 1 receptor antibody: Anakinra e. Janus kinase enzyme inhibitor: Tofacitinib f. CD80/86 receptor inhibitor: Abatacept	3–5 mg/kg/day at 0, 2, and 6 weeks followed by 3 mg/kg/day every 8 weeks 1000 mg on day 1 and day 15 25 mg twice weekly 100 mg/day 5 mg twice daily 500–1000 mg/day for day 0, week 2, week 4, and then every 4 weekly

autoimmune condition alone and do not have much effect on the mortality rate [3]. The drug may be administered in intravenous form of pulsed methylprednisolone, 1 g/day for 3 consecutive days. This can be followed by tapering dose of oral prednisolone, 1 mg/kg/day with maximum dosing of 60 mg/day. The tapering is done based on the response to treatment and onset of side effects. Commonest side effects are osteoporosis, electrolyte imbalance with weight gain and Cushinoid facies, gastric erosions, dyslipidemia, worsening of diabetes and hypertension [4, 8]. Steroids need to be supplemented with immunosuppressive or immunomodulatory drugs for long-term control of the disease.

B. ***Cytotoxic agents***: These drugs form the first-line therapy along with corticosteroids. These drugs are placed in three categories:

1. *Antimetabolites*: These include methotrexate, azathioprine, mycophenolate mofetil, and leflunomide. They are structural analogs of natural metabolites, thus inhibiting pathways of synthesis for these metabolites. Oral methotraxate is the commonly used first-line medication in a dose of 7.5–25 mg/week along with corticosteroids [3, 102]. Azathioprine is given in 1.0–2.5 g/kg/day dosing [3, 102] and mycophenolate in 1.0 g twice daily [102–104]. Leflunomide is started as a loading dose of 100 mg once daily for 3 days followed by maintenance dose of 20 mg once daily [105]. Complete blood counts including platelet counts, liver function test, renal function test, vital parameters including blood pressure are checked before initiating therapy. The antimetabolite drug is continued with timely monitoring of systemic status.

Side effects of antimetabolite therapy range from generalized flu-like condition with malaise and skin rashes to more severe conditions such as low leucocyte count, impaired renal and hepatic function, ulcerative stomatitis, pneumonia and gastric symptoms with severe nausea and vomiting. Methotraxate blocks folic acid synthesis, hence neurological toxicity has to be avoided with folic acid

supplement. Alopecia is reported with use of leflunomide [105].

2. *Alkylating agents*: These include cyclophosphamide and chlorambucil. These drugs interfere with DNA replication and induce cell apoptosis [102]. Cyclophosphamide is preferred in severe rheumatoid arthritis, systemic lupus erythematosus, and severe angitis where antimetabolites are ineffective in controlling inflammation. It is given in a dose of 1.5–2.5 mg/kg/day orally or in intravenous dose weekly. The drug has to be combined with mesna (sodium 2-mercaptoethane sulfonate) to avoid haeorrhagic cystitis and risk of malignancy due to its by-product acrolein which accumulates in the urinary bladder [106]. Other serious side effects include bone marrow suppression with risk of infections, myeloproliferative neoplasms, infertility, and cardiotoxicity. Common side effects include flu-like condition, alopecia and gastrointestinal upsets with nausea and vomiting. The patient needs to be monitored with weekly blood counts and renal profile while on therapy. Once the disease is in control, the regime can be changed to drugs with lower toxicity. Joint inflammation is not well controlled with alkylating drugs and need biological agents.
3. *T-cell inhibitors*: These include cyclosporine A and hydroxychloroquine. Cyclosporine A is a calcineurin inhibitor which prevents dephosphorylation of enzymes responsible for synthesis of various cytokines such as interleukin 2, 4, 10, and 17 [107]. The effects are noted on both T lymphocytes and B lymphocytes, leading to decrease in their activation and inflammatory action. Cyclosporine A is administered in a dose of 2.5 mg/kg/day and increased stepwise to maximal dose of 5 mg/kg/day. The adverse effects include gingival hypertrophy, fever, nausea and vomiting, hirsutism, tingling and numbness of peripheries and dyslipidemia. The drug is nephrotoxic and hepatotoxic, hence renal parameters with liver function tests need to be done periodically.

   Hydroxychloroquine is an antimalarial drug with strong anti-inflammatory properties. It increases lysosomal pH in antigen presenting cells and also blocks toll-like receptors on dendritic cells, thereby reducing the inflammatory cascade of B-cell and T-cell activation [108]. Treatment is started with 200–400 mg/day orally. Once disease control occurs, dose is reduced to 200 mg daily. Adverse effects include corneal deposits, nausea, vomiting, abdominal colic, skin rashes, anemia, hearing disorder, altered hepatic function, and muscle weakness. A serious side effect is bull's eye maculopathy with cumulative dose of more than 1000 mg. This is due to the progressive destruction of macular rods and cones with sparing of foveal cones [109]. Patients have to be monitored with visual acuity and visual field testing, color vision, multifocal electroretinogram, and fundus fluorescein angiography.

C. ***Biological agents***: These are proteins which are modified by molecular biotechnology as recombinant forms of biologically available inhibitors of immune processes. The prototype molecule is infliximab which is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF alpha) [110–112]. TNF alpha stimulates production of matrix metalloproteinases. Infliximab binds to TNF alpha receptors on cell membrane and in cytoplasm, thereby blocking the inflammatory action. The drug is administered intravenously from 3 to 5 mg/kg/day at 0, 2, and 6 weeks followed by 3 mg/kg/day every 8 weeks. Initial therapy is usually combined with an antimetabolite drug. A minimum of 1.5–2 years is needed before the treatment can be discontinued.

Other newer biological agents include etanarcept (dimeric fusion protein for TNF alpha receptors), rituximab (chimeric antibody against CD20 alpha found in B lymphocytes), anakinra (interleukin 1 receptor antagonist), abatacept (Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4), and tofacitinib (janus kinase enzyme inhibitor) [113]. Adalimumab and golimumab have similar mechanism of action as infliximab. Newer molecules are in research for biological control of immune status.

The advantage of biologic agents over conventional therapy is the targeted approach toward specific proteins involved in the inflammatory pathways rather than an overall immunosuppression of the body as with conventional therapy. Multiple case reports of improvement of PUK with infliximab and rituximab are present [110–112, 114, 115]. However, there are no large-case series or randomized trials comparing the efficacy of these drugs as compared to cytotoxic agents in resolution of PUK. The best results of these agents are in controlling joint inflammation in the body.

The biologic agents are associated with certain side effects such as injection site rash, diarrhea, venous thrombosis, opportunistic infections such as tuberculosis and hepatotoxicity. Serious adverse effects such as increased risk of cardiac failure and lymphoproliferative malignancies have been reported. Most of the adverse effects are associated with higher dosing and long-term usage of the agents [113].

Management of corneal ulcer

A. ***Medical management***

PUK is a rapidly progressive, sight threatening disease and needs prompt management. The use of topical steroids is controversial as these drugs can prevent new collagen formation, thereby disrupting the healing process [2, 6, 116]. However, topical corticosteroids are always instituted in frequent doses to decrease local inflammation.

Lubrication to overcome tear film dysfunction, especially preservative-free topical medications are preferred. Superadded infections should be promptly managed with necessary medications.

Progressive stromal melting can also be minimized with oral tetracycline through protease inhibition [117, 118]. Topical N acetyl cysteine 20% is a collagenase synthesis inhibitor and can control collagen loss in a limited manner.

B. ***Surgical management***

Surgical intervention is needed for ulcers that are rapidly progressive and can perforate the cornea. However, surgery is not the mainstay of management of PUK when associated with autoimmune diseases. Medical control of the underlying disease leads to better outcome of any surgical procedure done in such eyes.

Extreme thinning and perforations around 1–2 mm in diameter can be sealed with tissue adhesive (N butyl/iso amyl 2 cyanoacrylate glue) and bandage contact lens application [6, 119]. As the lesions are close to the limbus, the glue can induce early corneal neovascularisation. Once the inflammation is brought under control, collagen formation and epithelialisation occur leading to loosening of the glue, necessitating its removal. These eyes have compromised tear functions; hence the clinician should be vigilant about superadded infections.

For perforations greater than 2 mm, tissue adhesive alone cannot provide tectonic support. Corneal transplantation is needed, with grafts being crescent shaped or round patch grafts based on the size and shape of the ulcerated area. Lamellar keratoplasty can be done in corneas with extreme thinning without perforation. However, without adequate control of underlying immune reaction, outcomes

of keratoplasty in these cases are disappointing [120]. Recent studies shows a good recovery rate of 82% with a mean follow up of 4.6 years [119]. The visual recovery is average, with most studies reporting visual acuities of 20/200 or worse in nearly 40–50% of cases [14, 119, 121, 122]. Epitheliopathy with a compromised tear film is a prime factor in reducing the visual acuity in these grafted eyes. Studies have also shown that primary grafts done in emergency situations usually fail due to inadequate immunosuppressive therapy [122, 123]. Repeat grafts with adequate immunosuppression have better anatomical outcomes.

Conjunctival resection is a minor surgical procedure to halt the progress of the peripheral ulcer. It is postulated that this resection reduces the availability of cytokines and immune complexes from the conjunctival blood vessels to the cornea [1, 2, 8]. Although the usefulness of this technique is documented in Mooren's ulcer, its utility in PUK with systemic disease association is questionable as the effect is likely to be nullified once the conjunctiva grows back.

Human amniotic membrane (HAM) has multiple factors to reduce inflammation such as anti-inflammatory cytokines such as interleukin-10, inhibin, activin, and interleukin-1 receptor antagonist. It has the innate ability to engulf leucocytes in the extracellular matrix and cause apoptosis of these cells. HAM also has inhibitory action of proteases like trypsin [124]. All these properties make it a useful adjunct to surgical therapy in PUK. HAM is used for sealing perforations less than 2 mm size. It is also used to promote reepithelialization of the cornea after conjunctival resection and corneal transplantation.

Patients with concomitant keratoconjunctivitis sicca may need punctual occlusion either with collagen or silicon plugs or by punctual cautery for tear preservation.

Recent Advances

The use of new biological agents as monotherapy or adjuvant therapy to conventional immunosuppressant has been studied in multiple trials in recent times [113, 125].

1. TNF alpha inhibitor: Certolizumab pegol is currently showing good results in controlling rheumatoid arthritis and Crohn's disease. It is a PEGylated Fab' fragment of TNF alpha inhibitor molecule.
2. Interleukin 1 inhibitor: Canakinumab is a specific interleukin 1 beta antibody. It has shown good results in cryopyrin-associated periodic syndrome (CAP), a rare genetic disease due to interleukin oversecretion in the body causing autoimmune conditions. Trials on rheumatoid arthritis and gout arthritis show good results with lesser side effects compared to anakinra.
3. Interleukin 6 inhibitor: Tocilizumab has shown good results in rheumatoid arthritis when combined with methotrexate, especially in refractory cases.
4. Interleukin 17 inhibitor: Secukinumab and ustekinumab have been approved by US FDA for treatment of psoriasis. There are trials going on to assess their efficacy in other autoimmune disorders
5. Other inhibitors of TNF family: Baminercept inhibits lymphotoxin beta, while belimumab inhibits B-cell activating factor. However, phase III trials have not shown much efficacy of these antibodies in rheumatoid arthritis.
6. B-cell inhibitors: Ocrelizumab and ofatumumab have shown promising results in cases of rheumatoid arthritis refractory to methotraxate and TNF inhibitors. The smaller molecule size of these antibodies enhances tissue availability with lesser side effects.
7. Small molecules: These newer molecules are less than 1 KDalton in weight, increasing their bioavailability and lowering the side effects. Oral formulations are being tested for

ease of use. Some of these small molecules are

a. Inhibitors of p38 kinase
b. Inhibitors of Syk kinase (Fostamatinib)
c. Inhibitor of JAK3 kinase
d. Inhibitor of interleukin 12/23
e. Inhibitor of CD80-CD28 costimulation.

Plant derived immunosuppressants: There is much interest in plant extracts with immunomodulatory properties [126]. Curcumin, resveratrol, colchicine, epigallocatechin-3-gallate, quercetin, capasaicin, and genestein are some of the derivatives under trial. However, robust evidence is still lacking in the exact role played by these substances in disease modification.

Conclusion

PUK is a sight threatening condition if not treated adequately. More important is the fact that it may be a clinical marker for life-threatening autoimmune diseases. Ophthalmologists should have a high index of suspicion in such cases and a prompt referral to a physician or rheumatologist is needed. As the systemic conditions follow a chronic waxing and waning course, the patient should have periodic ocular evaluation to manage the localized eye problems as they arise.

Conflict of Interest Statement No conflict of interest is present among the authors for this article.

No human studies were carried out by the authors for this article.

No animal studies were carried out by the authors for this article.

References

1. Bartly J, Mondino BJ. Inflammatory diseases of the peripheral cornea. Ophthalmology. 1988;95:463–72.
2. Tauber J, de la Maza MS, Hoang-Xuan T, Foster CS. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea. 1990;9:66–73.
3. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis: effects of systemic immunosuppression. Ophthalmology. 1984;91:1253–63.
4. Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. Curr Opin Ophthalmol. 2000;11:468–71.
5. Mondino BJ. Experimental aspects and models of peripheral corneal disease. Int Ophthalmol Clin. 1986;26:5–14.
6. Gregory JK, Foster CS. Peripheral ulcerative keratitis in the collagen vascular diseases. Int Ophthalmol Clin. 1996;36:21–30.
7. Shiuey Y, Foster CS. Peripheral ulcerative keratitis and collagen vascular disease. Int Ophthalmol Clin. 1998;38:21–32.
8. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43:379–96.
9. Reynolds I, Tullo AB, John SL, et al. Corneal epithelial-specific cytokeratin 3 is an autoantigen in Wegener's granulomatosis-associated peripheral ulcerative keratitis. Invest Ophthalmol Vis Sci. 1999;40:2147–51.
10. Geerling G, Joussen AM, Daniels JT, et al. Matrix metalloproteinases in corneal melts. Ann N Y Acad Sci. 1999;878:571–4.
11. Smith VA, Hoh HB, Easty DL. Role of ocular metalloproteinases in peripheral ulcerative keratitis. Br J Ophthalmol. 1999;83:1376–83.
12. Feder RS, Krachmer JH. Conjunctival resection for treatment of the rheumatoid corneal ulceration. Ophthalmology. 1984;91:111–5.
13. Sevel D. Rheumatoid nodule of the sclera. Trans Ophthalmol Soc UK. 1965;85:357–67.
14. Messmer EM, Foster CS. Destructive corneal and scleral disease associated with rheumatoid arthritis. Cornea. 1995;14:408–17.
15. Koffler D. The immunology of rheumatoid arthritis. Clin Symp. 1979;31:2125.
16. Vandenbroucke JP, Havevoet HM, Cats A. Survival and causes of death in rheumatoid arthritis: a 25-year prospective follow-up. J Rheumatol. 1984;11:158–61.
17. Cruickshank B. The arteritis of rheumatoid arthritis. Ann Rheum Dis. 1954;13:136–46.
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
19. Schumacher HR, Bautista BB, Krauser RE, et al. Histological appearance of the synovium in early rheumatoid arthritis. Semin Arthritis Rheum. 1994;23:3–10.

20. Vollertson RS, Conn DL. Vasculitis associated with rheumatoid arthritis. Rheum Dis Clin North Am. 1990;16:445–6.
21. Reddy SC, Gupta SD, Jain IS, Deodhar SD. Ocular manifestations of rheumatoid arthritis. Indian J Ophthalmol. 1977;25:20–6.
22. de la Maza MS, Nicolas M, Luis Alonso GG, Priyanka PD, Tauber J, Foster CS. Clinical characteristics of a large cohort of patients with scleritis and episcleritis. Ophthalmology. 2012;119:43–50.
23. McGavin DDM, Williamson J, Forrester JV, et al. Episcleritis and scleritis: a study of their clinical manifestations and association with rheumatoid arthritis. Br J Ophthalmol. 1976;60:192–226.
24. Hemady R, Chu W, Foster CS. Keratoconjunctivitis sicca and corneal ulcers. Cornea. 1990;9:170–3.
25. Henkind P, Gold DH. Ocular manifestations of rheumatic disorders. In: Ehrlich GE, editor. Oculocutaneous manifestations of rheumatic diseases, vol. 4. Basel: Karger; 1973. p. 13–59.
26. Maffett MJ, Johns KJ, Parrish CM, et al. Sterile corneal ulceration after cataract extraction in patients with collagen vascular disease. Cornea. 1990;9:279–85.
27. de la Maza MS, Foster CS. Necrotizing scleritis after ocular surgery. Ophthalmology. 1991;98:1720–6.
28. Tidman M, Olander R, Svalander C, Danielsson D. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975–95: organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. J Intern Med. 1998;244:133–41.
29. Watts RA, Lane SE, Bentham G, Scott DGI. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. Arthritis Rheum. 2000;43:414–9.
30. Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine. 1973;52:535–61.
31. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488–98.
32. Robin JB, Schanzlin DJ, Verity SM, et al. Peripheral corneal disorders. Surv Ophthalmol. 1986;31:1–36.
33. Carrington CB, Liebow AA. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med. 1966;41:497–527.
34. Cassan SM, Coles DT, Harrison EG. The concept of limited forms of Wegener's granulomatosis. Am J Med. 1970;49:366–79.
35. Nolle B, Specks U, Ludemann J, et al. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener's granulomatosis. Ann Intern Med. 1989;64:28–36.
36. Soukiasian SH, Foster CS, Niles JL, Raizman MB. Diagnostic value of antineutrophil cytoplasmic antibodies in scleritis associated with Wegener's granulomatosis. Ophthalmology. 1992;99:125–32.
37. Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine. 1973;52:535–61.
38. Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. Ophthalmology. 1983;90:279–90.
39. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983;98:76–85.
40. Perry SR, Rootman J, White VA. The clinical and pathologic constellation of Wegener granulomatosis of the orbit. Ophthalmology. 1997;104(4):683–94.
41. Woo TL, Francis IC, Wilcsek GA, et al. Australasian orbital and adnexal Wegener's granulomatosis. Ophthalmology. 2001;108(9):1535–43.
42. Austin P, Green WR, Sallyer DC, Walsh FB, Kleinfelter HT. Peripheral corneal degeneration and occlusive vasculitis in Wegener's granulomatosis. Am J Ophthalmol. 1978;85:311–7.
43. Frayer WC. The histopathology of perilimbal ulceration in Wegener's granulomatosis. Arch Ophthalmol. 1960;64:58–64.
44. Douglas G, Bird K, Flume P, Silver R, Bolster M. Wegener's granulomatosis in patients with rheumatoid arthritis. J Rheumatol. 2003;30:2064–9.
45. Ohashi H, Itoh M, Ogawa N, et al. Wegener's granulomatosis in a patient with a rheumatoid arthritis. Intern Med. 1992;31:1128–31.
46. Pritchard MH. Wegener's granulomatosis presenting as rheumatoid arthritis (2 cases). Proc R Soc Med. 1976;69:501–4.
47. Sturrock RD, Ratnesar P. Wegener's granulomatosis occurring in a patient with pre-existing rheumatoid arthritis. Br J Clin Pract. 1974;28:183–4.
48. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271–7.
49. Locke IC, Cambridge G. Autoantibodies to neutrophil granule proteins: pathogenic potential in vasculitis? Br J Biomed Sci. 1996;53:302–16.
50. Spaeth GL. Corneal staining in systemic lupus erythematosus. N Engl J Med. 1967;276:1168–71.
51. Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. Rheumatology. 2007;46:1757–62.
52. Carli L, Tani C, Querci F, Della Rossa A, Vagnani S, Baldini C, Talarico R, d'Ascanio A, Neri R, Tavoni AG, Bombardieri S, Mosca M. Analysis of the prevalence of cataracts and glaucoma in systemic lupus erythematosus and evaluation of the rheumatologists' practice for the monitoring of glucocorticoid eye toxicity. Clin Rheumatol. 2013;32(7):1071–3.
53. Ushiyama O, Ushiyama K, Koarada S, Tada Y, Suzuki N, Ohta A, et al. Retinal disease in patients with systemic lupus erythematosus. Ann Rheum Dis. 2000;59:705–8.

54. Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: a review of the literature. Autoimmune Dis 2012;2012, Article ID 290898.
55. Nika M, Blachley TS, Edwards P, Lee PP, Stein JD. Regular examinations for toxic maculopathy in long-term chloroquine or hydroxychloroquine users. JAMA Ophthalmol. 2014;132(10):1199–208.
56. Abdou NI, Sagawa A, Pascual E, et al. Suppressor T-cell abnormality in idiopathic systemic lupus erythematosus. Clin Immunol Immunopathol. 1976;6:192–9.
57. Alarcon-Segovia D, Ruiz-Arguelles A. Decreased circulating thymus-derived cells with receptors for the Fc portion of immunoglobulin G in systemic lupus erythematosus. J Clin Invest. 1978;62:1390–4.
58. Han S, Zhuang H, Shumyak S, Yang L, Reeves WH. Mechanisms of autoantibody production in systemic lupus erythematosus. Front Immunol. 2015;13(6):22.
59. Squatrito D, Emmi G, Silvestri E, Ciucciarelli L, D'Elios MM, Prisco D, Emmi L. Pathogenesis and potential therapeutic targets in systemic lupus erythematosus: from bench to bedside. Auto Immun Highlights. 2014;5(2):33–45.
60. Heiligenhaus A, Dutt JE, Foster CS. Histology and immunopathology of systemic lupus erythematosus affecting the conjunctiva. Eye. 1996;10:425–32.
61. Nuttall A, Isenberg DA. Assessment of disease activity, damage and quality of life in systemic lupus erythematosus: new aspects. Best Pract Res Clin Rheumatol. 2013;27(3):309–18.
62. Wise GN. Ocular periarteritis nodosa. Arch Ophthalmol. 1952;47:1–11.
63. Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? Semin Arthritis Rheum. 1995;25:28–34.
64. Iudici M, Puéchal X, Pagnoux C, Quartier P, Agard C, Aouba A, Büchler M. Brief report: childhood-onset systemic necrotizing vasculitides: long-term data from the French Vasculitis Study Group Registry. Arthritis Rheumatol. 2015;67 (7):1959–65.
65. Hernández-Rodríguez J, Alba MA, Prieto-González S, Cid MC. Diagnosis and classification of polyarteritis nodosa. J Autoimmun. 2014;48–49:84–9.
66. Purcell JJ, Birkenkamp R, Tsai CC. Conjunctival lesions in periarteritis nodosa. Arch Ophthalmol. 1984;102:736–8.
67. Akova YA, Jabbur NS, Foster CS. Ocular presentation of polyarteritis nodosa. Clinical course and management with steroid and cytotoxic therapy. Ophthalmology. 1993;100:1775–81.
68. Fronert PP, Scheps FG. Long-term follow up study of periarteritis nodosa. Am J Med. 1967;43:8–14.
69. Niles JL. Antineutrophil cytoplasmatic antibodies in the classification of vasculitis. Annu Rev Med. 1996;47:303–13.
70. Chumbley LC, Harrison EG Jr, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome): report and analysis of 30 cases. Mayo Clin Proc. 1977;52:477–84.
71. Acheson JF, Cockerell OC, Bentley CR, Sanders MD. Churg- Strauss vasculitis presenting with severe visual loss due to bilateral sequential optic neuropathy. Br J Ophthalmol. 1993;77:118–9.
72. Kattah JC, Chrousos GA, Katz PA, et al. Anterior ischemic optic neuropathy in Churg-Strauss syndrome. Neurology. 1994;44:2200–2.
73. Nissim F, Von der Valde J, Czernobilsky B. A limited form of Churg-Strauss syndrome: ocular and cutaneous manifestations. Arch Pathol Lab Med. 1982;106:305–7.
74. Shields CL, Shields JA, Rozanski TI. Conjunctival involvement in Churg-Strauss syndrome. Am J Ophthalmol. 1986;102:601–5.
75. Vitale C, Genovesi-Ebert F, Romani A, et al. Ophthalmological and neuro-ophthalmological involvement in Churg-Strauss syndrome: a case report. Graefes Arch Clin Exp Ophthalmol. 1996;234:404–8.
76. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine. 1976;55:193–215.
77. Yoo JH, Chodosh J, Dana R. Relapsing polychondritis: systemic and ocular manifestations, differential diagnosis, management, and prognosis. Semin Ophthalmol. 2011;26(4–5):261–9.
78. Wong JS, Chee CK. Behcet's disease: corneal perforation as an ocular manifestation. Aust N Z J Ophthalmol. 1996;24:151–2.
79. Murphy C, Gregory ME, Ramaesh K. Peripheral ulcerative keratitis: an unusual primary ocular manifestation in Behcet's disease? Rheumatology. 2009;48:1490.
80. Gunduz A, Cumurcu T, Demirel EE, Akpolat N, Karincaoglu Y. The ocular surface in the Behcet's disease patient. Can J Ophthalmol. 2012;47:429–34.
81. Ji YS, Yoon KC. A rare case of peripheral ulcerative keratitis associated with Behcet's disease. Int Ophthalmol. 2014;34:979–81.
82. Gul A. Behcet's disease: an update on the pathogenesis. Clin Exp Rheumatol. 2001;19(Suppl 24): S6–12.
83. Mady R, Grover W, Butrus S. Ocular complications of inflammatory bowel disease. Sci World J. 2015;2015, Article ID 438402.
84. de la Maza MS, Foster CS. Peripheral ulcerative keratitis and malignancies. Cornea. 1994;13(4):364–7.
85. Morjaria R, Barge T, Mordant D, Elston J. Peripheral ulcerative keratitis as a complication of acute myeloid leukaemia. BMJ Case Rep. 2014;31:2014.
86. Lim LT, Ramamurthi S, Collins CE, Mantry S. Peripheral ulcerative keratitis associated with multiple myeloma. Ann Acad Med Singapore. 2011;40 (12):550–1.
87. Harthan JS, Reeder RE. Peripheral ulcerative keratitis in association with sarcoidosis. Cont Lens Anterior Eye. 2013;36(6):313–7.

88. Siracuse-Lee D, Saffra N. Peripheral ulcerative keratitis in sarcoidosis: a case report. Cornea. 2006;25(5):618–20.
89. Grunewald J. Review: role of genetics in susceptibility and outcome of sarcoidosis. Semin Respir Crit Care Med. 2010;31(4):380–9.
90. Kriegova E, Fillerova R, Tomankova T, Hutyrova B, Mrazek F, Tichy T, Kolek V, du Bois RM, Petrek M. T-helper cell type-1 transcription factor T-bet is upregulated in pulmonary sarcoidosis. Eur Respir J. 2011;38:1136–44.
91. Soni ND, Ingole AB, Murade SM. An unusual case of peripheral ulcerative keratitis as a presenting feature in an otherwise healthy patient with undiagnosed human immunodeficiency virus infection and low CD4 counts. Indian J Ophthalmol. 2013;61(3):138–9.
92. Gharai S, Venkatesh P, Tandon R, Garg S. Peripheral ulcerative keratitis and central retinal vein occlusion as the initial manifestation of HIV infection. Ocul Immunol Inflamm. 2007;15:407–9.
93. Neves RA, Rodriguez A, Power WJ, Muccioli C, Lane L, Belfort R Jr, Foster CS. Herpes zoster peripheral ulcerative keratitis in patients with the acquired immunodeficiency syndrome. Cornea. 1996;15(5):446–50.
94. Srinivasan M, Zegans ME, Zelefsky JR, Lietman T, Whitcher JP, Cunningham ET Jr. Clinical characteristics of Mooren's ulcer in South India. Br J Ophthalmol. 2007;91:570–5.
95. Garg P, Sangwan VS. Mooren's ulcer. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis: Elsevier; 2011.
96. Austin P, Brown SI. Inflammatory Terrien's marginal corneal disease. Am J Ophthalmol. 1981;92:189–92.
97. Keenan DJ, Mandel MR, Margolis TP. Peripheral ulcerative keratitis associated with vasculitis manifesting asymetrically as Fuchs superficial marginal keratitis and Terrien's marginal degeneration. Cornea. 2011;30:825–7.
98. Ueta M, Sotozono C, Takahashi J, Kojima K, Kinoshita S. Examination of Staphylococcus aureus on the ocular surface of patients with catarrhal ulcers. Cornea. 2009;28(7):780–2.
99. Ficker L, Seal D, Wright P. Staphylococcal infection and the limbus: study of the cell-mediated immune response. Eye (Lond). 1989;3(Pt 2):190–3.
100. Chung G. Phlyctenular keratoconjunctivitis and marginal staphylococcal keratitis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis: Elsevier; 2011.
101. Browning DJ, Proia AD. Ocular rosacea. Surv Ophthalmol. 1986;31:145–58.
102. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130:492–513.
103. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology. 2008;115:1826–32.
104. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology. 2005;112:1472–7.
105. Wiacek R, Kolossa K, Jankowski T, Jeka S, Karmowski A, Karmowski M, Gworys B. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis. Adv Clin Exp Med. 2012;21(3):337–42.
106. Radis CD, Kahl LE, Baker GL, et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year follow-up study. Arthritis Rheum. 1995;38(8):1120–7.
107. McCarthy JM, Dubord PJ, Chalmers A, Kassen BO, Rangno KK. Cyclosporin A for the treatment of necrotising scleritis and corneal melting in patients with rheumatoid arthritis. J Rheumatol. 1992;19:1358–61.
108. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology. 2015;23(5):231–69.
109. Costedoat-Chalumeau N, Dunogué B, Leroux G, Morel N, Jallouli M, Le Guern V, Piette JC, Brézin AP, Melles RB, Marmor MF. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol. 2015.
110. Odorcic S, Keystone EC, Ma JJ. Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up. Cornea. 2009;28:89–92.
111. Oh YJ, Kim MK, Wee WR. Infliximab for progressive peripheral ulcerative keratitis in a patient with juvenile rheumatoid arthiritis. Jpn J Ophthalmol. 2011;55:70–1.
112. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn's disease. Am J Ophthalmol. 2011;152:183–8.
113. Senolt L, Vencovský J, Pavelka K, Ospelt C, Gay S. Prospective new biological therapies for rheumatoid arthritis. Autoimmun Rev. 2009;9(2):102–7.
114. Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J InternMed. 2005;257:540–8.
115. Freidlin J, Wong IG, Acharya N. Rituximab treatment for peripheral ulcerative keratitis associated with Wegener's granulomatosis. Br J Ophthalmol. 2007;91(10):1414.

116. Virasch VV, Brasington RD, Lubniewski AJ. Corneal disease in rheumatoid arthritis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis: Elsevier; 2011.
117. Golub LM, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. Crit Rev Oral Biol Med. 1991;2:297–321.
118. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea. 2000;19:274–7.
119. Cartwright NEK, Tole DM, Georgoudis P, Cook SD. Peripheral ulcerative keratitis and corneal melt: a 10-year single center review with historical comparison. Cornea. 2014;33:27–31.
120. Maneo A, Naor J, Lee HM, Hunter WS, Rootman DS. Three decades of corneal transplantation: indications and patient characteristics. Cornea. 2000;19:7–11.
121. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, Tandon R, Vajpayee RB. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. Br J Ophthalmol 2015;0:1–6.
122. Palay DA, Stulting RD, Waring GO III, Wilson LA. Penetrating keratoplasty in patients with rheumatoid arthritis. Ophthalmology. 1992;99:622–7.
123. Squirrell DM, Winfield J, Amos RS. Peripheral ulcerative keratitis 'corneal melt' and rheumatoid arthritis: a case series. Rheumatology (Oxford). 1999;38(12):1245–8.
124. Shimmura S, Shimazaki J, Ohashi Y, Tsubota K. Antiinflammatory effects of amniotic membrane transplantation in ocular surface disorders. Cornea. 2001;20:408–13.
125. Gomez-Reino J. Biologic monotherapy as initial treatment in patients with early rheumatoid arthritis. Rheumatology. 2012;51:v31–7.
126. Jantan I, Ahmad W, Bukhari SNA. Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials. Front Plant Sci. 2015;25(6):655.

Infectious Causes

8

Ana Luísa Hofling-Lima and Eduardo Gayger Müller

Introduction

Peripheral ulcerative keratitis (PUK) refers to a crescent shaped destructive inflammatory lesion affecting the juxtalimbal corneal tissue. The peripheral cornea demonstrates stromal thinning with a leading edge of subepithelial infiltrate and an associated overlying epithelial defect. Usually, there is an adjacent inflammation of the conjunctiva, episclera and sclera as well. It is a rare and sight-threatening condition that may progress to corneal perforation, especially if left untreated.

PUK can be caused by both local and systemic conditions. It is helpful to divide the differential diagnosis into local ocular causes and systemic causes. Ocular causes of PUK can be categorized as infectious (associated or not to surgical or mechanical trauma), malignancy related, autoimmune. Systemic causes of PUK may be manifestation of infectious diseases, autoimmune, dermatologic, or related to malignancy.

PUK can be caused by exogenous or systemic infections. Bacteria, Virus, Fungus, and Acanthamoeba can cause local exogenous infection. Systemic infections causing PUK described in the literature are: Varicella zoster, tuberculosis, syphilis, AIDS, hepatitis C, Lyme Disease, bacillary dysentery.

When infection spreads to the scleral tissue, treatment becomes more difficult due to the lack of vascularization and antibiotic penetration in the scleral tissue.

PUK: Infectious Causes

The exogenous infectious causes of PUK are very similar to the ones of infectious keratitis affecting other areas of the cornea. They include bacteria (coagulase-negative Staphylococcus—CNS, *S. aureus*, Pseudomonas sp. Haemophilus), Herpes family viruses, fungi (Aspergillus, Fusarium, Scedosporium) and Acanthamoeba.

The systemic infections related to PUK are usually associated to immune reactions. The infecting agent may stimulate an autoimmune response to corneal antigens in the case of hepatitis C or even parasitic infestations. Other systemic infectious diseases associated to PUK described in the literature are: Varicella Zoster, tuberculosis, syphilis, AIDS, Lyme disease, and bacillary dysentery.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_8

Sharma et al. [1] evaluated 76 eyes of 65 consecutive patients with PUK in a prospective interventional study over an 18-month period. Local exogenous infection was identified as the cause of PUK in 15 eyes (19.7%). In this group, 73.3% was related to bacteria, 13.3% due to fungi, and 13.3% to herpes.

In the presence of infectious PUK, it is important to rule out adjacent infectious scleritis. Infection of the peripheral cornea that spreads to the limbus will first demonstrate limbal erythema, usually with edema and infiltrate. There may be no conjunctival epithelial defect. Pain may increase with infection of the sclera. Scleral involvement in cases of keratitis decreases the prognosis for control of the infection, but can be successfully treated.

Most cases of infectious scleritis result from severe bacterial infections of the cornea, but viral, fungal, and parasitic keratitis may also evolve into a keratoscleritis. Gram-negative bacteria, most commonly *Pseudomonas aeruginosa*, can spread from the cornea to the sclera, which is the most common situation [2–5], but also from the sclera to the cornea [6]. *S. aureus*, *Streptococcus pneumoniae* [7], *Mycobacterium chelonae*, herpes simplex, herpes zoster, Aspergillus, Acremonium, and Acanthamoeba [8, 9] have also been reported to cause keratoscleritis.

Difficulties related to the treatment of infectious scleritis are mostly due to poor drug penetration and difficulty to achieve minimal inhibitory concentration. Topical drugs can be used along with systemic antibiotics, antifungals, or antivirals.

In case of peripheral amoebic keratitis with concomitant scleritis, it is always important to rule out the presence of cysts in the scleral tissue. The investigation can be done by scleral biopsy and the result often will determine the treatment, either with or without immunosuppressant agent.

Etiopathogenesis

Because the peripheral cornea is adjacent to the rich vascular supply of the limbus, the limbal lymphatic tissue, and inflammatory cells, microbial keratitis may be thought to be less frequent than in the central cornea. However, other factors like contact lens wear and corneal exposure can increase the likelihood of a peripheral corneal infection.

Ishibashi et al. [10] compared the development of keratomycosis after central or peripheral corneal inoculation, Candida albicans was inoculated in the central portion and in the peripheral cornea of rabbits. The clinical scores of the central ulcers were significantly higher than those of the peripheral lesions. Histopathologic examination showed earlier and more extensive inflammatory reactions in eyes with peripheral lesions, compared with those in eyes with central lesions.

Contact lens wear can be associated with peripheral corneal disease. Wearing contact lenses reduces the amount of oxygen available to the cellular components of the cornea and the tear flow under the contact lens is less than that which would otherwise pass over the cornea. Additionally, the insertion and removal of lenses may produce regions of micro trauma to the corneal surface, limbus, and adjacent conjunctiva [11].

In addition, other factors, such as dry eye and lagophthalmos or certain systemic diseases, such as diabetes, can increase the risk of ocular infections.

Ocular surgeries like pterygium excision can also predispose PUK or sclerokeratitis, days or even months after the surgery [12, 13].

Bacterial and fungal keratitis, which occurs in the inferior third of the cornea, could be secondary to corneal exposure. This should especially be considered in an individual who has suffered multiple ocular infections.

Diagnosis

The first thing to rule out in a patient with PUK is a local infectious etiology. The patient with a peripheral corneal infiltrate should have bacterial, fungal, and in, some cases, Acanthamoeba cultures taken. After sample collection for cultures treatment can be initiated based on the clinical appearance and with the laboratory results

Table 8.1 List of standard and specific complimentary exams for PUK

Standard	Directed based on history and physical examination
Complete blood count	Tuberculin skin test
Complete metabolic panel	Sacroiliac joint x-rays
UA with microscopic analysis	Sinus imaging
ANCA, ANA, RF, anti-CCP	Viral hepatitis panel
CXR	IgE levels
RPR; FTA-ABS	GI evaluation
Lyme antibody	Scleral biopsy

therapy can be reevaluated. While many organisms affect the central cornea, they are also capable of affecting the periphery.

Even when infection has been diagnosed, there is need to investigate other causes of PUK which can be underlying the infection. This investigation can be done following a standard exam list but also aimed on history and physical examination characteristics as provided in Table 8.1.

It may be difficult to differentiate a marginal ulcer caused by Staphylococcus from an early ulcer of PUK. Herpes simplex and Herpes Zoster are both able to cause peripheral corneal thinning as well. These viruses are also capable of causing neurotrophic keratitis, which can lead to peripheral corneal thinning long after active disease has been present.

Exogenous Infections

Bacterial PUK

Bacteria are the most common causes of infectious keratitis and sclerokeratitis. Prevalent pathogens usually described in series of cases are Pseudomonas and *S. aureus* [3, 12–14]. *Haemophilus influenzae*, *S. pneumoniae,* and *N. gonorrhoeae* may also be causative organisms, the latter being very aggressive with peripheral corneal melting and perforation.

Sharma et al. [1] described 85% positivity to bacteria in 13 eyes with culture proven infectious PUK. Coagulase negative Staphylococci was isolated in seven cases, *S. aureus* in 2 cases, *Proteus vulgaris* and *P. aeruginosa* in 1 case each.

Several other case reports have shown multiple pathogenic organisms. Mattern and Ding [15] reported an unusual case of peripheral ulcerative keratitis in a patient with severe vitamin A deficiency. Two bacteria of the family Micrococcaceae were cultured and identified by genome sequence analysis, namely Kocuria palustris and Rothia mucilaginosa.

Ovodenko et al. [16] described a prevalence of 21.8% of peripheral localization from 78 Propionibacterium acnes ulcers. Three of these patients had previous diagnosis of PUK. Bullington et al. [17] documented the first case of *M. chelonae* sclerokeratitis. Tay et al. [18] described a case of Listeria monocytogenes sclerokeratitis. The corneal lesion was cheesy white and raised with nasal scleritis.

Gonococcal PUK

Gonococcal conjunctivitis is one of the few bacterial diseases associated with preauricular lymphadenopathy and the formation of conjunctival membranes. Keratitis, the principal cause of sight-threatening complications, has been reported to occur in 15–40% of cases. Corneal involvement may consist of diffuse epithelial haze, epithelial defects, marginal infiltrates, and ulcerative keratitis that can rapidly progress to perforation. Important conjunctival inflammation, chemosis, discharge, and accumulation of necrotic material can predispose to PUK and perforation (Fig. 8.1).

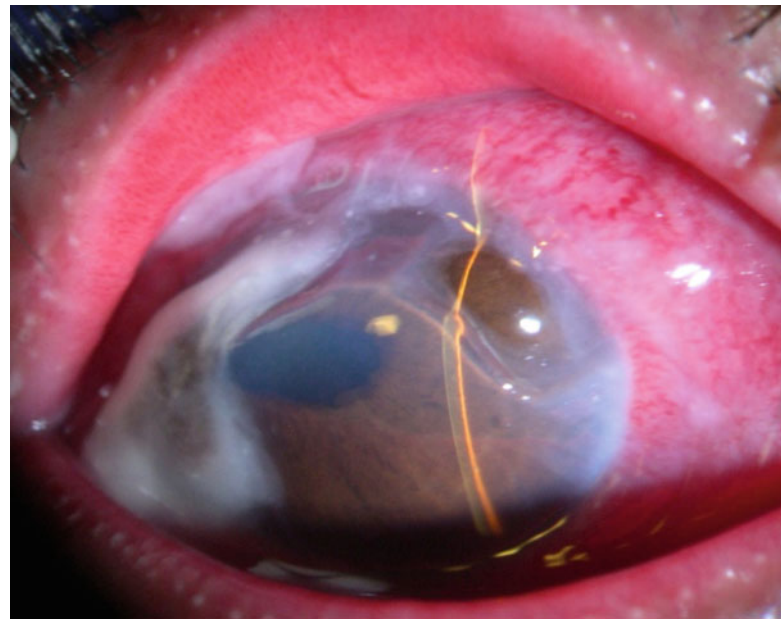

Fig. 8.1 Conjunctival inflammation, chemosis, discharge, and accumulation of necrotic material can predispose to PUK and perforation

'Ophthalmia neonatorum' encompasses any purulent neonatal conjunctivitis that develops within the first 28 days of life. The most important cause is *N. gonorrhoeae*, as it can rapidly lead to peripheral ulcerative keratitis, abscess formation, and corneal perforation if left untreated. The risk of bilateral involvement and hence bilateral low vision and blindness is also high.

Viral PUK

Herpes family viruses may affect the cornea in multiple ways. Herpes epitheliopathy is the most common presentation, but the infection or its immune reactions can manifest also as stromal keratitis, endothelitis, necrotizing keratitis, or even limbitis. Usually the disease is unilateral and the localization on the cornea may vary from central to periphery, which sometimes may confuse the diagnosis.

Thygeson [19] described a marginal Herpes simplex keratitis (HSK) simulating catarrhal ulcer and Praidou et al. [20] reported a case of bilateral HSK masquerading as PUK. Bilateral HSK, as opposed to PUK, is very rarely reported in the literature, and bilateral herpetic keratitis presenting as PUK is considered an even rarer manifestation of herpetic disease.

Zaher et al. [21] reported two cases of herpes simplex virus (HSV) PUK misdiagnosed as rheumatoid arthritis (RA)-associated PUK. In these two patients with known sero-positive RA, isolation of HSV led to a complete modification in management.

RA-related PUK and HSV stromal disease have several features in common. Both conditions are immune mediated and characterized by corneal necrosis, infiltration of lymphocytes, macrophages, up-regulation of Langerhans cells, liberation of collagenolytic, and proteolytic enzymes. In both conditions, immune complexes trigger the inflammatory cascades that result in corneal ulceration, and both conditions respond to immune modulation. In short, the major underlying pathophysiologic mechanism of PUK in both cases is a result of degradation and tissue necrosis of corneal stroma produced by degradative enzymes, which are released primarily by neutrophils attracted into the area by diverse stimuli [22].

Fungal PUK

Sharma et al. [1] in their case series reported two PUK due to *Aspergillus niger*. The cases were treated with 5% nathamycin 5 times a day and voriconazole tablets 200 mg twice a day.

Hayashi et al. [23] described a case of polymicrobial sclerokeratitis caused by *Scedosporium apiospermum* and Aspergillus cibarius. Amiel et al. [24] reported a case of sclerokeratitis due to a filamentous fungus, identified as *Metarhizium anisopliae*.

Fusarium, Petriellidium boydii, and Scedosporium inflatum were described by Moriarty et al. [13] in their case series of sclerokeratitis following pterygium surgery. Scedosporium was also reported presenting as scleritis, sclerokeratitis or keratitis alone by Jhanji et al. [25]. The risk factors included a previous pterygium excision with or without beta-radiation and trauma.

Acanthamoeba PUK

Acanthamoeba corneal infections are usually related to contact lens use. The typical presentation is a central corneal ring-shaped infiltrate, however, the ulcer can also appear in the peripheral cornea, sometimes leading to scleral involvement.

Moreira and Prajna [26] described a 37-year-old woman with a history of PUK. Microbiological investigations of the corneal infiltrate revealed Acanthamoeba cysts.

Acanthamoeba keratitis can evolve to adjacent scleritis and will be called Acanthamoeba sclerokeratitis (ASK), which is an aggressive and sight-threatening complications of this type of infection. It is presumed to be either an immune-mediated, or infective process or both. This uncertainty has hindered formulation of effective management guidelines and the outcome of this condition often remains poor [8, 27].

Iovieno et al. [28] described a series of 36 eyes with ASK from 178 patients with Acanthamoeba (18.5%). Mild scleritis/limbitis was treated with systemic NSAIDS and topical corticosteroids and moderate/severe scleritis was treated with immunosuppression. Control of scleral inflammation and pain was achieved in all but two eyes (2 enucleations). Keratoplasty was performed in 21 of 36 eyes (58%), 9 therapeutic/tectonic and 12 for visual rehabilitation. The mild scleritis group had better outcomes in terms of visual improvement and need for keratoplasty.

Systemic Infections

Varicella Zoster

Neves et al. [29] described three cases of PUK secondary to herpes varicella-zoster virus in patients with the acquired immunodeficiency syndrome (AIDS). All of them had skin involvement, and two of them had bilateral keratouveitis. All were treated with high-dose oral acyclovir (4 g/day) with or without topical antiviral therapy. Two of the patients responded well to oral acyclovir, but one of them stopped the treatment, and bilateral progressive outer retinal necrosis and lethal encephalitis developed. The third patient had a recurrent episode of inflammation with PUK, extensive stromal scarring, and deep neovascularization.

Mondino et al. [30] reported four patients with herpes zoster ophthalmicus, which developed peripheral corneal ulcers with steep central edges.

Gupta et al. [31] described one case of peripheral ulcerative keratitis in a population of 18 young adults with HZV keratitis and Naseri et al. [32] described a case of HZO sclerokeratitis three years after HZV vaccination.

The peripheral cornea can also be affected as an extension of HZV scleritis approximately 1 month after the onset of Herpes zoster ophthalmicus, creating a limbal vascular keratitis. It may manifest with scleralization, vascularization, stromal thinning, or peripheral faceting of the cornea. The underlying etiology is probably a vasculitis or immune complex deposition.

Tuberculosis

Mycobacterium tuberculosis may affect any structure of the eye or adnexae. The manifestations of anterior segment tuberculosis are chronic and insidious. *M. tuberculosis* may lead to formation of conjunctival granuloma, nodular scleritis, and interstitial keratitis. The recognition of clinical signs of ocular tuberculosis is of utmost importance as it can provide clinical pathway toward tailored investigations and decision making for initiating anti-tuberculosis therapy [33].

Ocular tissue involvement is the result of systemic dissemination of the organism reaching the eye through the blood circulation. Exogenous infection of the conjunctiva is rare [34].

Phlyctenulosis is a localized hypersensitivity reaction to antigens of *M. tuberculosis*. Phlyctenules may occur on the conjunctiva, but are more frequently observed at the limbus. The lesions appear as localized, elevated pinkish-gray nodules with a soft center and a leash of blood vessels. Sharma et al. [35] described a case of tuberculous phlyctenulosis in a 7-year-old girl. The ocular exam showed presence of discrete, raised, conjunctivae lesions near the corneal limbus with surrounding inflamed conjunctival vessels in the right and the left eye.

Tabbara [34] studied 22 cases of ocular tuberculosis. The most frequently encountered anterior segment findings included conjunctival granuloma, sclerokeratitis, interstitial keratitis, and anterior granulomatous uveitis. *M tuberculosis* was isolated from the eyes of two patients. Sclerokeratitis was seen with peripheral stromal inflammation in a triangular fashion associated with localized scleritis, which can be localized or diffuse.

Gupta et al. [36] described a case of Sweet syndrome associated with PUK and necrotizing scleritis. The patient was treated with oral corticosteroids with subsequent deterioration of the ocular manifestation. The culture growth indicated the presence of *M. tuberculosis*. The patient was started on oral anti-tubercular therapy with complete regression of the ocular lesions after 9 months.

It should be realized that ocular tuberculosis may occur without pulmonary findings. Early diagnosis and prompt treatment are mandatory for the prevention of serious ocular complications of tuberculosis [34].

Syphilis

Syphilis is a sexually transmitted, chronic, systemic infection caused by the spirochete Treponema pallidum. Frequent syphilitic ocular manifestations, which can occur at any stage of the disease, include interstitial keratitis, anterior, intermediate, and posterior uveitis, chorioretinitis, retinitis, retinal vasculitis and cranial nerve, and optic neuropathies [37].

Stromal keratitis is a manifestation of late congenital syphilis that generally appears between 5 and 15 years of age. Bilateral postinflammatory corneal opacification with ghost vessels is still occasionally encountered in older patients who had syphilitic keratitis during childhood, but active stromal keratitis among adults with syphilis is uncommon. The pathogenesis of syphilitic stromal keratitis has yet to be explained. A corneal autoimmune reaction that involves antigenic mimicry is feasible [38].

Wilhelmus and Jones [38] reported five patients with syphilitic keratitis characterized by stromal keratitis, central corneal edema and vascularization. Three of them had peripheral inflammation (two superior and one inferior).

The preferred treatment for all stages of syphilis remains parenteral penicillin G. With proper diagnosis and prompt antibiotic treatment, the majority of cases of syphilis can result in a cure [37].

AIDS

Soni et al. [39] reported the case of a 40-year-old female HIV-infected patient with a crescentic lesion involving the nasal corneal margin from 1 to 5 o'clock in the clockwise direction with associated stromal thinning; conjunctival involvement in the form of nodular lesion with

dilated tortuous vessels and underlying scleral thinning. The patient had no history of chicken pox, no evidence of herpes zoster or any systemic condition known to be associated with PUK in HIV infection. Vasculitis in HIV infection is an uncommon but important pathogenic factor that might manifest as organ-based disease process. HIV vasculopathy is an indirect effect of HIV infection via the immune complex-mediated mechanism or direct infection of vascular/perivascular tissue.

Hepatitis C

Multiple studies including collaborative studies have reported association between PUK and hepatitis C (HCV) infection [40–42]. Antibodies to HCV have been detected in serum from patients with the ulcer utilizing second-generation assay, and have been confirmed by a liver biopsy. Many of these patients responded to interferon therapy [43, 44]. These authors proposed that molecular mimicry might be involved, with the infecting agent stimulating an autoimmune response to corneal antigens through cross-reacting epitopes. Alternatively, they also proposed that deposition of immune complexes in limbal or peripheral corneal tissues led to an immune response and release of proteolytic enzymes.

Johnson and Ohlstein [45] reported a case of necrotizing scleritis and PUK one month after repair of a traumatic scleral defect with patch grafting in a patient with mixed cryoglobulinemia due to HCV infection and Kedhar et al. [46] also described a patient with necrotizing scleritis and PUK associated with HCV-related cryoglobulinemia.

Wilson et al. [40] and Baratz et al. [41] reported the improvement of the ocular disease of three patients with PUK related to HCV using interferon alfa-2b. Two of theses cases had recurrence after discontinuation of therapy.

In conclusion, all patients with Mooren-type ulcers should be tested for evidence of HCV infection in consultation with a liver specialist. Even when improvement is obtained with interferon alfa-2b treatment, however, continued follow-up is important because relapse is common and repeat treatment may be effective [40].

Parinaud and Lyme Disease

Prasher et al. [47] described a case of a 66-year-old woman with the diagnosis of Parinaud oculoglandular syndrome in her right eye. She subsequently experienced recurrent episodes of bilateral peripheral ulcerative keratitis associated with diffuse thinning, neovascularization, and conjunctivalization of the peripheral corneas.

DeLuise and O'Leary [48] described a case of peripheral ulcerative keratitis related to Lyme disease and Huppertz et al. [49] studied the ocular manifestations in children and adolescents with Lyme arthritis, reporting three cases in a group of 84 patients with arthritis. One of them had severe keratitis of the upper third of both corneas with marked neovascularization, but without intraocular inflammation.

Parasitic Diseases and Bacillary Disintery

Ocular associations have been reported with hookworm infestation [50–53].

van der Gaag et al. [52] tested 16 patients with clinical diagnosis of Mooren's ulcer and 15 local controls from Sierra Leone with respect to serum immunoglobulin levels, circulating antibody to hookworm, circulating antibodies to corneal epithelium, stool smears, and eosinophil and lymphocyte levels. Both patients and healthy controls had circulating antibodies to corneal epithelium and to hookworm. In the controls, the titers of hookworm antibodies were significantly lower than in the patients, though in both groups most people had intestinal parasite infestations as detected by the stool smear.

Majekodunmi [51] suggested an autoimmune phenomenon in this disease due to the presence of lymphocytes and plasma cells in the histopathology of the excised tissue in a case of PUK associated with Helminthosis. The authors

also described the finding of Helmintosis in four of five patients with Mooren's ulcer in Nigeria.

In one reported case, bilateral Mooren's ulcer was followed by a case of Salmonella gastroenteritis [54]. The PUK gradually resolved in both eyes after appropriate systemic antibiotic therapy and local ocular care. Those patients with Mooren's ulcer but not HCV may have a similar molecular mimicry with another systemic disease.

Infection as PUK Trigger

Pokharel et al. [55] reported a case of PUK following acute bacterial conjunctivitis (conjunctival congestion with discharge on the eyelids) in a 60-year-old lady with the diagnosis of Rheumathoid arthritis.

PUK Secondary Infections

In a case series Mathur et al. [56] described 14 eyes with peripheral ulcerative keratitis in children. Three eyes developed secondary infective keratitis, two of which had infection following keratoplasty. *S. pneumoniae* was identified as the causative organism. The infection resolved in two cases, while one developed endophthalmitis.

Lin et al. [57] described seven cases of perforated or near-perforated PUK due to rheumatoid arthritis. The cases were surgically managed with patch grafts using glycerol-preserved corneas. Wound culture revealed 1 *S. aureus* and 1 filamentary fungal infection.

Treatment

Depending on the severity, cases of PUK can be managed medically or surgically. Surgical management is done in cases presenting with actual or impending perforation and in cases of medical treatment failure [1].

Initial therapy of infectious PUK follows that for bacterial keratitis, with intensive topical broad-spectrum antibiotics (e.g., 4th generation fluorquinolones). Topical therapy may be altered based on Gram stain, culture, and sensitivity results. It is common for clinicians to add intravenous antibiotics when infection of the sclera is associated with keratitis. Parenteral therapy is generally accepted in clinical practice when there is scleral compromise, although controlled studies have not been done to clarify the added benefit. Given the poor outcome in most cases of bacterial keratoscleritis treated with drops alone, more aggressive approaches would seem reasonable. Use of a combination of intravenous ceftazidime and an aminoglycoside (tobramycin or gentamicin) in combination with topical fortified antibiotics has been reported to be effective in three patients with Pseudomonas scleritis or sclerokeratitis [58]. Topical third-and fourth-generation fluoroquinolones can also be used to treat Pseudomonas PUK, scleritis or sclerokeratitis. Fortified vancomycin and intravenous vancomycin are recommended to treat cases of methicillin-resistant *S. aureus* [12]. Antibiotic treatment via sub palpebral lavage may provide an alternative route to improve scleral penetration in severe infections [59]. Subconjunctival antibiotics can be used as adjuvant therapy specially in cases with scleral compromise taking care not to use those that present scleral necrosis risk (e.g., amphotericin B).

In case of fungal PUK or sclerokeratitis intensive topical antifungals should be used (5% natamycin, 0.15% amphotericin B). Treatment with systemic antifungals (e.g., voriconazole, ketoconazole) can be useful to aid topical treatment, with close follow-up regarding hepatotoxicity [1, 60]. In selected cases, intracameral injection of amphothericin B might be performed as adjuvant therapy [61], as well as intrastromal injection of voriconazole [62].

The initial treatment of Acanthamoeba keratitis is done with topical biguanides (polyhexamethylbiguanide 0.02% or chlorhexidine 0.02%) as monotherapy or in combination with diamidines (propamidine isethionate 0.1% or hexamidine 0.1%) used hourly day and night for 1–2 days, then hourly during the day for 1 week, and then tapered according to clinical severity and signs of ocular surface toxicity [63]. Higher

concentrations of polyhexamethylbiguanide (0.06%) and chlorhexidine (0.2%) can be used in recalcitrant cases [28].

Acanthamoeba sclerokeratitis can be treated according to the stepladder approach described by Lee et al. [8]. The initial treatment uses oral NSAIDs and topical steroids. In severe and nonresponsive cases, oral steroids should be added and immunossupressive agents, such as cyclosporine, mycophenolate or azathioprine are used as steroid-sparing drugs [28].

Sharma et al. [1] in their case series started on intensive topical antibacterial (5% cefazolin sodium with 1.3% tobramycin sulfate every hour round the clock for initial 3 days and then every 2 h), antiviral (3% acyclovir ointment five times a day) or antifungal (5% natamycin five times a day) therapy depending on etiology. Systemic antimicrobials (ciprofloxacin 500 mg twice a day, voriconazole tablets 200 mg twice a day and acyclovir tablets 400 mg five times a day) were instituted as appropriate for 10–14 days. Topical antimicrobial agents were stopped after the healing of the infection occurred. Topical lubricating drops, gels and ointments were added to aid re-epithelialization. Topical cycloplegics (2% homatropine bromide or 1% atropine sulfate) were also added as an adjunctive treatment.

All patients with PUK can benefit from oral Vitamin C (500 mg four times a day) and those above 15 years can be also supplemented with oral doxycycline 100 mg twice a day. Vitamin C helps in healing as it is involved in all phases of corneal healing such as synthesis, maturation, and secretion of collagen [64].

Various surgical modalities for treatment include tissue adhesives, multilayered amniotic membrane graft or tectonic procedures like penetrating keratoplasty, lamellar keratoplasty and corneoscleral patch grafts. Small perforations (less than 3 mm in diameter) can be treated with application of tissue adhesive (N-butyl cyanoacrylate) followed by placement of soft contact lens. Aggressive surgical debridement of infected tissue with appropriate antibiotic therapy may further improve response [65]. Severe destruction of the cornea or scleral perforation may require lamellar or full-thickness grafting [65]. Penetrating keratoplasty may be indicated in some cases of keratitis threatening scleral invasion. Grafting should probably be reserved for sclerokeratitis cases that do not respond to surgical debridement in combination with topical and parenteral antibiotics, or in those cases where perforation has occurred and is not sufficiently closed with tissue adhesive. Despite these aggressive treatments, 60% of eyes with infectious scleritis may require evisceration, enucleation, or have no light perception [3, 7].

Crescentic or circular patch grafts can be fashioned depending on the dimensions of the peripheral ulcer. Conjunctival peritomy adjacent to the ulcer must be done to discern the extent of perforation and the involvement of the sclera, if any. The anterior chamber can be formed with viscoelastic material and prolapsed iris can be either reposited or excised depending on the duration of exposure and viability. The margins of the bed of the corneoscleral ulcer must be revised and the dimensions of the recipient bed measured. The donor tissue is then prepared either using a circular trephine (for circular beds) or free hand dissection (for crescentic beds) from a corneoscleral rim. The donor corneoscleral graft is then sutured using interrupted 10–0 monofilament nylon sutures. The anterior chamber should be washed with balanced salt solution.

Lateral, medial, or both types of tarsorrhaphy may be required to protect the ocular surface and prevent subsequent episodes of infectious keratitis.

Cryotherapy appears to be a useful and safe adjunct to antibiotics, especially in cases of Pseudomonas infection [7]. Direct treatment of necrotic sclera with the cryoprobe after conjunctival resection may be effective for several reasons, including organism destruction, altering the host tissue to enhance the elimination of organisms and the healing process, and better antibiotic penetration.

Conclusions

Initial therapy of infectious PUK follows that for keratitis, with intensive topical broad-spectrum antibiotics (e.g., 4th generation fluorquinolones). Topical therapy may be altered based on Gram stain, culture, and sensitivity results.

Aggressive surgical debridement of infected tissue with appropriate antibiotic therapy may further improve response. Severe destruction of the cornea or scleral perforation may require lamellar or full-thickness grafting.

Conflict of Interest Ana Luísa Höfling-Lima and Eduardo Gayger Müller declare that they have no conflict of interest.

Informed Consent
No human studies were carried out by the authors for this chapter. No animal studies were carried out by the authors for this chapter.

References

1. Sharma N, Sinha G, Shekhar H, Titiyal JS, Agarwal T, Chawla B, Tandon R, Vajpayee RB. Demographic profile, clinical features and outcome of peripheral ulcerative keratitis: a prospective study. Br J Ophthalmol 2015.
2. Raber IM, Laibson PR, Kurz GH, Bernardino VB. Pseudomonas corneoscleral ulcers. Am J Ophthalmol. 1981;92:353–62.
3. Alfonso E, Kenyon KR, Ormerod LD, Stevens R, Wagoner MD, Albert DM. Pseudomonas corneoscleritis. Am J Ophthalmol. 1987;103:90–8.
4. Nanda M, Pflugfelder SC, Holland S. Fulminant pseudomonal keratitis and scleritis in human immunodeficiency virus-infected patients. Arch Ophthalmol. 1991;109:503–5.
5. Womack LW, Liesegang TJ. Complications of herpes zoster ophthalmicus. Arch Ophthalmol. 1983;101:42–5.
6. Codère F, Brownstein S, Jackson WB. Pseudomonas aeruginosa scleritis. Am J Ophthalmol. 1981;91:706–10.
7. Reynolds MG, Alfonso E. Treatment of infectious scleritis and keratoscleritis. Am J Ophthalmol. 1991;112:543–7.
8. Lee GA, Gray TB, Dart JKG, Pavesio CE, Ficker LA, Larkin DFP, Matheson MM. Acanthamoeba sclerokeratitis: treatment with systemic immunosuppression. Ophthalmology. 2002;109:1178–82.
9. Ebrahimi KB, Green WR, Grebe R, Jun AS. Acanthamoeba sclerokeratitis. Graefes Arch Clin Exp Ophthalmol. 2009;247:283–6.
10. Ishibashi Y, Kaufman HE, Kagawa S. Differences in development of keratomycosis after Candida inoculation in the central and peripheral cornea. J Med Vet Mycol. 1986;24:437–44.
11. Dart JK, Stapleton F, Minassian D. Contact lenses and other risk factors in microbial keratitis. Lancet. 1991;338:650–3.
12. Lee J-E, Oum BS, Choi HY, Lee JS. Methicillin-resistant *Staphylococcus aureus* sclerokeratitis after pterygium excision. Cornea. 2007;26:744–6.
13. Moriarty AP, Crawford GJ, McAllister IL, Constable IJ. Severe corneoscleral infection. A complication of beta irradiation scleral necrosis following pterygium excision. Arch Ophthalmol. 1993;111:947–51.
14. Hodson KL, Galor A, Karp CL, Davis JL, Albini TA, Perez VL, Miller D, Forster RK. Epidemiology and visual outcomes in patients with infectious scleritis. Cornea. 2013;32:466–72.
15. Mattern RM, Ding J. Keratitis with Kocuria palustris and Rothia mucilaginosa in Vitamin A deficiency. Case Rep Ophthalmol. 2014;5:72–7.
16. Ovodenko B, Seedor JA, Ritterband DC, Shah M, Yang R, Koplin RS. The prevalence and pathogenicity of *Propionibacterium acnes* keratitis. Cornea. 2009;28:36–9.
17. Bullington RH, Lanier JD, Font RL. Nontuberculous mycobacterial keratitis. Report of two cases and review of the literature. Arch Ophthalmol. 1992;110:519–24.
18. Tay E, Rajan M, Tuft S. Listeria monocytogenes sclerokeratitis: a case report and literature review. Cornea. 2008;27:947–9.
19. Thygeson P. Marginal herpes simplex keratitis simulating catarrhal ulcer. Invest Ophthalmol. 1971;10:1006.
20. Praidou A, Androudi S, Kanonidou E, Konidaris V, Alexandridis A, Brazitikos P. Bilateral herpes simplex keratitis presenting as peripheral ulcerative keratitis. Cornea. 2012;31:570–1.
21. Zaher SS, Sandinha T, Roberts F, Ramaesh K. Herpes simplex keratitis misdiagnosed as rheumatoid arthritis-related peripheral ulcerative keratitis. Cornea. 2005;24:1015–7.
22. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43:379–96.
23. Hayashi Y, Eguchi H, Toibana T, Mitamura Y, Yaguchi T. Polymicrobial sclerokeratitis caused by *Scedosporium apiospermum* and *Aspergillus cibarius*. Cornea. 2014;33:875–7.
24. Amiel H, Chohan AB, Snibson GR, Vajpayee R. Atypical fungal sclerokeratitis. Cornea. 2008;27:382–3.
25. Jhanji V, Yohendran J, Constantinou M, Sheorey H, Vajpayee RB. Scedosporium scleritis or keratitis or both: case series. Eye Contact Lens. 2009;35:312–5.
26. Moreira AT, Prajna NV. Acanthamoeba as a cause of peripheral ulcerative keratitis. Cornea. 2003;22:576–7.

27. Chatterjee S, Agrawal D, Vemuganti GK. Granulomatous inflammation in Acanthamoeba sclerokeratitis. Indian J Ophthalmol. 2013;61:300–2.
28. Iovieno A, Gore DM, Carnt N, Dart JK. Acanthamoeba sclerokeratitis: epidemiology, clinical features, and treatment outcomes. Ophthalmology. 2014;121:2340–7.
29. Neves RA, Rodriguez A, Power WJ, Muccioli C, Lane L, Belfort R, Foster CS. Herpes zoster peripheral ulcerative keratitis in patients with the acquired immunodeficiency syndrome. Cornea. 1996;15:446–50.
30. Mondino BJ, Brown SI, Mondzelewski JP. Peripheral corneal ulcers with herpes zoster ophthalmicus. Am J Ophthalmol. 1978;86:611–4.
31. Gupta N, Sachdev R, Sinha R, Titiyal JS, Tandon R. Herpes zoster ophthalmicus: disease spectrum in young adults. Middle East Afr J Ophthalmol. 2011;18:178–82.
32. Naseri A, Good WV, Cunningham ET. Herpes zoster virus sclerokeratitis and anterior uveitis in a child following varicella vaccination. Am J Ophthalmol. 2003;135:415–7.
33. Gupta V, Shoughy SS, Mahajan S, Khairallah M, Rosenbaum JT, Curi A, Tabbara KF. Clinics of ocular tuberculosis. Ocul Immunol Inflamm. 2015; 23:14–24.
34. Tabbara KF. Ocular tuberculosis: anterior segment. Int Ophthalmol Clin. 2005;45:57–69.
35. Sharma K, Kalakoti P, Juneja R, Sahu S, Singh V, Subramanian PS. Re-emphasizing Thygeson's warning: conjunctival phlyctenulosis as presenting sign of impending clinical tuberculosis. Can J Ophthalmol. 2014;49:e135–7.
36. Gupta N, Chawla B, Venkatesh P, Tandon R. Necrotizing scleritis and peripheral ulcerative keratitis in a case of Sweet's syndrome found culture-positive for *Mycobacterium tuberculosis*. Ann Trop Med Parasitol. 2008;102:557–60.
37. Kiss S, Damico FM, Young LH. Ocular manifestations and treatment of syphilis. Semin Ophthalmol. 2005;20:161–7.
38. Wilhelmus KR, Jones DB. Adult-onset syphilitic stromal keratitis. Am J Ophthalmol. 2006;141: 319–21.
39. Soni ND, Ingole AB, Murade SM. An unusual case of peripheral ulcerative keratitis as a presenting feature in an otherwise healthy patient with undiagnosed human immunodeficiency virus infection and low CD4 counts. Indian J Ophthalmol. 2013; 61:138–9.
40. Wilson SE, Lee WM, Murakami C, Weng J, Moninger GA. Mooren-type hepatitis C virus-associated corneal ulceration. Ophthalmology. 1994; 101:736–45.
41. Baratz KH, Fulcher SF, Bourne WM. Hepatitis C-associated keratitis. Arch Ophthalmol. 1998;116: 529–30.
42. Pluznik D, Butrus SI. Hepatitis C-associated peripheral corneal ulceration: rapid response to intravenous steroids. Cornea. 2001;20:888–9.
43. Moazami G, Auran JD, Florakis GJ, Wilson SE, Srinivasan DB. Interferon treatment of Mooren's ulcers associated with hepatitis C. Am J Ophthalmol. 1995;119:365–6.
44. Erdem U, Kerimoglu H, Gundogan FC, Dagli S. Treatment of Mooren's ulcer with topical administration of interferon alfa 2a. Ophthalmology. 2007;114:446–9.
45. Johnson CC, Ohlstein DH. Peripheral ulcerative keratitis and necrotizing scleritis initiated by trauma in the setting of mixed cryoglobulinemia. Case Rep Ophthalmol. 2011;2:392–7.
46. Kedhar SR, Belair M-L, Jun AS, Sulkowski M, Thorne JE. Scleritis and peripheral ulcerative keratitis with hepatitis C virus-related cryoglobulinemia. Arch Ophthalmol. 2007;125:852–3.
47. Prasher P, di Pascuale M, Cavanagh HD. Bilateral chronic peripheral ulcerative keratitis secondary to cat-scratch disease. Eye Contact Lens. 2008;34: 191–3.
48. Deluise VP, O'Leary MJ. Peripheral ulcerative keratitis related to Lyme disease. Am J Ophthalmol. 1991;111:244–5.
49. Huppertz HI, Münchmeier D, Lieb W. Ocular manifestations in children and adolescents with Lyme arthritis. Br J Ophthalmol. 1999;83:1149–52.
50. Kuriakose ET. Mooren's ulcer. Etiology and treatment. Am J Ophthalmol. 1963;55:1064–9.
51. Majekodunmi AA. Ecology of Mooren's ulcer in Nigeria. Doc Ophthalmol. 1980;49:211–9.
52. van der Gaag R, Abdillahi H, Stilma JS, Vetter JC. Circulating antibodies against corneal epithelium and hookworm in patients with Mooren's ulcer from Sierra Leone. Br J Ophthalmol. 1983;67:623–8.
53. Zelefsky JR, Srinivasan M, Kundu A, Lietman T, Whitcher JP, Wang K, Buyse M, Cunningham ET. Hookworm infestation as a risk factor for Mooren's ulcer in South India. Ophthalmology. 2007;114: 450–3.
54. Yang J, Baltatzis S, Foster CS. Peripheral ulcerative keratitis after Salmonella gastroenteritis. Cornea. 1998;17:672–4.
55. Pokharel A, Subedi S, Bajracharya M. Peripheral ulcerative keratitis triggered by bacterial conjunctivitis. Nepal J Ophthalmol. 2010;2:71–3.
56. Mathur A, Ashar J, Sangwan V. Mooren's ulcer in children. Br J Ophthalmol. 2012;96:796–800.
57. Lin HC, Lee YS, Chia JH. Management of rheumatoid arthritis-related peripheral ulcerative keratitis using glycerol-preserved corneas. Asia Pac J Ophthalmol (Phila). 2013;2:291–4.
58. Helm CJ, Holland GN, Webster RG, Maloney RK, Mondino BJ. Combination intravenous ceftazidime and aminoglycosides in the treatment of pseudomonal scleritis. Ophthalmology. 1997;104:838–43.

59. Meallet MA. Subpalpebral lavage antibiotic treatment for severe infectious scleritis and keratitis. Cornea. 2006;25:159–63.
60. Reddy JC, Murthy SI, Reddy AK, Garg P. Risk factors and clinical outcomes of bacterial and fungal scleritis at a tertiary eye care hospital. Middle East Afr J Ophthalmol. 2015;22:203–11.
61. Shao Y, Yu Y, Pei C-G, Tan Y-H, Zhou Q, Yi J-L, Gao G-P. Therapeutic efficacy of intracameral amphotericin B injection for 60 patients with keratomycosis. Int J Ophthalmol. 2010;3:257–60.
62. Sharma N, Agarwal P, Sinha R, Titiyal JS, Velpandian T, Vajpayee RB. Evaluation of intrastromal voriconazole injection in recalcitrant deep fungal keratitis: case series. Br J Ophthalmol. 2011;95:1735–7.
63. Alvarenga LS, Freitas D, Hofling-Lima AL. Acanthamoeba keratitis. Arq Bras Oftalmol. 2000;63:155–9.
64. Moores J. Vitamin C: a wound healing perspective. Br J Commun Nurs. 2013;S6:S8–11.
65. Huang FC, Huang SP, Tseng SH. Management of infectious scleritis after pterygium excision. Cornea. 2000;19:34–9.

Noninfectious Causes

9

Jessica Chow and Vincent P. deLuise

Introduction

Peripheral ulcerative keratitis (PUK) usually presents as a crescent-shaped thinning of the perilimbal cornea, characterized by an epithelial defect, stromal inflammation, and keratolysis [1]. Associated ocular findings may include conjunctivitis, episcleritis, and scleritis. PUK may progress to corneal melt and frank perforation with poor visual prognosis. About half of the cases of noninfectious PUK are associated with connective tissue disease, which can involve systemic vasculitis and result in significant systemic morbidity and mortality [2].

Clinical Features

The hallmark sign of inflammatory PUK is a peripheral crescentic ulceration, which represents keratolysis of the juxtalimbal cornea (Fig. 9.1a). Symptomatically, patients may complain of pain, tearing, photophobia and eye redness. Decreased vision may result from astigmatism, corneal scarring, or in severe cases, corneal melting and perforation.

On examination, early PUK manifests as peripheral corneal opacities composed of stromal cellular infiltrates in the perilimbal cornea. Progressive disease is exhibited by breakdown of the overlying epithelium and the presence of crescent-shaped corneal ulcers, usually associated with stromal thinning and adjacent corneal neovascularization (Fig. 9.1b). PUK secondary to connective tissue disease often presents with other ocular manifestations of that connective tissue disease, including keratoconjunctivitis sicca, anterior uveitis, and scleritis. In one retrospective review, 100% of scleritis-associated PUK patients had impending corneal perforation, 67% had associated anterior uveitis, and 83% had decreased vision [3]. In another review, 9% of PUK patients had associated anterior uveitis and 34% had impending or frank corneal perforations [2].

Differential Diagnosis

The differential diagnosis of inflammatory PUK includes ocular conditions that cause peripheral corneal thinning or scarring (Table 9.1) Peripheral corneal ulceration can result from a variety of etiologies including infectious causes, local trauma (chemical and thermal injury),

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_9

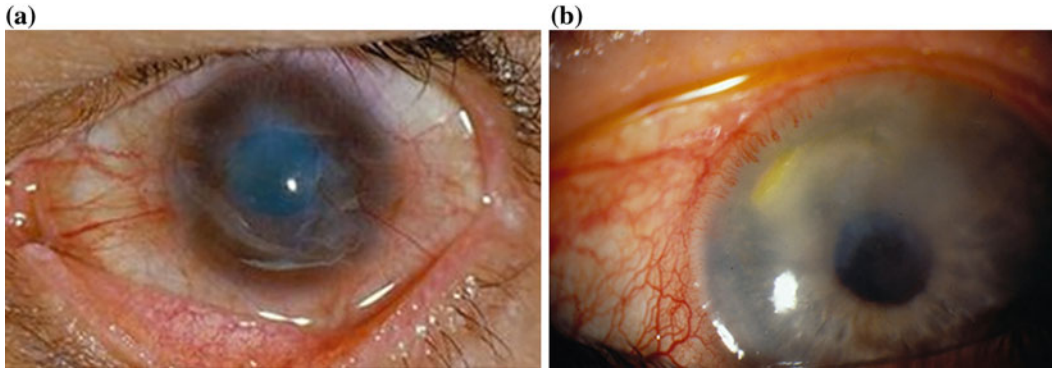

Fig. 9.1 **a**, **b** Peripheral ulcerative keratitis

Table 9.1 Differential diagnosis of peripheral ulcerative keratitis

Infectious	Bacterial (including spirochetes and mycobacteria) Viral (hepatitis C, herpes simplex, varicella zoster) Amebic Fungal
Local, traumatic	Chemical injury Thermal injury
Local, non-inflammatory	Neurotrophic (post-herpetic, diabetes mellitus) Eyelid/eyelash abnormalities (entropion, ectropion, lagophthalmos, trichiasis, cicatricial exposure) Dermatologic (rosacea)
Degenerative disease	Terrien's marginal degeneration Furrow degeneration Pellucid marginal degeneration
Local, inflammatory	Mooren's ulcer Post-surgical Staphylococcal marginal disease Phlyctenules
Systemic, inflammatory	Dermatological (ocular cicatricial pemphigoid, Stevens-Johnson syndrome) Connective tissue disease (rheumatoid arthritis, Wegener's granulomatosis, systemic lupus erythematosis, polyarteritis nodosa, relapsing polychondritis) Lacrimal (Keratoconjunctivitis sicca, Sjogren's syndrome, graft-versus-host disease) Inflammatory bowel disease (Crohn disease)
Systemic, non-inflammatory	Nutritional deficiency Malignancy (leukemia

neurotrophic changes (diabetic or post-herpetic), eyelid abnormalities (entropion, ectropion, lagophthalmos, trichiasis), and rosacea-associated keratitis.

Non-inflammatory causes of peripheral corneal thinning include Terrien's marginal degeneration, furrow degeneration, pellucid marginal degeneration. Systemic malnutrition and malignancy (leukemia) have also been reported to cause peripheral corneal thinning [4, 5].

Inflammatory causes of corneal ulceration include systemic conditions such as dermatologic disorders (Stevens-Johnson Syndrome, ocular cicatricial pemphigoid), and autoimmune connective tissue diseases such as rheumatoid arthritis, polyarteritis nodosa, dermatomyositis,

and inflammatory bowel disease. Mooren's ulcer is a diagnosis of exclusion. It is a type of inflammatory PUK characterized by a local autoimmune reaction without systemic involvement. Local inflammatory conditions such as staphylococcal marginal keratitis ("catarrhal" infiltrates), Fuchs superficial marginal keratitis, and post-surgical inflammation can also cause peripheral corneal ulceration.

Connective Tissue Diseases

Fully half of all cases of noninfectious peripheral ulcerative keratitis are due to an associated connective tissue disease [2]. Corneal involvement in these systemic conditions often portends severe disease in the setting of a systemic vasculitis, which can lead to significant morbidity and mortality. The pathophysiologic process is theorized to involve immune complex deposition in the peripheral cornea from inflammation of limbal and conjunctival vessels, leading to the release of collagenases and proteases by inflammatory cells and subsequent keratolysis. Rheumatoid arthritis, Wegener granulomatosis, polyarteritis nodosa, systemic lupus erythematosus, and relapsing polychondritis have all been identified as causes of PUK.

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is the most common connective tissue disease associated with PUK. Rheumatoid arthritis is diagnosed by the presence of arthritis in three or more joints, morning stiffness, positive IgG rheumatoid factor, and serum autoantibodies to IgG. IgM rheumatoid factor is also correlated with disease activity, but is not specific to RA. Anticyclic citrullinated peptide (anti-CCP) antibody has high specificity but low sensitivity for RA, and its presence identifies patients who are more likely to have severe aggressive disease.

In one study, RA accounted for 34% of noninfectious PUK [2]. PUK tends to occur in rheumatoid patients with chronic disease of longstanding duration, often over 20 years, and in patients with high RF and anti-CCP antibody titers. PUK in the setting of RA occurs bilaterally in nearly 50% of cases. Keratoconjunctivitis sicca and erosive arthritis are also predisposing factors for the development of rheumatoid PUK, may herald the presence of systemic vasculitis and potentially life-threatening disease. Other ocular manifestations of RA include episcleritis, diffuse anterior scleritis, necrotizing scleritis, and scleromalacia perforans. Severe keratoconjunctivitis sicca may lead to the formation of corneal epithelial defects, non-inflammatory corneal melts, and perforation, but dry eye alone does not cause PUK.

Corneal involvement in RA may manifest as peripheral corneal thinning or marginal furrows. The corneal epithelium may remain intact with peripheral guttering. There may be corneal neovascularization and an associated scleritis. PUK is a more severe form of RA-associated corneal pathology. Infiltration by inflammatory cells and neovascularization of the cornea results in inflammatory ulceration of the perilimbal cornea, with epithelial breakdown and progressive thinning to the point of corneal perforation. Keratoconjunctivitis sicca contributes to the rapid progression of keratolysis, as severe aqueous tear deficiency causes ocular surface instability and leads to epithelial defects. In later stages of PUK, the cornea exhibits diffuse neovascularization and scarring. Sterile ulceration and corneal melt in RA patients has also been reported in the postoperative setting after routine cataract surgery. The pathophysiology of RA-associated PUK has not been clearly elucidated. It has been theorized to result from an imbalance between matrix metalloproteinases and their inhibitors, or an immune complex-mediated limbal vasculitis that results in localized stromal keratolysis [4, 6]. Activation of local collagenases is believed to contribute to the corneal melt [6].

PUK-associated RA should be considered a life-threatening disease and its management therefore necessitates aggressive systemic immunosuppression in addition to treatment of local ocular pathology [7]. The use of topical corticosteroid therapy is controversial. In cases of infiltrative keratitis, topical steroids may be used cautiously with frequent follow-up. However, topical steroid use can cause corneal perforation in some cases of peripheral ulceration and can impair corneal wound healing.

Collagenase inhibitors such as 1% topical medroxyprogesterone and oral doxycycline (100 mg PO bid) may slow the keratolytic process in rheumatoid PUK. Bandage contact lenses, punctal occlusion, topical cyclosporine, and autologous serum tears are also helpful in the management of associated keratoconjunctivitis sicca in PUK cases. In cases of impending or frank perforation, tissue adhesive (cyanoacrylate glue) may stabilize and preserve ocular integrity.

Corneal grafting (lamellar tectonic patch grafts or full-thickness corneal transplants) may be necessary to restore ocular integrity in cases of severe ulceration. However, the prognosis of corneal grafting for PUK in RA tends to be poor, especially in cases of active local inflammation or corneal neovascularization. Control of the underlying inflammatory process is crucial prior to tectonic or full-thickness corneal transplantation.

The management of RA-associated vasculitis involves systemic corticosteroids as first-line therapy, unless contraindicated by the rheumatologist. Both oral and intravenous pulsed corticosteroids have rapid onset and demonstrate potent anti-inflammatory effects. Other immunomodulatory drugs such as azathioprine, methotrexate, and cyclosporine (which will be discussed later in this chapter) may be necessary both as steroid-sparing agents and as adjunctive immunosuppressive therapy. More recently, biologic agents such as infliximab, rituximab, and to a lesser extent, etanercept, have demonstrated efficacy even as either adjuvant or even monotherapy, both for control of the systemic connective tissue disease, and its associated PUK [8, 9].

Wegener's Granulomatosis

Wegener's granulomatosis (WG), also termed Granulomatosis with Polyangiitis, is a necrotizing granulomatous vasculitis of small arteries and veins that involves the respiratory tract and renal system. WG typically presents in the fourth to fifth decades, with a male to female predominance of 3:2. Symptoms include sinus infections, nosebleeds, hemoptysis, fever, fatigue with general malaise, and weight loss. Pulmonary involvement manifests as infiltrative lesions, nodules, or cavitations in the lungs, while upper respiratory tract involvement can lead to sinus fistulae and nasal septal perforation. Focal necrotizing glomerulonephritis can cause impaired renal function and hematuria, and heralds poor systemic prognosis with high mortality rate.

Laboratory testing is helpful in the diagnosis of WG. Antineutrophil cytoplasmic antibody toward proteinase PR3 with the cytoplasmic immunofluorescence pattern (c-ANCA) has specificity of over 90% for WG. Rheumatoid factor is positive in over 50% of WG patients. Histopathologic studies reveal a systemic granulomatous occlusive vasculitic process of the affected organs with tissue necrosis and giant cell reaction. The pathophysiology of WG is believed to represent immune complex-mediated vasculitis.

PUK is a common ocular manifestation in WG and occurs secondary to a necrotizing vasculitic involvement of the anterior ciliary arteries or perilimbal arteries. Unlike in RA, where PUK tends to occur with chronic, late-stage disease, PUK may be the presenting manifestation of WG. It often presents bilaterally and is always associated with scleritis, which may lead to severe scleral necrosis. PUK in WG may also be triggered by local trauma in the postoperative period, similar to RA. Other ocular manifestations of WG result from granulomatous paranasal sinus disease, which can cause severe orbital inflammation, nasolacrimal duct obstruction, ocular muscle involvement, and optic neuropathy.

Local treatment of WG-associated PUK is similar to that for rheumatoid PUK. Conjunctival resection, preservation of globe integrity with tissue adhesive, and anti-collagenolytic agents may be beneficial to prevent corneal perforation, but systemic immunosuppression is required for definitive cure, especially given the high mortality rate of systemic disease.

Although systemic corticosteroids are a mainstay of WG therapy, they do not affect long-term prognosis when used alone. However, the combination of corticosteroids with the alkylating agent cyclophosphamide usually given intravenously, have proven quite effective to achieve remission in advanced WG disease. Biologic agents such as rituximab, a chimeric monoclonal antibody against CD20, have some efficacy in treating WG-associated PUK. There are case reports of WG-associated ocular disease, with PUK recalcitrant to corticosteroids and cyclophosphamide or methotrexate, that have responded to rituximab therapy [10, 11].

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a necrotizing nongranulomatous vasculitis of small to medium-sized vessels. PAN can be divided into three main categories: classic PAN, allergic granulomatosis/Churg-Strauss angiitis, or and overlap syndrome of systemic necrotizing vasculitis. Classic PAN occurs more in middle-aged males and most commonly presents in 20- to 40-year-olds. [1] The diagnosis is made by clinical signs and histopathologic findings on biopsy of affected tissues. PAN can be associated with hepatitis B or C antigenemia, suggesting a molecular mimicry process involving the hepatitis viruses, with immune complex-mediated vasculitis.

PAN presents with a variety of clinical symptoms, including fever, malaise, muscle loss, arthralgia, and myalgia. It is typically a progressive disease involving multiple organ systems. Polyarteritis of the renal system can manifest as proteinuria, hematuria, and renal failure, a major cause of death in PAN. Skin involvement in the form of tender subcutaneous nodules is known as livedo reticularis. Cardiovascular complications such as myocardial infarction and congestive heart failure due to coronary arteritis are a major cause of morbidity in PAN. Gastrointestinal involvement is also common. Bowel infarction secondary to superior mesenteric arteritis and hepatic infarction from vasculitis can occur in PAN.

The diagnosis of PAN is based on the presence of the above clinical disease combined with histopathologic findings of nongranulomatous vasculitis of small and medium-size arteries. Laboratory tests are generally not useful. Biopsy of skin lesions and affected muscles may demonstrate immunoglobulin and complement deposits.

Ocular manifestations of PAN are secondary to diffuse vasculitis and include painful diffuse or nodular scleritis, retinal vasculitis, choroiditis, optic atrophy from involvement of posterior ciliary vessels, exudative retinal detachment, and central retinal artery occlusion. Hypertensive retinopathy may occur secondary to renal involvement.

PUK is the most common corneal manifestation of PAN and may be its presenting manifestation [1]. Clinically, PAN-associated PUK may exhibit similar features to Mooren's ulcer. However, associated adjacent scleritis distinguishes this from classic Mooren's ulcer, which typically does not demonstrate scleral involvement. Management strategies for PAN-associated PUK include conjunctival resection, tissue adhesive, and the use of topical collagenase inhibitors 1% medroxyprogesterone acetate and oral doxycycline. Topical corticosteroids may be deleterious as they can inhibit new collagen synthesis, delay wound healing, and lead to corneal melt. As with other types of inflammatory PUK, definitive treatment requires control of systemic disease. Untreated PAN has a high mortality rate, with a reported 5-year-survival rate of 13%. Treatment of systemic disease includes systemic immunosuppression with corticosteroids and alkylating agents, and can increase the 5-year-survival rate to 80% [12].

Microscopic Polyangiitis and Churg-Strauss Syndrome

Microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) are ANCA-positive vasculitides distinct from PAN. MPA is a rare vasculitis of small vessels and can cause glomerulonephritis and respiratory tract lesions. Unlike WG, the inflammation in MPA and CSS is nongranulomatous. 50% of MPA patients are ANCA- positive, and 70% of these patients have antineutrophil cytoplasmic antibodies against myeloperoxidase (p-ANCA) [1]. CSS presents as a systemic necrotizing vasculitis accompanied by asthma and eosinophilia. Both MPA and CSS may be associated with PUK. For milder disease, methotrexate may be effective, while severe systemic vasculitis requires systemic corticosteroids and alkylating agents.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic relapsing autoimmune disease with the production of antinuclear antibodies (ANA). 90% of patients are women, and the disease typically presents in the fourth or fifth decade of life. The pathophysiology of SLE is hypothesized to be related to dysfunction of suppressor T-lymphocytes, resulting in the production of autoantibodies and immune complex formation and deposition in various tissues. Activation of the complement pathway in these organs leads to local tissue destruction.

SLE involves inflammation in multiple organ systems. It is diagnosed by the presence of clinical and laboratory criteria, along with dermatologic findings (discoid lupus, facial rash, alopecia, photosensitivity, Raynaud phenomenon), renal involvement (proteinuria, urinary sediment cellular casts), hematologic abnormalities (anemia, leukopenia, thrombocytopenia), pleuritis, and pericarditis. Corneal involvement in the form of keratoconjunctivitis sicca is the most common ocular manifestation of SLE, whereas PUK is rare. Treatment of SLE-associated PUK should include therapy for sicca with topical anti-inflammatory medications, bandage contact lenses, punctal occlusion, and ocular surface lubrication with artificial tears or autologous serum tears. Close follow-up of the ocular surface is required, especially in cases wherein bandage contact lenses have been used. Corneal ulceration, while uncommon, signals active systemic vasculitis and necessitates therapy with oral corticosteroids or immunomodulators such as cyclophosphamide, azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil [13, 14].

Relapsing Polychondritis

Relapsing polychondritis (RP) is a connective tissue disease characterized by inflammation of cartilaginous tissues especially in the ears and nose. There is no gender predilection and onset is typically in the fourth through sixth decade of life. RP is an autoimmune disease associated with anti-type II collagen antibodies, and typically responds to high-dose systemic corticosteroids and anti-inflammatory medications. Clinical features include red, swollen, and painful ears, destruction of nasal cartilage, and nasal deformities. Relapsing polychondritis may lead to cardiovascular and respiratory morbidity with involvement of the aortic ring and trachea. Ocular findings include episcleritis, conjunctivitis, iridocyclitis, scleritis, and keratitis. The prevalence of PUK in RP is less than 10% [15].

PUK associated with RP has been reported to respond to high-dose systemic corticosteroids, as well as immunomodulators such as azathioprine, cyclosporine, cyclophosphamide, and chlorambucil [15]. Variable response to methotrexate has been reported in the literature. Refractory RP has also been successfully treated with biologics such as infliximab [16].

Other Causes of Inflammatory Peripheral Corneal Ulceration

Sarcoidosis

Rare cases of PUK associated with sarcoidosis have been reported in the literature. In one report, a patient with recently diagnosed, biopsy-proven sarcoidosis, presented with PUK that was successfully stabilized with cyclophosphamide and lamellar keratoplasty. Extensive workup did not reveal any other seropositive vasculitic disease [17]. Another case of sarcoidosis-associated PUK resolved with topical prednisolone acetate and did not require systemic management [18].

Inflammatory Bowel Disease

Crohn disease, an inflammatory bowel disorder, is associated with ocular involvement in up to 10% of patients. Uveitis, episcleritis, and scleritis are the most common ocular manifestations while corneal involvement is less common. PUK has been reported in 1–2% of Crohn patients with ocular findings, and rare cases of PUK leading to corneal perforation have been reported in the literature [19–21].

PUK associated with Crohn disease may be managed similarly to connective tissue disease-associated PUK, with systemic corticosteroid and immunomodulatory therapy as first-line treatments. Although corneal involvement in Crohn disease is rare, two reports detail the effective management of Crohn-associated PUK with infliximab. In one case series, two patients with PUK refractory to systemic steroid or cyclophosphamide therapy demonstrated rapid response to infliximab, with improvement in pain and decrease in inflammation and keratolysis [21].

Mooren's Ulcer

Mooren's ulcer is a rare, idiopathic form of peripheral corneal ulceration that may be unilateral or bilateral. It is characterized by severe pain in an inflamed eye, photophobia, and tearing, without associated scleritis. The corneal ulceration classically demonstrates an "overhanging" edge (Fig. 9.2). Progressive peripheral corneal ulceration results in significant irregular astigmatism and decreased vision, especially with proximity of the lesion to the central cornea [22]. Mooren's ulcer is more common in Africa,

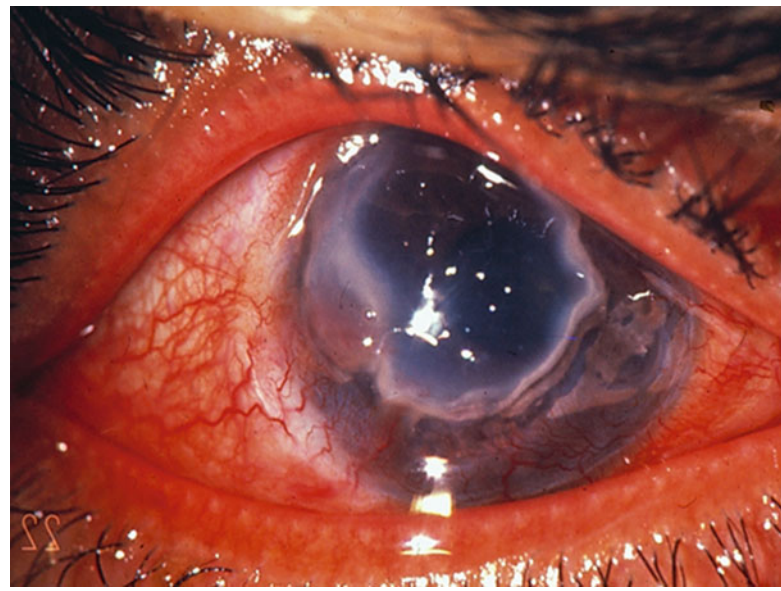

Fig. 9.2 Mooren's ulcer

China, and India. There is an association with environmental factors such as exposure to viral (hepatitis C) and helminthic infections, as well as a genetic component with susceptibility in the presence of HLA-DR17 or DQ2 antigens [23]. Mooren's ulcer can be classified into three types:

1. Unilateral Mooren's ulcer manifests as a painful progressive corneal ulceration in elderly patients. There is vascular nonperfusion of the adjacent conjunctiva and superficial vascular plexus.
2. Bilateral aggressive Mooren's occurs in young patients and demonstrates vascular leakage and neovascularization into the ulcer.
3. Bilateral indolent Mooren's occurs in middle-aged patients and progresses with peripheral corneal guttering, with little inflammatory response and a relatively normal vascular architecture [24].

The treatment of Mooren's ulcer is distinct from that for systemic inflammatory PUK and varies according to the type of presentation. Given the relative rarity of cases, there is a lack of prospective randomized control trials comparing interventions for Mooren's ulcer [25]. Multiple medical and surgical interventions have been reported with variable success [26]. In one study, unilateral Mooren's responded to aggressive systemic and local immunosuppression and resection of the corneal stroma to remove the source of the inciting antigen [24]. Bilateral aggressive Mooren's requires intense therapy with intravenous steroids and simultaneous treatment of any underlying infective process. In contrast, the indolent form of Mooren's responds to topical treatment with corticosteroids and cyclosporine A. Of note, peripheral corneal pathology similar to Mooren's ulcer has been reported in chronic hepatitis C infection, which responded to subcutaneous interferon alfa-2b treatment [27]. Typically, a stepwise approach is recommended: local immunosuppression, systemic immunosuppression, removal of local antigens, and removal of distant antigens.

Staphylococcus-Associated Marginal Keratitis

Staphylococcus-associated marginal keratitis (Staphylococcal "catarrhal" ulcer) is an immune-mediated peripheral corneal ulceration secondary to blepharoconjunctivitis. The pathophysiology

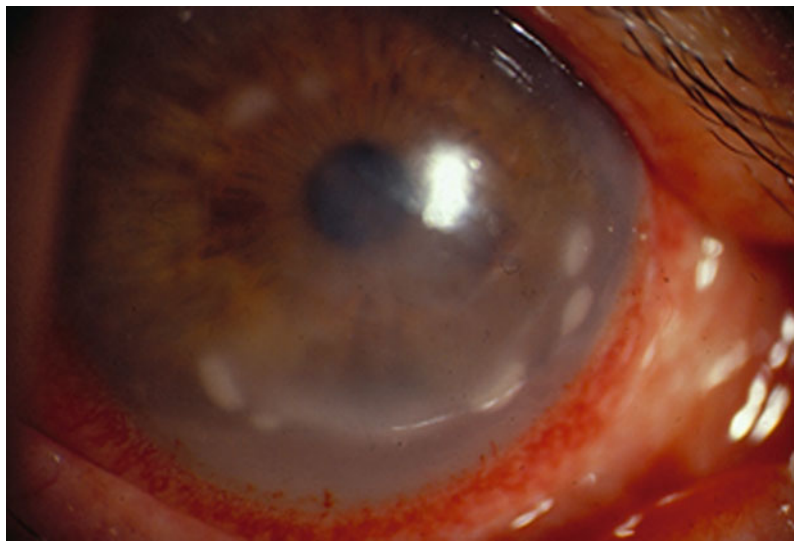

Fig. 9.3 Staphyloccoccus-associated marginal keratitis

is believed to be a type IV hypersensitivity reaction against antigens from the cellular wall of Staphylococcal species, as well as a direct effect on the peripheral cornea by staphylococcal exotoxins. Marginal infiltrates ("catarrhal" infiltrates) are well-circumscribed gray lesions and typically occur 1 mm inside the limbus. Unlike inflammatory PUK associated with systemic disorders, there is typically an intervening clear zone between the limbus and the peripheral infiltrates (Fig. 9.3). Superficial corneal pannus may be observed as well.

Management of Staphylococcus-associated marginal keratitis includes eyelid hygiene to reduce bacterial colonization of the eyelids, topical antibiotics, and topical corticosteroids. Topical 0.05% cyclosporine has also been reported as an effective treatment [28].

Fuchs' Superficial Marginal Keratitis

Fuchs' superficial marginal keratitis is a rare disorder causing inflammatory peripheral corneal thinning. It typically presents in young to middle-aged adults, and is characterized by recurrent marginal infiltrates that may lead to progressive stromal thinning [29]. In advanced cases, pseudopterygium may develop over the recurrent infiltrates. Severe thinning has been reported to progress to cystic hydrops and perforation, and some cases have required the use of lamellar patch grafts to preserve globe integrity [30, 31].

Management of Inflammatory PUK

Proper management of peripheral ulcerative keratitis requires a thorough history and workup to determine the etiology. A medical or family history of connective tissue disease or autoimmune disease should be elicited, as well as a detailed review of systems including signs of dermatologic, neurologic, and rheumatologic disease. On exam, careful attention to the ocular surface and eyelids may help differentiate between various etiologies of corneal thinning. Local infection should be excluded by corneal culture, as microbial keratitis usually responds well to topical antibiotic therapy, and conversely, may worsen with immunosuppressive therapy for PUK. Systemic laboratory workup for inflammatory PUK includes a complete blood count, rheumatoid factor, erythrocyte sedimentation rate, anti-neutrophil cytoplasmic antibodies, antinuclear antibody, urinalysis, and chest X-ray. These tests may help distinguish between the various connective tissue diseases associated with PUK (Table 9.2). However, many of these connective tissue diseases are diagnosed by a combination of rheumatologic clinical criteria, as the above tests may be nonspecific. Rheumatology referral should be offered to patients with inflammatory PUK, both for diagnosis and management of systemic disease.

Appropriate therapy for inflammatory PUK is determined by the etiology and severity of ocular pathology at presentation. Treatment should target control of both corneal disease and the

Table 9.2 Diagnostic testing for PUK

Test	Systemic disease
Rheumatoid factor (RF)	Rheumatoid arthritis, but nonspecific
Anticyclic citrullinated peptide (anti-CCP) antibody	Rheumatoid arthritis
Antineutrophil cytoplasmic antibodies (ANCA)	c-ANCA in Wegener's granulomatosis p-ANCA in microscopic polyangiitis syndrome
Antinuclear antibody (ANA)	Abnormal titers in systemic lupus erythematosus but not specific
Urinalysis (UA) with microscopic analysis	Proteinuria and red blood cell casts in Wegener's granulomatosis, polyarteritis nodosa
Chest radiograph (CXR)	Pulmonary nodules and cavitations in Wegener's granulomatosis

underlying systemic condition. The corneal process typically does not respond to local therapy alone and requires control of systemic inflammation. Systemic vasculitis can result in significant morbidity and mortality, and co-management with an internal medicine physician or rheumatologist is highly recommended. Immunosuppressive therapy requires frequent monitoring with blood work and clinic visits, and many of the systemic medications for PUK have the potential to cause serious side effects.

Medical Therapy

Local treatment of ocular disease

The primary goal of local therapy for PUK is the preservation of ocular integrity. As the pathophysiology of PUK involves release of collagenases and local proteases from perilimbal neutrophil invasion and activation, a variety of medications targeted at these enzymes have been employed to slow or halt the keratolytic process in PUK. Topical medroxyprogesterone 1% and acetylcysteine may be useful to manage corneal melt. Oral cyclines such as doxycycline, an irreversible inhibitor of corneal matrix metalloproteinase-2, may also be beneficial for the peripheral corneal ulceration in PUK. The usual dosing of doxycycline is 100 mg by mouth twice daily. Topical and oral ascorbate (1–2 grams by mouth daily) promote corneal wound healing by stimulating the secretion of collagen by corneal fibroblasts and may be of use in preventing corneal perforation in PUK. However, the above interventions are targeted specifically at the treatment of corneal disease, and are usually insufficient for control of PUK, as the corneal process is a local manifestation of systemic disease.

Systemic Immunosuppression

Systemic corticosteroids are the first-line therapy for the management of inflammatory PUK. Corticosteroids are a rapidly effective and potent anti-inflammatory agent and are effective in treating PUK associated with systemic vasculitides, inflammatory bowel disease-associated PUK, and the aggressive variant of Mooren's ulcer. The recommended dose of oral prednisone is 1 mg/kg/day with subsequent taper as determined by clinical response to treatment. Intravenous pulse methylprednisolone at 1 g/day for 3 days should be administered in cases of impending visual loss [32]. Chronic use of systemic corticosteroids can lead to potentially severe side effects. Prophylaxis against osteoporosis and gastric ulcers should be administered for all patients on chronic steroid therapy. Other potential complications of corticosteroids include poor control of hypertension and diabetes and electrolyte imbalance.

Several classes of steroid-sparing immunosuppressive agents have efficacy for inflammatory PUK. Antimetabolites such as methotrexate (7.5–2.5 mg/week), azathioprine (1.0–2.5 mg/kg/day), and mycophenolate mofetil (1.0 g bid) have proven useful in cases of rheumatoid PUK [3, 33–36]. T-cell inhibitors such as cyclosporine A are a reasonable immunosuppressive agent in cases of rheumatoid PUK, but may not be potent enough to treat systemic vasculitis. Nephrotoxicity may occur in susceptible patients. Topical cyclosporine A 0.05% is also useful for the treatment of keratoconjunctivitis sicca, which is often associated with inflammatory PUK.

Alkylating agents such as cyclophosphamide (1–2 mg/kg/day orally or intravenously pulsed every 3–4 weeks) may be used either as an alternative to or as adjunct therapy with chronic steroid use. Cyclophosphamide has proven particularly for Wegener's-associated PUK, which in severe cases does not respond well to corticosteroids.

Surgical Management

Surgical intervention may be indicated in severe PUK to maintain the integrity of the globe. Small corneal perforations (<2 mm in diameter) may be managed with cyanoacrylate adhesive and bandage contact lens. With systemic

immunosuppression, these glued corneal perforations can heal well without the use of corneal grafting. Larger impending or frank perforations require lamellar or full-thickness keratoplasty to preserve corneal integrity, but have a high failure rate even with appropriate immunosuppressive therapy. Amniotic membrane transplantation may be used alone or in conjunction with corneal grafting to reduce inflammation and promote graft re-epithelization. Amniotic membrane on the ocular surface promotes epithelial healing and reduces inflammation, scarring, and angiogenesis. In one recent case series of severe PUK, amniotic membrane transplantation in combination with anterior chamber washout and topical corticosteroid therapy, showed favorable results with stabilization of the ocular surface and healing of corneal ulceration in twelve patients [37].

Resection of perilimbal conjunctiva has been used with some success for various types of PUK. Removal of the source of immune complexes and collagenases and proteinases that contribute to corneal ulceration may promote resolution of inflammation, but the treatment is controversial, as the ulcerative process may recur with regeneration of the resected conjunctiva [1, 2, 32].

Recent Advances

Recent advances in the management of PUK originate from the development of biologic agents that directly target specific mediators in the inflammatory pathway. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), is approved for the treatment of RA and Crohn disease. TNF-α stimulates the production of matrix metalloproteinases that cause keratolysis in PUK. Infliximab is administered at an intravenous dose of 3 mg/kg for RA and 5 mg/kg for Crohn disease at weeks 0, 2, and 6, then every 8 weeks thereafter. Etanercept, a human recombinant dimeric fusion protein that mimics TNF-α receptors, has also been used for the treatment of inflammatory keratitis but is less effective than infliximab [38]. It is given at a subcutaneous dosage of 25 mg twice weekly. As mentioned above, rituximab, a chimeric antibody against CD20-α, has been used to treat refractory WG-associated PUK with some success. Rituximab is administered as weekly intravenous infusions of 1000 mg.

Biologic agents should be used with caution, as they may increase the risk of opportunistic infections such as tuberculosis and atypical Mycobacterial disease. Other potential adverse effects include congestive heart failure, anaphylaxis, lymphoproliferative disorders, malignancy, increased risk of thromboembolic events, and hepatotoxicity. Typically, these medications are administered with close monitoring by a rheumatologist.

Newer biologic agents including monoclonal antibodies against interleukins, such as IL-17 (secukinumab), IL-l (gevokizumab), and IL-6 (tocilizumab and sarilumab), antibody fragments against inflammatory cytokines such as TNF-α (ESBA 105) and T-cell inhibitors such as the fusion protein abatacept, have been used as investigational therapies for noninfectious uveitis, and may prove useful for the management of inflammatory PUK in the future [39].

Conclusion

Peripheral ulcerative keratitis is associated with a variety of inflammatory disorders. The diagnosis of PUK should exclude infectious causes of peripheral corneal ulceration, as immunosuppressive therapy can potentially worsen infectious keratitis. When associated with systemic vasculitis, PUK should be treated as a life-threatening disease, with management to control both local ocular pathology and systemic inflammation. Corticosteroids and immunomodulatory agents are effective immunosuppressive therapies, and newer biologic agents have recently proven to be excellent alternatives to refractory disease. A multidisciplinary approach between the ophthalmologist and internist or rheumatologist is recommended for PUK patients with systemic disease.

Compliance with Ethical Requirements

Conflict of Interest
Jessica Chow and Vincent de Luise declare that they have no conflict of interest.

Informed Consent
No human studies were carried out by the authors for this article.

Animal Studies
No animal studies were carried out by the authors for this article.

References

1. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43 (5):379–96.
2. Tauber J, Sainz de la Maza M, Hoang-Xuan T, Foster CS. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea. 1990;9 (1):66–73.
3. Sainz de la Maza M, Foster CS, Jabbur NS, Baltatzis S. Ocular characteristics and disease associations in scleritis-associated peripheral keratopathy. Arch Ophthalmol. 2002;120(1):15–9.
4. Gregory JK, Foster CS. Peripheral ulcerative keratitis in the collagen vascular diseases. Int Ophthalmol Clin. 1996;36(1):21–30.
5. Ladas JG, Mondino BJ. Systemic disorders associated with peripheral corneal ulceration. Curr Opin Ophthalmol. 2000;11(6):468–71.
6. Riley GP, Harrall RL, Watson PG, Cawston TE, Hazleman BL. Collagenase (MMP-1) and TIMP-1 in destructive corneal disease associated with rheumatoid arthritis. Eye (Lond). 1995;9(6):703–18. doi:10.1038/eye.1995.182.
7. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Effects of systemic immunosuppression. Ophthalmology. 1984;91(10):1253–63.
8. Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea. 2005;24(6):742–4.
9. Watanabe R, Ishii T, Yoshida M, Takada N, Yokokura S, Shirota Y, Fujii H, Harigae H. Ulcerative keratitis in patients with rheumatoid arthritis in the modern biologic era: A series of eight cases and literature review. Int J Rheum Dis. 2015. doi:10.1111/1756-185X.12688.
10. Freidlin J, Wong IG, Acharya N. Rituximab treatment for peripheral ulcerative keratitis associated with Wegener's granulomatosis. Br J Ophthalmol. 2007;91(10):1414. doi:10.1136/bjo.2006.113316.
11. Huerva V, Sanchez MC, Traveset A, Jurjo C, Ruiz A. Rituximab for peripheral ulcerative keratitis with wegener granulomatosis. Cornea. 2010;29(6):708–10. doi:10.1097/ICO.0b013e3181c296ed.
12. Leib ES, Restivo C, Paulus HE. Immunosuppressive and corticosteroid therapy of polyarteritis nodosa. Am J Med. 1979;67(6):941–7.
13. Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. Rheumatology (Oxford). 2007;46 (12):1757–62. doi:10.1093/rheumatology/kem173.
14. Read RW. Clinical mini-review: Systemic lupus erythematosus and the eye. Ocul Immunol Inflamm. 2004;12(2):87–99. doi:10.1080/09273940490895308.
15. Yoo JH, Chodosh J, Dana R. Relapsing polychondritis: systemic and ocular manifestations, differential diagnosis, management, and prognosis. Semin Ophthalmol. 2011;26(4–5):261–9. doi:10.3109/08820538.2011.588653.
16. Jabbarvand M, Fard MA. Infliximab in a patient with refractory necrotizing scleritis associated with relapsing polychondritis. Ocular immunology and inflammation. 2010;18(3):216–7.
17. Siracuse-Lee D, Saffra N. Peripheral ulcerative keratitis in sarcoidosis: A case report. Cornea. 2006;25(5):618–20.
18. Harthan JS, Reeder RE. Peripheral ulcerative keratitis in association with sarcoidosis. Contact Lens Anterior Eye. 2013;36(6):313–7.
19. Tan MH, Chen SDM, Rubinstein A, Bron AJ. Corneal perforation due to severe peripheral ulcerative keratitis in Crohn disease. Cornea. 2006;25(5):628–30.
20. Angioi K, Kaminsky P, Peyrin-Biroulet L. Infliximab for severe peripheral ulcerative keratopathy revealing Crohn's disease. Inflamm Bowel Dis. 2011;17 (3):866–867. doi:10.1002/ibd.21358.
21. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn disease. Am J Ophthalmol. 2011;152(2):183–188.e182.
22. Angioi K, Kaminsky P, Peyrin-Biroulet L. Infliximab for severe peripheral ulcerative keratopathy revealing Crohn's disease. Inflamm Bowel Dis. 2011;17 (3):866–867. doi:10.1002/ibd.21358.
23. Zegans ME, Srinivasan M. Mooren's ulcer. Int Ophthalmol Clin. 1998;38(4):81–8.
24. Watson PG. Management of Mooren's ulceration. Eye (Lond). 1997;11(Pt 3):349–56. doi:10.1038/eye.1997.74.
25. Alhassan MB, Rabiu M, Agbabiaka IO. Interventions for Mooren's ulcer. The Cochrane database of systematic reviews (6). doi:10.1002/14651858.CD006131.pub2.
26. Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer: Current concepts in management. Indian J Ophthalmol. 1997;45(1):7–17.

27. Wilson SE, Lee WM, Murakami C, Weng J, Moninger GA. Mooren-type hepatitis C virus-associated corneal ulceration. Ophthalmology. 1994;101(4):736–45.
28. Ozcura F. Successful treatment of staphyloc occus-associated marginal keratitis with topical cyclosporine. Graefes Arch Clin Exp Ophthal mol. 2010;248(7):1049–50. doi:10.1007/s00417-009-1290-4.
29. Bierly JR, Dunn JP, Dawson CR, Ostler HB, Wong IG. Fuchs' superficial marginal keratitis. Am J Ophthalmol. 1992;113(5):541–5.
30. Goldberg MA, Lubniewski AJ, Williams JM, Smith ME, Pepose JS. Cystic hydrops and spontaneous perforation in Fuchs' superficial marginal keratitis. Am J Ophthalmol. 1996;121(1):91–3.
31. Mejia LF, Santamaria JP, Gaviria AM, Rodriguez AM. Fuchs' superficial marginal keratitis managed with circumferential marginal corneoscleral lamellar patch graft. Eur J Ophthalmol. 2013;23 (6):925–7. doi:10.5301/ejo.5000356.
32. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007;33 (4):835–854, vii. doi:10.1016/j.rdc.2007.08.002.
33. Galor A, Jabs DA, Leder HA, Kedhar SR, Dunn JP, Peters GB 3rd, Thorne JE. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology. 2008;115(10):1826–32. doi:10.1016/j.ophtha.2008.04.026.
34. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, Nussenblatt RB, Stiehm ER, Tessler H, Van Gelder RN, Whitcup SM, Yocum D. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: Recommendations of an expert panel. Am J Ophthalmol. 2000;130(4):492–513.
35. Cuchacovich M, Solanes F, Perez C, Verdaguer JI, Verdaguer J, Castiglione E, Carpentier C, Traipe L, Villarroel F. Mycophenolate mofetil therapy in refractory inflammatory eye disease. J Ocul Pharmacol Ther. 2015;. doi:10.1089/jop.2015.0044.
36. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology. 2008; 115(8):1416–1421, 1421 e1411. doi:10.1016/j.ophtha.2007.12.011.
37. Jia Y, Gao H, Li S, Shi W. Combined anterior chamber washout, amniotic membrane transplantation, and topical use of corticosteroids for severe peripheral ulcerative keratitis. Cornea. 2014;33(6):559–64. doi:10.1097/ico.0000000000000130.
38. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol. 2012;6:747–54. doi:10.2147/opth.s24947.
39. Maya JR, Sadiq MA, Zapata LJ, Hanout M, Sarwar S, Rajagopalan N, Guinn KE, Sepah YJ, Nguyen QD. Emerging therapies for noninfectious uveitis: what may be coming to the clinics. J Ophthalmol. 2014;2014:310329. doi:10.1155/2014/310329.

Part III
Guide to Treatment

Medical Therapy Algorithms

10

Archita Singh, Radhika Tandon
and Virender Singh Sangwan

Introduction

Peripheral ulcerative keratitis is a complex clinical entity which requires a tailored and step-wise approach in management for adequate control of the underlying disease process. The main goals of therapy in cases of PUK are to achieve control of the inflammatory process with minimal damaging consequences and this is achieved by measures which include identification of the causative factor, suppression of the inflammatory cascade, stimulation of the healing process and prevention of complications. For the sake of convenience and better understanding of the best approach to follow in handling such cases, a practical guide has been provided following a logical sequence as would be required in practical clinical settings.

Treatment for Presumed Infectious Peripheral Ulcerative Keratitis

When treating a case of ulcerative keratitis it is a pre-requisite to rule out any infectious aetiology. The presence of infiltrates and/or hypopyon along with a history of inciting factors such as trauma, contact lens use usually raise a suspicion of an underlying microbial aetiology. The points favouring an infectious cause have been enumerated in Table 10.1 and can be useful to identify and consider an appropriate line of management. In case of a suspected infectious aetiology the ulcer scrapings should always be collected for microbiological evaluation before considering therapy. As a routine procedure empirical therapy in the form of topical fortified antibiotic drops along with cycloplegics is started. The therapy can be altered once the microbial agent has been identified and tested for antibiotic sensitivity. Adjuvant agents such as anti-glaucoma medication maybe required in cases with associated secondary rise of intraocular pressure. Oral antimicrobial agents are started in malignant cases and when chances of secondary complications to set in are higher. The indications for oral anti-microbials in patients have been listed in Fig. 10.1.

After starting disease specific therapy for ulcer, it is mandatory to re-evaluate an ulcer after a

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_10

Table 10.1 Features suggestive of an infectious aetiology

Points Suggestive of Infectious Aetiology
• History of trauma/injury with vegetative matter
• History of Contact lens use
• Past history of viral keratitis
• Slit lamp evaluation suggestive of poor ocular surface, presence of corneal infiltrates and hypopyon

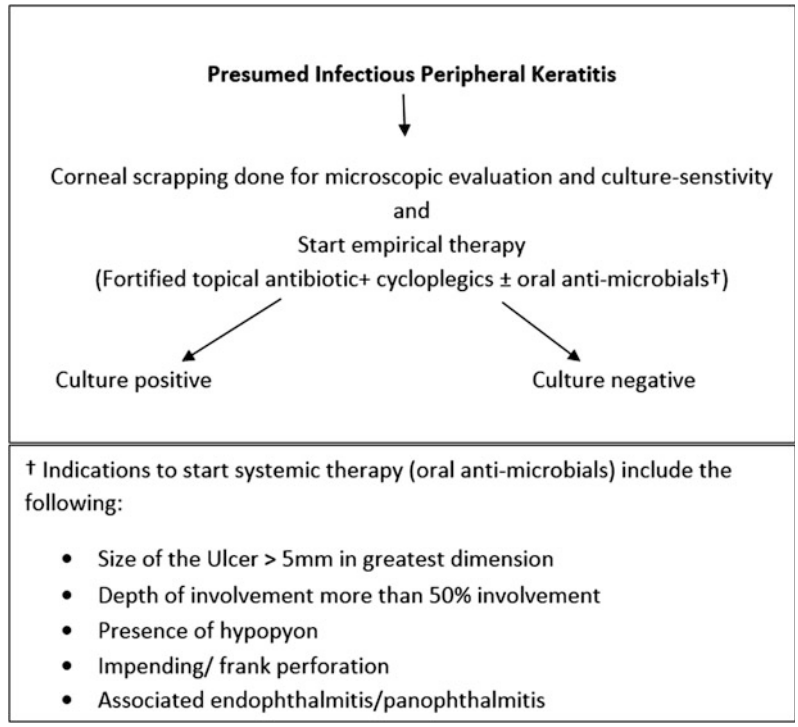

Fig. 10.1 Treatment algorithm for presumed infectious peripheral ulcerative keratitis

period of 48 h of medication. An improvement is suggestive of a correct line of management and should be followed and tapered as and when required. Failure to show improvement at the end of 48 h is suggestive of microbial resistance or improper treatment protocol. The management in such cases includes assessing the microbial cultures for antibiotic sensitivity, repeating collection of samples for microbial evaluation and systemic evaluation of the individual. A non healing ulcer may require early surgical intervention.

The following has been summarised in Figs. 10.2 and 10.3 for ease of understanding.

Treatment for Non-infectious Peripheral Ulcerative Keratitis [1–3]

In case an infectious aetiology has been ruled out and an inflammatory peripheral keratitis is confirmed, a systemic evaluation to identify underlying systemic inflammatory conditions and connective tissue disorders is a must. The main aim of our treatment protocols should be to control inflammation, support the healing and reparative process and to prevent complications (Figs. 10.4, 10.5 and 10.6).

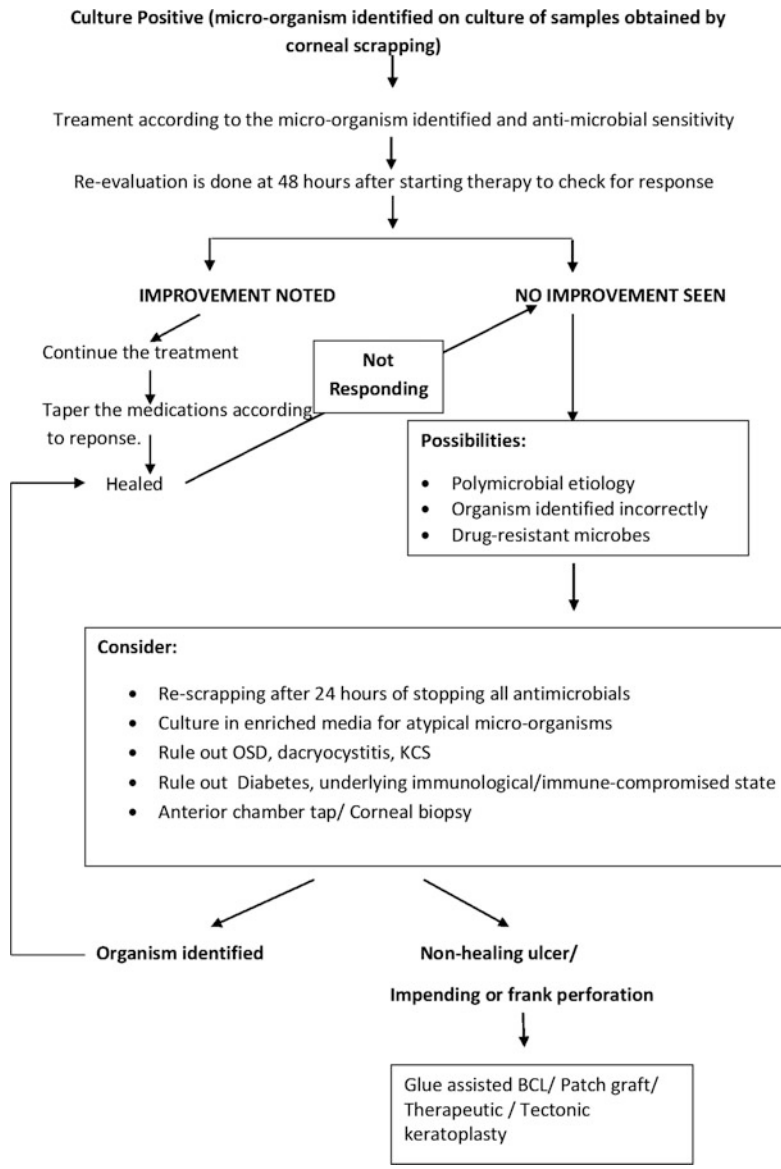

Fig. 10.2 Treatment algorithm in cases of infectious peripheral ulcerative keratitis

A. Steroid Therapy:

The first line of management for a non-infectious peripheral ulcerative keratitis is corticosteroids. Local steroid therapy in the form of topical preparations is preferred in unilateral cases when no systemic association is detected on evaluation. They are started at an initial frequency of hourly to two hourly administration followed by a slow and gradual tapering. It is important to remember that corneal melting has been noted in cases where systemic immune conditions are responsible for inflammatory peripheral ulcers.

Systemic steroids are the preferred agents in these conditions where ocular disease is a manifestation of underlying systemic inflammatory condition. Steroids as a first line drug help control inflammation in the initial window period when the effect of immune-modulatory agent has

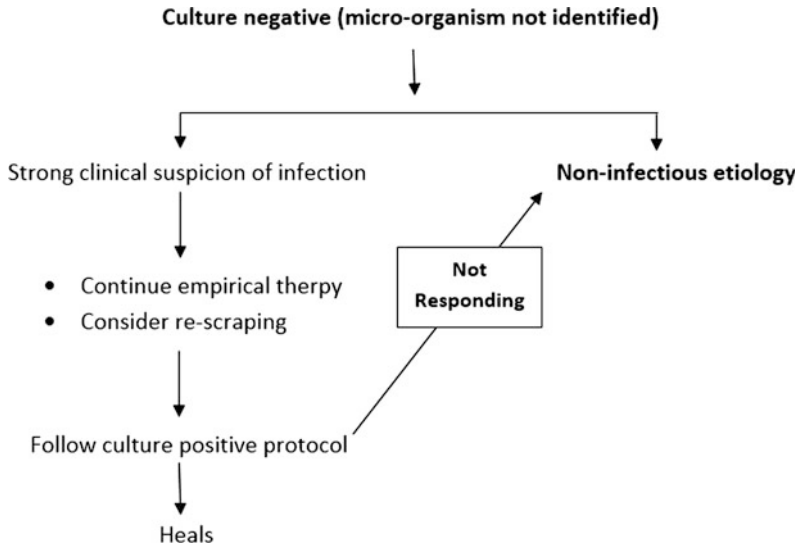

Fig. 10.3 Treatment algorithm in cases of suspected infectious aetiology (culture negative)

Fig. 10.4 The goals of treatment in cases of an ulcerative keratitis to control the underlying inflammatory process, to promote healing of the ulcer and to avoid or prevent progression and complications

not reached its full potential. Steroids may be administered as intravenous pulse therapy initially in acute cases followed by oral steroids (Dose: 1–1.5 mg/kg body wt.). The regimen for intravenous pulse therapy is administration of 1 gm methylprednisolone for three consecutive days. A full dose of oral corticosteroids based on body weight is given for initial 4 weeks and then tapered, preferably over a period of about 8 weeks. In cases where steroid induced serious side effects are seen or an inappropriate response at the end of initial 1 month is noted a shift to immune-modulators is considered. The side effects of long term steroid therapy include hypertension, dyslipidemia, hyperglycemia, osteoporosis, predisposition to fractures, acne-like lesion, easy bruisability, hormonal imbalance, altered fat distribution in the body

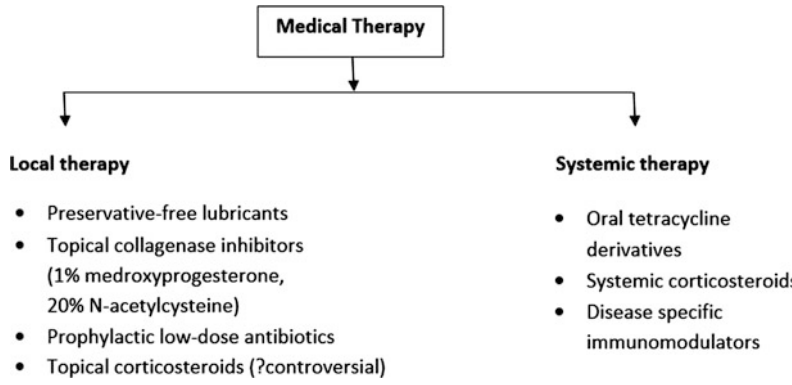

Fig. 10.5 Medical management in cases of inflammatory peripheral ulcerative keratitis

(cushinoid facies, buffalo hump) and weight gain. Thus it is important to monitor weight, blood pressure, blood glucose and lipid profile at three monthly intervals along with bone scans annually. While the patient is on long term steroid therapy, calcium and vitamin D supplements should be given routinely.

B. Adjuvant Agents [4–6]:
The therapy should always include use of tear supplements, cycloplegics, anti-glaucoma medications, oral and topical collagenase inhibitors. These adjuvant agents help support the healing process

- Artificial tear supplements help improve the ocular surface and tackle the keratoconjunctivitis sicca that is usually associated with systemic immune-mediated conditions. Preservative-free formulations are preferred agents. They help in the epithelial healing process and also dilute the local inflammatory factors. Gel formulations when available can be given along with eyedrops for they coat the ocular surface longer and provide protection.
- Cycloplegic agents decrease the ciliary spasm and provide symptomatic treatment by controlling pain.
- Anti-glaucoma agents control the intraocular pressure which maybe secondary to local inflammatory process.
- Collagenase inhibitors help improve the healing process by inhibiting breakdown of collagen and help in the repair process.

C. Immunomodulators and Immunosupressant Therapy [7–16]:
Immunomodulators refers to a group of therapeutic agents that alter the normal immune response of the body. They can either suppress or activate the immune system. Here we are referring to the group of drugs that suppress the immune system aka "*immunosuppressant*".

The immunosuppressants are broadly classified as

1. Alkylating Agents: Cyclophosphamide, Chlorambucil.
2. Anti-metabolites: Methotreaxate, Azathioprine, Mycophenolate mofetil.
3. T-cell inhibitors: Cyclosporine, Tacrolismus.
4. Biological agents: anti-TNF agents.

The commonly used immunosuppressants in ophthalmology, their mode of action and adverse effects have been listed in Table 10.2.

Before beginning therapy with immunemodulatory agents a number of questions need to be answered. These include:

- What is the indication for use of these drugs?
- Need to shift from steroid therapy to use of immune-modulatory agents?
- Underlying systemic status of the patient?
- Contra-indications, if any?
- What is the first line drug for specific disease conditions?
- How to monitor effect and adverse effects?
- When do we need to step-down therapy?
- Are we treating over-zealously? (Fig. 10.7).

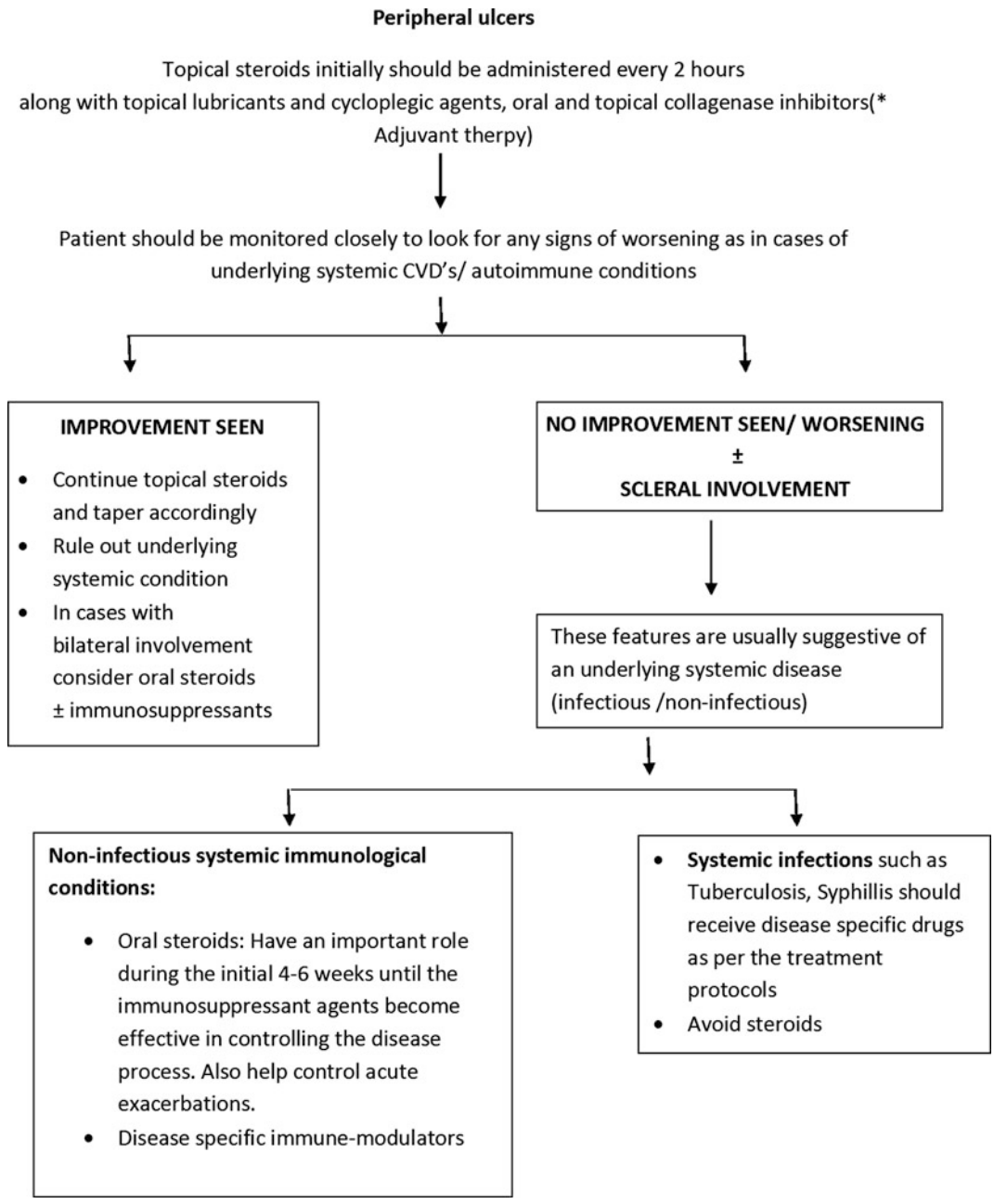

Fig. 10.6 Treatment algorithm for non-infectious immune-inflammatory peripheral ulcers

The specific indications for use of these agents include an underlying known connective tissue disorder or specific immunological condition, PUK associated with scleritis, bilateral cases, non-responsive to conventional medical and surgical management.

The preferred immune-modulatory agent depends upon the underlying systemic condition. For example, cyclophosphamide inspite of its adverse effects is considered as a first line drug in treatment of Wegner's granulomatosis, Rheumatoid arthritis and sclerokeratitis. Methotrexate and

Table 10.2 Commonly used medications in the treatment of Peripheral ulcerative keratitis

S. No.	Medications	Mechanism of action	Dose	Frequency	Duration	Side effects
1	Prednisolone	Blocks transcription of anti-inflammatory genes	1 mg/kg/day	Single dose	Taper over 8–12 weeks [16]	Hyperglycemia, Hypertension, osteoporosis, Gastric ulcers
2	Methotrexate	Antimetabolite which inhibits formation of THFR* thus decreasing DNA synthesis It induces apoptosis of T-Helper cells	5– 25 mg/week	Once a week	Taper as required	Hepatotoxity,low WBC count, ulcerative stomatitis, nausea, fatigue, renal failure
3	Cyclophosphamide	Alkylating agent Decreases replication of T-cells	2 mg/kg/day	Single dose	Taper as required	Bone marrow suppression, nausea, vomiting, stomach aches, haemorrhagic cystitis, diarrhoea
4	Azathioprine	Purine synthesis inhibitor. It inhibits enzyme required for DNA synthesis, thus affecting proliferating cells	1– 2.5 mg/kg/day	Single/two divided doses	Taper as required	Hypersenstivity reaction, skin rashes, predisposition to neoplasias, nausea, vomiting, hepatic and renal damage
5	Cyclosporine	Calcineurin inhibitor Inhibits the T-cell activity	2.5– 5 mg/kg/day	Divided doses	Taper as required	Gum hyperplasia, hypertension, hyperkalemia, hirsutism, fever, vomiting, dyspnea, convulsions
6	Mycophenolate Mofetil	Inhibits purine synthesis pathway inhibits replication of T and B cells	1–3 gm/day	Two divided doses	Taper as required	Gastrointestinal upset, elevated liver enzymes, bone marrow suppression, malaise, fatigue
Recent advances						
1	Infliximab	Anti-TNF-α chimeric monoclonal antibody	3 mg/kg (I.V.)	0, 2 and 6 weeks, and then 2 monthly	18 months	Infections, drug induced lupus, psoriatic lesions, demyelinating diseases, new onset vitiligo

(continued)

Table 10.2 (continued)

S. No.	Medications	Mechanism of action	Dose	Frequency	Duration	Side effects
2	Etanercept	TNF inhibitor (decoy receptor)			Taper as required	Serious infections, reactivation of tuberculosis and hepatitis B
3	Rituximab	Anti-CD20 chimeric monoclonal antibody			Taper as required	Infusion reaction, cardiac arrest, reactivation of infections

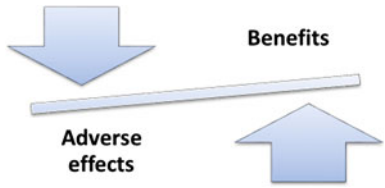

Fig. 10.7 Risk versus benefit maintaining the balance: Immuno-modulator therapy requires an essential balance between the adverse effects and the therapeutic advantages of the drugs. Goal is to treat the patient in totality thus maintaining the essential balance and achieving a favourable outcome in the patients under treatment

azathioprine are considered second line agents for therapy.

Therapy with immune-modulatory agents is always started in a "step—ladder pattern" and requires constant surveillance by an ophthalmologist and an immunologist. To step-up or to climb down the ladder is decided based upon the healing process, control of inflammation and adverse effects, if any. Usually a period of 6 months is considered ideal for an immune-modulatory agent to be effective. If no

Table 10.3 Investigations required for monitoring of therapy with immune-suppressants

S. No.	Drug	Investigation (Laboratory investigations can be carried out at monthly to three monthly intervals)	Common Drug Interactions
1.	Methotrexate	• Complete haemogram • Liver function tests • Renal function tests	• Cyclosporine worsens haematological adverse effects • Interaction with NSAIDs can be fatal • Proton pump inhibitors increase plasma concentration
2.	Cyclophosphamide	• Complete haemogram • Liver function tests • Renal function tests	• Increased risk of hepatotoxicity with azathioprine • ACE inhibitors worsens haematotoxicity • Increased nephrotoxicity when used with Indomethacin or amphotericin B
3.	Azathioprine	• Complete haemogram • Liver function tests • Renal function tests	• Alleviates anticoagulant effect of warfarin • Interferes with Vitamin B3 metabolism
4.	Cyclosporine	• Blood pressure • Renal function tests and serum electrolytes	• HIV protease inhibitors increase serum cyclosporine levels • Convulsions have been reported when simultaneously used with high dose methylprednisolone • Increase serum levels of methotrexate
5.	Mycophenolate Mofetil	• Complete haemogram • Liver function tests • Renal function tests	• Acyclovir impairs excretion of MMF • Anatacids and Cholestyramine decrease absorption of MMF

improvement is seen a revision of the therapy protocol is necessary. A favourable response at 6 months is suggestive of correct line of therapy and drugs can be tapered to avoid serious adverse effects.

Monitoring of the adverse effects related to immunomodulators is another important aspect which requires due attention of the treating physician. They can be easily monitored by a battery of clinical and laboratory investigations which can be carried out at periodic intervals. The various tests required to monitor effect of immune-modulators have been listed in Table 10.2. Table 10.3 shows the investigations required for monitoring of therapy with immune-suppressants.

As a clinician, one should always look at the patient as a whole and always assess for the benefit to the risk ratio. The beneficial effects of the chosen agent should always be weighted against the expected adverse outcomes (Fig. 10.7).

D. Immunosuppressants in Special Situations:

- Paediatric Age Group [17]:

One has to be extra cautious when treating systemic immune disease in younger age group because of its effect on the growth and development. Methotrexate is the immunosuppressant of choice in children. The dose of methotreaxate is usually higher in children as compared to adults because of faster metabolism. Cyclosporine may also be used in cases non-responsive to methotreaxate.

- Pregnancy:

Immunosuppressants are best avoided during pregnancy for the high risk of teratogenicity, abortions and pregnancy related problems. Steroids though require a vigilant surveillance, are considered the best drug to control inflammatory disorders in pregnancy.

Thus we conclude that the treatment pattern in cases of peripheral keratitis should always be carried out in a step-wise manner. This helps in improving the therapeutic outcomes and allows adequate titration. We can step-up or down depending upon the response of the individual to the treatment. Adjuvant agents are required in the majority of the cases as they enhance and improve the healing process. Anti-inflammatory agents such a steroids form an essential component so as to control inflammation. High end anti-inflammatory agents including disease specific immune-modulators are required in special conditions. This has been summarised in Fig. 10.8.

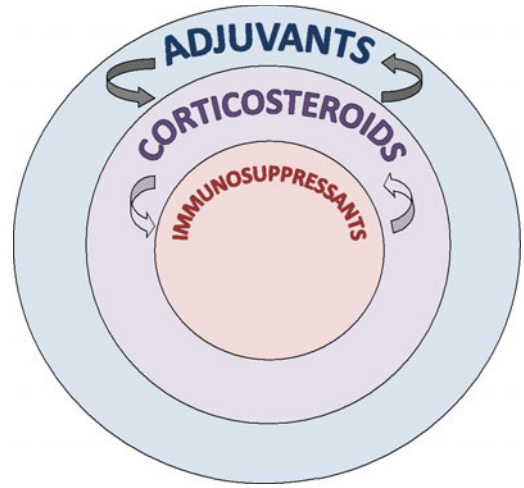

Fig. 10.8 A diagrammatic representation of step-wise approach to manage the patient. The idea being, all patients will receive adjuvants to promote the healing in form of tear supplements, cycloplegics, etc. and the medication to control inflammation needs to be titrated depending on individual patient's requirement and response. This implies that almost all patients would require adjuvant agents and a small subset only would need to be given the higher grades of therapy in the form of immune-modulators. The treatment can be stepped up and down as and when required

Management of Mooren's Ulcer [18–21]

Mooren's ulcer is a diagnosis of exclusion. It is an autoimmune condition which is characterised by absence of scleritis. Though it is relatively resistant to therapy a step-ladder pattern of treatment protocol for management has been described.

Corticosteroids are the most important component of therapy in cases of Mooren's ulcer. These ulcers respond very well to topical steroids. Steroid therapy is given in a frequency of one hourly to two hourly initially and depending on the response of ulcer the drugs are slowly tapered. Steroids should always be accompanied with use of topical adjuvant agents such as cycloplegics and preservative-free artificial tears to help the healing process.

In case of ulcers not responding to steroid therapy conjunctival resection can be considered. The advantage of a localised conjunctival resection is that it helps decrease the antigen load, decrease the inflammatory cells influx thus decreasing localised antibody production.

Systemic immunosuppressants have a role in those cases which fail to respond to the conventional management. Bilateral rapidly progressive cases which fail to respond to the described conventional management treatment protocol maybe successfully treated with immunosuppressants. The commonly used agents include cyclophosphamide, azathioprine and methotrexate. As discussed previously adequate monitoring of associated adverse effects is important when using these agents in clinical practice. (Refer to Table 10.2 for the commonly used agents.)

Surgical interventions include glue assisted bandage contact lens, amniotic membrane grafts, patch grafts, keratoepithelioplasty and superficial keratectomy (Fig. 10.9).

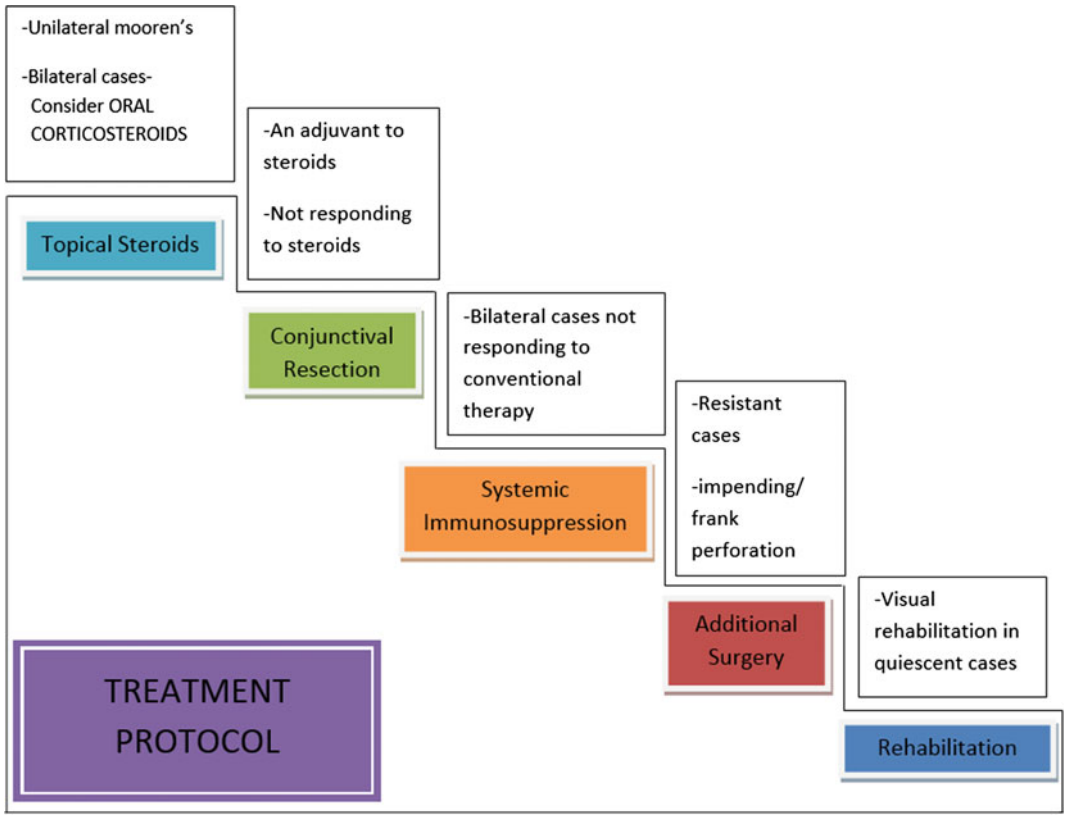

Fig. 10.9 Step-by-step treatment protocol for Mooren's ulcer. After Brown SI, Mondno BJ. Therapy of Mooren's ulcer. Am J Ophthalmol 1984; 981–6

Conclusions

The main goals of therapy in cases of PUK are to achieve control of the inflammatory process with minimal damaging consequences and this is achieved by measures which include identification of the causative factor, suppression of the inflammatory cascade, stimulation of the healing process and prevention of complications.

Compliance with Ethical Requirements Archita Singh, Radhika Tandon, and VirenderSangwan declare that they have no conflict of interest.

"No human or animal studies were carried out by the authors for this article."

References

1. Messmer E, Foster S. Destructive corneal and scleral disease associated with rheumatoid arthritis: medical and surgical management. Cornea. 1995;14:408–17.
2. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol. 2012;6:747–54.
3. Messmer EM, Foster CS. Vasculitic peripheral ulcerative keratitis. Surv Ophthalmol. 1999;43:379–96.
4. Perry HD, Golub LM. Systemic tetracyclines in the treatment of noninfectedcorneal ulcers: a case report and proposed new mechanism of action. Ann Ophthalmol. 1985;17:742–4.
5. Golub LM, Ramamurthy NS, McNamara TF, Greenwald RA, Rifkin BR. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. Crit Rev Oral Biol Med. 1991;2:297–321.
6. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. Cornea. 2000;19:274–7.
7. Virasch VV, Brasington RD, Lubniewski AJ. Corneal disease in rheumatoid arthritis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals, diagnostic, management. 3rd ed. St Louis, MO: Elsevier; 2011.
8. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Ophthalmolo. 1984;91:1253–63.
9. Akpek EK, Thorne JE, Qazi FA, Do DV, Jabs DA. Evaluation of patients with scleritis for systemic disease. Ophthalmolo. 2004;111:501–6.
10. Messmer E, Foster S. Destructive corneal and scleral disease associated with rheumatoid arthritis: medical and surgical management. Cornea. 1995; 14:408–17.
11. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:430–44.
12. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000;130:492–513.
13. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid sparing therapy for noninfectious ocular inflammation. Ophthalmolo. 2008;115:1826–32.
14. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmolo. 2005; 112:1472–7.
15. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmolo. 2008;115:1416–21.
16. Saw VPJ. Immunotherapy for corneal inflammatory disorders: stepping up and down the ladder. Br J Ophthalmol. 2013;97:1364–7. doi:10.1136/bjophthalmol-2013-303359.
17. Polito C, La Manna A, Papale MR, Villani G. Delayed pubertal growth spurt and normal adult height attainment in boys receiving long-term alternate-day prednisone therapy. Clin Pediatrics. 1999;38:279–85.
18. Brown SI, Mondino BJ. Therapy of Mooren's ulcer. Am J Ophthalmol. 1984;98:1–6.
19. Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer. current concepts in management. Indian J Ophthalmol. 1997;45:7–17.
20. Mathur A, Ashar J, Sangwan VS. Mooren's ulcer in children. Br J Ophthalmol. 2011. doi:10.1136/bjophthalmol-2011-300985.
21. AsharJn, Mathur A, Sangwan VS. Immunosuppression for Mooren's ulcer: evaluation of the stepladder approach—topical, oral and intravenous immunosuppressive agents. Br J Ophthalmol. 2013;97:1391–1394.

C-shaped Lamellar Corneal Patch Grafts "Match and Patch" Technique

11

Hui Chen Charmaine Chai, Hazel Anne Lin and Donald Tan

Introduction

Compared to full thickness keratoplasty, lamellar keratoplasty allows the conservation of the host endothelial layer, removing the risk of corneal endothelial rejection, reducing postoperative endothelial cell loss, and minimizing unintended intraocular complications [1]. A peripheral corneal patch graft with a C-shaped configuration allows for tectonic reconstruction of the peripheral cornea, without replacing healthy central cornea. Such concentric grafts also respect the central corneal contour, minimizing the amount of postoperative astigmatism [2] and spare the central visual axis.

We describe our preferred technique of performing a C-shaped lamellar corneal patch graft to match the peripheral corneal melt. This takes the form of a ***"match and patch" technique*** to restore tectonic integrity of the cornea and yet negate any induced peripheral ectasia and irregular astigmatism by adopting a minimally sized graft width along with strong compression sutures, which flattens any ectasia. These grafts are also easily repeatable in the event of a recurrence. Figure 11.1 demonstrates a case with severe extensive peripheral corneal thinning before and after surgical intervention using the "match and patch" technique.

Concept of "Match and Patch"

The concept of "match and patch" is to clearly define and regularize a semi-circular "C"-shaped or "banana"-shaped area of tissue immediately around the peripheral melt, which fully encompasses the melting area, but minimally involved unaffected corneal tissue, using calipers and various circular trephines of predetermined diameters, and then to replicate this same shape in the donor cornea. The donor tissue is therefore carefully sized to "match" the recipient bed, and "patches" the peripheral defect accordingly.

Concept of Lamellar Dissection of the Recipient Bed

Ideally, lamellar dissection of the recipient bed should be performed carefully to avoid inadvertent perforation, but also to regularize the overall depth of bed dissection so as to prevent an irregular surface contour when the donor is sutured on. If the dissection is deep enough, i.e., within 100–150 microns of Descemet's membrane (DM), then a full thickness donor tissue patch may be simply utilized, after peeling away the underlying DM. However, if only half

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_11

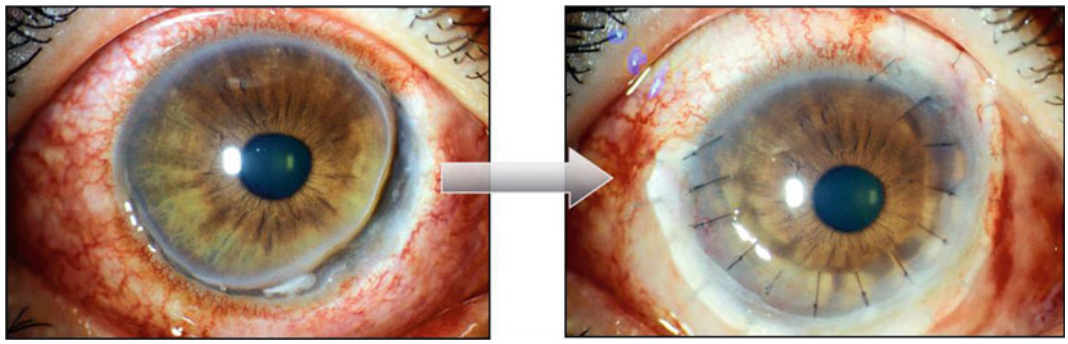

Fig. 11.1 Photograph demonstrating a case with severe extensive (Almost 270°) peripheral corneal thinning before and after surgical intervention using the "match and patch" technique

thickness dissection of the recipient bed is performed, then a similar half thickness lamellar dissection of the donor cornea should be performed.

Patient Preparation

The surgery is preferably done under general anesthesia, as the duration of surgery may take an excess of 1–2 h, but could be done under regional anesthesia, as the procedure is essentially extraocular. After the patient is cleaned and draped, the area of dissection is measured using a pair of calipers to determine the optimum corneal graft size. Conjunctival peritomy is performed adjacent to the area of thinning. Marking corneal trephines and dermatological trephines are used to mark the cornea and delineate the dissection bed in a structured step-by step technique (Fig. 11.2).

The outer and inner circumferential limits of the area of thinning are marked with corneal trephines. The distance between the two arcs is measured using a pair of calipers at the two edges of the melt and at the midpoint of the dissection bed. Dermatological trephines of appropriate sizes (or nearest size) are used to mark the edges of the dissection bed. The furthest distance between the two corners of the dissection bed is measured. This completes the outline of the C-shaped dissection bed. The use of marking trephines allows regularization of the area of dissection and subsequent replication of the same matching shape on the donor cornea. The area of dissection may include adjacent sclera depending on the extent of melt.

Freehand partial thickness vertical dissection of the marked area to attain vertical and regular graft margin is performed using a diamond blade. Care is taken to avoid causing an inadvertent perforation. A smooth and regular vertical edge of the dissection bed is ideal for good apposition of donor graft-to-host, especially during suturing. Careful lamellar dissection is performed with a crescent blade, a mini-crescent blade or similar lamellar dissector, while ensuring that a reasonably uniform dissection bed is created.

Intraoperative pachymetry can be used to guide the depth of dissection. The dissection bed is kept dry so that in the event of perforation, aqueous leak can be quickly identified.

In the event of a perforation, intra-cameral air can be injected to stabilize the anterior chamber. Lamellar dissection should then be performed at unaffected areas of the dissection bed first, leaving the area of perforation to be tackled last. In cases of existing perforation, the same principles of lamellar dissection all around the perforation site can be utilized, leaving the perforation site to be dissected last. It is generally easier to continue lamellar bed dissection if the chamber remains formed with air, but in cases of larger perforations where this is not possible, the hole may be temporally sealed with fibrin glue or histoacryl glue, so as to complete lamellar dissection, or else it is still possible to complete

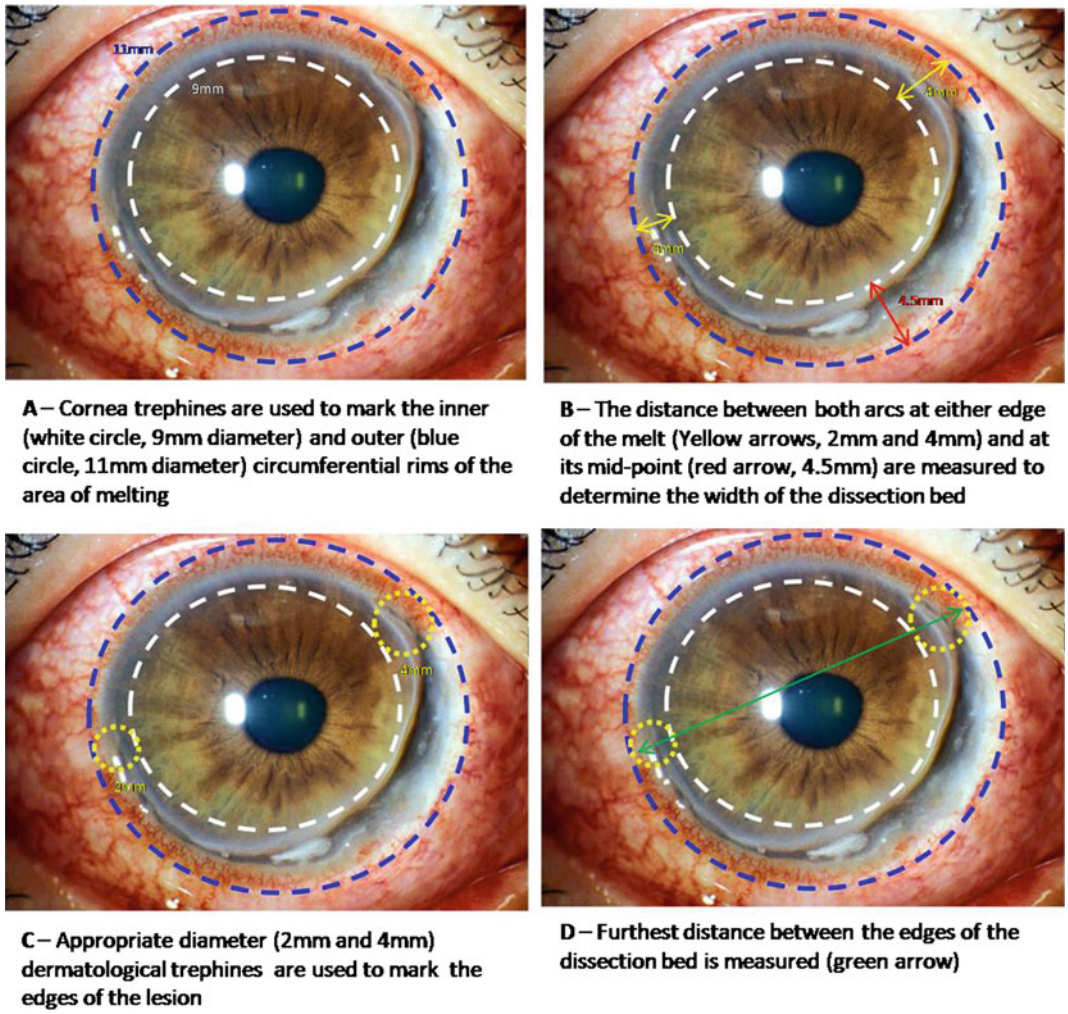

Fig. 11.2 Illustration of technique used to mark cornea to delineate dissection bed and determine the size of donor cornea required

lamellar dissection with iris plugging the wound and a flat chamber. The donor tissue can then be used to tamponade the perforation site, and after suturing the donor in place, any iris adhesions or synechiae may be released with a sinsky hook introduced from a separate paracentesis. In cases of a large perforation, which is likely to cause a double chamber in the postoperative period, denoting separation of the recipient lamellar bed and the donor, a large air bubble tamponade coupled with dilatation of the pupil or an inferior peripheral iridotomy (to prevent pupillary block) should be considered.

Donor Preparation

Donor cornea preparation is performed using our previously described Lamellar Ball Technique (Fig. 11.3), or can be performed on a standard disposable artificial chamber maintainer [3]. The advantage of the Lamellar Ball Technique is that if

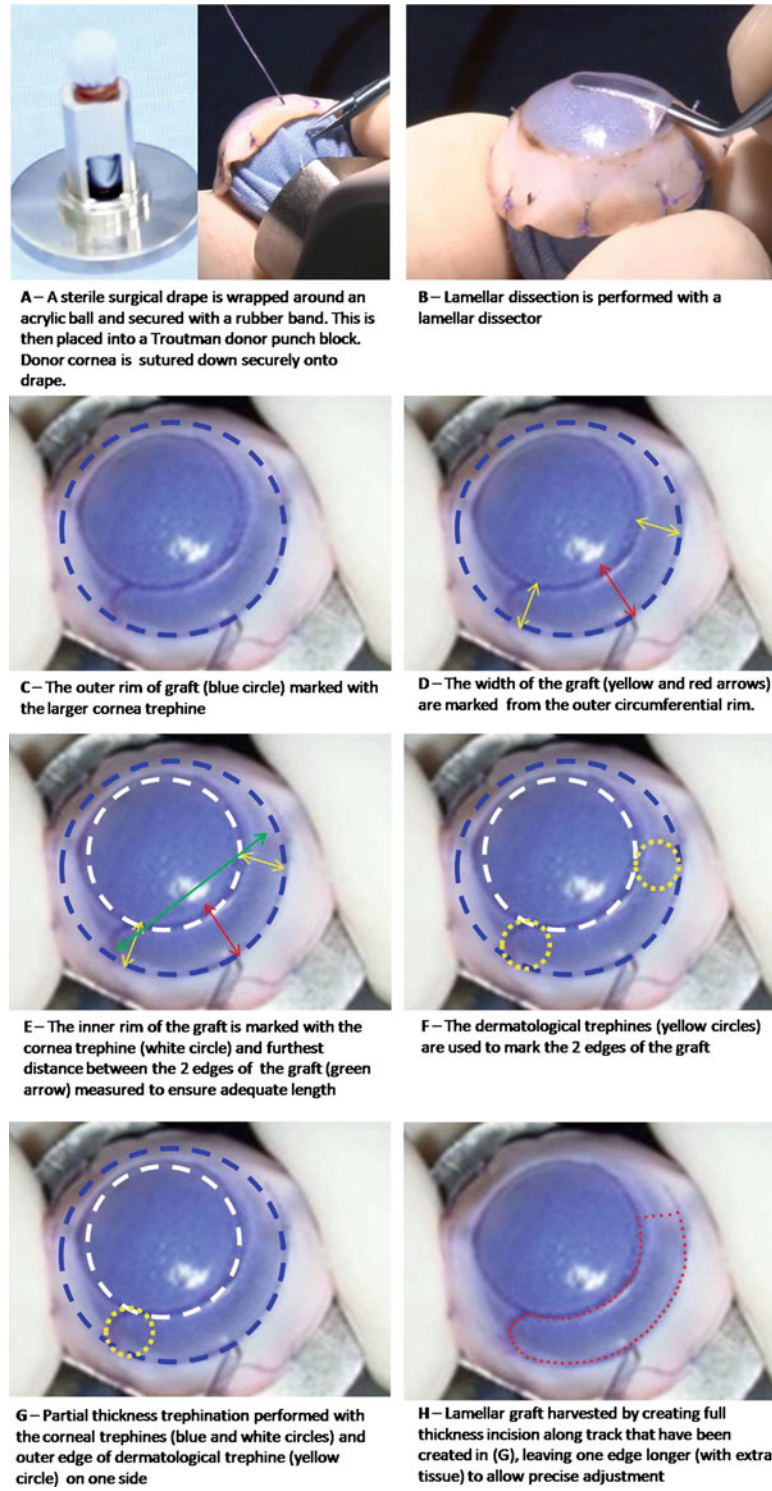

Fig. 11.3 Illustration of donor preparation and replicating shape of recipient dissection bed on donor cornea

inadvertent perforation of DM occurs during deep lamellar dissection, a new more anterior lamellar dissection can be immediately performed, whereas in standard disposable artificial chamber maintainers, perforation of DM usually results in leakage of BSS and chamber collapse, obviating any further lamellar dissection. Fresh frozen corneas or lamellar grade corneas with poor endothelial status can be used for tectonic purposes. A doubly folded sterile surgical drape is wrapped around a 14 mm acrylic orbital ball and secured with a rubber band. This is then placed in a Troutman donor punch block for stability and to allow precise incision and dissection to be performed. Eight interrupted sutures are used to secure the corneo-scleral button firmly to the drape.

A partial thickness limbal incision is created to allow entry of the lamellar dissector. Lamellar dissection is then performed ensuring adequate dissection of donor graft. For very deep melts (such as a residual cornea thickness of 100–150 microns down to Descemet membrane), it will not be necessary to perform lamellar dissection of the donor. Full thickness donor tissue with stripping of the Descemet's membrane can instead be used. The donor cornea is marked in a similar fashion using the same trephines to replicate the exact dimensions of the recipient dissection bed ("match" and "patch").

Partial thickness trephination over the markings on the donor cornea is created using the corneal trephines. A dermatological trephine is used to create a partial thickness trephination of the outer edge of one corner of the donor graft. These cuts create a partial thickness track outlining the graft margins, leaving out one corner of the graft. Freehand dissection is then completed using a disposable sharp blade along the partial thickness track. One end of the donor is cut, leaving additional length to allow precise adjustment over the recipient bed.

The donor patch graft is carefully transferred to the recipient and placed over the recipient bed. Interrupted 10/0 or 9/0 nylon sutures are then carefully placed to ensure correct positioning of the graft along the length of the graft, leaving the uncut end till last. Once the graft is accurately positioned and secured down, the uncut exposed end of the graft can be trimmed carefully to match the recipient bed. This end is intentionally left uncut simply because the recipient cornea is unlikely to be of the same diameter as the acrylic orbital ball used as an artificial chamber, and leaving one end long for final trimming obviates the risk of attaining a graft which turns out to be just too short in length. At the end of suturing, an intraoperative keratometer or keratoscope may be used to ensure that the sutures around the graft are tight enough to cause with-the-rule astigmatism perpendicular to the graft, so that in the postoperative state, loosening of the sutures will result in reduction in astigmatism, or selective suture removal can be used to reduce the suture-induced astigmatism. Finally, the conjunctival peritomy is closed with 8/0 vicryl or virgin silk sutures. Subconjunctival dexamethasone and gentamicin is injected and a bandage contact lens is placed over the cornea.

A case example illustrating the surgical step-by-step is described in Fig. 11.4.

Special Considerations

In patients with severe astigmatism in peripheral corneal ectasia, a modified "compressive" form of "C"-shaped lamellar keratoplasty has been described [4]. Peripheral ectatic corneas with severe astigmatism can be seen in conditions such as Terrien's marginal degeneration and Pellucid Marginal Degeneration, but ectasia can also occur in other forms of acute or chronic peripheral ulcerative keratitis, where the severe loss of tectonic integrity in the peripheral affected area results in a bulging ectatic state of the remaining thin cornea.

In these situations, a "compressive" patch graft may be performed, by deliberately undersizing the graft with a width which is narrower than the recipient bed width, perhaps by 0.25 or 0.5 mm. When combined with tight compression sutures (best using 9/0 nylon or nonabsorbable 9/0 prolene sutures), this results in significant anterior corneal compression and flattening of the bulging cornea in that meridian, correcting the ectasia and astigmatism. A significant overcorrection when viewed by an intraoperative keratoscope is usually preferred as compression sutures will invariably loosen over the ensuing

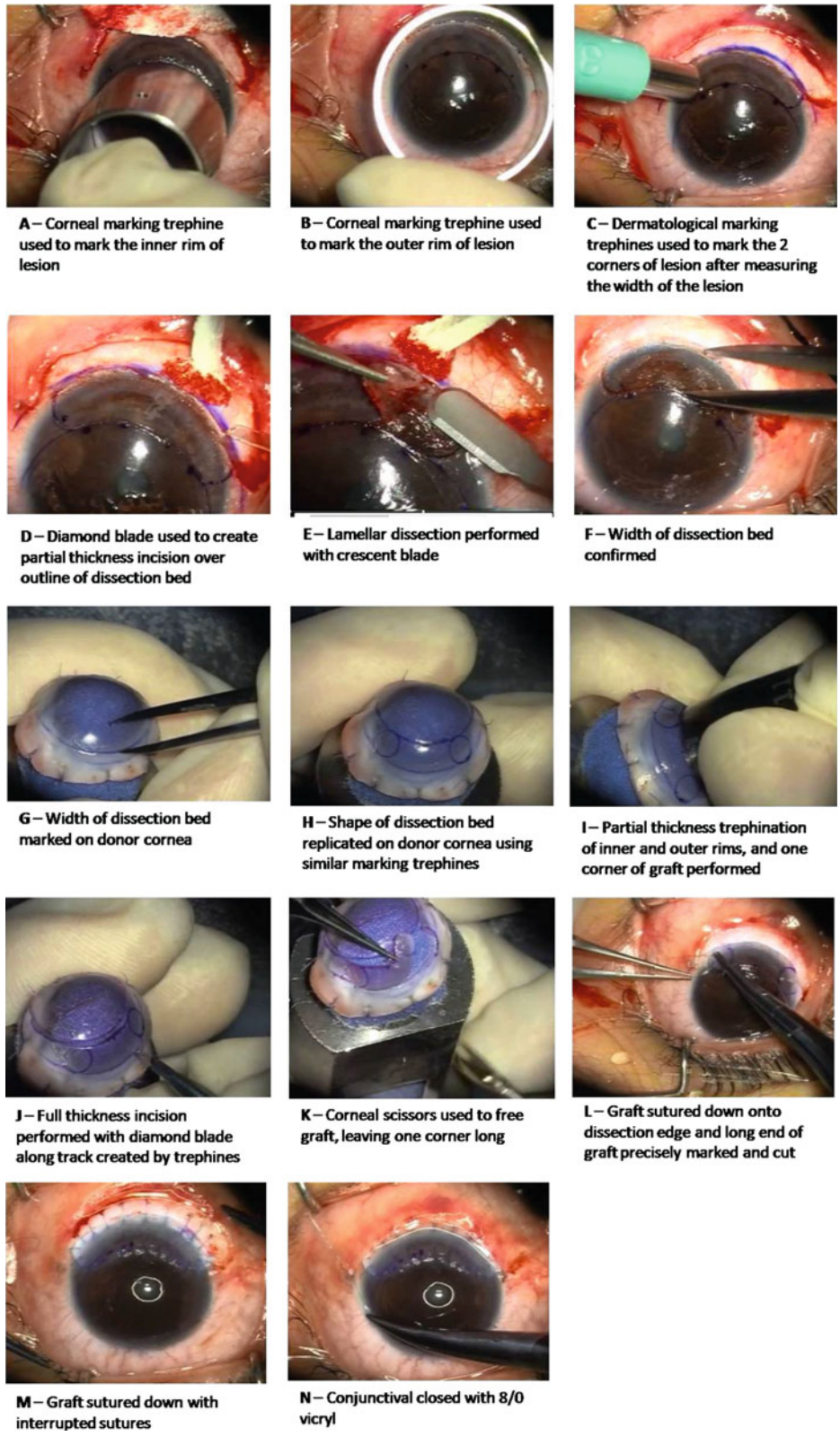

Fig. 11.4 Surgical step-by-step of a case example

weeks, and in the event that high levels of suture-induced astigmatism is still present 2–4 months after surgery, judicious selective suture removal can easily be performed.

Postoperative Regime

The patient should be started on a topical steroid and antibiotics such as Levofloxacin and Prednisolone Acetate eye drops. This is initially administered at a high frequency after surgery and progressively tapered down according to clinical response. Our recommended regime is to start at 3 hourly intervals. This same frequency is maintained for 2–3 weeks before reducing it to 4 times a day. Prednisolone acetate is reduced to about twice a day after 4–5 months. Topical medications are slowly tapered and typically stopped 6 months postoperatively.

Selective postoperative suture removal can be done at a later stage to improve visual outcome. These patients will require long term follow-up to watch for possible complications and monitoring for possible recurrences. It is also important to ensure optimal management of their primary medical condition, and often continuation of systemic immunosuppressive therapy may be required in autoimmune melting conditions to prevent recurrence of melting over the grafted area, or often in new areas around the limbus. Lamellar patch grafts can be repeated in the same eye at various affected locations in the event of recurrence, but replacement of too many clock hours of limbus may result in secondary limbal stem cell insufficiency and an unstable ocular surface.

Conclusion

Peripheral melting disorders require surgical intervention when medical intervention has failed and there is risk of impending perforation. Peripheral lamellar "C"-shaped grafts can effectively restore tectonic integrity, while maintaining a reasonable corneal contour to preserve good visual acuity. The use of compressive patch grafts can effectively restore accompanying ectasia and reduce corneal distortion and severe astigmatism.

Conflict of Interest Declaration Hui Chen Charmaine Chai, Hazel Anne Lin, and Donald Tan declare that they have no conflict of interest.

This article is compliant with the ethical requirements.

No human studies were carried out by the authors for this article.

No animal studies were carried out by the authors for this article.

References

1. Borderie VM, Sandali O, Bullet J, Gaujoux T, Touzeau O, Laroche L. Long-term results of deep anterior lamellar versus penetrating keratoplasty. Ophthalmolo. 2012;119(2):249–55.
2. Huang T, Wang Y, Ji J, Gao N, Chen J. Evaluation of different types of lamellar keratoplasty for treatment of peripheral corneal perforation. Graefes Arch Clin Exp Ophthalmol. 2008;246(8):1123–31.
3. Wong DWK, Chan W-K, Tan DTH. Harvesting a lamellar graft from a corneoscleral button: a new technique. Am J Ophthalmolo. 1997;123(5):688–9.
4. Cheng CL, Theng JT, Tan DT. Compressive C-shaped lamellar keratoplasty: a surgical alternative for the management of severe astigmatism from peripheral corneal degeneration. Ophthalmolo. 2005;112(3):425–30.

Practical Guide to Immunomodulatory Agents

12

Ramana S. Moorthy and Shailaja Valluri

Peripheral ulcerative keratitis with or without necrotizing scleritis is often associated with systemic autoimmune disease. Macro-ulcerative peripheral keratitis can be a local manifestation of systemic vasculitis such as rheumatoid arthritis, granulomatosis and polyangiitis, systemic lupus erythematosus, polyarteritis nodosa, and Crohn disease [1–3]. Mooren ulcer is the most common local ocular immunologic cause of peripheral ulcerative keratitis [1–3]. The association of peripheral ulcerative keratitis with systemic vasculitis is the reason that the treatment of this condition often warrants the use of aggressive systemic immunomodulatory therapy early in the disease course. Both necrotizing scleritis and peripheral ulcerative keratitis should be typically treated with systemic corticosteroids and systemic immunomodulatory therapy (preferably alkylating agents) [1–3]. This is based on mostly anecdotal and retrospective evidence of relatively small-case series of patients with these conditions. Although there is limited level I and II evidence of the efficacy of immunomodulatory agents to control corneal melting and scleral inflammation, extensive Level 1, II, and III evidence of the effect of these agents in treating systemic vasculitides, particularly rheumatoid arthritis, exists in the rheumatologic literature [4–9]. Based on extrapolations from these rheumatologic findings, and based on extensive clinical experience among experts in the management ocular inflammatory diseases, early initiation of immunomodulatory therapy for the treatment of necrotizing scleritis and peripheral ulcerative keratitis is essential. It must be emphasized that management of patients with peripheral ulcerative keratitis and necrotizing scleritis with immunomodulatory therapy should be performed by clinicians who are expert in the use of these medications such as an ocular immunologist, rheumatologist, and/or oncologist. It is imperative that ophthalmologists refer the patient who has peripheral ulcerative keratitis and/or necrotizing scleritis to a rheumatologist and/or ocular immunologist immediately for a thorough evaluation of systemic vasculitis. Appropriate management of underlying systemic vasculitides is essential since peripheral ulcerative keratitis not only carries with it a grave ocular prognosis but potential for increased morbidity and mortality [10, 11].

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*, Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9_12

Mechanisms of Action: General Principles

The mechanism of action of immunomodulatory therapeutic agents is directed at inhibition of T_{helper}-cell replication, inhibition of natural killer cell induced cytotoxicity, enhanced T suppressor cell activity, improved surveillance and immunologic control of aberrant autoimmune responses by direct inhibition of inflammatory cytokines [12]. Immunomodulatory agents are also called disease modifying antirheumatic drugs (DMARDs) [6]. DMARDs may be subdivided into four broad categories, namely, antimetabolites, calcineurin inhibitors, alkylating agents, and biologic response modifiers (Biologics). The most commonly used immunomodulatory agents are the antimetabolites. These agents typically interfere with the replication of T cells (sometimes preferentially of the helper cells or B cells), by inhibiting purine synthesis and DNA replication. The antimetabolites include methotrexate, azathioprine, and mycophenolate mofetil. The calcineurin inhibitors include cyclosporine A, tacrolimus, and sirolimus. Cyclosporine and tacrolimus are most commonly used. These bind to cyclophilin and inhibit calcineurin, which in turn inhibits transcription and translation of the interleukin-2 gene, which subsequently inhibits T-cell proliferation. The alkylating agents include cyclophosphamide and chlorambucil. These agents prevent cellular proliferation by causing DNA cross-linking and ultimately cell death. Toxic metabolites of these agents may also have a secondary effect of cellular protein damage and apoptosis. The newest agents, the biologic response modifiers, are usually monoclonal antibodies or receptor analogs that specifically interfere with membrane-bound or soluble inflammatory cytokines and can rapidly and profoundly reduce inflammation. In addition, some of these agents are monoclonal antibodies that are directed toward cell surface regulatory markers such as CD20 (rituximab). These can have very profound anti-inflammatory effects by complete clonal deletions of large populations of cells containing these markers, such as CD20 positive B cells in the case of rituximab [13].

Treatment Paradigm

Once the cause of the necrotizing scleritis and/or peripheral ulcerative keratitis (PUK) has been determined to be noninfectious based on clinical history and appearance, serologic studies, and local cultures, systemic corticosteroids are usually begun. Oral prednisone at 1–1.5 mg/kg per day may be utilized with a taper over the course of 6–12 weeks. Pulsed intravenous methylprednisolone for 3 days followed by high-dose oral prednisone may be used for the most severe cases [12]. The role of topical and who periocular corticosteroid therapy in the management of peripheral ulcerative keratitis and necrotizing scleritis is potentially contraindicated, and at best controversial. Systemic corticosteroids however are extremely important in the early management of this disease. A very gradual taper of oral corticosteroids followed by the establishment of low-dose maintenance therapy is a cornerstone of initial therapy. Corticosteroid monotherapy, however, may be ineffective for complete control of the disease and is often associated with significant and numerous systemic side effects such as exacerbation of hypertension, diabetes, weight gain, and long-term osteoporosis risk. To mitigate the risk posed by chronic oral corticosteroid use, and their relative limited efficacy in many cases of peripheral ulcerative keratitis, immunomodulatory therapy is often simultaneously begun [1]. If the patient has serologic (e.g., elevated ANA, cANCA, pANCA titers) and clinical (e.g., crippling arthritis, cutaneous, pulmonary, and/or renal) evidence of systemic vasculitis, early institution of alkylating agents is preferred [10, 14, 15]. Antimetabolites or calcineurin inhibitors can be used in milder disease but the choice of agent is empiric [3, 16]. In the presence of rapidly progressive corneal melting, or if one eye has already been lost to the disease and the second eye is rapidly worsening, alkylating agents or antimetabolites may be

combined with biologic response modifiers [3, 17–20]. Special cases of rapidly progressive systemic vasculitis such as granulomatosis and polyangiitis, polyarteritis nodosa or relapsing polychondritis, especially with the presence of life-threatening pulmonary or renal lesions, may necessitate the institution of rituximab infusions along with antimetabolites or alkylating agents and systemic corticosteroids [21–24]. Once quiescence and disease control is achieved, immunomodulatory therapy is continued for 6–12 months in the case of alkylating agents or for 2–5 years for antimetabolites, calcineurin inhibitors, and biologics in order to achieve durable steroid-free remission of disease [12].

Laboratory Testing

In general, when immunomodulatory therapy is utilized, baseline laboratory evaluation of complete blood count, hepatic function testing, and complete metabolic panel are often obtained [12]. If biologic response modifiers are utilized, a thorough evaluation for underlying demyelinating neurologic disease, congestive heart failure, latent tuberculosis, or latent histoplasmosis in endemic areas is usually performed prior to the initiation of therapy [25, 26]. Once the patient has initiated therapy, periodic complete blood count and hepatic function tests are performed every 2–4 weeks initially and then less frequently based on dosing and patient tolerance [12]. Additional testing specific to each immunomodulatory therapeutic agent may be necessary. If there is laboratory evidence of drug toxicity, a temporary discontinuation of the medications for a few weeks followed by reinstitution of medications at lower doses and reevaluation of hematologic or metabolic abnormalities is indicated. If toxicity is severe, and dosing reduction has not relieved toxicity, switching to a different agent in the same class or a different class of immunomodulatory medications may be required. The choices of such agents are tailored to individual patient needs, comorbidities, and constraints of underlying disease.

Special Considerations: Pregnancy and Fetal Risk

Most steroid sparing immunomodulatory agents should be avoided in women of childbearing age [8, 12] (Table 12.1). Contraception in at least two different forms should be utilized by both partners to avoid pregnancy. Those agents that have a very high risk of fetal harm include the alkylating agents and most of the antimetabolites with the exception of azathioprine. Azathioprine, corticosteroids, biologic agents, such as tumor necrosis factor alpha inhibitors, as well as calcineurin inhibitors may be utilized selectively during pregnancy. Consultation with a high-risk obstetrics specialist is indicated in the management of these patients if these immunomodulatory therapeutic agents are to be utilized during pregnancy. Similarly men who are taking these agents should practice contraception in order to avoid potential fetal risk and malformations caused by abnormal spermatogenesis. Some agents, such as the alkylators, cause azoospermia and in some cases permanent sterility [27]. This should be discussed at length with patients prior to initiation of therapy. Sperm banking prior to initiation of therapy may be a useful method for younger men who require immunomodulatory therapy but who still wish to have children.

Specific Agents (Table 12.2)

Antimetabolites

1. Methotrexate

Methotrexate is a folic acid analog that inhibits the conversion of dihydrofolate to tetrahydrofolate and thus has the effect of inhibiting de novo purine synthesis and some transmethylation reactions necessary for synthesis of RNA and DNA. In addition, it causes extracellular release of adenosine, which may have additional anti-inflammatory properties. It is metabolized in the liver and as such has the potential risk of causing significant hepatotoxicity. Methotrexate is given orally weekly medications in the dose

Table 12.1 Immunomodulatory therapy—special considerations: pregnancy: Maternal and fetal risk

• Minimal fetal or maternal risk
Hydroxychloroquine
Sulfasalazine
• Selective use allowed during pregnancy
NSAIDs and aspirin
Glucocorticoids
Azathioprine and 6-MP
TNF inhibitors
Intravenous immune globulin
Cyclosporine
Tacrolimus
• Contraindicated during pregnancy: moderate to high risk of fetal harm
Cyclophosphamide
Methotrexate
Mycophenolate mofetil
Leflunomide
Third trimester use of NSAIDs and aspirin
• Unknown risk
Anakinra
Rituximab
Abatacept
Tocilizumab

range of 7.5–25 mg per week [16, 28, 29]. Oral bioavailability, however, is variable and is associated with significant gastrointestinal irritation at higher dosages. As a result, subcutaneous injection of methotrexate may have better bioavailability and greater therapeutic effect with less gastrointestinal irritation [30]. The onset of action is relatively slow. Methotrexate may take up to 3–6 months to have a full effect on intraocular tissues [28]. It is particularly safe to use in children, as it is associated with no risk of long-term secondary neoplasia. Leukopenia, elevation of liver enzymes, long-term development of cirrhosis and even pulmonary fibrosis are potential complications of methotrexate use. Since methotrexate can affect rapidly dividing cells, it does tend to cause nausea, fatigue, mucous membrane ulceration, and dry eyes symptoms. Folic acid supplementation at 1–2 mg per day usually decreases the severity of side effects [12, 31]. Avoidance of alcohol to reduce hepatotoxicity is essential. Since methotrexate is a category X medication for pregnancy, appropriate dual methods of contraception are required in women of childbearing age. There is also potential for spermatic mutation, and males should be off the drug for at least 4 months prior to attempting conception [12].

There is substantial Level I and II evidence of the efficacy of methotrexate in the treatment of rheumatoid arthritis [6, 8, 32]. In addition there is extensive level II-2 evidence of the efficacy of methotrexate in the management of ocular inflammatory diseases [1, 12, 28]. The SITE study has shown that 66% of patients on systemic methotrexate have no inflammation after 1 year of therapy and nearly 60% are able to reduce maintenance prednisone dosage to less than 10 mg per day [28].

Table 12.2 Specific Immunomodulatory Agents for the Treatment of Peripheral Ulcerative Keratitis and Necrotizing Scleritis

Medication	Mechanism of action	Dosage/route	Potential complications
Antimetabolites			
Methotrexate	Folate analog; inhibits dihydrofolate reductase	7.5–25.0 μg/wk PO, SC,IM	GI upset, fatigue, hepatotoxicity, pneumonitis
Azathioprine	Alters purine metabolism	100–250 mg/d PO	GI upset, hepatotoxicity
Mycophenolate mofetil	Inhibits purine synthesis	1–3 gm/d PO	Diarrhea, nausea, GI ulceration
Alkylating agents			
Cyclophosphamide	Cross-links DNA	1–2 mg/d PO	Hemorrhagic cystitis, sterility, increased risk of malignancy
Chlorambucil	Cross-links DNA	2–12 mg/d PO	Sterility, increased risk of malignancy
Calcineurin inhibitors			
Cyclosporine	Inhibits NF-AT (nuclear factor of activated T cells) activation	2.5–5.0 mg/kg/d PO	Nephrotoxicity, hypertension, gingival hyperplasia, GI upset, paresthesias
Tacrolimus	Inhibits NF-AT activation	0.1-0.2 mg/kg/d PO	Nephrotoxicity, hypertension, diabetes mellitus
Biologic response modifiers			
Infliximab	TNF-α inhibitor	3 mg/kg IV Week 0, 2, 6 and then Q6-8 weeks (may need Q 4wk)	Infusion reactions, Infections (TB reactivation), Malignancy/lymphoproliferative diseases Autoantibodies/Lupus like syndrome Congestive heart failure
Adalimumab	TNF-α inhibitor	40 mg q 1 week or q 2 weeks	Headache, nausea, rash, stomach upset
Rituximab	Anti-CD20 antibody	375 mg/m^2 IV qWeek x4 weeks	Profound Lymphopenia, Hypersensitivity reactions Infusion reactions: Fevers, Nausea

2. Azathioprine

Azathioprine is a purine analog and prodrug, which is converted to 6 mercaptopurine, a competitive inhibitor of purine synthesis. Azathioprine produces its immunosuppressive effect by inhibiting DNA and RNA synthesis and actively dividing cells such as lymphocytes [12]. It is absorbed well orally and typically is given at an oral dose of 1–3 mg/kg per day. It is hepatically metabolized and carries with it some potential risk for hepatotoxicity. Patients who are homozygous for deficiency of thiopurine methyltransferase or TPMT should not be treated with azathioprine since they are at particularly great risk for developing pancytopenia from azathioprine [33]. Patients who are heterozygous for this deficiency may require dose adjustment. The presence of TPMT enzyme deficiency should be part of the pretreatment evaluation of patients who are being considered for azathioprine therapy [33]. Like methotrexate, azathioprine may take up to 6 months to have full therapeutic effect of reducing ocular inflammation. Complications of therapy include nausea,

leukopenia with potentially rapid onset of bone marrow suppression particularly in patients who are homozygous for the TPMT mutation, elevation of liver enzymes, and possible increased risk of lymphoma or leukemia [12, 34]. Routine monitoring of complete blood count and liver function tests are essential. Relatively strong level II-2 evidence of the efficacy of azathioprine and ocular inflammatory diseases exists. The SITE study showed that 62% of patients had no inflammation 1 year after initiation of azathioprine, and nearly 50% were able to reduce prednisone maintenance dosing to less than 10 mg per day [34].

3. Mycophenolate mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid. It is a selective inhibitor of de novo purine synthesis by selectively and reversibly binding inosine monophosphate dehydrogenase. This enzyme is particularly active in T- and B lymphocytes which are dependent on de novo purine synthesis. This may be the reason why mycophenolate mofetil may have greater efficacy in reducing clonal T_{helper} and B lymphocyte populations than azathioprine [12]. In addition, mycophenolate suppresses antibody synthesis, interferes with cellular adhesion to vascular endothelium, and reduces recruitment of leukocytes [12]. It is particularly well absorbed when given orally. Therapeutic dosing for adults is usually between 1000 and 3000 mg daily. Unlike azathioprine and methotrexate, mycophenolate mofetil has a slightly more rapid onset of action in ocular tissues. Therapeutic effects may be seen as quickly as 2–3 months after initiation of therapy. Complications of mycophenolate mofetil include gastrointestinal disturbances (most common), leukopenia (rarely red cell aplasia), progressive multifocal leukencephalopathy, and possible increased risk of lymphoma and leukemia [12, 35–37]. It is teratogenic and should be avoided in women of childbearing age who wish to become pregnant. Routine monitoring of complete blood count and liver function tests is required. Gastrointestinal complications such as diarrhea, constipation, or nausea are usually due to inappropriate oral administration of the medication. Mycophenolate mofetil should be given 2–3 h prior to or after meals on an empty stomach. This approach significantly reduces gastrointestinal distress and side effects. In addition dose reductions can also dramatically reduce gastrointestinal side effects. There is strong level II-2 evidence for the use of mycophenolate mofetil in ocular inflammatory disease [12, 36–40]. The SITE studies have shown that 73% of patients treated with mycophenolate mofetil had no inflammation 1 year after initiation of therapy, and 55% were able to reduce prednisone maintenance dosing to less than 10 mg per day [12, 35].

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

Both cyclosporine and tacrolimus inhibit calcineurin which in turn inhibits nuclear factor of activated T cells resulting in downregulation of the interleukin-2 gene and reduction of interleukin-2 production [12, 41, 42]. This results in a dramatic reduction of the stimulus for T_{helper}-cell proliferation. These agents are noncytotoxic and selectively and reversibly inhibit helper T lymphocytes-mediated immune responses [41]. These agents do not affect suppressor T cells or T-cell-independent antibody-mediated immunity. Cyclosporine has two different formulations that have different bioavailabilities. Dosing of cyclosporine must be adjusted depending on the formulation used. A modified microemulsion formulation has greater bioavailability than the unmodified cyclosporine A [12]. Cyclosporine does cross the placenta and is found in breast milk. Cyclosporine and tacrolimus should be avoided in pregnancy. Foods and medications such as grapefruit juice, some cholesterol-lowering medications, and macrolide antibiotics increase blood levels of cyclosporine [12]. Cyclosporine has a high risk of causing renal toxicity if given orally at dosages greater than 5 mg/kg per day. Baseline renal and hepatic function tests, serum cholesterol and

triglycerides, complete blood count, and blood pressure should be performed along with routine follow-up of these parameters during therapy. Measurements of trough serum levels of cyclosporine are no longer performed. Cyclosporine has a myriad of side effects. Renal toxicity, hypertension requiring therapy, hirsutism, gingival hyperplasia, tremors and paresthesia, acne, headache, nausea, potential increased risk of secondary malignancy, and central nervous system dysfunction or peripheral neuropathies have all been reported [12, 41]. Due to these numerous side effects, Cyclosporine is often used as an adjunctive with other antimetabolites at lower doses to reduce side effects and improve therapeutic efficacy in controlling ocular inflammatory disease. Tacrolimus has less nephrotoxicity and is utilized at an oral dosage of 0.1–0.2 mg/kg per day. Although there is ample clinical evidence of the efficacy of cyclosporine and tacrolimus in the treatment of retinal vasculitis, Behçet disease, and prevention of organ transplant rejection, mostly anecdotal evidence exists for its efficacy in the treatment of necrotizing scleritis and peripheral ulcerative keratitis [12, 42]. Level II-2 evidence for treatment of ocular inflammatory disease exists for calcineurin inhibitors. The SITE studies showed that 52% of patients had no inflammation 1 year after initiation of cyclosporine or tacrolimus and that 36% were able to reduce prednisone maintenance dosage to less than 10 mg per day [42].

Alkylating Agents: Cyclophosphamide and Chlorambucil

Cyclophosphamide, an alkylating agent, is metabolized following oral administration in the liver to phosphoramide mustard, the active component, and acrolein, a toxic metabolite [12, 27, 43]. Phosphoramide mustard inhibits T- and B-cell proliferation by producing cross-linkage in the DNA between clonidine and thymidine resulting in aberrant base pairing, DNA strand breakage, and interruption of transcription [12]. This results in inhibition of both the resting and actively dividing lymphocytes and suppresses both the cellular and humoral immune responses. Acrolein causes hemorrhagic cystitis but may also have the effect of causing intracellular protein damage [12]. Chlorambucil is also a nitrogen mustard derivative and has a similar mechanism of action although it is slower acting and has a more prolonged effect on inhibition of lymphocyte proliferation. Both drugs are well absorbed orally and are metabolized in the liver. In certain conditions such as necrotizing scleritis, granulomatosis with polyangiitis, relapsing polychondritis, or polyarteritis nodosa, cyclophosphamide is indicated as first-line therapy where it is particularly efficacious in controlling inflammatory ocular disease and also plays a pivotal role in life-saving therapy [27, 44, 45]. Both chlorambucil and cyclophosphamide have been shown to induce long-term remission in patients who have otherwise intractable sight threatening noninfectious uveitis, scleritis, or peripheral ulcerative keratitis [1, 12, 14, 27, 43, 45, 46]. Baseline complete blood count, liver function tests, hepatic function tests, and urinalysis along with routine follow-up evaluation of these parameters are essential. The dosing of cyclophosphamide is typically given orally at 1–3 mg/kg per day over a period of approximately 6 months usually to a maximum cumulative dose of around 35 g. Cumulative dosage greater than 35 g is associated with a substantial increase in secondary leukemia, especially acute myelogenous leukemia in adults [27, 44, 45]. Alternatively, a pulsed intravenous monthly 500 mg dose of cyclophosphamide for 6–12 months can also be given [43]. Oral or intravenous hydration is essential in patients receiving cyclophosphamide therapy. Aggressive hydration can reduce the risk of hemorrhagic cystitis. Chlorambucil may be given as low-dose therapy over 12 months at 0.1–0.2 mg/kg per day orally and dose adjusted to the leukocyte count; or, it may be given as short-term high-dose therapy over 3–6 month period with an initial daily dose of 2 mg per day for 1 week increasing the dose by 2 mg per day each week until inflammation is suppressed or the leukocyte count drops [12, 47]. Unlike other immunomodulatory agents, cyclophosphamide and chlorambucil are dose adjusted based on a

target leukocyte count of 3000–4000 cells per microliter off of systemic corticosteroids. The induced leukopenia is proportional to and indicative of the control of inflammatory disease. Complications of cyclophosphamide and chlorambucil include leukopenia, secondary infection especially from *Pneumocystis jeroveci* (requires Bactrim prophylaxis), hemorrhagic cystitis (cyclophosphamide), permanent infertility from gonadal suppression, pulmonary fibrosis, and significant long-term risk of secondary malignancies of the bladder, skin, leukemia, and lymphoma [12, 27, 43, 44]. These medications are also highly teratogenic. Patients should be advised to use two methods of contraception when these medications are utilized. Due to the relatively high risk of toxicity, these agents are reserved for use by those experienced in the recognition and treatment of potential complications associated with these medications. Strong level II-1 evidence exists for the efficacy of alkylating agents in the treatment of ocular cicatricial pemphigoid [48] and level I and level II-1 evidence exists for the efficacy of these agents in the treatment of systemic vasculitis [1, 3, 27, 43, 47]. The SITE studies demonstrated that 76% of patients treated with alkylating agents had no inflammation 1 year after initiation of therapy and 61% were able to reduce prednisone maintenance dosages to the less than 10 mg per day [27].

Biologic Response Modifiers

Biologic response modifiers are the newest class of agents used for the treatment of systemic autoimmune diseases and noninfectious uveitis, necrotizing scleritis, and peripheral ulcerative keratitis [1, 7, 8, 49, 50]. Biologic response modifiers are considered if antimetabolite therapy has failed to control ocular or systemic inflammatory disease [1, 8, 49–51]. Biologic response modifiers may be utilized in conjunction with other antimetabolites such as methotrexate. Biologic response for modifiers may be utilized prior to or after a course of alkylating agent therapy. They can be subdivided into major classes that include tumor necrosis factor alpha inhibitors, anti-lymphocyte drugs, cytokine receptor blockade blockers, recombinant human cytokine/cytokine analogs, co-stimulation modulators, and selective lymphocyte elimination drugs such as rituximab. Of these classes, the tumor necrosis factor alpha inhibitors have the most favorable impact in the treatment of advanced rheumatoid arthritis [8], ankylosing spondylitis, psoriasis, inflammatory bowel disease, Behçet disease, and numerous ocular inflammatory diseases including peripheral ulcerative keratitis [12, 50, 51].

Of the tumor necrosis factor alpha inhibitors, etanercept, a receptor analog, has been found to be ineffective for the treatment of ocular inflammatory disease [51]. It is typically not used in the management of ocular inflammatory disease although it may have a beneficial role in the management of systemic autoimmune inflammatory disease processes. Infliximab and adalimumab are the most commonly utilized tumor necrosis factor alpha inhibitors for the treatment of ocular inflammatory disease [51]. Small-case series of level II and in some cases level I evidence does exist showing the efficacy of these agents in the treatment of ocular inflammatory disease [3, 17, 18, 21, 49, 51–54]. Most uveitis specialists would not manage the administration of these agents but will refer the patient to a rheumatologist for appropriate pretreatment evaluation and administration and follow-up. At this point these agents, like all of the other immunomodulatory agents, remain off label for the treatment of ocular inflammatory disease alone except for adalimumab which was recently approved by the FDA and the European Commission for the treatment of non-infectious intermediate, posterior, and pan-uveitis based on two phase III clinical trials, VISUAL I [55] and VISUAL II [56]. Patients treated with adalimumab every other week had a significantly lower risk for treatment failure (a combination of uveitic flare and decrease in visual acuity) compared with placebo. No new safety risks were identified in this patient population. Adalimumab is still considered off-label for peripheral ulcerative keratitis and/or scleritis. However, a

plethora of clinical information exists on the efficacy of these agents when other immunomodulatory therapeutic agents fail [3, 17, 18, 21, 49, 51–54]. Prior to initiation of therapy with tumor necrosis factor alpha inhibitors, chest X-ray and purified protein derivative or interferon gamma release assay to rule out the possibility of latent tuberculosis, neurologic evaluation to rule out underlying multiple sclerosis, metabolic panel, complete blood count, and an evaluation of a history or risks for congestive heart failure, and serum antinuclear antibody levels should be obtained [51]. Infliximab is usually given as intravenous infusions at 3–10 mg/kg per dose on day 0, week 2, week 4, then every 4–6 weeks based on control of inflammatory response [12]. Infusions are performed in a rheumatologic infusion center setting supervised by physicians and nursing personnel. Adalimumab is usually self-administered at 40 mg subcutaneously every 2 weeks but can be increased to weekly interval if needed [12]. The dosing, administration, and education on self-administration should be performed by the rheumatologist. Complications of tumor necrosis factor alpha inhibitor therapy include infusion reactions, exacerbation of underlying demyelinating disease, exacerbation of latent tuberculosis or latent histoplasmosis, heart failure, reduction of neutralizing antibodies, drug-induced lupus with elevated antinuclear antibodies, and secondary neoplasia including acute leukemia with infliximab [7, 12, 51, 53]. Numerous Level I, II, and III reports and small-case series exist showing the efficacy of infliximab and adalimumab in halting the progression of progressive corneal melting from peripheral ulcerative keratitis and reduction of inflammatory activity in necrotizing and non-necrotizing scleritis [3, 17, 18, 49, 54]. These findings are consistent with reports in the rheumatologic literature of the efficacy of these agents in the treatment of refractory rheumatoid arthritis and systemic vasculitides. There is only anecdotal evidence of efficacy against ocular inflammatory diseases for newer tumor necrosis factor alpha inhibitors such as certolizumab and golimumab [7, 8, 49, 51, 53].

Rituximab is anti-CD20 monoclonal antibody. By binding the CD20 molecule on the surface of the lymphocytes, this monoclonal antibody induces cell death and clonal deletion of entire populations of CD20 positive lymphocytes [12]. This can have a very profound effect on the control of immune mediated disease. The efficacy of rituximab in the treatment of fulminant extraocular manifestations of granulomatosis and polyangiitis has been well established in the rheumatologic literature [57]. There is level I and II–1 evidence of efficacy of rituximab in the treatment of refractory scleritis, systemic vasculitides such as granulomatosis with polyangiitis, ocular cicatricial pemphigoid, recalcitrant pediatric uveitis, and orbital inflammation [21–24, 58, 59]. Rituximab is typically given as a one-time infusion and methotrexate is often simultaneously begun for the treatment of systemic vasculitis. Periodic repeat infusions of rituximab may be given based on the patient's clinical response [12, 57]. Profound lymphopenia can occur and hypersensitivity and infusion reactions are also common.

Newer agents (e.g., secukinumab) directed at the inhibition of interleukin-17 have shown promise in producing a sustained anti-inflammatory effect that is long-lasting. At this point little evidence exists for the efficacy of these agents in the treatment of necrotizing scleritis or peripheral ulcerative keratitis. But inhibition of interleukin-17 shows promise in the treatment of autoimmune inflammatory disorders.

Conclusions

Severe necrotizing scleritis with peripheral ulcerative keratitis is best managed by early institution of high doses of corticosteroids that are gradually tapered with simultaneous or early institution of alkylating agents for a 6–12 month period to gain rapid control of inflammation and hopefully obtain sustained durable remission of disease. The presence of fulminant and severe systemic vasculitis involving extraocular tissues such as the sinuses, lung, or kidney may require early initiation of rituximab infusion therapy

combined with long-term immunomodulatory therapy using antimetabolites, calcineurin inhibitors, or even alkylating agents along with tapering systemic corticosteroid therapy. Milder disease (non-necrotizing scleritis) should be managed empirically using milder immunomodulatory agents such as antimetabolites or calcineurin inhibitors. These treatment paradigms have been shown over the last 2-1/2 decades to be the most successful in controlling ocular inflammation and systemic vasculitis, improving visual prognosis, and ultimately reducing systemic morbidity and mortality associated with severe systemic vasculitides that often underlie cases of peripheral ulcerative keratitis and necrotizing scleritis.

Compliance with Ethical Requirements Ramana S. Moorthy and Shailaja Valluri declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this article.

References

1. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007;33:835–54, vii.
2. Wilson DM, John GR, Callen JP. Peripheral ulcerative keratitis—an extracutaneous neutrophilic disorder: report of a patient with rheumatoid arthritis, pustular vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. J Am Acad Dermatol. 1999;40:331–4.
3. Yagci A. Update on peripheral ulcerative keratitis. Clin Ophthalmol (Auckland, N.Z.). 2012;6:747–54.
4. Artifoni M, Rothschild PR, Brezin A, Guillevin L, Puechal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:108–16.
5. Atchia II, Kidd CE, Bell RW. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. J Clin Rheumatol: Pract Rep Rheum Musculoskelet Dis. 2006;12:291–3.
6. Kemper AR, Van Mater HA, Coeytaux RR, Williams JW Jr, Sanders GD. Systematic review of disease-modifying antirheumatic drugs for juvenile idiopathic arthritis. BMC Pediatr. 2012;12:29.
7. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, van der Heijde D, Winthrop K, Landewe R. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014;73:529–35.
8. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgereit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492–509.
9. Watanabe R, Ishii T, Yoshida M, Takada N, Yokokura S, Shirota Y, Fujii H, Harigae H. Ulcerative keratitis in patients with rheumatoid arthritis in the modern biologic era: a series of eight cases and literature review. Int J Rheum Dis. 2015.
10. Foster CS. Ocular manifestations of the potentially lethal rheumatologic and vasculitic disorders. J Fr Ophtalmol. 2013;36:526–32.
11. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis. Effects of systemic immunosuppression. Ophthalmology. 1984;91:1253–63.
12. Castilblanco C, Foster CS. Review of systemic immunosuppression for autoimmune uveitis. Ophthalmol Ther. 2014;3:17–36.
13. Miserocchi E, Modorati G. Rituximab for noninfectious uveitis. Dev Ophthalmol. 2012;51:98–109.
14. Tarabishy AB, Schulte M, Papaliodis GN, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. Surv Ophthalmol. 2010;55:429–44.
15. Tauber J, Sainz de la Maza M, Hoang-Xuan T, Foster CS. An analysis of therapeutic decision making regarding immunosuppressive chemotherapy for peripheral ulcerative keratitis. Cornea. 1990;9:66–73.
16. Galor A, Jabs DA, Leder HA, Kedhar SR, Dunn JP, Peters GB 3rd, Thorne JE. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology. 2008;115:1826–32.
17. Cordero-Coma M, Mendez RS, Blanco AC, Corral AL, Calleja-Antolin S, de Morales JM. Adalimumab for refractory peripheral ulcerative keratitis. J Ophthalmic Inflamm Infect. 2012;2:227–9.
18. Doctor P, Sultan A, Syed S, Christen W, Bhat P, Foster CS. Infliximab for the treatment of refractory scleritis. Br J Ophthalmol. 2010;94:579–83.
19. Odorcic S, Keystone EC, Ma JJ. Infliximab for the treatment of refractory progressive sterile peripheral ulcerative keratitis associated with late corneal perforation: 3-year follow-up. Cornea. 2009;28:89–92.

20. Pham M, Chow CC, Badawi D, Tu EY. Use of infliximab in the treatment of peripheral ulcerative keratitis in Crohn disease. Am J Ophthalmol. 2011;152:183–188.e182.
21. Taylor SR, Salama AD, Joshi L, Pusey CD, Lightman SL. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. Arthritis Rheum. 2009;60:1540–7.
22. Freidlin J, Wong IG, Acharya N. Rituximab treatment for peripheral ulcerative keratitis associated with Wegener's granulomatosis. Br J Ophthalmol. 2007;91:1414.
23. Huerva V, Sanchez MC, Traveset A, Jurjo C, Ruiz A. Rituximab for peripheral ulcerative keratitis with wegener granulomatosis. Cornea. 2010;29:708–10.
24. Recillas-Gispert C, Serna-Ojeda JC, Flores-Suarez LF. Rituximab in the treatment of refractory scleritis in patients with granulomatosis with polyangiitis (Wegener's). Graefes Arch Clin Exp Ophthalmol. 2015;253:2279–84.
25. Murphy CC, Ayliffe WH, Booth A, Makanjuola D, Andrews PA, Jayne D. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. Ophthalmology. 2004;111:352–6.
26. Theodossiadis PG, Markomichelakis NN, Sfikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina (Philadelphia, PA). 2007;27:399–413.
27. Pujari SS, Kempen JH, Newcomb CW, Gangaputra S, Daniel E, Suhler EB, Thorne JE, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Foster CS. Cyclophosphamide for ocular inflammatory diseases. Ophthalmology. 2010;117:356–65.
28. Gangaputra S, Newcomb CW, Liesegang TL, Kacmaz RO, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Kempen JH. Methotrexate for ocular inflammatory diseases. Ophthalmology. 2009;116:2188–2198.e2181.
29. Jachens AW, Chu DS. Retrospective review of methotrexate therapy in the treatment of chronic, noninfectious, nonnecrotizing scleritis. Am J Ophthalmol. 2008;145:487–92.
30. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004;31:645–48.
31. van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2001;44.
32. Nurmohamed MT, Dijkmans BA. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. Drugs. 2005;65:661–94.
33. Anstey A, Lennard L, Mayou SC, Kirby JD. Pancytopenia related to azathioprine–an enzyme deficiency caused by a common genetic polymorphism: a review. J R Soc Med. 1992;85:752–6.
34. Pasadhika S, Kempen JH, Newcomb C, Liesegang TL, Pujari SS, Rosenbaum JT, Thorne JE, Foster CS, Jabs DA, Levy-Clarke GA, Nussenblatt RB, Suhler EB. Azathioprine for Ocular Inflammatory Diseases. Am J Ophthalmol. 2009;148:500–509.e502.
35. Daniel E, Thorne JE, Newcomb CW, Pujari SS, Kacmaz RO, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Foster CS, Jabs DA, Kempen JH. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol. 2010;149:423–32.e421–22.
36. Kolomeyer AM, Ragam A, Shah K, Jachens AW, Tu Y, Chu DS. Mycophenolate mofetil in the treatment of chronic non-infectious, non-necrotizing scleritis. Ocul Immunol Inflamm. 2012;20:113–8.
37. Thorne JE, Jabs DA, Qazi FA, Nguyen QD, Kempen JH, Dunn JP. Mycophenolate mofetil therapy for inflammatory eye disease. Ophthalmology. 2005;112:1472–7.
38. Sen HN, Suhler EB, Al-Khatib SQ, Djalilian AR, Nussenblatt RB, Buggage RR. Mycophenolate mofetil for the treatment of scleritis. Ophthalmology. 2003;110:1750–5.
39. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology. 2008;**115**:1416–21, 1421.e1411.
40. Yalcindag FN, Amer R, Forrester JV. Mycophenolate mofetil in the treatment of ocular inflammation in ANCA-associated vasculitis. J Ocul Pharmacol Ther: Official J Assoc Ocul Pharmacol Ther. 2008;24:249–54.
41. Graham RM. Cyclosporine: mechanisms of action and toxicity. Cleve Clin J Med. 1994;61:308–13.
42. Kacmaz RO, Kempen JH, Newcomb C, Daniel E, Gangaputra S, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Jabs DA, Levy-Clarke GA, Foster CS. Cyclosporine for ocular inflammatory diseases. Ophthalmology. 2010;117:576–84.
43. Khan IJ, Barry RJ, Amissah-Arthur KN, Carruthers D, Elamanchi SR, Situnayake D, Murray PI, Denniston AK, Rauz S. Ten-year experience of pulsed intravenous cyclophosphamide and methylprednisolone protocol (PICM protocol) in severe ocular inflammatory disease. Br J Ophthalmol. 2013;97:1118–22.
44. Kempen JH, Gangaputra S, Daniel E, Levy-Clarke GA, Nussenblatt RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Jabs DA, Helzlsouer KJ. Long-term risk of malignancy among patients treated with immunosuppressive agents for ocular inflammation: a critical assessment of the evidence. Am J Ophthalmol. 2008;146:802–812.e801.
45. Watkins AS, Kempen JH, Choi D, Liesegang TL, Pujari SS, Newcomb C, Nussenblatt RB, Rosenbaum JT, Thorne JE, Foster CS, Jabs DA,

Levy-Clarke GA, Suhler EB, Smith JR. Ocular disease in patients with ANCA-positive vasculitis. J Ocul Biol Dis Inform. 2010;3:12–9.
46. Sainz de la Maza M, Molina N, Gonzalez-Gonzalez LA, Doctor PP, Tauber J, Foster CS. Scleritis therapy. Ophthalmology. 2012;119:51–8.
47. Tessler HH, Jennings T. High-dose short-term chlorambucil for intractable sympathetic ophthalmia and Behçet's disease. Br J Ophthalmol. 1990;74:353–7.
48. Foster CS. Cicatricial pemphigoid. Tran Am Ophthalmol Soc. 1986;84:527–663.
49. de Fidelix TS, Vieira LA, de Freitas D, Trevisani VF. Biologic therapy for refractory scleritis: a new treatment perspective. Int Ophthalmol. 2015;35:903–12.
50. Lim L, Suhler EB, Smith JR. Biologic therapies for inflammatory eye disease. Clin Exp Ophthalmol. 2006;34:365–74.
51. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121:785–796.e783.
52. Ragam A, Kolomeyer AM, Fang C, Xu Y, Chu DS. Treatment of chronic, noninfectious, nonnecrotizing scleritis with tumor necrosis factor alpha inhibitors. Ocul Immunol Inflamm. 2014;22:469–77.
53. Rifkin LM, Birnbaum AD, Goldstein DA. TNF inhibition for ophthalmic indications: current status and outlook. BioDrugs: Clin Immunotherapeutics Biopharmaceuticals Gene Ther. 2013;27:347–57.
54. Sen HN, Sangave A, Hammel K, Levy-Clarke G, Nussenblatt RB. Infliximab for the treatment of active scleritis. Can J Ophthalmol/J Can Ophtalmol. 2009;44:e9–12.
55. Jaffe GJ, et al. Adalimumab in patients with active noninfectious uveitis. N Engl J Med 2016; 375:932–43.
56. Nguyen QD, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet. 2016; 388:1183–92.
57. Moog P, Thuermel K. Spotlight on rituximab in the treatment of antineutrophil cytoplasmic antibody-associated vasculitis: current perspectives. Ther Clin Risk Manag. 2015;11:1749–58.
58. Joshi L, Tanna A, McAdoo SP, Medjeral-Thomas N, Taylor SR, Sandhu G, Tarzi RM, Pusey CD, Lightman S. Long-term outcomes of rituximab therapy in ocular granulomatosis with polyangiitis: impact on localized and nonlocalized disease. Ophthalmology. 2015;122:1262–8.
59. Suhler EB, Lim LL, Beardsley RM, Giles TR, Pasadhika S, Lee ST, de Saint Sardos A, Butler NJ, Smith JR, Rosenbaum JT. Rituximab therapy for refractory scleritis: results of a phase I/II dose-ranging, randomized, clinical trial. Ophthalmology. 2014;121:1885–91.

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R. Tandon et al. (eds.), *Peripheral Ulcerative Keratitis*,
Essentials in Ophthalmology, DOI 10.1007/978-3-319-50404-9