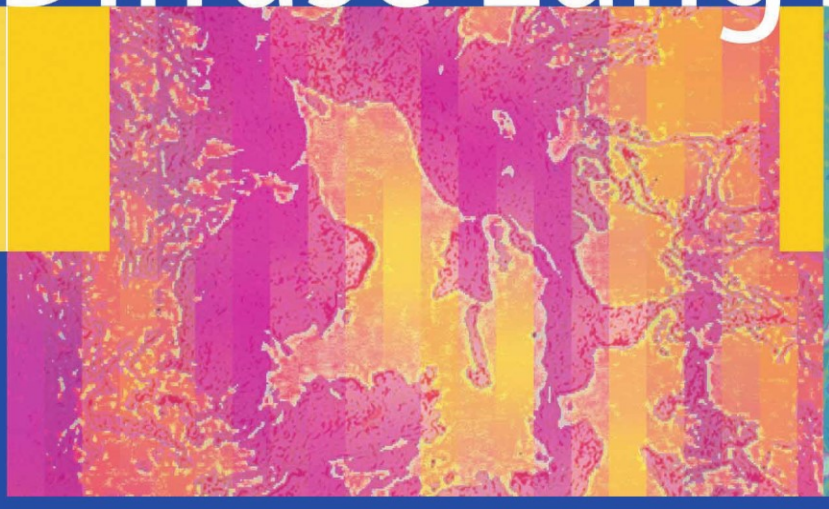
M. Maffessanti
G. Dalpiaz
Editors

A. Cancellieri
G. Dalpiaz
M. Maffessanti
A. Pesci
R. Polverosi
M. Zompatori
Authors

Diffuse Lung Diseases



Clinical Features
Pathology
HRCT

Springer

Diffuse Lung Diseases

Clinical Features, Pathology, HRCT

Editors
Mario Maffessanti & Giorgia Dalpiaz

Authors
A. Cancellieri
G. Dalpiaz
M. Maffessanti
A. Pesci
R. Polverosi
M. Zompatori

Springer

MARIO MAFFESSANTI, M.D.
Associate Professor of Diagnostic Imaging, University of Trieste, Italy - maffe@gnbts.univ.trieste.it

GIORGIA DALPIAZ, M.D.
Unit of Radiology, Bellaria Hospital, Bologna, Italy - giorgia.dalpiaz@ausl.bologna.it

ALESSANDRA CANCELLIERI, M.D.
Department of Pathology, Maggiore Hospital, Bologna, Italy - alessandra.cancellieri@ausl.bologna.it

ALBERTO PESCI, M.D.
Associate Professor of Respiratory Diseases, University of Parma, Italy - alberto.pesci@unipr.it

ROBERTA POLVEROSI, M.D.
Department of Radiology, San Bassiano Hospital, Bassano del Grappa, Italy - rpolve@libero.it

MAURIZIO ZOMPATORI, M.D.
Professor of Diagnostic Imaging, University of Parma, Italy - maurizio.zompatori@unipr.it

Originally pubblished as:
Pneumopatie Infiltrative Diffuse
Clinica, Anatomia Patologica, HRTC
a cura di Mario Maffessanti & Giorgia Dalpiaz

Library of Congress Control Number: 2005937063

ISBN-10 88-470-0429-2 Springer Milan Berlin Heidelberg New York
ISBN-13 0978-88-470-0429-0

Springer is a part of Springer Science+Business Media
springer.com

Printed in Italy

Cover design: eStudio Calamar, Barcelona, Spain
Design and typesetting: Daniele Kirchmayer, Trieste, Italy
Printing: Arti Grafiche Nidasio, Assago (MI), Italy
Translation: Itala Brancaleone and Alexander Cormack, Trieste, Italy

Foreword

Introducing a book dealing with Radiology is always a pleasure, but it is a special pleasure on this occasion as the invitation came from a very dear friend, Mario Maffessanti. The idea of producing a guide to the interpretation of the diffuse lung diseases via high-resolution CT, as the authors state in the preface, arose at the end of a day's work brilliantly orchestrated by Mario on the snowfields of Corvara, Italy, several years ago. The same level of thoroughness and precision then can be found among the pages of this undoubtedly useful volume in order to arrive at a diagnosis from the basis of a radiological sign.

It is certainly an innovative book in terms of the way in which it is designed to be consulted, which brings together thorough descriptions of the radiological signs and complete clinical and pathological references to create a comprehensive understanding of each individual disease. The interdisciplinary team of authors is an absolute guarantee of quality, given the brilliant scientific, academic and professional activities they have performed over the years.

Having in part been the prime mover of this book and having it dedicated to me fills me with pleasure and pride, which prompts me to wish the reader a useful and productive read.

Lorenzo Bonomo, M.D.

Professor of Radiology and Chairman
Department of Bioimaging and Radiological Sciences
Catholic University, Rome, Italy

Foreword

The Springer book “Diffuse Lung Diseases”, edited by two prominent Italian radiologists, Mario Maffessanti and Giorgia Dalpiaz, and authored by some of the most expert clinicians and pathologists in the field of diffuse lung diseases, was published last year in Italian. Since this innovative book became available to the Italian medical community, it has become tangible evidence of the need for a multidisciplinary approach to the diagnosis and treatment of patients affected by diffuse lung disorders. In the last few decades, major technological advances in different disciplines, particularly respiratory medicine, radiology, pathology and thoracic surgery, have contributed to the elucidation of crucial key points in the pathogenesis of diffuse lung diseases, such as idiopathic pulmonary fibrosis and sarcoidosis. Certainly, high-resolution computed tomography of the chest has significantly contributed to these important achievements: the unexpectedly high level of detail of its images has allowed chest physicians to create the ideal link between the patients seen in daily clinical practice and the granulomas or fibroblastic foci seen under the pathologist’s microscope. In this book, this ideal link becomes concrete and the authors have been able to simplify the fundamental pathways from clinic to pathology. This has been done through the unprecedented and meticulous classification of a few simple radiological patterns, followed by the pathological “evidence” of the disease.

Overall, this is a well-written and referenced book, thoroughly illustrated, and easy to read and consult. The inclusion of comprehensive images, graphs, tables and references, and the detailed discussions of different patterns of disease presentation make this book an invaluable tool for the training of post-graduate students and scientists in the difficult field of diffuse interstitial disorders of the lung. Also, these characteristics make this book extremely valuable to the doctors and healthcare professionals who have decided to make education and research an integral part of the treatment process of their patients.

This book is now published in English. As an Italian chest physician, I am proud that such a prestigious book, edited entirely by Italian specialists, will now have the opportunity to cross borders, and I hope that it will reach many English-speaking healthcare professionals. I’m certain that this will contribute to the growth of the already established interdisciplinary and international network dedicated to the study of the diffuse interstitial disorders of the lung.

Leonardo M. Fabbri, M.D.
Professor of Respiratory Medicine
University of Modena and Reggio Emilia, Modena, Italy

Foreword

The future of medical textbooks appears to have finely arrived with the publication of "Diffuse Lung Diseases" edited by Drs. Maffessanti and Dalpiaz, with contributions from a stellar cast of experts in the field. This diagnostic medical textbook utilizes a simplified pattern-based approach to high-resolution computed tomographic scan findings, as well as lung pathology, and joins a limited offering of such works in the medical literature. Dr. A. Bernard Ackerman whose textbook on the histopathology of inflammatory skin disease revolutionized the field in his day would be proud. I am especially impressed that the authors were able to limit their initial number of patterns, a very difficult challenge and one that makes this work truly usable.

Few busy medical practitioners have the available time to read a book from beginning to end. This constraint does not reduce the critical need for "real-time" authoritative information regarding complex combinations of diagnostic findings as encountered in day-to-day practice. The time has come for experts in the field to find ways to distill their knowledge into a user friendly format for "just in time" continued medical education at the bedside, at the CT monitor, and at the microscope. I applaud the efforts of these authors and commend them on their execution and the quality of their final product.

Kevin O. Leslie, M.D.
Consultant and Professor of Pathology
Department of Pathology and Laboratory Medicine
Mayo Clinic Scottsdale
Arizona, USA

Would you set off on a car journey…

Would you set off on a car journey without first having filled up with gas? Would you travel around the South of France without a roadmap? Would you head off for Ireland without first finding out about its history? Would you go trekking in Nepal without first finding out who your traveling companions were? Would you take part in a tour of India without knowing what you were to see and the difficulties you would face?

How this book came about

The idea for this book came about some time ago at Corvara (Italy, in the Alps). Lorenzo Bonomo had decided to organize Radiology courses in the snowfields according to the undeniable principle "mens sana in corpore sano", entitling them "High Altitude Radiology". Each day was devoted to an organ and that year was dedicated to the diffuse diseases. We were responsible for the chest and we had organized our lessons in an entirely interdisciplinary fashion, because either diffuse infiltrative lung diseases are treated in this way, or not much is understandable.

Who are the authors

From the idea to its realization, the development of the volume was not easy. We began with a clinician, a pathologist and four radiologists. With time someone was lost along the way and someone new came on board, as often happens on any long journey.

What has remained unaltered, however, is the distribution of effort and it can be seen here in each chapter. We trust we have done a good job - the commitment has been enormous.

Who are the intended readers

Given the spectrum of diseases covered, a wide variety of healthcare workers may benefit from reading this volume, and not only in the specialist fields of pneumology, pathology and radiology, but perhaps even more so in the broad and complex field of general medicine. Often it is here that the patient is first examined before seeing the specialist and so there is even greater need for this kind of book.

Some diseases have links with oncology, pediatrics, hematology, infectious diseases, intensive care, occupational medicine and thoracic surgery.

It has been our intention to provide a thorough and well structured guide, which can be used easily in clinical practice. We have tried to present it in a complete but accessible manner even for a not strictly specialist audience. Understanding this motivation, the experts of the field will undoubtedly forgive us for the simplifications which proved necessary.

Why use the book as a work tool

Readers with little experience in diffuse infiltrative lung diseases or who feel uncomfortable in trying to grasp their multiplicities may approach them using CT like Arianna's thread with the key patterns.

Those who are already experts, but wish to broaden their understanding of the individual diseases may do so directly, remembering that they are listed in alphabetical order and grouped on the basis of their prevalent pattern.

We wanted the book to be interdisciplinary, so the contributions of the various specialists have been tightly interwoven throughout the book.

Some diseases appear in the index more than once for two reasons.

The first reason is that an identical cause (e.g. sarcoidosis, a drug) can manifest in the lung with different pathological and therefore radiological patterns.

The second reason is that the same disease (e.g. pulmonary edema, idiopathic pulmonary fibrosis) can change in appearance during its natural course. In both cases the clinical, functional and bronchological data can also change, and therefore such diseases deserve to be treated as separate entities.

What are its limitations

A volume such as this cannot exhaustively cover such a broad range of diseases in little over 200 pages. For this purpose there are reference books, which nonetheless have the drawback of being cumbersome.

Limiting ourselves to the field of Radiology we feel it is only right to mention the work of W. Richard Webb, which has not been cited in this book merely because we would have had to cite it continuously. The same could easily be said for other clinical and pathology texts.

There are chapters of pathology (e.g. on drug toxicity or collagen vascular diseases) which are so extensive that a complete coverage would require a whole book in itself. The choice was therefore made to limit the description to a single entity, either because it is the most common or is considered paradigmatic. If this book is successful, these parts would certainly deserve to be covered more thoroughly.

Finding your way around the book

Begin with the patient's CT, note the prevailing pattern and compare it with the images in the chapter "Key pattern – quick reference". Then check how the lesions are distributed and verify the presence of associated signs using the tables accompanying the images. In this way you can deduce the possible diagnoses and read the description in the appropriate chapter.

The book uses various symbols to facilitate orientation; their meaning is summarized on the inside flap of the front cover.

With reference to the images, we have used symbols inserted directly in the text so as not to overburden it with legends which would prove repetitive.

The bibliographic references have been also included in the context of the topic to which they refer, so as to avoid the need to chase them up at the end of the chapter. For practical purposes only the first author is cited (although often there are others who are no less important)

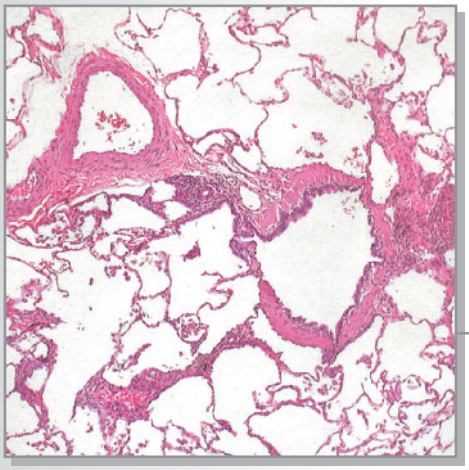
Readers of this book should not think that things are (always) so easy or that learning the four tables of the inside cover by heart is enough to master such a complex and varied field.

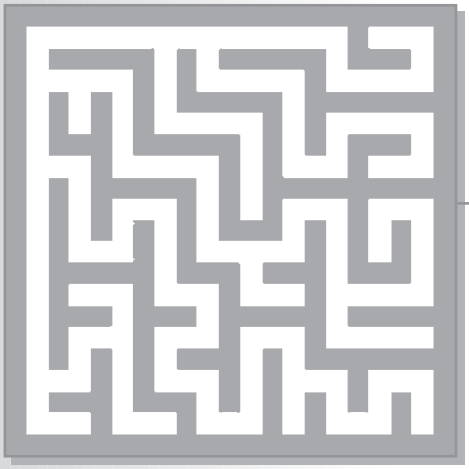
The appealing presentation of the topics, the simplified algorithms and the multidisciplinary approach, however, will be useful for approaching this complexity in an orderly manner and acquiring the basis for a better understanding.

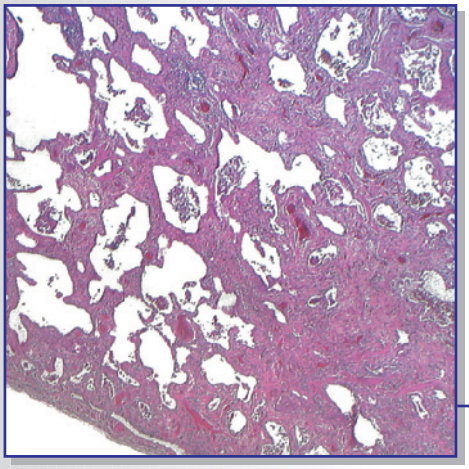
To whom the book is dedicated

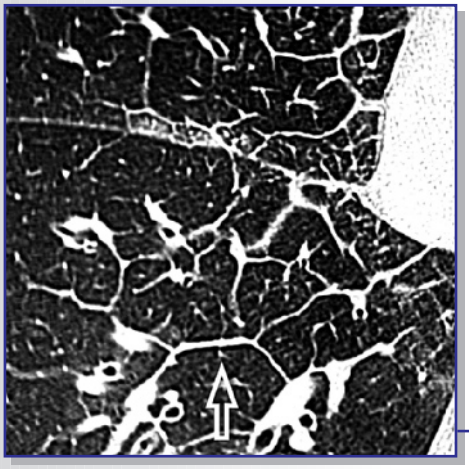
We would like to dedicate this book to Lorenzo Bonomo, not only due to his "High Altitude Radiology" courses which constituted the prime motive for it, or because he is the first author of a volume which for years was the only Italian work dedicated to high-resolution CT of the chest, but also because among his courses at Chieti, Italy, he proposed high-resolution CT of the chest in such an appealing and effective manner enjoyed by all and greatly contributed to the broadening of interest in the field throughout the country.

Mario Maffessanti & Giorgio Dalpiaz

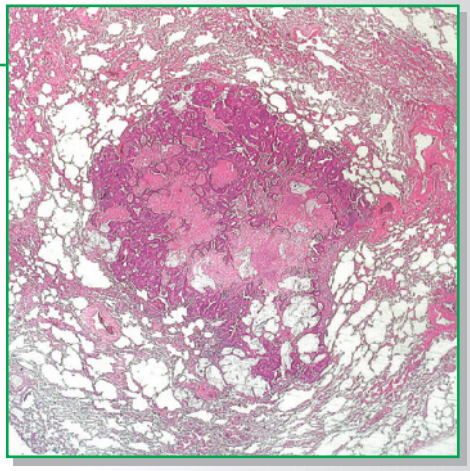


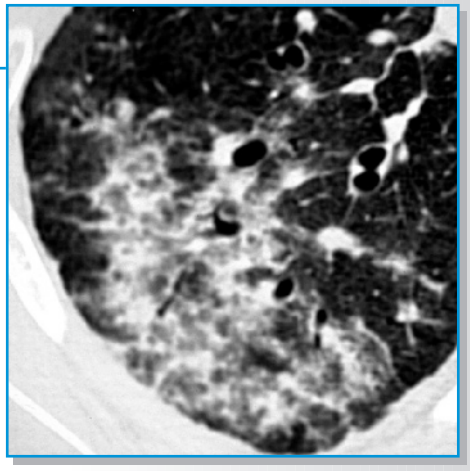


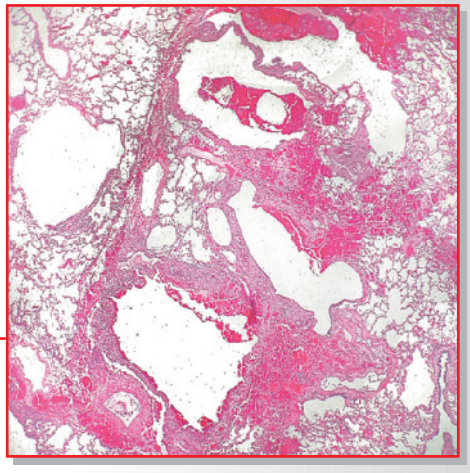




Contents







Anatomy

Pathology	**Alessandra Cancellieri**
Radiology	**Mario Maffessanti**

Anatomy

Definition

The anatomical organization of the lungs consists of the bronchovascular bundles and the secondary lobules

The bronchovascular bundles are made up of the main bronchi, the pulmonary vessels and the interstitial framework around them (central interstitium)

The secondary lobules are the peripheral units of parenchyma where the airways meet the capillaries within the interstitial framework supporting them (peripheral interstitium)

Weibel ER. Fleischner Lecture. Looking into the lung: what can it tell us? AJR Am J Roentgenol 1979, 133: 1021

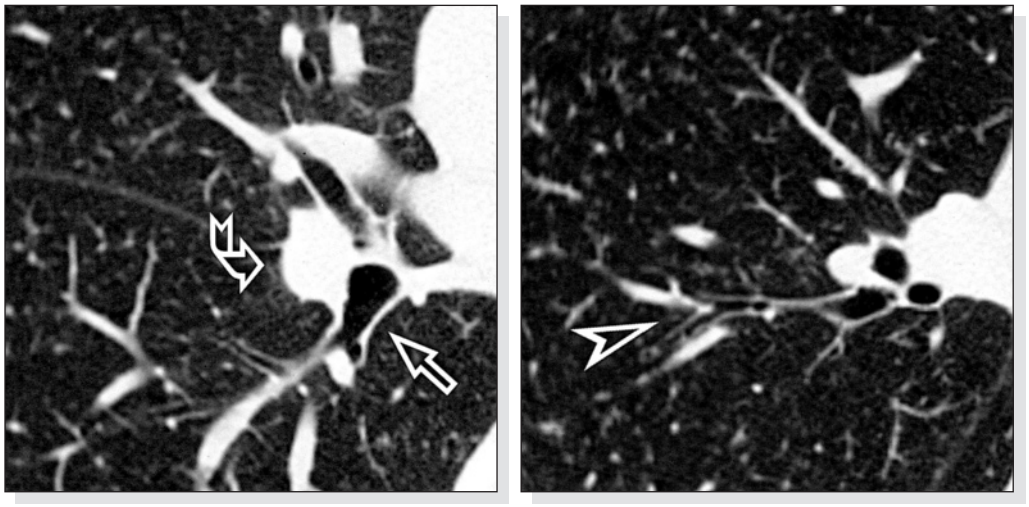
Weibel ER. Structural organization of the pulmonary interstitium. In: The Lung, vol 1, Raven Press, 1991

BRONCHOVASCULAR BUNDLES

Bronchi and arteries

The bronchovascular bundles are therefore made up of the bronchi (⇨), the main arteries (↳) and the surrounding connective tissue (peribronchovascular interstitium) and extend from the hilar-parahilar regions (main arteries and bronchi) to the most peripheral prelobular branches. These structures become narrower at each dichotomous branching (➢)

The vessels and bronchi are usually readily identified on high-resolution computed tomography (HRCT)



Lung pattern

The inhaled air is transported from the trachea to the alveoli through various generations of bronchi and bronchioles, from the hilum to the peripheral regions: these are the airways

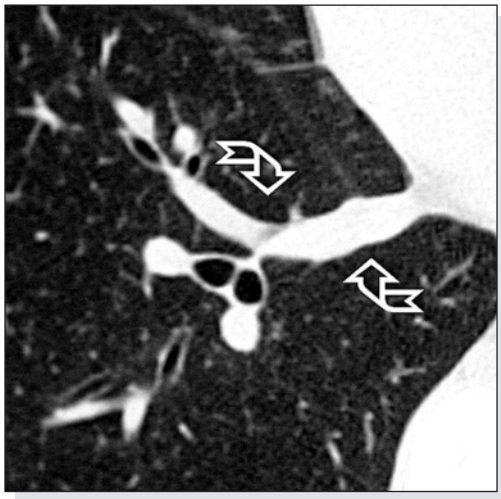
The bronchial walls, which are rich in cartilage at their origin, are composed entirely of muscular tissue at their distal ends (terminal bronchioles)

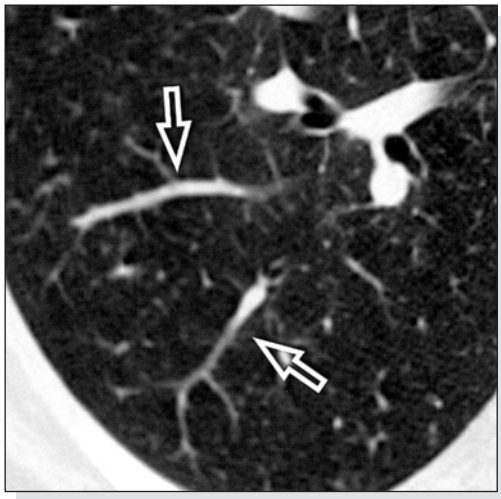
✓ On CT, the arteries imaged along their main axis have the appearance of branching linear opacities which progressively taper as they approach the periphery. The bronchi imaged in the same plane appear as finer linear opacities running parallel to the arteries (“railway track” appearance)

In transverse sections the arteries have the appearance of opaque white circles, and are often closely associated with a fine ring of the same color representing the wall of the accompanying bronchus

Veins

The pulmonary veins, which also make up part of the lung pattern, have in contrast a distinct course, as they flow into the left atrium below the arterial hilum (↳); the smaller branches flow into the main collecting vessels in a monopodial fashion (⇨)

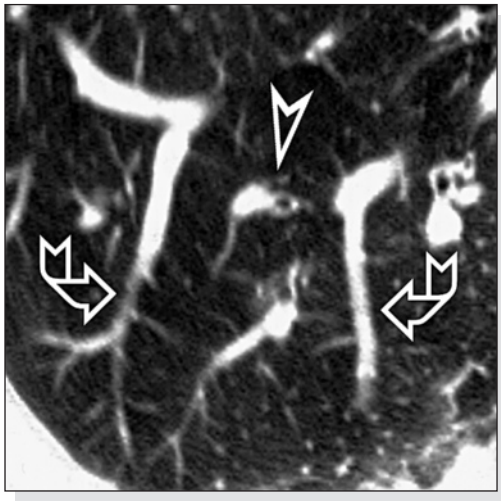


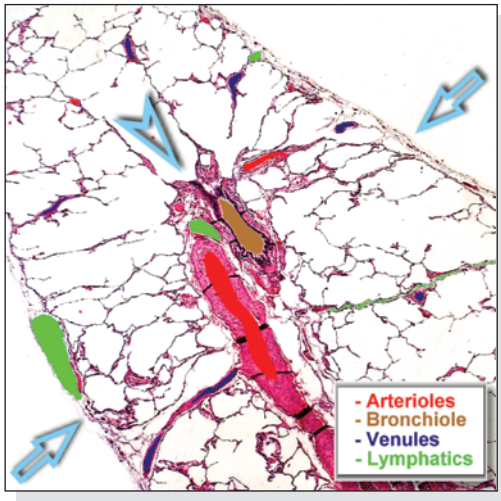


SECONDARY LOBULE

Definition

The secondary lobule can be thought of as a polyhedral structure up to about 2 cm in size. On CT, its architecture, which consists of a central lobule (⩥) and perilobular veins (↳), can be best identified peripherally, in the subpleural regions of the lung (⇨)

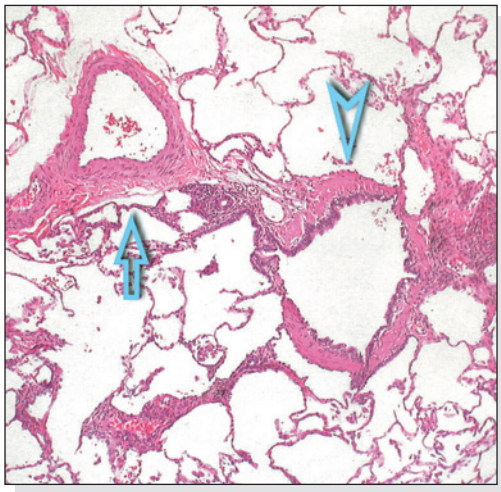


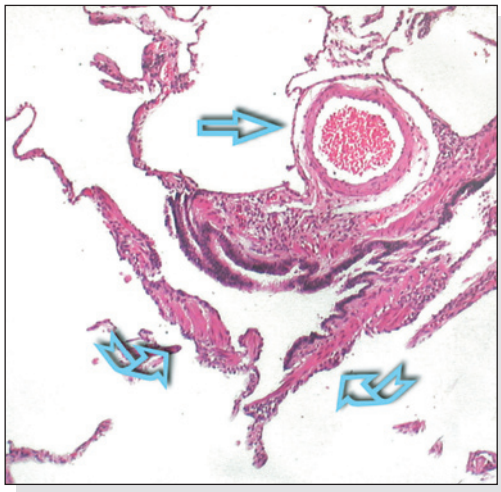


Colby TV. Anatomic distribution and histopathologic patterns in diffuse lung disease: correlation with HRCT. J Thorac Imaging 1996, 11: 1

Centrilobular interstitium

The most peripheral branches of the central interstitium, that is, the centrilobular arterioles (⇨) and the bronchioles (➢) enter the central portion of the secondary lobule (core). Emerging from the centrilobular bronchioles are 3-5 terminal bronchioles, the most distal branches with muscular walls (↳), which are tributaries of the sublobular units of parenchyma known as acini





Bergin C. The secondary pulmonary lobule: normal and abnormal CT appearances. AJR Am J Roentgenol 1988, 151: 21

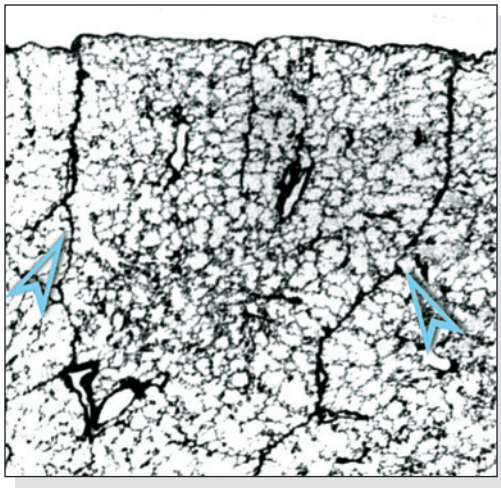
✓ The centrilobular arteriole is often visible on CT at the centre of the lobule, whereas the bronchiole is not, since the thickness of its walls (0.1 mm) is below the resolution power of the scanners

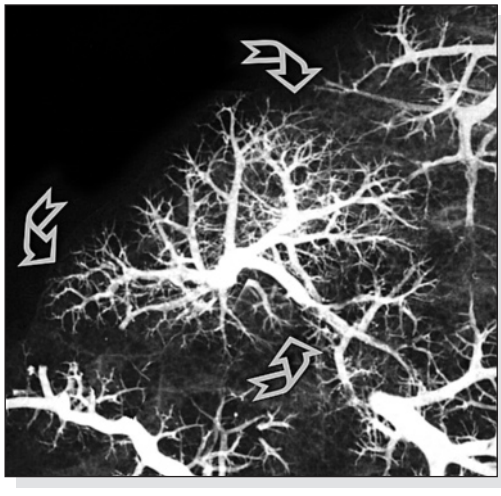
Webb WR. Normal and diseased isolated lungs: high-resolution CT. Radiology 1988, 166: 81

The structure of the terminal bronchiole plays an important part in the development of many diseases, owing to its diameter, the absence of cilia and of mucous-secreting cells, and its muscular walls. Its diameter is such that particles between 0.5 and 5 microns tend to accumulate on the walls, the absence of cilia and mucous renders their elimination difficult, while the muscular component makes the terminal bronchiole the preferential site for bronchospasm and air-trapping. The distal structures which suffer are the acini, and once again the unit comprising them, the secondary lobule

Intralobular interstitium

Within the lobule (➢), a fine stromal network of intralobular septa make up the framework of the acini, and more specifically, of the anatomical units responsible for gas exchange: respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. The intralobular septa contain the arterioles (↳) and small venules as well as the capillary network. Lymphatics are found throughout the lobule, both centrally and peripherally

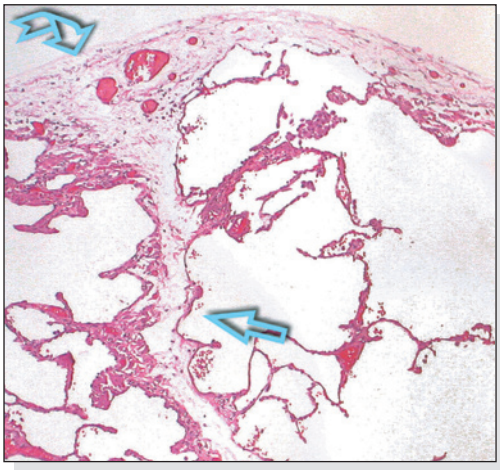


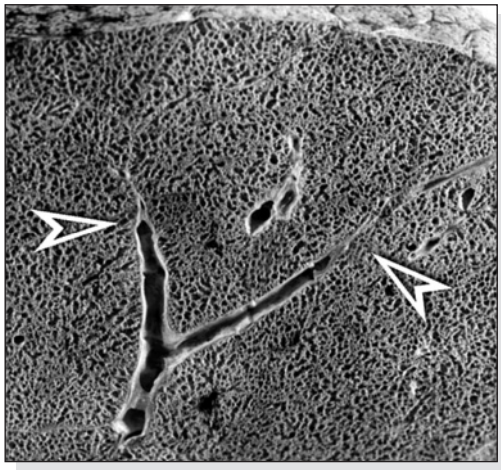


Under normal conditions, the intralobular interstitium is only partly visible on CT: the most peripheral millimeters of the subpleural lung are homogeneously lucent (black). An important consequence of this is that if branching lucencies or opacities are identified in the peripheral subpleural lung, they are likely to be pathological, and are often due to bronchiolar dilatation, either empty or filled with mucous

Perilobular interstitium

The perilobular interstitium (⇨) surrounds and delimits the lobules. At the peripheral regions of the lobule, the interlobular septa are arranged more or less regularly, parallel to each other and perpendicular to the pleural surface (↳). Within the interlobular septa are lymphatic ducts and perilobular venules (➢) which are identifiable radiologically, making them a reliable anatomical landmark



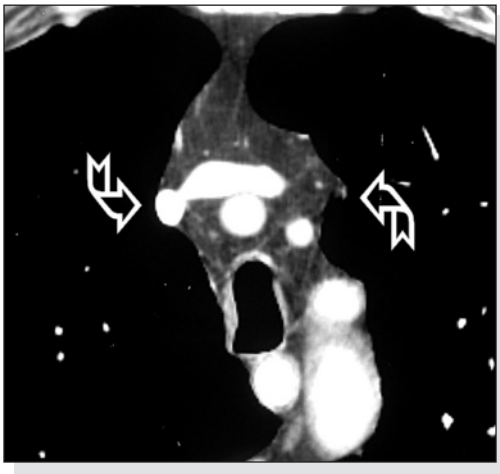


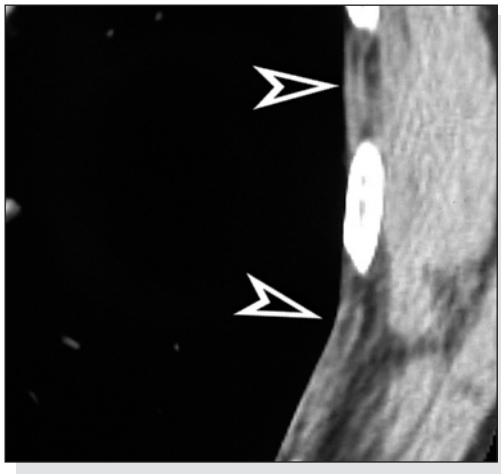
The concept of the secondary lobule and its importance in interpreting various conditions dates back to long before the advent of HRCT, a technique which merely facilitated its identification even under normal conditions. The radiological identification of the secondary lobule came about thanks to ER Heitzman as early as 1969, who developed our understanding of the crucial role of this anatomical structure in his work “The Lung” published in 1973 - about fifteen years before the development of HRCT!

PLEURAL-PARENCHYMAL INTERFACE

Pleura and subpleural space

The pleural-parenchymal interface is the boundary which separates the pulmonary lucency (black) from the mediastinal fat (at the centre) and the subpleural space (towards the ribcage). It is generally smooth, although the border around the mediastinum may be gently undulating, owing to the dips and projections formed by the structures occupying it (↳). The subpleural space is for the most part made up of a varying quantity of fat (in part depending on the subject’s build), although under normal conditions it is barely recognizable (➢) except for being a little more evident in the costophrenic angles. Occasionally, vascular elements can be identified in the subpleural space





Key Pattern

The morning sun shimmered on the bronze sword
Now there was not a trace of blood left on it
"Can you believe it, Ariadne?" said Theseus. "The Minotaur scarcely defended itself"

JL Borges, The House of Asterion

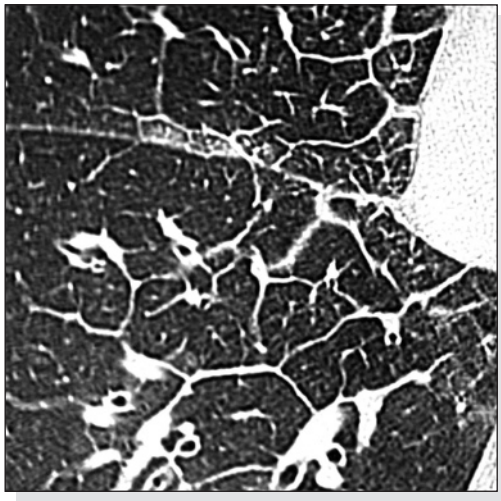
RETICULAR PATTERN

Definition

The main finding consists of thin interlacing linear opacities creating a more-or-less tight mesh

This finding is produced by a thickening of the structures of the lobular interstitium, and often of the central interstitium as well

The interstitial thickening may be due to a variety of causes (fluid accumulation, amyloid deposits, cellular infiltration, fibrosis) and the pattern may vary accordingly. The distribution of the lesions and other associated signs are often useful for diagnosis



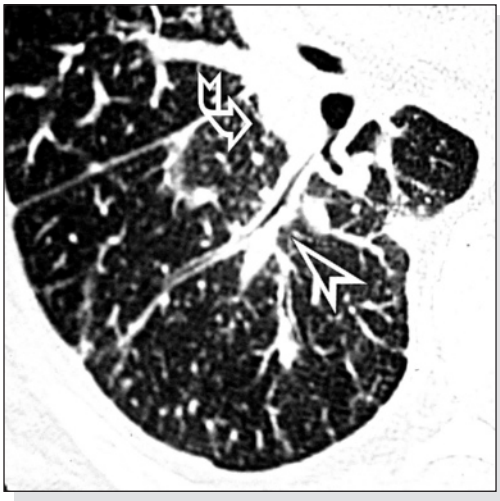
As well as in reticular diseases, in which this pattern is dominant, there are other diseases in which reticulation may be found, albeit less important or sporadic. They are therefore described in the relevant chapter: ● RB-ILD; ● Large rounded opacities: High-grade primary lymphoma; ⌘ AIP; ⌘ ARDS; ⌘ BAC; ⌘ CEP; ⌘ DIP; ⌘ Drug toxicity; ⌘ MALToma; ⌘ PAP; ⌘ PCP; ⌘ PE, alveolar; ○ Asbestosis, advanced; ○ Collagen vascular diseases, advanced; ○ UIP, advanced

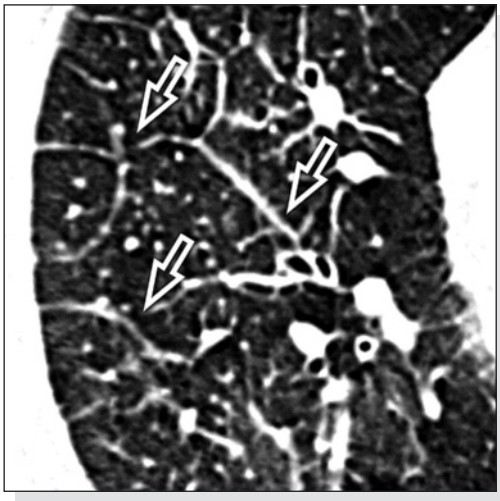
Smooth

Definition

Centrally, the alteration is characterized by a uniform thickening of the bronchial walls (➢) and an increase in the diameter of the adjacent vessels (↳). Peripherally, the thickening of the interstitium appears as an exaggeration of the interstitial borders (⇨) and by a fine reticulation crossing them. In the centrilobular region the arteriole is more prominent and the bronchiolar walls, normally not evident in CT, are visible

Interstitial thickening may be caused by edema, organic substances or cellular infiltration. The lobular architecture is preserved, only is more recognizable than in the normal lung, at times with an exaggerated appearance





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Often unilateral, patchy	Variable	Variable	Well-defined nodules, hilar and mediastinal adenopathies, unilateral pleural effusion	**LC**
Bilateral, diffuse	Peribroncho-vascular, gravity-dependent	Middle and lower zones	Acinar-sized, ill-defined nodules, patchy ground-glass and consolidations, cardiomegaly, bilateral pleural effusion	**PE, interstitial**
Bilateral, patchy	Peripheral	Basal	Calcificed micronodules, consolidations, mediastinal adenopathies, tracheal thickening	**Amyloidosis, interstitial**

Nodular

Definition

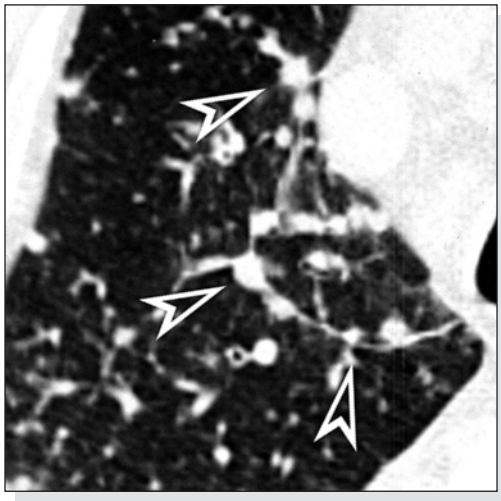
Thickening of the central and/or peripheral interstitium with associated micronodules (≫)

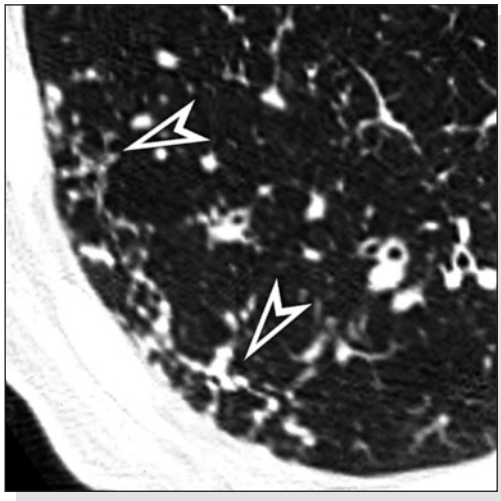
If the interstitium is thickened simply because of a focal accumulation of cells or substance, the architecture of the lobule is preserved

Beaded appearance

If the interstitium is thickened because of fibrosis and the nodular elements are due to focal fibrosis, the architecture of the lobule may be distorted

Dotlike opacities





From pattern to disease

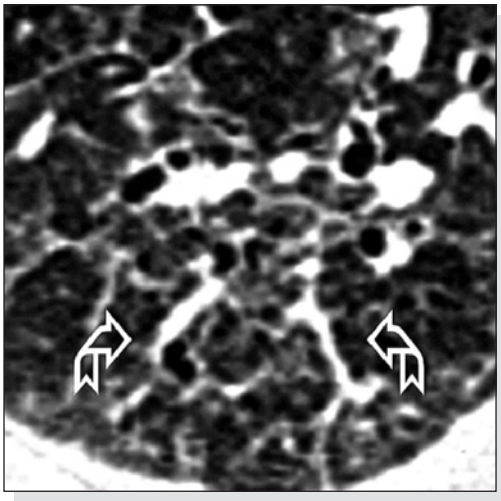
Distribution	◆▶	▲▼	Associated signs	DISEASE
Often unilateral, patchy	Variable	Variable	Smooth reticular pattern, hilar and mediastinal adenopathies, unilateral pleural effusion	**LC**
Bilateral, patchy	Peripheral	Basal	Calcified micronodules, consolidations, mediastinal adenopathies, tracheal thickening	**Amyloidosis, interstitial**
Bilateral, diffuse or patchy	Peripheral, dorsal	Basal	Subpleural dotlike opacities, irregular intralobular reticulation, subpleural lines, parenchymal bands, pleural plaques	**Asbestosis, early**

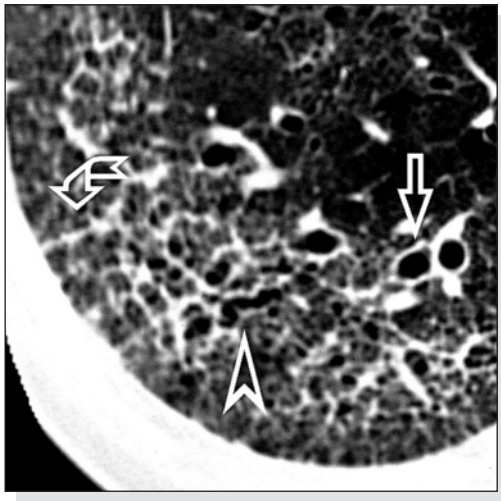
Irregular

Definition

The interstitium presents various degrees of thickening along the lobular margins (↳) and peribroncho-vascular bundles (⇨). The interstitial structures show an irregular course with a zigzag conformation which distorts their architecture and renders it increasingly unrecognizable

This pattern is characteristic of the fibrosing diseases, as fibrosis accounts for the distortion of the lobular anatomy. An irregularly thickened intralobular network is often seen together with the loss of the separation between lobules. The pattern is also accompanied by traction bronchiectasis and bronchiolectasis (➢), with vessels and bronchi following an irregular, corkscrew-like path





From pattern to disease

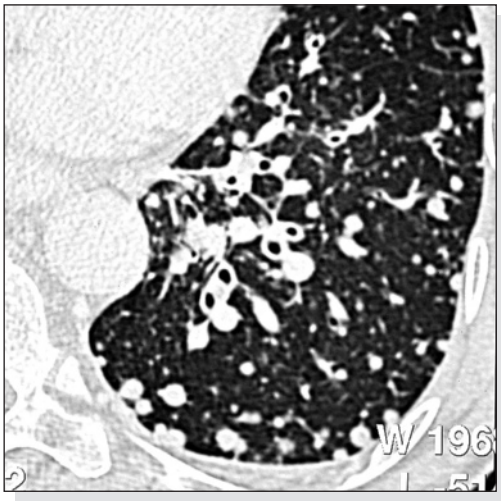
Distribution	◆▸	▲▼	Associated signs	DISEASE
Bilateral, patchy	Central, especially dorsal	Upper zones	Parahilar conglomerations with traction bronchiectasis, perilymphatic nodules, hilar-mediastinal adenopathies	**Sarcoidosis, fibrosing**
Bilateral, patchy	Subpleural, but also peribroncho-vascular	Variable	Interface sign, traction bronchiectasis, ground-glass and ill-defined centrilobular nodules, mosaic oligemia with air-trapping	**HP, chronic**
Bilateral, patchy	Variable	Variable	Ground-glass, consolidations with air-bronchogram, possible honeycombing	**Drug toxicity**
Bilateral, diffuse	Peripheral, subpleural, dorsal	Basal	Ground-glass and consolidations with traction bronchiolectasis, specific signs of each disease	**Collagen vascular diseases, early**
Bilateral, uniform or patchy	Peripheral, but also dorsal	Basal	Ground-glass and consolidations with bronchiolectasis, bronchial walls thickening, rare honeycombing	**NSIP**
Bilateral, patchy in normal parenchyma	Typically subpleural, especially dorsal	Basal, but also peripherally up to the upper regions	Sporadic ground-glass, early honeycombing, moderate mediastinal adenopathies	**UIP, early**
Bilateral, diffuse or patchy	Peripheral, dorsal	Basal	Subpleural dotlike opacities, irregular intralobular reticular pattern, subpleural lines, parenchymal bands, pleural plaques	**Asbestosis, early**

NODULAR PATTERN

Definition

The main alteration consists of small rounded opacities (micronodules if the diameter is less than 3 mm, macronodules if between 3 mm and 1 cm) which tend to be localized in definite positions within the secondary lobule and in relation to the pleural surface

The nodular pattern may be due to a variety of granulomatous diseases arising directly in the lung or arriving via the bloodstream down to small vessels where they develop concentrically, or via the bronchi, for example, when a reaction to an inhaled substance develops in a small bronchus and the adjacent area



☝ In the nodular diseases, this pattern is dominant; however there are other diseases in which nodules may be found, albeit less important or sporadic. They are therefore described in the relevant chapter: ☐ Amyloidosis, interstitial; ☐ Collagen vascular diseases, early; ☐HP, chronic; ☐ LC; ☐ Sarcoidosis, fibrosing; ⌘ BAC; ⌘ CEP; ⌘ HP, acute; ⌘ Infections, endobronchial; ⌘ MALToma; ⌘ OP; ⌘ PCP; ○ LCH, advanced

✓ Multiple round lesions larger than 1 cm are not classified in the nodular pattern as they size is no longer comparable to the size of the lobule. Such lesions are nonetheless covered at the end of the Nodular Diseases section under the heading: ● Large rounded opacities

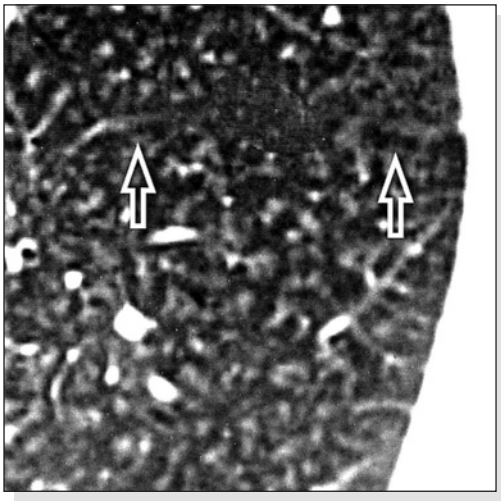
Centrilobular

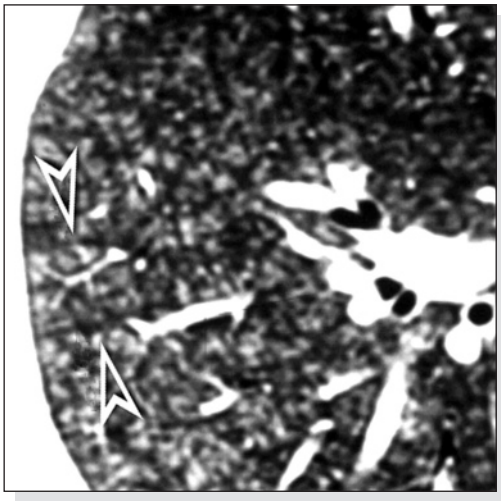
Definition

The nodules tend to be centered at a certain distance from the pleural surface (⇨) and at times also from the interlobular septa (➢). As a consequence they are separated from the lobular margins, the costal margins and the fissures by a transparent rim

Centrilobular distribution is more typical of diseases in which the elementary lesions originate from or near the peripheral bronchioles

When the adjacent peribronchiolar airspaces are involved, the nodules tend to present low density and ill-defined borders (nodular ground-glass)





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral, patchy	Uniform distribution	Upper and middle zones	Patchy ground-glass, centrilobular emphysema, bronchial wall thickening, intralobular reticular pattern (rare)	**RB-ILD**
Bilateral, diffuse	Uniform distribution	Upper and middle zones	Well-defined, high density nodules possibly cavitated sparing the costophrenic angles, air-trapping	**LCH, early**
Diffuse, uniform	Uniform distribution	Possible middle and lower predominance	Dense well-defined perilymphatic nodules, ground-glass, nodular reticulation, thin-walled cysts, adenopathies in AIDS	**LIP**
Diffuse or patchy	Uniform distribution	Possible middle and lower predominance	Patchy ground-glass, at times mixed with areas of lobular air-trapping (head-cheese pattern)	**HP, subacute**

Random

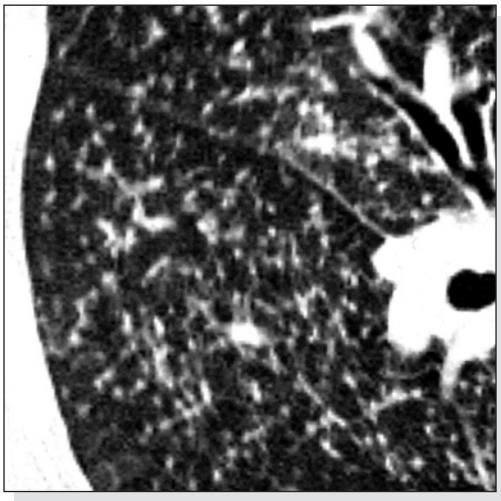
Definition

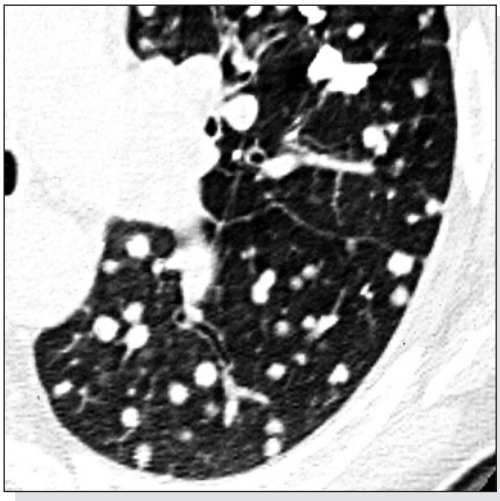
These nodules are often of a good density with sharp borders mainly because they are confined to the interstitium

Their distribution is reasonably uniform in the secondary lobule and the parenchyma

At times they can be seen in contact with the extremities of the vascular structures, from which they appear to originate (feeding vessel sign), and their origin is often hematogenous

However, they can also be found near the pleural surface, but this is not the rule. In short, their spatial distribution appears uniform





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral, some right-sided prevalence	Tendency to predominate posteriorly	Prevalence in middle and upper zones	Pseudoplaques, "egg-shell" mediastinal adenopathy, larger opacities and conglomerated parahilar masses	**Silicosis**
Bilateral, symmetrical	Uniform distribution	Uniform distribution	Diffuse or localized ground-glass, mediastinal adenopathies with central hypodensities, possible tree-in-bud	**TB, miliary**
Bilateral, often symmetrical	Possible subpleural	Especially basal	Nodules of different size, possibily cavitated or calcified, feeding vessel sign, mediastinal adenopathies	**Metastases**

Perilymphatic

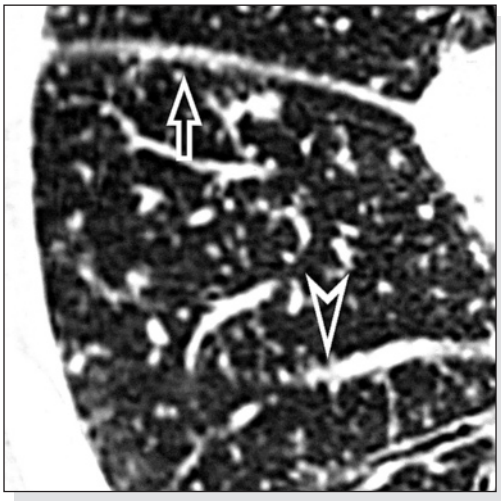
Definition

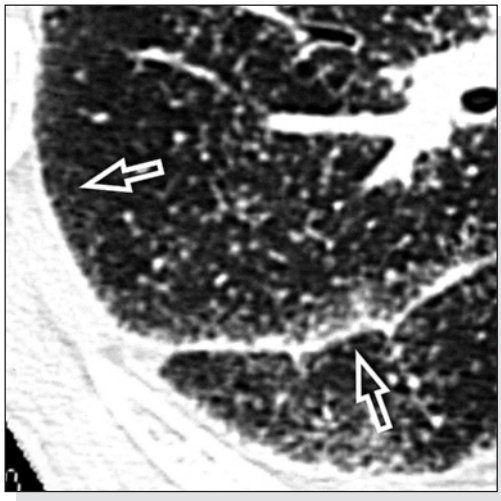
These nodules tend to be prevalent in the perilobular and subpleural interstitium (⇨) and are therefore profuse along the costal margins and the fissures

They are more common in diseases which spread along the lymphatics, and may therefore be found within the lobule, but also along the vessels (➢) and bronchi (beaded appearance)

The nodules have well-defined margins as well as high and uniform opacity

The spatial arrangement of the lesions tends to be patchy, interspersed with areas of normal parenchyma





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral, patchy	Perihilar regions, mainly dorsal and subpleural	Middle and upper predominance	Bronchovascular nodules, pseudoplaques, hilar and mediastinal adenopathies, micronodular ground-glass, lobular air-trapping	**Sarcoidosis, granulomatous**
Diffuse, uniform	Uniformly distributed	Possible predominance in middle and lower zones	Centrilobular ground-glass, nodular reticulation, thin-walled cysts, adenopathies in AIDS	**LIP**

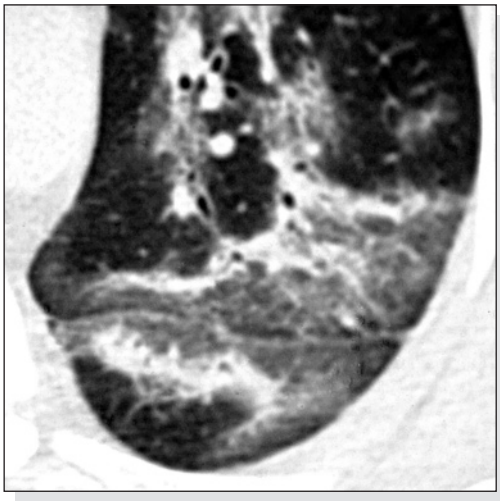
ALVEOLAR PATTERN

Definition

The main finding consists of opacities resulting from alveolar filling

Their density varies in proportion to the extent of this filling, from partial (ground-glass) to complete (consolidation)

Involvement of the small airways may either take the form of luminal narrowing (indirect signs of which are hypodensities of the distal parenchyma due to regional oligemia), or filling by various materials (in which case they become ectatic and their opacity can stand out against the surrounding lung parenchyma)



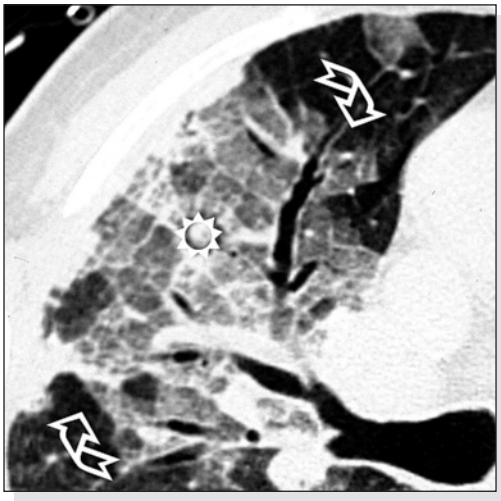
In the alveolar diseases, this pattern is dominant; however, there are other diseases in which alveolar opacities may be found, albeit less important or sporadic. They are therefore described in the relevant chapter: ☐ Amyloidosis, interstitial; ☐ Asbestosis, early; ☐ Collagen vascular diseases, early; ☐ Drug toxicity; ☐ HP, chronic; ☐ NSIP; ☐ PE, interstitial; ☐ UIP, early; ● HP, subacute; ● LCH, early; ● RB-ILD; ● Sarcoidosis, granulomatous; ● TB, miliary; ● Large rounded opacities: Aspergillosis; BAC; High-grade primary lymphoma; Kaposi's sarcoma; OP; Septic emboli; Tuberculomas; Wegener's granulomatosis; ○ Bronchiectasis, cystic; ○ CF; ○ Collagen vascular diseases, advanced; ○ LAM; ○ LCH, advanced; ○ UIP, advanced

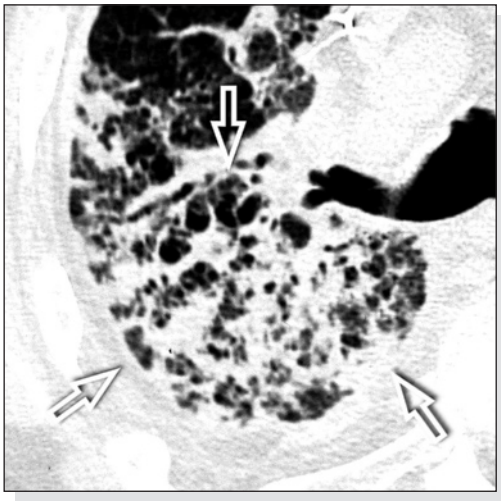
Mixed-density, acute

Definition

This pattern is recognizable by the presence of the two characteristic findings of the alveolar diseases, ground-glass (↬) and consolidation (⇨), combined in varying proportions. The ground-glass may be accompanied by a reticular pattern (☼)(crazy paving). The simultaneous finding of bronchial involvement (bronchial wall thickening, bronchiectasis) and ill-defined centrilobular nodules due to alveolar filling is not uncommon

The acute form usually presents with bilateral and often extensive consolidations which may change in appearance, location, and size within hours or days





From pattern to disease

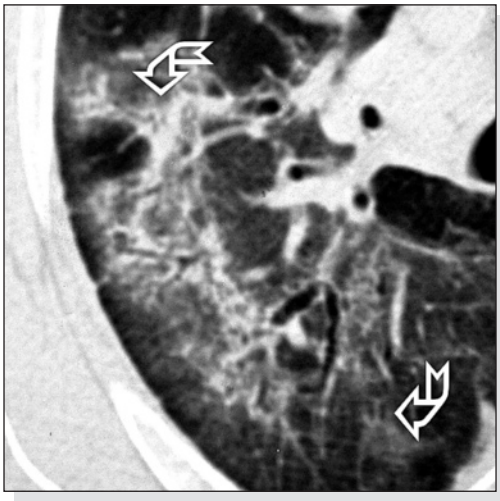
Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral symmetrical, patchy or diffuse	Often parahilar	Middle and upper zones	Walled cysts, crazy paving, hazy micronodules, mediastinal adenopathies, pleural effusion	PCP
Bilateral, diffuse or patchy	Parahilar or diffuse, not peripheral	Variable	Wegener: hazy centrilobular nodules, crazy paving, large cavitating nodules and mediastinal findings	DAH
Bilateral symmetrical, diffuse or patchy	Usually peripheral, gravity-dependent	Variable	Reticular pattern, parenchymal distortion, traction bronchiectasis, sporadic honeycombing	AIP
Bilateral, patchy, occasionally uniform	Uniform	Variable, most often basal	Hazy centrilobular nodules, mediastinal adenopathies, mosaic oligemia with air-trapping	HP, acute
Bilateral symmetrical, patchy	Prevalence in dependent lung	More extensive at the lung bases	Asymmetrical and less gravity-dependent if pulmonary ARDS. Crazy paving, minor pleural effusions	ARDS
Bilateral symmetrical, diffuse or patchy	Subpleural, gravity-dependent	Basal prevalence	Redistribution of pulmonary perfusion, smooth reticular pattern, pleural effusion, cardiomegaly	PE, alveolar

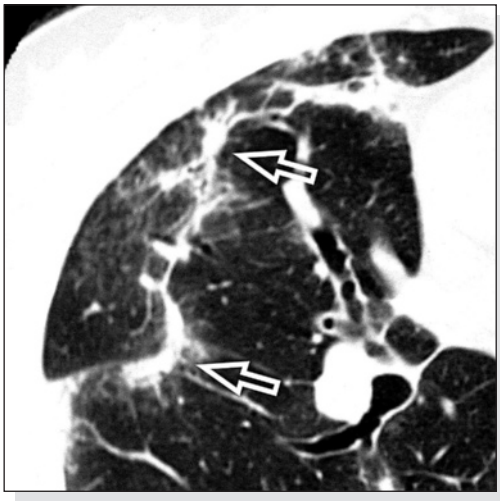
Mixed-density, chronic

Definition

This pattern is recognizable by the presence of the two characteristic findings of the alveolar diseases, ground-glass (↳) and consolidation (⇨), combined in varying proportions. The ground-glass may be accompanied by a reticular pattern (☼)(crazy paving). The simultaneous finding of bronchial involvement (bronchial wall thickening, bronchiectasis) and ill-defined centrilobular nodules due to alveolar filling is not uncommon

The chronic form usually presents with consolidations often localized and patchy which progress slowly, even over weeks or months





From pattern to disease

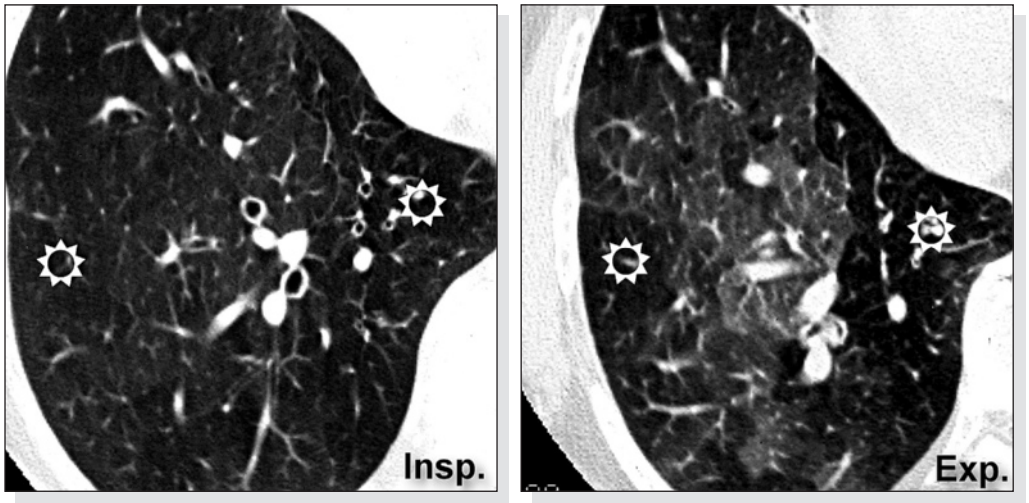
Distribution	◆▸	▲▼	Associated signs	DISEASE
Bilateral, patchy	Peripheral and subpleural	Middle and upper zones	Ill-defined nodules, mediastinal adenopathies, rarely pleural effusion	CEP
Bilateral or unilateral, diffuse or patchy	Peribronchial	Variable	Bronchi stretched and thinned within the consolidations; centrilobular nodules, small or large masses, halo sign	MALToma
Bilateral, diffuse or patchy	Variable	Variable	Predominant ground-glass, extensive crazy paving, sharp interfaces with the healthy parenchyma	PAP
Uni or bilateral, asymmetrical, patchy	Often peripheral and subpleural	Often basal	Possible pseudocavitations, nodules and hazy ground glass, crazy paving, adenopathies, pleural effusion	BAC
Bilateral symmetrical, patchy	Subpleural but also diffuse	Prevalently basal	Ground-glass predominant, limited parenchymal distortion with traction bronchiolectasis, microcysts	DIP
Bilateral, patchy	Peripheral but also peribronchial	Basal	Air bronchogram and bronchiolectasis within the opacities, centrilobular nodules with ill-defined margins, macronodules or masses	OP
Bilateral symmetrical, patchy	Peripheral	Basal	Amiodarone: hyperdense consolidations (compared to the muscles), reticular pattern and micronodules, pleural thickening	Drug toxicity

Mosaic oligemia with air-trapping

Definition

The main characteristics of this pattern are areas of patchy hyperlucency (☼), often with lobular distribution, associated with vessels reduced in number and diameter. This pattern is a typical expression of small airways obstruction. The oligemia is due to hypoxic vasoconstriction secondary to alveolar hypoventilation. The surrounding normal parenchyma appears "relatively" hyperdense partially because of hyperperfusion (pseudo-ground-glass). While oligemia from vascular obstruction (e.g. in patients with chronic pulmonary thromboembolism) does not change during expiration, hypoxic oligemia accentuates (air-trapping)

☯ Mosaic perfusion



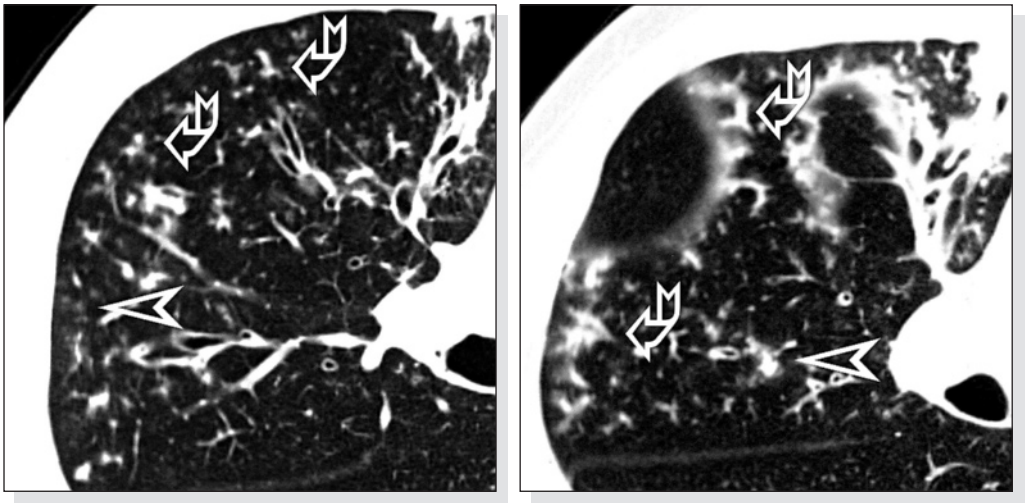
From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral asymmetrical, patchy	Variable	Variable	Direct signs of airway disease (bronchiectasis), pseudo-ground-glass in the normally ventilated areas	CB

Tree-in-bud

Definition

This pattern is identified by the presence of thin branching opacities in the peripheral lung, which terminate with small nodular opacities of different density (↳)
The branching opacities (the tree) reflect the presence of dilated bronchioles filled with material other than air, whereas the nodular opacities (the buds) are due to clusters of partially or completely filled alveoli, usually with poorly-defined margins (⩾)(centrilobular nodules)
The tree-in-bud sign is typical of diseases with bronchogenic spread



From pattern to disease

Distribution	◆▸	▲▼	Associated signs	DISEASE
Uni or bilateral, patchy	Variable, often in relation to the bronchi	Variable	Atypical mycobacteriosis: bronchial wall thickening, bronchiectasis, cavitation, possibly cavitated consolidations	Infections, endobronchial

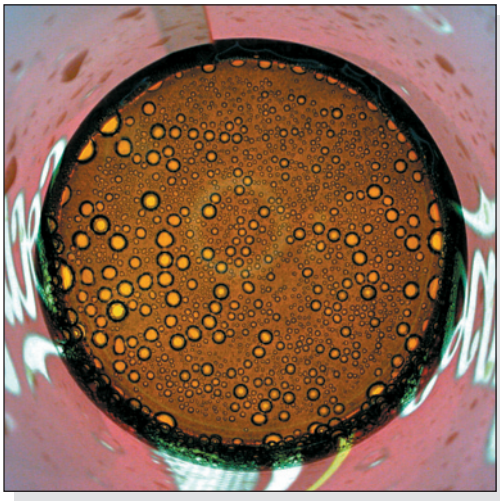
CYSTIC PATTERN

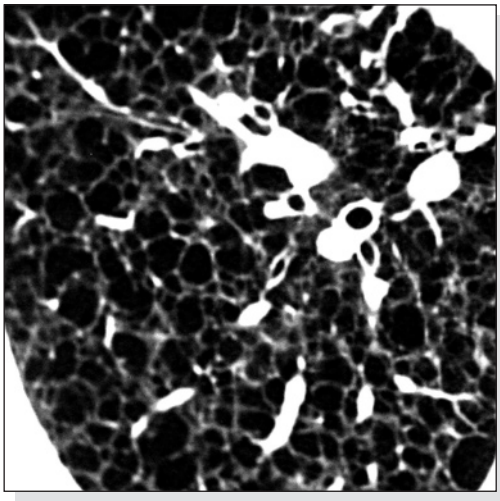
Definition

The main finding consists of small areas of absolute hyperlucency (cysts) - black holes which more-or-less extensively occupy the lung parenchyma

They may or may not be delimited by walls

Cyst formation may result from bronchial and bronchiolar enlargement due to wall distention, traction, increased endoluminal pressure, or a focal hyperinflation of the air spaces with rupture of the walls





In the cystic diseases, this pattern is dominant; however, there are other diseases in which cystic lesions may be found, albeit less important or sporadic. They are therefore described in the relevant chapters: ☐ Collagen vascular diseases, early; ☐ Drug toxicity; ☐ HP, chronic; ☐ NSIP; ☐ Sarcoidosis, fibrosing; ☐ UIP, early; ● LCH, early; ● LIP; ● RB-ILD; ⌘ BAC; ⌘ DIP; ⌘ PCP

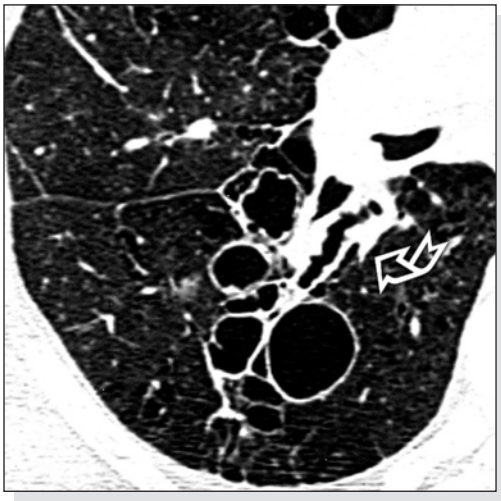
Clusters of grapes

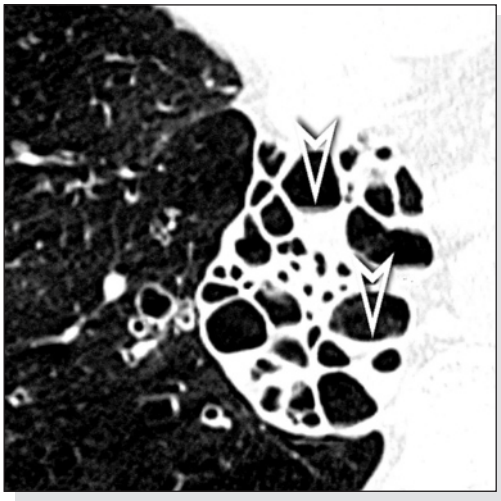
Definition

The cysts are arranged in grape-like clusters, often around a stem (the bronchovascular pedicle)(↳). Usually, these lesions have thick walls; their diameter may not be uniform

Air-fluid levels or inclusions inside the cysts (➢) are common. The fluid may be of varying nature: mucus, pus or blood. An intracystic mass is often due to a mycetoma, more rarely neoplastic; however, only a mycetoma moves when the patient's position is changed!

At times the cysts may be completely full of material and assume a pseudo-nodular appearance





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Uni or bilateral, patchy	Central or peripheral	Middle and upper zones	Air-fluid levels, tubular or varicose bronchiectasis and tree-in-bud, oligemia with air-trapping	**Bronchiectasis, cystic** **CF**

String of pearls

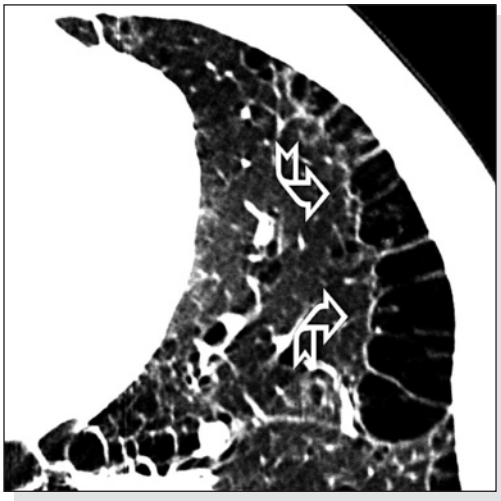
Definition

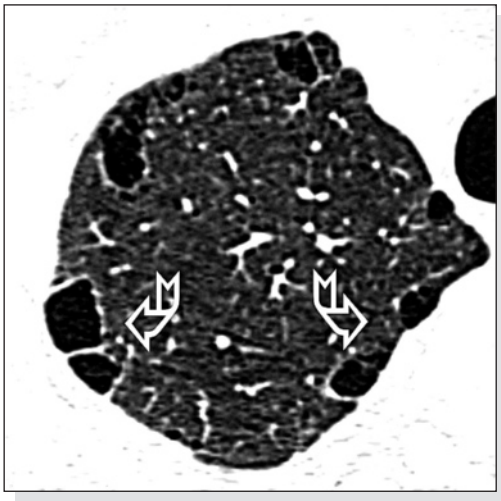
The cysts are arranged in a single layer in the subpleural region (↳) and resemble a string of pearls

Usually, these lesions have thin walls (comparable to the thickness of a fissure), which are interlobular septa at times thickened by minimal fibrosis

If the diameter of the cysts is greater than 1 cm, the term bulla is used

Bullae tend to have thicker walls owing to a greater quantity of fibrosis





From pattern to disease

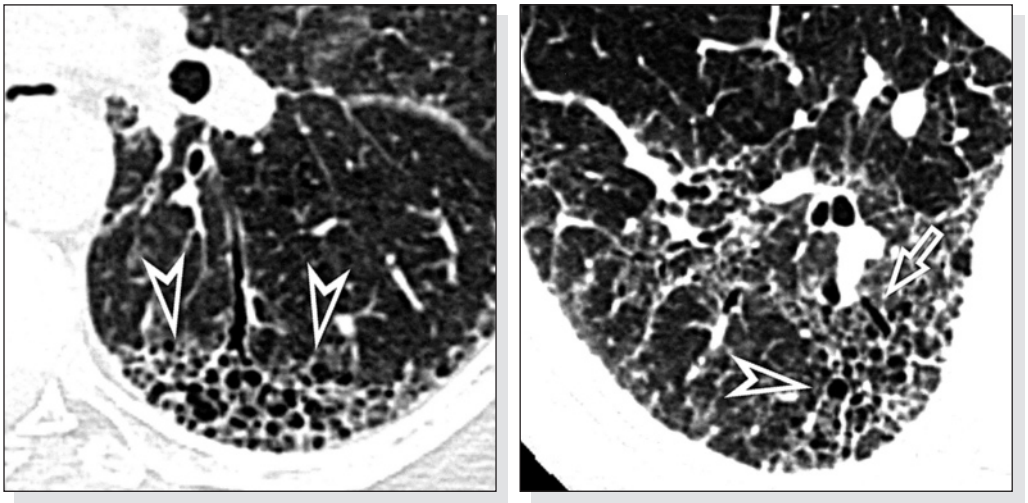
Distribution	◆▶	▲▼	Associated signs	DISEASE
Uni or bilateral, patchy	Peripheral and subpleural	Middle and upper zones	Centrilobular emphysema, spontaneous pneumothorax	**Emphysema, paraseptal**

Honeycombing

Definition

This pattern refers to thick-walled, rounded cysts arranged in several layers (➢). In the affected regions, the pulmonary architecture is distorted and traction bronchiectasis and bronchiolectasis (⇨) are often present

Honeycombing is the expression of the end phase of a number of fibrotic diseases (end-stage lung). The lung volume is characteristically reduced; an early sign of loss of volume is the dislocation of thin structures such as the fissures, whereas in the more advanced phases the bronchovascular bundles and the mediastinum are also displaced



From pattern to disease

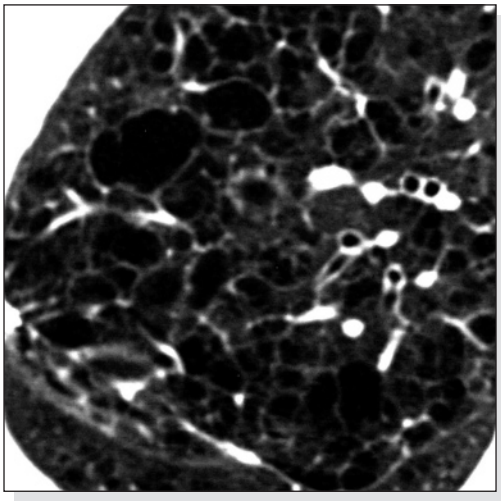
Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral, patchy	Peripheral, subpleural	Basal and peripheral	Traction bronchiectasis and bronchiolectasis, irregular reticular pattern, mediastinal adeno-pathies	**UIP, advanced**
Bilateral, patchy	Peripheral, subpleural	Basal	Traction bronchiectasis and bronchiolectasis, irregular reticular pattern, disease-specific signs	**Collagen vascular diseases, advanced**
Bilateral, patchy	Peripheral, subpleural	Basal	Traction bronchiectasis and bronchiolectasis, irregular reticular pattern, subpleural lines, pleural plaques	**Asbestosis, advanced**

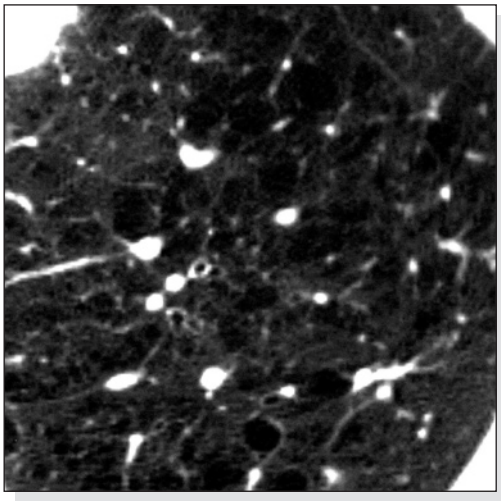
Random cysts

Definition

The cysts are randomly arranged without obvious aggregations. Their walls are of variable thickness, and in some diseases they are absent. The presence of a minute central hyperdensity can indicate the presence of a centrilobular arteriole. The distribution of the cysts is relatively homogeneous in the affected parenchyma, so their profusion is uniform

The overall appearance of the diseases presenting with this pattern can be very similar. The differential diagnosis, therefore, requires a careful assessment of the craniocaudal distribution of the lesions and the involvement of the costophrenic angles





From pattern to disease

Distribution	◆▶	▲▼	Associated signs	DISEASE
Bilateral, symmetrical or asymmetrical	Uniformly distributed	Middle and upper zones	Lack of walls, visible centrilobular artery, paraseptal emphysema, saber-sheath trachea	**Emphysema, centrilobular**
Bilateral, symmetrical	Uniformly distributed	Middle and upper zones, costophrenic angles spared	Thick walls, bizarre coalescent cysts, associated cavitated nodules, possible pneumothorax	**LCH, advanced**
Bilateral, symmetrical	Uniformly distributed	Diffuse, also in the costophrenic angles	Thin walls, lacy appearance, frequent pneumothorax, unilateral pleural effusion, mediastinal adenopathies	**LAM**

Reticular Diseases

Clinical features	**Alberto Pesci**
Pathology	**Alessandra Cancellieri**
Radiology	**Roberta Polverosi**

Amyloidosis

Definition

Amyloidosis is a general term which refers to the extracellular accumulation of fibrillar proteins composed of low molecular-weight subunits. There are three main patterns of pulmonary involvement: tracheobronchial, nodular parenchymal and diffuse alveolar-septal amyloidosis

Amyloidosis may be divided into primary (there are no other associated diseases with the exception of multiple myeloma) and secondary (associated with chronic inflammatory diseases). Amyloidosis may also be divided into localized (with the involvement of only one organ) or generalized: in the thorax, in addition to the parenchyma, amyloidosis may also affect the pleura, the pulmonary arteries, the hilar and mediastinal lymph nodes, and the diaphragm

DEMOGRAPHICS

Etiology and pathogenesis

The basic alteration is the extracellular deposit of amyloid L (AL) (primary form) or amyloid A (AA) (secondary form). Most pulmonary amyloidosis are AL and it has been estimated that 30-90% of all primary amyloidosis affect the lungs, although other organs may be involved

Epidemiology

The disease is very rare: the incidence of the primary (most common) form is nine cases per million

Risk factors

Chronic inflammatory disease or plasma cell dyscrasia

CLINICAL FEATURES

History

Patients affected by diffuse alveolar-septal amyloidosis often present dyspnea and at times a dry cough. Hemoptysis has been described in patients with pulmonary hypertension and involvement of the pulmonary arteries. Most patients present signs of extrathoracic diseases, particularly multiple myeloma

In patients with systemic disease, the dyspnea may also depend on the involvement of the heart or diaphragm

Physical findings

Diffuse fine bilateral rales

Pulmonary function tests

Respiratory function tests reveal a restrictive defect and mild-to-moderate D_LCO impairment

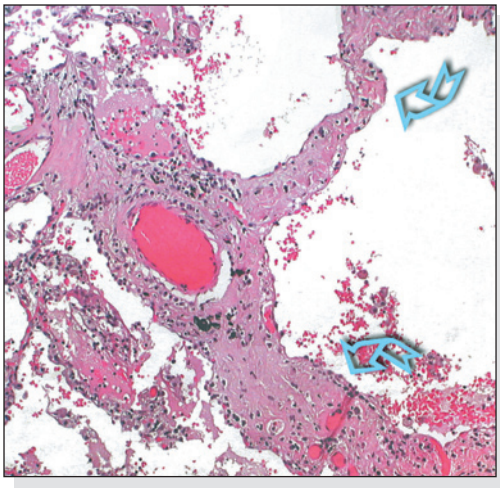
Gillmore JD. Amyloidosis and the respiratory tract. Thorax 1999, 54: 444

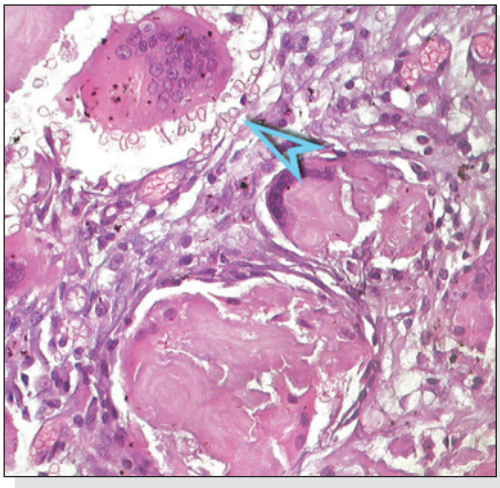
PATHOLOGY

Basic lesions

Diffuse interstitial amyloidosis presents in the form of:

- Deposits of amorphous, eosinophilic and homogenous extracellular material in the septal and perivascular interstitium
- Frequent slight lymphoplasmacellular infiltrate with characteristic multinucleated giant cell reaction
- Calcification and ossification may be present





Amyloid is a protein-derived substance which deposits in the extracellular spaces. It appears homogeneous and slightly eosinophilic in hematoxylin and eosin sections, positive to Congo red staining, exhibiting a green birefringence under polarized light and fluorescent after thioflavin staining

Distribution

In the interstitium of the alveolar and perivascular septa

Differentials

Histopathologic differential diagnoses:

- Fibrosing diseases such as chronic HP, fibrosing NSIP, sarcoidosis, etc. The presence of dense connective tissue of the alveolar septa can simulate amyloid deposits, but it is negative to thioflavin and Congo red staining (beware of artifacts in thick sections!), not birefringent under polarized light, and typically stains as the connective tissue

Deposits of amyloid may be seen in lymphoproliferative lesions (myeloma, monoclonal gammopathy of uncertain significance, low grade B-cell lymphoma, LIP, etc.), collagen vascular diseases and neuroendocrine tumors (carcinoids, small cell carcinomas, etc.)

Poh SC. Primary diffuse alveolar septal amyloidosis. Thorax 1975, 30: 186

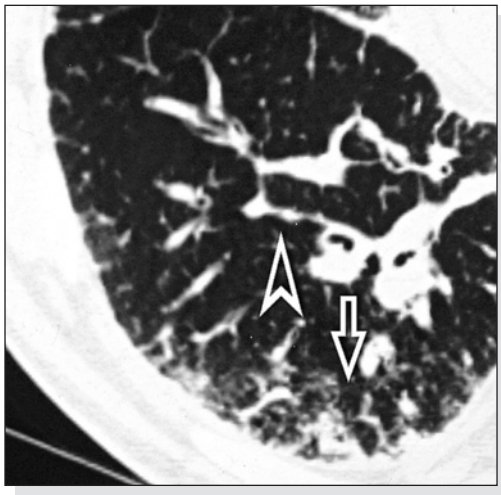
Sumiya M. Diffuse interstitial pulmonary amyloidosis in rheumatoid arthritis. J Rheumatol 1996, 23: 933

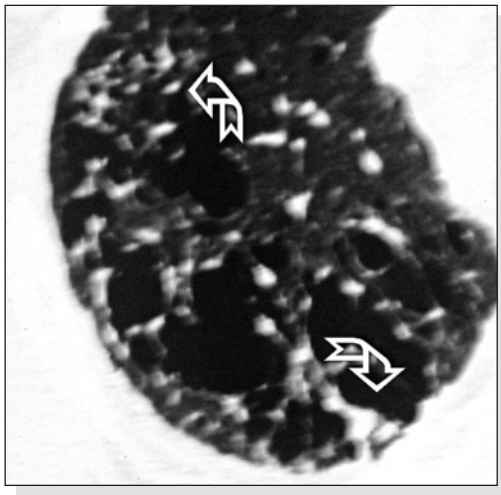
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Smooth or nodular interlobular reticular pattern (➢)
- Intralobular linear opacities (⇨)
- Micronodules with well-defined margins, often calcific (↳)





Geusens EA. Primary pulmonary amyloidosis as a cause of interlobular septal thickening. AJR Am J Roentgenol 1997, 168: 1116

Graham. High-resolution CT appearance of diffuse alveolar septal amyloidosis. AJR Am J Roentgenol 1992, 158: 265

Distribution

Bilateral, patchy

Pickford HA. Thoracic cross-sectional imaging of amyloidosis. AJR Am J Roentgenol 1997, 168: 351

Dorsal subpleural

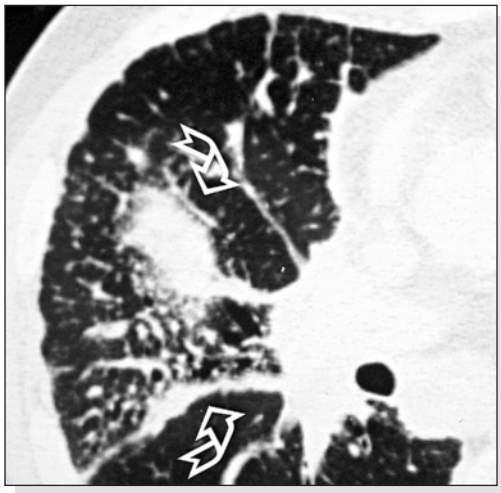
Middle and basal zones

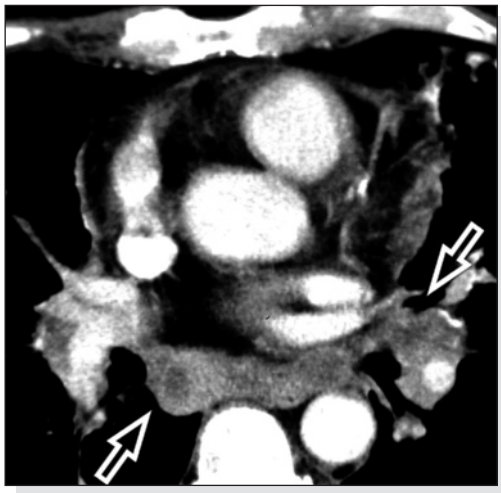
Lung volume is normal

Other signs

Other characteristics:

- Ground-glass
- Consolidations or masses (↳)
- Hilar-mediastinal lymphadenopathies (⇨)
- Pleural effusion
- Thickening of the walls of the larynx, trachea and bronchi (tracheobronchial amyloidosis)





Differentials

The coexistence of reticular and nodular patterns significantly broadens the radiological differential diagnosis. The appearance of the calcifications may help diagnosis:

- Sarcoidosis: the calcifications are sporadic in the parenchymal opacities, at times scattered in the mediastinal adenopathies. Lesions are prevalent in the upper lobes
- Silicosis and pneumoconiosis: only nodular opacities are present. The calcifications are seen within the large masses formed by the confluence of nodules and predominate in the upper lung zones
- Alveolar microlithiasis: only a large number of small, evenly distributed calcifications are present

Korn MA. Pulmonary alveolar microlithiasis: findings on high-resolution CT. AJR Am J Roentgenol 1992, 158: 981

Lee KS. Diffuse micronodular lung disease: HRCT and pathologic findings. J Comput Assist Tomogr 1999, 23: 99

COURSE and COMPLICATIONS

Associated diseases

The deposit of amyloid material in the lungs may be associated with several diseases affecting the lungs (chronic tuberculosis, bronchiectasis, pulmonary abscess, chronic aspergillosis, rheumatoid pleuritis, extrinsic allergic alveolitis, fibrosis) or other organs (Crohn's disease, Hodgkin's disease, renal carcinoma)

Clinical course

The disease is progressive and may lead to severe respiratory failure and death, often brought about by the involvement of other organs (heart and kidneys). The mean survival time from diagnosis is only 16 months

Radiological course

As the disease progresses basic lesions tend to become more diffuse. A certain degree of honeycombing may also appear

LABORATORY FINDINGS

In primary amyloidosis monoclonal immunoglobulin light chains may be found in the peripheral blood, these being more commonly lambda than kappa. In the secondary form there may be either an increase or a decrease in quantitative immunoglobulins

CLINICAL DIAGNOSIS

In the appropriate clinical setting, the association of a reticular-nodular pattern with calcifications on HRCT has a diagnostic accuracy of 95%

Utz JP. Pulmonary amyloidosis. The Mayo Clinic experience from 1980 to 1993. Ann Intern Med 1996, 124: 407

INVASIVE DIAGNOSIS

Diagnosis requires the histologic demonstration of amyloid deposits in the extracellular space and is obtained with fine needle aspiration biopsy from the periumbilical fat or a biopsy of the rectal mucosa or other involved organ, including the lungs. Lung parenchyma for diagnostic purposes can be obtained with fine needle aspiration, transbronchial or surgical biopsy

Bronchoalveolar lavage

The few studies available suggest that BAL in amyloidosis is characterized by an increase in lymphocytes and the CD4/CD8 ratio. In addition, paraprotein may be encountered in higher concentration in BAL fluid than in serum in the primary form of the disease

Morgan JE. Pulmonary immunologic features of alveolar septal amyloidosis associated with multiple myeloma. Chest 1987, 92: 704

Asbestos-induced pneumoconiosis

Definition

Asbestosis is a pneumoconiosis caused by the inhalation of asbestos fibers and characterized by a slowly progressive fibrosis up to the end-stage cystic disease (O Asbestosis, advanced)

DEMOGRAPHICS

Etiology and pathogenesis

A toxic effect is thought to be produced by the asbestos fibers on the lung parenchyma with recruitment of inflammatory cells and release of various mediators (reactive oxygen species, cytokines, proteases and growth factors)

Epidemiology

The precise epidemiology of the disease is unknown because of its long clinical latency (up to 20-30 years from initial exposure)

Risk factors

Asbestosis affects workers involved in the extraction of the mineral, in the manufacture and installation of products containing asbestos (industrial textiles, insulation, cement-asbestos manufactured goods) and in the repair and removal of the same (naval and railway demolition)

CLINICAL FEATURES

History

Patients may be asymptomatic for up to 20-30 years from initial exposure. The first symptom is dyspnea on exertion associated at times with a dry cough

Physical findings

Physical examination of the lungs may be normal or characterized by diffuse fine bibasilar rales (32-64%)

Pulmonary function tests

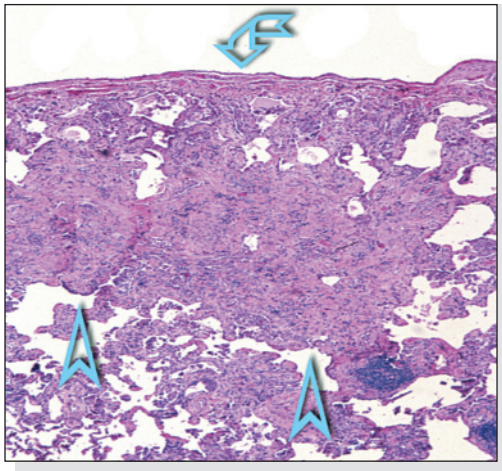
The earliest functional changes include reduced D_LCO and hypoxemia with exercise. A restrictive pattern is observed in a later stage. The presence of airway obstruction is generally due to cigarette smoking

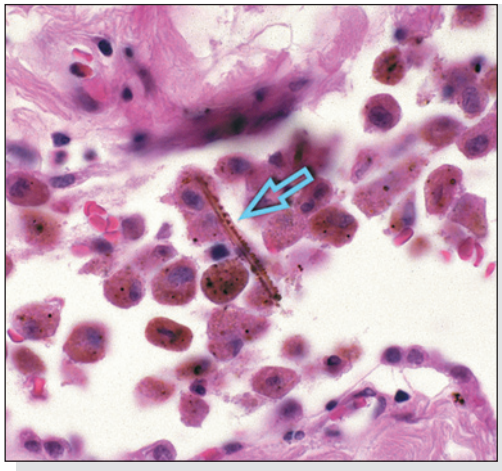
Mossman BT. Asbestos-related diseases. N Engl J Med 1989, 320: 1721

PATHOLOGY

Basic lesions

These include interstitial fibrosis, initially around the small airways and alveolar ducts and then involving extensive areas of parenchyma (➢), with the possible association of fibrosis of the visceral pleura (↳) and honeycombing. Asbestos bodies may also be present (⇨)





The diagnosis of asbestosis requires the presence of fibrosis associated with asbestos bodies (at least 1 or 2 according to various authors). The presence of asbestos bodies without fibrosis indicates exposure, but not disease

✓ Clinical signs associated with the disease include mucostasis, OP, mild lymphoplasmacellular infiltrate or heavy infiltrate of macrophages with hemosiderin or anthracotic pigment, often intraalveolar, which create DIP-like changes. Multinucleated giant cells elicited by asbestos bodies (asbestos fibers with an iron protein coat) may also be present

Distribution

Initially peribronchiolar and subpleural, then progressively diffuse

Histologic grading schemes have been proposed based on the extent of fibrosis. However, rarely is sufficient material available to apply them

Differentials

Histopathologic differential diagnoses:

- UIP: prevalently perilobular fibrosis with bronchiolectasis; fibroblastic foci at the interface with normal parenchyma, absence of asbestos bodies
- NSIP: diffuse fibrosis of the alveolar septa, non-centrilobular; absence of asbestos bodies
- Sarcoidosis: fibrosis with a lymphatic distribution, residual granulomas, absence of asbestos bodies
- DIP: dense and diffuse accumulation of intraalveolar macrophages with slight septal fibrosis, absence of asbestos bodies

Craighead JE. The pathology of asbestos-associated diseases of the lungs and pleural cavities: diagnostic criteria and proposed grading schema. Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. Arch Pathol Lab Med 1982, 106: 544

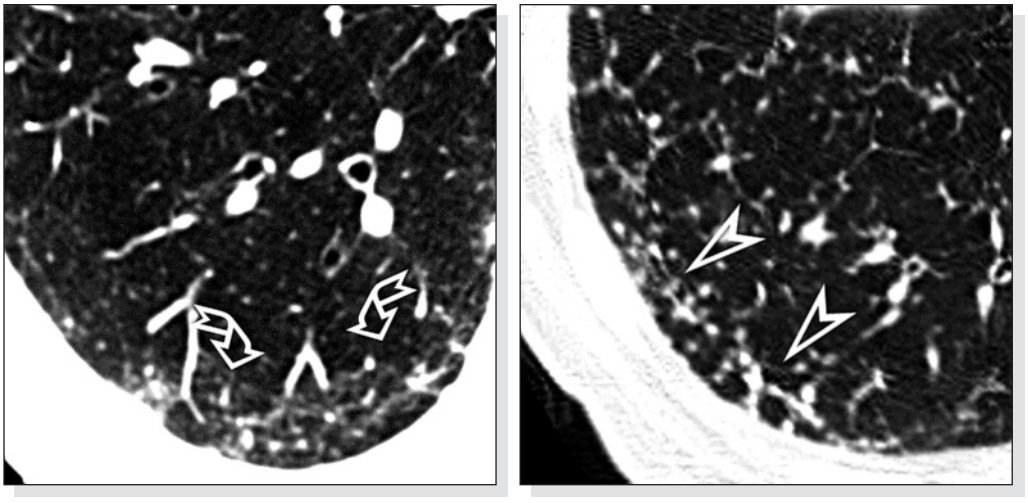
Mossman BT. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 1998, 157: 1666

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Irregular reticular pattern, interlobular and intralobular
- Subpleural branching or dotlike opacities with a nodular reticular appearance
- Subpleural lines
- Parenchymal bands



Akira M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. AJR Am J Roentgenol 2003, 181: 163

Distribution

Bilateral and symmetrical

Peripheral, dorsal

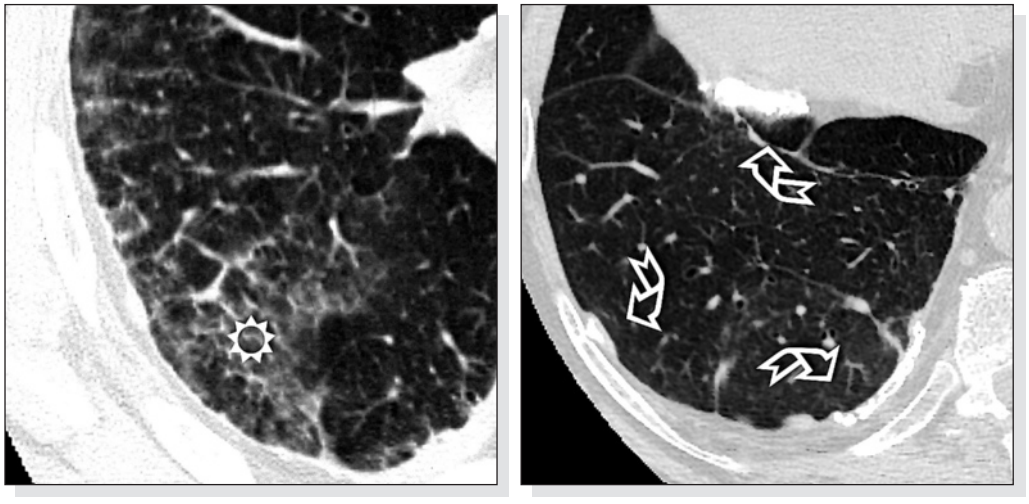
Prevalently basal

Initially normal, lung volume becomes progressively reduced

Other signs

Other radiological characteristics:

- Ground-glass (☼)
- Pleural plaques, 10-15% of which calcified (↳)
- Pleural effusion
- Rounded atelectasis



Pleural plaques: these may be bilateral, of varying length, but with a thickness <1 cm and calcified in 10-15% of cases; they are typically absent in the apices and the costophrenic sinuses and tend to be arranged in a spiral pattern extending superoanterior to posteroinferior

Rounded atelectasis: these are identifiable as rounded or ellipsoid areas of increased density with a parietal supporting base in correspondence with pleural thickening; the vessels and bronchi around the areas are gently arched with a "comet-tail" appearance. The consolidation is markedly hyperdense following administration of contrast material as it is composed of collapsed parenchyma which is not aerated but rather perfused

Akira M. High-resolution CT in the evaluation of occupational and environmental disease. Radiol Clin North Am 2002, 40: 43

Polverosi R. [Pleural and parenchymal lung diseases from asbestos exposure. CT diagnosis]. Radiol Med 2000, 100: 326. Italian

Differentials

The signs described may be present in other fibrosing diseases:

- UIP: honeycombing is prevalent with frequent evidence of traction bronchiolectasis
- NSIP: ground-glass and bronchiolectasis are prevalent
- Collagen vascular diseases: in addition to signs of fibrosis, ground-glass, consolidation and pleural effusion are present
- Drug toxicity: ground-glass is often dominant, while progression to fibrosis is rare

COURSE and COMPLICATIONS

Associated diseases

Patients affected by asbestosis are almost always carriers of pleural plaques, which are often calcified; they are also at increased risk of developing cancer, particularly mesothelioma and lung cancer

Clinical course

The disease may progress to respiratory failure (30%), albeit more slowly than in UIP; respiratory failure is the cause of death in about one fifth of patients with asbestosis. Cigarette smoking may accelerate the progression of pulmonary fibrosis

Radiological course

The radiological appearance progresses from an early irregular reticular pattern towards cystic honeycombing (○ Asbestosis, advanced)

LABORATORY FINDINGS

Increased ESR, the presence of antinuclear antibodies and rheumatoid factor are frequently found, but they are not correlated with the disease activity

CLINICAL DIAGNOSIS

In the appropriate clinical setting, a detailed history of asbestos exposure and a long period of latency from initial exposure to the onset of clinical signs are diagnostic of asbestosis

In 20-30% of patients with a significant history of exposure, symptoms or altered pulmonary function tests, but with a normal radiograph, HRCT allows detection of parenchymal abnormalities. Nonetheless, a normal CT does not exclude the possibility of disease

Staples CA. High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. Am Rev Respir Dis 1989, 139: 1502

The presence of pleural plaques is a hallmark of asbestos exposure

INVASIVE DIAGNOSIS

In doubtful cases a surgical lung biopsy should be performed

Bronchoalveolar lavage

Asbestos bodies are frequently found in BAL, and their number correlates with those in the tissues. Cell count may reveal an increase in both lymphocytes and polymorphonucleated neutrophils. The lymphocytes show a predominance of CD8+ cells

The number of asbestos bodies increases when BAL is performed in the lower lobes. Asbestos bodies may be present in exposed subjects who do not have asbestosis

Karjalainen A. Asbestos bodies in bronchoalveolar lavage in relation to asbestos bodies and asbestos fibres in lung parenchyma. Eur Respir J 1996, 9: 1000

Scleroderma

Definition

Collagen vascular diseases are a heterogeneous group of diseases characterized by the presence of circulating autoantibodies which cause inflammatory damage to various organs or tissues. The patterns of lung disease in collagen vascular diseases include fibrosing alveolitis, bronchiolitis, OP, parenchymal nodules, pleuritis, and vasculitis

Scleroderma is a collagen vascular disease which will be covered in this chapter as a representative example. The lungs are affected by a diffuse-fibrotic infiltrate, with a reticular radiological appearance in the early stages, although this may progress to cystic disease (Collagen vascular diseases, advanced)

Progressive Systemic Sclerosis (PSS)

Other collagen vascular diseases which may affect the lungs in the form of fibrosing alveolitis are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), CREST syndrome, Sjögren's syndrome, dermatomyositis-polymyositis (DM/PM), mixed connective tissue disease (MCTD)

Hunninghake GW. Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 1979, 119: 471

DEMOGRAPHICS

Etiology and pathogenesis

The precise pathogenesis of lung involvement is unknown. Experimental data suggest that a fundamental role is played by alveolar macrophages which are thought to produce factors involved in chemotaxis and the activation of fibroblasts such as tumor necrosis factor-alpha, transforming growth factor-beta, fibronectin and insulin-like growth factor-I. Alveolar macrophages are also thought to produce increased amounts of interleukin-8, a powerful chemokine for neutrophils which are regularly found in the BAL of patients with scleroderma

Mastocytes and their mediators are also thought to play a role in the pathogenesis of the disease, together with endothelin-1, a factor produced by endothelial cells which directly stimulates the fibroblasts. The "coordinating" cells of these processes are thought to be CD8+ T cells of mostly Tc2 phenotype

Epidemiology

Scleroderma is a rare disease (12 cases per million/year) which primarily afflicts adults between the age of 30 and 50 years, with women being more commonly affected (3:1). The lung is affected in more than 70% of patients with scleroderma, which makes it the second most frequently affected organ after the esophagus

Risk factors

Lung involvement is more common in patients with genetic markers such as HLA-DR3/DR52a, specific autoantibodies (ScL-70, anti-U3RNP, antitopoisomerase I, antihistone) and in African American patients

CLINICAL FEATURES

History

The most common symptoms in this early phase are dyspnea on exertion and dry cough. Chest pain and hemoptysis are less common

Physical findings

Almost 50% of patients present diffuse fine bibasilar rales

Pulmonary function tests

Reduced D_LCO is the earliest functional change and this is present in 70% of patients, including asymptomatic patients with a normal chest X-ray. Another early sign of functional deficit is the alveolar-arterial oxygen gradient during exercise. Lung function is worse in smokers than in non-smokers

The clinical and physiologic features of the fibrosing infiltrative lung disease seen in scleroderma are similar to those in UIP

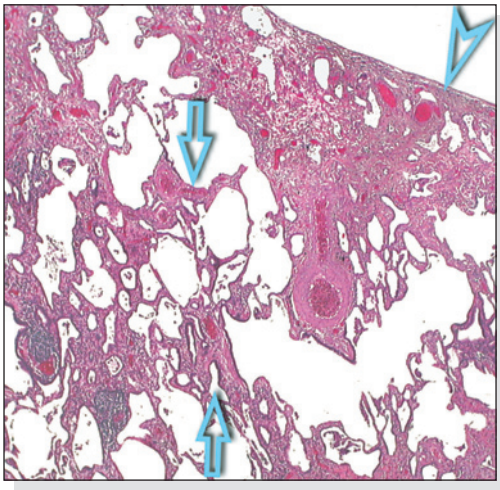
Lamblin C. Interstitial lung diseases in collagen vascular diseases. Eur Respir J Suppl 2001, 32: 69s

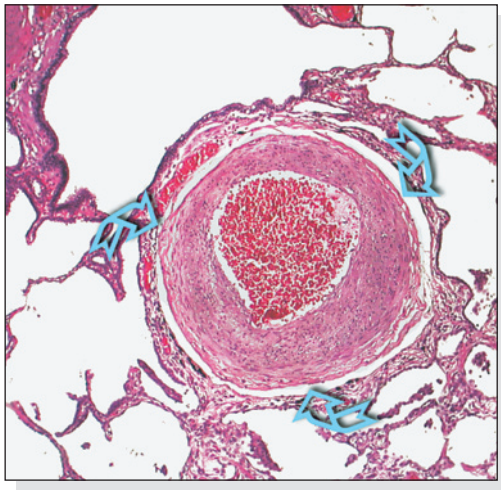
PATHOLOGY

Basic lesions

In the early phase scleroderma presents with:

- Interstitial fibrosis (⇨) with mainly lymphoplasmacellular infiltrate: this is frequently associated with pleural fibrosis (➢) with adhesions
- Vascular lesions (independent of fibrosis): medial smooth muscle hypertrophy (↳) and intimal fibrosis of the pulmonary arteries may be seen, while fibrinoid necrosis and plexiform lesions are rarer findings





✓ The pattern of fibrosis in progressive systemic sclerosis is most similar to that of fibrosing NSIP or UIP

Distribution

Diffuse interstitial and subpleural

Differentials

Histopathologic differential diagnoses:

- NSIP and UIP: the lesions are often morphologically indistinguishable, except that the vascular changes are less pronounced and related to fibrosis

Colby TV. Pulmonary pathology in patients with systemic autoimmune diseases. Clin Chest Med 1998, 19: 587

Fujita J. Non-specific interstitial pneumonia as pulmonary involvement of systemic sclerosis. Ann Rheum Dis 2001, 60: 281

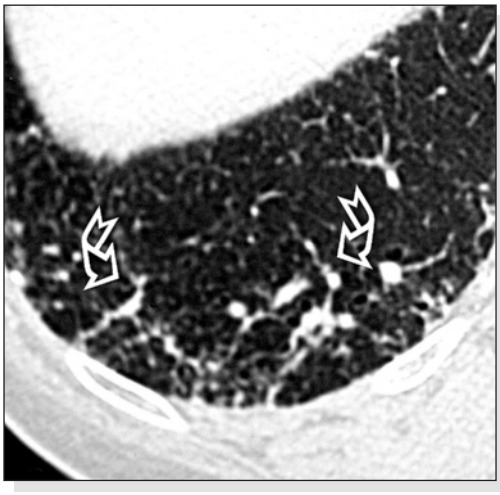
Yousem SA. The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol 1990, 21: 467

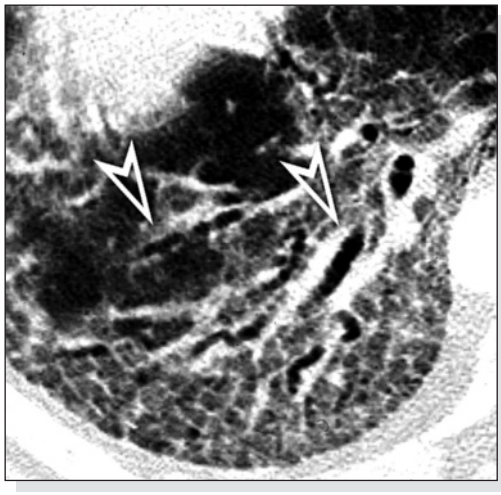
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Fine interlobular and intralobular irregular reticular pattern (↯)
- Interface signs
- Ground-glass and consolidations containing traction bronchiectasis and bronchiolectasis (➢)





Ooi GC. Interstitial lung disease in systemic sclerosis. Acta Radiol 2003, 44: 258

Distribution

Bilateral, diffuse

Peripheral, subpleural, dorsal

Basal

Lung volume is slightly reduced

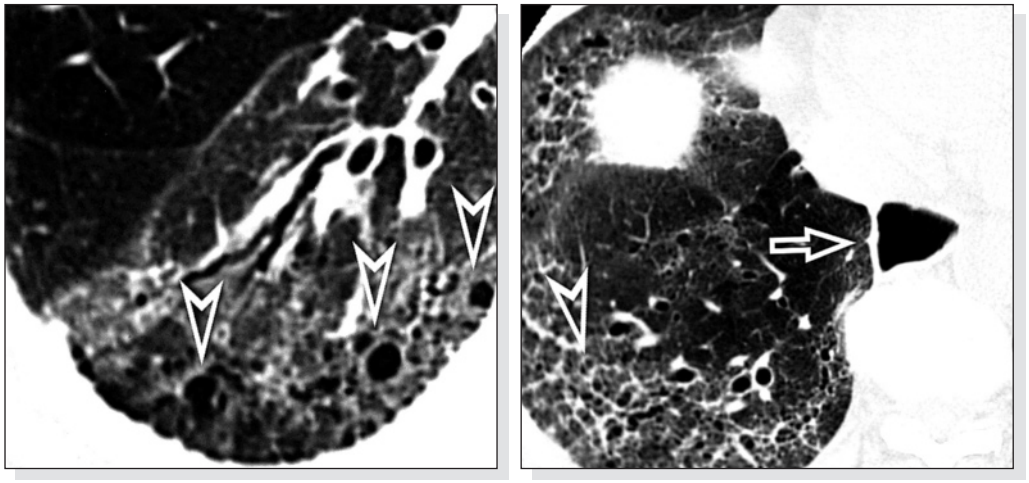
Gamsu G. Radiographic manifestations of thoracic involvement by collagen vascular diseases. J Thorac Imaging 1992, 7: 1

Mayberry JP. Thoracic manifestations of systemic autoimmune diseases: radiographic and high-resolution CT findings. Radiographics 2000, 20: 1623

Other signs

Other characteristics:

- Honeycombing composed of minute cysts (≻)
- Small centrilobular nodules
- Esophageal dilatation (40-80%)(⇨)
- Mediastinal lymphadenopathy (60%)
- Pleural thickening



In collagen vascular diseases honeycombing is less common and the air spaces are smaller than in UIP. Parenchymal consolidation is bilateral and can be caused by fibrosis, alveolar hemorrhage, aspiration pneumonia or OP. Centrilobular nodules result from associated follicular bronchiolitis, which is common in this disease

Bhalla M. Chest CT in patients with scleroderma: prevalence of asymptomatic esophageal dilatation and mediastinal lymphadenopathy. AJR Am J Roentgenol 1993, 161: 269

Franquet T. High-resolution CT of lung disease related to collagen vascular disease. Radiol Clin North Am 2001, 39: 1171

Differentials

Radiological differential diagnoses are:

- UIP: subpleural honeycombing prevails and the cysts are larger
- Asbestosis: ground-glass is less frequent and bronchiolectasis is rare; subpleural lines, parenchymal bands and pleural plaques coexist
- Drug-toxicity: ground-glass prevails, while progression towards fibrosis is rare
- Collagen vascular diseases: all the described signs (appearance and distribution) may be equally present in the other collagen vascular diseases. Differential elements include:
  - RA: bronchiectasis is isolated and not in the context of consolidation (associated with chronic infections); air-trapping and mosaic perfusion (from bronchiolitis obliterans); centrilobular nodules with hazy margins (from follicular bronchiolitis); cavitating subpleural

rounded opacities; pleural effusion
- LES: pleural and/or pericardial effusion, more frequent parechymal consolidation (hemorrhage, lupus pneumonia due to diffuse alveolar damage, OP)

Kim EA. Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. Radiographics 2002, 22: S151

Ooi GC. Systemic lupus erythematosus patients with respiratory symptoms: the value of HRCT. Clin Radiol 1997, 52: 775

Salaffi F. [Subclinical interstitial lung involvement in rheumatic diseases. Correlation of high resolution computerized tomography and functional and cytologic findings]. Radiol Med 1999, 97: 33. Italian

COURSE and COMPLICATIONS

Associated diseases

About 10% of scleroderma patients develop pulmonary hypertension. Other less common manifestations are pleuritis, aspiration pneumonia, spontaneous pneumothorax, drug-induced pneumonia, tumors, and amyloid deposits

The differential diagnosis of the lung involvement in scleroderma must take into account other possible causes such as drug-associated pneumonia (□ Drug toxicity; ⌘ Drug toxicity); opportunistic infections induced by immunosuppressive drugs; concurrent neoplasm

Clinical course

The disease progresses towards fibrosis and respiratory failure. Lung involvement is the most frequent cause of death in patients with scleroderma

Radiological course

Progression towards fibrosis with the prevalence of honeycombing (○ Collagen vascular diseases, advanced) is slower compared to UIP

LABORATORY FINDINGS

Antinuclear antibodies are found in most patients. The presence of antitopoisomerase I (topo I or Scl-70) or antihistone is associated with more severe lung fibrosis. Patients with fibrosing alveolitis in the course of scleroderma are reported to have increased serum levels of KL-6, a glycoprotein mainly present in type-II pneumocytes and alveolar macrophages. According to some authors, KL-6 levels are useful in diagnosing and monitoring the disease

CLINICAL DIAGNOSIS

In patients with scleroderma, a CT scan exhibiting characteristic features can be considered sufficient for diagnosing fibrosing lung involvement without the need for lung biopsy

INVASIVE DIAGNOSIS

Surgical lung biopsy is indicated in the following circumstances: D_LCO is notably reduced relative to lung volumes, there is massive pleural involvement, and HRCT is unable to clearly identify a reticular pattern. Transbronchial lung biopsy is only useful for excluding concurrent infections or tumors

Bronchoalveolar lavage

BAL is characterized by an increase in total cell count and granulocytes, particularly neutrophils and eosinophils. In some cases an increase in lymphocytes and mastocytes is present. BAL plays a part in prognosis, since the presence of persistent alveolitis is associated with more severe lung function deterioration and faster progression of the disease

BAL is useful in the diagnosis of complications (aspiration pneumonia, drug-induced pneumonia, concomitant infections or tumors, etc.)

A correlation exists between the BAL findings and the extent of disease seen on HRCT: the number of lymphocytes increases in the still unaffected lung areas, the eosinophils are the first cells to increase detected by HRCT, and neutrophils predominate when at least 50% of the lavaged lobe is affected by disease

Manganelli P. Clinical and subclinical alveolitis in connective tissue diseases assessed by bronchoalveolar lavage. Semin Arthritis Rheum 1997, 26: 740

Silver RM. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. Am J Med 1990, 88: 470

Methotrexate-induced lung disease

Definition

A number of drugs can cause lung damage, which is expressed by different histopathologic patterns (see the table "Drug-induced lung damage: histopathologic patterns" at the end of this chapter)
Methotrexate, a drug which will be covered in this chapter as a representative example, causes chronic interstitial pneumonia, which presents with a reticular HRCT pattern

It should nonetheless be noted that the same drug may cause different types of damage in the lung tissue, even in sequence. For example, methotrexate itself may also cause pulmonary edema (⌘ PE, alveolar), OP (⌘ OP) and even diffuse alveolar damage (DAD) typical of AIP (⌘ AIP) and ARDS (⌘ ARDS), although less frequently than chronic interstitial pneumonia

Rosenow EC 3rd. Drug-induced pulmonary disease. An update. Chest 1992, 102: 239

DEMOGRAPHICS

Etiology and pathogenesis

It has not yet been established whether lung damage caused by methotrexate is due to hypersensitivity reaction or direct toxic effect. The observation of regression of damage despite continued exposure to the drug suggested a concomitant abnormal response to a viral infection (cytomegalovirus and Epstein-Barr virus)

Epidemiology

Methotrexate-induced lung disease may occur in all those diseases where the drug is administered (lung and breast cancer, osteosarcoma, epidermoid carcinoma of the head-neck, non-Hodgkin's lymphoma, psoriasis and severe rheumatoid arthritis). The incidence of lung damage during treatment with methotrexate, in its various manifestations, varies from 5% to 10%

Risk factors

The following risk factors have been identified in rheumatoid arthritis patients receiving methotrexate: >60 years of age, rheumatoid lung involvement, diabetes mellitus, hypoalbuminemia and the prior use of disease-modifying antirheumatic drugs. No correlation between cumulative dose and lung damage has been observed. Concomitant treatment with drugs which reduce the protein bond of methotrexate (aspirin, chlorambucil, sulfonamide, penicillin, phenylbutazone, barbiturates, NSAIDs) seems to increase the toxicity of methotrexate

CLINICAL FEATURES

History

Pulmonary toxicity generally arises during treatment and only rarely afterwards. Patients experience subacute fever with a dry cough and dyspnea 3-4 months after beginning treatment. Acute symptoms of fever, chills, cough, dyspnea and chest pain only occur in 5-10% of cases

Physical findings

Clinical signs include diffuse fine bibasilar rales, tachypnea and at times cyanosis. A small percentage of patients may present with skin reactions (15%) and signs of pleural effusion

Pulmonary function tests

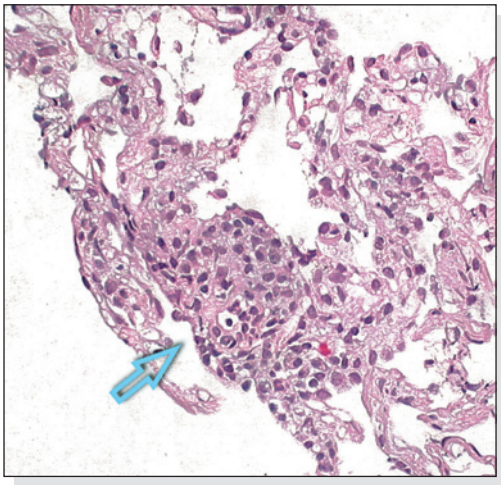
Most patients do not have functional deficits. In rare cases there is a restrictive deficit with a decrease on D_LCO and at times hypoxemia. It has been shown that pulmonary function tests are unable to predict lung involvement caused by methotrexate

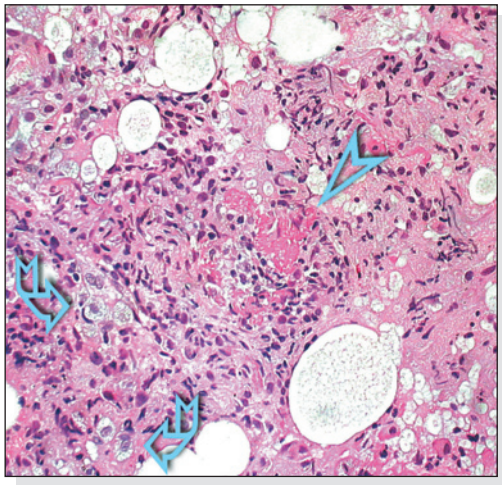
PATHOLOGY

Basic lesions

These include:

- Diffuse lymphocytic interstitial infiltrate, often with perivascular, mostly perivenular, distribution (⇨); non-necrotizing granulomas may be present
- Fibrosis to varying degrees, without honeycombing
- Type II pneumocyte hyperplasia





Methotrexate-induced toxicity in the lung may also have the clearly alveolar features of DAD, either acute or organized. Other possible manifestations include the presence of foamy intraalveolar macrophages (↳), and eosinophils, mucostasis and organizing thrombi (➢)

Distribution

Diffuse interstitial

Differentials

Histopathologic differential diagnoses:

- NSIP: methotrexate-induced chronic interstitial pneumonia may have essentially a cellular NSIP pattern
- MALToma and well-differentiated lymphocytic lymphoma: diffuse, dense and uniform lymphoid infiltrate, infiltration of the pleura and lymphoepithelial complexes in MALT
- HP: intense lymphoplasmacellular infiltrate, poorly-formed interstitial granulomas, centrilobular lesions

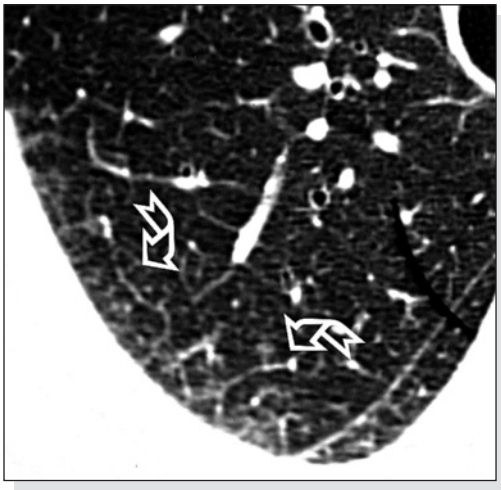
Imokawa S. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000, 15: 373

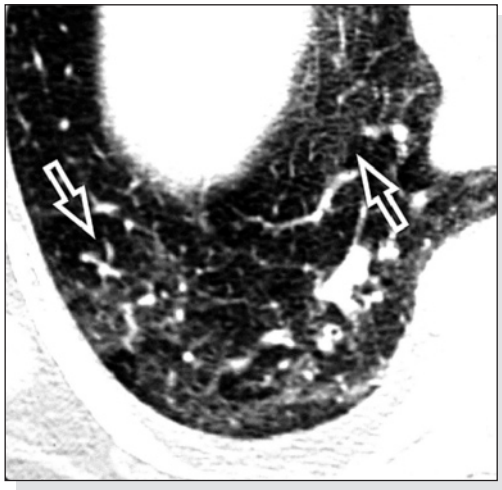
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Irregular reticular opacities (20%) (↳)
- Ground-glass (100%) (⇨)





Distribution Bilateral, patchy

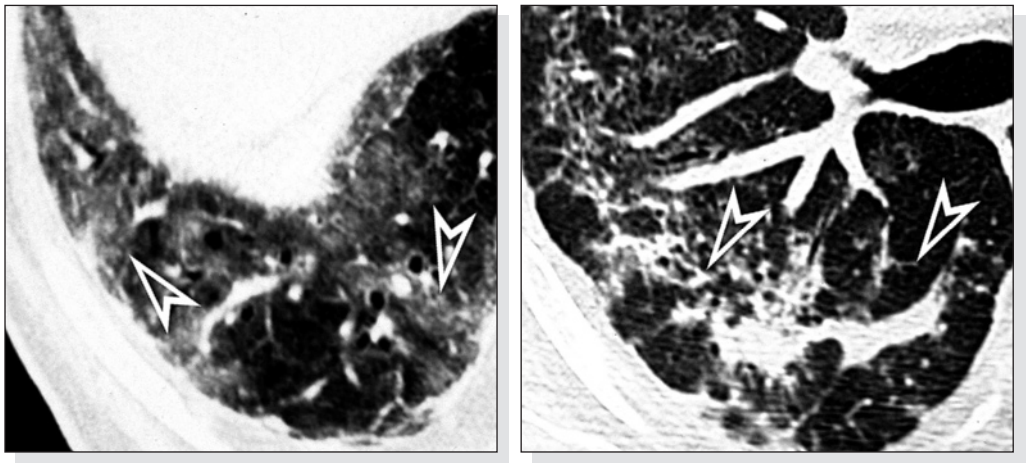
Variable

Variable

Lung volume is normal or slightly reduced

Other signs Other radiological characteristics:

- Parenchymal consolidation with air-bronchogram sign (≻)
- Honeycombing (rare)



Pietra GG. Pathologic mechanisms of drug-induced lung disorders. J Thorac Imaging 1991, 6: 1

Rossi SE. Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics 2000, 20: 1245

Differentials Radiological differential diagnoses include:

- UIP: honeycombing prevails and is typically found in subpleural and basal zones
- Collagen vascular diseases: signs of fibrosis prevail at the lung bases
- Asbestosis: ground-glass is less frequent, while subpleural lines and bands and pleural plaques coexist

Erasmus JJ. High-resolution CT of drug-induced lung disease. Radiol Clin North Am 2002, 40: 61

McAdams HP. The alphabet soup revisited: the chronic interstitial pneumonias in the 1990s. Radiographics 1996, 16: 1009

COURSE and COMPLICATIONS

Associated diseases Treatment with cytotoxic drugs such as methotrexate not only causes direct lung damage, but may also promote the onset of infection (most commonly pneumocystis) or lung cancers (especially non-Hodgkin's lymphomas)

Clinical course Most patients make a practically complete recovery, with mortality being below 10%. Progression to respiratory failure may also occur, whereas in about 10% the disease progresses towards diffuse pulmonary fibrosis

Radiological course The lesions described may regress (consolidation and ground-glass) if the drug is discontinued, or in contrast there may be progression towards honeycombing with traction bronchiectasis

LABORATORY FINDINGS

Peripheral eosinophilia may be seen (40-65%)

CLINICAL DIAGNOSIS

Most cases are diagnosed clinically and only a minority of patients need a lung biopsy. Improvement after discontinuation of the drug and/or response to steroid treatment provide important clues. It is imperative to exclude opportunistic lung infection before treating

INVASIVE DIAGNOSIS

In the appropriate clinical setting, BAL findings and transbronchial lung biopsy may provide further diagnostic support

Bronchoalveolar lavage

Most patients present a high-intensity CD4+ lymphocytic alveolitis, although a prevalence of CD8+ T-cells has been described. Neutrophilia is present in some cases. BAL is particularly useful in ruling out opportunistic infections. The presence in the BAL fluid of atypical epithelial cells may be an early sign of progression towards fibrosis. The table at the end of this chapter entitled "Drug-induced lung damage: BAL findings" summarizes the main features which may be encountered

CD4+ lymphocytic alveolitis is not a specific finding in that it may also be seen in sarcoidosis, berylliosis, tuberculosis and rheumatoid arthritis

Schnabel A. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. Thorax 1997, 52: 377

DRUG TOXICITY TABLES

On the following pages are two detailed tables which present:

- Drug-induced lung damage: histopathologic patterns
- Drug-induced lung damage: BAL findings

DRUG-INDUCED LUNG DAMAGE: HISTOPATHOLOGIC PATTERNS

Chronic interstitial pneumonia	Amiodarone, BCNU, busulfan, cyclophosphamide, chlorambucil, cocaine, fluoxetine, gold salts, melphalan, methotrexate, methyl-CCNU, nilutamide, nitrofurantoin, nitrogen mustard, phenytoin, pindolol, procarbazine, quinidine, sulfasalazine, tocainide, tryptophan
Diffuse Alveolar Damage (DAD)	Amiodarone, amitriptyline, azathioprine, BCNU, bleomycin, busulfan, CCNU, cocaine, colchicine, cyclophosphamide, cytosine arabinoside, gold salts, hexamethonium, melphalan, methotrexate, mitomycin, nitrofurantoin, penicillamine, procarbazine, streptokinase, sulfasalazine, teniposide, vinblastine, zinostatin
OP	Amiodarone, bleomycin, chlorozotocin, cocaine, cyclophosphamide, disodium chromoglycate, gold salts, hexamethonium, interferon, mecamylamine, methotrexate, mitomycin, nilutamide, phenytoin, sulfasalazine, tocainide
BO	CCNU, penicillamine
CEP	Acetominophen, ampicillin, bleomycin, carbamazepine, chlorpropamide, cocaine, disodium chromoglycate, imipramine, mephenesin, nabumetone, naproxen, nitrofurantoin, PAS, phenylbutazone, procarbazine, prontosil, propranolol, pyrimethamine, sulfasalazine, tetracycline, trazodone
Hemorrhagic alveolitis	Amphoteracin B, anticoagulants, cocaine, codeine, cyclophosphamide, epinephrine, haloperidol, heroin, hydralazine, hydrochlorothiazide, mitomycin, nitrofurantoin, penicillamine, propylthiauracil, streptokinase, sulfonamide, urokinase
PE	Buprenorphine, chlordiazepoxide, cocaine, codeine, cytosine arabinoside, epinephrine, haloperidol, heroin, hydrochlorothiazide, isoxsuprine, lidocaine, magnesium sulfate, methadone, methotrexate, mitomycin, nalbuphine, naloxone, nifedipine, paraldehyde, penicillin, propoxyphene, propranolol, ritodrine, salbutamol, salicylates, sulindac, terbutaline
Granulomatous inflammation	Acebutolol, BCG, cocaine, disodium chromoglycate, fluoxetine, methotrexate, nitrofurantoin, procarbazine

DRUG-INDUCED LUNG DAMAGE: BAL FINDINGS

Drugs	Damage induced	BAL findings
Bleomycin, busulfan, cyclophosphamide, methotrexate, nitrosourea	Cytotoxic reaction	Atypical cells Lipoproteinaceous material Increase in eosinophils
Acebutolol, amiodarone, azathioprine, bleomycin, busulfan, cyclophosphamide, gold salts, methotrexate*, nitrofurantoin, propranolol, sulfasalazine	Lymphocytic alveolitis	Lymphocytosis >40% Increased T CD8+ lymphocytes Decreased CD4:CD8 ratio *Increased CD4+ lymphocytes
Bleomycin, busulfan	Neutrophilic alveolitis	Increase in neutrophils
Ampicillin, bleomycin, nitrofurantoin, penicillin, sulfasalazine, tetracycline	Eosinophilic alveolitis	Increase in eosinophils
Amphoteracin B, penicillamine	Hemorrhagic alveolitis	Red blood cells and hemosiderin-laden alveolar macrophages
Amiodarone	Storage disease	Foamy macrophages
Mineral oil	Lipoid pneumonia	Vacuolated alveolar macrophages Sudan stain or Oil red O-positive in alveolar macrophages

Hypersensitivity Pneumonitis

Definition

Hypersensitivity pneumonitis (HP) refers to a group of diffuse granulomatous parenchymal lung diseases caused by the repeated inhalation of and sensitization to a broad variety of low molecular weight organic antigens and chemicals. Clinical presentation may be acute (⌘ HP, acute), subacute (● HP, subacute) or chronic. This chapter deals with the chronic form

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

Etiology and pathogenesis

The number of inciting antigens responsible is high (more than 300) and new antigens are constantly being identified. The most commonly known diseases are "Farmer's lung" caused by the inhalation of Faeni rectivirgula present in moldy hay and "Bird fancier's lung" caused by exposure to avian proteins

Gell- and Coombs type III and type IV immune reactions lie at the basis of the immunopathogenesis of the disease. The progressive fibrotic changes appear to be linked to a dysregulation of fibroblasts in susceptible subjects

Epidemiology

The incidence and prevalence of the disease is difficult to estimate, since individual susceptibility, intensity of exposure in different occupational settings, seasons, geographical areas and proximity of industry vary greatly. The prevalence of "Farmer's lung" varies between 2 and 9%, whereas that of "Bird fancier's lung" varies between 6 and 15%

Risk factors

The chronic form appears to be due to continued exposure to low levels of antigens. Non-smokers are more commonly affected

CLINICAL FEATURES

History

The inciting antigen can be difficult to detect and may remain unknown in some cases. Symptoms of the chronic form are the insidious onset of cough, dyspnea, fatigue and weight loss. Patients may also lack a history of acute episodes

Physical findings

Diffuse fine bibasilar rales are often noted on physical examination. Patients may present signs of wasting and digital clubbing

Pulmonary function tests

Patterns include moderate-to-severe restrictive defect, mixed restrictive and obstructive defect, or rarely an isolated obstructive defect. There is hypoxemia at rest and D_LCO is always reduced

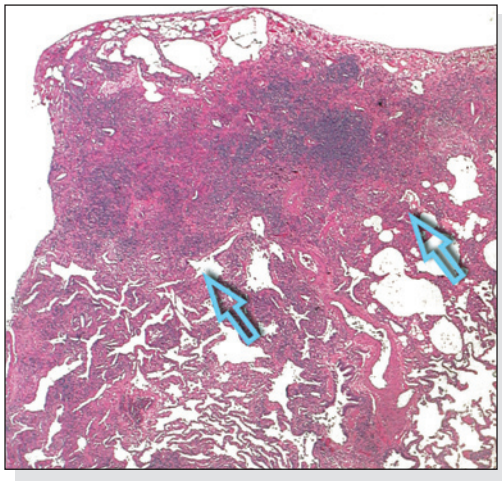
Patel AM. Hypersensitivity pneumonitis: current concepts and future questions. J Allergy Clin Immunol 2001, 108: 661

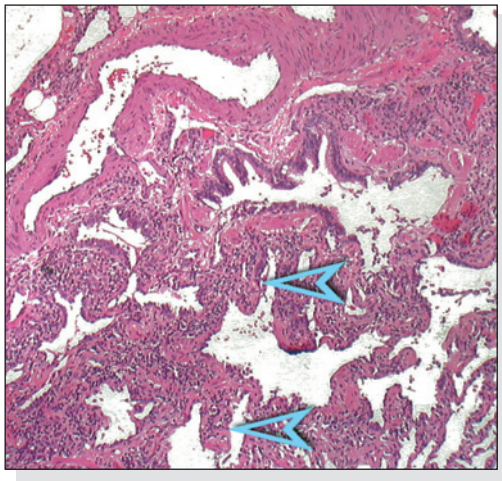
PATHOLOGY

Basic lesions

In the advanced stages, the classic histological triad of HP (mononuclear cell bronchiolitis at times with intraluminal fibroblastic plugs, diffuse chronic inflammatory infiltrates (➢), small non-necrotizing granulomas) may be progressively replaced by:

- Temporally homogeneous fibrosis, which is more or less extensive and non-specific (⇨)
- Remodeled architecture with possible honeycombing





Distribution

Pulmonary fibrosis begins in the peribronchiolar regions and then extends to the alveolar septa

Differentials

Histopathologic differential diagnoses:

- UIP: temporal heterogeneity, distribution of the fibrosis beginning from the subpleural region, scant inflammatory infiltrate
  Absence of granulomas and intraluminal fibroblastic plugs
- NSIP: diffuse, non-bronchiolocentric lesions; granulomas are rare
- Sarcoidosis: well-formed granulomas, often along the lymphatic routes and in the lamina propria of the larger airways; inflammatory infiltrate is scant
  Absence of intraluminal fibroblastic plugs and fibrosis is lamellar

In the series published by Katzenstein and Fiorelli, examples of hypersensitivity pneumonitis were probably included among the cases of NSIP

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127

Coleman A. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 1988, 12: 514

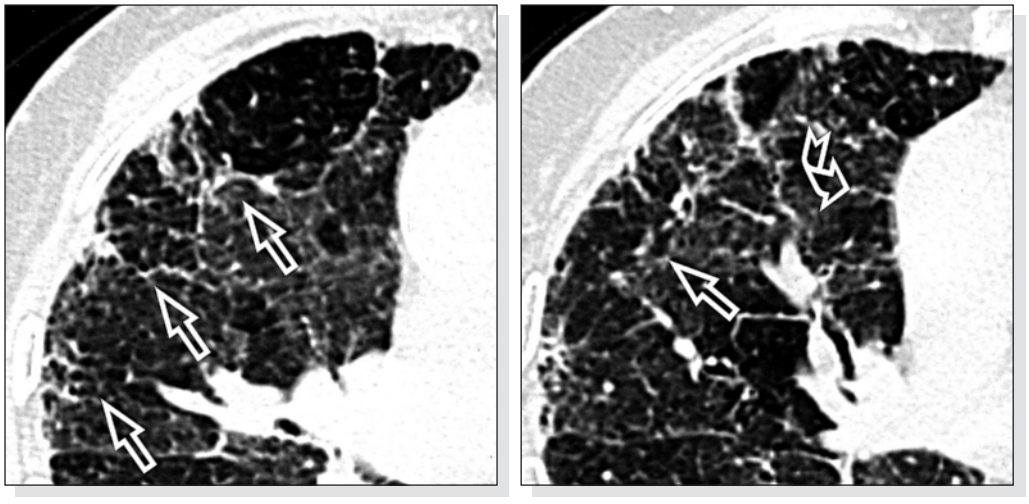
Katzenstein AL. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994, 18: 136

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Irregular interlobular and intralobular nodules (⇨)
- Interface signs (↳)



Distribution

Bilateral, patchy

Variable, possible in peripheral subpleural regions, although also in the peribronchovascular interstitium

Variable

Adler BD. Chronic hypersensitivity pneumonitis: high-resolution CT and radiographic features in 16 patients. Radiology 1992, 185: 91

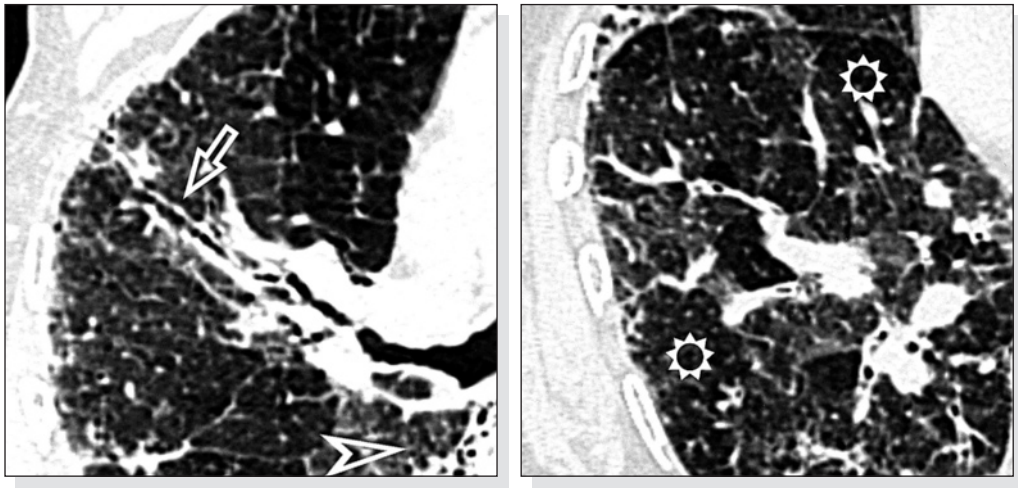
Buschman DL. Chronic hypersensitivity pneumonitis: use of CT in diagnosis. AJR Am J Roentgenol 1992, 159: 957

Lung volume is reduced

Other signs

Other characteristics:

- Traction bronchiectasis and bronchiolectasis (⇨)
- Honeycombing (➢)
- Patchy ground-glass attenuation and subtle centrilobular nodules
- Mosaic oligemia and air-trapping with lobular extension or beyond (☼)



Mosaic oligemia is due to the constrictive bronchiolitis so frequent in this disease

Small JH. Air-trapping in extrinsic allergic alveolitis on computed tomography. Clin Radiol 1996, 51: 684

Parenchymal architecture is deranged. Ground-glass attenuation and nodules typical of the subacute phase are indicative of at least partially reversible disease

Glazer CS. Clinical and radiologic manifestations of hypersensitivity pneumonitis. J Thorac Imaging 2002, 17: 261

Differentials

Radiological differential diagnoses:

If the alterations are prevalently in the lung bases:

- UIP: honeycombing is extensive, patchy, prevalently basal and peripheral
- NSIP: ground-glass attenuation predominates; limited progression towards honeycombing
- Asbestosis: subpleural lines, pleural plaques and rounded atelectasis are often associated; limited progression towards honeycombing
- Collagen vascular diseases: more varied appearances and at times characteristic of the individual diseases

If the alterations are prevalently in the mid-upper zones:

- Sarcoidosis: micronodules are perilymphatic, lymphadenopathies are paratracheal, hilar and mediastinal

Collins J. CT signs and patterns of lung disease. Radiol Clin North Am 2001, 39: 1115

Lynch DA. Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonary fibrosis? AJR Am J Roentgenol 1995, 165: 807

COURSE and COMPLICATIONS

Associated diseases

There is a greater incidence of chronic bronchitis. About one quarter of patients present aspecific bronchial hyperreactivity to methacholine. Pneumothorax or pneumomediastium are rare

The associated chronic bronchitis appears to be linked more to exposure to the inciting antigens than to cigarette smoking

Clinical course

Once fibrosis has developed, the disease is irreversible. Its progression can be more or less rapid, leading to chronic respiratory failure with pulmonary hypertension. Removal from exposure results in only partial improvement and chronic steroid therapy is often necessary. Digital clubbing is observed in the advanced stages of the disease and is a sign of poor prognosis

Radiological course

The radiological progression of the lesions depends on the progression of the disease; when the disease worsens, the reticular pattern and honeycombing are more extensive

Remy-Jardin M. Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. Radiology 1993, 189: 111

Zompatori M. Chronic hypersensitivity pneumonitis or idiopathic pulmonary fibrosis? Diagnostic role of high resolution Computed Tomography (HRCT). Radiol Med 2003, 106: 135

LABORATORY FINDINGS

The presence of serum precipitating antibodies against the offending antigen is a characteristic feature. A slight increase in inflammatory indices (ESR and CRP) as well as a significant increase in quantitative immunoglobulins may be observed

The presence of precipitating IgG and IgM serum antibodies may be considered markers of antigen exposure, although they are not diagnostic, nor does their presence correlate with disease activity

CLINICAL DIAGNOSIS

The chronic form is clinically difficult to differentiate from forms of idiopathic interstitial pneumonia such as UIP or NSIP. An accurate occupational and environmental history is needed to ascertain the potential exposure to the offending antigen. There is little agreement regarding the usefulness of inhalation challenge to the offending antigen. HRCT can be useful with a positive predictive value of 80%

INVASIVE DIAGNOSIS

At this stage, transbronchial lung biopsy rarely reveals parenchymal regions still affected by small, poorly-formed epithelioid non-caseating granulomas. In cases where the history and transbronchial biopsy are not diagnostic, a surgical lung biopsy is required

Bronchoalveolar lavage

At this advanced stage, unlike in the acute form where there are high percentages of lymphocytes, the sediment of the lavage is characterized by an increase in neutrophils (>5%) and eosinophils (>5%). Sometimes lymphocytes (10-20%) may still be present

This mixed alveolitis with an increase in neutrophils, eosinophils and lymphocytes may also be observed in BAL of OP and NSIP

Costabel U. Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med 2001, 7: 255

Pardo A. Increase of lung neutrophils in hypersensitivity pneumonitis is associated with lung fibrosis. Am J Respir Crit Care Med 2000, 161: 1698

Lymphangitic Carcinomatosis

Definition

Lymphangitic carcinomatosis (LC) is the metastatic spread in the lung of intra- or extrapulmonary tumors

In most cases the primary tumor is located in the breast, stomach, pancreas, prostate or in the lung itself

DEMOGRAPHICS

Etiology and pathogenesis

Lymphatic involvement may occur in three ways: hematogenous spread to the pulmonary arterioles followed by invasion of the adjacent interstitium and lymphatics with subsequent spread to the hilum or lung periphery; retrograde dissemination from mediastinal lymph nodes; communication between superior abdominal lymph nodes or lymph nodes of the peritoneal cavity and the lymphatics of the diaphragmatic pleura

Epidemiology

Lymphangitic carcinomatosis is a frequent pattern of cancer spread to the lungs (35-55%)

Risk factors

Primary neoplasm

CLINICAL FEATURES

History

The onset of symptoms is insidious, although disease course is rapid (few months). The most frequent symptom is dyspnea, while a minority of patients present with dry irritative cough (due to involvement of the bronchial submucosa lymphatics). In some patients the symptoms are similar to those of bronchial asthma

Physical findings

Diffuse fine rales can at times be heard in the basal regions

Pulmonary function tests

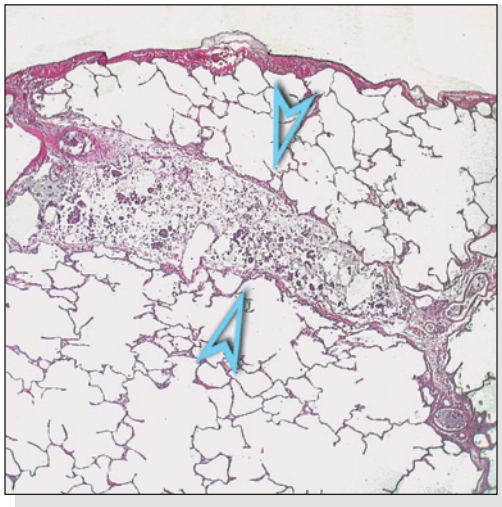
There is a restrictive ventilatory defect with reduced compliance and D_LCO. A rapid respiratory failure, complicated by tumor emboli, leads to hypoxemia and pulmonary arterial hypertension

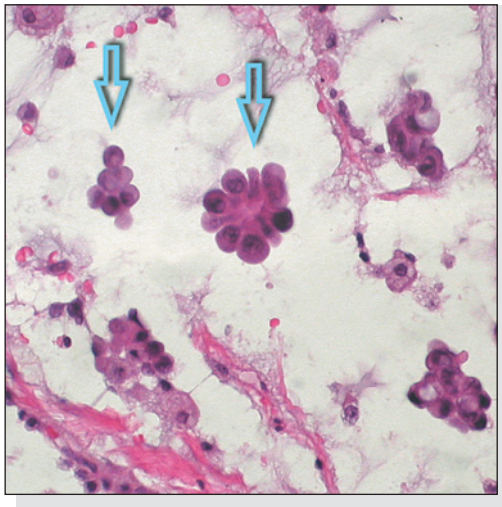
Soares FA. Pulmonary tumor embolism to arterial vessels and carcinomatous lymphangitis. A comparative clinicopathological study. Arch Pathol Lab Med 1993, 117: 827

PATHOLOGY

Basic lesions

Pulmonary architecture is preserved, although the lymphatic vessels appear distended (➢) by cancer cells (⇨). A fibrotic reaction of perilymphatic connective tissue is often present





Distribution

Lymphatic distribution (along the bronchovascular bundles, the pleura, and the interlobular septa)

Differentials

Histopathologic differential diagnoses:

- PE: interalveolar septa are edematous and there are no cancer cells
- Sarcoidosis: granulomas are often present whereas lymphangectasias with cancer cells are lacking
- Hematological malignancies (lymphomas, leukemias): lymphatics contain cancer cells characteristic of each lesion; immunohistochemistry may aid diagnosis

✓ Immunohistochemical techniques can be helpful in identifying the site of the primary lesion

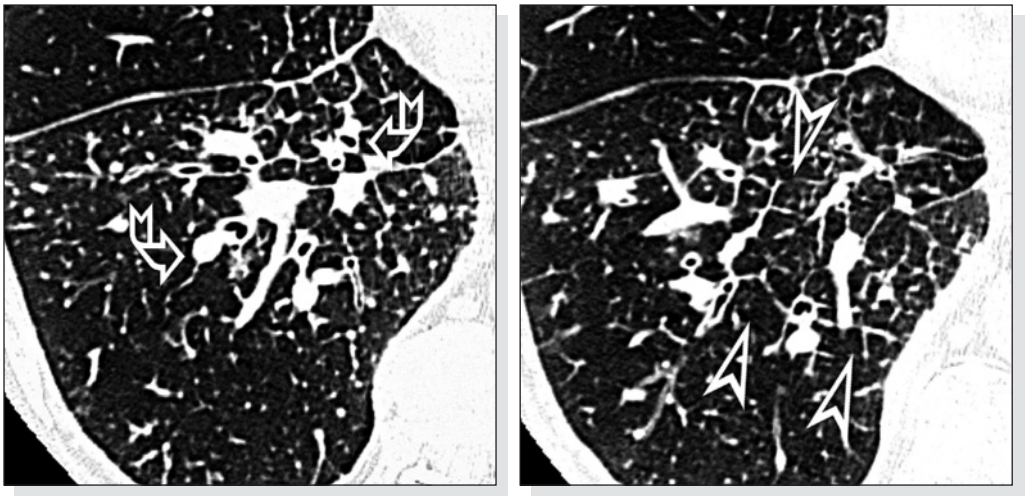
Sweeney S. Vasculitis carcinomatosa occurring in association with adenocarcinoma of the stomach. Ann Diagn Pathol 1998, 2: 247

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Smooth or nodular pattern (beaded appearance) of the interstitium:

- Central peribronchovascular (↳)
- Centrilobular
- Septal (➢)
- Subpleural



Nodular reticular pattern, beaded appearance

Pulmonary architecture is preserved: the lobules, which are more visible than normal in relation to the septal thickening, maintain their morphology

Johkoh T. CT findings in lymphangitic carcinomatosis of the lung: correlation with histologic findings and pulmonary function tests. AJR Am J Roentgenol 1992, 158: 1217

Distribution

Monolateral, more rarely bilateral, patchy

Variable

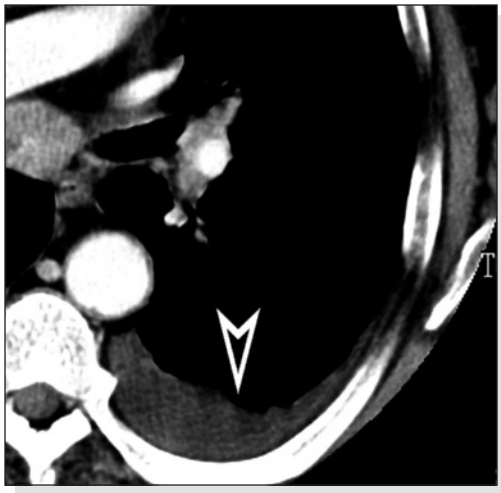
Variable

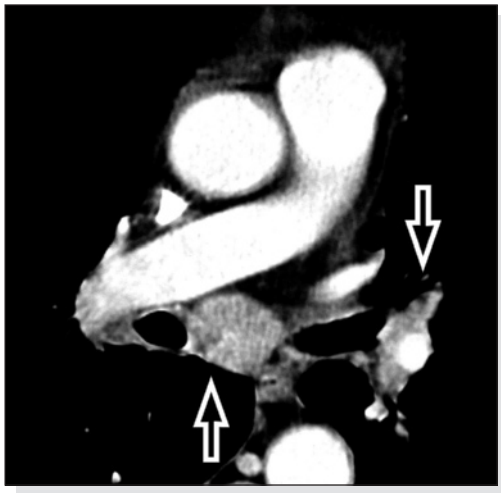
Lung volume is normal

Other signs

Other non-constant characteristics:

- Pleural effusion, often monolateral (50%) (≽)
- Hilar and mediastinal lymphadenopathy (25-50%) (⇨)





Differentials

Radiological differential diagnoses:

- PE: perilymphatic nodules are absent, while ground-glass and consolidation due to associated alveolar edema coexist
- Sarcoidosis: signs are bilateral and located in the upper lobes with possible distortion of lobular architecture; the perilymphatic nodular pattern prevails while pleural effusion is absent
- Silicosis: centrilobular and subpleural nodules in the upper lobes prevail, associated with masses and distortion of the architecture while pleural effusion is absent
- LIP: centrilobular nodules prevail, which may have hazy margins, associated with ground-glass and occasionally cysts

Schaefer-Prokop C. High-resolution CT of diffuse interstitial lung disease: key findings in common disorders. Eur Radiol 2001, 11: 373

COURSE and COMPLICATIONS

Associated diseases

During the course of the disease, episodes of tumor embolism with acute cor pulmonale may arise, and associated pleural effusion is not uncommon

Clinical course

The clinical picture rapidly deteriorates up to the onset of severe pulmonary arterial hypertension. Half of all patients die within three months of diagnosis and only 15% survive longer than six months

Radiological course

The radiological picture may progress towards the presence of numerous metastatic rounded opacities (● Large rounded opacities: Metastases) arising from hematogenous spread of the primary tumor

LABORATORY FINDINGS

The spread of the primary tumor to other organs and the bone marrow may cause microangiopathic hemolytic anemia, thrombocytopenia and lead to the presence of immature granulocytes and nucleated red blood cells in the circulation

CLINICAL DIAGNOSIS

The clinical-radiological picture of the lung is characteristic and in the presence of a known primary tumor may be considered diagnostic, with an HRCT accuracy of 92%

INVASIVE DIAGNOSIS

In the presence of an unknown primary tumor, the diagnosis is based on cytologic (BAL, bronchial washing, pulmonary artery blood sampling, transthoracic needle aspirate, pleural fluid) or pathologic specimens (transbronchial or surgical lung biopsy)

Bronchoalveolar lavage

Bronchoalveolar lavage fluid often reveals cancer cells (65-70%) and a non-specific increase in lymphocytes

The reactive type II pneumocytes seen in the BAL fluid during various idiopathic interstitial pneumonias and in the organizing phase of diffuse alveolar damage may appear so atypical as to be confused with cancer cells

Levy H. The value of bronchial washings and bronchoalveolar lavage in the diagnosis of lymphangitic carcinomatosis. Chest 1988, 94: 1028

Non-Specific Interstitial Pneumonia

Definition

Non-specific interstitial pneumonia (NSIP) is one of the idiopathic interstitial pneumonias which in certain aspects is similar to UIP (□ UIP, early), although it often has a more favorable prognosis

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

The general term idiopathic interstitial pneumonias (IIP) includes various diseases, and in particular usual interstitial pneumonia (□ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

DEMOGRAPHICS

Etiology and pathogenesis

Although the etiology is unknown, the temporal appearance of the histologic changes regardless of the stage of disease suggests a single triggering event

Epidemiology

The mean age at onset is 40-50 years, although children may also be affected. The disease equally affects males and females. NSIP is less common than UIP, but much more common than the other idiopathic interstitial pneumonias. There is no correlation between the disease and cigarette smoking

Risk factors

None are known

CLINICAL FEATURES

History

Onset is mainly subacute. The duration of symptoms to the moment of diagnosis varies from 18 to 31 months. The most common symptoms are exertional dyspnea, cough and fatigue, while half of patients report weight loss and one third fever

Physical findings

Physical examination is characterized by fine bibasilar crackles and in some cases inspiratory squeaks. Clubbing has been reported in 10 to 35 percent of cases

Pulmonary function tests

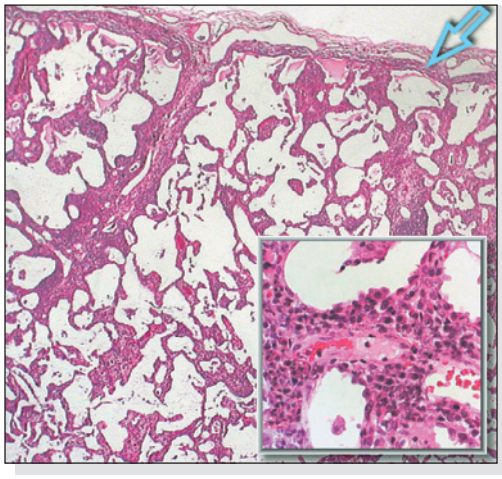
All patients have reduced D_LCO, and there is a concurrent restrictive defect in 90 percent of cases. A minority of patients also have a mild obstructive syndrome, whereas two thirds show exertional hypoxemia

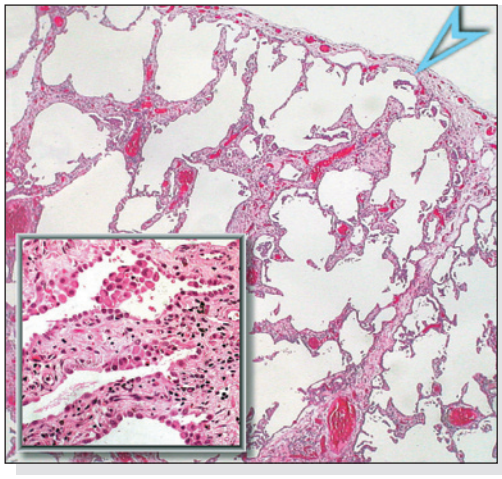
PATHOLOGY

Basic lesions

Histologic features are fibrosis and inflammation of the alveolar interstitium to varying degrees. The distribution of the lesions is uniform (spatial homogeneity) and the disease appears in the same phase (temporal homogeneity), with rare or absent fibroblastic foci. Two types of disease can be identified according to whether fibrosis or inflammation is prevalent:

- Cellular NSIP (⇨): the inflammatory infiltrate, composed of lymphocytes and plasma cells, is moderately intense and prevails over the fibrosis
- Fibrosing NSIP (⩾): dense or loose fibrosis predominates and expands the alveolar septa, while the inflammatory infiltrate, composed of lymphocytes and rare plasma cells, is mild





Although NSIP may also present with a patchy distribution, with a relatively normal intercurring parenchyma, in contrast to UIP the appearance within each individual focus is characteristically uniform

Distribution

Diffuse interstitial

In the fibrosing form, if the fibrosis has an irregular and subpleural distribution, the lack of fibroblastic foci is critically important. In contrast to UIP, such foci are neither common nor situated at the interface between normal parenchyma and fibrotic areas

Differentials

Histopathologic differential diagnoses:

- UIP: spatial and temporal heterogeneity with fibroblastic foci at the interface between normal parenchyma and fibrotic areas. The fibrosis is prevalent in subpleural regions
- HP: intense lymphoplasmacellular infiltrate, poorly-formed interstitial granulomas, centrilobular lesions
- Organizing diffuse alveolar damage (DAD): loose fibrosis and septal thickening; marked type II pneumocyte hyperplasia
- Well-differentiated lymphocytic lymphoma: dense and diffuse neoplastic lymphoid infiltrate composed mainly of small lymphocytes with frequent pleural infiltration; lymphoepithelial complexes in BALT
- DIP: The alveoli are filled with pigmented macrophages; inflammatory infiltrate and interstitial fibrosis are mild

Katzenstein AL. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994, 18: 136

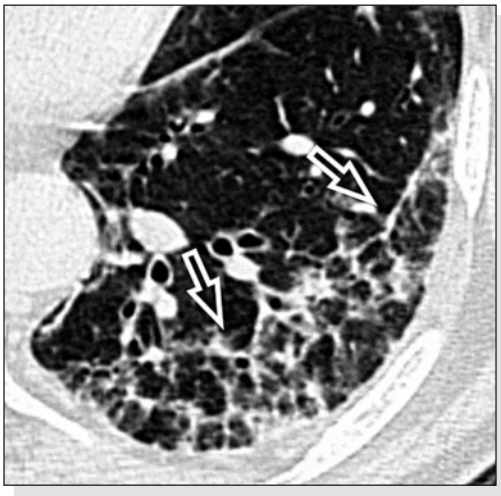
Travis WD. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000, 24: 19

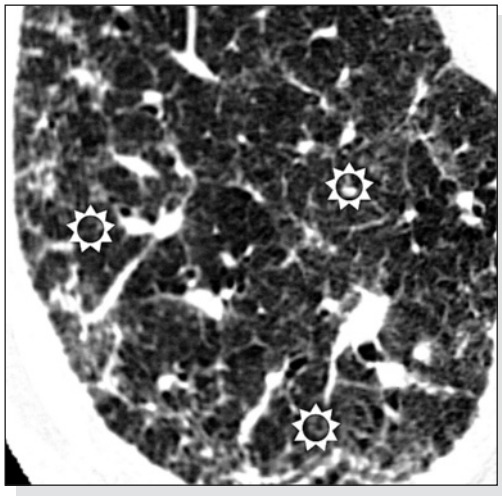
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Reticular opacities (>30%) (⇨)
- Ground-glass (100%) (☼)
- Areas of parenchymal consolidation (40-70%)





Hartman TE. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. Radiology 2000, 217: 701

Johkoh T. Nonspecific interstitial pneumonia: correlation between thin-section CT findings and pathologic subgroups in 55 patients. Radiology 2002, 225: 199

Distribution

Bilateral, symmetrical, often patchy

Peripheral, although also central; less commonly diffuse

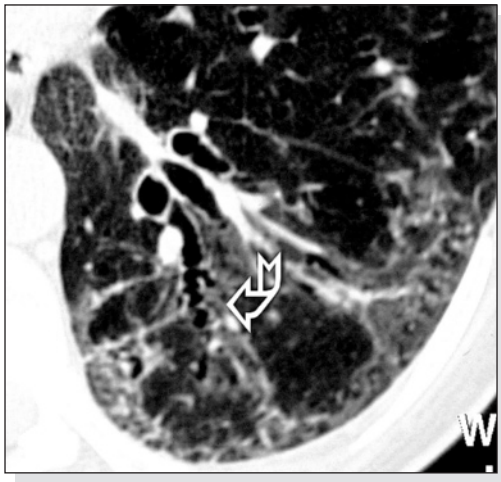
Basal

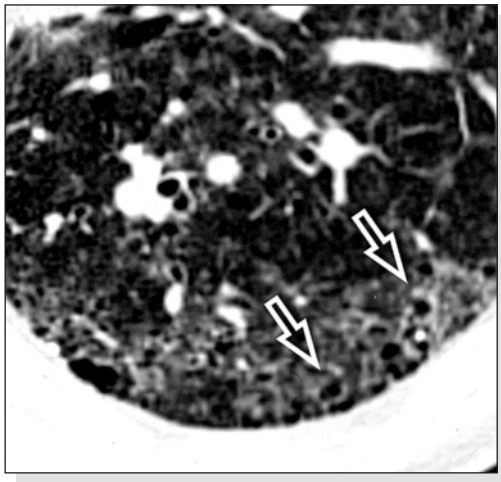
Lung volume is normal or slightly reduced

Other signs

Other non-constant characteristics:

- Bronchial wall thickening
- Traction bronchiectasis (↯) within the opacities
- Honeycombing (< 25%) (⇨)





In NSIP, bronchiectasis is not necessarily an indication of irreversible fibrosis, as the fibrosis may regress with therapy (in contrast to UIP)

Johkoh T. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999, 211: 555

Kim TS. Nonspecific interstitial pneumonia with fibrosis: high-resolution CT and pathologic findings. AJR Am J Roentgenol 1998, 171: 1645

Differentials

Radiological differential diagnoses:

- UIP: clearly peripheral reticular pattern, even in the upper lung regions; ground-glass is limited and honeycombing is more common
- DIP: ground-glass is dominant and the reticular pattern is limited or absent
- OP: consolidations prevail and tend to be peripheral but also bronchocentric
- HP: clear predominance of the reticular pattern over ground-glass

Polverosi R. Idiopathic interstitial pneumonias. Radiol Med 2003, 105: 403

COURSE and COMPLICATIONS

Associated diseases

It should be noted that an NSIP histopathologic pattern may be present in association with other clinical conditions such as collagen vascular diseases (☐ Collagen vascular diseases, early), hypersensitivity pneumonitis (☐ HP, chronic), drug-induced pneumonia (☐ Drug toxicity), radiation, infections and immunodeficiencies including HIV+ status. NSIP in these cases is a pattern of lung reaction to different stimuli

Clinical course

The prognosis of NSIP is more favorable than that of UIP (☐ UIP, early) and appears to be correlated with the extent of fibrosis present at surgical biopsy. Although there have been no reported cases of spontaneous remission, the literature does report cases of stabilization, improvement and even complete recovery in up to 75% of treated cases, even though relapse is possible if treatment is discontinued. Only in a minority of cases does the disease progress, leading to death from respiratory failure

Radiological course

The areas of ground-glass and consolidation may decrease with cortisone treatment (>80% of cases), whereas in cases of disease progression the irregular reticular opacities may develop into fibrosis with honeycombing

Akira M. Non-specific interstitial pneumonia: findings on sequential CT scans of nine patients. Thorax 2000, 55: 854

Nishiyama O. Serial high resolution CT findings in nonspecific interstitial pneumonia/fibrosis. J Comput Assist Tomogr 2000, 24: 41

LABORATORY FINDINGS

ESR is elevated and about half of patients also have increased CRP and fibrinogen. Some patients may have low-titer antinuclear antibody positivity

CLINICAL DIAGNOSIS

In a patient with suspected idiopathic interstitial pneumonia, the presence of patchy or subpleural ground-glass opacities and limited reticulation is strongly suggestive of NSIP, whereas if honeycombing is predominant on HRCT, the most likely diagnosis is UIP. In contrast to other diseases, however, lung biopsy is essential given the possible association of the two conditions in different lobes or even in the same lobe, a feature which influences prognosis and treatment options

Flaherty KR. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 2001, 164: 1722

INVASIVE DIAGNOSIS

Diagnostic confirmation can only be provided by surgical lung biopsy. Transbronchial lung biopsy is of no use

Bronchoalveolar lavage

About 50% of patients present with increased lymphocytes and reduced CD4:CD8 ratio (cellular NSIP), whereas another 50% of cases present with increased neutrophils and eosinophils (fibrosing NSIP). These two patterns may also be present simultaneously. BAL is unable to distinguish between UIP and fibrosing NSIP

Nagai S. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998, 12: 1010

Veeraraghavan S. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003, 22: 239

Pulmonary Edema

Definition

Pulmonary edema refers to the accumulation of fluid in the interstitium and in more severe cases in the alveoli (⌘ PE, alveolar)

Cardiogenic, hemodynamic edema

DEMOGRAPHICS

Etiology and pathogenesis

The volume of water and the movement of proteins in the lung depend on the equilibrium achieved between the hydrostatic and intra- and extravascular osmotic pressures and the permeability of the alveolar-capillary membrane. An increase in hydrostatic pressure produces an increase in the transudation of excess fluid (edema) from the microcirculation to the extravascular compartment, with an accumulation initially in the pulmonary interstitium and then in the alveolar spaces

The most common cause of pulmonary edema is cardiogenic (left ventricular systolic or diastolic dysfunction, left atrial outflow impairment). Less common causes result from a reduction in capillary osmotic pressure (renal disease, liver cirrhosis, fluid overload), neurogenic alterations (head injury, increase in intracranial pressure, non-hemorrhagic stroke) and diseases of the pulmonary veins (idiopathic veno-occlusive disease, fibrosing mediastinitis)

Epidemiology

Pulmonary edema is a frequent cause of admission to the hospital

Risk factors

These include diseases affecting the function of the left atrium and ventricle, liver cirrhosis and kidney failure

CLINICAL FEATURES

History

In this stage of the disease (interstitial edema) the onset of symptoms is gradual and insidious. At times the main symptoms of dry cough and dyspnea are only present on exertion. Orthopnea and paroxysmal nocturnal dyspnea are relatively rare

Physical findings

Physical examination of the lung is often negative, although wheezes may be heard. Auscultation may reveal a gallop rhythm in cases of valvular dysfunction. Some patients present hepatojugular reflux without peripheral edema

Pulmonary function tests

In interstitial edema, the only functional deficits observed are reduced compliance and increased lung resistance. Some patients present bronchial hyperreactivity, while mild hypoxemia with normal-hypocapnia may also be present

In these patients the most common differentials are bronchial asthma and chronic obstructive lung disease

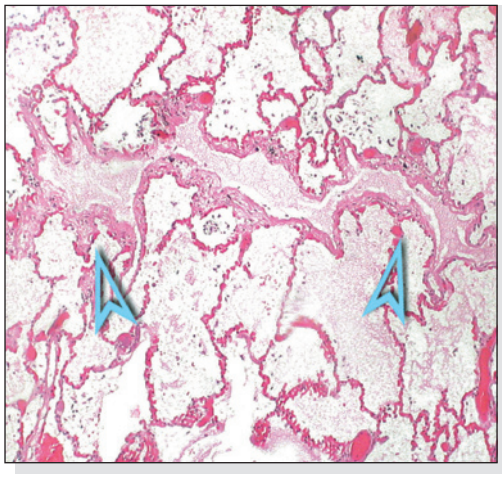
Gandhi SK. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001, 344: 17

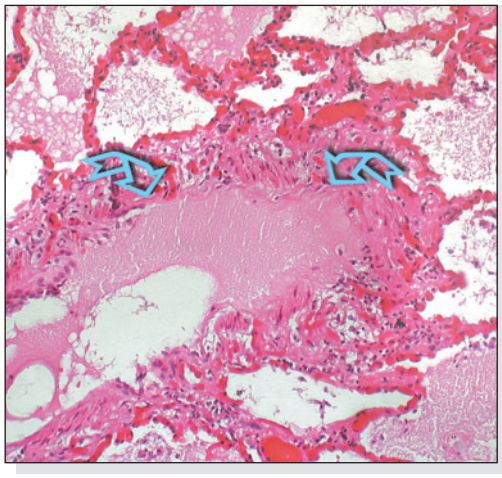
Gropper MA. Acute cardiogenic pulmonary edema. Clin Chest Med 1994, 15: 501

PATHOLOGY

Basic lesions

These include interstitial accumulation of fluid, particularly in the interlobular septa (➢) which appear expanded. Lymph vessel ectasia also occurs (➴)





Distribution

Interlobular, perivascular, peribronchial and subpleural interstitium

Differentials

Histopathologic differential diagnoses:

- Normal lung parenchyma: no lymphangiectases, and normal interlobular septa
- ARDS and AIP: presence of hyaline membrane, and thrombosis of small vessels
- LC: dilated lymph vessels contain carcinomatous cells

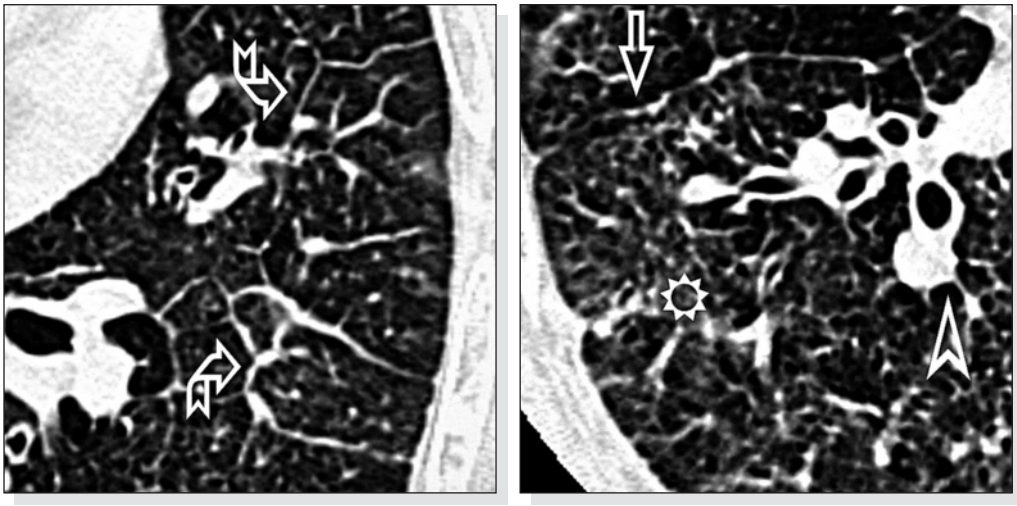
Colby TV. Pulmonary histology for the surgical pathologist. Am J Surg Pathol 1988, 12: 223

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Smooth thickening of the interlobular (↳) and intralobular (☼) interstitium
- Smooth thickening of peribronchovascular connective tissue (➢)
- Smooth thickening of subpleural connective tissue (⇨)



Storto ML. Hydrostatic pulmonary edema: high-resolution CT findings. AJR Am J Roentgenol 1995, 165: 817

Distribution

Bilateral, diffuse

Central, peribronchovascular in parahilar and dependent regions

Basal, gravity-dependent

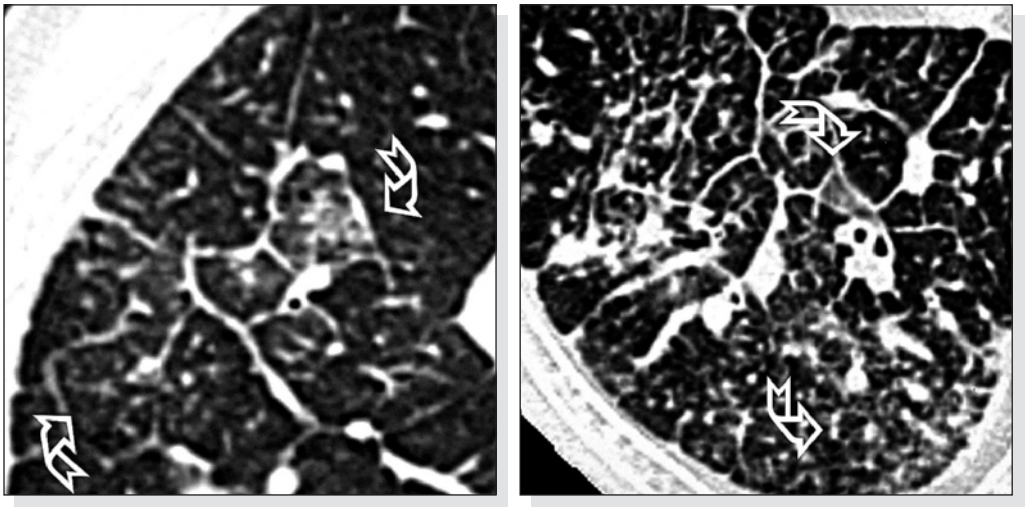
Lung volume is normal

Gluecker T. Clinical and radiologic features of pulmonary edema. Radiographics 1999, 19: 1507

Other signs

Other characteristics:

- Patchy ground-glass (↳)
- Acinar-sized hazy nodules
- Pleural effusion, which is often bilateral
- Increased diameter of pulmonary vessels and enlargement of left heart



Differentials

The main radiological differential diagnosis is:

- LC: changes with less uniform distribution, while the reticular pattern is more commonly nodular with well-defined margins

Schaefer-Prokop C. High-resolution CT of diffuse interstitial lung disease: key findings in common disorders. Eur Radiol 2001, 11: 373

COURSE and COMPLICATIONS

Associated diseases

In the presence of suspected pulmonary edema, the function of the various organs (heart, kidneys, etc.) involved in the pathogenesis of edema should be investigated

Clinical course

Interstitial pulmonary edema may progress towards alveolar pulmonary edema and acute respiratory failure (⌘ PE, alveolar). The progression from chronic pulmonary edema to mild interstitial fibrosis has also been reported

Radiological course

Interstitial edema may regress or progress towards the alveolar stage (⌘ PE, alveolar); in the latter case, the interstitial signs become increasingly masked by alveolar signs

LABORATORY FINDINGS

Basic lab studies may be performed, although they are not indispensable for the diagnosis or for planning treatment. Nonetheless, they may be useful for excluding possible precipitating factors, such as concurrent infections or anemia

Cardiac enzyme levels are important for excluding the presence of myocardial infarction, just as altered creatinin may reveal underlying renal failure. Measurement of plasma brain natriuretic peptide (BNP) may be useful to distinguish heart failure from lung disease as a cause of dyspnea

CLINICAL DIAGNOSIS

Diagnosis is often achieved on the basis of clinical and radiological settings. Clinical suspicion may be confirmed by non-invasive instrumental investigations such as BNP plasma levels, electrocardiogram and echocardiography

HRCT is performed when there is a discrepancy between clinical history and radiological progression

INVASIVE DIAGNOSIS

Bronchoalveolar lavage

Pulmonary edema is not an indication to perform BAL, which even if performed would reveal a pattern similar to that of diffuse hemorrhagic alveolitis (⌘ DAH), associated with an increased number of red blood cells, siderophages and neutrophils

Nakos G. Proteins and phospholipids in BAL from patients with hydrostatic pulmonary edema. Am J Respir Crit Care Med 1997, 155: 945

Sarcoidosis

Definition

Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology characterized by non-caseating epithelioid granulomas in involved organs. As a result the disease tends to present an HRCT nodular pattern (● Sarcoidosis, granulomatous), although it may occasionally have a fibrosing reticular appearance. The latter of these two forms will be covered in this chapter

DEMOGRAPHICS

Etiology and pathogenesis

The mechanism which causes the progression towards fibrosis is thought to be a shift of pulmonary T cells towards the production of Th2-type cytokines with a consequent fibroproliferative response with extracellular matrix deposition

Epidemiology

Fewer than 10% of lung sarcoidosis cases progress to the fibrosing form

Risk factors

The disease is 3-4 times more common and more severe among Afro-Americans than whites. Negative prognostic factors include lupus pernio, chronic uveitis, hypercalcemia, nephrocalcinosis, cystic bone lesions and nervous system involvement

CLINICAL FEATURES

History

At this stage patients present with dyspnea on exertion and dry cough

Physical findings

Physical examination may be normal, although at times fine localized rales may be present. Clubbing is not frequently found in chronic fibrosing sarcoidosis. In the more severe cases, chronic cor pulmonale (jugular turgor, peripheral edema, hepatomegaly, systolic ejection murmur at the pulmonary foci, etc.) may be observed

Pulmonary function tests

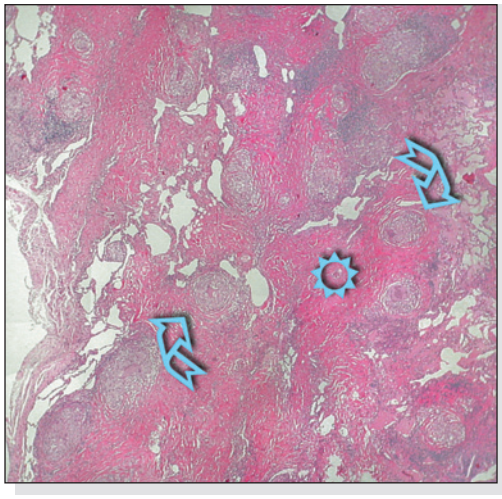
A more or less serious restrictive syndrome may be present in relation to the extent of fibrosis, and reduction in D_LCO. Patients present with hypoxemia on exertion and in the more severe cases even at rest

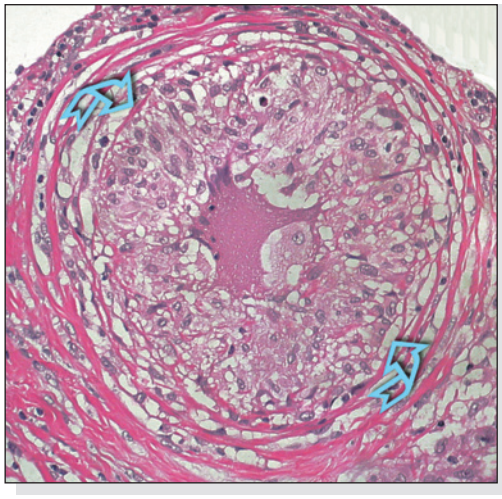
Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Am J Respir Crit Care Med 1999, 160: 736

PATHOLOGY

Basic lesions

Non-caseating epithelioid granulomas (↳) typical of sarcoidosis are associated with a variable amount of fibrosis (☼). The fibrosis in the individual granulomas displays a centripetal pattern (from the outer edge to the center of the granuloma). Hyaline and lamellar fibrosis deposits in the interstitium, at first maintaining its distribution along the lymphatics, whereas in advanced disease the fibrosis extends to the lung, transforming it into a fibrotic mass. There may even be a mild interstitial inflammatory infiltrate





✓ In cases of extensive fibrosis, the underlying disease can be identified by the presence of residual granulomas

Distribution Along the lymphatic routes in the early stages (along the bronchovascular bundles, in the interlobular septa and subpleural) and diffuse in the advanced stages

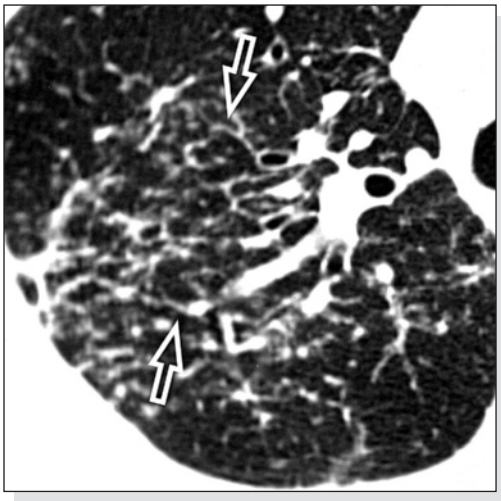
Differentials Histopathologic differential diagnoses:

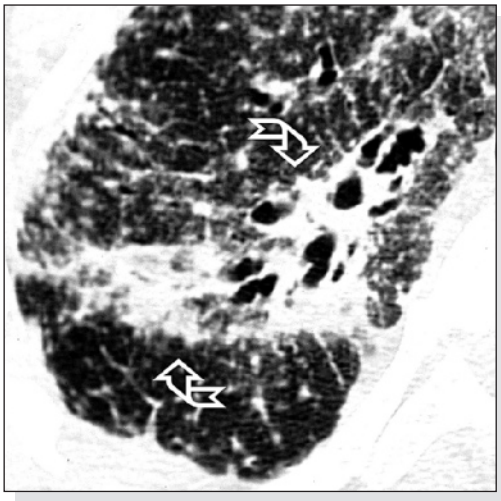
- NSIP: alveolar septa are uniformly thickened without a prevalently lymphatic distribution, while granulomas are rare
  The interstitial inflammatory infiltrate is more abundant
- HP: lesions are centrilobular, there is intense lymphoplasmacellular inflammation, and granulomas are poorly formed
- UIP: fibrosis tends to be distributed in the subpleural regions and along the interlobular septa
  Fibroblastic foci are present at the interface with normal parenchyma; granulomas are absent

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions Basic radiological signs:

- Irregular reticular pattern with parenchymal distribution (⇨)
- Conglomerates of hilar-parahilar opacities (↳)
- Traction bronchiectasis within the opacities





Distribution Bilateral, patchy

Predominantly central, especially dorsal

Upper lung regions

Lung volume is reduced, and the bronchi and major vessels tend to be displaced posteriorly

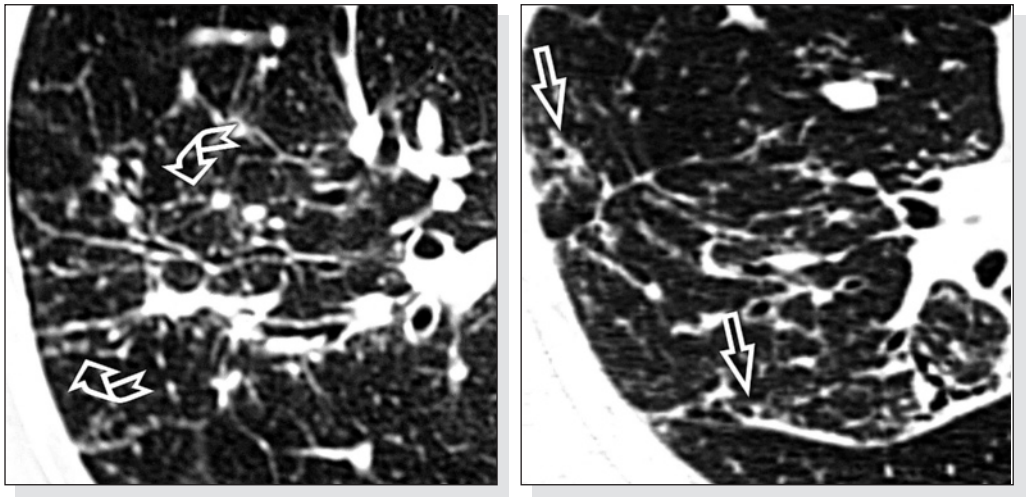
Abehsera M. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 2000, 174: 1751

Traill ZC. High-resolution CT findings of pulmonary sarcoidosis. AJR Am J Roentgenol 1997, 168: 1557

Other signs

Other radiological characteristics:

- Nodules in subpleural zones and along the peribronchovascular connective tissue (↳)
- Hilar-mediastinal lymphadenopathy, possibly calcified
- Sporadic honeycombing (⇨)



Lynch DA. Computed tomography in pulmonary sarcoidosis. J Comput Assist Tomogr 1989, 13: 405

Differentials

Radiological differential diagnoses:

- HP: alterations are predominantly subpleural with a patchy distribution, whereas perilymphatic nodules are absent
- Radiation-induced lung injury: fibrosis selectively affects the irradiated site
- UIP: alterations are prevalently located in the peripheral regions and lung bases, with a predominance of honeycombing

COURSE and COMPLICATIONS

Associated diseases

In this stage superinfection of the cystic spaces created by the fibrosis may be seen, particularly by aspergillus, whereas pneumothorax is relatively rare

The presence of hemoptysis is sufficient cause for suspecting aspergillus superinfection

Clinical course

Spontaneous resolution of the disease in this stage has never been documented. The fibrosis may gradually lead to respiratory failure and chronic cor pulmonale

Radiological course

Conglomerates of the bronchi and vessels may be seen within the opacities, with possible cavitations and mycetomas

LABORATORY FINDINGS

The increase in ESR and serum ACE is less pronounced in the fibrosing form than in the nodular form (● Sarcoidosis, granulomatous). In two thirds of patients the Mantoux skin test is negative

CLINICAL DIAGNOSIS

The diagnosis is based on a compatible clinico-radiological setting and the definite exclusion of other granulomatous diseases

INVASIVE DIAGNOSIS

When active lung disease is still present (nodular or ground-glass radiological appearance), a transbronchial lung biopsy is useful for confirming the granulomatous nature of the lesions

Bronchoalveolar lavage

BAL is not as characteristic as in the nodular form (● Sarcoidosis, granulomatous), exhibiting an increase in total cells, lymphocytes (smaller than the nodular form) and neutrophils (>3%). An increase in CD8+ T-cells and mastocytes (>1%) has been documented

Poulter LW. The value of bronchoalveolar lavage in the diagnosis and prognosis of sarcoidosis. Eur Respir J 1990, 3: 943

Usual Interstitial Pneumonia

Definition

Usual interstitial pneumonia (UIP) is the histopathologic pattern of idiopathic pulmonary fibrosis (IPF), a chronic fibrosing interstitial lung disease of unknown etiology. The term UIP has become so well known as to often be used as a substitute of IPF even in clinical practice. If studied in the early stage, the condition exhibits a predominantly reticular pattern

Idiopathic Pulmonary Fibrosis (IPF), Cryptogenic Fibrosing Alveolitis (CFA)

The general term idiopathic interstitial pneumonias (IIP) includes various diseases, and in particular usual interstitial pneumonia (□ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

DEMOGRAPHICS

Etiology and pathogenesis

The etiology of IPF is unknown. There are two prevailing theories regarding pathogenesis:

1. Inflammatory theory. In the early stage of disease, chronic interstitial and alveolar inflammation (macrophages, neutrophils, eosinophils) damages the lung structure and increases production of fibrogenic cytokines with a consequent exaggerated reparative response leading to end-stage fibrotic disease

2. Fibroblast dysregulation. Following an unknown insult, an exaggerated reparative response characterized by the migration and proliferation of fibroblasts, reduced apoptosis of the fibroblasts themselves and increased response to fibrogenic cytokines takes place. This situation is associated with an absence of re-epithelization of the alveolar structures and inappropriate remodeling of the extracellular matrix

Epidemiology

A prevalence rate of 20.2 cases per 100,000 for males and 13.2 cases for females has been reported. Mean age at diagnosis is 66 years, and the incidence increases with age. The disease has no geographical or racial predilection, although familial cases have been reported

Risk factors

These are thought to include antidepressant drugs, chronic gastroesophageal reflux, inhalation of metal and wood dust, and smoking (1.6-2.3 times), although their importance in the pathogenesis of the disease is unknown

CLINICAL FEATURES

History

The onset of symptoms is insidious; in most patients symptoms are present for > 6 months before diagnosis. The most common symptoms are breathlessness with exertion and dry cough. Constitutional symptoms are rare and include weight loss and fatigue. Joint and muscle pain may also be present

Physical findings

Most patients present with tachypnea. In the early stages, fine diffuse bilateral rales are detected in the posterior lung bases. With progression of the disease the rales extend throughout the lungs. Clubbing occurs in 25-50% of cases

Pulmonary function tests

Lung function tests reveal a mild-to-moderate restrictive defect, reduced D_LCO and mild hypoxemia at rest which worsens on exertion. Smokers may also exhibit an obstructive defect. Although rare, normal pulmonary function tests have been reported at diagnosis

Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000, 161: 646

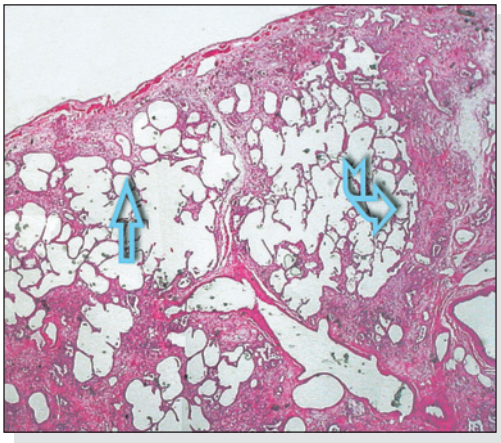
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

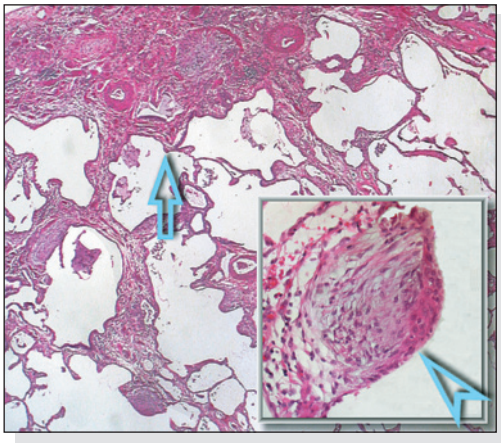
PATHOLOGY

Basic lesions

The lesions in early UIP are:

- Small fibrotic areas starting in the subpleural regions (⇨) or in the interlobular septa (↳), and less commonly along the bronchovascular bundles. The lung architecture is slightly modified
- Extensive areas of normal parenchyma between pathological areas
- Characteristic fibroblastic foci (➢) at the interface between normal lung and fibrotic areas





☝ Spatial heterogeneity (areas of fibrosis alternating with areas of normal parenchyma) and temporal heterogeneity ("old" fibrosis alternating with areas with "young" fibroblastic foci) are characteristic

Distribution

Subpleural and paraseptal

Differentials

Histopathologic differential diagnoses:

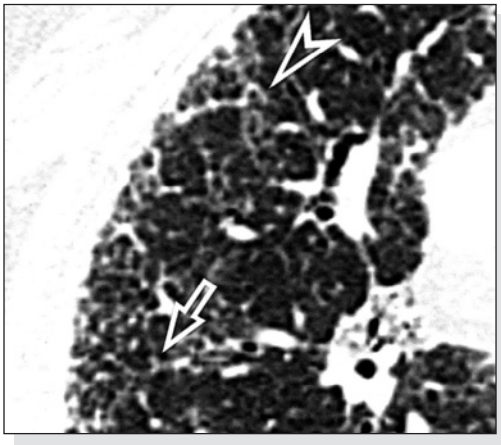
- NSIP: lesions are spatially and temporally homogeneous, lacking fibroblastic foci
- HP: peribronchiolar distribution, presence of granulomas and a more intense inflammatory interstitial infiltrate
- LCH: centrilobular stellate nodules containing a mixed infiltrate with Langerhans' cells and often eosinophils
- Asbestosis: fibrosis is centrilobular, at least in the early stages, and asbestos bodies are present

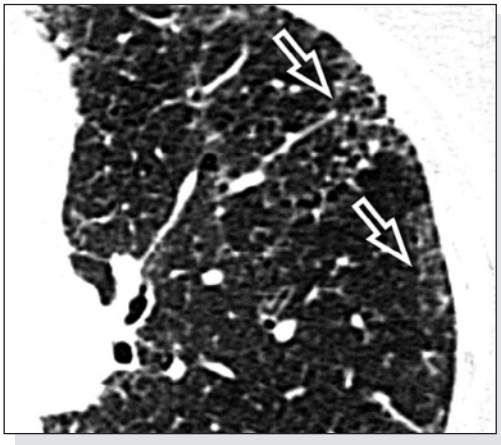
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

The HRCT pattern commonly shows irregular reticulation:

- Intralobular (more evident) (⇨)
- Interlobular (less evident) (➢)





A characteristic feature of the disease is the subversion of the lobular architecture produced by the fibrosis

Muller NL. Idiopathic interstitial pneumonias: high-resolution CT and histologic findings. Radiographics 1997, 17: 1016

Distribution

Bilateral, patchy, interspersed between more-or-less extensive areas of unaffected parenchyma in relation to which the pathological zones are clearly defined

Preferentially peripheral (subpleural), predominantly dorsal

From the apices to the bases along the entire subpleura, but predominant basal

Hunninghake GW. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. Chest 2003, 124: 1215

Polverosi R. Idiopathic interstitial pneumonias. Radiol Med 2003, 105: 403

Lung volume is normal or only slightly reduced in this phase

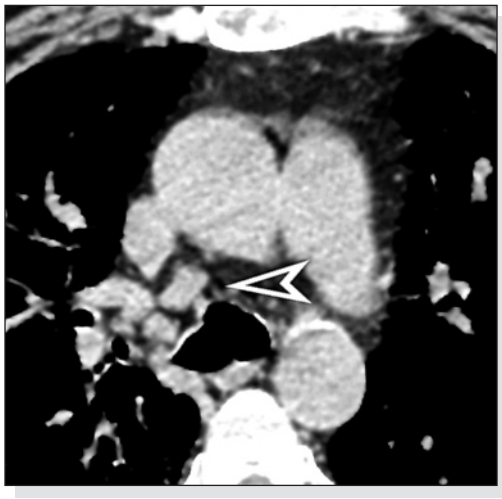
McAdams HP. The alphabet soup revisited: the chronic interstitial pneumonias in the 1990s. Radiographics 1996, 16: 1009

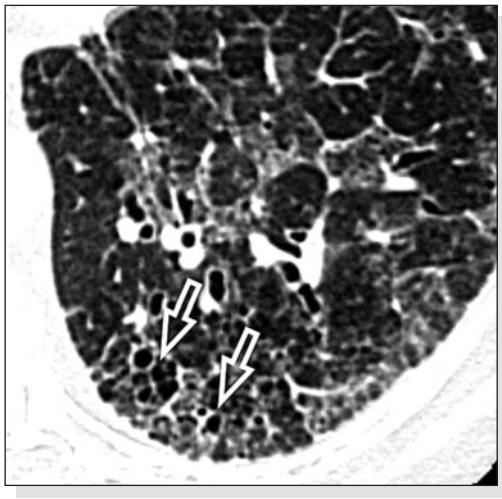
Johkoh T. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999, 211: 555

Other signs

Other radiological characteristics:

- Reactive enlargement of mediastinal lymph nodes (70-90%) (≥)
- Ground-glass (limited)
- Honeycombing (⇨) (limited in this phase of the disease)





The ground-glass may be linked not only to the presence of areas of alveolitis and active fibroblast proliferation, but also to the intralobular septal thickening caused by mild fibrosis

The presence of irregular dilatation within the ground-glass areas is a sign of irreversible fibrosis, as is a cystic pattern, which indicates progression from reticular alterations towards honeycombing

Bergin C. Mediastinal lymph node enlargement on CT scans in patients with usual interstitial pneumonitis. AJR Am J Roentgenol 1990, 154: 251

Lee JS. Fibrosing alveolitis: prognostic implication of ground-glass attenuation at high-resolution CT. Radiology 1992, 184: 451

Differentials

Radiological differential diagnoses:

- NSIP: ground-glass prevails and the lesions are less noticeably peripheral. Involvement of upper subpleural zones is rare, as is honeycombing
- Asbestosis: subpleural branching or dotlike opacities, subpleural lines and parenchymal bands
- Collagen vascular diseases: ground-glass and consolidations containing bronchiectasis and bronchiolectasis
- Drug toxicity: ground-glass and consolidations prevail

COURSE and COMPLICATIONS

Associated diseases

Subjects with idiopathic pulmonary fibrosis tend to have an increased incidence of lung carcinoma, both adenocarcinoma and squamous cell carcinoma

Park J. Lung cancer in patients with idiopathic pulmonary fibrosis. Eur Respir J 2001, 17: 1216

Clinical course

The disease follows a relentlessly progressive course (O UIP, advanced). Mean survival time from diagnosis is 2.5-3.5 years. Most patients (40%) die of respiratory failure, often hastened by concurrent infections, while 20% die of cardiovascular complications. A small percentage of IPF patients may present acute exacerbation of their disease (accelerated phase of IPF), characterized by diffuse alveolar damage (DAD)

In the event of rapid worsening of the patient's condition, the differential diagnosis between an acute exacerbation of their underlying disease and possible complications such as pneumothorax, pulmonary embolism, infection, left heart failure and drug toxicity is vital

Radiological course

Progress towards honeycombing (O UIP, advanced) is accompanied by a progressive reduction in lung volume in relation to the severity of fibrosis

Gay SE. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998, 157: 1063

Lee JS. Usual interstitial pneumonia: relationship between disease activity and the progression of honeycombing at thin-section computed tomography. J Thorac Imaging 1998, 13: 199

LABORATORY FINDINGS

Non-specific increases in ESR, quantitative immunoglobulins and LDH levels may be seen. In 10-20% of patients low titer-positive antinuclear antibodies or rheumatoid factor may be slightly increased

The presence of a titer-positive antinuclear antibodies higher than 1:160 should suggest a collagen vascular disease. Indeed, some collagen vascular diseases (particularly scleroderma) may present with lung involvement similar to that of IPF which may even precede by months or years the more typical systemic manifestations

CLINICAL DIAGNOSIS

In an immunocompetent adult the presence of all of the following major diagnostic criteria as well as at least three of the four minor criteria is considered suggestive of IPF in the absence of a surgical lung biopsy

Major criteria: 1) exclusion of other known causes of diffuse infiltrative lung disease such as drug toxicities, environmental exposures and connective tissue diseases; 2) Abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity often with an increased FEV1/FVC ratio) and impaired gas exchange (decreased D_LCO or increased alveolar-arterial oxygen gradient); 3) bibasilar reticular abnormalities with minimal ground-glass opacities at HRCT scans; 4) transbronchial lung biopsy or BAL showing no features support an alternative diagnosis

Minor criteria: 1) age > 50 years; 2) insidious onset of otherwise unexplained dyspnea on exertion; 3) duration of illness > 3 months; 4) bibasilar, inspiratory crackles (Velcro-like)

In subjects above 65 years of age, severely obese with severe respiratory failure or severe and chronic co-existing diseases of other organs, surgical lung biopsy is considered high-risk

INVASIVE DIAGNOSIS

Surgical lung biopsy is the most definitive method of establishing diagnosis (UIP pattern) and is always performed when the above mentioned criteria have not been met. Transbronchial lung biopsy cannot be used to diagnose IPF but is useful in excluding alternative specific diagnosis (fourth clinical major criteria)

Bronchoalveolar lavage

The BAL fluid shows an increase in total cells and polymorphonucleated neutrophils (>5%) which correlate with the extension of the reticular lesions seen at CT. Polymorphonucleated eosinophils may also be increased (>5%). This pattern is much the same as most idiopathic interstitial pneumonias or other fibrosing lung conditions. The number and type of cells found in the BAL fluid have no prognostic value and therefore serial BAL for monitoring disease progression or response to treatment are not advised

A lone increase in eosinophils (>20%) is suggestive of eosinophilic pneumonia just as a lone increase in lymphocytes (>15%) is uncommon in IPF. A mixed alveolitis (an increase in lymphocytes, neutrophils and eosinophils) is suggestive of a non-specific interstitial pneumonia (NSIP) or a cryptogenic organizing pneumonia (COP)

Haslam PL. Bronchoalveolar lavage fluid cell counts in cryptogenic fibrosing alveolitis and their relation to therapy. Thorax 1980, 35: 328

Veeraraghavan S. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003, 22: 239

Nodular Diseases

Clinical features	**Alberto Pesci**
Pathology	**Alessandra Cancellieri**
Radiology	**Mario Maffessanti**

Hypersensitivity Pneumonitis

Definition

The subacute form of hypersensitivity pneumonitis (HP) tipically presents a nodular pattern. HP represents a group of diffuse granulomatous parenchymal lung diseases caused by the repeated inhalation of, and sensitization to, a broad variety of low molecular weight organic antigens and chemicals. Clinical presentation may be acute (⌘ HP, acute) or chronic (☐ HP, chronic)

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

Etiology and pathogenesis

The number of responsible inciting antigens is high (more than 300) and new antigens are constantly being identified. The most commonly known diseases are "Farmer's lung", caused by the inhalation of Faeni rectivirgula present in moldy hay and "Bird fancier's lung", caused by exposure to avian proteins. The subacute form of the disease seems to be produced by a less intense exposure to the inciting antigen than occurs in the acute form. Gell and Coombs type III and type IV immune reactions lie at the basis of the immunopathogenesis of the disease

Epidemiology

The incidence and prevalence of the disease is difficult to estimate, since individual susceptibility, intensity of exposure in different occupational settings, seasons, geographical areas and proximity of industry vary greatly. The prevalence of "Farmer's lung" varies between 2 and 9%, whereas that of "Bird fancier's lung" varies between 6 and 15%

Risk factors

Non-smokers are more commonly affected

CLINICAL FEATURES

History

Onset in the subacute form is insidious, with symptoms characterized by slowly worsening cough, dyspnea, fatigue, anorexia and weight loss. Acute exacerbation of symptoms occasionally occurs. In contrast to the acute form, clinical history is not always able to identify a temporal correlation (4-12 h) between onset of symptoms and exposure to the inciting agent (e.g. moldy hay, avian proteins, etc.)

Physical findings

Diffuse fine bibasilar rales are often noted on physical examination. Patients may present signs of wasting

Pulmonary function tests

Patterns include moderate-to-severe restrictive defects and mixed restrictive and obstructive defects. There is hypoxemia at rest and D_LCO is reduced in most cases

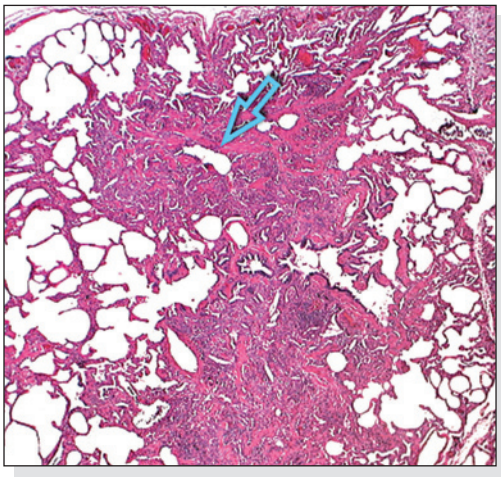
Patel AM. Hypersensitivity pneumonitis: current concepts and future questions. J Allergy Clin Immunol 2001, 108: 661

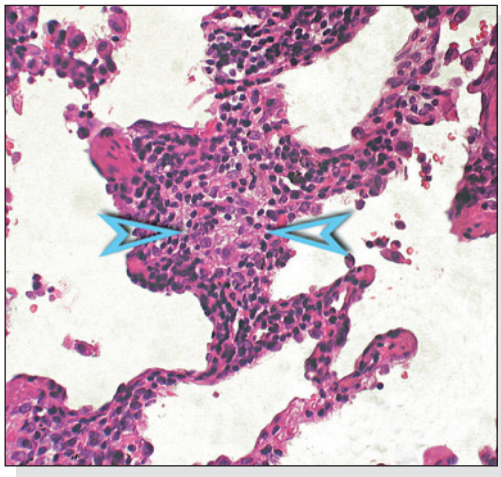
PATHOLOGY

Basic lesions

Interstitial granulomatous pneumonitis, in 75-80% of cases consisting of the following histological triad:

- Chronic interstitial pneumonitis with bronchiolocentric distribution (⇨)(cellular bronchiolitis) The often intense infiltrate consists of lymphocytes and plasma cells
- Small, poorly-formed, non-necrotizing granulomas (➢), mostly consisting of small aggregates of epithelioid histiocytes scattered in the peribronchiolar interstitium
- Foci of organizing pneumonia





✓ Additional findings:

- Scattered multinucleated giant cells, often containing cholesterol crystals
- Obstructive pneumonia with foamy histiocytes in the air spaces

Distribution Bronchiolocentric

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127

Coleman A. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 1988, 12: 514

Differentials Histopathologic differential diagnoses:

- Sarcoidosis: numerous, well-formed granulomas, surrounded by fibrosis with mild mononuclear infiltrate distributed along the lymphatics with a tendency to coalesce
- NSIP: inflammatory infiltrate with uniform and diffuse distribution, no granulomas
- LIP: the lymphoid infiltrate is diffuse or distributed along the lymphatics
- Mycobacterial infections: well-formed caseating granulomas, detection of mycobacteria with various techniques

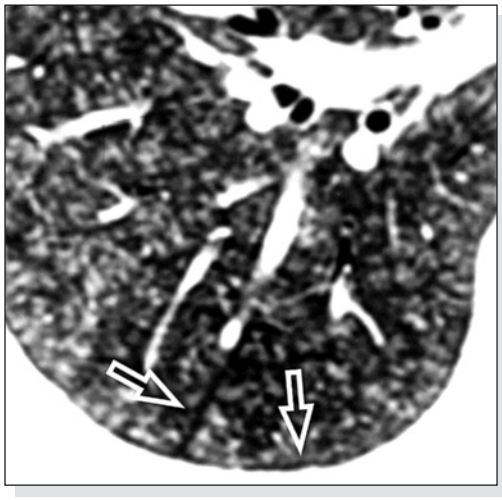
A form of interstitial granulomatous pneumonitis was recently described in immunocompetent hosts exposed to an aerosol contaminated with intracellular Mycobacterium avium. This form, known as hot tub lung, has many similarities with hypersensitivity pneumonitis (e.g. interstitial infiltrate, rarely caseating bronchiolocentric granulomas). The search for mycobacteria is characteristically negative

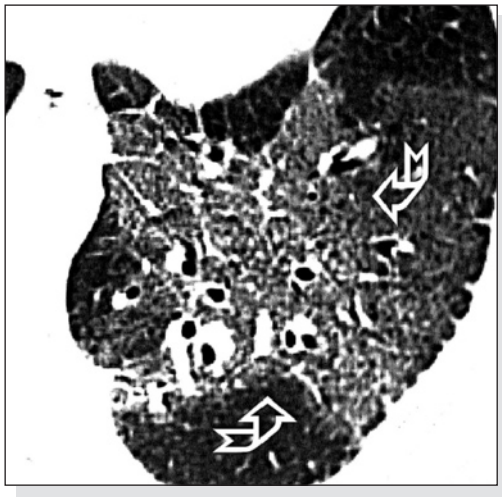
Khoor A. Diffuse pulmonary disease caused by nontuberculous mycobacteria in immunocompetent people (hot tub lung). Am J Clin Pathol 2001, 115: 755

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions Basic radiological signs:

- Centrilobular nodules (⇨): low density with ill-defined margins and a 1-5 mm diameter
- Ground-glass: diffuse or patchy, possibly overlying the nodules (↳) (common)





Distribution Diffuse or patchy

Uniformly distributed

Variable with possible middle-lower predominance

Hansell DM. High-resolution computed tomography in extrinsic allergic alveolitis. Clin Radiol 1991, 43: 8

Lynch DA. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 1992, 159: 469

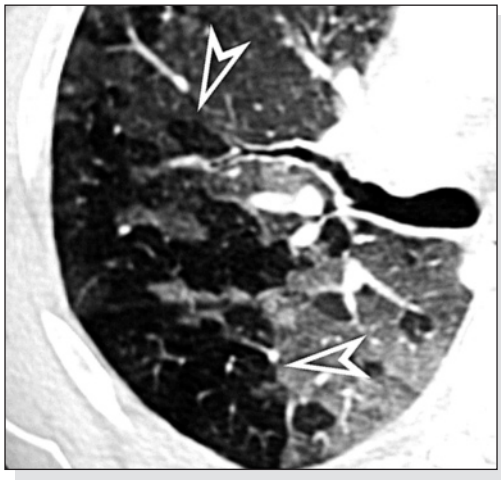
Remy-Jardin M. Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. Radiology 1993, 189: 111

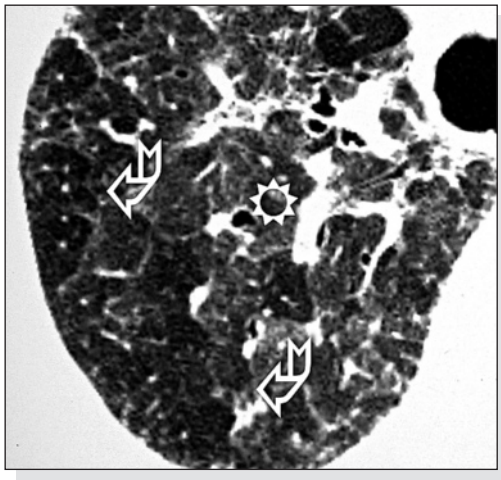
Lung volume is normal

Other signs

Other radiological findings:

- Air-trapping, often lobular, but also extensive (⩾) mosaic appearance (common, up to 86%)
- Ground-glass (☼) + air-trapping (↳): head-cheese pattern





Chung MH. Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. J Thorac Imaging 2001, 16: 69

Hansell DM. Hypersensitivity pneumonitis: correlation of individual CT patterns with functional abnormalities. Radiology 1996, 199: 123

Small JH. Air-trapping in extrinsic allergic alveolitis on computed tomography. Clin Radiol 1996, 51: 684

Differentials

Radiological differential diagnoses:

- Infectious bronchiolitis: tree-in-bud opacities are also present
- Respiratory bronchiolitis: patchy, predominantly middle-upper distribution, absence of mosaic perfusion with air-trapping
- BAC: absence of expiratory air-trapping, areas of parenchymal consolidation often associated
- LIP: nodules also in the subpleural regions and possible concomitant microcystic appearance
- LCH: the nodules are more dense and often cavitating

COURSE and COMPLICATIONS

Associated diseases

There is a greater incidence of chronic bronchitis. About one quarter of patients present aspecific bronchial hyperreactivity to methacholine

The associated chronic bronchitis appears to be linked more to exposure to the inciting antigens than to cigarette smoking

Clinical course

Removal from exposure to the inciting antigens is usually sufficient for complete remission, although corticosteroid treatment may be required. Recovery is slower than in the acute form (months). Continued exposure to the inciting antigens may lead to the development of the chronic form of the disease with diffuse pulmonary fibrosis (☐ HP, chronic)

✓ The prognosis of "Bird fancier's lung" is worse than that of "Farmer's lung". The appearance of digital clubbing is a negative prognostic factor

Radiological course

The progression towards the chronic phase is characterized by a reduction in nodules and their replacement by a reticular pattern (☐ HP, chronic)

LABORATORY FINDINGS

The presence of serum precipitating antibodies against the offending antigen is a characteristic feature. A slight increase in inflammatory indices (ESR and CRP), as well as a significant increase in quantitative immunoglobulins may be observed

☝ The presence of precipitating IgG and IgM serum antibodies may be considered markers of antigen exposure, although they are not diagnostic (30-40% of farmers have precipitanting antibodies without clinical disease), nor does their presence correlate with disease activity

CLINICAL DIAGNOSIS

There are no well-defined diagnostic criteria in the subacute HP form, as there are in the acute form (⌘ HP, acute). The diagnosis may be posed on the basis of a positive history of exposure to an antigen capable of producing the disease and/or the appropriate clinical, radiological and functional findings. There is little agreement regarding the usefulness of inhalation challenge to the offending antigen

INVASIVE DIAGNOSIS

In cases where the inciting antigen cannot be detected, or in cases of non-characteristic clinical, radiological and functional findings, fiberoptic bronchoscopy with BAL and transbronchial lung biopsy are indicated. Only in exceptional cases is surgical lung biopsy required

Bronchoalveolar lavage

If performed within 2-3 days of the most recent exposure, BAL may reveal an aspecific finding with a predominance of neutrophils. On the other hand, BAL performed after a greater time interval from the most recent exposure to the inciting antigen is characterized by a marked increase in total cell count with a predominance of lymphocytes (often >50%) and the presence of foamy macrophages and mastocytes (>1%). The lymphocytes are predominantly CD3+ (T cells) and CD8+ (cytotoxic suppressors). The CD4+/CD8+ ratio is usually decreased to less than 1.0

☝ A predominantly CD8+ lymphocytic alveolitis may also be observed in BAL fluid of OP, NSIP and asbestosis

📖 Costabel U. Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med 2001, 7: 255

Drent M. Bronchoalveolar lavage in extrinsic allergic alveolitis: effect of time elapsed since antigen exposure. Eur Respir J 1993, 6: 1276

❖

Langerhans' Cell Histiocytosis

Definition

Langerhans' cell histiocytosis (LCH) is a rare disease which predominantly affects young adults. The lung may be affected in isolation or in addition to other organs and/or systems. In the early stages, LCH exhibits a diffuse nodular pattern, but if the disease progresses there is a radiological evolution to the cystic pattern (O LCH, advanced)

Pulmonary eosinophilic granuloma, pulmonary Langerhans' cell granulomatosis, histiocytosis X

DEMOGRAPHICS

Etiology and pathogenesis

The precise pathogenesis of the disease is unknown, although epidemiological data strongly suggest an altered response to cigarette smoke. Viral and neoplastic causes have also been suggested

Epidemiology

The disease is rare and the true incidence and prevalence are unknown. It predominantly affects young adults (20-40 years) and has no sex predilection. The disease is more common among the white population than among blacks

Risk factors

Almost all patients are smokers or ex-smokers. There are no known geographical or occupational risk factors

Vassallo R. Pulmonary Langerhans' cell histiocytosis. N Engl J Med 2000, 342: 1969

CLINICAL FEATURES

History

Early LCH may be detected as an incidental finding. The patient may have dry cough and/or systemic symptoms (fever, weight loss, fatigue)

Physical findings

They are generally normal

Pulmonary function tests

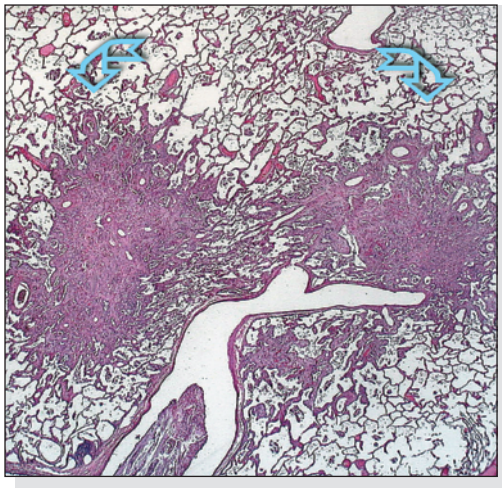
The early phase of the disease is characterized by essentially normal pulmonary function parameters

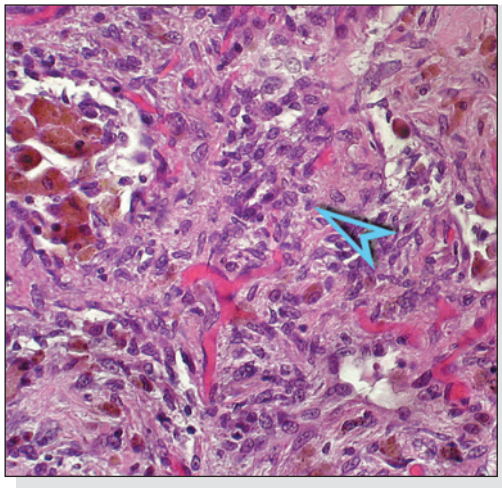
PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Small nodular infiltrates around bronchioles or alveolar ducts extending at the periphery into the surrounding interstitium (↳)
- The infiltrate in the nodules (➢) is made up of Langerhans' cells with characteristic nuclear foldings mixed with a variable number of eosinophils, pigmented macrophages, lymphocytes, fibroblasts and giant cells





The nodules vary in size and cellular composition and overtime progress from cellular lesions to foci of stellate fibrosis. The presence of Langerhans' cells can be confirmed with immuno-cytochemistry (positive staining for S-100 and CD1a)

Distribution

Smaller lesions are bronchiolocentric. The site of origin is often unidentifiable in advanced lesions

Differentials

Histopathologic differential diagnoses:

- DIP: accumulation of macrophages is intraalveolar and not present in the interstitium. Langerhans' cells are also absent
- CEP: involvement is mainly alveolar and Langerhans' cells are absent; eosinophilic infiltrate is intense
- UIP: fibrosis is subpleural and not centrilobular; discrete stellate nodules are absent

Colby TV. Histiocytosis X in the lung. Hum Pathol 1983, 14: 847

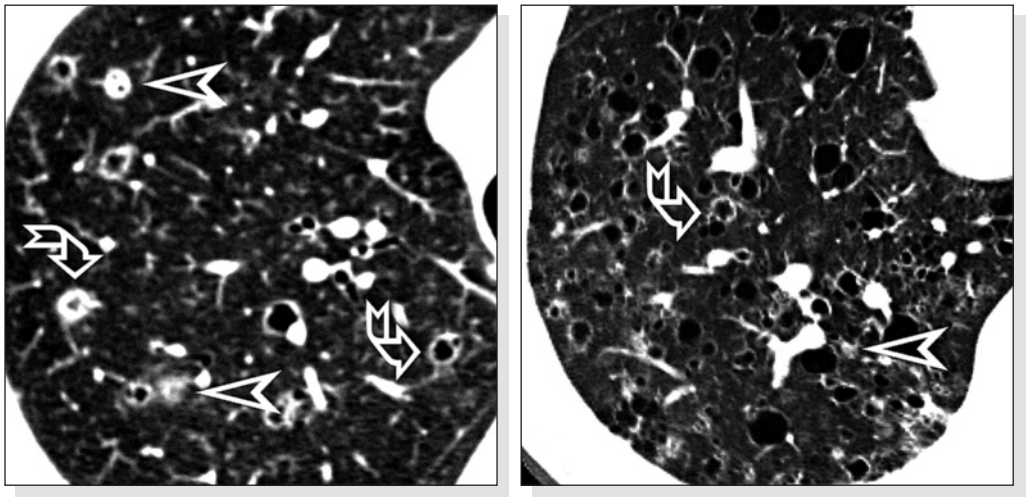
Travis WD. Pulmonary Langerhans' cell granulomatosis (histiocytosis X). A clinicopathologic study of 48 cases. Am J Surg Pathol 1993, 17: 971

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- High-density centrilobular nodules with well-defined margins and finely irregular borders (➢). Cavitation is common (↳) (cheerios pattern)
- The number of nodules may vary from very few to a multitude; the surrounding parenchyma is normal



The presence of linear opacities between the nodules is indicative of cystic progression of the disease

Giron J. Contribution of high resolution x-ray computed tomography to the diagnosis of pulmonary histiocytosis X. Apropos of 12 cases. Ann Radiol 1990, 33: 31

Grenier P. Chronic diffuse interstitial lung disease: diagnostic value of chest radiography and high-resolution CT. Radiology 1991, 179: 123

Distribution

Bilateral and symmetrical

Uniformly distributed

Upper and middle lung zones: lesions are typically absent in the costophrenic angles

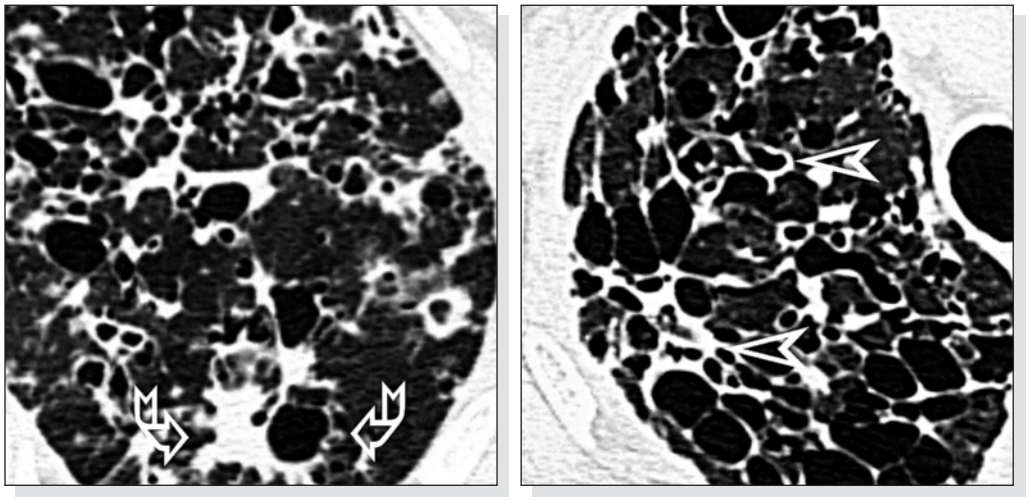
Lung volume is normal or slightly increased

Moore AD. Pulmonary histiocytosis X: comparison of radiographic and CT findings. Radiology 1989, 172: 249

Other signs

Other less frequent findings:

- Micronodules, possibly cavitating (↳)(25-30%)
- Thick-wall cysts (➢)
- Mosaic oligemia with air-trapping



Brauner MW. Pulmonary histiocytosis X: evaluation with high-resolution CT. Radiology 1989, 172: 255

Stern EJ. Cystic lung disease associated with eosinophilic granuloma and tuberous sclerosis: air-trapping at dynamic ultrafast high-resolution CT. Radiology 1992, 182: 325

Differentials

Radiological differential diagnoses:

- TB: the nodules are smaller, more numerous, and non cavitating
- Metastases: the opacities tend to show different diameters, they are predominant in the lung bases and present also in the costophrenic angles
- Silicosis: no cavitation, but rather a tendency towards confluence

Gruden JF. Multinodular disease: anatomic localization at thin-section CT-multireader evaluation of a simple algorithm. Radiology 1999, 210: 711

COURSE and COMPLICATIONS

Associated diseases

LCH may be associated with a number of benign or malignant tumors, especially bronchogenic carcinoma (5%), lymphomas and pulmonary carcinoid

Clinical course

In the systemic form affecting adolescents (Hand-Schüller-Christian disease) there may be involvement of bone (lytic lesions) or the hypothalamus (diabetes insipidus)

In this phase, the disease may spontaneously regress, especially in patients who stop smoking. However, progression towards a cystic pattern is more common. Cases of relapse after years of radiological remission have been reported

Radiological course

Uniform and thick-walled cystic nodules may regress if smoking is stopped. Thin-walled cystic nodules tend to remain the same or patently progress towards a cystic appearance with the involvement of increasingly widespread areas of parenchyma (○ LCH, advanced)

Brauner MW. Pulmonary Langerhans' cell histiocytosis: evolution of lesions on CT scans. Radiology 1997, 204: 497

LABORATORY FINDINGS

Laboratory findings are normal

✓ The peripheral eosinophil count is normal. The term eosinophilic granuloma should not be mistaken, as this refers to the presence of eosinophils in the histological lesions, but not in the peripheral blood

CLINICAL DIAGNOSIS

In this phase of the disease a clinical diagnosis cannot be made, even though the radiological findings may be suggestive

✓ The presence of lytic bone lesions and/or diabetes insipidus may be suggestive of the systemic form in adolescents (Hand-Schüller-Christian disease)

INVASIVE DIAGNOSIS

If BAL findings are not diagnostic (CD1+ cells <5%), histological diagnosis is required, which occasionally may be obtained with a transbronchial biopsy, although surgical biopsy is generally definitive

Bronchoalveolar lavage

BAL fluid is characterized by elevated total cell count, elevated percentage of neutrophils and a possible elevated percentage of eosinophils. These findings are aspecific. In the appropriate clinical-radiological setting, however, a finding of a percentage of Langerhans' cells (CD1+) greater than 5% is diagnostic

☝ Increased CD1+ cells in BAL fluid can occur also in healthy heavy smokers

Auerswald U. Value of CD-1-positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991, 169: 305

Lymphocytic Interstitial Pneumonia

Definition

Lymphocytic interstitial pneumonia is a rare syndrome which may be idiopathic or associated with other diseases. It is characterized by infiltration of the interstitium by lymphocytes, plasma cells and other elements of the lymphoreticular system

✓ The idiopathic form is currently classified among the idiopathic interstitial pneumonias. Some researchers, however, suggest that it is a lymphoproliferative disease in its own right

The general term idiopathic interstitial pneumonias (IIP) include various diseases, in particular, usual interstitial pneumonia (□ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

DEMOGRAPHICS

Etiology and pathogenesis

In addition to the theory of idiopathic hyperplasia of the pulmonary lymphatic tissue and a low-grade non-Hodgkin's lymphoma, an autoimmune and infectious (especially viral) etiology has been proposed

Epidemiology

The incidence of LIP is unknown, but it appears rare. It predominantly affects subjects aged 40-50 years, with a higher incidence among women

Risk factors

There are no known risk factors

CLINICAL FEATURES

History

Onset is insidious, with the main symptoms being cough (71%) and worsening dyspnea (61%). Other symptoms, such as fever (10%), weight loss (16%), chest pain (6%) and joint pain may also be present

Physical findings

Most patients present with diffuse fine rales. Peripheral adenopathy and/or splenomegaly may be present. Digital clubbing is rare (<10%)

Pulmonary function tests

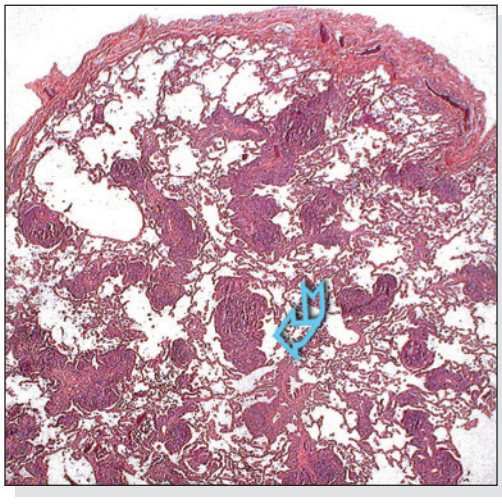
The most common functional change is a restrictive defect and lowered D_LCO

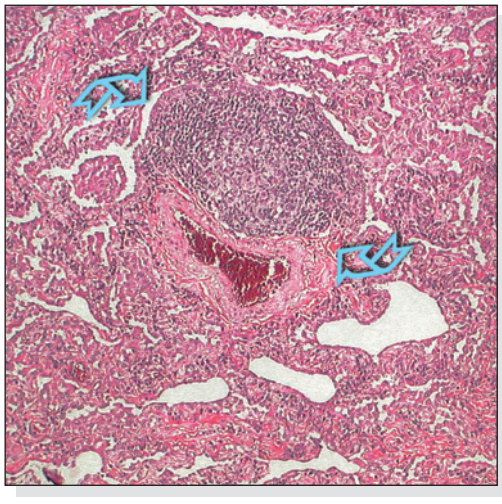
PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Intense interstitial infiltrate consisting of small lymphocytes and plasma cells in the alveolar septa or with a lymphatic distribution
- Lymphoid follicles (↳) with germinal centers are often present, usually with a lymphatic distribution





Lymphoid proliferation is polyclonal, often with a significant number of T-cells

Intraalveolar macrophages and foci of organizing pneumonia may be associated, together with interstitial fibrosis and non-necrotizing granulomas

Distribution

Peribronchiolar, lymphatic or diffuse

Differentials

Histopathologic differential diagnoses:

- MALToma, small lymphocytic lymphoma: dense monomorphic infiltrate with destruction of pulmonary architecture, and pleural, lymph node and cartilage infiltration. Lymphoid proliferation is monoclonal. Lymphoepithelial lesions are present in MALToma
- Nodular lymphoid hyperplasia: lesions are localized and not diffuse, the lymphoid infiltrate is predominant around the airways and lymphatics with more numerous and prominent germinal centers
- HP: less intense infiltrate, peribronchiolar distribution, poorly-formed granulomas, and cellular bronchiolitis
- NSIP: the infiltrate is less dense and diffuse, while lymphoid follicles with germinal centers are rare

LIP belongs to a group of proliferative lymphoid pulmonary lesions including follicular bronchiolitis, nodular lymphoid hyperplasia and low grade lymphomas. Some cases initially classed as LIP have been subsequently reclassified as low grade lymphomas

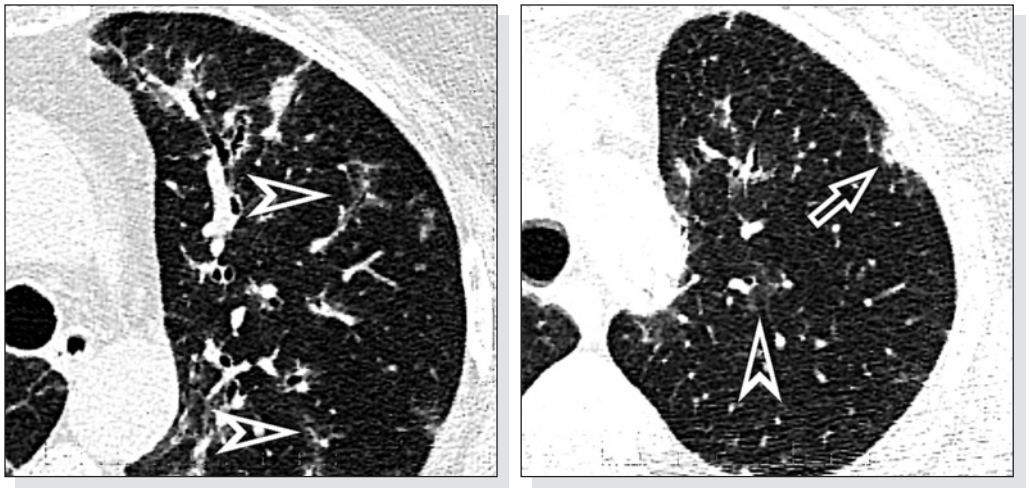
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Small centrilobular nodules with low density and ill-defined margins (≻)
- Subpleural and perilobular nodules with well-defined margins and higher density (⇨) (86%)



Johkoh T. Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1999, 212: 567

Distribution

Diffuse, uniform

Uniformly distributed

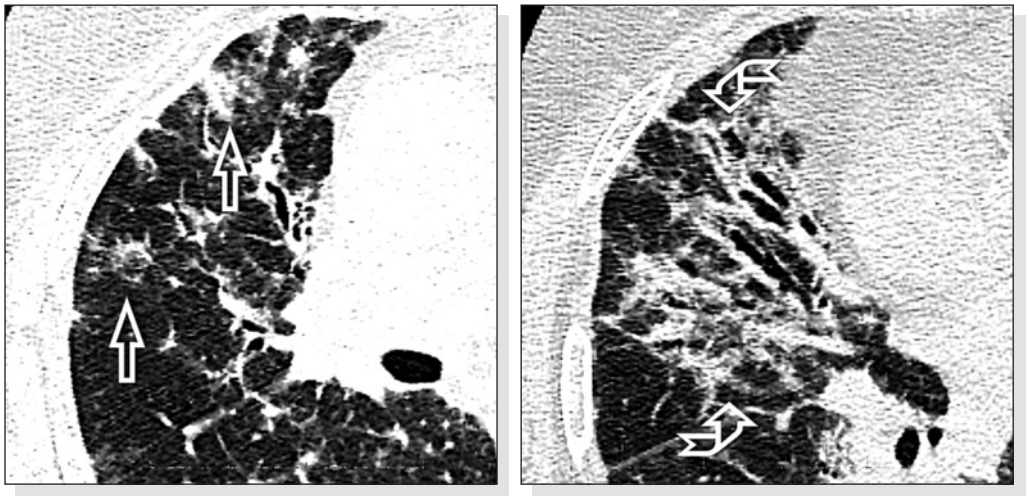
No predominance or middle-to-basal tendency

Lung volume is normal

Other signs

Other radiological findings:

- Ground-glass opacities (⇨) (70-100%)
- Nodular thickening of the peribronchovascular and perilobular interstitium (80%)
- Thin-walled cysts with 1-3 cm diameter (60-80%)
- Patchy parenchymal consolidations (↳) (20-40%)
- Mediastinal adenopathy, especially in AIDS patients (70%)



Ichikawa Y. Lung cyst formation in lymphocytic interstitial pneumonia: CT features. J Comput Assist Tomogr 1994, 18: 745

Differentials

Radiological differential diagnoses:

- Follicular bronchiolitis: the nodules are exclusively centrilobular: they are the result of a hyperplasia of the bronchus-associated lymphoid tissue (BALT)
- RB-ILD: the lesions are predominant in the middle and upper regions, where only hazy centrilobular nodules are present
- HP: there is no thickening of the peribronchovascular and the perilobular interstitium and the lymph nodes are normal
- LCH: presence of high density, possibly cavitating nodules; ground-glass densities and consolidations are rare
- Sarcoidosis: the nodules are predominantly peribronchovascular and subpleural with well-defined margins and good density, distributed in the middle-upper lung regions

Howling SJ. Follicular bronchiolitis: thin-section CT and histologic findings. Radiology 1999, 212: 637

COURSE and COMPLICATIONS

Associated diseases

Lymphocytic interstitial pneumonia may be isolated, or appear in association with other diseases such as rheumatoid arthritis, Sjögren's syndrome, Hashimoto's disease, pernicious anemia, active chronic hepatitis, systemic lupus erythematosus, autoimmune hemolytic anemia, primary biliary cirrhosis, myasthenia gravis, dysproteinemias and immunodeficiency (especially AIDS in children). When other diseases are present LIP is considered secondary

Clinical course

In over one third of patients the disease progresses towards lung fibrosis, although cases of spontaneous remission or in response to steroid or immunosuppressive treatment have been reported. Progression to lymphoma may occur in some cases (5%), even years after diagnosis. Patients with lymphomas evolving from LIP generally have a good survival rate

Radiological course

The radiological course may improve or worsen, with the appearance of honeycombing

Johkoh T. Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients. J Thorac Imaging 2000, 15: 162

LABORATORY FINDINGS

Slight anemia and dysproteinemia with polyclonal or monoclonal gammopathy (IgG or IgM) is present in 75% of cases

CLINICAL DIAGNOSIS

A diagnosis of LIP cannot be made without using invasive procedures

INVASIVE DIAGNOSIS

A definitive diagnosis requires surgical lung biopsy

Bronchoalveolar lavage

BAL is characterized by the presence of a predominantly CD4+ high-intensity T-cell alveolitis, without monoclonal characteristics

Betsuyaku T. Establishing diagnosis of pulmonary malignant lymphoma by gene rearrangement analysis of lymphocytes in bronchoalveolar lavage fluid. Am J Respir Crit Care Med 1994, 149: 526

Metastases

Definition

Secondary neoplastic involvement of the lungs is extremely common. Tumor cells may reach the lung via direct extension, via the pulmonary arteries, less commonly via the bronchial arteries and pulmonary lymphatics. This chapter covers hematogenous metastases, the primary manifestation of which is one or more nodules within the lung parenchyma

Any malignant neoplasm can metastasize to the lung, a high incidence is seen in tumors that posses a rich vascular supply and that drain directly into the systemic venous system (renal cell carcinoma, osteosarcomas and germ-cell tumors)

DEMOGRAPHICS

Etiology and pathogenesis

The development of tumor emboli depends on a number of factors, including local inflammatory and immunologic response, the organization rate of thrombus, the viability of the tumor cells in their new environment and the effect on tumor cells of embolization trauma. In the event they survive, tumor cells will proliferate in the adjacent parenchyma

Pulmonary metastases are generally so small that they do not cause pulmonary infarction

Epidemiology

The radiological finding of multiple rounded opacities in the lung is indicative of metastases in 84-98% of cases (especially in testicular, ovarian, renal and breast carcinomas, melanomas and sarcomas). In contrast, the probability that an isolated nodule is due to secondary neoplastic disease is only 2-10% (especially in colon, renal, breast and testicular carcinomas, melanomas and sarcomas)

While the finding of a solitary pulmonary nodule in a patient with high-grade malignant sarcoma or invasive melanoma is more likely due to a metastases, the same nodule in a patient with squamous-cell carcinoma of the oropharynx is more likely to be a synchronous primary neoplasm

Risk factors

Neoplastic disease in any organ or system. A positive history of extrapulmonary neoplasm is found in 80-90% of patients with multiple pulmonary metastases

✓ The incidence of multiple nodular metastases varies, depending on the number of cases of infectious granulomatosis included in the case series from different countries

CLINICAL FEATURES

History

Patients with multiple pulmonary nodules are generally asymptomatic. The following symptoms, however, may be present: 1. cough, hemoptysis or wheezing in cases of disease spread to the tracheobronchial wall; 2. chest pain in cases of pleural involvement; 3. dyspnea in cases of large and numerous metastases; 4. signs and symptoms of thromboembolism in cases of massive tumor embolization

Physical findings

Physical findings are unremarkable except in the presence of pleural involvement. In cases of paraneoplastic syndrome the relevant signs and symptoms may be present (clubbing, watch glass nails, unilateral gynecomastia etc.)

Pulmonary function tests

Pulmonary function tests are normal and only in cases of very diffuse lesions might a restrictive pattern be present

Libshitz HI. Pulmonary metastases. Radiol Clin North Am 1982, 20: 437

PATHOLOGY

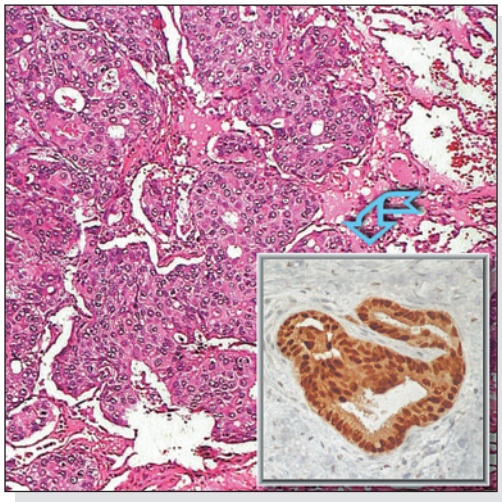
Basic lesions

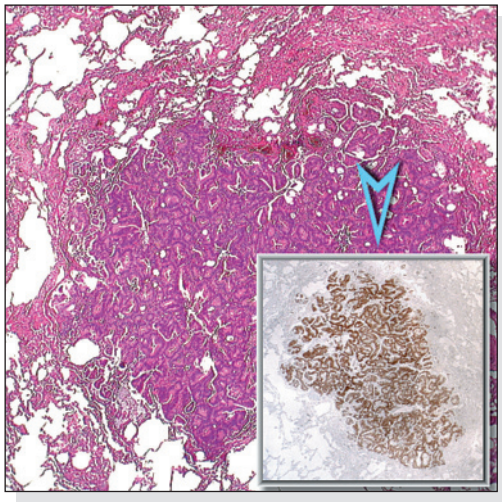
The histopathologic findings are the following:

- Single or multiple nodular lesions, often with well-defined margins and a possible vascular distribution
- Both the morphology and the immunohistochemical features are those of the primary neoplasm

For example:

- Metastases from primary breast carcinoma: positive staining for estrogen and progesterone receptors (↳) and GCD-FP15 (gross cystic disease fluid protein 15) and negative staining for TTF-1
- Metastases from primary colo-rectal carcinoma: positive staining for CDX-2 (⩾) and cytokeratin 20 and negative staining for cytokeratin 7 and TTF-1. A lepidic growth pattern may be present at the periphery of the nodule, thus mimicking mucinous BAC
- Metastases from primary renal carcinoma: positive staining for vimentin and cytokeratin and negative staining for TTF-1. Primary renal carcinoma may metastasize to the lung both hematogenously and via the lymphatics and even grow as an intrabronchial mass. Differential diagnoses include primary pulmonary neoplasms such as large cell, clear cell type carcinoma and benign clear-cell "sugar" tumor
- Metastases from primary melanoma: positive staining for S-100 and HMB-45 and negative staining for cytokeratin (in most cases) and TTF-1. These lesions may also be endobronchial





✓

Distribution

Both primary and secondary squamous-cell neoplasms tend to cavitate more frequently than others

Random

Barbareschi M. CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. Am J Surg Pathol 2003, 27: 141

Gaffey MJ. Clear cell tumor of the lung. Immunohistochemical and ultrastructural evidence of melanogenesis. Am J Surg Pathol 1991, 15: 644

Differentials

Histopathologic differential diagnoses:

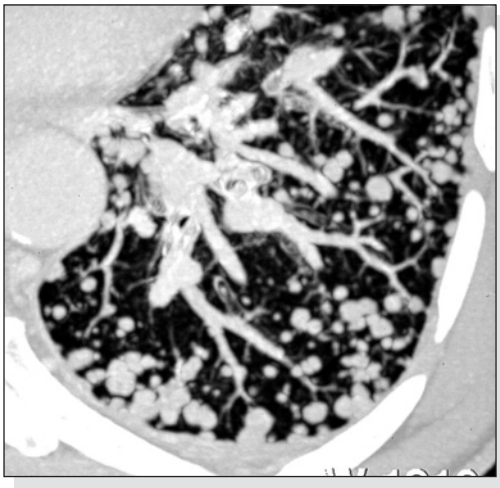
- Primary pulmonary neoplasm: in cases of known extrapulmonary malignancy, the pulmonary, possibly metastatic, lesion should be compared with the primary tumor. In the absence of a known primary tumor, immunohistochemistry, electron microscopy and molecular biology can be used to identify the origin of the metastases
- Primary or secondary squamous-cell carcinoma: metastases from squamous-cell carcinoma (uterine cervix, head and neck) are relatively rare and in the presence of this histological type a primary pulmonary neoplasm is more likely

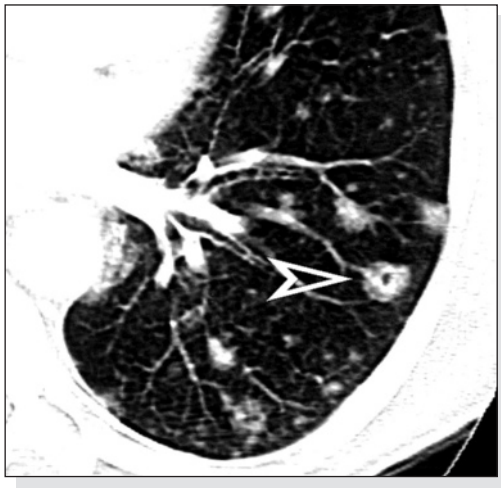
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Nodules with well-defined margins, often varying in diameter from micronodules to large opacities
- The nodules have uniform solid density, although they may be cavitated (≻) (cheerios pattern) or calcified





✓ There may be a close connection between nodules and the peripheral vessels, which is indicative of the hematogenous origin of the lesions (feeding vessel sign)

Murata K. Pulmonary metastatic nodules: CT-pathologic correlation. Radiology 1992, 182: 331

Remy-Jardin M. Diffuse infiltrative lung disease: clinical value of sliding-thin-slab maximum intensity projection CT scans in the detection of mild micronodular patterns. Radiology 1996, 200: 333

The non-uniform diameter of the lesions may be related to subsequent episodes of metastatic spread. The presence of an intranodular hyperlucency gives the lesion a characteristic appearance known as cheerios pattern. The cavitation is indicative of a squamous-cell carcinoma of the head or neck, uterine cervix, bladder or, less frequently, of an adenocarcinoma (especially gastrointestinal) or sarcoma. Calcifications are suggestive of an osteosarcoma, chondrosarcoma, papillary thyroid carcinoma, giant-cell tumor of the bone, synovial sarcoma, treated metastases, breast or gastrointestinal mucinous adenocarcinoma

Distribution

Bilateral, often symmetrical, random

Early predominance in subpleural regions

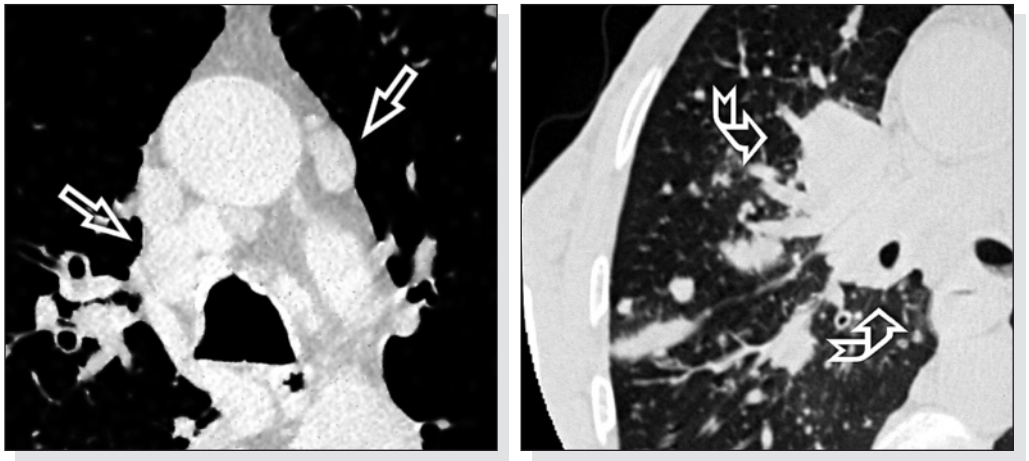
Often at the lung bases

Lung volume is normal

Other signs

Other possible findings:

- Mediastinal adenopathy (⇨)
- Lymphangitic carcinomatosis (☐ LC)
- Primary thoracic neoplasm (↳)



Seo JB. Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 2001, 21: 403

Differentials

Radiological differential diagnoses:

- TB: uniform nodules of miliary size without basal predominance
- LCH: centrilobular nodules predominant in the upper lung regions
- Septic emboli: cavitation is more common, and the association of peripheral opacities resulting from pulmonary infarction may be present
- "Cystic" BAC: consolidations, often peripheral; basal and nodular or patchy areas of ground-glass attenuation usually coexist

COURSE and COMPLICATIONS

Associated diseases

Cavitating metastases in peripheral subpleural regions may rupture into the pleural cavity with consequent pneumothorax and neoplastic dissemination

Clinical course

The prognosis is unfavorable. Cases of complete remission from metastases after removal of the primary tumor (renal cell carcinoma or choriocarcinoma) have been described

Radiological course

As the disease progresses the lesions increase in number and size and become progressively more widespread

LABORATORY FINDINGS

Neoplastic cells may be present in the sputum (35-50%). An increase in neoplastic markers indicative of the primary tumor site is often found in the serum

CLINICAL DIAGNOSIS

In the appropriate clinical setting (presence of known primary neoplasm), the finding of neoplastic cells in the sputum of a patient with multiple pulmonary nodules is diagnostic

INVASIVE DIAGNOSIS

In cases of negative cytology, a histological diagnosis can be obtained (according to the size and the site of the opacities) via transbronchial or CT-guided transthoracic needle lung biopsy. Bronchial washing and brushing are complementary procedures. If these techniques fail to confirm the diagnosis, surgical lung biopsy is a further option

Bronchoalveolar lavage

BAL can be useful in the diagnosis of peripheral tumors not visible endoscopically. The diagnostic accuracy of the technique is 65-70%

Linder J. Bronchoalveolar lavage in the cytologic diagnosis of carcinoma of the lung. Acta Cytol 1987, 31: 796

Respiratory Bronchiolitis-Interstitial Lung Disease

Definition

Respiratory bronchiolitis-interstitial lung disease (RB-ILD) is a smoking-related disease in which a pattern of chronic respiratory bronchiolitis is associated with fibrous scarring into the surrounding alveolar walls

Smoker's bronchiolitis

DEMOGRAPHICS

Etiology and pathogenesis

Subjects suffering from the disease are probably a subset of individuals with a more severe response to cigarette smoke than simple respiratory bronchiolitis, a pathological alteration common in smokers

Epidemiology

The disease affects individuals aged 30-50 years with a history of smoking of more than 30 packs-year. Males are more commonly affected than females (2:1)

Risk factors

Cigarette smoking

CLINICAL FEATURES

History

The most common subacute symptoms are dyspnea and cough, which are generally mild. Digital clubbing is rare

Physical findings

Bibasilar end-respiratory crackles may be heard in nearly 50% of patients

Pulmonary function tests

Pulmonary function tests may be normal. A mixed restrictive-obstructive pattern and a slight reduction in D_LCO may be present. An isolated increase in residual volume has also been described

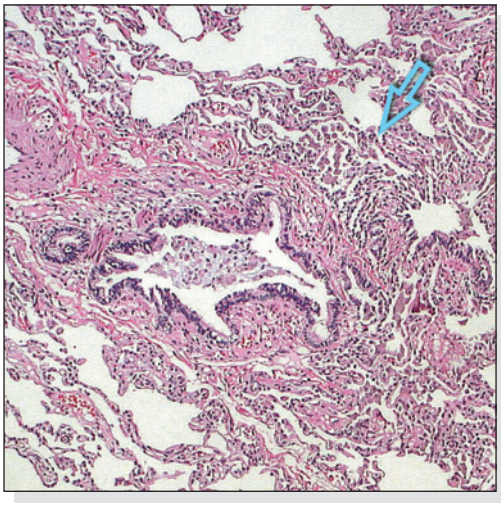
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

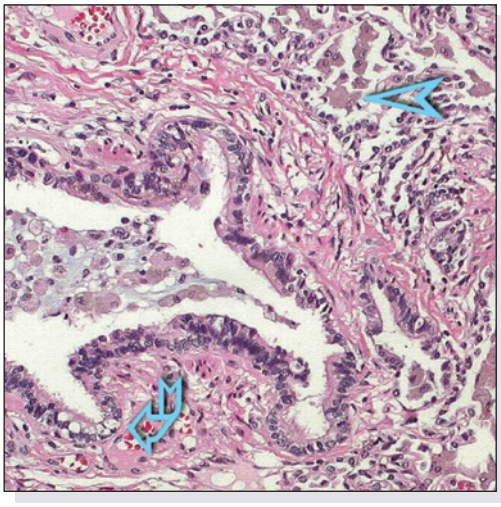
PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Multifocal accumulation of pigmented macrophages in the respiratory bronchioles and the surrounding alveolar spaces (⇨). The cytoplasmic pigment is yellow-brown and finely granular (➢)
- The airways may show mild fibrosis, mild chronic peribronchiolar inflammation and goblet-cell metaplasia of the bronchiolar epithelium (↯)
- The peribronchiolar alveolar septa may be slightly thickened and lined with bronchiolar epithelium (bronchiolar metaplasia or lambertosis). The intervening parenchyma is substantially normal





Distribution

Bronchiolocentric

Differentials

Histopathologic differential diagnoses:

- DIP: the process is diffuse and the bronchiolar component is absent or less pronounced. The macrophages form less compact aggregates, while the alveolar septal thickening is diffuse and not limited to the peribronchiolar alveoli
- Cellular bronchiolitis: pigmented macrophages are absent and there is no peribronchiolar septal thickening, while the inflammatory infiltrate in the bronchiolar walls is more intense
- Asbestos-induced bronchiolitis: fibrosis is more pronounced and involves respiratory bronchioles and especially alveolar ducts. Asbestos bodies are present
- Intraalveolar hemorrhage: bronchiolitis is absent. The lesion is diffuse with no peribronchiolar distribution. The granules of hemosiderin within the macrophages are coarse
- LCH: scars with stellate borders and cysts containing Langerhans' cells and other inflammatory elements (NB: LCH and RB-ILD are both affect smokers and can coexist!)
- HP: presence of intense lymphoplasmacellular interstitial infiltrate and poorly-formed granulomas

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

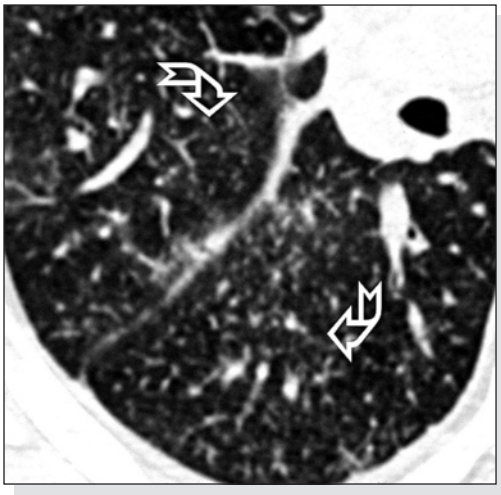
Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989, 64: 1373

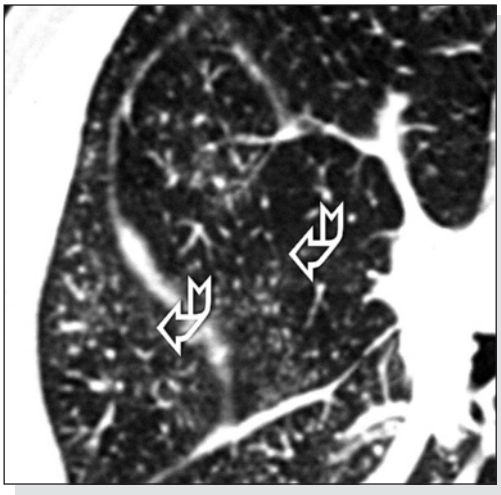
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Low-density centrilobular micronodules (3-5 mm diameter) with ill-defined margins (↳)





Distribution

Bilateral, patchy

Random

Upper and middle lung regions

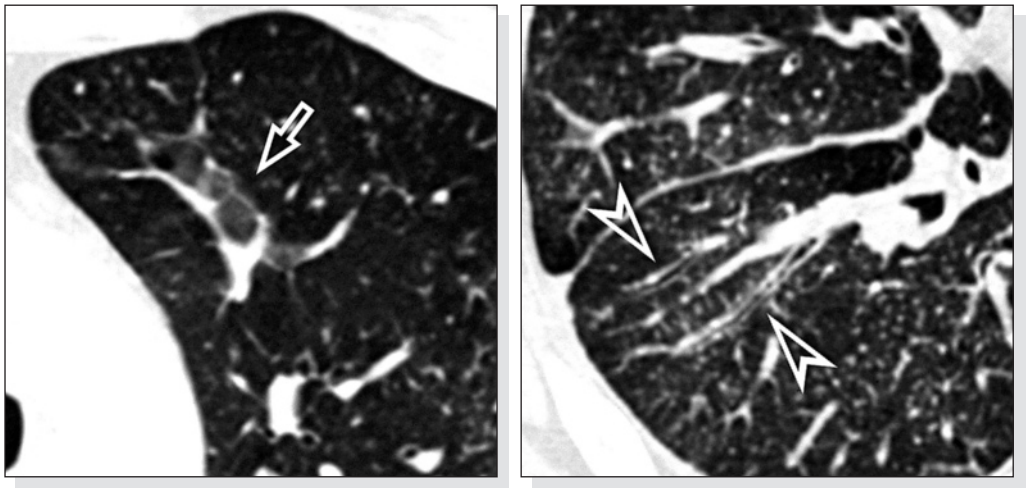
Lung volume is normal

Heyneman LE. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? AJR Am J Roentgenol 1999, 173: 1617

Other signs

Other radiological findings:

- Patchy ground-glass in the middle and upper lung fields (⇨)(85%)
- Bronchial wall thickening (➢)(94%)
- Centrilobular emphysema (50%)
- Intralobular reticular pattern (rare)



Holt RM. High resolution CT in respiratory bronchiolitis-associated interstitial lung disease. J Comput Assist Tomogr 1993, 17: 46

Park JS. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 2002, 26: 13

Differentials

Radiological differential diagnoses:

- RB: this is the asymptomatic form of RB-ILD, and therefore the findings are similar, even though generally limited to nodules and ground-glass
- HP: possible middle-lower predominance, and frequent association with oligemia with air-trapping
- LIP: possible middle-lower distribution. The nodules may also be subpleural and perilobular, their margins well-defined and parenchymal consolidations may coexist. Possible association of cystic lesions

Remy-Jardin M. Morphologic effects of cigarette smoking on airways and pulmonary parenchyma in healthy adult volunteers: CT evaluation and correlation with pulmonary function tests. Radiology 1993, 186: 107

COURSE and COMPLICATIONS

Associated diseases

The disease may be associated with other smoking-related diseases, especially centrilobular emphysema. It is not clear whether RB-ILD is an early stage of desquamative interstitial pneumonia (DIP), which also affects smokers and with which RB-ILD has histopathologic similarities (⌘ DIP)

Clinical course

Most patients improve or have a stable clinical course after smoking cessation. Progress towards diffuse pulmonary fibrosis has not been reported

Radiological course

The lesions may totally regress or, in contrast, increase in patients who fail to stop smoking

Remy-Jardin M. Longitudinal follow-up study of smoker's lung with thin-section CT in correlation with pulmonary function tests. Radiology 2002, 222: 261

LABORATORY FINDINGS

Routine laboratory examinations are neither specific nor of diagnostic utility

CLINICAL DIAGNOSIS

In an appropriate clinical and radiological setting, a diagnosis of RB-ILD may be suspected in the presence of a history of cigarette smoking

INVASIVE DIAGNOSIS

Only surgical lung biopsy is capable of providing diagnostic confirmation and is also indispensable to distinguish RB-ILD from more serious causes of diffuse infiltrative lung diseases, especially NSIP and DIP. Transbronchial lung biopsy does not provide useful data for diagnostic purposes

Bronchoalveolar lavage

BAL fluid contains alveolar macrophages with brown pigmented inclusions which are characteristic and indistinguishable from those found in normal smokers. The absence of these cells renders the diagnosis of RB-ILD unlikely. A slight increase in polymorphonucleated neutrophils may be present

Nagai S. Classification and recent advances in idiopathic interstitial pneumonia. Curr Opin Pulm Med 1998, 4: 256

Sarcoidosis

Definition

Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology characterized by the presence of non-caseating granulomas in involved organs

DEMOGRAPHICS

Etiology and pathogenesis

The etiology of the disease remains unknown. It is thought that the pathogenesis of the disease involves the exposure of a genetically susceptible individual to specific antigens (propionobacteria and mycobacteria)

This pathogenetic theory, suggesting conventional antigenic stimulation, is supported by the presence of activation and proliferation of helper T cell type 1 (Th1) and oligoclonality in TCR Vß repertoire

Epidemiology

Sarcoidosis mainly affects adults below the age of 40 years (with a peak in the third decade of life) and has a prevalence of 10-20 cases per 100,000 population. The disease is diffuse throughout the world and both sexes are almost equally affected. Familial clustering of cases has been described

Risk factors

Sarcoidosis is 3-4 times more common and severe among African Americans than among Caucasians, and prevalence is higher among non-smokers than smokers. The disease appears to be more common among certain occupational groups, such as nurses, fire-fighters and transportation service workers, even though one reason for this peculiar prevalence might be the more numerous medical check-ups these workers are required to undergo by law

CLINICAL FEATURES

History

Lung involvement is frequently found (90%). In 50% of cases the disease is incidentally detected at routine chest radiograph. The predominant symptoms are dry cough, dyspnea and chest pain (30-50%). Systemic symptoms such as weakness, fatigue, mild fever, polyarthritis and weight loss are reported in 30% of cases. Symptoms involving other organs are less common; skin (20%), eyes (20%), CNS (5%), etc.

Acute onset of erythema nodosum and polyarthralgias in a young adult with radiologically evident mediastinal adenopathy is strongly suggestive of sarcoidosis (Löfgren's syndrome)

Physical findings

Physical examination of the chest is negative in most cases. The finding of rales is rare

Pulmonary function tests

Reduced D_LCO is the earliest functional change, while lung volumes are often normal. A restrictive pattern may appear as the disease progresses. Irreversible bronchoconstriction is present in some patients

Bronchoconstriction can result from intrabronchial lesions or the compression exerted by granulomas present in the peribronchial lymphatics

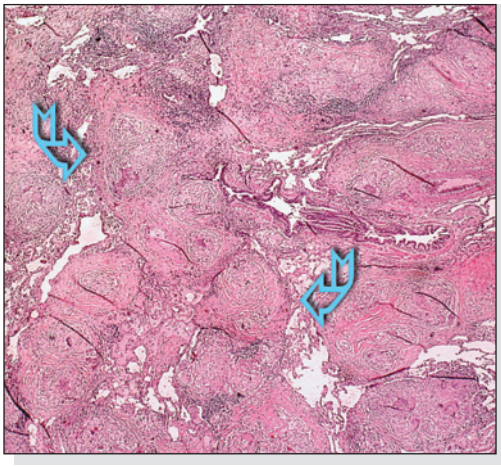
Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Am J Respir Crit Care Med 1999, 160: 736

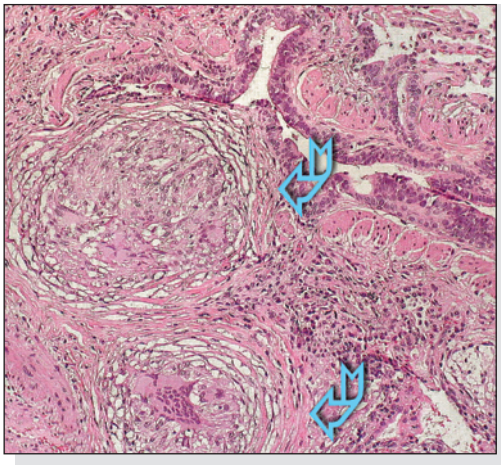
PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Multiple non-caseating giant-cell granulomas (↳) with a lymphatic distribution (along bronchovascular bundles, interlobular septa and subpleural connective tissue)
- The granulomas are discrete compact aggregates of epithelioid histiocytes, rare lymphocytes and multinucleated giant cells, sometimes with cytoplasmic inclusions (Schaumann bodies, asteroid bodies, Hamazaki-Wesenberg bodies). The granulomas often merge and tend to be surrounded by hyaline fibrosis





Granulomas may occasionally exhibit focal coagulative necrosis or fibrinoid degeneration. The interstitial inflammatory infiltrate is mild. Granulomatous or lymphoplasmacellular vasculitis may be present

Distribution

Lymphatic distribution (along the bronchovascular bundles, the interlobular septa and the subpleural connective tissue)

Along the airways granulomas are often found in the lamina propria of the mucosa and in the submucosal connective tissue, rendering them easily accessible to biopsy during bronchoscopy

Differentials

Histopathologic differential diagnoses:

- HP: the granulomas consist of small aggregates of epithelioid macrophages in the alveolar septa and in the peribronchiolar interstitium (poorly-formed granulomas) associated with intense inflammatory infiltrate
- Mycobacterial and fungal infections: randomly distributed necrotizing granulomas which may be bronchiolocentric, associated with inflammatory infiltrate. Positive staining for acid-fast bacilli and fungi
- Chronic berylliosis: histologically indistinguishable from sarcoidosis. History of exposure to beryillium

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127

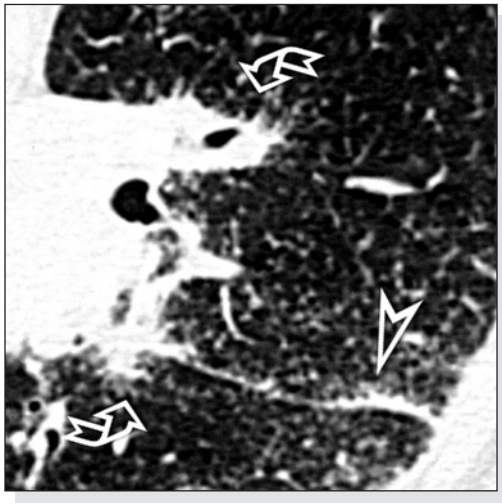
Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Am J Respir Crit Care Med 1999, 160: 736

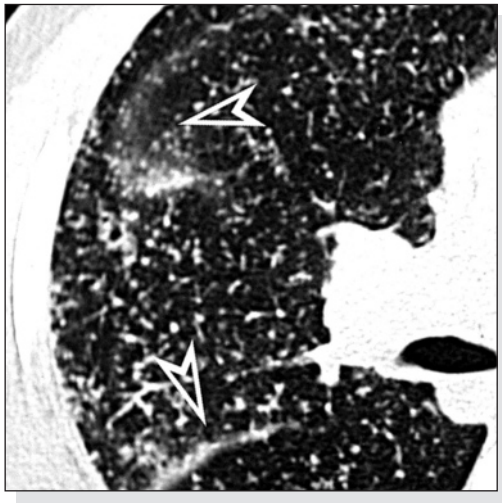
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Small nodules with well-defined margins, distributed along bronchovascular bundles (↳), beneath the visceral pleura and along fissures (⩾) (perilymphatic pattern)





Distribution

Bilateral, patchy

Hilar-perihilar, dorsal and in the subpleural regions

Middle-upper lung fields (two thirds of cases)

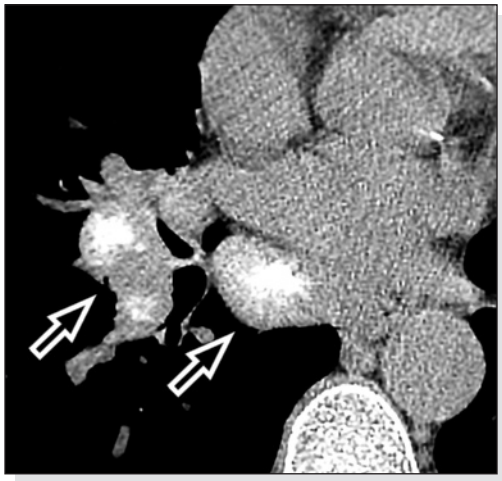
Brauner MW. Pulmonary sarcoidosis: evaluation with high-resolution CT. Radiology 1989, 172: 467

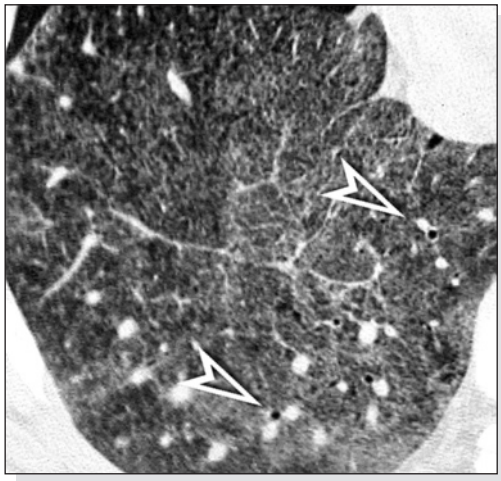
Lung volume is normal

Other signs

Less frequent manifestations:

- Hilar-mediastinal adenopathies (⇨)
- Pseudoplaques: peripheral, small elongated opacities with long axis parallel to the adjacent costal boundaries
- Ground-glass: non-uniform, patchy and finely granular with small bronchi and vessels visible in the areas of increased attenuation (➢)
- Round opacities: dense opacities with well-defined margins and irregular borders, up to several centimeters in diameter with a halo of tiny satellite nodules (galaxy sign) (15-25%) (● Large rounded opacities: Sarcoidosis)
- Parenchymal consolidation: bilateral and symmetrical with opaque strands radiating from the hilar-parahilar regions and often containing narrowed or ectatic bronchi. Signs of distortion of the pulmonary architecture may also be present
- Air-trapping: often lobular but also more widespread, with the appearance of the mosaic pattern (common)





The adenopathies are bilateral, symmetrical, not only hilar but also in the right paratracheal space, subcarinal space and aortopulmonary window. Adenopathies may contain "stippled" calcifications

Parenchymal consolidation and rounded opacities with galaxy signs are produced by the confluence of granulomas. Even the pseudoplaques are early aggregates of granulomas in the subpleural regions

The ground-glass pattern is produced by a multitude of small granulomas below the spatial resolution of HRCT. Granulomas situated in the small airways can cause lobular air-trapping or more significant mosaic oligemia

Chiles C. Imaging features of thoracic sarcoidosis. Semin Roentgenol 2002, 37: 82

Gleeson FV. Evidence of expiratory CT scans of small-airway obstruction in sarcoidosis. AJR Am J Roentgenol 1996, 166: 1052

Johkoh T. CT findings in "pseudoalveolar" sarcoidosis. J Comput Assist Tomogr 1992, 16: 904

Nishimura K. Pulmonary sarcoidosis: correlation of CT and histopathologic findings. Radiology 1993, 189: 105

Differentials

Radiological differential diagnoses:

- LC: the nodules are only one aspect of a prevalent reticular pattern
- Silicosis: the nodules have no predilection for the subpleural regions, the extensive areas of consolidation are a late manifestation of the disease and they do not contain the air-bronchogram. Ground-glass is absent
- LIP: small low-density centrilobular nodules with poorly-defined margins are often present with possible association of thin-walled cysts and a distribution predominantly in the middle and upper lung regions

COURSE and COMPLICATIONS

Associated diseases

Associations between sarcoidosis and neoplasms, lymphoproliferative diseases and connective tissue diseases have been reported without any clear indication of a pathogenetic link between them

Clinical course

Spontaneous remission occurs in nearly 50-70% of cases. Löfgren's syndrome typically has a high rate of spontaneous remission and therefore requires no treatment, only monitoring over time. Favorable prognostic factors include erythema nodosum and acute inflammatory manifestations (e.g. fever, polyarthritis), whereas lupus pernio, chronic uveitis, hypercalcemia, nephrocalcinosis, cystic bone lesions, neurosarcoidosis and progressive pulmonary sarcoidosis are adverse prognostic factors. Relapse may occur in 16-74% of patients if corticosteroid treatment is reduced or discontinued. Patients with chronic or progressive disease may develop lung fibrosis (☐ Sarcoidosis, fibrosing). Irreversible organ damage occurs in 10-20% of patients. Mortality is about 1% and mainly due to cardiac involvement, CNS involvement and respiratory failure

Radiological course

The number of nodules may decrease or the disease may become chronic with the appearance of signs of parenchymal fibrosis (☐ Sarcoidosis, fibrosing)

Abehsera M. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 2000, 174: 1751

LABORATORY FINDINGS

Laboratory findings may include leucopenia (5-10%), eosinophilia (25%), hypergammaglobulinemia (30-80%), hypercalcemia (10%) and hypercalciuria (30%), while anemia and thrombocytopenia are less common. ESR is often elevated, but this is not correlated with disease activity. Elevated serum levels of angiotensin converting enzyme (ACE) are found in 75% of non-treated patients, although the clinical significance of this finding is unknown. Elevated serum levels of lysozyme and alkaline phosphatase have also been reported in patients with sarcoidosis. The Mantoux skin test is negative in two thirds of patients

The finding of elevated serum levels of ACE is of little diagnostic utility owing to its low specificity. The finding can in fact be observed in pneumoconiosis, Gaucher's disease, hyperthyroidism, tuberculosis and other granulomatous diseases

CLINICAL DIAGNOSIS

The diagnosis of sarcoidosis is established in the presence of non-caseating granulomas by biopsy, compatible clinical-radiological findings and with the exclusion of other granulomatous disease (particularly tuberculosis). In the presence of clinical-radiological findings suggestive of classical Löfgren's syndrome (98% probability), biopsy proof may not be required

INVASIVE DIAGNOSIS

Biopsies should be performed at the most easily accessible site such as the skin, superficial lymph nodes or lachrymal glands. In the absence of this possibility, fiberoptic bronchoscopy with bronchial biopsy (diagnostic in 41-57% of cases) and/or transbronchial lung biopsy (diagnostic in 40-90% of cases) may be used. As a last resort, mediastinoscopy (diagnostic in more than 90% of cases) or surgical lung biopsy (diagnostic in more than 90% of cases) may be performed

Erythema nodosum should not be considered a site for skin biopsy since the granulomatous lesions indispensable for diagnostic confirmation are absent in this skin condition (thus erythema nodosum should never be biopsied)

Bronchoalveolar lavage

BAL findings are characterized by an elevated total cell count and an increased percentage of lymphocytes, even though the latter finding is neither sensitive nor specific. A large number of BAL lymphocytes are CD4+ T-cells, so an elevated CD4/CD8 ratio is found. A CD4/CD8 ratio >3.5 has a sensitivity of 53% and specificity of 94%

Neither the number of lymphocytes nor their activation state have any prognostic value, nor can these findings be used to guide treatment

Poulter LW. The value of bronchoalveolar lavage in the diagnosis and prognosis of sarcoidosis. Eur Respir J 1990, 3: 943

Silica-induced pneumoconiosis

Definition

Pneumoconiosis is a general term for a group of diseases caused by the chronic inhalation of mineral dust capable of producing lung damage. The group includes a number of morbid conditions, the best known of which are silicosis (silica), coal worker's pneumoconiosis (coal dust), asbestosis (asbestos), talcosis (talc), siderosis (iron), beryllosis (beryllium) and hard metal pneumoconiosis (cobalt, tungsten). Silicosis will be covered in this chapter as a representative example

DEMOGRAPHICS

Etiology and pathogenesis

The interaction between silica (particles < 5 μm) and macrophages is the primum movens in the pathogenesis of the disease. Alveolar macrophages are recruited at the site where the particles are deposited. The macrophages become activated and release numerous cytokines, including tumor necrosis factor, transforming growth factor-beta, interferon, fibronectin and interleukin-1, inducing a proliferation of lymphocytes and fibroblasts at the sites involved. The interaction between these cellular components initially produces a granulomatous reaction which can evolve into pulmonary fibrosis

Epidemiology

Although there are no precise data regarding the incidence and prevalence of the disease, silicosis was undoubtedly the most common pneumoconiosis in the last quarter of a century. In the United States, the disease was recognized as the primary cause of death in more than 4,000 workers between 1979 and 1991. In developing countries where occupational health regulations are less stringent the disease is undoubtedly still widespread

Risk factors

Occupational or environmental exposure to the inhalation of silica particles (e.g. stone cutting, rock mining, foundry, tunneling through rock, sand blasting, etc)

CLINICAL FEATURES

History

There is typically a latency of about 20 years from initial exposure to clinical onset. Subjects affected by the mild form of disease are generally asymptomatic, whereas in the advanced stages dyspnea, cough and sputum production may be found, often due to chronic bronchitis produced by cigarette smoking or concurrent infections. They can also be minimally symptomatic in spite of advanced radiographic abnormalities

The appearance of mild fever, hemoptysis and weight loss are suggestive of mycobacterial infection, which is a frequent complication of silicosis

Physical findings

Auscultation of the lungs generally fails to identify abnormal breath sounds, except in cases of associated chronic bronchitis (wheezes). Digital clubbing is rare

Pulmonary function tests

Functional changes are absent in simple nodular silicosis, whereas in the advanced forms restrictive, obstructive or mixed patterns may be observed. Some patients may have a reduction in D_LCO, a reduction in air flow and a hyperinflation similar to that found in emphysema

Spirometry can detect physiological abnormalities that may precede radiographic changes

In fact, no good correlation exists between radiographic abnormalities and ventilatory impairment

It is not clear whether the inhalation of silica particles has a synergetic effect with cigarette smoke in promoting the onset of chronic bronchitis and later emphysema

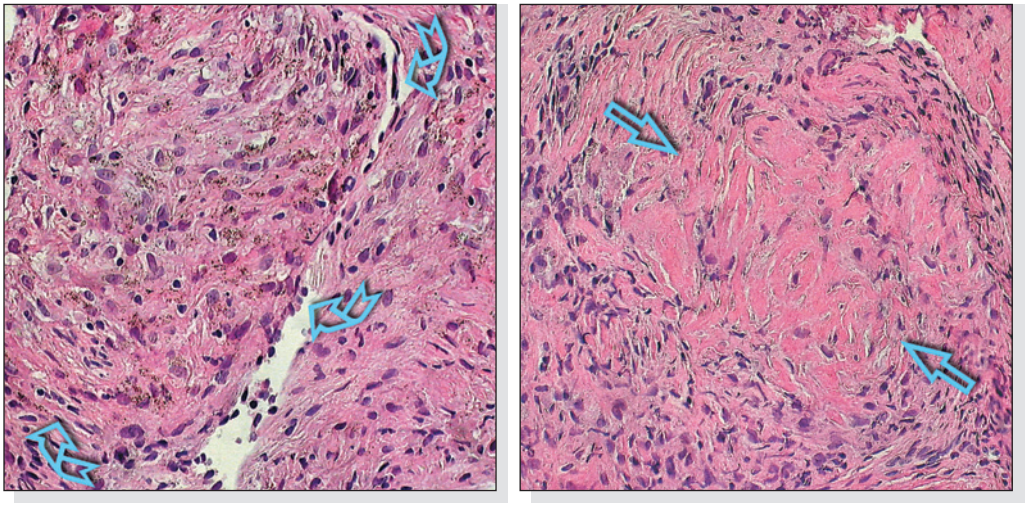
Balaan MR. Clinical aspects of coal workers' pneumoconiosis and silicosis. Occup Med 1993, 8: 19

PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Firm, rounded and non-confluent nodules, 3-6 mm in diameter and containing variable quantities of gray-black pigment. The surrounding pulmonary parenchyma is normal
- The nodules (↳) consist of concentric bands of collagen (⇨) surrounded by a variable quantity of dust-laden macrophages



Early lesions are more cellular (even containing only pigment-laden macrophages), while advanced lesions consist predominantly of acellular collagen, sometimes with calcifications

The nodules often contain 1-2 micron diameter needle-like particles of silica and are weakly birefringent to polarized light. Silicates, on the other hand, are found in larger and more irregular aggregates, and are more intensely birefringent. The presence of silica particles is neither a hallmark of the disease, nor is it necessary for diagnosis

Nodular lesions with irregular or stellate margins in a "medusa head" appearance are more likely due to the association of various dusts and are referred to as mixed dust pneumoconiosis

Distribution

The nodules are distributed along the lymphatics, around the bronchovascular bundles and in the subpleural and paraseptal regions

Differentials

Histopathologic differential diagnoses:

- TB and mycobacteriosis: caseating granulomas with multinucleated giant cells. Mycobacteria are present, whereas pigmented macrophages and the characteristic whorled collagen deposits are absent. In older lesions, necrosis and mycobacteria may be absent while fibrosis dominates, rendering the differential diagnosis difficult
- Sarcoidosis: non-necrotizing granulomas with multinucleated giant cells with a lymphatic distribution. Pigmented macrophages are absent, as is a significant fibroblastic component and the whorled collagen arrangement
- Other infectious granulomas: presence of necrosis and neutrophils; isolation of the etiologic agent

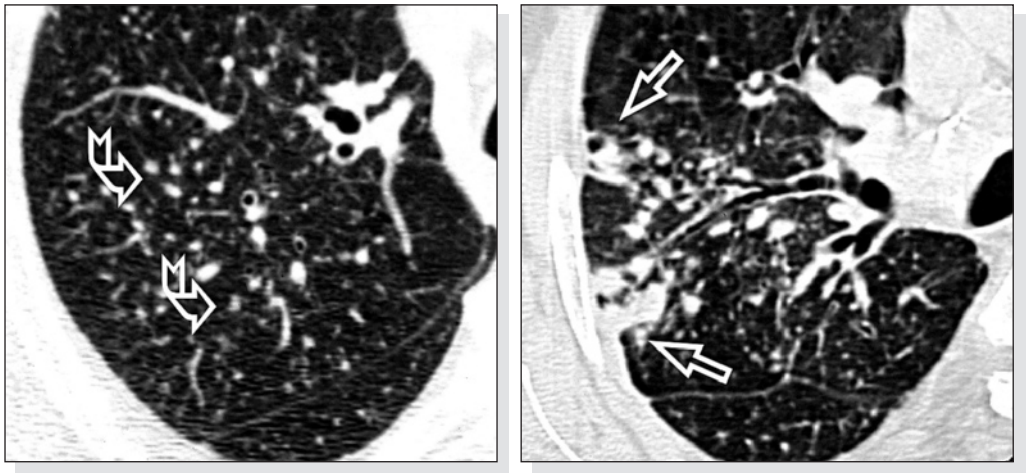
Mossman BT. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 1998, 157: 1666

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Centrilobular (↳) and subpleural (⇨) nodules with a diameter variable up to several millimeters



The margins of smaller nodules (1-2 mm) tend to be less well-defined than those of larger nodules (> 3 mm); the latter progressively lose their rounded appearance and become irregular

Akira M. Radiographic type p pneumoconiosis: high-resolution CT. Radiology 1989, 171: 117

Distribution

Bilateral, symmetrical, although a right-sided predominance may be observed

Random distribution with a tendency to posterior predominance, especially in the dorsal segment of the upper lobe and the apical segment of the lower lobe

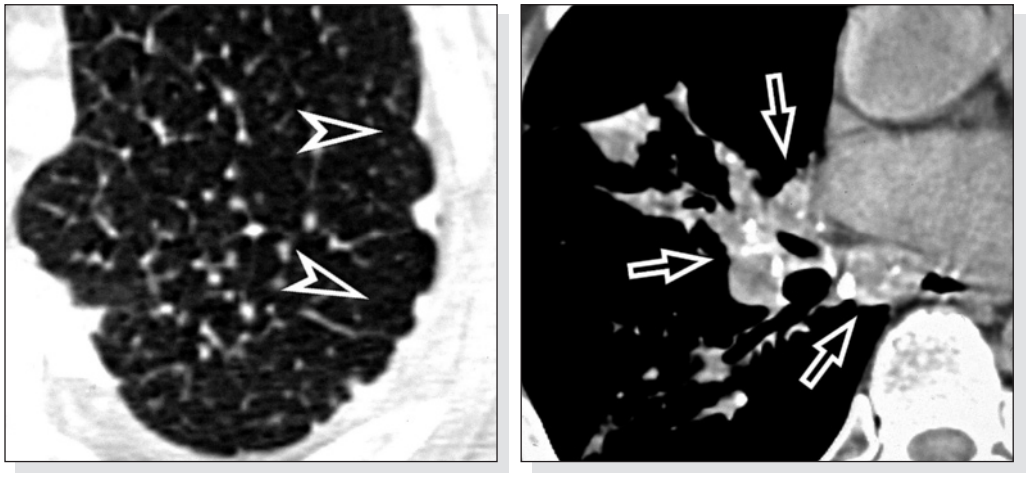
Upper and middle lung regions

Lung volume is normal or increased

Other signs

Other characteristics:

- Pseudoplaques (➢): aggregates of nodules along the costal margins, which mimic pleural plaques (early)
- Mediastinal adenopathies (⇨)(15-40%): their "egg-shell" calcification is characteristic (late)



Grenier P. Chronic diffuse infiltrative lung disease: determination of the diagnostic value of clinical data, chest radiography, and CT and Bayesian analysis. Radiology 1994, 191: 383

Remy-Jardin M. Subpleural micronodules in diffuse infiltrative lung diseases: evaluation with thin-section CT scans. Radiology 1990, 177: 133

Exposure to high concentrations of silica may cause progressive disease (accelerated silicosis) or even an acute form (silicoproteinosis). In accelerated silicosis, a reticular appearance is associated with nodular opacities. In acute silicosis the nodules are absent, and the HRCT appearance mimics the alveolar proteinosis

Akira M. High-resolution CT in the evaluation of occupational and environmental disease. Radiol Clin North Am 2002, 40: 43

Differentials

Radiological differential diagnoses:

- Sarcoidosis: the nodules tend to be distributed along the bronchovascular bundles in the parahilar and especially subpleural regions. The distribution also tends to be patchy
- TB: the nodules are smaller, more numerous and uniform in size
- Metastases: the opacities tend to be more variable in size with a predilection for the lung bases
- LIP: possible middle-lower distribution. Small, low-density nodules with ill-defined margins, also centrilobular. Ground-glass opacities and parenchymal consolidation may be present, and cystic lesions may be associated
- LCH: the nodules may be cavitating

COURSE and COMPLICATIONS

Associated diseases

Silicosis may be complicated by tuberculosis (silica is thought to reduce the intracellular killing ability of the alveolar macrophages), lung carcinoma (silica is classified as an occupational carcinogen) and collagen vascular diseases (especially scleroderma, rheumatoid arthritis and systemic lupus erythematosus)

Clinical course

The clinical course of the disease is often insidious with progression even in the event of removal from exposure. The prognosis is worse in cases of associated chronic bronchitis and complications such as tuberculosis or carcinoma. Advanced forms of silicosis are associated with progressive respiratory failure with or without cor pulmonale

Radiological course

Confluence of nodules in masses which progressively become more numerous towards the center leaving a peripheral subpleural emphysema with parenchymal destruction

If greater than 4 cm, the masses present central hypodensities due to necrosis or cavitations. The masses may also calcify

Remy-Jardin M. Coal worker's pneumoconiosis: CT assessment in exposed workers and correlation with radiographic findings. Radiology 1990, 177: 363

LABORATORY FINDINGS

An increase in rheumatoid factor, immunocomplexes, antinuclear antibodies and hypergammaglobulinemia may be found

CLINICAL DIAGNOSIS

The diagnosis of silicosis is generally radiological in the presence of a compatible occupational history and the absence of other nodular lung diseases

✓ Because the disease may persist even in cases of removal from exposure to silica particles, a detailed patient history is important, with particular attention paid to all of the occupations performed even in the remote past, given the long latency of the disease

INVASIVE DIAGNOSIS

Surgical lung biopsy is required only in the absence of a definite history of exposure or when the clinical-radiological findings are atypical

Bronchoalveolar lavage

The BAL fluid of patients with silicosis shows elevated alveolar macrophages, interleukin-1 and fibronectin. The massive fibrosis of the progressive form results in an increase in polymorphonucleated neutrophils. Exposed workers not affected by the disease may have an increase in lymphocytes which is suggestive of the presence of subacute alveolitis

Light and electron microscope examination of BAL fluid is able to confirm exposure or reveal unrecognized exposure

Christman JW. Effects of work exposure, retirement, and smoking on bronchoalveolar lavage measurements of lung dust in Vermont granite workers. Am Rev Respir Dis 1991, 144: 1307

Miliary tuberculosis

Definition

The term miliary tuberculosis encompasses all forms of progressive tuberculosis (TB) with hematogenous seeding

Although the lung is the preferred target organ (over 50% of patients), the disease may affect any other organ (e.g. spleen, liver, bone marrow, etc.)

DEMOGRAPHICS

Etiology and pathogenesis

In most cases TB is caused by Mycobacterium tuberculosis (MT), while in others M. bovis and M. africanus are the offending pathogens. A distinction needs to be made between primary infection and the development of the disease proper, which in turn may be either primary or secondary. Miliary TB bears all of the characteristic clinical manifestations of the secondary form. Cases of the disease have been reported after lithotripsy for kidney stones, ureteral catheterization and cardiac valve implant. MT is an aerobic acid alcohol-fast bacterium with slow growth (doubling time 12-18 h), Interleukin-12 and interferon gamma are thought to be essential cytokines for the development of granulomas and the defense against MT

Hematogenous seeding is less common in the primary form, probably owing to the lower number of bacteria in the body, which also presents a more effective immune host defence

The latency period between hematogenous seeding and the development of radiological lesions is probably several weeks

Epidemiology

Miliary TB is more common among the elderly and children below the age of 1 year. About 1.3-4% of all cases of TB are miliary forms

Risk factors

The various risk factors include socioeconomic status (malnutrition and poverty), drug and alcohol abuse (probable negative action against the immune system), sex and age (the disease is more common among elderly males), race and genetic factors (disease more common and severe among African Americans than among whites), associated diseases (silicosis, diabetes, chronic renal failure, alveolar proteinosis, gastric resection) and immunosuppression (HIV, steroid treatment, transplant patients)

CLINICAL FEATURES

History

Onset is often insidious, with a mean duration of symptoms to diagnosis of 16 weeks. The most common symptoms are aspecific and include fatigue, weakness, anorexia, weight loss, fever and night sweats. Respiratory symptoms are characterized by dry cough. Headache, mental status changes and abdominal pain are suggestive of involvement of the meninges or the peritoneum. Acute onset with fever and dyspnea is not rare, nor are fulminating forms with multiorgan failure or septic shock with ARDS

Physical findings

Physical chest examination is generally normal. Rales and rhonchi are rare findings, as is the presence of pleural effusion. Fundus examination of the eye may reveal multiple choroid tubercles in 30-60% of patients. Hepatomegaly with or without splenomegaly is not uncommon

Pulmonary function tests

Miliary TB produces a restrictive ventilatory defect with a marked deficiency in D_LCO

Diagnostic Standards and Classification of Tuberculosis in Adults and Children. Official statement of the American Thoracic Society and the Centers for Disease Control and Prevention. Am J Respir Crit Care Med 2000, 161: 1376

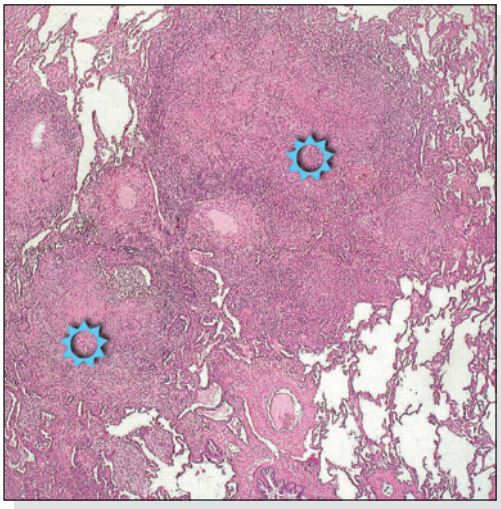
Kim JH. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990, 12: 583

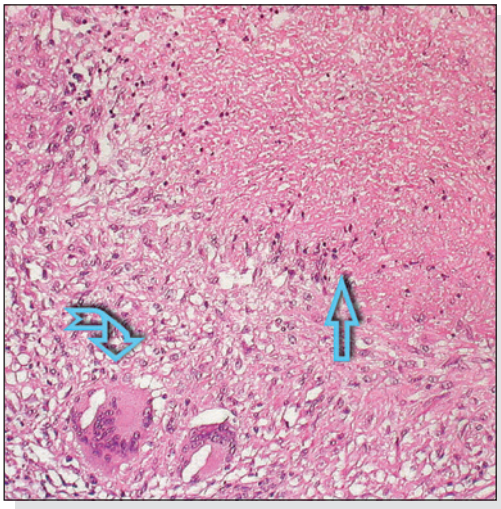
PATHOLOGY

Basic lesions

The histopathologic findings are the following:

- Multiple small granulomas (2-3 mm), often caseating and usually randomly distributed, although they may be clustered along vessel walls and airways (☼)
- The lesions are uniform in size and age, and classically consist of foci of caseating necrosis (⇨) surrounded by a wall of epithelioid macrophages mixed with Langhans' giant cells (with nuclei arranged peripherally in a horseshoe-like pattern) (↳)
- A variable quantity of neutrophils and small satellite granulomas with or without necrosis may be associated





In HIV-infected patients the tuberculous lesions may appear as poorly-formed granulomas or completely lose their granulomatous appearance, and even the caseating necrosis may be absent

Distribution

Random, sometimes peribronchiolar

Differentials

Histopathologic differential diagnoses:

- Fungal infections: isolation of the etiologic agent
- Wegener's granulomatosis: non-caseating necrosis with patchy distribution, "blue" in appearance due to the high number of neutrophils; vasculitis; absence of mycobacteria
- Sarcoidosis: non-caseating granulomas distributed along the lymphatics and absence of mycobacteria
- HP: granulomas are small, poorly-formed and non-caseating with a centrilobular distribution An intense lymphoplasmacellular interstitial infiltrate is associated and mycobacteria are absent

The mycobacteria are negative to hematoxylin-and-eosin staining but may be detected with special stains of which the best known is the Ziehl-Neelsen technique, which stains mycobacteria red, rendering them visible under the light microscope. However, at least 10^5-10^6 bacilli/ml of tissue are required for the stain to be positive. Far more sensitive methods of mycobacteria detection include molecular hybridization and DNA amplification

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127

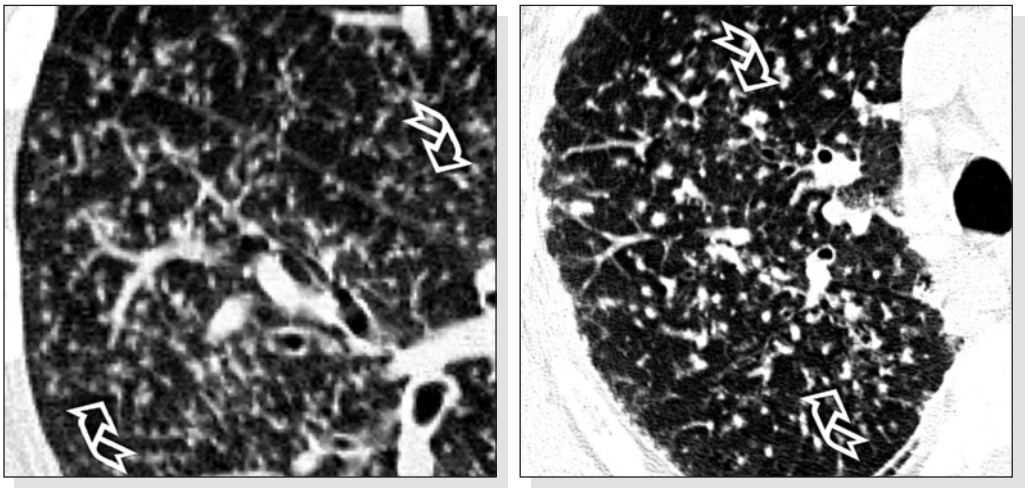
Ikonomopoulos JA. Multiplex polymerase chain reaction for the detection of mycobacterial DNA in cases of tuberculosis and sarcoidosis. Mod Pathol 1999, 12: 854

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Nodules with a diameter of 1-3 mm randomly distributed within the lobule. Their size is uniform (↳)



Hong SH. High resolution CT findings of miliary tuberculosis. J Comput Assist Tomogr 1998, 22: 220

Oh YW. High-resolution CT appearance of miliary tuberculosis. J Comput Assist Tomogr 1994, 18: 862

Distribution

Bilateral, symmetrical, diffuse

Uniformly distributed

Uniformly distributed

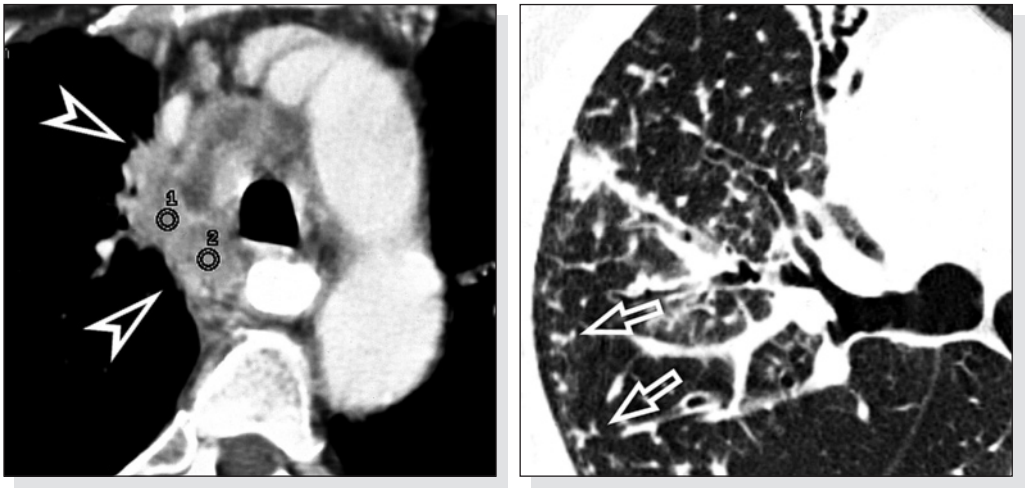
Lung volume is normal

Nodules may be observed also in the subpleural regions or along the fissures, but the general impression is of random distribution with no predilection of site. At times, a relationship may be observed with the most peripheral vessels

Other signs

Other characteristics:

- Diffuse or localized ground-glass
- Mediastinal adenopathies with possible central hypodensities due to necrosis (➢)
- Signs of bronchogenic spread of the disease with tree-in-bud (⇨)



Ground-glass is recognizable in varying percentages. When extensive, it may be the expression of massive lung involvement and be a prelude to or accompany an acute respiratory failure

Differentials

Radiological differential diagnoses:

- Metastases: the diameter of the lesions is often non-uniform and the nodules have a predominantly basal distribution
- Sarcoidosis: the nodules are situated along the bronchial walls, their distribution is patchy with a predilection for the subpleural regions. The nodules are also predominant in the upper and hilar-perihilar regions
- Silicosis: the nodules may be very similar in appearance and distribution within the lobe, but they predominate in the upper lobes and the posterior regions. The patient history is also disease specific
- LIP: possible middle-lower distribution. Small, low-density nodules with ill-defined margins, also centrilobular. Ground-glass may be present, and cystic lesions may be associated
- TB: centrilobular nodules with hazy margins and peripheral tree-in-bud. The lesions are of variable size, patchy distributed and may be cavitated

COURSE and COMPLICATIONS

Associated diseases

A number of clinical conditions may be associated with miliary TB, especially those producing immunosuppression (e.g. HIV, corticosteroid therapy, transplant, diabetes) or others such as silicosis, alveolar proteinosis, collagen vascular diseases, neoplasms, pregnancy or post partum

Clinical course

Miliary TB has a variable prognosis due to the fact that it is a disseminated disease, various risk factors may coexist and diagnosis may be delayed. A mortality of 20% has been reported, especially in cases of ARDS or associated disseminated intravascular coagulation

Radiological course

Confluence of nodules and possible cavitation if the infection progresses, or a progressive reduction in the density, number and size of nodules if the infection regresses

LABORATORY FINDINGS

Normochromic anemia and hyponatremia are frequently encountered. Hypercalcemia may be observed in 5-50% of patients, while a lesser number present inappropriate ADH secretion and hypopotassemia. Leukemoid reactions, pancytopenia, hemophagocytic syndrome and disseminated intravascular coagulation have all been reported. Sterile pyuria is found in 30% of patients

The Mantoux skin test is negative in 25-50% of patients

CLINICAL DIAGNOSIS

The diagnosis of miliary TB is often first posed by radiological findings, either together with or even in the absence of appropriate clinical findings. The diagnosis may only be confirmed by the detection of MT with direct examination or culture procedures of any biological sample available. Mycobacteria may be isolated in sputum, gastric aspirate, urine, and pleural or ascitic fluid. The detection of MT, however, is only positive in 30-35% of cases. Molecular biology techniques capable of increasing diagnostic accuracy are still burdened by the inability to distinguish between active and inactive forms of infection. The occasional autopsy finding of miliary TB is not uncommon, particularly in the elderly (20%)

INVASIVE DIAGNOSIS

Transbronchial lung biopsy associated with BAL has a diagnostic accuracy of 65%. Liver or bone marrow biopsy may also prove diagnostic

Bronchoalveolar lavage

BAL may be useful in the detection of MT in cases in which the bacilli were not detected in the sputum. Cytological examination of the BAL fluid shows the presence of an elevated number of lymphocytes and neutrophils. The CD4+/CD8+ ratio of T-cells in the BAL of patients affected by miliary TB is generally normal or elevated

The microscopic examination of the BAL needs to be performed with extreme care because the bacilli may be found only within the cytoplasm of the alveolar macrophages

Hoheisel GB. Bronchoalveolar lavage cytology and immunocytology in pulmonary tuberculosis. Am J Respir Crit Care Med 1994, 149: 460

Large rounded opacities

Definition

Rounded opacities from one to several centimeters in diameter, possibly associated with small-sized diffuse alterations, provide the specificity of the diseases. The diffuse lung diseases characterized by these features include:

- Aspergillosis
- Amyloidosis
- BronchioloAlveolar Carcinoma (BAC)
- High-grade primary lymphoma
- Kaposi's sarcoma
- Metastases
- Organizing Pneumonia (OP)
- Rheumatoid Arthritis (RA)
- Sarcoidosis
- Septic emboli
- Tuberculomas
- Wegener's granulomatosis

Although they are most commonly multiple, solitary opacities may occasionally appear. In such cases the intrinsic imaging characteristics of the lesion are the only non-invasive system for posing a diagnosis

ASPERGILLOSIS

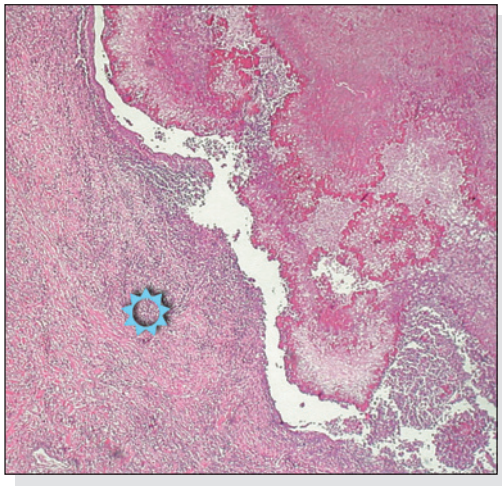
Clinical features

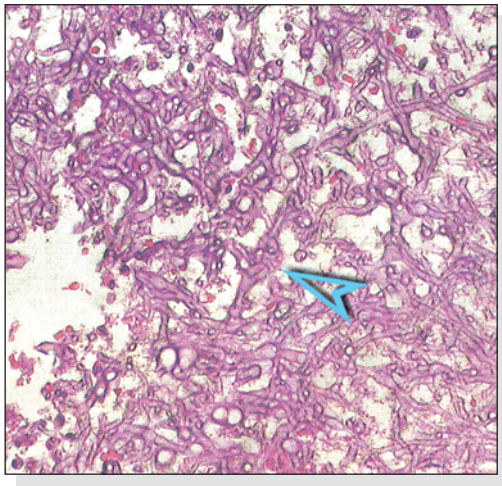
Invasive aspergillosis is a severe and often fatal infection which almost exclusively affects immunosuppressed subjects. Fever and cough are the most common symptoms (80% and 70%, respectively), while dyspnea, which often appears in the diffuse forms, is less frequently encountered (60%). In cases of cavitation hemoptysis may be observed. In the appropriate clinical-radiological setting, detection of aspergillus in pulmonary secretions alone can be sufficient to justify specific treatment. Chronic necrotizing aspergillosis (semi-invasive) is more common in patients with COPD, fibrosis or pneumoconiosis. A condition of mild immunosuppression does, however, facilitate colonization. Affected subjects may be asymptomatic or have symptoms such as productive cough, hemoptysis and fever. The clinical course is indolent (months to years). The disease may, however, prove fatal

Miller WT. Pulmonary aspergillosis in patients with AIDS. Clinical and radiographic correlations. Chest 1994, 105: 37

Pathology

The acute invasive form is characterized by nodular infarct of the lung associated with angioinvasion by aspergillus hyphae. The necrotic lesions may cavitate or contain a fungus ball. The chronic necrotizing form is characterized by a combination of granulomatous inflammation, necrosis and fibrosis of varying degrees (☼). Often the fungal hyphae and spores (➢) cannot be detected with routine staining, and special stains and techniques are required (e.g. PAS, methenamine silver, immunofluorescence, tissue cultures, etc.)





Sarosi GA. Fungal diseases of the lung. 3rd ed. Lippincott William and Wilkins, 2000

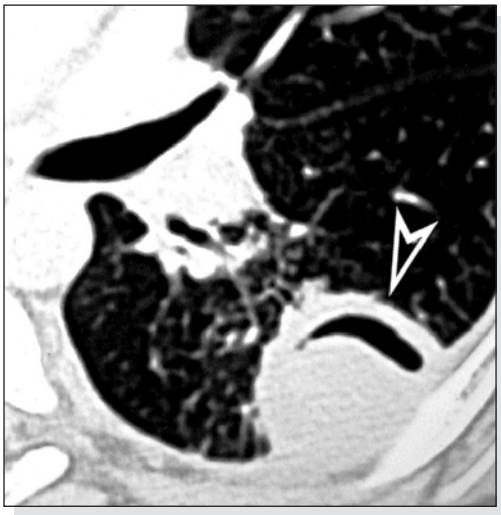
Yousem SA. The histological spectrum of chronic necrotizing forms of pulmonary aspergillosis. Hum Pathol 1997, 28: 650

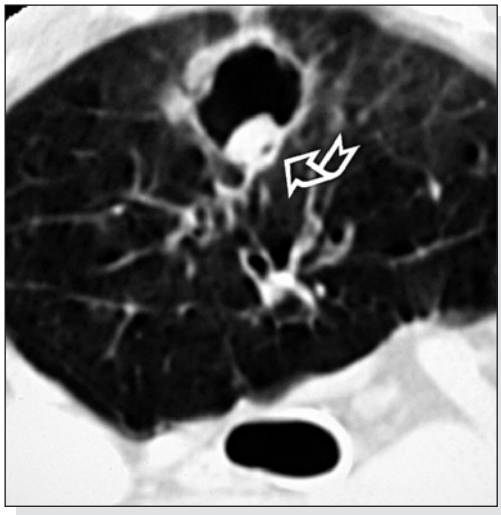
HRCT

In the angioinvasive form, multiple rounded opacities may be seen varying in shape and size and typically surrounded by a halo of ground-glass, an expression of perilesional hemorrhage (halo sign). The opacities may be cavitating, and an inclusion may be seen inside separated from the wall of the cavity by a hyperlucent meniscus (≫) (air crescent sign). Patchy areas of wedge-shaped pleural-based parenchymal consolidation may be associated

In the chronic necrotizing form, multiple opacities larger than 1 cm may be seen. They often cavitate and are associated with parenchymal consolidation, also cavitating. Inclusions (↬) of fungus balls are very often present within the cavitations

Consolidations and cavitations may mimic TB when found in the upper lobes





Logan PM. High-resolution computed tomography and pathologic findings in pulmonary aspergillosis: a pictorial essay. Can Assoc Radiol J 1996, 47: 444

AMYLOIDOSIS

Clinical features

Patients with nodular amyloidosis are usually asymptomatic and the lesions are often discovered as incidental findings on chest radiographs. Only one case with massive hemoptysis has been described. When multiple nodules are present, symptoms such as cough and hemoptysis occur

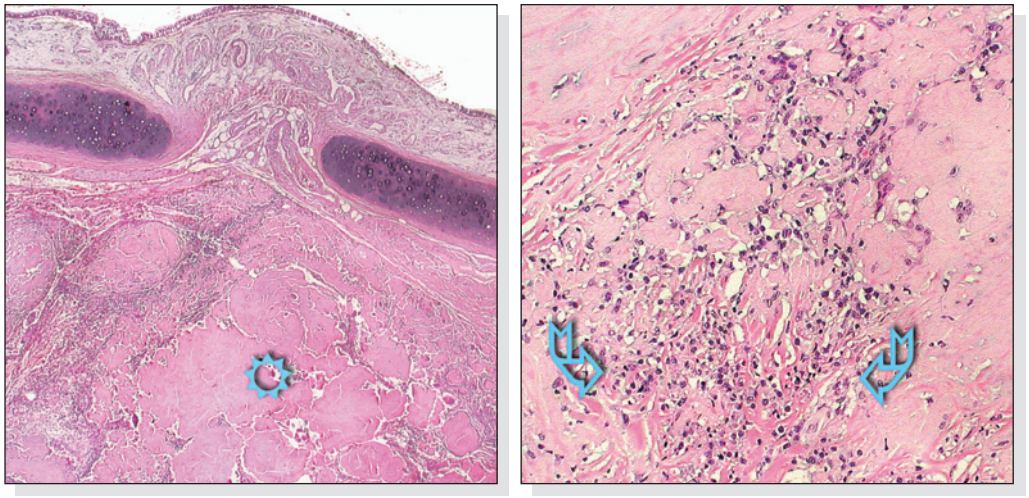
Physical lung examination and pulmonary function tests are generally normal and the prognosis is favorable

In most cases the nodules are characterized by stability or slow growth. Diagnosis is generally obtained by surgical lung biopsy

Gillmore JD. Amyloidosis and the respiratory tract. Thorax 1999, 54: 444

Pathology

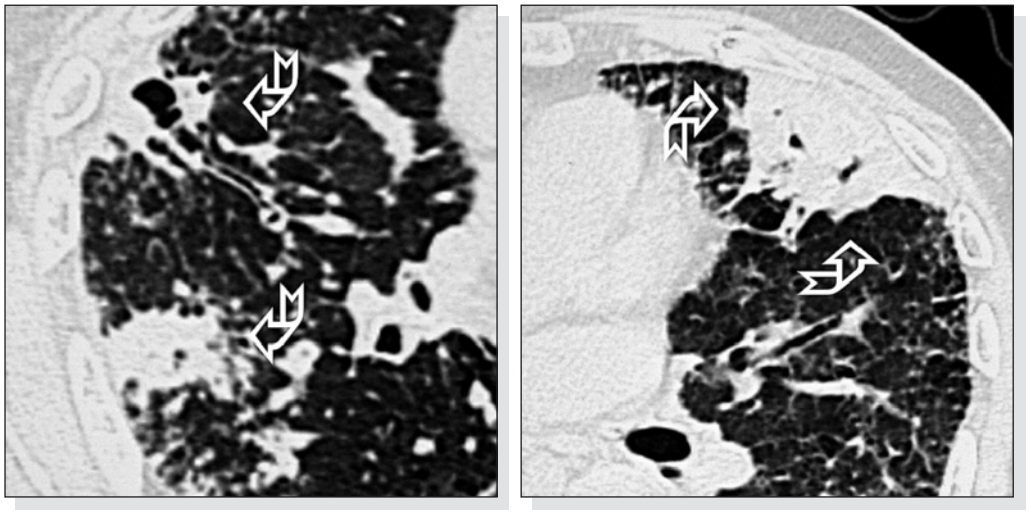
In nodular amyloidosis the amyloid deposits consist of circumscribed masses of amorphous, eosinophilic and homogenous extracellular material, which replace the normal pulmonary architecture (☼). Foci of osseous metaplasia or calcifications can be seen within these deposits, while lymphoplasmacellular infiltrates (☟) and a multinucleated giant-cell reaction are common at the periphery. Amyloid is positive to Congo red staining, exhibiting a green birefringence in polarized light, and is fluorescent after thioflavin staining



Dacic S. Nodular amyloidoma and primary pulmonary lymphoma with amyloid production: a differential diagnostic problem. Mod Pathol 2000, 13: 934

HRCT

The disease is characterized by multiple rounded opacities (☟)(although solitary nodules may be found) ranging in size up to several centimeters in diameter. Calcifications may be found (20-50%); cavitation is rare. The distribution is (⬌) peripheral and (⬍) basal. The lesions may grow slowly to large masses. Associated LIP may be observed (● LIP)



Urban BA. CT evaluation of amyloidosis: spectrum of disease. Radiographics 1993, 13: 1295

BRONCHIOLOALVEOLAR CARCINOMA (BAC)

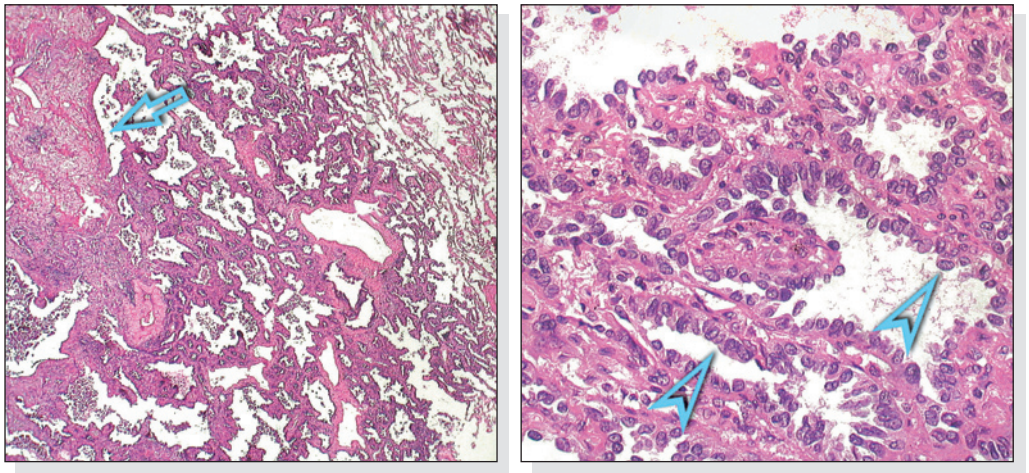
Clinical features

About half of all patients are asymptomatic. When present, the most common symptoms (onset from 6 months to 1 year prior to diagnosis) include cough (50-70%), sputum production >100 ml/day (5-25%), chest pain (30-50%), dyspnea (25-50%), hemoptysis (10-25%) and weight loss (25%). Bronchorrhea is a symptom of disseminated disease and may cause hypovolemia with prerenal failure and hyponatremia. Physical examination may find rales and occasional signs of pleural effusion. Pulmonary function tests are often normal. A restrictive defect may be found with diffusion deficiency and even hypoxemia. Diagnosis of a BAC can be obtained by transbronchial lung biopsy, although only surgical lung biopsy is capable of diagnosing a pure BAC

Harpole DH. Alveolar cell carcinoma of the lung: a retrospective analysis of 205 patients. Ann Thorac Surg 1988, 46: 502

Pathology

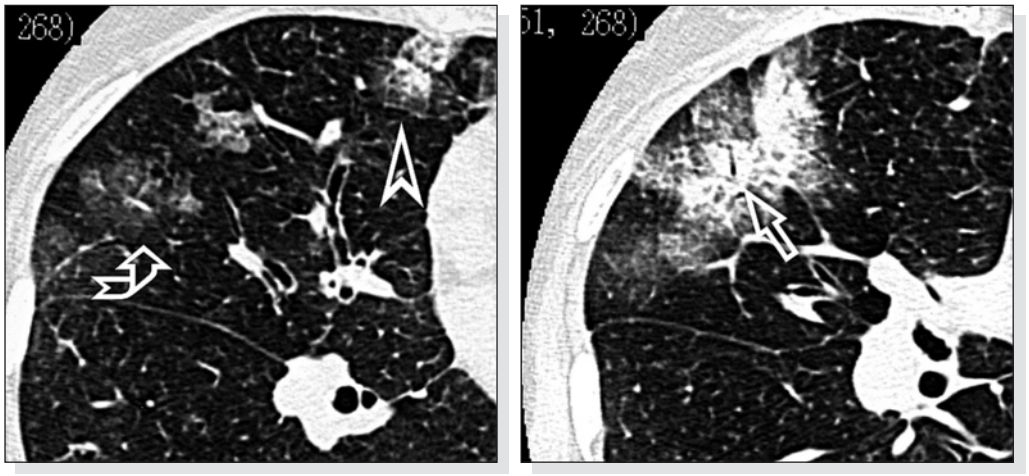
Histologically, lesions are characterized by growth along the alveolar walls (➢)(lepidic growth) without evidence of stromal, pleural, or vascular invasion. Large nodules often display a central sclerotic zone (⇨) where possible interstitial infiltration should be sought to exclude adenocarcinoma



Travis WD. Histological typing of lung and pleural tumors, 3rd ed. Springer, 1999

HRCT

The opacities may be numerous, varying in size up to 3 cm. Typically, they show ill-defined margins (↳) and often a halo sign (➢). A bronchocentric distribution is common (⇨). Cavitation is possible. A characteristic feature is the presence of narrowed bronchi inside the lesions, whereas calcifications are absent. The nodules tend to be distributed (⇹) peripherally but (⇳) without predilection along the craniocaudal axis. Patchy ground-glass and parenchymal consolidation are often present



Akira M. High-resolution CT findings of diffuse bronchioloalveolar carcinoma in 38 patients. AJR Am J Roentgenol 1999, 173: 1623

Gaeta M. Ground-glass attenuation in nodular bronchioloalveolar carcinoma: CT patterns and prognostic value. J Comput Assist Tomogr 1998, 22: 215

HIGH-GRADE PRIMARY LYMPHOMA

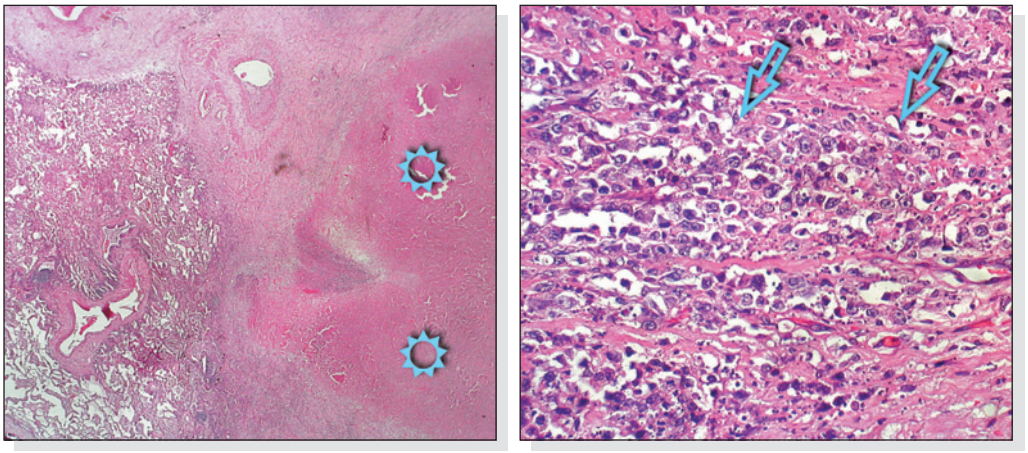
Clinical features

Lymphoma is a particularly common neoplasm in immunodepressed patients. In 80-90% of cases the neoplasm is of intermediate or high-grade malignancy and almost all are B-cell type. Pulmonary symptoms (e.g. cough, dyspnea and hemoptysis) are rare and aspecific. Patients more commonly report symptoms of systemic involvement such as fever, sweating and weight loss. Diagnosis generally requires surgical lung biopsy even though transbronchial (58-75%) or transthoracic (5-10%) lung biopsy may prove diagnostic. Prognosis is highly unfavorable, with a mean survival time of 6.5 months

Ray P. AIDS-related primary pulmonary lymphoma. Am J Respir Crit Care Med 1998, 158: 1221

Pathology

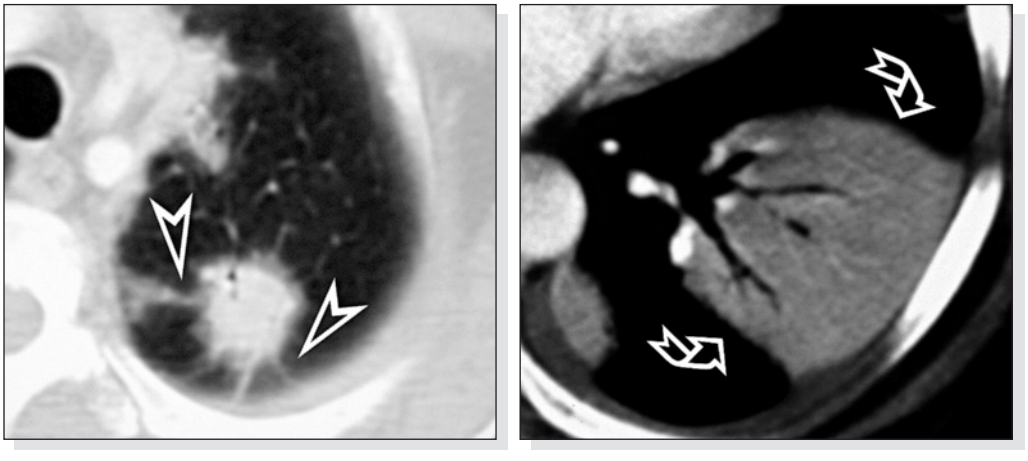
Lymphomas which develop in transplant or immunodepressed patients show clear similarities with angiocentric lymphoma/lymphomatoid granulomatosis (AIL/LYG). The histologic appearance varies from a polymorphous infiltrate consisting of small transformed lymphocytes to a monomorphous proliferation which is almost indistinguishable from a large cell lymphoma (⇨). An EBV infection is present in most cases. Necrosis (☼) and infiltration of the vessel walls may be the dominant features in the histopathologic pattern



Saxena A. Posttransplant diffuse large B-cell lymphoma of "lymphomatoid granulomatosis" type. Virchows Arch 2002, 441: 622

HRCT

The opacities, multiple with well-defined margins, usually have a spiculated appearance (➢) and often are centered on the bronchi with an air-bronchogram sign. The diameter of the lesions may reach 5 cm. Cavitation is possible while calcifications are absent. Reticular opacities, parenchymal consolidations (↳), mediastinal adenopathies and pleural effusion (common) may also be present. There is a tendency towards (⬌) central distribution but (⬍) without craniocaudal predilection



Eisner MD. The pulmonary manifestations of AIDS-related non-Hodgkin's lymphoma. Chest 1996, 110: 729
Lee KS. Imaging of pulmonary lymphomas. AJR Am J Roentgenol 1997, 168: 339

KAPOSI'S SARCOMA

Clinical features

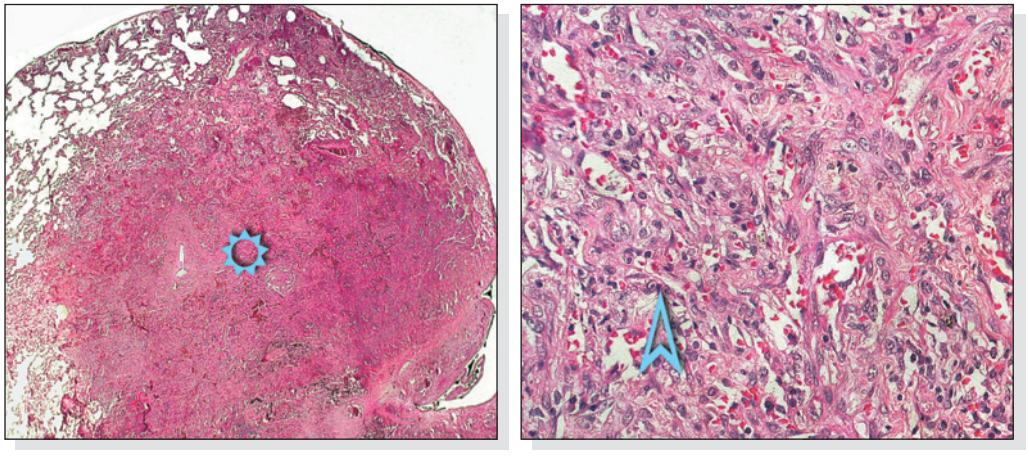
About one third of patients with Kaposi's sarcoma have clinically evident lung involvement. Kaposi's sarcoma may involve the lung parenchyma in either a nodular (25%) or interstitial pattern. The airways, the pleura and the intrathoracic lymph nodes may also be involved. Symptoms generally include dyspnea and cough, while hemoptysis and fever are less common. Clinical diagnosis is confirmed with fiberoptic bronchoscopy in cases where typical endobronchial lesions are present (bronchial and transbronchial lung biopsies have low diagnostic accuracy and cause significant hemorrhage in 30% of cases). In the remaining cases surgical lung biopsy is required. Diagnosis may also be suspected on the basis of the detection (PCR analysis) of the offending pathogen in BAL fluid (human herpes virus-8 – HHV8)

Miller RF. Bronchopulmonary Kaposi's sarcoma in patients with AIDS. Thorax 1992, 47: 721

Tamm M. Diagnosis of pulmonary Kaposi's sarcoma by detection of human herpes virus 8 in bronchoalveolar lavage. Am J Respir Crit Care Med 1998, 157: 458

Pathology

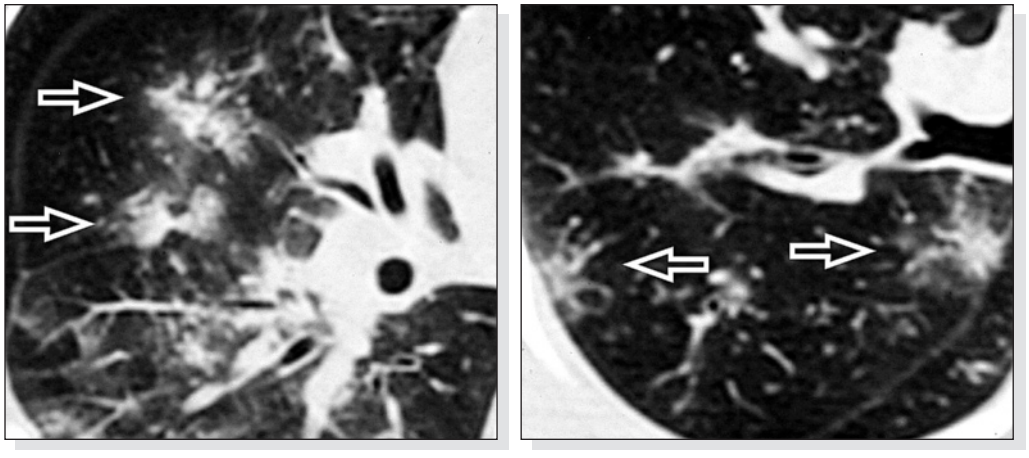
The tumor is composed of hemorrhagic nodules distributed along the lymphatics which originates around vessels and then extends to the surrounding structures (☼). Histologically it consists of a proliferation of spindle cells separated by interanastomosing vascular channels (➢) with extravased erythrocytes and hemosiderin deposits in the interstitium. The cytoplasm of the neoplastic cells contains characteristic PAS-positive eosinophilic globules. Also associated are varying degrees of chronic inflammatory infiltrate and vascular ectasia of the surrounding parenchyma



Purdy LJ. Pulmonary Kaposi's sarcoma. Premortem histologic diagnosis. Am J Surg Pathol 1986, 10: 301

HRCT

The nodules have hazy and irregular margins, often with a flame-like appearance and a diameter which can reach several centimeters (⇨). The non-cavitating and non-calcifying lesions tend to be bronchocentric (⇹) in parahilar regions (⇳), especially at the lung bases. Other signs: peribronchial interstitial thickening, pleural effusion (35%), adenopathies (50%), consolidations and areas of ground-glass (30%)



Hartman TE. Diagnosis of thoracic complications in AIDS: accuracy of CT. AJR Am J Roentgenol 1994, 162: 547

METASTASES

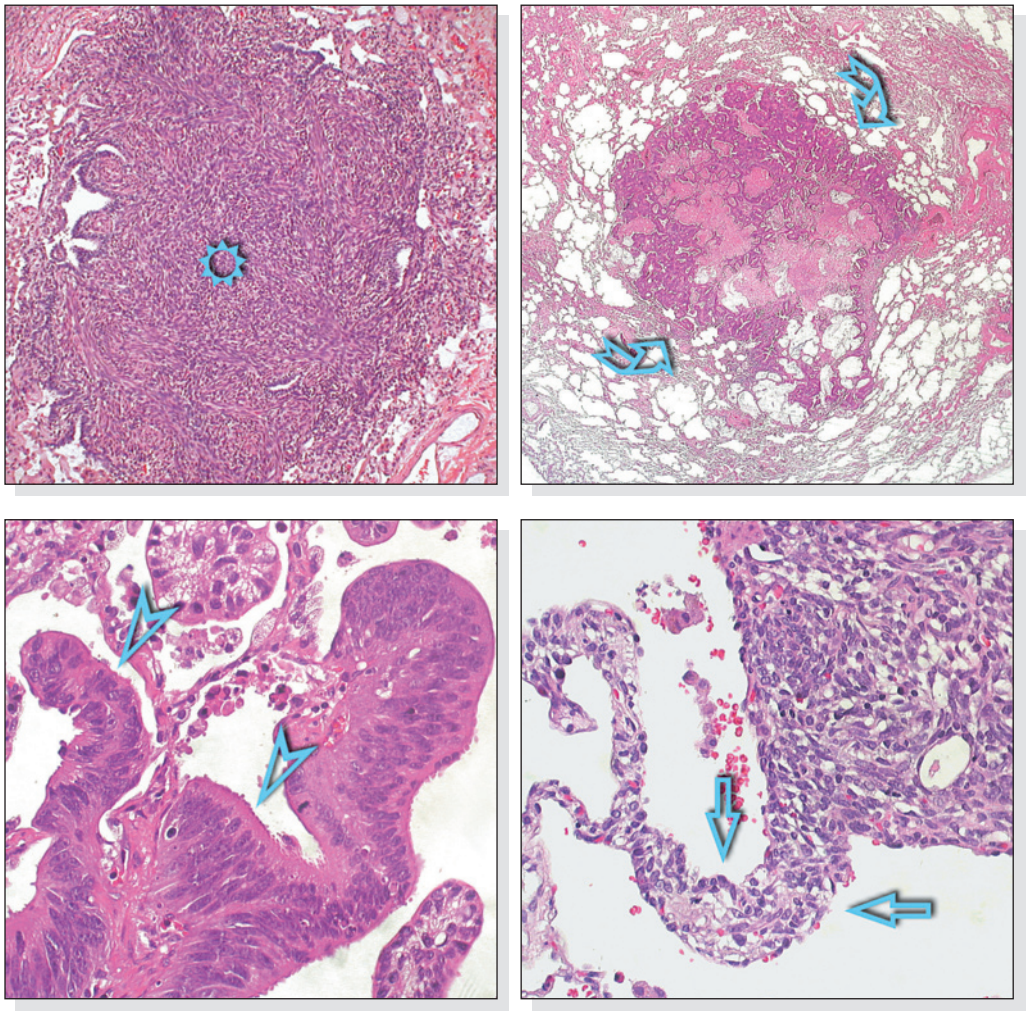
Clinical features

Between 84% and 98% of multiple pulmonary coin lesions are metastatic. The primary neoplasm often originates in the testicles, ovaries, kidneys or breasts, or is a melanoma or sarcoma. Patients are generally asymptomatic, and symptoms of cough, hemoptysis (airways) and chest pain (pleura) are only occasionally observed in cases of tumor extension to the adjacent structures. In cases of numerous large lesions dyspnea may be present. Rarely and after the removal of the primary neoplasm (e.g. renal carcinoma or choriocarcinoma) cases of spontaneous remission have been reported

Libshitz HI. Pulmonary metastases. Radiol Clin North Am 1982, 20: 437

Pathology

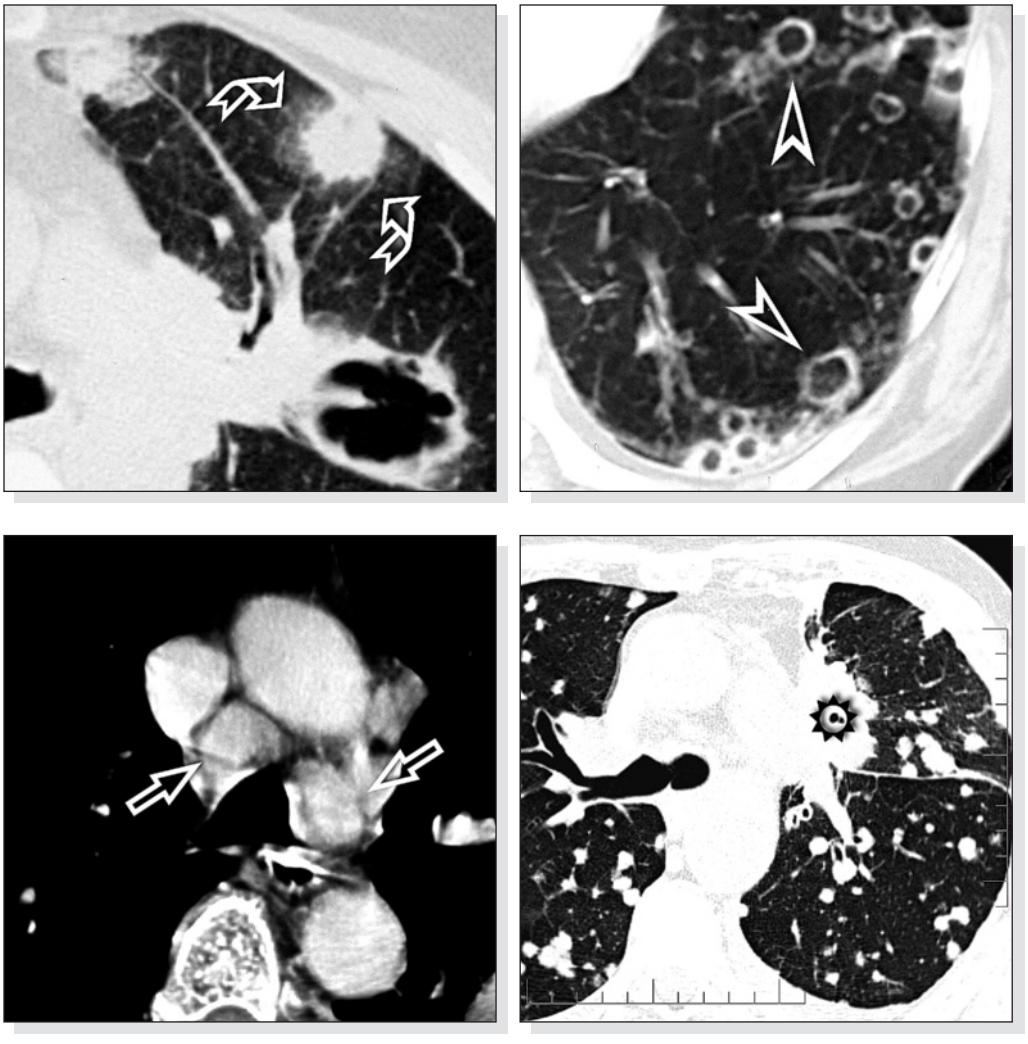
While miliary nodules are common in metastases from melanomas, renal carcinomas and thyroid medullary carcinoma, "cannonball" metastases are typical of sarcomas (☼) and colo-rectal carcinomas (☟), as well as the above-mentioned renal carcinomas and melanomas. Histologically, the growth pattern of metastases can be classified in five groups: 1. lepidic growth (➢) (typical of bronchioloalveolar carcinoma) may be shared by various adenocarcinomas, especially colo-rectal adenocarcinoma; it is frequently necrotic and displays no anthracotic pigment in the areas of fibrosis; 2. interstitial growth with no involvement of the overlying alveolar epithelium is typical of low-grade malignant sarcomas (⇨) (e.g. leiomyosarcomas, endometrial stromal sarcomas, etc.); 3. cavitation is frequent in metastases from carcinomas of the head and neck, cervix, bladder, colon and breast; 4. thin-walled cysts may be observed in sarcomas; 5. cavitation and cysts are seen in teratomas, lymphomas and melanomas



Askin FB. Something old? Something new? Second primary or pulmonary metastasis in the patient with known extrathoracic carcinoma. Am J Clin Pathol 1993, 100: 4

HRCT

The number of lesions is variable and their diameter may also vary within the same patient up to several centimeters. The opacities have regular and well-defined margins, but are sometimes hazy with a halo sign (↳) in choriocarcinomas and angiosarcomas. Cavitation (⩾) is possible in metastases from squamous-cell carcinomas of the head and neck, cervix or bladder, gastrointestinal adenocarcinomas and sarcomas. Calcifications are possible within the lesions from osteosarcoma, chondrosarcoma, thyroid papillary carcinoma, giant-cell bone tumors, synovial sarcomas, mucinous carcinomas of the gastrointestinal tract, breast and in treated metastases. The distribution is (↔) peripheral (↕) with a predilection for the lung bases. Mediastinal adenopathy (⇨), lymphangitic carcinomatosis (☐ LC) and primary pulmonary neoplasms (☼) may also be present



Diederich S. Helical CT of pulmonary nodules in patients with extrathoracic malignancy: CT-surgical correlation. AJR Am J Roentgenol 1999, 172: 353

Seo JB. Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 2001, 21: 403

ORGANIZING PNEUMONIA (OP)

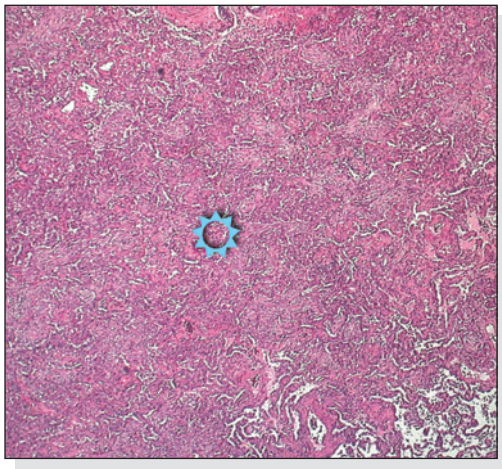
Clinical features

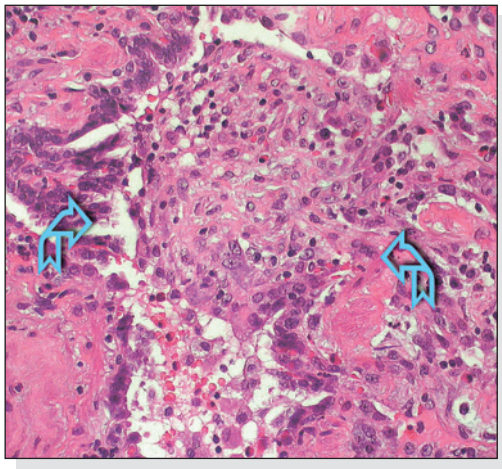
Organizing pneumonia is a clinical condition which manifests in a cryptogenic form (⌘OP) or secondary to various diseases, both infectious and non-infectious. The disease generally has a pneumonia-like appearance, but may also present large rounded pulmonary opacities. Seventy-five percent of patients have symptoms for at least 3 months prior to diagnosis. The clinical manifestations of disease onset are often similar to those of influenza

Lohr RH. Organizing pneumonia. Features and prognosis of cryptogenic, secondary, and focal variants. Arch Intern Med 1997, 157: 1323

Pathology

Early descriptions of the disease used the acronym BOOP to indicate the two components of the disease, i.e. bronchiolitis obliterans (↳) and organizing pneumonia (☼). Bronchioles, alveolar ducts and alveoli are filled with plugs of loose connective tissue containing fibroblasts and inflammatory cells in a mucopolysaccharide-rich matrix. The lesion is temporally uniform

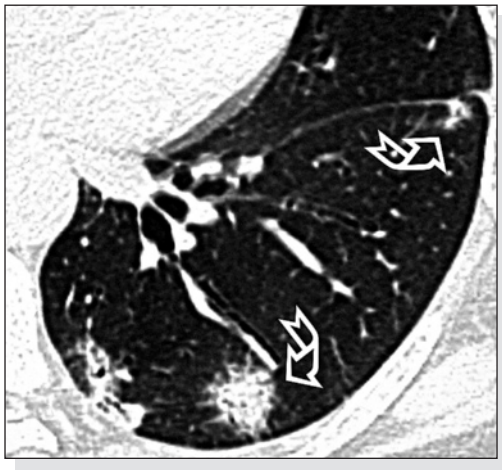


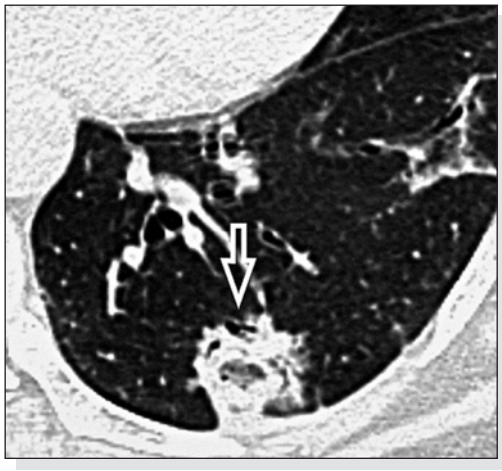


American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

HRCT

The radiological appearance is characterized by multiple opacities (↳) (from 2 to 8) with mixed well- and ill-defined irregular margins which may be spiculated and in contact with the pleura (38%). A reversed halo sign (atoll sign) (⇨) may be also present. The diameter of the lesions vary from 1 to 5 cm. Bronchi can often be observed in the context of the lesions. Calcifications are absent. Lesions tend to be distributed (⇹) peripherally (⇳) without craniocaudal predilection. Consolidations, interlobular septal thickening, parenchymal bands and pleural thickening may be present





Akira M. Bronchiolitis obliterans organizing pneumonia manifesting as multiple large nodules or masses. AJR Am J Roentgenol 1998, 170: 291

Zompatori M. Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign). A case report. Radiol Med 1999, 97: 308

RHEUMATOID ARTHRITIS (RA)

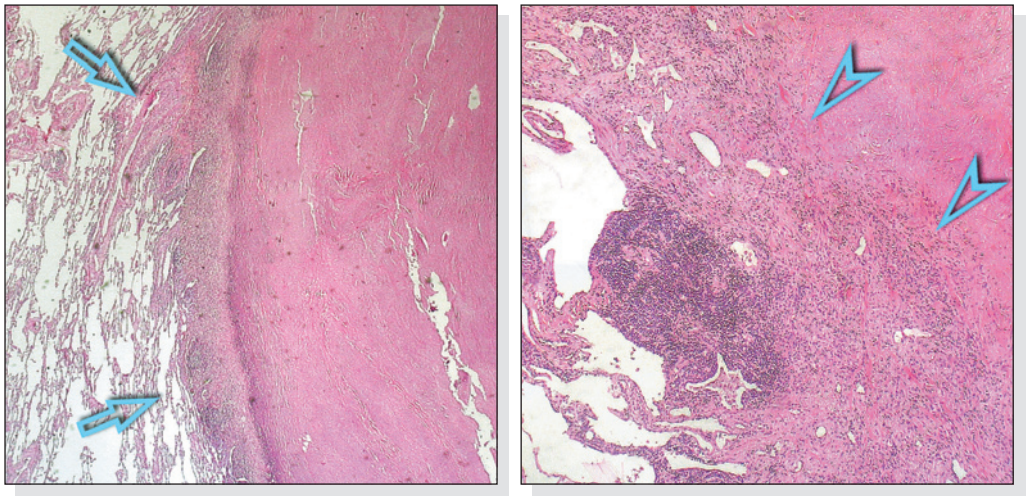
Clinical features

Rheumatoid nodules are the only pulmonary hallmark of this disease. Their precise prevalence is unknown, ranging from 0.5% at radiology to 32% at biopsy examination. They generally produce no symptoms, although they may be complicated by infection and/or cavitation with pneumothorax, pyopneumothorax, bronchopleural fistula and hemoptysis. Prognosis is usually favorable with spontaneous remission

Yousem SA. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985, 131: 770

Pathology

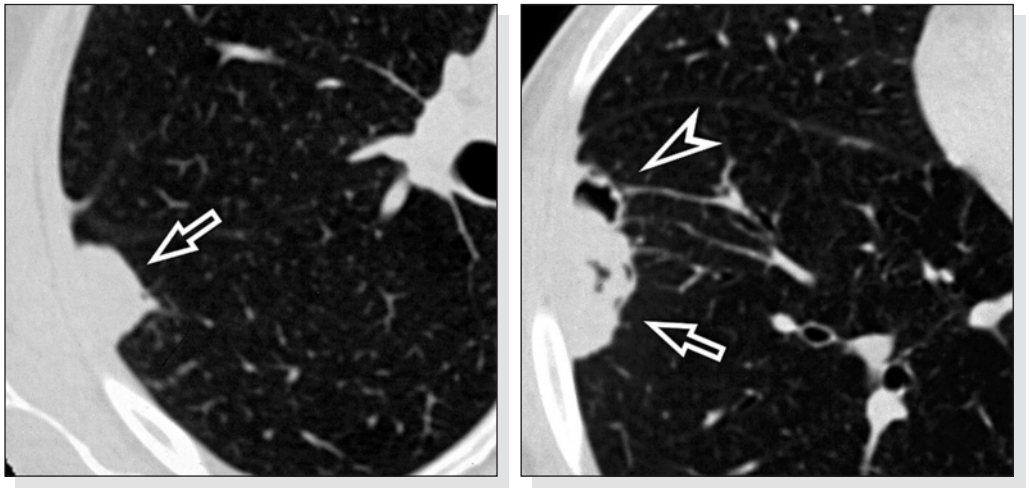
The nodules (⇨) are necrotic, surrounded by palisading histiocytes and possibly by a fibrous capsule (➢), in subpleural and paraseptal regions. They may become infected and cavitate, or be the site of hemorrhage. The characteristic lesions of the disease can be seen in the surrounding parenchyma



Yousem SA. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985, 131: 770

HRCT

Isolated opacities up to several centimeters in diameter; the size may increase during the acute phases of the disease proportional to the antibody titre. The nodules are well-defined with lobulated margins (⇨). Cavitation (➢) is common (50%), whereas calcifications are absent. Distribution is (⇹) peripheral, adjacent to the pleura and (⇳) without predilection along the craniocaudal axis. Associated tracheobronchial nodules may be observed



Sarkar TK. Pulmonary necrobiotic nodule. J Rheumatol 1984, 11: 557

Walters MN. Pleuropulmonary necrobiotic rheumatoid nodules. A review and clinicopathological study of six patients. Med J Aust 1986, 144: 648

SARCOIDOSIS

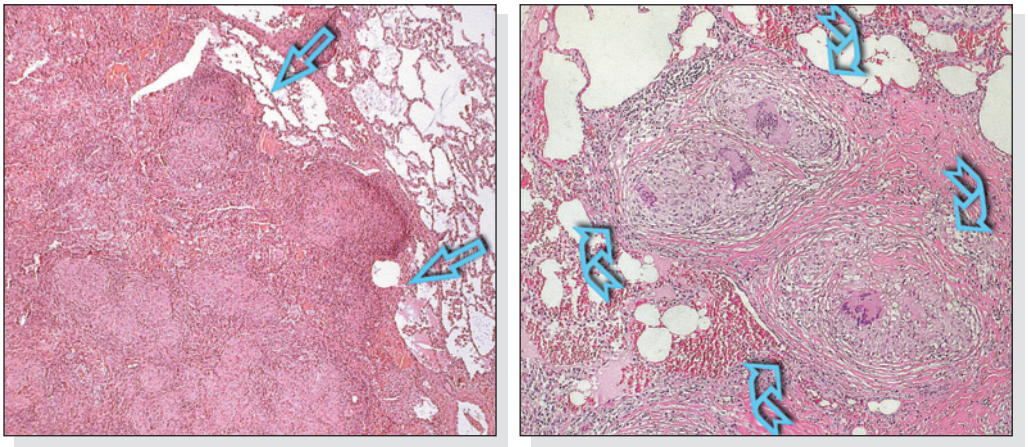
Clinical features

Sarcoidosis presenting as solitary or multiple large nodules occurs in less than 5% of cases. In about 50% of cases the finding occurs incidentally on chest radiographs. Respiratory symptoms include dry cough, dyspnea and chest pain. If the opacities are cavitating, hemoptysis may be observed. Systemic symptoms such as weakness, fatigue, mild fever, polyarthralgia and weight loss may appear in 30% of cases. Less common symptoms include the involvement of extrapulmonary organs: skin (20%), eye (20%), CNS (5%) etc. Physical examination of the chest is generally normal. Diagnosis may be performed with transbronchial or surgical lung biopsy

Costabel U. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999, 14: 735

Pathology

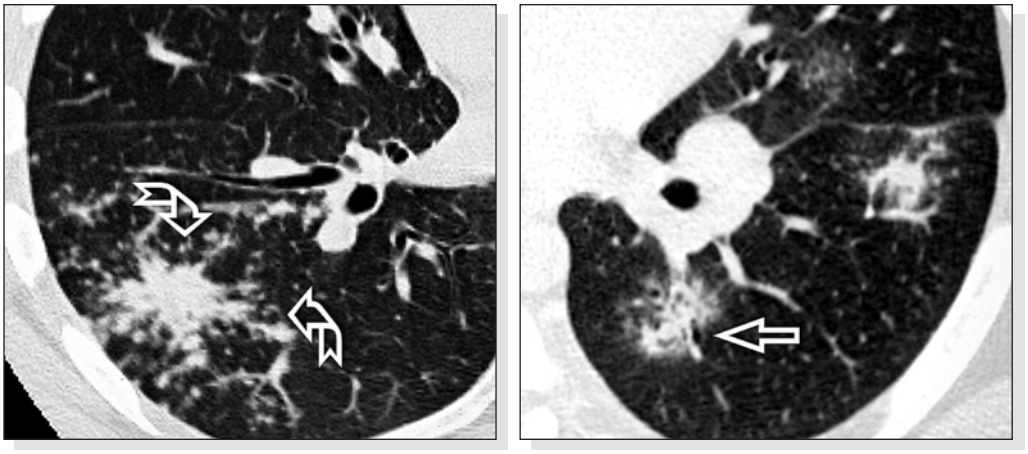
Sarcoidosis rarely presents in the lungs as large nodules (⇨) distributed predominantly along the airways and in subpleural regions. These larger lesions are formed by the coalescence of single, non-necrotizing, epithelioid granulomas (↳), with multinucleated giant cells often containing cytoplasmic inclusions and surrounded by fibrosis. The parenchyma between the lesions is normal or exhibits well-formed non-necrotizing epithelioid granulomas with a lymphatic distribution



Abramowicz MJ. Tumour-like presentation of pulmonary sarcoidosis. Eur Respir J 1992, 5: 1286

HRCT

The opacities of nodular sarcoidosis may be single or multiple, and the diameter may rise up to several centimeters. The lesions may have well-defined margins and irregular borders surrounded by multiple tiny satellite nodules (↳) (galaxy sign) or hazy margins and irregular borders and contain narrowed bronchi (⇨), whereas calcifications are absent. A necrotizing variant may be observed. The distribution of the lesions (⬌) tends to be bronchocentric (⬍) with a predilection for the upper lung zones. Large opacities are usually associated with perilymphatic micronodules, and hilar and mediastinal adenopathies



Muller NL. Ground-glass attenuation, nodules, alveolitis, and sarcoid granulomas. Radiology 1993, 189: 31

Nakatsu M. Large coalescent parenchymal nodules in pulmonary sarcoidosis: "sarcoid galaxy" sign. AJR Am J Roentgenol 2002, 178: 1389

SEPTIC EMBOLI

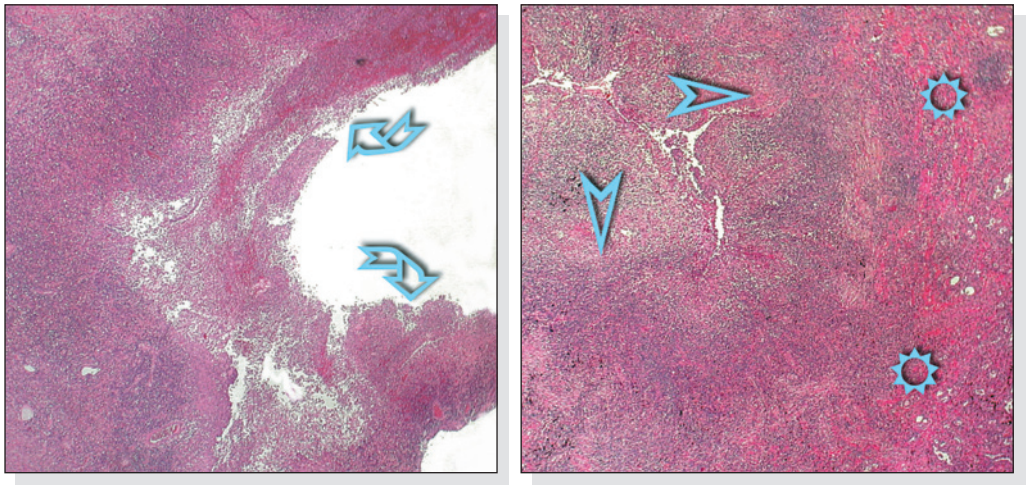
Clinical features

The main origin of septic emboli is septic deep venous thrombosis of the lower limbs or pelvis, with central venous lines, tricuspid endocarditis and intravenous drug use being less common. The most frequent complications include pulmonary abscess or septic pulmonary infarction, empyema (30%) and broncho-pleural fistula (rare). The symptoms are the same as those of pulmonary embolism (e.g. dyspnea, chest pain and hemoptysis) accompanied by septicemia. Pulmonary hypertension with signs of right-sided heart failure may develop rapidly

Libby LS. Pulmonary cavitation following pulmonary infarction. Medicine 1985, 64: 342

Pathology

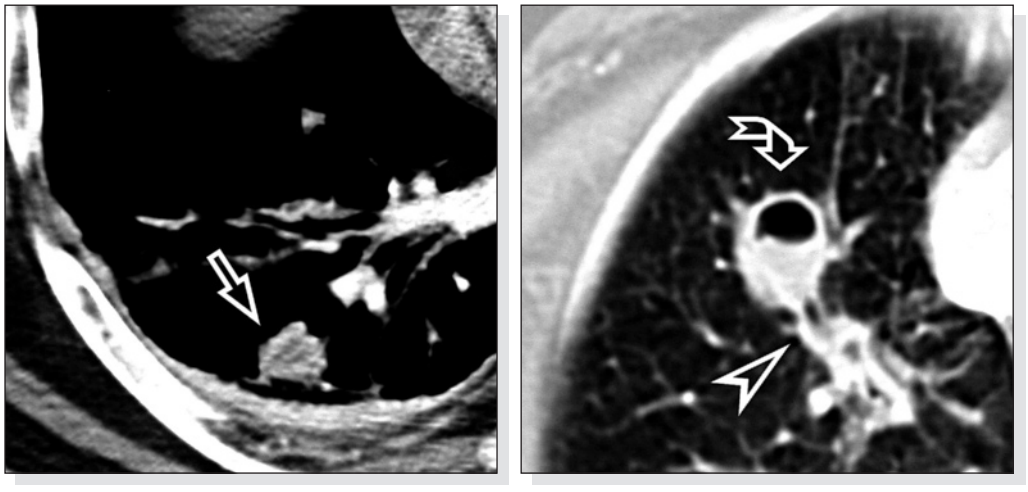
The pulmonary abscess consists of a cavitating lesion that at some time during its development contains purulent material. In the acute phase, pus and necrotic material are abundant at the center of the thin-walled cavity (↳); in the chronic phase, the granulocytic infiltrate is substituted by lymphocytes, plasma cells and macrophages (➢) and the cavity walls are thickened due to the presence of fibrosis (☼) and granulation tissue



Kumar V. Robbins. Basic Pathology. Elsevier Science, 2002

HRCT

Rounded opacities (⇨) typically multiple with well-defined or hazy margins, size variable up to 3 cm and usually a peripheral vascular distribution (➢). Cavitation (↳) is common while calcifications are absent. The opacities tend to be distributed (⇹) peripherally with (⇳) a predilection for the basal regions. Peripheral wedge-shaped pleural-based opacities due to parenchymal infarction, thereafter typically hypodense after contrast medium, may be found in association (50-70%)



Huang RM. Septic pulmonary emboli: CT-radiographic correlation. AJR Am J Roentgenol 1989, 153: 41

Kuhlman JE. Pulmonary septic emboli: diagnosis with CT. Radiology 1990, 174: 211

TUBERCULOMAS

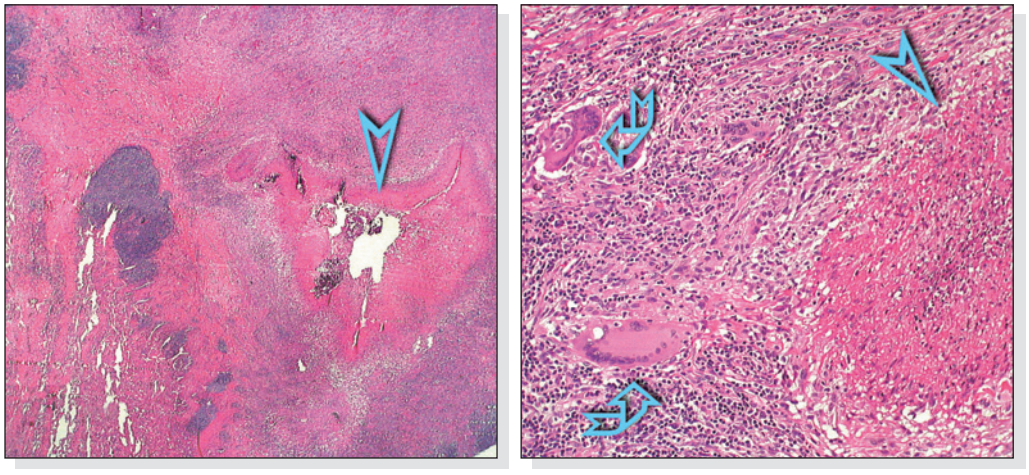
Clinical features

Tuberculoma may develop during a primary infection or when a secondary focus of tubercular reactivation becames encapsulated. These lesions are often solitary and may be cavitating. Patients are almost always asymptomatic, thus tuberculoma is generally an incidental finding on chest radiographs. Diagnosis is difficult because bronchial washing, BAL and tissue culture assays are often negative. Surgical lung biopsy or transthoracic needle biopsy are therefore required

Congregado Loscertales M. Usefulness of video-assisted thoracoscopy for the diagnosis of solitary pulmonary nodules. Arch Bronconeumol 2002, 38: 415

Pathology

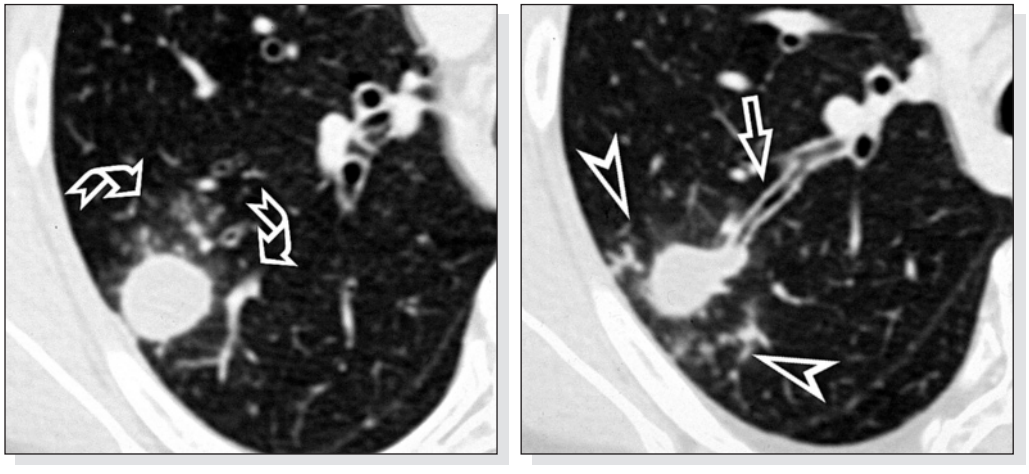
Histologically, the lesions share the features of tubercular infection. The solitary nodule has a necrotic (caseous) center (➢), multinucleated giant cells with nuclei distributed peripherally in a horseshoe pattern (Langhans' type cells) (↳) and surrounded by palisading histiocytes admixed with epithelioid cells and varying degrees of lymphocellular infiltrate. The capsule is usually thick and cavitation is frequent



American Thoracic Society and the Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000, 161: 1376

HRCT

Opacities are most frequently solitary, but may be also multiple and bilateral. In the advanced phase, the tuberculomas are dense lesions with well-defined margins and characteristic central calcifications. In the early phase, the lesions display low density and a hyperdense rim after contrast medium, with possible cavitation. In this phase the margins are well-defined although a halo sign may be present (↳). The distribution of the lesions (◆▶) is relatively peripheral, possibly centered by a bronchus (⇨) and often surrounded by satellite lesions (➢) (hazy micronodules, thick-walled bronchi, tree-in-bud opacities)



Lee JY. Pulmonary tuberculosis: CT and pathologic correlation. J Comput Assist Tomogr 2000, 24: 691
Gaeta M. Computed tomography halo sign in pulmonary nodules: frequency and diagnostic value. J Thorac Imaging 1999, 14: 109

WEGENER'S GRANULOMATOSIS

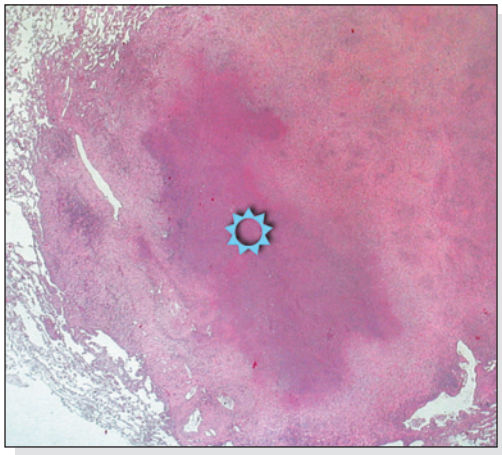
Clinical features

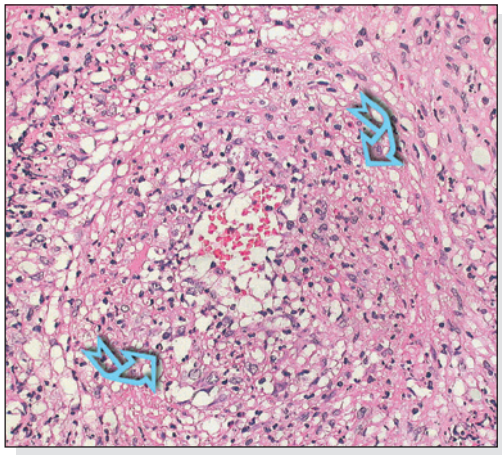
Symptoms of lower respiratory tract involvement in Wegener's granulomatosis include cough (60-77%), hemoptysis (30-40%), dyspnea and chest pain. These may be associated with systemic symptoms, such as fever, anorexia, weight loss and malaise, as well as signs and symptoms of the involvement of other organs and/or systems (kidney in 75-85%, polyneuritis in 20-35%, ocular symptoms in 10-15%, skin alterations in 10-15%, alterations of the musculoskeletal system in 30%). Nodule cavitation can cause cough and hemoptysis. In cases of large pulmonary lesions the chest examination may reveal signs of consolidation. Positive staining for antineutrophil cytoplasmic antibodies (ANCA) and especially C-ANCA against the target antigen proteinase 3 is diagnostic in the appropriate clinical-radiological setting

Hoffman GS. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992, 116: 488

Pathology

Histologically, nodules represent areas of pulmonary consolidation with necrosis on an inflammatory background. The characteristic features are necrosis (☼) (both geographic and often basophilic due to the presence of numerous neutrophils, and in the form of microabscesses), vasculitis (↳) (which may involve arteries, veins or capillaries and is usually focal and eccentric to the vessel wall) and an inflammatory infiltrate (consisting of a mixture of neutrophils, lymphocytes, plasma cells, macrophages, eosinophils and giant cells). Intraalveolar hemorrhage, OP or tissue eosinophilia may be found in the surrounding lung and may be the dominant feature in some variants of the disease (⌘ DAH)

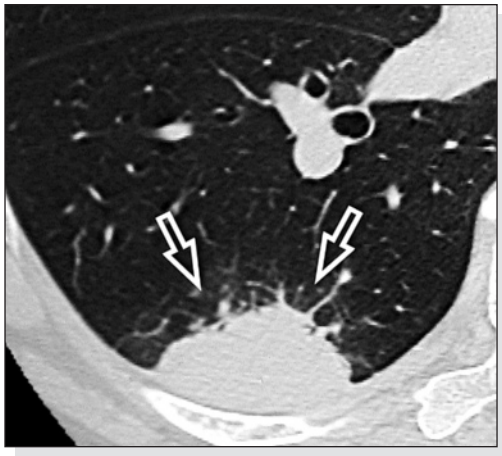


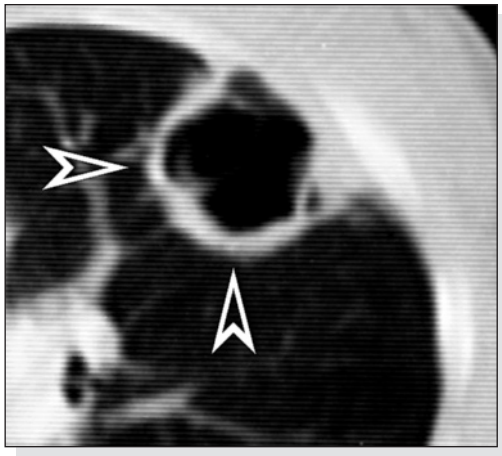


Katzenstein AL. Solitary lung lesions in Wegener's granulomatosis. Pathologic findings and clinical significance in 25 cases. Am J Surg Pathol 1995, 19: 545

HRCT

Scattered uni- or bilateral opacities, multiple in 85% of cases. The margins may be well-defined; the borders are irregular (⇨). The diameter may reach 10 cm. Cavitation (≻) is common, with thick and irregular walls. Calcifications are absent. The lesions may be distributed along the bronchovascular bundles (⇹) peripherally but (⇳) with no craniocaudal predilection. Ground-glass opacities and parenchymal consolidations are often present





Aberle DR. Thoracic manifestations of Wegener granulomatosis: diagnosis and course. Radiology 1990, 174: 703

⌘ Alveolar Diseases

Clinical features	**Alberto Pesci**
Pathology	**Alessandra Cancellieri**
Radiology	**Maurizio Zompatori**

Acute Interstitial Pneumonia

Definition

Acute interstitial pneumonia (AIP) is a rare and rapidly progressive form of lung damage that arises abruptly in apparently healthy individuals. The disease has no known cause and is classified among the idiopathic interstitial pneumonias

Hamman-Rich syndrome, fulminant interstitial pneumonia

The general term idiopathic interstitial pneumonias (IIP) include various diseases, in particular usual interstitial pneumonia (☐ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (☐ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

DEMOGRAPHICS

Etiology and pathogenesis

Although the etiology and pathogenesis are unknown, the lung damage is thought to be caused by the release of toxic oxygen species and proteases by polymorphonuclear neutrophils

Epidemiology

Mean age at onset is 50 years. Both sexes are equally affected and there is no correlation with tobacco smoking

Risk factors

There are no known risk factors

CLINICAL FEATURES

History

The onset is acute and the most common presenting symptoms are cough (100%), dyspnea (80-100%) and fever. Patients often report a prodromal flu-like illness (joint and muscle pain, fever, chills and malaise)

Physical findings

Physical examination reveals tachypnea and peripheral cyanosis. In 50% of cases fine rales can be heard throughout the lung fields

Pulmonary function tests

All patients have reduced D_LCO and a restrictive pattern. Moderate to severe hypoxemia, at times refractory to oxygen therapy, rapidly ensues. Rapid progression to respiratory failure similar to acute respiratory distress syndrome (ARDS) is common

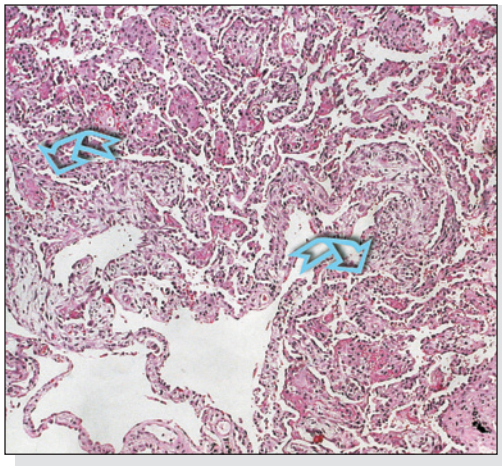
Vourlekis JS. Acute interstitial pneumonitis. Case series and review of the literature. Medicine 2000, 79: 369

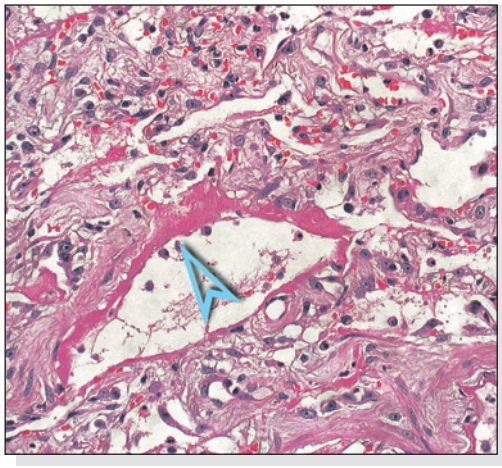
PATHOLOGY

Basic lesions

The histologic features of AIP are those of diffuse alveolar damage (DAD):

- Acute (exudative) phase, rarely biopsied: hyaline membranes, an expression of acute epithelial damage, line the alveolar walls. The alveolar septa show edema and varying amounts of acute and chronic inflammatory infiltrate. Thromboses of small and medium-size arterioles are common
- Organizing (proliferative) phase: proliferation of myofibroblasts that migrate from the interstitium to the alveolar spaces: the hyaline membranes (➢) are resorbed and organized within the alveolar septa, which become thickened (↯). Proliferation of hyperplastic type II pneumocytes restores the alveolar epithelium
- Chronic (fibrotic) phase: dense fibrosis with possible distortion of lung architecture





Distribution

Diffuse (alveoli and alveolar septa)

Differentials

Histopathologic differential diagnoses:

- DAD associated with infections: granulomas, viral inclusions, necrotic foci, abscesses; identification of the microorganism with special stains
- DAD superimposed on UIP (accelerated UIP): associated with the characteristic UIP pattern
- DAD due to other causes: not idiopathic but secondary to other causes (shock, trauma, physical or chemical causes, etc.)
- OP: predominantly intraalveolar foci of fibroblastic organization, intense inflammatory infiltrate, bronchiolar involvement (not constant)

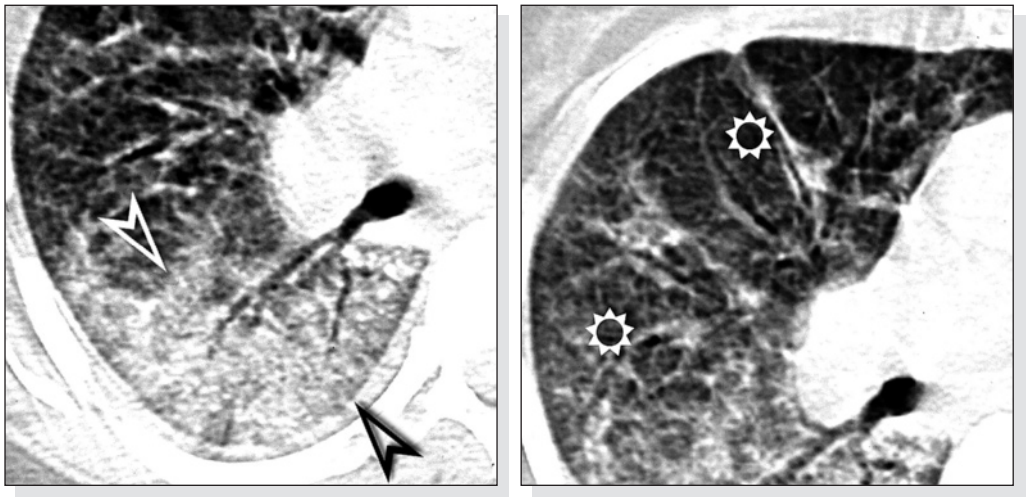
Katzenstein AL. Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986, 10: 256

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs, typical of the early stage (1-7 days):

- Parenchymal consolidation (≥)
- Ground-glass opacities (☼)



Akira M. Computed tomography and pathologic findings in fulminant forms of idiopathic interstitial pneumonia. J Thorac Imaging 1999, 14: 76

Distribution

Diffuse or patchy, generally bilateral and symmetrical

Lesions may predominate in the peripheral and lower regions of the lung

Variable

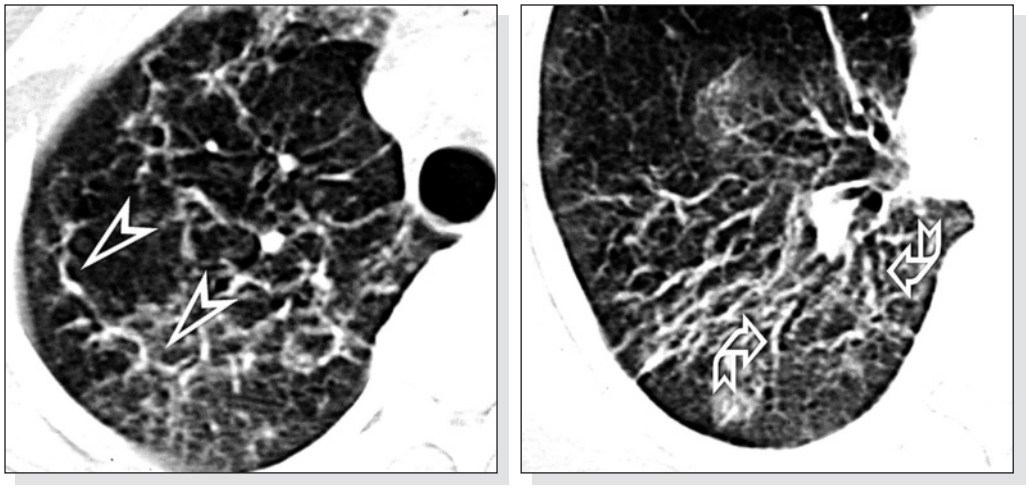
Lung volume is normal or reduced

Primack SL. Acute interstitial pneumonia: radiographic and CT findings in nine patients. Radiology 1993, 188: 817

Other signs

Transition to the proliferative fibrotic stage may manifest with:

- Reticular pattern (≫) with distortion of parenchymal architecture
- Traction bronchiectasis (↳) and mild honeycombing



Ichikado K. Acute interstitial pneumonia: high-resolution CT findings correlated with pathology. AJR Am J Roentgenol 1997, 168: 333

Johkoh T. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999, 211: 555

Differentials

Radiological differential diagnoses:

- Atypical pneumonias in immunocompetent subjects and opportunistic pneumonias in immunodepressed subjects: the differential diagnosis cannot be made clinically and requires surgical biopsy
- OP: the peripheral and/or peribronchial consolidations tend to be triangular or polygonal in shape; accelerated forms exhibit patterns similar to those of AIP
- DAH: the consolidation tends to be centrally distributed and absent in the subpleural regions
- PE: more distinctly gravitational and hilar-parahilar, with smooth thickening of the septal and peripheral interstitium

Ichikado K. A case of acute interstitial pneumonia indistinguishable from bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia: high-resolution CT findings and pathologic correlation. Radiat Med 1998, 16: 367

Mihara N. Can acute interstitial pneumonia be differentiated from bronchiolitis obliterans organizing pneumonia by high-resolution CT? Radiat Med 2000, 18: 299

COURSE and COMPLICATIONS

Associated diseases

There are no known associated diseases

Clinical course

The disease tends to progress to respiratory failure requiring mechanical ventilation. The mortality rate is 50% mostly within 1-2 months of presentation. Those who recover may develop chronic interstitial lung diseaselesions that progress to fibrosis

Radiological course

In survivors, the alveolar opacities tend to regress, whereas the more-or-less extensive irregular reticular changes and honeycombing may persist indefinitely

LABORATORY FINDINGS

Peripheral neutrophilic leukocytosis is a common finding. Increased serum creatinine levels and reduced hematocrit are considered unfavorable prognostic factors

CLINICAL DIAGNOSIS

Acute clinical onset with severe and refractory respiratory failure associated with a radiological picture of diffuse, bilateral, air-space opacification should suggest a diagnosis of AIP, in the absence of any possible cause

INVASIVE DIAGNOSIS

The large number of differential diagnoses, the poor prognosis and the need to institute high-dose immunosuppressive therapy all call for a definitive diagnosis that can only be obtained by surgical lung biopsy. Transbronchial lung biopsy is of no diagnostic value, however, it can significantly narrow the differential diagnosis

Bronchoalveolar lavage

BAL fluid reveals an increased total cell count, signs of alveolar hemorrhage by the finding of red blood cells and hemosiderin-laden macrophages, increased levels of polymorphonuclear neutrophils (>50%) and occasionally lymphocytes. The cytologic preparations of BAL fluid should also examined for reactive type II pneumocytes (the atypia of these cells may be severe enough to mimic carcinoma), as well as fragments of hyaline membranes

In intensive care units, BAL is particularly useful for differentiating AIP from: 1. diffuse alveolar hemorrhage (bloody fluid, erythrocytes and hemosiderin-laden macrophages); 2. acute eosinophilic pneumonia (marked increase in eosinophils); 3. drug-induced pulmonary toxicity (CD8+ lymphocytosis and foamy macrophages); 4. fast-growing neoplasms (cancer cells); 5. infections with associated acute lung injury (direct visualization or positive quantitative culture of the causative microorganism); 6. cryptogenic organizing pneumonia (CD8+ lymphocytosis, neutrophils and foamy macrophages)

Bonaccorsi A. Acute interstitial pneumonia: report of a series. Eur Respir J 2003, 21: 187

Pesci A. Bronchoalveolar lavage in intensive care units. Monaldi Arch Chest Dis 2004, 61: 39

Adult Respiratory Distress Syndrome

Definition

Adult respiratory distress syndrome (ARDS) is a form of severe acute respiratory failure characterized by severe hypoxia (PaO_2/FiO_2 ratio <200), pulmonary capillary wedge pressure <18 mmHg and diffuse lung opacities on chest radiograph. A trigger mechanism can always be identified (sepsis, trauma, surgery, burns, infections, drugs, etc.)

Non-cardiogenic pulmonary edema, edema due to membrane damage, shock lung

DEMOGRAPHICS

Etiology and pathogenesis

The edema is caused by disruption of the alveolocapillary barrier: the alveoli become engulfed with protein-rich fluid, blood cells and cellular debris; the loss of surfactant leads to atelectasis. This early exudative stage may be followed by a organizing phase with fibroblast proliferation in the alveolar spaces and interstitium, and type II cell hyperplasia

The pathogenesis of lung injury is complex and linked to inflammatory phenomena involving cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha), granulocyte macrophage colony stimulating factor (GM-CSF), chemokynes (IL-8) and inflammatory mediators (leukotriene B4). These in turn recruit polymorphonuclear neutrophils, which become activated and release toxic oxygen species and proteases capable of damaging the epithelial and endothelial cells

Epidemiology

The reported incidence of ARDS varies from 1.5% to 13.5% per year

Risk factors

The main risk factors are sepsis, gastric content aspiration, severe trauma, multiple transfusions, near drowning, acute pancreatitis, prolonged hypotension, severe bacterial pneumonia, and disseminated intravascular coagulation. The presence of multiple risk factors increases the likelihood of developing ARDS

CLINICAL FEATURES

History

The signs and symptoms of ARDS may develop insidiously 8-48 hours after the initiating event, or acutely immediately after the event. The main symptoms are rapidly progressive dyspnea, dry cough, chest pain and agitation. The presence of mild or massive hemoptysis indicates full-blown ARDS

Physical findings

Patients present with marked dyspnea, tachypnea, cyanosis and agitation; auscultation of the lung reveals bilateral rales. Pulmonary hypertension with right-sided cardiac failure (jugular venous distension, tender hepatomegaly, peripheral edema) is often associated

Pulmonary function tests

Lung function testing reveals low D_LCO, functional residual capacity, and decreased lung compliance. Patients typically have severe hypoxia refractory to oxygen supplementation, mechanical ventilation with positive end expiratory pressure (PEEP) or other resuscitation procedures. The severity of functional impairment does not correlate with prognosis

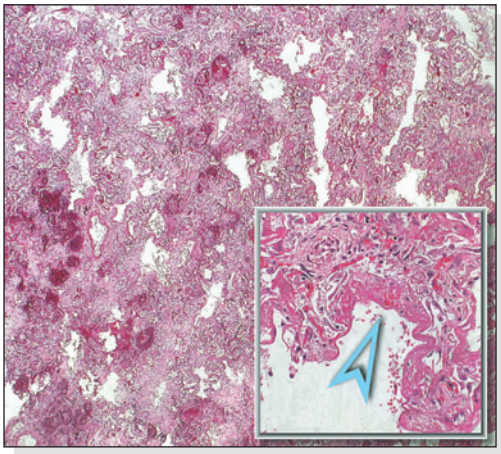
Ware LB. The acute respiratory distress syndrome. N Engl J Med 2000, 342: 1334

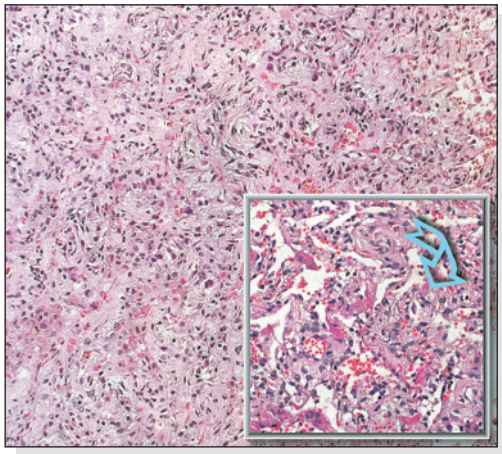
PATHOLOGY

Basic lesions

ARDS is the clinical syndrome associated with the histologic picture of diffuse alveolar damage (DAD) secondary to various diseases conditions. The process is characterized by different histologic changes depending on the stage of disease:

- In the acute (exudative) phase there is a predominance of hyaline membranes. These are sheets of eosinophilic material made up of necrotic type I pneumocytes and plasma proteins that line the alveolar surfaces (➢). These are also associated with interstitial edema and microthromboses
- In the organizing (proliferative) phase there is a proliferation of type II pneumocytes, fibroblasts and myofibroblasts. The latter migrate from the interstitium to the intraalveolar exudate turning it into granulation tissue (↳), which may eventually be completely reabsorbed with complete healing of the lesions or progress towards fibrosis
- In the chronic (fibrotic) phase there is deposition of dense fibrous tissue which causes remodeling of the lung architecture





Distribution

Diffuse (alveoli and alveolar septa)

Differentials

Histopathologic differential diagnoses:

- DAD associated with infections: granulomas, viral inclusions, necrotic foci, abscesses; demonstration of the microorganism with special stains
- DAD superimposed on UIP (accelerated UIP): the characteristic UIP pattern appears, that is, spatially and temporally heterogeneous fibrosis originating from the subpleural regions, with fibroblastic foci at the interface with normal parenchyma
- OP: predominantly intraalveolar foci of fibroblastic organization, intense inflammatory infiltrate, bronchiolar involvement (not constant)

A possible variant of DAD, acute fibrinous and organizing pneumonia (AFOP), has recently been reported, which is histologically characterized by intraalveolar fibrin accumulation in the form of "fibrin balls" without the classic hyaline membranes and associated with foci of organizing pneumonia in the bronchioles and alveolar ducts

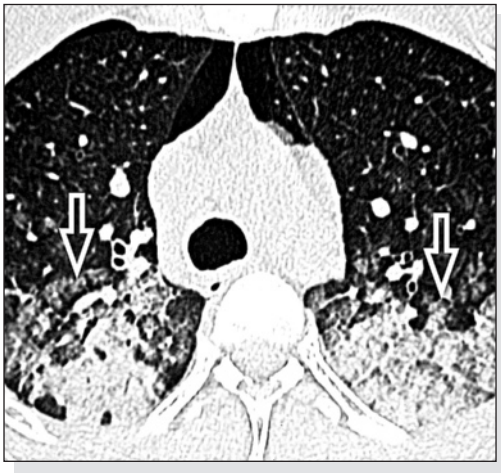
Beasley MB. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. Arch Pathol Lab Med 2002, 126: 1064

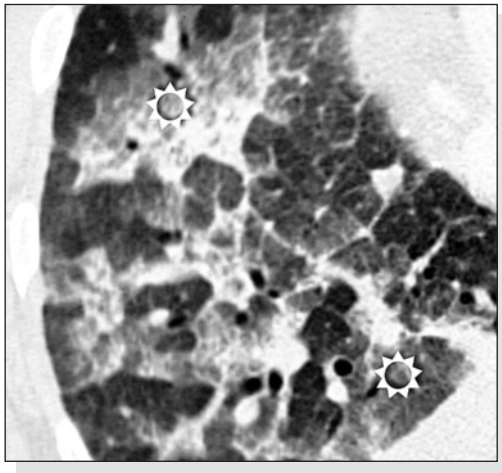
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation with air bronchogram (⇨)
- Ground-glass opacities associated with air bronchogram (☼)





Goodman LR. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. Radiology 1999, 213: 545

Distribution

Bilateral and patchy, prevalently symmetrical in ARDS due to extrapulmonary causes, and asymmetrical in ARDS due to a primary pulmonary cause

Diffuse, although the opacities tend to become more uniform and dense in the dependent areas, especially in ARDS due to extrapulmonary causes

Diffuse, although consolidation is more extensive at the lung bases

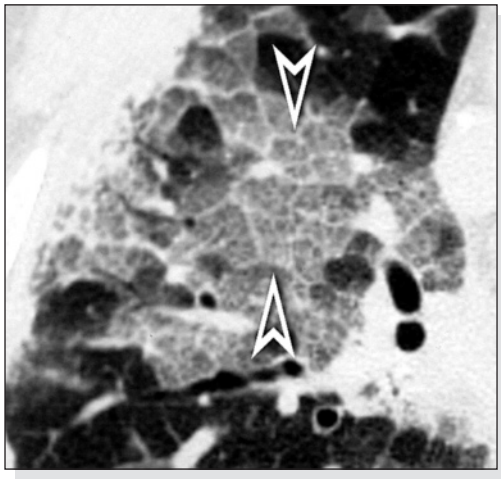
The degree of opacification tends to increase in the more dependent regions as a result of the parenchyma progressively collapsing under the weight of the dense lung above

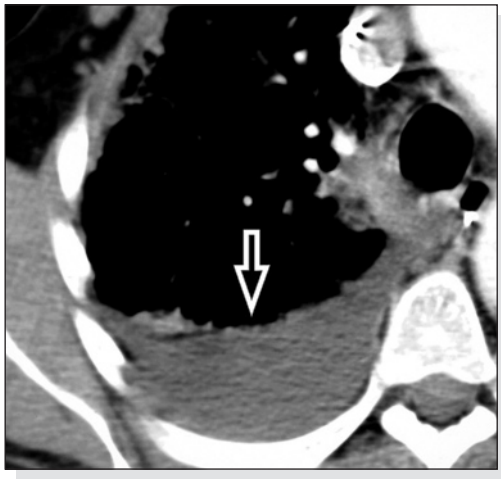
Lung volume may be reduced

Other signs

Other non-constant radiological signs:

- Regular reticular pattern due to septal thickening
- Association of reticular pattern and ground-glass attenuation (≥)(crazy paving)
- Pleural effusion (moderate)(⇨)





Desai SR. Acute respiratory distress syndrome: imaging of the injured lung. Clin Radiol 2002, 57: 8

Differentials

Radiological differential diagnoses:

- AIP: the radiological pattern may be identical since AIP is an idiopathic form of ARDS
- PE: the opacities are more uniform, frankly gravitational and without air bronchogram. A reticular pattern is almost always present, and cardiomegaly and pleural effusion are common
- Fluid overload: increase in the diameter of the superior vena cava (due to increased volume of circulating blood) and thickening of the chest wall soft tissues

Gluecker T. Clinical and radiologic features of pulmonary edema. Radiographics 1999, 19: 1507

Ketai LH. A new view of pulmonary edema and acute respiratory distress syndrome. J Thorac Imaging 1998, 13: 147

COURSE and COMPLICATIONS

Associated diseases

Patients requiring mechanical ventilation have a higher risk of developing the typical complications of ARDS (ventilator-associated pneumonia, multiple organ failure) or complications associated with treatment (barotraumas with pneumothorax, pneumomediastinum and chest wall emphysema)

Clinical course

Prognosis is poor and the disease may be fatal in 35-40% of cases. Ninety percent of deaths occur within the first 2 weeks of onset of the symptoms. The presence of infections or multiorgan failure has negative prognostic implications. Survivors may recover normal pulmonary function or in some cases experience pulmonary fibrosis

Radiological course

Depending on the clinical course, the following radiological patterns may be observed:

- Progressive regression of opacities with complete healing of lesions
- Regression of the alveolar opacities with persisting reticular pattern and distortion of lung parenchyma anteriorly
- Progressive increase in opacities with appearance of linear opacities and remodeling of the lung architecture (fibrosis) and formation of paradoxical hyperlucencies due to vascular obstruction

Desai SR. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology 1999, 210: 29

LABORATORY FINDINGS

Neutrophilic leukocytosis in the peripheral blood is a common finding, and hematological changes ascribable to disseminated intravascular coagulation (DIC) are relatively common

CLINICAL DIAGNOSIS

The diagnosis is made on the basis of the clinical picture (acute onset in the absence of left cardiac failure and with apparent predisposing condition), radiological pattern (bilateral opacities at chest radiograph) and functional findings (PaO_2/FiO_2 <200; pulmonary capillary wedge pressure <18 mmHg)

INVASIVE DIAGNOSIS

Surgical lung biopsy is rarely required. Transbronchial lung biopsy is of no diagnostic value, however, it can significantly narrow the differential diagnosis

Bronchoalveolar lavage

In early ARDS, the BAL fluid shows a marked increase in neutrophils, whereas in late ARDS lymphocytes and eosinophils predominate. The finding of a high number of neutrophils in late stage ARDS indicates a negative prognosis. The cytologic preparations of BAL fluid should also examined for reactive type II pneumocytes (the atypia of these cells may be severe enough to mimic carcinoma), as well as fragments of hyaline membranes. Increased concentrations of toxic oxygen species, proteases and cytokines/chemokines (TNF-alpha, IL-1 and IL-8) have been found in the supernatant

In intensive care units, BAL is particularly useful for differentiating ARDS from: 1. diffuse alveolar hemorrhage (bloody fluid, erythrocytes and hemosiderin-laden macrophages); 2. acute eosinophilic pneumonia (marked increase in eosinophils); 3. drug-induced pulmonary toxicity (CD8+ lymphocytosis and foamy macrophages); 4. fast-growing neoplasms (cancer cells); 5. infections with associated acute lung injury (direct visualization or positive quantitative culture of the causative microorganism); 6. cryptogenic organizing pneumonia (CD8+ lymphocytosis, neutrophils and foamy macrophages)

Nakos G. Bronchoalveolar lavage fluid characteristics of early intermediate and late phases of ARDS. Alterations in leukocytes, proteins, PAF and surfactant components. Intensive Care Med 1998, 24: 296

BronchioloAlveolar Carcinoma

Definition

Bronchioloalveolar carcinoma (BAC) is a primary lung tumor that may present in a focal (more frequent) or diffuse form, both at onset and during the course of the disease. This chapter will cover only the diffuse form

Alveolar carcinoma, pulmonary adenomatosis

DEMOGRAPHICS

Etiology and pathogenesis

BAC is thought to originate from a bronchiolar stem cell capable of differentiating into different cell types. The multifocal form may result from a single lesion spreading through the airways or the synchronous growth of independent neoplastic clones. A viral etiology (retrovirus) has also been suggested based on the morphological similarity of BAC to jaagsiekte (a contagious viral disease in sheep)

Epidemiology

BAC accounts for 1-9% of all primary lung tumors. Age at diagnosis ranges from 50 to 70 years, and there is no racial or gender predilection

Risk factors

BAC features may be seen in old focal or diffuse scar lesions

CLINICAL FEATURES

History

In the diffuse form of BAC the most common symptoms (often present 6 months to 1 year before diagnosis) are cough (50-70%), sputum production (20-50%), bronchorrhea >100 ml/day (5-25%), chest pain (30-50%), dyspnea (25-50%), hemoptysis (10-25%) and weight loss (25%)

Physical findings

Physical examination reveals localized or diffuse rales and at times signs of pleural effusion

Pulmonary function tests

Lung function tests are often normal. There may be a restrictive ventilatory defect with reduced D_LCO and hypoxemia, which may be severe due to a physiologic shunt

Bronchorrhea is indicative of diffuse disease and may be so massive as to cause hypovolemia and prerenal failure with hyponatremia

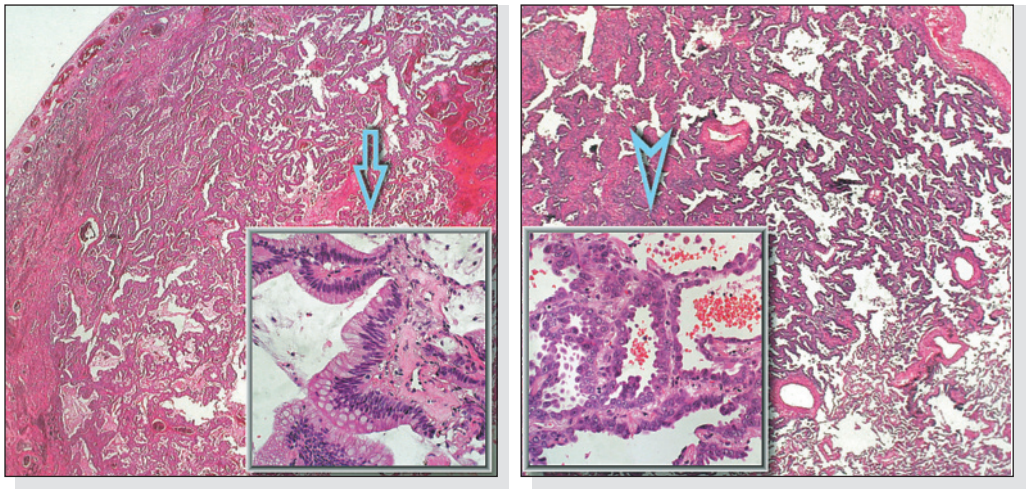
Harpole DH. Alveolar cell carcinoma of the lung: a retrospective analysis of 205 patients. Ann Thorac Surg 1988, 46: 502

PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Adenocarcinoma with tumor cells growing along the alveolar walls (lepidic growth pattern). By definition there is no stromal, vascular or pleural invasion
- Septa and interstitium may be thickened by fibrosis or chronic inflammatory infiltrate
- Tumor cells may or may not secrete mucous and, based on their prevalence, bronchioloalveolar carcinomas are classified into mucinous (⇨), non-mucinous (≻) and mixed



Mucinous BAC consists of columnar cells with round basal nuclei and abundant clear cytoplasm rich in mucin that often form micropapillae. In this variant, which may present as a solitary nodule, multiple nodules or alveolar consolidation (diffuse pneumonitis variant), dissemination often occurs through the airways with the formation of satellite nodules and rapid development of diffuse intrathoracic disease

Non-mucinous BAC may exhibit the two distinct cell types of the distal lobule: one is similar to Clara cells, with cuboid or cylindrical eosinophilic cytoplasm with apical projections and PAS-positive granules; the other is similar to type II pneumocytes, and consists of squamoid cells with round nuclei and finely vacuolated or even foamy cytoplasm. The nuclei of either of these cell types may show eosinophilic inclusions surrounded by a clear halo. Dissemination through the airways is rare in this variant

Mixed or indeterminate BAC consists of a mixture of mucinous and non-mucinous cells or indeterminate cells which grow along the alveolar walls without invading the stroma

Non-mucinous BAC is often associated with central alveolar collapse leading to fibrosis. The fibrosis should not be mistaken for the scars seen at the center of peripheral adenocarcinomas (scar cancer)

Distribution

Diffuse along the alveolar septa

It is not uncommon to find foci of adenocarcinoma with stromal invasion associated with features of bronchioloalveolar growth; consequently, the histopathologic diagnosis of a "pure" BAC requires extensive sampling to exclude the presence of stromal invasion

A four-point grading system for stromal invasion has recently been proposed which has prognostic implications. Invasion is absent in BAC (grade 0) and present to varying degrees in adenocarcinoma (grades 1, 2, 3)

Brambilla E. The new World Health Organization classification of lung tumours. Eur Respir J 2001, 18: 1059

Sakurai H. Grade of stromal invasion in small adenocarcinoma of the lung: histopathological minimal invasion and prognosis. Am J Surg Pathol 2004, 28: 198

Differentials

Histopathologic differential diagnoses:

- Atypical adenomatous hyperplasia: the lesion is smaller than 5 mm, the cells are arranged in a single layer, and cytological atypia is not prominent
- Bronchiolar metaplasia (lambertosis): the lesion is centrilobular and originates from the bronchiole. There may be an identifiable connection with clearly benign epithelium. The cells are often ciliated and show no evidence of malignancy or nuclear inclusions
- Type II pneumocyte hyperplasia: the cellular monotony and lepidic growth pattern typical of BAC are absent, and the transition to normal epithelium is gradual
- Clara cell, papillary and alveolar adenomas: small, well-circumscribed lesions without cytologic atypia
- Sclerosing hemangioma: papillary, well-circumscribed lesion with areas of recent and old hemorrhage and sclerosis
- Metastases: infiltration of the septa, marked atypia, history of neoplasm

Although both primary and metastatic adenocarcinomas (e.g. of the colon and pancreas) may exhibit bronchioloalveolar-type (lepidic) growth patterns at the periphery, they also show stromal, vascular (hematic or lymphatic) or pleural invasion

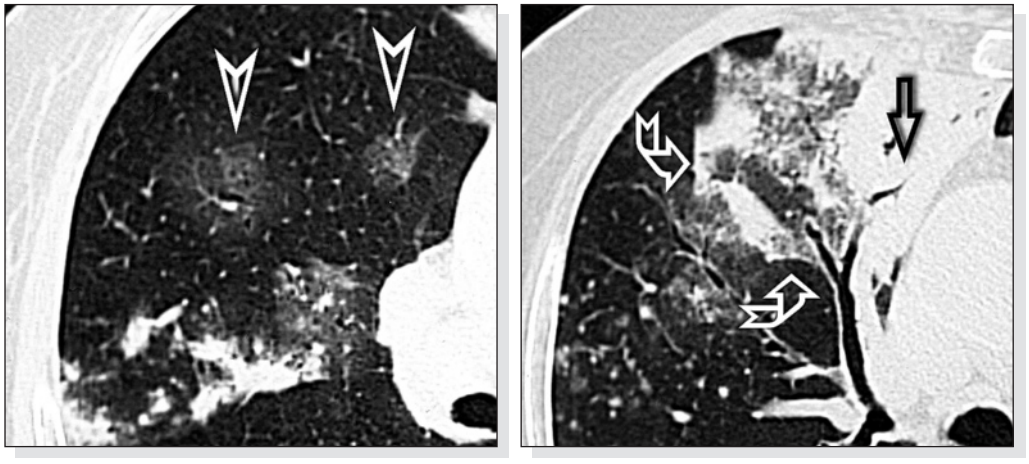
Travis WD. Histopathologic typing of lung and pleural tumours: World Health Organization International Histological Classification of Tumours, 3rd ed. Springer, 1999

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Multiple areas of parenchymal consolidation (↳)
- Ground-glass opacities with irregular hazy contours (➢)
- Air bronchogram within the lesions giving the appearance of a leafless tree (⇨)



Adler B. High-resolution CT of bronchioloalveolar carcinoma. AJR Am J Roentgenol 1992, 159: 275

Akira M. High-resolution CT findings of diffuse bronchioloalveolar carcinoma in 38 patients. AJR Am J Roentgenol 1999, 173: 1623

✓ One of the parenchymal opacities usually predominates in terms of density or extension

Distribution

Unilateral or bilateral, usually asymmetrical, often patchy

Peripheral and subpleural (50%)

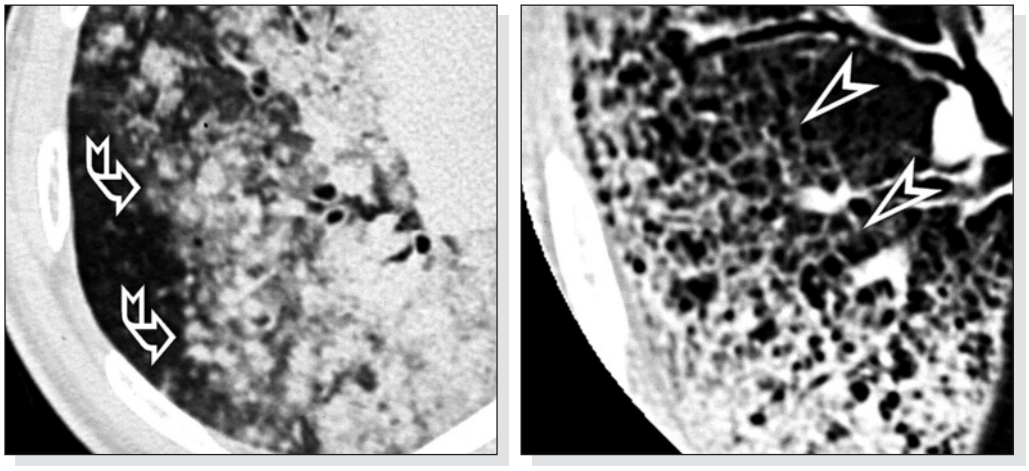
Basal (50%)

Other signs

Lung volume is normal, although bulging of the fissural border may be noted in extensive lobar consolidation

Other radiological characteristics:

- Nodules with hazy margins (↳) or true large opacities (● Large rounded opacities: BAC)
- Internal hyperlucencies appearing as pseudocavitations or pseudocysts
- Low-attenuating parenchymal consolidation with enhancing vessels after administration of contrast material (angiogram sign)
- Linear bands of septal thickening associated with the ground-glass opacity (crazy paving) (➢)
- Adenopathy, pleural effusion, calcifications (of the mucoid matrix)



Im JG. Lobar bronchioloalveolar carcinoma: "angiogram sign" on CT scans. Radiology 1990, 176: 749

Recent research suggests that a pattern of well-defined nodules, once thought to be possible in BAC, is instead due to hematogenous spread of components of classical adenocarcinoma

The pseudocavitary hyperlucencies are related to bronchiolar obstruction, even though true cavitations may also occur (rarely)

Gaeta M. Radiolucencies and cavitation in bronchioloalveolar carcinoma: CT-pathologic correlation. Eur Radiol 1999, 9: 55

Differentials

All diseases characterized by chronic parenchymal consolidation enter the differential diagnoses:

- Slowly resolving infections: the clinical history and the regression of the opacities in subsequent radiograms are the key to the diagnosis
- OP: the peripheral and/or peribronchial areas of consolidation tend to be triangular or polygonal in shape
- PAP: bilateral, symmetrical, more extensive in the axial plane; widespread crazy paving
- CEP: the areas of consolidation are more distinctly subpleural and prevail in the upper lung fields
- MALToma: differentiation may be impossible, except for a slower progression; the differential diagnosis is based on the biopsy findings
- Exogenous lipoid pneumonia: clinical history, at times negative density at CT

Aquino SL. Distinction of consolidative bronchioloalveolar carcinoma from pneumonia: do CT criteria work? AJR Am J Roentgenol 1998, 171: 359

COURSE and COMPLICATIONS

Associated diseases

Superimposed acute bacterial diffuse or localized pneumonia

Clinical course

The clinical progression of the diffuse form of BAC is very rapid, with death sometimes occurring within weeks of diagnosis. The most frequent causes of death are respiratory failure, pulmonary embolism, cardiac tamponade, pneumothorax and pneumonia

Radiological course

The existing areas of consolidation become more compact and homogeneous, and new areas of consolidation appear, even contralaterally, as a result of bronchogenic spread, in a relentless progression

LABORATORY FINDINGS

About half of patients show increased serum carcinoembryonic antigen levels, whereas a smaller proportion have increased amylasemia and CA 19-9. Patients with bronchorrhea may have elevated azotemia due to prerenal failure and electrolyte disturbances

CLINICAL DIAGNOSIS

In an appropriate clinical and radiological setting, the repeated finding of well-differentiated cancer cells in the sputum is considered diagnostic (25-50% of cases)

INVASIVE DIAGNOSIS

In some cases, the diagnosis requires a histological sample which may be obtained by transbronchial or transthoracic lung biopsy. However, the diagnostic certainty of a “pure” BAC requires extensive samples and therefore surgical lung biopsy

Bronchoalveolar lavage

Analysis of the BAL fluid often reveals the presence of well-differentiated neoplastic alveolar cells, although this finding is not sufficient for differentiating BAC from a primary or metastatic adenocarcinoma

The cytologic preparations of BAL fluid during AIP or ARDS may show reactive type II pneumocytes with consistent atypia

Sprigmeyer SC. Bronchioloalveolar cell carcinoma diagnosed by bronchoalveolar lavage. Chest 1983, 83: 278

Constructive Bronchiolitis

Definition

Bronchiolitis refers to a heterogeneous group of diseases characterized by non-specific inflammation of the small airways. This chapter, devoted to the forms in which the dominant histopathologic change is a narrowing of the distal bronchioles, will mainly cover idiopathic constrictive bronchiolitis (CB)

☯ Bronchiolitis obliterans

✓ Various diseases may have histological changes of CB and the corresponding clinical and radiological presentations:

- Healed infections (e.g. adenovirus, respiratory syncytial virus, mycoplasma, influenza)
- Collagen vascular diseases (e.g. rheumatoid arthritis)
- Exposure to toxic fumes
- Damage induced by Sauropus androgynus, a vegetable of the Euphorbiaceae family taken for weight reduction purposes
- Lung, heart-lung and allogenic bone marrow transplant (graft versus host disease - GVHD)
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Bronchial asthma
- Sarcoidosis
- HP

DEMOGRAPHICS

Etiology and pathogenesis

The causative agent and pathogenesis are unknown

Epidemiology

Idiopathic CB is a rare clinical-pathological syndrome seen in middle-aged adults, and more commonly in females. It accounts for 4% of all obstructive pulmonary diseases

Risk factors

There are no known risk factors, not even cigarette smoking

CLINICAL FEATURES

History

The main symptoms are dyspnea, dry cough and rarely wheezing. Systemic symptoms such as malaise and asthenia may also be noted. The symptoms may be present for several months before diagnosis

Physical findings

Chest physical examination is generally unhelpful, although there have been rare reports of wheezes, rales and ronchi

Pulmonary function tests

Typically there is an irreversible obstructive ventilatory pattern. The obstruction is often severe and accompanied by a reduced D_LCO

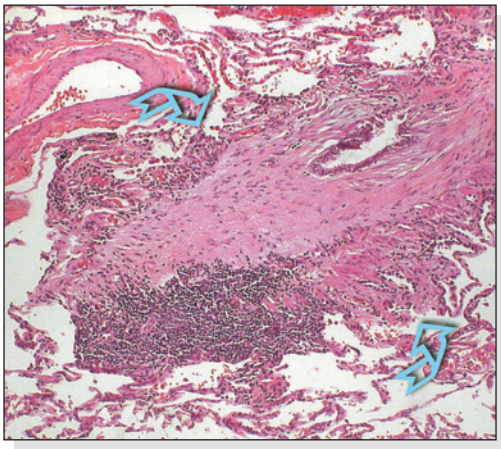
📖 Kraft M. Cryptogenic constrictive bronchiolitis. A clinicopathologic study. Am Rev Respir Dis. 1993, 148: 1093

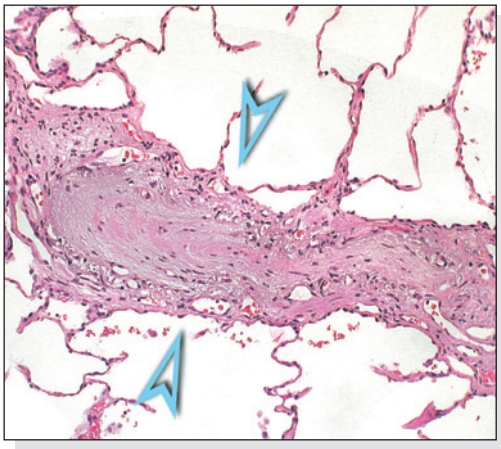
PATHOLOGY

Basic lesions

CB usually presents as an isolated lesion of the bronchioles, with only minimal, if any, changes to the surrounding parenchyma. The basic lesions include:

- Narrowing and distortion of the lumen of the small airways due to submucosal or adventitial fibrosis (↳). In the more severe cases the lumen may be completely obliterated (≻)
- Hypertrophy of the bronchiolar wall smooth muscle
- Bronchiolar ectasia with mucostasis
- Bronchiolar metaplasia of the alveolar epithelium (“bronchiolization” or “lambertosis”)





Distribution

Centrilobular

Differentials

Histopathologic differential diagnoses:

- Normal lung: the bronchiole and accompanying branch of the pulmonary artery have similar diameters, and no fibrosis is present in the bronchiolar wall
- LCH: peribronchiolar nodules and cysts consisting of fibrous tissue with inflammatory cells such as Langerhans' cells and eosinophils
- RB: pigmented macrophages in the peribronchiolar alveolar spaces associated with slight changes in the bronchiolar wall
- OP: the lumen of the distal respiratory bronchioles is obliterated by plugs of granulation tissue

Colby TV. Bronchiolitis. Pathologic considerations. Am J Clin Pathol 1998, 109: 101

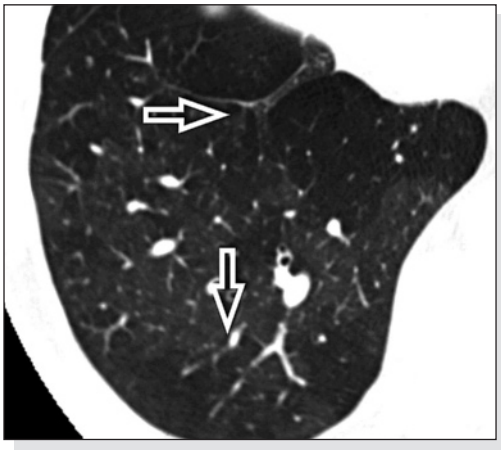
The bronchiole and accompanying branch of the pulmonary artery have a similar diameter and are uniformly distributed in the peripheral parenchyma. Any variation to this condition suggests small airways disease. In addition, the normal bronchiole has a layer of loose connective tissue beneath the epithelium. In patients with small airways disease fibrous tissue is deposited in this area

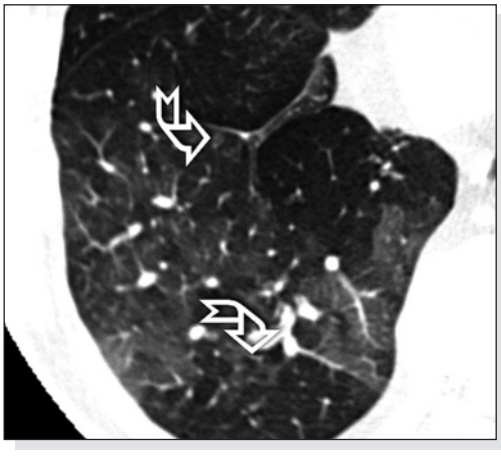
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Well-defined patchy areas of reduced parenchymal density (⇨), which stand out on a background of normal lung
- Paucity (reduction in number and diameter) of vascular structures within the pathological areas without distortion of the lobular architecture (mosaic pattern)
- Expiratory air-trapping (↳)





In about one third of cases the diseased areas are visible on expiratory scans only

The hypoperfusion results from reflex vasoconstriction in the areas of the lung which are less ventilated due to bronchiolar narrowing. The narrowing also produces air-trapping in these areas which is well-depicted on expiratory CT scans

Hansell DM. HRCT of obliterative bronchiolitis and other small airways diseases. Semin Roentgenol 2001, 36: 51

Stern EJ. Small-airway diseases of the lungs: findings at expiratory CT. AJR Am J Roentgenol 1994, 163: 37

Distribution

Generally bilateral, asymmetrical and patchy

In some secondary forms of localized CB, such as post-infectious CB in Swyer-James syndrome (MacLeod), the lesions may predominate in one lung or lobe

In contrast, severe and extensive disease (rare) may have an almost uniform distribution similar to emphysema

Swyer-James syndrome is the effect of post-infectious CB usually due to viral infections contracted in early infancy. Damage to the bronchioles leads to incomplete development of the distal respiratory structures and to the formation of bronchiectasis proximally. Pulmonary vascularity is consequently reduced

Variable

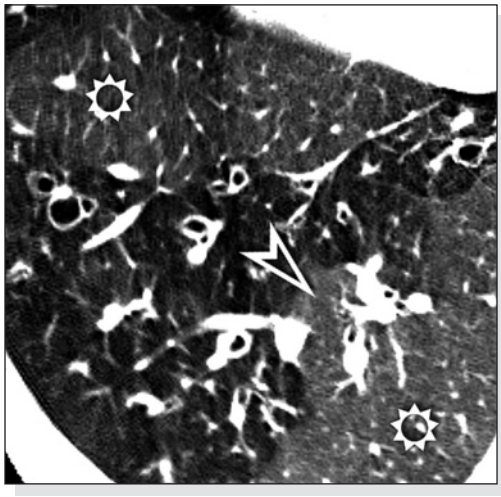
Variable

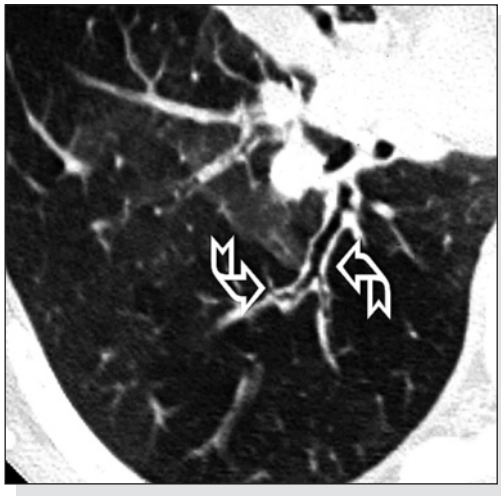
Lung volume is normal or increased, except in Swyer-James syndrome in which the volume of the affected areas is reduced

Other signs

Other radiological signs:

- Increased density of the normally ventilated areas (☼) where the vessels are enlarged (≽) due to hyperperfusion, at times to the point of simulating disease (pseudo-ground-glass opacity)
- Direct signs of airway disease (bronchial wall thickening (↳), bronchiolectasis, etc.)





A number of diseases, such as extrinsic allergic alveolitis, and airway infections (mycoplasma) may show an alternation of areas of three different levels of density (head-cheese pattern): true ground-glass opacities, areas of normally ventilated parenchyma, and hyperlucent areas due to air-trapping

Waitches GM. High-resolution CT of peripheral airways diseases. Radiol Clin North Am 2002, 40: 21

Differentials

Radiological differential diagnoses:

- Chronic pulmonary thromboembolism: the vessels within the areas of oligemia are reduced in number and diameter, but there is no expiratory air-trapping. The central pulmonary arteries may be dilated due to chronic arterial hypertension
- Diseases responsible for patchy ground-glass opacities: the pulmonary vessels are equally well-depicted and have similar diameters both in the hypodense and hyperdense areas. There is no expiratory air-trapping
- Panlobular emphysema: the hyperlucency is diffuse rather than patchy and bilaterally symmetrical with lower lobe predominance. In addition, there is distortion with straightening and rigidity of the vascular markings
- Postobstructive emphysema: the hyperlucency is uniform rather than patchy even if the affected area is limited. The cause of the obstruction can usually be identified

Overall, HRCT is able to differentiate CB from other causes of mosaic perfusion in more than 70% of cases

Copley SJ. Thin-section CT in obstructive pulmonary disease: discriminatory value. Radiology 2002, 223: 812

Worthy SA. Mosaic attenuation pattern on thin-section CT scans of the lung: differentiation among infiltrative lung, airway, and vascular diseases as a cause. Radiology 1997, 205: 465

COURSE and COMPLICATIONS

Associated diseases

Recurrent bronchiolar superinfections, with clinically obrious flare-ups

Clinical course

Clinical course varies from rapid evolution to long periods of stability. There is no definitely effective treatment.

Radiological course

Radiological course is variable. Among the secondary forms of CB, those due to rheumatoid arthritis, graft versus host disease in bone marrow transplant, and chronic rejection in lung transplant are progressive and have a poor response to therapy. The microgranulomatous forms (sarcoidosis, HP) may regress completely or partially with regression of the disease

LABORATORY FINDINGS

Laboratory findings are usually non-specific and unhelpful for diagnosis

CLINICAL DIAGNOSIS

Idiopathic CB should be suspected in the presence of an irreversible obstructive ventilatory defect without a previous history or clinical findings of associated diseases. The diagnostic suspicion can be confirmed by HRCT in the majority of cases

INVASIVE DIAGNOSIS

Transbronchial lung biopsy is rarely diagnostic and surgical lung biopsy may become indispensable for reaching a diagnosis in doubtful cases, in cases with possible multifactorial etiology or when considering a lung transplant

Bronchoalveolar lavage

The BAL fluid shows marked neutrophilia (>25%) and an increase in neutrophil products such as collagenase and myeloperoxidase. BAL neutrophilia tends to decrease in patients responding to treatment

Dorinsky PM. Adult bronchiolitis. Evaluation by bronchoalveolar lavage and response to prednisone therapy. Chest 1985, 88: 58

Chronic Eosinophilic Pneumonia

Definition

Chronic eosinophilic pneumonia (CEP) is an idiopathic condition characterized by an abnormal accumulation of eosinophils in the lungs. The clinical course lasts more than 3 months

DEMOGRAPHICS

Etiology and pathogenesis

The etiology is unknown, although there have been occasional reports of association with aspergillus infection, rheumatoid arthritis, and cutaneous vasculitis. The frequent association with atopy and elevated IgE levels suggests a Gell and Coombs type I immune reaction mechanism. The lungs of these patients contain a high number of activated eosinophils that produce eosinophil cationic protein (ECP) and an increase in activated helper lymphocytes (CD4+) that produce interleukins (IL): IL-5, IL-6 and IL-10

Epidemiology

The disease is rare and the true prevalence and incidence are unknown. Women are more frequently affected (2:1), with a peak incidence between 20 and 50 years of age. There have been rare reports of familial cases

Risk factors

Atopy, allergen immunotherapy

CLINICAL FEATURES

History

The onset of disease is insidious, with symptoms being present for at least 2-3 months before diagnosis. The most common symptoms are: cough (80-90%), fever as high as 40°C (80-90%), dyspnea, weight loss, night sweats and malaise. Asthma accompanies or precedes the illness in about 50% of cases. Hemoptysis, chest pain and myalgia are rarely noted

Physical findings

Chest physical examination is non-specific, with wheezes, rales and signs of pulmonary consolidation

Pulmonary function tests

These often reveal a restrictive or mixed ventilatory pattern with reduced D_LCO. In the acute phases there may be severe hypoxemia. After remission, an obstructive ventilatory defect is common at times associated with irreversible small airways obstruction

Allen JN. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994, 150: 1423

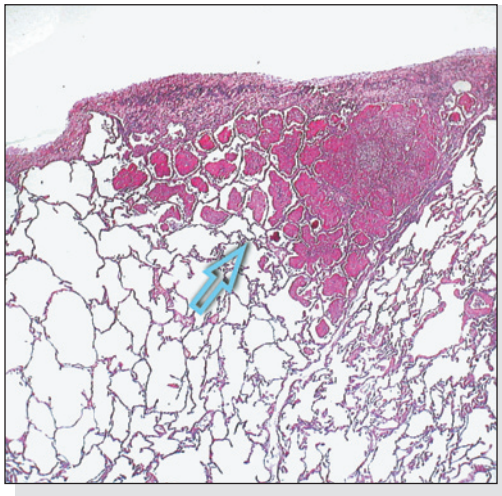
Naughton M. Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. Chest 1993, 103: 162

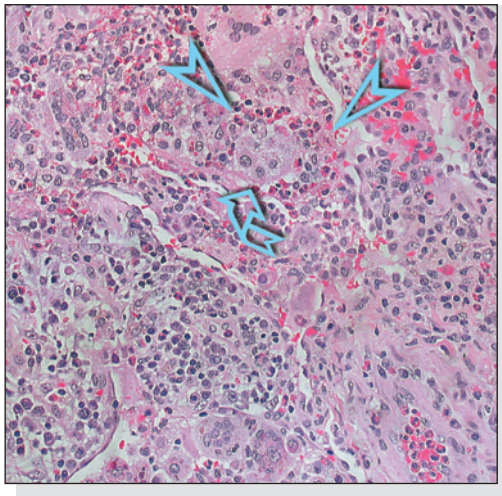
PATHOLOGY

Basic lesions

CEP is characterized by:

- Aggregates of eosinophils (➢) and macrophages (↳) filling the air spaces (⇨)
- Type II pneumocyte hyperplasia
- Increased interstitial eosinophils





The intraalveolar aggregates of eosinophils often contain necrotic foci (eosinophilic abscesses). Macrophages and pneumocytes typically have dense eosinophilic cytoplasm. There may be numerous foci of intraalveolar fibroblastic organization as in OP, and interstitial lymphoplasmacellular infiltrate. Giant cells and mild non-necrotizing vasculitis of arterioles and venules may also be present

Distribution

Diffuse intraalveolar

Differentials

Histopathologic differential diagnoses:

- DIP: eosinophils are rare in the alveolar spaces, and there is a predominance of macrophages. Type II pneumocyte hyperplasia is less prominent, and there is no necrosis within the intra-alveolar aggregates
- LCH: stellate scars and small cysts with Langerhans' cells. Eosinophils are fewer and interstitial
- Churg-Strauss syndrome: necrotizing granulomas rich in eosinophils ("red" necrosis). Necrotizing vasculitis is also present
- Wegener's granulomatosis, eosinophilic variant: patchy necrosis containing neutrophils ("blue" necrosis) and intense vasculitis. The eosinophilic infiltrate is interstitial and mixed with granulomatous inflammation

Jederlinic PJ. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine 1988, 67: 154

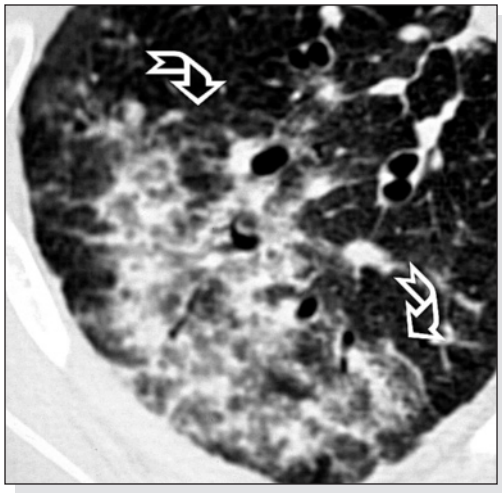
Olopade CO. Chronic eosinophilic pneumonia and idiopathic bronchiolitis obliterans organizing pneumonia: comparison of eosinophil number and degranulation by immunofluorescence staining for eosinophil-derived major basic protein. Mayo Clin Proc 1995, 70 : 137

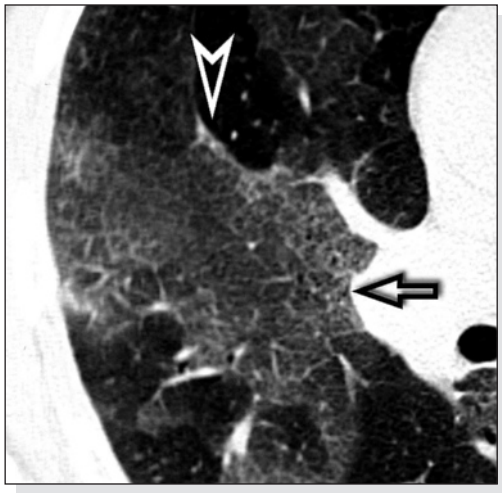
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Multiple areas of consolidation (↳) with non-segmental distribution
- Ground-glass opacities (≻)
- Patchy ground-glass opacities associated with smooth septal thickening (crazy paving)(⇨)





Distribution

Unilateral or bilateral, patchy

Peripheral, subpleural

Often predominant in the upper or central lung regions

✓ The classical appearance has been described as photographic negative of the "butterfly" or "batwing" pattern seen in alveolar edema

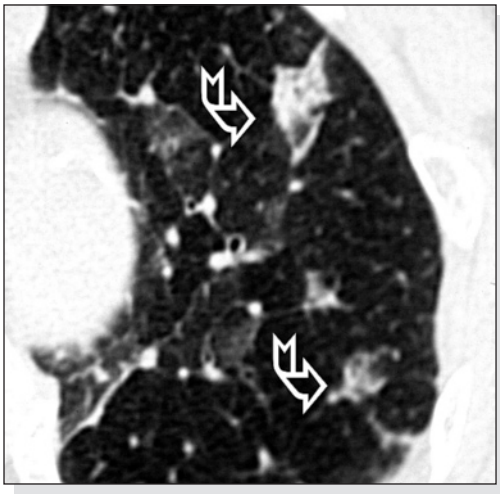
Johkoh T. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. Radiology 2000, 216: 773

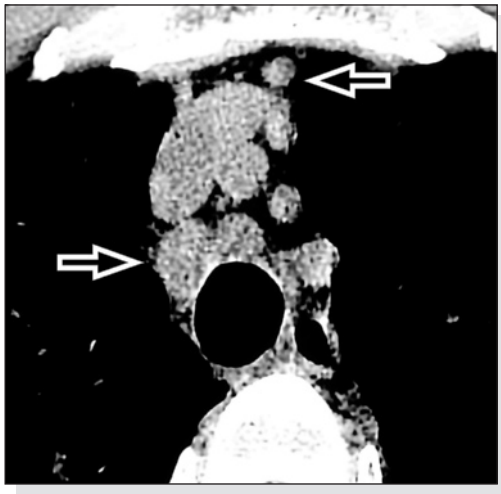
Other signs

Lung volume is preserved

Other radiological signs:

- Nodular opacities with hazy contours (↳)(20%)
- Areas of atelectasis
- Mediastinal adenopathy (⇨)
- Pleural effusion (rare)





Jederlinic PJ. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine 1988, 67: 154

Mayo JR. Chronic eosinophilic pneumonia: CT findings in six cases. AJR Am J Roentgenol 1989, 153: 727

Differentials

Radiological differential diagnoses:

- OP: the lesions are not only confined to the lung periphery, but are also bronchocentric and predominate in the lower lobes. In addition, a macronodular appearance or a pattern of round opacities is frequent. There may be patchy air-trapping. Septal thickening or parenchymal bands are uncommon
- Slowly-resolving bacterial infections: distribution is different from that typically seen in CEP, and the clinical findings are not suggestive of CEP
- Churg-Strauss syndrome: the areas of consolidation may have a random distribution and be migratory. The differential diagnosis is nonetheless difficult
- Drug toxicity (amiodarone-induced lung disease): the areas of parenchymal consolidation are often hyperdense and tend to be located in the lower lobes. Hyperdensity of the liver and spleen and at times of the myocardium may be present

Arakawa H. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. AJR Am J Roentgenol 2001, 176: 1053

Bain GA. Pulmonary eosinophilia. Eur J Radiol 1996, 23: 3

Worthy SA. Churg-Strauss syndrome: the spectrum of pulmonary CT findings in 17 patients. AJR Am J Roentgenol 1998, 170: 297

COURSE and COMPLICATIONS

Associated diseases

Asthma is present in almost 50% of patients

Clinical course

Response to steroid treatment is generally dramatic with improvement of symptoms within 24 hours and clinical and radiological remission within 3 weeks. Progression to diffuse lung fibrosis is rare. The disease tends to recur frequently after discontinuation of steroid treatment (75%)

☝ Steroid treatment failure should prompt reconsideration of the diagnosis of CEP

Radiological course

During regression, consolidation tends to disappear centrifugally and may be temporarily followed by subpleural curvilinear bands. If the disease is left untreated, the opacities may progressively increase in number and even migrate

📖 Ebara H. Chronic eosinophilic pneumonia: evolution of chest radiograms and CT features. J Comput Assist Tomogr 1994, 18: 737

LABORATORY FINDINGS

In 85% of patients, peripheral eosinophilia is present (10-40% of white blood cells or more than 500 eosinophils/mmc). Erythrocyte sedimentation rate (ESR) may exceed 100 mm/hour. There may be hypochromic anemia, thrombocytosis and elevated IgE levels

✓ Persistence of peripheral eosinophilia >1500 cells/mmc for more than 6 months should suggest a diagnosis of hypereosinophilic syndrome

CLINICAL DIAGNOSIS

The association of characteristic clinical, laboratory and radiological findings are required for diagnosis

☝ In addition to CEP, a number of other conditions can cause pulmonary eosinophilia (see the table "Eosinophilic lung diseases" at the end of this chapter). Differential diagnosis among these diseases is complex. However, the following criteria apply: 1. normal total IgE levels in a patient with eosinophilic pneumonia rule out allergic bronchopulmonary aspergillosis and helminth infestation; 2. asthma is usually present in subjects with allergic bronchopulmonary aspergillosis, in 50% of CEP cases and is a characteristic feature of Churg-Strauss syndrome; 3. atopy is unusual in eosinophilic pneumonia due to drug toxicity, helminth infestation, and acute eosinophilic pneumonia

INVASIVE DIAGNOSIS

Transbronchial lung biopsy and/or BAL, is indicated if the clinical, radiological and laboratory findings are uncharacteristic and in particular, in the absence of peripheral eosinophilia

☝ If a biopsy is performed, this should be done under radiological guidance as areas of consolidation may rapidly migrate from one zone to another within the lungs

The biopsy should be performed before steroid treatment, since steroids can drastically reduce the number of intraalveolar and interstitial eosinophils

Bronchoalveolar lavage

The BAL fluid is characterized by eosinophilia >25-40%. The eosinophils often appear degranulated. The finding of degenerating alveolar macrophages is frequent. Significantly high concentrations of ECP may be found in the supernatant

The highest proportion of eosinophils in BAL fluid are found in association with CEP and Churg-Strauss syndrome

📖 Allen JN. Diagnostic significance of increased bronchoalveolar lavage fluid eosinophils. Am Rev Respir Dis 1990, 142: 642

Olivieri D. Eosinophilic alveolitis in immunologic interstitial lung disorders. Lung 1990, 168 Suppl: 964

TABLE

On the following page is a table which presents:

- Eosinophilic lung diseases

EOSINOPHILIC LUNG DISEASES

CEP	Condition characterized by bilateral peripheral airspace consolidations with fever, dyspnea, weight loss and malaise of several weeks duration. Usually there is eosinophilia and high serum levels of IgE
Parasitic infections	Many parasite infestations may cause eosinophilic pneumonia, including Ascaris lumbricoides, Strongyloides stercoralis, Toxocara canis, etc
Hypereosinophilic syndrome	A condition in which mature eosinophils infiltrate different organs; the heart and nervous system are most frequently involved, whereas the lung is affected in 30-40% of cases. Usually there is peripheral eosinophilia >1500 cells/mmc for more than 6 months
Churg-Strauss syndrome	This is a small vessel systemic vasculitides that may affect various organs. The most typical features are asthma, rhinosinusitis and peripheral eosinophilia. Pulmonary infiltrates are present in about two thirds of patients
Drug-toxicity	Many drugs can cause eosinophilic pneumonia, including anti-infectious, anti-inflammatory, cytotoxic agents, and L-tryptophan
Allergic bronchopulmonary aspergillosis	A clinical syndrome seen in patients with chronic asthma who develop hypersensitivity to fungal antigens, and in particular to Aspergillus fumigatus. About one third of patients may exhibit eosinophilic pulmonary infiltrates
Acute idiopathic eosinophilic pneumonia	Lung disease characterized by acute (<7 days) respiratory failure often requiring mechanical ventilation. There is no blood eosinophilia

DAH in Wegener's granulomatosis

Definition

Systemic vasculitides are diseases characterized by an inflammatory process of the vessel wall. The forms most frequently presenting with pulmonary involvement are Wegener's granulomatosis, Churg-Strauss allergic angiitis and granulomatosis, and microscopic polyangiitis

This chapter will deal with Wegener's granulomatosis as a representative example, and in particular with its diffuse lung involvement in the form of diffuse alveolar hemorrhage (DAH) (see the table entitled "Vasculitides syndromes associated with DAH" at the end of the chapter)

Diffuse Alveolar Hemorrhage

Travis WD. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 1990, 14: 1112

Travis WD. Vasculitis of the lung. Pathology 1996, 4: 23

The anatomical and radiological manifestations of Wegener's granulomatosis are not limited to DAH, but also include large nodules or masses (● Large rounded opacities: Wegener's granulomatosis)

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis are unknown, although various causative agents and pathogenetic mechanisms have been implicated in the development of Wegener's granulomatosis. These include genetic predisposition, infectious agents, autoantibodies, (in particular anti-neutrophil cytoplasmic antibodies C-ANCA), immune complex deposition, and involvement of cell-mediated immunity. The etiology is most likely to be multifactorial

Epidemiology

The prevalence is about 1.5-3 cases per 100,000 people. The disease primarily affects adults between 30 and 50 years of age, without sex predilection. DAH is present in approximately 5% of cases at presentation

Risk factors

Spring months, pregnancy, silica exposure, allergic syndrome (cutaneous, drug-induced, reaction to insect bites). Advanced age and renal involvement at onset are negative prognostic factors

CLINICAL FEATURES

History

Onset is usually abrupt with dyspnea, cough, and hemoptysis (which may however be absent in up to one third of patients with DAH). Patients may report symptoms secondary to upper airway involvement (50-75% of cases), as well as symptoms ascribable to involvement of other organs (kidney in 75-85% of cases, polyneuritis in 20-35%, eye in 10-15%, skin in 10-15%, and muscles and joints in 30%)

Physical findings

If DAH is present, physical examination of the chest reveals fine diffuse rales or signs of pulmonary consolidation. There may be physical signs of the underlying systemic vasculitis in other organs

Pulmonary function tests

DAH causes an increase in D_LCO due to the abundance of hemoglobin in the airspaces. Hypoxemia, moderate to severe, is frequent

In the follow-up, D_LCO monitoring may reveal disease recurrence

DAH in Wegener's granulomatosis needs to be differentiated from other forms of vasculitis with capillaritis (see the table entitled "Vasculitis syndromes associated with DAH" at the end of the chapter) as well as from other conditions responsible for DAH, such as lung damage induced by drugs (penicillamine, nitrofurantoin, propylthiouracil) (⌘ Drug toxicity) or toxic inhalation (trimellitic anhydride, cocaine, paraquat, pesticides, isocyanates)

Imoto EM. Pulmonary capillaritis and hemorrhage. A clue to the diagnosis of systemic necrotizing vasculitis. Chest 1989, 96: 927

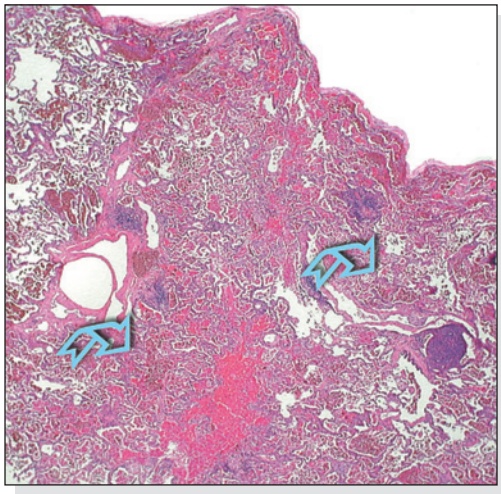
Langford CA. Wegener's granulomatosis. Thorax 1999, 54: 629

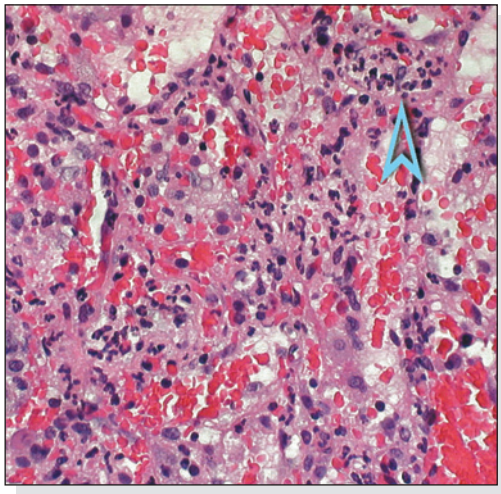
PATHOLOGY

Basic lesions

DAH in Wegener's granulomatosis presents as:

- Intraalveolar accumulation of red blood cells and hemosiderin-laden macrophages (↳). This may be associated with capillaritis, consisting of an intense neutrophilic infiltrate around the capillaries of the alveolar septa (➢), as well as foci of organizing pneumonia (OP)
- In chronic hemorrhage there is also fibrous septal thickening and the presence of hemosiderin-laden septal and intraalveolar macrophages





✓ Capillaritis is often a focal and transient process: its presence may therefore depend on the timing of the biopsy

☝ The characteristic lesions of Wegener's granulomatosis should be sought in the interstitium: these may be primary or secondary

The primary lesions are necrosis, vasculitis and background granulomatous inflammation. Necrosis may present in the form of both neutrophil microabscesses and extensive patchy ("geographic") basophilic ("blue") areas due to the prevalence of neutrophils. Vasculitis may affect the arteries, veins or capillaries. The lesion is often focal and all types of inflammatory cells are implicated. Granulomatous inflammation may be expressed both by giant cells, sparse or in small groups, and by palisading histiocytes around the necrotic foci

Secondary lesions, bronchial or parenchymal, include alveolar hemorrhage, OP, lymphoid hyperplasia, endogenous lipoid pneumonia, acute, chronic and follicular bronchiolitis, tissue eosinophilia. Secondary lesions sometimes dominate the morphological pattern

Distribution

Diffuse intraalveolar

The finding of "endogenous pneumoconiosis" is frequent during chronic hemorrhage

It consists of hemosiderin deposition in the vessel walls with fragmentation of the elastic lamina and consequent giant cell granulomatous reaction (not to be mistaken for Wegener's granulomatous inflammation)

Differentials

Histopathologic differential diagnoses:

- Traumatic hemorrhage (biopsy-related): this is the most common cause of intraalveolar bleeding. The macrophages show no hemosiderin or erythrophagocytosis and the red blood cells are not mixed with fibrin. Capillaritis is absent
- Neutrophilic margination: the neutrophils within the lumen of capillaries may adhere to the vessel walls and simulate capillaritis
- Microscopic polyangiitis (MPA): absence of granulomas
- Churg-Strauss syndrome: prominent eosinophilic infiltrate ("red" necrosis)
- Idiopathic pulmonary hemosiderosis: capillaritis is uncommon, but differentiation requires clinical and radiological data
- Other pulmonary hemorrhagic syndromes (diffuse pulmonary hemorrhage due to anti-basal membrane antibodies, systemic lupus erythematosus (SLE), idiopathic glomerulonephritis, drugs, Henoch-Schönlein purpura, IgA disease, cryglobulinemia, pulmonary-renal syndrome): differentiation is based on clinical-serological data, immunofluorescence and electron microscopy findings. The characteristic lesions of Wegener's granulomatosis are absent
- Hemorrhagic DAD (due to crack, cocaine): presence of acute-phase hyaline membranes, and marked hyperplasia of type II pneumocytes
- Infectious hemorrhagic pneumonia: the neutrophils are predominantly intraalveolar and peribronchial
- DIP and RB-ILD, smoker's lung: the macrophages contain finely dispersed granules of pigment which are negative or weakly positive for iron, whereas the granules in chronic hemorrhage are coarse and strongly positive for iron

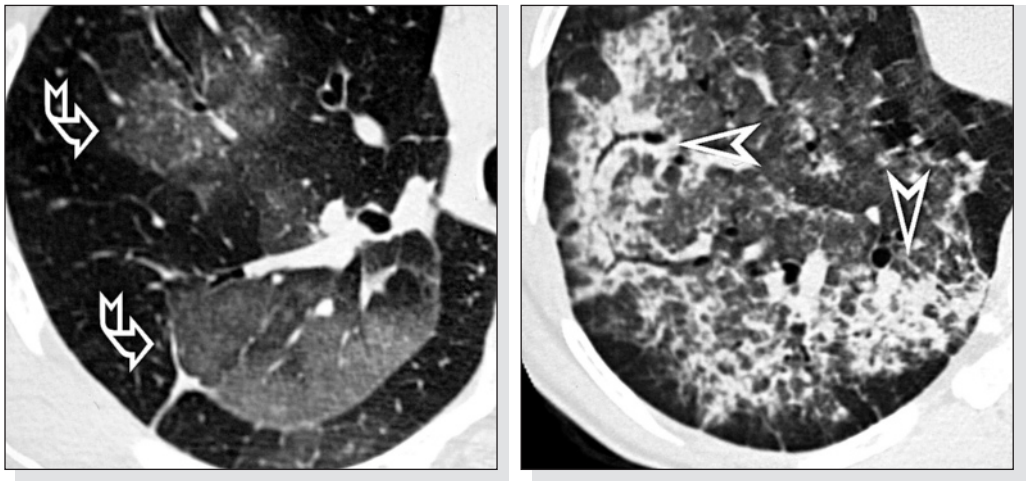
Travis WD. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 1990, 14: 1112

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Areas of ground-glass attenuation (↳)
- Multiple areas of parenchymal consolidation (➢)



Parenchymal consolidation may reflect alveolar hemorrhage, edema or superimposed infections (favored by pharmacological immunosuppression). At times there are true peripheral wedge-shaped opacities due to tissue infarction in connection with the pulmonary vessels

Hansell DM. Small-vessel diseases of the lung: CT-pathologic correlates. Radiology 2002, 225: 639

Primack SL. Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. AJR Am J Roentgenol 1995, 164: 295

Distribution

Bilateral (even though unilateral predominance is also possible), diffuse or patchy

Diffuse, at times predominant in the parahilar region ("butterfly" or "batwing" pattern) with absence in the subpleural regions

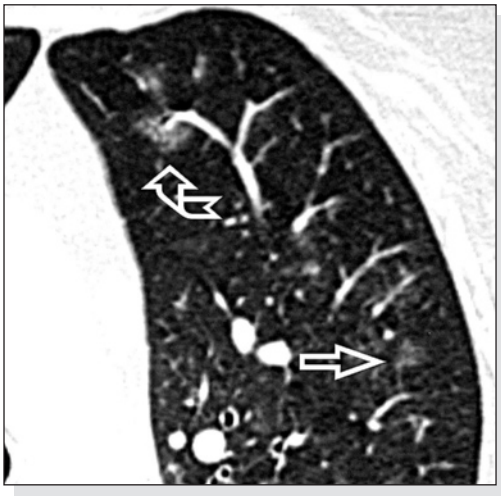
Variable; when diffuse, the lung apices and costophrenic sinuses are relatively unaffected

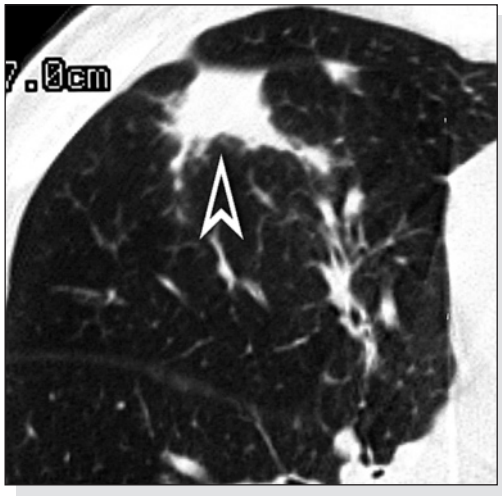
Lung volume is normal

Other signs

Other radiological signs:

- Scattered low-density nodules (⇨) (nodular ground-glass pattern), at times in connection with the small vessels (↳)
- Smooth septal thickening and crazy paving
- Round opacities with diameter varying between 1 and 4 cm, usually bilateral (75%), often cavitated and with irregular thick walls
- Macronodules (➢) and masses with ill-defined borders
- Hilar or mediastinal adenopathy (2-15%)
- Smooth or irregular tracheal stenosis with wall thickening and possible calcifications
- Pleural effusion (less than 10%)





In some cases the round opacities and masses are the dominant or exclusive sign of disease (● Large rounded opacities: Wegener's granulomatosis)

Tracheal stenosis tends to involve the subglottic cervical trachea; diffuse stenosis involving the central bronchi with lobar atelectasis or the entire lung is rare

Maguire R. Unusual radiographic features of Wegener's granulomatosis. AJR Am J Roentgenol 1978, 130: 233

Maskell GF. Computed tomography of the lung in Wegener's granulomatosis. Clin Radiol 1993, 48: 377

Stein MG. Computed tomography of diffuse tracheal stenosis in Wegener granulomatosis. J Comput Assist Tomogr 1986, 10: 868

Differentials

The radiological differential diagnoses are:

- Other vasculitis syndromes, hemorrhage collagen vascular diseases and immune diseases: the differential diagnosis is based on the clinical and laboratory findings, although the presence of nodules and masses with a tendency to cavitate is less common
- PE: pleural effusion (common), widening of the vascular pedicle, possible cardiomegaly, absence of macronodules or masses
- Infectious pneumonias: the pattern is often indistinguishable, especially in immunodepressed patients. Ground-glass attenuation in perihilar regions or in the upper lobes prevails in PCP, and thick/thin-walled cysts are possible

Specks U. Granulomatous vasculitis. Wegener's granulomatosis and Churg-Strauss syndrome. Rheum Dis Clin North Am 1990, 16: 377

COURSE and COMPLICATIONS

Associated diseases

An association with immune-mediated diseases such as Hashimoto's thyroiditis and CREST syndrome has been described

Clinical course

The clinical course of DAH is often dramatic and may be fatal if the disease is not promptly treated. Pulmonary interstitial fibrosis or progressive broncho-obstructive disease have been reported in patients with repeated episodes of DAH

Radiological course

Hemorrhagic alveolar consolidations typically evolve rapidly, even within days. During the resolution phase, a reticular pattern may be present which may persist in the case of relapsing hemorrhage

LABORATORY FINDINGS

A typical finding is the rapid development of anemia. Non-specific findings include: leukocytosis, thrombocytosis, and elevated ESR. Renal involvement produces changes in renal function indices (azotemia, creatinemia), and in urinalysis (red blood cells, proteinuria, cell casts). More than 90% of patients with active disease and pulmonary-renal involvement have C-ANCA (directed against proteinase) in the serum

The role of C-ANCA in the diagnosis of Wegener's granulomatosis is well-established, and according to some studies, C-ANCA might also be useful in monitoring the disease. However, the possibility of false positives should be kept in mind. These may occur both with other forms of vasculitis and with non-vasculitic diseases (tuberculosis, HIV infection, endocarditis, nasal septal perforation, monoclonal gammopathy, neoplastic disease, drug-toxicity, polyneuritis). A negative C-ANCA test undoubtedly has a strong negative predictive value (90%)

CLINICAL DIAGNOSIS

In the appropriate clinical setting, positive serum C-ANCA and anti-proteinase-3 antibodies are considered to be strongly suggestive of Wegener's granulomatosis. Histologic confirmation should nonetheless be sought, with demonstration of necrotizing vasculitis at the affected sites (kidney, lung, skin, etc.)

INVASIVE DIAGNOSIS

Surgical lung biopsy is the method of choice for a definitive diagnosis. Transbronchial lung biopsy does not provide diagnostic material

Bronchoalveolar lavage

BAL may reveal the presence of DAH in patients without hemoptysis or significant anemia. The BAL fluid is hemorrhagic and the cytological analysis reveals hemosiderin-laden macrophages. C-ANCA may be assayed in the supernatant, but the prognostic significance of the titer is unknown

BAL is useful in differentiating disease recurrence from opportunistic infection or drug toxicity in the event that new pulmonary infiltrates appear in the follow-up

Hoffman GS. Bronchoalveolar lavage analysis in Wegener's granulomatosis. A method to study disease pathogenesis. Am Rev Respir Dis 1991, 143: 401

VASCULITIDES SYNDROMES ASSOCIATED WITH DAH

- Wegener's granulomatosis
- Churg-Strauss allergic angiitis and granulomatosis
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Bechet's disease
- Mixed cryoglobulinemia
- Collagen vascular diseases: Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), polymyositis
- Antiphospholipid antibody syndrome
- Goodpasture's syndrome
- Isolated pulmonary capillaritis

Desquamative Interstitial Pneumonia

Definition

Desquamative interstitial pneumonia (DIP) is a discrete clinical and pathologic entity characterized by abnormal and uniform accumulation of intraalveolar macrophages. A rare disease, it is classified among the idiopathic interstitial pneumonias

Alveolar macrophage pneumonia

The general term idiopathic interstitial pneumonias (IIP) includes various diseases, and in particular usual interstitial pneumonia (□ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis are unknown. Similarities with RB-ILD (● RB-ILD) suggest that the two entities represent the extremes of a spectrum of diseases caused by cigarette smoking. The cells which accumulate in the alveolar spaces are now known to be alveolar macrophages attracted to the site by chemotactic stimuli (probably cigarette smoke antigens) rather than sloughed epithelial cells

Epidemiology

The disease tends to affect smokers in their 4th or 5th decades of life, and is more common in men than in women by a ratio of 2:1

Risk factors

Cigarette smoking

CLINICAL FEATURES

History

DIP develops insidiously with dyspnea (87%) and cough (43%) over a course of weeks or months before diagnosis. Chest pain may be observed, albeit rarely (17%)

Physical findings

Bibasilar fine rales may be heard. About 25% of patients have digital clubbing

Pulmonary function tests

The earliest functional alteration is reduced D_LCO (35%) on a background of a mild restrictive ventilatory defect (30%)
Lung volumes may be normal (20%)

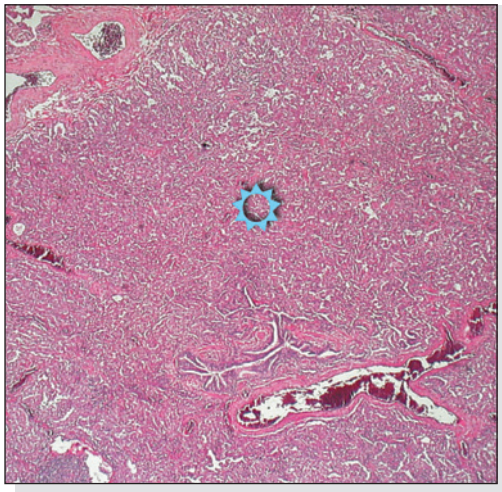
Rju JH. Desquamative interstitial pneumonia and respiratory bronchiolitis - associated interstitial lung disease. Chest 2005, 127:178

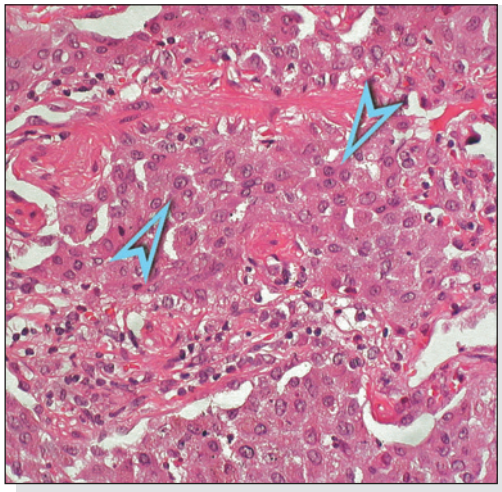
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Extensive accumulation of macrophages in the alveolar spaces (☼). The alveolar septa may be slightly thickened by fibrosis and mild lymphoplasmacellular infiltrate with rare eosinophils
- The intraalveolar macrophages have dense eosinophilic cytoplasm (➢) containig particles of golden-brown pigment. They tend to form monotonous aggregates. Necrosis, fibrin, intraalveolar organization and intense interstitial infiltrate are usually absent





✓ **Distribution Differentials**

Pulmonary architecture is basically preserved

Diffuse intraalveolar

Histopathologic differential diagnoses:

- DIP-like reaction: associated with other conditions such as drug- or asbestos-induced disease, eosinophilic pneumonia, infections or simply as a consequence of smoking
- RB-ILD: the proliferation is not diffuse but bronchiolocentric with sparing of the alveoli
- NSIP: septal thickening due to inflammation and fibrosis are more pronounced and there is less involvement of the alveolar spaces
- LCH: centrilobular nodules with stellate margins associated with cysts, and interstitial infiltrate consisting of eosinophils and Langerhans' cells

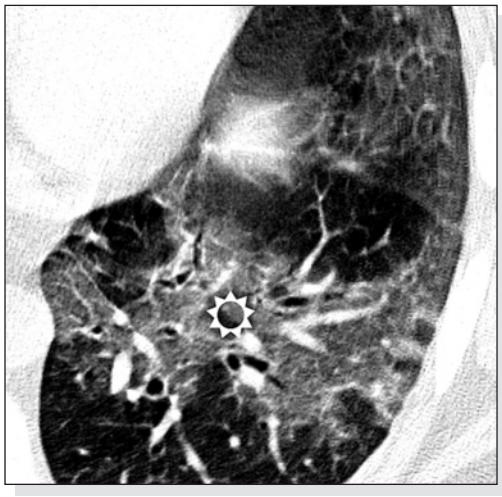
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

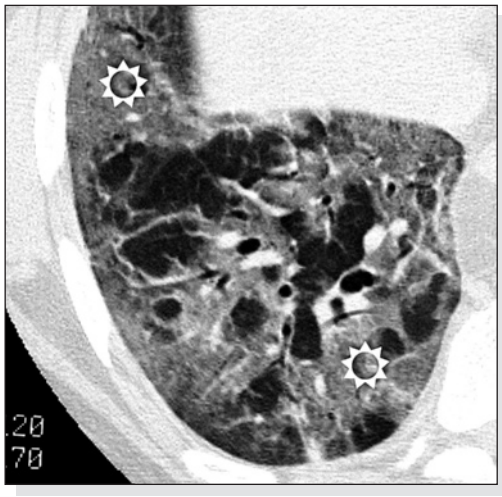
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Patchy ground-glass opacities (☼)





Distribution

Bilateral, generally symmetrical

Diffuse, at times predominant in the peripheral and subpleural regions

Basal

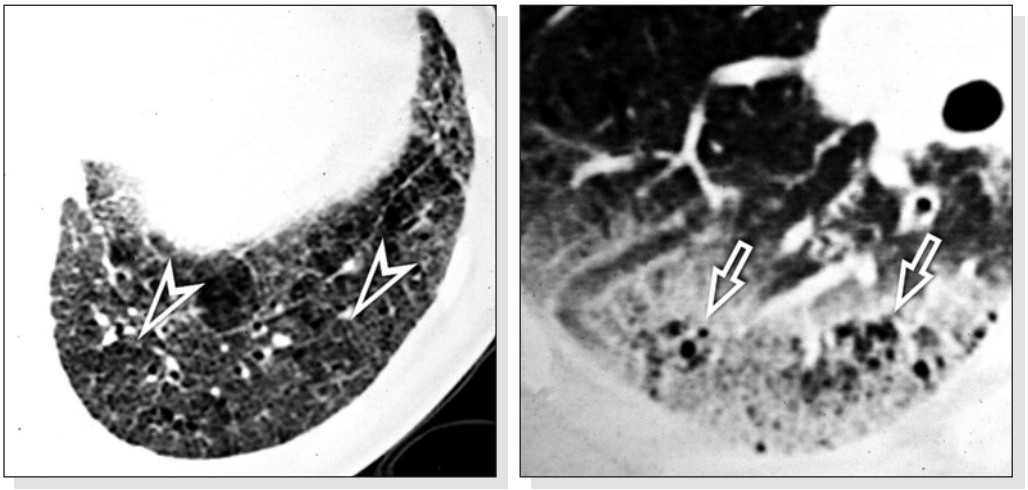
Lung volume is normal or slightly reduced

Hartman TE. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1993, 187: 787

Other signs

Other non-constant signs:

- Basal reticular opacities (≽)
- Moderate distortion of the pulmonary architecture and traction bronchiectasis
- Small air-filled cysts within the areas of ground-glass attenuation (⇨)



The cysts, which are due to dilatation of the alveolar ducts and respiratory bronchioles, are smaller than those seen in UIP; in addition, there is no fibrotic distortion!

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomogr 2002, 26: 5

Differentials

The main radiological differential diagnoses are:

- NSIP: more evident reticular changes, bronchiectasis and traction bronchiolectasis
- PCP: acute onset in immunodepressed subjects, frequent localization in the middle-upper regions
- HP: the patchy areas of ground-glass attenuation are more randomly distributed. Centrilobular nodules are often associated

Heyneman LE. Respiratory bronchiolitis, respiratory bronchiolitis-associated interstitial lung disease, and desquamative interstitial pneumonia: different entities or part of the spectrum of the same disease process? AJR Am J Roentgenol 1999, 173: 1617

COURSE and COMPLICATIONS

Associated diseases

The disease may be associated with other smoke-induced lung diseases such as respiratory bronchiolitis and centrilobular emphysema

Clinical course

The majority of patients demonstrate a stable clinical course with favorable prognosis. However, there have been sporadic reports of progression of disease with death (26-32%) despite smoking cessation and corticosteroid treatment

Radiological course

The lesions may become stable or even regress after smoking cessation. The small air-filled cysts within the areas of ground-glass attenuation may disappear spontaneously

LABORATORY FINDINGS

Laboratory findings are usually unremarkable

CLINICAL DIAGNOSIS

In smokers with chronic dyspnea, dry cough, restrictive ventilatory pattern and reduced D_LCO, the HRCT pattern can raise the suspicion of DIP. The diagnosis, however, requires histological confirmation by surgical lung biopsy. The differential diagnosis will mainly consider the other idiopathic interstitial pneumonias, in particular NSIP (□ NSIP) and RB-ILD (● RB-ILD)

INVASIVE DIAGNOSIS

Surgical lung biopsy is mandatory for a definite diagnosis. The usefulness of BAL and transbronchial lung biopsy is limited to the exclusion of infectious or neoplastic diseases

Bronchoalveolar lavage

BAL typically shows increased numbers of alveolar macrophages with yellow, golden, brown or black inclusions (which are also seen in healthy smokers). The absence of these cells makes a diagnosis of DIP highly unlikely. There may be increases in neutrophils, eosinophils and, at times, lymphocytes

Nagai S. Classification and recent advances in idiopathic interstitial pneumonia. Curr Opin Pulm Med 1998, 4: 256

Veeraraghavan S. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003, 22: 239

Amiodarone-induced lung disease

Definition

A number of drugs can cause lung injury, which is expressed by different histopathological patterns (see the table "Drug-induced lung injury: histopathologic patterns" at the end of this chapter). This chapter covers amiodarone-induced lung disease as a representative example of drug-induced alveolar damage

It should nonetheless be noted that the same drug may cause different types of lung injury, even in sequence. For example, amiodarone itself may also cause OP (⌘ OP) or chronic interstitial pneumonia (☐ Drug toxicity) or diffuse alveolar damage (DAD) such as AIP (⌘ AIP) and ARDS (⌘ ARDS)

Rosenow EC 3rd. Drug-induced pulmonary disease. An update. Chest 1992, 102: 239

DEMOGRAPHICS

Etiology and pathogenesis

The lung injury induced by amiodarone is thought to result in part from a direct toxic effect (altered phospholipid turnover, toxic oxygen species) and in part from an immune reaction (hypersensitivity pneumonitis). Inhibition of phospholipid degeneration within the lysosomes is responsible for the characteristic "foamy" appearance of the alveolar macrophages

Epidemiology

Amiodarone causes pulmonary toxicity in 5-10% of patients treated with the drug

Risk factors

A higher risk of pulmonary toxicity is associated with: 1. daily dose (maintenance therapy) ≥400 mg; 2. duration of treatment longer than 2 months: 3. age over 60 years; 4. pre-existing lung disease; 5. surgery (thoracic and non-thoracic); 6. angiographic investigations. There is no correlation between duration of treatment or cumulative dose and the extent of lung damage

CLINICAL FEATURES

History

The onset of disease is insidious, with dry cough and dyspnea arising within months of starting therapy. Systemic symptoms such as low-grade fever, weight loss and weakness are also common. In one third of patients the onset is acute and mimics a pulmonary infection

Physical findings

Patients are tachypneic, and chest auscultation reveals fine diffuse rales and at times pleural rubs. Digital clubbing has not been reported

Pulmonary function tests

Pulmonary function tests reveal a restrictive ventilatory defect with decreased D_LCO. Hypoxemia is present in all patients

Martin WJ 2nd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part I). Chest 1988, 93: 1067

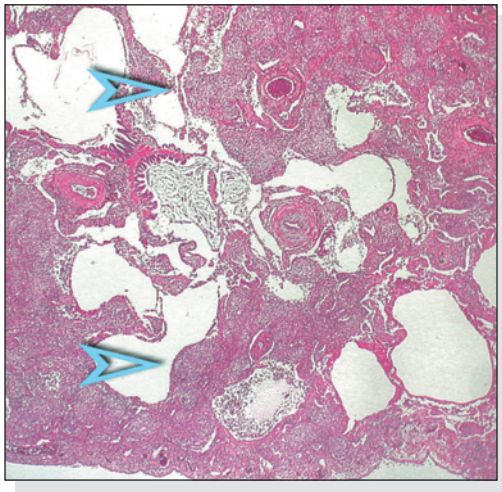
Martin WJ 2nd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 2). Chest 1988, 93: 1242

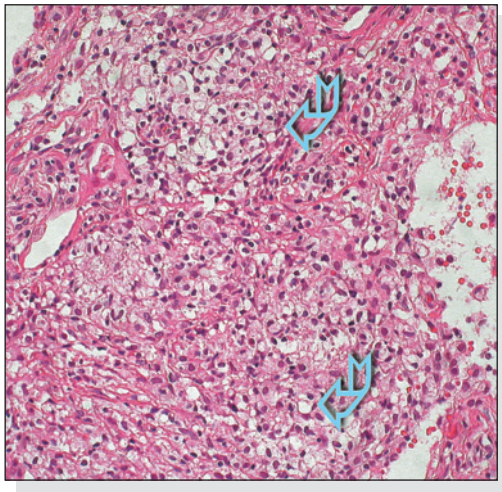
PATHOLOGY

Basic lesions

The most common lesion associated with amiodarone-induced pulmonary toxicity is the following:

- Chronic interstitial pneumonia with lymphoid hyperplasia and accumulation of foamy macrophages (↳) with finely vacuolated cytoplasm predominantly in the alveolar spaces, but also in the interstitium (➢)





At low magnification the histologic appearance is similar DIP

Non-specific inflammatory pleural infiltrate, with or without effusion, may be observed

In addition to chronic interstitial pneumonia, amiodarone may occasionally produce OP and DAD patterns with the presence of foamy macrophages

The presence of foamy macrophages is not confined to amiodarone-induced pneumonia, as they can also be observed in other conditions associated with airway obstruction

Distribution

Alveolar and, to a lesser extent, septal

Differentials

Histopathologic differential diagnoses:

- Obstructive pneumonia: there is obstruction of large or small airways
- Diffuse panbronchiolitis (DPB) and DPB-like pattern (e.g. associated with idiopathic inflammatory bowel disease): centrilobular lesions with cellular bronchiolitis containing numerous foamy macrophages in the alveolar spaces, but mostly in the pulmonary interstitium
- Erdheim-Chester disease: interstitial infiltrate of foamy macrophages along the lymphatic routes associated with fibrosis
- TB and mycobacteriosis: presence of numerous mycobacteria in immunodepressed patients
- NSIP: interstitial fibrosis and inflammation are more pronounced

Bedrossian CW. Amiodarone pulmonary toxicity: cytopathology, ultrastructure, and immunocytochemistry. Ann Diagn Pathol 1997, 1: 47

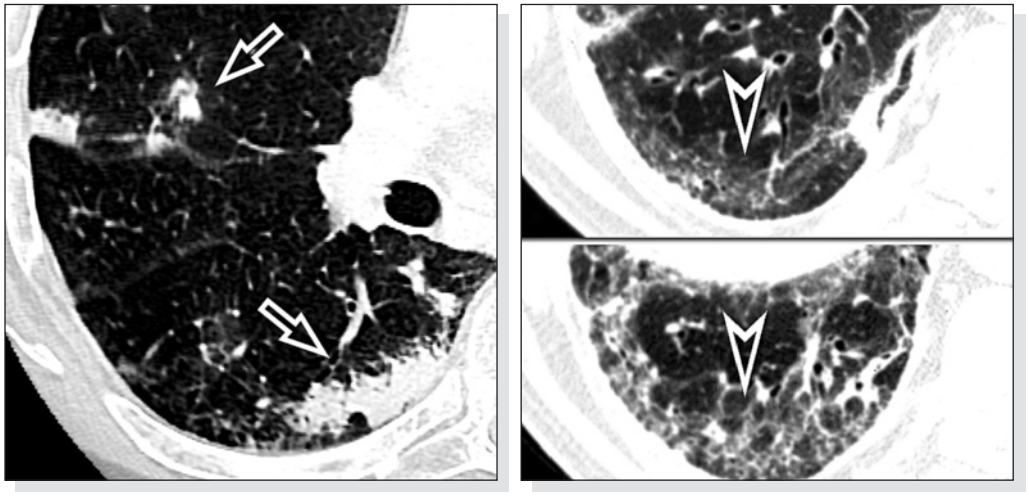
Ott MC. Pulmonary toxicity in patients receiving low-dose amiodarone. Chest 2003, 123: 646

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (⇨) often hyperdense compared to muscle (80-180 HU)
- Patchy ground-glass opacities (≫)



These findings correspond to NSIP possibly associated with OP: the two patterns may coexist in the same patient. The hyperdensity of the lesions is due to the accumulation of amiodarone (which contains iodine) in the macrophages and type II pneumocytes. In some patients, the consolidation appears as a single pneumonia-like opacity or as a solitary pseudoneoplastic mass

Kuhlman JE. Amiodarone pulmonary toxicity: CT findings in symptomatic patients. Radiology 1990, 177: 121

Padley SP. High-resolution computed tomography of drug-induced lung disease. Clin Radiol 1992, 46: 232

Polverosi R. [Thoracic radiography and high resolution computerized tomography in the diagnosis of pulmonary disorders caused by amiodarone]. Radiol Med 1996, 92: 58. Italian

Distribution

Bilateral and asymmetrical, patchy

Predominantly peripheral

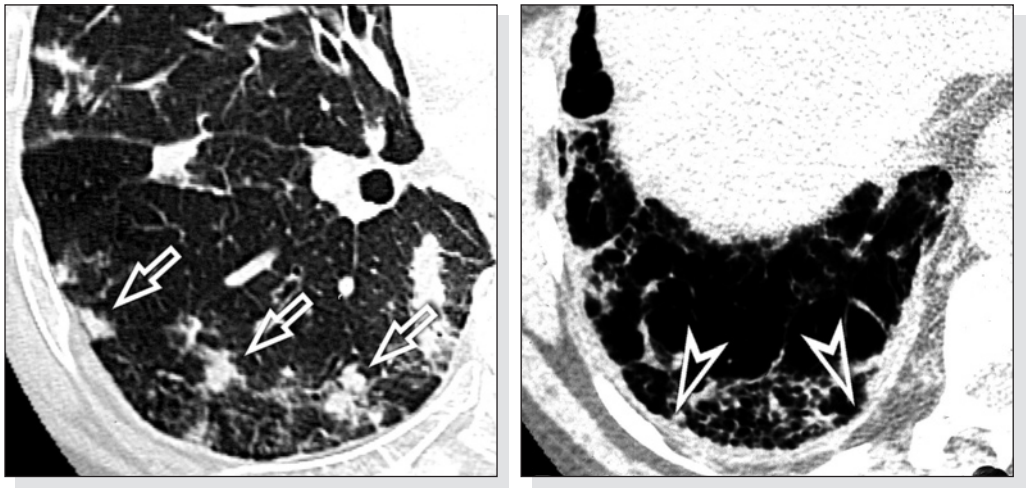
Predominantly basal

Lung volume is normal or reduced

Other signs

Other radiological signs:

- Reticular opacities and micronodules (⇨)
- Hyperdense pleural thickening (➢)
- Pleural effusion
- Hyperdense liver and spleen (80%) and heart (20%)



Rossi SE. Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics 2000, 20: 1245

Differentials

The presence of hyperdensities within the areas of consolidation needs to be differentiated from:

- Amyloidosis: possible presence of more pronounced hyperdensities due to calcifications within the areas of consolidation and, above all, nodules

The radiological differential diagnoses also include other conditions responsible for consolidation with subacute or acute clinical courses:

- Slow-healing infections: the differential diagnosis is made on the basis of the clinical and bronchological findings
- CEP: the areas of consolidation are located in the upper lung regions and are always peripheral ("photographic negative" of the butterfly or batwing edema pattern)
- OP: the pattern is similar
- Churg-Strauss syndrome: the differential diagnosis is challenging. The areas of consolidation may be not only peripheral but also randomly distributed and migratory
- BAC and MALToma: the diagnosis is based on bronchoscopy and biopsy

Leung AN. Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. Radiology. 1993, 188: 209

COURSE and COMPLICATIONS

Associated diseases

Amiodarone is used to treat cardiopathic patients affected by supraventricular arrhythmias unresponsive to conventional therapy

Clinical course

Discontinuation of the drug and administration of corticosteroids have proven to be very effective. Recurrences have been reported following interruption of steroid treatment. Amiodarone-induced lung disease has a mortality rate below 10% which increases to 50% in cases complicated by ARDS

Radiological course

The areas of parenchymal consolidation resolve with steroid therapy and only in a small minority of patients do they progress to fibrosis

Ellis SJ. Drug-induced lung disease: high-resolution CT findings. AJR Am J Roentgenol 2000, 175: 1019

LABORATORY FINDINGS

The laboratory findings are non-specific: leukocytosis, > lactate dehydrogenase (LDH), > ESR. The serum levels of amiodarone are not predictive of lung damage. It has been suggested that serum concentrations of the glycoprotein KL-6 may predict lung damage

CLINICAL DIAGNOSIS

Amiodarone-induced lung disease is a diagnosis of exclusion made on the basis of the clinical, radiological and, where possible, BAL findings

INVASIVE DIAGNOSIS

In the appropriate clinical setting, surgical lung biopsy is unnecessary, in part because the findings would not be specific. Transbronchial lung biopsy may be useful in identifying OP pattern

Bronchoalveolar lavage

A common BAL pattern in patients receiving amiodarone, whether or not they have lung disease, is the presence of numerous "foamy" macrophages. In addition to this, patients with lung disease also have an increase in lymphocytes, neutrophils and eosinophils (mixed alveolitis). The lymphocytes are predominantly of the CD8+ subset. These findings may assist in the diagnosis, although they have no prognostic significance

The BAL finding of mixed alveolitis in a patient with amiodarone-induced lung damage is similar to that seen in HP, idiopathic OP and at times NSIP. BAL may be of value in ruling out infection or malignancy

Coudert B. Amiodarone pneumonitis. Bronchoalveolar lavage findings in 15 patients and review of the literature. Chest 1992, 102: 1005

The table entitled "Drug-induced lung injury: BAL findings" at the end of this chapter summarizes the main BAL features encountered in lung disease induced by various drugs

TABLES

On the following pages are two detailed tables which present:

- Drug-induced lung injury: histopathologic patterns
- Drug-induced lung injury: BAL findings

DRUG-INDUCED LUNG INJURY: HISTOPATHOLOGIC PATTERNS

Chronic interstitial pneumonia	Amiodarone, BCNU, busulfan, cyclophosphamide, chlorambucil, cocaine, fluoxetine, gold salts, melphalan, methotrexate, methyl-CCNU, nilutamide, nitrofurantoin, nitrogen mustard, phenytoin, pindolol, procarbazine, quinidine, sulfasalazine, tocainide, tryptophan
Diffuse Alveolar Damage (DAD)	Amiodarone, amitriptyline, azathioprine, BCNU, bleomycin, busulfan, CCNU, cocaine, colchicine, cyclophosphamide, cytosine arabinoside, gold salts, hexamethonium, melphalan, methotrexate, mitomycin, nitrofurantoin, penicillamine, procarbazine, streptokinase, sulfasalazine, teniposide, vinblastine, zinostatin
OP	Amiodarone, bleomycin, chlorozotocin, cocaine, cyclophosphamide, disodium chromoglycate, gold salts, hexamethonium, interferon, mecamylamine, methotrexate, mitomycin, nilutamide, phenytoin, sulfasalazine, tocainide
BO	CCNU, penicillamine
CEP	Acetominophen, ampicillin, bleomycin, carbamazepine, chlorpropamide, cocaine, disodium chromoglycate, imipramine, mephenesin, nabumetone, naproxen, nitrofurantoin, PAS, phenylbutazone, procarbazine, prontosil, propranolol, pyrimethamine, sulfasalazine, tetracycline, trazodone
Hemorrhagic alveolitis	Amphoteracin B, anticoagulants, cocaine, codeine, cyclophosphamide, epinephrine, haloperidol, heroin, hydrochlorothiazide, mitomycin, nitrofurantoin, penicillamine, propylthiauracil, streptokinase, sulfonamide, urokinase
PE	Buprenorphine, chlordiazepoxide, cocaine, codeine, cytosine arabinoside, epinephrine, haloperidol, heroin, hydrochlorothiazide, isoxsuprine, lidocaine, magnesium sulfate, methadone, methotrexate, mitomycin, nalbuphine, naloxone, nifedipine, paraldehyde, penicillin, propoxyphene, propranolol, ritodrine, salbutamol, salicylates, sulindac, terbutaline
Granulomatous inflammation	Acebutolol, BCG, cocaine, disodium chromoglycate, fluoxetine, methotrexate, nitrofurantoin, procarbazine

DRUG-INDUCED LUNG INJURY: BAL FINDINGS

Drugs	Type of injury	BAL findings
Bleomycin, busulfan, cyclophosphamide, methotrexate, nitrosourea	Cytotoxic reaction	Atypical cells Lipoproteinaceous material Increase in eosinophils
Acebutolol, amiodarone, azathioprine, bleomycin, busulfan, cyclophosphamide, gold salts, methotrexate*, nitrofurantoin, propranolol, sulfasalazine	Lymphocytic alveolitis	Lymphocytosis >40% Increased T CD8+ lymphocytes Decreased CD4:CD8 ratio *Increased CD4- lymphocytes
Bleomycin, busulfan	Neutrophilic alveolitis	Increase in neutrophils
Ampicillin, bleomycin, nitrofurantoin, penicillin, sulfasalazine, tetracycline	Eosinophilic alveolitis	Increase in eosinophils
Amphotericin B, penicillamine	Hemorrhagic alveolitis	Red blood cells and hemosiderin-laden alveolar macrophages
Amiodarone	Storage disease	Foamy macrophages
Mineral oil (oil nose-drops, laxatives)	Lipoid pneumonia	Vacuolated alveolar macrophages Sudan stain or Oil red O-positive in alveolar macrophages

Hypersensitivity Pneumonitis

Definition

Hypersensitivity pneumonitis (HP) refers to a group of diffuse granulomatous parenchymal lung diseases caused by the repeated inhalation of, and sensitization to, a broad variety of low molecular weight antigens and chemicals. Clinical presentation may be subacute (● HP, subacute), chronic (□ HP, chronic) or more rarely, acute. This chapter deals with the acute form

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

Etiology and pathogenesis

The number of responsible inciting agents is high (more than 300) and new antigens are constantly being identified. The most commonly known diseases are "Farmer's lung", caused by the inhalation of Faeni rectivirgula present in moldy hay and "Bird fancier's lung", caused by exposure to avian proteins

Gell and Coombs type III and type IV immune reactions lie at the basis of the immunopathogenesis of the disease. The acute form seems to be related to heavy exposure to antigens and working conditions (environmental antigen concentration, duration and frequency of exposure, type of work)

Epidemiology

Little is known about the incidence and prevalence of hypersensitivity pneumonitis, since individual susceptibility, intensity of exposure in different occupational settings, seasons, geographical areas and proximity of industry vary greatly. The prevalence of "Farmer's lung" varies between 2% and 9%, whereas that of "Bird fancier's lung" varies between 6% and 15%

Risk factors

The disease is more common in non-smokers

CLINICAL FEATURES

History

Symptoms of the acute form are cough, dyspnea, fever, chills, malaise and myalgia. A careful clinical history may reveal massive exposure to an inciting antigen and a temporal relationship between exposure and onset of symptoms (4-12 hours)

Physical findings

Patients present with tachypnea, and auscultation of the lungs may be normal or reveal fine diffuse rales. Wheezes and stridors are rarely heard

Pulmonary function tests

Patients typically have a restrictive ventilatory defect with reduced D_LCO or, in rare cases, an obstructive pattern. Mild hypoxemia at rest is common

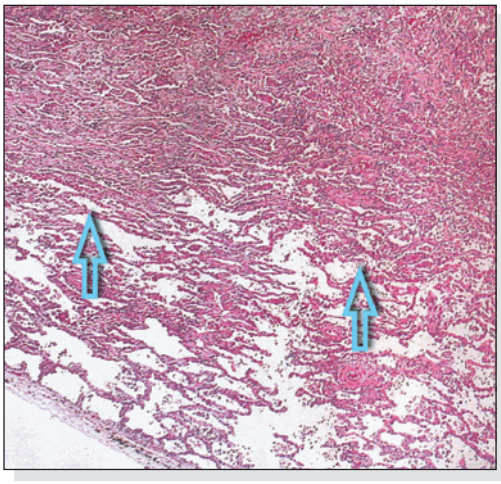
Patel AM. Hypersensitivity pneumonitis: current concepts and future questions. J Allergy Clin Immunol 2001, 108: 661

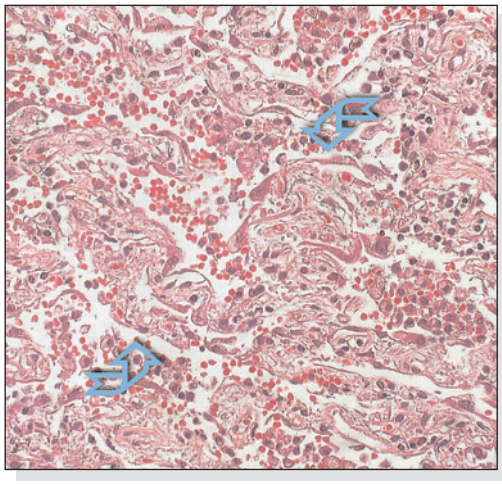
PATHOLOGY

Basic lesions

In the acute stage, the histologic pattern is characterized by:

- Neutrophilic infiltrate in the alveolar spaces and respiratory bronchioles (acute bronchiolitis)
- Extensive foci of organizing pneumonia (⇨)
- Acute or organizing DAD (↳) with hyaline membranes and necrosis in severe cases





✓ Additional findings:

- Interstitial granulomatous pneumonia characterized by cellular bronchiolitis with diffuse interstitial lymphoplasmacellular infiltrates. Small poorly-formed non-necrotizing granulomas are also present

Ancillary findings:

- Giant cells containing refractile crystals
- Foci of obstructive pneumonia with foamy macrophages histiocytes in the alveolar spaces

Distribution Centrilobular

Seal RM. The pathology of the acute and chronic stages of farmer's lung. Thorax 1968, 23: 469

Tasaka S. Fatal diffuse alveolar damage from bird fancier's lung. Respiration 1997, 64: 307

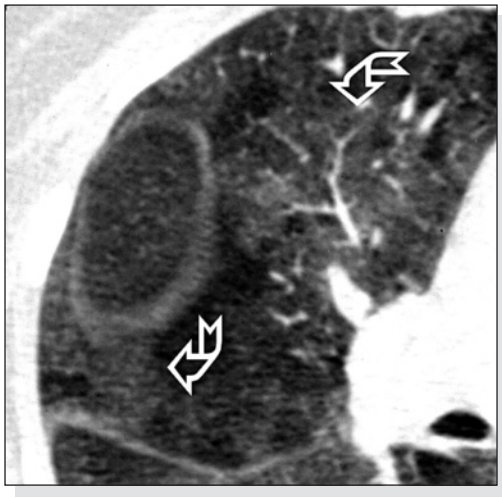
Differentials Histopathologic differential diagnoses:

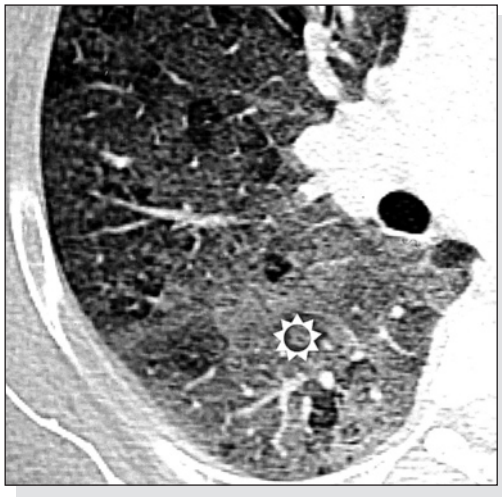
- NSIP: diffuse rather than bronchiolocentric lesions; granulomas and foci of organizing pneumonia may be present, but they are not characteristic
- DAD: the process is diffuse rather than bronchiolocentric, and there is marked hyperplasia of type II pneumocytes
- OP: less intense interstitial infiltrate and absence of granulomas

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions Basic radiological signs:

- Ground-glass opacities (↳)
- Parenchymal consolidation (☼)





Distribution Bilateral and patchy; rarely homogeneous

Random

Variable but more commonly basal

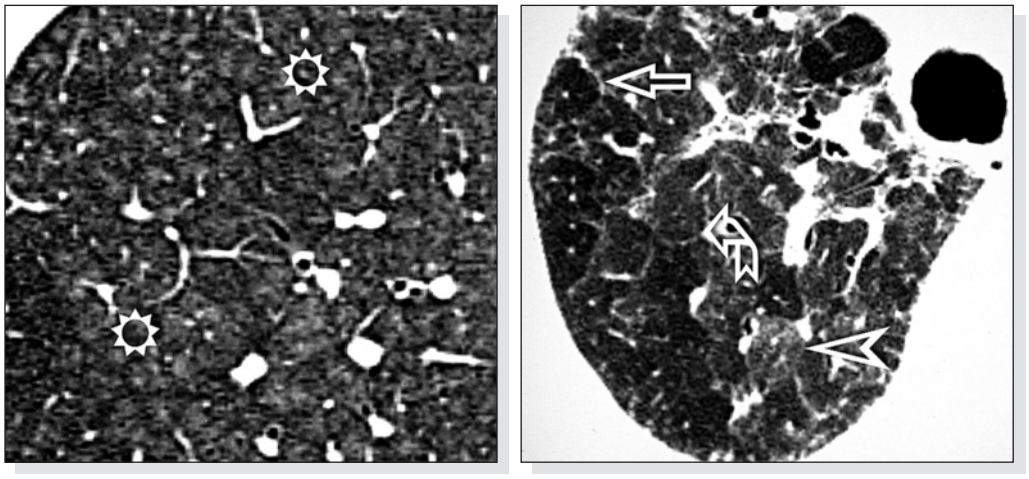
Lung volume is normal

Silver SF. Hypersensitivity pneumonitis: evaluation with CT. Radiology 1989, 173: 441

Other signs

Other radiological features:

- Low-density poorly-defined centrilobular nodules 1-5 mm in diameter (☼)
- Mediastinal adenopathy
- Mosaic oligemia with air-trapping (⇨), possibly associated with areas of normal parenchyma (↳) alternating with areas of ground-glass attenuation (≫) (head-cheese pattern)



Cormier Y. High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. Eur Respir J 2000, 16: 56

Differentials

Radiological differential diagnoses:

If the ground-glass attenuation prevails:

- PCP: in immunodepressed patients only. Ground-glass attenuation is present in the parahilar regions and in the upper lobes in patients treated with aerosol pentamidine. Thin- or thick-walled cysts may be seen

If consolidation prevails:

- AIP: reticular pattern associated with consolidation, parenchymal distortion, traction bronchiectasis and limited honeycombing
- OP: the peripheral and/or peribronchial consolidation tends to be triangular or polygonal in shape. The accelerated form tends to have an AIP-like appearance

Herraez I. Hypersensitivity pneumonitis producing a BOOP-like reaction: HRCT/pathologic correlation. J Thorac Imaging 2002, 17: 81

Remy-Jardin M. Computed tomography assessment of ground-glass opacity: semiology and significance. J Thorac Imaging 1993, 8: 249

COURSE and COMPLICATIONS

Associated diseases

About one quarter of patients with HP have non-specific bronchial hyperreactivity to methacholine

Clinical course

If the patient avoids exposure to the antigen, single acute episodes may resolve spontaneously within days. The pulmonary function tests and radiological alterations return to normal within weeks: only D_LCO takes longer to normalize. The disease may recur with re-exposure. If areas of fibrosis, or honeycombing at HRCT, develop, the disease may become irreversible

✓ "Bird fancier's lung" has a worse prognosis than "Farmer's lung"

Radiological course

If exposure continues, the disease progresses to the subacute form (● HP, subacute) and may eventually become chronic (□ HP, chronic)

LABORATORY FINDINGS

The presence of serum precipitating antibodies against the offending antigen is a characteristic feature. There may also be a slight increase in inflammatory indices (ESR and C-reactive protein - CRP), as well as a significant increase in quantitative immunoglobulins which return to normal once the acute phase is over. Some patients may also test positive for rheumatoid factor and circulating immune complexes

CLINICAL DIAGNOSIS

The disease is diagnosed on the basis of a history of exposure to an offending antigen with onset of compatible clinical, radiographical or physiological findings within 4-12 hours. Other diagnostic criteria include clinical improvement after removal from exposure and recurrence on re-exposure. There is little agreement regarding the usefulness of inhalation challenge to the offending antigen

INVASIVE DIAGNOSIS

In cases where the inciting antigen cannot be identified or in the presence of conflicting clinical, radiological and functional findings, fiberoptic bronchoscopy with BAL and transbronchial lung biopsy are indicated. Surgical lung biopsy is only required if these prove inconclusive

Bronchoalveolar lavage

If performed within 2-3 days of the most recent exposure, BAL may reveal an aspecific finding with a predominance of neutrophils. On the other hand, BAL performed after a greater time interval from the most recent exposure to the inciting antigen is characterized by a marked increase in total cell count with a predominance of lymphocytes (often > 50%) and the presence of foamy macrophages and mastocytes (> 1%). The lymphocytes are predominantly CD3+ (T cells) and CD8+ (cytotoxic suppressors). The CD4+/CD8+ ratio is usually decreased to less than 1.0

Similar patterns (CD8+ lymphocytic alveolitis, foamy macrophages, and mastocytes) may also be seen in drug-induced lung disease (⌘ Drug toxicity), in OP (⌘ OP), and in NSIP (☐ NSIP)

Costabel U. Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med 2001, 7: 255

Drent M. Bronchoalveolar lavage in extrinsic allergic alveolitis: effect of time elapsed since antigen exposure. Eur Respir J 1993, 6: 1276

Atypical mycobacteriosis

Definition

Pulmonary infections characterized by endobronchial spread may be caused by a variety of pathogens, including mycobacteria other than Mycobacterium (M.) tuberculosis, commonly referred to as non-tuberculous mycobacteria (NTM). This chapter will cover these forms. The radiological hallmark of endobronchial spread is known as the tree-in-bud pattern (see the table entitled "Diseases with radiological tree-in-bud pattern" at the end of the chapter)

DEMOGRAPHICS

Etiology and pathogenesis

The main causative agents are M. avium-intracellulare, M. Kansasii, M. fortuitum, and M. chelonei, traditionally classified into 4 groups based on pigment production and growth rate: photochromogens, scotochromogens, nonchromogens and fast-growers. These mycobacteria are ubiquitous and infection generally occurs through environmental contamination rather than human-to-human transmission

Epidemiology

A North-American surveillance study from the pre-AIDS era (early 1980s) reported that 65% of mycobacterial isolates were M. tuberculosis, 21% were M. avium-intracellulare (MAI) (nonphotochromogen), 6.5% M. fortuitum and M. chelonei (fast-growing), 3.5% M. Kansasii (photochromogen) and 2.3% M. scrofulaceum (scotochromogen). The overall incidence of NTM disease was 1.78 cases per 100,000 with variations due to geographical differences in the mycobacterial habitats

The advent of AIDS has brought about an increase in the incidence of M. avium-intracellulare infection. Atypical mycobacteriosis is more common in white males over 50 years of age, and rare in children

Risk factors

Immunodepressed states such as AIDS or conditions such as alcoholism, rheumatoid arthritis, gastric resection, organ transplant and diabetes mellitus facilitate infection by atypical mycobacteria. Most patients have co-existing lung diseases such as chronic obstructive bronchitis, bronchiectasis, cystic fibrosis, lung cancer, silicosis, lipoid pneumonia, or a history of tuberculosis

A form of diffuse interstitial granulomatous pneumonia has been described in immunocompetent subjects who had inhaled aerosolized water contaminated with MAI (hot tub lung). These cases exhibit small granulomas with or without necrosis that involve the bronchiolar wall and at times the lumen

Khoor A. Diffuse pulmonary disease caused by nontuberculous mycobacteria in immunocompetent people (hot tub lung). Am J Clin Pathol 2001, 115: 755

CLINICAL FEATURES

History

The clinical pulmonary manifestations are those of tuberculosis (TB). Immunocompetent subjects with atypical mycobacteriosis due to MAI present with cough, low-grade fever, malaise and, at times, hemoptysis. Systemic symptoms are rare in immunocompetent individuals but frequent in HIV+ subjects, in whom pulmonary involvement is, however, rare

Physical findings

The physical examination is often unremarkable. Bronchiolar crackles may occasionally be heard

Pulmonary function tests

Mycobacterial infections predominantly affect the upper lobes. Because these have limited functional importance, lung function impairment tends to be mild, and possible alterations should therefore be ascribed to the underlying disease

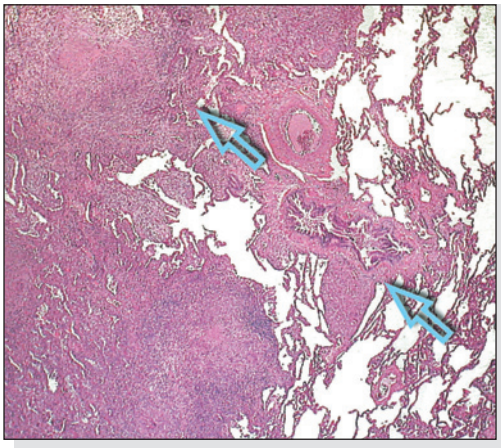
Griffith DE. Nontuberculous mycobacteria. Curr Opin Pulm Med 1997, 3: 139

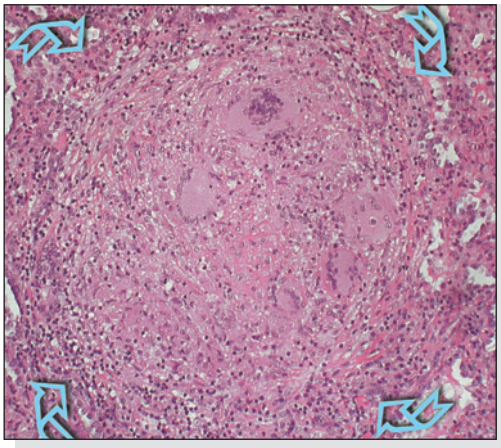
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Epithelioid necrotizing granulomas (↳) with Langhans' type giant cells, distributed along the airways (⇨)(bronchi, bronchioles, and alveolar ducts). The caseating necrosis is less extensive in atypical mycobacteriosis compared to the typical form
- In AIDS patients, well-formed granulomas are often absent and the infiltrate consists of foamy macrophages with cytoplasm filled with numerous mycobacteria





Distribution

Along the airways

✓

It is almost impossible to distinguish between tuberculous and non-tuberculous mycobacteria on the basis of morphology alone: the differential diagnosis requires special stains (PAS), and cultures or molecular biology assays

Differentials

Histopathologic differential diagnoses:

- Sarcoidosis: small non-necrotizing granulomas. The search for mycobacteria by any method, is negative
- Fungal infections: presence of mycetes
- Wegener's granulomatosis (endobronchial): necrosis is patchy ("geographic") and "blue" as it is rich in neutrophilic debris. The infiltrate is more intense and granulomas are not associated with marked fibrosis
- HP: poorly-formed granulomas associated with intense interstitial lymphoplasmacellular infiltrate. Presence of giant cells containing needle-shaped clefts, and absence of necrosis

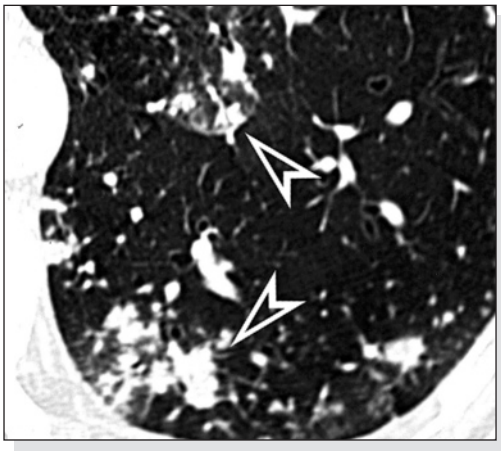
Fujita J. Pathological and radiological changes in resected lung specimens in Mycobacterium avium intracellulare complex disease. Eur Respir J 1999, 13: 535

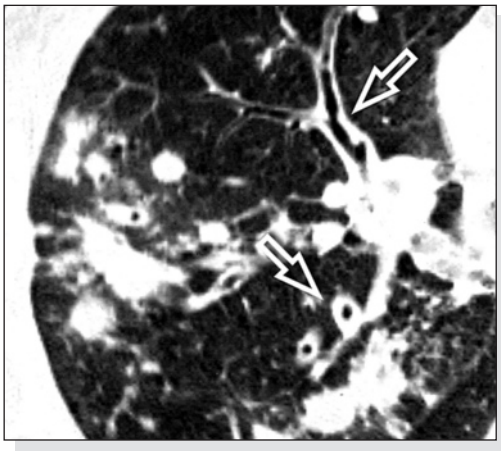
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Mycobacteriosis, classic form (70% of cases):

- Poorly-defined centrilobular nodules, often clustered into "rosettes" (➢)
- Branching opacities with tree-in-bud appearance
- Bronchial wall thickening (⇨) with or without bronchiectasis
- Multiple areas of consolidation of acinar or lobular size; cavitation is common





In addition to the classic presentation (70%), which strongly resembles that of tuberculosis with endobronchial spread, there is another less frequent presentation (non-classic, 30%) typical of elderly women (80%) and characterized by bronchiectasis and bronchiolectasis, centrilobular nodules and patchy mosaic hypoperfusion (Lady Windermere syndrome). More rarely, mycobacterial infection may give rise to pneumonia-like areas of consolidation or centrilobular nodular ground-glass opacities due to the extrinsic allergic alveolitis produced by the mycobacterial infection

Erasmus JJ. Pulmonary nontuberculous mycobacterial infection: radiologic manifestations. Radiographics 1999, 19: 1487

Reich JM. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest 1992, 101: 1605

Distribution

Unilateral or bilateral, patchy

Variable but more prominent in the peripheral areas and usually showing a clear connection with the bronchi

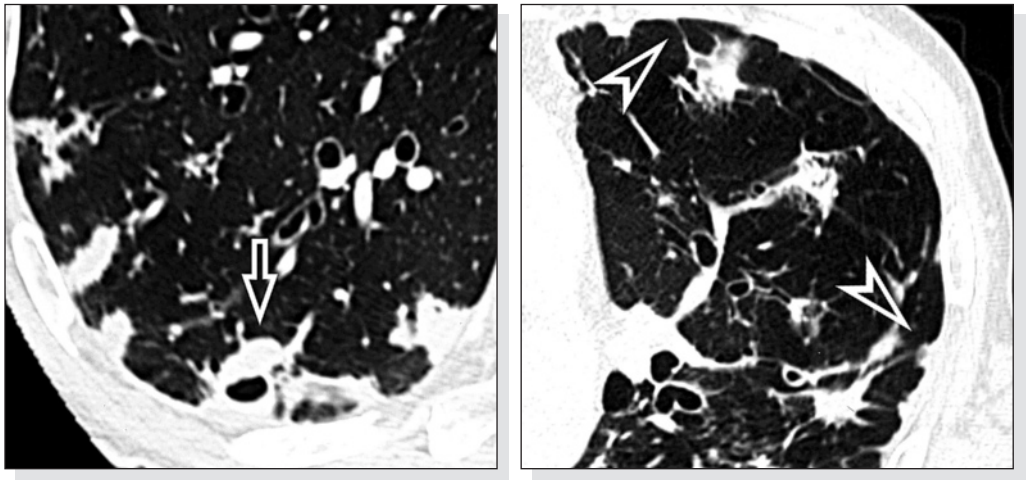
In the classic form, decreasing craniocaudal severity of lesions originating from an apical focus; in non classic forms, predominance of lesions in the middle lobe and lingula

Overall lung volume is preserved, although retraction in correspondence with the areas of consolidation is common

Other signs

Other possible radiological manifestations:

- Cavitating consolidations (⇨), particularly in the dorsal regions as in post-primary TB
- Retraction along the pleural borders adjacent to the areas of consolidation (≻)
- Pleural effusion associated with mediastinal and hilar adenopathy (rare)
- Superimposed hematogenous miliary form



Levin DL. Radiology of pulmonary Mycobacterium avium-intracellulare complex. Clin Chest Med 2002, 23: 603

Miller WT Jr. Spectrum of pulmonary nontuberculous mycobacterial infection. Radiology 1994, 191: 343

Differentials

The radiological differential diagnoses include:

- Diseases producing a tree-in-bud pattern (see the table at the end of this chapter)
- Mycosis: uncommon in immunocompetent individuals; in immunodepressed subjects the invasive forms show nodules or cavitating masses frequently associated with a perilesional halo sign
- Branching micrometastases within the vessels (beaded vessel sign)

Goo JM. CT of tuberculosis and nontuberculous mycobacterial infections. Radiol Clin North Am 2002, 40: 73

Worthy SA. Small airway diseases. Radiol Clin North Am 1998, 36: 163

COURSE and COMPLICATIONS

Associated diseases

Obstructive chronic bronchitis, bronchiectasis, cystic fibrosis, history of tuberculosis, lung cancer, silicosis, lipoid pneumonia

Clinical course

If left untreated, NTM infections follow a variable course depending on the underlying lung disease. Even after healing of the parenchymal lesions, an active bronchial infection may persist, which becomes a constant source of infection. The advent of new treatments relying on macrolides and rifabutin has markedly improved the prognosis of these patients

Radiological course

If the disease regresses, the opacities will disappear progressively. If it progresses, the bronchiectasis, which are generally more pronounced than in TB, tend to worsen, above all in the forms due to MAI infection

LABORATORY FINDINGS

Sputum microbiology and culture can identify the colonizing or pathogenic mycobacterium. The culture, staining and detection techniques used for atypical mycobacteria are very similar to those used for tuberculosis. The advent of genetic probes will enable a faster and more specific diagnosis, whereas laboratory tests are not specific

CLINICAL DIAGNOSIS

In immunocompetent individuals, the diagnosis is based on radiological criteria (cavitating lung disease in the absence of other identifiable causes and/or tree-in-bud pattern) and microbiological findings (detection of the mycobacterium in at least 3 sputum samples). The differential diagnosis mainly includes the other forms of infectious necrotizing granulomatosis, such as tuberculosis and fungal infections

☝ Isolation of the microorganism (even on repeated occasions) in the absence of pulmonary cavitations indicates colonization rather than infection. These patients should not be treated but instead, closely monitored

INVASIVE DIAGNOSIS

Transbronchial lung biopsy can provide material for the direct detection of the microbic agent or for microbiological culture. Surgical lung biopsy to confirm the diagnosis is rarely required

Bronchoalveolar lavage

BAL may be used in the event that sputum is unavailable. The search for atypical mycobacteria in the BAL fluid must be carried out with extreme care (in particular for M. avium-intracellulare) as often the germs are only present inside the alveolar macrophages. These may have a Gaucher-like appearance due to the massive number of germs distending their cytoplasm

DISEASES WITH TREE-IN-BUD PATTERN

The radiological pattern known as tree-in-bud may be found in different diseases characterized by the presence of distended centrilobular bronchioles with a mucous- or pus-filled lumen and often inflammation of the peribronchiolar airspaces. These include:

- TB with endobronchial spread
- Atypical mycobacteriosis
- Infectious bronchopneumonia and bronchiolitis
- CF
- Bronchiectasis of any cause
- Asian panbronchiolitis
- Allergic bronchopulmonary aspergillosis (ABPA)
- BAC

Mucosa-Associated Lymphatic Tissue lymphoma

Definition

Mucosa-associated lymphatic tissue lymphoma (MALToma) is an extranodal pulmonary B-cell lymphoma with a low grade of malignancy. The cells arise from the marginal zone (centrocyte-like cells) of the normal or hyperplastic bronchus-associated lymphoid tissue (BALT)

MALT lymphoma, BALT lymphoma, marginal zone B-cell lymphoma

These tumors express CD19, 20, 22 and 79a, are negative for CD5, CD 23 and CD10 and do not present bcl-1 and bcl-2 gene rearrangements

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis of the disease are unknown. It is thought, however, that certain stimuli (cigarette smoking, infections, asbestos exposure, various collagen vascular diseases) are capable of provoking BALT hyperplasia with subsequent malignant transformation

In contrast to other pulmonary lymphomas, no association with Epstein-Barr virus has been described for MALToma

Epidemiology

MALToma primarily affects adults in their fifth decade of life, without gender predilection. It is the most common primary pulmonary lymphoma (60-80%)

Risk factors

Collagen vascular diseases such as RA, Sjögren's syndrome and SLE. Hepatitis C virus infection

CLINICAL FEATURES

History

Half of the patients are asymptomatic. When present, the most common symptoms are cough and dyspnea, whereas pleural pain and hemoptysis are rare. Systemic symptoms such as fever, night sweats or weight loss are encountered in 20-40% of cases

Physical findings

In the presence of a large lymphomatous mass, physical examination may reveal lung consolidation. Pleural effusion is uncommon (10%)

Pulmonary function tests

Most patients have normal lung function tests, although a restrictive or obstructive defect may be present

The presence of systemic symptoms is indicative of extrapulmonary involvement, in which case the prognosis is worse (5 year survival rate of 55%)

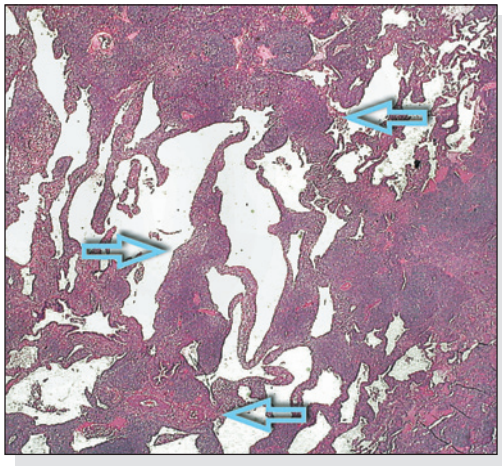
Koss MN. Pulmonary lymphoid disorders. Semin Diagn Pathol 1995, 12: 158

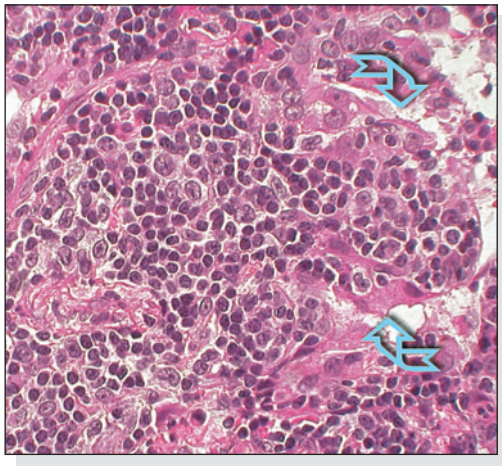
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Dense and monotonous lymphoid infiltrate, forming cuffs or micronodules along the lymphatic vessels (⇨)
- Lymphoepithelial complexes of neoplastic lymphocytes within the bronchial and bronchiolar epithelium (↳)





The neoplastic population is composed of different cell types in varying proportions: 1. small lymphocytes with round nuclei; 2. "monocytoid" lymphocytes with slightly larger and more irregular nuclei and abundant, pale cytoplasm; 3. lymphocytes with plasmocytoid appearance and plasma cells; 4. occasional large "transformed" lymphocytes, with round vesicular nucleolated nuclei and abundant cytoplasm. This pattern is often associated with a non-neoplastic (polyclonal) reactive lymphoplasmacellular infiltrate and, in 70% of cases, with numerous germinal centers. Amyloid deposits, bands of dense fibrosis and granulomas may also be present. Although non-specific, lymphoepithelial complexes are a characteristic feature of MALT lymphomas. Infiltration of the pleura and bronchial cartilage is rare but, when present, is strongly suggestive of lymphoma

Many cases now interpreted as MALT lymphomas were previously classified as pseudolymphomas or LIP (● LIP) depending on whether the lesions were localized or diffuse

Distribution

Along the lymphatics. In macronodular lesions, lung architecture is effaced in the center of the nodule and lymphatic distribution can therefore only be identified at the periphery

Differentials

Histopathologic differential diagnoses:

- LIP, diffuse lymphoid hyperplasia, pseudolymphoma: the lymphocyte population is heterogeneous and polyclonal. Absence of dense monotypic lymphocytic infiltrate around the germinal centers and in the septa, which is typical of lymphomas. Infiltration of the pleura and the bronchial cartilage is rare, as is the presence of lymphoepithelial complexes
- Chronic lymphocitic leukemia: although neoplastic infiltrates which are histologically indistinguishable from those of MALToma, may be present along the lymphatics lymphoepithelial complexes rare

Begueret H. Primary lung small B-cell lymphoma versus lymphoid hyperplasia: evaluation of diagnostic criteria in 26 cases. Am J Surg Pathol 2002, 26: 76

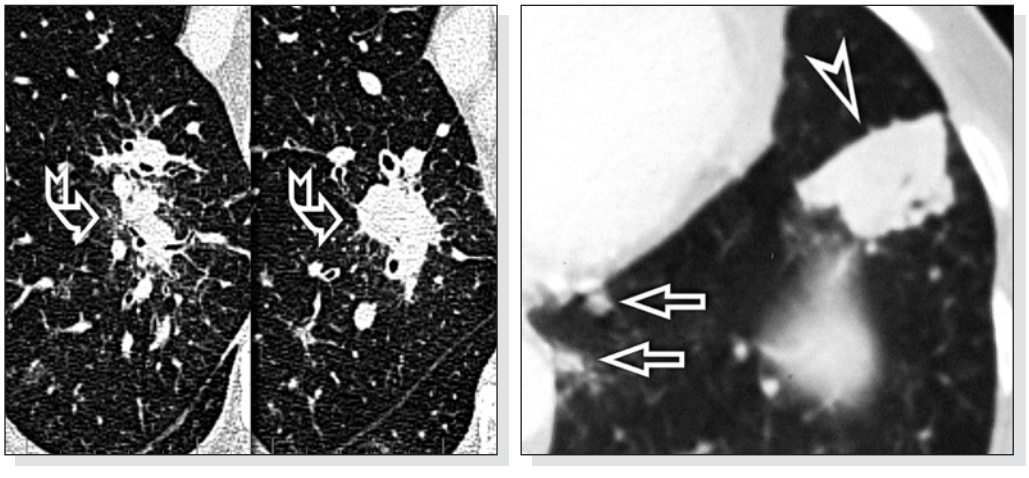
Kurtin PJ. Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. Am J Surg Pathol 2001, 25: 997

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (60%) with air bronchogram (↳)(50-90%); the bronchi appear stretched and narrowed
- Masses with variable diameter up to several centimeters (➢)
- Nodules with hazy margins (⇨) due to airspace filling (60%)



The above HRCT signs are frequently seen in combination

Distribution

Frequently bilateral (60%), but also unilateral, diffuse, or patchy with involvement of extensive areas (80%)

Tendency towards peribronchial distribution

Variable

Lung volume is normal

Kinsely BL. Pulmonary mucosa-associated lymphoid tissue lymphoma: CT and pathologic findings. AJR Am J Roentgenol 1999, 172: 1321

Lee DK. B-cell lymphoma of bronchus-associated lymphoid tissue (BALT): CT features in 10 patients. J Comput Assist Tomogr 2000, 24: 30

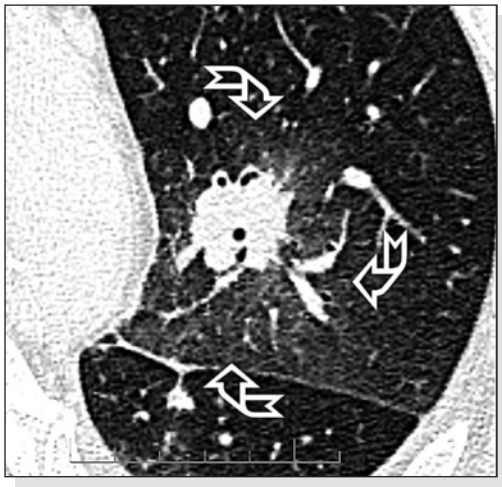
Other signs

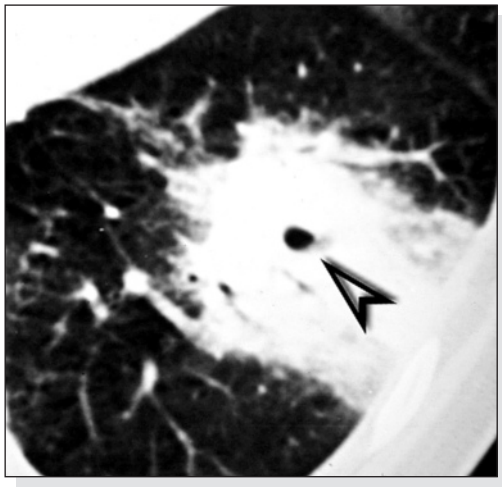
Common:

- Perinodular halo sign (↳)
- Air alveologram and small cysts (⩾) within the consolidation (due to bronchiolar dilatation)
- Angiogram sign after contrast material administration
- Bronchial wall thickening, luminal stenosis or signs of fibrosis with bronchiectasis (50%)

Uncommon:

- Pleural effusion (10-25%) generally associated with the parenchymal lesions
- Hilar and mediastinal adenopathy (10%)
- Lymphangitis-like septal thickening





King LJ. Pulmonary MALT lymphoma: imaging findings in 24 cases. Eur Radiol 2000, 10: 1932

Rodallec M. Imaging of MALT lymphomas. Eur Radiol 2002, 12: 348

Differentials

Radiological differential diagnoses:

- OP: the consolidations are basal and peripheral, at times migratory, and respond readily to steroid treatment
- BAC: the differential diagnosis is histological; however, the form with endobronchial spread tends to progress more rapidly
- Metastases: consolidation is present in a limited number of cases (hemorrhagic metastases, or metastases from angiosarcoma or choriocarcinoma)
- Angioinvasive mycosis: associated nodules or masses with a tendency to cavitate
- Lymphomatoid granulomatosis: nodules or masses without air bronchogram and with a tendency to coalesce; consolidation is rare

COURSE and COMPLICATIONS

Associated diseases

Pleural effusion (10%), lymphadenopathy (5%). In some subjects, the disease may manifest with signs and symptoms in other regions, such as the upper respiratory tract or the stomach (33%). The signs of lung involvement may appear later. Besides the above-mentioned elements, an association with LCH and sarcoidosis has been described in a small number of instances

Clinical course

If appropriately treated, patients with low-grade pulmonary B-cell lymphoma have a good prognosis (84% survival at 5 years). Progression of the disease into a high-grade lymphoma is rare

Radiological course

Progression of the lesions is very slow: they can initially appear months, or even years, before diagnosis

LABORATORY FINDINGS

If plasmcytoid differentiation develops, monoclonal gammopathy, usually IgM, may be detected in the peripheral blood. Free light chains may be detected in the urine, including Bence-Jones protein. The leucocyte count is generally normal, although lymphocytosis can be detected in a small number of cases. In the case of pleural effusion, the exudate will contain predominantly B lymphocytes

CLINICAL DIAGNOSIS

Normally, diagnosis neccesitates invasive techniques

INVASIVE DIAGNOSIS

Diagnosis can be based on histologic-immunohistochemical analysis of pulmonary tissue obtained by transbronchial biopsy or surgery, or, more rarely, based upon typification of lymphocytes in the BAL or pleural fluid

Bronchoalveolar lavage

The BAL results are pathognomonic where cytofluorometry demonstrates an increase in the B lymphocyte population (>5%) with monoclonal aspects (k or λ light chains). In this case, use of the polymerase chain reaction (PCR), can allow analysis of the gene re-arrangement of the tumor cells

Betsuyaku T. Establishing diagnosis of pulmonary malignant lymphoma by gene rearrangement analysis of lymphocytes in bronchoalveolar lavage fluid. Am J Respir Crit Care Med 1994, 149: 526

Cryptogenic Organizing Pneumonia (COP)

Definition

Cryptogenic organizing pneumonia (COP) is a disease entity classified among the idiopathic interstitial pneumonias, which presents clinically with pneumonia-like features

Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

The general term idiopathic interstitial pneumonias (IIP) include various diseases, in particular, usual interstitial pneumonia (□ UIP, early; ○ UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

An identical histological and radiological pattern (BOOP-reaction pattern) may be seen in a number of diseases where the lung responds non-specifically to different noxae (see the table entitled "BOOP-reaction pattern" at the end of this chapter)

Katzenstein AL. Katzenstein and Askin's surgical pathology of non-neoplastic lung disease. WB Saunders, 1997

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis of idiopathic COP is unknown. The disease is thought to result from alveolar epithelium injury due to an unknown cause, capable of triggering angiogenesis and exaggerated reparative response by the fibroblasts

Epidemiology

Mean age at onset varies from 50 to 60 years. The two sexes are equally affected, with a prevalence in non-smokers (2:1). The incidence of COP on hospital admissions is 6-7 per 100,000

Risk factors

There are no known specific risk factors

CLINICAL FEATURES

History

At the time of diagnosis, 75% of patients report symptoms of less than 2 months duration. The most common presentation is that of a community-acquired pneumonia, at times preceded by a flu-like illness. The most frequent symptoms are cough and dyspnea upon exertion at times associated with mucous production. Systemic symptoms are also frequent and include weight loss (57%), chills, sweats, intermittent fever and myalgia

Physical findings

Localized or diffuse fine rales are noted in 74% of patients. Digital clubbing is absent

Pulmonary function tests

The most common findings are a restrictive ventilatory defect (mild to moderate) and reduced D_LCO. An obstructive ventilatory defect is present in a minority of patients (20%), usually smokers. More than 80% of affected individuals have mild resting hypoxemia

The main clinical differential diagnoses are infectious pneumonia and CEP (⌘ CEP)

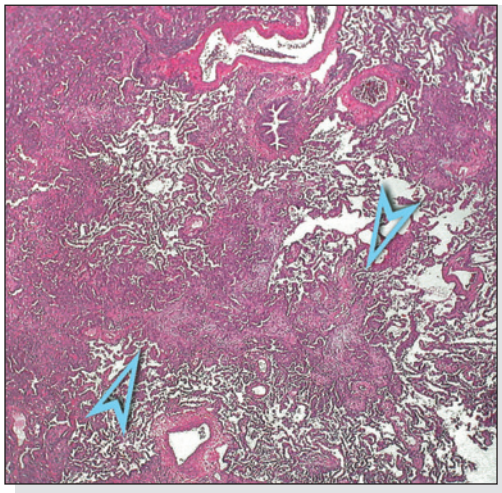
Nagai S. Bronchiolitis obliterans with organizing pneumonia. Curr Opin Pulm Med 1996, 2: 419

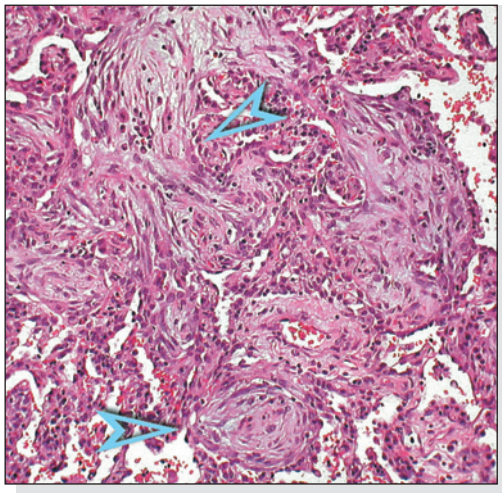
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- "Polyps" of loose connective tissue (≥) within the terminal or respiratory bronchioles (bronchiolitis obliterans, BO), in the alveolar ducts and surrounding alveoli (organizing pneumonia, OP)
- The alveolar septa are often distended by a more-or-less intense chronic inflammatory infiltrate of lymphocytes, histiocytes and plasma cells, and are sometimes lined by hyperplastic type II pneumocytes
- Intense infiltrate of foamy macrophages and other changes typical of obstructive pneumonia





Because the bronchiolar component may be lacking, there is a tendency to replace the acronym BOOP with OP. However, the term BOOP remains commonly used

The disease process involves multiple temporally uniform foci (the connective tissue is young and at the same stage of maturation throughout). Lung architecture is preserved

On hematoxylin-and-eosin stain, the "polyps" appear as pale serpiginous plugs reproducing the shape of the airways in which they form. These plugs consist of fibroblasts arranged parallel to one another and immersed in a mucopolysaccharide-rich matrix containing inflammatory cells

As the disease progresses the "polyps" become covered by bronchiolar or alveolar epithelium and incorporated within the septa, resulting in the healing of the lesions

Distribution

Bronchiolar and peribronchiolar

Differentials

Histopathologic differential diagnoses:

- Infections: suppurative or granulomatous inflammation, presence of necrosis. Identification of the infectious agent
- Obstructive pneumonia: predominance of foamy macrophages in the inflammatory infiltrate
- Organizing DAD: the process is diffuse rather than patchy, the fibrosis is interstitial with uniformly distended and edematous septa. The septal infiltrate is less intense and hyperplasia of type II pneumocytes is more pronounced. In addition, a bronchiolar component is absent
- Wegener's granulomatosis (BOOP-like variant): vasculitis and necrosis with an infiltrate often rich in eosinophils are present
- HP: poorly-formed granulomas, very intense inflammatory infiltrate
- CEP: intense eosinophilic infiltrate in the interstitium and alveoli
- UIP: subpleural fibrosis with fibroblastic foci at the edges of the fibrotic areas; temporal heterogeneity and remodeling with honeycombing. There is no bronchiolar involvement

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

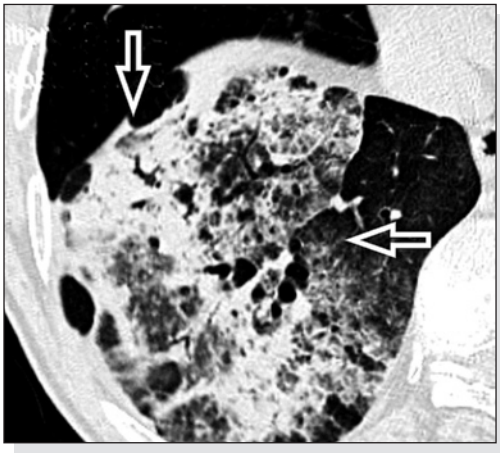
Colby TV. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. Chest 1992, 102: 38S

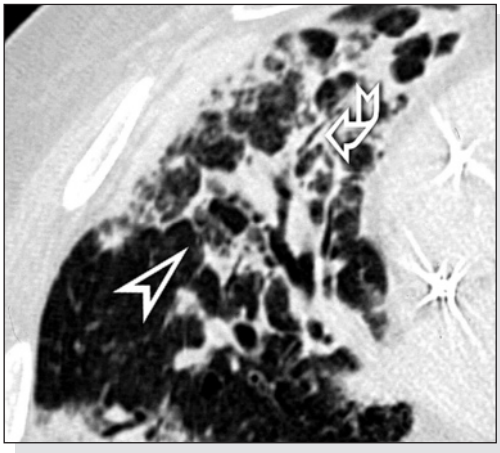
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Patchy areas of consolidation (⇨), often triangular (➢) or polygonal in shape, with hazy borders (80%)
- Ground-glass opacities with patchy (60%) or perilobular distribution (↳)
- Air bronchogram within the areas of consolidation, at times mild bronchiectasis





The ground-glass pattern is the dominant feature in immunodepressed subjects, and may be associated with the presence of inflammatory nodules

Johkoh T. Perilobular pulmonary opacities: high-resolution CT findings and pathologic correlation. J Thorac Imaging 1999, 14: 172

Muller NL. Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 1990, 154: 983

Distribution

Usually bilateral (although unilateral is also possible), characteristically patchy

Peripheral subpleural, although also peribronchial

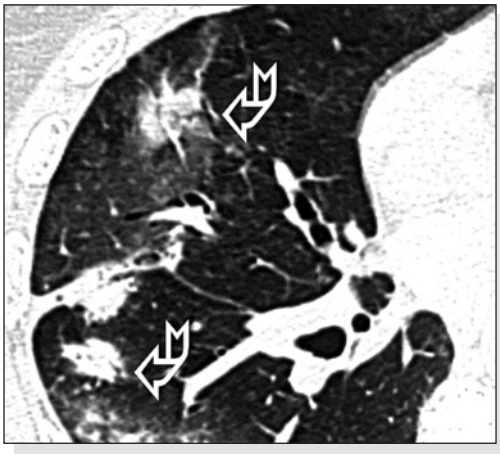
Prevalently basal

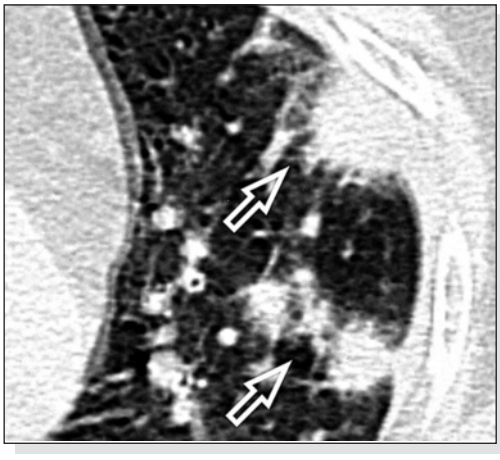
Lung volume is normal

Other signs

Other radiological signs:

- Centrilobular, often peribronchial (↳)(50%), nodules with ill-defined borders
- Bronchial wall thickening and cylindrical bronchiectasis within the areas of consolidation
- One or more large nodules or masses (⇨)(● Large rounded opacities: Organising Pneumonia)
- Moderate pleural effusion





Lee KS. Cryptogenic organizing pneumonia: CT findings in 43 patients. AJR Am J Roentgenol 1994, 162: 543

Differentials

The differential diagnoses of the typical pattern (patchy consolidation and ground-glass attenuation) include:

- Slow-resolving bacterial infections: clinical history and regression of the opacities at follow-up are the key to the diagnosis
- BAC: the radiological pattern may be similar
- TB: the differential diagnosis is based on bronchological studies especially in elderly, diabetic, debilitated or mildly immunodepressed patients
- Sarcoidosis: associated subpleural nodules, hilar and mediastinal adenopathy
- CEP: consolidation predominates in the upper lung fields and has strictly subpleural distribution

In contrast, the differential diagnosis of the pattern seen in immunodepressed patients (ground-glass opacities and nodules) includes:

- Opportunistic infections: the differential diagnosis is based on the biopsy

Arakawa H. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. AJR Am J Roentgenol 2001, 176: 1053

Johkoh T. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999, 211: 555

COURSE and COMPLICATIONS

Associated diseases

The various diseases that result in the development of a BOOP-like pattern (see the table "BOOP-reaction pattern" at the end of this chapter)

Clinical course

Two thirds of subjects treated with corticosteroids make a full recovery: most patients recover within several weeks or months and some respond dramatically with improvements appearing even within 1 or 2 weeks. Only a minority of patients, however, experience spontaneous remission and about half of those treated relapse when treatment is reduced or discontinued

One third of patients have persistent disease which rarely, however, progresses to respiratory failure or death. On the other hand, rare hyperacute forms are possible which rapidly lead to death (accelerated BOOP)

Radiological course

The opacities may resolve spontaneously and then form elsewhere, usually more cranially and at times in the contralateral lung (migratory opacities). Left untreated, the disease may progress to permanent damage with fibrosis and bronchiectasis

LABORATORY FINDINGS

Common findings include elevated ESR, often more than 100 mm in one hour (70-80%), and raised CRP. Leukocytosis is present in 50% of cases. Autoantibodies are usually absent or the titer is low

CLINICAL DIAGNOSIS

A definitive diagnosis cannot be made on the basis of the clinical features alone. The HRCT findings will enable the correct diagnosis to be included among the first three in 50% of cases and, in the appropriate clinical setting, can provide the diagnosis in 80% of cases

BOOP-pattern should be considered in patients with areas of parenchymal consolidation labeled as pneumonia, which persist or migrate after antibiotic therapy

INVASIVE DIAGNOSIS

In the presence of a characteristic clinical-radiological setting, transbronchial lung biopsy alone may be sufficient for histological confirmation, with BAL providing further support for the diagnosis. The diagnosis of COP is, however, a diagnosis of exclusion made only after ruling out all the other conditions characterized by a BOOP-reaction pattern

If biopsy is needed, it should be performed under radiological guidance since the areas of consolidation may rapidly migrate from one zone to another within the lungs

Bronchoalveolar lavage

The BAL fluid is characterized by elevated total cell count, with a reduction in the percentage of macrophages and an increase in lymphocytes (>40%), neutrophils and eosinophils (mixed alveolitis pattern). The CD4/CD8 ratio is reduced. Foamy macrophages are typically present and mast cells and plasma cells are increased

A mixed alveolitis pattern (increased CD8+ lymphocytes, neutrophils and at times eosinophils) is not specific to COP, and may also be observed in HP (⌘ HP, acute), NSIP (☐ NSIP) and drug-induced lung disease (⌘ Drug toxicity)

Costabel U. Bronchiolitis obliterans organizing pneumonia (BOOP): the cytological and immunocytological profile of bronchoalveolar lavage. Eur Respir J 1992, 5: 791

Pesci A. Mast cells in bronchiolitis obliterans organizing pneumonia. Mast cell hyperplasia and evidence for extracellular release of tryptase. Chest 1996, 110: 383

TABLE

On the following page is a table providing further information on the:

- BOOP-reaction pattern

BOOP-REACTION PATTERN

The histological pattern known as "BOOP-reaction pattern" occurs when the lung responds non-specifically to different noxae. As a result, it is seen in varying extents and severity in a number of diseases

BOOP as a disease:	• COP • RA • Toxic respiratory agents • Drugs and medications • Other collagen vascular diseases • Viral and bacterial infections • Radiotherapy
BOOP as an associated reaction in the course of:	• Malignancies • Infectious granulomas • Vasculitides • Pulmonary infarction
BOOP as a minor reaction accompanying:	• HP • NSIP • LCH • Allogeneic bone marrow transplant • Lung transplant

Pulmonary Alveolar Proteinosis

Definition

Pulmonary alveolar proteinosis (PAP) is a chronic disease of unknown etiology characterized by the accumulation of amorphous PAS-positive lipoproteinaceous material in the alveoli

DEMOGRAPHICS

Etiology and pathogenesis

The etiology of the disease is unknown, although similar histopathologic findings have been reported in acute silicosis, exposure to dusts containing aluminium, titanium or silicon, Pneumocystis carinii (jiroveci) infection, hematologic malignancies and immunosuppressive disorders. The pathogenesis of the disease is related to changes in the production or degradation of surfactant resulting from altered macrophage function and/or diminished production or inhibition (neutralizing antibodies) of the cytokine granulocyte-macrophage colony stimulating factor (GM-CSF)

Epidemiology

The disease is rare and its incidence is unknown. It primarily affects subjects aged 20 to 50 years, with a predominance of males (2:1), without racial or geographic predilection

Risk factors

Exposure to mineral dusts and cigarette smoking

CLINICAL FEATURES

History

Approximately one third of patients are asymptomatic. The main symptoms at onset are progressive exertional dyspnea, and less frequently productive cough with expectoration of gelatinous material, low-grade fever, fatigue, hemoptysis, chest pain and weight loss

Physical findings

Breath sounds are often normal, although fine rales may be heard in about 50% of patients. Digital clubbing is rare, as is cyanosis

Pulmonary function tests

The most common physiologic alteration is a restrictive ventilatory defect associated with a reduction in D_LCO. Hypoxemia at rest is present in only one third of patients, whereas oxygen desaturation with exercise is seen in over half

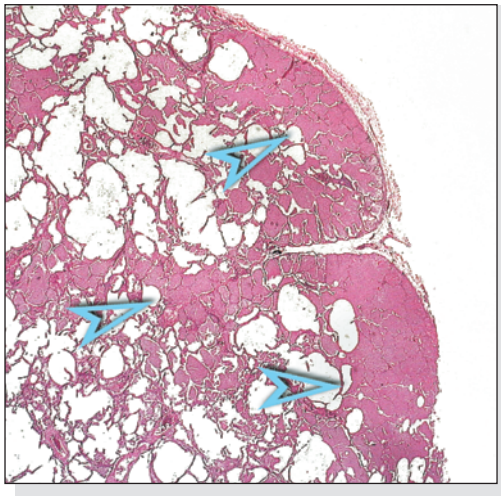
Shah PL. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax 2000, 55: 67

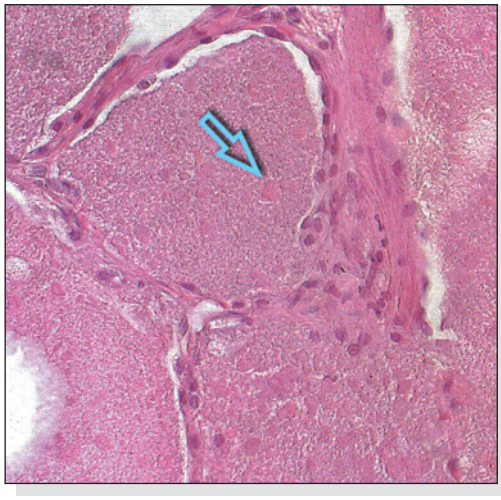
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Alveolar spaces filled with granular eosinophilic PAS-positive material (➢) containing needle-like cholesterol clefts, eosinophilic globules (⇨), scattered macrophages, and cellular debris
- Minimal interstitial involvement consisting of slight septal thickening





Distribution

Diffuse in the alveolar spaces, sometimes extending to the bronchi and alveolar ducts

The lesions are more numerous in the peripheral and subpleural regions, but may also affect the peribronchial airspaces. These features often make it possible to diagnose the disease with transbronchial biopsy

In alveolar proteinosis secondary to infection and in long-standing disease, marked interstitial alterations may be seen, which are due to intense inflammatory infiltrate and septal fibrosis, respectively

Differentials

Histopathologic differential diagnoses:

- PE: the material is neither granular, nor PAS-positive; macrophages and cholesterol clefts are lacking
- Infections: demonstration of the infectious agent in PCP
- DAD: in the exudative phase, presence of fibrin in the form of hyaline membranes associated with hyperplasia of type II pneumocytes; in the proliferative phase, foci of fibroblastic organization

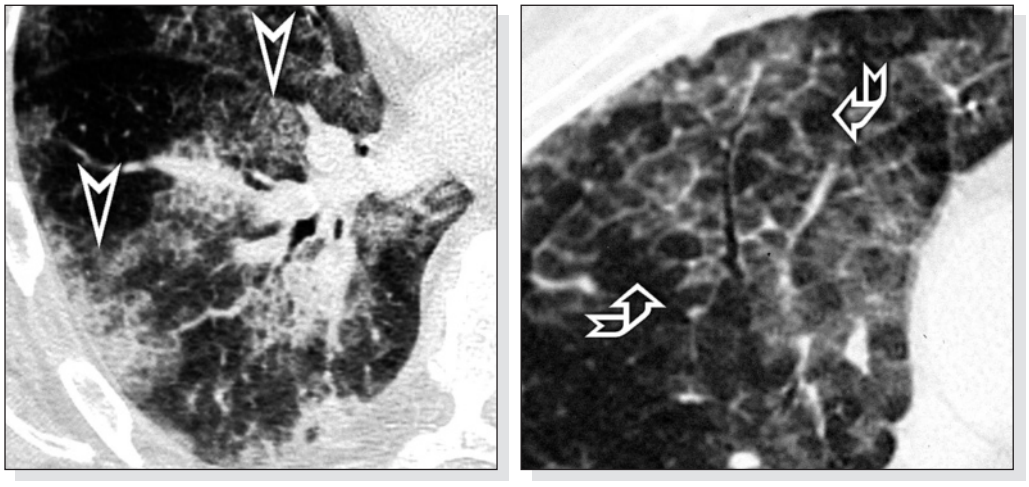
Seymour JF. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002, 166: 215

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Ground-glass opacities (≥)
- Patchy ground-glass opacities associated with smooth septal thickening (↳)(crazy paving)



Reticular septal thickening is exclusively seen within the areas of ground-glass attenuation

Holbert JM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 2001, 176: 1287

Murch CR. Computed tomography appearances of pulmonary alveolar proteinosis. Clin Radiol 1989, 40: 240

Distribution

Bilateral, patchy and sharply demarcated from normal lobules or groups of lobules

Variable, without clear predilections

Variable

Lung volume is normal

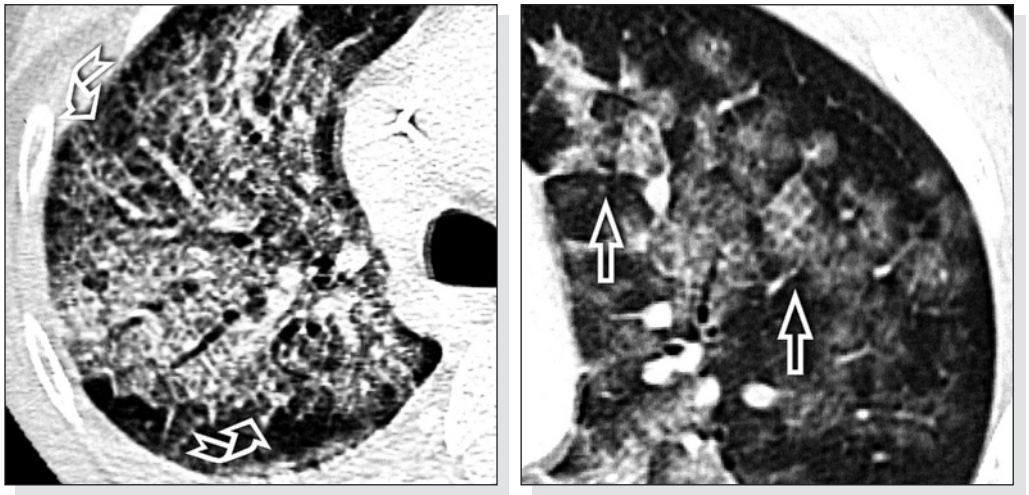
Lee KN. Pulmonary alveolar proteinosis: high-resolution CT, chest radiographic, and functional correlations. Chest 1997, 111: 989

Wang BM. Diagnosing pulmonary alveolar proteinosis. A review and an update. Chest 1997, 111: 460

Other signs

Other radiological signs:

- Diffuse (↳) or focal (⇨) areas of parenchymal consolidation



Parenchymal consolidation may be caused both by the underlying disease and by supervening opportunistic infection. The latter is suspected when the consolidation is focal

Godwin JD. Pulmonary alveolar proteinosis: CT findings. Radiology 1988, 169: 609

Differentials

The differential diagnosis includes all chronic consolidative diseases exhibiting a crazy paving pattern:

- BAC: crazy paving is not the dominant feature, and is associated with hazy nodules. Lesion distribution is asymmetrical, often peripheral and basal, and pleural effusion and adenopathy may be present
- Slow-resolving bacterial pneumonia: frank areas of consolidation predominate and crazy paving is rare
- Lipoid pneumonia: negative density at CT
- CEP: peripheral distribution in the middle and upper regions. Crazy paving is not a constant feature and, when present, has limited extension. Ill-defined nodular opacities and mediastinal adenopathy may be associated

Johkoh T. Crazy-paving appearance at thin-section CT: spectrum of disease and pathologic findings. Radiology 1999, 211: 155

Zompatori M. [Crazy paving]. Radiol Med 1999, 98: 432. Italian

COURSE and COMPLICATIONS

Associated diseases

Hematological malignancies are associated in 8% of cases (acute myeloblastic leukemia, chronic myelocytic leukemia, paraproteinemia). Secondary alveolar proteinosis has also been described in AIDS, dermatomyositis and pulmonary tuberculosis

Clinical course

Left untreated, the disease proves fatal in about 25% of patients with death due to respiratory failure or pulmonary superinfections. Spontaneous recovery may occur in 20-30% of cases, whereas progression to fibrosis is rare. In 15% of cases, the disease may become complicated by opportunistic infections (Nocardia, Aspergillus, Cryptococcus, Histoplasma, Mucor, Mycobacterium, Pneumocystis, Cytomegalovirus)

Radiological course

In patients treated with repeated therapeutic bronchial lavage, follow-up radiology demonstrates regression or improvement of the opacities, which may, however, recur. Progression to fibrosis is rare. Transient alveolar opacities noted immediately after therapeutic bronchial lavage may be due to the procedure itself

Clague HW. Pulmonary interstitial fibrosis associated with alveolar proteinosis. Thorax 1983, 38: 865

LABORATORY FINDINGS

Serum levels of LDH are typically increased. Less common findings include polycytemia and hypergammaglobulinemia, as well as elevated serum levels of surfactant proteins A and D (SP-A and SP-D)

Elevated levels of SP-A and SP-D are not specific and may also be observed in idiopathic pulmonary fibrosis

CLINICAL DIAGNOSIS

Alveolar proteinosis is suspected on the basis of the clinical and radiological setting and in particular in the presence of extensive crazy paving visualized by HRCT. In patients with a productive cough, the diagnosis can be confirmed by the detection of PAS-positive macrophages and lamellar bodies in the sputum. More often, the diagnosis is provided by bronchoscopy with BAL and transbronchial biopsy. The possibility of diagnosing idiopathic alveolar proteinosis based on the presence of serum antibodies against GM-CSF has recently been reported

Kitamura T. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000, 162: 658

INVASIVE DIAGNOSIS

Surgical lung biopsy is rarely required

Bronchoalveolar lavage

The BAL fluid is strongly opaque or "milky". Total cell count is reduced and there are large acellular eosinophilic bodies in a background of amorphous granular eosinophilic material. The proteinaceous component typically stains positive for PAS and negative for Alcian blue. The macrophages are engulfed by PAS-positive material. There are elevated levels of SP-A. Finally, electron microscopy reveals the presence of concentric layers of laminated structures (lamellar bodies). These findings are diagnostic

Milleron BJ. Bronchoalveolar lavage cell data in alveolar proteinosis. Am Rev Respir Dis 1991, 144: 1330

Pneumocystis Carinii Pneumonia

Definition

Pneumocystis carinii (recently renamed Pneumocystis jiroveci) pneumonia (PCP) is a clinically significant lung infection, found only in immunosuppressed subjects

Pneumocystosis

DEMOGRAPHICS

Etiology and pathogenesis

The mode of transmission of the infectious agent is unknown. Some studies have suggested an exogenous infection transmitted through inhalation, whereas others have implicated a reactivation of a latent infection acquired during childhood

Infection is undoubtedly favored by the subject's immunosuppressed state and in particular by CD4+ T-cell deficiency (circulating CD4+ count below 200/mm^3) and impairment of the bactericide action of alveolar macrophages and neutrophils

Epidemiology

Prior to advent of highly active antiretroviral therapy (HAART), 15% of HIV+ patients receiving prophylactic treatment and 45% of those not on prophylaxis developed PCP. PCP is decreasing in frequency due to use of prophylaxis and HAART

Risk factors

Immunodeficiency: HIV+, post-transplant immunosuppression, lymphatic system malignancies, and immunosuppressive treatments

CLINICAL FEATURES

History

Onset is generally insidious. In patients with full-blown AIDS, however, the disease may manifest abruptly with fever and hypoxemia. The most common symptom is dyspnea (95%) often associated with dry cough (90%). Less frequent symptoms include chills, malaise, weight loss and chest pain. Sputum production may be present in 25% of patients, whereas hemoptysis is unusual. About 7% of patients are asymptomatic

Physical findings

Patients have fever (84%) and tachypnea (62%). The most common finding on chest auscultation is fine rales heterogeneously distributed throughout the lung fields. At times ronchi and wheezes are heard. Chest examination is normal in 50% of cases. Patients may have splenomegaly and skin lesions. Digital clubbing is rare

Pulmonary function tests

Most patients have reduced D_LCO (<70% of the predicted value) with increased alveolar-arterial oxygen gradient. A finding of normal D_LCO and alveolar-arterial oxygen gradient has a strong negative predictive value for PCP

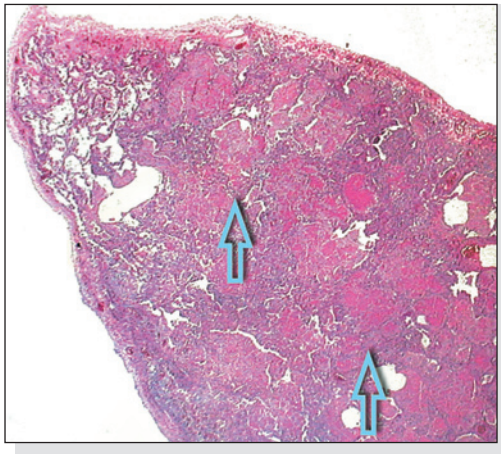
Santamauro JT. Pneumocystis carinii pneumonia. Med Clin North Am 1997, 81: 299

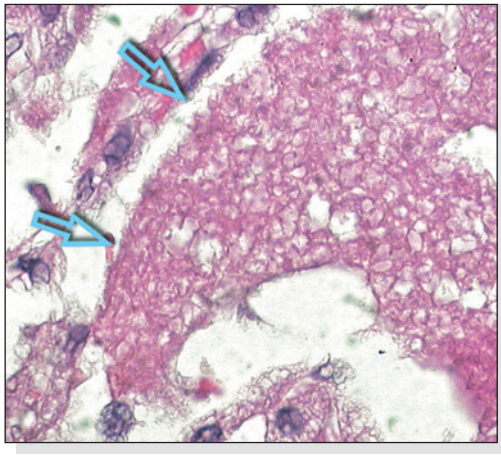
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Colonies of Pneumocystis carinii consisting of intraalveolar eosinophilic masses with a foamy appearance as they are made up of tiny cysts approximately the size of a red blood cell (⇨). At the center of these cysts is a small gray-blue spot that is poorly appreciable upon hematoxylin-and-eosin stain but clearly evident with silver stains (methenamine silver). The walls of the microcysts are PAS-positive
- Sparse inflammatory elements are commonly observed in the interstitium associated with hyperplasia of type II pneumocytes





Other possible histopathologic patterns include: 1. DAD with hyaline membranes; 2. non-specific cellular, granulomatous or desquamative interstitial pneumonia; 3. intraalveolar hemorrhage; 4. fibrosis and micro-calcification; 5. alveolar proteinosis-like pattern. Colonies of Pneumocystis may also be found in the context of a normal lung

Distribution

Intraalveolar

Differentials

Histopathologic differential diagnoses:

- Intraalveolar fibrin or edema: the intraalveolar material is not foamy and is negative upon PAS and silver stainings
- PAP: the intraalveolar material is not foamy and is negative upon silver stainings. Although PAS may be positive, it does not selectively stain the microcyst walls

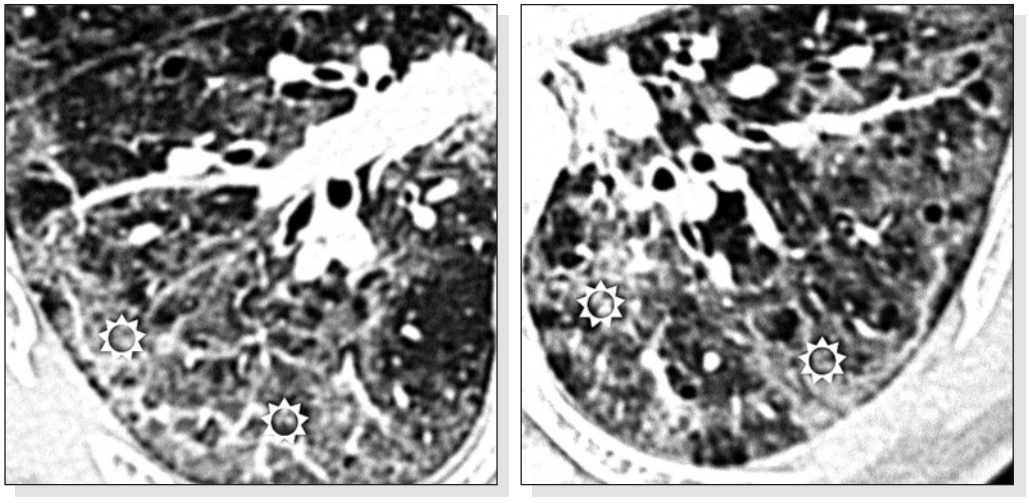
Travis WD. Atypical pathologic manifestations of Pneumocystis carinii pneumonia in the acquired immune deficiency syndrome. Review of 123 lung biopsies from 76 patients with emphasis on cysts, vascular invasion, vasculitis, and granulomas. Am J Surg Pathol 1990, 14: 615

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- More or less extensive ground-glass opacities (☼)
- Associated parenchymal consolidation



Kuhlman JE. Pneumocystis carinii pneumonia: spectrum of parenchymal CT findings. Radiology 1990, 175: 711

Distribution

Bilateral and asymmetrical, diffuse or patchy

Often central and parahilar

Middle-upper lung regions

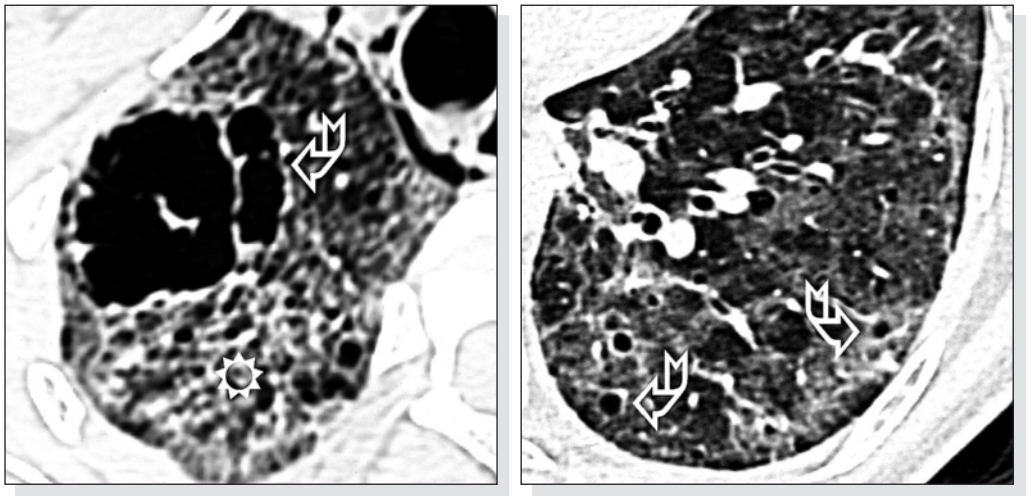
The lesions tend to predominate in the upper lobes in subjects receiving aerosol pentamidine

Lung volume is normal, or moderately reduced in the more extensive forms

Other signs

Other radiological signs:

- Cysts (↳) within the ground-glass opacities (35% of cases)
- Reticular opacities (☼) due to smooth interlobular septal thickening possibly associated with ground-glass density with resulting crazy paving pattern
- Small diffuse or parahilar nodules with ill-defined borders (due to granulomatous reaction); more rarely large nodules or true masses (pneumocystomas) may be seen
- Mediastinal or hilar adenopathy
- Pleural effusion (about 5% of cases)
- At times signs of infectious bronchiolitis with tree-in-bud pattern, bronchial wall thickening, and bronchiectasis



The cysts, which are often arranged in clusters in the upper lobes, have thick walls and bizarre shapes. At times the cysts are septated and may become very large

A reticular pattern associated with ground-glass attenuation is often seen in the subacute phase of the disease. This is the result of interstitial organization of the intraalveolar exudate

Moskovic E. High resolution computed tomography of Pneumocystis carinii pneumonia in AIDS. Clin Radiol 1990, 42: 239

Differentials

The differential diagnosis includes other diseases characterized by acute alveolar pattern:

- Viral infections: the radiological patterns may be similar, but the cysts are absent
- DAH: the longitudinal distribution is variable. In Wegener's disease large round cavitating opacities may be present
- PE: predominantly basal distribution, and frequent cardiomegaly and pleural effusion

COURSE and COMPLICATIONS

Associated diseases

Infections in other organs, in particular due to Cytomegalovirus, or neoplastic disease (Kaposi's sarcoma or lymphomas). Pneumothorax due to rupture of a cyst into the pleural space in 5-10% of cases

The appearance of severe dyspnea in a patient with PCP should raise the suspicion of pneumothorax

Feurestein IM. Thin-walled cavities, cysts, and pneumothorax in Pneumocystis carinii pneumonia: further observations with histopathologic correlation. Radiology 1990, 174: 697

Clinical course

PCP is a severe infection which may be fatal if overlooked. If promptly treated, on the other hand, it has a favorable prognosis (50-95% survival). In 50-75% of AIDS patients, the disease will relapse unless appropriate chemoprophylaxis has been instituted

Radiological course

If treatment is effective the radiological consolidative changes may resolve completely. A minority of cases show persistence of mild fibrosis in the form of retracting strands. The cysts may even persist for weeks or months after the pneumonia has resolved, and in this case they have thin walls

In cases not responding to therapy, the consolidative changes may progress to a clinical and radiological pattern of ARDS (⌘ ARDS)

Chow C. Lung cysts associated with Pneumocystis carinii pneumonia: radiographic characteristics, natural history, and complications. AJR Am J Roentgenol 1993, 161: 527

LABORATORY FINDINGS

Most patients have moderate leukocytosis with lymphopenia. In 50% of cases, the CD4/CD8 ratio is reduced (often the absolute count of CD4+ T-cells is <200/mm^3). Elevated serum levels of LDH are common (90%), as are high serum levels of angiotensin-converting enzyme (ACE). Recent studies showed undetectable plasma levels of S-adenosylmethionine in PCP patients

The finding of elevated LDH levels is a negative prognostic factor

LDH has been suggested to be an index of pneumonia extension more than a marker of PCP infection

CLINICAL DIAGNOSIS

Although the clinical and radiological setting may often be strongly suggestive of PCP, the presence of Pneumocystis carinii (jiroveci) in the respiratory specimens should always be demonstrated (first in induced sputum)

The sensitivity of HRCT is close to 100% and its specificity is greater than 80%, with good interobserver agreement

The negative predictive value of HRCT is so high that a negative scan allows a diagnosis of PCP to be confidently ruled out. HRCT has replaced gallium scintigraphy

INVASIVE DIAGNOSIS

Given the high diagnostic yield of induced sputum and BAL, histological confirmation, which is mostly obtained by transbronchial lung biopsy, is rarely required. When performing a biopsy, the high risk of post-biopsy bleeding due to the typical thrombocytopenia found in HIV+ subjects should be borne in mind

Bronchoalveolar lavage

BAL is recommended if sputum induction is non-diagnostic. A characteristic BAL finding is “foamy exudate”: the “foamy” effect is due to the presence of empty cysts within the pathological secretions. This exudate, which can be seen with May-Grunwald-Giemsa or Papanicolau stains, is diagnostic of PCP even without special stains. Sporozoites may be observed inside, and free trophozoites outside the cysts

The diagnostic yield of BAL in HIV+ subjects in 97-100%, which drops to 62% in those on pentamidine prophylaxis. Increased levels of interleukin-8 or the presence of cysts in the BAL fluid have been reported to be negative prognostic factors

Golden JA. Bronchoalveolar lavage as the exclusive diagnostic modality for Pneumocystis carinii pneumonia. A prospective study among patients with acquired immunodeficiency syndrome. Chest 1986, 90: 18

Pulmonary Edema

Definition

Pulmonary edema (PE) refers to the accumulation of extravascular fluid in the alveoli

Cardiogenic, hemodynamic edema

DEMOGRAPHICS

Etiology and pathogenesis

The volume of water and the movement of proteins in the lung depend on the equilibrium achieved between the hydrostatic and intra- and extravascular osmotic pressures and the permeability of the alveolar-capillary membrane. An increase in hydrostatic pressure produces an increase in the transudation of excess fluid (edema) from the microcirculation to the extravascular compartment, with an accumulation initially in the pulmonary interstitium and then in the alveolar spaces

The most common cause of PE is cardiogenic (left ventricular systolic or diastolic dysfunction, left atrial flow impairment). Less common causes result from a reduction in capillary osmotic pressure (renal disease, liver cirrhosis, fluid overload), neurogenic alterations (head injury, increased intracranial pressure, non-hemorrhagic stroke) and diseases of the pulmonary veins (idiopathic veno-occlusive disease, fibrosing mediastinitis)

Epidemiology

PE is a frequent cause of admission to hospital

Risk factors

These include liver cirrhosis, kidney failure, heart disease, valvulopathy

CLINICAL FEATURES

History

The onset of symptoms is often acute and dramatic. Patients present with orthopnea and are in an obvious state of respiratory distress (use of accessory respiratory muscles). Peripheral and central cyanosis, tachycardia, pallor, cold clammy skin, anxiety and often elevated systemic pressure are all common findings. In the more severe cases, the patients have productive cough with expectoration of pink frothy sputum up to frank hemoptysis. Patients often have a long history of orthopnea and/or paroxysmal nocturnal dyspnea

Physical findings

The physical examination reveals indirect signs of increased venous return such as jugular venous distention, tender hepatosplenomegaly and peripheral edema. Examination of the lung is characterized by fine diffuse inspiratory rales and expiratory wheezees. In patients with valvular dysfunction, a gallop rhythm may be noted on cardiac auscultation. In the end stages of disease, loss of consciousness and cardiocirculatory failure occur

Pulmonary function tests

Lung function testing is rarely performed in patients with full-blown PE. Nonetheless, the findings will include a reduction in compliance, vital capacity and total lung capacity, and an acute increase in pulmonary resistance and closing volume

Bronchial hyperreactivity has been reported in some patients. Severe hypoxemia and normocapnia or hypercapnia are also encountered

The differential diagnosis of PE includes fulminant pneumonia, acute asthma, acute exacerbation of COPD and acute hemorrhagic alveolitis

Gandhi SK. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001, 344: 17

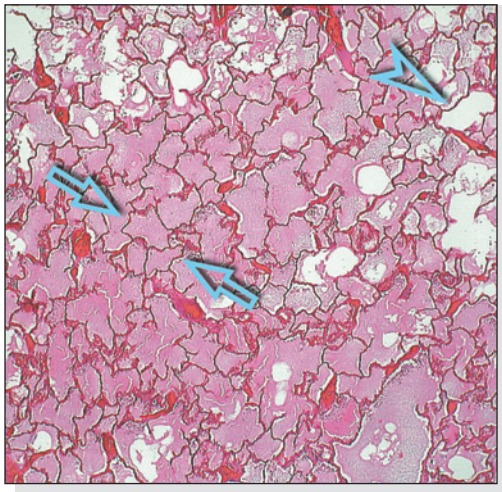
Gropper MA. Acute cardiogenic pulmonary edema. Clin Chest Med 1994, 15: 501

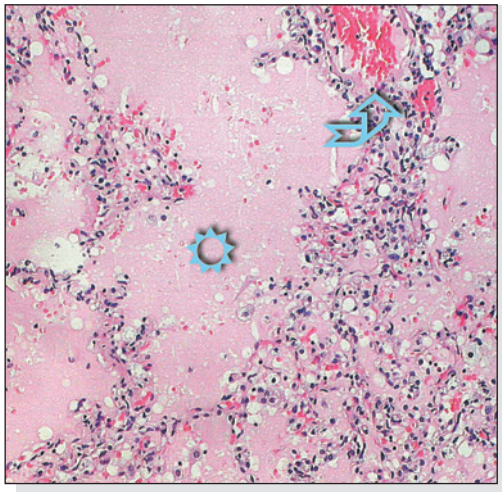
PATHOLOGY

Basic lesions

The histopathologic features of PE are the following:

- Accumulation of intraalveolar fluid (⇨): the lungs are heavier than normal, with frothy fluid oozing out of the cut surface of the lung and bronchi, either spontaneously or following compression
- The alveolar spaces appear overdistended and often optically empty (≻) as their content is easily lost during tissue processing
- Less frequently, slightly eosinophilic granular and proteinaceous material may be seen within the alveolar spaces (☼)
- Interstitial edema associated with congested capillaries in the intraalveolar septa (↯)





Distribution

Intraalveolar

Differentials

Histopathologic differential diagnoses:

- Normal parenchyma: normal lung weight and optically empty alveoli; there is no edema in the pulmonary interstitium
- DAD: the edema is associated with the presence of hyaline membranes
- PAP: the alveoli are filled with granular and PAS-positive material

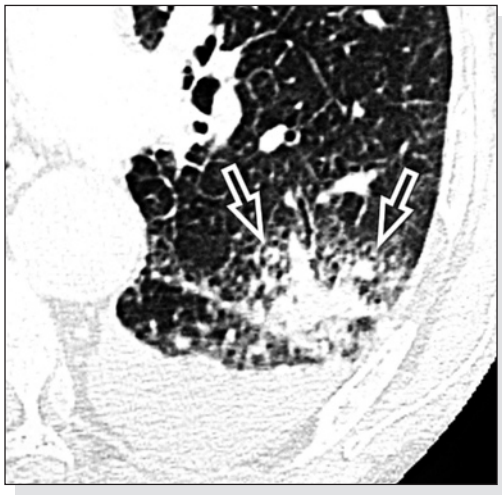
Colby TV. Pulmonary histology for the surgical pathologist. Am J Surg Pathol 1988, 12: 223

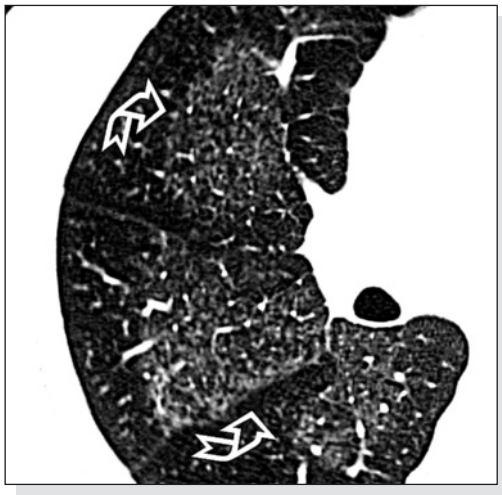
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (⇨)
- Associated ground-glass (↳)
- Limited or absent air bronchogram





Distribution

Bilateral, symmetrical

The edema may be unilateral, as in patients in protracted lateral decubitus, or asymmetric and bizarre-shaped, as in patients with regional emphysema (because edema does not form in the affected area)

In patients with acute pulmonary thromboembolism, hemodynamic edema due to hyperperfusion may develop in the otherwise unaffected areas

Predominantly subpleural and gravitational, although also diffuse

Peripheral edema is more characteristic of cardiogenic edema because the movement of the fluid towards the hilum (mediated by the lymphatics) is hindered by the elevated central venous pressure. Instead, a hilar distribution is more typical of hypervolemic edema since the central pressures are relatively normal

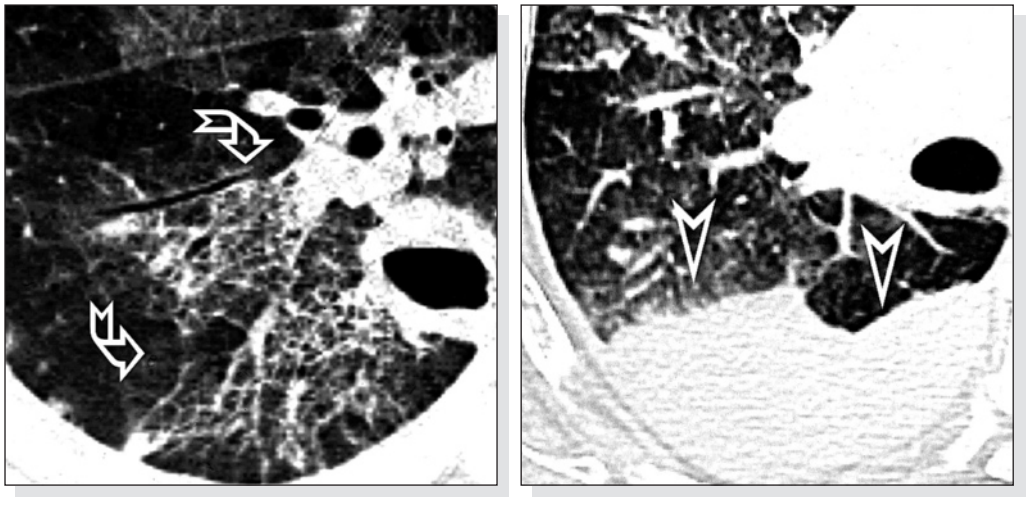
Predominantly basal

Lung volume is slightly reduced

Other signs

Other radiological characteristics:

- Smooth reticular pattern (↳), prevalent in the initial stages of disease (☐ PE, interstitial)
- Subpleural thickening and pleural effusion (➢)
- Cardiomegaly



An increase in the thickness of the chest wall may reflect an accumulation of fluid in the "third space", whereas a widening of the vascular pedicle indicates an increase in the blood volume circulating in the venous district

Gluecker T. Clinical and radiologic features of pulmonary edema. Radiographics 1999, 19: 1507

Storto ML. Hydrostatic pulmonary edema: high-resolution CT findings. AJR Am J Roentgenol 1995, 165: 817

Differentials

The differential diagnoses include the various causes of acute parenchymal consolidation:

- ARDS: patchy opacities with air bronchogram without clear gravitational predominance. There is no reticular pattern or pleural effusion, and the vascular pedicle and heart volume are normal
- AIP: there are no cardiovascular signs of hemodynamic edema
- Acute eosinophilic pneumonia: the appearance is similar to lesional edema (AIP associated with DAD or ARDS)
- HP: patchy distribution, with associated hazy centrilobular nodules, and mosaic pattern with air-trapping
- DAH: "butterfly" or "batwing" pattern with perihilar distribution and sparing of the subpleural regions. Cardiomegaly is absent
- PCP: crazy paving, thick-walled cysts, and distribution in the middle-upper lung regions

Desai SR. Acute respiratory distress syndrome: imaging of the injured lung. Clin Radiol 2002, 57: 8

Primack SL. Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. AJR Am J Roentgenol 1995, 164: 295

COURSE and COMPLICATIONS

Associated diseases

Various valvular and non-valvular heart diseases may also be present

Clinical course

Alveolar PE is a dramatic condition that may become life-threatening if not treated promptly

Radiological course

Acute onset and rapid regression with treatment are characteristic features of this form of edema, and may assist in the differential diagnosis

There may be a time lag between the regression of edema and pleural effusion and the return to normal of the pulmonary capillary wedge pressure

LABORATORY FINDINGS

Laboratory findings are useful for ruling out infection or anemia which may act as precipitating factors. Normal cardiac enzymes allow exclusion of an underlying myocardial infarction, and renal function indices enable detection of concurrent renal failure

Brain natriuretic peptide (BNP) levels are increased in PE and therefore can be helpful in differentiating between cardiogenic and lesional PE

CLINICAL DIAGNOSIS

The diagnosis is clinical and may be aided by instrumental investigations such as BNP serum levels, chest radiographs, electrocardiogram and echocardiography

INVASIVE DIAGNOSIS

Bronchoalveolar lavage

There is no indication to perform BAL in PE. The small amount of data available in the literature suggests that the BAL findings are similar to those seen in hemorrhagic alveolitis

Nakos G. Proteins and phospholipids in BAL from patients with hydrostatic pulmonary edema. Am J Respir Crit Care Med 1997, 155: 945

Cystic Diseases

Clinical features	**Alberto Pesci**
Pathology	**Alessandra Cancellieri**
Radiology	**Giorgia Dalpiaz**

Asbestos-induced pneumoconiosis

Definition

Asbestosis is a pneumoconiosis caused by the inhalation of asbestos fibers and characterized by a slowly progressive fibrosis

The early stage of the disease is characterized by an irregular reticular pattern (☐ Asbestosis, early), whereas the cystic pattern is characteristic of the advanced stage. This chapter will cover the latter

DEMOGRAPHICS

Etiology and pathogenesis

A toxic effect is thought to be produced by the asbestos fibers on the lung parenchyma with recruitment of inflammatory cells and release of various mediators (reactive oxygen species, cytokines, proteases and growth factors)

Epidemiology

The precise epidemiology of the disease is unknown since working environment are significantly different throughout the world and the disease has such a long clinical latency (up to 20-30 years from initial exposure)

Risk factors

Asbestosis affects workers involved in the extraction of the mineral, in the manufacture and installation of products containing asbestos (industrial textiles, insulation, cement-asbestos manufactured goods) and in the repair and removal of the same (naval and railway demolition)

CLINICAL FEATURES

History

The main symptoms at this stage of the disease are dyspnea on exertion and dry cough. Digital clubbing is present in 30-40% of cases

Physical findings

Physical examination of the lung reveals diffuse fine bibasilar rales (32-64%) and in the more advanced cases the signs of cor pulmonale (peripheral edema, jugular venous distension, hepatojugular reflux) may be seen

Sputum production and wheezing are not common findings and may be ralated more to cigarette smoking than to asbestosis

Pulmonary function tests

A restrictive ventilatory defect to a varying degrees and reduced D_LCO and compliance are seen, while hypoxemia at rest is present in the more advanced forms

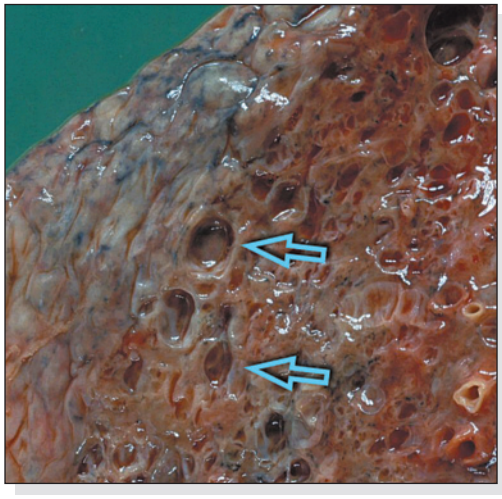
Mossman BT. Asbestos-related diseases. N Engl J Med 1989, 320: 1721

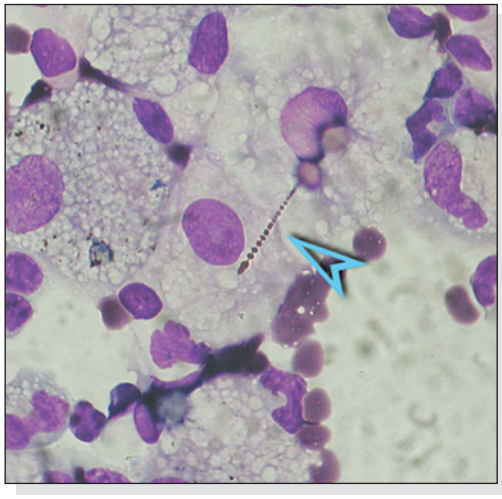
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Cystic spaces (⇨)(honeycombing) alternating with fibrosis; presence of asbestos bodies (➢)
- Fibrosis is more frequent and extensive in subpleural regions





In the advanced stages, the fibrosis in asbestosis may be macroscopically indistinguishable from the fibrosis in UIP

Distribution

Diffuse, more extensive in subpleural regions

Differentials

Histopathologic differential diagnoses:

- UIP: fibroblastic foci are present, while asbestos bodies are absent
- NSIP: asbestos bodies are absent and the lesions are uniformly distributed with no subpleural prevalence

Churg A. Pathology of occupational lung disease. 2nd ed. Baltimore, Williams & Wilkins, 1998

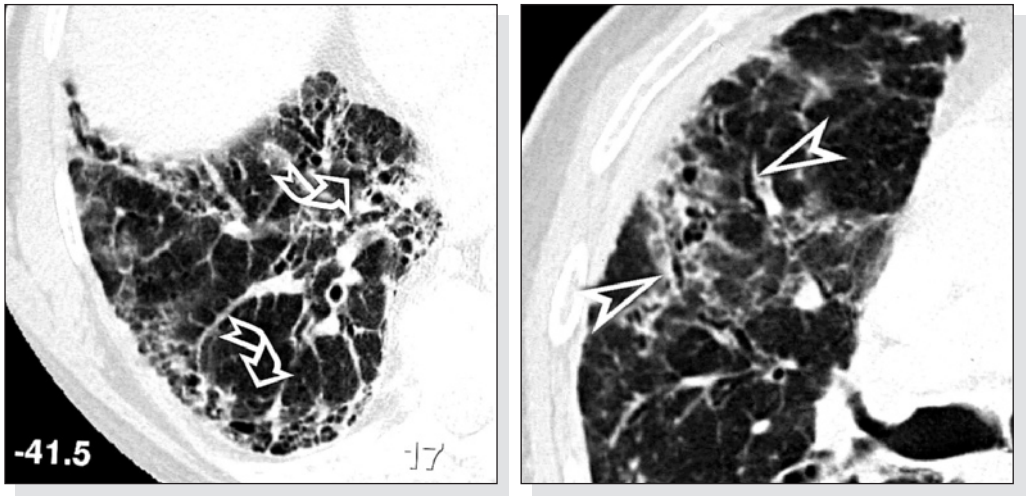
Gaensler EA. Idiopathic pulmonary fibrosis in asbestos-exposed workers. Am Rev Respir Dis 1991, 144: 689

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Small rounded cysts (2-10 mm) which share thick walls and are distributed in several concentric layers in the subpleural regions (↳)(honeycombing)
- Traction bronchiectasis and bronchiolectasis (➢) with highly irregular morphology and thick walls



Distribution

Bilateral, patchy

Peripheral subpleural, more pronounced posteriorly

Predominantly basal

Lung volume is reduced

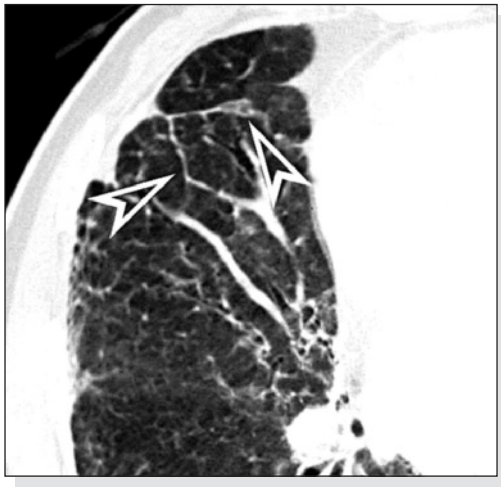
Aberle DR. High-resolution computed tomography of asbestos-related diseases. Semin Roentgenol 1991, 26: 118

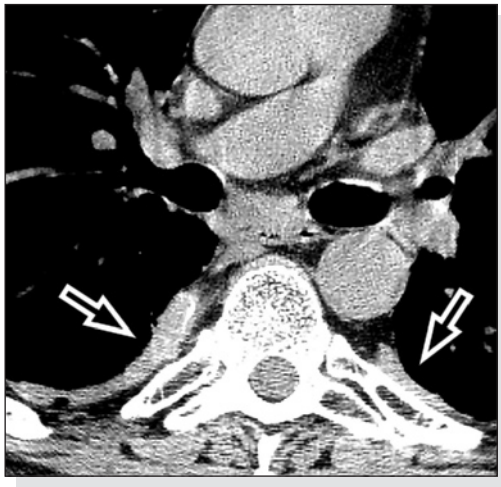
Kim KI. Imaging of occupational lung disease. Radiographics 2001, 21: 1371

Other signs

Other non-constant radiological signs:

- Irregular reticular pattern
- Subpleural lines and parenchymal bands (➢)
- Pleural plaques (⇨)
- Uni- or bilateral effusion
- Diffuse uniform pleural thickening <1 cm not involving the mediastinal pleura
- Rounded atelectasis: unilateral, found most commonly in the basal-posterior portions of the lower lobes





Pleural plaques: these may be bilateral, of varying length, but with a thickness <1 cm and calcified in 10-15% of cases; they are typically absent in the apices and in the costophrenic sinuses and tend to be arranged in a spiral pattern extending superoanterior to posteroinferior

Rounded atelectasis: a rounded or ellipsoid area of increased density with a parietal base in correspondence with pleural thickening; the vessels and bronchi around the area are gently arched with a "comet-tail" appearance. The area is markedly hyperdense following administration of contrast material as it is composed of collapsed parenchyma which is not aerated, but rather perfused

Gevenois PA. Asbestosis, pleural plaques and diffuse pleural thickening: three distinct benign responses to asbestos exposure. Eur Respir J 1998, 11: 1021

Peacock C. Asbestos-related benign pleural disease. Clin Radiol 2000, 55: 422

Differentials

Radiological differential diagnoses:

- UIP: honeycombing is more pronounced, while pleural plaques are absent
- Collagen vascular diseases: other characteristic findings of the individual diseases often coexist (esophageal dilatation in scleroderma, pleural effusion or thickening in rheumatoid arthritis, etc.)
- LCH: the cysts are diffuse in the axial plane and absent in the bases, while the individual cysts are more irregular and at times confluent with bizarre morphology

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomog 2002, 26: 5

Primack SL. End-stage lung disease: CT findings in 61 patients. Radiology 1993, 189: 681

COURSE and COMPLICATIONS

Associated diseases

Pleural plaques and malignant tumors, particularly lung cancer (3-5 times increased risk) and pleural mesothelioma (2.5 times increased risk, especially in smokers) are the main associated diseases

Pleural plaques are the characteristic signs of the disease. Radiologically, mesothelioma appears in the form of a diffuse and unilateral nodular pleural and/or mediastinal thickening. The pleural thickening is more than 1 cm in thickness, and is often associated with pleural effusion

Hillerdal G. Pleural plaques and risk for bronchial carcinoma and mesothelioma. A prospective study. Chest 1994, 105: 144

Van Loon AJ. Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. Occup Environ Med 1997, 54: 817

Clinical course

The progression towards respiratory failure and cor pulmonale may be accelerated by the presence of an asbestos- and/or smoking-related tumor

Radiological course

Slow spatial extension of the characteristic lesions, with a possible increase in the size of the cysts and decrease in the thickness of their walls

LABORATORY FINDINGS

Increased erythrocyte sedimentation rate (ESR), the presence of antinuclear antibodies and rheumatoid factor are frequently found, they are not correlated with the disease activity

CLINICAL DIAGNOSIS

In the appropriate clinical setting, a detailed history of asbestos exposure and a long period of latency from initial exposure to the onset of clinical signs, and radiological findings are diagnostic of asbestosis

✓ The presence of pleural plaques is pathognomic of previous exposure

INVASIVE DIAGNOSIS

In this phase, surgical or transbronchial lung biopsy are not useful, because they are likely to result in the generic histological diagnosis of end-stage fibrotic lung disease. Biopsy may be useful in the presence of infectious complications or suspected concomitant malignancy

Bronchoalveolar lavage

Asbestos bodies are frequently encountered in BAL fluid, and their number correlates with the number present in the tissues. Cell count shows an increase in polymorphonucleated neutrophils and eosinophils. Elevated fibronectin levels are also seen in the supernatant

Recovery of asbestos bodies improves when BAL is performed in the lower lobes. Asbestos bodies may be encountered in BAL fluid of exposed subjects who do not have asbestosis

According to some studies, the intensity of neutrophilia correlates with the severity of lung fibrosis

Karjalainen A. Asbestos bodies in bronchoalveolar lavage in relation to asbestos bodies and asbestos fibres in lung parenchyma. Eur Respir J 1996, 9: 1000

Cystic bronchiectasis

Definition

Bronchiectasis is the permanent abnormal dilatation of the bronchi due to various causes (see the table "Causes of bronchiectasis" at the end of this chapter)

DEMOGRAPHICS

Etiology and pathogenesis

The disease is caused by impaired clearance of inflammatory secretions and microbes, which produces airway obstruction, airway damage and recurrent infection. The bronchi become involved in a vicious circle of infection, transmural inflammation, the release of various mediators and even peribronchial fibrosis. The bronchial walls are infiltrated by neutrophils and T-cells, while the sputum shows an increased presence of neutrophils, interleukin-8, tumor necrosis factor alpha and prostanoids

Epidemiology

Bronchiectasis presents at all ages and affects both sexes. Bronchiectasis resulting from cystic fibrosis and infection is the most common form

Risk factors

Immunodeficient states, repeated bronchopulmonary infections, bronchial obstruction

CLINICAL FEATURES

History

Nearly all patients present with cough and chronic purulent sputum. At times hemoptysis is present and can be massive. Seventy-five percent of patients have dyspnea and wheezing, while 50% may suffer from chest pain. Bronchitic exacerbation refers to the presence of at least four of the following symptoms: (1) increased sputum production; (2) increased dyspnea; (3) increased cough; (4) temperature >38°C; (5) increased wheezing; (6) malaise, fatigue or reduced tolerance for exercise; (7) reduction in functional parameters; (8) new radiological alterations; (9) increased lung sounds

Physical findings

Seventy percent of patients have persistent and localized rales, while rhonchi are present in 44%, wheezes in 34%, and digital clubbing in 3% of patients

Pulmonary function tests

A mixed obstructive-restrictive ventilatory defect is common. Bronchial obstruction can be reversed in 50% of cases by administering beta-2 agonists, while 30-69% of patients present bronchial hyperreactivity to methacholine

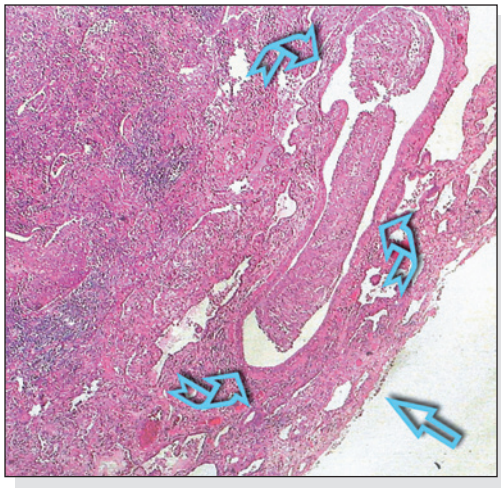
Barker AF. Bronchiectasis. N Engl J Med 2002, 346: 1383

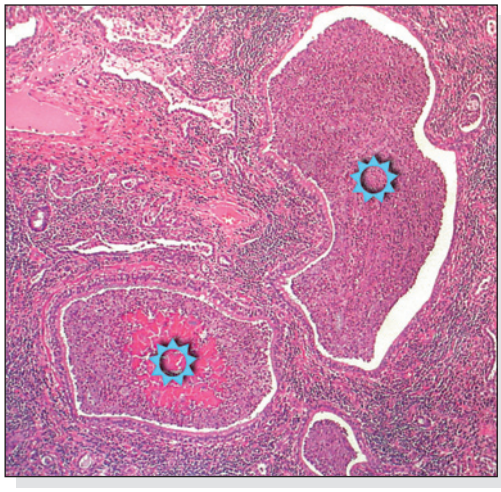
PATHOLOGY

Basic lesions

The following histopathologic changes are seen:

- Bronchial dilatation (↳) which may almost extend to the pleural surface (⇨). The bronchi show accentuated transverse ridges due to hypertrophied smooth muscle bundles and pouches formed by dilated bronchial glands
- The bronchial lumen is often filled with muco-purulent secretions and necrotic debris (☼)
- Histologically, the lesions vary from small changes in the bronchial wall to intense, acute and chronic inflammatory infiltrate, sometimes associated with granulation tissue. The mucosa may be ulcerated, and the respiratory epithelium may be replaced by squamous epithelium





The bronchial vessels may show smooth muscle hypertrophy and endarteritis obliterans may be seen in the areas of fibrosis. The bronchioles may be partially or completely obliterated, and proliferation of neuroendocrine cells (tumorlets) may be seen. Foci of acute or organizing pneumonia or post-obstructive changes (foamy macrophages) may be seen in the alveoli. Areas of fibrosis with honeycombing may be seen in the lung in some cases

Distribution

Bronchocentric and bronchiolocentric

Differentials

Histopathologic differential diagnoses:

- Bronchiectasis and bronchiolectasis in UIP: the fibrosis has a subpleural and paraseptal distribution and is associated with fibroblastic foci at the interface with normal parenchyma
- Post-obstructive bronchiectasis (e.g. in pulmonary carcinoma): presence of obstruction; foamy macrophages may be seen in the alveoli

Possible causes of obstructions should always be looked for in lungs resected for bronchiectasis

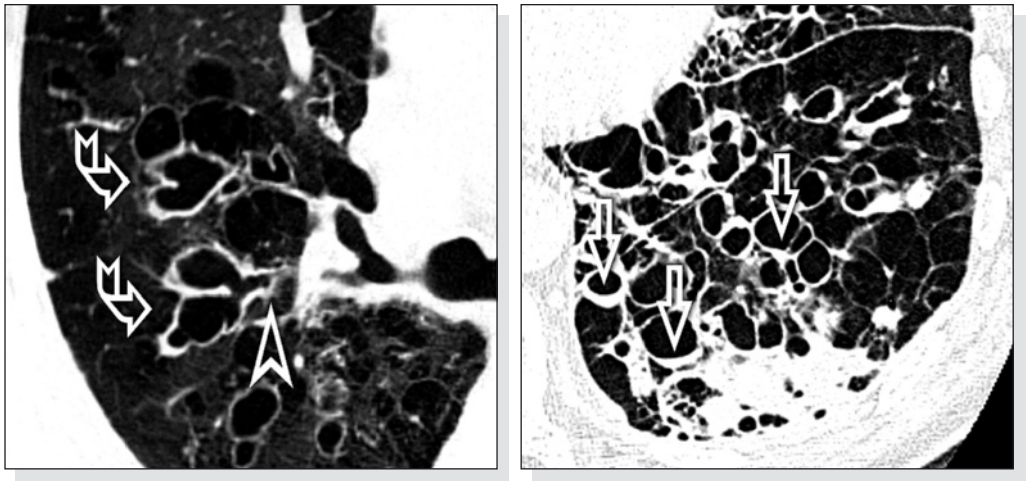
Thurlbeck WM. Chronic airflow obstruction in lung disease. WB Saunders, 1976

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Clusters of rounded or oval cysts with thick walls (↳), often found adjacent to the bronchial tree (➢)
- Air-fluid levels in the dilated cystic spaces (⇨)



Cystic bronchiectasis is the most severe manifestation of bronchial dilatation. These alterations are at times isolated, whereas at others they are found in the presence of smaller dilatations with a cylindrical or varicose appearance. The material in the cystic spaces has a fluid or superfluid density (pus) which remains unchanged in the presence of contrast material. Isolated opacities of variable density (mycetomas, clots, dense mucus), which move with the patient's position may also be seen

McGuinness G. CT of airways disease and bronchiectasis. Radiol Clin North Am 2002, 40: 1

Distribution

Bilateral or unilateral; patchy asymmetrical in localized forms with possible segmental or lobular extension

Variable with possible predominance in the central parahilar regions

Variable, but predominantly in the upper lobes in cystic fibrosis (CF) particularly on the right side, in allergic bronchopulmonary aspergillosis (ABPA), in Mounier-Kuhn syndrome (a congenital deficiency of muscle fibers and the tracheobronchial myenteric plexus with tracheomegaly) and in Williams-Campbell syndrome (a rare condition associated with congenital bronchial wall cartilage deficiency)

Cartier Y. Bronchiectasis: accuracy of high-resolution CT in the differentiation of specific diseases. AJR Am J Roentgenol 1999, 173: 47

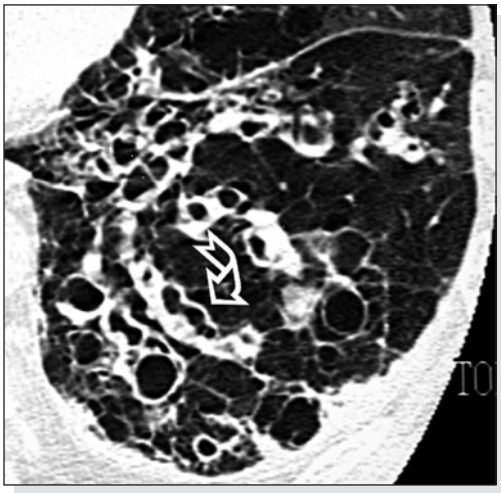
Hartman TE. CT of cystic diseases of the lung. Radiol Clin North Am 2001, 39: 1231

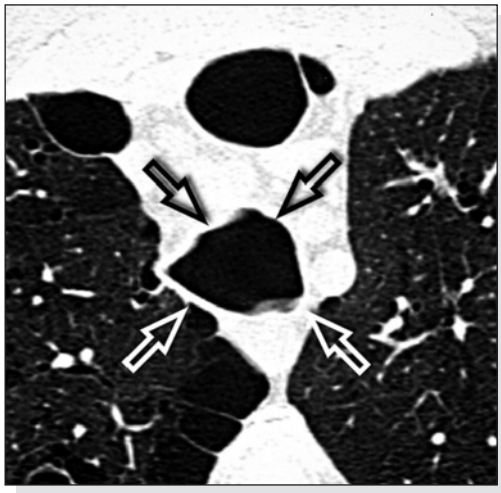
Lung volume is normal or locally reduced

Other signs

Other radiological signs:

- Central, tubular or varicoid bronchiectasis (↳); empty or filled bronchiolectasis (tree-in-bud)
- Scattered areas of mosaic perfusion with air-trapping produced by associated constrictive bronchiolitis
- Inflammatory consolidations
- Hilar and/or mediastinal lymph node enlargement due to chronic infections
- Dilated and dysmorphic appearance of the trachea (⇨)(tracheomegaly) and the main bronchi in cases of Mounier-Kuhn syndrome





Grenier PA. New frontiers in CT imaging of airway disease. Eur Radiol 2002, 12: 1022

Hansell DM. Bronchiectasis. Radiol Clin North Am 1998, 36: 107

Differentials

Radiological differential diagnoses:

- Cavitating metastases: lesions predominate in the basal regions, are random in the axial plane, and often coexist with other non-cavitating nodules
- LCH: cysts are random and diffuse, they are not found adjacent to the bronchial structures and air-fluid levels are never present
- PCP: cysts are situated within areas of ground-glass opacity, and air-fluid levels are never present

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomog 2002, 26: 5

COURSE and COMPLICATIONS

Associated diseases

Infection plays an important role in causing and perpetuating the bronchiectasis. There are three main colonizing microorganisms involved: Pseudomonas aeruginosa, intracellular Mycobacterium avium, and Aspergillus fumigatus. Aspergillus causes an asthmatic condition known as ABPA. The presence of coexisting sinusitis, bronchial amyloidosis and peripheral neural disease have been reported

Clinical course

In most patients, bronchiectasis progresses slowly and leads to frequent hospitalization due to recurrent infection. The mortality level lies between those of asthma and chronic obstructive pulmonary disease (COPD). Prognosis has markedly improved over the last 50 years owing to antibiotic treatment, with mortality decreasing from 92% in the 1940s to 9-19% in the 1980s

Radiological course

Over time the cystic lesions may become progressively extensive, particularly in the event of repeated infections, scarring with retraction, etc.

LABORATORY FINDINGS

Neutrophilic leukocytosis is a common finding, and some patients may have selective or panhypogammaglobulinemia. Sputum microscopy and culture may reveal, Haemophilus influenzae (29-42%), Pseudomonas aeruginosa (13-31%) and Streptococcus pneumoniae (6-13%)

CLINICAL DIAGNOSIS

HRCT is currently the gold-standard for the diagnosis of bronchiectasis with a sensitivity and specificity above 90%. The technique is indicated in bronchiectasis for: (1) assessing the site and extension of the lesion (particularly useful in the planning of postural drainage therapy); (2) planning possible surgery; and (3) follow-up

Young K. High resolution CT and bronchography in the assessment of bronchiectasis. Acta Radiol 1991, 32: 439

INVASIVE DIAGNOSIS

There are no special indications for biopsy

Bronchoalveolar lavage

BAL plays no part in the diagnosis and treatment of bronchiectasis

BRONCHIECTASIS TABLE

On the following page is a table which presents:

- Causes of bronchiectasis

CAUSES OF BRONCHIECTASIS

Post-infection conditions	Bacteria (Pseudomonas, Haemophilus) Mycobacteria Fungi (Histoplasmosis, Pneumocystosis) Virus (Adenovirus, Morbillivirus, Influenzavirus, HIV)
Congenital conditions	Primary ciliary dyskinesia (including Kartagener's syndrome) Alpha-1 antitrypsin deficiency CF Tracheobronchomegaly (Mounier-Kuhn syndrome) Cartilage deficiency (Williams-Campbell syndrome) Pulmonary sequestration Marfan syndrome
Immunodeficiency	Hypogammaglobulinemia Due to tumors, chemotherapy or organ transplant
Aspiration or inhalation of toxic substances	Chlorine Heroin Aspiration of gastric fluid Ingestion of paraquat Foreign bodies or broncholiths Tumors
Rheumatic diseases	RA SLE Sjögren's syndrome Polychondritis
Parenchymal fibrosis	Chronic tuberculosis Sarcoidosis
Other	ABPA Intestinal inflammatory diseases (ulcerative colitis and Crohn's disease) Young's syndrome (secondary ciliary dyskinesia) Yellow nail syndrome

Cystic Fibrosis

Definition

Cystic fibrosis (CF) is a hereditary multisystem disease characterized by the production of thickened and viscous secretions in various exocrine glands, such as the salivary and sweat glands, the pancreas, and the mucous glands of the colon and tracheobronchial tree

Mucoviscidosis

DEMOGRAPHICS

Etiology and pathogenesis

CF is an inherited autosomal recessive disorder. The gene responsible for the disease is situated on the long arm of chromosome 7

The protein produced by the gene is formed by 1,480 amino acids and is known as cystic fibrosis transmembrane conductance regulator (CFTR). The mutation of the gene and the production of altered CFTR is thought to cause a number of disturbances, including: (1) excessive transmural transport of sodium followed by the dessication of luminal secretions; (2) an increased affinity of epithelial cells for bacteria such as Pseudomonas aeruginosa; (3) altered bacterial killing; and (4) disruption of epithelial tight junctions. These changes in the lung are thought to lead to an alteration in the rheology of the bronchial secretions and mucociliary clearance. This facilitates bronchial bacterial colonization, with massive recruitment of polymorphonuclear cells, release of elastase and collagenase and subsequent permanent structural damage to the bronchial walls (bronchiectasis)

Epidemiology

CF is the most common fatal hereditary disease in the white population. Males and females are equally affected, with an estimated prevalence of 1 case per 2,000-3,500 live births. The disease is most commonly found in the white population

Risk factors

Mutations of the CFTR gene

CLINICAL FEATURES

History

CF is generally diagnosed in early infancy, and much less commonly in adolescence or adulthood. The main symptoms are productive cough, hemoptysis, wheezing and dyspnea. Patients are subject to recurrent lung infections. Hemoptysis is often limited, but fatal cases of hemoptysis are not rare

Patients of both sexes are frequently sterile (95% of males and 20% of females)

Physical findings

A variety of extrapulmonary manifestations may accompany the lung disease: meconium ileus in the newborn (10-20%), esophageal dysfunction, gastroesophageal reflux, rectal prolapse, joint disease (2-9%), hepatic steatosis, focal biliary cirrhosis (2-5%), pancreatic failure, chronic sinusitis (90-100%) and nasal polyposis (10-32%)

Physical examination reveals diffuse or less frequently localized rales. There may be wheezes and stridor, and digital clubbing is constant

Pulmonary function tests

The earliest functional parameters that change involve small airway patency (FEF 25-75, MEF 25). As the disease progresses, vital capacity decreases, residual volume increases, and FEV1 and D_LCO decline. Because of the gas exchange abnormalities the patients become hypoxemic, and only later hypercapnic

There have been reports of oxygen desaturation during sleep (REM phase), which is caused by hypoventilation and only partly by central or peripheral apnea

Many patients exhibit bronchial hyperresponsiveness. Patients with CF have declining exercise tolerance as a result of both functional impairment and reduced muscle mass related to undernutrition

Robinson P. Cystic fibrosis. Thorax 2001, 56: 237

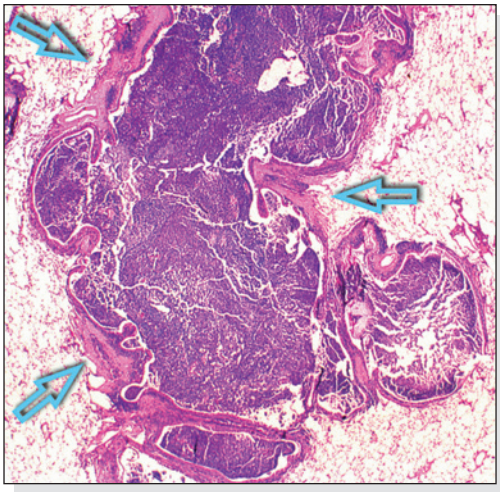
Stern RC. The diagnosis of cystic fibrosis. N Engl J Med 1997, 336: 487

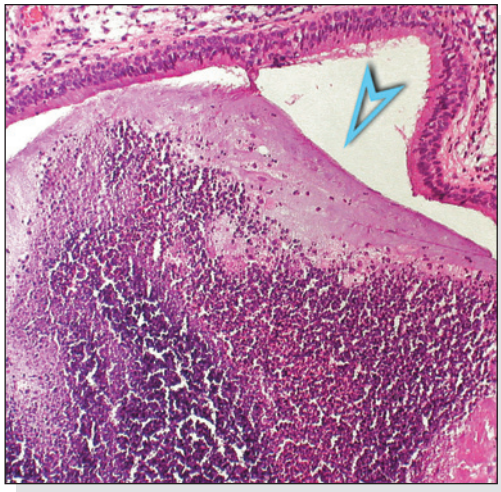
PATHOLOGY

Basic lesions

The histopathologic changes are the following:

- Bronchiectasis filled with inspissated mucus firmly adhering to the walls (⇨). The mucoid material, admixed with neutrophilic granulocytes and often bacterial colonies (➢) extends to the bronchioles and sometimes to the peribronchiolar parenchyma
- Foci of acute and organizing pneumonia or interstitial pneumonia, with or without fibrosis, may be seen in the peribronchiolar parenchyma
- Acute and chronic bronchiolitis may be seen in the small airways with peribronchiolar fibrosis and constrictive bronchiolitis





There are no pulmonary histologic features which distinguish bronchiectasis produced by cystic fibrosis from that due to other causes

✓ Other characteristics:

- Large airways: hypertrophy of the submucosal glands, acute and chronic bronchitis, bronchial wall fibrosis with stenosis and squamous superficial metaplasia with hyperplasia of the goblet cells
- Pleura: thickening with adherences
- Subpleural parenchyma: possible bullous and interstitial emphysema

Distribution

Bronchocentric, bronchiolocentric

Differentials

Histopathologic differential diagnoses:

- Primary ciliary dyskinesia (including ciliary dyskinesia syndrome, Kartagener's syndrome and immotile cilia syndrome): hereditary conditions with autosomal recessive inheritance; presence of ultrastructural changes in the airway's cilia
- Post-obstructive bronchiectasis: presence of obstruction, foamy intraalveolar macrophages
- ABPA: presence of Aspergillus fumigatus mixed with numerous eosinophils
- Plastic bronchitis: large bronchial casts composed of inspissated mucus, fibrin and inflammatory cells

Bedrossian CW. The lung in cystic fibrosis. A quantitative study including prevalence of pathologic findings among different age groups. Hum Pathol 1976, 7: 195

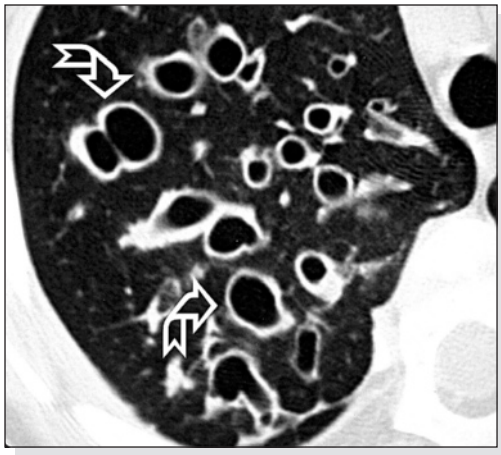
Vawter GF. Cystic fibrosis in adults: an autopsy study. Pathol Annu 1979, 2: 357

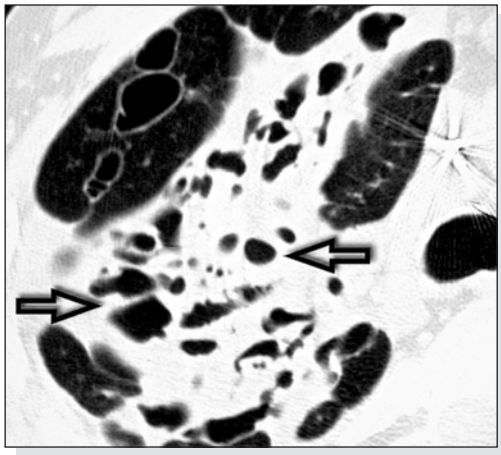
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Cystic bronchiectasis (↳)(30-50%) associated with thick-walled varicoid and cylindrical bronchiectasis
- Cystic spaces within dense fibrotic and post-infectious conglomerates (⇨)





✓ The bronchiectasis may be filled with air, mucous or an exudate produced by superinfections, in which case they exhibit air fluid levels or appear totally opaque (mucoid impaction)

Helbich TH. Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology 1999, 213: 537
Ruzal-Shapiro C. Cystic fibrosis. An overview. Radiol Clin North Am 1998, 36: 143

Distribution

Bilateral, patchy

Central parahilar, but also peripheral

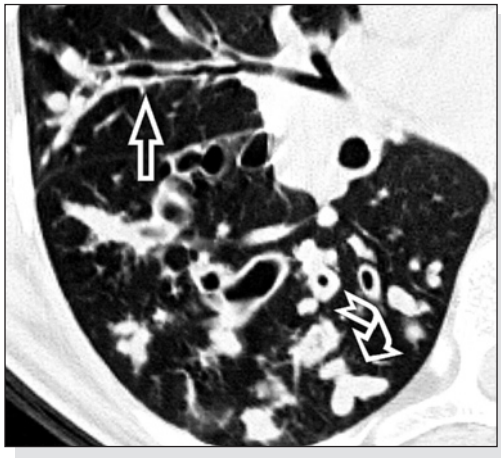
Predominance in the upper lobes and the dorsal segment of the lower lobes, especially right-sided

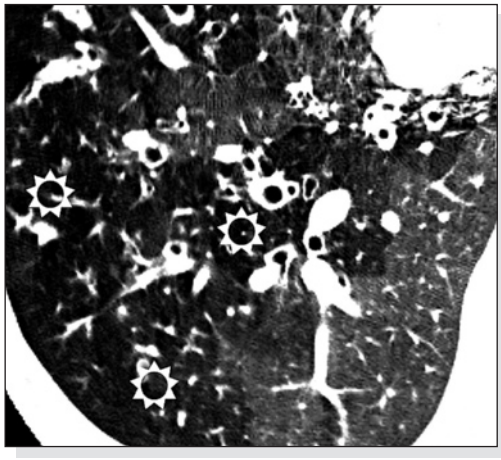
Lung volume is increased

Other signs

Other radiological signs:

- Varicose and cylindrical bronchiectasis (⇨), either empty or filled; bronchiolectasis with tree-in-bud pattern (↳)
- Scattered areas of mosaic perfusion (☼) with air-trapping from concurrent bronchiolitis obliterans
- Inflammatory consolidations
- Hilar and mediastinal lymph node enlargement due to chronic infection
- Chronic cor pulmonale in the advanced stages of disease





Maffessanti M. Cystic fibrosis in children: HRCT findings and distribution of disease. J Thorac Imaging 1996, 11: 27

Differentials

Radiological differential diagnoses:

- ABPA: the bronchiectasis is decidedly more central, although the radiological appearance is similar in more involved cases
- Tracheobronchomegaly (Mounier-Kuhn syndrome): the trachea and the main bronchi are dilated and deformed
- Williams-Campbell syndrome: the bronchiectasis is almost exclusively cystic, while mosaic oligemia with air-trapping is extensive
- LCH: the cysts are diffuse and randomly distributed, and not noticeably adjacent to the bronchial structures. Air fluid levels are never present

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomogr 2002, 26: 5

COURSE and COMPLICATIONS

Associated diseases

In 5-10% of patients, ABPA may develop. Pneumothorax is seen in 7-49% of cases. CF patients have a higher incidence of atopy and asthma compared to patients with bronchiectasis unrelated to CF

Clinical course

Failure of mucociliary clearance results in bronchiectasis and recurrent bacterial infection (Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Burkholderia cepacia). There is a gradual worsening in lung function which ultimately leads to respiratory failure, pulmonary arterial hypertension and right heart failure (the main cause of death). Infection also causes a chronic state of malnutrition which can accelerate the progression of the disease. Recent advances in medical treatment and early diagnosis have markedly improved the life expectancy of patients with CF (40 years). Airway colonization by Pseudomonas and Burkholderia negatively affects prognosis

Radiological course

Serial CT follow-up has demonstrated a progressive spread of cystic spaces in the lung, alternating between empty and filled bronchiectasis even in relation to postural drainage, and consolidation linked to infectious exacerbations

Helbich TH. Evolution of CT findings in patients with cystic fibrosis. AJR Am J Roentgenol 1999, 173: 81

Shah RM. High-resolution CT in the acute exacerbation of cystic fibrosis: evaluation of acute findings, reversibility of those findings, and clinical correlation. AJR Am J Roentgenol 1997, 169: 375

LABORATORY FINDINGS

Most patients with CF have a positive sweat chloride test (Cl>60 mEq/L). Neutrophilic leukocytosis is also common

CLINICAL DIAGNOSIS

The diagnosis suggested by family history, persistent respiratory symptoms and clinical evidence of pancreatic insufficiency requires confirmation by a sweat chloride test or chromosome analysis. HRCT may at times be the first investigation to suggest the disease in adults and is valuable in providing a spatial analysis of lung changes, as well as being useful in planning postural drainage and follow-up

INVASIVE DIAGNOSIS

Lung biopsy is indicated only in cases of pulmonary complications unidentifiable with other methods

Bronchoalveolar lavage

BAL total cell count is highly increased (10-14 times) and the fluid is rich in polymorphonuclear neutrophils (50-60%). An increase in interleukin-8, leukotriene B4, elastase and metalloproteinase in the supernatant has also been reported. According to some authors, BAL is useful for microbiological testing in acute infectious exacerbations when antibiotic treatment, either based on sputum culture or empirically established, has failed

Konstan MW. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. Am J Respir Crit Care Med 1994, 150: 448

Scleroderma

Definition

Collagen vascular diseases are a heterogeneous group of diseases characterized by the presence of circulating autoantibodies which cause inflammatory damage to various organs or tissues. The patterns of lung disease in collagen vascular diseases include fibrosing alveolitis, bronchiolitis, OP, parenchymal nodules, pleuritis, and vasculitis

Scleroderma in its advanced phase will be covered in this chapter as a representative example of collagen vascular diseases. In the early phase the lungs are affected by fibrosing alveolitis with a reticular radiological appearance (☐ Collagen vascular diseases, early), while in the advanced stage they show a diffuse cystic pattern

Progressive Systemic Sclerosis (PSS)

Other collagen vascular diseases which may affect the lungs in the form of fibrosis and diffuse infiltrative disease are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), CREST syndrome, Sjögren's syndrome, dermatomyositis-polymyositis (DM/PM), mixed connective tissue disease (MCTD)

Hunninghake GW. Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 1979, 119: 471

DEMOGRAPHICS

Etiology and pathogenesis

The precise pathogenesis of lung involvement is unknown. Experimental data suggest that a fundamental role is played by alveolar macrophages which are thought to produce factors involved in chemotaxis and the activation of fibroblasts such as tumor necrosis factor-alpha, transforming growth factor-beta, fibronectin and insulin-like growth factor-I. Alveolar macrophages are also thought to produce increased amounts of interleukin-8, a powerful chemokine for neutrophils. Mastocytes and their mediators are also thought to play a role in the pathogenesis of the disease, together with endothelin-1, a factor produced by endothelial cells which directly stimulates the fibroblasts. The "coordinating" cells of these processes are thought to be CD8+ T cells of mostly Tc2 phenotype

Epidemiology

Scleroderma is a rare disease (12 cases per million/year) which primarily afflicts adults between the age of 30 and 50 years, with women being more commonly affected (3:1). The lung is affected in more than 70% of patients with scleroderma, which makes it the second most frequently affected organ after the esophagus

Risk factors

Lung involvement is more common in patients with genetic markers such as HLA-DR3/DR52a, specific autoantibodies (Scl-70, anti-U3RNP, antitopoisomerase I, antihistone) and in African American patients

CLINICAL FEATURES

History

The most common symptoms in this advanced phase are dyspnea at rest and dry cough. Chest pain and hemoptysis are rare

Physical findings

The main physical findings are diffuse fine bibasilar rales. Pulmonary hypertension (increased second heart sound, epigastric pulsation) and right-sided heart failure (jugular venous distension, enlarged and tender liver, peripheral edema) may also be present

Pulmonary function tests

In addition to pronounced reduction in D_LCO functional tests in this phase of the disease, a more-or-less marked restrictive defect and respiratory failure are present, characterized by hypoxemia with normocapnia or hypocapnia. Fibrosing involvement of chest skin rarely alters pulmonary function tests

The clinical findings of scleroderma lung disease are similar to UIP

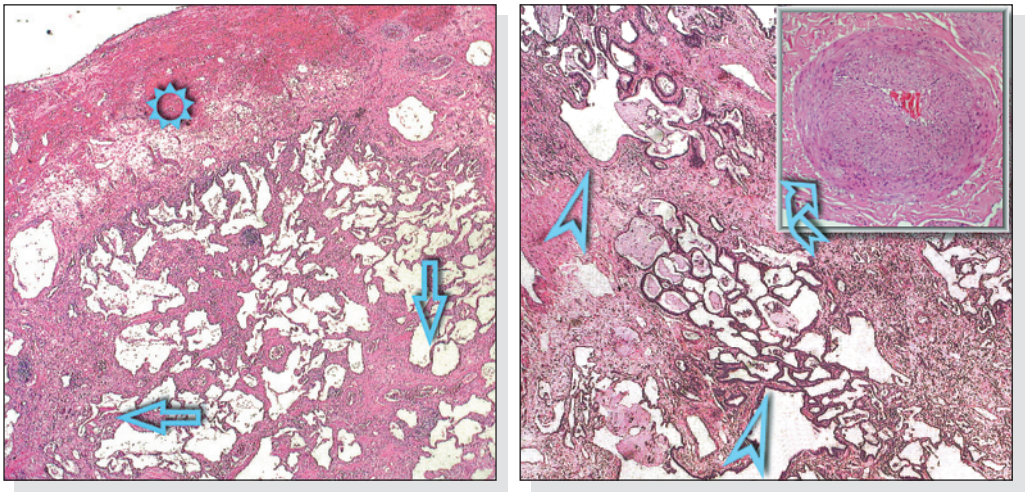
Lamblin C. Interstitial lung diseases in collagen vascular diseases. Eur Respir J Suppl 2001, 32: 69s

PATHOLOGY

Basic lesions

Histopathologic changes include:

- Interstitial fibrosis (⇨) associated with pleural fibrosis (☼)
- Vascular lesions (medial smooth muscle hypertrophy (↳) and intimal proliferation)
- Microcystic and macrocystic changes (honeycombing)(➢)



Distribution

Diffuse interstitial and subpleural

Differentials

Histopathologic differential diagnoses:

- UIP: lesions are often morphologically indistinguishable, even though vascular changes are less marked and fibroblastic foci more numerous
- Asbestosis: uniform fibrosis with limited fibroblastic foci; presence of asbestos bodies
- HP: distribution may be peribronchiolar with poorly-formed granulomas; in advanced stages the primary disease may no longer be identifiable
- Sarcoidosis: confluent non-necrotizing granulomas within areas of extensive fibrosis; a lymphatic distribution may be seen. Fibroblastic foci are absent

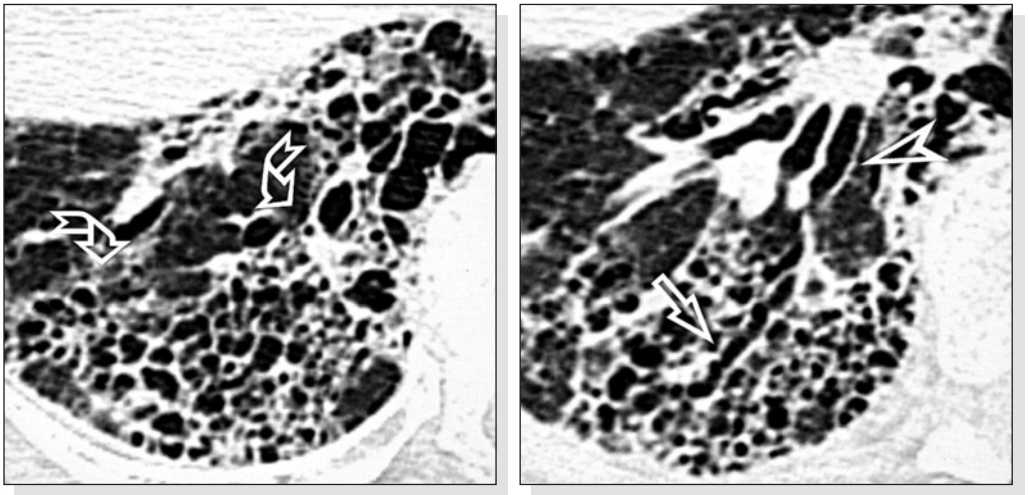
Bouros D. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002, 165: 1581

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Small rounded cysts (2-10 mm) which share thick walls. The cysts are distributed in concentric layers in the subpleural region (↳)(honeycombing)
- Corkscrew-like traction bronchiectasis (➢) and bronchiolectasis (⇨)



Schurawitzki H. Interstitial lung disease in progressive systemic sclerosis: high resolution-CT versus radiography. Radiology 1990, 176: 755

Distribution

Bilateral, patchy

Peripheral subpleural, more prominent posteriorly

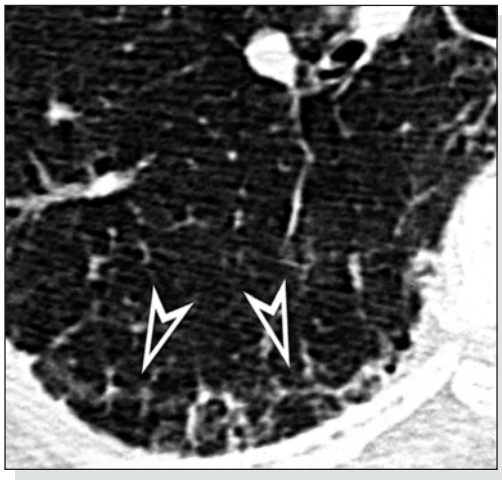
Predominantly basal

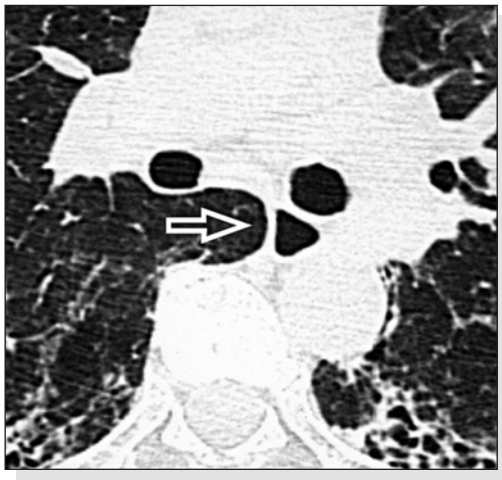
Lung volume is reduced

Other signs

Other signs:

- Irregular intralobular reticular pattern (➢)
- Ground-glass opacity with bronchiolectasis (fibrotic ground-glass opacity)
- Unilateral pleural thickening or effusion (one third of cases)
- Mediastinal lymph node enlargement (60%)
- Esophageal dilatation (⇨)(40-80%)





The simultaneous presence of ground-glass opacity, bronchiolectasis and a reticular pattern in the same lung zones is a sign of irreversible fibrosis

Bhalla M. Chest CT in patients with scleroderma: prevalence of asymptomatic esophageal dilatation and mediastinal lymphadenopathy. AJR Am J Roentgenol 1993, 161: 269

Mayberry JP. Thoracic manifestations of systemic autoimmune diseases: radiographic and high-resolution CT findings. Radiographics 2000, 20: 1623

Differentials

Radiological differential diagnoses:

- UIP: the CT pattern is similar, although the honeycombing is more marked and coarser. The typical findings associated with each collagen vascular disease are absent
- Asbestosis: pleural plaques that are often calcific are also present
- HP: patchy ground-glass opacity associated with hazy centrilobular nodules, with a distribution which may be predominant in the middle-upper regions
- Collagen vascular diseases: all of the findings presented (appearance and distribution) are essentially shared by all of the collagen vascular diseases. The differential features are:
  - Mosaic perfusion and/or air-trapping due to BO in RA
  - Peripheral nodules and opacities with well-defined margins, possibly cavitating, together with cylindrical bronchiectasis in RA
  - Bilateral consolidations in RA, SLE and DM

Chan TY. Cryptogenic fibrosing alveolitis and the fibrosing alveolitis of systemic sclerosis: morphological differences on computed tomographic scans. Thorax 1997, 52: 265

Kim EA. Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. Radiographics 2002, 22: S151

COURSE and COMPLICATIONS

Associated diseases

These include opportunistic lung infections (these patients are immunosuppressed by their disease and the use of immunosuppressive drugs), aspiration pneumonia, drug-associated pneumonia (☐ Drug toxicity; ⌘ Drug toxicity), pleuritis, and alveolar hemorrhage, spontaneous pneumothorax due to cyst rupture, and lung tumors. Ten percent of cases are associated with pulmonary hypertension due to direct involvement of the pulmonary circulation without fibrosing lung disease

Clinical course

Progression of the fibrosis leads to respiratory failure and consequent pulmonary hypertension. Lung involvement is the most common cause of death in these patients, with a 5 year survival rate of 49-67%

Radiological course

Slow extension and progression of the reticular pattern and honeycombing; possible increase in cyst diameter and reduction in wall thickness, with signs of chronic cor pulmonale

Remy-Jardin M. Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. Radiology 1993, 188: 499

LABORATORY FINDINGS

Antinuclear antibodies are found in most patients. The presence of antitopoisomerase I (topo I or Scl-70) or antihistone is associated with more severe lung fibrosis. Patients with fibrosing alveolitis in the course of scleroderma are reported to have increased serum levels of KL-6, a glycoprotein mainly present in type-II pneumocytes and alveolar macrophages. According to some authors, KL-6 levels are useful in diagnosing and monitoring the disease

CLINICAL DIAGNOSIS

In patients with scleroderma, a CT scan exhibiting characteristic features can be considered sufficient for diagnosing fibrosing lung involvement without the need for lung biopsy

INVASIVE DIAGNOSIS

Biopsy may be useful in diagnosing infectious complications or concomitant malignancy

Bronchoalveolar lavage

BAL is characterized by an increase in total cell count and granulocytes, particularly neutrophils and eosinophils. BAL plays a part in prognosis, since the presence of persistent alveolitis is associated with more severe lung function deterioration and faster progression of the disease

BAL is useful in the diagnosis of complications (aspiration pneumonia, drug-induced pneumonia, concomitant infections or malignancy, etc.)

Manganelli P. Clinical and subclinical alveolitis in connective tissue diseases assessed by bronchoalveolar lavage. Semin Arthritis Rheum 1997, 26: 740

Silver RM. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. Am J Med 1990, 88: 470

Centrilobular and paraseptal emphysema

Definition

Emphysema is the abnormal permanent enlargement of the air spaces distal to the terminal bronchiole, accompanied by the destruction of their walls

There are three types of emphysema - panlobular, centrilobular and paraseptal - only the latter two present a diffuse cystic pattern and therefore only these two are covered in this chapter. In addition, centrilobular and paraseptal emphysema often coexist

Centrilobular emphysema: this form involves the respiratory bronchioles and the adjacent alveoli. This pattern is typical of smokers with chronic obstructive pulmonary disease and is predominant in the upper and posterior portion of the lung

Paraseptal emphysema: this form involves the distal part of the lobule along the interlobular septa and the subpleural regions. This pattern generally does not cause clinical disturbances unless it progresses to bullous emphysema or is complicated by pneumothorax

Centriacinar and distal acinar emphysema

DEMOGRAPHICS

Etiology and pathogenesis

The pathogenesis is thought to be due to an imbalance in the protease-antiprotease ratio. Another hypothesis suggests an inflammatory mechanism playing a pathogenetic role in the development of emphysema. It is likely that both mechanisms are involved

Epidemiology

Although the precise epidemiology of emphysema is uncertain, chronic obstructive pulmonary disease (COPD), which includes both emphysema and chronic bronchitis, is currently the twelfth most common disease throughout the world and the forth leading cause of death in the United States

Risk factors

The protease-antiprotease imbalance in centrilobular emphysema is triggered by cigarette smoke, environmental pollution and occupational exposure to toxic dusts or fumes. Paraseptal emphysema is idiopathic

CLINICAL FEATURES

History

Clinical and functional signs may be totally absent in patients with paraseptal emphysema

The presenting manifestations of patients with centrilobular emphysema are constant and worsening dyspnea on exertion. Patients with associated bronchitis also report chronic productive cough

Physical findings

Patients with centrilobular emphysema have an increased respiratory rate and often breathe with pursed lips. They may show cyanosis and, once pulmonary hypertension has developed, signs of right-sided heart failure (jugular venous distension and peripheral edema)

On percussion the entire lung field is hyperresonant, and the area of superficial cardiac dullness is no longer definable

Auscultation reveals distant cardiac sounds, markedly diminished breath sounds, prolonged expiration and at times expiratory wheezes and ronchi

Pulmonary function tests

Spirometry shows non-reversible airflow obstruction with increased residual volume. The D_LCO is commonly low, the arterial PaO_2 is mildly or moderately reduced with or without hypercapnia in proportion to the severity of airflow obstruction

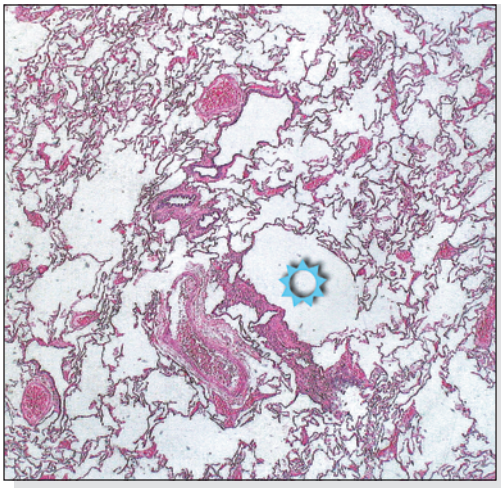
Chitkara RK. Recent advances in diagnosis and management of chronic bronchitis and emphysema. Curr Opin Pulm Med 2002, 8: 126-36

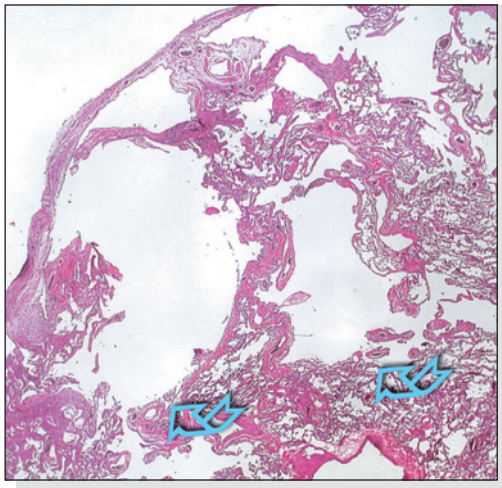
PATHOLOGY

Basic lesions

Abnormal and permanent enlargement of the air spaces distal to the terminal bronchiole, with destruction of the walls, in the absence of significant fibrosis

- In centrilobular emphysema the respiratory bronchioles are enlarged and destroyed at the centre of the acinus (☼). The resulting spaces may coalesce to form macroscopic parenchymal "holes". Frequently associated are other smoke related lesions, such as respiratory bronchiolitis
- In paraseptal emphysema the distal acinus is involved
  The alveolar ducts are enlarged and destroyed, sometimes leading to the formation of subpleural blebs or even bullae (↳)





Distribution

Conventionally, bullae are air spaces larger than 1 cm, with thick fibrous walls. The pleura above the bullae may exhibit an inflammatory infiltrate, sometimes rich in eosinophils (eosinophilic pleuritis)

Around the respiratory bronchioles in centrilobular emphysema, and along the interlobular septa and below the pleura in paraseptal emphysema

Differentials

Histopathologic differential diagnoses:

- Compensatory overinflation (e.g. following unilateral pneumonectomy): air spaces are dilated, but without wall destruction
- Artifacts: alveolar walls are destroyed through manipulation of the surgical specimen
- LAM: presence of interstitial smooth muscle positive to HMB45
- LCH: cysts have fibrous walls and stellate nodules are also present
- Honeycombing: fibrosis is associated with parenchymal remodeling, whereas the cysts are often covered by metaplastic bronchiolar epithelium
- Bronchiolectasis: "cysts" are dilatations of the bronchiolar lumina and therefore lined by bronchiolar epithelium. The walls may contain bundles of smooth muscles of the muscularis mucosae. Varying degrees of inflammation and fibrosis are often present
- Panlobular emphysema: enlargement of the air spaces is diffuse throughout the acinus

Snider GL. Pathogenesis and terminology of emphysema. Am J Respir Crit Care Med 1994, 149: 1382

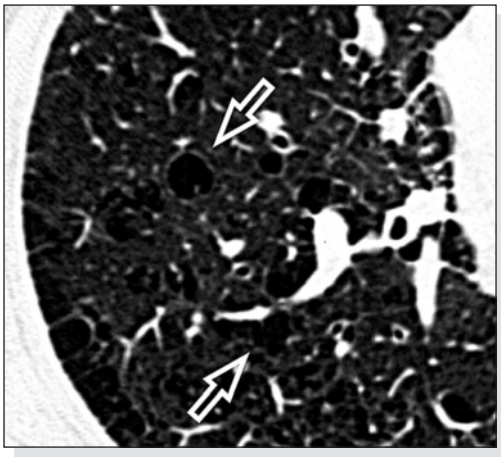
Wright JL. Emphysema: concepts under change-a pathologist's perspective. Mod Pathol 1995, 8: 873

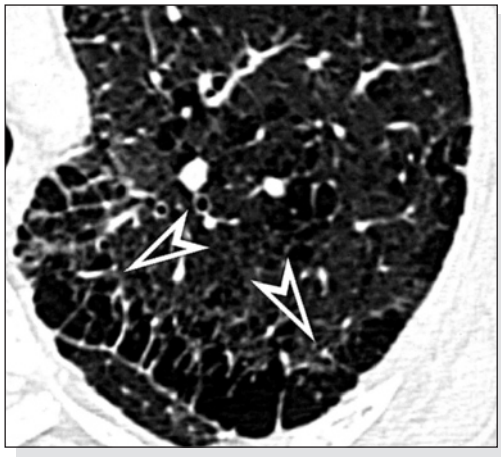
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

The radiological findings depend on the type of emphysema:

- Centrilobular emphysema: small lucencies lacking visible walls, surrounded by normal parenchyma (⇨). They may be rounded or oval in shape and are often smaller than one centimeter
- Paraseptal emphysema or bullae: small lucencies arranged in a single layer (➢), with thin walls (these are formed by interlobular septa at times thickened by minimal fibrosis). If the diameter of the areas of low attenuation exceeds one centimeter, the term bullae is used





In centrilobular emphysema the lucencies may be "centered" by a small hyperdense area produced by the centrilobular arteriole. Occasionally a thin opaque border produced by the limited fibrotic component may be visible

Thurlbeck WM. Emphysema: definition, imaging, and quantification. AJR Am J Roentgenol 1994, 163: 1017

Distribution

Bilateral, often symmetrical

In centrilobular emphysema there is random distribution. In paraseptal emphysema the cysts are subpleural, even along the visceral surfaces of the pleura

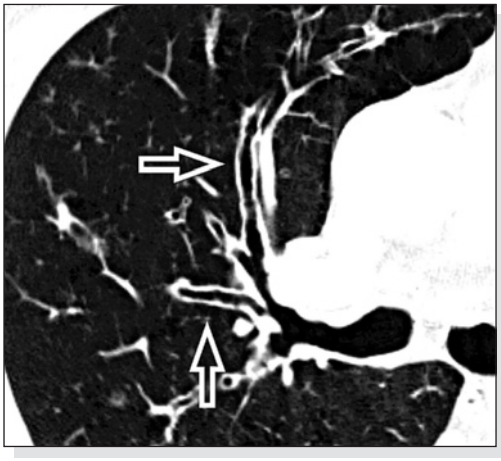
Upper-lobe predominance

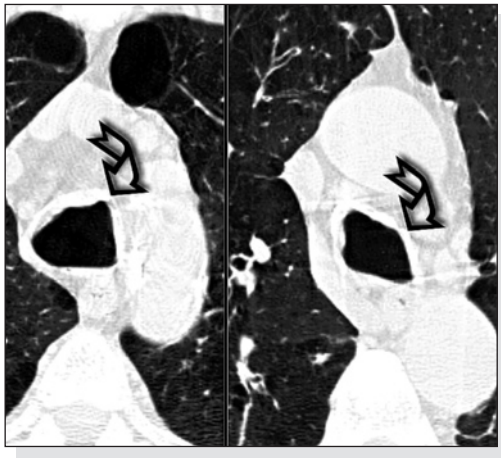
Other signs

Normal in the early forms and pure paraseptal emphysema; increased in advanced centrilobular emphysema

Other radiological signs:

- Bronchial wall thickening (⇨) (due to concomitant bronchitis)
- Pulmonary arterial hypertension (diameter of the main artery >27 mm)
- Moderate mediastinal lymphadenomegaly (due to chronic airway infection)
- Luminal changes in the intrathoracic trachea (↯)





Arakawa H. Computed tomography measurements of overinflation in chronic obstructive pulmonary disease: evaluation of various radiographic signs. J Thorac Imaging 1998, 13: 188

Differentials

Radiological differential diagnoses:

- LAM: cysts have thin walls and involve the lungs extensively from the apices to the bases, including the costophrenic sinuses. Unilateral pleural effusion and angiomyolipomas may be seen
- LCH: cysts have clearly defined walls of uneven thickness. Their appearance is less regular and the individual lesions may coalesce giving rise to bizarre shapes
- UIP: thick-walled cysts in basal lung zones are subpleural as in paraseptal emphysema but are in several concentric layers. Traction bronchiectasis and bronchiolectasis may also be seen
- Panlobular emphysema: there are no cysts, but rather widespread areas of low attenuation. Lucencies are dominant in the lower lobes

Bonelli FS. Accuracy of high-resolution CT in diagnosing lung diseases. AJR Am J Roentgenol 1998, 170: 1507

Takasugi JE. Radiology of chronic obstructive pulmonary disease. Radiol Clin North Am 1998, 36: 29

COURSE and COMPLICATIONS

Associated diseases

Patients with emphysema have an increased susceptibility to respiratory infections and may easily develop bronchiectasis. Pneumothorax is not rare, particularly in paraseptal emphysema

Clinical course

The natural progression is towards chronic respiratory failure, with pulmonary arterial hypertension in the more severe cases

Radiological course

Increase in the size of lucencies which tend to coalesce to involve the entire lobule and occupy increasingly extensive areas of parenchyma. The bullae may become very large

The extension of an initially centrilobular lesion to the entire lobule and the involvement of several adjacent lobules creates a pattern of diffuse low attenuation similar to that seen in panlobular emphysema; the lucencies, however, are always predominant in the upper lung regions

LABORATORY FINDINGS

During acute exacerbation the patients may have neutrophilic leucocytosis. Erithrocytosisis is observed when arterial PaO_2 falls below 55 mmHg

CLINICAL DIAGNOSIS

Diagnosis of emphysema is made on the basis of clinical, radiological and functional findings

INVASIVE DIAGNOSIS

There is no need for invasive diagnostic procedures. Moreover, emphysema is a frequent histopathologic finding in patients who have undergone biopsy or lung resection for other reasons

Transbronchial biopsy is contraindicated in emphysema due to the risk of pneumothorax

Bronchoalveolar lavage

Bronchoalveolar lavage has been performed in patients with emphysema only for research purposes. Findings have demonstrated an increase in neutrophils and their products such as proteases (elastases and metalloproteinases) and toxic oxygen radicals

Finlay GA. Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysematous patients. Thorax 1997, 52: 502

Lymphangioleiomyomatosis

Definition

Lymphangioleiomyomatosis (LAM) is a rare lung disease affecting young premenopausal women and characterized by the proliferation of atypical smooth muscle cells and the presence of cysts in the lungs

DEMOGRAPHICS

Etiology and pathogenesis

Although the pathogenesis of the disease is unknown, a number of studies suggest the loss of tumor-suppression function by certain cellular enzymes, or an abnormality in proteins involved in the synthesis of catecholamines. The influence of hormones is also important, given that the disease almost exclusively affects premenopausal women

Epidemiology

Little is known about the epidemiology of LAM. Estimates suggest it accounts for about 1% of all diffuse infiltrative lung diseases. The white population is affected more commonly than others, and two thirds of patients are aged 20-40 years at the time of diagnosis

Risk factors

Pregnancy and the use of estrogen may accelerate the progression of the disease. Estrogen replacement therapy in menopause is a risk factor

CLINICAL FEATURES

History

Almost all patients report gradual onset dyspnea on exertion. Acute dyspnea, on the other hand, is due to associated pneumothorax. Other common symptoms include cough and chest pain

Physical findings

Although physical examination may be normal, 22% of patients may have diffuse fine rales and/or decreased breath sounds. Clubbing is uncommon

Pulmonary function tests

Pulmonary function tests show an obstructive or mixed pattern. Residual volume and total lung capacity are increased. Most patients also have a marked reduction in D_LCO

Hancock E. Lymphangioleiomyomatosis: a review of the literature. Respir Med 2002, 96: 1

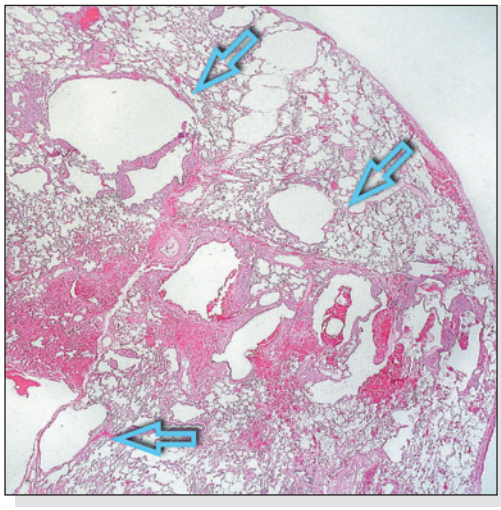
Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. Thorax 1999, 54: 254

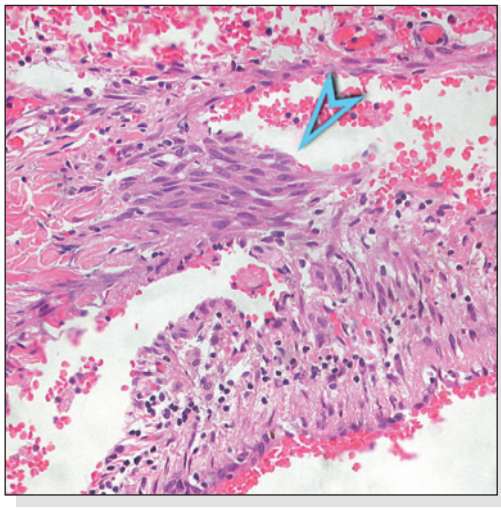
PATHOLOGY

Basic lesions

The histopathologic changes are the following:

- Intraparenchymal cystic spaces (⇨) associated with subpleural emphysema
- Cyst walls are irregularly thickened by disarranged and immature smooth muscle tissue (➢), with shorter bundles





The smooth muscle tissue stains positive for HMB45, muscle markers (actin, desmin) and often for estrogen and progesterone receptors

LAM is an abnormal and multifocal proliferation of immature smooth muscle cells of the pulmonary interstitium which may extend to the pulmonary veins (with passive congestion responsible for intraparenchymal microhemorrhages), the bronchovascular bundles (with air-trapping), the thoracic duct and the thoracic and retroperitoneal lymphatics (with possible rupture into the pleural cavity and chylothorax)

Distribution

The distribution of the disease is predominantly lymphatic. The lesions are often situated along the interlobular septa, the subpleural regions and sometimes around the bronchovascular bundles

Differentials

Histopathologic differential diagnoses:

- LCH: cystic lesions are associated with nodules and do not contain smooth muscle tissue in their walls. The lesions are positive for S-100 and CD1a, and negative for HMB45, muscle markers, and estrogen and progesterone receptors
- Centrilobular emphysema: thin-walled cysts without muscle cell proliferation
- Benign metastasizing leiomyoma: predominantly nodular (although cysts may form within) and negative for HMB45

Corrin B. Pulmonary lymphangiomyomatosis. A review. Am J Pathol 1975, 79: 348

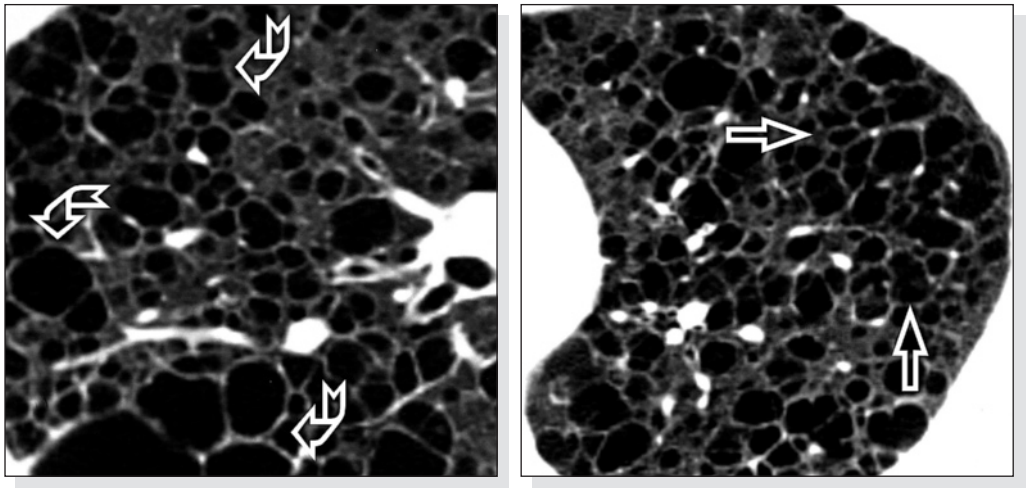
Taylor JR. Lymphangioleiomyomatosis. Clinical course in 32 patients. N Engl J Med 1990, 323: 1254

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Rounded cysts (↳) 1-2 cm in diameter. No vessels are identifiable within the cysts
- Lesions are uniform in shape and have thin walls (⇨), tending to give an overall homogeneous, "lacy" appearance



Kirchner J. Pulmonary lymphangioleiomyomatosis: high-resolution CT findings. Eur Radiol 1999, 9: 49

Distribution

Bilateral, homogeneous and symmetrical

Diffuse, random

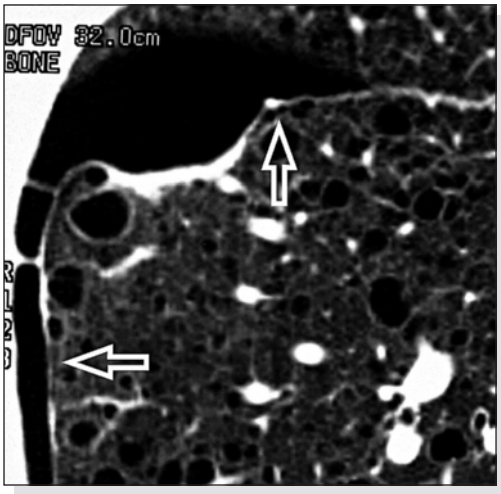
From the apices to the bases, including the costophrenic sinuses

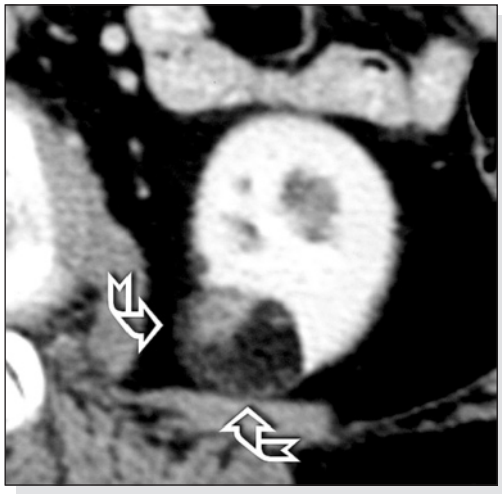
Lung volume is normal or increased (50%)

Other signs

Other radiological signs:

- Pneumothorax (⇨)(50%)
- Enlargement of hilar, mediastinal and retrocrural lymph nodes (40%)
- Unilateral pleural effusion (14%); less commonly pericardial
- Ground-glass opacity due to hemorrhage and smooth thickening of the interlobular septa due to edema (rare)
- Renal angiomyolipomas (↳)(50%), often bilateral
- Chylous ascites and enlargement of retroperitoneal lymph nodes





Avila NA. Lymphangioleiomyomatosis: abdominopelvic CT and US findings. Radiology 2000, 216: 147

Chu SC. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999, 115: 1041

Differentials

Radiological differential diagnoses:

- LCH: cysts have thick walls, irregular morphology with bizarre shapes and are absent in the costophrenic sinuses. Cavitating micronodules may also be present, while pleural effusion is absent
- Cystic bronchiectasis: cysts are clustered together with a patchy distribution and air fluid levels are often present. There is also cylindrical and varicose bronchiectasis

Bonelli FS. Accuracy of high-resolution CT in diagnosing lung diseases. AJR Am J Roentgenol 1998, 170: 1507

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomog 2002, 26: 5

COURSE and COMPLICATIONS

Associated diseases

About 50% of patients have renal angiomyolipomas. An increased incidence of meningiomas has also been reported

Clinical course

The prognosis is variable and the median survival time is 8-10 years from the time of diagnosis. Possible complications include spontaneous pneumothorax (50%), which is often recurrent and at times bilateral, chylothorax (28%), and hemoptysis (40%), that may be life-threatening. Other non-pulmonary complications include chylous ascites, chyluria and chylopericardium

According to some authors, prognosis is correlated with the percentage of tissue involvement in the two major features of LAM: cystic lesions and abnormal smooth muscle cell proliferation (LHS = LAM histologic score)

Matsui K. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. Am J Surg Pathol 2001, 25: 479

Radiological course

Over the years the cysts tend to increase in number and size. There may be a recurrence of LAM even in a transplanted lung

Nine JS. Lymphangioleiomyomatosis: recurrence after lung transplantation. J Heart Lung Transplant 1994, 13: 714

LABORATORY FINDINGS

Hematological examinations show no alterations, with the exception of rare cases of increased serum levels of angiotensin-converting enzyme

CLINICAL DIAGNOSIS

The diagnosis of LAM should be strongly considered in the case of a young woman presenting recurrent pneumothorax or emphysema or chylous pleural effusion. HRCT has a high level of diagnostic accuracy (>80%), which becomes almost total when associated with a compatible history. Diagnostic certainty can only be obtained by biopsy

INVASIVE DIAGNOSIS

Transbronchial lung biopsy may collect sufficient pathological tissue for diagnostic purposes. The use of specific immunohistochemical staining for smooth muscle (desmin or HMB-45 antibody) increases diagnostic accuracy, thus reducing the need for surgical biopsy

Bronchoalveolar lavage

BAL fluid often shows hemorrhagic alveolitis (erythrocytes and siderophages), although this finding has no diagnostic implications

Chu SC. Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999, 115: 1041

Langerhans' Cell Histiocytosis

Definition

Langerhans' cell histiocytosis (LCH) is a rare disease which predominantly affects young adults. The disease is characterized by pulmonary proliferation of special histiocytes known as Langerhans' cells
In the early stages, LCH exhibits a diffuse nodular pattern (● LCH, early), while in advanced stages the pattern is prevalently cystic. This chapter will cover the latter

☯ Pulmonary eosinophilic granuloma, pulmonary Langerhans' cell granulomatosis, histiocytosis X

DEMOGRAPHICS

Etiology and pathogenesis

The pathogenesis of the disease is unknown, although epidemiological data strongly suggest an altered response to cigarette smoke. Viral and neoplastic causes have also been suggested

Epidemiology

The disease is rare and its true incidence and prevalence are unknown. It predominantly affects young adults (20-40 years) and has no sex predilection. The disease is more common among the white population than among blacks

Risk factors

Almost all patients are smokers or ex-smokers. There are no known geographical or occupational risk factors

📖 Vassallo R. Pulmonary Langerhans'-cell histiocytosis. N Engl J Med 2000, 342: 1969

CLINICAL FEATURES

History

Clinical presentation is variable: (1) incidental finding upon chest radiography (20-25%); (2) following a spontaneous pneumothorax; and (3) the presence of respiratory or constitutional symptoms. The most common symptoms are dry cough (55-70%), dyspnea (40-85%), fatigue (30%), weight loss (20-30%), chest pain (10-20%), and fever (15%)

Physical findings

Physical examination is generally unremarkable. Rare findings include crackles and digital clubbing

Pulmonary function tests

A reduction in D_LCO is the first functional alteration detectable. In the advanced stage a mixed restrictive-obstructive defect may be seen with an increase in residual volume

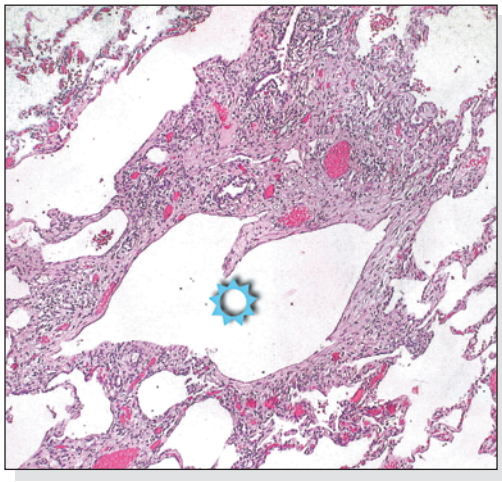
📖 Crausman RS. Pulmonary histiocytosis X: pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med 1996, 153: 426

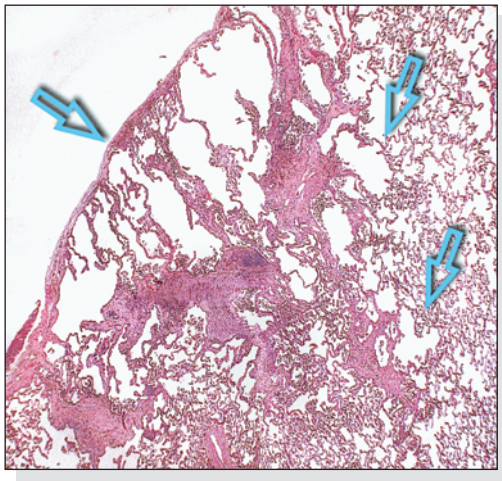
PATHOLOGY

Basic lesions

The nodular lesions of Langerhans' cell histiocytosis may progress to small stellate scars with the most active areas at the periphery, followed by the formation of:

- Cavitating lesions/cysts (☼) within the stellate scars
- Foci of microscopic emphysema (around the fibrous tissue) in the adjacent parenchyma (⇨)
- Diffuse fibrosis secondary to the coalescence of single fibrotic lesions (rare)





In advanced cases, Langerhans' cells may be few or absent, and it becomes difficult to establish the etiology of the disease at this stage

Distribution

Many lesions are centered on the small airways. A point of origin may not be identifiable in advanced lesions

Differentials

Histopathologic differential diagnoses:

- LAM: presence of interstitial smooth muscle, positive to HMB45 staining
- Centrilobular emphysema: neither nodules nor fibrosis are seen

Colby TV. Histiocytosis X in the lung. Hum Pathol 1983, 14: 847

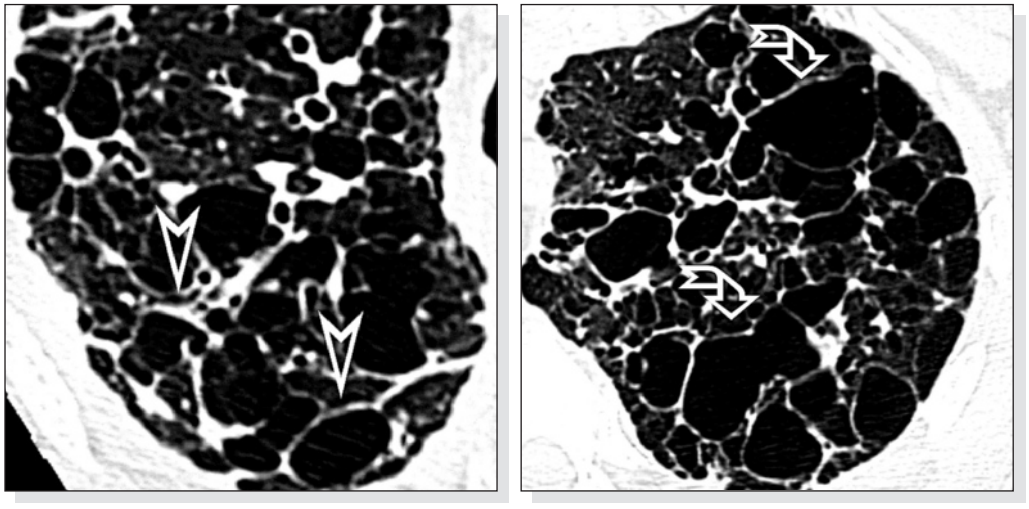
Desai SR. Smoking-related interstitial lung diseases: histopathological and imaging perspectives. Clin Radiol 2003, 58: 259

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Thick-walled cysts of varying size, with a diameter 1-2 cm (≥)
- Cyst morphology is highly variable, with some cysts exhibiting bizarre shapes due to coalescence (↳)



The cysts are completely empty. No structures, particularly vascular structures, are ever seen inside them

Abbott GF. From the archives of the AFIP: pulmonary Langerhans' cell histiocytosis. Radiographics 2004, 24: 821

Brauner MW. Pulmonary Langerhans' cell histiocytosis: evolution of lesions on CT scans. Radiology 1997, 204: 497

Kulwiec EL. Imaging of pulmonary histiocytosis X. Radiographics 1992, 12: 515

Distribution

Bilateral, homogeneous and symmetrical

Random

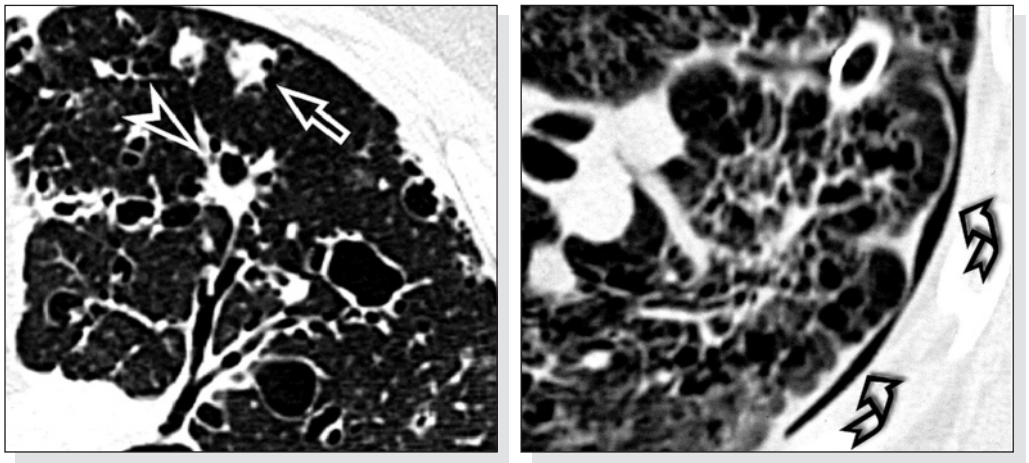
The lesions predominate in the middle-upper regions and are absent in the bases and costophrenic sinuses

Lung volume is increased

Other signs

Other radiological signs:

- Dense centrilobular nodules with diameter <10 mm (⇨), often cavitating (➢)(cheerios pattern)
- Mosaic oligemia perfusion with air-trapping due to bronchiolar obstruction
- Lymphadenomegaly is relatively uncommon
- Pneumothorax (↯)(10%)



The nodules are an expression of disease activity, and are predominant finding in the early stages (● LCH, early)

Stern EJ. Cystic lung disease associated with eosinophilic granuloma and tuberous sclerosis: air trapping at dynamic ultrafast high-resolution CT. Radiology 1992, 182: 325

Differentials

Radiological differential diagnoses:

- LAM: cysts have thin walls, regular shape, uniform size, are not confluent and also involve the costophrenic sinuses. Pleural effusion may also be present
- Centrilobular emphysema: cysts have no walls, or on rare occasions have a thin border. A small opacity produced by the arteriole is often identifiable within the cysts. Subpleural cysts in a single layer due to paraseptal emphysema often coexist
- Cystic bronchiectasis: cysts are clustered with a patchy distribution and air fluid levels are often present. Cylindrical and varicose bronchiectasis are also present

Bonelli FS. Accuracy of high-resolution CT in diagnosing lung diseases. AJR Am J Roentgenol 1998, 170: 1507

Hansell DM. Bronchiectasis. Radiol Clin North Am 1998, 36: 107

COURSE and COMPLICATIONS

Associated diseases

A number of benign or malignant tumors have been reported, particularly bronchogenic carcinoma (5%), Hodgkin's and non-Hodgkin's lymphoma, and pulmonary carcinoid tumor. There may also be pulmonary hypertension due to venous occlusive disease

In the systemic form affecting adolescents (Hand-Schüller-Christian disease) there may be involvement of bone (lytic lesions) or hypothalamus (diabetes insipidus)

Clinical course

More than 25% of patients develop recurrent spontaneous pneumothorax, while 13% have episodes of hemoptysis which is indicative of an infection in the cystic spaces (e.g. Aspergillus). At this stage the disease does not regress, even if the patient quits smoking. Cases have been reported of relapse after years of radiological remission, and recurrence is even possible after lung transplant. Pulmonary arterial hypertension appears to be common in the advanced stages

Etienne B. Relapsing pulmonary Langerhans' cell histiocytosis after lung transplantation. Am J Respir Crit Care Med 1998, 157: 288

Radiological course

The cysts tend to enlarge and their walls become thin with a pattern which may be indistinguishable from that of LAM and confluent emphysema. This pattern is indicative of the inactive or advanced phase of the disease. With the appearance of pulmonary arterial hypertension, the diameter of the main pulmonary artery increases (>27 mm)

Abbott GF. From the archives of the AFIP: pulmonary Langerhans' cell histiocytosis. Radiographics 2004, 24: 821

LABORATORY FINDINGS

Laboratory investigations are normal

The peripheral eosinophil count is normal. The term eosinophilic granuloma should be used accordingly, as this refers to the presence of eosinophils in the histological lesion, but not in the peripheral blood

CLINICAL DIAGNOSIS

Even though the clinical (smoking history, recurrent pneumothorax, etc.) and HRCT findings may be strongly suggestive of LCH, cytological (CD1+ cells in the BAL fluid) or histological confirmation should always be sought

The presence of lytic bone lesions and/or diabetes insipidus in adolescents suggests the systemic form (Hand-Schüller-Christian disease)

INVASIVE DIAGNOSIS

BAL and transbronchial biopsy can be sufficient for diagnosis without the need for surgical biopsy

Transbronchial biopsy should be planned with great care to avoid possible complications (pneumothorax)

Transbronchial biopsy may result in a substantial number of false negative and non-diagnostic biopsies due to inadequate sampling. The immunohistochemical study of CD1+ cells increases diagnostic accuracy

Bronchoalveolar lavage

BAL shows an increase in total cells and neutrophils, as one would expect in smokers. A non-specific increase in eosinophils may also be seen. A proportion of Langerhans' cells (CD1+) of more than 5% is diagnostic. In this advanced stage of the disease the number of CD1+ cells in BAL fluid decreases in comparison to the early stage

Auerswald U. Value of CD-1-positive cells in bronchoalveolar lavage fluid for the diagnosis of pulmonary histiocytosis X. Lung 1991, 169: 305

Usual Interstitial Pneumonia

Definition

Usual interstitial pneumonia (UIP) is the histopathologic pattern of idiopathic pulmonary fibrosis (IPF), a chronic fibrosing interstitial lung disease of unknown etiology. The term UIP has become so widely-used as to often be used as a substitute even in clinical practice

If studied in the advanced stage, the condition exhibits a predominantly cystic pattern

Idiopathic Pulmonary Fibrosis (IPF), Cryptogenic Fibrosing Alveolitis (CFA)

The general term idiopathic interstitial pneumonia (IIP) includes various diseases, and in particular usual interstitial pneumonia (□ UIP, early; O UIP, advanced), non-specific interstitial pneumonia (□ NSIP), desquamative interstitial pneumonia (⌘ DIP), acute interstitial pneumonia (⌘ AIP), lymphocytic interstitial pneumonia (● LIP) and cryptogenic organizing pneumonia (⌘ OP)

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

DEMOGRAPHICS

Etiology and pathogenesis

The etiology of IPF is unknown. There are two prevailing theories regarding pathogenesis:

1. Inflammatory theory. In the early stage of disease chronic inflammation (macrophages, neutrophils, eosinophils) is thought to arise in the septa and alveoli damaging the lung structure and increasing production of fibrogenic cytokines with a consequent exaggerated reparative response leading to end-stage lung fibrotic disease

2. Fibroblast dysregulation theory. Following an unknown insult, there is thought to be an exaggerated reparative response characterized by the migration and proliferation of fibroblasts, reduced apoptosis of the fibroblasts themselves and increased response to fibrogenic cytokines. This situation is associated with an absence of re-epithelization of alveoli and inappropriate remodeling of the extracellular matrix

Epidemiology

A population-based study reported a prevalence rate of 20.2 cases per 100,000 for males and 13.2 cases for females. Mean age at diagnosis is 66 years, and the incidence increases with older age. The disease has no geographical or racial predilection, although familial cases have been reported

Risk factors

The exposure to antidepressant drugs, inhalation of metal and wood dust, cigarette smoking (1.6-2.3 times), and chronic gastroesophageal reflux have been implicated in development of IPF. The importance of these factors in the pathogenesis of the disease is unknown

CLINICAL FEATURES

History

In this advanced stage of the disease, dyspnea is present on minimal exertion and at times at rest. The dry persistent cough may be intractable, and rib fractures due to coughing fits have been reported. Systemic symptoms include weight loss and fatigue

Physical findings

Patients usually have tachypnea and cyanosis at rest. Diffuse fine crackles ("velcro" rales) are heard over all lung fields. In this advanced stage of the disease, signs of pulmonary hypertension (increased second pulmonic sound, epigastric pulsation) and right-sided heart failure (jugular venous distension, enlarged and tender liver, peripheral edema) may also be present. A mean pulmonary pressure greater than 30 mmHg at rest is associated with a serious prognosis. Clubbing is noted in 25-50% of cases

Pulmonary function tests

Pulmonary function tests show a moderate-to-severe restrictive pattern, a severe reduction in D_LCO and hypoxemia at rest. Smokers may also present an obstructive defect, in which case lung volumes may be normal

Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000, 161: 646

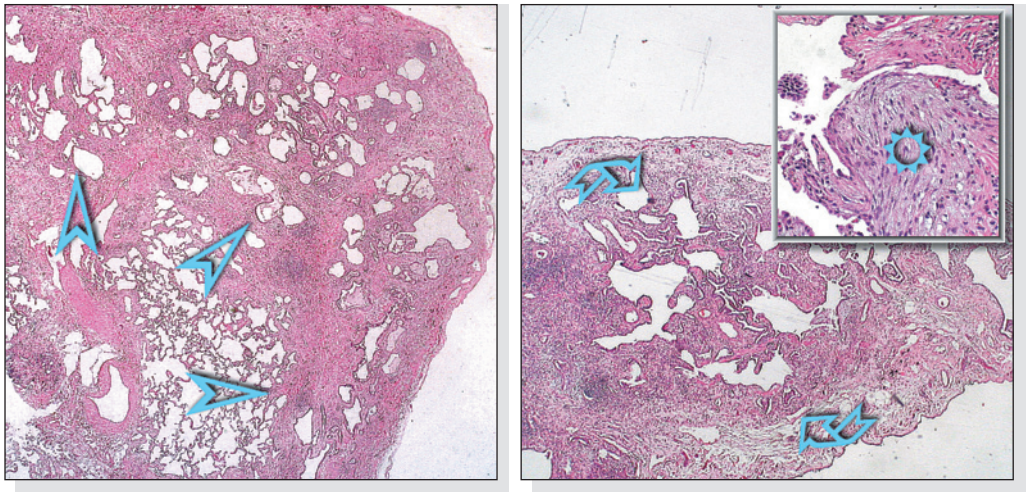
Wiggins J. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. Respir Med 1990, 84: 365

PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Irregularly distributed dense fibrosis predominantly in the subpleural regions (➢) and various degrees of honeycombing (↳)
- Fibroblastic foci (☼)(loose connective tissue rich in mucopolysaccharides and containing myofibroblasts) at the interface between areas of fibrosis and normal parenchyma
- Mild inflammatory infiltrate may be seen within the areas of fibrosis, together with smooth muscle tissue hyperplasia and fatty metaplasia of the subpleural parenchyma



Pseudocysts in honeycombing arise from the coalescence of air spaces within fibrotic areas due to the rupture of the alveolar walls. The cavities are bounded by thick fibrous walls and lined with bronchiolar epithelium or hyperplastic pneumocytes

Spatial heterogeneity (pathological areas alternating with areas of normal parenchyma) and temporal heterogeneity ("old" fibrosis alternating with "young" fibroblastic foci) are characteristic histological features of UIP. Even in the advanced stages, the presence of fibroblastic foci is the diagnostic hallmark of the disease

According to some authors, the fibroblastic component involves the organization of small foci of diffuse alveolar damage that is rarely identifiable either clinically or histologically. True diffuse alveolar damage with hyaline membranes and type-II pneumocyte hyperplasia in UIP is instead seen in the so-called "accelerated UIP"

Distribution

Subpleural and paraseptal although the latter cannot be seen in areas of extensive fibrosis or honeycombing

Differentials

Histopathologic differential diagnoses:

- NSIP: the overall appearance is uniform, while spatial and temporal heterogeneity are absent
- Collagen vascular diseases: the inflammatory infiltrate is more intense, with lymphoid follicles and less numerous fibroblastic foci, and associated pleuritis
- Asbestosis: fibrosis without the spatial and temporal heterogeneity of UIP, and the presence of asbestos bodies
- HP: peribronchiolar distribution, and more intense interstitial inflammatory infiltrate with granulomas
- Sarcoidosis: non-necrotizing granulomas confluent in broad areas of fibrosis with a distribution which, at least initially, is lymphatic; fibroblastic foci are absent

Katzenstein AL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998, 157: 1301

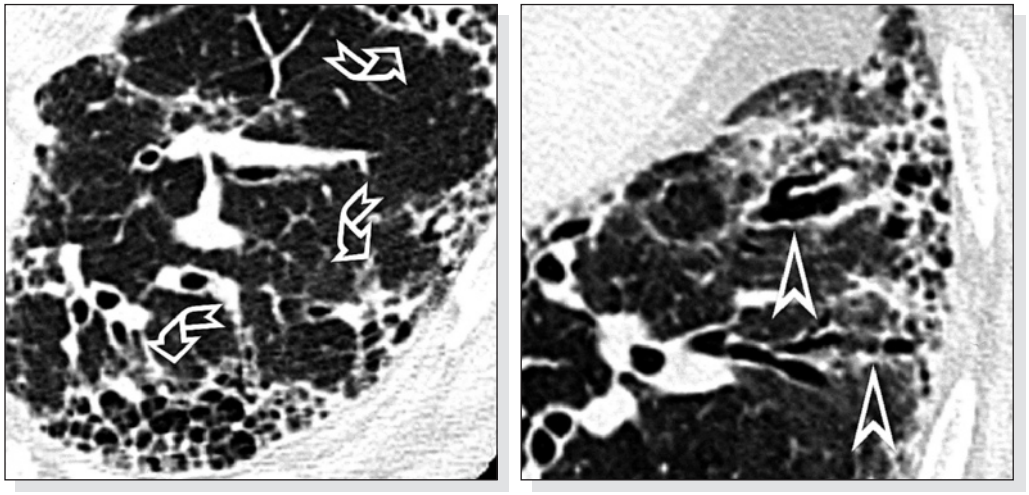
Katzenstein AL. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol 2002, 26: 1567

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological findings:

- Small rounded cysts (2-10 mm) which share thick walls, distributed in several concentric layers in the subpleural region (↳)(honeycombing)
- Traction bronchiectasis and bronchiolectasis (➢): the dilated bronchi have thick walls and a tortuous, corkscrew-like form



Muller NL. Fibrosing alveolitis: CT-pathologic correlation. Radiology 1986, 160: 585

Primack SL. End-stage lung disease: CT findings in 61 patients. Radiology 1993, 189: 681

Distribution

Bilateral and patchy

Peripheral subpleural, more prominent posteriorly

Predominantly basal

Despite the predominantly basal distribution, there is always a certain degree of subpleural involvement even in the middle and upper zones. In fact, involvement is predominant in these zones in 10% of cases

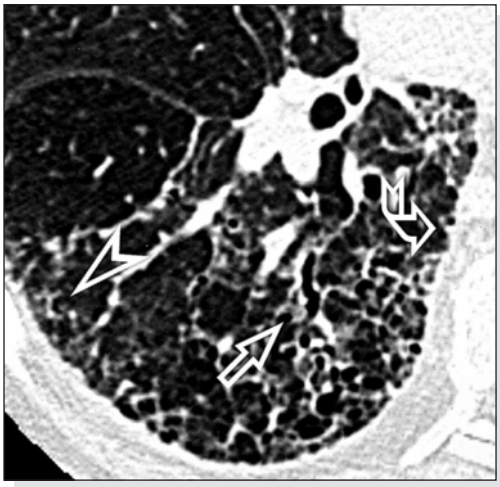
Wells AU. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR Am J Roentgenol 1993, 161: 1159

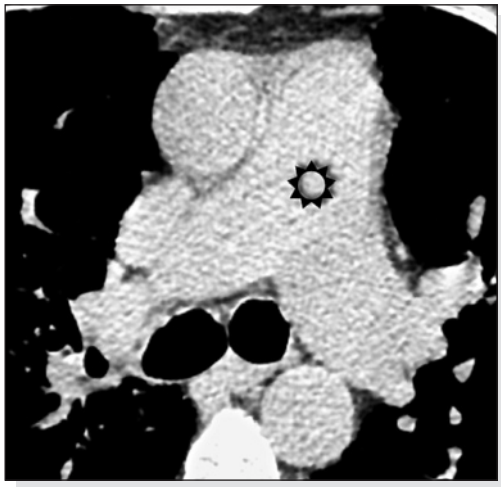
Lung volume is reduced

Other signs

Other radiological signs:

- Inter-and intralobular irregular reticular pattern (➢)
- Interface sign (↳)
- Fibrotic ground-glass opacity with associated bronchiolectasis (⇨)
- Mediastinal lymph node enlargement (50-90%), more commonly in the extensive forms. As this is a reactive process, it can be reduced with steroid treatment
- Pulmonary arterial hypertension: diameter of the main pulmonary artery (☼) > 27 mm





Franquet T. Mediastinal lymphadenopathy in cryptogenic fibrosing alveolitis: the effect of steroid therapy on the prevalence of nodal enlargement. Clin Radiol 1998, 53: 435

Nishimura K. Usual interstitial pneumonia: histologic correlation with high-resolution CT. Radiology 1992, 182: 337

Differentials

Radiological differential diagnoses:

- Collagen vascular diseases: honeycombing is less conspicuous, and the typical findings of each disease may be present
- Asbestosis: subpleural lines, parenchymal bands, calcific pleural plaques, rounded atelectasis
- HP: possible preferential involvement of the middle-upper lung zones with peribronchovascular distribution. Ill-defined centrilobular nodules and scattered areas of ground-glass opacity also be present
- Sarcoidosis: the lesions are situated in the upper lobes and in the parahilar region; perilymphatic nodules are also present

Mayberry JP. Thoracic manifestations of systemic autoimmune diseases: radiographic and high-resolution CT findings. Radiographics 2000, 20: 1623

Primack SL. End-stage lung disease: CT findings in 61 patients. Radiology 1993, 189: 681

COURSE and COMPLICATIONS

Associated diseases

An increased incidence of pulmonary carcinoma has been reported, especially squamous-cell carcinoma and adenocarcinoma (13-30%). During the course of the disease pneumothorax with pneumomediastinum and intracystic mycetomas may appear

Lee HJ. Lung cancer in patients with idiopathic pulmonary fibrosis: CT findings. J Comput Assist Tomogr 1996, 20: 979

Zompatori M. [Really an intruder!] Radiol Med 2000, 99: 406. Italian

Clinical course

IPF is usually progressive. The median survival time from diagnosis is 2.5-3.5 years. Most patients (40%) die of respiratory failure which is often aggravated by infection, while about 20% die from heart complications. On rare occasions the disease may have an acute exacerbation (accelerated phase of UIP) with rapid progression due to underlying diffuse alveolar damage (DAD)

Radiological course

Characteristic features include the progressive extension of honeycombing to the middle and upper lung zones, possible increase in the size of the cysts and a reduction in the thickness of their walls, and a progressive reduction in lung volume

LABORATORY FINDINGS

Laboratory findings include a non-specific increase in ESR, immunoglobulin and LDH. Positive circulating anti-nuclear autoantibodies (ANA) or rheumatoid factor occur in 10-20% of patients

✓ The presence of an ANA titer greater than 1:160 would suggest the presence of a collagen vascular disease which may be indistinguishable from IPF on the sole basis of radiological techniques

CLINICAL DIAGNOSIS

In an immunocompetent adult, the presence of all of the following major diagnostic criteria as well as at least three of the four minor criteria is considered suggestive of IPF in the absence of a surgical lung biopsy

Major criteria: 1) exclusion of other known causes of diffuse infiltrative lung disease such as drug toxicities, environmental exposures and connective tissue diseases; 2) Abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity often with an increased FEV1/FVC ratio) and impaired gas exchange (decreased D_LCO or increased alveolar-arterial oxygen gradient); 3) bibasilar reticular abnormalities with minimal ground-glass opacities at HRCT scans; 4) transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor criteria: 1) age > 50 years; 2) insidious onset of otherwise unexplained dyspnea on exertion; 3) duration of illness > 3 months; 4) bibasilar, inspiratory crackles (Velcro-like)

INVASIVE DIAGNOSIS

Transbronchial lung biopsy plays a role in excluding other specific disorders and may be useful in the diagnosis of complications. Surgical lung biopsy is the most definitive method of establishing diagnosis (UIP pattern) and is always performed when the above-mentioned criteria have not been met. However, surgical lung biopsy is not indicated when the HRCT findings show frank and diffuse honeycombing, since the pathological analysis of end-stage lung parenchyma provides no useful diagnostic information. In addition, surgical biopsy is contraindicated in patients with cardiovascular problems, serious respiratory failure, who are severely obese or above 65 years of age

Bronchoalveolar lavage

The BAL findings in this phase of the disease are similar to those of the early or reticular phase (☐ UIP, early). BAL is not diagnostic of IPF, however it may be useful in narrowing the differential diagnosis

Haslam PL. Bronchoalveolar lavage in pulmonary fibrosis: comparison of cells obtained with lung biopsy and clinical features. Thorax 1980, 35: 9

Veeraraghavan S. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003, 22: 239

Glossary

Long years I devoted to learning the order and arrangement of the shapes

Some made circles; others formed transverse stripes on the inside of its legs; others, ringlike, occurred over and over again

Perhaps they were the same sound, or the same word

JL Borges, The God's Script

The glossary includes the definition of characteristic radiological signs, often expressed with fanciful terms such as tree-in-bud, cheerios pattern, halo sign, etc.

These terms which are part of the radiological jargon are useful because they immediately and unequivocally identify one or more characteristic images of these diseases

The terms in the glossary can be found within the text printed in a distinctive font style (e.g. …rounded opacities with the galaxy sign are produced by…)

Glossary HRCT

A

Air bronchogram

Visualization of patent bronchial structures within areas of parenchymal consolidation

Wong JS. Bronchioloalveolar carcinoma and the air bronchogram sign: a new pathologic explanation. J Thorac Imaging 1994, 9: 141

Air crescent sign

Crescent-shaped or circumferential area of radiolucency within a nodular opacity. The latter may be linked to the presence of opaque material within a preexisting cavity or formed by necrosis and cavitation

Abramson S. The air crescent sign. Radiology 2001, 218: 230

Air-trapping

Abnormal retention of gas caused by an obstruction of the small airways. Air-trapping may be recognized by patchy areas of low-attenuation (mosaic oligemia) and is particularly evident at suspended expiration

Arakawa H. Expiratory high-resolution CT: diagnostic value in diffuse lung diseases. AJR Am J Roentgenol 2000, 175: 1537

Angiogram sign

Marked visualization of vessels revealed by contrast material in areas of hypodense parenchymal consolidation (because the air spaces are filled with mucous, lipidic material, etc.)

Shah RM. CT angiogram sign: incidence and significance in lobar consolidations evaluated by contrast-enhanced CT. AJR Am J Roentgenol 1998, 170: 719

Atoll sign

Reversed halo sign

B

Beaded appearance

Nodular thickening of the central or peripheral interstitium (interlobular septa) in which small lung nodules (micronodules) are visible

Ren H. Computed tomography of inflation-fixed lungs: the beaded septum sign of pulmonary metastases. J Comput Assist Tomogr 1989, 13: 411

C

Cheerios pattern

Cavitating nodules with a central area of decreased attenuation

Reed SL. Cheerios in the chest. Chest 1993, 104: 1267

Crazy paving

Scattered or diffuse ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines. The marked visualization of the interlobular septa may be due to an effective thickening, as well as the concentration of materials along the walls of the adjacent air spaces

Colonial-era pavement

Rossi SE. "Crazy paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 2003, 23: 1509

D

Dark bronchogram sign

"Overly good" visualization of bronchial structures within areas of ground-glass opacity. Appreciating this finding may prove useful when faced with faint and uniform darkening which is otherwise difficult to distinguish from normal parenchyma

Remy-Jardin M. Computed tomography assessment of ground-glass opacity: semiology and significance. J Thorac Imaging 1993, 8: 249

Dotlike opacities

Micronodular opacities in the subpleural zones described by Akira in relation to early asbestosis. Dotlike opacities are due to a focal centrilobular concentration of fibrotic tissue and often with the association of branching linear opacities and curvilinear subpleural lines

Akira M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. AJR Am J Roentgenol 2003, 181: 163

E

End-stage lung

The final stage of a fibrosing lung disease, in which more-or-less extensive areas of lung are replaced by thick-walled cystic spaces

Honeycomb lung

Primack SL. End-stage lung disease: CT findings in 61 patients. Radiology 1993, 189: 681

F

Feeding vessel sign

Nodules connected to peripheral vascular branches from which they appear to originate. This finding is evidence of the hematogenous genesis of random nodulation

Iwasaki Y. Spiral CT findings in septic pulmonary emboli. Eur J Radiol 2001, 37: 190

G

Galaxy sign

Large opacity with irregular margins surrounded by tiny satellite nodules. The large opacities are due to the coalescence of numerous smaller-sized nodules

Nakatsu M. Large coalescent parenchymal nodules in pulmonary sarcoidosis: "sarcoid galaxy" sign. AJR Am J Roentgenol 2002, 178: 389

Geographic distribution

Term used to describe the distribution of a lesion characterized by an alternation of areas of affected lung and areas of normal parenchyma

Patchy

Ground-glass opacity

Increased hazy opacity within the lung, not associated with obscured underlying vessels

This finding reflects the relative reduction of the quantity of air in the alveoli, either due to partial filling of the air spaces or thickening of the septa (intralobular interstitium)

Ground-glass attenuation

Remy-Jardin M. Computed tomography assessment of ground-glass opacity: semiology and significance. J Thorac Imaging 1993, 8: 249

H

Halo sign

A halo of ground-glass attenuation around a nodular opacity

Pinto PS. The CT Halo Sign. Radiology 2004, 230: 109

Head-cheese pattern

Combination of geographic areas of normal parenchyma, ground-glass opacity and mosaic oligemia with air-trapping. The changes often have a lobular distribution

Chung MH. Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. J Thorac Imaging 2001, 16: 69

Honeycombing

Small thick-walled cystic spaces arranged in several concentric layers. Honeycombing is the radiological hallmark of end-stage lung disease, and therefore traction bronchiectasis and bronchiolectasis as well as interface signs are often present

Akira M. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology 1994, 192: 582

I

Interface sign

Presence of irregular interfaces at the edges of the bronchi, the vessels and especially the pleural surfaces which become finely irregular with a saw-tooth pattern. The sign is common in fibrosing diseases which cause traction on the adjacent structures

Zerhouni E. Computed tomography of the pulmonary parenchyma. An overview. Chest 1989, 95: 901

M

Mosaic oligemia

Areas of low parenchymal density in which the vessels are reduced in size and number. The extent of oligemia may be lobular or segmental, while the distribution is typically patchy

☯ Mosaic perfusion

Mosaic oligemia may be secondary to vascular diseases or related to obstruction of the small airways. In the latter case lung density further decreases upon expiration (air-trapping)

📖 Stern EJ. CT mosaic pattern of lung attenuation: etiologies and terminology. J Thorac Imaging 1995, 10: 294

Mosaic perfusion

Mosaic oligemia

P

Parenchymal bands

Linear opacities 2-5 cm in length, usually perpendicular to the costal margins. This finding is due to thickening of contiguous interlobular septa in relation to scarring, to atelectasis associated with fibrosis or simply to the thickening of variously arranged connective septa

📖 Akira M. Asbestosis: high-resolution CT-pathologic correlation. Radiology 1990, 176, 389

Perilymphatic

Term used to describe the distribution of nodules which tend to be concentrated in the perilobular and subpleural interstitium (although they may have an intralobular location) and therefore located along the costal margins and major fissures.

These nodules are most commonly found in diseases which spread along the lymphatics and are therefore also found in other lymphatic locations, typically along the vessels and the bronchi, which take on a beaded appearance

📖 Gruden JF. Multinodular disease: anatomic localization at thin-section CT-multireader evaluation of a simple algorithm. Radiology 1999, 210: 711

Pseudo-ground-glass

An increase in the size of vessels and diffuse hyperdensity of areas of normal lung, mimicking patchy ground-glass attenuation

Pseudoplaques

A grouping of small subpleural nodules adjacent to the costal margins. They are due to agglomerates of nodules (e.g. granulomas) and arranged linearly along the pleural surfaces, thus mimicking focal thickening

📖 Remy-Jardin M. Subpleural micronodules in diffuse infiltrative lung diseases: evaluation with thin-section CT scans. Radiology 1990, 177: 133

R

Random

Term used to describe the distribution of nodules or cysts within the secondary lobule and therefore within the parenchyma when the lesions are situated without predilection

Reversed halo sign

Rounded opacity composed of a peripheral ring of consolidation surrounding an area of ground-glass attenuation, indicating the peculiar involvement of the air spaces and the interstitium

☯ Atoll sign

📖 Kim SJ. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. AJR Am J Roentgenol 2003, 180: 1251

S

Subpleural interstitial thickening

This finding manifests as a thickening at the chest wall, the mediastinum and the major fissures produced by an accumulation of liquid or cells in the corresponding interstitium

✓ The interstitial thickening is more clearly evident adjacent to the major fissures where the two layers belonging to the pulmonary lobes are present

📖 Zerhouni E. Computed tomography of the pulmonary parenchyma. An overview. Chest 1989, 95: 901

Subpleural lines

Thin linear opacities running usually 0.5-1 cm from the pleural surface and paralleling the pleura. They are commonly seen in the posterior regions of the lung

Subpleural lines are formed by peribronchiolar fibrotic thickening associated with collapse of the adjacent alveolar structures, such that they are found mainly in fibrosing diseases beginning in the centrilobular zone

With the patient in the supine position (as usually occurs in CT) a similar appearance may be observed due to artifacts related to the force of gravity: the wedge-shaped underlying portion of the lung collapses under the weight of the overlying portion, thus tending to opacify. The differential diagnosis can be made by performing a scan with the patient in the prone position: the functional features disappear, whereas anatomical changes such as the lines remain

Yoshimura H. Pulmonary asbestosis: CT study of subpleural curvilinear shadow. Work in progress. Radiology 1986, 158: 653

T

Tree-in-bud

Thin branching opacities which terminate with small nodular opacities, usually visible in the lung periphery

This finding is particularly common in diseases with endobronchial spread of infection. Its appearance is due to the presence of dilated adjacent bronchioles and air spaces filled with material such as pus, mucous or fluid

Eisenhuber E. The tree-in-bud sign. Radiology 2002, 222: 771

Subject Index

A large horn of mead passed from hand to hand while the man conversed with the god about poetry. The god listed the metaphors to be used: divine catalogue that now assists me

This list does not exclude the *kenningar* that I have already mentioned. Making it gave me an almost philatelic pleasure

JL Borges, The kenningar

The following index lists all the diseases covered in the four chapters. Many have a variety of different names which are often accompanied by abbreviations and acronyms

A number of diseases are presented more than once in the book, either because they present different radiological patterns or because they change appearance during their natural course

All of these features have been included in the index. The page reference in bold indicates the detailed explanation of the disease, while the page reference in normal type indicates the HRCT pattern with which it manifests

Subject Index

I

K

L

M

N

O

P

R

S

T

U

W

Index of tables