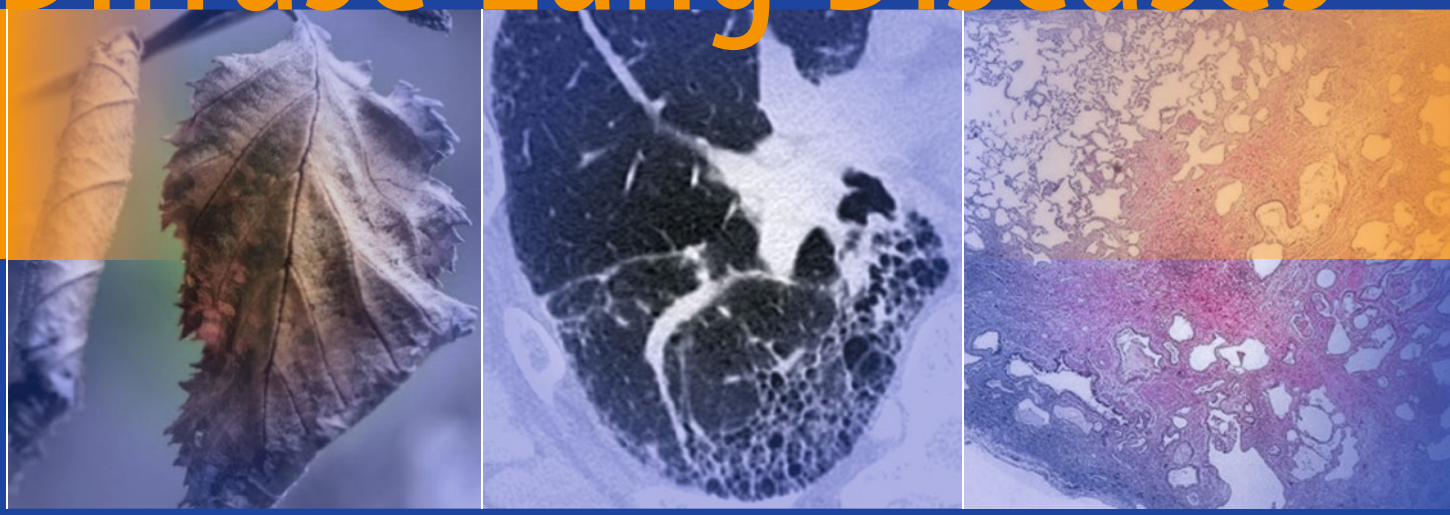
Giorgia Dalpiaz
Alessandra Cancellieri
Editors

Atlas of Diffuse Lung Diseases



A Multidisciplinary Approach

In collaboration with
L. Cardinale · A. Cavazza · M. Patelli
M. Romagnoli · N. Sverzellati
R. Trisolini · M. Zompatori

Springer

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Editors
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ISBN 978-3-319-42750-8
ISBN 978-3-319-42752-2 (eBook)
DOI 10.1007/978-3-319-42752-2

Library of Congress Control Number: 2016959558

Printed on acid-free paper

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

Foreword

For many clinicians and radiologists, particularly those with limited experience, the recognition and characterisation of diffuse lung disease can be an uncomfortable challenge. Any aid that increases the confidence and accuracy of HRCT interpretation is thus very welcome. This handsomely produced guide to understanding diffuse interstitial lung disease and multidisciplinary diagnosis, using practical divisions based on broad patterns, is an excellent addition to the literature. The underpinning of CT interpretation by superb pathology illustrations is a real strength, and will remind readers that extracting the most out of HRCT images requires a good grasp of the pathology of diffuse lung diseases.

Many radiologists have mental "thumbnail sketches" of diffuse lung diseases, that is to say they can compress what may be a complex diffuse lung disease, with potentially variable appearances, into surprisingly succinct descriptions. For example, the HRCT findings in pulmonary veno-occlusive disease can be summarised as: "widespread ground glass, septal thickening, big pulmonary artery and small effusions". This approach allows a large bank of HRCT diagnoses to be stored in the otherwise crowded hippocampus of a radiologist. The beauty of this book is the way it echoes this method which means that the thumbnail sketches of common and rare diffuse lung diseases can be readily assimilated.

The authors are drawn from the foremost practitioners of multidisciplinary diagnosis of diffuse lung disease, and there is no doubt that the enthusiastic and critical approach to HRCT by expert Italian clinicians, radiologists and pathologists over many years has helped to establish the crucial imaging technique of HRCT in the modern practice of respiratory medicine.

David M. Hansell
Professor of Thoracic Imaging
Royal Brompton Hospital
London, UK

Foreword

Since the first evidences published in literature in the early 1980s demonstrating the usefulness of HRCT scans in evaluating lung interstitium and the related lung diseases with excellent anatomical details, a tremendous progress has been made in the knowledge of diffuse lung diseases (DLDs).

This remarkable book is structured as an atlas, but it is much more than that. It explores the DLDs through a reading key centered on the correlation between radiological findings and pathological appearance, without overlooking the most relevant clinical aspects of the diseases and the updatings from literature.

The easiest approach to the complex topic of DLDs is to understand the reasons why a disease manifests certain characteristics on HRCT scans and this work represents an excellent example of it. The authors brilliantly describe patterns and diseases in a creative and original manner which facilitates the learning process by taking pictures not only from HRTC scans and pathological specimens, but also from nature, art, and real life. Furthermore, differential diagnosis is complete, concise, and effectively discussed in all the sections.

I would like to congratulate the authors on this outstanding volume which attests their great and continuous collaboration, born in the daily practice. In an age in which the multidisciplinary approach to DLDs is becoming essential to an accurate diagnosis, this atlas is timely perfect.

I highly recommend it to all the physicians who are involved in diagnosing and managing DLDs, as a stunning example of how radiologists, pulmonologists, and pathologists can successfully cooperate to ensure the wellbeing of patients.

Anna Rita Larici
Assistant Professor of Thoracic Imaging
Catholic University
Rome, Italy

Foreword

Medical textbooks have evolved over the years, but most still serve as encyclopedic tomes, designed for reference use once a diagnosis is being closely considered. But what written guidance exists for the physician seeking diagnostic answers in real time, when the diagnosis is completely unknown?

The exceptional body of work presented by Dalpiaz and coworkers is just such a reference. The approach has tremendous value for radiologists, pneumologists, and pathologists alike, emphasizing differential diagnosis based on key observations of *pattern* and *distribution* of abnormalities identified on HRCT. Further, the work is constructed to provide maximum benefit to the user through the application of a consistent format throughout including special annotations that serve to guide the reader in an efficient and highly user-friendly way.

Kevin O. Leslie, MD
Professor and Consultant
Laboratory Medicine and Pathology
Mayo Clinic Arizona
Scottsdale, AZ, USA

Foreword

As a clinician with a longstanding passion and a research interest for interstitial lung diseases, I still remember distinctly the day when, back in 2006, I had for the first time in my hands a new volume on the clinical features, pathology and HRCT patterns in diffuse lung diseases. I was surprised to find such a clear and rational description of the complex diagnostic algorithm behind the recognition of the many and so different HRCT patterns for this group of patients. Even more so when I recognised the two authors as well know Italian colleagues and friends! At that time, I was still working in Italy, more specifically in Modena, part of a prolific Italian region, from which one of the authors was a native of. That book authored by Mario Maffessanti and Giorgia Dalpiaz has been since then a faithful and useful companion of my clinical and research activity. Moreover, it has been a reliable and friendly starting point for the younger colleagues interested in this challenging field of our discipline.

When some weeks ago I received a nice message from Giorgia, anticipating the publication of a new *Atlas of Diffuse Lung Diseases* (and kindly asking me for this preface), I became very excited to see if and how the previous excellent book, still sitting in my bookcase (now in the United Kingdom) had been improved. Looking at the pre-print version of the atlas, three characteristics did catch my eye. First, now the team is an all-female duo, both native from the same Emilia region: certainly one more reason to be proud of our strong, dedicated, strong-willed and smart women, now that I have been working for the last 3 years abroad. Second, a colour-coded structure is even more clear than in the previous book and now the BEST approach (please refer to the preface from the authors to know more about this), together with the six colours strategy, is opening the mind while reading the text and is helping to have a comprehensive, but still detailed, view of the diagnostic process. Lastly, the magic word "multidisciplinary" is on the front page, clearly anticipating the different and complementary expertise of the two colleagues.

In fact, since 2006 a lot of change happened in this evolving and dynamic field of respiratory medicine. We discovered that the traditional combination of steroid and immunosuppressive therapy is associated with increased hospitalisation and mortality. This new, groundbreaking discovery strongly argues now against the empiric use of this (and other) therapeutic combination in patients with idiopathic pulmonary fibrosis. Similarly, the lack of consistent efficacy of a simple regimen based on *N*-acetyl-cysteine and the availability of effective and safe anti-fibrotic therapies has increased the urgency to make an accurate diagnosis in patient with suspected idiopathic pulmonary fibrosis. Although the field of diffuse lung diseases has benefited from updated clinical practice guidelines that address multiple subtypes of interstitial lung diseases, nonetheless there remains significant heterogeneity and uncertainty in the practical application of existing classification schema, with resulting heterogeneity in case classification and important implications for both clinical practice and future research. It is widely recognised that with clear divergence in the management pathways of different disease subtypes, there is a need for a consistent and reproducible approach to diagnosis and classification that can be applied across diverse centres, ideally on a global scale.

In this context, it is now clear to me that this *Atlas of Diffuse Lung Diseases* is the perfect companion of the first book and together will help to address the future challenges for clinicians dedicated to this important area of respiratory medicine. These beautiful books will always occupy a privileged place in my bookshelf, wherever it will be.

Luca Richeldi
Professor of Respiratory Medicine
Chair of Interstitial Lung Disease
University of Southampton
Southampton, UK

The BEST Points of the Atlas

This preface is inspired by the Italian author Beppe Severgnini's book *Life is a Journey*. In choosing BEST, we did not wish to give ourselves a pat on the back; in fact, it is the acronym for this atlas's four guiding concepts:

- Brevity
- Encouragement
- Simplicity
- Teaching

Beppe Severgnini is a columnist for *Corriere della Sera* (one of Italy's leading daily newspapers) and a contributing opinion writer for *The New York Times*. He is the author of 16 books and teaches at the University of Milan's School of Journalism. *Severgnini was awarded the O.B.E. and is a Commendatore della Repubblica Italiana.*

Brevity

Briefness and *precision* are essential qualities in these busy times, and the importance of having quick guides is crucial. This atlas is designed as an easy-to-use reference guide that identifies and illustrates the key patterns of diffuse lung diseases observed on high-resolution computed tomography (HRCT). This atlas documents in great detail each pattern's signs with close Rad-Path correlations. This book also allows a rapid view of HRCT characteristics and appearances of the individual diseases grouped on the basis of their prevalent radiological pattern.

Brevity is the soul of wit. From the second act of *Hamlet*, this is one of the countless expressions coined by William Shakespeare that has entered into common usage. With appropriate conciseness, it extols the virtue of expressing ideas in as few words as possible.

Encouragement

We all need a little encouragement! One should not to be concerned or put off by the wide number of DLDs that exist; in this atlas the task is made much easier by the inclusion of many diagnostic tools as well as a variety of tips and tricks (examples of which can be found in the Case-Based Glossary).

We would also *nudge* you to deal with DLDs using a multidisciplinary approach. Multidisciplinary diagnosis is considered the gold standard: it can improve the accuracy of diagnosis, avoid unnecessary tests (e.g. lung biopsies), and optimize patient management.

Nudge: *Improving Decisions about Health*, *Wealth*, *and Happiness*. Richard H. Thaler Cass R. Sunstein, 2008 Yale University Press.

Simplicity

Simplicity is the ultimate sophistication (Steve Jobs). Jobs saw simplicity as the means for conquering complex realities. He later added: *It takes a lot of hard work to make something simple, to truly understand the underlying challenges and come up with elegant solutions*.

In this atlas, we have removed anything that was not essential and used a simple and visually pleasing layout.

Teaching

We have employed an innovative format that we believe is effective for achieving optimal learning and memorization. In a way similar to color-code maps (geographic, political, railway, etc.), different colors are used so as to assist in the quick memorization of the six different patterns.

The six pattern colors are:

- **Purple (septal pattern)**
- **Pink (fibrosing pattern)**
- **Green (nodular pattern)**
- **Sky blue (alveolar pattern)**
- **Red (cystic pattern)**
- **Dark grey (dark lung pattern)**

In addition to the description of each pattern's signs and a selected choice of signs in the Case-Based Glossary, we also provide some images that are easy to remember and recognize; some of these resemble everyday things (e.g., butterfly sign, cheerio sign, etc.).

Symbols

Symbols are used to allow quick identification of important concepts

Synonyms commonly used in clinical practice

Tips and tricks

Caveat! Be careful! Remember!

Expansion of a concept just outlined

Bibliographic reference related to the topic in the specific context

Differential diagnosis

About the Atlas

This new atlas is a *companion volume* to the book entitled *Diffuse Lung Diseases*: *Clinical Features*, *Pathology*, *HRCT*, Mario Maffessanti & Giorgia Dalpiaz (Eds), Springer 2006. Both volumes share the same layout, use of graphics, and multidisciplinary approach to DLDs, but this atlas contains a greater number of Rad-Path figures.

About the Editors

Giorgia Dalpiaz (radiologist) and Alessandra Cancellieri (pathologist) are close friends and a longstanding Rad-Path team. This atlas is the result of decades of professional collaboration in daily practice as well as for the preparation of joint lectures and talks.

Target Readership

This atlas is intended for a wide range of healthcare professionals, in particular *radiologists*, *pulmonologists*, and *pathologists*. A further feature of this book is its interdisciplinary content.

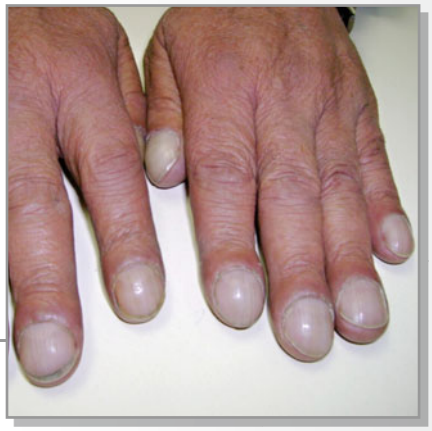
Dedication

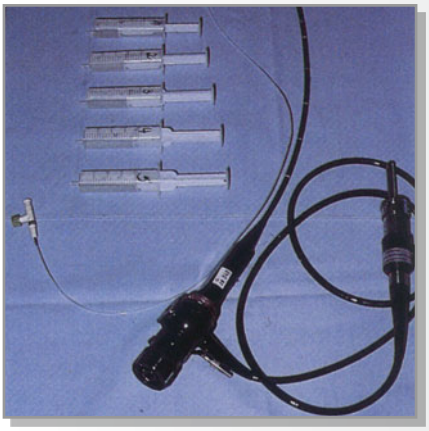
Both of us affectionately dedicate this atlas to Prof. Mario Maffessanti, a very special and brilliant person.

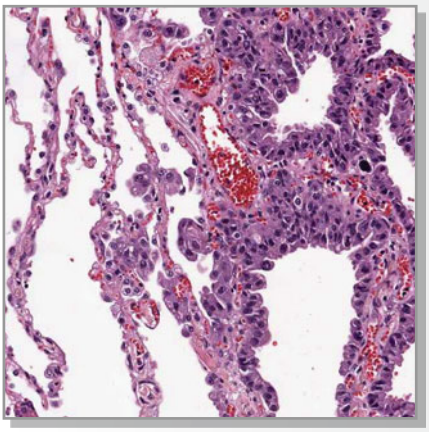
We also wish to thank our families for their loving support.

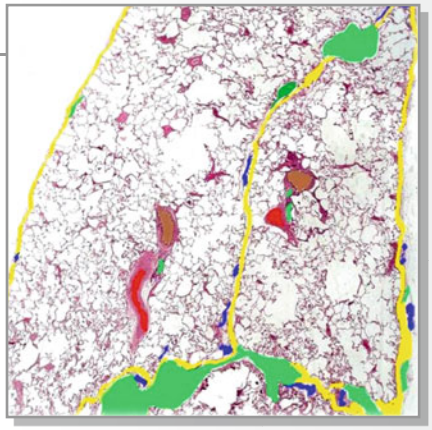
Bologna, Italy — Giorgia Dalpiaz
Bologna, Italy — Alessandra Cancellieri

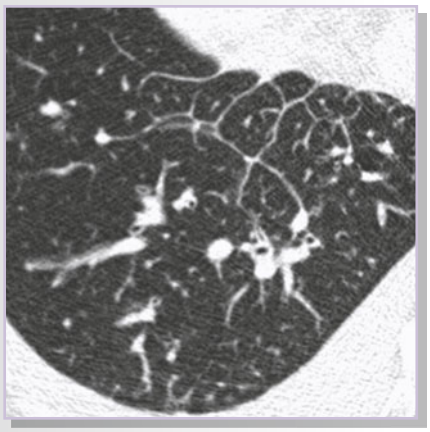
Contents

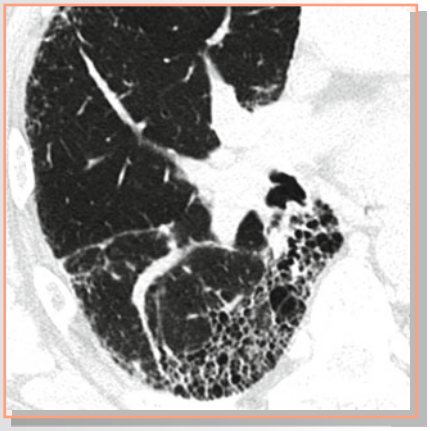




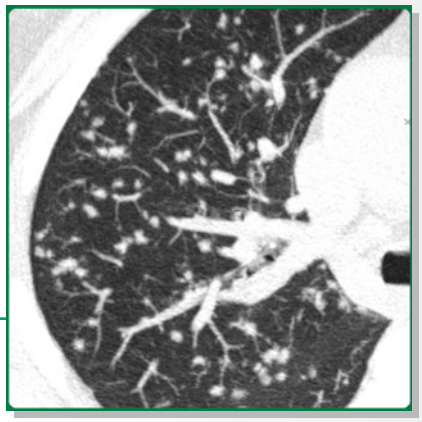




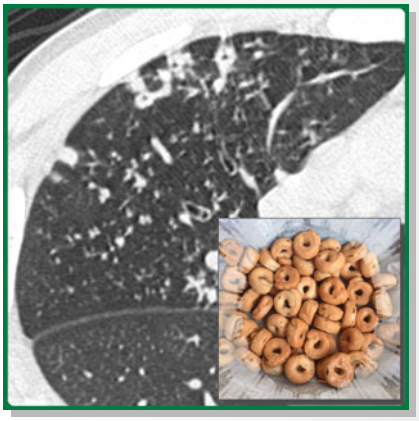


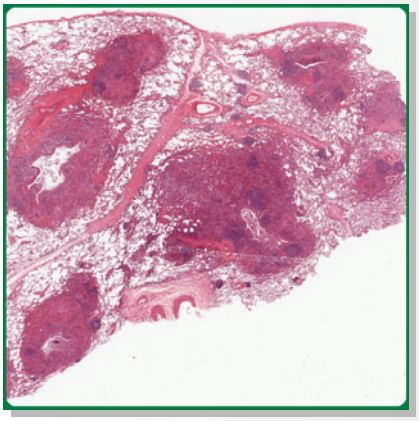


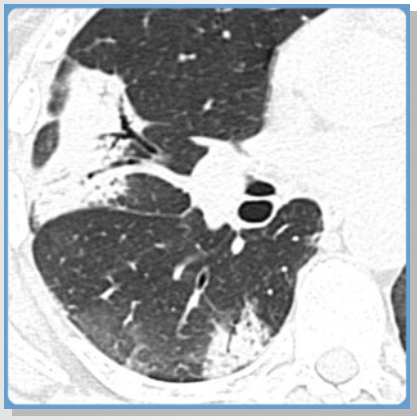
Nodular Pattern

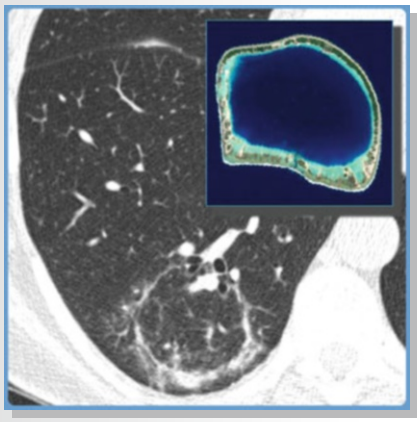


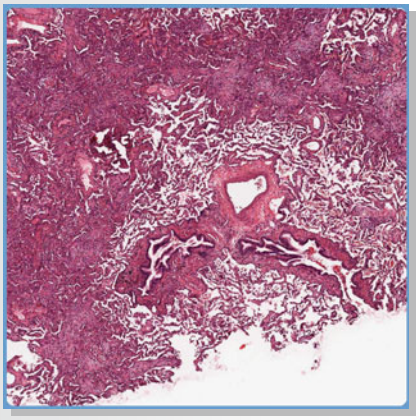
Nodular Diseases





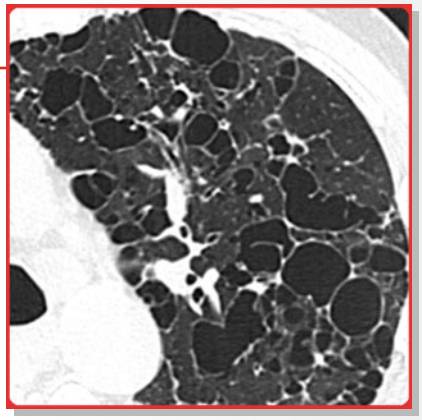


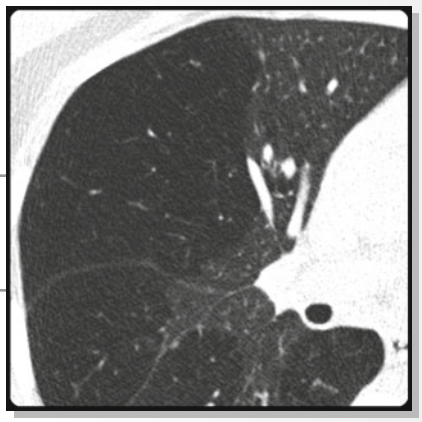




Alveolar Pattern

Alveolar Diseases





Clinical Approach to Diffuse Lung Diseases

Clinical features	**Micaela Romagnoli** **Rocco Trisolini**
Pathology	**Alessandra Cancellieri**

G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_1

CLASSIFICATION OF DLDs

Diffuse lung diseases (DLDs) are a heterogeneous group of lung disorders, consisting of inflammation and/or fibrosis of the pulmonary parenchyma, classified together because of some similar clinical, radiographic, physiologic or pathologic manifestations.
The differential diagnosis includes a broad range of diseases, and the treatment choices and prognosis significantly vary among the different causes and types of DLDs, so ascertaining the correct diagnosis is important.

DLD, interstitial lung disease (ILD) and diffuse parenchymal lung diseases (DPLD)

DLDs Associated to Known Causes

DLDs associated to known causes (~35 % of all patients with DLDs) are:

- Connective tissue diseases (CTD)
- Drug-induced lung diseases
- Dust-associated pneumoconiosis
- Familial pulmonary fibrosis
- Hypersensitivity pneumonia (HP)
- IgG4-related disease
- Immunodeficiency (HIV, GVHD)

Idiopathic DLDs

Idiopathic DLDs (iDLDs) (~65 % of all patients with DLDs) may be classified according to the incidence in:

Major idiopathic interstitial pneumonias:

- Idiopathic pulmonary fibrosis (IPF)
- Idiopathic non-specific interstitial pneumonia (NSIP)
- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Cryptogenic organizing pneumonia (COP)
- Acute interstitial pneumonia (AIP)

Rare idiopathic interstitial pneumonias:

- Idiopathic lymphoid interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

*Unclassifiable idiopathic interstitial pneumonias**

*Causes of unclassifiable ILDs include (a) insufficient clinical, radiologic or pathologic data and (b) discordance between clinical, radiologic and pathologic findings that may occur in patients previously treated or new pathologic entities/unusual variants of recognized entities.

Idiopathic DLDs

Idiopathic DLDs might also be classified according to clinical presentation:

Acute/subacute iDLDs:

- Cryptogenic organizing pneumonia (COP)
- Acute interstitial pneumonia (AIP)

Chronic fibrosing iDLDs:

- Idiopathic pulmonary fibrosis (IPF)
- Idiopathic non-specific interstitial pneumonia (NSIP)

Smoking-related iDLDs:

- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

American Thoracic Society, European Respiratory Society (2002) American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 165:277

IPAF

Interstitial pneumonia with autoimmune features (IPAF) is a new entity in the DLDs context:

- Many patients with an idiopathic DLD have clinical features suggesting an underlying autoimmune process, but do not meet established criteria for a definite CTD.
- The 'European Respiratory Society/American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease' was formed to reach a consensus regarding the nomenclature and classification criteria for patients with DLD and features of autoimmunity.
- The proposed term 'interstitial pneumonia with autoimmune features' (IPAF) gives classification criteria mainly based on the combination of features from three domains: (1) clinical characteristics consisting of specific extra-thoracic features, (2) serologic characteristics consisting of specific autoantibodies and (3) morphologic characteristics based on specific chest imaging, histopathologic or functional features.
- The term IPAF should be used to identify individuals with DLD and features suggestive of, but not definitive for, a CTD.

Fischer A (2015) An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 46(4):976

Cottin V (2016) Idiopathic interstitial pneumonias with connective tissue diseases features: a review. Respirology 21(2):245

Kim HC (2015) Interstitial pneumonia related to undifferentiated connective tissue disease: pathologic pattern and prognosis. Chest 147(1):165

Solomon JJ (2015) Connective tissue disease-associated interstitial lung disease: a focused review. J Intensive Care Med 30(7):392

Epidemiology and Prognosis

- Registries of epidemiology of different DLDs remain scarce, since these conditions are rare. Many of the available data come from prospective registries of data reported by respiratory physicians in Belgium, Germany, Italy, Spain and Greece. The data show that the most frequent DLDs are IPF and sarcoidosis, which together comprise about 50 %.
- Prognosis significantly differs depending on DLD subtype. The 5-year survival rate is only about 20 % in IPF, about 60 % in LIP, 80 % in cellular NSIP, above 90 % in sarcoidosis and close to 100 % in COP. In general, DLDs that are associated with connective tissue diseases are recognized to have a better prognosis, although there are some conflicting data in literature on this issue.

The risk prediction is challenging in DLDs because of the heterogeneity in disease-specific and patient-specific variables.

The validated GAP model, a clinical prediction model based on sex, age and lung physiology, has been validated in patients with IPF and with DLDs other than IPF. The ILD-GAP model accurately predicts mortality in major chronic ILD subtypes and at all stages of disease.

Ley B (2012) A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 156(10):684

Ryerson CJ (2014) Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 145(4):723

The European Lung white book. Interstitial lung diseases 256, 2013 ERS

CLINICAL EVALUATION

All successful diagnostic strategies begin with the patient. First of all it is an absolute requirement to know the *tempo* of the patient's respiratory symptoms. Shortness of breath is the main clinical complaint when DLD is present, often accompanied by cough. Knowing whether these symptoms are *acute* (hours to several days), *subacute* (a few weeks to a few months) or *chronic* (many months to years) allows inclusion of some diseases and exclusion of others from the differential diagnosis. This knowledge also helps us to determine the nature of the critical pathology for this patient. Tables below present a view of the diseases most commonly associated with these three clinical presentations listed in alphabetical order.

Acute Diseases

The main *acute* (hours to several days) diseases are:

- Acute exacerbation of chronic DLD
- Acute injury related to drugs
- Acute eosinophilic pneumonia (AEP)
- Acute injury related to fumes and toxins
- Acute interstitial pneumonia (AIP)
- ARDS
- Diffuse alveolar haemorrhage (DAH)
- Infection
- Vasculitis

☝ In the patient with acute clinical manifestations, further knowledge about his/her immunological status is very helpful, as suspicion for infection is always higher in immunocompromised hosts, and if bronchoalveolar lavage (BAL) and/or transbronchial biopsies are done, specimens always require additional studies to exclude an infectious organism (cultures and special stains for microorganisms).

Subacute Diseases

The main *subacute* (weeks to several months) diseases are:

- Cryptogenic organizing pneumonia (COP)
- Infection
- Pulmonary alveolar proteinosis (PAP)
- Smoking-related disease
- Subacute hypersensitivity pneumonitis (HP)
- Subacute injury related to CVD
- Subacute injury related to drugs

Chronic Diseases

The main *chronic* (months to several years) diseases are:

- Amyloidosis
- Chronic eosinophilic pneumonia (CEP)
- Chronic injury related to CVD
- Chronic injury related to drugs
- Idiopathic pulmonary fibrosis (IPF)
- Lymphoid interstitial pneumonia (LIP)
- Non-specific interstitial pneumonia (NSIP)
- Pneumoconioses
- Pulmonary alveolar proteinosis (PAP)
- Sarcoidosis/berylliosis
- Small airways disease
- Smoking-related disease

📖 Leslie KO (2009) My approach to interstitial lung disease using clinical, radiological and histopathological patterns. J Clin Pathol 62(5):387

Palmucci S (2014) Clinical and radiological features of idiopathic interstitial pneumonias (IIPs): a pictorial review. Insights Imaging 5(3):347

History

In about one-third of patients with a DLD, the aetiology of the lung injury pattern is known, and it can be depicted by a detailed clinical history, taking into account all the possible known causes of lung injury (please see the above section 'DLDs associated to known causes').

A complete history should include information about:

- Occupational and environmental exposure (asbestos, inorganic particles, organic dusts or animal antigens)
- Smoking history
- Drugs exposure
- Pulmonary infection
- Recent travel history
- Immune disorders
- Autoimmune disorders, e.g. connective tissue disease (CTD)
- Family history (familial fibrosis)

When all these causes might be excluded, then the diagnosis will be of an idiopathic DLD.

Key Pulmonary Symptoms and Signs

- Dyspnea (acute, subacute or chronic), mainly progressive exertional dyspnea
- Dry cough
- Chest pain
- Hemoptysis
- Wheezing
- Inspiratory crackles at lower lobes (mainly in IPF, asbestosis, chronic HP)
- Tachypnea (10–15 % of patients)

Inspiratory crackles, *velcro sounds* and rales

Dyspnea

- Most of the patients with DLD present to the pulmonologist attention mainly because of *chronic* progressive dyspnea, which is mainly experienced during exertion, but it can also occur at rest at the end-stage disease, or it can present in an *acute* form during an exacerbation.
- Differential diagnosis for *acute dyspnea*: pulmonary embolism, upper airway obstruction (foreign body aspiration, laryngospasm), acute asthma, pneumothorax, pneumonia, pulmonary oedema and cardiac ischaemia.
- Differential diagnosis for *chronic dyspnea* includes asthma, chronic obstructive pulmonary disease (COPD) and cardiac failure.
- Some patients with mild forms of DLDs, or at earlier stages, might be asymptomatic, and the radiologic or pulmonary function abnormalities can be discovered incidentally.

When in DLD the severity of dyspnea is worse than expected based on the extent of radiologic and functional abnormalities, one should consider the possibility of a complicating factor, e.g. pulmonary hypertension, or of a coexisting cardiac disorder.

Seeger W (2013) Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol 62(25 Suppl):D109

Ryu JH (2007) Pulmonary hypertension in interstitial lung diseases. Mayo Clin Proc 82

Dry Cough

- Dry cough is typically observed in patients with DLDs, and it may precede the onset of dyspnea.
- Differential diagnosis for *dry cough* includes postnasal drip, gastroesophageal reflux disease, asthma and lung cancer.

Brown KK (2006) Chronic cough due to chronic interstitial pulmonary diseases: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl):180S

Chest Pain

Chest pain is related to a pleural disorder. In DLDs, chest pain might be present because of a pleuritis or a pleural effusion, e.g. in CTD-related DLDs, drug-induced DLDs, or because of a spontaneous pneumothorax, e.g. in LAM and LCH.

Hemoptysis

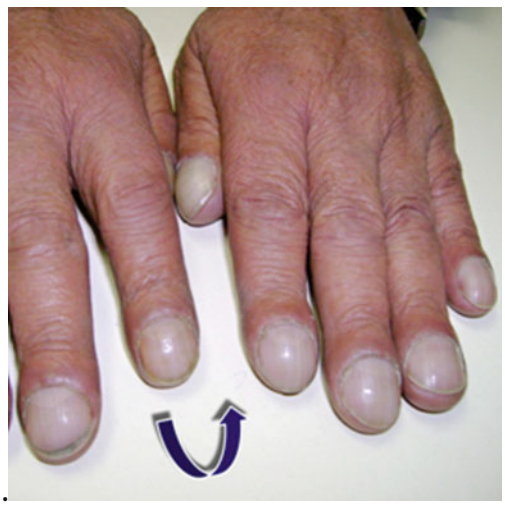
Coughing up of blood is not a frequent symptom in DLDs. However, it might be present in some specific DLDs, e.g. pulmonary vasculitis, CTD-DLDs, Goodpasture's syndrome, drug-induced alveolar haemorrhage and idiopathic pulmonary hemosiderosis.

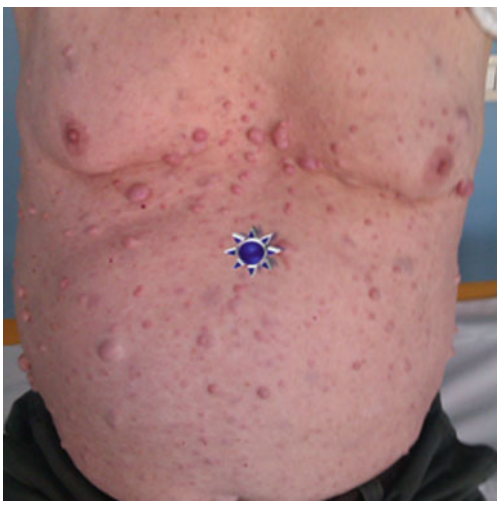
Wheezing

Wheezing is uncommon in patients with DLDs. However, some DLDs might be associated with airflow obstruction and wheezing, e.g. in sarcoidosis, eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome), respiratory bronchiolitis-associated ILD (RB-ILD), lymphangioleiomyomatosis (LAM) and hypersensitivity pneumonitis.

Key Extrapulmonary Symptoms and Signs

- Clubbing of the fingers and toes (). It is common in IPF but also in other chronic conditions: lung carcinoma, asbestosis, cystic fibrosis and arterio-venous malformation.
- Cutaneous neurofibromas () are the hallmarks of Recklinghausen neurofibromatosis.
- Erythema nodosum, uveitis, parotid enlargement and acute arthritis (sarcoidosis).
- Fever.
- Gastroesophageal reflux disease (GERD) often present in scleroderma and IPF.
- Haematuria (vasculitis).
- Multiorgan involvement (connective tissue disease, vasculitis, amyloidosis, neurofibromatosis).
- Neurologic symptoms (vasculitis, sarcoidosis, miliary TB).
- Pulmonary hypertension.
- Weight loss





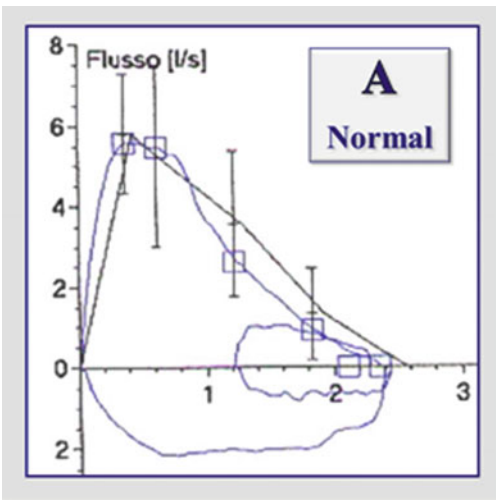
All the symptoms and signs, pulmonary and/or extrapulmonary, are not specific *per se* of DLDs, as they can be found in many other different respiratory diseases and heart dysfunction (lung cancer, emphysema, COPD, heart failure). Their presence together with the clinical context, chest X-ray and chest high-resolution computed tomography (HRCT) findings makes the physician confident for the suspicion of a DLD, necessitating for further investigations.

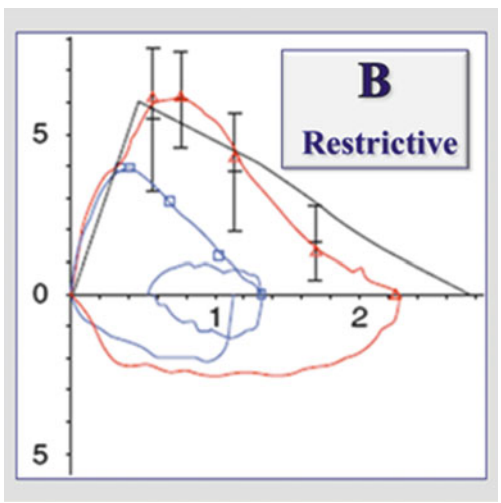
FUNCTIONAL TESTING

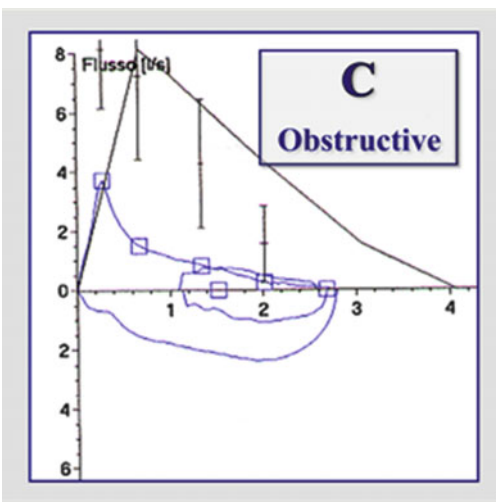
Spirometry

- *Normal*: FVC, FEV_1 and FEV_1/FVC ratio are above the lower limit of normal. ATS recommendations: lower limit of normal is the result of the mean predicted value (based on the patient's sex, age and height) minus 1.64 times the standard error of the estimate from the population study on which the reference equation is based. If the lower limit of normal is not available, the FVC and FEV_1 should be greater than or equal to 80 % of predicted, and the FEV_1/FVC ratio should be no more than 8–9 absolute percentage points below the predicted ratio.
- *Restrictive*: FEV_1/FVC ratio is normal, with relative preservation of the RV/TLC percentage, and reduced values of TLC, RV, FVC and FEV_1.
- *Obstructive*: FEV_1/FVC ratio is reduced, with reduced FEV_1, relative preservation of TLC and FVC and increased RV.

In DLDs spirometry might be normal, e.g. in the earlier stages of the disease, but most often it shows a typical restrictive pattern.







- In some cases, severe obstructive defects, especially when they present acutely, e.g. during an asthma attack, can mimic a restrictive pattern, showing a normal FEV_1/FVC ratio, and reduced values of both FVC and FEV_1.

- It is important in these cases to also measure TLC and RV, since contrarily to real restrictive trouble, TLC in these cases is normal or increased (and not reduced) and RV is increased (and not reduced).

Quanjer PH (1993) Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 6(Suppl 16):S5

DL_{CO}

- The diffusing capacity of carbon monoxide (DL_{CO}, mL/min/mmHg) is usually decreased in DLDs. The decrease of DL_{CO} is due in part to the thickening of the alveolo-capillary membrane, but also importantly to the mismatching of ventilation and perfusion of the alveolus.
- The DL_{CO} may be falsely decreased in severe restrictive or obstructive disease as patients may not be able to inspire an adequate amount of CO. Therefore, the DL_{CO} is often adjusted by the alveolar volume (VA) and listed as the DL_{CO}/VA. A normal DL_{CO}/VA is considered to be >80 %.

Recently, a proposed computer-aided method for quantitative computed tomography (CT) analysis of honeycombing area showed in 36 IPF patients that there is a correlation between the measured honeycombing area and parameters of PFTs, e.g. DLCO and FVC, furtherly underlying the importance of the use of these functional parameters in the follow-up of IPF patients.

Nakagawa H (2016) Quantitative CT analysis of honeycombing area in idiopathic pulmonary fibrosis: correlations with pulmonary function tests. Eur J Radiol 85(1):125

Cotes JE (1993) Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 6(Suppl 16):S41

AUTOIMMUNITY

- Pulmonary manifestations of connective tissue disease (CTD), also defined as collagen vascular disease (CVD), may precede systemic onset, and, therefore, pulmonologists may have the chance to diagnose a systemic rheumatic disease.
- For the discrimination of CTD-related DLDs and idiopathic DLDs, serological testing and depiction of systemic symptoms/signs are recommended.
- Laboratory findings for autoimmunity and systemic symptoms/signs are always to be detected in the initial evaluation of patients with a DLD and during their follow-up.

Laboratory Findings

- ANA (antinuclear antibody, Ab)
- ANCA (anti-neutrophil cytoplasmic, Ab)
- Anti-CCP (anti-cyclic citrullinated peptide, Ab)
- Anti-Jo1 (anti-histidyl, Ab)
- Rheumatoid factor (RF)
- Sedimentation rate and C-reactive protein
- SSA (Sjögren's syndrome-A Ab – Ro ribonucleoprotein: Ro52/Ro60)
- SSB (Sjögren's syndrome-B Ab – La ribonucleoprotein domain family)
- TSH (thyroid-stimulating hormone), FT3 (triiodothyronine) and FT4 (thyroxin)

- The above suggested list of basic tests to perform in the suspicion of, or to exclude, a CTD is based on practical clinical routine and mentioned to help physicians dealing with DLDs. These laboratory tests should be performed at the initial evaluation of a DLD patient and at follow-up (e.g. annually).
- The screening for ANA is generally accepted, and it represents a basic diagnostic tool for screening CTD with high sensitivity, but poor specificity. The probability to detect an underlying CTD is higher in patients with high ANA titres. However, as there are frequent screening failures in the ANA test, the following routine screenings are also recommended:
- The most common positive test in myositis and antisynthetase is Jo-1 Ab, with other tests, e.g. PL7 and PL12 in an advanced laboratory workup.
- SSA and SSB should also be tested to detect an underlying Sjögren's syndrome or SLE (systemic lupus erythematosus).
- Rheumatoid arthritis is the most common CTD, often associated with DLDs. Therefore RF and anti-CCP Ab screening should be included in routine screening laboratory testing.
- In microscopic polyangiitis (MPA), DLD also can be the first apparent symptom, which makes a routine screening for ANCA (especially p-ANCA) reasonable and recommendable.
- Autoimmune thyroiditis has been found to develop during the follow-up of idiopathic NSIP patients, up to 30 % of cases. Thus, testing for thyroid function should also be recommended.

Systemic Symptoms and Signs

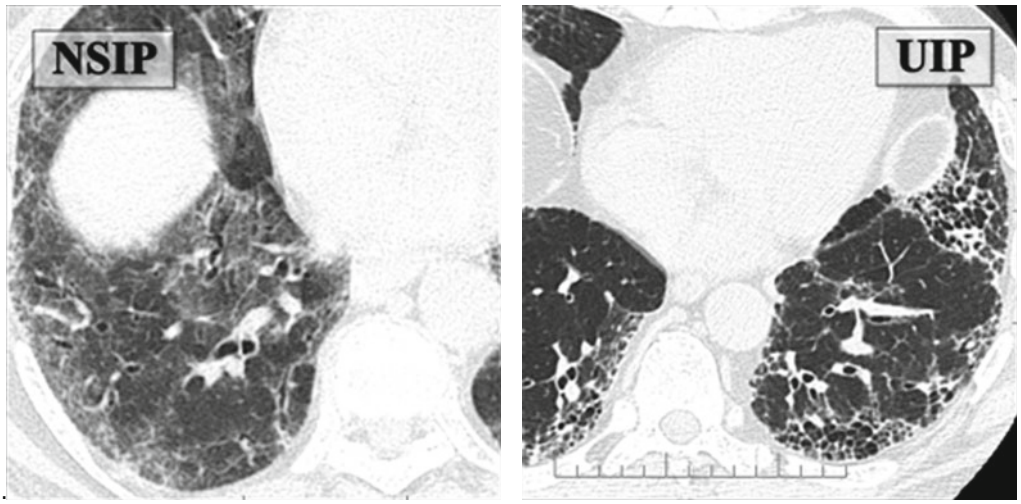
- Arthralgias/multiple joint swelling
- Dry mouth or dry eyes (*sicca* features)
- Dysphagia
- Gastroesophageal reflux
- Morning stiffness
- Nonandrogenic alopecia
- Oral ulceration
- Photosensitivity
- Proximal muscle weakness
- Raynaud's phenomenon
- Recurrent unexplained fever
- Skin changes (rash)
- Unintentional weight loss

The above-mentioned systemic symptoms and signs are characteristic of the different CTDs. There also exists, however, a group of systemic autoimmune disorders with signs and symptoms not sufficiently evolved to fulfil any of the accepted classification criteria for the defined connective tissue diseases. These conditions have been defined as undifferentiated connective tissue diseases (UCTD).

The presence of at least one of the above-mentioned symptoms/signs, together with positive findings for at least one of the above-cited laboratory tests, is now internationally accepted as sufficient to define an UCTD.

DLD in Sjögren's Syndrome and in RA

- In Sjögren's syndrome DLDs occur in <5 %. NSIP and UIP are the most frequent patterns (and LIP), with NSIP pattern found in 60 % of patients with ILD-Sjögren.
- In patients with rheumatoid arthritis (RA), DLD is the most common lung disease and UIP affects 15–20 % of patients with RA. In 10 % of cases, ILD may be the first manifestation of RA, especially with the histological NSIP pattern.



Mosca M (1999) Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 17:615

Kinder BW (2007) Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 176(7):691

Bahmer T (2016) The use of autoantibody testing in the evaluation of interstitial lung disease (ILD) – a practical approach for the pulmonologist. Respir Med 113:80

THE MOST FREQUENT CLINICAL SETTINGS

Based on the described different clinical onset of the disease, history, pulmonary and extrapulmonary symptoms/signs, functional features, the presence or absence of an autoimmune context and imaging at chest HRCT, how can the clinician orientate to recognize the main clinical different settings?
On the basis of the comprehensive analysis of clinical, functional, radiologic and pathologic data and of some specific details in some clinical settings.

IPF

IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP and characterized by a median survival of 3–5 years following diagnosis.
Clinical presentation and diagnosis:

- Predominantly in smokers or previous smoker men averaged 70 years of age.
- Presenting with dry cough and rapid progressive exertional dyspnea.
- Showing in most cases a progressive restrictive ventilatory defect on lung function testing and decreased DLCO.
- Need for chronic oxygen therapy at end-stage disease.
- Other known causes of DLDs (e.g. genetic disorders, domestic and occupational environmental exposures, connective tissue disease and drug toxicity) must be excluded.
- Chest HRCT: the presence of a typical UIP pattern (please refer to IPF in chapter "Fibrosing Diseases").
- Natural history is variable and unpredictable: (a) most patients with IPF demonstrate a gradual worsening of lung function over the years; a minority of patients remains stable or declines rapidly; (b) some patients may experience episodes of acute respiratory worsening despite previous stability.
- The need for lung histology when the disease is suspected but chest HRCT does not show a definite UIP pattern (e.g. in the presence of a "possible UIP" pattern, or in the presence of a "inconsistent with UIP" pattern).

Raghu G (2011) ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183(6):788

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

Spagnolo P (2015) Idiopathic pulmonary fibrosis: An update. Ann Med 47(1):15

In the presence of a UIP pattern at chest HRCT scan, always think of an IPF and exclude all the known causes for a UIP pattern (e.g. CTD, fibrosing drug toxicity).

There is no available treatment to cure this fatal disease, except for lung transplantation.

However, in the last years, two new drugs (pirfenidone and nintedanib) have shown some beneficial effects (e.g. reducing the FVC decline) for those patients with mild/moderate disease, whereas neither one has a clear advantage on mortality outcomes.

NSIP

Idiopathic NSIP is recognized since 2008 as a distinct clinical entity among idiopathic DLDs.
Clinical presentation and diagnosis:

- Predominantly in never-smoking women averaged 50 years of age
- Presenting with shortness of breath and cough of usually 6–7 months' duration
- Showing in most cases a restrictive ventilatory defect on lung function testing and decreased DLCO
- Chest HRCT: bilateral, symmetric, predominantly lower lung fibrosing reticulation and ground-glass opacity (GGO) with traction bronchiectases and lower lobe volume loss that is usually diffuse or subpleural in the axial dimension, but sometimes spares the subpleural lung (please also refer to NSIP in chapter "Fibrosing Diseases")
- Lung histology: cellular and/or fibrosing NSIP
- Relative good response to systemic corticosteroid treatment, although controlled studies are not available
- Good prognosis with a 5-year mortality rate estimated at less than 18 %

In the presence of a patient with a final diagnosis of idiopathic NSIP, always carefully check for autoimmunity, both at initial evaluation and at follow-up, since almost 30 % of cases have a UCTD or a CTD from the beginning, and almost 50 % of cases develop an autoimmune disease in the next 3 years after initial diagnosis.

Travis WD (2008) Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 177(12):1338

Romagnoli M (2011) Idiopathic nonspecific interstitial pneumonia: an interstitial lung disease associated with autoimmune disorders? Eur Respir J 38:384

COP

Clinical presentation and diagnosis:

- COP affects both sexes indiscriminately between the ages of 50 and 60, with a relative prevalence of non-smoking patients.
- Within a few days, the patient might develop hyperthermia and/or malaise and/or cough and/or dyspnea, all of which can become severe, often (but not always) associated with signs of inflammation and an increase in blood neutrophil levels.
- Chest HRCT: patchy peripheral and/or peribronchial consolidations with ground-glass opacities; possible 'reversed' halo sign (also defined Atoll sign) (please also refer to COP in chapter "Alveolar Diseases" and also to Reversed halo sign in the "Case-Based Glossary with Tips and Tricks").
- Rapid regression of symptoms and radiologic improvement/healing with systemic corticosteroids, which should be continued with a tapering regimen for 6 months.

Baque-Juston M (2014) Organizing pneumonia: what is it? A conceptual approach and pictorial review. Diagn Interv Imaging 95(9):771

Sarcoidosis

Different clinical presentations:

- Bilateral hilar adenopathy on the chest radiograph in an asymptomatic patient
- Löfgren syndrome (erythema nodosum skin rash coupled with bilateral hilar adenopathy on the chest radiograph and often fever and arthritis)
- Heerfordt syndrome (uveitis, parotiditis and fever)

Diagnosis: the presence of granulomas alone is inadequate for the diagnosis of sarcoidosis. The diagnosis is established when clinico-radiographic findings are supported by histologic evidence of noncaseating granulomatous inflammation, and other causes of granulomas and local reactions have been reasonably excluded.

Chest X-ray staging system:

- Stage 0: no adenopathy or infiltrates
- Stage 1: hilar and mediastinal adenopathy alone
- Stage 2: adenopathy and pulmonary infiltrates
- Stage 3: pulmonary infiltrates alone
- Stage 4: pulmonary fibrosis

Pathologic diagnosis: at present, it only relies on the demonstration of noncaseating granulomatous inflammation.

For the pathologic diagnosis of sarcoidosis, endosonographic techniques (EBUS-TBNA and EUS-FNA) are superior to the combination of endobronchial mucosa and transbronchial lymph node biopsies (TBNA) for the demonstration of noncaseating granulomatous inflammation.

At present, serologic ACE (angiotensin-converting enzyme) test and BAL are not considered anymore as first-step diagnostic tests.

Baughman RP (2011) A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med 183(5):573

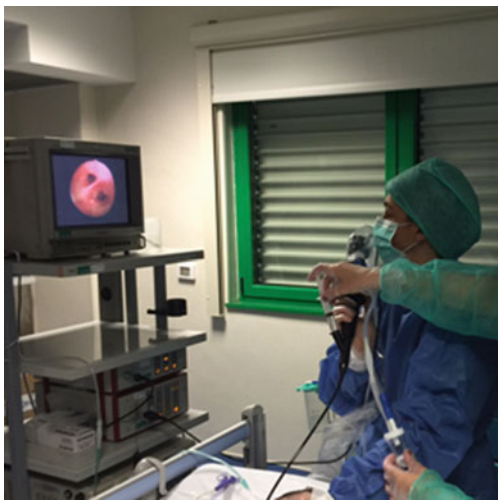
Jenssen C (2015) Ultrasound techniques in the evaluation of the mediastinum, part 2: mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography. J Thorac Dis 7(10):E439

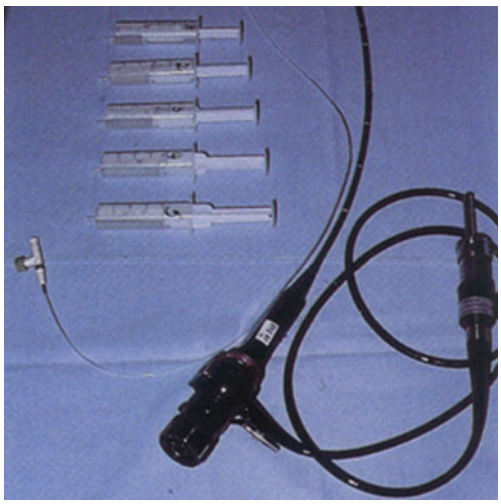
BRONCHOALVEOLAR LAVAGE (BAL)

Bronchoalveolar lavage (BAL) and transbronchial biopsy are no more essential in the diagnostic algorithm of 2002 ATS/ERS consensus classification. However, BAL might be diagnostic in several DLD clinical settings, and some researchers use it as an additional tool in the multidisciplinary approach to DLDs.
Thus, BAL has a central role in the diagnosis of a number of rare disorders and in excluding opportunistic infection in treated patients.
The use of BAL in the diagnosis of the more prevalent DLDs is not well addressed in the medical literature, as most published studies predate changes in disease classification and fail to integrate BAL data with other clinical and radiological information.
Further studies to quantify the value added by bronchoalveolar lavage in routine practice are required.

Procedure

- Bronchoscope placed in a wedge position within the selected bronchopulmonary segment.
- Total volume between 100 and 300 ml of normal saline at room T°, divided into 3–5 aliquots.
- Use negative suction pressure <than 100 mmHg.
- The minimal total volume retrieved should be ≥to 5 % (optimal ≥30 %).





Normal Values

The BAL normal values in healthy never-smoking individuals are:

- Total cells: 2–64 × 10^6 or 100–150 × 10^3/mL
- Alveolar macrophages: 80–90 %
- Lymphocytes: 5–15 %
- Neutrophils: ≤3 %
- Eosinophils: < 1 %

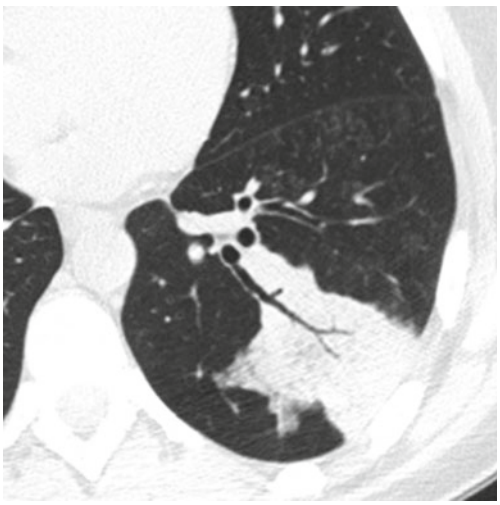
Diagnostic Role

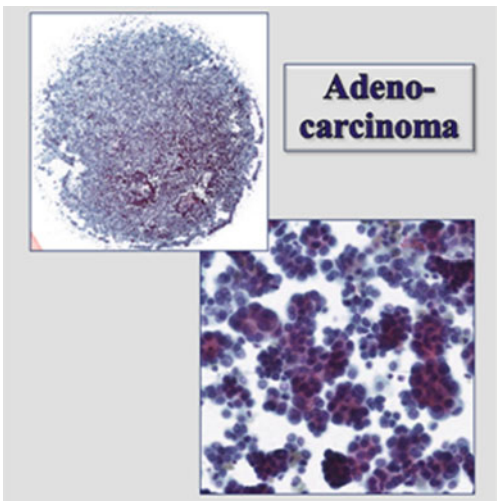
In the correct clinical setting, BAL findings might be diagnostic in:

- Cancer (especially in adenocarcinoma)
- Chronic eosinophilic pneumonia (CEP)
- Diffuse alveolar damage (DAD)
- Diffuse alveolar haemorrhage (DAH)
- Drug-induced lung disease
- Dust exposure
- Infection (opportunistic)
- Langerhans cell histiocytosis (LCH)
- Lipoid pneumonia (LP)
- Pulmonary alveolar proteinosis (PAP)
- Pulmonary lymphoma

BAL in Adenocarcinoma

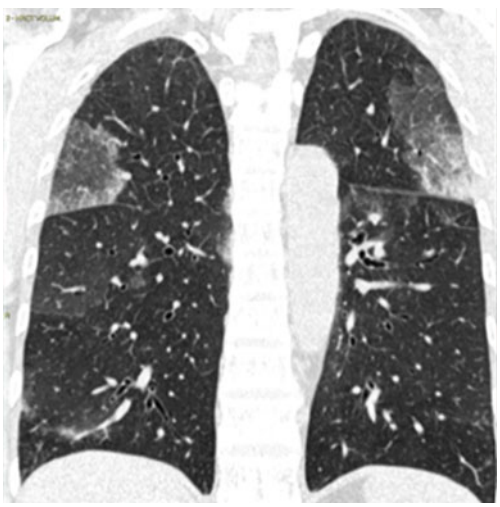
Axial HRCT: basal consolidation with air bronchogram (please also refer to Adenocarcinoma in the chapter "Alveolar Diseases").
Pathology: neoplastic cells from adenocarcinoma are present.

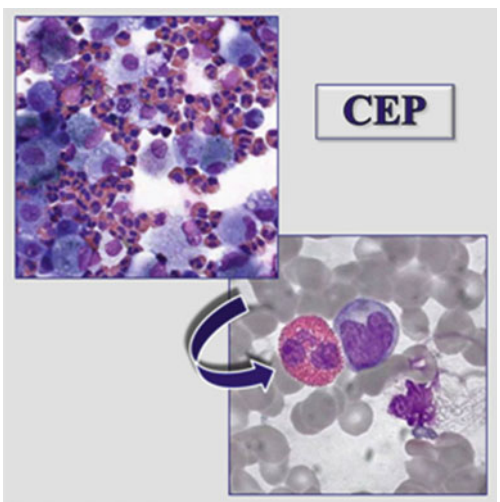




BAL in CEP

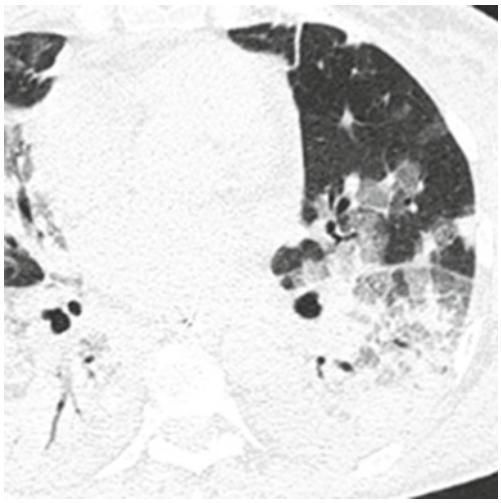
Coronal HRCT: peripheral ground-glass opacities in the upper lobes (please also refer to Reverse batwing sign in the "Case-Based Glossary with Tips and Tricks" and to chronic eosinophilic pneumonia-CEP in the chapter "Alveolar Diseases").
Pathology: a very high number of eosinophils (>40 %) are visible. At higher power, the eosinophil (↘) shows a bilobated nucleus and an intensely red, granular cytoplasm.

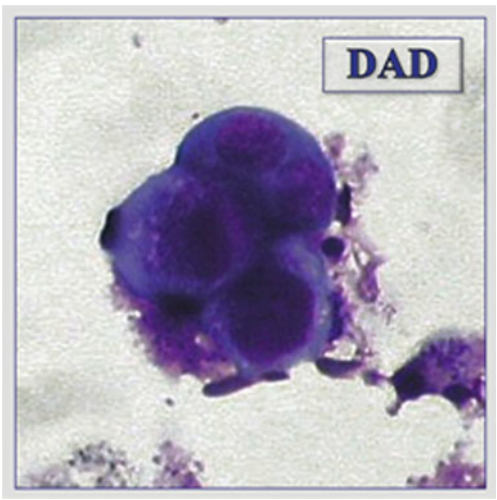




BAL in DAD

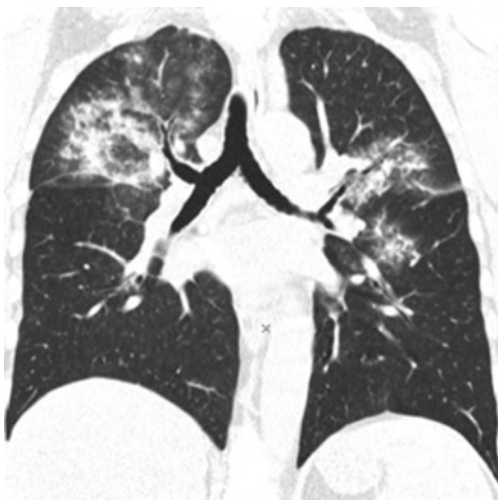
Axial HRCT in AIP: extensive bilateral ground-glass opacities and gravity-dependent consolidations with air bronchogram (please also refer to AIP in the chapter "Alveolar Diseases")
Pathology: diffuse alveolar damage (DAD) cells, with reactive atypia, are present.

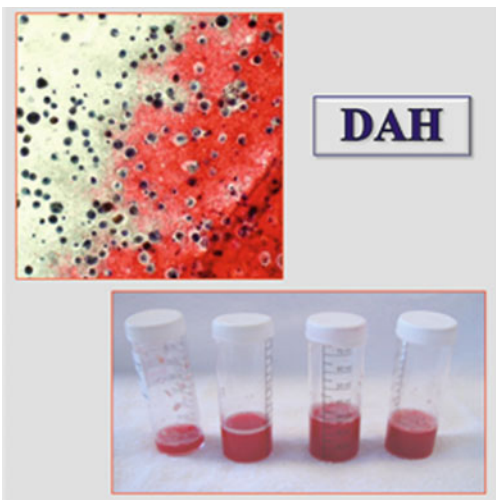




BAL in DAH

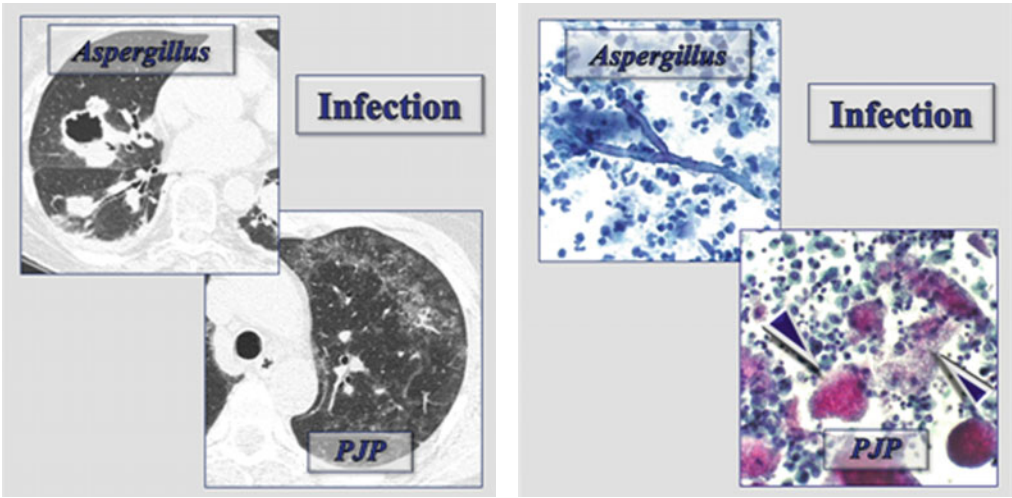
Coronal HRCT: bilateral consolidations and ground-glass opacities being predominant in the parahilar region with the absence in the subpleural regions ('butterfly' or 'batwing' distribution) (please also refer to Butterfly sign in the "Case-Based Glossary with Tips and Tricks" and to DAH in the chapter "Alveolar Diseases").
Pathology: hemosiderin-laden macrophages and fresh blood cells are present.





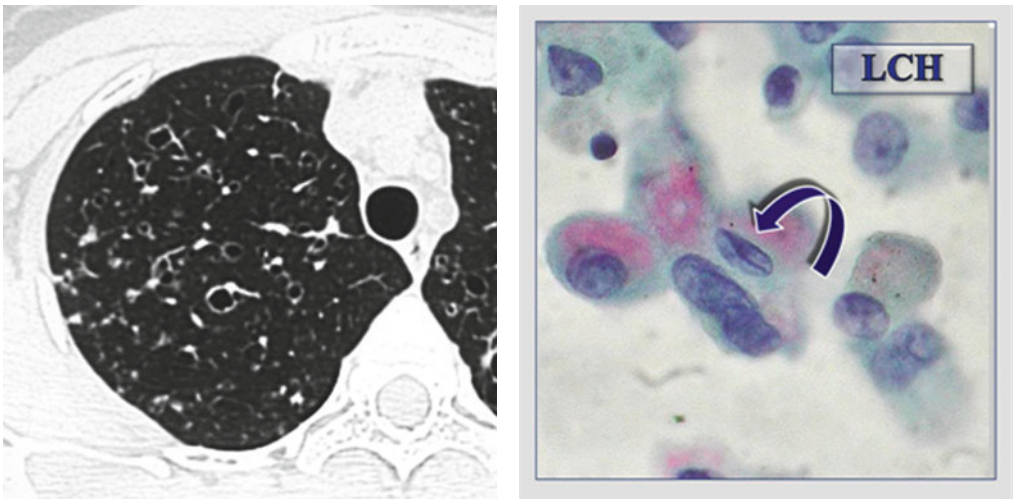
BAL in Infection (e.g. *Aspergillus*, *PJP*)

Axial HRCT in *Aspergillus* infection: multiple macronodules, some of them cavitated.
Axial HRCT in *PJP* infection: patchy GGO.
Pathology: in *Aspergillus* infection, septate hyphae branching at 45° are present on a necrotic background (please also refer to Air crescent sign in the "Case-Based Glossary with Tips and Tricks").
PJP infection shows characteristic foamy alveolar casts (►).



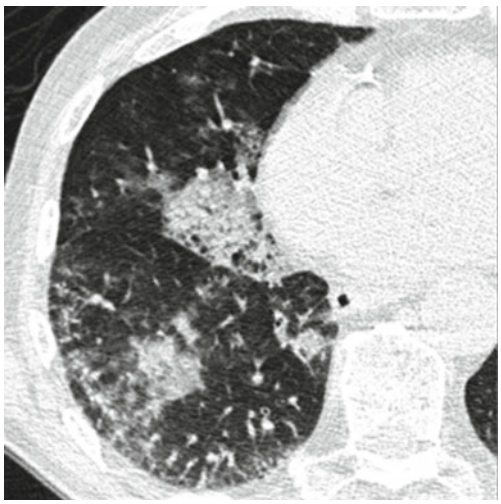
BAL in LCH

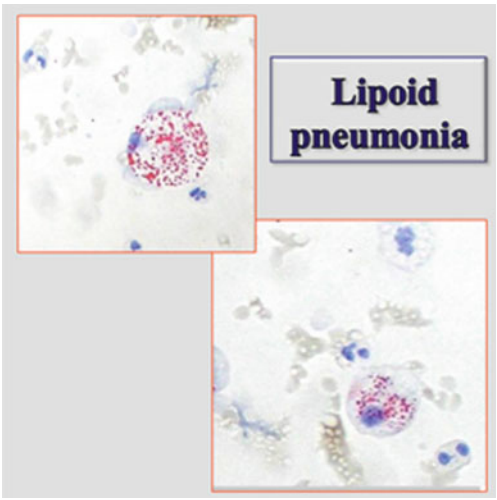
Axial HRCT: thick-walled and thin-walled cysts associated with some small solid nodules (please also refer to LCH in the chapter "Cystic Diseases").
Pathology: in BAL fluid, together with pigmented macrophages, a few Langerhans cells, with elongated, cleaved nuclei, are appreciable (↳).



BAL in Lipoid Pneumonia

Axial HRCT: basal patchy areas of ground-glass opacities (please also refer to Lipoid Pneumonia in the chapter "Alveolar Diseases").
Pathology: Oil-red positive macrophages.





Meyer KC (2012) An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 185(9):1004

Harari S (2012) Bronchoscopic diagnosis of Langerhans cell histiocytosis lymphangioleiomyomatosis. Respir Med 106:1286

Wells AU (2010) The clinical utility of bronchoalveolar lavage in diffuse parenchymal lung disease. Eur Respir Rev 19(117):237

BAL in IPF

BAL cellularity was considered not determinant in discriminating among the different idiopathic DLDs. However, a cut-off level of 30% for lymphocytes in BAL has shown to demonstrate a favourable discriminative power for the diagnosis of IPF.

Ohshimo S (2009) Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 179(11):1043

Ryu YJ (2007) Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. Respir Med 101(3):655

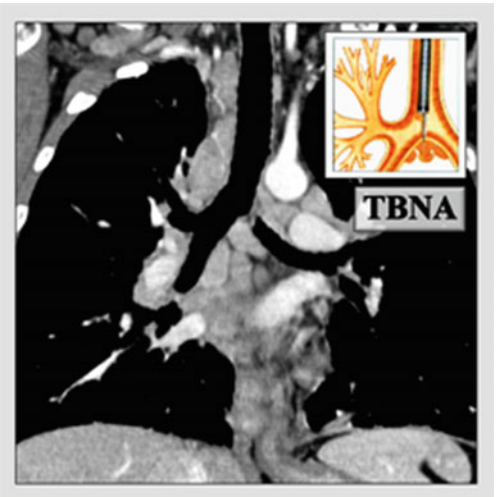
BAL in Sarcoidosis

CD4/CD8 ratio is highly specific but not sensitive for sarcoidosis diagnosis. Thus, BAL flow cytometry is not diagnostic alone without appropriate clinicoradiological and/or histopathological findings.

Tanriverdi H (2016) Comparison of the diagnostic value of different lymphocyte subpopulations in bronchoalveolar lavage fluid in patients with biopsy proven sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 32: 305

TBNA, EBUS-TBNA, EUS-FNA AND EUS-B-FNA

- *TBNA* (transbronchial needle aspiration) was developed for use with flexible bronchoscopy in the 1980s and was mainly used for the diagnosis and mediastinal staging of lung cancer. It showed later successful results also for the diagnosis of inflammatory/infectious and mediastinal lymphadenopathies (mainly sarcoidosis and tuberculosis).
- Ultrasound imaging has gained importance in pulmonary medicine over the last decades including endobronchial ultrasound (*EBUS*) and esophageal endoscopic ultrasound (*EUS*) for mediastinal lymph node assessment in both neoplastic and inflammatory mediastinal lymphadenopathy. Thus, mediastinal nodes can be sampled from the airways [endobronchial ultrasound combined with transbronchial needle aspiration (*EBUS-TBNA*)] or from the oesophagus [endoscopic ultrasound fine-needle aspiration (*EUS-FNA*)].
- EBUS and EUS have a complementary diagnostic yield and in combination virtually all mediastinal lymph nodes can be biopsied.
- These procedures might be useful in DLDs presenting with mediastinal lymphadenopathy, especially in sarcoidosis (and tuberculosis).
- Endosonography has been shown to have an excellent yield in assessing granulomas in patients suspected of sarcoidosis.



Procedures

The procedures are performed according to the mediastinal lymph node anatomy as classified by the International Association for the Study of Lung Cancer (IASLC).

- *TBNA* is performed in the conventional, 'blind' fashion, with either 19-gauge or 22-gauge needles, during standard flexible bronchoscopy, mostly on an outpatient basis, with the patient under local anaesthesia. Only lymph nodes with a short axis greater than 1 cm at CT are selected for aspiration. At least three passes per node are recommended. Each TBNA specimen is collected on clean glass slides. If a histologic core of tissue is obtained, it is gently removed from the slide and placed in a formalin solution. The remaining cytologic material is smeared on clean glass slides ('smear technique') which might be half air-dried and half ethanol fixed.
- *EBUS-TBNA* is performed with a dedicated ultrasonic bronchoscope, an endoscope with an ultrasound transducer engineered into its tip, and a linear one for the mediastinal approach (a radial probe is also available). It is introduced orally via a laryngeal mask/endotracheal tube under local anaesthesia and additional sedation usually with midazolam, with or without propofol depending on the presence of an anaesthesiologist, mostly on an outpatient basis. Images can be obtained by directly contacting the probe or by attaching a balloon on the tip and inflating with saline. When a lesion is outlined, the needle is introduced via the biopsy channel of the endoscope. Power Doppler examination is used immediately before the biopsy in order to avoid unintended puncture of vessels between the wall of the bronchi and the lesion. Under real-time ultrasonic guidance, the needle will be placed in the lesion. Suction is applied with a syringe and

the needle is moved back and forth inside the lesion. EBUS-TBNA specimen are collected as mentioned above.

- *EUS-FNA.* Similarly to EBUS, EUS is performed with a 'dedicated' echoendoscope. The echoendoscope for transesophageal endoscopic ultrasound is known by its acronym from the English language 'EUS' (endoscopic ultrasound). Linear EUS (similarly to linear EBUS) provides a view with a scanning angle variable from 120 to 180°, that is, parallel to the shaft of the echoendoscope, allowing real-time visualization of fine-needle aspiration (FNA). The procedure is performed with the patient lying on his/her left side, and it begins once the patient is adequately sedated, under mild sedation with midazolam, or deep sedation with anaesthesiologic care, based on the internal structure organization. The instrument is introduced through the mouth (through the use of a mouthpiece) and pushed gently until the gastric wall can be individualized at the ultrasound, and the left hepatic lobe, which presents cranially the hepatic vein flowing into the inferior vena cava, can be visualized. Through the introduction in the operating channel of the echoendoscope of a needle 22 gauge (also available needles 19 and 25 gauge) placed in suction, EUS-FNA can be performed under real-time ultrasound guidance.
- *EUS-B-FNA.* The EBUS bronchoscope can also be introduced into the oesophagus for mediastinal evaluation and sampling, a technique described as transesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-B-FNA). For EUS-B-FNA, the flexible EBUS endoscope is inserted and advanced through the oesophagus with the patient in the supine position while examining the structure and blood vessels around the oesophagus by ultrasound with Doppler flow imaging. Needle aspirations are performed as previously mentioned.

Diagnostic Role

The main role of these procedures in the evaluation of DLDs is in the presence of mediastinal adenopathies for the diagnosis of sarcoidosis, pulmonary lymphoproliferative disorders, and mainly for the differential diagnosis between sarcoidosis and tuberculosis.

Sarcoidosis:

- Both EBUS-TBNA and EUS-FNA are suitable for a final diagnosis of sarcoidosis, whereas pure TBNA fails in about one-third of cases.
- Published data indicate that the sensitivity (80–90 %) and accuracy of EUS-FNA and EBUS-TBNA are superior compared to simple mucosa biopsies with and without 'blind' TBNA.
- Special techniques (cytology and cell-block analysis) might even improve the diagnostic yield of ultrasound-guided specimens.
- A meta-analysis of 14 studies including 2,097 patients showed a diagnostic yield of 79 % for the diagnosis of sarcoidosis by EBUS-TBNA, with a pooled sensitivity and specificity of 84 % and 100 %, respectively.
- Complications may be encountered. Mediastinitis with abscess formation has been observed after EUS-FNA. Therefore, prophylactically administered antibiotics may be considered for EUS-guided biopsies.
- In the clinical suspicion of sarcoidosis, the presence at smear cytology/histology of typical epithelioid granulomas without necrosis, with or without some multinucleated giant cells, can confirm the diagnosis.

Tuberculosis:

- Several studies have shown a good diagnostic accuracy for the diagnosis of tubercular mediastinal adenopathies by EUS-FNA and EBUS-TBNA. Cytopathological criteria, the search for acid-fast bacilli using Ziehl-Neelsen technique as well as culture techniques and PCR are helpful for the final diagnosis.

Lymphoma:

- EBUS-FNA and EUS-FNA have a variable diagnostic yield for diagnosing and subtyping mediastinal Hodgkin and non-Hodgkin lymphoma. Often, a histology specimen – obtained by mediastinoscopy – is needed. However, the cell-block processing of the material obtained by EBUS-TBNA or EUS-FNA may have nearly similar diagnostic yield as histology, with an accuracy in some reports for EBUS-TBNA of 84 and 91 %, with correct subtyping possible in >2/3 of cases.

ROSE: the rapid on-site evaluation

- Although rapid on-site cytologic evaluation (ROSE) is widely used during EBUS-TBNA and EUS-FNA, its role remains unclear.
- Most studies on the role of ROSE during EBUS-TBNA demonstrate that ROSE is associated with a significantly lower need for additional bronchoscopic procedures and puncture number.
- ROSE prevents the need to repeat invasive diagnostic procedures aimed at molecular profiling, as when ROSE is performed patients are less likely to have samples suitable only for pathologic diagnosis because of minimal tumour burden.

Wang KP (1983) Flexible transbronchial needle aspiration for staging of bronchogenic carcinoma. Chest 84(5):571

Jenssen C (2015) Ultrasound techniques in the evaluation of the mediastinum, part 2: mediastinal lymph node anatomy and diagnostic reach of ultrasound techniques, clinical work up of neoplastic and inflammatory mediastinal lymphadenopathy using ultrasound techniques and how to learn mediastinal endosonography. J Thorac Dis 7(10):E439

Trisolini R (2015) Endobronchial ultrasound-guided transbronchial needle aspiration for diagnosis of sarcoidosis in clinically unselected study populations. Respirology 20:226

Grosu HB (2015) Endobronchial ultrasound-guided transbronchial needle aspiration accurately diagnoses and subtypes lymphoma. Ann Am Thorac Soc 12:1336

Oki M (2013) Rapid on-site cytologic evaluation during endobronchial ultrasound-guided transbronchial needle aspiration for diagnosing lung cancer: a randomized study. Respiration 85(6):486

Trisolini R (2015) Randomized trial of endobronchial ultrasound-guided transbronchial needle aspiration with and without rapid on-site evaluation for lung cancer genotyping. Chest 148(6):1430

TRANSBRONCHIAL BIOPSY (TBB)

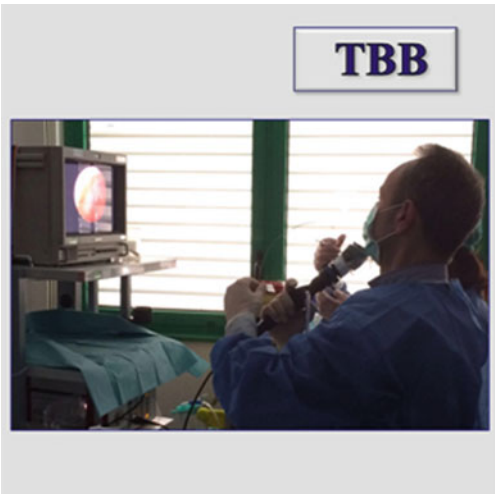
TBBs are biopsies containing lung parenchyma, usually performed during rigid bronchoscopy by the flexible bronchoscope inserted through the small airways containing lung parenchyma. The forceps used in conventional TBB reachs the lung parenchyma through the bronchial routes, and specimens come from the centrilobular regions. By this procedure, only disorders which are centred around terminal and respiratory bronchioles or are distributed along the lymphatic routes (e.g. sarcoidosis – see Figure below, carcinomatous lymphangitis) might be successfully diagnosed.

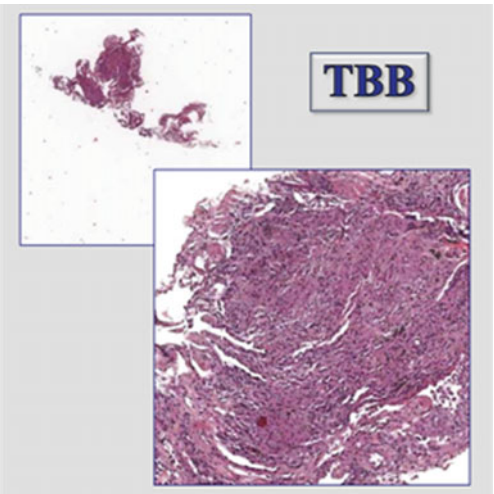
The role of transbronchial biopsy in the diagnosis of usual interstitial pneumonia (UIP) is controversial. Diagnostic findings of usual interstitial pneumonia are variably found in TBB specimens from 9.4 to 41 %, depending on the different reports. The primary and main role of transbronchial biopsy in the diagnosis of usual interstitial pneumonia is not to confirm a diagnosis, but to exclude other infiltrative diseases, such as malignancy, sarcoidosis or infections.

TBB has a low complication rate, with pneumothorax occurring in up to 8 % of cases, major bleeding in less than 1 % of cases and other complications (e.g. acute exacerbation of fibrotic lung disease) even more rarely.

Procedure

TBB can be carried out using rigid bronchoscopy under deep sedation, with anaesthesiologic assistance, under assisted spontaneous ventilation. TBBs are performed under fluoroscopic guidance, using flexible bronchoscope with flexible forceps. For each patient a number of at least six transbronchial biopsies are usually obtained. To minimize major complications in case of haemorrhage, a non-inflated Fogarty balloon and a rigid aspirator (diameter 4 mm) are placed in the lobar bronchus, before performing TBB in the more involved lobe, as shown by HRCT scan.





Diagnostic Role

Disorders centred around terminal and respiratory bronchioles routes:

- Alveolar filling disorders
- Arterial/bronchiolocentric peripheral nodules or masses
- Cellular bronchiolitis
- Infectious pneumonia
- Organizing pneumonia (OP)
- Respiratory bronchiolitis (RB)
- Tuberculosis

Disorders distributed along the lymphatic routes:

- Carcinomatous lymphangitis
- Kaposi sarcoma
- Sarcoidosis

Complication Rate

- Mortality: 0.01–0.1 %
- Haemorrhage: 1–2 % (15–26 % in immunocompromised patients)
- Pneumothorax: under fluoroscopic control, 1–2 %; blind, 3–8 %

Katzenstein (2012) Smoking-related interstitial fibrosis (SRIF), pathogenesis and treatment of usual interstitial pneumonia (UIP), and transbronchial biopsy in UIP. Mod Pathol 25(Suppl 1):S68

Shim HS (2010) Histopathologic findings of transbronchial biopsy in usual interstitial pneumonia. Pathol Int 60(5):373

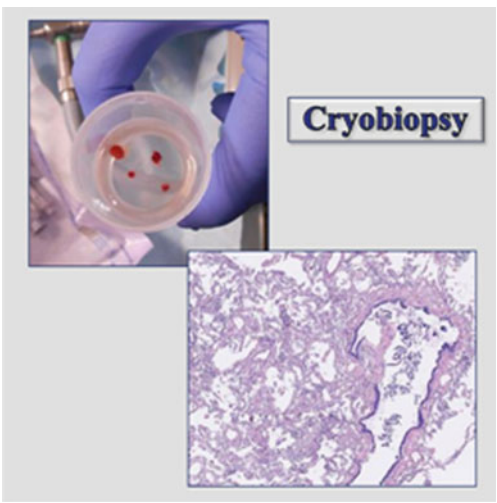
Romagnoli M (2008) The role of transbronchial lung biopsy for the diagnosis of diffuse drug-induced lung disease: a case series of 44 patients. Sarcoidosis Vasc Diffuse Lung Dis 25(1):36

TRANSBRONCHIAL CRYOBIOPSY

- At present, the gold standard procedure to obtain histology in DLDs is the surgical lung biopsy (SLB), allowing a histologic diagnosis up to the 95–98 % of cases. However, due to its complexity, cost and risk of mortality, the eligible patients are around one-third of all cases. Thus, the decision for a histologic diagnosis should be made on a case-by-case basis, weighing the morbidity of the procedure, the balance between the likely diagnoses and treatment options and, of course, the values and preferences of the patient.
- Unfortunately, endoscopic transbronchial biopsy (TBB) – although less invasive – is much less likely to be helpful for the histologic diagnosis in ILDs.
- Transbronchial (TB) cryobiopsy has been shown in the last 5 years to represent a useful, safe and poorly invasive diagnostic tool for the histologic diagnosis of DLDs.

Procedure

- Patients are intubated with a rigid bronchoscope under deep sedation.
- TB cryobiopsies are obtained under fluoroscopic guidance using the flexible bronchoscope inserted through the rigid tube.
- A flexible cryoprobe is used, after insertion in the working channel of the flexible bronchoscope.
- To better control a possible haemorrhage, before performing biopsies, a non-inflated Fogarty balloon will be placed through the rigid bronchoscope into the lobar bronchus chosen for cryobiopsies. The Fogarty balloon will be always inflated after each biopsy and then deflated in case of the absence of haemorrhage. In case of bleeding, the Fogarty will be deflated only after bleeding cessation.
- The cryoprobe is cooled with carbon dioxide (CO_2) to a temperature in the probe's tip of –75 °C within several seconds and is placed perpendicular to the chest wall.
- Once brought into the right position, the probe is cooled for approximately 5″–6″ and then retracted together with the flexible bronchoscope carrying the frozen lung tissue attached on the probe's tip.
- The procedure does not require hospitalization, unless complications occur.



Diagnostic Role

- TB cryobiopsy is a novel promising technique for histological diagnosis of DLDs, providing larger specimen size than classic transbronchial biopsy, less crush artefacts, more viable lung parenchyma and more alveolated tissue suitable for immunohistochemical analysis. It represents a less invasive technique than surgical lung biopsy, it needs shorter hospitalizations, and in the absence of complications, it might be performed on an outpatient setting.
- TB cryobiopsy has a diagnostic yield up to 74–80 % in DLDs, likely representing an 'innovative' way to obtain lung samples for the diagnosis of DLDs.
- TB cryobiopsy can dispense with the need of surgical lung biopsy in up to 50 % of cases.
- Samples obtained by TB cryobiopsy have significant larger size than 'classical' transbronchial biopsy, with an average surface area of 9 mm^2, with 70 % alveolated tissue.

- Complications are not negligible, with 2.6–28 % pneumothorax rate depending on different publications and 4–24 % bleeding rate, with different definitions of bleeding severity depending on different studies. However, no mortality and no haemodynamic instability are reported because of bleeding. Iced-cold saline, diluted vasoconstrictive agents, electrocoagulation, endobronchial blocker and Fogarty balloon should be immediately available, as these can aid in controlling bleeding.
- Limitations of this technique might be represented by the mentioned complications, and by the risk of missing the main and a second histology pattern, since lung samples obtained by TB cryobiopsy are smaller than those obtained by surgical lung biopsy.

Ganganah O (2016) Efficacy and safety of cryobiopsy versus forceps biopsy for interstitial lung diseases and lung tumours: a systematic review and meta-analysis. Respirology 21(5):834–841. doi: 10.1111/resp.12770

Yarmus L (2013) Cryoprobe transbronchial lung biopsy in patients after lung transplantation. A pilot safety study. Chest 143(3):621

Fruchter O (2014) Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. Respirology 19(5):683

Casoni GL (2014) Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS One 9(2):e86716

Babiak A (2009) Transbronchial cryobiopsy: a new tool for lung biopsies. Respiration 78:203

Romagnoli M et al. (2015) Transbronchial cryobiopsy in the evaluation of interstitial lung diseases: time for a positioning in the diagnostic work-up approach? Respirology 20(4):684

SURGICAL LUNG BIOPSY IN VATS

Surgical lung biopsy (SLB) is performed using a VATS (video-assisted thoracoscopic surgery).

Procedure

- Surgical lung biopsy is executed in VATS with the patient under general anaesthesia, using a one-lung ventilation to collapse the ipsilateral lung.
- Three access sites with 5-, 10- and 12-mm ports are used. A 10-mm videothoracoscope is introduced through the seventh or eighth intercostal space on the midaxillary line, and the placement of the latter two additional ports will be determined according to the site of biopsy. The biopsy sites are chosen on the basis of CT scan abnormalities.
- Two surgical biopsies are taken from different lobes, avoiding the middle lobe and the lingula. The lung is grasped and wedge resections are performed with an endostapler.
- At the end, a chest tube is inserted through the anterior incision and connected to an underwater seal suction with a negative pressure (30-cm water).
- Hospitalization is required.

Diagnostic Role

- SLB does still represent the gold standard for the histologic diagnosis of DLDs without a chest HRCT pattern of definite UIP pattern.
- SLB might be associated with a significant mortality at 90 days, mainly related to acute exacerbation. The overall 30-day mortality for video-assisted thoracoscopic surgery (VATS) biopsy is around 2.1 % depending on casistics, with non-lethal complications of 10 %. The pooled post-operative mortality rate is around 3.5 %. Given these potential complications, performing an SLB is not always possible due to age, severity of the DLD, comorbidities or patient refusal to undergo the procedure.
- The median diagnostic yield is pretty high, with a 95 % (range, 42–100 %), with UIP as the most frequent diagnosis (33.5 %). SLB is not recommended in the suspicion or certainty of a CTD-related DLD. The indication for SLB should always follow the multidisciplinary discussion at the MDA.

Nguyen W (2013) Surgical lung biopsy for the diagnosis of interstitial lung disease: a review of the literature and recommendations for optimizing safety and efficacy. Sarcoidosis Vasc Diffuse Lung Dis 30(1):3

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

Kondoh Y (2006) Acute exacerbation of interstitial pneumonia following surgical lung biopsy. Respir Med 100:1753

THE MULTIDISCIPLINARY APPROACH (MDA)

The Role of MDA

- Multidisciplinary approach (MDA) is the current 'gold standard' in DLD diagnosis and comprises interdisciplinary discussion (including pulmonologists, radiologists, thoracic surgeons, pathologists and rheumatologists) of multiple forms of information to provide diagnostic and management outputs.
- Every expert centre dealing with DLDs should involve regular dynamic MDA for DLDs diagnosis and treatment decisions.
- Surgical lung biopsy (SLB) still plays a key role in distinguishing specific DLDs in patients whose imaging studies lack features diagnostic of UIP, although it cannot be considered as a diagnostic procedure *per se.*
- Histopathologic information has the greatest impact on the final diagnosis, especially when the initial clinical/radiographic diagnosis is not idiopathic pulmonary fibrosis. The dynamic interactions between clinicians, radiologists and pathologists improve interobserver agreement and diagnostic confidence.

☝ Concerns on SLB and MDA:

- Although SLB provides a pathologic diagnosis for the majority of patients, a very interesting recent series showed that SLB was inconclusive in a considerable number of cases and did not lead to a therapeutic change for more than half of all patients.
- It must be also considered that SLB is not without risk and can be associated with a prolonged hospital stay. Consequently, SLB should be performed in a select group of patients with DLD after discussion by a multidisciplinary panel.
- There is no consensus regarding the appropriate constitution and governance of MDA, with a consequent significant heterogeneity in attendee speciality group type, and approach to diagnosis formulation and a considerable difference between expert centres.

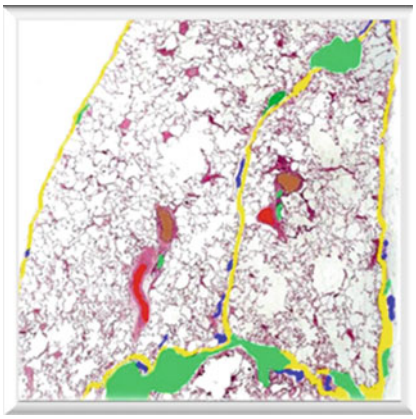
📖 Flaherty KR (2004) Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 170(8):904

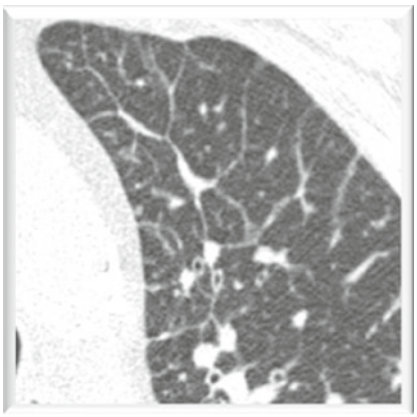
Blackhall V (2013) The role of surgical lung biopsy in the management of interstitial lung disease: experience from a single institution in the UK. Interact Cardiovasc Thorac Surg 17(2):253

Jo HE (2016) Evaluating the interstitial lung disease multidisciplinary meeting: a survey of expert centres. BMC Pulm Med 16(1):22

Thinking Through Pathology

Pathology	**Alessandra Cancellieri** **Alberto Cavazza**
Radiology	**Giorgia Dalpiaz**

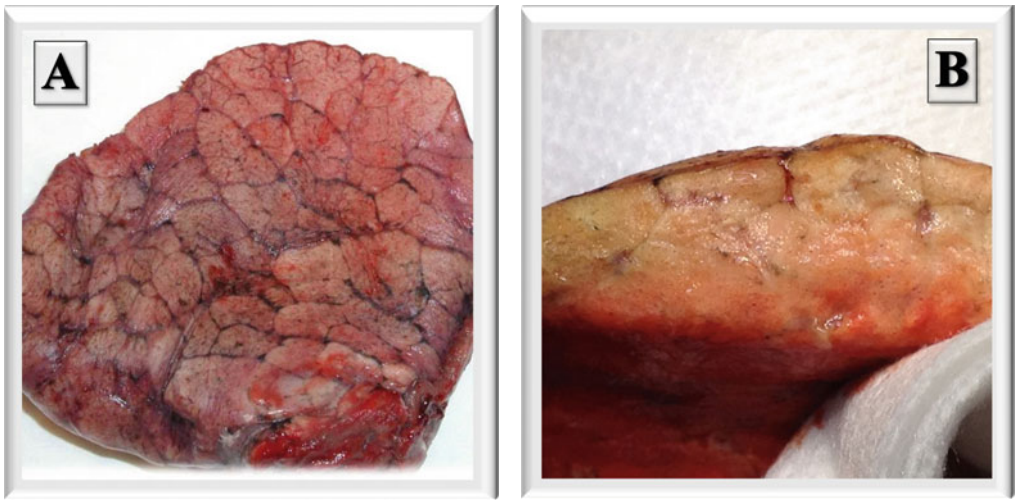




G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_2

SECONDARY LOBULE

The lesions of interstitial lung diseases populate the framework of the secondary lobule. These are polygonal structures, 1–2 cm in diameter, bound by complete or incomplete connective tissue (interlobular septa), well visible on the pleural surface as thin anthracotic lines due to the deposition of pigment along the lymphatic routes.

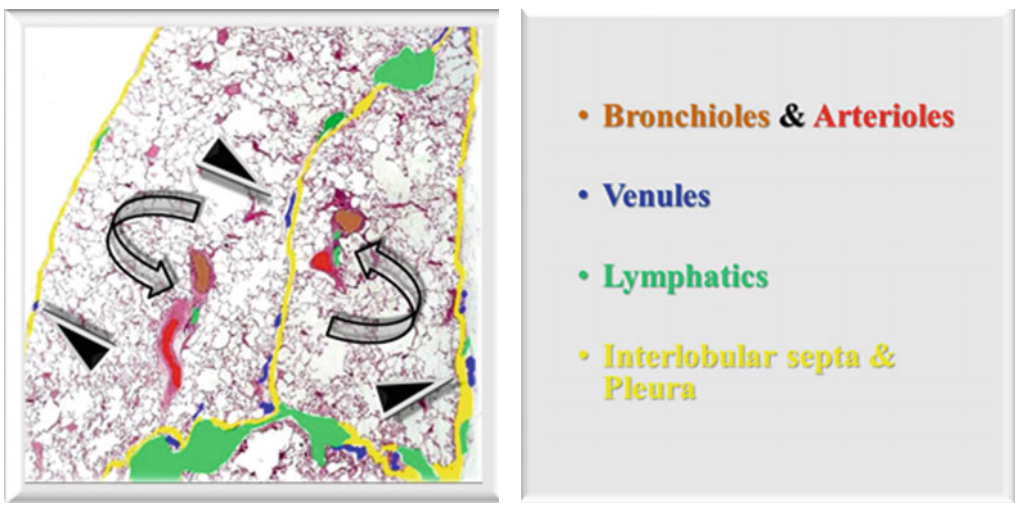


In the above figures, interlobular septa are particularly well recognizable because of the black anthracotic material along the perilobular lymphatics. Both on the pleura (A) and on the cut surface (B).

Main Components of Secondary Lobule

The main components of secondary lobule are:

- *Bronchioles and arterioles* constitute the bronchovascular bundle in the center of the lobule (⇲). Bronchioles and arterioles come along together following the same routes.
- *Venules*, on the contrary, can be found peripherally, in the *interlobular septa* and along the *pleura* (►).
- *Lymphatics*, of variable caliber but usually smaller than bronchioles and arterioles, are present in all the above-mentioned compartments (i.e., bronchovascular bundle, interlobular septa, and pleura).

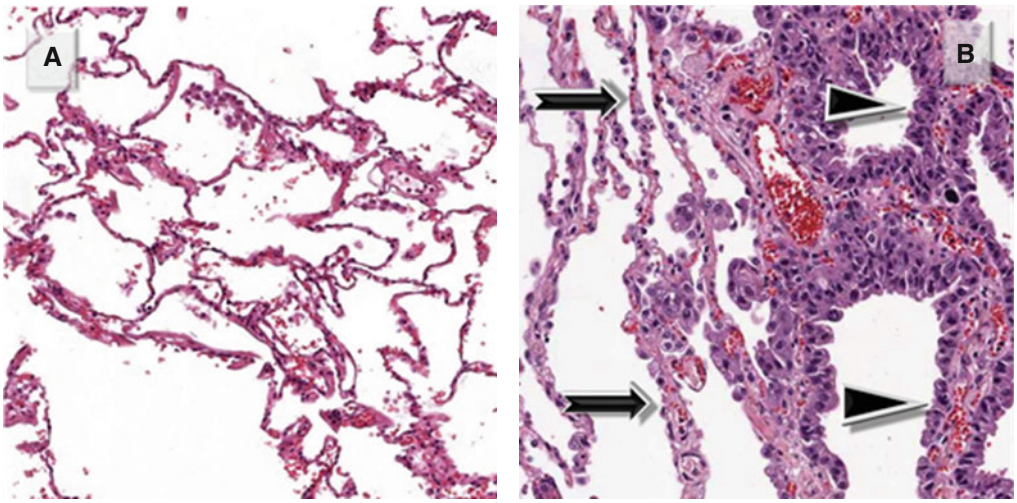


Rule of thumb: no matter how they are cut, bronchioles and arterioles should have approximately comparable size (and – therefore – lumen diameter) and, often, shape. When arterioles and bronchioles are of different caliber, something is abnormal.

Intralobular Interstitium/ Septa

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 (alveolar) septa contain the smallest branches of arterioles and venules, as well as the capillary network.

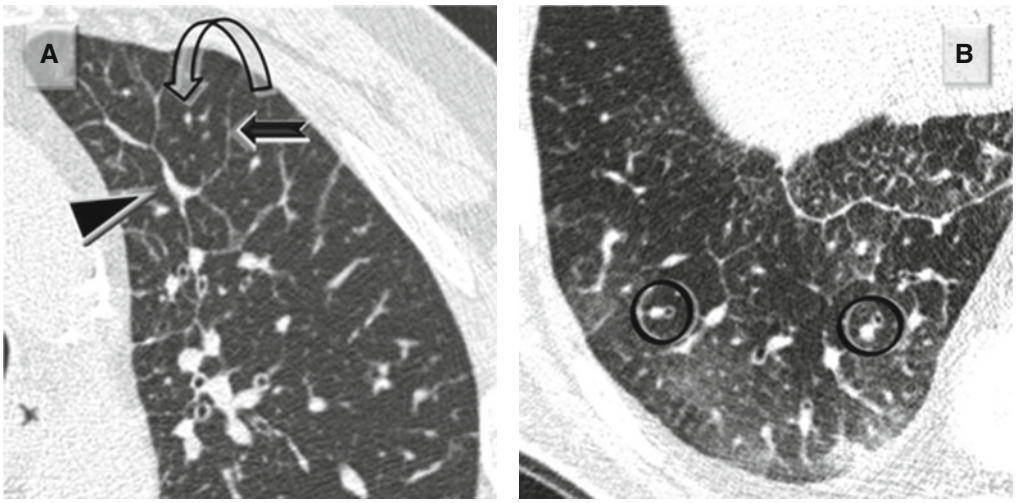
Figure A below shows normal intralobular septa. Figure B shows normal intralobular septa (➡) and thickened septa due to "lepidic growth" (►) in a patient with adenocarcinoma.



HRCT

On HRCT, secondary lobules appear to be of various sizes and shapes, depending at least partially on the relationship of the lobule to the plane of scan. They may be thought of as having three primary components:

- *Interlobular septa and septal structures* (Figure A below). At the periphery of lobule, the interlobular septa are arranged more or less regularly, parallel to each other and perpendicular to the pleural surface (➡). Venules can sometimes be seen as linear or arcuate structures (►).
  In healthy patients, a few septa are often visible in the lung periphery, but they tend to be inconspicuous; normal septa are most often seen in the apices.
- *Centrilobular region and centrilobular structures* (Figure A and Figure B below). Centrilobular arterioles and bronchioles measure approximately 1 mm in diameter. Arterioles can always be easily resolved on HRCT (☟). Pathologic thickened bronchioles are visible close to arterioles (O).
  In healthy patients, bronchioles are not visible because the wall thickness measures approximately 0.15 mm; this is at the lower limit of thin-section CT resolution.
- *Intralobular interstitium (lobular parenchyma).* 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 capillary network which connects the arterial and venous system.
  In healthy patients, the intralobular interstitium is only partly visible on CT: the most peripheral millimeters of the subpleural lung are homogeneously black.



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

Webb WR (2006) Thin-section CT of the secondary pulmonary lobule: anatomy and the image – the 2004 Fleischner lecture. Radiology 239(2):322

Elementary lesions of the lung can be separated into two groups:

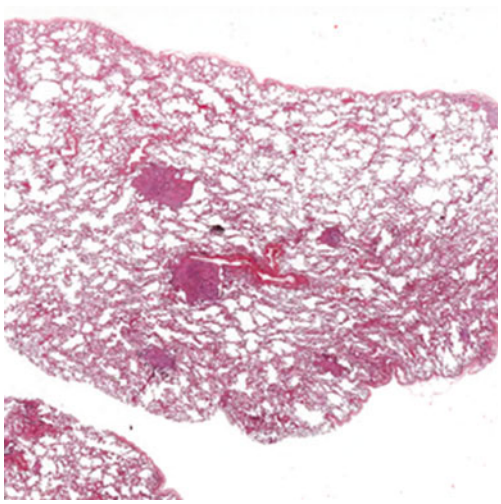
- *Defining lesions*: lesions which are *per se* explanatory, regardless of their topography within the secondary lobule (neoplasms and mixture)
- *Non-defining lesions*: lesions which are similar almost everywhere, their peculiarity being mainly due to their topography (inflammation and fibrosis)

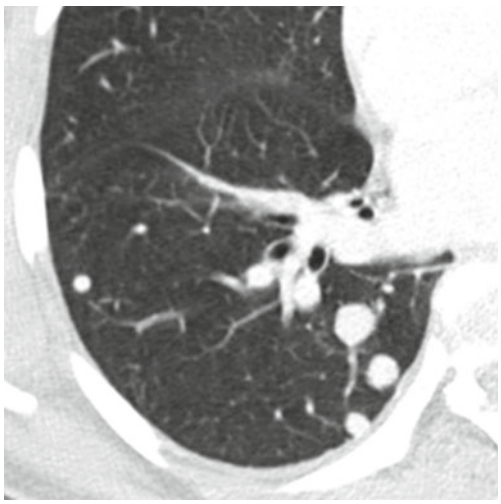
DEFINING LESIONS: NEOPLASM

A systematic description of the histological and cytological features of the single lesions is beyond the aim of this atlas. All the possible histotypes can be involved, namely, epithelial, lymphoid, and mesenchymal. According to the modality of growth of the neoplastic cells, several presentations may be identified.

Multiple Neoplastic Nodules

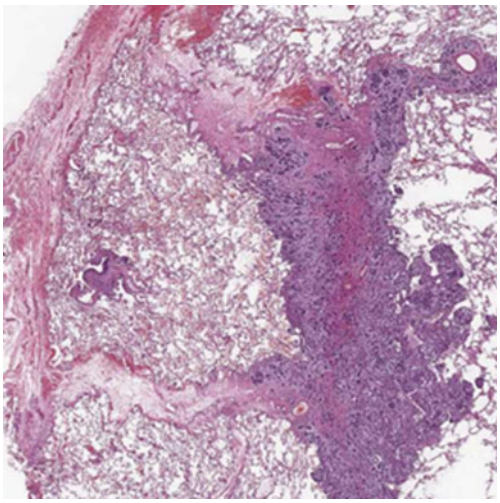
As a rule of thumb, neoplastic lesions in the lung are similar to malignancies elsewhere, that is, they present as solitary or multiple discrete nodules. Metastases often have random distribution and different size. Please also refer to hematogenous metastases in the chapter "Nodula Diseases".

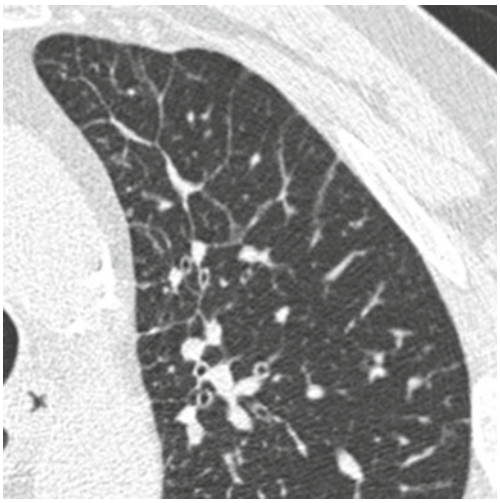




Interstitial Neoplastic Thickening

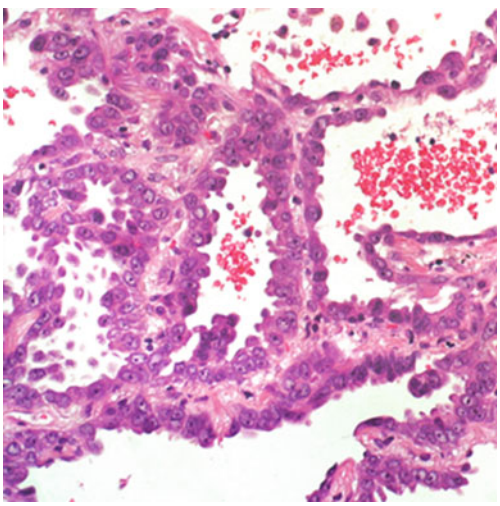
This modality of growth along the bronchovascular bundles, in the interlobular septa, and within the pleura is called carcinomatous lymphangitis (CL). Please also refer to carcinomatous lymphangitis in the chapter "Septal Diseases".

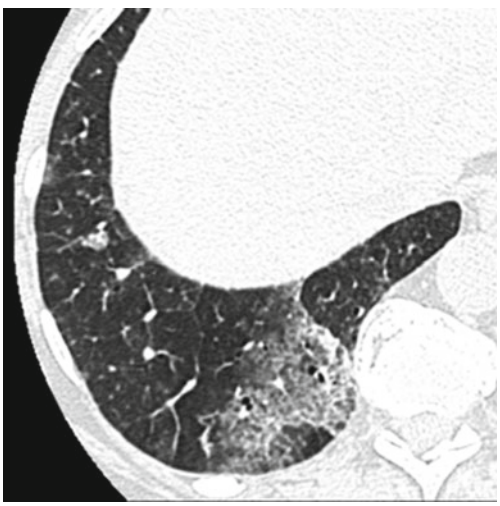




Lepidic Growth

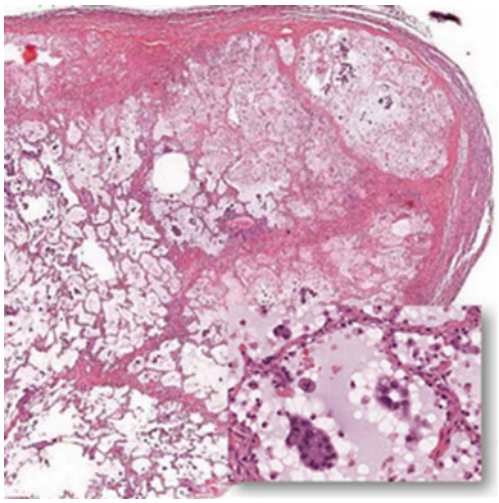
A peculiar pattern of presentation frequently responsible for the so-called ground-glass opacity (GGO) in CT is due to a lepidic growth of the neoplasm along alveolar septa. Please also refer to Adenocarcinoma in the chapter "Alveolar Diseases".

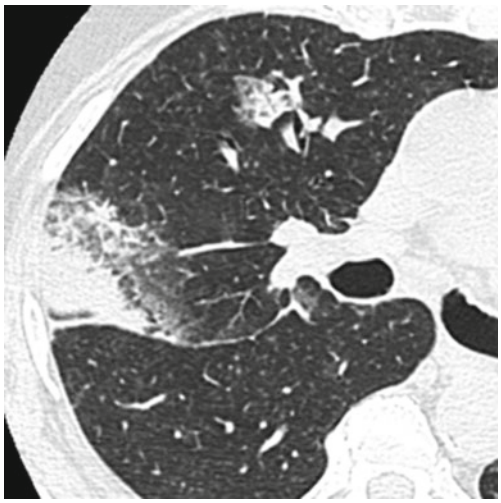




Partial or Complete Neoplastic Alveolar Filling

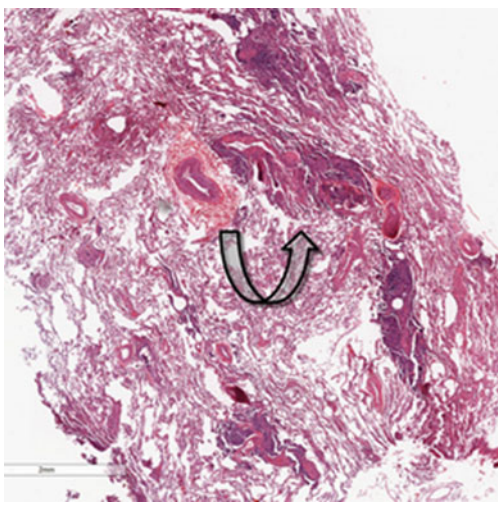
In the context of a malignancy, this can be due to the presence of mucus as in pneumonia-like pattern of invasive mucinous adenocarcinoma, formerly mucinous BAC, or to the presence of neoplastic cells. In these cases, ground-glass opacity (GGO) and consolidations are the radiological expression of the disease, and more often a mixed pattern, where the two aspects coexist, is present. Please also refer to Adenocarcinoma in the chapter "Alveolar Diseases".

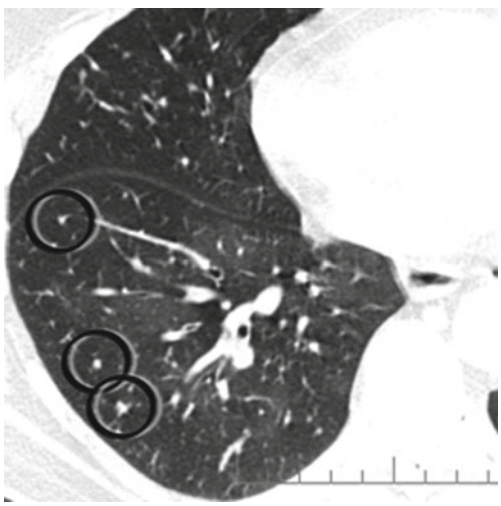




Peribronchial and Peribronchiolar Neoplastic Growth

Some tumors preferentially grow along bronchial and bronchiolar walls eventually invading their lumen. Also, preinvasive conditions such as DIPNECH (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia) can exhibit this pattern of growth (↬). Expiratory HRCT shows patchy areas of black and white aspect due to air trapping. Some small solid nodules, consisting of tumorlets or typical carcinoids, also coexist (O). Please also refer to DIPNECH in the chapter "Dark Lung Diseases".





Engeler CE (1993) Ground-glass opacity of the lung parenchyma: a guide to analysis with high-resolution CT. AJR Am J Roentgenol 160(2):249

Davies SJ (2007) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognized spectrum of disease. Thorax 62(3):248

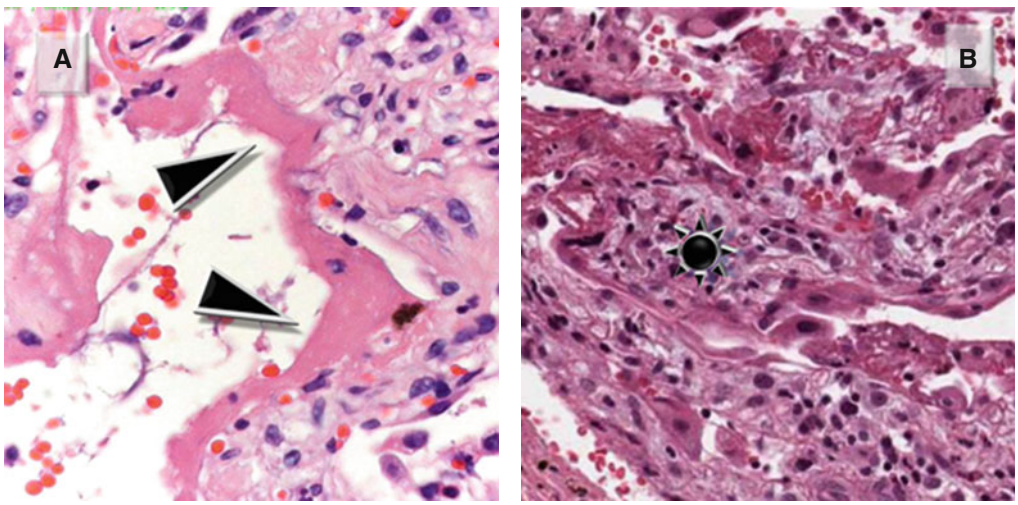
DEFINING LESIONS: MIXTURE

Miscellaneous elementary lesions that can be encountered in the presence of a diffuse lung disease are (among the others) the following:

Hyaline Membranes

Characteristic of the exudative phase of a diffuse alveolar damage (DAD), they consist of proteinaceous exudate which adheres to the inner surface of the alveoli (Figure A ►).

During the subsequent proliferative phase, the membranes are incorporated within the alveolar septa, which become thick (Figure B ✸).

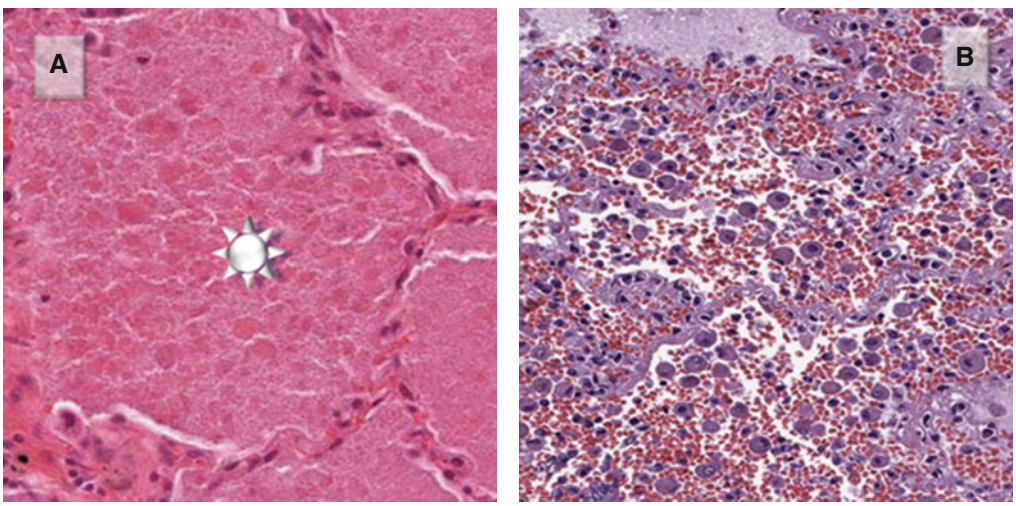


Pulmonary Alveolar Proteinosis (PAP)

Pulmonary alveolar proteinosis (PAP) consists of amorphous, lipid-rich, eosinophilic material with small globules and cholesterol clefts, within the alveolar spaces, with a rim of retraction at the edge (Figure A ✸).

Diffuse Alveolar Hemorrhage (DAH)

Diffuse alveolar hemorrhage (DAH) is characterized by fibrin and hemosiderin-laden macrophages, which can be appreciated both on cytology in BAL fluid and at histology (Figure B). Capillaritis is often part of the picture; nevertheless, it represents a transient phenomenon and therefore it is not constantly seen.

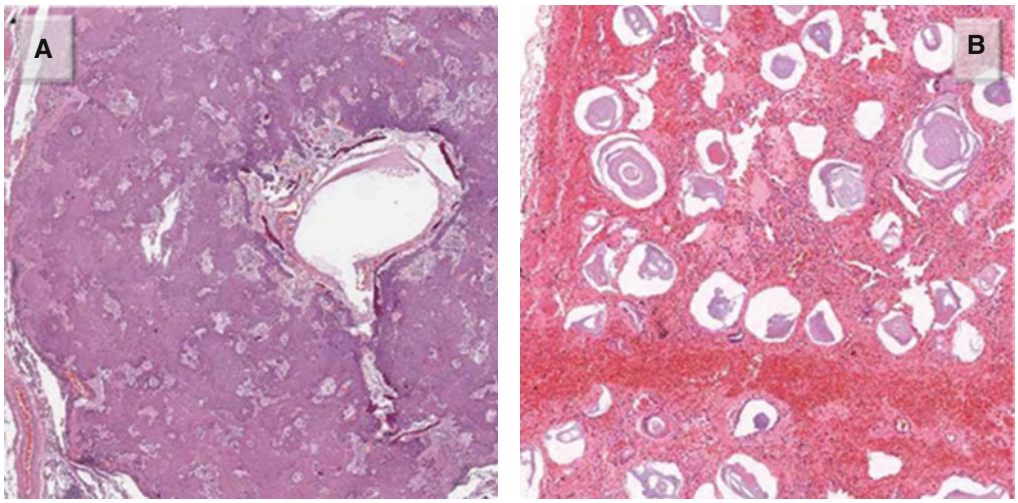


Amyloid

Amyloid, whether nodular or interstitial, isolated finding or associated to chronic inflammation or low-grade lymphomas consists of the deposition of a homogeneous, acellular, pink material which can calcify or ossify (Figure A).

Microlitiasis

Microlitiasis appears as tiny, calcified micronodules filling the alveolar spaces (Figure B).



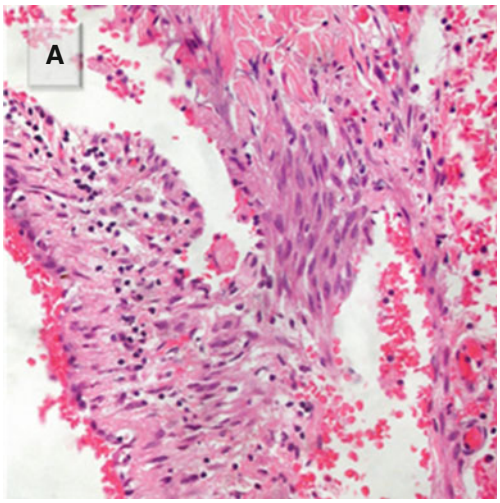
LAM

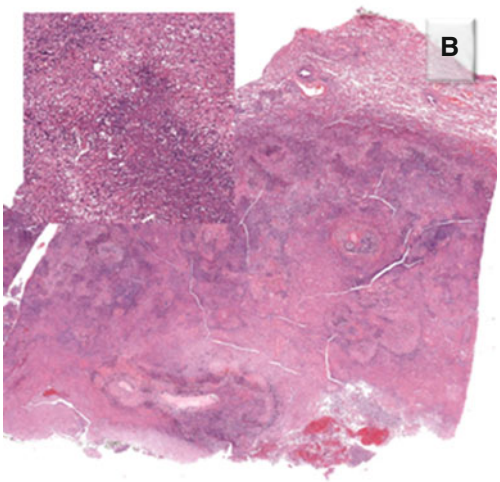
Lymphangioleiomyomatosis (LAM) is characterized by the presence of cysts with thin wall containing smooth muscle bundles (Figure A). LAM cells are spindle shaped and plump, with vacuolated cytoplasm.

Necrosis

Necrosis refers to the premature death of cells in living tissues; this is a detrimental event as opposed to apoptosis, which is actually the programmed cell death. It mostly appears as amorphous material with or without inflammatory cells (Figure B). Histologically, viable tissue cells and lung architecture (including vessels) are no longer appreciable in any kind of necrosis; so, the necrotic portion of a process results avascular in a computed tomography performed after the administration of contrast medium. Cavitation of the necrotic areas is also possible and frequent.

- *Coagulative necrosis* is characteristic of hypoxic conditions, such as infarction. It consists of homogeneous, eosinophilic material almost devoid of inflammatory cells. Ghost images of the necrotic structures are often identifiable.
- *Suppurative (colliquative) necrosis*, on the contrary, is characteristic of infectious diseases (bacterial, viral, or fungal), but it can also be observed in other clinical contexts (toxic, immunological, aspiration, etc.), and it is also characteristic of vasculitides, such as granulomatosis with polyangiitis (Wegener's, Figure B) and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome -CSS). Suppurative necrosis is characterized by numerous neutrophils associated with fibrin and abscess formation, filling and often destroying the alveolar structures.
- *Caseous necrosis* refers to the gross appearance of this necrosis of mycobacterial, namely, tubercular, origin. Its amount, architecture, and distribution depend on the immunological settings of the patient.
- *Tumor necrosis.* This necrosis presents intermediate features between coagulative and colliquative and may be observed in several types of malignancy, mostly epithelial (e.g., large-cell neuroendocrine carcinoma-LCNEC) and lymphoid (e.g., large-cell lymphoma).


A


B

NON-DEFINING LESIONS: INFLAMMATION

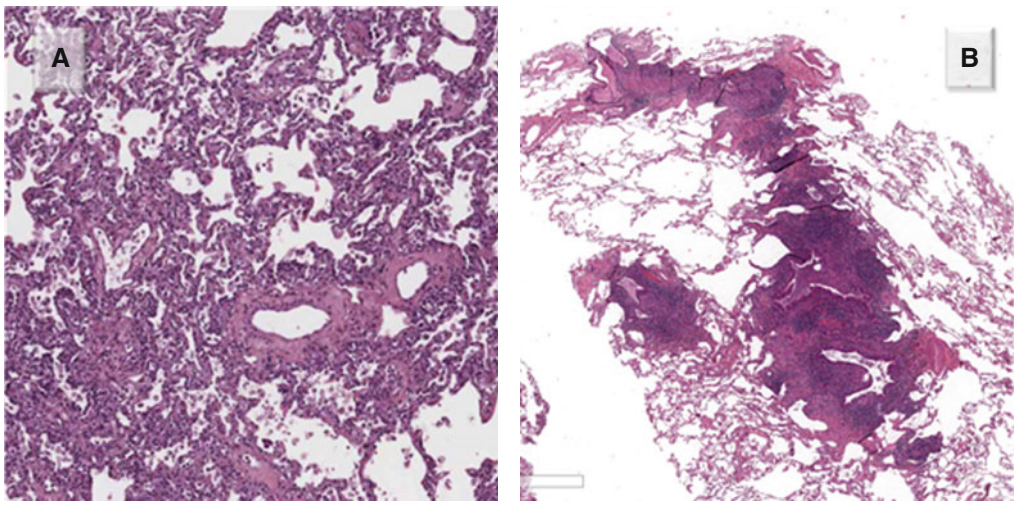
The presence of an inflammatory infiltrate to a variable extent, from scant to heavy, is so common in the lung that it can hardly be considered other than a normal finding. It is otherwise appropriate to consider it as an elementary lesion when it is huge, is readily apparent on low-power magnification, and represents the main feature of the histologic picture. In most cases (namely, lympho-plasmacellular in composition), it appears blue in H&E.

Diffuse Uniform Inflammation

The inflammatory cells are uniformly distributed as in cellular NSIP, in which alveolar septa are expanded by a diffuse, blue, interstitial infiltrate (Figure A below).

Centrilobular Peribronchial Inflammation

The inflammatory cells are limited to the peribronchiolar areas, as in cellular bronchiolitis of any etiology, in which blue spots centered on bronchioles are visible even at low power (Figure B below).

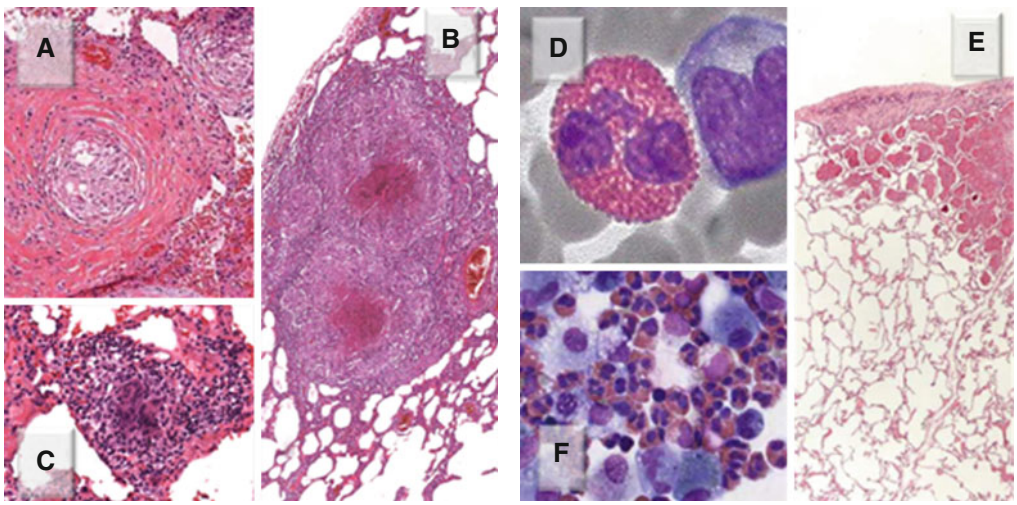


Granulomas

Histiocytes, together with multinucleated giant cells and other inflammatory elements, are the main component of granulomas, a common finding in different conditions: sarcoidosis (Figure A), infection (Figure B), and hypersensitivity pneumonia (HP) (Figure C).

Eosinophils

They are other inflammatory cells worth being recognized by the pathologist. They belong to the granulocytic line and show a bilobed nucleus (differently from the multilobular nucleus of polymorphous granulocytes) and a red granular cytoplasm (Figure D). Easily recognized on histology and BAL fluid (Figure F), they are the main cellular component of eosinophilic pneumonia, with the typical peripheral infiltrate (Figure E).



Cheung OY (2003) Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 7(2):127

Cancellieri A, Dalpiaz G (2010) Granulomatous lung disease. Pathologica 102(6):464

NON-DEFINING LESIONS: FIBROSIS

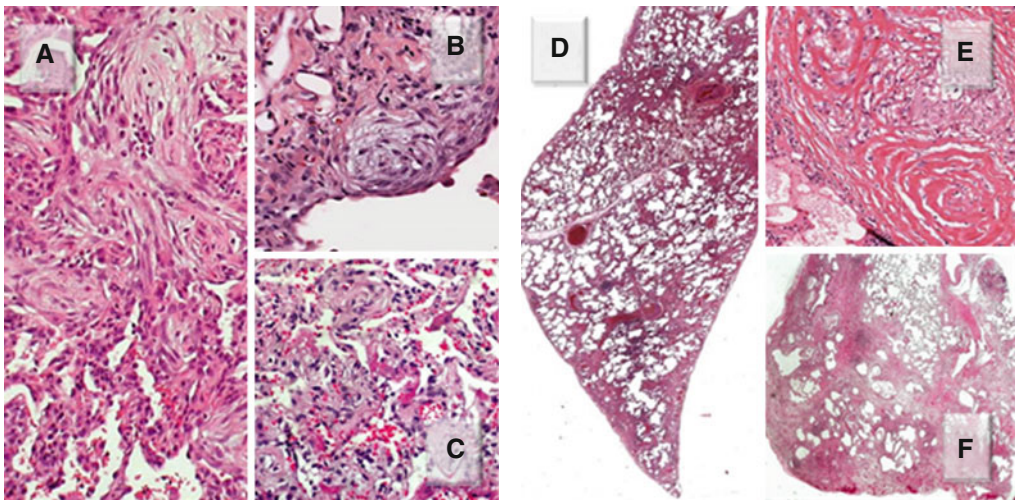
Fibrosis consists of dense collagen deposition, usually associated with a variable degree of structural remodeling. It appears pink in H&E. Please also refer to chapter "Fibrosing Pattern".

"Young" Fibrosis

"Young" fibrosis, rich in fibroblasts and mucopolysaccharides, somewhat pale "grayish" in H&E, is characteristic of recent or ongoing processes (Figure A). With the exception of fibroblast foci (Figure B), this type of fibrosis is typically associated with an acute/subacute clinical presentation, e.g., organizing pneumonia, OP (Figure A), and organizing diffuse alveolar damage, DAD (Figure C).

"Old" Fibrosis

"Old" fibrosis, dense, hyaline, and intensely "pink," is typical of long-standing processes, usually with a chronic clinical presentation, e.g., fibrosing NSIP (Figure D), sarcoidosis (Figure E), and UIP (Figure F).

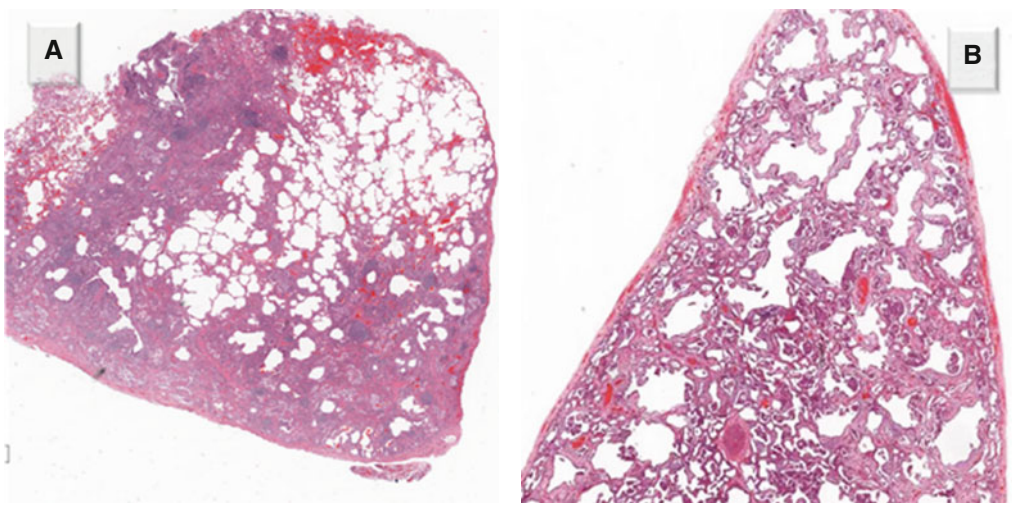


Diffuse Fibrosis of Patchy Type

When diffuse, the typical presentation is an effacement of the pulmonary architecture by dense tissue mainly found at the periphery of the lobule and patchily involving the parenchyma (spatial heterogeneity). Lung parenchyma may be involved to different extents, from minimal down to massive in end-stage lung. The prototype is UIP (Figure A below).

Diffuse Fibrosis of Uniform Type

This fibrosis is quite homogeneous from the spatial point of view, so uniformly distributed throughout the lobule. The prototype is fibrosing NSIP (Figure B below).

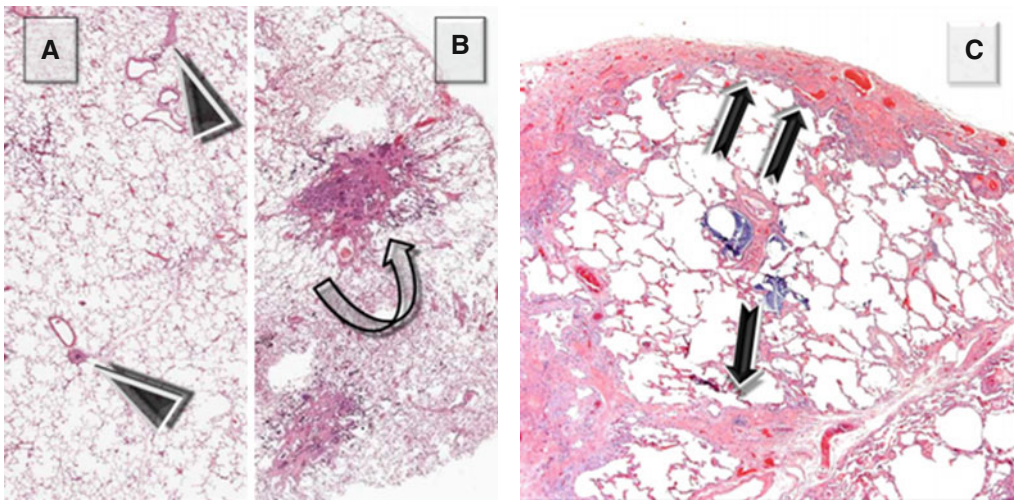


Centrilobular Fibrosis

The size of the process varies from the punctate fibrosis which is barely visible at low power (Minimal changes) because it is concentrically limited to the bronchiole, typically in constrictive bronchiolitis (Figure A ►) to more extended areas of eccentrically radiating stripes, often surrounding an irregularly ectatic bronchiole (typically, in Langerhans cell histiocytosis) (Figure B ☟).

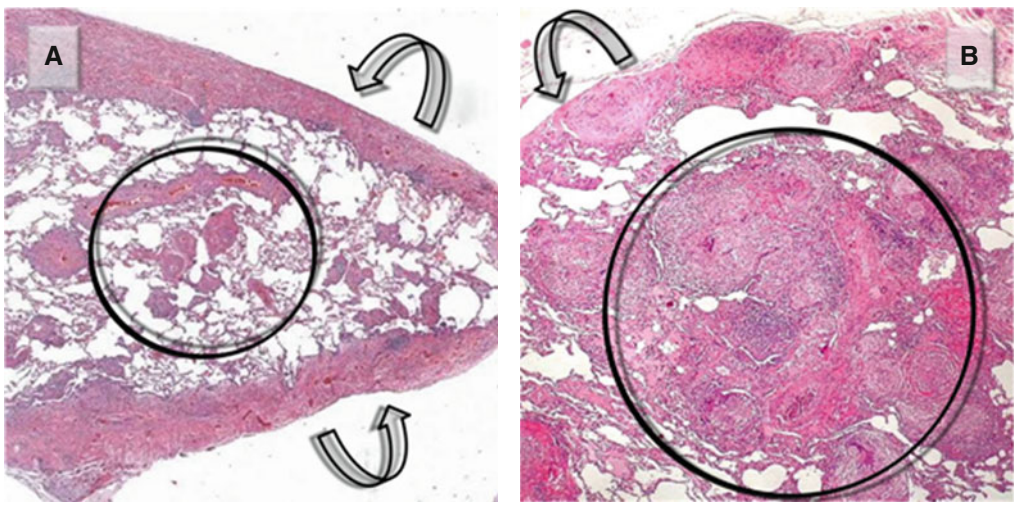
Peripheral Fibrosis

The prototype disease is early usual interstitial pneumonia (UIP), with small scars in a peripheral (subpleural, Figure C ➡ ➡) and paraseptal (➡) distribution.



Lymphatic Distribution

Finally, centrilobular and peripheral fibrosis testifies the existence of a disease moving through the lymphatics, namely, in the centrilobular area, where bronchioles are present (O), but in the interlobular septa and pleura as well (☟). Figure A shows lymphatic distribution of fibrosis in patients with Erdheim–Chester disease (ECD). Figure B shows the central and peripheral distribution of the pink fibrosis in sarcoidosis, the paradigm of lymphatic disorders.



Smith ML (2016) Update in pulmonary fibrosis. Arch Pathol Lab Med 140:221
Mazor RD (2013) Erdheim-Chester disease: a comprehensive review of the literature. Orphanet J Rare Dis 8:137

The pathologic approach to the diseases may be schematized according to:

- *Anatomic distribution*
- *Patterns*
- *Ancillary histologic findings*

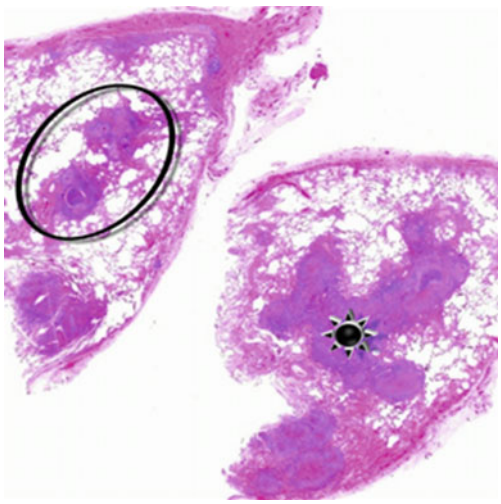
The evaluation of anatomic localization, histologic pattern, and further histologic findings together generally allows the pathologist to generate a list of diagnostic possibilities that can be correlated with the clinical and radiological data.

ANATOMIC DISTRIBUTION

Many diseases of the lung have a preferential distribution in relationship to the secondary lobule, so the evaluation by the pathologist of where the lesion is localized is helpful in narrowing the differential diagnosis.

Bronchiolocentric

This is the presentation of diseases arriving to the lung through the airways and/or developing just next to the bronchiole in the centrilobular area. A good example is the cellular bronchiolitis due to mycobacterial infection, consisting in centrilobular inflammatory nodules sparing the subpleural regions (O). Note the focal ramified appearance (✸), corresponding to the tree-in-bud sign at CT scan. Please also refer both to the Tree-in-bud, bronchiolar sign in the chapter "Alveolar Pattern" and in the "Case-Based Glossary with Tips and Tricks".

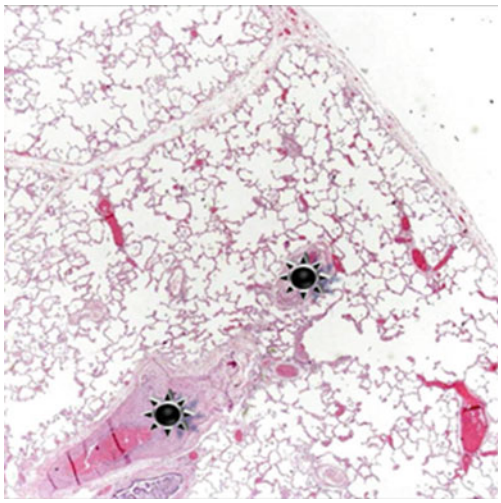


Bronchiolocentric

- Allergic BronchoPulmonary Aspergillosis (ABPA)
- Aspiration
- Bronchiolitis
- Hypersensitivity Pneumonitis (HP)
- Infection
- Inflammatory bowel disease
- Langerhans Cell Histiocytosis (LCH)
- Organizing Pneumonia (OP), some cases
- Respiratory Bronchiolitis - ILD - (RB-ILD)
- Silicosis

Angiocentric

This is the presentation of diseases arriving to the lung through the arteries. An example is the thromboembolic disease, consisting in acute or organizing thrombi obliterating the lumen of a small artery (✸). The centrilobular peribronchiolar location is a guarantee that the involved vessel is an artery and not a vein. Please also refer to Chronic Pulmonary Thromboembolism (CTPE) in the chapter "Dark Lung Diseases".

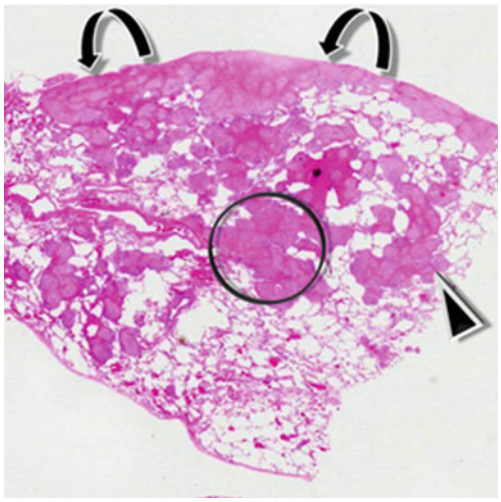


Angiocentric

- Thromboembolic disease (CTPE)
- Pulmonary tumor thrombotic microangiopathy (PTTM)
- Plexiform arteriopathy

Lymphatic

Lymphatic distribution is another typical presentation of specific disorders. Sarcoidosis is a prototype disease of lymphatic distribution with multiple noncaseating compact giant-cell granulomas visible along bronchovascular bundles (O), interlobular septa (►), and subpleural connective tissue (☟). Please also refer to Sarcoidosis in the chapter "Nodular Diseases".

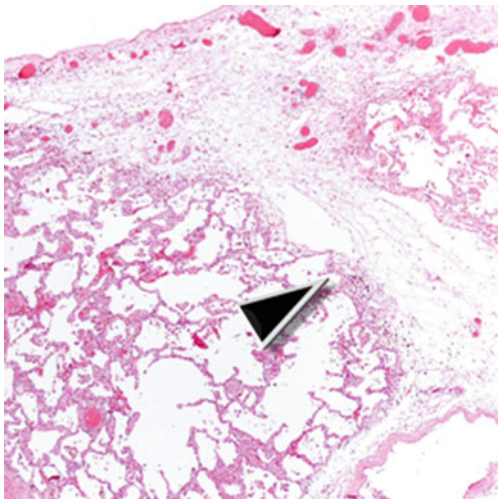


Lymphatic

- Berylliosis
- Diffuse lymphoid hyperplasia
- Erdheim–Chester Disease (ECD)
- Kaposi sarcoma
- Lymphangitic carcinomatosis (LC)
- Lymphoma
- Sarcoidosis
- Silicosis

Septal

This is the appearance of diseases causing an elective enlargement of the interlobular septa. Pulmonary edema (PE) secondary to heart failure is a prototype disease (►). Please also refer to interstitial PE in the chapter "Septal Diseases".

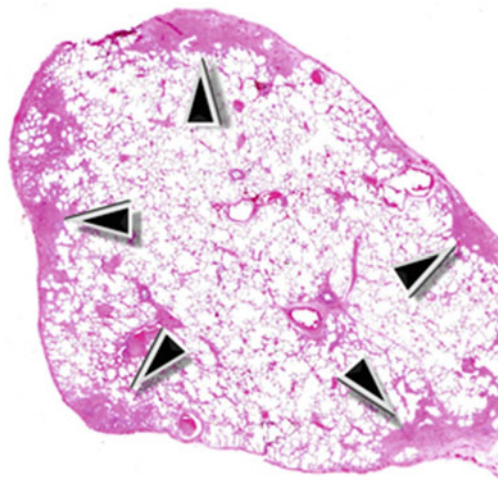


Septal

- Amyloidosis, interstitial
- Erdheim–Chester disease (ECD)
- Lymphangitic Carcinomatosis (LC)
- Pulmonary edema (PE), interstitial
- Venoocclusive disease (VOD)

Peripheral

Some diseases tend to involve the lobule at its periphery. The prototype disease is early usual interstitial pneumonia (UIP), with small scars in a peripheral subpleural (►) and paraseptal distribution. Please also refer to UIP in the chapter "Fibrosing Diseases".

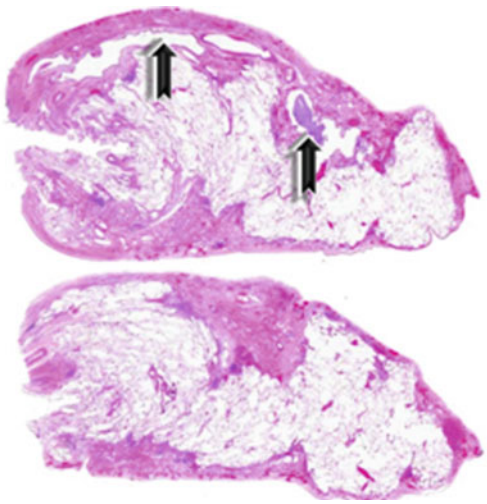


Peripheral

- UIP, early
- Perilobular opacities (OP)

Pleural/ Subpleural

The image shows a case of pleuroparenchymal fibroelastosis (PPFE), a rare disease consisting in elastotic tissue with a subpleural localization. The arrows (➡) show a dilated bronchiole almost reaching the pleura (traction bronchiolectasis). Please also refer to PPFE in the chapter "Fibrosing Diseases".

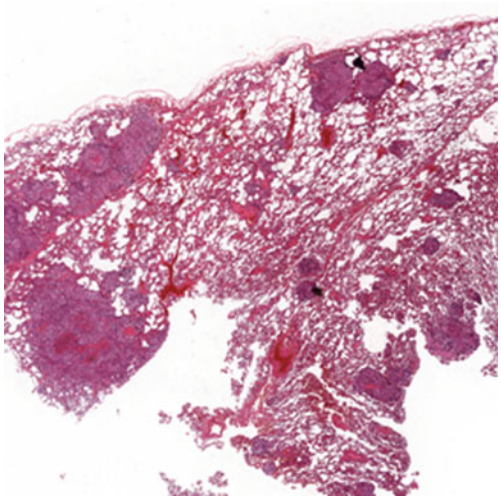


Pleural/Subpleural

- Pleuro-Pulmonary Fibro-Elastosis (PPFE)

Random

The lesions appear randomly scattered throughout the lung (e.g., miliary tuberculosis, figure below). Please also refer to HRCT chapter "Nodular Pattern" and miliary TB in the chapter "Nodular Diseases".

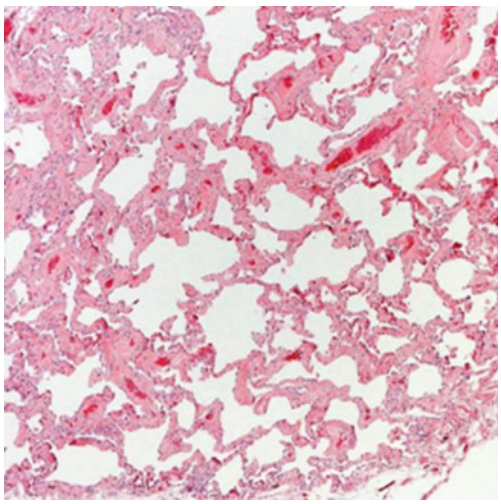


Random

- Amyloidosis, nodular
- Churg–Strauss syndrome
- IgG4 syndrome
- Immunoglobulin deficiency
- Infection (e.g. miliary TB)
- Inflammatory bowel disease
- Neoplasm (e.g. metastases)
- Organizing Pneumonia (OP)
- Rheumatoid nodule
- Granulomatosis with Polyangiitis (GPA), formerly defined Wegener Granulomatosis (WG)

Interstitial

The alveolar septa are thickened, due to material growing inside them. Interstitial expansion by cells (cellular NSIP) or by fibrosis (fibrotic NSIP, figure below). Please also refer to NSIP in the chapter "Fibrosing Diseases".

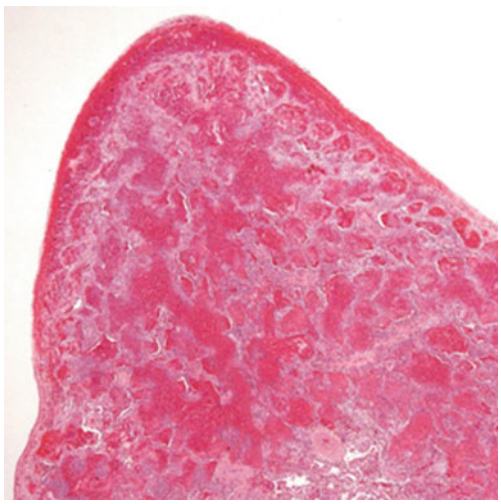


Interstitial

- Collagen Vascular Diseases (CVD)
- Non-Specific Interstitial Pneumonia (NSIP)
- Lymphocytic Interstitial Pneumonia (LIP)
- Hypersensitivity Pneumonitis (HP), subacute
- Drug toxicity
- Lymphoma

Intra-alveolar

The elements of the disease fill more or less entirely the alveoli. An example is diffuse alveolar hemorrhage (DAH), consisting in blood filling the alveolar spaces (figure below). Please also refer to DAH in the chapter "Alveolar Diseases".



Intra-alveolar

- Acute Fibrinous and Organizing Pneumonia (AFOP)
- Alveolar microlithiasis
- Pulmonary alveolar proteinosis (PAP)
- Diffuse alveolar hemorrhage (DAH)
- Diffuse ossification
- Desquamative Interstitial Pneumonia (DIP)
- Eosinophilic pneumonia
- Infection (e.g. acute bacterial)
- Metabolic diseases
- Neoplasm
- Cryptogenic Organizing Pneumonia (COP)
- Pulmonary edema (PE)

Fukuoka J (2001) Pathologic approach to pulmonary hemorrhage. Ann Diagn Pathol 5(5):309

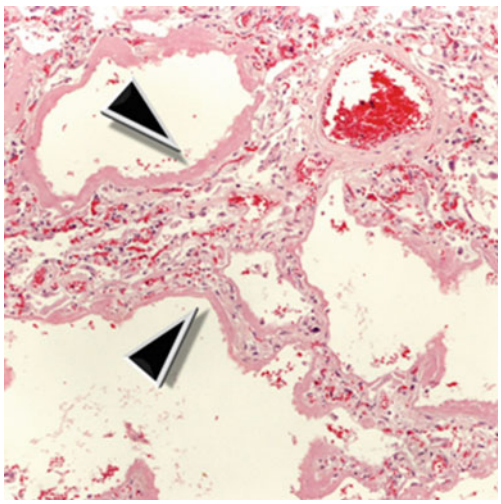
PATTERNS

When trying to pigeonhole the diffuse lung disorders, one could also use the approach through patterns. Pattern is the *ensemble* of elements that, all together, indicate a limited number of possible causative diseases.

The pathological patterns are illustrated below through suitable examples. Please remember that for each pattern, not all the possibilities, only selected examples useful to catch the concept, are listed.

Acute Lung Injury (ALI)

Acute lung injury (ALI) has a spectrum of histologic features, ranging from diffuse alveolar damage (DAD) with hyaline membranes (►), to organizing pneumonia (OP) with intra-alveolar plugs of pale granulation tissue, to acute fibrinous and organizing pneumonia (AFOP) consisting in intra-alveolar accumulation of fibrin.

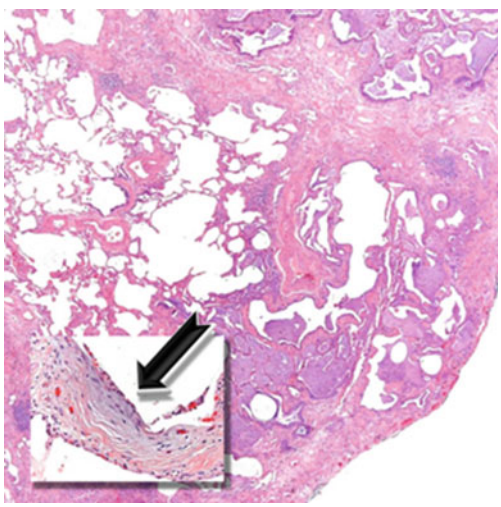


ALI

- Accelerated phase of chronic ILD
- Idiopathic AFOP
- Aspiration
- Cryptogenic OP (COP)
- Collagen Vascular Diseases (CVD)
- Drug reaction, acute
- Eosinophilic pneumonia
- Acute interstitial pneumonia (AIP)
- Infection
- Vasculitis

Fibrosis

Pulmonary fibrosis is defined as the abnormal deposition of dense collagen (old, pink-staining fibrosis) in lung parenchyma. Usual interstitial pneumonia (UIP) is an example of fibrotic pattern, consisting in old scars obliterating the alveolar architecture with an abrupt transition to normal lung (so-called patchy fibrosis). A pale fibroblastic focus is shown in the inset (➡). Please also refer to chapter "Fibrosing Pattern".

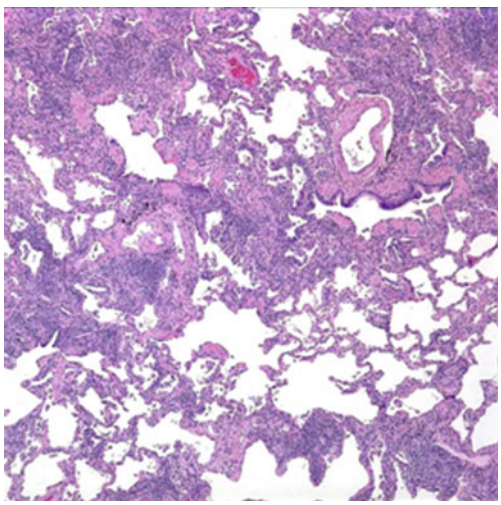


Fibrosis

- Aspiration, chronic
- Collagen Vascular Diseases (CVD)
- Drug reaction, chronic
- Hypersensitivity Pneumonitis (HP), chronic
- Infection, chronic
- Inhalation, chronic
- IPF (idiopathic UIP)
- Non-Specific Interstitial Pneumonia (NSIP), idiopathic
- Pneumoconioses
- Sarcoidosis, chronic
- Smoking-related ILD (DIP, chronic LCH)

Cellular Infiltrate

An example of cellular infiltrate, consisting in inflammatory cells (lymphocytes and plasma cells) expanding the interstitium due to hypersensitivity pneumonitis (HP) is shown in the image below.

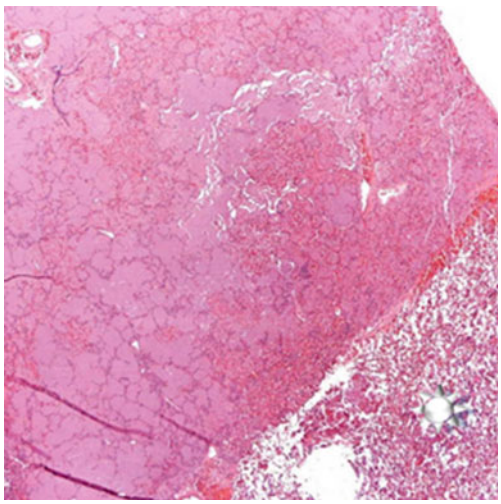


Cellular Infiltrate

- Collagen Vascular Diseases (CVD)
- Drug reaction
- Hypersensitivity Pneumonitis (HP), subacute
- Immuno-mediated diseases (e.g., immunodeficiencies, primary biliary cirrhosis, Crohn's disease, IgG4-related diseases)
- Infections (e.g. pneumocystis, viral)
- Lymphocytic Interstitial Pneumonia (LIP)
- Lymphoma
- NSIP, idiopathic cellular

Alveolar Filling

Alveolar filling by cells or noncellular material is very frequent. An example, illustrated here in the figure below, is pulmonary alveolar proteinosis (PAP). Note the abrupt transition between the area in which alveoli are filled by proteinaceous material and the normal lung (☼). Please also refer to chapter "Alveolar Pattern".

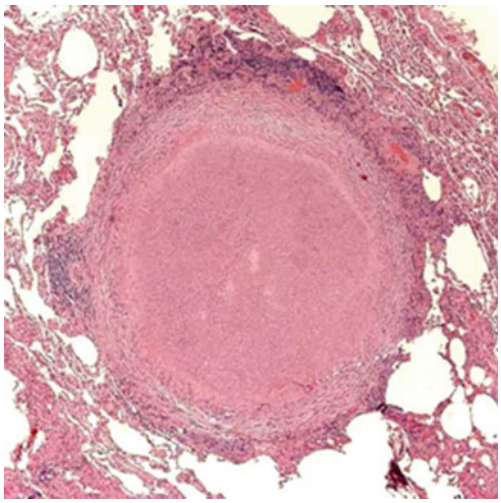


Alveolar Filling

- Acute Fibrinous and Organizing Pneumonia (AFOP)
- Alveolar microlithiasis
- Pulmonary alveolar proteinosis (PAP)
- Diffuse ossification
- Desquamative Interstitial Pneumonia (DIP)
- Pulmonary edema (PE)
- Eosinophilic pneumonia
- Diffuse alveolar hemorrhage (DAH)
- Infections (e.g., acute bacterial)
- Neoplasms
- OP, cryptogenic

Nodules

A necrotic nodule due to a previous varicella infection is an example of a disease presenting with a nodular pattern (Figure below). Please also refer to chapter "Nodular Pattern".

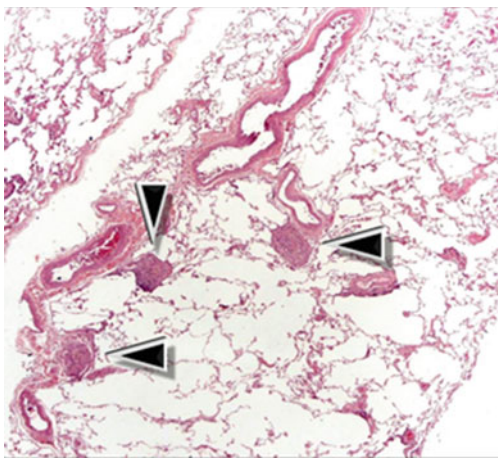


Nodules

- Aspiration
- Follicular bronchiolitis (FB)
- Hypersensitivity Pneumonitis (HP), subacute
- Infections
- Langerhans Cell Histiocytosis (LCH)
- Neoplasms (primary or metastatic)
- Organizing Pneumonia (OP)
- Pneumoconioses (e.g., silicosis)
- Respiratory Bronchiolitis-ILD (RB-ILD)
- Rheumatoid nodule
- Sarcoidosis
- Granulomatosis with Polyangiitis (GPA), formerly defined Wegener Granulomatosis (WG)

Minimal Changes

The minimal changes pattern consists in subtle lesions, easily overlooked by the pathologist. Constrictive bronchiolitis is an example, consisting in small scars obliterating the bronchiolar lumina (►). Please also refer to chapters "Dark Lung Pattern" and "Cystic Pattern".



Minimal Changes

- Constrictive bronchiolitis (CB)
- Emphysema
- Lymphangioleiomyomatosis (LAM)
- Vascular disease (thrombosis/ embolism, plexiform arteriopathy, veno-occlusive disease)

Leslie KO (2009) My approach to interstitial lung disease using clinical, radiological and histopathological patterns. J Clin Pathol 62:387

Leslie KO, Wick MR (2011) Practical Pulmonary Pathology: A Diagnostic Approach, 2nd Edition, Elsevier Sciences

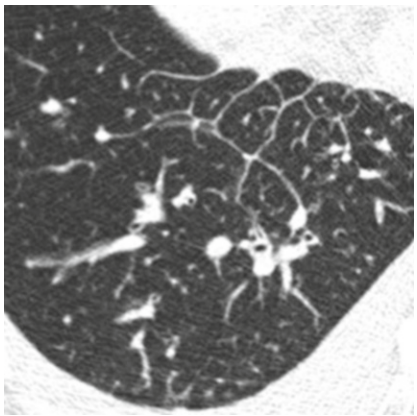
ANCILLARY HISTOLOGIC FINDINGS

Going at higher magnification, the pathologist can further try to find more specific histologic clues. Some of these are diagnostic *per se* (see also Defining/Non-defining elementary lesions), for example, microorganisms, neoplastic cells, LAM cells, and accumulation of Langerhans cells; others are not diagnostic *per se* but helpful to further narrow the differential diagnosis, for example, granulomas, necrosis, eosinophils, etc. (please see the table below).

Ancillary histologic findings	Diseases
Microorganism	Infection
Neoplastic cells	Neoplasm
Accumulations of Langerhans cells	Langerhans Cell Histiocytosis (LCH)
LAM cells	Lymphangioleiomyomatosis (LAM)
Proteinosic material	Pulmonary alveolar proteinosis (PAP)
Exogenous material	Aspirations, pneumoconiosis, embolization of exogenous material
Granulomas	Infection, sarcoidosis, HP, aspiration, Wegener
Necrosis	Infection, Wegener, neoplasm, infarct
Neutrophils	Infection, Wegener, aspirations
Eosinophils	Eosinophilic infiltrate (many causes), incidental finding
Blood, hemosiderin, capillaritis	Hemorrhagic syndrome
Pleuritis	Collagen Vascular Diseases (CVD), infection

Septal Pattern

Radiology — **Giorgia Dalpiaz**
Pathology — **Alessandra Cancellieri**



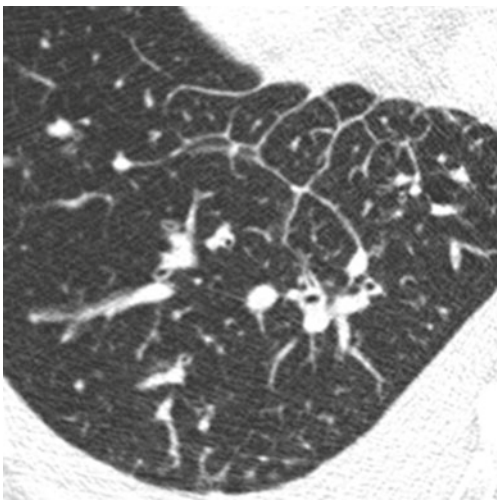
G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_3

SEPTAL PATTERN

Definition

A septal pattern is present when thickening of the perilobular interstitium and bronchovascular bundle, both in the centrilobular core and at the central level, is visible. The final effect is that of a regular network of white lines. Lobular architecture is preserved. Septal pattern can be smooth or nodular in contour depending on the different pathological processes.
The septal pattern may be due to the filling of the interstitium by fluid, neoplastic cells, or inflammation.

Reticular pattern with preserved architecture, regular linear pattern



Reticular pattern may be also “irregular” due to fibrosis, and therefore this subtype is included and explained in the fibrosing pattern. In this case, the architecture is not preserved resulting in a distorted net.

The signs of septal pattern are:

- Septal thickening
- Subpleural interstitial thickening
- Peribronchovascular thickening

The prevalent distribution of the signs together with the presence of non-parenchymal signs may be helpful for the diagnosis of a specific disease (please see also the tables at the end of this chapter).

As well as in septal diseases, in which this pattern is predominant, there are other diseases in which septal pattern (reticular pattern with preserved architecture) may be found, albeit less important or sporadic. They are therefore described in the relevant chapter (e.g., associated with ground-glass opacity in diffuse alveolar hemorrhage, pneumonia, and NSIP or associated with nodules and/or cysts in LIP).

Andreu J (2004) Septal thickening: HRCT findings and differential diagnosis. Curr Probl Diagn Radiol 33(5):226

Hansell DM (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

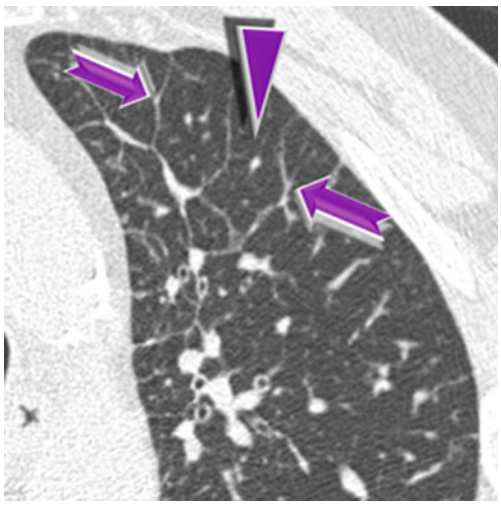
Webb WR (2006) Thin-section CT of the secondary pulmonary lobule: anatomy and the image – the 2004 Fleischner lecture. Radiology 239(2):322

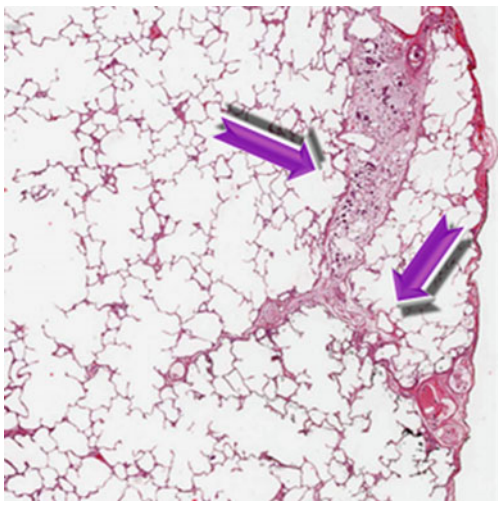
SEPTAL SIGNS

Septal Thickening

White lines 1–2 cm in length outlining the polygonal boundaries of secondary lobules. A few lines inside the lobule may be also visible. Lobules delineated by thickened septa (➡) commonly contain a visible dot-like or branching centrilobular pulmonary artery (►).
Pathologically, septal thickening may be due to interstitial fluid or cellular infiltration; the latter may be secondary to nonneoplastic or neoplastic diseases (e.g., lymphangitic carcinomatosis; please see both pictures below ➡).

Interlobular septal thickening, septal lines, Kerley's lines



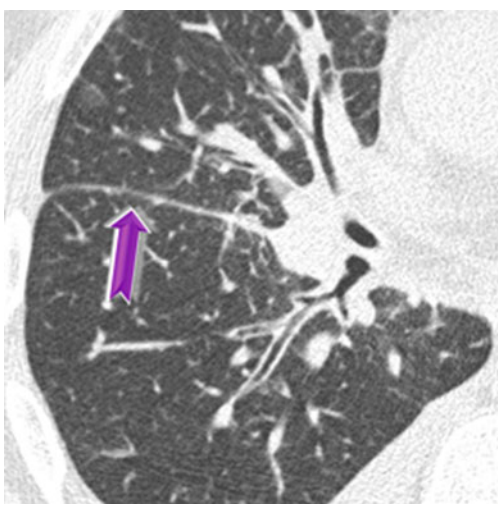


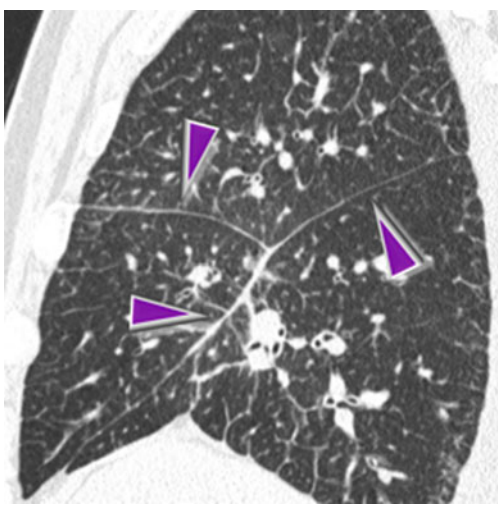
Diffuse interlobular septal thickening outlines numerous pulmonary lobules. They appear to be of various sizes and shapes, depending at least partially on the location of the lobule and its relationship with the plane of scan. Many of them are conical in shape.

History: on chest X-ray, septal thickening corresponds to Kerley's lines. Kerley B: 2-cm lines oriented perpendicular to the pleura. Kerley A: 2–6-cm lines oriented toward the hila.

Subpleural Interstitial Thickening

Subpleural interstitial thickening is easier to identify at the fissural level, where two layers of subpleural interstitium coexist (➡). Sagittal multiplanar reconstruction (MPR) is the best choice to quickly see the thickened fissures along their whole course (►). Subpleural thickening may be difficult to recognize where the lung gets in contact with the chest wall or the mediastinum.



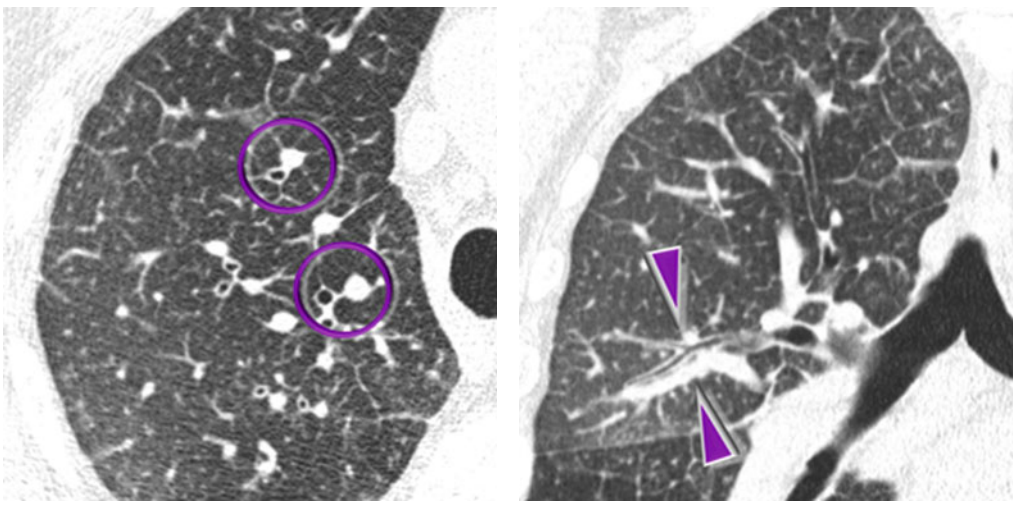


At fissural level, it may be difficult to distinguish subpleural interstitial thickening from fluid.

Peribronchovascular Thickening

Thickening of the peribronchovascular interstitium is usually appreciated on HRCT as an "apparent" increase in the bronchial wall thickness and in the diameter of pulmonary artery branches (○ and ►). This feature is due to the fact that the thickened interstitium cannot be distinguished from the underlying opacity of the bronchial wall and pulmonary artery.
Peribronchovascular interstitial thickening is easy to identify if it is marked and patchy/unilateral. As a rule, bronchial walls in corresponding regions of one or both lungs should be similar in thickness.

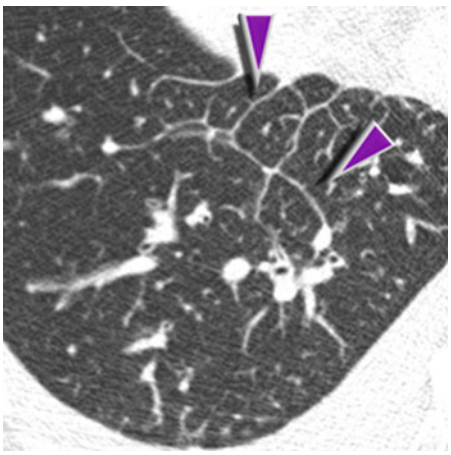
Peribronchial cuffing

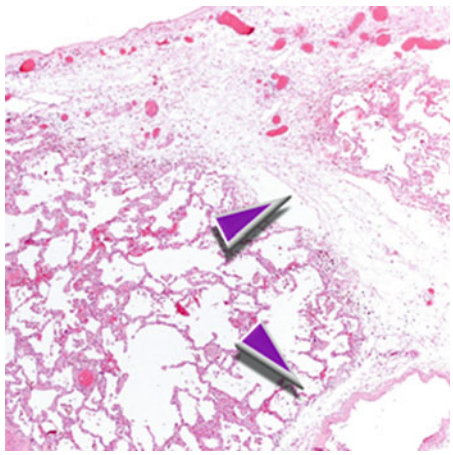


In patients with peribronchovascular interstitial thickening due to congestive heart failure, the correlation between the size of the bronchus and the artery may not be maintained due to dilatation of arteries and veins.

SUBSET SMOOTH

The interstitial compartments are thickened with smooth profiles. The anatomy of the three interstitial compartments (perilobular, peribronchovascular, and subpleural) is visible without focal abnormalities. Smooth septal thickening typically occurs in patients with venous diseases (e.g., interstitial pulmonary edema ►) and lymphatic diseases. Rarely, it may be due to an infiltrative disease (e.g., Erdheim-Chester disease).





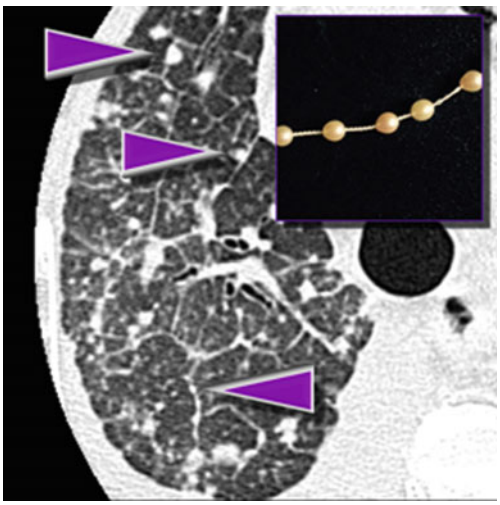
Smooth septal thickening may appear as an ancillary sign also in other diseases, in particular in patients with pulmonary hemorrhage or infection. Even if it is not the main radiologic feature, it is usually associated with airspace consolidation, ground-glass areas, or centrilobular branching structures (please see also chapter "Alveolar Pattern").

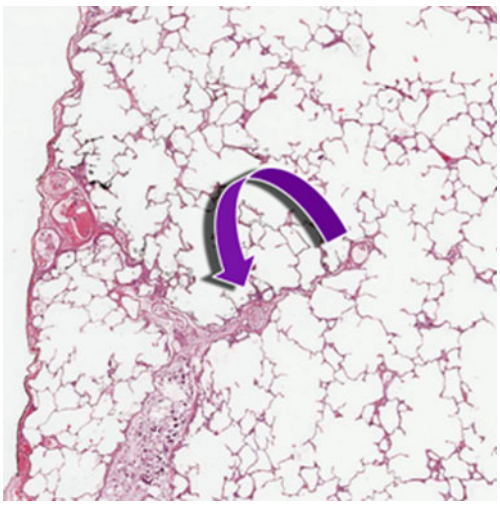
Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Smooth septal disease
Smooth thickening of septa, fissures, and bronchovascular bundles	Mainly in the apical, anterior, and peripheral regions	Rarely GGO	Pleural and pericardial thickening and/or effusion, "hairy kidney," osteosclerosis of the long bones	**Erdheim-Chester disease (ECD)**
Smooth thickening of septa, fissures, and bronchovascular bundles	If bilateral, abnormalities are asymmetric. Possibly nongravity dependent	Possible nodular thickening of septa, fissures, and bronchovascular bundles, patchy GGO	Lymph node enlargement, pleural effusion, pleural thickening, lytic or sclerotic skeletal lesions	**Lymphangitic carcinomatosis (LC)**
Smooth thickening of septa, fissures, and bronchovascular bundles	Diffuse and random distribution	GGO, possible crazy paving and low-density ill-defined centrilobular nodules, enlargement of pulmonary veins	Enlargement of left cardiac chambers, bilateral pleural effusion, enlarged mediastinal lymph nodes	**Pulmonary edema (PE), interstitial**
Smooth septal thickening, GGO	Patchy involvement of both lungs with nongravity-dependent distribution; septal thickening may be diffuse over time	Centrilobular ground-glass opacities	Enlargement of arteries and right heart chambers, enlarged lymph nodes; pleural and pericardial effusion may be seen	**Veno-occlusive disease (VOD)**

SUBSET NODULAR

Interstitial compartments are thickened in a nodular form, testifying to the existence of locally growing cells or extracellular deposits within the interstitial boundaries. Being interstitial, these nodules are dense with well-defined margins, embedded as they are inside the thickened interlobular septa and interstitial lines with an overall beaded appearance (►).
Nodular or "beaded" septal thickening often occurs in lymphatic diseases (e.g., lymphangitic carcinomatosis). Nodular subset may be also due to infiltrative diseases.

Beaded septum sign (please also refer to the chapter "Case-Based Glossary with Tips and Tricks")





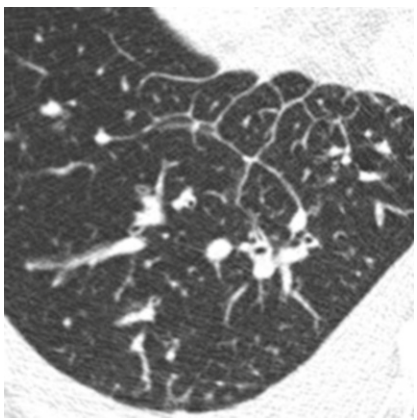
Nodular septal thickening may appear as an ancillary sign also in other diseases, particularly in patients with nodular diseases (sarcoidosis, silicosis, and coal workers' pneumoconiosis; please see chapter "Nodular Pattern").

In some cases, smooth and nodular thickening may coexist due to edema secondary to hilar lymphatic blockage.

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Nodular septal disease
Nodular septal thickening	Usually symmetric, mainly subpleural and basal	Nodules (calcified in 50 %), maybe cysts and smooth septal thickening	Adenopathy (also calcified), pleural thickening	**Amyloidosis**
Nodular septal thickening	Diffuse, patchy, or unilateral	Possible associated smooth thickening of septa, fissures, and bronchovascular bundles	Lymph node enlargement, pleural effusion, pleural thickening, lytic or sclerotic skeletal lesions	**Lymphangitic carcinomatosis (LC)**

Septal Diseases

Radiology	Nicola Sverzellati Mario Silva	



G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_4

Definition

Amyloidosis is a group of diseases caused by extracellular accumulation of abnormal misfolded autologous proteins (amyloid deposit), in a variety of organs and tissues. Current classification of amyloidosis is based on the type of fibrillar protein in the amyloid deposit (fibrillar amyloid light chain, AL, and serum amyloid A, AA, are the most common).

Amyloidosis can be primary or secondary in origin; hereditary forms are described but usually do not involve the chest. Localized and systemic forms of amyloidosis are described, with two main patterns of pulmonary involvement at HRCT, namely, nodular or diffuse. The interstitial diffuse form is more symptomatic than the nodular one.

Interstitial amyloidosis

Berk JL (2002) Pulmonary and tracheobronchial amyloidosis. Semin Respir Crit Care Med 23(2):155

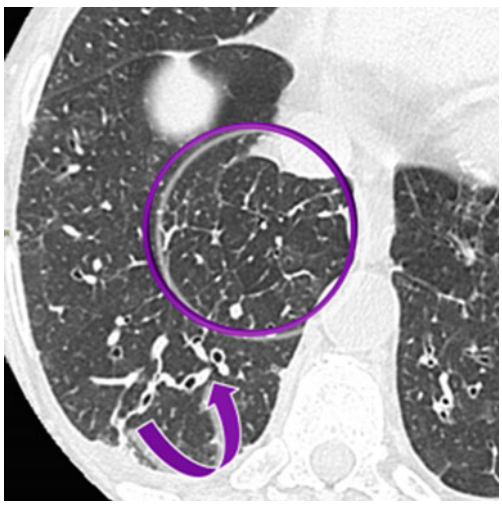
HIGH-RESOLUTION CT: HRCT

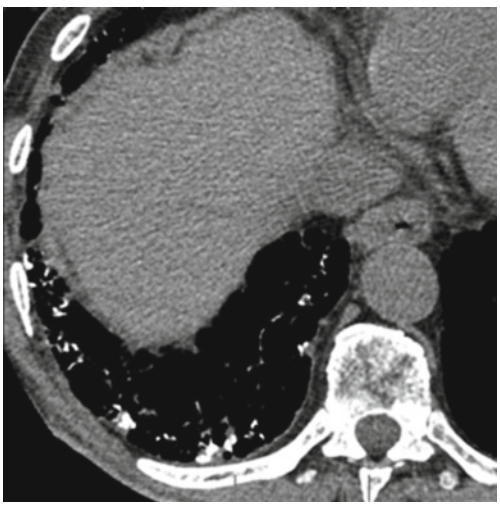
Key Signs

- Nodular interlobular septal thickening (beaded septum sign)
- Smooth interlobular septal thickening (O)
- Thickening of the bronchovascular bundles ( )
- Nodules (calcified in up to 50 % of cases) (see the image with mediastinal window)

Distribution

Usually symmetric and diffuse, but selective involvement with segmental distribution can be seen. Reticular opacities are predominantly subpleural and basal.





The beaded septum sign consists of nodular thickening of interlobular septa reminiscent of a row of beads. The beaded septum sign was initially described as a sign of lymphangitic spread of cancer although other diseases may be responsible of this sign (please also refer this sign in chapters "Septal Pattern" and "Case-Based Glossary with Tips and Tricks").

The reticular and nodular findings might be unspecific. The identification of coexisting nodules may help radiologists suggest the correct diagnosis. Nevertheless, pulmonary edema should always be considered in differential diagnosis, notably because it is frequent in subjects with myocardial amyloid deposits.

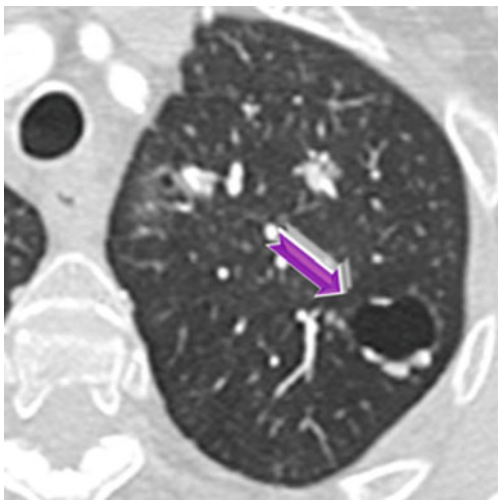
Pickford HA (1997) Thoracic cross-sectional imaging of amyloidosis. AJR Am J Roentgenol 168(2):351

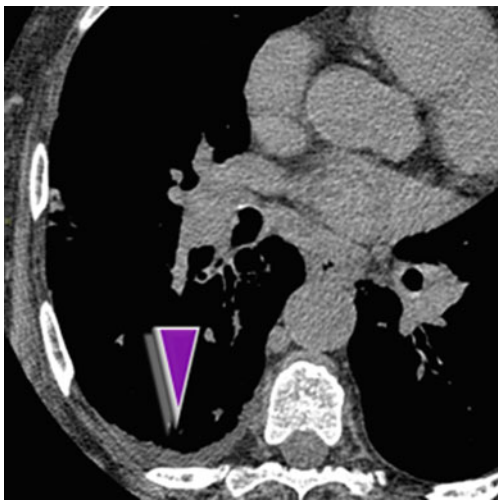
Ancillary Signs

- Ground-glass opacity.
- Patchy bilateral consolidations could show calcifications, some of them with punctate aspect.
- Lung cysts may coexist (➡), particularly in cases associated with lymphoproliferative disorders (e.g., LIP).

Non-parenchymal Signs

- Pleural thickening may be associated with pleural effusion (►).
- Hilar and mediastinal lymphadenomegaly with calcification is common in AL form of amyloidosis but uncommon in AA variant.
- Myocardial infiltration (wall thickening of the left ventricle with systolic and diastolic dysfunction and subendocardial or transmural late enhancement at MRI).





Differential diagnosis includes sarcoidosis because of beaded reticulation associated with lymph node enlargement with coarse calcifications. Also, it is important to differentiate between interstitial involvement from systemic amyloidosis and localized forms of diffuse alveolar septal amyloidosis, because the latter has more severe prognosis from pulmonary impairment.

Cordier JF (2009) Pulmonary amyloidosis in hematological disorders. Semin Respir Crit Care Med 26(5):502

Boydking A (2009) Localized interstitial pulmonary amyloid: a case report and review of the literature. Curr Opin Pulm Med 15(5):517–520

Course and Complications

- Treatment of underlying disease warrants resolution of interstitial involvement in the majority of cases of AA amyloidosis.
- AL amyloidosis related to hematologic disorders resolves in 30 % of cases treated with stem cell transplantation.

Clinical and radiological findings of the lung are usually secondary in pulmonary involvement from systemic amyloidosis. Cardiac involvement is a major prognostic factor; complications of cardiac involvement can overlap the pattern of interstitial amyloidosis. Assessment of myocardial involvement is suggested to provide comprehensive evaluation of cardiopulmonary involvement.

Czeyda-Pommersheim F (2015) Amyloidosis: modern cross-sectional imaging. Radiographics 35(5):1381

Definition

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis, with systemic infiltration by CD68+ and CD1a– histiocytes without Birbeck granules. Diagnosis in adulthood is a distinctive feature of ECD compared to other forms of non-Langerhans histiocytosis. The clinical manifestation is heterogeneous due to the variability in organ involvement. However, long bones are primarily affected in 95 % of patients. Extra-osseous manifestation is also seen, particularly in the retroperitoneum (perirenal rind of soft tissue), central nervous system (sellar with diabetes insipidus or extra-sellar), and thorax (myocardium, pericardium, lung, mediastinum, pleura, and vessels).

ECD

Campochiaro C (2015) Erdheim-Chester disease. Eur J Intern Med 26(4):223

Zaveri J (2014) More than just Langerhans cell histiocytosis: a radiologic review of histiocytic disorders. Radiographics 34(7):2008

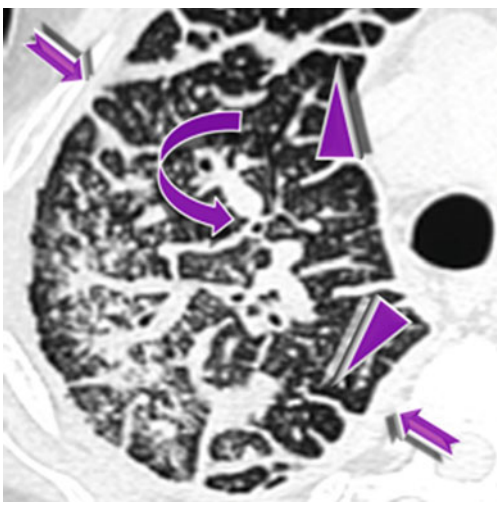
HIGH-RESOLUTION CT: HRCT

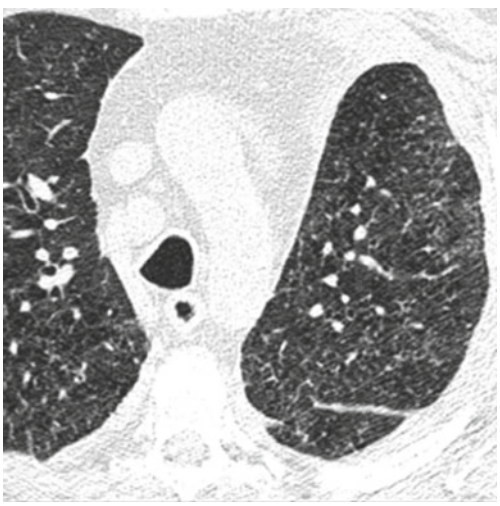
Key Signs

- Smooth thickening of interlobular septa (►)
- Smooth bronchovascular thickening (peribronchial cuffing) (↳)
- Smooth subpleural thickening (➡)
- Prominence of centrilobular structures

Distribution

Apical, anterior, and peripheral regions of the lungs are predominantly involved by symmetric smooth interlobular reticulation; also patchy or unilateral.





The thickening may be very marked assuming a “caricatural” aspect.

Pulmonary involvement is variable (14–54 % in different series), though it contributes significantly to symptoms and mortality. Pulmonary abnormalities may be due to either histiocytic infiltration or cardiogenic edema (from primary cardiac involvement).

Differential diagnosis includes lymphangitic carcinomatosis, as the differential diagnosis with systemic spread of neoplastic disease might be complicated in cases with atypical skeletal findings.

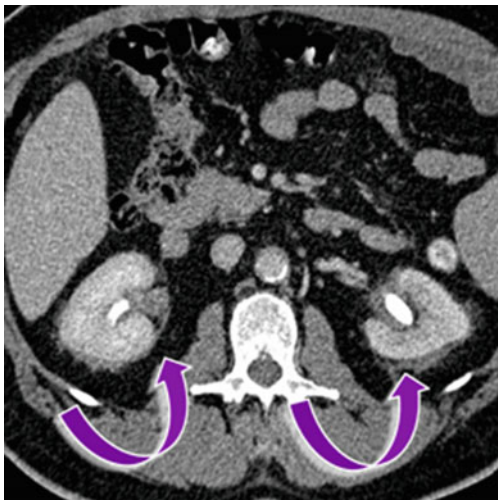
Arnaud L (2010) Pulmonary involvement in Erdheim-Chester disease: a single-center study of thirty-four patients and a review of the literature. Arthritis Rheum 62(11):3504

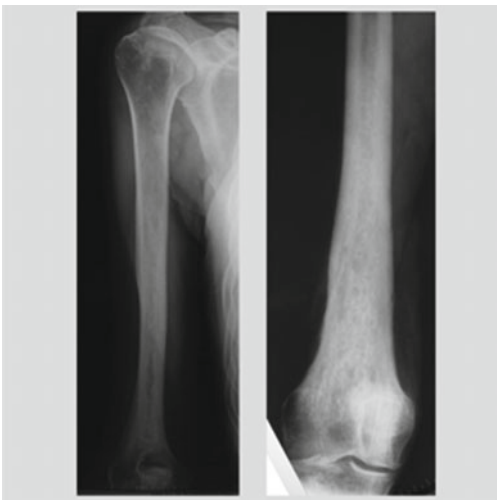
Ancillary Signs

- Variable ground-glass opacities or consolidation is seen in a small percentage of cases (please see image above).

Non-parenchymal Signs

- Pericardial effusion (up to tamponade); smooth or nodular pericardial thickening.
- Pleural thickening with late enhancement after injection of contrast agent.
- "Hairy kidney" from retroperitoneal fibrosis (☟) can be seen at bottom slides of thoracic scans (30 % of cases); urologic complications are rather common due to encasement of ureters from retroperitoneal fibrosis.
- Symmetric osteosclerosis of long bones, typically periarticular in lower limbs (tibia and distal femur).
- "Coated aorta" due to periaortic infiltration.
- Gadolinium-enhanced lesions of the central nervous system.





✓ The systemic involvement is a key feature of ECD that needs to be assessed when pulmonary and cardiac signs are seen at chest CT. Skeletal and retroperitoneal findings are therefore of paramount importance to target the differential diagnosis.

📖 Wittenberg KH (2000) Pulmonary involvement with Erdheim-Chester disease: radiographic and CT findings. AJR Am J Roentgenol 174(5):1327

Dion E (2004) Imaging of thoracoabdominal involvement in Erdheim-Chester disease. AJR Am J Roentgenol 183(5):1253

Course and Complications

- Serial imaging of the involved organ is warranted (3–6 months) to monitor pharmacological treatment, notably at its beginning.
- FDG-PET is helpful to assess disease activity.
- Worsening of cardiopulmonary abnormalities are among the most frequent life-threatening complications.

📖 Haroche J (2012) Erdheim-Chester disease. Curr Opin Rheumatol 24(1):53

Yahng SA (2009) Erdheim-Chester disease with lung involvement mimicking pulmonary lymphangitic carcinomatosis. Am J Med Sci 337(4):302

De Filippo M (2009) Erdheim-Chester disease: clinical and radiological findings. Radiol Med 114(8):1319

Definition

Lymphangitis carcinomatosis (LC) is caused by the infiltration of pulmonary lymphatics by neoplastic cells. The primary tumor is most frequently located in the bronchial tree, breast, pancreas, stomach, colon, and prostate. Invasion of lymphatics may vary according to the site of primary tumor: direct spread from intrathoracic neoplasms, retrograde diffusion from hilar lymph nodes for upper abdomen tumors, and contiguity from hematogenous metastasis

Pulmonary lymphangitic carcinomatosis (PLC), LC

Biswas A (2015) Getting the whole picture: lymphangitic carcinomatosis. Am J Med 128(8):837

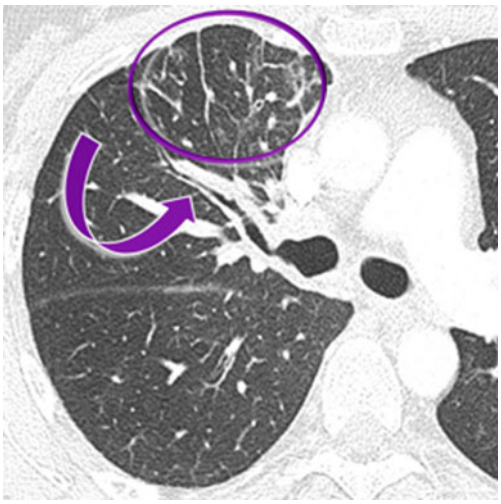
HIGH-RESOLUTION CT: HRCT

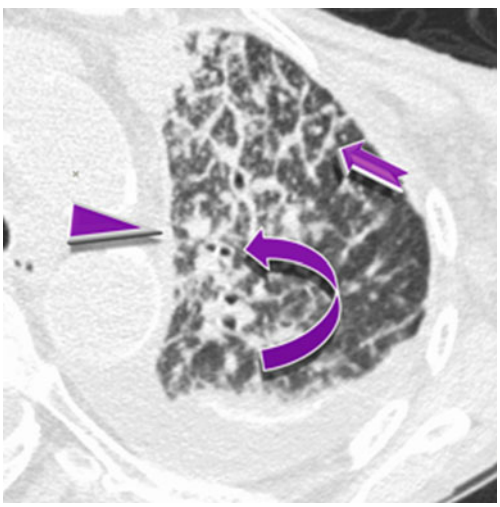
Key Signs

- Smooth interlobular septal thickening (O)
- Nodular interlobular septal thickening (beaded septum sign) (➡)
- Smooth or nodular peribronchovascular interstitial thickening (peribronchial cuffing) (⇳)
- Smooth or nodular thickening of fissures or pleural surface (►)

Distribution

Bilateral distribution is as common as unilateral involvement. If bilateral, abnormalities are asymmetric. Possible nongravity-dependent distribution (O)





Pulmonary edema represents the main differential diagnosis. Coexisting perilymphatic nodules and nonsymmetric or nongravity-dependent distribution of the septal lines are features more consistent with lymphangitis (in axial CT image, note the anterior nongravity-dependent septal thickening O).

Other disorders may also mimic lymphangitis carcinomatosis: pulmonary leukemia, eosinophilic pneumonia, veno-occlusive disease, and metabolic disorders are indeed characterized by predominant interlobular septal thickening. Thickened interlobular septa may be spurious in other disorders (e.g., infections, sarcoidosis, etc.), which, however, display other more distinctive CT features.

The beaded septum sign consists of nodular thickening of interlobular septa reminiscent of a row of beads. The beaded septum sign was initially described as a sign of lymphangitic spread of cancer although thoracic sarcoidosis in literature has been called the "great mimic" and can manifest with various patterns on HRCT like nodular septal thickening simulating the lymphangitic carcinomatosis. Other diseases responsible of this sign are amyloidosis and lymphoproliferative diseases (lymphoma, leukemia); please also refer to beaded septum sign in chapters "Septal Pattern" and "Case-Based Glossary with Tips and Tricks."

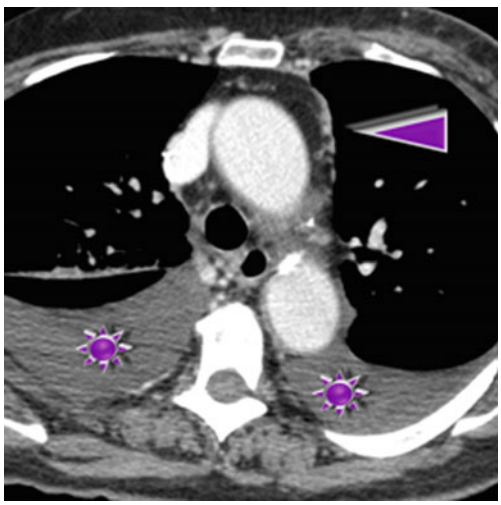
Honda O (1999) Comparison of high resolution CT findings of sarcoidosis, lymphoma, and lymphangitic carcinoma: is there any difference of involved interstitium? J Comput Assist Tomogr 23(3):374

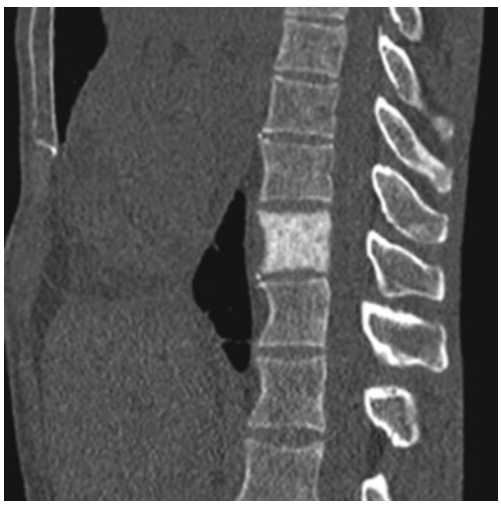
Ancillary Signs

- Intralobular septal thickening
- Patchy GGO
- Wedge densities located in the periphery of the lung, usually small in size (one or few contiguous lobules)

Non-parenchymal Signs

- Pleural effusion (✸)
- Pleural thickening, also nodular (►)
- Hilar and mediastinal lymphadenopathy
- Association with systemic metastasis (e.g., lytic and or sclerotic skeletal lesions)





Johkoh T (1992) CT findings in lymphangitic carcinomatosis of the lung: correlation with histologic findings and pulmonary function tests. AJR Am J Roentgenol 158(6):1217

Course and Complications

- Interlobular septal and bronchovascular bundle thickening and pulmonary nodules may increase in extent and size.
- CT signs of lymphangitic carcinomatosis may reduce after chemotherapy.
- Pleural and pericardial involvement may complicate lymphangitic carcinomatosis.

Lymphangitic carcinomatosis may happen through different pathways and usually progress by contiguity with involvement of interlobular septa (beaded reticulation), intralobular interstitium (ground-glass or small consolidations with geometric shape, sometimes into the crazy-paving pattern), and peribronchovascular bundle.

Follow-up: radiation therapy in oncologic patients can be a confounding factor because lung damage from radiation therapy and lymphangitic carcinomatosis look alike. The differential diagnosis can be based on the spatial distribution because diffuse lung abnormalities outside the radiation volume and bilateral distribution increase the level of confidence toward lymphangitic carcinomatosis.

Larici AR (2011) Lung abnormalities at multimodality imaging after radiation therapy for non-small cell lung cancer. Radiographics 31:771

Definition

Pulmonary edema is classified as cardiogenic (increase in interstitial fluid from high pulmonary hydrostatic pressure) or noncardiogenic (increase in interstitial fluid from high vascular permeability). Interstitial edema is characterized by infiltrates in the interstitial spaces of the lung, mostly in the loose peribronchovascular tissues and the interlobular septa.

PE

In more severe cases of pulmonary edema, the fluid accumulation is in the alveoli (please see PE, alveolar).

Komiya K (2013) Comparison of chest computed tomography features in the acute phase of cardiogenic pulmonary edema and acute respiratory distress syndrome on arrival at the emergency department. J Thorac Imaging 28:322

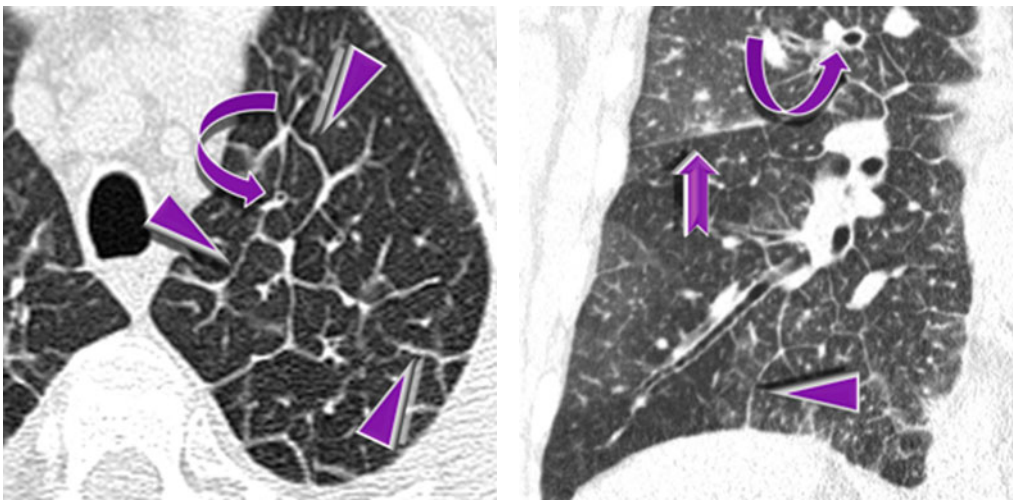
Key Signs

HIGH-RESOLUTION CT: HRCT

- Smooth thickening of interlobular septa (►)
- Smooth bronchovascular thickening (peribronchial cuffing) (⇘)
- Smooth subpleural thickening, easy visible at the fissural level (➡)
- Ground-glass opacity (GGO), patchy or lobular

Distribution

In most patients, pulmonary edema has a diffuse and random distribution, with some lobes more severely affected than others.



The absence of distortion of lung parenchyma and the more linear, smooth septal thickening, despite extensive involvement, helps to differentiate cardiogenic interstitial edema from fibrosing interstitial lung diseases.

In permeability edema vessels are not dilated and diffuse septal lines are rarely observed, whereas they are often the major feature associated with cardiogenic edema.

Scillia P (2004) Computed tomography assessment of lung structure and function in pulmonary edema. Crit Rev Comput Tomogr 45(5–6):293

Milne EN (1985) The radiologic distinction of cardiogenic and noncardiogenic edema. Am J Roentgenol 144:879

In papillary muscle rupture from myocardial infarction, acute mitral valve regurgitation causes pulmonary edema with selective involvement, usually the right upper lobe. Moreover, monolateral edema may be due to prolonged lateral decubitus.

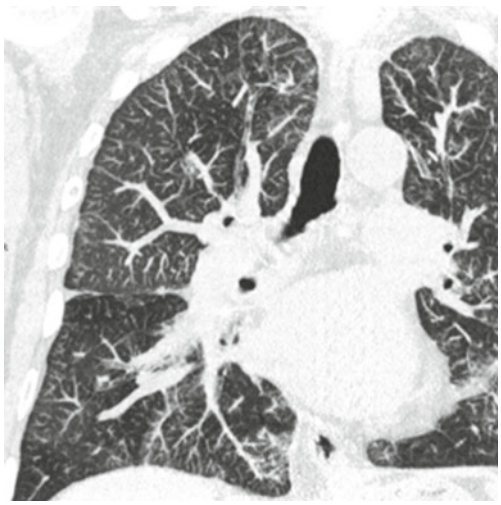
Gurney JW (1989) Pulmonary edema localized in the right upper lobe accompanying mitral regurgitation. Radiology 171(2):397

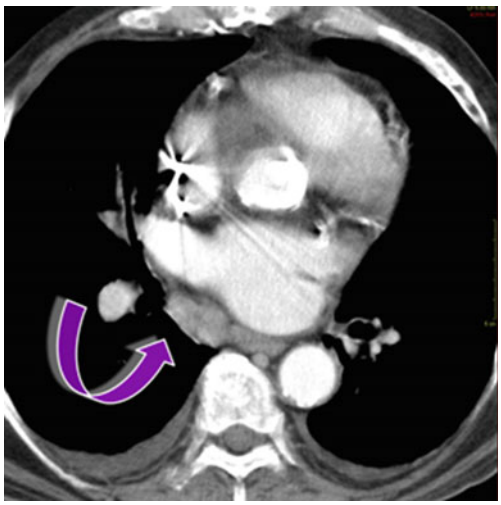
Ancillary Signs

- Possible crazy paving
- Low-density ill-defined centrilobular nodules
- Transient subpleural curvilinear opacities (possibly representing engorged lymphatics)

Non-parenchymal Signs

- Pleural effusion, more commonly bilateral
- Enlargement of pulmonary veins up to the left atrium and left cardiac chambers
- Enlarged mediastinal lymph nodes in nearly up to 50 % of cases ( )
- Haziness of mediastinal fat





Course and Complications

- Cardiogenic edema generally resolves with reduction of fluid overload.
- In cases of chronically elevated pulmonary venous hypertension, interstitial fibrosis-like changes might be expected on CT.

Marano R (2015) Comprehensive CT cardiothoracic imaging: a new challenge for chest imaging. Chest 147(2):538

Definition

Pulmonary veno-occlusive disease (VOD) is a rare disease characterized by narrowing of pulmonary venules and small veins caused by intimal fibrosis. Such abnormalities are associated to *postcapillary* pulmonary arterial hypertension (PAH).

VOD, pulmonary veno-occlusive disease (PVOD)

Montani D (2009) Pulmonary veno-occlusive disease. Eur Respir J 33:189

Mandel J (2000) Pulmonary veno-occlusive disease. Am J Respir Crit Care Med 162(5):1964

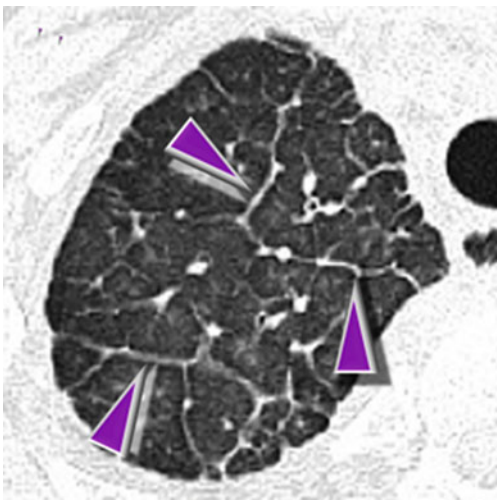
HIGH-RESOLUTION CT: HRCT

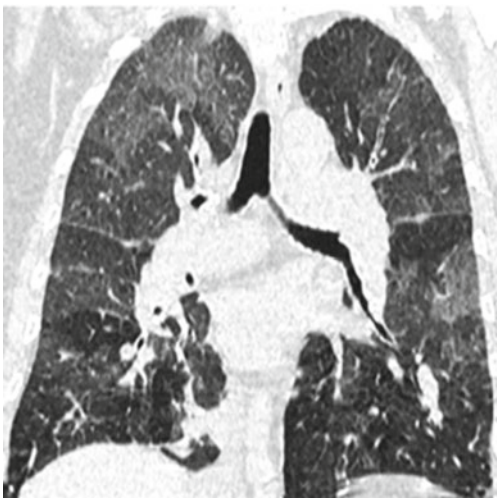
Key Signs

- Smooth thickening of interlobular septa (►)
- Ground-glass opacity, patchy or lobular (see coronal image below)

Distribution

Patchy involvement of both lungs with nondependent distribution; septal thickening may be diffuse over time.





Histologic correlation with CT findings has shown that thickened interlobular septa corresponded to the presence of septal fibrosis and venous sclerosis. GGO may be related to alveolar wall thickening or pulmonary edema.

The diagnosis is challenging and multidisciplinary (including pulmonary function test, hemogasanalysis, and right-heart catheterization); the presence of key signs provides good diagnostic accuracy in the appropriate clinical scenario. However, lung biopsy may be required to confirm diagnosis. PVOD is associated with extremely poor prognosis.

Frazier AA (2007) Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Radiographics 27:867

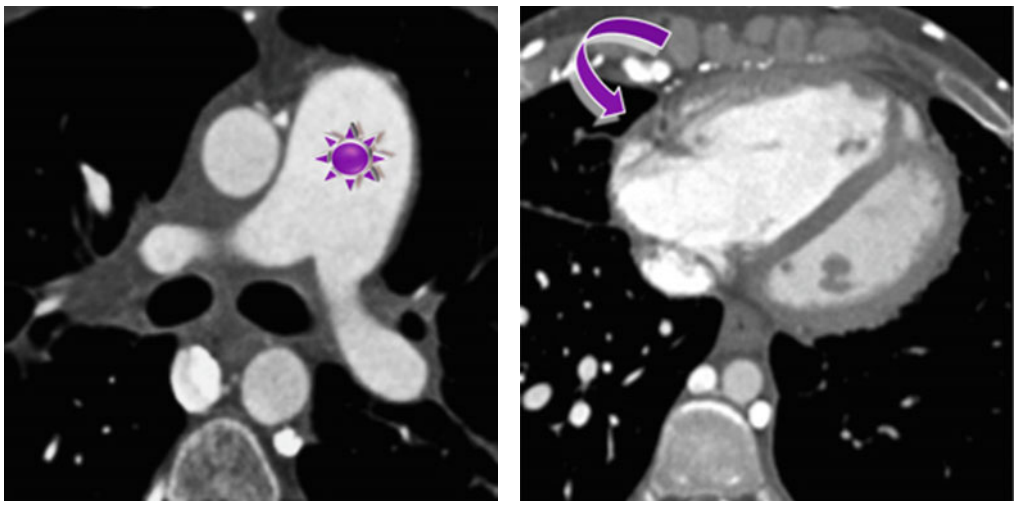
Miura A (2013) Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis. Cardiovasc Pathol 22(4):287

Ancillary Signs

- Centrilobular ground-glass opacities
- Late-phase alveolar consolidation caused by edema, hemorrhage, or infarction

Non-parenchymal Signs

- Cardiovascular signs consistent with pulmonary hypertension, e.g., enlargement of pulmonary arteries (✸) and right-heart chambers (↻) with normal pulmonary veins and normal left cardiac chambers.
- Mediastinal lymph node enlargement.
- Pleural and pericardial effusion may be seen.



Early PVOD may show scant parenchymal findings that are easy to overlook. In addition, it may be observed in association with other conditions such as connective tissue disease.

Mineo G (2014) Pulmonary veno-occlusive disease: the role of CT. Radiol Med 119:667–673

Course and Complications

Interlobular septal thickening increases in extent. Ground-glass opacity and pleural effusion may appear and mimic pulmonary edema associated with pulmonary hypertension.

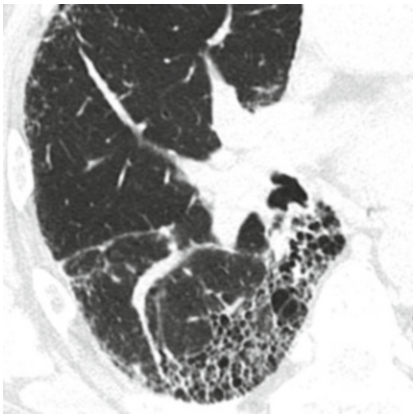
Thickened interlobular septa are more frequently associated with PVOD rather than pulmonary capillary hemangiomatosis (PCH), the latter being characterized by larger centrilobular ground-glass opacities.

Rossi A (2014) Rare causes of pulmonary hypertension: spectrum of radiological findings and review of the literature. Radiol Med 119(1):41

Fibrosing Pattern

Radiology
Pathology

Giorgia Dalpiaz
Alessandra Cancellieri



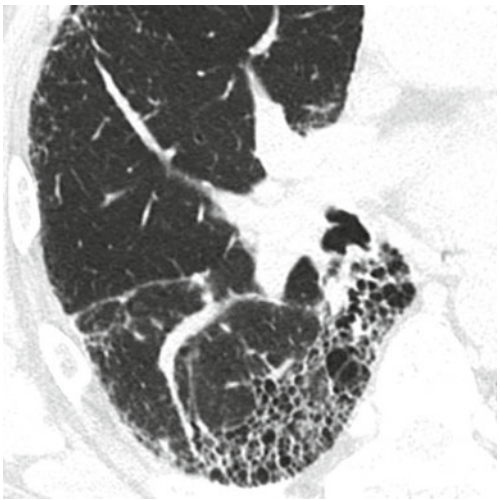
G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_5

FIBROSING PATTERN

Definition

Fibrosing pattern is defined when retraction and/or remodeling of thoracic structures is visible at the lobular level, often extended to larger portions of the lungs.
Pulmonary fibrosis is histologically defined as the abnormal deposition of dense collagen in lung parenchyma (pink-staining fibrosis). Regardless of the underlying mechanism and duration of injury, fibrosis results into structural damage and pathological remodeling (Please refer to "Non-defining lesions: fibrosis" in the chapter "Thinking trough pathology").

Fibrotic pattern



The HRCT signs of fibrotic disease are associated with the direct visualization of fibrotic lesions or the effects of retraction and remodeling on pulmonary structures.

Key signs are:

- Honeycombing
- Fibrosing reticulation and interface sign
- Traction bronchiectasis and bronchiolectasis
- Volume loss

Ancillary signs are:

- Ground-glass opacity
- Lobular air trapping
- Disseminated pulmonary ossification

The prevalent distribution of the signs, together with the presence of non-parenchymal signs, may be helpful for the diagnosis of a specific disease (please see the table at the end of this chapter).

As well as in fibrosing diseases, in which this pattern is predominant, there are other diseases in which fibrotic signs may be found, albeit less important or sporadic. They are therefore described in the relevant chapter.

Jacob J, Hansell DM (2015) HRCT of fibrosing lung disease. Respirology 20(6):859

Leslie KO (2009) My approach to interstitial lung disease using clinical, radiological and histopathological patterns. J Clin Pathol 62(5):387–401

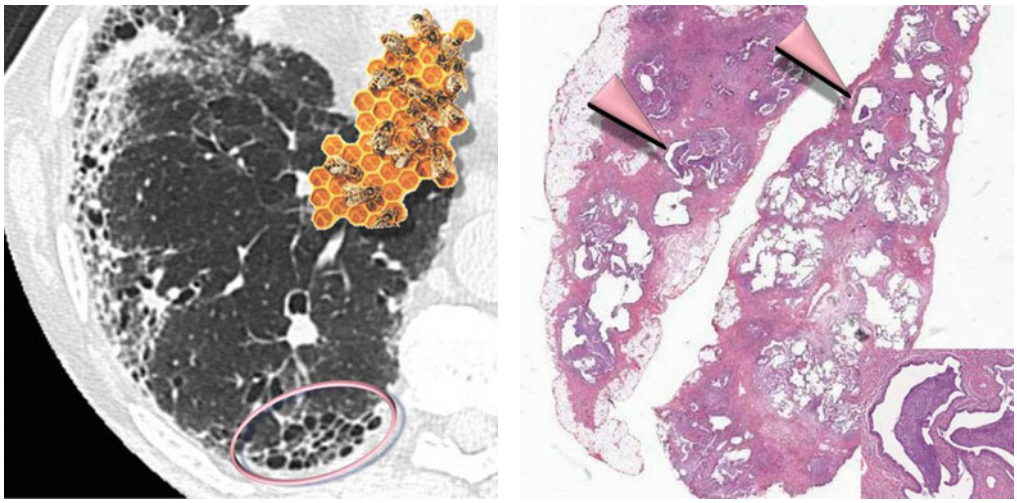
Dalpiaz G (2017) Fibrosing pattern. In Leslie KO, Wick MR (eds). Practical lung pathology, 3rd edn. Saunders, Philadelphia

Hodnett PA (2013) Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med 15;188(2):141

FIBROSING KEY SIGNS

Honeycombing

In the latest version from the Fleischner Society on HRCT, honeycomb lung is defined as clustered cystic airspaces, typically of comparable diameters on the order of 3–10 mm but occasionally as large as 2.5 cm. Honeycombing is usually subpleural and is characterized by well-defined walls 1–3 mm in thickness. Although often cited in the literature as being layered (O), a single layer of subpleural cysts may also be a manifestation of honeycombing. Unfortunately, the HRCT identification of honeycombing is not always straightforward, and there is some disagreement regarding its imaging features, mainly due to conditions that may mimic honeycombing in the axial plane, in particular, severe traction bronchiolectases and emphysema. The coronal or sagittal reconstruction may be useful for the differential diagnosis. Pathology of honeycombing consists of enlarged airspaces lined by bronchiolar epithelium and frequently filled by mucus and inflammatory cells (►, inset). The background architecture has to be altered in order to distinguish honeycombing from peribronchiolar metaplasia, a nonspecific finding in many conditions.



The differential diagnosis between honeycombing and paraseptal emphysema may be difficult; however, honeycombing is usually associated with other features of lung fibrosis, such as volume loss, architectural distortion, fibrosing reticulation, traction bronchiectases, and bronchiolectases. Subpleural cysts without other signs of fibrosis likely represent subpleural emphysema. But one must also keep in mind that emphysema and honeycombing may coexist. The latter entity is defined combined pulmonary fibrosis and emphysema syndrome (CPFE). In these cases, it may be difficult to determine where emphysema ends and honeycombing begins.

Diseases with honeycombing:

- *IPF*: honeycombing is a strong predictor of histologic UIP because it is seen in most cases (about 70 %) and mainly involves subpleural regions and lung bases. However keep in mind that in patients with fibrotic ILD and absence of CT honeycombing, the probability of IPF exceeds 80 % in subjects over age 60 years with one-third of total lung having fibrosing reticulation
- *Asbestosis*: honeycombing is a common finding in advanced-stage disease, predominantly at the basal periphery and posterior region, similarly to what is observed in patients with IPF. Bilateral pleural plaques are crucial for the diagnosis
- *HP*, *chronic*: honeycombing is common in advanced disease (about 60 %) with possible (non-basal) upper-lobe distribution. Bilateral lobular air trapping is a key for the diagnosis
- *CVD and drug toxicity*: based on the pathologic classification, the frequently observed NSIP pattern related to CVDs (mostly, in patients with scleroderma and rheumatoid arthritis) may be associated with mild honeycombing. In patient with pathologic UIP pattern, honeycombing is frequent. Pleural and pericardial thickening or effusion may coexist and useful for the diagnosis of CVD and drug toxicity. In scleroderma pulmonary arterial hypertension and esophageal dilation (up to 80 % of cases) may be visible
- *NSIP*: honeycombing is uncommon and of minimal extent

- *Sarcoidosis*, *fibrotic*: occasionally, honeycomb-like cysts are seen in the upper lobes, associated with peribronchovascular fibrosis. Bilateral, symmetric mediastinal and hilar and right paratracheal lymph node enlargement, often calcified, are crucial for the diagnosis. May be present perilymphatic nodules that may be difficult to distinguish from interface sign

☝ Honeycombing in patient with biopsy-proven NSIP may reflect foci of UIP in spite of the histologic diagnosis, since heterogeneity is known to exist among biopsy samples (so-called discordant UIP).

Honeycombing in PPFE is often due to coexistent UIP. Marked irregular pleural thickening and "tags" in the upper zones that merges with fibrotic changes in the subjacent lung are the key signs for the diagnosis.

📖 Hansell D (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

Arakawa H (2011) Honeycomb lung: history and current concepts. AJR Am J Roentgenol 196(4):773

Watadani T (2013) Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology 266(3):936

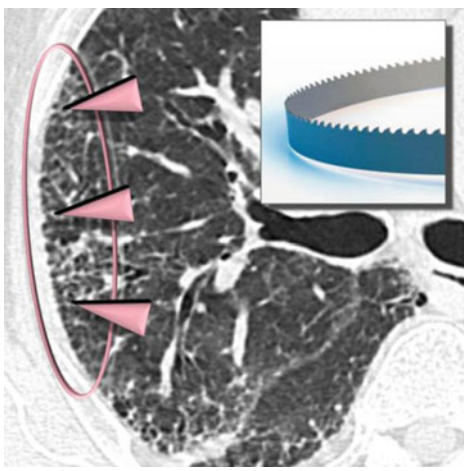
Fibrosing Reticulation and Interface Sign

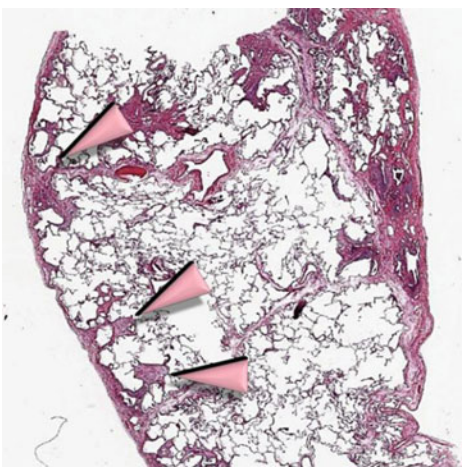
Fibrosing reticular abnormality appears as wavering fine intralobular lines as if they were traced on the lung background by an unsteady hand. The distortion due to fibrosis tends to reduce the recognition of the lobular architecture (O). Although interlobular septal thickening can be seen on thin-section CT scans with possible association with honeycombing, it is not usually a predominant feature. In the presence of fibrosis, distortion of lung architecture makes the recognition of lobules and thickened septa difficult.

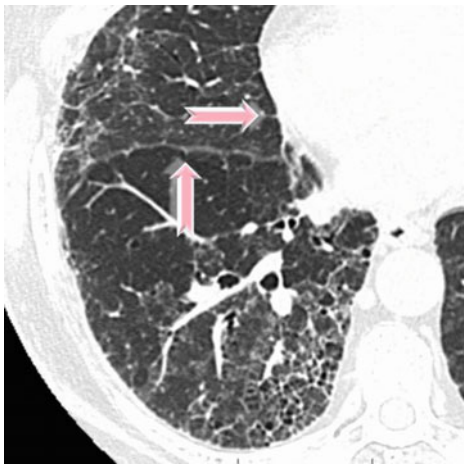
Subpleural fibrosing reticulation is associated with shaggy interfaces between the lung and pulmonary vessels, bronchi, and pleural surfaces with an aspect resembling the blame of a saw (►) or the spines of roses (➡), corresponding to interface sign.

Pathologically, when alveolar septa are thick enough to produce a reticular pattern at CT scan, interstitial fibrosis generally consists of dense scars obscuring the alveolar architecture. The fibrosis may have a "peripheral acinar distribution," correlating at CT scan with the interface sign and fibrosing reticulation (►).

☯ Irregular septal thickening, reticulation with distorted architecture







Intralobular interstitial thickening can be seen in non-fibrosing interstitial lung diseases. When this is the case, distortion and other signs are absent. Non-fibrosing intralobular interstitial thickening may be seen in association with interlobular septal thickening or ground-glass opacity in conditions such as pulmonary edema or hemorrhage, atypical pneumonia, and lymphangitic spread of carcinoma (please see also chapter "Septal Pattern" and "Alveolar Pattern").

Interface sign is frequently visible in patients with fibrotic ILDs, but it may be also be seen in patients with non-fibrosing ILDs, showing in the latter a regular outline.

Diseases with fibrosing reticulation and interface sign:

- *IPF*: a fibrosing reticular pattern is the most common radiographic finding, described in approximately 70–90 % of patients with biopsy-proven IPF. Although these opacities may be diffuse throughout both lungs, in 50–80 % of cases, they involve predominantly or exclusively the lower-lung zones. A "propeller blade" distribution from caudal to cranial (being predominantly posterior to anterior) is frequent. According to the recent international guidelines, reticular abnormalities must be present for a HRCT diagnosis of definite or possible UIP pattern. Interface sign is reported in more 90 % of patients with IPF
- *Asbestosis*: in early asbestosis, thickened intra- and interlobular lines are often visible. Bilateral pleural plaques are crucial for diagnosis
- *NSIP*: a fibrosing reticular HRCT abnormality is present in 80–90 % of patients, more frequently in patients with the fibrotic variant of NSIP. It is often associated with traction bronchiectases and bronchiolectases. Reticulation is often extended in the axial plane
- *HP chronic*: reticulation is common, mainly in the middle portion of the lungs or fairly evenly throughout the lungs but with relative sparing of the extreme apices and bases. Lobular air trapping is crucial for diagnosis
- *CVD and drug toxicity*: fibrosing reticulation is frequent in either pathologic pattern fibrosing NSIP and UIP related to both drug toxicity and CVD (mainly in patients with scleroderma and rheumatoid arthritis). Pleural and pericardial thickening or effusion may coexist and useful for the diagnosis of CVD and drug toxicity. In scleroderma pulmonary arterial hypertension and esophageal dilation (up to 80 % of cases) may be visible
- *Sarcoidosis*, *fibrosing*: fibrotic linear opacities stretch the hila with posterior displacement of the main and upper-lobe bronchi (tug of war aspect). Bilateral, symmetric mediastinal and hilar and right paratracheal lymph node enlargement, often calcified, are crucial for the diagnosis. Perilymphatic nodules that may be difficult to distinguish from interface sign

Sverzellati N (2015) American Thoracic Society-European Respiratory Society Classification of the Idiopathic Interstitial Pneumonias: Advances in Knowledge since 2002. Radiographics 35(7):1849

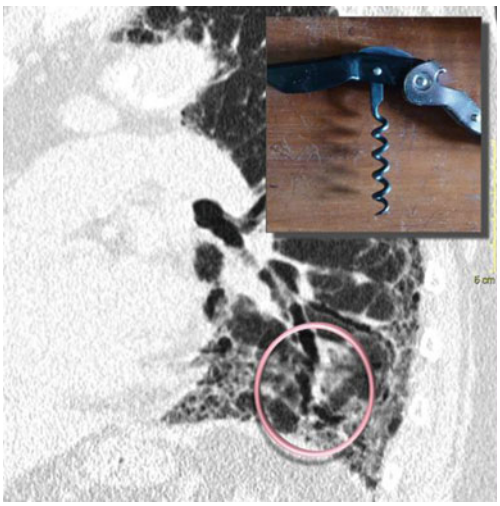
Raghu G (2014) Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. Lancet Respir Med 2(4):277

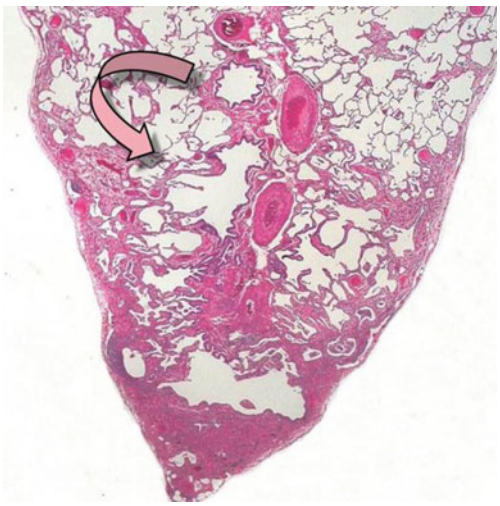
Salisbury ML (2016) Predictors of idiopathic pulmonary fibrosis in absence of radiologic honeycombing: A cross sectional analysis in ILD patients undergoing lung tissue sampling. Respir Med 118:88

Traction Bronchiectasis and Bronchiolectasis

Traction bronchiectasis and bronchiolectasis, respectively, represent irregular bronchial and bronchiolar dilatation caused by surrounding retractile pulmonary fibrosis. The bronchi are irregularly ectatic with no-thickened, shaggy walls and winding or corkscrew appearance (O). Dilated airways are usually identifiable as such, but they may be seen on the axial plane as cysts (bronchi) or microcysts (bronchioles in the lung periphery) mimicking honeycombing. Coronal or sagittal reconstructed images (O) may be useful for the differentiation of a traction bronchiectasis and bronchiolectasis from its mimics, especially from honeycombing.

Traction bronchiectases and bronchiolectases visible on HRCT images correspond at histology to ectatic bronchi or bronchioles localized in a fibrotic lung (↬), a quite frequent finding in any fibrosing ILD.





Traction bronchiectases and bronchiolectases can be seen in all patients with an underlying fibrotic lung disease, and therefore its diagnostic value by itself is limited; however, the distribution and the associated signs may be helpful (please see the table at the end of this chapter).

- *IPF*: bronchiectasis are often present and they may have a semicircular course often touching the subpleural space ("subpleural involvement") because the disease start from subpleural space and progressively expand to the central space
- *NSIP*: reported high prevalence of traction bronchiectasis (80 %) that may don't touch the subpleural space ("subpleural sparing"; please see the CT figure "fibrosing NSIP" in the ancillary sign)

Hansell D (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

Cantin L (2009) Bronchiectasis. AJR Am J Roentgenol 193(3):W158

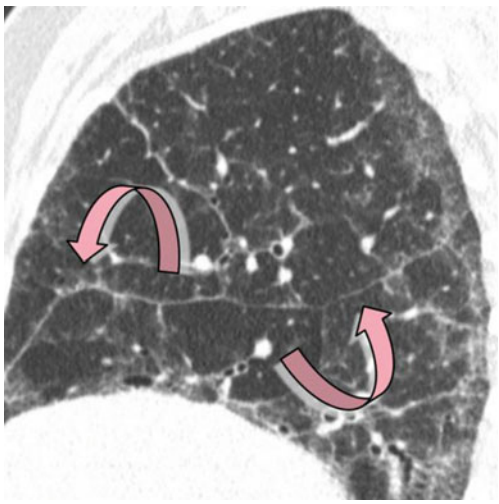
Milliron B (2015) Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. Radiographics 35(4):1011

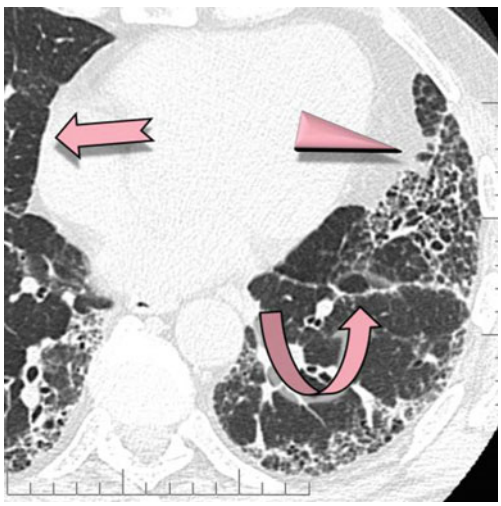
Volume Loss

Volume loss is a basic sign of fibrotic ILDs but not easy to recognize in the early phase of diseases or in the presence of minimal fibrosis. The fissure shape is a good early marker of volume loss. The angulation and displacement of fissures are indirect signs of peripheral fibrosing disease and may assume a "festooned" course due to traction phenomena (↬). Sagittal and coronal reconstruction may be useful

for an easy recognition of the displacement of the fissures (☟). Right image below refers to a close-up of stained-glass window representing the love story of Psyche and Cupid in Chateau de Chantilly, France.

A sign of volume loss can also be visible along the mediastinal contour appearing as a lobulated profile attracted toward the more affected lung. This process results as an enlargement of mediastinal outline. This aspect is easy to recognize comparing the pathological profile (►) with the normal one (➡). Another sign of volume loss is the displacement of bronchovascular bundles, sometimes assuming a winding course. In advanced fibrotic disease, the volume loss may be very significant and, as a result, the lung is screwed and rigid as a dead leaf.





☝ Volume loss may have a crucial role for the diagnosis of fibrosing ILDs when other key signs are absent or equivocal.

Volume loss may be minimal than expected in some patients because of an early phase of the disease or coexisting emphysema.

🚹🚺 The presence of volume loss in fibrotic ILDs is not specifically described in most articles; however, it is a useful indirect sign for a diagnosis of fibrosing lung disease. The site of the prevalent volume loss may be useful for the diagnosis (please see the table at the end of this chapter).

🕮 Dalpiaz G, Maffessanti M (2013) Diffuse lung diseases. In Guglielmi G, Peh W, Guermazi A (ed) Geriatric Imaging. Springer-Verlag Berlin-Heydelberg, 2013

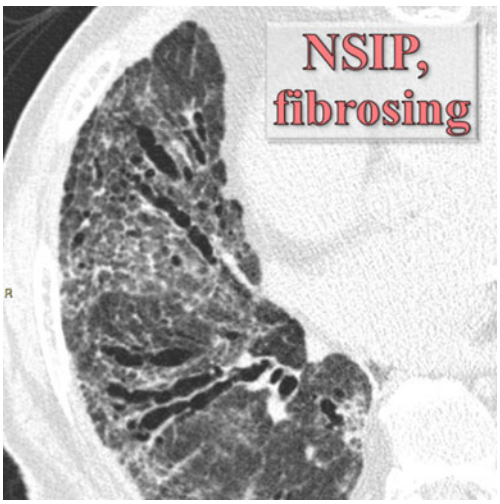
ANCILLARY SIGNS

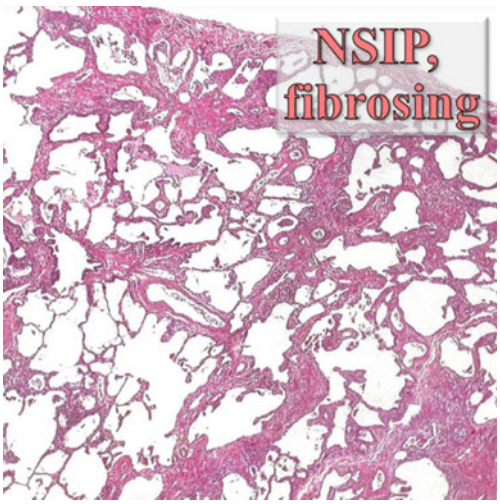
Ground-Glass Opacity

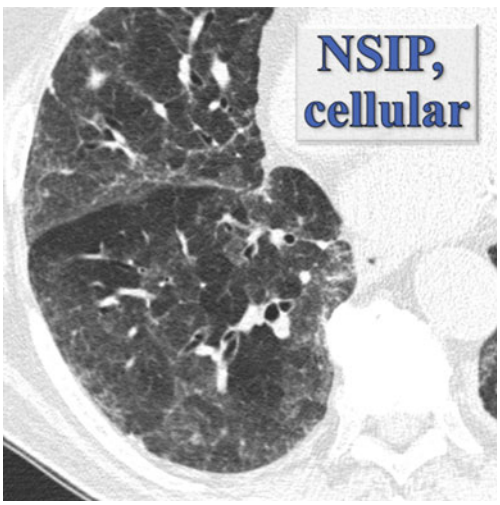
On CT scans, ground-glass opacity appears as a hazy increased opacity of the lung, with preservation of bronchial and vascular margins.
Ground-glass opacity associated with traction bronchiectases and bronchiolectases, fibrotic reticular abnormality, and volume loss represents fine fibrosis rather than inflammation (e.g., in fibrosing NSIP).

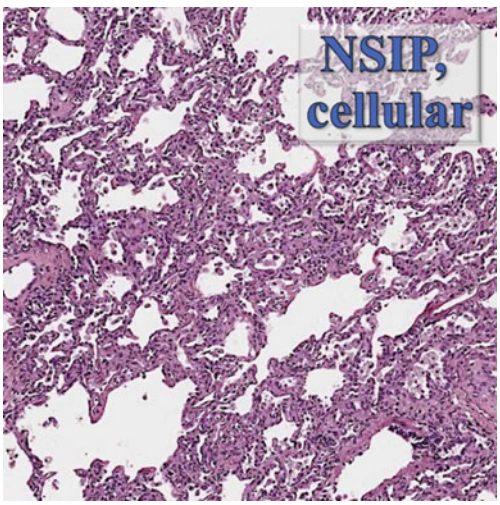
Ground-glass opacity should be interpreted as "active," potentially reversible disease when not associated with other findings suggestive of fibrosis (e.g., in cellular NSIP).

GGO









Diseases with ground-glass opacity (GGO):

- *NSIP*: the presence of wide areas with ground-glass opacity is the salient CT feature of NSIP and is found in nearly all cases; fibrotic or non-fibrotic GGO may be variously present depending on the pathologic type (see the images above). In fibrosing NSIP, in the areas of fibrotic GGO always coexist traction bronchiectases that may don't touch the subpleural space ("subpleural sparing"; please see the CT figure above "fibrosing NSIP")
- *CVD and drug toxicity*: the GGO reflects the NSIP histologic pattern frequently related to both conditions. Pleural and pericardial thickening or effusion may coexist and useful for the diagnosis of

CVD and drug toxicity. In scleroderma pulmonary arterial hypertension and esophageal dilation (up to 80 % of cases) may be visible
- *HP*, *chronic*: often presents with possible associated lobular air trapping
- *IPF*: not extended

In other fibrotic ILDs (chronic sarcoidosis, PPFE, and asbestosis), GGO is minimal or absent.

In patients with chronic history of fibrotic ILD, the onset of acute symptoms and widespread GGO on CT may suggest an accelerated phase of the disease, supervening heart failure edema, opportunistic infection (PJP/CMV), or drug reaction.

Kligerman SJ (2009) Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics 29(1):73

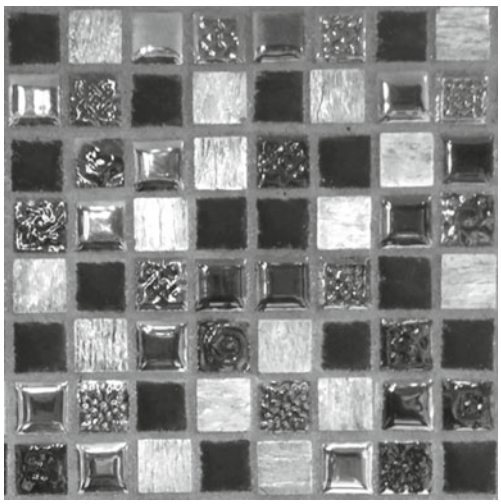
Hodnett PA (2013) Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med 15;188(2):141

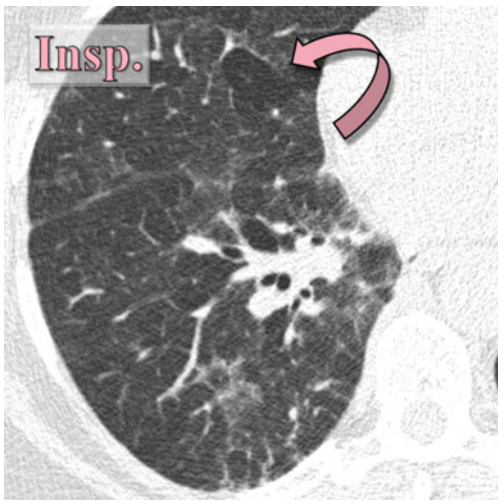
Maffessanti M, Dalpiaz G (2006) Diffuse lung diseases: clinical features, pathology, HRCT. Springer

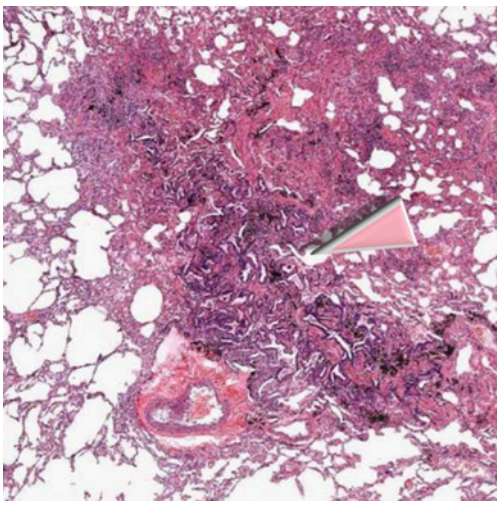
Lobular Air Trapping

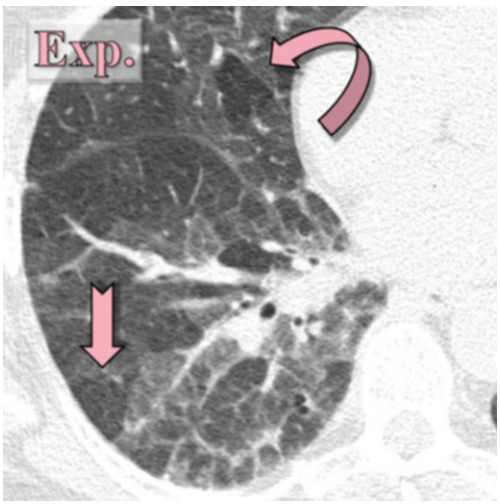
Areas of low attenuation (the so-called mosaic attenuation) with air trapping, more visible (⇳) or only evident (➡) on expiratory CT, indicate the presence of small airways obstruction. Lobular air trapping, in the context of a fibrosing ILD, appears often patchy and must be recognized in areas of relatively spared, non-fibrotic lung.

The histologic substrate of mosaic attenuation is bronchiolar obstruction due to fibrosis and/or inflammation (►). Irregularity of the bronchiolar wall with some impairment of the airflow is almost universal in scarred lung of any cause, whereas bronchiolar inflammation and/or fibrosis in non-fibrotic lung is less frequent and represents a more significant finding in the differential diagnosis.









Diseases with lobular air trapping:

- *HP*, *chronic*: 80 % of patients, often more visible in post-expiratory CT scans
- *Sarcoidosis*, *chronic*: most often results from small airways involvement by granulomas or fibrosis

Sometimes lobular air trapping may be present in UIP and NSIP (20–30 %).

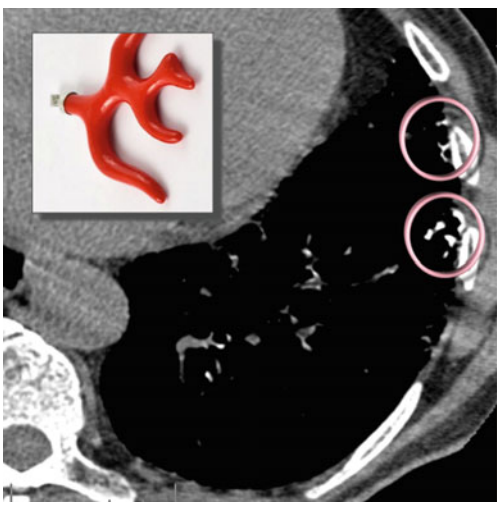
Silva CI (2007) Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. AJR Am J Roentgenol 188(2):334

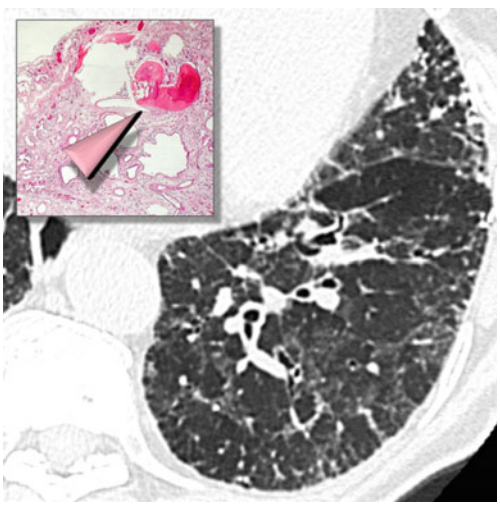
Jeong YJ (2014) Chronic hypersensitivity pneumonitis and pulmonary sarcoidosis: differentiation from usual interstitial pneumonia using high-resolution computed tomography. Semin Ultrasound CT MR 35(1):47

Disseminated Pulmonary Ossification

In patients with fibrosing ILDs, disseminated pulmonary ossification is more visible on HRCT using the appropriate window settings (mediastinal window) as tiny calcific dot-like or dendritic coral-like opacities in the fibrotic area in the periphery of the lung (○).

Pathologically, pulmonary ossification is characterized by the presence of mature bone in alveolar or interstitial spaces, either localized or disseminated throughout the lung (►). Although the exact pathogenesis of disseminated pulmonary ossification is unclear, the condition is postulated to be a reaction to chronic lung insult.





The presence of disseminated pulmonary ossification in fibrotic ILDs is not specifically described in most articles and only in patients with IPF (6 %).

Diffuse pulmonary ossification can be also idiopathic or associated with heart disease. Most cases had been diagnosed on autopsy.

Kim TS (2005) Disseminated dendriform pulmonary ossification associated with usual interstitial pneumonia: incidence and thin-section CT-pathologic correlation. Eur Radiol 15(8):1581

Peros-Golubicić T (2008) Diffuse pulmonary ossification: an unusual interstitial lung disease. Curr Opin Pulm Med 14(5):488

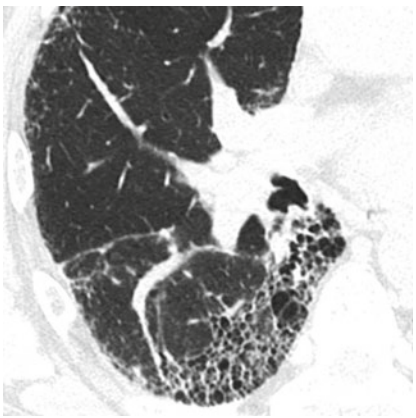
Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Fibrosing disease
Subpleural dot-like and curvilinear opacities, fine fibrosing reticulation, interface sign, traction bronchiolectases	Basal predominance, often symmetric, subpleural	Fibrosing GGO, traction bronchiectasis, honeycombing in advanced phase	Pleural thickening or plaques, sometimes calcified	**Asbestosis**
GGO, fine fibrosing reticulation, traction bronchiectases and bronchiolectases, volume loss	Basal predominance, often symmetric. Variously distributed in axial plane	Possible patchy consolidation and honeycombing	Esophageal dilation, signs of pulmonary arterial hypertension, pleural and pericardial thickening or effusion	**Collagen Vascular Diseases (CVD) – scleroderma**
GGO, fine fibrosing reticulation, traction bronchiectases and bronchiolectases, volume loss	Basal predominance, often symmetric. Variously distributed in axial plane	Possible patchy consolidation and honeycombing	Possible pericardial or pleural effusion and thickening	**Drug toxicity, chronic - Methotrexate**
Fibrosing reticulation, architectural distortion, variable volume loss, lobular air trapping	Mainly in the middle portion of the lungs; possible central peribronchovascular predominance	GGO, centrilobular low-density (subsolid) nodules, mild honeycombing, and traction bronchiectases and bronchiolectases	Enlargement of mediastinal lymph nodes, possible pulmonary arterial hypertension	**Hypersensitivity Pneumonitis (HP), chronic**
Honeycombing, fibrosing reticulation, interface sign, traction bronchiectases and bronchiolectases, volume loss	Basal peripheral predominance, “propeller blade” distribution from caudal to cranial. At times asymmetric	Disseminated pulmonary ossification	Enlargement of mediastinal lymph nodes, possible pulmonary arterial hypertension	**Idiopathic Pulmonary Fibrosis (IPF)**

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Fibrosing disease
GGO, fine fibrosing reticulation, traction bronchiectases and bronchiolectases, volume loss	Basal predominance, often symmetric. Variously distributed in axial plane with possible "subpleural sparing"	Possible patchy consolidation and honeycombing	Enlargement of mediastinal lymph nodes	**Non-Specific Interstitial Pneumonia (NSIP)**
Subpleural fibrotic coarse reticulation, volume loss, traction bronchiectases	Bilateral apical	Possible honeycombing	Marked irregular pleural thickening and "tags"	**PleuroPulmonary FibroElastosis (PPFE)**
Distorted linear opacities mainly at the periphery of hila that stretch the latter, volume loss, traction bronchiectases	Predominantly in the upper and middle zones	Perilymphatic nodules	Bilateral, symmetric mediastinal and hilar lymph node enlargement, often calcified	**Sarcoidosis, chronic**

Fibrosing Diseases

Radiology

Giorgia Dalpiaz
Sara Piciucchi



G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_6

Definition

Asbestosis is a pneumoconiosis that occurs secondary to the inhalation of asbestos fibers. Disease usually occurs approximately 20 years following the initial exposure.
Histologically, asbestosis is defined as an interstitial pulmonary fibrosis associated with the presence of intrapulmonary asbestos bodies or asbestos fibers. The earliest changes of fibrosis occur in the peribronchiolar region of the lobular core. As the fibrosis progresses, it involves alveolar walls and lobular periphery and interlobular septa. Visceral pleural thickening often overlies areas of parenchymal fibrosis.

☯ Pneumoconiosis

📖 Ross RM (2003) The clinical diagnosis of asbestosis in this century requires more than a chest radiograph. Chest 124:1120

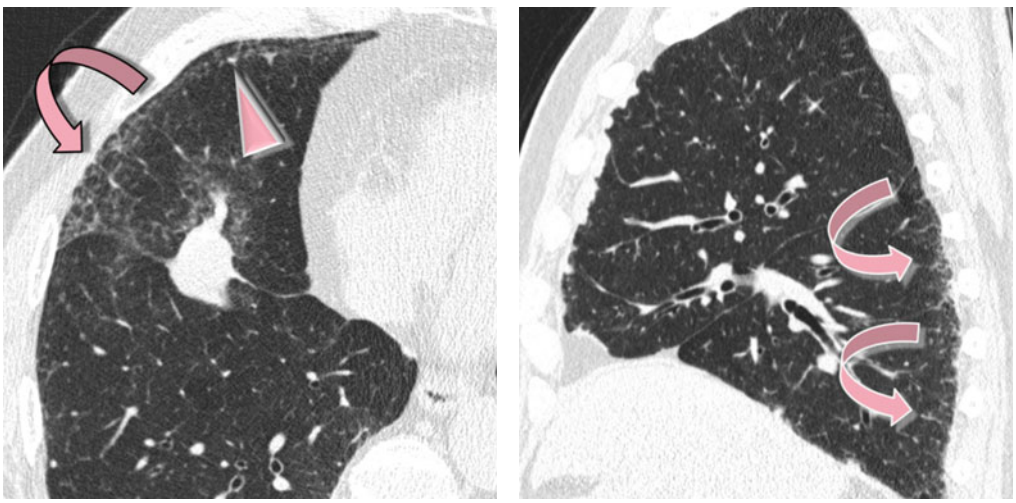
HIGH-RESOLUTION CT: HRCT

Key Signs

- In patients with early asbestosis, dot-like opacities are visible in the subpleural lung (►). Subpleural, confluent curvilinear opacities are also present. These correlate with the presence of peribronchiolar fibrosis extending to involve the contiguous airspaces and alveolar interstitium.
- Fine fibrosing reticulation such as intralobular interstitial thickening (☟).
- Irregular thickening of interlobular lines and irregular interfaces.
- Traction bronchiolectases.
- Architectural distortion.
- Parenchymal bands, with possible "Crow's foot" appearance (50–80 %).
- Subpleural lines.

Distribution

Basal predominance of pulmonary abnormalities. It is also characteristic for these lung abnormalities being most severe in the posterior lung and subpleural regions (sagittal image ☟). The abnormalities are usually bilateral and symmetric.



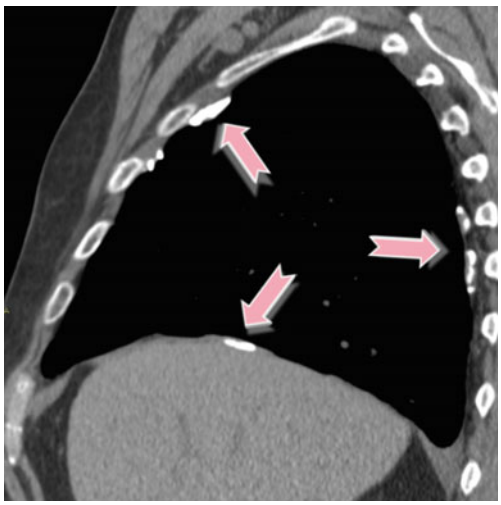
☝ CT scans obtained in a prone position may be useful for distinguishing normal increased opacity from dependent lung regions and mild fibrosis.

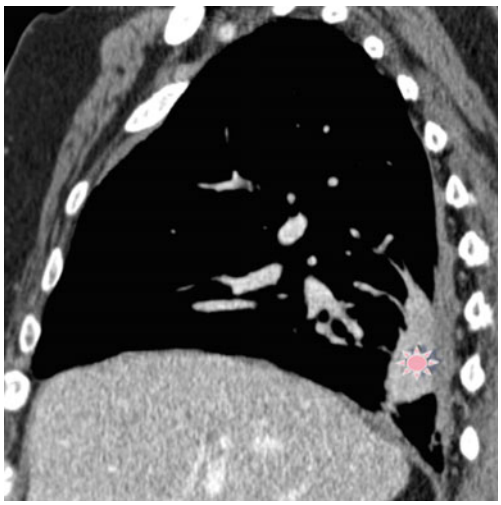
Ancillary Signs

- Ground-glass opacity (GGO), when present, is usually seen in association with reticulation (see the axial image above) and traction bronchiectases and reflects fibrosis. When seen in isolation, GGO correlates with the presence of mild alveolar wall and interlobular septal fibrosis or edema.

Non-parenchymal Signs

- Pleural thickening or 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 or in the costophrenic sinuses and tend to be arranged in a spiral pattern extending superoanterior to posteroinferior ("propeller blade" distribution). The presence of pleural plaques often lends support to the radiologic diagnosis of asbestosis. Pleural disease is often present (80 %). The diaphragmatic pleura is commonly involved in patients who have asbestos-related pleural disease.
- Rounded atelectasis (✸) is a form of peripheral lobar collapse that develops in patients with pleural disease and in 80 % of patients with asbestos exposure. It usually occurs in the subpleural, posterior, or basal region of the lower lobes. This lesion has oval morphology and is strictly adhering to a pleural plaque. It has a curvilinear tail, frequently referred to as the "comet tail sign". Volume loss of the involved area is also visible. The contrast enhancement of the "nodule" is homogenous. Rounded atelectasis is often unilateral (please also refer to Comet tail sign in the "Case-Based Glossary with Tips and Tricks").





It is important to distinguish rounded atelectasis from lung cancer, which has an increased incidence in asbestos-exposed individuals. For the differential diagnosis contrast-enhanced CT scan and CT-PET can be useful in making differential diagnosis. Because rounded atelectasis represents collapsed parenchyma, it appears vascularized (hyperdense) and with little SUV on CT-PET.

Course and Complications

- The early stage may progress to severe fibrosis with honeycombing and traction bronchiectases with complete destruction of the alveolar architecture.
- Pleuropulmonary malignancy may occur, with a period of latency of at least 20 years between the initial exposure to asbestos and the development of a pulmonary carcinoma or pleural mesothelioma.

HRCT findings of advanced asbestosis are similar to those seen in patients with IPF. However, when the lung fibrosis is associated with typical asbestos-related pleural abnormalities, the diagnosis of asbestosis may be suggested.

Chong S (2006) Pneumoconiosis: comparison of imaging and pathologic findings. Radiographics 26(1):59–77

Kim KI (2001) Imaging of occupational lung disease. Radiographics 21(6):1371

Definition

Collagen vascular disease (CVD) is a heterogeneous group of diseases, with a pleomorphic involvement of various organs or tissues, characterized by the presence of circulating autoantibodies. CVD can cause variety of ILDs, with an histology identical to the idiopathic interstitial pneumonias. The most common patterns include NSIP (the most frequent), UIP, OP, and LIP. The pattern of scleroderma, including also the pleuritic and vasculitis form, will be covered in this Chapter as the representative example of a fibrosing CVD. Based on international collaborative data, interstitial lung disease is considered as the most frequent cause of death in progressive systemic sclerosis (scleroderma).

CVD – progressive systemic sclerosis (PSS)

Other collagen vascular diseases which can induce a fibrosing alveolitis are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), CREST syndrome, Sjögren's syndrome, dermatomyositis–polymyositis (DM/PM), and mixed connective tissue disease (MCTD). Lung fibrosis is the most common pattern of abnormality, with NSIP pattern as much more common than UIP pattern (the so-called "secondary" NSIP or UIP pattern).

Tanaka N (2004) Collagen vascular disease-related lung disease: high-resolution computed tomography findings based on the pathologic classification. J Comput Assist Tomogr 28(3):351

HIGH-RESOLUTION CT: HRCT

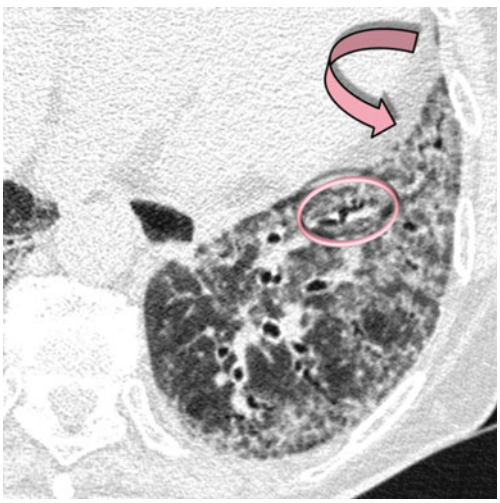
Key Signs

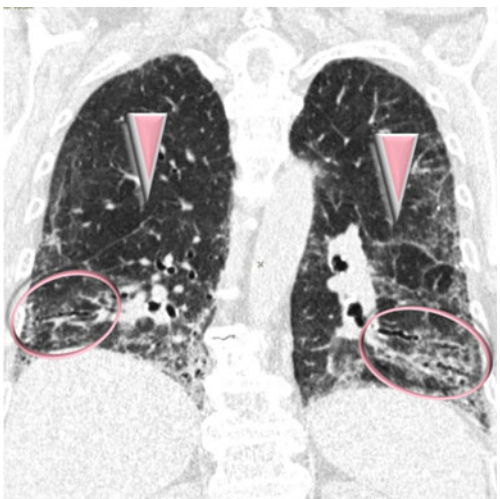
Findings reflect the frequent NSIP histological pattern (80 %) related to scleroderma and are characterized by:

- Confluent ground-glass opacity (GGO)
- Fine fibrosing reticulation (80–90 %) and irregular interface sign
- Traction bronchiectasis and bronchiolectasis (○)
- Volume loss of different entity associated to angulation and low-displacement of the fissure. The finding assumes a festooned course (►): possible traction effect of the mediastinal outline (⇘)

Distribution

Often symmetric lower lobe distribution. It is variously distributed in its axial plane (peripherally predominant or diffuse).





Predominant GGO often correlates with the presence of inflammation. On the other hand, the presence of a reticular pattern correlates with the presence of fibrosis on the pathologic specimens. However, keep in mind that GGO may also represent fibrosis in a context of fibrosing reticulation, traction bronchiectasis, and bronchiolectasis ("fibrotic GGO"). The lung fibrosis related with scleroderma is associated with a much better prognosis than that found in IPF, most likely due to predominant NSIP histology.

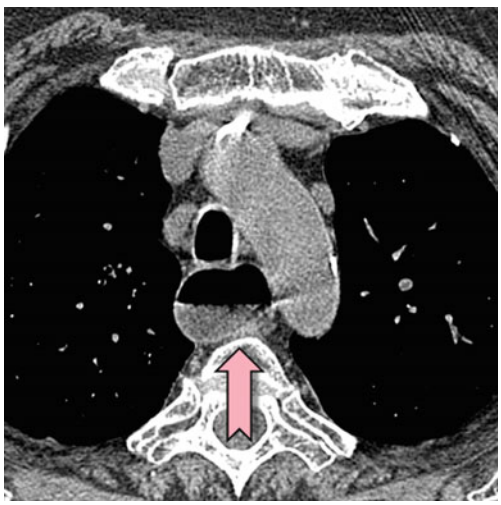
Lynch DA (2009) Lung disease related to collagen vascular disease. J Thorac Imaging 24(4):299

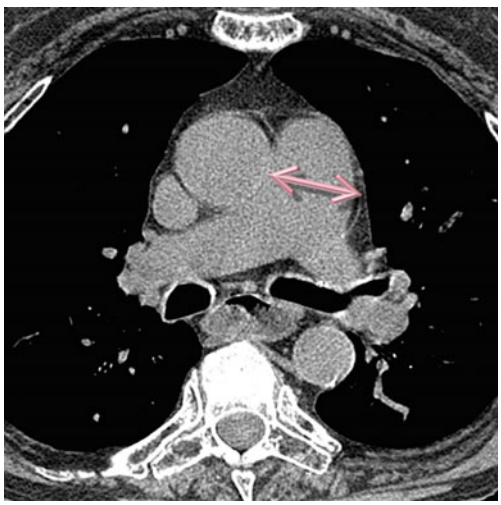
Ancillary Signs

- Honeycombing, when present, is usually mild. In patients with pathologic UIP pattern, honeycombing is more frequent.
- Possible small nodules have been reported in association to follicular bronchiolitis.
- Consolidation.

Non-parenchymal Signs

- Esophageal dilation is found in up to 80 % of cases (➡).
- Pulmonary arterial hypertension confirmed by cardiac catheterization is present in about 10–30 % of patients. It is also present especially in the limited form of scleroderma (CREST syndrome). Usually, it causes enlargement of the main and proximal pulmonary arteries (⟷); however, normal-sized pulmonary arteries do not exclude the diagnosis.
- Pleural thickening or effusion is not a common manifestation, and when it occurs, it is usually accompanied by parenchymal lung disease. Asymptomatic pericardial effusions commonly occur in scleroderma.
- Enlarged mediastinal nodes (60 %).





Parenchymal consolidation can be present in association with organizing pneumonia (OP) or aspiration pneumonia.

In the majority of these patients, the degree of pulmonary hypertension (and degree of pulmonary arterial involvement) is out of proportion to the extent of lung disease, because CVD directly affect the pulmonary vasculature.

Pleural or pericardial involvement is not present in IPF and therefore it results useful in the differential diagnosis of PPS from this disease.

Course and Complications

- In the majority of cases, the fibrosis progresses on long-term follow-up with worsening due to an increasing extent of GGO and honeycombing. The latter correlates with the decrease of DLCO.
- Pulmonary arterial hypertension is a leading cause of death related to progressive systemic sclerosis.
- Several studies have demonstrated an increased frequency of some malignancies.

Mayberry JP (2000) Thoracic manifestations of systemic autoimmune diseases: radiographic and high-resolution CT findings. Radiographics 20(6):1623

Capobianco J (2012) Thoracic manifestations of collagen vascular diseases. Radiographics 32(1):33

Definition

Initially administrated as antineoplastic drug, methotrexate (MTX) has been shown as an effective anti-inflammatory agent and is now widely used in nonneoplastic inflammatory conditions, including psoriasis, primary biliary cirrhosis, inflammatory bowel diseases, and, most commonly, rheumatoid arthritis. Methotrexate-induced pulmonary toxicity occurs in 5–10 % of patients and is unrelated to the duration of treatment or cumulative dose.

☯ MTX pneumonitis

☝ It should be noted that the same drug may cause different types of damage in the lung tissue, even in sequence. For example, methotrexate itself may cause pulmonary edema (PE), organizing pneumonia (OP), diffuse alveolar damage (DAD), and hypersensitivity pneumonitis (HP), although less frequently than chronic interstitial pneumonia such as nonspecific interstitial pneumonia (NSIP).

🕮 Bonniaud P (2014) Drug-induced interstitial lung diseases. Rev Prat 64(7):951
www.pneumotox.com

HIGH-RESOLUTION CT: HRCT

Key Signs

Histological NSIP pattern is the most common manifestation of MTX-induced lung disease appearing as:

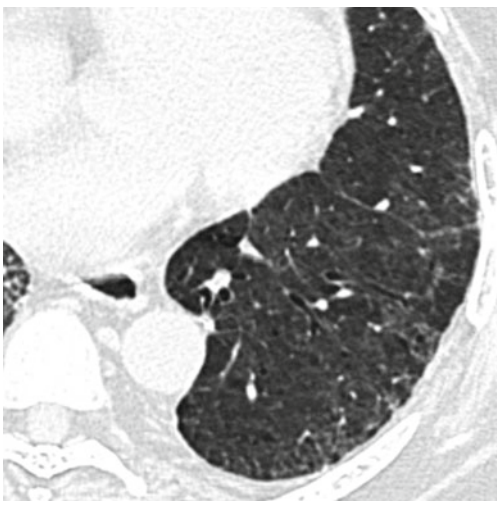
- Scattered or diffuse areas of ground-glass opacity (GGO)
- Fine fibrosing reticulation and architectural distortion (○)
- Traction bronchiectases and bronchiolectases
- Variable volume loss

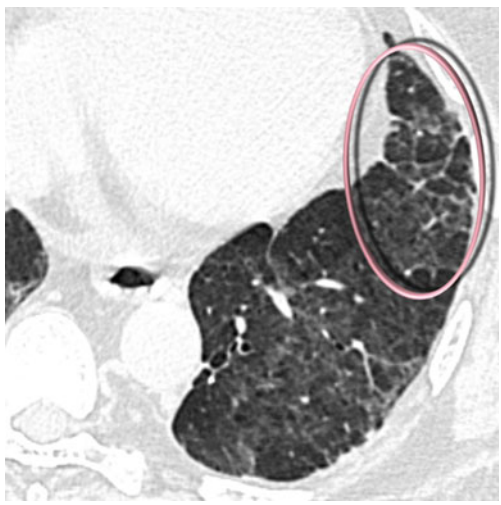
Occasionally, patients may develop a UIP pattern:

- Traction bronchiectases and honeycombing

Distribution

Lesions predominate in a basal distribution, bilateral





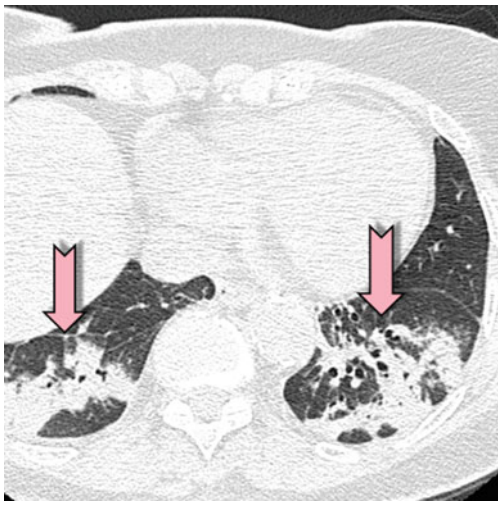
🕮 Arakawa H (2003) Methotrexate-induced pulmonary injury: serial CT findings. J Thorac Imaging 18(4):231
Erasmus JJ (2002) High-resolution CT of drug-induced lung disease. Radiol Clin North Am 40:61

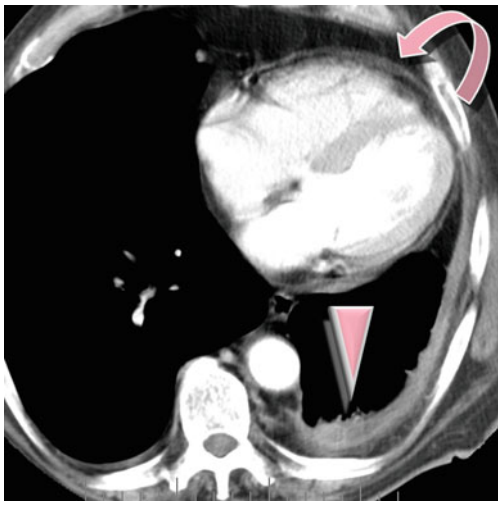
Ancillary Signs

- Patchy consolidations due to OP pattern (➡)
- Centrilobular nodules, tree-in-bud opacities, and bronchial dilatation

Non-parenchymal Signs

- Pericardial effusion (↬) and pleural thickening and effusion (►)





✓ Diagnostic criteria for methotrexate (MTX) pneumonitis may include (a) exposure to MTX preceding the onset of pulmonary symptoms, (b) exclusion of infection, (c) new or evolving infiltrates on HRCT, and (d) lung pathology consistent with drug-induced lung toxicity.

📖 Rossi SE (2000) Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics 20(5):1245

Piciucchi S (2011) Prospective evaluation of drug-induced lung toxicity with high-resolution CT and transbronchial biopsy. Radiol Med 116(2):246

Course and Complications

- Potentially reversible lesions (GGO, consolidation, nodules) may regress if the drug is discontinued, or in contrast there may be a progression toward honeycombing with traction bronchiectases.
- 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).

📖 Imokawa S (2000) Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 15(2):373–81

Definition

Hypersensitivity pneumonitis is an immunologically mediated inflammation of the lung parenchyma and airways in response to the repeated inhalation of organic antigens or low-molecular-weight inorganic molecules.

Chronic hypersensitivity pneumonitis is thought to develop slowly after a period ranging from months to years without discrete episodes of acute respiratory symptoms. This exposure is to an unrecognized persistent or intermittent, relatively low level of antigens.

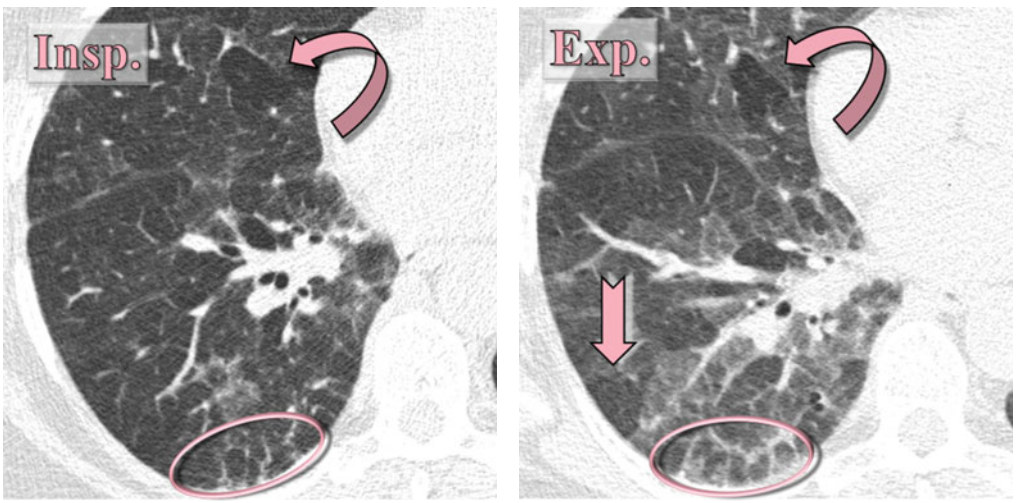
☯ HP, extrinsic allergic alveolitis (EAA)

📖 Hirschmann JV (2009) Hypersensitivity Pneumonitis: a historical, clinical, and radiologic review. Radiographics 29:1921

HIGH-RESOLUTION CT: HRCT

Key Signs

- Fibrosing reticulation is often present appearing as extensive intralobular and irregular interlobular septal thickening (please see axial images but also the coronal one below) (O).
- Architectural distortion also at fissural level, the latter appearing distorted and associated with interface sign (spine of roses) (►).
- Lobular air trapping in 80 % of patients in spared (non-fibrotic) lung due to the obliterative bronchiolitis so frequent in this disease (☟). It is easily visible on the expiratory high-resolution CT scans. Sometimes, air trapping may be visible only on expiratory CT scans (➡).



📖 Silva CI (2008) Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 246(1):288

Silva CI (2007) Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. AJR Am J Roentgenol 188(2):334

Distribution

Mainly in the middle portion of the lungs or fairly evenly throughout the lungs but with sparing of the extreme apices and bases; possible central peribronchovascular predominance. Sometimes, there may be a basal UIP-like distribution.

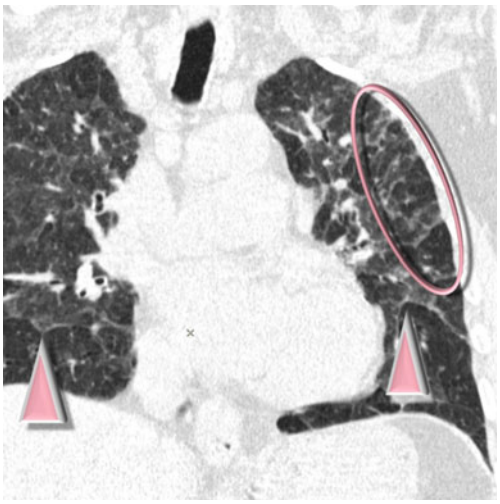
Ancillary Signs

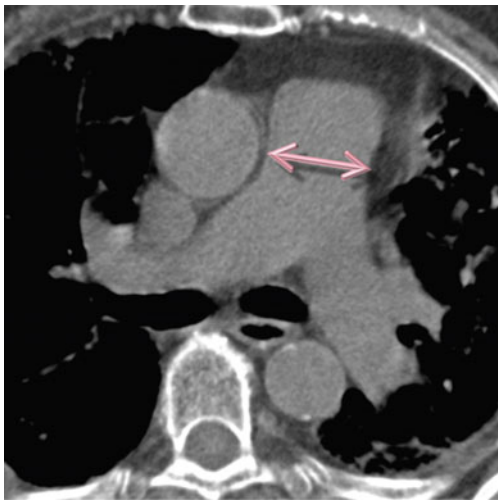
The vast majority of patients with chronic HP have superimposed signs of subacute disease:

- Ground-glass opacity (GGO)
- Centrilobular small low-density (subsolid) nodules (snowflake-like nodules)
- Mild honeycombing
- Traction bronchiectasis and bronchiolectasis

Non-parenchymal Signs

- Reactive nonspecific mild enlargement of mediastinal lymph nodes
- Possible pulmonary arterial hypertension (diameter of the main pulmonary artery > 28 mm ⟷)





Silva et al. observed no significant difference in the frequency of honeycombing in patients with chronic HP (64 %) and IFP (67 %). The different distribution may be the key point for the diagnosis.

High-resolution CT and pathologic features of chronic HP (CHP) frequently overlap with those of NSIP and UIP. Lobular areas of mosaic attenuation and centrilobular nodules together with non-basal distribution are the keys for differentiating chronic HP from IPF and NSIP.

Sahin H (2007) Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. Radiology 244(2):591

Course and Complications

- HRCT patterns, in particular severity of traction bronchiectasis and extent of honeycombing in CHP, have a high predictable value in mortality more than pulmonary function tests.
- Patients with chronic HP may develop acute exacerbation similar to those observed in IPF. The histologic findings of acute exacerbation of CHP consist of DAD or, less commonly, OP superimposed on histologic features of chronic HP or UIP. Prognosis is poor; the majority of patients die because of acute respiratory failure.

The HRCT findings of acute exacerbation of CHP are similar to those seen in acute exacerbation of IPF and consist of extensive bilateral ground-glass opacities with or without associated dependent areas of consolidation superimposed on underlying fibrosis.

Walsh SL (2012) Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. Eur Radiol 22(8):1672

Miyazaki Y (2008) Clinical predictors and histologic appearance of acute exacerbations in chronic hypersensitivity pneumonitis. Chest 134(6):1265

Definition

IPF is defined as a specific form of chronic progressive fibrosing interstitial pneumonia of unknown cause that occurs primarily in older adults. Prognosis is poor, with a median survival of less than 5 years. IPF is one of the major idiopathic interstitial pneumonias (IIP). Usual interstitial pneumonia (UIP) is the histopathological pattern of IPF. The term UIP has become so widely used as to often be used as a substitute even in clinical practice.

IPF, idiopathic usual interstitial pneumonia (UIP), cryptogenic fibrosing alveolitis (CFA)

In the updated American Thoracic Society–European Respiratory Society classification of the IIPs, the major entities have been preserved and grouped into (a) "chronic fibrosing IIPs": idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP); (b) "smoking-related IIPs": respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP); and (c) "acute or subacute IIPs": cryptogenic organizing pneumonia (COP) and acute interstitial pneumonia (AIP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

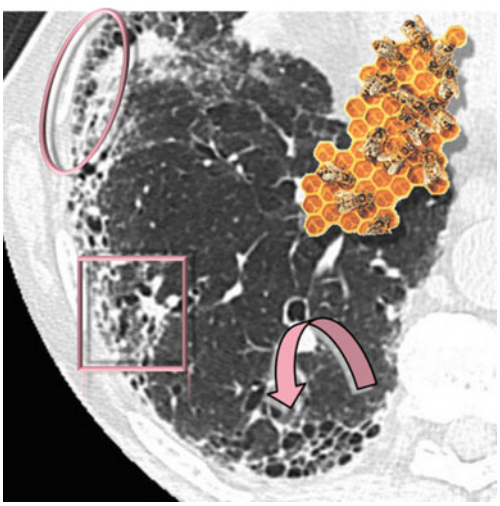
HIGH-RESOLUTION CT: HRCT

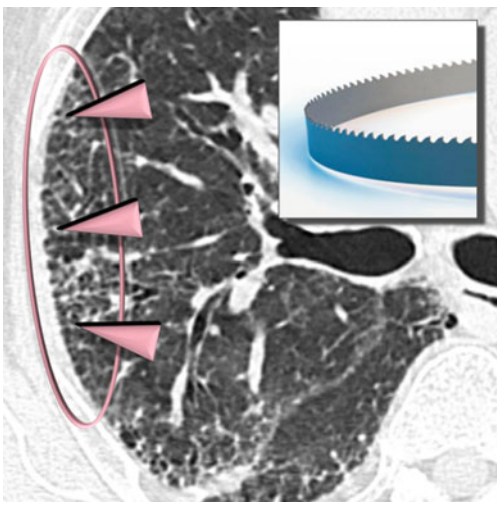
Key Signs

- Honeycombing ( ) is a strong predictor of histologic UIP because it is seen in most cases (about 70 %). However, it must be kept in mind that, in patients with fibrotic ILDs and absence of CT honeycombing, the probability of IPF exceeds 80 % in subjects over age 60 years, with one-third of total lung having fibrosing reticulation.
- Fibrosing reticulation is the most common radiographic finding in IPF, described in approximately 70–90 % of patients with biopsy-proven IPF. It appears as fine intralobular interstitial thickening with associated architectural distortion of involved areas ( ).
- Irregular interfaces between the lung and pulmonary vessels, bronchi, and pleural surfaces resembling the blame of saw or spines of rose (►).
- Traction bronchiectasis and bronchiolectasis ( ).
- Volume loss with angulation and downward displacement of the fissure which assumes a festooned course (please see the sagittal image below ➡).

Distribution

Patchy with prevalent basal and peripheral localization; "propeller blade" distribution from caudal to cranial (being predominantly posterior to anterior). The distribution may be asymmetric in as many as 25 % of cases.





The identification of honeycombing is not always straightforward, and in association with emphysema and traction bronchiectases, the agreement among observer can be relatively low. Indeed, it must be looked for carefully also in the coronal and sagittal reconstruction (please also refer to Honeycombing in the chapter "Fibrosing Pattern"). A confident CT diagnosis of UIP is not usually made unless honeycombing is depicted. However, according to several recent studies, investigators have suggested that subjects with typical clinical features and CT appearances of UIP, but without honeycombing, are highly likely to have UIP.

Raghu G (2011) An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183(6):788

Raghu G (2014) Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial. Lancet Respir Med 2(4):277

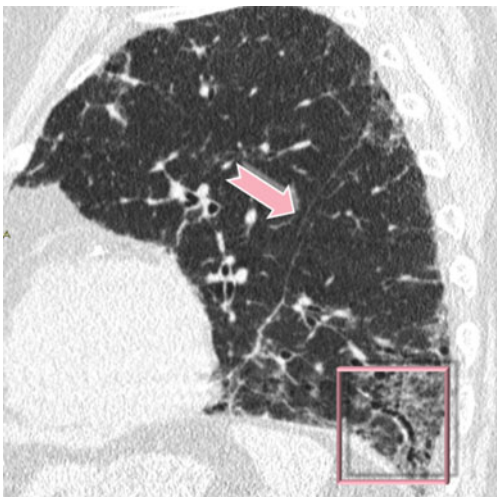
Sverzellati N (2015) American Thoracic Society-European Respiratory Society classification of the idiopathic interstitial pneumonias: advances in knowledge since 2002. Radiographics 35(7):1849

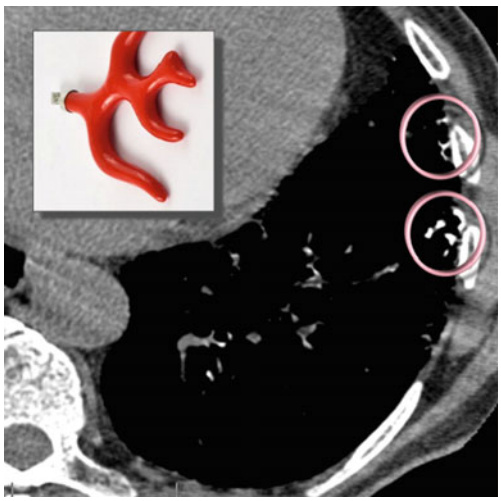
Ancillary Signs

- Ground-glass opacity may be present usually less extensive than reticular abnormalities. It often reflects the presence of microscopic fibrosis.
- Disseminated pulmonary ossification (6 %) appearing as tiny calcific dot-like or dendritic coral-like opacities in the fibrotic area in the periphery of the lung (○).
- Persistent peripheral nodule or mass is often due to associate neoplasm; it is more frequent in patients with associated emphysema.

Non-parenchymal Signs

- Mild reactive nonspecific enlargement of mediastinal lymph nodes (70–90 %); possible large adenopathy due to associate neoplasm
- Possible pulmonary arterial hypertension (diameter of the main pulmonary artery > 28 mm)





Course and Complications

- The clinical course of IPF is usually chronic. Serial HRCTs show increase in extent of the fibrosis over months or years. Reticulation often progresses to honeycombing, and honeycomb cysts increase in extent and size.
- An acute exacerbation of IPF is characterized by ground-glass opacification and/or consolidations (representing histologically diffuse alveolar damage or, less commonly, organizing pneumonia) superimposed on a background of fibrosis. This radiologic presentation can rapidly progress to death of the patient.

Acute exacerbation is essentially a diagnosis of exclusion. Differential diagnosis includes concomitant infection (such as *Pneumocystis* pneumonia or *Cytomegalovirus* infection), pulmonary edema, due to left ventricular failure, pulmonary embolism, and pneumothorax. IPF is associated with increased lung cancer risk. The cancer will often develop in the area of major fibrosis.

Lloyd CR (2011) High-resolution CT of complications of idiopathic fibrotic lung disease. Br J Radiol 84(1003):581

Definition

Nonspecific interstitial pneumonia (NSIP) is a chronic interstitial lung disease. It is subclassified into cellular and fibrosing. NSIP may be idiopathic being one of the major idiopathic interstitial pneumonias (IIPs). The median age of onset of symptoms is 40–50 years, which is more than 10 years younger than patients with IPF. Although the prognosis of idiopathic NSIP is heterogeneous, it is overall (reported as) better than that of IPF.

NSIP pattern is more frequently non-idiopathic, occurring as a pattern of collagen vascular disease (CVD), hypersensitivity pneumonitis (HP), and drug-induced lung disease. This form is called "secondary NSIP".

NSIP

The general term idiopathic interstitial pneumonias (IIPs) includes various diseases. The major IIPs include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), and cryptogenic organizing pneumonia (COP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

HIGH-RESOLUTION CT: HRCT

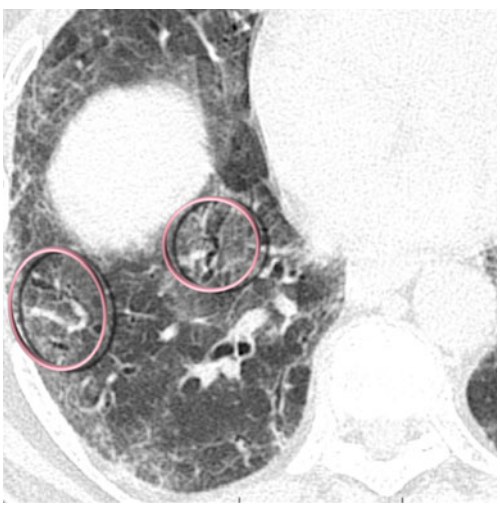
Key Signs

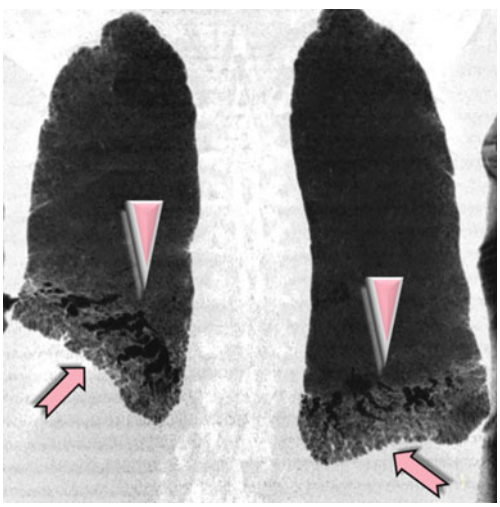
The CT features of idiopathic NSIP may vary according to the underlying proportion of inflammation (cellular component) and fibrosis:

- Wide-extent areas with ground-glass opacity (GGO) is the salient CT feature of NSIP mostly in patients with cellular NSIP; minimal traction bronchiolectases may coexist (○).
- Fine fibrosing reticulation and interfaces are often visible (80–90 %) largely in patients with fibrotic NSIP (➡).
- Traction bronchiectases or bronchiolectases (80–100 %), almost universal in patients with fibrotic NSIP (►) visible.
- Volume loss (70 %) in patients with fibrotic NSIP (downward displacement of the fissures and crowding of lower lobe bronchi and vessels).

Distribution

Often symmetric lower lobe distribution. NSIP is variously distributed in its axial plane (peripherally predominant or diffuse). The possible subpleural sparing can be helpful in distinguishing NSIP from UIP.





The different prevalence of GGO and reticulation in the various studies reflects the different prevalence of cellular and fibrotic NSIP or the timing of CT. In some cases of cellular NSIP, ground-glass opacity is present in the absence of traction bronchiectases and volume loss, and thus it likely represents areas of inflammation ("non-fibrosing" GGO). However, the majority of the patients with GGO also have other signs of fibrosis and may more frequently have fibrotic NSIP.

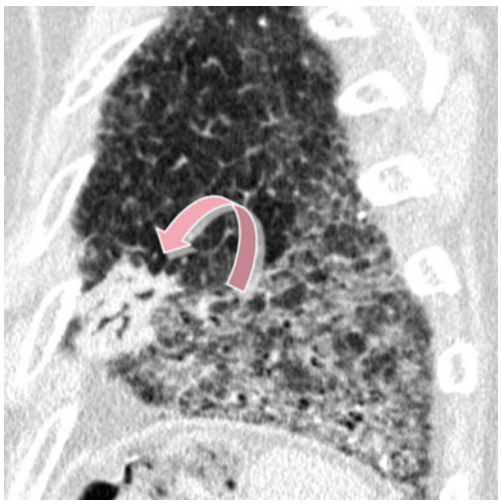
Kligerman SJ (2009) Nonspecific interstitial pneumonia: radiologic, clinical, and pathologic considerations. Radiographics 29(1):73

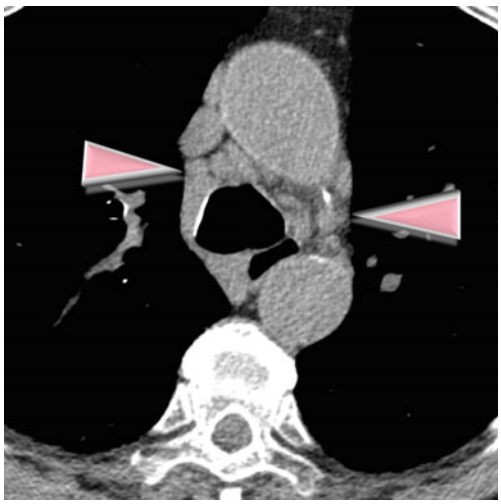
Ancillary Signs

- Chronic consolidation is often related to a component of associated organizing pneumonia (OP) (↭).
- The presence of honeycombing can occasionally be seen in fibrotic NSIP or it reflects foci of coexistent UIP.

Non-parenchymal Signs

- Nonspecific reactive mediastinal lymphadenomegaly (80%) correlates with the extent of disease (►).





Associated findings which may suggest a "secondary" NSIP due to collagen vascular disease include esophageal abnormalities, pleural or pericardial effusion, or thickening (please refer to CVD in this Chapter).

Course and Complications

- The extent of ground-glass attenuation may decrease with time, but the extent of reticular abnormality persists.
- The majority of patients with NSIP who show progression of fibrosis on follow-up maintain a CT pattern more suggestive of NSIP; however, a minority progress to a UIP pattern.
- Similarly to patients with IPF, patients with NSIP may develop the so-called acute exacerbation due to DAD or, less commonly, due to OP. It appears as rapidly developing extensive ground-glass opacities and/or airspace consolidation.

Silva CI (2007) Acute exacerbation of chronic interstitial pneumonia: high-resolution computed tomography and pathologic findings. J Thorac Imaging 22(3):221

Definition

Pleuroparenchymal fibroelastosis is a recently described rare condition listed among the rare idiopathic interstitial pneumonias (IIPs). It is an entity characterized by circumscribed elastotic fibrosis of the pleura and subjacent lung. Most cases are considered idiopathic although a variety of associated conditions have been described, including carcinoma treated with chemo- and/or radiotherapy, hematopoietic malignancies treated with chemotherapy and bone marrow transplantation, autoimmune diseases, inhalatory exposures, infections, gastrointestinal reflux disease, post-lung transplantation, and in coexistence with usual interstitial pneumonia (UIP). Familial cases have been described. Disease progression occurs in 60 % of patients, with death from the disease in 40 %.

PPFE

The general term idiopathic interstitial pneumonias (IIPs) includes various diseases. The major IIPs include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), and cryptogenic organizing pneumonia (COP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

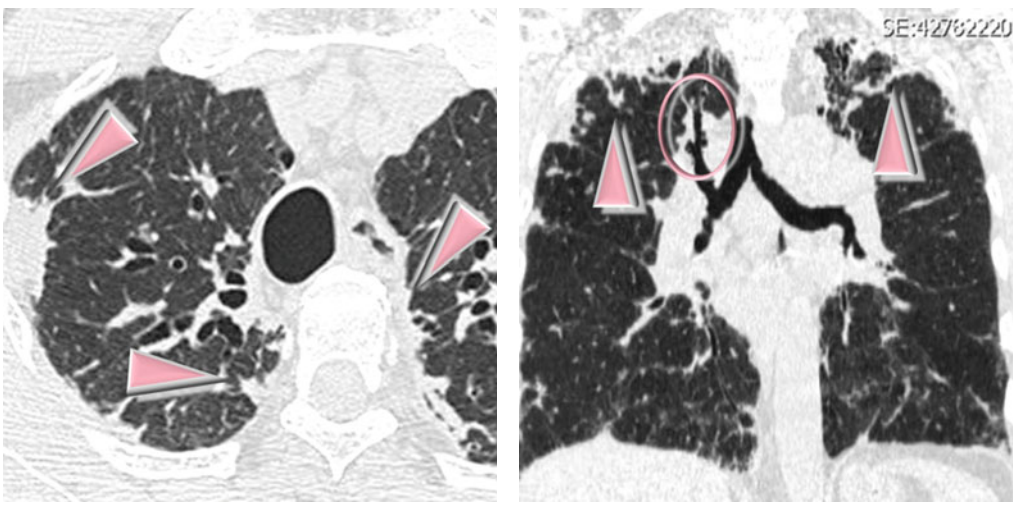
HIGH-RESOLUTION CT: HRCT

Key Signs

- Marked irregular pleural thickening and "tags" in the upper zones merging with fibrotic coarse reticulation in the subjacent lung (►)
- Upper-lobe volume loss with upward displacement of both fissures and tracheobronchial structures
- Architectural distortion
- Traction bronchiectases (O)

Distribution

Bilateral apical with upper-lobe volume loss. The hila tend to be retracted upward. The lower pleural-pulmonary zones are less involved or spared.



Radiological and histological features of PPFE may overlap with disorders that mainly involve the upper lobes: collagen vascular diseases (particularly ankylosing spondylitis), fibrotic sarcoidosis, and chronic hypersensitivity pneumonitis (HP) and apical caps. The latter may be difficult to distinguish from PPFE and probably the difference in mainly quantitative.

Frankel SK (2004) Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. Chest 126(6):2007

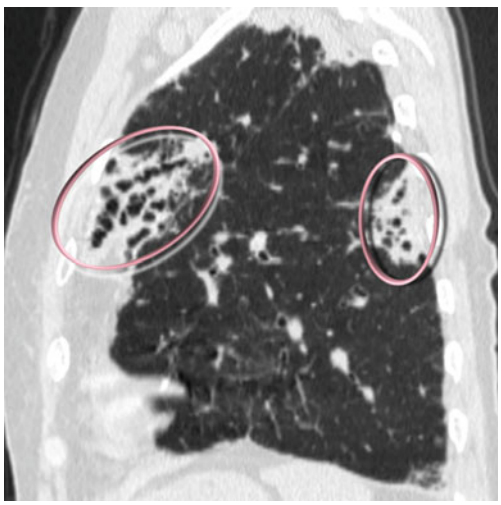
Watanabe K (2013) Pleuroparenchymal fibroelastosis: its clinical characteristics. Curr Respir Med Rev 9:299

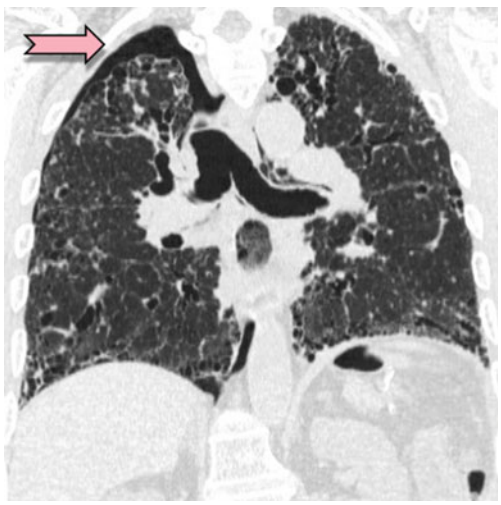
Ancillary Signs

- Honeycomb remodeling that may signify coexistent UIP

Non-parenchymal Signs

- Pleural thickening
- Uni- (➡) or bilateral spontaneous pneumothorax complicates the disease course in approximately 30 % of cases and can occur at presentation or during the course of the disease; possible pneumomediastinum.





Piciucchi S (2011) High resolution CT and histological findings in idiopathic pleuroparenchymal fibroelastosis: features and differential diagnosis. Respir Res 12:111

English JC (2015) Pleuroparenchymal fibroelastosis: a rare interstitial lung disease. Respirol Case Rep 3(2):82

Course and Complications

- In about 60 % of patients with PPFE, the clinical course is progressive despite treatment.
- In about 40 % PPFE progresses rapidly, with a poor prognosis.

Kusagaya H (2015) Co-occurrence of pneumoperitoneum and pneumothorax in a patient with pleuroparenchymal fibroelastosis. Am J Respir Crit Care Med 191(10):120

Noh HJ (2014) Idiopathic pleuroparenchymal fibroelastosis presenting in recurrent pneumothorax: a case report. Tuberc Respir Dis 77(4):184

Definition

Sarcoidosis is a multisystemic disorder which may affect almost any organ. It is characterized by the histologic presence of non-caseous epithelioid cell granulomas. Thoracic involvement is relatively common. Thoracic radiologic abnormalities are seen at some stage in approximately 90 % of patients, and an estimated 20–50 % develop chronic lung disease leading to pulmonary fibrosis.

☯ Stage IV sarcoidosis, fibrosing sarcoidosis

📖 Abehsera M (2000) Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 174(6):1751

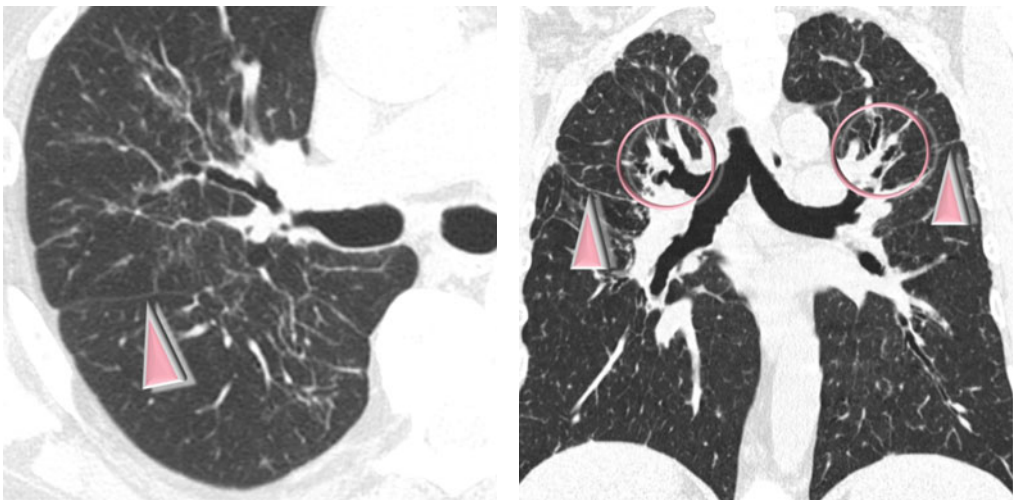
HIGH-RESOLUTION CT: HRCT

Key Signs

- Distorted linear opacities of irregular thickness, mainly on periphery of hila (25 %) which stretch the latter with displacement of the main and upper-lobe bronchi (tug of war aspect)
- Distortion and displacement of the fissures (►) which indicate loss of volume of the upper lobes
- Bronchial irregularity with traction bronchiectases (O)

Distribution

Predominantly in upper and middle zones with volume loss; predominant central bronchovascular distortion



✓ The distinction of fibrosing sarcoidosis from other diseses with upper zone distribution such as chronic HP and PPFE is mandatory. The presence in sarcoidosis of bilateral, symmetric, hilar and right paratracheal lymph node enlargement, often calcified, is the key for the differential diagnosis (please see the coronal CT image below with mediastinal window).

📖 Valeyre D (2014) Advanced pulmonary sarcoidosis. Curr Opin Pulm Med 20(5):488

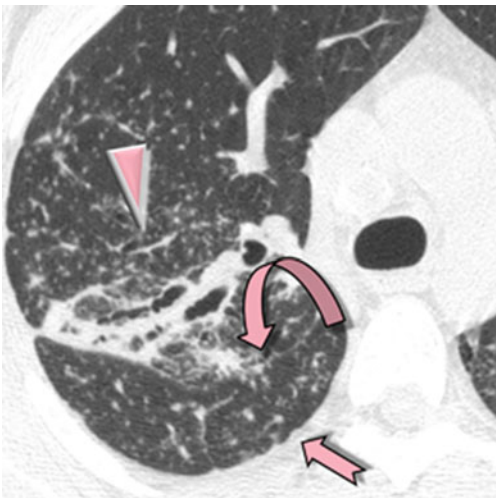
Jeong YJ (2014) Chronic hypersensitivity pneumonitis and pulmonary sarcoidosis: differentiation from usual interstitial pneumonia using high-resolution computed tomography. Semin Ultrasound CT MR 35(1):47

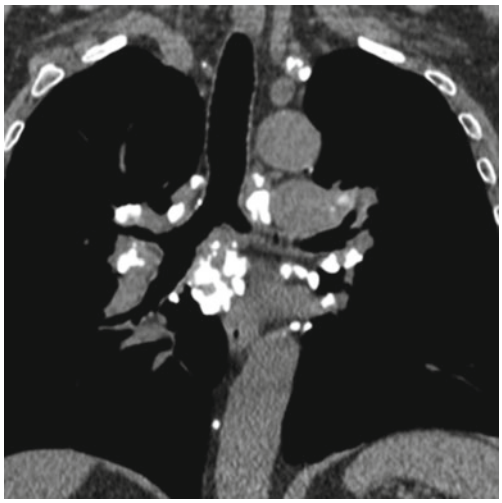
Ancillary Signs

- Small solid nodules with well-defined margins, distributed along the bronchovascular bundles (►), the visceral pleura (➡), and the fissures (⇨) (perilymphatic distribution – avid of pleura). Keep in mind that perilymphatic nodules may sometimes be difficult to distinguish from interface sign.
- Possible mosaic attenuation results from small airway involvement by granulomas or fibrosis.

Non-parenchymal Signs

- Bilateral, symmetric mediastinal and hilar and right paratracheal lymph node enlargement, often calcified.
- Enlargement of main pulmonary artery and right ventricle related to pulmonary arterial hypertension. Pulmonary hypertension is suspected on CT when the diameter of the main pulmonary artery is greater than 29 mm or when the ratio of the diameters of the main pulmonary artery to the ascending aorta is greater than 1.





Perilymphatic nodules and calcified lymph nodes represent a crucial keypoint in the diagnosis. The occurrence of lymph node calcification is closely related to the duration of disease (in 3 % after 5 years and in 20 % after 10 years). The calcifications may have an amorphous, punctate, popcorn-like, or eggshell-like appearance. Eggshell-like calcifications may also be seen in silicosis, and the other patterns of lymph node calcification in sarcoidosis may be indistinguishable from those seen in tuberculosis and histoplasmosis.

Patients with end-stage sarcoidosis may uncommonly develop a UIP-like pattern; however, sarcoidosis should be suspected if the cysts are large.

Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30(6):1567

Spagnolo P (2014) Imaging aspects of the diagnosis of sarcoidosis. Eur Radiol 24(4):807

Course and Complications

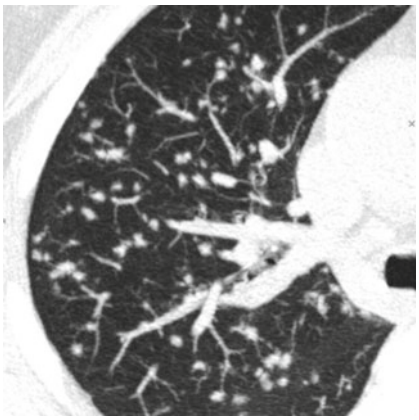
- Progressive fibrosis leads to mass-like opacities of the parahilar region.
- Cavitation is seen in an estimated 10 % of patients with end-stage disease. Most cavities observed on chest radiographs and CT images are actually bullae and blebs.
- Mycetomas may develop inside preexisting bullae and cysts (10 %) typically in the upper lobes due to chronic pulmonary aspergillosis.

The other diseases which commonly result in conglomerate masses of fibrosis with or without traction bronchiectases are silicosis, tuberculosis, and talcosis.

Koyama T (2004) Radiologic manifestations of sarcoidosis in various organs. Radiographics 24(1):87

Nodular Pattern

Radiology	**Giorgia Dalpiaz**
Pathology	**Alessandra Cancellieri**

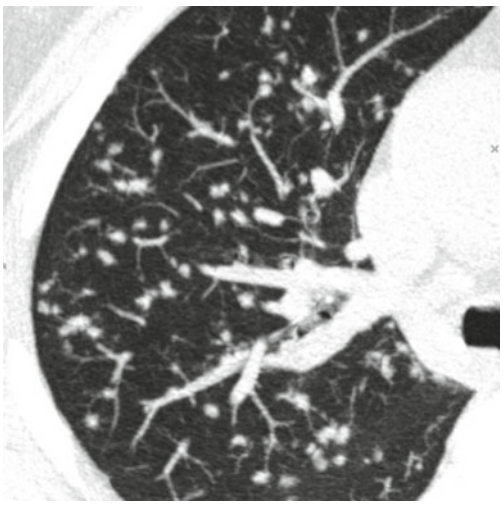


G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_7

NODULAR PATTERN

Definition

Nodular pattern is defined by the presence of multiple roundish pulmonary opacities ranging in diameter from 2 to 10 mm. Morphology, density, and distribution of the nodules depend on the route of arrival and the modality of spread.
Nodular pattern may be due to a variety of diseases arising directly in the lung or arriving via the bloodstream down to small vessels where they develop concentrically or via the bronchi.



The Nomenclature Committee of the Fleischner Society has recommended that the term “micronodule” be reserved for opacities less than 3 mm in diameter.

The signs of nodular pattern may be:

- Low-density (subsolid) nodules
- High-density (solid) nodules
- Cavitated nodules
- Calcified nodules
- Nodules with halo sign

The prevalent distribution of the nodules together with the presence of non-parenchymal signs may be helpful for the diagnosis of a specific disease (please see the tables in this chapter).

As well as in nodular diseases, in which this pattern is predominant, there are other diseases in which nodules may be found, albeit less important or sporadic. They are therefore described in the corresponding chapters.

Boitsios G (2010) Diffuse pulmonary nodules. AJR Am J Roentgenol 194(5):W354

Chou SH (2013) Cheerio sign. J Thorac Imaging 28(1):W4

Gruden JF (1999) Multinodular disease: anatomic localization at thin-section CT – multireader evaluation of a simple algorithm. Radiology 210(3):711

Hansell DM (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

Okada F (2007) Clinical/pathologic correlations in 553 patients with primary centrilobular findings on high-resolution CT scan of the thorax. Chest 132(6):1939

Pinto PS (2004) The CT halo sign. Radiology 230(1):109

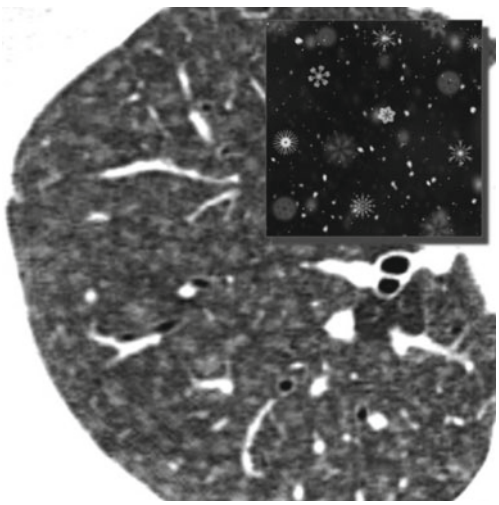
Raoof S (2006) Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm. Chest 129(3):805

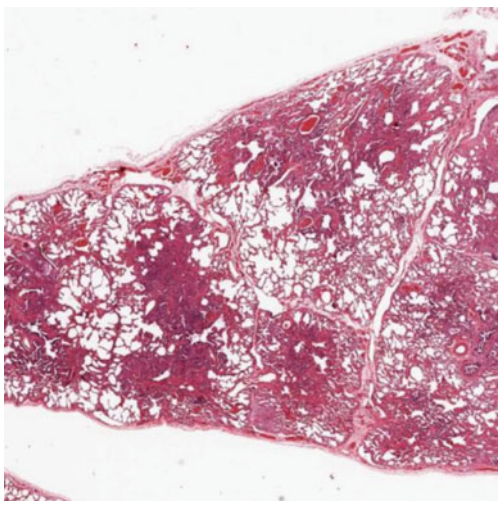
NODULAR SIGNS

Low-density (subsolid) nodules

With a snowflake aspect (fluffy nodules), sometimes tiny and hence difficult to recognize, these low-density (subsolid) nodules may coalesce, resulting in the appearance of more or less extensive, patchy GGO. They are commonly seen in patients with diseases primarily affecting small airways and surrounding areas. The low-density CT aspect is due to minimal thickening of the peribronchiolar interstitium or partial filling of the peribronchiolar alveoli (e.g., subacute hypersensitivity pneumonitis; please see the pictures below). Both conditions are below the CT spatial resolution, and thus the common final effect is a focal low-density lesion. The ill-defined margins are due to a progressive reduction of interstitial or alveolar involvement extending away from the centrilobular area to the periphery.

Snowflake nodules, fluffy nodules, nodular GGO, ill-defined nodules, airspace nodules





Frequent diseases with low-density (subsolid) nodules:

- *Hypersensitivity pneumonitis* (*HP*), *subacute*: it is the prototype disease of the snowflake nodules which are several and centrilobular (please see the figures above). The associated key sign for the diagnosis is the coexistence of sporadic lobular areas of air trapping appearing as patches of black lung. Another significant diagnostic finding, whenever present, is the so-called headcheese sign (please also refer to headcheese sign in chapters "Alveolar Pattern" and "Case-Based Glossary with Tips and Tricks"). Often the patient is a nonsmoker.
- *Respiratory bronchiolitis-interstitial lung disease* (*RB-ILD*): in young heavy smokers, the presence of very tiny centrilobular snowflake nodules predominantly in the upper zones is suggestive for RB-ILD. These features are often in combination with areas of GGO and moderate centrilobular emphysema.

Rare diseases with Low-density (subsolid) nodules:

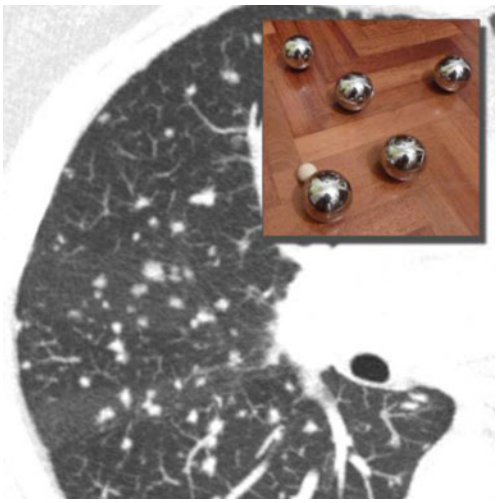
- *Follicular bronchiolitis* (*FB*): in patients with collagen vascular disease (CVD), the presence of centrilobular tiny nodules associated with nodules mimicking a tree-in-bud pattern (peribronchiolar distribution) and cysts is suggestive for FB.
- *Hemorrhage* (*e.g.*, *in endometriosis*): the snowflake nodules are scattered and angiocentric, associated with patchy ground-glass opacities. Predictably, these lesions may vary in size during the menstrual cycle and may disappear after the cessation of menstruation.
- *Hot tub lung* (*HTL*): the signs overlap with the reported findings of subacute HP. The key for the diagnosis is the possible coexistence of tiny, randomly distributed solid nodules with, of course, an anamnestic data of hot tub exposure.
- *Metastatic pulmonary calcification* (*MPC*): in asymptomatic patients with hyperparathyroidism, the presence of centrilobular fluffy nodules (ground-glass nodular opacities) also containing foci of calcification mainly in the upper zones is suggestive for MPC. The frequently associated calcifications in the vessels of the chest wall support the diagnosis.

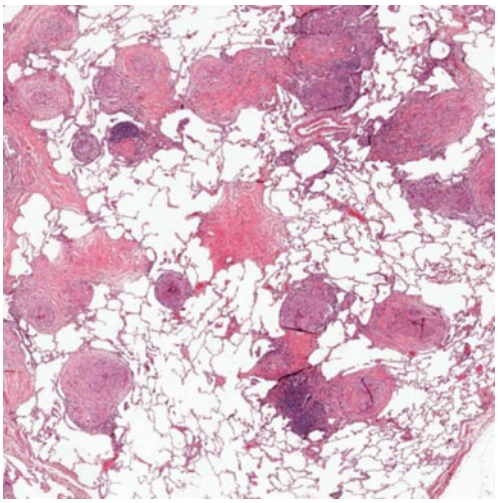
- *Pulmonary capillary hemangiomatosis* (*PCH*): in young adults, the coexistence of widespread tiny snowflake nodules and lobular areas of ground-glass opacity with signs of pulmonary arterial hypertension is suggestive for PCH.

High Density (solid) Nodules

Being solid, these nodules obscure the edges of the vessels or other adjacent structures. Usually due to diseases primarily affecting the interstitium, they may coalesce in larger opacities or pseudoplaques. Regular or lobulated contours and even shaggy profiles are possible especially in diseases with a fibrotic component (e.g., sarcoidosis; please see the pictures below).

Interstitial nodules, ball-like nodules





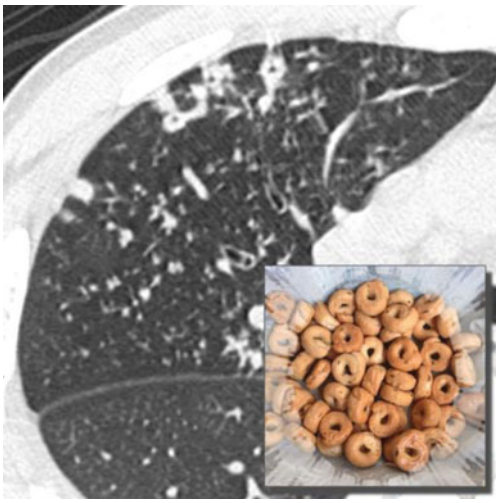
Diseases with solid nodules:

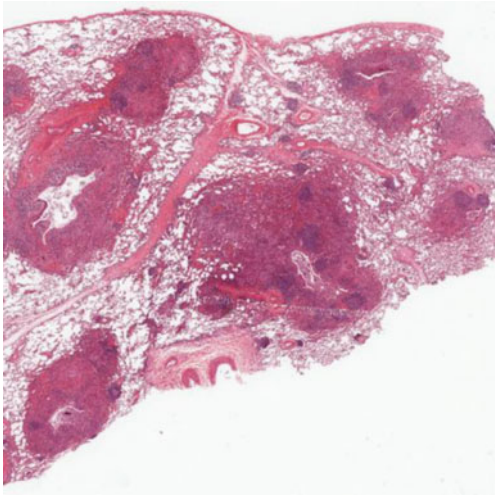
- *Metastases*, *hematogenous*: random solid nodules with well-defined margins and often prevalent at the bases and not uniform in diameter; crucial for the diagnosis are the other possible associated features of hematogenous diffusion such as pleural involvement and bone lesions, the latter often visible only with bone CT window.
- *Tuberculosis*, *miliary*: numerous random tiny solid nodules, which are uniform in size; other associated findings which may possibly suggest the diagnosis include cavitation and signs of bronchogenic spread of the disease with tree-in-bud pattern; crucial also is the possible coexistence of hematogenous extrapulmonary involvement (please see the table in chapters "Alveolar Pattern" and "Alveolar Diseases" >Infection, chronic TB).
- *Sarcoidosis*: lymphatic, with well-defined or shaggy margins and prevalent in the upper lobes (see the images above); crucial for the diagnosis is the coexistence of symmetrical hilar and mediastinal lymph nodes, also partially calcified.
- *Silicosis*: lymphatic solid nodules often have well-defined margins, sometimes with calcifications; the nodules mainly involve the upper and posterior lung zones; crucial of course is the anamnesis of pneumoconiosis.
- *Lymphocytic interstitial pneumonia* (*LIP*): the possible association of subpleural solid nodules with well-defined margins with sporadic cysts and ground-glass opacities is suggestive of LIP in patients with immunodeficiency syndromes and autoimmune disorders.
- *Langerhans cell histiocytosis* (*LCH*), *early*: in smokers, the presence in the upper lobes of solid centrilobular, often cavitated, nodules, with possible shaggy margins and thick-walled cysts, is suggestive for LCH in florid phase.
- *Epithelioid hemangioendothelioma* (*EHE*): multiple, usually bilateral, small solid nodules, mainly distributed in the subpleural space similar to metastatic lesions. EHE mainly affects young women and is usually asymptomatic.

Cavitated Nodules

Cavitated nodules relate to pulmonary nodules with a central lucent cavity as seen on CT. It is due to the proliferation of (both neoplastic and nonneoplastic) cells around an airway or to necrosis (e.g., tuberculosis; please see the pictures below). They are named Cheerios after their resemblance to the breakfast cereals Cheerios.

Cheerio sign, Tarallucci sign (please also refer to the "Case-Based Glossary with Tips and Tricks")





Diseases with "cavitated" nodules:

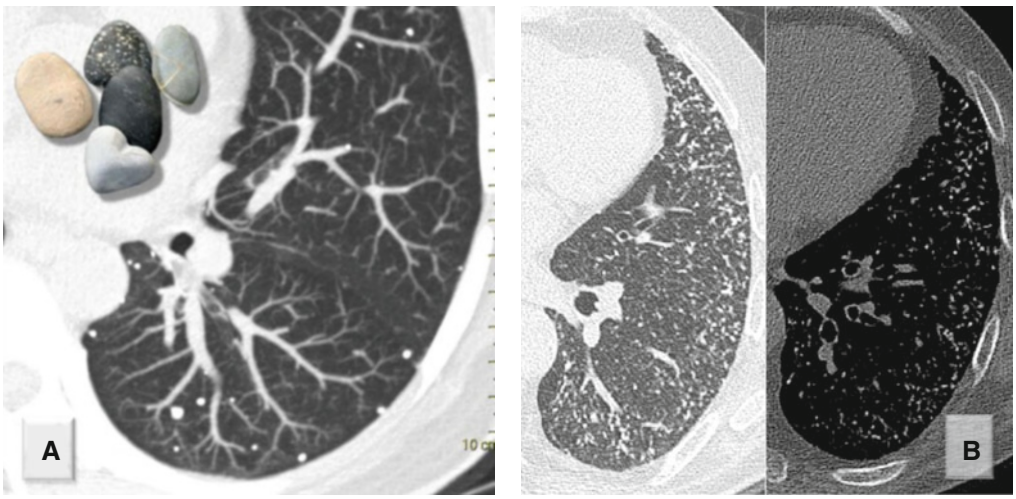
- *Infection*: often due to mycobacterial (see the figures above) or fungal infections; the presence of tree in bud due to bronchial diffusion and both cavitated consolidation and lymphadenomegaly may be crucial for the diagnosis.
- *Neoplasm* (*often adenocarcinoma*, *primary or metastatic*): cavitated nodules are often associated with patchy of unresolving consolidations and GGO. Mucinous adenocarcinomas arising elsewhere, such as those from the gastrointestinal and genitourinary systems, can also present with the Cheerio sign when metastasized to the lungs (please also refer to Cheerio sign in the "Case-Based Glossary with Tips and Tricks").
- *Langerhans cell histiocytosis* (*LCH*): in smokers, the presence of solid Cheerio nodules and cysts predominantly in the upper lobes is suggestive of LCH.
- *Necrobiotic rheumatoid nodules*: sporadic cavitated nodules can occur in a patient with rheumatic disease.

Granulomatosis with polyangiitis (former Wegener's granulomatosis) and septic embolism due to bacteria may appear as "cavitated" macronodules.

Calcified Nodules

Calcified pulmonary nodules are a specific group of hyperdense nodules with density similar to that of stone or bone on CT. The most common causes of nodular calcification are granulomas, usually in the healing phase to infections, often appearing as sporadic, random, and calcified nodules (e.g., chicken pox pneumonia; please see the image A below). Calcified nodules may be numerous (e.g., pulmonary alveolar microlithiasis, image B). Pathogenesis: dystrophic calcification follows caseation, necrosis, or fibrosis. It may also be the consequence of calcium deposition in normal pulmonary parenchyma.

Stonelike nodules



Diseases with calcified nodules:

- *Healed infection* (*e.g.*, *chicken pox pneumonia*, image A above): small (1–3 mm) scattered stonelike nodules with random distribution and feeding vessel sign, predominantly in the upper lobes. Calcifications can also be observed inside the lymph nodes.
- *Healed TB*: in postprimary TB, sporadic stonelike nodules prevail in the upper lobes and are usually associated with fibrotic distortion and calcification of hilar/mediastinal nodes.
- *Silicosis and coal workers' pneumoconiosis* (*CWP*): multiple, small, densely calcified nodules in mid and upper zones associated with nodal eggshell calcification. These calcified nodules are commonly seen with massive fibrosis. The anamnesis of an occupational or environmental prolonged exposure to the inhalation of silica particles is crucial.
- *Amyloidosis*: calcified nodules are present in up to 50 % of cases, often associated with smooth and nodular interlobular septal thickening (beaded septum sign). Hilar and mediastinal lymphadenomegaly with calcification is common in AL (amyloid light-chain) form of amyloidosis.
- "*Metastatic*" *pulmonary calcification* (*MPC*): it is the consequence of calcium deposition in normal pulmonary parenchyma in patients with primary and secondary hyperparathyroidism, often asymptomatic. HRCT findings are characterized by centrilobular, fluffy, ground-glass nodular opacities which may contain foci of calcification. Typically, MPC is most marked in the upper lobes.
- *Chronic hemorrhagic conditions* (*e.g.*, *idiopathic pulmonary hemosiderosis*): it is an uncommon cause of alveolar hemorrhage that occurs predominantly in infants and young adults. Secondary hemosiderosis can occur, due to mitral stenosis. HRCT shows dense centrilobular nodular opacities due to recurrent hemorrhage.
- *Pulmonary alveolar microlithiasis* (image B above): it is characterized by diffuse sandlike calcifications within the alveoli. Characteristic HRCT findings consist of innumerable tiny sandlike calcified micronodules which tend to merge throughout both lungs. Other findings include calcified interlobular septa and small subpleural cysts.

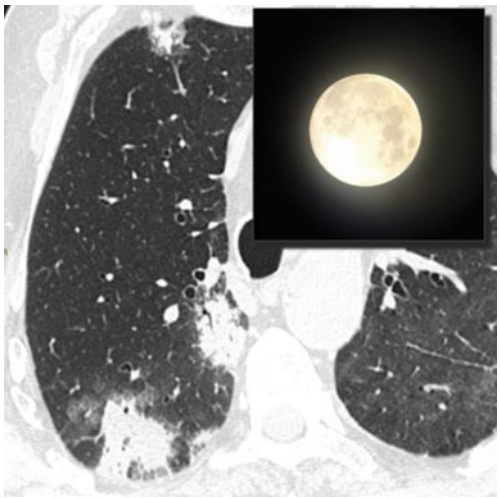
Multiple dense nodular opacities are rarely seen in siderosis, stannosis, and baritosis, in which iron, tin, and barium, respectively, are deposited in the lungs. In siderosis, nodular opacities are less dense and less profuse than those in silicosis. HRCT shows extremely dense opacities due to barium aspiration in baritosis, usually located in the basal segments of the lower lobes.

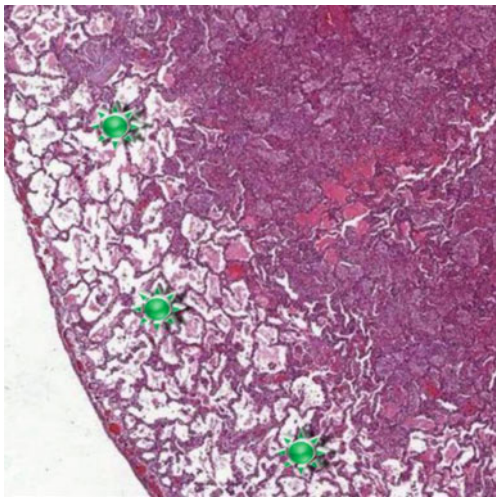
Calcified metastases appear as large calcified nodules. Calcification in pulmonary metastases is rare and can result from either sarcomas or carcinomas (mucin-producing carcinomas, thyroid carcinomas, and

treated metastatic choriocarcinomas). Osteosarcoma may lead to multiple, calcified parenchymal and pleural metastases.

Nodules with Halo Sign

The halo sign is a CT finding of ground-glass opacity surrounding a nodule or mass. The halo sign has been related to a hemorrhagic or nonhemorrhagic material partially filling the surrounding alveoli (e.g., in organizing pneumonia – OP, ✸). It may also be due to tumoral perinodular lepidic growth.
Please also refer to halo sign in the "Case-Based Glossary with Tips and Tricks."





Infection Diseases

- *Fungi*, *viruses*, *bacteria*, *mycobacteria*, *and parasites*: areas of consolidation and GGO may coexist, also cavitated.

Noninfectious

- *Hemorrhage due to endometriosis*: in young women with hemoptysis, the presence of scattered small random nodules with halo sign, snowflake nodules, and patchy GGO during menstruation is suggestive of catamenial pulmonary endometriosis.
- *Organizing pneumonia* (*OP*) (see figures above): macronodules and peripheral consolidation coexist, often basal.

Neoplastic Diseases

- *Haemorrhagic metastases*: in patients with hemoptysis and random solid nodules with halo sign, a neoplastic etiology may be considered, in particular due to angiosarcoma, choriocarcinoma, osteosarcoma, and renal cell carcinoma.
- *Nonhemorrhagic metastases*: they can represent metastases of adenocarcinoma of the lung, digestive tube, or pancreas. Halo sign is often secondary to perinodular neoplastic spread into the lung along the intact alveolar walls (lepidic growth).

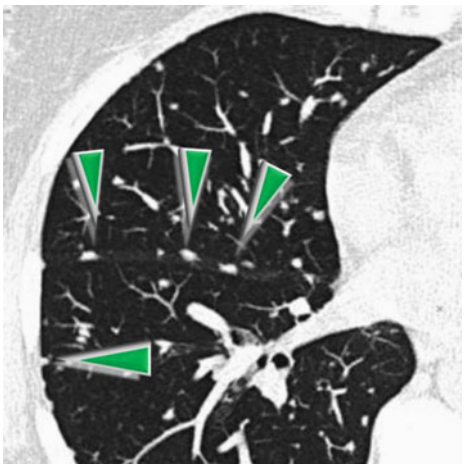
Please also refer to halo sign in the "Case-Based Glossary with Tips and Tricks."

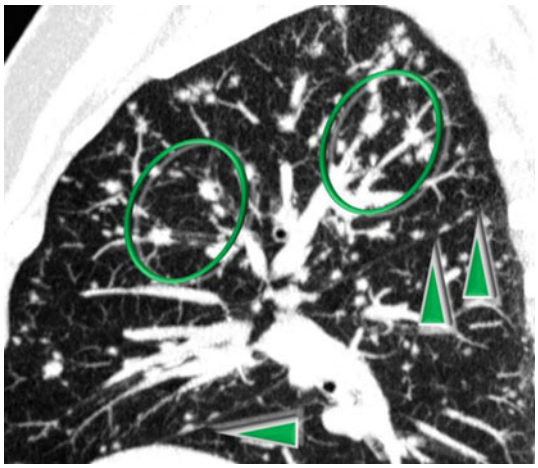
Granulomatosis with polyangiitis (former Wegener's granulomatosis), eosinophilic diseases, and amiodarone-induced toxicity may have macronodules with halo sign.

SUBSET LYMPHATIC

Several small nodules, mainly with well-defined margins and high density, are distributed along the costal margins and the fissures (►). They are also visible along the bronchovascular bundles (◯). The sagittal MIP view beautifully shows the affinity of the nodules for the subpleural spaces at the level of fissures.

☯ Perilymphatic, "avid for pleura"



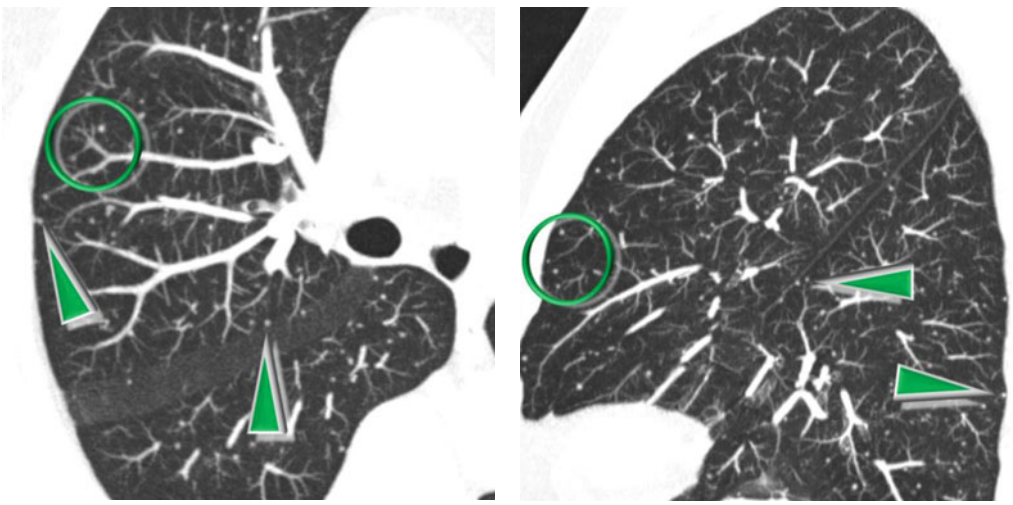


Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Lymphatic nodular disease
Solid lymphatic nodules	Basal predominance	Centrilobular low-density (subsolid) nodules, cysts	Mediastinal and hilar lymphadenopathy	**Lymphocytic Interstitial Pneumonia (LIP)**
Solid lymphatic nodules	Upper lobe predominance	Pseudoplaques, galaxy sign	Mediastinal and symmetric hilar lymph node enlargement, maybe calcified	**Sarcoidosis**
Solid lymphatic nodules	Upper lobe predominance	Pseudoplaques	Calcified mediastinal lymph nodes	**Silicosis**

SUBSET RANDOM

They can be found near the pleural surface (►) and in the core. At times they can be seen in contact with the extremities of vascular structures, from which they appear to originate (feeding vessel sign) (O), and their origin is often hematogenous.
Random nodules show a quite homogeneous distribution, here and there like sown seeds, occasionally touching the pleural surfaces but without a consistent relationship with them. More frequently, they exhibit high-density and well-defined margins. The sagittal MIP view beautifully shows that nodules are "indifferent to the pleura."

☯ "Indifferent to the pleura"

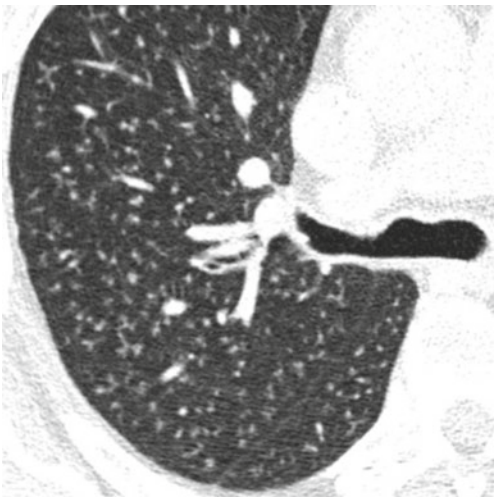


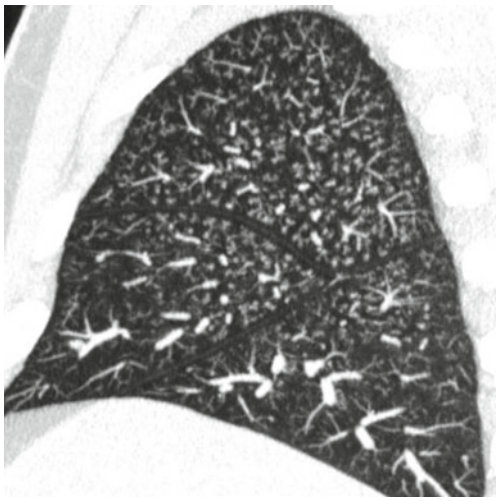
Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Random nodular disease
Solid random nodules	Mostly bilateral	Possible punctate calcification and ossification inside the nodules	Mediastinal lymphadenomegaly, pleural and bone metastases	**Epithelioid hemangioendothelioma (EHE)**
Low-density random nodules, solid nodules with halo sign	Diffuse and bilateral	Focal GGO	Catamenial and non-catamenial PNX	**Hemorrhage in endometriosis**
Tiny innumerable random solid nodules	Diffuse and bilateral	Possible parenchymal cavitated lesions, tree in bud	Possible pleural effusion and lymph node enlargement. Hematogenous extrapulmonary involvement	**Infection, miliary TB**
Solid random nodules, also cavitated (Cheerio sign)	Prevalence in lower lobes	Possible associated signs of LC	Lymph node enlargement, metastatic pleural thickening	**Metastases, hematogenous**

SUBSET CENTRILOBULAR

A centrilobular distribution can be assumed when the nodules, patchily or randomly distributed, stop at a certain distance from pleural surfaces and interlobular septa. Diseases caused by inhaled substances typically show centrilobular nodules of low-density and ill-defined margins. Nodules due to focal accumulation of cells, however, may show well-defined margins. The sagittal MIP image highlights the centrilobular arrangement of the nodules that stop at a certain distance from the pleural surface. As a result, they are separated from the fissures by a dark rim.

"Pavid of the pleura"





Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Centrilobular nodular disease
Centrilobular low-density or solid nodules	Diffuse with possible basal predominance	Bronchial dilatation or bronchial wall thickening, cysts	Absent	**Follicular bronchiolitis (FB)**
Centrilobular low-density (subsolid) nodules	Diffuse	Possible tiny solid nodules randomly distributed, GGO	Small reactive lymph nodes	**Hot tub lung (HTL)**
Centrilobular low-density (subsolid) nodules, lobular air trapping	Homogeneous distribution	Patchy GGO, headcheese sign, cysts	Small reactive lymph nodes	**Hypersensitivity Pneumonitis (HP), subacute**
Centrilobular solid nodules with shaggy margins, also "cavitated" (Cheerio sign)	Predominate in the upper lobes	Bizarre cysts	Possible pneumothorax	**Langerhans Cell Histiocytosis (LCH), early**

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Centrilobular nodular disease
Centrilobular low-density (subsolid) nodules with possible foci of calcification	Mainly in the upper zones	Fluffy lobular or sublobular areas of GGO	Vascular calcifications	**"Metastatic" pulmonary calcification (MPC)**
Centrilobular pseudo-GGO, either ill or well defined	All lobes symmetrically with relative sparing of the periphery	Large ground-glass opacities	Enlargement of pulmonary arteries and right cardiac chambers, lymph node enlargement	**Pulmonary capillary hemangiomatosis (PCH)**
Tiny centrilobular low-density (subsolid) nodules	Predominate in the upper lobes	Patchy GGO, bronchial wall thickening, centrilobular emphysema	Small reactive lymph nodes	**Respiratory Bronchiolitis-ILD (RB-ILD)**

UNUSUAL DISTRIBUTION OF SMALL NODULES

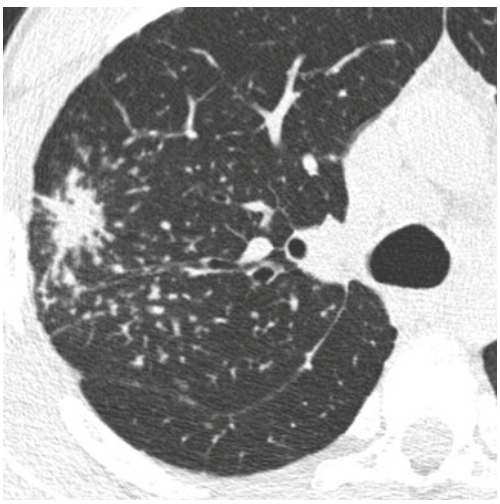
Small lung nodules are recognized as belonging to one of the three distribution patterns: perilymphatic, random, or centrilobular (please see above). Nevertheless, atypical distributions have been described, especially for granulomatous diseases such as sarcoidosis and tuberculosis (TB). The prevalent distribution of the signs together with the presence of non-parenchymal signs may be helpful for the diagnosis of a specific disease (please see the table at the end of this chapter).

Marchiori E (2011) Atypical distribution of small nodules on high resolution CT studies: patterns and differentials. Respir Med 105(9):1263

Galaxy Sign

The galaxy sign is a large parenchymal nodule arising from coalescent small nodules and surrounded by many tiny satellite nodules. The nodule often also present shaggy profiles
Pathologically, the galaxy sign represents numerous coalescent granulomas. Granulomas were described as being much more concentrated toward the center of the galaxy than at the periphery (please also refer to galaxy sign in the "Case-Based Glossary with Tips and Tricks").

Sarcoid galaxy sign



Galaxy sign occurs in some granulomatous diseases:

- *Sarcoidosis*: the galaxy sign is often multiple.
- *Tuberculosis (TB)*: the galaxy sign is often single.

For the differential diagnosis between this two granulomatous diseases, please look for the possible associated signs listed in the table at the end of this chapter.

Nakatsu M (2002) Large coalescent parenchymal nodules in pulmonary sarcoidosis: "sarcoid galaxy" sign. AJR 178:1389

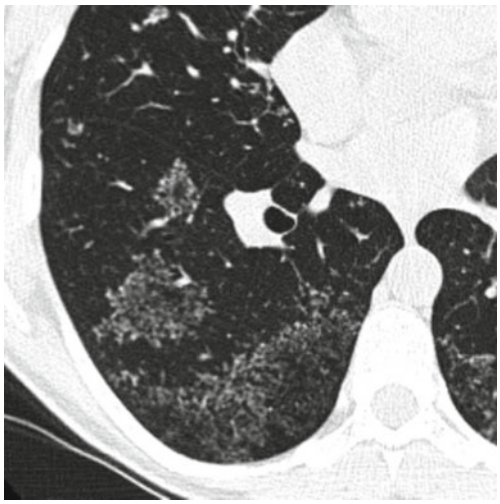
Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30(6):1567

Aikins A (2012) Galaxy sign. J Thorac Imaging 27(6):W164

Nodular Cluster Sign

The nodular cluster sign corresponds to rounded or elongated clusters of multiple tiny nodules in the pulmonary parenchyma, close to each other but not confluent, somewhat reminiscent of pomegranate. These tiny nodules represent noncaseating, non-coalescing granulomas (please also refer to reversed bat wing sign in the "Case-Based Glossary with Tips and Tricks").

"Sarcoid" cluster sign



Nodular cluster sign occurs in some granulomatous diseases:

- Sarcoidosis
- Tuberculosis (TB)
- Cryptococcosis: rarely

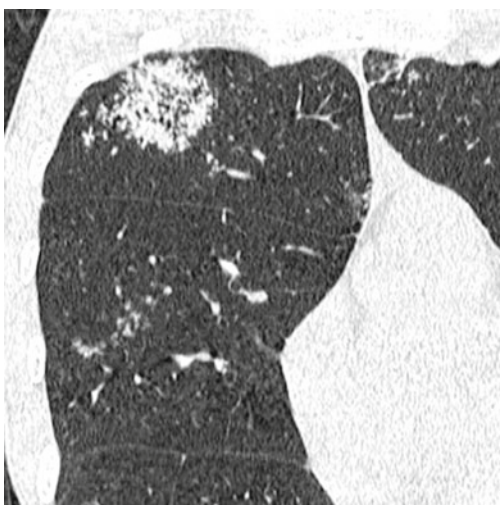
Herráez Ortega I (2009) The “sarcoid cluster sign”. A new sign in high resolution chest CT. Radiology 51(5):495

Cardinale L (2015) A new variant of “Sarcoid Cluster Sign” in tuberculosis. J Belgian Soc Radiology 99(1): 89

Nodular Reversed Halo Sign

The nodular reversed halo sign can be considered a variant of the reversed halo sign. It is defined as focal, rounded ground-glass area surrounded by a ring of consolidation, “nodular” in appearance. Tiny nodules may also be present in the inner area of the nodular reversed halo (HRCT image courtesy of Edson Marchiori, Universidade Federal do Rio de Janeiro, Brazil).
At histology, specimens from such cases have revealed the presence of granulomas within the ring portion of the “nodular” reversed halo sign and/or inside the reversed halo sign.

Fairy ring sign, nodular atoll sign



In 1999, K. Marlow et al. named this lesion the "fairy ring" sign, based on Celtic mythology. Western European, including English, Scandinavian, and Celtic, traditions claimed that fairy rings are the result of elves or fairies dancing. Such a legend dated to at least the Medieval period; the Middle English term elferingewort ("elf-ring"), meaning "a ring of daisies caused by elves' dancing," dates to the twelfth century. A fairy ring, also known as fairy circle, elf circle, elf-ring, or pixie ring, is a naturally occurring ring or arc of mushrooms.

A reversed halo sign with a nodular border indicates a granulomatous disease, such as sarcoidosis and TB, while a reversed halo sign with a smooth contour often suggests organizing pneumonia, the latter being a less common feature (please also refer to reversed halo sign in "Case-Based Glossary with Tips and Tricks" and chapters "Alveolar Pattern").

"Nodular" reversed halo sign is associated with some granulomatous diseases:

- Sarcoidosis
- TB
- Paracoccidioidomycosis: rarely

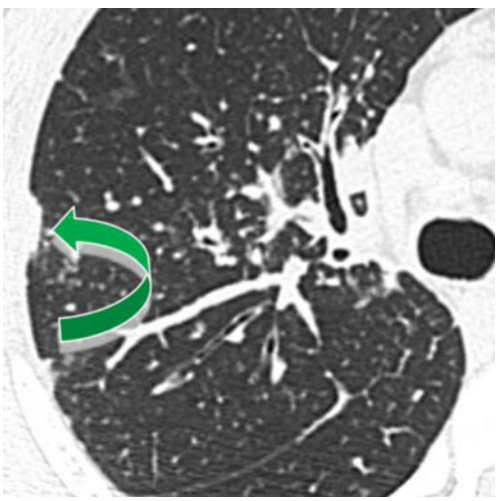
Marchiori E (2012) Reversed halo sign on computed tomography: state-of-the-art review. Lung 190(4):389

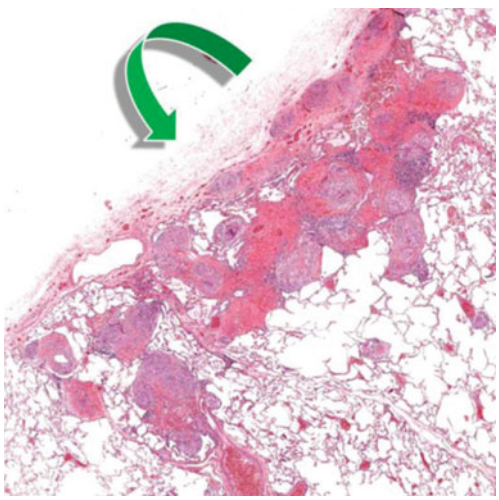
Queiroz RM (2016) Pulmonary paracoccidioidomycosis showing reversed halo sign with nodular/coarse contour. Radiol Bras 49(1):59

Pseudoplaques

Pseudoplaques result from a grouping of coalescent small subpleural nodules, several millimeters thick, that form a focal subpleural opacity simulating the appearance of an asbestos-related parietal pleural plaque ( ). The presence of pseudoplaques correlates significantly with the profusion of subpleural nodules.

Pleural plaquelike opacities





Pseudoplaques are visible along the costal contour but also at the fissural level.

Pseudoplaques occur in some granulomatous diseases:

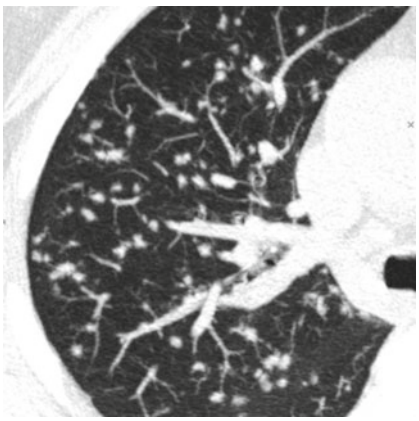
- Sarcoidosis
- Silicosis
- Coal workers' pneumoconiosis (CWP)

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Granulomatous disease
Perilymphatic nodules	Upper and middle lobes	Galaxy sign (often multiple) Cluster sign "Nodular" reversed halo sign Pseudoplaque	Bilateral hilar and mediastinal lymphadenopathy, possible calcification	**Sarcoidosis**
Perilymphatic nodules	Upper and posterior lung zones	Pseudoplaque	Mediastinal lymphadenopathy with eggshell calcifications	**Silicosis**
Cavitation is frequent, Tree-in-bud opacities	Upper lobes and superior segment of the lower lobes	Galaxy sign (often single) Cluster sign "Nodular" reversed halo sign	Lymphadenopathy, possible necrotic	**Tuberculosis (TB)**

Nodular Diseases

Radiology

Nicola Sverzellati
Mario Silva



G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_8

Definition

Epithelioid hemangioendothelioma is a rare neoplasm (prevalence <1/1,000,000) of vascular endothelial origin with low-to-intermediate malignant potential that can arise in the lung, liver, bones, and soft tissue. Pulmonary epithelioid hemangioendothelioma mainly affects young women (median age of onset is 36 years) and is usually asymptomatic.

EHE

Shao J (2014) Clinicopathological characteristics of pulmonary epithelioid hemangioendothelioma: a report of four cases and review of the literature. Oncol Lett 8(6):2517

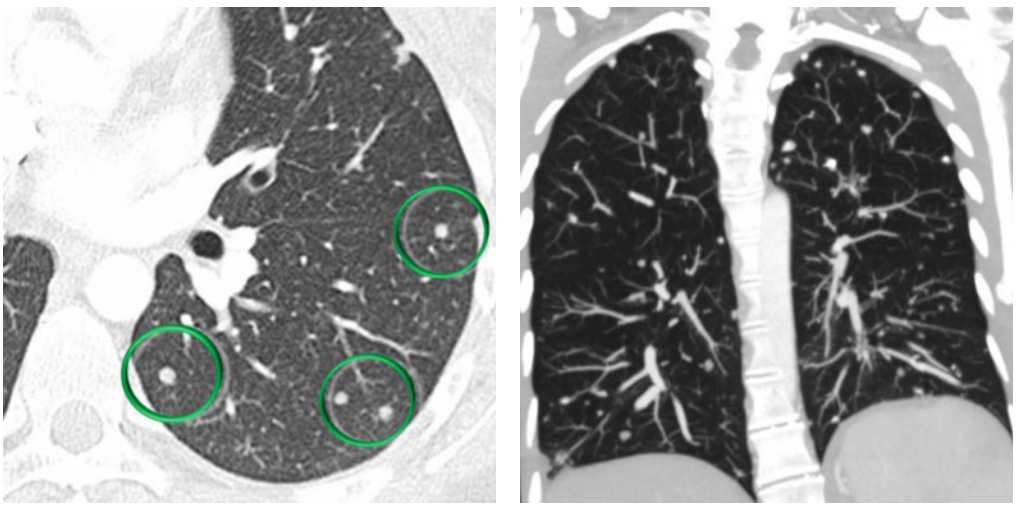
HIGH-RESOLUTION CT: HRCT

Key Signs

- Multiple small solid (O) and subsolid pulmonary nodules (<1 cm), also with irregular margins. More rarely, nodules can be up to 5 cm.

Distribution

Mostly bilateral, however, unilateral distribution was reported in 25 % of cases. Nodules are frequently subpleural (e.g., < 2 cm from the pleura), with perivascular distribution, namely, adjacent to small- and medium-sized vessels and bronchi.



The nodules detected in EHE usually show clear boundaries, although in case of infiltration of vessels and bronchi, the margins can be irregular or ill-defined.

EHE is a neoplasm of mesenchymal origin characterized by the presence of multiple, usually bilateral, small nodules, mainly distributed in the subpleural space; the main differential diagnosis is represented by metastatic lesions.

Liu K (2014) The computed tomographic findings of pulmonary epithelioid hemangioendothelioma. Radiol Med 119(9):705

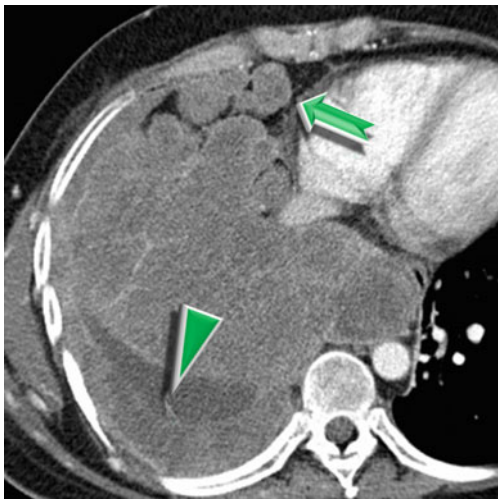
Kim M (2015) Pulmonary epithelioid hemangioendothelioma misdiagnosed as a benign nodule. World J Surg Oncol 13:107

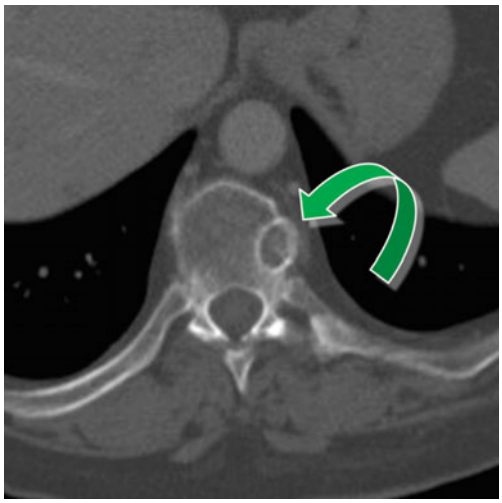
Ancillary Signs

- Punctate calcification and ossification inside the nodules may be observed.
- Reticulonodular opacities are a rare pattern of presentation.

Non-parenchymal Signs

- Thickening of the pleural layers (►) is a consequence of the pleural invasion, despite pleural effusion being quite rare.
- Enlargement of mediastinal lymph nodes (⇘).
- Bone metastases are usually osteolytic (➡) and show homogeneous enhancement after injection of contrast agent.





Small nodules are usually negative at 18 F-FDG-PET, while the bigger ones may show an uptake (SUV $\geq$ 2.5), thus suggesting more malignant behaviors.

Sardaro A (2014) Pulmonary epithelioid hemangioendothelioma presenting with vertebral metastases: a case report. J Medl Case Reports 8:201

Sakamoto N (2005) High resolution CT findings of pulmonary epithelioid hemangioendothelioma unusual manifestations in 2 cases. J Thorac Imaging 20:236–238

Course and Complications

- The prognosis is extremely variable, from long/indolent to cases of partial spontaneous regression. Therefore, life expectancy may range from 1 to 30 years.
- A wedge or anatomical resection is possible in case of a single lesion, while multiple nodules are treated with chemotherapy.

- Mizuno Y (2011) Pulmonary epithelioid hemangioendothelioma. Gen Thorac Cardiovasc Surg 59:297–300

Definition

Follicular bronchiolitis (FB) represents a nonneoplastic pulmonary lymphoid disorder characterized by lymphoid hyperplasia of the bronchus-associated lymphoid tissue (BALT). Hyperplastic lymphoid follicles and well-defined reactive germinal centers distributed along bronchovascular bundles characterize the histological pattern of FB.
FB is mainly secondary to collagen vascular disease – CVD (particularly, rheumatoid arthritis and Sjögren), AIDS, or hypersensitivity reaction – whereas the primary (idiopathic) form is rare. Follicular bronchiolitis usually affects middle-aged people. Dyspnea with insidious onset, cough, and weight loss are the main symptoms, which usually show insidious and unspecific onset.

FB

Tashtoush B (2015) Follicular Bronchiolitis: a literature review. J Clin Diagn Res 9(9):OE01

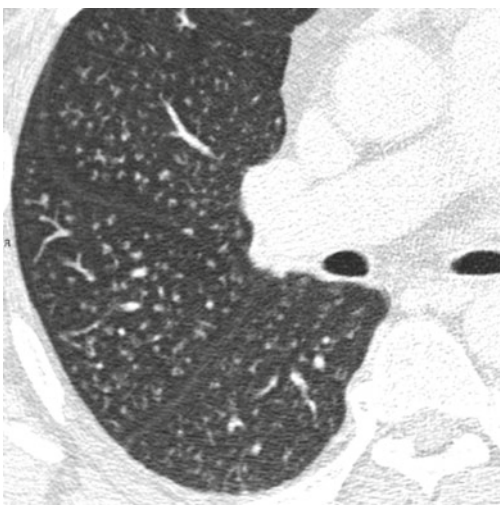
HIGH-RESOLUTION CT: HRCT

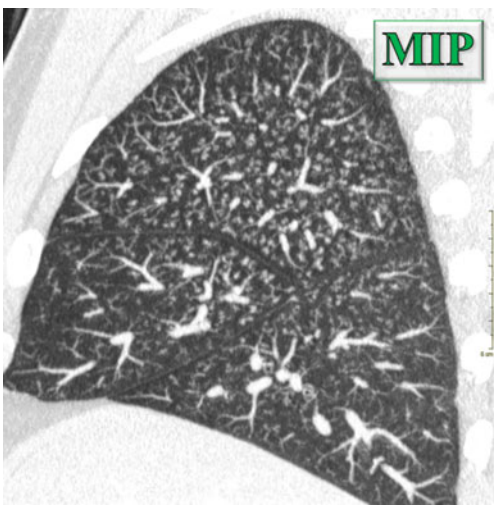
Key Signs

- Small bilateral centrilobular nodules, usually 3 mm in size (diameter ranges 1–12 mm)
- Nodules which mimic a tree-in-bud pattern (peribronchiolar distribution), more visible on MIP images (please see the sagittal MIP image below)

Distribution

The nodules are distributed throughout the lung, with possible slight basal predominance.





MIP image highlights the visibility and the profusion of the diffuse small nodules. The sagittal plane also confirms the centrilobular distribution of the nodules (nodules "pavid of pleura").

FB seldom represents the sole abnormality on HRCT as it often coexists with other lung abnormalities (e.g., interstitial lung disease and other lymphoid tissue disorders).

FB overlaps imaging features of other types of bronchiolitis. Indeed, the radiological diagnosis is very difficult if not impossible without any knowledge of the clinical background (e.g., collagen vascular disease).

Pipavath SJ (2005) Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol 185(2):354

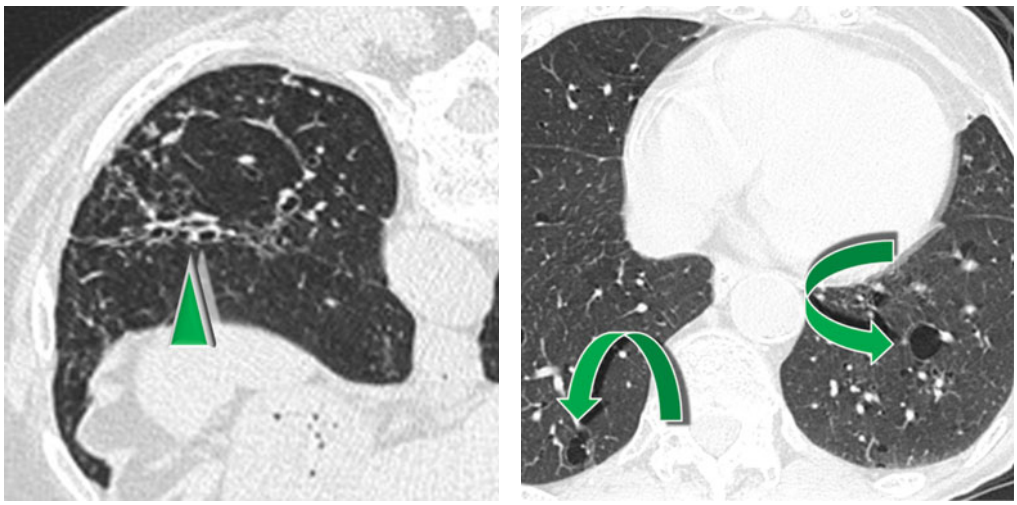
Kang EY (2009) Bronchiolitis: classification, computed tomographic and histopathologic features, and radiologic approach. J Comput Assist Tomogr 33(1):32

Ancillary Signs

- Bronchial dilatation or bronchial wall thickening (►).
- Lymphoid follicles in the bronchiolar wall narrow the bronchiolar lumen with obstruction to airflow variably associated with mosaic attenuation pattern on inspiratory CT; therefore, expiratory CT is granted to assess and quantify the air trapping.
- Mild ground-glass opacity, mostly reflecting coexisting interstitial lung disease.
- Cystic changes (☟).

Non-parenchymal Signs

Absent



Thin-walled cysts, randomly distributed and ranging from 3 mm to 1 cm, represent a finding also of lymphocytic interstitial pneumonia (LIP), which is itself associated with FB and represents a pathophysiological *continuum* of lymphocytic infiltration from hyperplasia of BALT to cellular expansion of the interstitium with fibrosis.

The cystic pattern associated with Sjögren's syndrome typically shows septa within cysts with heterogeneous size, parenchymal thinning into the so-called dissolving lung appearance (mainly basal and perivasal), and frequent association with ground-glass opacities and nodules.

Gupta N (2015) Diffuse cystic lung disease. Part II. Am J Respir Crit Care Med 192(1):17

Gupta N (2016) Diffuse cystic lung disease as the presenting manifestation of Sjögren's syndrome. Ann Am Thorac Soc 13(3):371

Howling SJ (1999) Follicular bronchiolitis: thin-section CT and histologic findings. Radiology 212(3):637

Course and Complications

Follicular bronchiolitis secondary to connective tissue diseases or AIDS are usually treated with pharmaceutical approach for the underlying disease.

Burgel PR (2013) Small airways diseases, excluding asthma and COPD: an overview. Eur Respir Rev 22(128):131

Carrillo J (2013). Lymphoproliferative lung disorders: a radiologic-pathologic overview. Part I: reactive disorders. Semin Ultrasound CT MR 34(6):525

Definition

Thoracic endometriosis syndrome (TES) encompasses a variety of symptoms and signs determined by migration of endometriosis foci through diaphragmatic defects (pleural implant) or microembolization from pelvic veins (parenchymal implant). TES is associated with pelvic endometriosis, with median age of presentation about 35 years (approximately 5 years later than pelvic symptoms onset). Catamenial pneumothorax and hemoptysis reflect pleural and pulmonary involvement, respectively. In parenchymal involvement, recurrent alveolar damage is caused by episodes of alveolar hemorrhage during the menstrual cycle. Pulmonary nodules represent the rarest form of presentation (6 %).

☯ TES, Catamenial hemorrhage

📖 Joseph J (1996) Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. Am J Med 100(2):164

Alifano M (2006) Thoracic endometriosis: current knowledge. Ann Thorac Surg 81:761

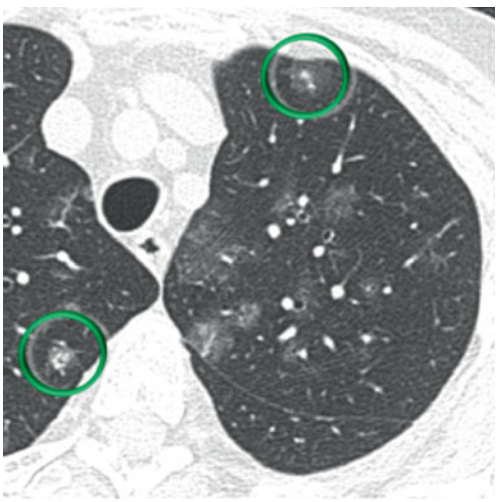
HIGH-RESOLUTION CT: HRCT

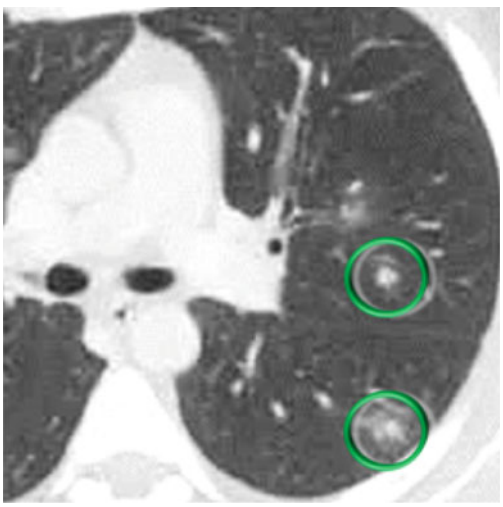
Key Signs

- Low-density (subsolid) nodules (snowflake nodules)
- Small solid nodules with halo sign (O)

Distribution

Bilateral. The right lung is involved in about 70 % of nodular presentation.





Halo sign refers to a ground-glass opacity that surrounds circumferentially pulmonary solid nodules due to hemorrhagic involvement. It may present both in hemorrhagic and nonhemorrhagic diseases (please also refer to halo sign in the chapter "Nodular Pattern" and in the "Case-Based Glossary with Tips and Tricks").

✓ Temporal heterogeneity of parenchymal findings is the CT hallmark of this rare presentation of TES. In the acute phase, atelectasis can be seen as consequence of endobronchial clots. In the chronic phase, band-like opacities reflect linear fibrosis from chronic hemorrhage.

📖 Rousset P (2014) Thoracic endometriosis syndrome: CT and MRI features. Clin Radiol 69(3):323

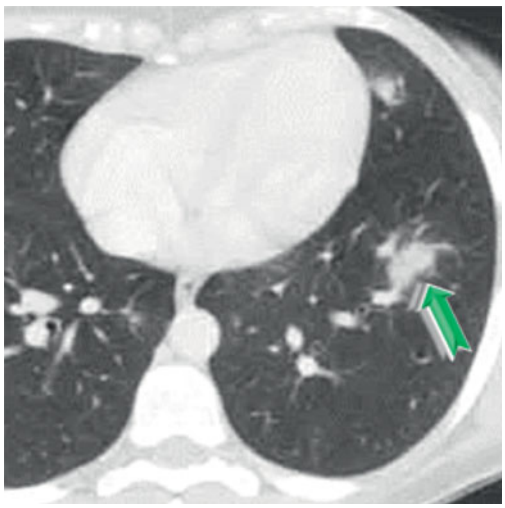
Huang Q (2015) Clinical and radiographic characteristics in pulmonary endometriosis: based on five cases. Clin Exp Obstet Gynecol 42(3):336

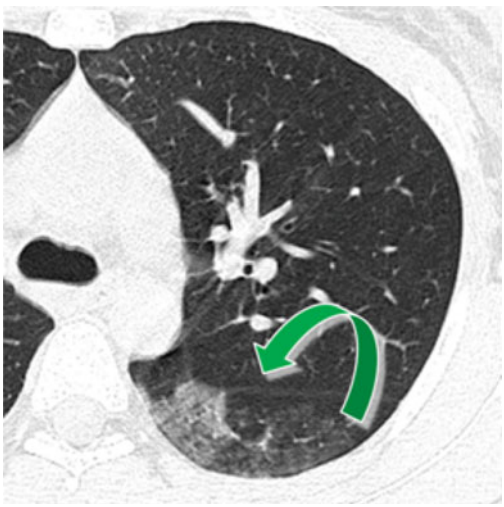
Ancillary Signs

- Macronodules (➡).
- Focal ground-glass opacities and consolidation reflecting alveolar filling from periodic bleeding (🔥) (image courtesy of Angelo Carloni, Terni).
- Cavitation can happen in nodules and pulmonary hematomas.

Non-parenchymal Signs

- Catamenial and non-catamenial pneumothorax
- Catamenial hemothorax with pleural thickening, notably right-sided





Pulmonary endometriosis is a rare presentation of TES which shows nodules on HRCT. The diagnosis is achieved on clinical ground; in particular catamenial hemoptysis and cyclical wax and wane of HRCT findings is hallmark of this rare abnormality. Pneumothorax and hemothorax are the most frequent symptoms of TES; they can coexist and are variably associated with the pulmonary involvement.

Pleural and diaphragmatic hemorrhagic lesions may be diagnosed by MRI, which shows typical signal features.

Korom S (2004) Catamenial pneumothorax revisited: clinical approach and systematic review of the literature. J Thorac Cardiovasc Surg 128(4):502

Haga T (2014) Thoracic endometriosis-related pneumothorax distinguished from primary spontaneous pneumothorax in females. Lung 192(4):583

Cassina PC (1997) Catamenial hemoptysis. Diagnosis with MRI. Chest 111(5):1447

Course and Complications

- Nodules may vary in size according with the menstrual cycle, up to resolution in some cases.
- Patients can report hemoptysis, which may be controlled by either surgical (e.g., VATS) or medical treatment (e.g., hormone therapy); chemoembolization of bronchial artery may be considered among therapeutic options.
- Pneumothorax is better treated by pleuroscopy and pleurodesis, rather than with medical therapy. Nevertheless, relapse is common despite either treatment.

Legras A (2014) Pneumothorax in women of child-bearing age: an update classification based on clinical and pathologic findings. Chest 145(2):354

Kervancioglu S (2008) Bronchial artery embolization in the management of pulmonary parenchymal endometriosis with hemoptysis. Cardiovasc Intervent Radiol 31(4):824

Definition

Hypersensitivity pneumonitis is caused by inhalatory exposure to organic particles, which engage an exaggerated immune response at the level of small airways and alveoli in susceptible individuals. Recognized antigens include proteins from different species (e.g., animals, insects, bacteria, and protozoa), fungi, and low-molecular-weight chemical compounds. The radiological findings are influenced by the stage of the disease.
The subacute form of hypersensitivity pneumonitis (HP) typically presents a prevalent nodular pattern.

HP, extrinsic allergic alveolitis (EAA – this term has been largely used in the past, currently it is obsolete).

Clinical presentation may be also acute or chronic (please refer to HP, Chronic in the chapter "Fibrosing Diseases").

Selman M (2012) Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. Am J Respir Crit Care Med 186(4):314

Spagnolo P (2015) Hypersensitivity pneumonitis: a comprehensive review. J Investig Allergol Clin Immunol 25(4):237

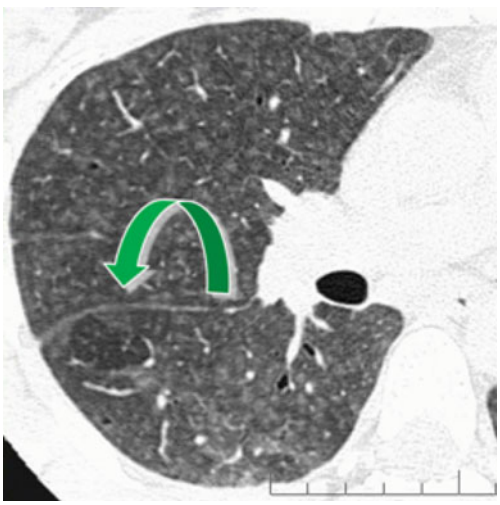
HIGH-RESOLUTION CT: HRCT

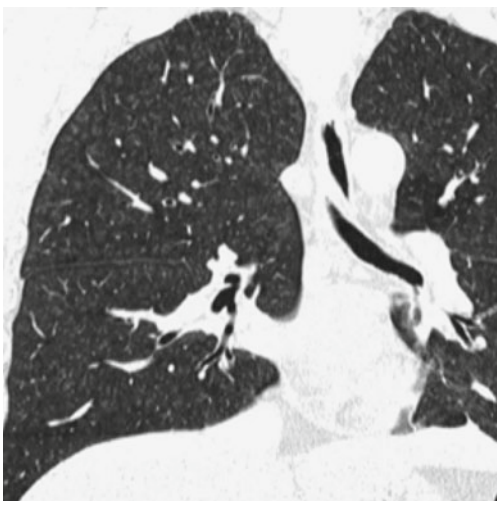
Key Signs

- Low-density centrilobular nodules (snowflake nodules) no larger than 5 mm
- Lobular areas of air trapping

Distribution

HP-related abnormalities are seen with homogeneous distribution to both lungs throughout the lung; although a mid-to-lower lung zone predominance has been variably reported.





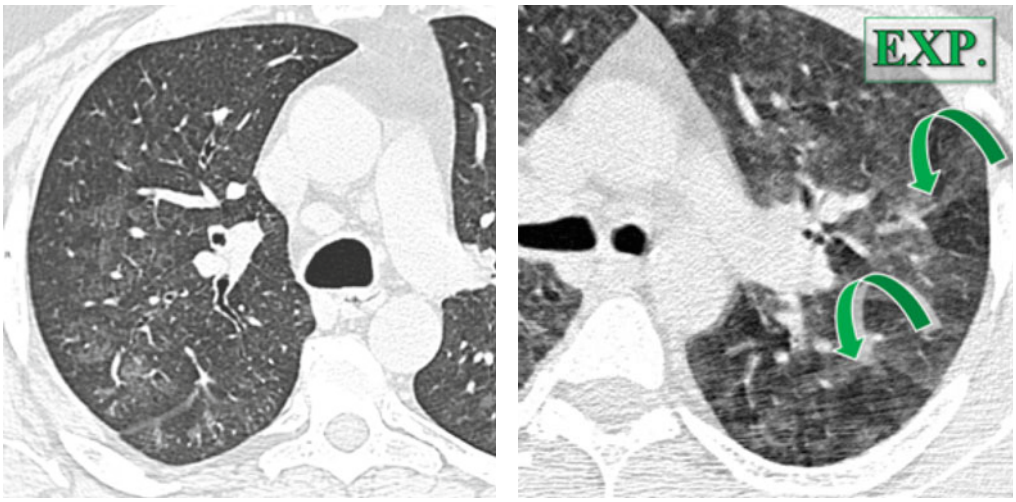
Silva CI (2007) Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. AJR Am J Roentgenol 188(2):334

Ancillary Signs

- Patchy ground-glass opacity may be present, though more commonly observed in acute phase.
- Headcheese sign with lobular air trapping easily visible on expiratory CT.
- Cysts in up to 12 % of cases.

Non-parenchymal Signs

- Pneumomediastinum can occur in case of subpleural cyst rupture.



✓ The "headcheese sign" results as the combination of ground-glass opacity, decreased attenuation areas (reflecting air trapping at expiratory CT scanning), and normal lung. Please also refer this sign to the "Case-Based Glossary with Tips and Tricks".

HRCT features of HP may overlap those of several disorders. Notably, the combination of features of infiltrative (ill-defined nodules and ground-glass opacity) and small airways disease (sporadic lobular areas of air trapping appearing as patches of black lung) may be useful for the differential diagnosis with RB-ILD. The distinction can usually be made also with knowledge of the smoking history.

HP has been described also in patients undergoing chemotherapy (e.g., docetaxel). Acute dyspnea and respiratory failure should prompt HRCT investigation. Discontinuation of chemotherapy and high-dose corticosteroid administration prevent worsening of the respiratory performance.

Genestreti G (2015) A commentary on interstitial pneumonitis induced by docetaxel: clinical cases and systematic review of the literature. Tumori 101(3):e92

Course and Complications

- In the subacute phase, the nodules usually regress with removal from exposure.
- Possible progression to the chronic form of HP. It is characterized by progressive fibrotic changes, with either UIP or NSIP pattern. Of note, air trapping and headcheese pattern should help in the differential between HP and idiopathic interstitial pneumonitis. At this stage, mixed restrictive and obstructive functional abnormalities are seen.

Elicker BM (2016). Multidisciplinary Approach to Hypersensitivity Pneumonitis. J Thorac Imaging;31(2):92

Definition

Hot tub lung (HTL) is a diffuse granulomatous lung disease affecting immunocompetent individuals, caused by inhalation of hot tub water containing nontuberculous mycobacteria such as *Mycobacterium avium* complex (MAC). MAC is commonly found in natural water and tap water and is resistant to most water decontaminants. Moreover, whirlpool and jets in hot tubs drizzle hot vapor, which is an extremely favorable medium for MAC growth. A recent report mentions occupational associations among possible causes of HTL. There is debate whether HTL should be classified as an independent disease or it should be included among hypersensitivity pneumonitis (HP), infections, or a crossing point of these two conditions. Of note, the histology of HTL shows the dominance of well-formed granulomas, as opposed to HP where interstitial inflammation is more represented. Granulomas in HTL can be randomly distributed in bronchioles, airspace, and interstitium.
According to the American Thoracic Society, HTL can be diagnosed by typical HRCT findings without histopathology, in case of subacute onset of symptoms (e.g., dyspnea, fatigue, low-grade fever, and unintentional weight loss) associated with hot tub exposure and positive mycobacterial culture from respiratory samples and water.

HTL

The pathogenesis of HTL consist in a hypersensitivity reaction toward mycobacterial cell wall antigens. The hypothesis of a hypersensitivity pneumonitis is supported by the complete recovery following antigen withdrawal and corticosteroid therapy.

Hanak V (2006) Hot tub lung: presenting features and clinical course of 21 patients. Respir Med 100(4):610

Fjällbrant H (2013) Hot tub lung: an occupational hazard. Eur Respir Rev 22(127):88

Cheung OY (2003) Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 7(2):127

Cancellieri A, Dalpiaz G (2010) Granulomatous lung disease. Pathologica 102(6):464

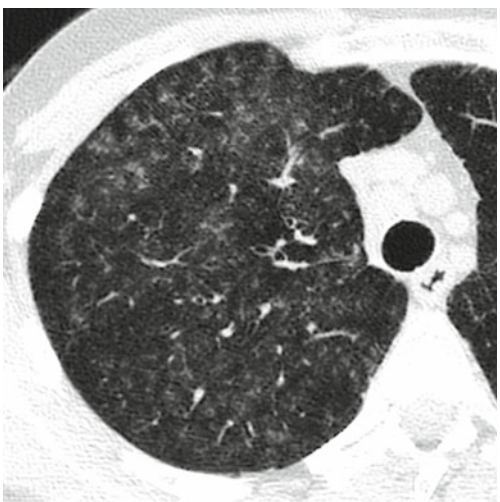
HIGH-RESOLUTION CT: HRCT

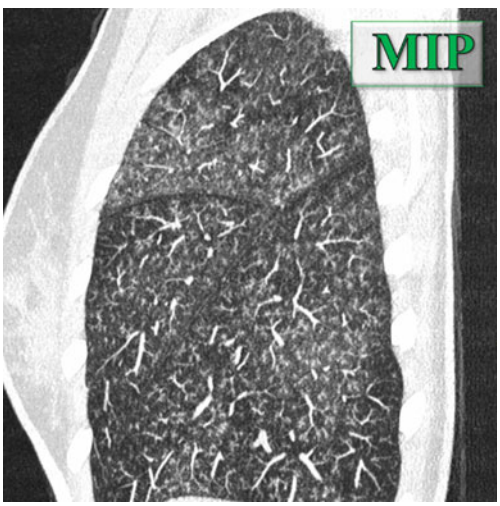
Key Signs

- Small centrilobular low density (snowflake nodules) (please see the axial CT image below).
- Possible tiny solid nodules randomly distributed (please see the sagittal and coronal MIP images below).
- Ground-glass opacities may coexist with the nodules (please see all images below).

Distribution

Both nodules and ground-glass opacity are usually bilateral, homogeneously distributed in throughout the lungs.





The HRCT findings of HTL may overlap HP.

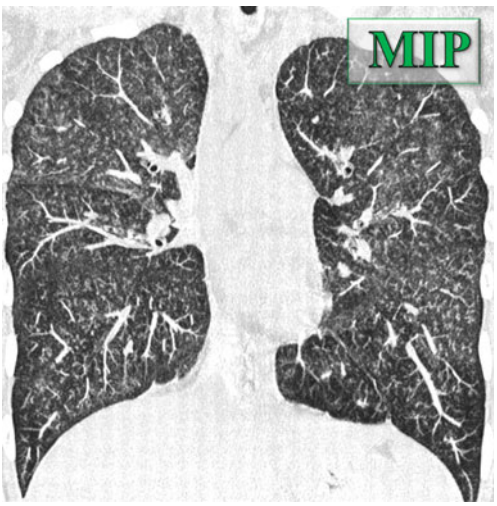
Hartman TE (2007) CT findings of granulomatous pneumonitis secondary to Mycobacterium avium-intracellulare inhalation: "hot tub lung". AJR Am J Roentgenol 188(4):1050

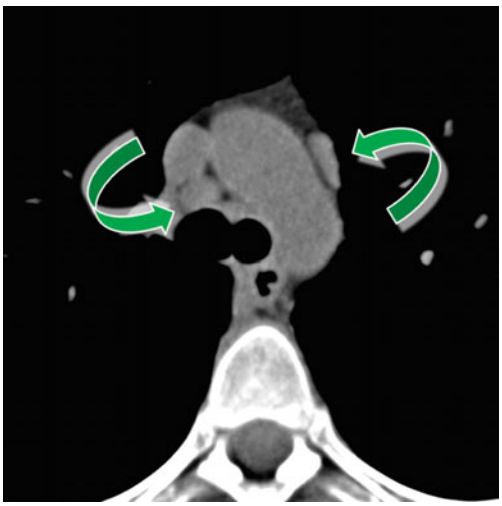
Ancillary Signs

- Air trapping on expiratory scan reflecting the bronchiolocentric distribution of granulomas causing a reduction of the bronchiolar lumen
- Thickening of the interlobular septa
- Cysts and emphysema

Non-parenchymal Signs

Small adenopathies may be present ( ).





Marchetti N (2004) Characterization of functional, radiologic and lung function recovery post-treatment of hot tub lung. A case report and review of the literature. Lung 182(5):271

Course and Complications

- Complete avoidance of exposure is of paramount importance, with most of the patients recovering within weeks without other treatment.
- Treatment with steroids is considered to fasten recovery in advanced cases, whereas antimycobacterial therapy is less effective.
- Improvement on follow-up HRCT is usually seen.
- No chronic or mortal cases have been reported.

Lacasse Y (2012) Recent advances in hypersensitivity pneumonitis. Chest 142(1):208

Pham RV (2003) High-resolution computed tomography appearance of pulmonary Mycobacterium avium complex infection after exposure to hot tub: case of hot-tub lung. J Thorac Imaging 18(1):48

Definition

Pulmonary miliary tuberculosis (TB) derives from the hematogenous spread of *Mycobacterium tuberculosis* to the lungs. Miliary spread can happen in both primary and postprimary TB, with an overall prevalence ranging 1–7 % among patients with tuberculosis.
Lung parenchyma is occupied by innumerable local granulomas with necrotic core and peripheral proliferation of epithelioid histiocytes with local fibrotic degeneration.

☯ Miliary TB

📖 Jeong YJ (2008) Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol 191(3):834

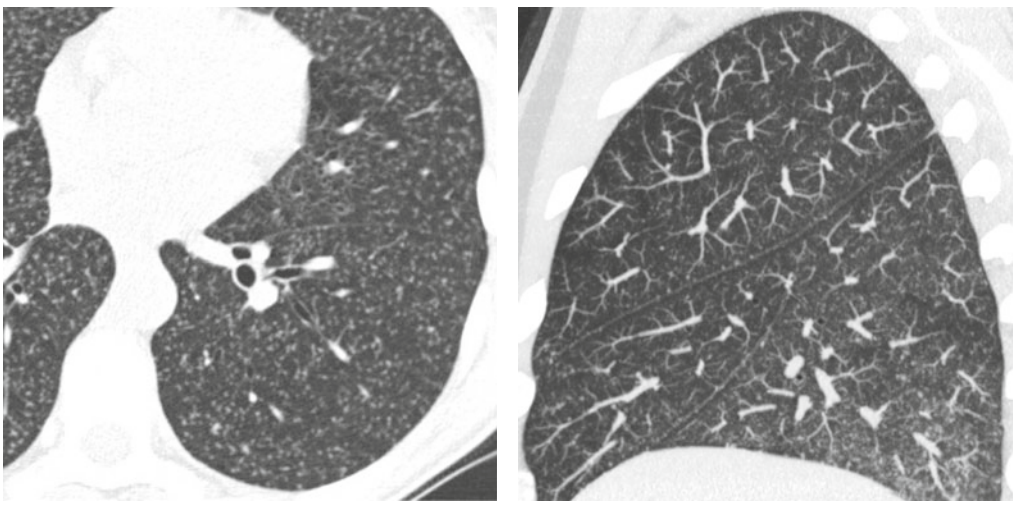
HIGH-RESOLUTION CT: HRCT

Key Signs

- Tiny innumerable solid nodules, homogenous in size (2–4 mm), with either smooth or ill-defined margins

Distribution

Nodules are uniformly and randomly distributed throughout both lungs; this pattern of distribution reflects a hematogenous dissemination. Nodules are homogeneously distributed within the secondary lobule; indeed subpleural and centrilobular involvement are equally represented into the so-called random distribution.



✓ The random distribution can help differentiate miliary hematogenous TB from reactivation of aerogenous TB, the latter selectively showing centrilobular nodules and tree-in bud.

☝ Miliary TB can also happen as iatrogenic disease, for instance, in case of adjuvant immunotherapy with intravesical bacillus Calmette-Guérin (BCG) after endoscopic resection of bladder urothelial carcinoma. Notably, the nodular pattern in BCG-treated patients has also been described in association with sarcoid-like reaction.

📖 Dalpiaz G, Cancellieri A (2014) Diffuse granulomatous lung disease: combined pathological-HRCT approach. Radiol Med 119:54

Rosati Y (2016). Intravesical BCG therapy as cause of miliary pulmonary tuberculosis. Urologia83(1):49

Ancillary Signs

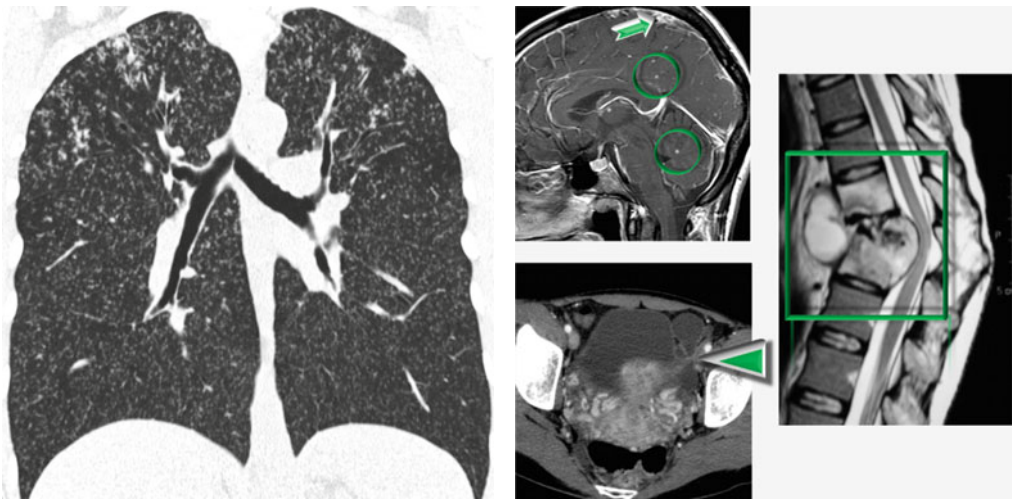
- Miliary tuberculosis may occur in patients with reactivation of TB; therefore upper-lobe predominant consolidation, cavitation, and tree-in-bud sign may be seen in association with miliary pattern (please see the upper lobes on the coronal HRCT image below).

Non-parenchymal Signs

- Pleural effusion either unilateral or bilateral.
- In case of postprimary tuberculosis, necrosis of mediastinal lymph nodes may be seen as a hypodense core of the lymph node that is highlighted by rim enhancement after contrast media injection.

Possible hematogenous extrapulmonary involvement:

- The central nervous system (CNS) involvement is seen in approximately 5 % of immunocompetent patients and up to 15 % of immunocompromised patients. Tuberculous meningitis is the most common manifestation of CNS involvement. The typical radiographic finding is abnormal meningeal enhancement (➡). The most common CNS parenchymal lesion of tuberculosis is tuberculoma. This lesion may be solitary, multiple, or miliary and may be seen anywhere within the brain parenchyma (O).
- The musculoskeletal system is involved in only 1 %–3 % of cases of tuberculosis. Approximately 50 % of skeletal tuberculosis involves the spine (Pott disease) with possible associated paraspinal abscess (□). The lower thoracic and upper lumbar levels are most commonly affected.
- Genital tuberculosis almost always involves the fallopian tubes in women (94 % of cases) (►).
- Neck TB, abdominal TB, urinary TB (please see the table of extrapulmonary TB in the alveolar diseases).



Miliary spread of TB is exceptionally common in immunocompromised subjects, where it should be differentiated from other etiologies (e.g., *Candida albicans*) which show similar HRCT findings.

Pereira M (2015) High-resolution CT findings of pulmonary Mycobacterium tuberculosis infection in renal transplant recipients. Br J Radiol 22:2015–0686

Fujita J (2007) Radiological findings of mycobacterial diseases. J Infect Chemother 13:8

Course and Complications

Nodules usually resolve without sequelae, namely, without scars or calcifications, after 2–6 months of treatment. Nevertheless, the nodular lesions may coalescence into bigger consolidation.

Van Dyck P (2003) Imaging of pulmonary tuberculosis. Eur Radiol 13:1771–1785

Burrill J (2007) Tuberculosis: a radiologic review. Radiographics 27(5):1255

Definition

Langerhans cell histiocytosis is a rare interstitial lung disease strongly associated with cigarette smoking. It encompasses different pathologic phases which reflect its variable CT appearance. Langerhans cells proliferate in the bronchiolar wall and insinuate into the surrounding alveolar septa, forming multiple stellate nodules centered on small airways.
In the early stages, LCH exhibits a diffuse nodular pattern.

LCH, pulmonary Langerhans cell histiocytosis (PLCH).

In the early stages, LCH exhibits a diffuse nodular pattern, but if the disease progresses, there is a radiological evolution to the cystic pattern (please see LCH, advanced in the HRCT Cystic Pattern).

Elia D (2015) Pulmonary Langerhans cell histiocytosis: a comprehensive analysis of 40 patients and literature review. Eur J Intern Med 26(5):351

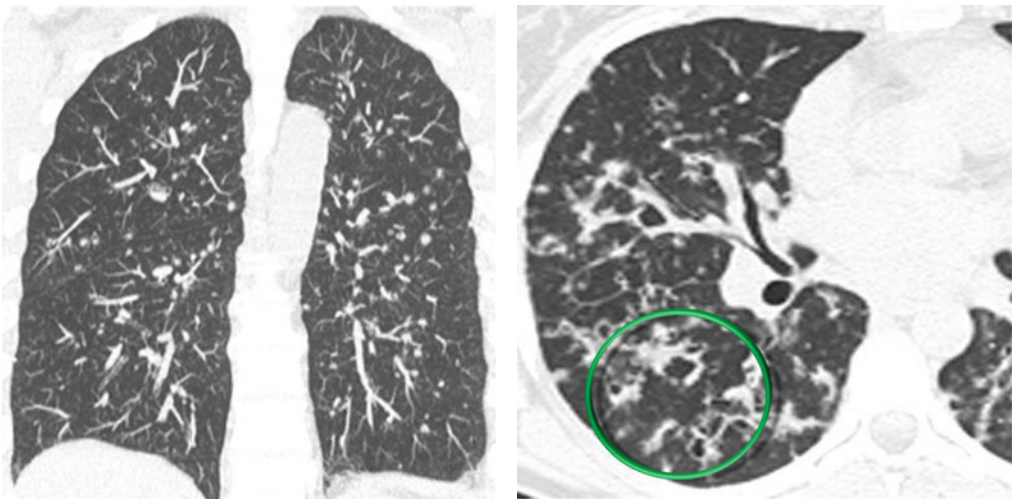
HIGH-RESOLUTION CT: HRCT

Key Signs

- Centrilobular solid nodules with irregular or spiculated margins reflect "florid" early granulomas. Nodule size is rather heterogeneous, generally ranging from 1 to 5 mm.
- Nodules may be "cavitated" (Cheerio sign) (O).

Distribution

PLCH nodules have a peribronchiolar and centrilobular distribution. They classically predominate in the upper lobes, relatively sparing the costophrenic sulci.



Cheerio sign is defined by a nodule with a central lucency seen on CT, similar to the ring-shaped "Cheerios breakfast cereal" and to Italian "Tarallucci". The sign was first described in 1993 in a low-grade adenocarcinoma of the lung.

Causes of Cheerio sign include both neoplastic and nonneoplastic diseases (please also refer to "Case-Based Glossary with Tips and Tricks").

Castoldi MC (2014) Pulmonary Langerhans cell histiocytosis: the many faces of presentation at initial CT scan. Insights Imaging 5(4):483

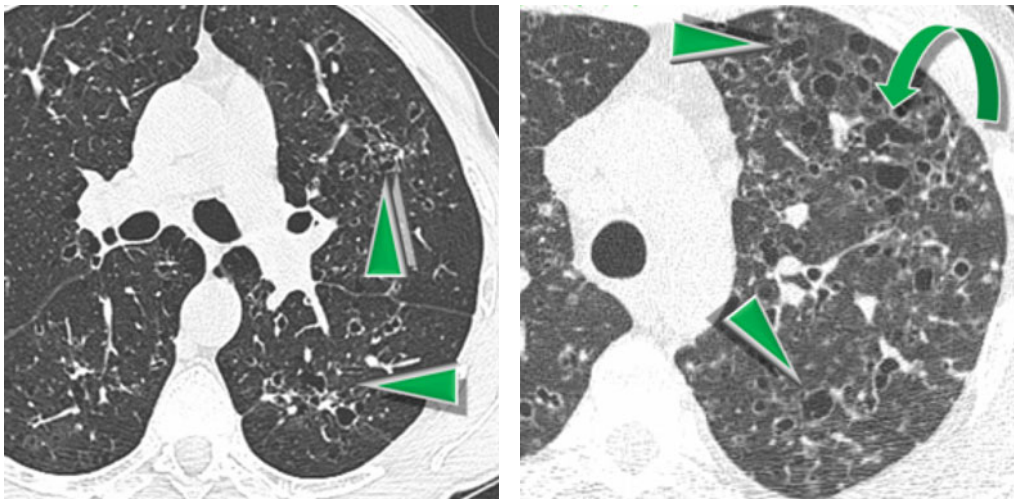
Seely JM (2012) Pulmonary Langerhans cell histiocytosis: a comparative study of computed tomography in children and adults. J Thorac Imaging 27(1):65

Ancillary Signs

- Coexisting bizarre cysts (►), also confluent (↬) (image courtesy of Riccardo Panzavolta, Rovigo).
- Ground-glass opacity may reflect other smoking-related interstitial lung abnormalities such as respiratory bronchiolitis.
- Bullae related to cigarette smoking.

Non-parenchymal Signs

- Pneumothorax may occur from subpleural cysts or even from emphysema.
- Extrathoracic disease, notably bone involvement, can be observed at chest CT.



Pediatric PLCH nodule distribution is more diffuse, also involving the costophrenic sulci.

Kim HJ (2011) Pulmonary Langerhans cell histiocytosis in adults: high-resolution CT-pathology comparisons and evolutional changes at CT. Eur Radiol 21(7):1406–1415

Tazi A (2015) The natural history of adult pulmonary Langerhans cell histiocytosis: a prospective multicentre study. Orphanet J Rare Dis 14;10:30

Course and Complications

- Resolution of pulmonary abnormalities is possible in case of early smoking cessation.
- Nodules progressively cavitate resulting in temporally heterogeneous pattern with nodules and bizarre cysts (please refer to LCH, advanced in the chapter "Cystic Pattern").

An association between PLCH and lung cancer has been shown. Large nodules or masses in a background of PLCH should be carefully investigated.

Mason RH (2014) Pulmonary Langerhans cell histiocytosis (PLCH): a new UK register. Thorax 69(8):766–7.

Definition

Lymphocytic interstitial pneumonia is characterized by abundant interstitial infiltrate of T cells, plasma cells, and histiocytes. It is more commonly associated with immunodeficiency syndromes and autoimmune disorders.
Clinical presentation includes dyspnea, nonproductive cough, and restrictive pulmonary function abnormality.

LIP, Lymphoid interstitial pneumonia

The definition of LIP on the latest ATS/ERS 2013 guidelines slightly changed with the inclusion of HRCT criteria (e.g., cysts). LIP is usually associated with other systemic diseases, but idiopathic cases are known.

Sverzellati N (2015) American Thoracic Society-European Respiratory Society classification of the idiopathic interstitial pneumonias: advances in knowledge since 2002. Radiographics 35(7):1849

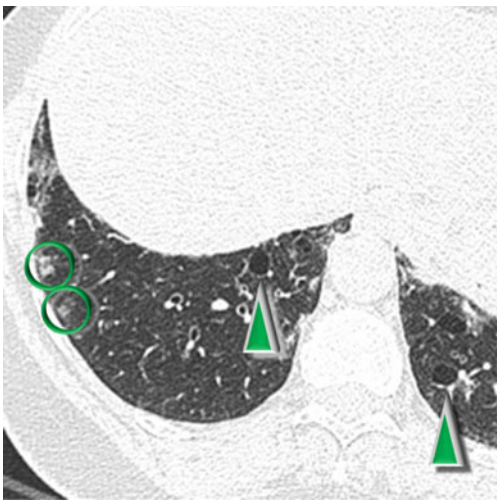
HIGH-RESOLUTION CT: HRCT

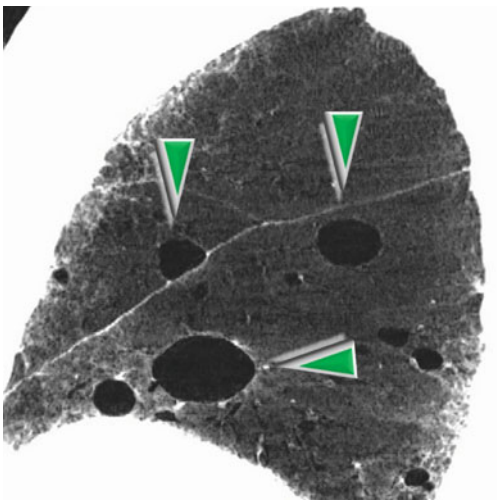
Key Signs

- Small centrilobular nodules with low-density and ill-defined margins (O)
- Subpleural solid nodules with well-defined margins
- Cysts (►)

Distribution

Basal predominance of parenchymal abnormalities is common, with distribution along peribronchovascular bundle.





The centrilobular nodules reflect discrete peribronchiolar infiltration, whereas more diffuse infiltration is seen as ground-glass opacities up to consolidations when alveolar component is relevant. Peribronchovascular infiltration can cause obstruction with dilation of small bronchi and bronchioles, likely reflected by cysts on imaging.

LIP may overlap hypersensitivity pneumonitis (HP) and nonspecific interstitial pneumonia (NSIP) in its histological and radiological presentation.

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

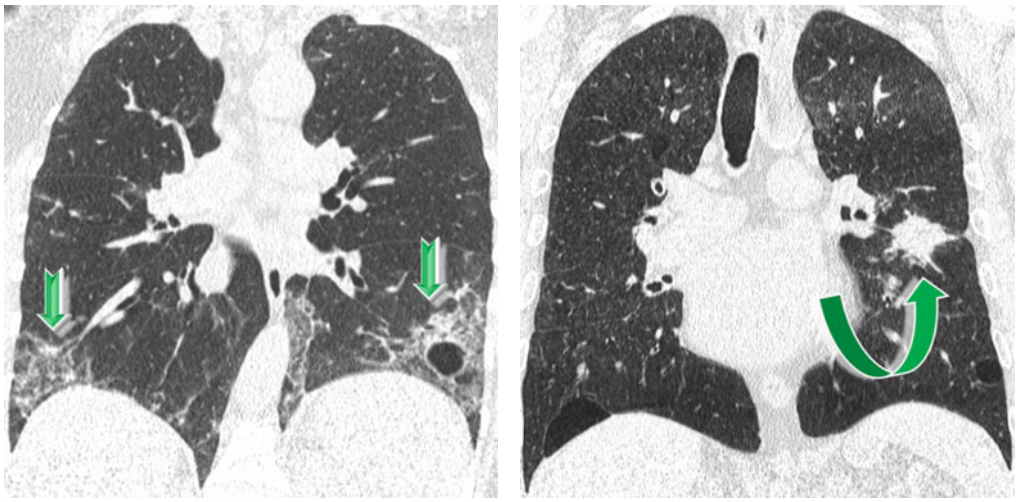
Silva CI (2006) Diffuse lung cysts in lymphoid interstitial pneumonia: high-resolution CT and pathologic findings. J Thorac Imaging;21(3):241

Ancillary Signs

- Ground-glass opacities (➡).
- Thickening of interlobular septa.
- Bronchiectases are more common in advanced stage.
- Lung masses may reflect coexisting lymphoma (↬).

Non-parenchymal Signs

- Mediastinal and hilar lymphadenopathy



In HIV infection, LIP usually occurs with normal CD4 cell count. It can be suspected when parenchymal findings persist after antibiotic treatment or show “wax and wane” with a chronic, indolent course. The clinical course is variable, including either spontaneous resolution or respiratory failure.

Chou SHS (2014) Thoracic diseases associated with HIV infection in the era of anti-retroviral therapy: clinical and imaging findings. Radiographics 34:895

Course and Complications

- Longitudinal evaluation can show worsening, stability, or even improvement of radiological findings.
- Improvement has been reported as the most common evolution.
- Progression of pulmonary involvement is characterized by fibrotic interstitial changes.
- Improvement can be seen for any radiological finding but cysts.

Johkoh T (2000) Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients. J Thorac Imaging15(3):162

Definition

Tumor cells may spread into the vascular stream, causing hematogenous metastases. Lung and liver are the main target of most hematogenous metastases, followed by bone and adrenals. The most common primary tumors metastasizing to the lung are breast, colon, kidney, gynecological, and head and neck cancers.

Chambers AF (2002) Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2(8):563

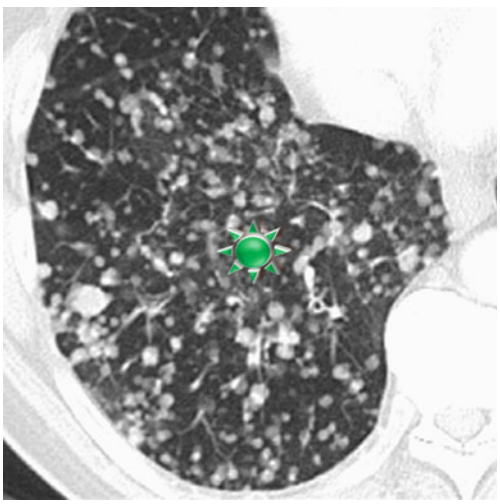
HIGH-RESOLUTION CT: HRCT

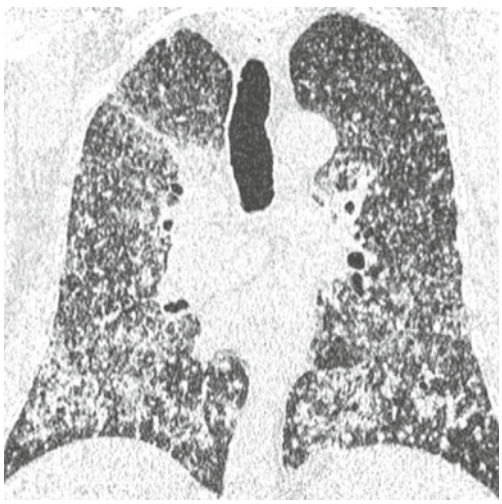
Key Signs

- The typical pattern consists of solid nodules heterogeneous in size, ranging from few millimeters to many centimeters (✸).
- Miliary metastases consist of multiple sharply defined small (3–5 mm) nodules (please see the coronal CT image below).
- Lung metastases may be round, oval, or lobulated in shape. Margins are generally smooth, though sometimes may appear spiculated or poorly defined.
- Lung metastasis density is extremely variable, namely, solid, partially solid, ground-glass, and cavitary (Cheerio sign, ➡).
- Additionally, lung metastases may show fatty or calcified components.

Distribution

Hematogenous metastases show random distribution within the secondary lobule (feeding vessel sign). Prevalence in lower lobes can be seen in relation to perfusion gradient.





✓ The "feeding vessel sign" has been associated with hematogenous origin, representing a pulmonary vessel leading directly to the nodule. Despite being attractive in theory, this hypothesis is currently debated. Indeed, it was shown that vessels "feeding" the lung nodules were pulmonary veins.

Cheerio sign is defined by a nodule with a central lucency seen on CT, similar to the ring-shaped "Cheerios breakfast cereal" and to the Italian "Tarallucci". It may reflect intralesional necrosis or proliferation of either neoplastic cells or nonmalignant cells around a patent airway. The Cheerio sign may be due to neoplastic or nonneoplastic diseases (please refer to Cheerio sign in the "Case-Based Glossary with Tips and Tricks").

Calcified nodules can reflect metastatic spread from osteosarcoma, chondrosarcoma, colon, ovary, breast, and thyroid malignancy. Calcification may derive from either intralesional bony degeneration in primary bone tumors or from dystrophic or mucoid calcification.

Occasionally a solitary pulmonary nodule may represent a single metastasis. Solitary metastases are more commonly associated with colon, renal, and testicular carcinoma and melanoma.

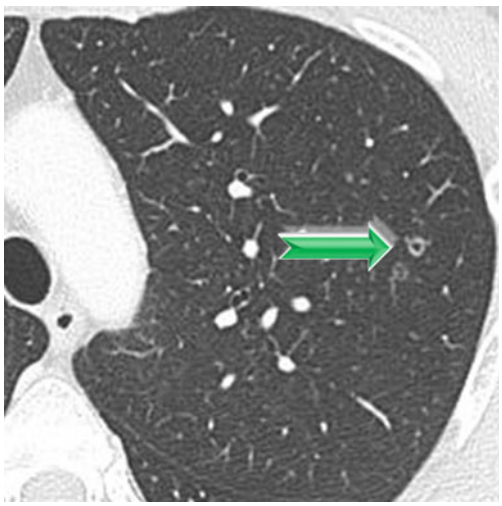
Aquino SL (2005) Imaging of metastatic disease to the thorax. Radiol Clin N Am 43:481

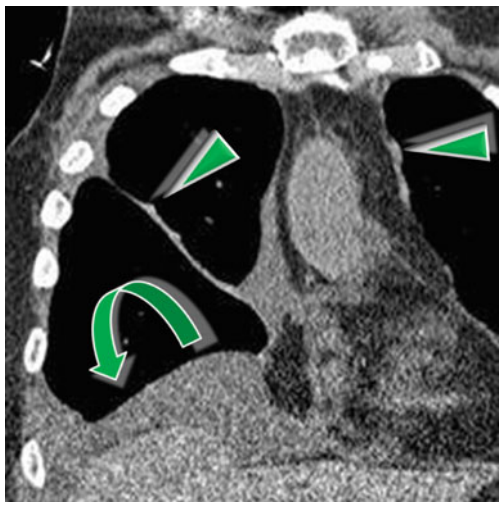
Ancillary Signs

- Hematogenous metastases may coexist with lymphangitis carcinomatosis.

Non-parenchymal Signs

- Lymph node enlargement
- Pleural effusion (☟) and nodular or smooth thickening of pleura due to metastatic involvement (►)





Martínez-Jiménez S (2014) Imaging features of thoracic metastases from gynecologic neoplasms. Radiographics 34(6):1742

Course and Complications

- Pulmonary metastases may change appearance following chemotherapy: they may change in size and density (notably cavitating ➡).
- Rarely, spontaneous pneumothorax can happen in case of necrotic degeneration of peripheral metastases abutting the pleura.
- Diffuse alveolar damage with ARDS can be associated with diffuse metastases to the lung. HRCT features can be hard to differentiate from ARDS from other causes. ARDS from metastatic damage can take advantage from specific chemotherapy, and therefore this option should be always considered.

CT is used in oncologic patients for screening of pulmonary metastases as well as for follow-up after neoadjuvant chemotherapy or radiation therapy. Temporal evolution by HRCT includes growth, shrinkage, cavitation, and calcification.

Seo JB (2001) Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 21(2):403

Definition

Metastatic pulmonary calcification is the consequence of calcium deposition in normal pulmonary parenchyma, predominantly in the alveolar epithelial basement membranes.
MPC is a subdiagnosed metabolic lung disease that is commonly associated with end-stage renal disease. This condition can occur in a variety of disorders (primary and secondary hyperparathyroidism, chronic renal failure, intravenous calcium therapy, and massive osteolysis due to metastases or multiple myeloma). "Metastatic" pulmonary calcification usually presents as an asymptomatic condition. MPC is seen at autopsy in 60-75 % of patients with renal failure. It is often asymptomatic, but can potentially progress to respiratory failure.

Chan ED (2002) Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med 165:1654

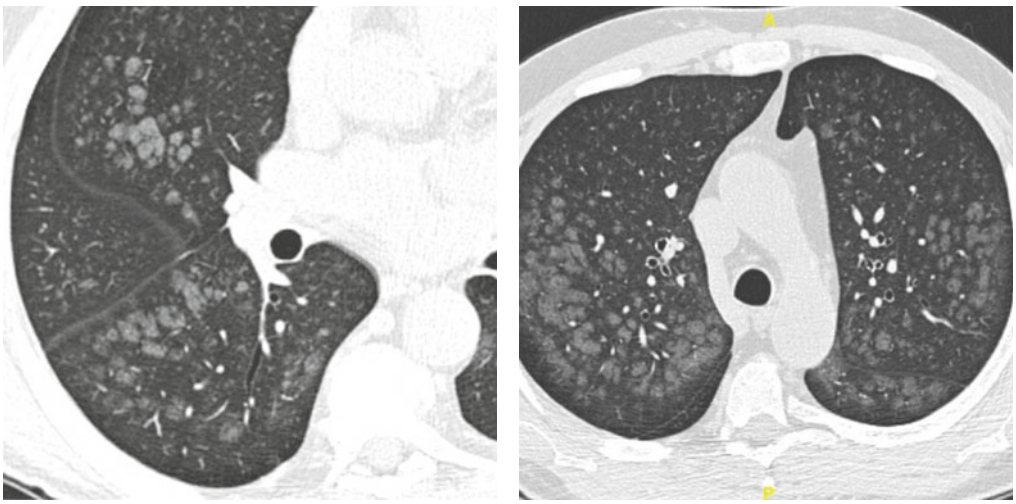
HIGH-RESOLUTION CT: HRCT

Key Signs

- Centrilobular low-density (subsolid) nodules (snowflake nodules)
- Fluffy lobular or sublobular areas of ground-glass opacities

Distribution

The lesions are seen mainly in the upper zones.



Images courtesy of Gaetano Rea, Department of Radiology, Monaldi Hospital, Naples, Italy

Note that both nodules and GGOs are distant from the fissures ("pavid of pleura"). The lesions are separated by a "black rim" being normal interlobular septa.

The nodules may contain tiny foci of calcification.

The most common parenchymal finding on HRCT is the presence of centrilobular ground-glass nodular opacities, with numerous fluffy and poorly defined nodules; however, two other patterns visible on high-resolution CT have been described: diffuse or patchy areas of ground-glass opacity or consolidation, and confluent high-attenuation parenchymal consolidation (see Figure below).

Features visible on CT are most marked in the upper zones of the lungs due to increased alkalinity at the apices, which encourages the deposition of calcium salts. This process can be explained by the higher ventilation/perfusion ratio at the apices, which produces a lower partial pressure of carbon dioxide in arterial blood (PaCO2) and higher blood pH.

Belém LC (2014) Metastatic pulmonary calcification: state-of-the-art review focused on imaging findings. Respir Med 108(5):668

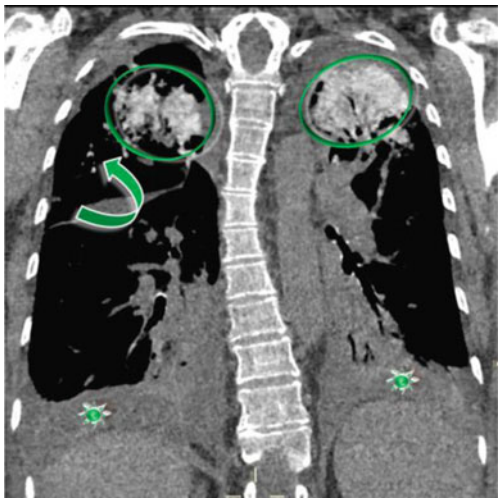
Marchiori E (2005) Diffuse high-attenuation pulmonary abnormalities: a pattern-oriented diagnostic approach on high-resolution CT. AJR Am J Roentgenol 184(1):273

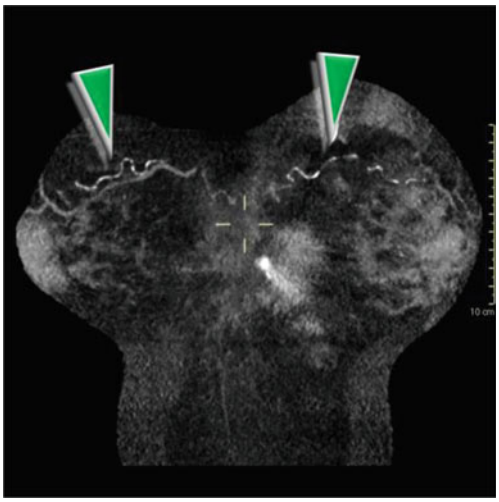
Ancillary Signs

- Multiple calcified nodules (↺)
- High-attenuation parenchymal consolidations with possible calcifications (○) (Images courtesy of Francesca Zanier & Blerti Troshani, Department of Radiology, Merano, Italy)

Non-parenchymal Signs

- Calcification of the vessels of the chest wall is frequently associated with MPC (►).
- Pleural effusion due to associated edema in patients with chronic renal failure (✸).
- Scintigraphy with bone-seeking radionuclides may demonstrate increased radioactive isotope uptake.





✓ The predilection of calcification for the upper lung area and its association with calcification in the vessels of the chest wall may support the diagnosis. Nuclear imaging with technetium-99m-methylene diphosphonate (Tc99m-MDP) is a more specific and less expensive method for diagnosis.

☝ PFT are usually normal in patients with MPC. Since alveolar septa are diffusely involved in MPC, diffusing capacity is decreased.

Course and Complications

- Pulmonary calcification generally progresses slowly and is often asymptomatic.
- Several reports have described acute respiratory insufficiency with a rapidly progressive chest shadow which mimics pneumonia or pulmonary edema.
- There is a poor correlation between the severity of respiratory distress and the degree of macroscopic calcification. Patients with extensive calcification may be asymptomatic, whereas those with subtle calcification or normal chest radiographs may have severe respiratory distress.
- It may progress to irreversible lung damage and respiratory failure.

Timmins S (2010) Images in clinical medicine. Metastatic pulmonary calcification. N Engl J Med 363(26):2547

Ceylan N (2010) CT findings of high-attenuation pulmonary abnormalities. Insights Imaging 1(4):287

Definition

Pulmonary capillary hemangiomatosis (PCH) is an extremely rare idiopathic vascular disease with poor prognosis (mean age 30 years; equal prevalence in both genders). It is characterized by a disproportionate proliferation of capillaries in the pulmonary interstitium with progressive invasion of the alveolar spaces and bronchi. Consequently, the increase in vascular resistance causes pulmonary hypertension. Although the combination of the HRCT pattern and signs of pulmonary hypertension may suggest PCH, the diagnosis demands histological evaluation.

PCH

Frazier AA (2007) From the archives of the AFIP pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Radiographics 27(3):867

Rossi A (2014) Rare causes of pulmonary hypertension: spectrum of radiological findings and review of the literature. Radiol Med 119(1):41

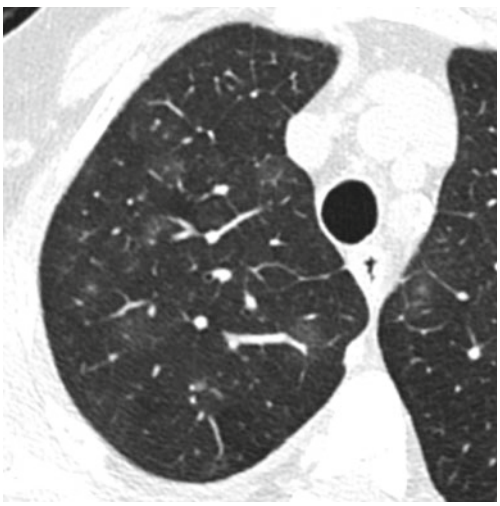
HIGH-RESOLUTION CT: HRCT

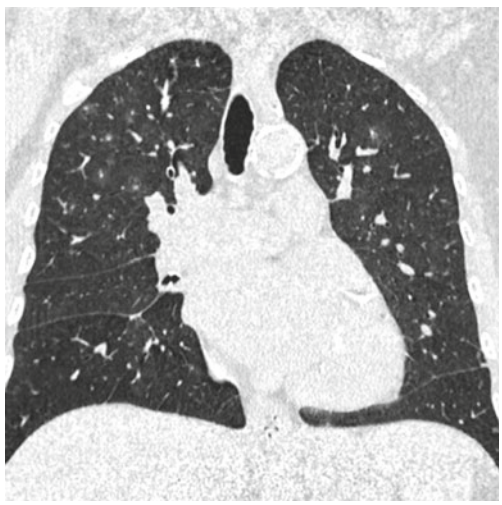
Key Signs

- Pseudonodular ground-glass opacities (snowflake nodules), either ill or well defined, with centrilobular distribution. These nodules reflect the angiomatoid proliferation within alveolar septa.

Distribution

The nodules typically affect all lobes in both lungs, symmetrically, with relative sparing of the periphery.





Snowflake nodules are nonspecific, as they are commonly seen in a variety of rare (e.g., pulmonary veno-occlusive disease – PVOD) and common pulmonary diseases (e.g., hypersensitivity pneumonitis or infectious pneumonitis). The differential between PCH and PVOD is variously approachable by the evaluation of centrilobular GGO size, which appears to be larger in PCH.

Miura A (2013) Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis. Cardiovasc Pathol 22(4):287

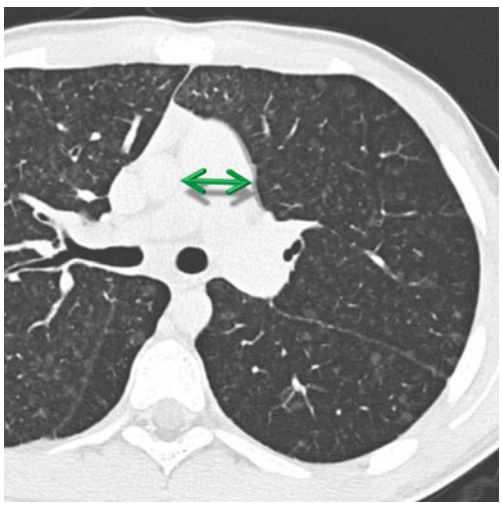
Faria IM (2013) Pulmonary capillary hemangiomatosis: an uncommon cause of pulmonary hypertension. J Bras Pneumol 39(3):390

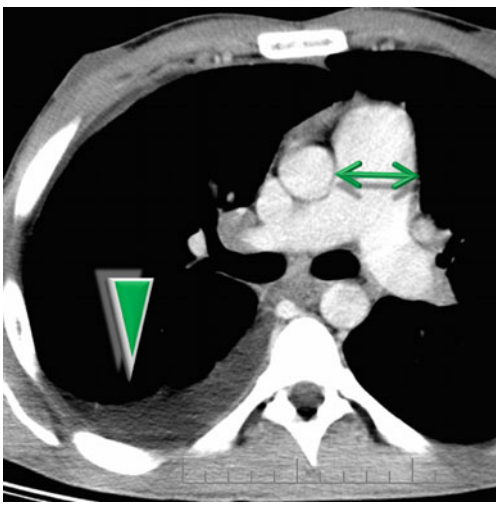
Ancillary Signs

- Smooth septal thickening reflecting pulmonary edema and reticulonodular pattern in association with advanced focal capillary proliferation.
- Ground-glass opacities may be associated with nodules.

Non-parenchymal Signs

- Pulmonary artery dilation (⇔) and enlargement of the right cardiac chambers; the left atrium is normal in size with preserved function as reflected by normal postcapillary pressure.
- Lymph node enlargement.
- Pleural and pericardial effusion (►).





The invasion of alveolar structure and blood vessels by overgrowing capillaries leads to a reduction of gas exchange, as well as recurrent pulmonary hemorrhage with thrombosis and pulmonary infarction.

El- Gabaly M (2007) Pulmonary capillary hemangiomatosis imaging findings and literature update. J Comput Assist Tomogr 31(4):608

Lawler LP (2005) Pulmonary capillary hemangiomatosis multidetector row CT findings and clinicopathologic correlation. J Thorac Imaging 20(1):61

Course and Complications

- HRCT shows progressive increase in the extent of centrilobular GGOs, which usually reflects the clinical worsening up to cor pulmonale.
- Complication with discrete pulmonary hemorrhage is seen on HRCT as patchy ground-glass opacification; overinfection of hemorrhagic foci can happen.
- Lung transplantation is the only definitive treatment that grants long-term survival.

Prostacyclins (e.g., epoprostenol) are life-threatening in patients with postcapillary pulmonary hypertension and in PCH, because they cause pulmonary edema. Therefore, patients with presumed primary pulmonary hypertension should undergo HRCT before treatment to exclude signs of PCH before therapy administration.

O'Keefe MC (2015) Pulmonary capillary hemangiomatosis: a rare cause of pulmonary hypertension. Arch Pathol Lab Med 139(2):274–7.

Definition

Respiratory bronchiolitis (RB) is a smoke-related lung disease, which is usually asymptomatic, and it theoretically involves all smokers. The association with symptoms defines the subtype called respiratory bronchiolitis interstitial lung disease (RB-ILD). Both RB and RB-ILD are characterized by the deposition of pigmented macrophages into the lumen of first- and second-order respiratory bronchioles. The HRCT pattern is identical between RB and RB-ILD, with the latter showing larger lung involvement.
Smoking-related RB-ILD is an obstructive inhalational lung disease characterized by centrilobular subsolid nodules and patchy faint ground-glass areas which reflect the deposition of pigmented macrophages in the terminal bronchioles.

☯ RB-ILD

📖 Madan R (2016) Spectrum of smoking-related lung diseases: imaging review and update. J Thorac Imaging 31(2):78

Fraig M (2002) Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 26(5):647

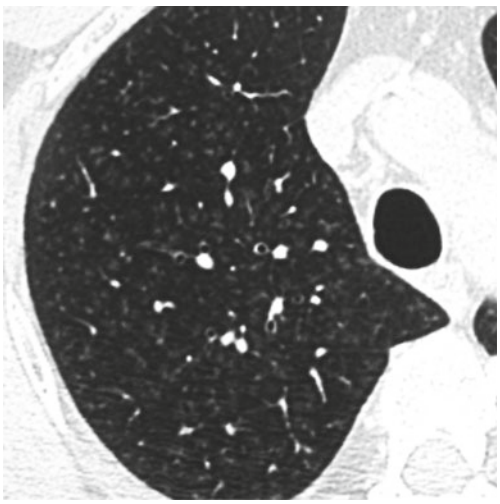
HIGH-RESOLUTION CT: HRCT

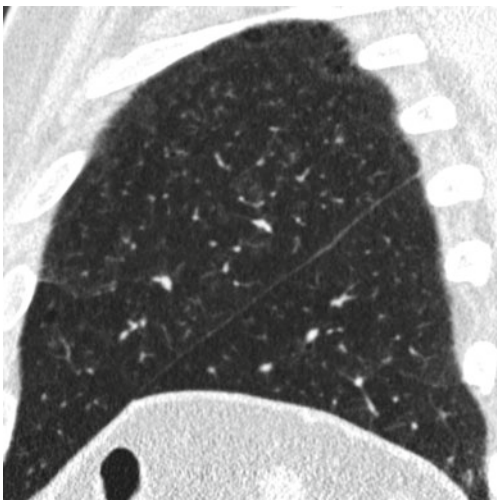
Key Signs

- Tiny centrilobular nodules with ground-glass attenuation (snowflake nodules) (please see the axial image below)
- Small areas of ground-glass attenuation with patchy distribution (please see the sagittal image below)

Distribution

Nodules may show apical dominance; however homogeneous distribution is also seen. With respect to the secondary lobule, nodules have consistent centrilobular location with constant sparing of subpleural parenchyma which appears relatively darker.





☝ The HRCT pattern of smoking-related RB and RB-ILD is seen also in environmental exposure to particles with inflammation and fibrosis of respiratory bronchioles. However, the histological pattern is different between smoke-related and environmental respiratory bronchiolitis. Therefore, parenchymal signs are faint and aspecific, though relatively specific when associated with cigarette smoke.

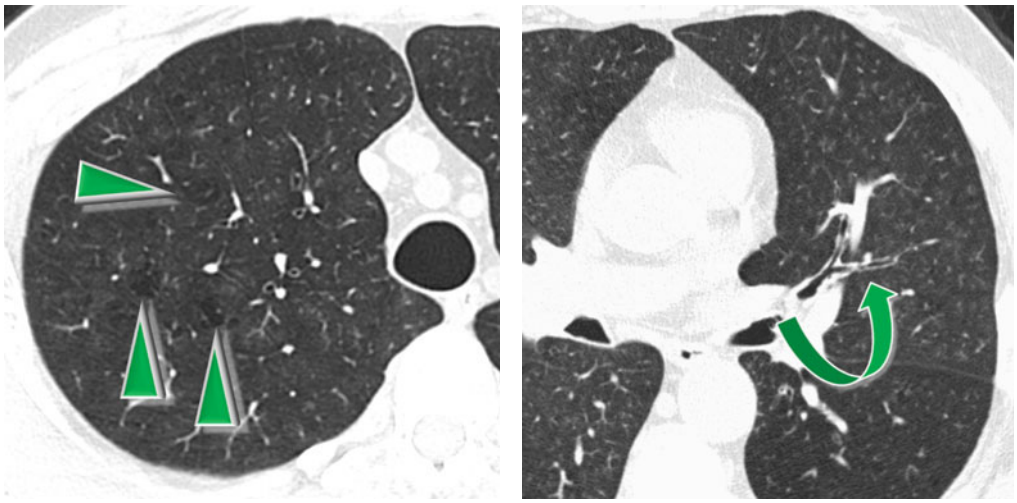
📖 Kligerman SJ (2015) Mosaic attenuation: etiology, methods of differentiation, and pitfalls. Radiographics 35:1360

Ancillary Signs

- Centrilobular emphysema (►)
- Bronchial wall thickening (⇩)

Non-parenchymal Signs

- Small reactive lymph nodes



Air trapping can be highlighted on expiratory scan in association with airflow obstruction in respiratory bronchioles. The differential between RB-ILD and HP is exceptionally challenging. RB is a smoke-related lung disease, and therefore it should be hypothesized exclusively in subjects with a history of smoke habit or passive smoke exposure. On the other hand, RB-ILD might result particularly similar to other smoking-related lung disease such as desquamative interstitial lung disease (DIP), where areas of ground-glass attenuation are more extensive and centrilobular ground-glass nodules are uncommon.

Remy-Jardin M (2002) Longitudinal follow-up study of smoker's lung with thin-section CT in correlation with pulmonary function tests. Radiology 222(1):261

Course and Complications

- Reversibility is complete after smoking cessation.
- In one original study, consequential correlation was proposed between ground-glass centrilobular nodules and progression toward centrilobular emphysema. However, the result has not been confirmed yet.

The subtle parenchymal HRCT findings make this disease hard to differentiate compared to other inhalational lung disease (e.g., HP, environmental particles), notably in case of smoking-related disease (e.g., desquamative interstitial lung disease, DIP). Discontinuation of smoking habit is associated with significant improvement of the symptoms and HRCT findings, up to complete radiological resilience.

Hansell DM (2010) Thin-section CT of the lungs: the hinterland of normal. Radiology 256(3):695–711

Definition

Sarcoidosis is a systemic granulomatous disorder of unknown etiology with a wide spectrum of radiological appearances and common pulmonary involvement. In typical cases, chest radiography may be sufficient to establish the diagnosis. However, CT can play a pivotal role in several clinical settings: atypical clinical and/or radiographic findings, normal or near-normal chest radiograph but clinical suspicion of sarcoidosis, and detection of complications.

Sarcoid, Besnier Boeck Schaumann disease

Valeyre D (2015) Pulmonary sarcoidosis. Clin Chest Med 36(4):631

Silva M (2015) Imaging of sarcoidosis. Clin Rev Allergy Immunol 49(1):45

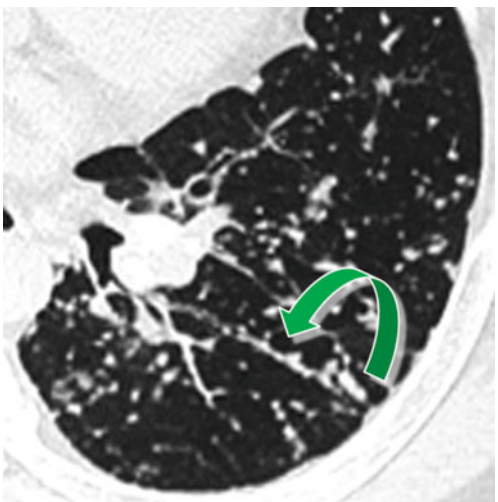
HIGH-RESOLUTION CT: HRCT

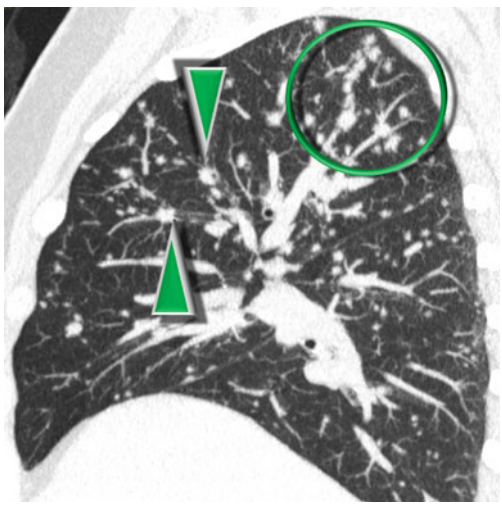
Key Signs

- Solid nodules with well-defined margins, distributed along bronchial (►) and vascular bundles (O), beneath the visceral pleura and along fissures, and interlobular septa (perilymphatic pattern, "avid for pleura") (☟).
- The nodules may have smooth or irregular (shaggy) margins and commonly measure 2–5 mm.

Distribution

Upper-lobe predominance



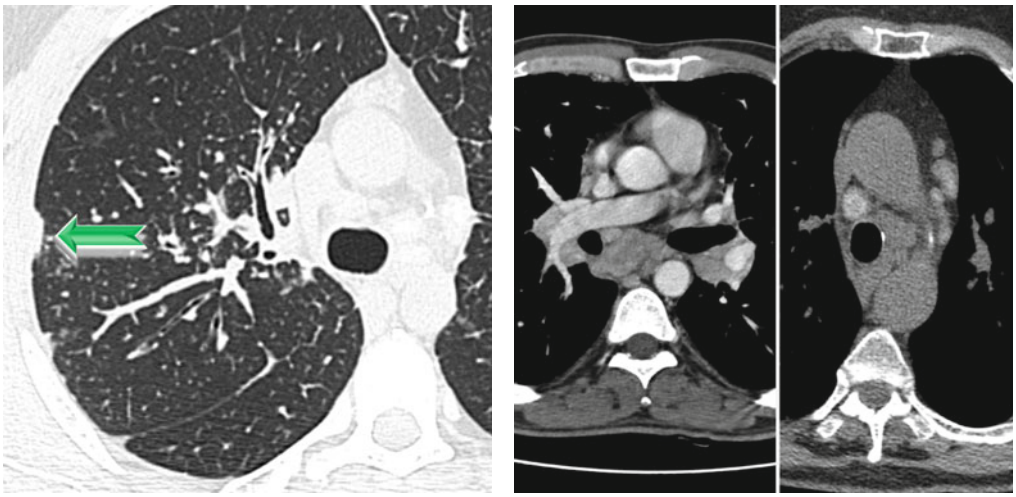


Ancillary Signs

- Nodules may coalesce (pseudoplaques) ➡.
- Air trapping on expiratory scan.

Non-parenchymal Signs

- Symmetric hilar lymph node enlargement
- Possible lymph node calcification with specific patterns described as "eggshell" or "icing sugar"
- Pulmonary artery dilation in case of pulmonary arterial hypertension



Pseudoplaques are peripheral, small, elongated opacities with long axis parallel to the adjacent costal boundaries (please see this sign in the chapter Nodular Pattern).

✓ In the appropriate clinical setting, a combination of mediastinal and parenchymal abnormalities on HRCT may be pathognomonic of sarcoidosis. This is particularly the case when lymph nodes show subcarenal and symmetric hilar enlargement and the typical perilymphatic distribution of nodules.

Hawtin KE (2010) Pulmonary sarcoidosis: the 'Great Pretender'. Clin Radiol 65:642

Spagnolo P (2014) Imaging aspects of the diagnosis of sarcoidosis. Eur Radiol 24(4):807

Course and Complications

- HRCT has prognostic value because it can differentiate between reversible and irreversible abnormalities; conversely, it is not necessary in the follow-up of sarcoidosis.
- Sarcoidosis can progress toward end-stage fibrotic lung disease in a limited number of cases (5 %) (please refer to Chronic Sarcoidosis in the chapter "Fibrosing Diseases").
- Among the complications of sarcoidosis, aspergillus-related lung disease (2 %) and pulmonary hypertension are to be suggested by radiologists.

For most patients, pulmonary sarcoidosis is a somewhat benign and self-limiting disorder. However, for others sarcoidosis can be a chronic and debilitating disease associated with significant mortality. An easy staging system integrating pulmonary function tests and HRCT measures of pulmonary hypertension identifies patients at high clinical risk.

Walsh SL (2014) An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med 2(2):123

Sarcoidosis in literature has been called the "great mimic" and can manifest with various patterns on HRCT. The most "typical" pulmonary findings of pulmonary involvement are listed in the previous two pages. The "atypical" pulmonary features are listed in Table 1 below:

Park HJ (2009) Typical and atypical manifestations of intrathoracic sarcoidosis. Korean J Radiol 10(6):623

Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30(6):1567

Table 1 "Atypical" sarcoidosis

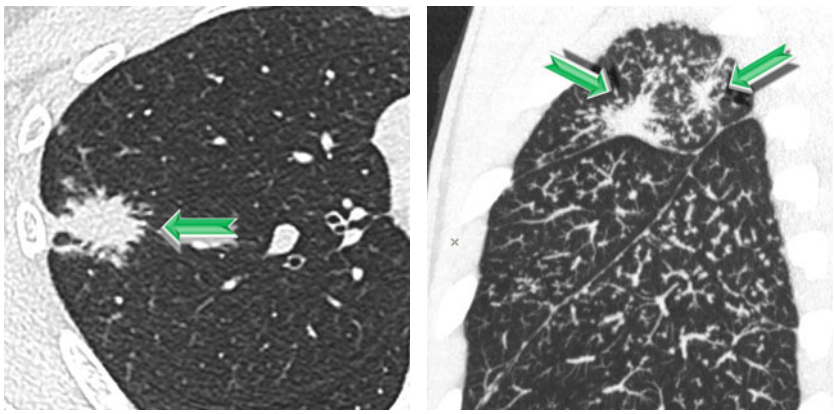
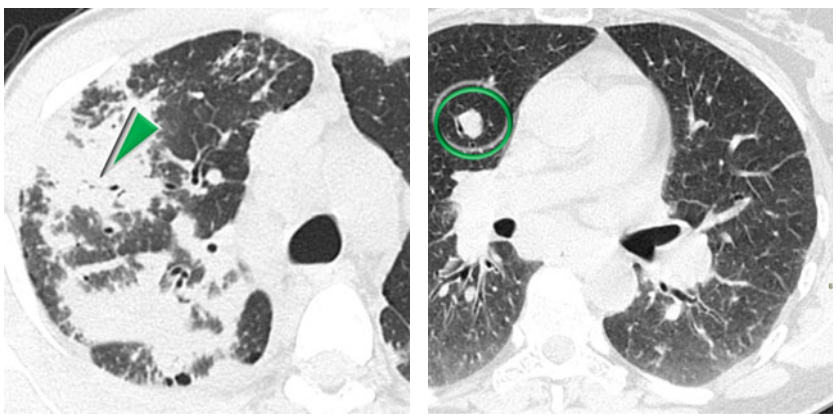
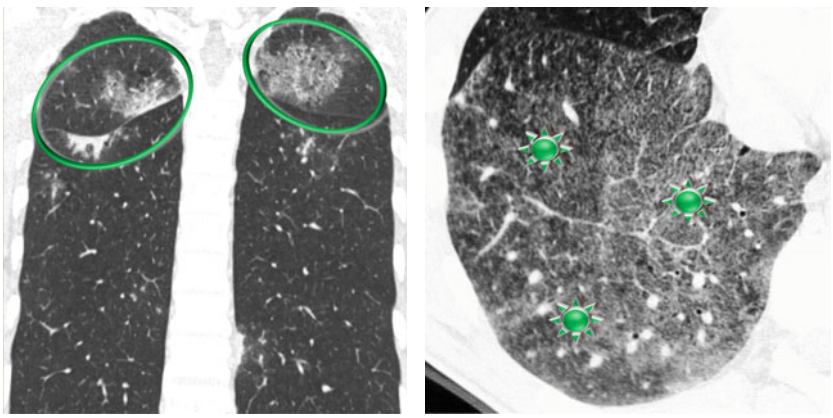
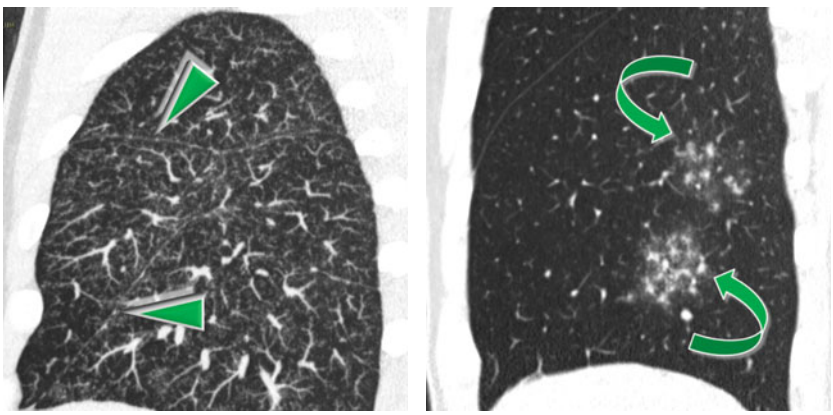
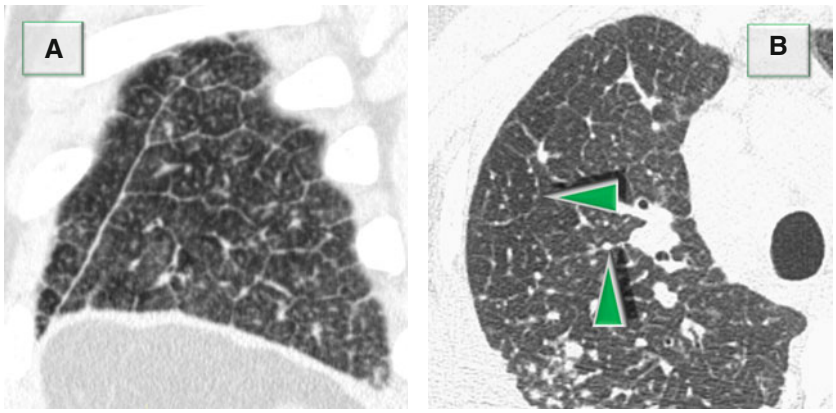
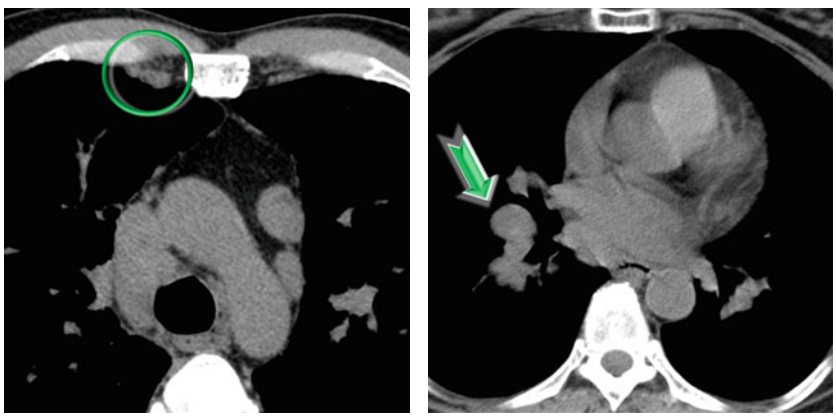
Galaxy sign	The galaxy sign is characterized by a main large solid nodule with satellite small peripheral nodules abutting its surface and distributed in its proximity (➡). In sarcoidosis, the galaxy sign may be single or multiple (➡ ➡). For the differential diagnosis of galaxy sign in different diseases, please refer to the "Nodular Pattern" and also in the "Case-Based Glossary with Tips and Tricks").
	
Macronodule; masses	Pulmonary macronodules and masses are seen in about 20 % of patients with parenchymal involvement from sarcoidosis. They represent coalescent interstitial granulomas. There is no specific location; indeed both perihilar and peripheral distribution are equally seen. Depending on the size and location, air bronchogram can occasionally be seen within the consolidation (►). They are usually multiple and bilateral, solitary lung mass or nodule is uncommon in sarcoidosis (O), and, therefore, it should prompt diagnostic work-up.
	

Table 1 (continued)

"Alveolar" sarcoid pattern	Airspace opacification is reported in about 15 % of patients with sarcoidosis. Middle-upper zones of the lung are preferentially involved, notably with bilateral distribution (O). Heterogeneous alveolar involvement is quite frequent in subjects with parenchymal involvement which may show patchy ground-glass areas in up to 40 % of cases (✸), variably associated with signs of fibrosis.
	
"Miliary" nodules; nodular cluster sign	Miliary pattern can be seen in sarcoidosis, which should be differentiated from other pathologies with different therapeutic approaches (e.g., tuberculosis) and prognoses (e.g., metastatic cancer). In sarcoidosis, solid micronodules represent granulomas, notably distributed along the main lymphatic network. Indeed, the differential of miliary pattern in sarcoidosis is provided by the typical so-called "avid of pleura" (►) distribution, which should be carefully confirmed along fissures, parietal pleura, and bronchovascular bundle. Moreover, clusters of nodules can appear heterogeneously distributed within the lung into the so-called nodular cluster sign (↬), to be differentiated from the galaxy sign by the absence of coalescence (please also refer to the Nodular Cluster Sign in chapter "Nodular Pattern").
	

(continued)

Table 1 (continued)

"Lymphangitic" septal spread	Smooth (Figure A) and beaded interlobular septal thickening (Figure B, ►) are seen in sarcoidosis. In particular, the "beaded septum sign" (►) reflects multiple granulomas along interlobular septa. The differential of beaded septum sign should first account lymphangitic carcinomatosis, where the in-line nodules are caused by neoplastic infiltration along the lymphatic stream.
	
Atypical patterns of lymphadenopathy	Provided that symmetric lymphadenopathy is the hallmark of sarcoidosis, asymmetric hilar enlargement can be seen in sarcoidosis as well as lymph node enlargement in atypical location, for instance, the internal mammary (O), paravertebral, and retrocrural regions. Atypical distribution of lymph node enlargement should always prompt a diagnostic work-up to rule out neoplastic (e.g., lymphoma, metastatic involvement) and infectious nature. It has been reported that asymmetric hilar enlargement has prevalence as low as 5 % in sarcoidosis (➡).
	

Definition

Silicosis is a pneumoconiosis caused by the chronic inhalation of fine particles of silica, which are responsible for lung toxicity possibly causing fibrotic evolution. The classic form of silicosis represents a chronic disease that can be divided into a simple and a complicated form. Silicosis is a pneumoconiosis that can reliably be diagnosed by integration of imaging findings and assessment of exposure.

Silicosis can be distinguished in different forms based on the presence of small nodules (simple) or soft-tissue masses (complicated). Symptoms are mainly associated with complicated silicosis, whereas a bare history of working exposition to silica dust is associated with an increased risk of infectious or neoplastic complications.

Progressive massive fibrosis (PMF) for the complicated form of classic silicosis

Chong S (2006) Pneumoconiosis: comparison of imaging and pathologic findings. Radiographics 26(1):59

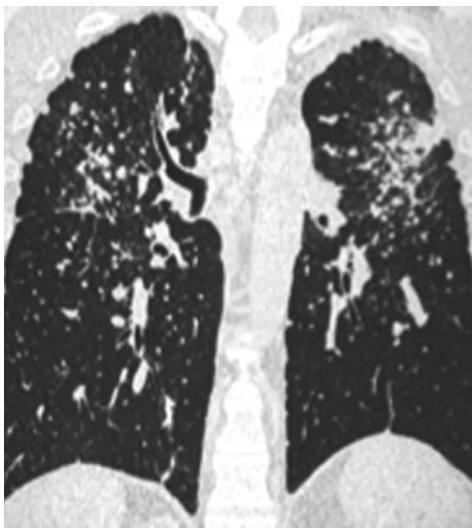
HIGH-RESOLUTION CT: HRCT

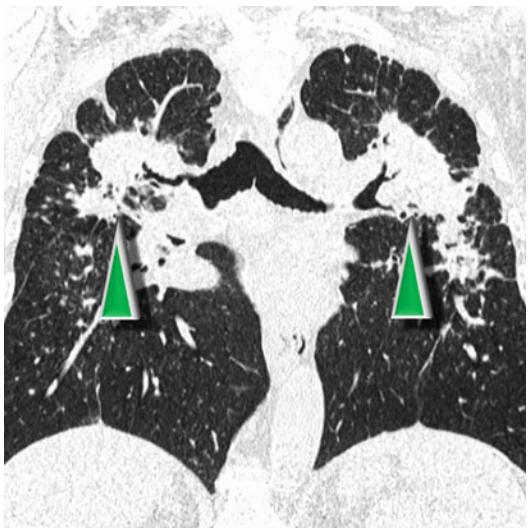
Key Signs

- Simple silicosis: solid bilateral nodules (1–10 mm) with perilymphatic distribution; the nodules tend to coalesce in the most peripheral pulmonary regions forming the so-called pseudoplaques.
- Progressive massive fibrosis: usually bilateral and symmetrical solid masses (diameter more than 1 cm) (►) surrounded by cicatricial emphysema.

Distribution

- Simple silicosis: nodules are mainly located in the upper and posterior lung zones.
- Progressive massive fibrosis (PMF): the masses tend to develop in the mid-zone or periphery of the upper lung showing a tendency to migrate toward the hila.





Upper and posterior lung zones are mostly involved by solid nodules, allegedly related to relatively slow lymphatic drainage. Perilymphatic distribution of nodules is typical, with typical coalescence of subpleural nodules into pseudoplaques.

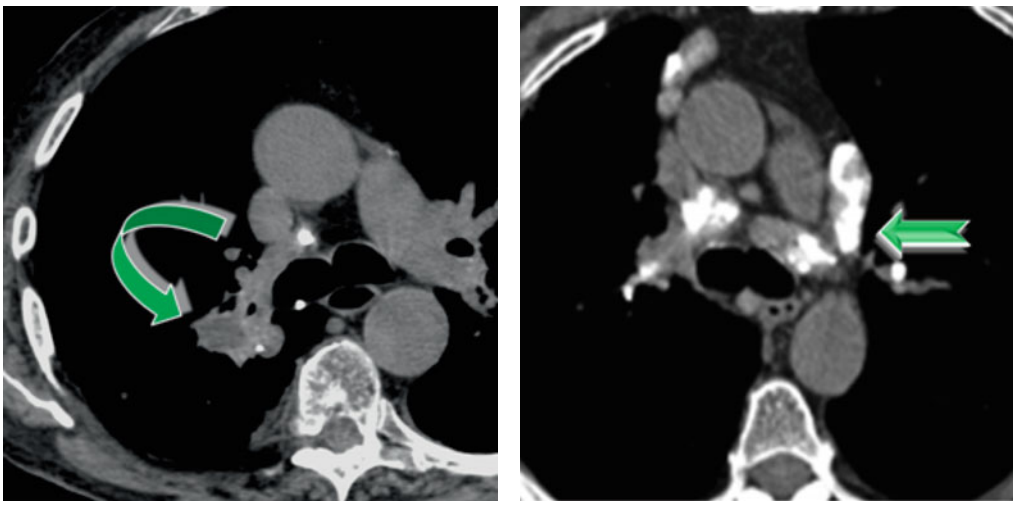
Kim KI (2001) Imaging of occupational lung disease. Radiographics 21(6):1371

Ancillary Signs

- Paracicatricial emphysema.
- The masses of PMF may show endolesional hypodensity (↬), cavitation, and calcification because of ischemic necrosis, tuberculosis, or infective complications (e.g., anaerobic bacteria).
- "Candle-wax lesions," histologically analogous to parenchymal nodules, are related to the coalescence of subpleural micronodules.
- Apical fibrotic scars.

Non-parenchymal Signs

- Eggshell calcifications are seen in mediastinal lymph nodes (➡).
- Diffuse or localized thickening of the visceral pleura may be present.



The masses of complicated silicosis derive from the coalescence of the underlying nodules, and therefore their appearance is associated with a numerical reduction of the small nodules.

Webb W.R (2010) Pneumoconiosis, thoracic imaging: pulmonary and cardiovascular radiology. Williams and Wilkins, Lippincott

Lopes AJ (2008) High-resolution computed tomography in silicosis: correlation with chest radiography and pulmonary function tests. J Bras Pneumol 34(5):264

Course and Complications

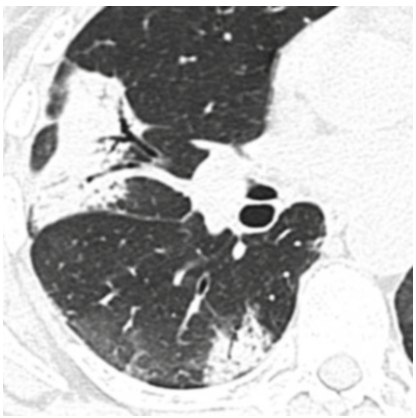
- Acute silicosis causes a rapidly progressive detriment of the pulmonary function with an increased risk of death due to respiratory failure.
- Although rare, acute exposure to silica dust may lead to silicoproteinosis, a life-threatening condition characterized by the alveolar filling of proteinaceous material.
- While simple silicosis is usually asymptomatic and is not responsible for a reduced lung function, complicated silicosis is associated with respiratory symptoms (i.e., exertional dyspnea) and lung function impairment.
- Silicosis is a known risk factor for mycobacterial infections (*M. tuberculosis*, *M. kansasii*, and *M. avium* complex) probably because of a toxic effect of silica on alveolar macrophages; lung cancer has been also shown to present an increased incidence in patients with silicosis.

Kim JS (2002) Imaging of nonmalignant occupational lung disease. J Thorac Imaging 17(4):238

Churg A (2006) Pathological reactions to inhaled particles and fibers, in imaging of occupational and environmental disorders of the chest. Springer, Berlin/Heidelberg

Alveolar Pattern

Radiology **Giorgia Dalpiaz**
Pathology **Alessandra Cancellieri**



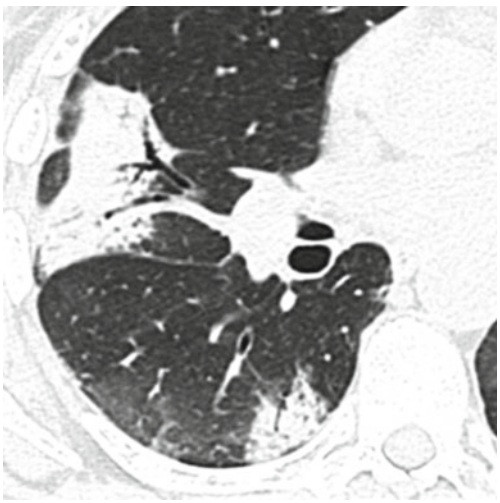
G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_9

ALVEOLAR PATTERN

Definition

An alveolar pattern is defined by the existence of more or less broad portions of the lung more opaque than normal due to partial or complete alveolar filling. With a few exceptions, the pulmonary architecture is overall preserved, and, if signs of interstitial involvement are present, they are not prevalent. On HRCT the different opacity of the alveolar pattern reminds the variable density of the clouds.

Air-space-filling pattern, cloudy opacities



Why are some clouds white and others gray? The color depends on a physical characteristic called reflectance, which indicates the percentage of light that is reflected from the cloud. In general, denser clouds have a reflectance of 90 % and are thus light in color.

In alveolar diseases, this pattern is predominant; however, there are other diseases in which alveolar opacities may be found, albeit less important or sporadic. They are therefore described in the relevant chapters.

The HRCT key signs are:

- Ground-glass opacity
- Consolidation

The ancillary signs are:

- Hypodense consolidation
- Hyperdense consolidation
- Cystic consolidation
- Crazy paving
- Head-cheese sign
- Reversed halo sign (atoll sign)
- Perilobular pattern
- Lobular/sublobular consolidation and GGO
- Tree-in-bud sign, bronchiolar

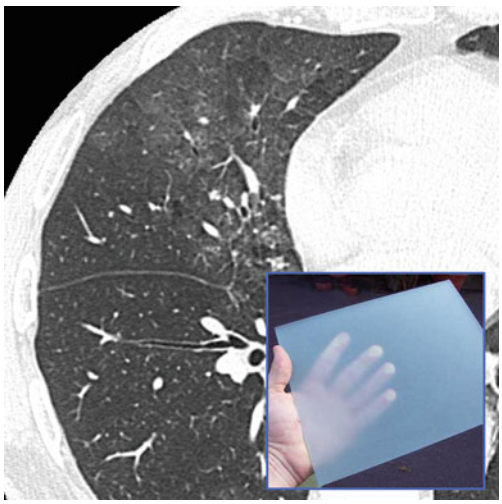
The prevalent distribution of the signs, together with the presence of non-parenchymal signs, may be helpful for the diagnosis of a specific disease (please see the tables at the end of this chapter).

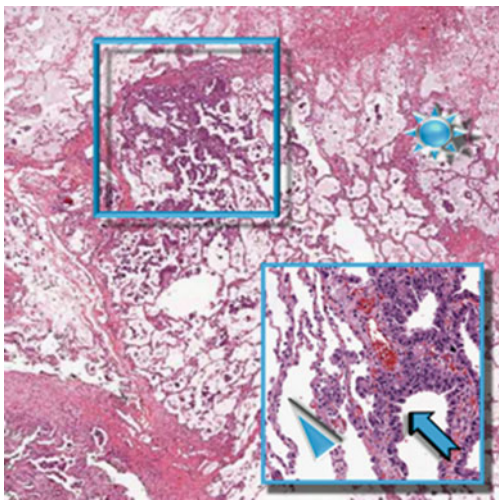
ALVEOLAR KEY SIGNS

Ground-Glass Opacity (GGO)

On CT scans, ground-glass opacity (GGO) appears as hazy increased opacity of the lung, with preservation of bronchial and vascular margins. Ground-glass opacity is less opaque than consolidation, in which bronchovascular details are obscured. The final effect is similar to the ground glass inserted in windows and doors (please see the left image below).
Pathologically, it may be caused by partial filling of air spaces and/or interstitial (mainly, alveolar septal) thickening due to fluid and/or cells. An example, illustrated in the figures below, is mucus in pneumonia-like pattern of mucinous adenocarcinoma. There are both a diffuse partial filling of air spaces due to mucus (✸) and the lepidic growth of the neoplasm along alveolar septa (□). In the close-up, note the comparison between the different thickening of the normal alveolar septa (►) and the pathological ones (➡). Please also refer to the chapter entitled "Thinking Through Pathology".

☯ GGO





☝ GGO may also be due to partial collapse of alveoli, increased capillary blood volume, or a combination of these, the common factor being the partial displacement of air.

GGO may also be due to interstitial fibrosis. It is variously associated with traction bronchiectases and bronchiolectases, fibrotic reticular abnormalities, and volume loss (please also refer to chapter "Fibrosing Pattern").

✓ Dark bronchogram sign ("overly good" visualization of bronchial structures within areas of ground-glass opacity) is a helpful mark to recognize minimal diffuse GGO.

🚹🚺 GGO can be seen in all patients with an underlying alveolar lung disease, so its diagnostic value in isolation is limited; however, the clinical context (*acute* or *chronic*), together with the distribution and in combination with associated signs, may be helpful (please see the tables at the end of this chapter).

🕮 Engeler CE (1993) Ground-glass opacity of the lung parenchyma: a guide to analysis with high-resolution CT. AJR Am J Roentgenol 160(2):249

Hansell D (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

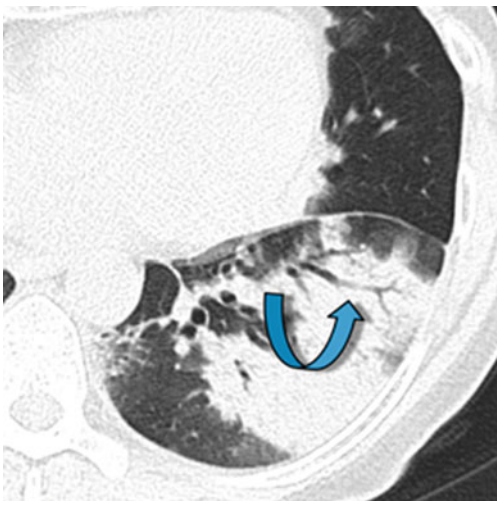
Miller WT Jr (2005) Isolated diffuse ground-glass opacity in thoracic CT: causes and clinical presentations. AJR Am J Roentgenol 184(2):613

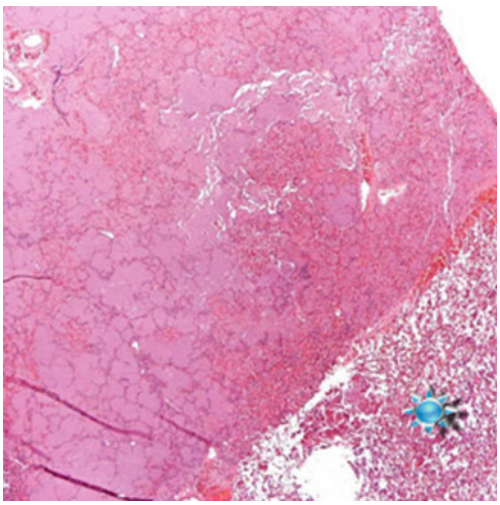
Consolidation

Consolidation appears as a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls. An air bronchogram may be present (☟).

Pathologically, consolidation is due to a complete filling of alveoli by any material (exudate, cells, or other disease product can cause a similar radiological aspect) – the common factor being the full displacement of air from alveoli. An example, illustrated in the figure below, is pulmonary alveolar proteinosis (PAP).

Note the abrupt transition between the area in which alveoli are filled by proteinaceous material and the normal lung (✸). Please also refer to the chapter entitled “Thinking Through Pathology >Pattern >Alveolar Filling.”





Consolidation can be seen in all patients with an underlying alveolar lung disease, so its diagnostic value by itself is limited; however, the clinical context (*acute* or *chronic*) and the distribution may be helpful together with the associated signs (please see the tables at the end of this chapter).

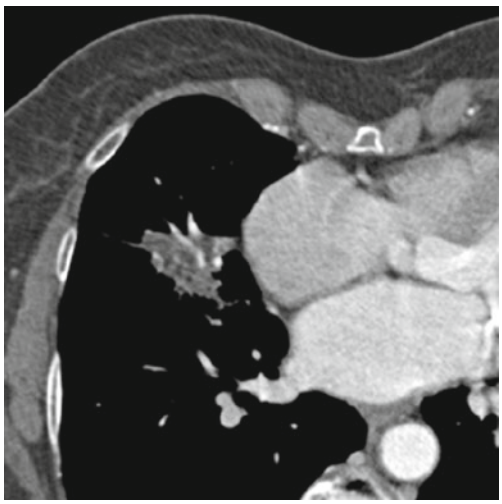
Hansell D (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

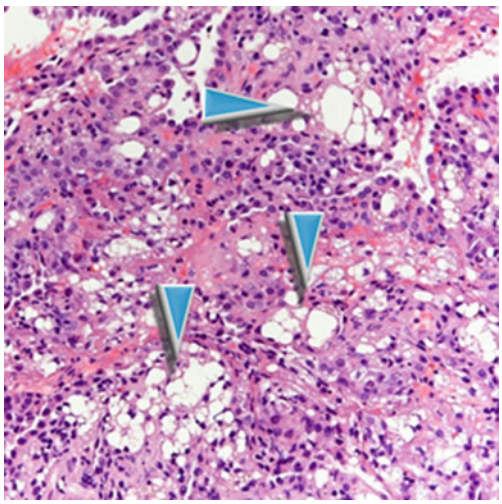
ANCILLARY SIGNS

Hypodense Consolidation

Using mediastinal window, an attenuation of consolidation is defined hypodense when it is lower than the muscle. It may be visible on CT after intravenous contrast material administration (please see CT image below). Sometimes the hypodense consolidation may be visible on unenhanced CT (HRCT) due to very low-density material (e.g., fat ► in lipoid pneumonia). Hypodense consolidations can result from ischemia (lung infarction) or from the presence in the air space of mucinous neoplasms (primary or metastatic mucinous adenocarcinoma), mucus (obstructive pneumonia with abundant accumulation of secretions), necrosis (necrotizing pneumonia), or fat (lipoid pneumonia, see the images below). With the exception of infarct, on enhanced CT you can also find the so-called angiogram sign, i.e., the visualization of pulmonary vessels within an airless, low-attenuation consolidation (please see CT image below). Please also refer to angiogram sign in "Case-Based Glossary with Tips and Tricks".

Low-attenuation consolidation, low-density consolidation





Fat-containing hypodense consolidation shows CT-negative Hounsfield units (values between –150 and –30 HU).

Hypodense consolidation is recognizable only with CT mediastinal window, and it is more visible on contrast enhancement CT (see the figure above).

Diseases with hypodense consolidation:

- *Lipoid pneumonia*: fatty consolidation (–150 and –30 HU) with dependent distribution (please see the figures above); patchy GGO and crazy paving often coexist.
- *Mucinous adenocarcinoma*, *primary or metastatic*: low-density consolidation with possible air-filled cystic spaces (please also refer to bubble-like sign in "Case-Based Glossary with Tips and Tricks"); patchy GGO often coexists.
- *Obstructive pneumonia*: crucial is the visibility of abundant accumulation of secretions inside the airways.
- *Lung infarction*: contrast enhancement CT shows filling defects within the pulmonary vasculature with acute pulmonary emboli.
- *Necrotizing pneumonia*: progression to a necrotizing pneumonia can occur from either virulence factor of the microorganism, predisposing factors of the host, or both. It can result from a large number of pathogens, mostly bacteria. Normal pulmonary parenchymal architecture within the necrotic segments is often lost.

MRI with "water-sensitive" sequences is useful in the diagnosis of patients with pulmonary consolidations suspected to be mucinous adenocarcinoma.

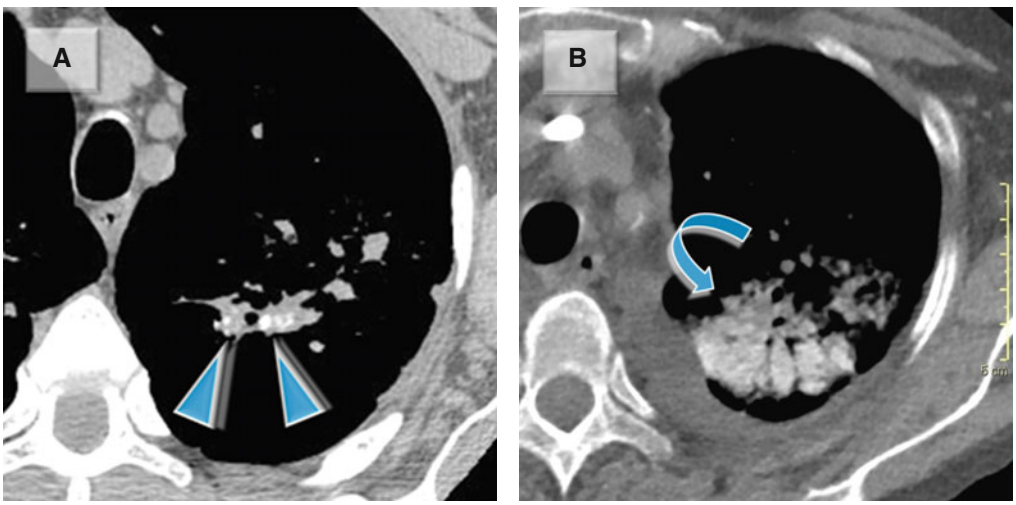
Betancourt SL (2010) Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol 194(1):103

Gaeta M (2012) MRI differentiation of pneumonia-like mucinous adenocarcinoma and infectious pneumonia. Eur J Radiol 81(11):3587

Hyperdense Consolidation

Attenuation higher than the muscle seen as dense/calcified diffuse or focal pulmonary opacities can result from a variety of different conditions. They can be due to deposition of calcium or, less commonly, other high-attenuation material such as talc, amiodarone, iron, mercury, iodinated substances, and barium sulfate. Small and *focal*, hyperdense opacities inside a consolidation can be secondary to dystrophic calcifications in previously damaged lung parenchyma or, most commonly, as a result of infection diseases (►).

High-attenuation consolidation, calcified consolidation



Diseases with multiple small *focal* hyperdense opacities inside the consolidation (Figure A above):

- *Tuberculosis*: parenchymal focal calcifications are frequently seen in tuberculosis (►). A sequela of dystrophic calcification follows caseation, necrosis, or fibrosis. These nodules are seen as well-circumscribed parenchymal calcifications with fibrosis. Most patients with pulmonary nodular calcifications secondary to tuberculosis are located in the upper lobes and the upper segments of lower lobes. Calcified hilar or mediastinal lymph nodes often coexist.
- *Amyloidosis*: the diffuse parenchymal pattern is mostly nodular and septal, although patchy consolidations may be seen. Basal and peripheral distribution is the dominant aspect. Areas of consolidations could show calcifications, some of them with punctate aspect. Lymph node enlargement, together with unilateral or bilateral pleural effusions, may be associated findings.
- *Calcified atelectasis*: chronic atelectasis can be rarely seen as calcified consolidation, often with gravity-dependent distribution.
- *Silicoproteinosis*: it may have focal calcifications, usually seen as small punctate calcified foci inside the areas of consolidation. This disease can also show hyperdense, often perihilar masses. Conglomerate masses are usually oval and have irregular borders.

Diseases with *diffuse* hyperdense consolidation (Figure B above):

- "*Metastatic" pulmonary calcification (MPC):* HRCT findings are characterized by high-attenuation consolidtations (↳) most marked in the upper zones. Nodules which may contain foci of calcification may coexist.
- *Drug toxicity* (*amiodarone*): the association of dense lung air-space consolidations with high density of the liver and spleen is characteristic of amiodarone impregnation. Consolidations are usually peripheral in location. High-attenuation nodules or masses sometimes coexist.
- *Pulmonary alveolar microlithiasis*: it is a rare chronic disease characterized by widespread calcific intra-alveolar concretions within alveolar spaces. In patients with long-standing disease, numerous

adjacent hyperdense nodules result in areas of high-attenuation consolidation. Clinical symptoms are usually absent and, when present, are characterized by dyspnea on exertion.
- *Talcosis*: in the late stage of the disease, hyperdense consolidations or confluent perihilar masses may be present. These lesions are similar to those seen in progressive massive fibrosis caused by silicosis.

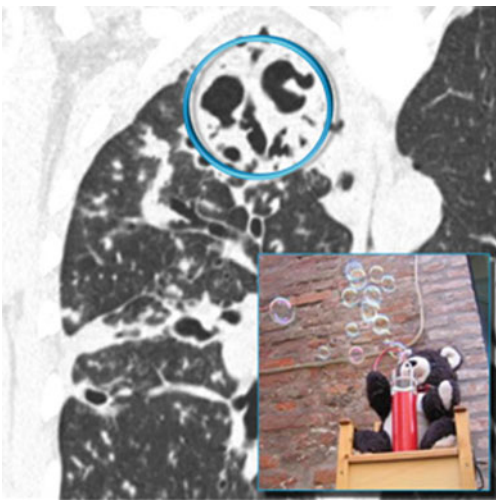
Marchiori E (2005) Diffuse high-attenuation pulmonary abnormalities: a pattern-oriented diagnostic approach on high-resolution CT. AJR 184:273

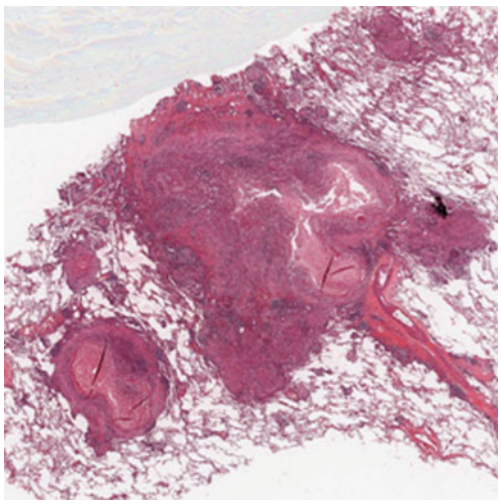
Chan E (2002) Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med 165:1654

Cystic Consolidation

Cysts (black holes) inside the consolidations and the GGO may be large or small, rounded, oval or serpentine, and sometimes confluent.
Pathogenesis: true cavitation (more often round or oval, e.g., TB – please see the HRCT and histologic images below), pseudo-cavitation (bubble-like lucencies following bronchiolar obstruction due to a check-valve mechanism), and air bronchiologram (serpentine or linear in shape due to ectatic phenomena)

Bubble-like lucencies





Nonneoplastic diseases with cystic consolidation:

- *Infection* (e.g., *TB*): the presence of cavitated consolidations or nodules in the apical and posterior segments of the upper lobes and/or the superior segments of lower lobes (please see the images above) is suggestive of TB. Another hallmark is hilar/mediastinal lymphadenopathy with possible central necrosis, more visible on contrast enhancement CT.
- *Pulmonary infarct*: cystic features are rarely present, often single unilateral consolidation with basal-peripheral distribution.
- *OP*: although cavitary infiltrates are not usually included in textbook descriptions of the disease, OP presenting with cavitating infiltrates has indeed been described, albeit rather rarely. They often present as multiple bilateral consolidations with basal-peripheral distribution.

Neoplastic diseases with cystic consolidation:

- *Adenocarcinoma*: patchy areas of non-resolving consolidation with possible halo sign and often with air bronchogram or air-filled cystic spaces. Possible lower lung predominance (please also refer to bubble-like lucencies in "Case-Based Glossary with Tips and Tricks").
- *Lymphomas*: cystic aspects are rarely present, possible mass-like aspect.

"Cystic lucencies" can be found in patients with BPCO. This pattern is caused by the coexistence of consolidations and underlying severe centrilobular/paraseptal emphysema.

Gaeta M (1999) Radiolucencies in bronchioloalveolar carcinoma: CT-pathologic correlation. Eur Radiol 9:55–9

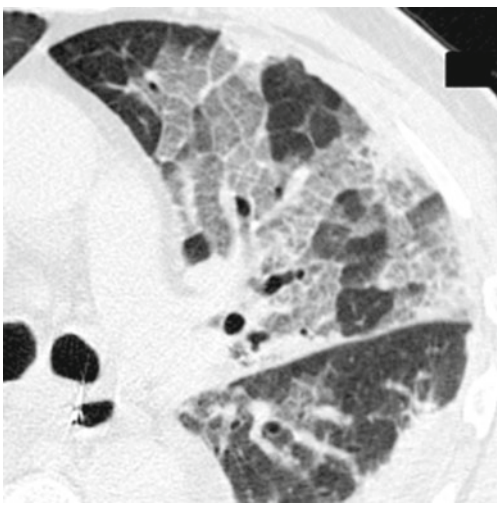
He H (2006) Pulmonary infarction: spectrum of findings on multidetector helical CT. J Thorac Imaging 21(1):1

Crazy Paving

Crazy paving appears as ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines. The crazy-paving pattern is often sharply demarcated from normal lung and may have a geographic outline, often with lobular or geographic sparing. The term crazy paving refers to the resemblance of this sign to paths made with broken pieces of stone or concrete.
In the crazy-paving sign, ground-glass opacity reflects the presence of air space or interstitial abnormalities; the lines of reticular opacities may represent interlobular septal thickening, thickening of the intralobular interstitium, irregular areas of fibrosis, or a preponderance of an air-space-filling process at the periphery of lobules or acini.

Please also refer to crazy paving in “Case-Based Glossary with Tips and Tricks”.

Colonial-era pavement, palladian sign



Acute diseases with crazy paving listed in alphabetic order:

- *Acute interstitial pneumonia (AIP)*
- *Acute respiratory distress syndrome (ARDS)*
- *Acute exacerbation of IPF*
- *Diffuse alveolar hemorrhage (DAH)*
- *Drug-induced pneumonitis*
- *Infection, acute*
- *Pulmonary edema (PE)*

Subacute/chronic diseases with crazy paving listed in alphabetic order:

- *Adenocarcinoma*
- *Chronic eosinophilic pneumonia (CEP)*
- *Lipoid pneumonia (LP)*
- *MALT lymphoma*
- *Nonspecific interstitial pneumonia (NSIP)*
- *Organizing pneumonia (OP)*
- *Pulmonary alveolar proteinosis (PAP)*
- *Radiation pneumonitis*
- *Sarcoidosis, alveolar*
- *Tuberculosis*

A crazy-paving sign can be seen as the dominant pattern only in some of the diseases listed above (e.g., PAP and lipoid pneumonia). It often represents an ancillary or uncommon finding.

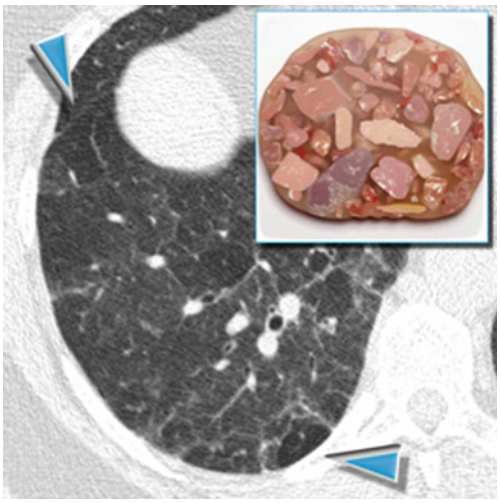
De Wever W (2011) The crazy-paving pattern: a radiological-pathological correlation. Insights Imaging 2(2):117

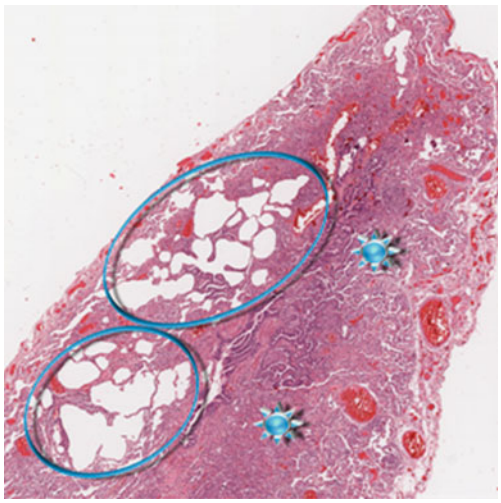
Rossi SE (2003) "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 23(6):1509

Head-Cheese Sign

On HRCT scan, head-cheese pattern is characterized by a combination of patchy lobular areas of normal parenchyma, ground-glass opacity, and mosaic oligemia with lobular air trapping (►). This definition is due to its resemblance to the variegated appearance of a sausage made of parts of the head of a hog. Pathologically head-cheese sign is indicative of a mixed infiltrative and obstructive process. The ground-glass opacity (GGO) component represents the infiltrative portion of the underlying disease (✸). Low-attenuation lobules reflect obstructive small airways disease with resultant air trapping (○) and vasoconstriction from localized hypoxia.
Please also refer to head-cheese sign in "Case-Based Glossary with Tips and Tricks".

Hog's head-cheese sign, mixed (infiltrative and obstructive) disease





Common diseases with head-cheese sign:

- *Hypersensitivity pneumonia* (*HP*), *subacute*: it is the prototype disease of head-cheese sign (see figures above). The coexistence of low-density centrilobular nodules (snowflake nodules) is helpful for the diagnosis.

Rare diseases with head-cheese sign:

- *Atypical infection with bronchiolitis* (e.g., *mycoplasma pneumonia*): frequent bilateral, lobular areas of GGO and consolidations with patchy distribution.
- *Respiratory bronchiolitis-interstitial lung disease (RB-ILD)*: although reports have cited mild emphysema in the upper lobes and small foci of GGO as distinct features of RB-ILD, it can still be difficult to distinguish RB-ILD from HP.
- *Sarcoidosis*: the presence of perilymphatic solid nodules (well-defined bronchovascular nodules and nodules along the pleural surface) helps to distinguish sarcoidosis from HP.

✓ Integrating clinical and laboratory findings may indicate the most likely diagnosis in the setting of the head-cheese sign.

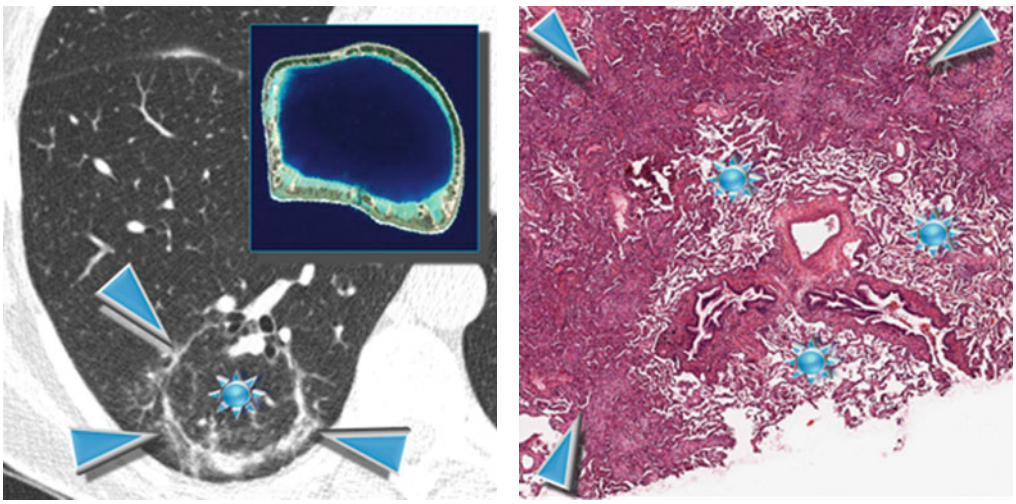
Chong BJ (2014) Headcheese sign. J Thorac Imaging 29(1):W13

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

Reversed Halo Sign

Reversed halo sign (RHS) is a rare sign. On HRCT images, it appears as a focal rounded area of ground-glass opacity (✸) surrounded by a more or less complete ring of consolidation (►). In organizing pneumonia (OP), the central ground-glass opacity corresponds histopathologically to an area of alveolar septal inflammation and cellular debris (✸), while the ring-shaped or crescentic, peripheral, air-space consolidation corresponds to the area of organizing pneumonia (►).
Please also refer to reversed halo sign in "Case-Based Glossary with Tips and Tricks".

Atoll sign, RHS



Noninfectious – nonneoplastic diseases with reversed halo sign:

- *Cryptogenic organizing pneumonia (COP) and secondary OP* (the most frequent)
- *Acute fibrinous organizing pneumonia (AFOP)*
- *Chronic eosinophilic pneumonia (CEP)*
- *Granulomatosis with polyangiitis (Wegener's granulomatosis)*
- *Hypersensitivity pneumonia (HP)*
- *Lipoid pneumonia (LP)*
- *Lymphoid interstitial pneumonia (LIP)*
- *Nonspecific interstitial pneumonia (NSIP)*
- *Post-embolic infarction*
- *Radiotherapy* and *percutaneous RF ablation*
- *Sarcoidosis*

Infection diseases with reversed halo sign:

- *Fungal pneumonia*: *angioinvasive aspergillosis*, *pneumocystosis*, *paracoccidioidomycosis*, *histoplasmosis*, *and mucormycosis*
- *Bacterial infections*: TB and bacterial pneumonia
- *Virus infection*: H1N1

Neoplastic diseases with reversed halo sign:

- *Adenocarcinoma*
- *Lymphoid granulomatosis*
- *Metastases*

Sarcoidosis and tuberculosis may present the so-called "nodular" reversed halo sign. The nodular aspect of the RHS usually corresponds to the presence of granulomatous inflammation and most likely represents active pulmonary sarcoidosis or the granulomatous infiltrate of tuberculosis. Please refer to chapter "Nodular Pattern."

Despite being no longer considered specific, the presence of RHS, in association with ancillary CT findings and an appropriate clinical history, can be useful in narrowing the differential diagnosis.

COP is the most common condition described in immunocompetent patients.

Invasive fungal pneumonia should be considered until differently proven in severely immunocompromised host.

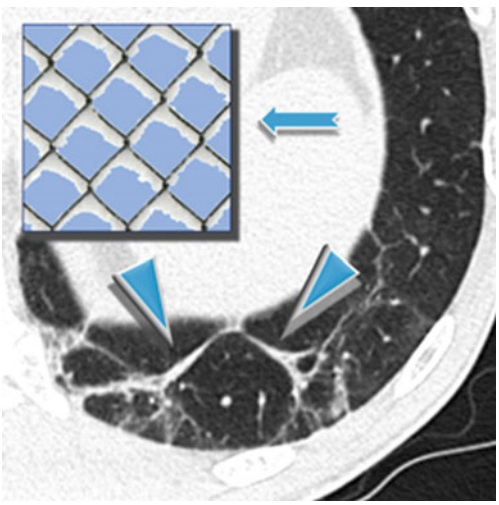
Zompatori M (1999) Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign): a case report. Radiol Med (Torino) 97:308

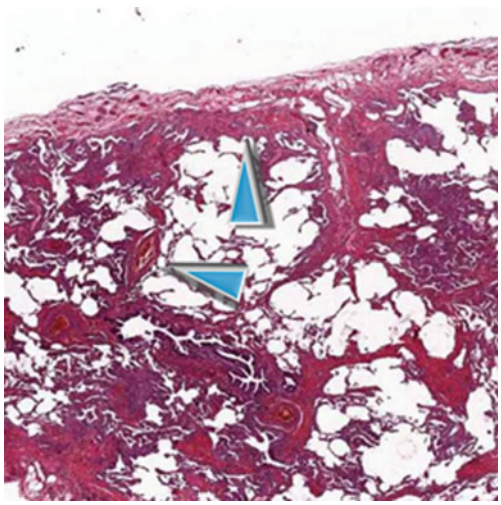
Godoy MC (2012) The reversed halo sign: update and differential diagnosis. Br J Radiol 85(1017):1226

Perilobular Opacities

The term is most frequently used in the context of diseases (e.g., perilobular organizing pneumonia – OP, images below) which are distributed mainly around the inner contour of the secondary pulmonary lobule (►). This may result in an indistinct thickening of the interlobular septa appearing as curvilinear opacities with an arcade-like or polygonal appearances similar to the snow along a wire net (➡). Perilobular pattern is thicker and, mostly, less sharply defined than those encountered in thickened interlobular septa (please compare to septal thickening visible in chapter "Septal Pattern").

Arcade-like, perilobular pattern





The term is most frequently used in the context of diseases (e.g., perilobular organizing pneumonia – OP, see images above) which are distributed mainly around the inner surface of the secondary pulmonary lobule.

Johkoh emphasized that a perilobular distribution of disease may reflect abnormalities of peripheral alveoli but also of the interlobular septa. Differential diagnosis: smooth interlobular septal thickening, nodular interlobular septal thickening, irregular (fibrosing) interlobular septal thickening, and peripheral lobular abnormalities (OP, UIP; please also refer to "Thinking Through Pathology >Pattern >Peripheral").

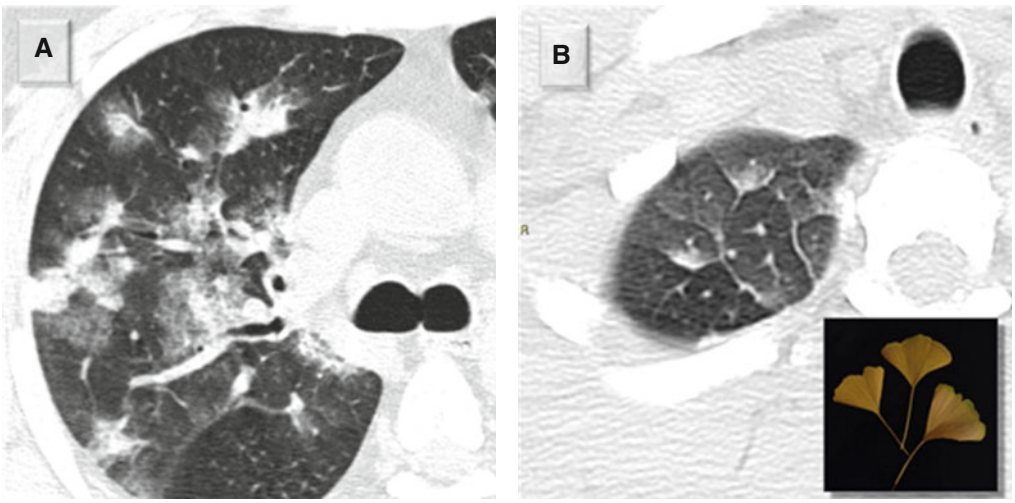
Johkoh T (1999) Perilobular pulmonary opacities: high-resolution CT findings and pathologic correlation. J Thorac Imaging 14(3):172

Ujita M (2004) Organizing pneumonia: perilobular pattern at thin-section CT. Radiology 232(3):757

Lobular/ Sublobular Opacities

Some lung diseases result in consolidation or ground-glass opacity (GGO) that involve individual lobules or groups of lobules as a whole, while adjacent lobules appear normal, giving the lung a patchwork appearance; sometimes, there may be a partial involvement of the lobule (sublobular opacities); please see Figure A. At times, lobular/sublobular consolidations and GGO may be associated with smooth septal thickening, reminiscent of a ginkgo biloba leaf. We defined this feature "ginkgo biloba sign" (Figure B). Note that the GGO sublobular areas present a gravitational-dependent distribution inside the lobules.

Lobular/sublobular consolidation/GGO, ginkgo biloba sign



Diseases with lobular/sublobular opacities:

- *Infection pneumonia* (Figure A above): e.g., pneumonia due to infection from *Staphylococci*, *Haemophilus* species, *Pseudomonas*, and *M. pneumoniae*.
- *Pulmonary edema (PE)*: bilateral pleural effusion and smooth septal thickening are often present.
- *Fat embolism syndrome (FES)* (Figure B): in patients with a fracture of a long bone, often young, the presence of lobular/sublobular consolidations, together with GGO and ginkgo biloba sign, is suggestive for FES. These signs result from the toxic and biochemical effects of free fatty acids (FFA) and of other, partly unknown, mediators with consequent edema, vasculitis, or inflammation.

Many other alveolar acute and chronic diseases may present with lobular/sublobular consolidations and GGO but not as the prevalent feature.

In some patients with lobular ground-glass opacity visible on thin-section CT scans, superimposition of a reticular pattern results in the crazy-paving appearance (please see this sign in this chapter but also in "Case-Based Glossary with Tips and Tricks").

Webb WR (2006) Thin-section CT of the secondary pulmonary lobule: anatomy and the image – the 2004 Fleischner lecture. Radiology 239(2):322

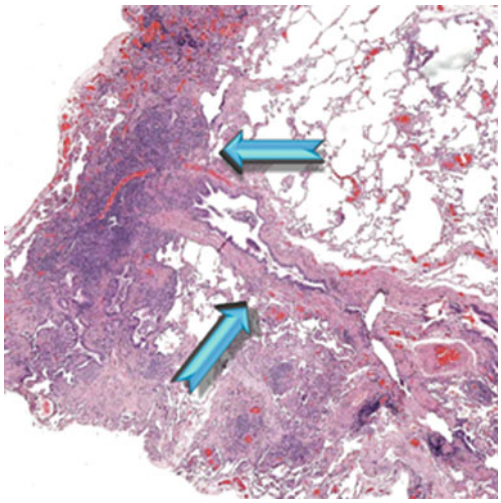
Piolanti M, Dalpiaz G (2016) Fat embolism syndrome: lung computed tomography findings in 18 patients. J Comput Assist Tomogr 40(3):335

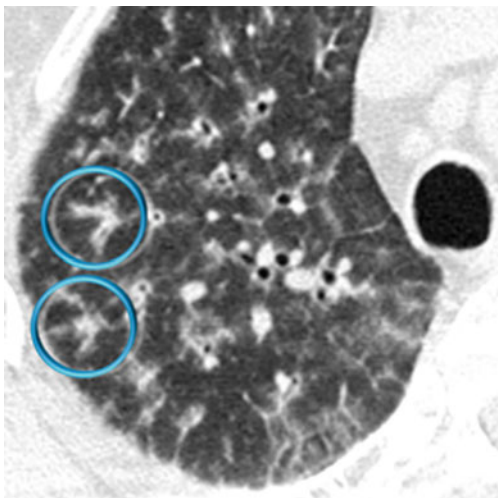
Tree-in-Bud Sign, Bronchiolar

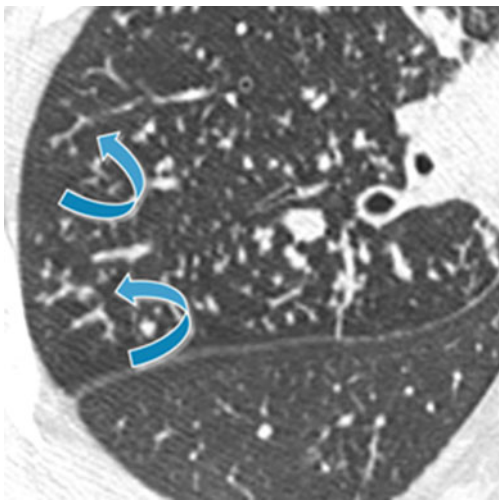
The tree-in-bud (TIB) pattern results in a V- or Y-shaped branching pattern together with centrilobular nodularity. This pattern also resembles the small objects used in the childhood game of jacks (see the image below).
The nodules and connecting branches are peripheral but spare the subpleural lung. In *acute* disease, TIB may present ill-defined margins (O). In chronic diseases TIB presents well-defined margins (⇳).

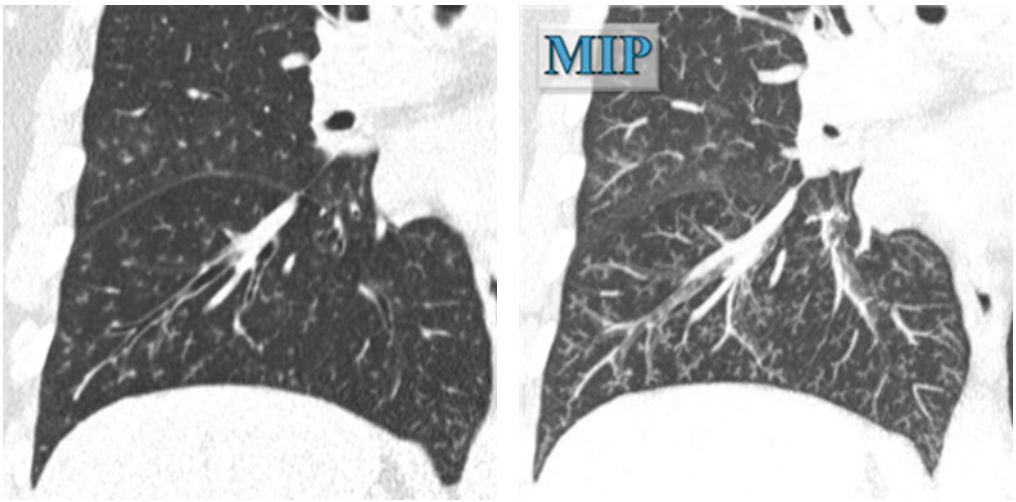
The bronchiolar tree-in-bud sign reflects a spectrum of endo- and peribronchiolar disorders, including mucoid impaction or inflammation of the wall (➡).
Please also refer to tree-in-bud sign, bronchiolar in "Case-Based Glossary with Tips and Tricks".

☯ TIB, centrilobular branching opacities, budding tree, jacks









✓ Post-processing techniques such as maximum-intensity projections (MIP) facilitate the recognition of the tree-in-bud pattern (please compare the two coronal images above).

Infection diseases with bronchiolar tree-in-bud:

- *Bacterial*: in infections caused by *Mycobacterium tuberculosis*, identification of the tree-in-bud sign along with other imaging findings, such as bronchial wall thickening or narrowing, bronchiectases, consolidation, cavitation, and/or necrotic lymphadenopathy, supports the diagnosis. In *nontuberculous mycobacterial pneumonia*, tree-in-bud sign and bronchiectases predominate, usually most severe in the right middle lobe and lingula. The tree-in-bud sign may also be present in other types of acute pneumonia (such as those caused by *Staphylococcus aureus* and *Haemophilus influenzae*), often appearing with ill-defined contours.
- *Fungal and viral*: airway-invasive aspergillosis and *Cytomegalovirus* infection typically occurs in immunocompromised patients.

Congenital diseases with bronchiolar tree-in-bud sign:

- *Cystic fibrosis*: a combination of upper lung predominant bronchiectases, bronchial wall thickening, mucus plugging, and air trapping or mosaic attenuation is commonly encountered.

Immunologic diseases with bronchiolar tree-in-bud sign:

- *Allergic bronchopulmonary aspergillosis (ABPA)*: the classic findings include central bronchiectases with an upper lobe predominance and mucoid impaction. Mucoid impaction typically appears as homogeneous, tubular, finger-in-glove opacities (please also refer to finger-in-glove sign in "Case-Based Glossary with Tips and Tricks").

Connective tissue diseases with bronchiolar tree-in-bud sign:

- *Rheumatoid arthritis and Sjögren syndrome*: the most common manifestations include follicular bronchitis, bronchiectases, bronchiolitis, and obliterative bronchiolitis.

Neoplastic diseases with bronchiolar tree-in-bud sign:

- *Endobronchial spread of adenocarcinoma*: CT features highly suggestive of aerogenous spread include persistent centrilobular nodules and branching opacities (tree-in-bud), typically with ill-defined margins and GGO attenuation. Well-defined nodules of soft tissue attenuation are less common. Nodules tend to be clustered and invariably show evidence of growth on serial images, in some cases progressing to confluent air-space disease.

Other causes of bronchiolar tree-in-bud sign:

- *Aspiration*: a gravitational and lower lung predominance of the tree-in-bud pattern is often observed. Predisposing factors such as structural abnormalities of the pharynx, esophageal disorders (achalasia, Zenker diverticulum, hiatus hernia and reflux, esophageal carcinoma), neurologic defects, and chronic illnesses are common.
- *Inhalation (toxic fumes and gases)*: acute bronchiolar damage with diffuse resultant ill-defined tree-in-bud.
- *Diffuse pabronchiolitis (DPB)*: DPB is reported almost exclusively in Asians. It is characterized by chronic inflammation of the paranasal sinuses and respiratory bronchioles. A diffuse tree-in-bud appearance predominantly affects the lung bases. Other findings include bronchial wall thickening and bronchiectases.

Rarely, neoplastic conditions such as pulmonary arterial metastases of adenocarcinoma may result in a "vascular" tree-in-bud sign (please also refer to vascular tree-in-bud in "Case-Based Glossary with Tips and Tricks").

Rossi SE (2005) Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 25(3):789

Miller WT (2013) Causes and imaging patterns of tree-in-bud opacities. Chest 144(6):1883

SUBSET ACUTE

Evaluation of the clinical onset of the symptoms for each patient is the suggested way to duly frame subsets of disorders. In particular, one should know if the onset of respiratory symptoms dates back from days to a few weeks (subset acute) or instead from months to years from the time of diagnosis (subset chronic). The *acute* alveolar pattern usually presents with bilateral and often extensive consolidations and ground glass which may change in appearance, location, and size within hours or days.

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Acute alveolar disease
GGO with possible patchy consolidations	GGO often bilateral and diffuse, consolidations with multifocal and peripheral basal distribution	Signs of fibrosing lung disease (UIP pattern)	Lymph node enlargement, pulmonary arterial hypertension	**Acute Exacerbation of IPF (AE-IPF)**
GGO, smooth interlobular septal thickening	Bilateral, patchy without zonal predominance	Possible crazy paving and consolidations	Small pleural effusion	**Acute Eosinophilic Pneumonia (AEP)**
First week: GGO and/or consolidations	Bilateral extensive GGO, mainly gravity-dependent consolidations	Second week: associated sign of fibrosis	Absent	**Acute Interstitial Pneumonia (AIP)**
First week: GGO and/or consolidations	Bilateral extensive GGO, mainly gravity-dependent consolidations	Second week: associated sign of fibrosis	Small pleural effusion	**Acute Respiratory Distress Syndrome (ARDS)**
GGO and/or patchy consolidations	Bilateral extensive GGO, patchy consolidations, possible perihilar (butterfly distribution)	Scattered feeding-vessels low-density (subsolid) nodules, solid and often cavitated macronodules	Hilar or mediastinal adenopathy, tracheal concentric wall thickening	**Diffuse Alveolar Hemorrhage in Wegener's granulomatosis (DAH in WG)**
DAD pattern: GGO, possible consolidations	Bilateral diffuse GGO, possible gravity-dependent consolidations	Possible crazy paving	Possible pleural effusion	**Drug toxicity (amiodarone)**
GGO and consolidations, also lobular	GGO and lobular consolidation prevail in the upper zones, while extended consolidations are gravity dependent	Nodules, often subsolid, possible ginkgo biloba sign	Possible pleural effusion	**Fat Embolism Syndrome (FES)**
GGO	Symmetric bilateral, diffuse, or patchy, mainly the upper lobes and perihilar regions (butterfly sign)	Possible cysts, consolidations in patients with more severe disease	Small hilar or mediastinal lymph nodes	**Infection, acute (PJP)**
GGO, peribronchial cuffing and vessel enlargement, smooth septal thickening	Bilateral, central, and gravitational, possible perihilar regions (butterfly sign)	Possible crazy paving	Bilateral pleural effusion, cardiomegaly, dilatation of arteries and veins, mediastinal lymph nodes	**Pulmonary edema (PE), alveolar**

SUBSET CHRONIC

The *chronic* form usually presents with consolidations often localized and patchy which progress slowly, even over weeks or months. GGO often coexists. There may be architectural distortion in long-time disease.
Other signs may be variously associated.

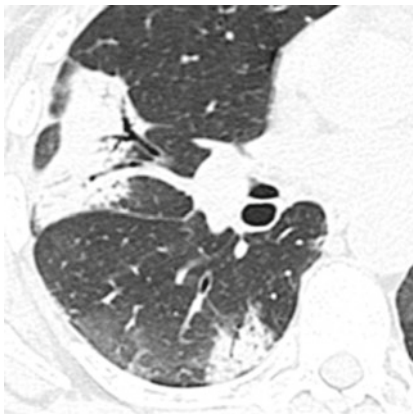
Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Chronic alveolar disease
Patchy areas of consolidation and GGO	Unilateral or bilateral, usually asymmetrical, often peripheral with lower lung predominance	Possible bubble-like lucencies, nodules, crazy paving	Adenopathies, possible pleural effusion	**Adenocarcinoma**
Patchy areas of consolidation and GGO	Bilateral peripheral (reverse bat wing sign), mainly the upper lobes	Possible crazy paving and low-density (subsolid) nodules	Adenopathies	**Chronic Eosinophilic Pneumonia (CEP)**
Patchy areas of consolidation and GGO	Bilateral peribronchial and/or subpleural, often with lower lobe predominance	Perilobular and reversed halo sign, possible crazy paving, rarely large nodules or masses	Possible mediastinal lymph node enlargement	**Cryptogenic Organizing Pneumonia (COP)**
Diffuse GGO	Bilateral symmetrical, often predominant in the peripheral regions	Possible tiny cysts within the areas of GGO, sometimes focal or lobular dark areas	Absent	**Desquamative Interstitial Pneumonia (DIP)**
OP pattern: patchy consolidations NSIP pattern: GGO and fibrosing reticulation	OP pattern: patchy NSIP pattern: diffuse, often peripheral	Nodules/masses (PET positive), crazy paving, possible hyperdense consolidations	Hyperdense liver and spleen (80 %) and heart (20 %)	**Drug toxicity (amiodarone)**
Consolidation and nodules, also cavitated, tree-in-bud sign	Patchy unilateral or bilateral, apical and posterior segments of the upper lobes, superior segments of lower lobes	Possible association with diffuse tiny random nodules	Pleural effusion (unilateral), pleural thickening, hilar/mediastinal lymphadenopathy with possible necrosis	**Infection, chronic: TB**
Patchy consolidations with possible low-density attenuation (negative values), GGO	Often bilateral, middle and lower lobes with posterior predominance	Crazy paving, low-density centrilobular nodules, signs of fibrosis	Lymph node enlargement	**Lipoid pneumonia (LP)**
Patchy consolidations	Often multiple and bilateral	Macronodules, masses	Lymph node enlargement, pleural effusion (rare)	**Mucosa-Associated Lymphatic Tissue (MALToma)**

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Chronic alveolar disease
Patchy GGO and consolidations	Prevalent lower lobe distribution	Low-density centrilobular nodules, possible clusters of tree-in-bud sign, possible beaded septum, and cheerio sign	Lymph node enlargement	**Metastases, aerogenous**
Crazy paving, GGO, possible low-density (subsolid) nodules	Bilateral diffuse, possible butterfly distribution, predominate in the lower lung	Consolidations	Lymph node enlargement, pleural effusion (rare)	**Pulmonary Alveolar Proteinosis (PAP)**

Alveolar Diseases

Radiology

Luciano Cardinale
Edoardo Piacibello
Giorgia Dalpiaz



G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_10

Definition

Adenocarcinoma has surpassed squamous cell carcinoma as the leading histologic type, accounting for 30 % of all cases of lung cancer. The new 2015 who classification provided the basis for a multidisciplinary approach emphasizing the close correlation among radiologic and histopathologic pattern of lung adenocarcinoma. The term "bronchioloalveolar carcinoma" has been eliminated, introducing the concepts of adenocarcinoma in situ (ais) and minimally invasive adenocarcinoma (mia) and the use of descriptive predominant patterns in invasive adenocarcinomas (lepidic, acinar, papillary, solid, and micropapillary patterns). Invasive mucinous adenocarcinoma is the new definition for mucinous bronchioloalveolar carcinoma.

Travis WD (2015) The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 10(9):1243

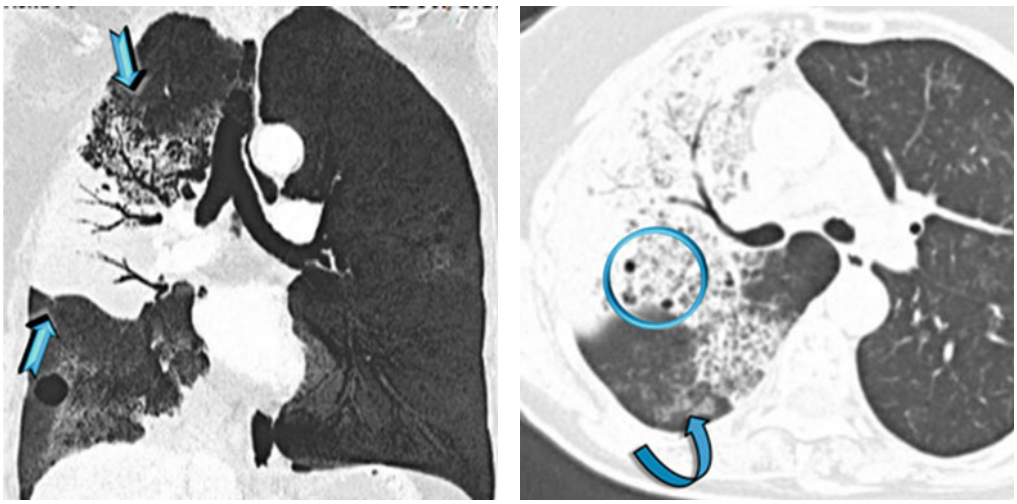
HIGH-RESOLUTION CT: HRCT

Key Signs

- Patchy areas of non-resolving consolidation (➡) with possible halo sign and often with air bronchogram or air-filled cystic spaces (bubble-like lucencies) (O)
- Patchy non-resolving ground-glass opacity

Distribution

Unilateral or bilateral, usually asymmetrical, and often patchy. The consolidation may be segmental or may involve an entire lobe or lung. Often peripheral distribution. Possible lower lung predominance.



Bubble-like lucencies are small lucencies inside consolidations (pseudocavitation). They can be formed by a valve mechanism by bronchiolar obstruction or by desmoplastic bronchiolar traction or paracicatricial emphysema. Also, lucency can result from spared pulmonary lobules (please also refer to Bubble-like lucencies in the "Case-Based Glossary with Tips and Tricks").

The stretching, sweeping, and widening of branching air-filled bronchi within an area of consolidation on computed tomography (CT) favor the diagnosis of cancer instead of pneumonia.

Areas of ground-glass attenuation and consolidation often have straight and angulated margins, suggesting demarcation by interlobular septum at the margin of the secondary pulmonary lobule. A halo sign may be present around the consolidation due to lepidic growth.

Patsios D (2007) Pictorial review of the many faces of bronchioloalveolar cell carcinoma. Br J Radiol 80(960):1015

Gaeta M (1999) Radiolucencies and cavitation in bronchioloalveolar carcinoma: CT-pathologic correlation. Eur Radiol 9(1):55

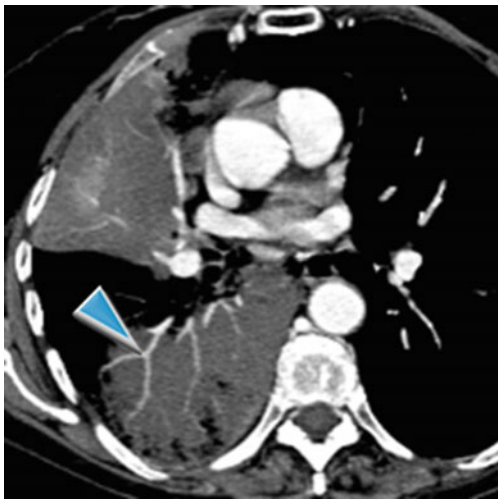
Ancillary Signs

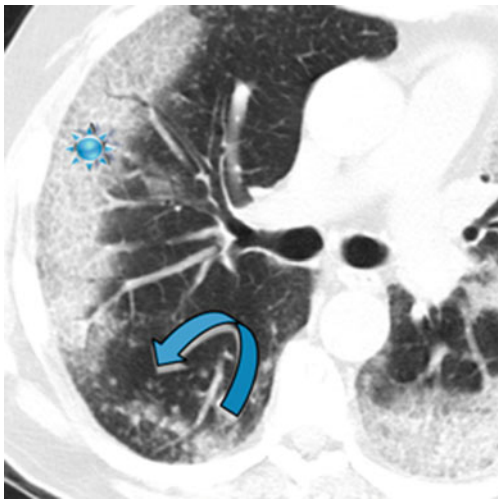
- Low-density consolidation with angiogram sign on contrast-enhanced CT (►)
- Crazy paving (✸)

- Centrilobular or feeding vessel nodules due to the aerogenous or hematogenous intrapulmonary spread of the tumoral cells
- Consolidation and/or nodules with halo sign (lepidic growth)

Non-parenchymal Signs

- Pleural effusion (10 %)
- Lymph node enlargement





Usually, inflammatory angiogram sign, pseudocavitation, and crazy paving are more frequent in adenocarcinoma than in consolidation.

CT angiogram sign may be visible because fluid and mucus produced by the tumor are of low attenuation if CT is performed with contrast infusion. This sign may be also observed in bacterial pneumonia, lipid pneumonia, pulmonary lymphoma, and metastasis of gastrointestinal adenocarcinomas (please also refer to Angiogram sign in the "Case-Based Glossary with Tips and Tricks").

Diffuse lung involvement may represent multifocal origin, endobronchial spread of tumor from primary focus, hematogenous metastases, or a combination of these.

Jung JI (2001) CT differentiation of pneumonic-type bronchioloalveolar cell carcinoma and infectious pneumonia. Br J Radiol 74(882):490

Piacibello E (2015) Lung cancer: one issue, many faces. ECR C-2202

Course

- Slow progression with continuous growth of neoplastic cells (lepidic growth).
- Intrapulmonary discontinuous spread of neoplastic cells through airspaces and airways; the discontinuous foci may be seen close to primary tumor as satellite foci or at distance, including the contralateral lung (aerogenous metastases).
- The discontinuous spread of neoplastic cells through lymphatic vessels can cause intrapulmonary metastasis along the lymphatic vessels or locoregional metastasis to the lymph nodes (lymphatic metastases).
- The discontinuous spread of neoplastic cells through blood vessels can cause intrapulmonary and systemic metastases (hematogenous metastases).

Gaikwad A (2014) Aerogenous metastases: a potential game changer in the diagnosis and management of primary lung adenocarcinoma. AJR Am J Roentgenol 203(6):W570

Warth A (2015) Prognostic impact of intra-alveolar tumor spread in pulmonary adenocarcinoma. Am J Surg Pathol 39:793

Kadota K (2015) Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I adenocarcinomas. J Thorac Oncol 10:806

Definition

The criteria for acute exacerbation (AE) of IPF include an unexplained worsening of dyspnea within 1 month, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic infiltrates, and an absence of an alternative cause of disease. Surgical lung biopsy or even surgical procedures in organs other than the lungs may also trigger AE. The annual incidence of AE-IPF is typically reported at 5–15 %. The histologic findings consist of diffuse alveolar damage (DAD) or, less commonly, prominent organizing pneumonia (OP) superimposed on the UIP pattern.

AE-IPF, accelerated phase

Collard HR (2007) Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 176(7):636

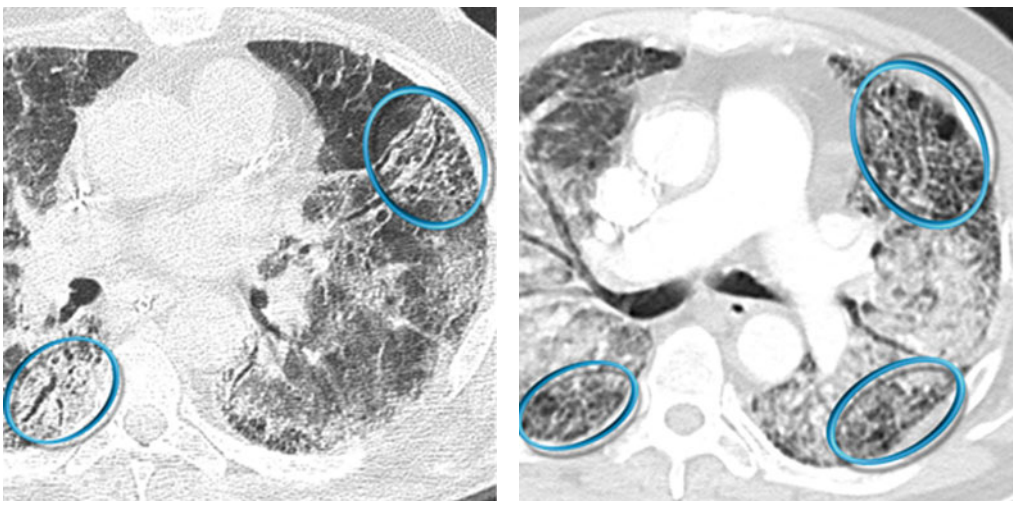
HIGH-RESOLUTION CT: HRCT

Key Signs

- Diffuse ground-glass opacity (GGO) is the dominant sign.
- Sometimes also consolidations can be visualized.
- Signs of fibrosing lung disease (O): fibrosing subpleural reticulation, traction bronchiectases, and honeycomb change typical of UIP pattern.

Distribution

Often bilateral and diffuse with possible multifocal and peripheral distribution. The consolidations tend to involve mainly the dorsal half of the lung.



Acute exacerbation is essentially a diagnosis of exclusion. Differential diagnoses include concomitant infection (such as *P. jirovecii* pneumonia or *Cytomegalovirus* infection), pulmonary edema due to left ventricular failure, pulmonary embolism, and pneumothorax.

When it is necessary to exclude the diagnosis of pulmonary thrombo-embolic disease with a CT pulmonary angiogram (CTPA), intravenous contrast enhancement increases the attenuation of the background lung parenchyma, which can complicate the evaluation of whether the lungs are of abnormally increased attenuation. In this situation, interspaced HRCT sections should be obtained prior to the acquisition of the contrast-enhanced CTPA.

Akira M (2008) Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 178(4):372

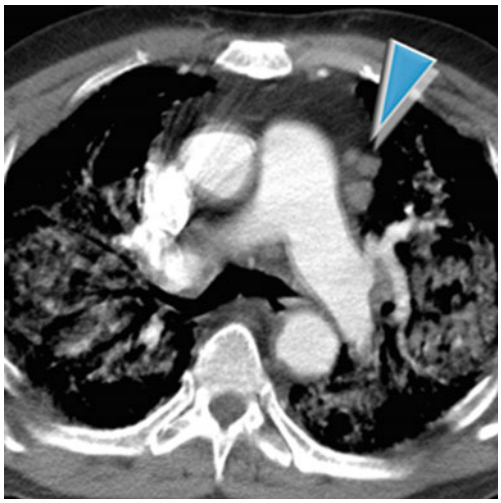
Lloyd CR (2011) High-resolution CT of complications of idiopathic fibrotic lung disease. Br J Radiol 84(1003):581

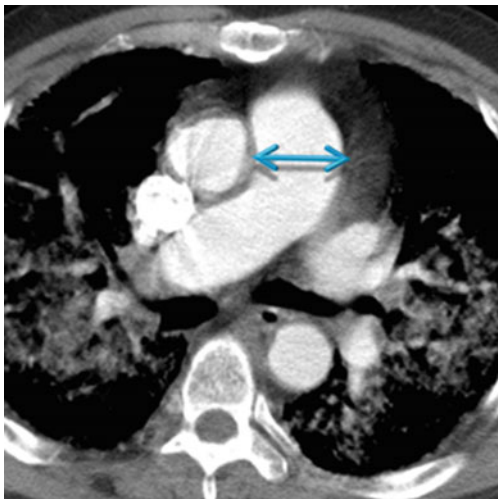
Ancillary Signs

- Crazy paving

Non-parenchymal Signs

- Lymph node enlargement (►).
- Pulmonary arterial hypertension: enlargement of the main (⬌) and proximal pulmonary arteries; however, normal-sized pulmonary arteries do not exclude the diagnosis.





Antoniou KM (2013) Acute exacerbations of idiopathic pulmonary fibrosis. Respiration 86(4):265

Luppi F (2015) Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. Intern Emerg Med 10(4):401

Course

- Patients with acute exacerbation have a poor prognosis with mortality exceeding 50 % despite therapy.
- Survival may be related to the degree of CT involvement. The extent of disease is a more important determinant of outcome than the distribution of disease.
- AE represents the most frequent cause of rapid deterioration requiring hospitalization of IPF patients.

AE have been reported in ILDs other than IPF, including nonspecific interstitial pneumonia (NSIP), chronic hypersensitivity pneumonitis (HP), and ILD associated with connective vascular disease (CVD), particularly rheumatoid arthritis.

Fujimoto K (2012) Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. Eur Radiol 22(1):83

Park IN (2007) Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 132(1):214

Definition

Acute eosinophilic pneumonia is an acute severe febrile illness associated with rapidly increasing respiratory failure. The diagnosis is based on clinical findings and the presence of markedly elevated numbers of eosinophils in BAL fluid. The majority of cases are idiopathic; occasionally, it may result from drug reaction or toxic inhalation. Patients respond rapidly to high doses of corticosteroids, usually within 24–48 h. The principal histologic finding in AEP is diffuse alveolar damage (DAD) associated with interstitial and alveolar eosinophilia.

AEP

Philit F (2002) Idiopathic acute eosinophilic pneumonia: a study of 22 patients. Am J Respir Crit Care Med 166(9):1235

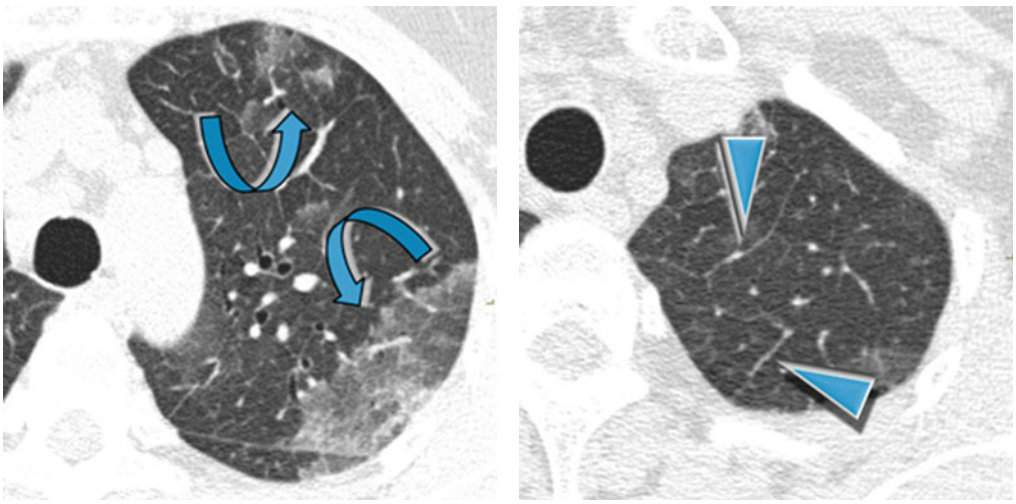
HIGH-RESOLUTION CT: HRCT

Key Signs

- Areas of ground-glass opacity (GGO) (↖)
- Smooth interlobular septal thickening (►)

Distribution

Bilateral, patchy in a random or peripheral distribution, no zonal predominance



Given that initial peripheral blood eosinophil counts are usually normal, therefore developing a clinicoradiologic differential diagnosis for AEP is often difficult.

The radiologic differential diagnosis for AEP includes hydrostatic pulmonary edema (PE), acute respiratory distress syndrome (ARDS) or acute interstitial pneumonia (AIP), and atypical bacterial or viral pneumonia. In contrast to these forms, patients with AEP usually have a dramatic response to corticosteroids, with rapid resolution of clinical signs and symptoms and radiographic abnormalities.

Obadina ET (2013) Acute pulmonary injury: high-resolution CT and histopathological spectrum. Br J Radiol 86 20120614

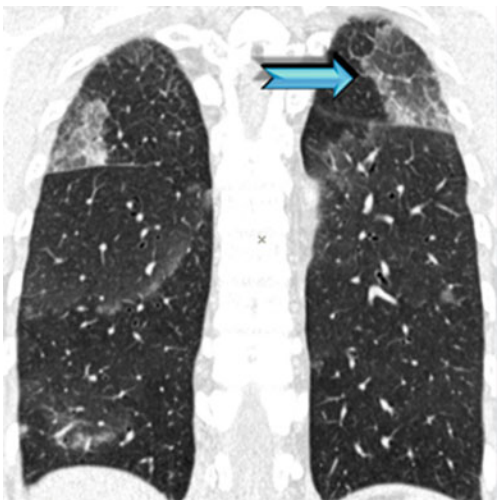
Jeong YJ (2007) Eosinophilic lung diseases: a clinical, radiologic, and pathologic overview. Radiographics 27(3):617

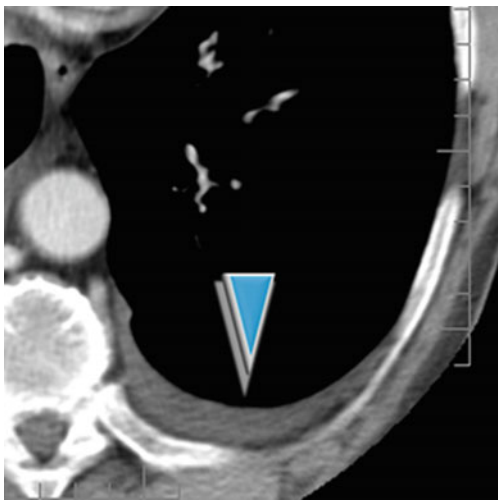
Ancillary Signs

- Possible crazy paving (➡) and consolidations
- Poorly defined centrilobular nodules and thickening of bronchovascular bundles

Non-parenchymal Signs

- Small pleural effusion is present in the majority of patients (►), absent cardiomegaly.





☝ Peripheral blood eosinophilia is often absent in contrast to chronic eosinophilic pneumonia. Eosinophilia on BAL (>25 % eosinophils) or lung biopsy is the key for diagnosis; however, eosinophils are exquisitely sensitive to corticosteroids and may disappear from blood-stream and BAL fluid within few hours after administration of corticosteroids.

📖 Cottin V (2016) Eosinophilic lung diseases. Clin Chest Med 37:535

Daimon T (2008) Acute eosinophilic pneumonia: thin-section CT findings in 29 patients. Eur J Radiol 65(3):462

Course

- Complete response to corticosteroids: no relapse after discontinuation of corticosteroids

Definition

Acute interstitial pneumonia is a term used for an idiopathic form of acute lung injury characterized clinically by acute respiratory failure with bilateral lung infiltrates and histologically by diffuse alveolar damage (DAD). The *acute*, *exudative phase* shows edema, hyaline membranes, and acute interstitial inflammation. In the *subacute*, *proliferative (organizing) phase*, the fibroblast proliferation mainly becomes prominent. In the *chronic*, *fibrotic phase*, 2 weeks or more after the injury, there is progressive fibrosis. The acute presentation and the histologic features are identical with those of DAD, so AIP has also referred to as idiopathic DAD. The average age at presentation is 50–60 years. It has no gender predominance and no association with cigarette smoking. It is classified among the idiopathic interstitial pneumonias.

AIP, Hamman–Rich syndrome, idiopathic DAD

The general term idiopathic interstitial pneumonias (IIPs) includes various diseases. The major IIPs include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), and cryptogenic organizing pneumonia (COP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

HIGH-RESOLUTION CT: HRCT

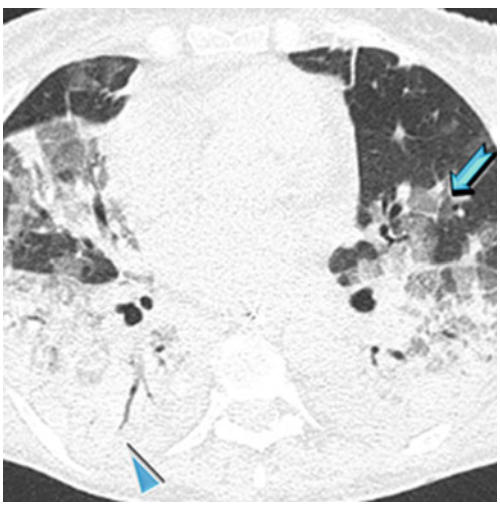
Key Signs

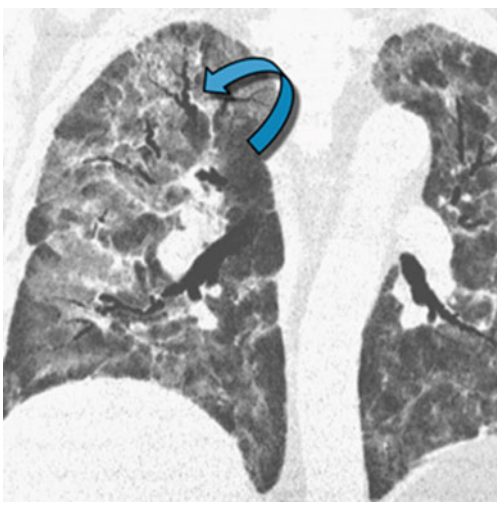
The HRCT findings are strictly correlated to the pathologic phases of DAD:

- *Acute or exudative phase* (first week): extensive ground-glass opacities (➡) and/or airspace consolidation with air bronchogram (►)
- *Proliferative phase* (second week): within areas of GGO and consolidation, the appearance of distortion of the architecture, volume loss, traction bronchiectases (☟), and bronchiolectases

Distribution

Patchy (geographic) or confluent and tends to involve mainly the dependent lung





Traction bronchiolectases or bronchiectases within areas of increased attenuation on HRCT scan is a sign of progression from the exudative to the proliferative and fibrotic phase.

Patients with greater extent of ground-glass attenuation or airspace consolidation without traction bronchiectases or bronchiolectases on HRCT scan have been shown to have a better prognosis than patients with greater extent of increased attenuation with traction bronchiectases or bronchiolectases.

Mukhopadhyay S (2012) Acute interstitial pneumonia (AIP): relationship to Hamman-Rich syndrome, diffuse alveolar damage (DAD), and acute respiratory distress syndrome (ARDS). Semin Respir Crit Care Med 33(5):476

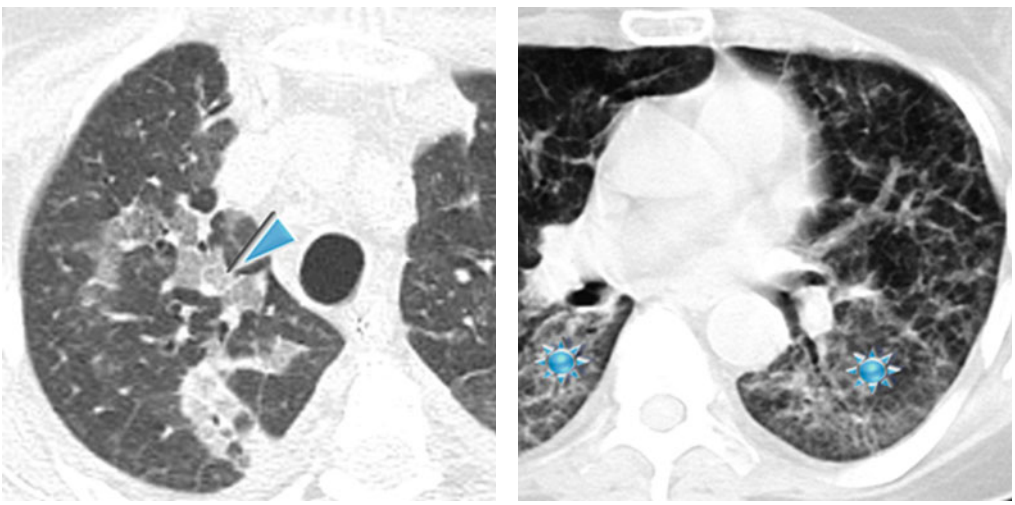
Ichikado K (2014) High-resolution computed tomography findings of acute respiratory distress syndrome, acute interstitial pneumonia, and acute exacerbation of idiopathic pulmonary fibrosis. Semin Ultrasound CT MR 35(1):39

Ancillary Signs

- Smooth septal thickening
- Crazy paving (►)

Non-parenchymal Signs

- Absent



Although the HRCT findings of AIP and ARDS reflect the presence of DAD and therefore overlap, patients with AIP are more likely to have a symmetric lower lobe distribution of abnormalities and a greater prevalence of honeycombing.

Tomiyama N (2001) Acute respiratory distress syndrome and acute interstitial pneumonia: comparison of thin-section CT findings. J Comput Assist Tomogr 25(1):28

Course

- The prognosis is poor, with the majority of studies reporting a mortality ranging from 50 to 100 %.
- In the surviving patients, HRCT may show mild residual fibrotic features (fibrosing reticulation, architectural distortion, fibrotic GGO) (please see the figure above ✸) and possible mild honeycombing.

Akira M (1999) Computed tomography and pathologic findings in fulminant forms of idiopathic interstitial pneumonia. J Thorac Imaging 14:76

Definition

Acute respiratory distress syndrome (ARDS) is a syndrome characterized by diffuse lung injury and progressive dyspnea and hypoxemia over a short time. The clinical criteria of acute lung injury or ARDS defined by the American-European Consensus Conference in 1994 have been revised as the Berlin definition in 2012. According to this latest definition, the diagnosis is based on the onset of hypoxemia and of bilateral chest opacities within 1 week of a known risk factor. From the radiological point of view, the presence of bilateral opacities remains one of the hallmarks for diagnosis. However, it was explicitly recognized that these findings could be detected by computed tomography (CT) instead of radiography.

Pathologically, ARDS is characterized by diffuse alveolar damage (DAD) and evolves over 2 or 3 weeks through exudative, fibroproliferative phases.

ARDS

ARDS Definition Task Force (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307(23):2526

HIGH-RESOLUTION CT: HRCT

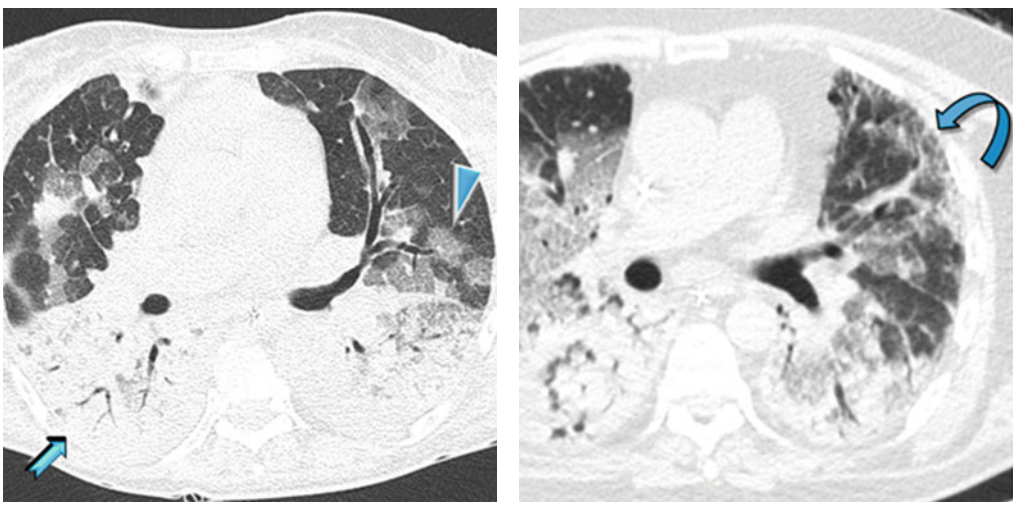
Key Signs

The HRCT findings closely correlate to pathologic phases of DAD:

- *Acute or exudative phase* (first week): HRCT may be normal in the early phase of DAD but is usually abnormal within 12 h with extensive ground-glass opacities (►) and/or airspace consolidation with air bronchogram (➡).
- *Proliferative phase* (second week): distortion of the architecture, volume loss, fibrosing reticulation, traction bronchiectases or bronchiolectases (), and honeycombing represent signs of early fibrosis.

Distribution

Bilateral, diffuse with a gravity-dependent gradient, with larger areas of consolidation in the posterobasal regions, as a result of compressive gravitational forces



Ichikado K (2014) High-resolution computed tomography findings of acute respiratory distress syndrome, acute interstitial pneumonia, and acute exacerbation of idiopathic pulmonary fibrosis. Semin Ultrasound CT MR 35(1):39

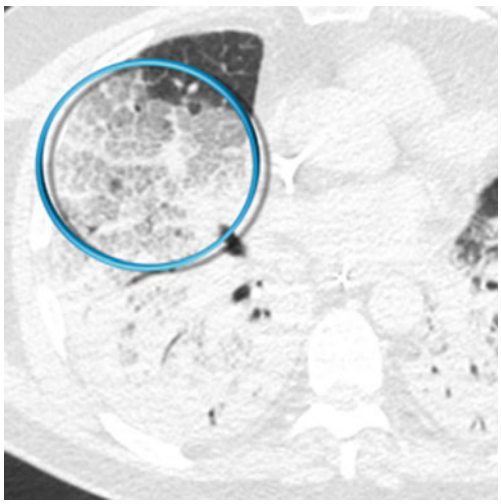
Zompatori M (2014) Overview of current lung imaging in acute respiratory distress syndrome. Eur Respir Rev 23(134):519

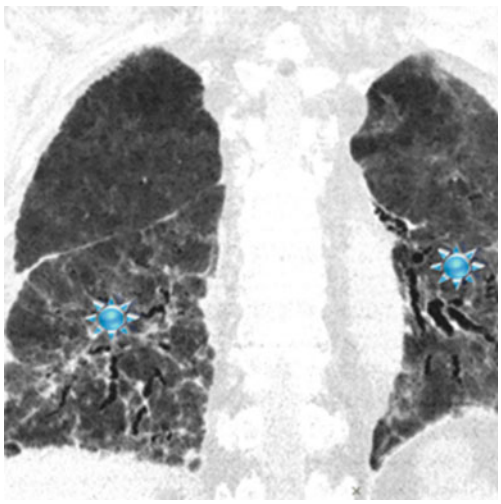
Ancillary Signs

- Reticular opacities
- Crazy paving (O)

Non-parenchymal Signs

- Small pleural effusion (less representative than decompensated heart failure)





In the *early stage* of disease (*exudative phase*), reticular opacities and crazy paving correspond histologically to alveolar collapse adjacent to interlobular septa and subsequent organization or correspond to edematous thickening.

In the *proliferative and fibrotic phase* (see Course below), reticulation is fibrosis (see figure with ✸ above) with associated distorted parenchyma.

The differential diagnosis of ARDS includes cardiogenic pulmonary edema, acute interstitial pneumonia (AIP), diffuse alveolar hemorrhage (DAH), and acute eosinophilic pneumonia (AEP); however, the most challenging differential diagnosis is still between ARDS and cardiogenic edema, especially in the acute phase.

Ellen L (2014) Detection of fibroproliferation by chest high-resolution CT scan in resolving ARDS. Chest 146(5):1196–1204.

Course

- In surviving patients in the later stages, CT may usually demonstrate progressive regression of opacities with complete healing of lesions.
- A rarer evolution is progressive lung fibrosis (*fibrotic phase)*: fibrosing reticulation, architectural distortion, fibrotic GGO (please see the figure above ✸), and possible mild honeycombing.
- Early signs of barotrauma often correspond to interstitial emphysema and subpleural cystic airspaces. Subsequently, imaging studies can demonstrate the development of pneumomediastinum, pneumothorax (often hypertensive in mechanically ventilated patients), and subcutaneous emphysema.
- Superimposed cardiac failure, pneumonia, pulmonary embolism, ventilator-induced lung injury, malposition of tubes, central venous catheters, and drainages or other conditions may suddenly worsen the clinical evolution.

Obadina ET (2013) Acute pulmonary injury: high-resolution CT and histopathological spectrum. Br J Radiol 86(1027):20120614

Desai SR (1999) Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology 210:29

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 1–3 months. Most patients are middle aged, and approximately 50 % have asthma.

CEP is almost always associated with increased numbers of eosinophils on BAL fluid and in peripheral blood. Radiologically, CEP is characterized by peripheral unresolving or migrating pneumonia.

☯ CEP

📖 Alam M (2007) Chronic eosinophilic pneumonia: a review. South Med J 100(1):49

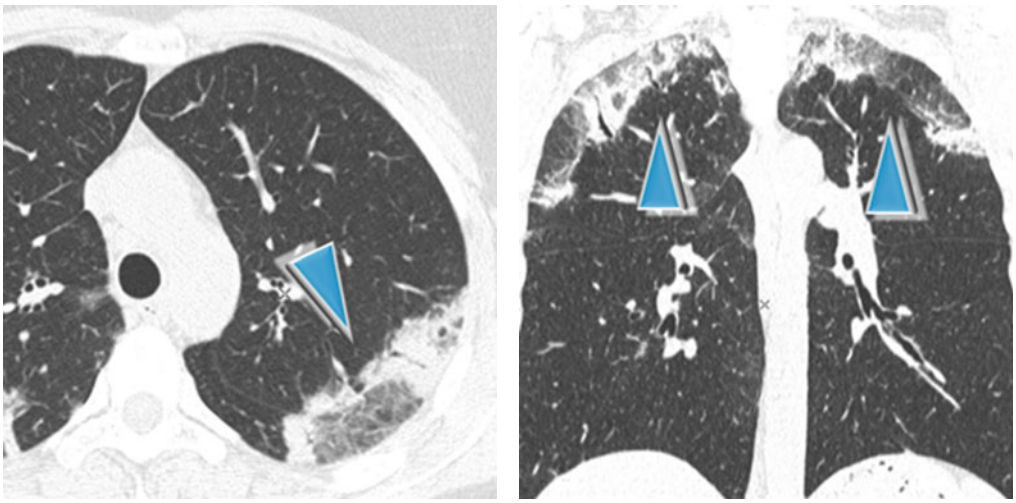
HIGH-RESOLUTION CT: HRCT

Key Signs

- Non-resolving airspace consolidations and ground-glass opacities are often associated (►) with changing in location over a matter of weeks.

Distribution

Peripheral in almost all cases (so-called reverse batwing sign or photographic negative shadow of pulmonary edema), mainly the upper lobes, patchy or confluent



☝ In CEP, the distribution of opacities is identical to that in Löffler syndrome, although in the latter, the lung opacities are self-limited. Also in COP, alveolar sarcoidosis, infarcts, and contusions consolidations can be seen in peripheral airspace (please also refer to Reverse batwing sign in the "Case-Based Glossary with Tips and Tricks").

Spontaneous migration of the opacities can be present in both CEP and OP.

📖 Yeong YJ (2007) Eosinophilic lung diseases: a clinical, radiologic, and pathologic overview. Radiographics 27(3):617

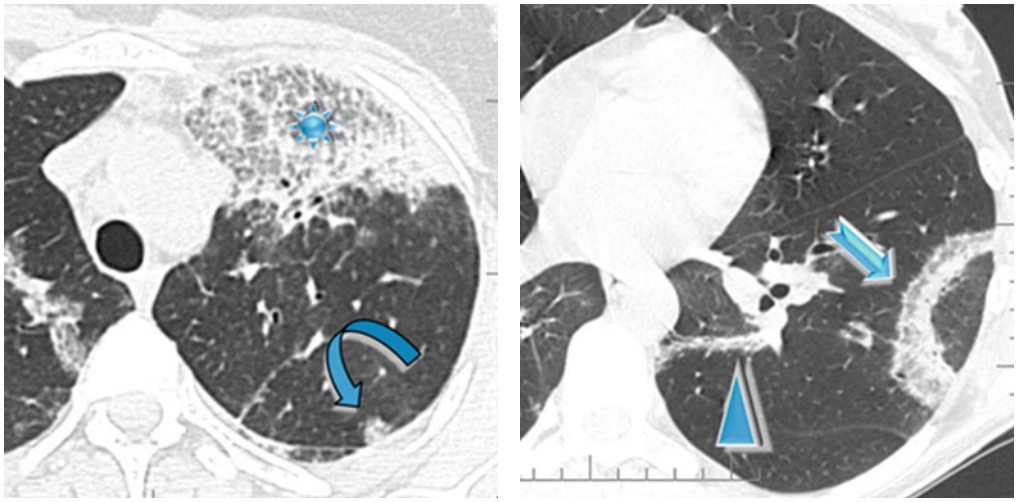
Ebara H (1994) Chronic eosinophilic pneumonia: evolution of chest radiograms and CT features. J Comput Assist Tomogr 18(5):737

Ancillary Signs

- Crazy paving (✸)
- Low-density (subsolid) nodules (20 %) with hazy contours (20 %) (⇦)
- Reversed halo sign (atoll sign), rarely (➡)
- Linear bandlike opacities seen during resolution (►)

Non-parenchymal Signs

- Pleural effusion (<10 %)
- Mediastinal lymph node enlargement



The diagnosis of eosinophilic pneumonia relies on both characteristic clinical imaging features and demonstration of alveolar eosinophilia. Lung biopsy is generally not necessary for the diagnosis of eosinophilic pneumonia.

☝ An identical appearance to that of CEP may be seen in patients who have simple pulmonary eosinophilia (Löffler syndrome) and in patients with Churg–Strauss syndrome (CSS).

An identical appearance of peripheral consolidations can be seen in OP. In this disease, the lesions are not only confined to the lung periphery but are also bronchocentric and often predominate in the lower lobes. In addition, a macronodular appearance or a pattern of round opacities is frequent. Septal thickening or parenchymal bands are uncommon.

📖 Sano S (2009) Chronic eosinophilic pneumonia: a case report and review of the literature. Cases J 2:7735

Cottin V (2012) Eosinophilic lung diseases. Immunol Allergy Clin North Am 32(4):557

Course

- Response to steroid treatment is generally dramatic with improvement of symptoms within 24 h 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 %).
- 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.

📖 Oyama Y (2015) Efficacy of short-term prednisolone treatment in patients with chronic eosinophilic pneumonia. Eur Respir J 45(6):1624

Definition

Cryptogenic organizing pneumonia (COP) is the idiopathic form of organizing pneumonia. OP is a well-known histopathologic pattern characterized by loose plugs of proliferating fibroblasts and myofibroblasts within the alveolar ducts and airspaces, accompanied by varying degrees of bronchiolar involvement. COP is classified among the idiopathic interstitial pneumonias (IIPs). Patients with COP typically present with a 2–4-month history of nonproductive cough, low-grade fever, malaise, and shortness of breath. The mean age of presentation is 50–60 years.

COP, idiopathic OP/BOOP

The general term idiopathic interstitial pneumonias (IIPs) includes various diseases. The major IIPs include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), and cryptogenic organizing pneumonia (COP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

OP may also be a reaction pattern associated with infection, connective diseases, drugs, inflammatory bowel disease, inhalation injury, hypersensitivity pneumonitis, malignancy, radiation therapy, and aspiration.

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

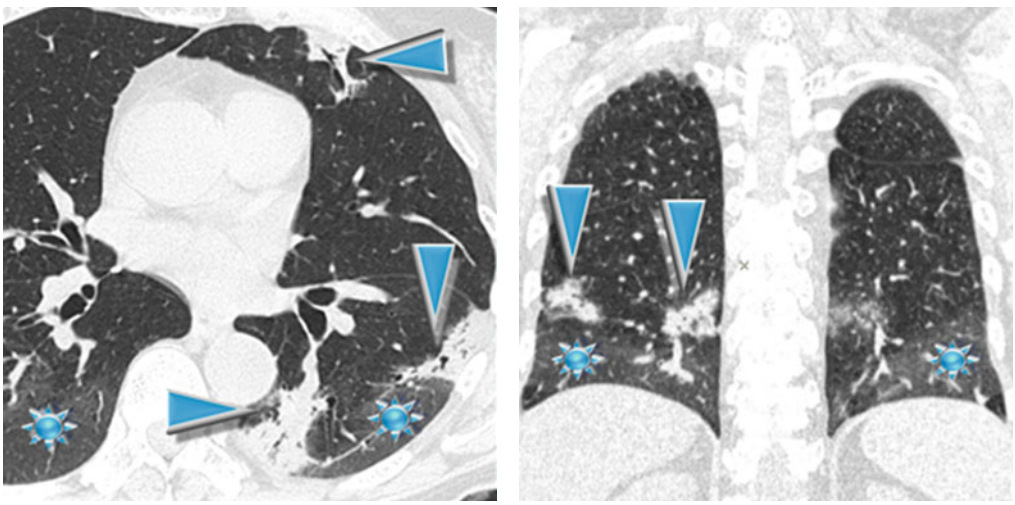
Key Signs

HIGH-RESOLUTION CT: HRCT

- Multifocal patchy consolidations (80–90 %) with air bronchogram (►) changing in location over a matter of weeks
- Ground-glass opacity (✸) (60 %), usually in association with areas of consolidation

Distribution

Patchy with predominant peribronchial and/or subpleural (60–80 %) distribution, often with lower lobe predominance



The subpleural distribution is also defined as “reverse batwing sign” (please also refer to this sign in the “Case-Based Glossary with Tips and Tricks”).

The predominant subpleural distribution together with migration over time and spontaneous regression of consolidation are important pointers, which are also possible in CEP. A peribronchial distribution of consolidations is more frequently observed in COP than in CEP (29 % vs. 9 %). The most helpful distinguishing feature on CT was the presence of nodules, seen in about 30 % of patients with COP and rarely (5 %) in patients with CEP.

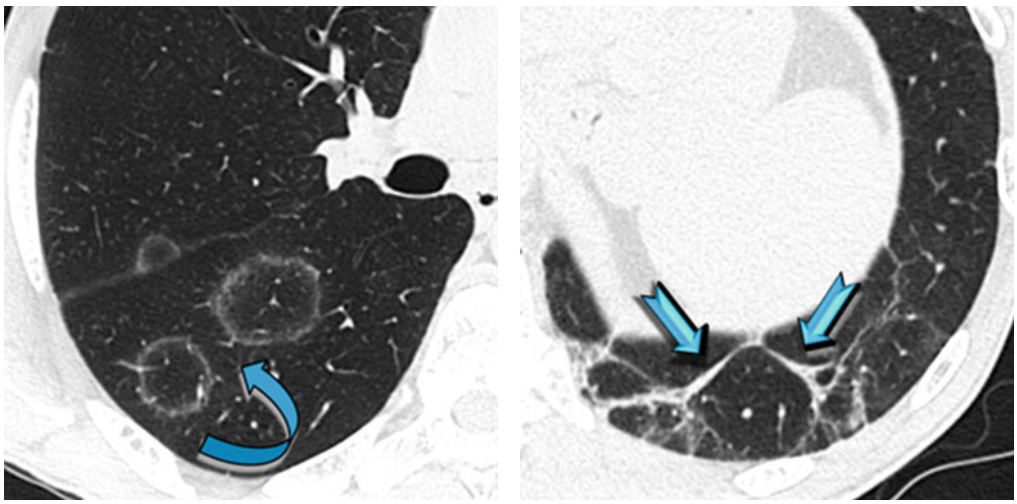
Arakawa H (2001) Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. AJR Am J Roentgenol 176(4):1053

Ancillary Signs

- Reversed halo sign (also defined as the atoll sign) (↻) in 20 % of patients
- Perilobular sign (60 %) (➡)
- Crazy paving
- Bandlike opacities
- Low-density (subsolid) nodules (30–50 %)
- Large nodules or masses

Non-parenchymal Signs

- Possible mediastinal lymph node enlargement (20–40 %)
- Small uni- or bilateral pleural effusion (10–30 %)



The reversed halo sign, also known as the atoll sign, is characterized by a central ground-glass opacity surrounded by a more or less complete ring of consolidation (please also refer to the Reverse halo sign in the "Case-Based Glossary with Tips and Tricks").

Perilobular pattern appears as poorly defined arcade-like polygonal structures, usually abutting the pleural surface.

Nodules are seen in 32 % of patients with COP and only 5 % of patients with CEP.

Zompatori M (1999) Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign). A case report. Radiol Med 97(4):308

Roberton BJ (2011) Organizing pneumonia: a kaleidoscope of concepts and morphologies. Eur Radiol 21(11):2244

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 OP).
- The opacities may resolve spontaneously and then form elsewhere, usually more cranially and at times in the contralateral lung (migratory opacities). If left untreated, the disease may progress to permanent damage with fibrosis and bronchiectases.

Definition

Diffuse alveolar hemorrhage (DAH) is defined as the presence of hemoptysis, diffuse alveolar infiltrates, and a drop in hematocrit level; it is one of the manifestations of primary pulmonary vasculitis, among other entities (idiopathic alveolar hemorrhage, collagen vascular diseases, drug reactions, anticoagulation disorders, and other entities).

Granulomatosis with polyangiitis (GPA, former Wegener's granulomatosis, WG) and microscopic polyangiitis (MPA) are the most common causes of DAH, representing 40 % of cases. Wegener granulomatosis is the most common among the ANCA-associated vasculitides. It is characterized clinically by the triad of upper airway disease (nasal, oral, or sinus inflammation), lower respiratory tract disease (airway or lung), and glomerulonephritis. The complete triad is often not present at initial presentation. The upper respiratory tract is affected in almost all patients, and the lungs and kidneys are involved in 90 % and 80 % of patients, respectively.

DAH in GPA (granulomatosis with polyangiitis/ANCA-associated granulomatous vasculitis)

Castañer E (2010) When to suspect pulmonary vasculitis: radiologic and clinical clues. Radiographics 30(1):33

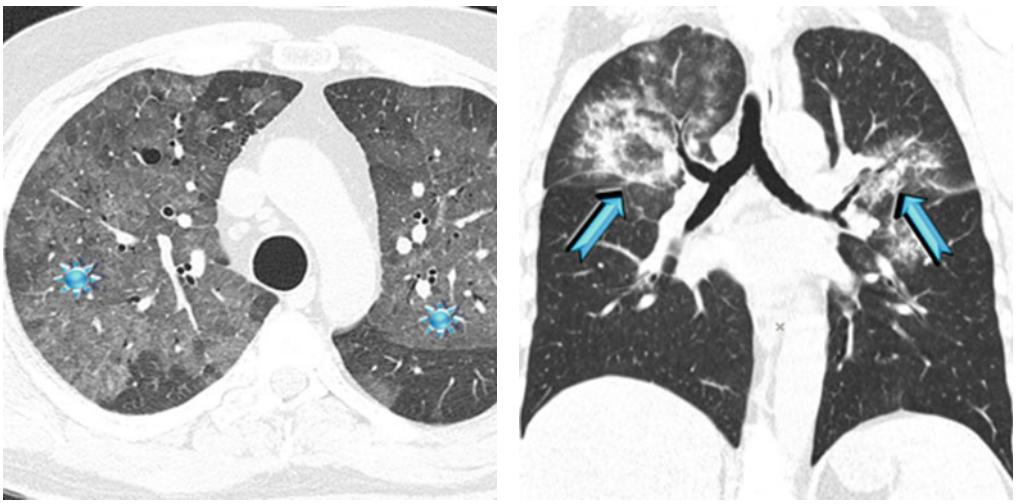
HIGH-RESOLUTION CT: HRCT

Key Signs

- Ground-glass opacity (✸)
- Consolidations (➡)

Distribution

Bilateral (even though unilateral predominance is also possible), diffuse, or patchy or lobular predominant in the parahilar region with sparing of the subpleural regions ("butterfly" or "batwing" distribution)



Butterfly or batwing pulmonary opacities are classically described in the chest X-ray but they are best appreciated on CT. Diseases responsible for butterfly pulmonary opacities may have acute or chronic behavior (please refer to Butterfly pulmonary opacities in the "Case-Based Glossary with Tips and Tricks").

The corresponding findings on thin-section CT are nonspecific, with ground-glass opacity as the leading feature without a characteristic distribution. Ill-defined centrilobular nodules may predominate in some patients. The presence of dense consolidation represents complete filling of the alveoli with blood.

Consolidations and ground-glass opacities can occur either in vasculitic pulmonary disease (in form of pneumonitis) or alveolar hemorrhage.

Primack SL (1995) Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. AJR Am J Roentgenol 164:295.

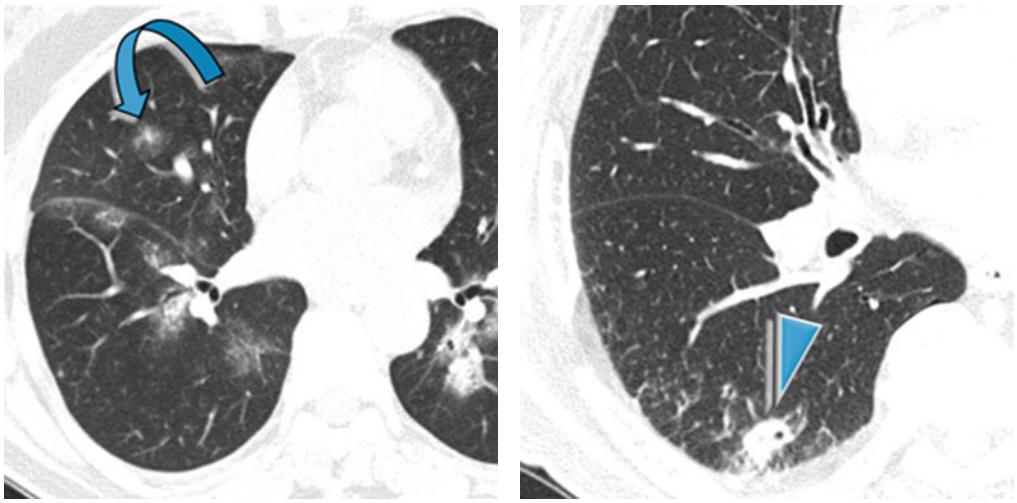
Ananthakrishnan L (2009) Wegener's granulomatosis in the chest: high-resolution CT findings. AJR Am J Roentgenol 192(3):676

Ancillary Signs

- Scattered low-density (subsolid) nodules, at times in connection with small vessels (☞).
- Smooth septal thickening and crazy paving.
- Solid macronodules with a diameter varying between 1 and 4 cm, usually bilateral (75 %), often cavitated (►), and with irregular thick walls, macronodules, and masses with ill-defined borders.
- Perinodular halo sign (a rim of ground-glass opacity surrounding the pulmonary lesion) is seen in up to 15 % of cases.

Non-parenchymal Signs

- Hilar or mediastinal adenopathy (2–15 %)
- Smooth or irregular tracheal stenosis with concentric wall thickening and possible calcifications
- Pleural effusion (less than 10 %)



Martinez F (2012) Common and uncommon manifestations of Wegener granulomatosis at chest CT: radiologic-pathologic correlation. Radiographics 32(1):51

Course

- The complete clearing of airspace and interstitial opacities usually occurs within 10 days to 2 weeks after an acute episode of hemorrhage. This is considerably slower than the clearing of pulmonary edema, which hemorrhage closely resembles.
- Masses show a decrease in the extent with residual scarring.
- If present, airway lesions show improvement with treatment in most patients.
- After repeated episodes of pulmonary hemorrhage, a persistent reticular pattern may be seen, with areas of peripheral honeycombing and traction bronchiectases.

Chung MP (2010) Imaging of pulmonary vasculitis. Radiology 255(2):322

Definition

Desquamative interstitial pneumonia (DIP) is a rare interstitial lung disease, and it is classified among the idiopathic interstitial pneumonias (IIPs). Pathologically, it is characterized by a widespread filling of alveoli with macrophages. Although DIP occurs in nonsmokers, it is strongly associated with cigarette smoking (60–90 %). DIP may also occur in association with passive exposure to cigarette smoke, heavy marijuana smoking, occupational dust exposure, drug reaction, collagen vascular disease, leukemia, and infection. DIP occurs most commonly in patients between 35 and 55 years of age. The clinical symptoms usually consist of slowly progressive exertional dyspnea and dry cough.

☯ DIP, alveolar macrophage pneumonia

The general term idiopathic interstitial pneumonias (IIPs) includes various diseases. The major IIPs include idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), and cryptogenic organizing pneumonia (COP). Rare idiopathic interstitial pneumonias include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

Travis WD (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733

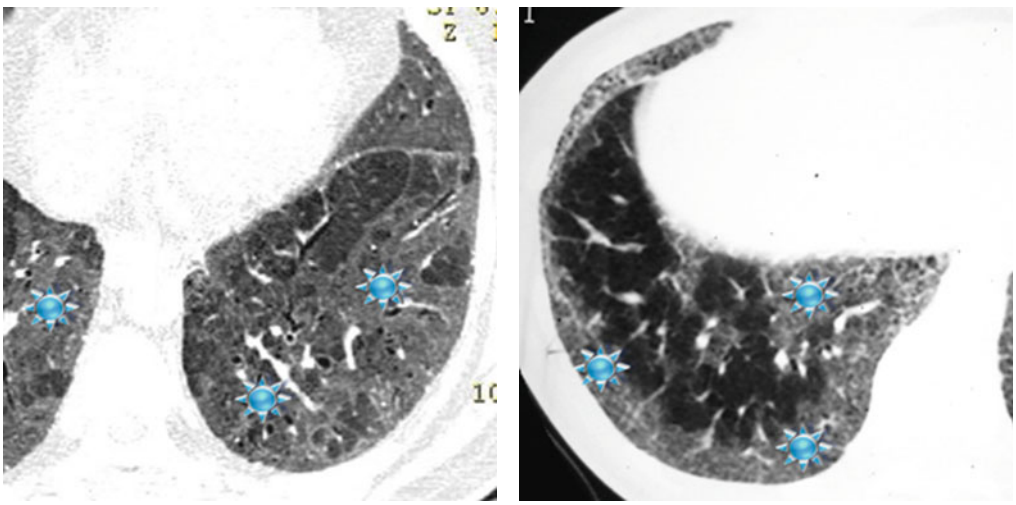
HIGH-RESOLUTION CT: HRCT

Key Signs

Extended areas of ground-glass opacity (GGO) (✸)

Distribution

Diffuse, often predominant in the peripheral and subpleural regions, bilateral, and generally symmetrical



Kadoch MA (2015) Idiopathic interstitial pneumonias: a radiology-pathology correlation based on the revised 2013 American Thoracic Society-European Respiratory Society classification system. Curr Probl Diagn Radiol 44(1):15

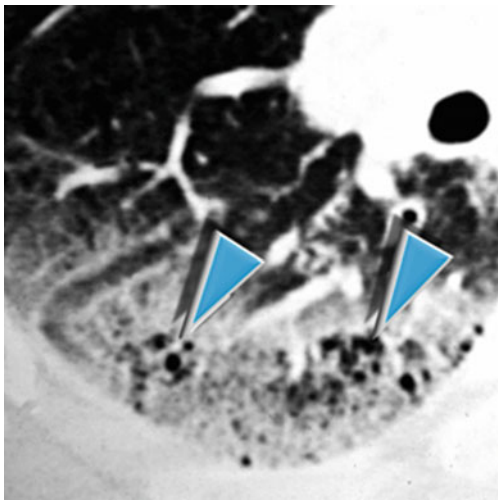
Attili AK (2008) Smoking-related interstitial lung disease: radiologic-clinical-pathologic correlation. Radiographics 28(5):1383

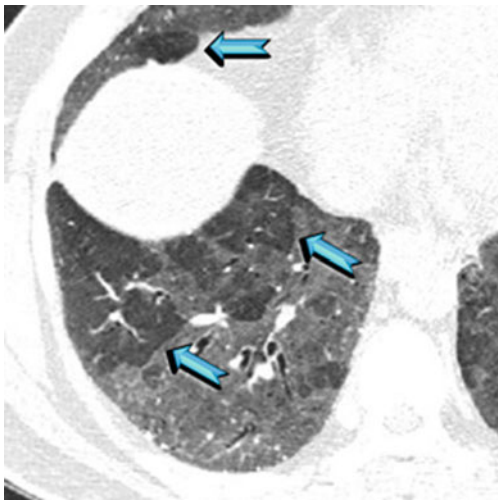
Ancillary Signs

- Occasionally smokers with DIP may also have low-density ill-defined centrilobular nodules and tiny air-filled cysts within the areas of ground-glass attenuation probably corresponding to dilated alveolar ducts or foci of emphysema (►).
- Focal or lobular dark areas are sometimes seen, perhaps representing areas of mosaic perfusion related to bronchiolitis and airway obstruction (➡).
- Reticular opacities, honeycombing, and traction bronchiectases are rare.

Non-parenchymal Signs

- Absent





The presence of centrilobular nodules is due to the considerable overlap between the HRCT findings of RB, RB-ILD, and DIP because these entities are part of the spectrum of the same disease process, representing different degrees of severity of reaction to cigarette smoke.

Park JS (2002) Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 26(1):13

Course

- Follow-up HRCT is variable showing usually a decrease or resolution of the ground-glass opacities, while sometimes it remains stable.
- A progression to severe fibrosis is rare.

Nair A (2014) High-resolution computed tomography features of smoking-related interstitial lung disease. Semin Ultrasound CT MR 35(1):59

Hartman TE (1996) Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assessment with serial CT. Chest 110(2):378

Definition

There are numerous agents with potential toxic effects on the lungs including cytotoxic and noncytotoxic drugs. Common causes of drug-induced lung disease include amiodarone, antibiotics, nonsteroidal anti-inflammatory drugs, and chemotherapeutic agents. The most common clinical manifestations of patients with pulmonary drug reaction are cough, progressive dyspnea, and fever. These symptoms are nonspecific, and therefore, the diagnosis requires a high index of suspicion by the clinician and the radiologist.

Amiodarone is a tri-iodinated drug used to treat refractory tachyarrhythmia. It accumulates in the lung, largely within macrophages and type 2 pneumocytes, where it forms lamellar inclusion bodies and has a very long half-life.

Nonetheless, it should be noted that drugs may cause different types of lung injury (see Table Drug-induced lung injury: major histopathologic reaction patterns). The HRCT features of drug-induced lung disease usually reflect the histopathologic patterns of reaction. Amiodarone itself may often cause subacute or chronic pattern (OP or NSIP) and sometimes acute (diffuse alveolar damage – DAD/ARDS).

Silva CI (2006) Drug-induced lung diseases: most common reaction patterns and corresponding high-resolution CT manifestations. Semin Ultrasound CT MR 27(2):111

HIGH-RESOLUTION CT: HRCT

Key Signs

OP amiodarone-induced pattern is often associated with:

- Patchy consolidations ()

NSIP amiodarone-induced pattern is often associated with:

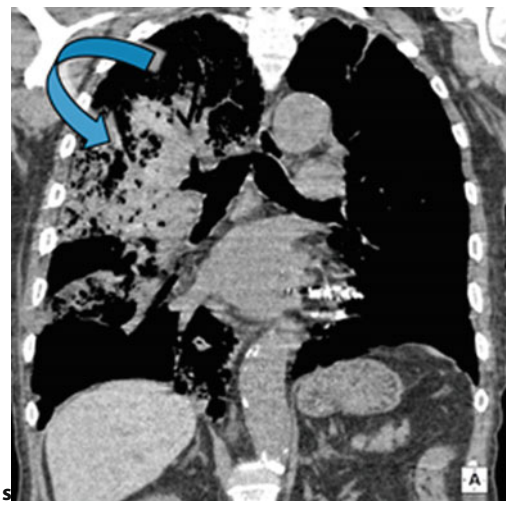
- Ground-glass opacities and fibrosing reticulation ()

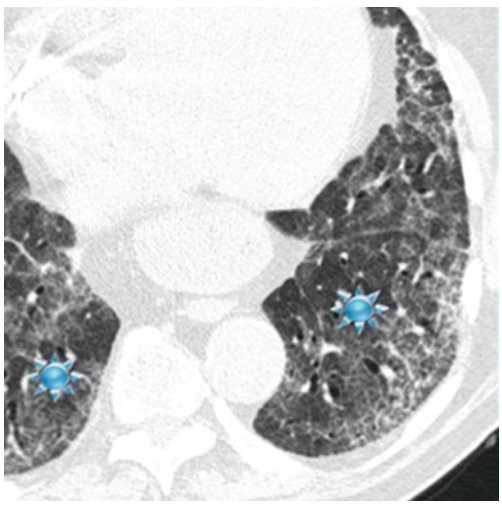
DAD amiodarone-induced pattern may be present in a minority of patients:

- Diffuse GGO (please see the third image below) with possible associated consolidations (ARDS-like aspect)

Distribution

- NSIP pattern: diffuse and often peripheral
- OP pattern: patchy
- DAD pattern: diffuse GGO, possibly gravity-dependent consolidation





The presence in the lung of foci of attenuation greater than that of soft tissues may be noted inside areas of consolidation or mass-like opacities. The same aspect may be present in the liver and spleen, related to the accumulation of amiodarone and its metabolites in tissue macrophages. The presence of hyperdensities within the areas of consolidation needs to be differentiated from other diseases (please refer to Hyperdense consolidation in the chapter "Alveolar Pattern").

Wolkove N (2009) Amiodarone pulmonary toxicity. Can Respir J 16(2):43

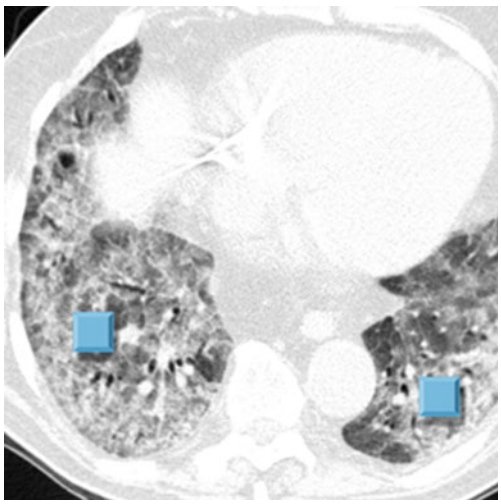
Rossi SE (2000) Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics 20(5):1245

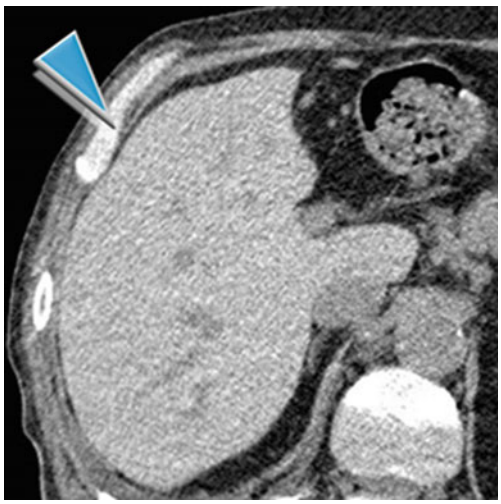
Ancillary Signs

- Nodules/masses (PET positive)
- Crazy paving

Non-parenchymal Signs

- Pleural thickening and pleural effusion (uncommon)
- The hyperdense liver (►) and spleen (80 %) and heart (20 %)





A minority of patients experience acute, severe lung injury culminating in death. The most dramatic manifestation is a rapidly progressing diffuse pneumonitis with acute respiratory failure and a picture typical of the acute respiratory distress syndrome (ARDS), characterized by diffuse alveolar damage (DAD).

Course

Amiodarone-induced pulmonary fibrosis develops in 5–7 % of patients following the amiodarone pneumonitis. On HRCT, there are coarse interstitial fibrosing reticular opacities and traction bronchiectases. Honeycombing is less common than in idiopathic pulmonary fibrosis.

Drug-induced lung injury: major histopathologic patterns	
Acute	Subacute – chronic
Acute eosinophilic pneumonia (AEP)	Chronic interstitial pneumonitis and fibrosis (NSIP or rarely UIP)
Diffuse alveolar damage (DAD/ARDS)	Chronic eosinophilic pneumonia (CEP)
Diffuse alveolar hemorrhage (DAH)	Hypersensitivity pneumonitis (HP)
	Nonspecific interstitial pneumonia (NSIP)
	Organizing pneumonia (OP/BOOP)
	Pulmonary edema (PE)

www.pneumotox.com

Definition

Fat embolism syndrome (FES) is a systemic syndrome due to pulmonary and systemic embolization from fat particles. It is a rare entity, and the most frequent cause is a fracture of a long bone. As a matter of fact, some degree of fat embolism is present in the majority of fractures of the long bones, but the clinical syndrome is not frequent. Most patients are males of young age. The diagnosis is clinical, and the most widely adopted criteria are those from Gurd and Wilson. Diagnosis requires the presence of two major criteria or one major criteria plus four minor. Major diagnostic criteria are cutaneous petechial rash, hypoxemia, and central nervous system involvement. Minor criteria are fever, tachycardia, and laboratory abnormalities such as thrombocytopenia, anemia, jaundice, and high ESR.

From a histopathological point of view, FES is a toxic vasculitis. The most severe cases may develop the ARDS/DAD complex, while in exceptional cases, the syndrome occurs in the fulminating or hyperacute form (with cardiorespiratory collapse).

Mechanical and biochemical pathophysiological mechanisms have been proposed. As a consequence of the fracture, fat globules from the bone marrow can access to the circulation and become embolic, causing pulmonary arterial mechanical obstruction. The accumulation of fat in the pulmonary microvasculature could also cause chemical pneumonitis with perivascular hemorrhage and edema, due to the local liberation of free fatty acids and glycerol with toxic effects to the lung parenchyma.

FES, posttraumatic pulmonary fat embolism

Akhtar S (2009) Fat embolism. Anesthesiol Clin 27(3):533

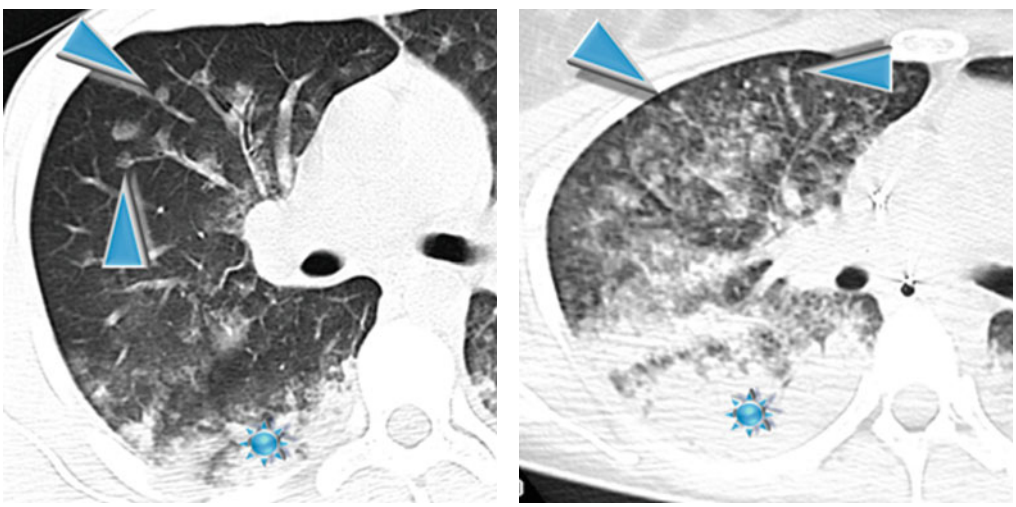
HIGH-RESOLUTION CT: HRCT

Key Signs

- Ground-glass opacities
- Consolidations (✸)
- Nodules, often subsolid (GGO nodules) (►)

Distribution

Pulmonary involvement is always bilateral. Nodules are often centrilobular with possible feeding vessels and subpleural distribution. Both nodules and GGO prevail in the upper lungs, while consolidations show gravity-dependent distribution in the lower lobes.



Malagari K, Economopoulos N, Stoupis C et al (2003) High resolution CT findings in mild pulmonary fat embolism. Chest 123(4):1196–1201

Gallardo X (2006) Nodular pattern at lung computed tomography in fat embolism syndrome: a helpful finding. J Comput Assist Tomogr 30(2):254–257

Piolanti M, Dalpiaz G (2016) Fat embolism syndrome: lung computed tomography findings in 18 patients. J Comput Assist Tomogr 40(3):335–342

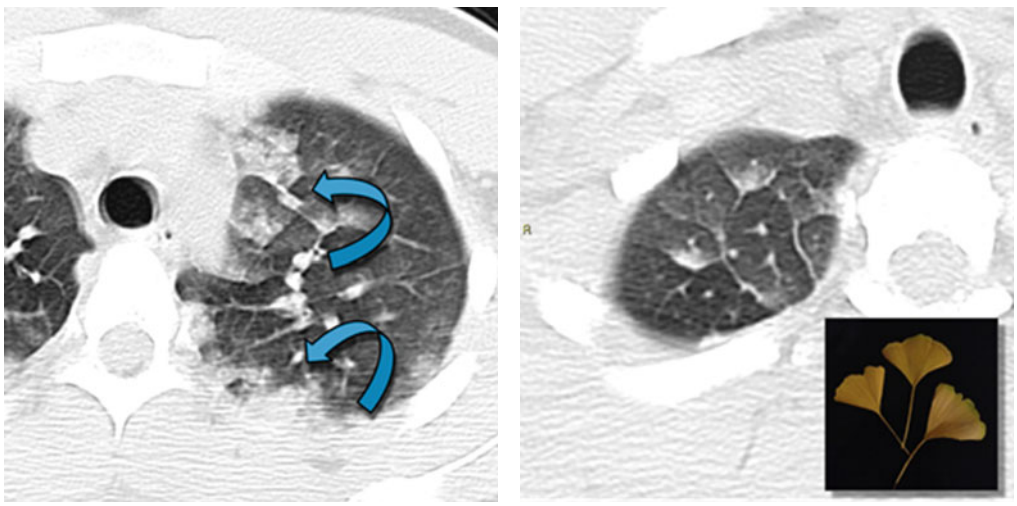
FES is essentially a posttraumatic disease that has to be differentiated from aspiration, contusions, pneumonia, and pulmonary edema. The presence of a nodular pattern is the most suggestive HRCT finding.

Ancillary Signs

- Lobular and sublobular consolidation and GGO ()
- Smooth septal thickening
- "Ginkgo biloba sign"

Non-parenchymal Signs

- Pleural effusions (not frequent)
- Macroscopic fat emboli in pulmonary CT angiogram (rare)



In the anterior lung, the combination of smooth septal thickening and lobular/sublobular GGO or consolidations may give rise to an aspect that reminds a ginkgo biloba leaf. We suggest this sign may be called "ginkgo biloba sign" and, like all other signs in thoracic radiology, is unlikely to be specific for FES, but rather it may suggest the presence of hemorrhage and edema.

Note that the sublobular consolidation/GGO may present a gravity-dependent distribution inside the lobes.

FES may be a likely cause for hypoxemia even in trauma patients with fractures and entirely negative imaging studies (chest roentgenogram and CT scan), provided that the chest wall involvement or pulmonary infectious complications have been ruled out.

Trisolini R (2010) Fat embolism may be responsible for hypoxemia in trauma patients with no radiological pulmonary abnormalities. J Trauma 68(2):E53

Course and Complications

- Most patients develop only a transitory respiratory failure, requiring only supportive care. A minority of patients develop ARDS, likely due to a combination of factors, not only FE.

Arakawa H (2000) Pulmonary fat embolism syndrome: CT findings in six patients. J Comput Assist Tomogr 24(1):24

Newbigin K (2016) Fat embolism syndrome: State-of-the-art review focused on pulmonary imaging findings. Respir Med 113:93–100

Definition

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection of the lungs. This fungus is common in the environment and rarely causes illness in healthy people. PJP is the most common opportunistic infection in individuals with HIV infection. Pathologically, PJP typically results in the presence of foamy, intra-alveolar exudates. A definitive diagnosis of PJP requires the demonstration of organisms in sputum or BAL fluid.

PJP, *Pneumocystis carinii*, or PCP pneumonia, opportunistic infection

Cushion MT (2010) Stealth and opportunism: alternative lifestyles of species in the fungal genus Pneumocystis. Annu Rev Microbiol 64:431

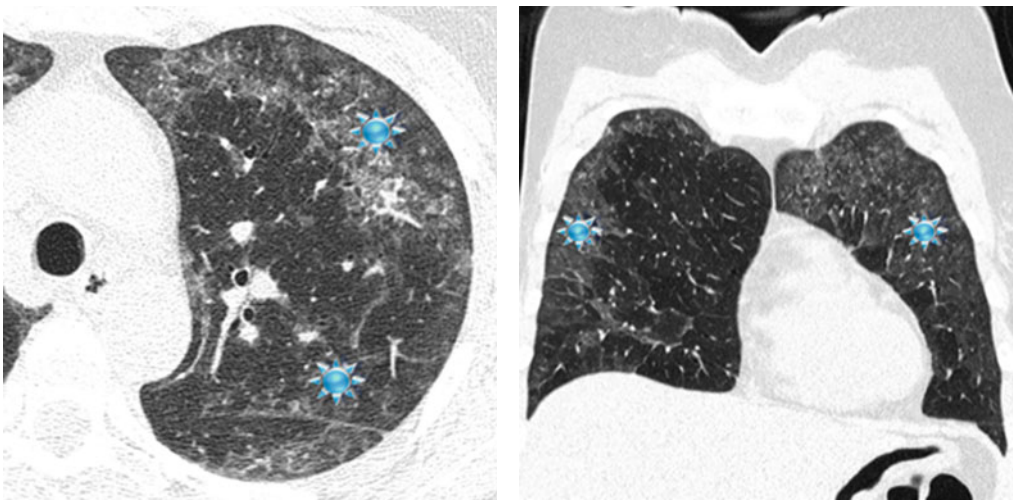
HIGH-RESOLUTION CT: HRCT

Key Signs

- Ground-glass opacities (✸)
- Consolidation in patients with more severe disease

Distribution

Symmetric bilateral, diffuse, or patchy (mosaic pattern); the lesions may involve mainly the upper lobes and perihilar regions (butterfly or batwing).



A butterfly or batwing distribution may be also present in other diseases (please also refer to "Butterfly pulmonary opacities" in the "Case-Based Glossary with Tips and Tricks").

Lung consolidation is more common in patients without HIV infection and tends to develop more rapidly, reflecting pulmonary damage from the host-immune response.

HRCT is useful in patients with suspected *PJP* who have a normal or equivocal chest X-ray finding. A negative HRCT may allow exclusion of *PJP* in such patients.

Sarkar P (2013) Clinical review: respiratory failure in HIV-infected patients – a changing picture. Crit Care 17(3):228

Hardak E (2010) Radiological features of Pneumocystis jirovecii Pneumonia in immunocompromised patients with and without AIDS. Lung 188(2):159

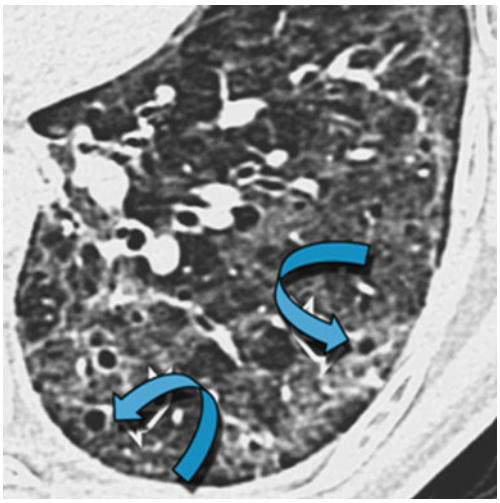
Ancillary Signs

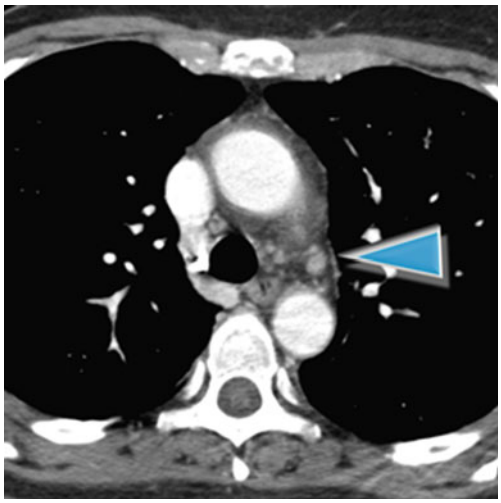
- Cystic lesions (20–35 % in patients with AIDS but only in 3 % of non-AIDS immunocompromised patients) (↬)
- Smooth interlobular septal thickening
- Crazy paving
- At times signs of infectious bronchiolitis with tree-in-bud pattern, bronchial wall thickening, and bronchiectases

- Less typical manifestations: centrilobular nodules, large nodules or masses, even cavitated, also cavitated due to granulomatous reaction mimicking carcinoma (↬)

Non-parenchymal Signs

- Small hilar or mediastinal lymph node enlargement, or both, may be seen in approximately 20 % of patients (►)
- Pneumothorax
- Pleural effusion (about 5 % of cases)





Pulmonary cysts (especially on upper lobes) of varying shape, size, and wall (complex, occurring in cluster, with an irregular shape) are common.

Cysts are associated with an increased frequency of spontaneous pneumothorax, although the latter can occur in the absence of definable lung cysts.

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 intra-alveolar exudate.

Kanne JP (2012) Pneumocystis jirovecii pneumonia: high-resolution CT findings in patients with and without HIV infection. AJR Am J Roentgenol 198(6):W555

Atwal SS (2014) High resolution computed tomography lung spectrum in symptomatic adult HIV-positive patients in South-East Asian Nation. J Clin Diagn Res 8(6):RC12

Course

- In the resolving disease, reticulation and septal thickening predominate representing organization of intra-alveolar exudates: it typically occurs in areas in which ground-glass opacity was visible during the acute phase of the disease.
- Rarely, infection with *PJP* results in diffuse parenchymal fibrosis (chronic *PJP*).
- Less frequently, *PJP* results in mild, peripheral bronchiectasis and/or bronchiolectasis, presumably the result of PJP bronchiolitis.
- Some authors noted the appearance of premature bullous disease in AIDS patients.

Wassermann K (1993) Chronic Pneumocystis carinii pneumonia in AIDS. Chest 104(3):667

Kuhlman JE (1989) Premature bullous pulmonary damage in AIDS: CT diagnosis. Radiology 173(1):23

Definition

Tuberculosis (TB), in the past also called phthisis or consumption, is a widespread and, in many cases, fatal, infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs but can also affect other parts of the body. The infections that do not have symptoms are known as latent tuberculosis. Pathologically, the typical form of TB consists of a necrotizing granulomatous inflammation associated with a variable amount of accompanying non-necrotizing granulomas.

TB (short for tubercle bacillus)

Menzies D (2013) Update in tuberculosis and nontuberculous mycobacterial disease 2012. Am J Respir Crit Care Med 188(8):923

Dalpiaz G (2014) Diffuse granulomatous lung disease: combined pathological-HRCT approach. Radiol Med 119(1):54

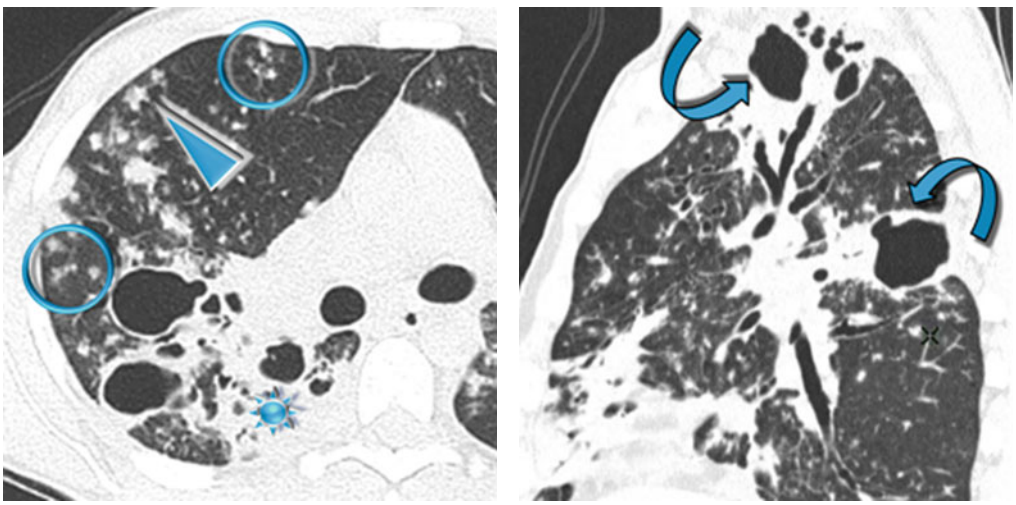
HIGH-RESOLUTION CT: HRCT

Key Signs

- Consolidation (✸)
- Macronodules and centrilobular micronodules (►)
- Tree-in-bud sign which reflects endobronchial spread of infection (O)
- Cavitation (50–58 %) visible both in the consolidation and in the nodules (⇲)

Distribution

Patchy unilateral or bilateral, frequently peribronchial in distribution, apical and posterior segments of the upper lobes, and superior segments of the lower lobes (⇲)



The cavities typically have thick, irregular walls, which become smooth and thin with successful treatment. When the amount of fluid content is significantly high, superinfection by other bacteria should be suspected. Cavities are usually multiple and occur within areas of consolidation. The resolution can result in emphysematous change or scarring.

Cardinale L (2015) The imaging spectrum of pulmonary tuberculosis. Acta Radiol 56(5):557

Woodring JH (1986) Update: the radiographic features of pulmonary tuberculosis. AJR Am J Roentgenol 146(3):497

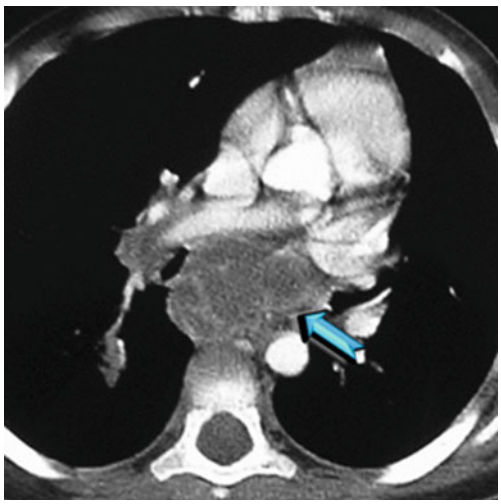
Yeong YJ (2008) Pulmonary tuberculosis: up-to-date imaging and management. AJR Am J Roentgenol 191(3):834

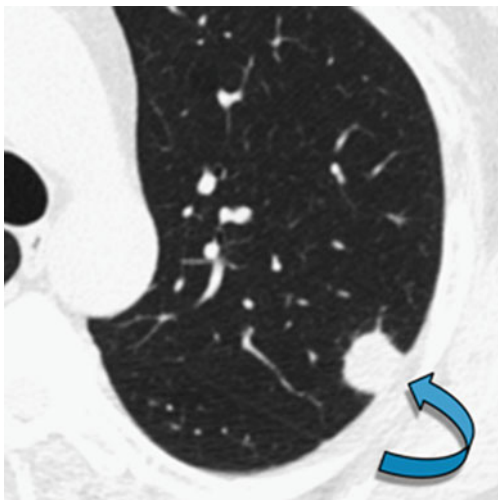
Ancillary Signs

- Possible association with diffuse, random, tiny and solid, well defined nodules, indicating nodules that indicate hematogenous spread of infection (please see miliary TB in the chapter "Nodular Diseases").
- Occasionally, active TB may be associated with a reversed halo sign (atoll sign). This sign in active TB typically has nodular margins and commonly has nodules within it, which allows distinction from the halo sign seen in OP or other entities which have smooth margins (please also refer to the Reversed halo sign in the chapter "Nodular Pattern").

Non-parenchymal Signs

- Pleural effusion (unilateral) and pleural thickening
- Hilar/mediastinal lymphadenopathy with central necrosis more visible on contrast-enhanced CT (➡)





TB may appear as solitary macronodules (tuberculomas) (please see the image above).

The principal CT findings of airway TB are circumferential wall thickening and luminal narrowing, with the involvement of a long segment of the bronchi. In active disease, the airways are irregularly narrowed in their lumina and have thick walls, whereas in fibrotic disease, the airways are smoothly narrowed and have thin walls.

Moon WK (1997) Tuberculosis of the central airways: CT findings of active and fibrotic disease. AJR Am J Roentgenol 169(3):649

Course

- Parenchymal lesions: thin wall cavities, calcified nodules, and end-stage lung destruction.
- Airway lesions: bronchiectasis, bronchial stenosis, and broncholithiasis.
- Rasmussen aneurysm represents a pulmonary artery aneurysm or pseudoaneurysm adjacent or within a tuberculous cavity.
- Empyema necessitates the leakage of tuberculous empyema through the parietal pleura and discharge of its contents into the subcutaneous tissues of the chest wall.
- Mycetoma, fungus ball is common in patients who have cavitary TB. It appears as a well-circumscribed intracavitary mass associated with an air crescent sign (please also refer to Air crescent sign in the "Case-Based Glossary with Tips and Tricks").

The best indicators of residual active disease are centrilobular nodules, tree-in-bud appearance, and cavitation.

Kim HY (2001) Thoracic sequelae and complications of tuberculosis. Radiographics 21(4):839

Table	Differential diagnosis with pulmonary TB
Nontuberculous mycobacteria	Cavitary form: in comparison with postprimary TB, cavities are more likely to be smaller or thin-walled; anyway, the differential diagnosis remains a challenge
Semi-invasive (chronic necrotizing) aspergillosis	Radiologic manifestations include unilateral or bilateral segmental areas of consolidation with or without cavitation or adjacent pleural thickening
Bacterial pneumonia	The appearance of the parenchymal consolidations in primary tuberculosis is most commonly dense and homogeneous but may also be linear, patchy, and nodular, very similar to bacterial pneumonia Lymphadenopathy and the lack of response to conventional antibiotics can suggest the correct diagnosis
Lung cancer	Tuberculomas can appear mass-like and tend to be mistaken for malignancy if typical characteristics are absent. Benign-type (diffuse, central, or lamellar) calcifications and upper lobe involvement may be clues to the imaging diagnosis of tuberculosis. In controversial situations, transthoracic needle biopsy can lead to a diagnosis
Sarcoidosis	Cavitation of parenchymal lesions is a rare finding in sarcoidosis. It is seen in an estimated 10 % of patients with end-stage disease

Franquet T (2001) Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics 21(4):825

Tan CH (2010) Tuberculosis: a benign impostor. AJR Am J Roentgenol 194(3):555

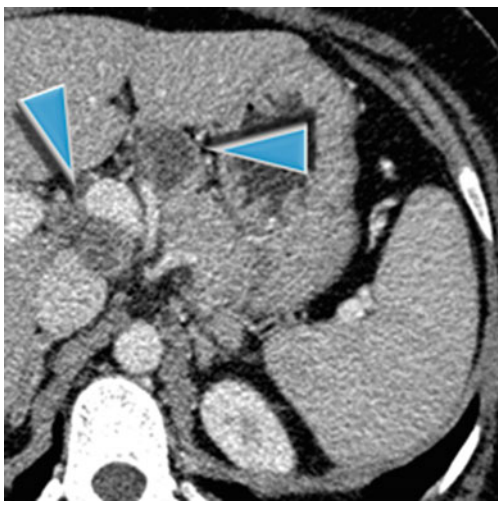
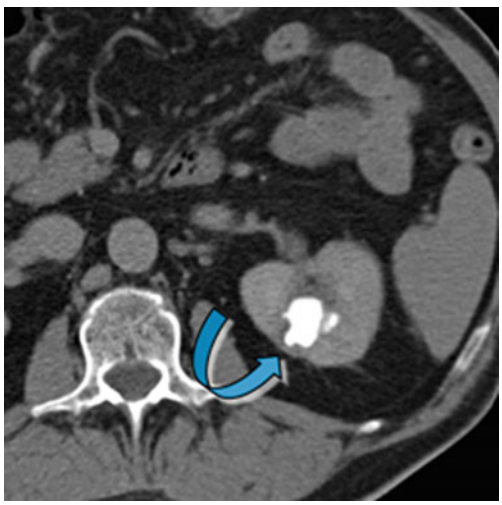
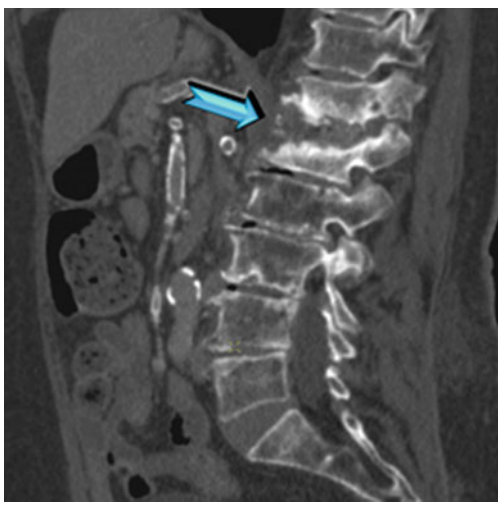
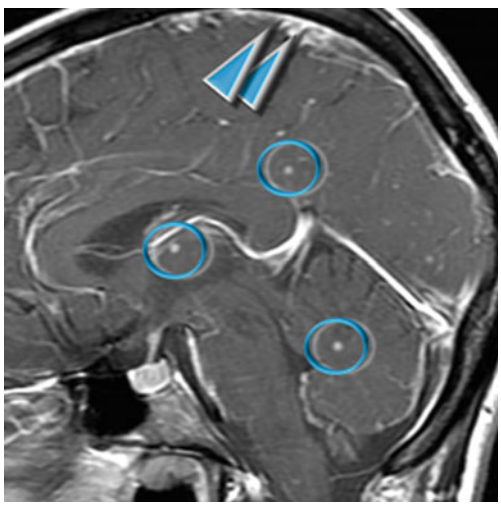
Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30(6):1567

Harisinghani MG (2000) Tuberculosis from head to toe. Radiographics 20(2):449

Burrill J (2007) Tuberculosis: a radiologic review. Radiographics 27(5):1255

Table	Extrapulmonary TB
Neck TB	Tuberculosis in the head and neck represents about 15 % of cases of extrapulmonary tuberculosis. The most common location is within the neck nodes, often manifesting as bilateral painless cervical lymphadenitis, also known as scrofula. The involved nodes are initially homogeneous but later undergo central necrosis, manifesting with central low attenuation at CT
Abdominal TB	The abdomen is the most common focus of extrapulmonary tuberculosis. Abdominal lymphadenopathy is the most common manifestation, observed in 55–66 % of patients. The majority (40–60 %) of patients with lymphadenitis have enlarged nodes with hypoattenuating centers and hyperattenuating enhancing rims at CT (▶). Peritonitis may be present. Gastrointestinal tuberculosis is rare; when present, however, it almost always involves the ileocecal region (90 % of cases). Hepatosplenic involvement is common in patients with disseminated disease and is either micronodular-miliary or macronodular
Urinary TB	Various patterns of hydronephrosis may be seen at CT depending on the site of the stricture and include focal caliectasis with mild thickening of adjacent parenchyma due to papillary necrosis (↪) and possible generalized hydronephrosis. Other common findings include parenchymal scarring and low-attenuation parenchymal lesions. CT is also useful in depicting the extension of disease into the extrarenal space

Table	Extrapulmonary TB
Musculoskeletal TB	The musculoskeletal system is involved in only 1–3 % of cases of tuberculosis. Approximately 50 % of skeletal tuberculosis involves the spine (Pott disease). The lower thoracic and upper lumbar levels are most commonly affected (➡). Isolated tuberculous osteomyelitis in the absence of associated tuberculous arthritis is relatively rare
TB involving the CNS	Involvement of the central nervous system (CNS) is seen in approximately 5 % of immunocompetent patients and up to 15 % of immunocompromised patients. Tuberculous meningitis is the most common manifestation of CNS. The typical radiographic finding is abnormal meningeal enhancement (►►). The most common CNS parenchymal lesion of tuberculosis is tuberculoma. This lesion may be solitary, multiple, or miliary and may be seen anywhere within the brain parenchyma (○). They demonstrate homogeneous or ring enhancement

Definition

Lipoid pneumonia (LP) is an uncommon condition which results from the pulmonary accumulation of fatlike compounds. The exogenous chronic form results from the recurrent aspiration or inhalation of oil or from the accidental aspiration of a large quantity of lipid material. It can have an animal, vegetable, or mineral origin. It is possible in patients with obstinate constipation and long-term use of laxative or in patients who use Vaseline for oiling tracheal cannula. Clinically, patients may be asymptomatic or present with nonspecific symptoms such as cough, tachypnea, and mild fever. As a result, the diagnosis of lipoid pneumonia is sometimes difficult to establish, and the history of ingestion or inhalation of oily material is often the key to diagnosis. Pathologically, macrophages containing phagocytosed oil fill in the alveoli and distend the alveolar walls and interlobular septa. Fibrosis is occasionally present and is of variable extent. The diagnosis of this disease requires a high index of suspicion and can be confirmed by the demonstration of lipid-laden macrophages in respiratory samples such as sputum, bronchoalveolar lavage fluid, or fine-needle aspiration cytology/biopsy from lung lesions.

☯ LP

📖 Marchiori E (2011) Exogenous lipoid pneumonia. Clinical and radiological manifestations. Respir Med 105(5):659

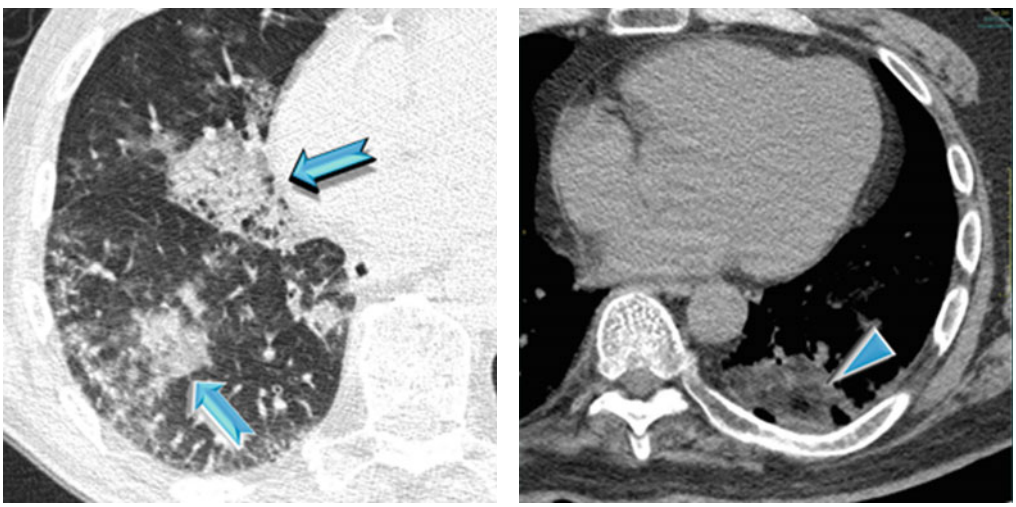
HIGH-RESOLUTION CT: HRCT

Key Signs

- Patchy ground-glass opacities
- Patchy airspace consolidations (➡) with possible low-density attenuation (negative values) (►)

Distribution

Patchy unilateral or more frequently bilateral, middle and lower lobes and geographic distribution with posterior predominance



✓ Low-attenuation consolidation with negative density values between –150 and –30 HU is highly suggestive of fat and consistent with lipoid pneumonia. These measures should be taken in the most hypodense part of the consolidation areas, free of any aerated parenchyma. Nevertheless, CT attenuation measurements are not always characteristic due to the averaging with attenuation values from surrounding inflammatory infiltrates.

The low-attenuation consolidation is better appreciated after contrast material administration.

📖 Baron SE (2003) Radiological and clinical findings in acute and chronic exogenous lipoid pneumonia. J Thorac Imaging 18(4):217

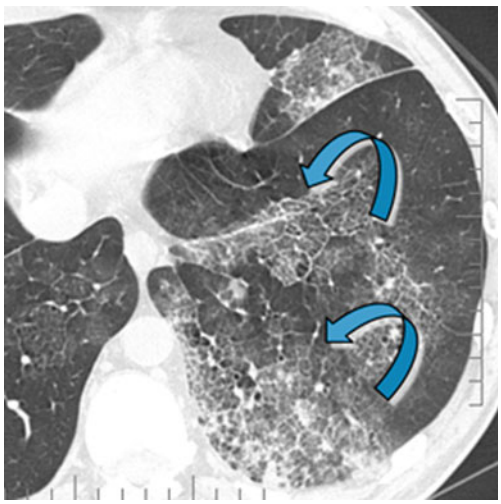
Ancillary Signs

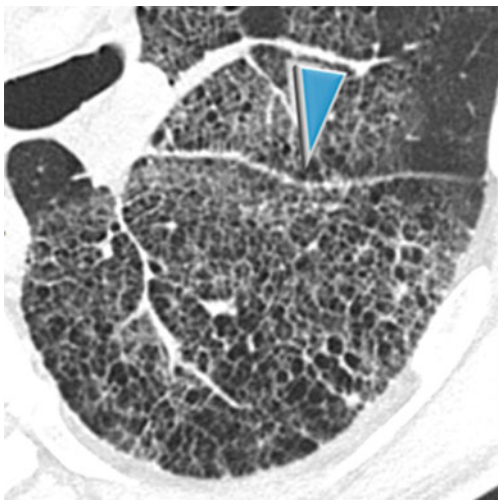
- Interlobular septal thickening and crazy paving have also been reported (⇨).
- Airspace nodules (low-density centrilobular nodules).
- Signs of fibrosis in the later stages appearing as fissure distortion, volume loss, and diffuse honeycombing (►).
- Tumorlike lesions often with spiculated profiles and mainly in the dorsal area of the lower lobes.

☝ Chronic crazy paving may be present in lipoid pneumonia but also in other alveolar diseases, often in pulmonary alveolar proteinosis (please also refer to Crazy-paving in the "Case-Based Glossary with Tips and Tricks").

Non-parenchymal Signs

- Reactive mild lymph node enlargement





☝ Lipoid pneumonia can present as a PET-positive lung nodule and should be considered in the differential diagnosis and workup of a solitary pulmonary nodule.

📖 Talwar A (2004) False-positive PET scan in a patient with lipoid pneumonia simulating lung cancer. Clin Nucl Med 29(7):426

Course

- None of the patients with chronic presentations improved either clinically or radiologically.
- The natural history and outcome of LP are variable. This and the low number of cases make it difficult to establish the optimal treatment. The first and foremost concern is the avoidance of further insult.

📖 Laurent F (1999) Exogenous lipoid pneumonia: HRCT, MR, and pathologic findings. Eur Radiol 9(6):1190

Betancourt SL (2010) Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol 194(1):103

Definition

Primary pulmonary mucosa-associated lymphoid tissue (p-MALT) lymphoma is an extranodal low-grade B-cell lymphoma. It is the most common primary pulmonary lymphoma. MALToma accounts for 54–58 % of the primary pulmonary lymphomas. This tumor tends to remain localized to the lung for long periods of time, follows an indolent course, and is associated with a good prognosis. MALT lymphomas are usually indolent lesions with possible association with autoimmune disease (collagen vascular diseases such as RA, Sjögren's syndrome, SLE, and hepatitis C virus infection). When present, symptoms, such as cough, mild dyspnea, and chest pain, are nonspecific. The median age is 60 years. About 50 % of patients have at least one extrapulmonary location of lymphoma.

MALToma, BALT lymphoma, extranodal marginal zone B-cell lymphoma

Poletti V (2013) Lymphoproliferative lung disorders: clinicopathological aspects. Eur Respir Rev 22(130):427

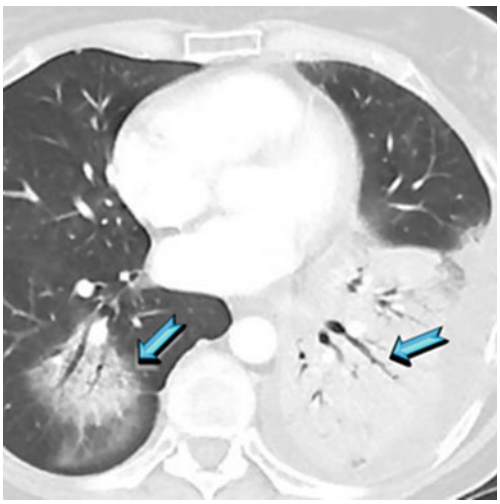
HIGH-RESOLUTION CT: HRCT

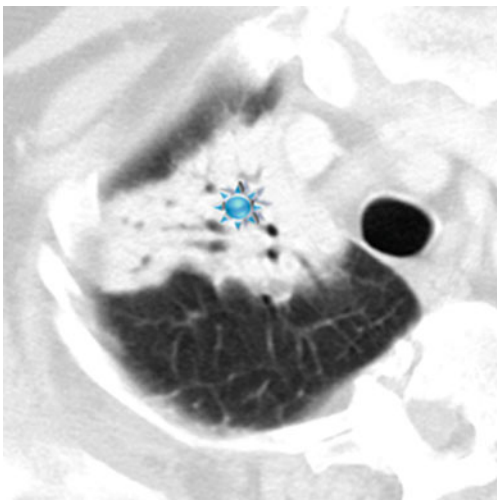
Key Signs

- Consolidations (60 %) with air bronchogram (50–90 %); bronchi within affected parenchyma may appear stretched and slightly narrowed (➡) or slightly dilated (✸).

Distribution

Solitary or often multiple (70 %) and bilateral (60–70 %), peribronchovascular and peripheral





Multifocal areas of consolidation may also be seen in other alveolar chronic diseases and in particular in minimally invasive adenocarcinoma (MIA), adenocarcinoma in situ (AIS), formerly known as bronchoalveolar carcinoma (BAC), and cryptogenic organizing pneumonia (COP). See also alveolar pattern, chronic subset.

Do KH (2005) Pulmonary parenchymal involvement of low-grade lymphoproliferative disorders. J Comput Assist Tomog 29(6):825

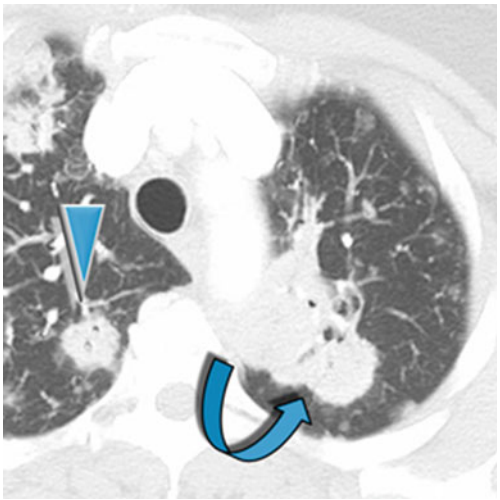
Hare SS (2012) The radiological spectrum of pulmonary lymphoproliferative disease. Br J Radiol 85(1015):848

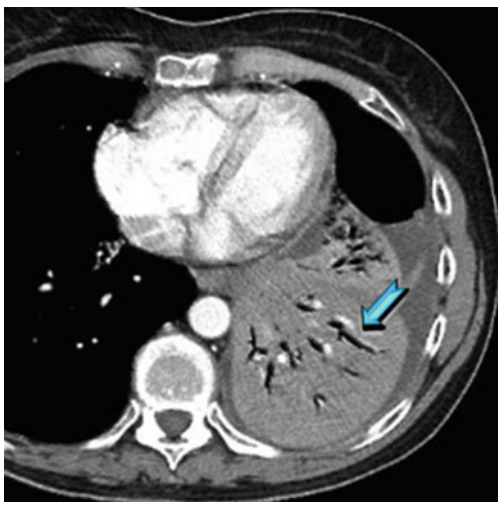
Ancillary Signs

- Macronodules (►) with hazy margins due to airspace filling (60 %)
- Masses (☟) with variable diameter up to several centimeters
- Possible halo sign around nodules or masses
- Angiogram sign after contrast material administration (➡)
- Interlobular septal thickening
- Bubble-like lucencies inside the lesions (rare)

Non-parenchymal Signs

- Hilar/mediastinal lymphadenopathy (30 %)
- Pleural effusion (10–30 %), generally associated with the parenchymal lesions





Halo sign is defined as a ground-glass opacity that surrounds circumferentially a pulmonary nodule or mass. The sign was originally described in association with invasive pulmonary aspergillosis, but, as a matter of fact, many infectious or noninfectious diseases may be associated with this sign.

Angiogram sign refers to the visualization of pulmonary vessels within an airless portion of the lung, on contrast-enhanced CT scanning. The vessels are prominently seen against a background of relatively low-attenuation lesion. It has been initially described in 1990 as a specific sign of lobar bronchoalveolar cell carcinoma. Thereafter, several retrospective studies reported that this sign can be seen in both benign and malignant diseases.

Bubble-like lucencies (pseudocavitations) inside the lesions are rare and are due to bronchiolar dilatation. Others diseases are more often responsible of bubble-like lucencies.

For all these tree signs, please refer to “Case-Based Glossary with Tips and Tricks”.

Think of primary pulmonary lymphomas in the presence of a tumorlike mas and an air bronchogram with bronchial dilatation in patients with autoimmune disease

Cardinale L (2005) CT findings in primary pulmonary lymphomas. Radiol Med 110(5–6):554

King LJ (2000) Pulmonary MALT lymphoma: imaging findings in 24 cases. Eur Radiol 10(12):1932

Course

- The parenchymal abnormalities typically show an indolent course, with slow growth over months or years.
- The survival data confirm the indolent nature of pulmonary MALT lymphoma.

Borie R (2009) Clinical characteristics and prognostic factors of pulmonary MALT lymphoma. Eur Respir J 34(6):1408

Definition

Metastases from an adenocarcinoma may spread into the lung along the intact alveolar walls (lepidic growth), in a fashion similar to a primary lung adenocarcinoma. Metastases may be from an adenocarcinoma of the lung or gastrointestinal tract/breast/ovary.

In primary lung adenocarcinoma, aerogenous metastases result as intrapulmonary discontinuous spread of neoplastic cells through airspaces and airways; the discontinuous foci may be seen close to primary tumor as satellite foci or at distance, including the contralateral lung. The radiologic features of this tumor growth pattern can mimic pneumonia.

Gaikwad A (2014) Aerogenous metastases: a potential game changer in the diagnosis and management of primary lung adenocarcinoma. AJR Am J Roentgenol 203(6):W570

Warth A (2015) Prognostic impact of intra-alveolar tumor spread in pulmonary adenocarcinoma. Am J Surg Pathol 39:793

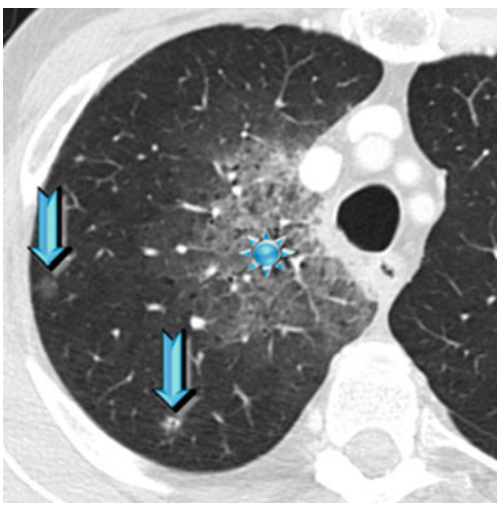
HIGH-RESOLUTION CT: HRCT

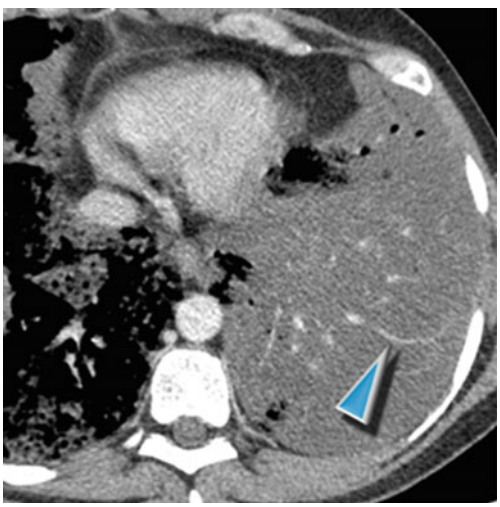
Key Signs

- Predominant or exclusive airspace disease: ground-glass opacities (✸) and consolidations
- Low-density persistent centrilobular nodules with ill-defined margins (snowflake nodules) (➡) and possible branching opacities (tree in bud)
- Possible low-attenuation consolidations with "angiogram sign" on contrast-enhanced CT (the vessels may be stretched and thin due to "mass effect") (►)

Distribution

Prevalent lower lobes and dependent distribution





The presence of a "dominant" consolidation may be due to primary or sometimes due to the advanced metastatic involvement of lepidic growth, more frequent in patients with gastrointestinal disease.

Possible low-attenuation consolidations with "angiogram sign" may be due to primary or metastatic mucinous adenocarcinoma. The CT findings include a uniform low attenuation and slight enhancement after intravenous injection of contrast medium. The differential diagnosis is with other diseases with hypodense consolidation and in particular with lipoid pneumonia (please see also "angiogram sign" in the "Case-Based Glossary with Tips and Tricks" "low-density consolidation" in the chapter "Alveolar Pattern").

Nodules tend to grow in clusters on serial images, in some cases progressing to confluent airspace consolidation. The differential diagnosis of centrilobular nodules and branching opacities at CT includes infectious bronchiolitis due to mycobacterial, viral or bacterial agents. Inflammatory centrilobular nodules commonly resolve with appropriate treatment, whereas aerogenous metastases persist and grow. The CT appearance reflects cancer cells lining the small airways and alveolar spaces in a lepidic pattern with variable amounts of intra-alveolar material (e.g., cells, secretions, and mucin).

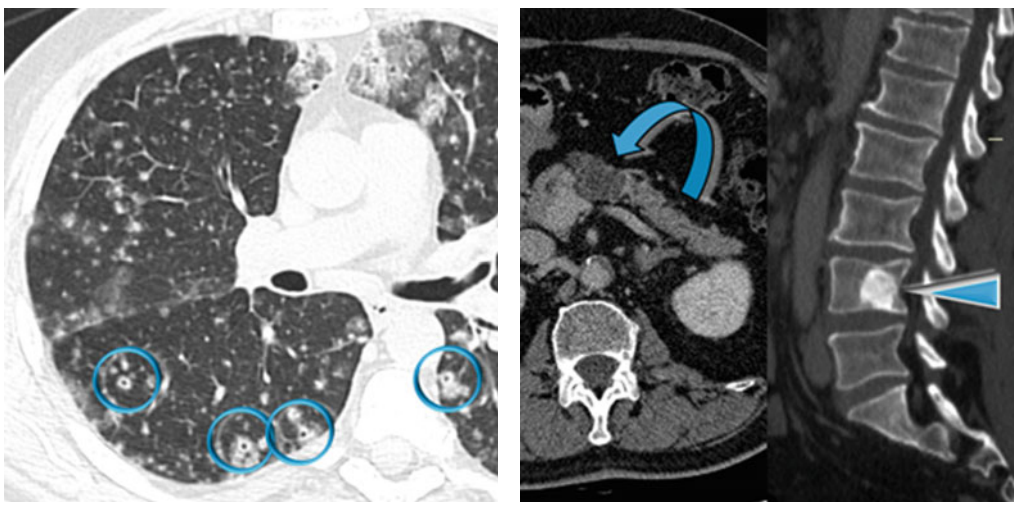
Gaeta M (2002) CT and MRI findings of mucin-containing tumors and pseudotumors of the thorax: pictorial review. Eur Radiol 12(1):181

Ancillary Signs

- Nodular thickening and solid nodules along lymphatic routes due to lymphangitic carcinomatosis
- Solid nodules due to hematogenous metastases, feeding vessels, and also "cavitated" (O) (please also refer to Cheerio sign in the chapter "Nodular Pattern" and in the "Case-Based Glossary with Tips and Tricks").

Non-parenchymal Signs

- Mediastinal and abdominal lymph node enlargement
- Mucus filling of airways
- Pleural effusion
- Abdominal solid neoplasm (e.g., pancreas, colon), often mucinous and consequently partially hypodense after intravenous injection of contrast medium
- Focal lytic or hyperdense bone lesions (►) due to hematogenous metastatic involvement in infiltrative carcinoma



Synchronous primary mucinous adenocarcinoma typically presents as multiple random peripheral subsolid nodules of variable size; in comparison, aerogenous metastatic lesions appear as small clustered centrilobular and "tree-in-bud" opacities. The temporal evolution on serial CT examinations is a key in the differential diagnosis.

Tateishi U (2005) Mucin producing adenocarcinoma of the lung: thin-section computed tomography findings in 48 patients and their effect on prognosis. J Comput Assist Tomogr 29:361–368

Seo JB (2001) Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 21(2):403

Course

- Slow progression with continuous growth of neoplastic cells (lepidic growth) with growing of the consolidative and ground-glass areas
- In invasive adenocarcinomas, onset or progression of metastatic disease through lymphatic and/or blood vessels

Definition

Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease characterized by the alveolar and interstitial accumulation of a periodic acid–Schiff (PAS) stain-positive phospholipoprotein derived from surfactant. Three distinct subgroups of PAP are currently recognized: idiopathic, secondary, and congenital. *Idiopathic/autoimmune* PAP (also termed "adult-type" PAP) accounts for the great majority of cases (90 %). *Secondary* PAP (5–10 % of cases) is associated with certain occupational exposures, particularly mineral dusts and fumes or an underlying hematologic malignancy or immunodeficiency disorders. *Congenital* PAP is quite rare (2 % of cases) and manifests in the neonatal period with severe hypoxia.

PAP

Frazier AA (2008) From the archives of the AFIP: pulmonary alveolar proteinosis. Radiographics 28(3):883

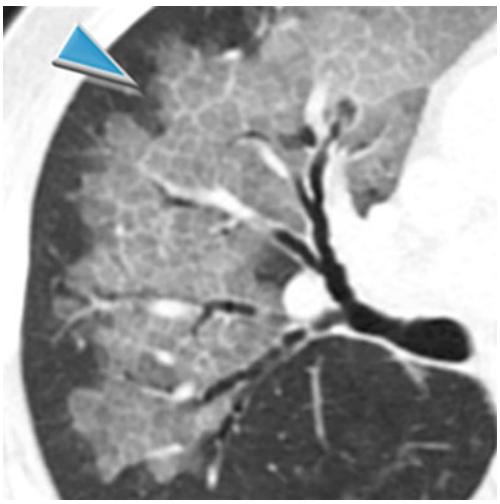
HIGH-RESOLUTION CT: HRCT

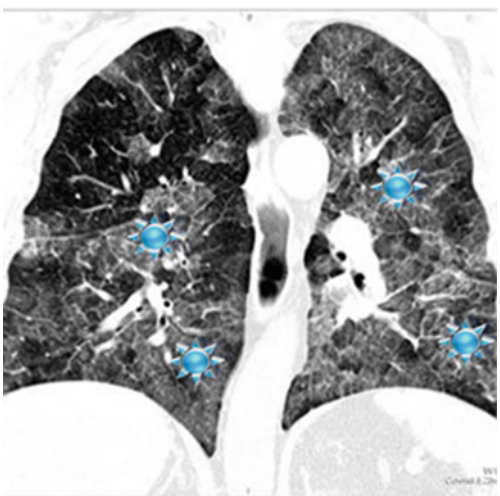
Key Signs

- Crazy paving (►)
- Areas of ground-glass opacity (GGO) (✸)

Distribution

Bilateral, diffuse, patchy, or geographic distribution with typically sharply demarcated marginations of areas of lung opacity. No specific zonal distribution with relative sparing of apices and costophrenic angles (butterfly distribution); in some patients the abnormalities predominate in the lower lung.





Crazy paving refers to the appearance of ground-glass opacity with superimposed interlobular septal thickening and intralobular reticular thickening, seen on chest HRCT. This sign is strongly suggestive of alveolar proteinosis in patients with subacute/chronic symptoms. Other diseases with *subacute/chronic alveolar pattern* may be lipoid pneumonia, chronic eosinophilic pneumonia (CEP), organizing pneumonia (OP), sarcoidosis (alveolar), tuberculosis, primitive pulmonary neoplasms (adenocarcinoma, MALT lymphoma), nonspecific interstitial pneumonia (NSIP), and radiation pneumonitis (please also refer to Crazy paving in the "Case-Based Glossary with Tips and Tricks").

The extent and zonal distribution of idiopathic PAP is bigger than that of secondary PAP, as some inhaled dusts may deposit according to the gravity and some other conditions (such as infectious, metastatic, or malignant processes) may spread to zones with higher vascular supply.

Mehrian P (2014) Features of idiopathic pulmonary alveolar proteinosis. in high resolution computed tomography. Pol J Radiol 79:65

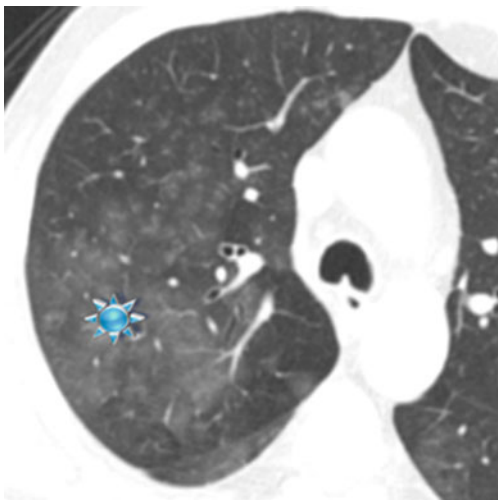
Shah PL (2000) Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax 55:67

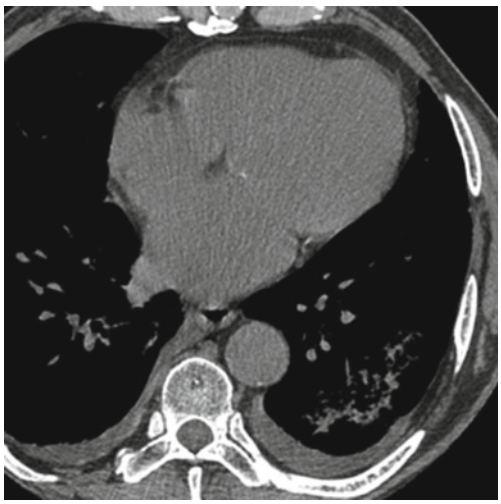
Ancillary Signs

- Ill-defined low-density (subsolid) nodules (snowflake nodules) (see figure below)
- Consolidation (►)

Non-parenchymal Signs

- Mediastinal and/or hilar lymphadenopathy
- Pleural effusion





Patients with PAP are at increased risk of developing pulmonary infection, usually caused by opportunistic agents such as *Nocardia*, *Aspergillus*, *Pneumocystis jirovecii*, and *Mycobacteria*. The presence of pleural effusion and enlarged lymph nodes in patients with PAP should be considered as highly suggestive of a superimposed infection.

Parenchymal consolidation may be caused both by the underlying disease and by supervening opportunistic infection. The latter is suspected when the consolidation is focal.

Souza CA (2012) Comparative study of clinical, pathological and HRCT findings of primary alveolar proteinosis and silicoproteinosis. Eur J Radiol 81(2):371

Course

- Patients with idiopathic PAP are treated with sequential therapeutic whole-lung lavage (WLL), a procedure to remove lipoproteinaceous material from pulmonary alveoli with the use of saline solution.
- In patients who undergo whole-lung lavage (WLL), both ground-glass opacity and interlobular septal thickening typically decrease. However, in some patients undergoing WLL, a reduction in GGO occurs, with the persistence of interlobular septal thickening. Sometimes this abnormality may become chronic; rarely it indicates the presence of fibrosis.

Abdelmalak BB (2015) Therapeutic whole-lung lavage for pulmonary alveolar proteinosis: a procedural update. J Bronchol Interv Pulmonol 22(3):251

Definition

Hydrostatic pulmonary edema is characterized by a transudative mechanism often due to increased intravascular pressure, heart failure being the most common cause. Low intravascular oncotic pressure resulting from hypoalbuminemia can also result in increased interstitial transudation of fluid. If pulmonary edema is severe enough to flood the alveoli, bilateral, patchy, or widespread "fluffy" lung opacities may become evident on chest radiography. Hydrostatic pulmonary edema is a frequent cause of admission to the hospital, in particular, in elderly patients.

A classification of pulmonary edema as (a) hydrostatic edema, (b) increased permeability edema without associated DAD, (c) mixed edema, and (d) permeability associated with DAD (ARDS) has been proposed, and either agrees with pathology, physiology, and radiological findings.

PE

Ketai LH (1998) A new view of pulmonary edema and acute respiratory distress syndrome. J Thorac Imaging 13(3):147

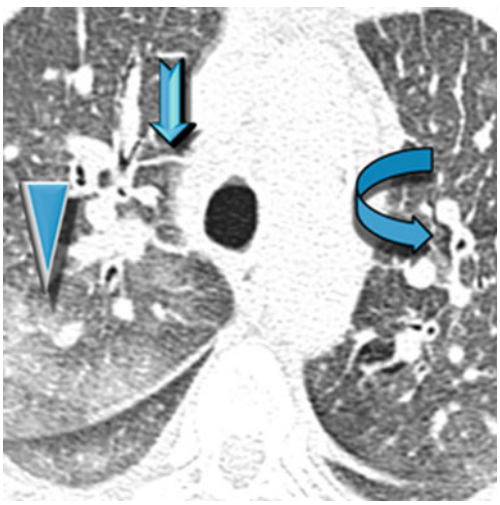
HIGH-RESOLUTION CT: HRCT

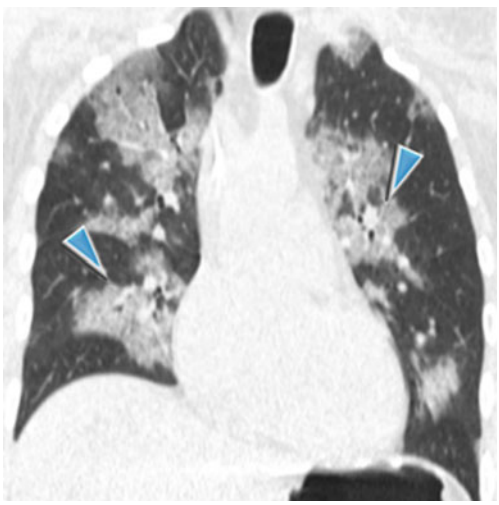
Key Signs

- Areas of ground-glass opacities (►)
- Peribronchial cuffing and vessel enlargement ( ) and smooth septal thickening (➡); all these signs are prevalent in the initial stages of disease, please see PE, interstitial in the chapter "Septal Diseases").

Distribution

Patchy or lobular (geographic) bilateral, central, and gravitational. Possible butterfly or batwing distribution (►)





Butterfly or batwing pulmonary opacities refer to the presence of bilateral parenchymal opacities, with perihilar distribution and sparing of the periphery of the lungs. It is classically described in the chest X-ray but is best appreciated on CT. It generally occurs with rapidly developing severe cardiac failure. It can be also caused by other diseases (see also the Butterfly pulmonary opacities in the "Case-Based Glossary with Tips and Tricks").

It is possible that increased blood volume is the cause of ground-glass opacity or that ground-glass opacity reflects very subtle interstitial edema.

Occasionally, edema may have unilateral distribution, as may occur in patients with a prolonged lateral decubitus, or asymmetric and even with bizarre distribution in patients with regional emphysema. Pulmonary edema may also localize to the right middle and upper lobes because of myocardial infarction with papillary muscle rupture and mitral acute valve insufficiency.

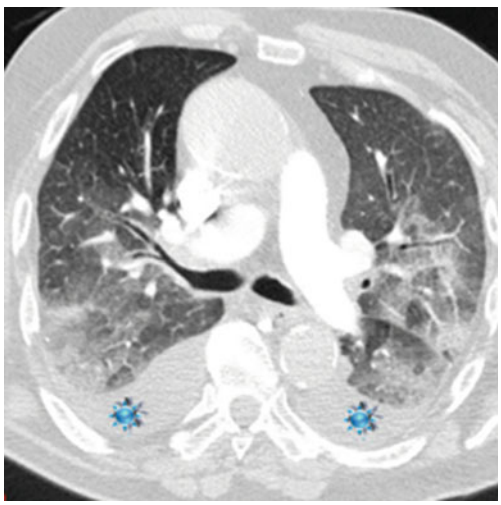
Storto ML (1995) Hydrostatic pulmonary edema: high-resolution CT findings. AJR Am J Roentgenol 165:817

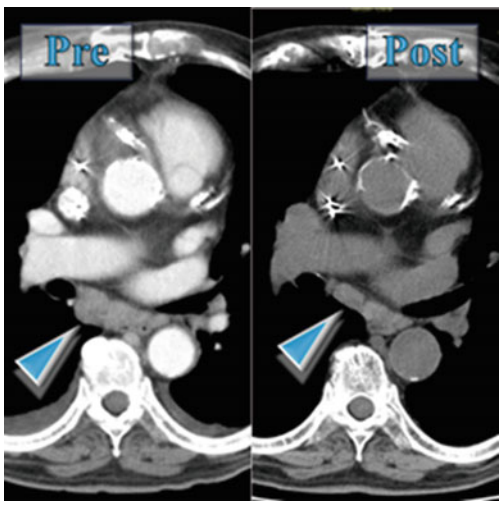
Ancillary Signs

- Crazy paving.
- Consolidation is inconspicuous or absent in most cases.

Non-parenchymal Signs

- Among the bilateral pleural effusion (✸), most are similarly sized but the right-sided can be larger. Possible unilateral pleural effusion, often on the right side.
- Cardiomegaly.
- Dilatation of pulmonary arteries and veins; vessels may become more visible at the periphery of the lung, and nongravity-dependent vessels may enlarge disproportionately, reflecting the process of "cephalization" seen on the chest radiograph.
- Enlargement of mediastinal lymph nodes due to fluid stagnation (in patients with left heart failure, identified in 40–60 %). Both the enlarged lymph nodes and pleural effusion often reduce or disappear after adequate diuretic therapy (►).





An increase in 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.

Cardinale L (2014) Effectiveness of chest radiography, lung ultrasound and thoracic computed tomography in the diagnosis of congestive heart failure. World J Radiol 6(6):230

Ribeiro CM (2006) Hydrostatic pulmonary edema: high-resolution computed tomography aspects. J Bras Pneumol 32(6):515

Course

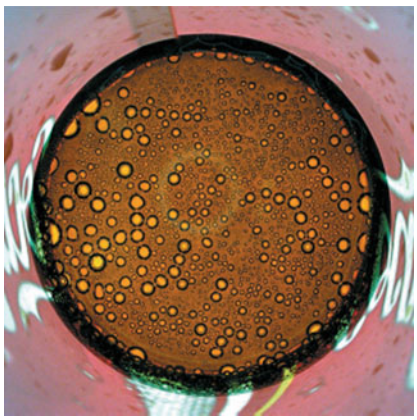
- Acute onset and rapid regression with treatment are characteristic features of this form of edema and may assist in the differential diagnosis.
- In patients with left heart failure, mediastinal lymphadenopathy often decreases after adequate treatment (60 %).

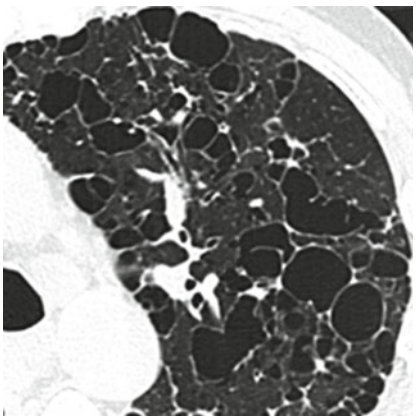
Chabbert V (2004) Mediastinal lymphadenopathy in congestive heart failure: a sequential CT evaluation with clinical and echocardiographic correlations. Eur Radiol 14(5):881

Cystic Pattern

Radiology
Pathology

Giorgia Dalpiaz
Alessandra Cancellieri





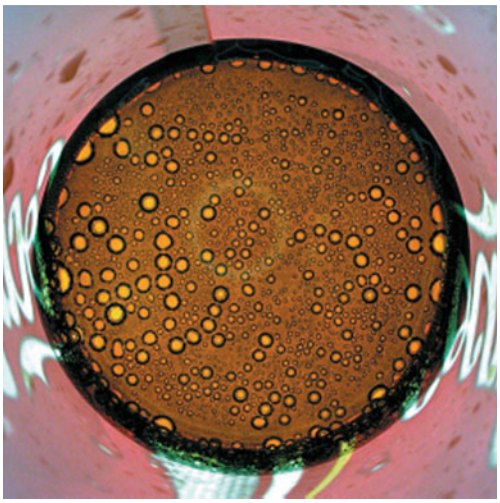
G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_11

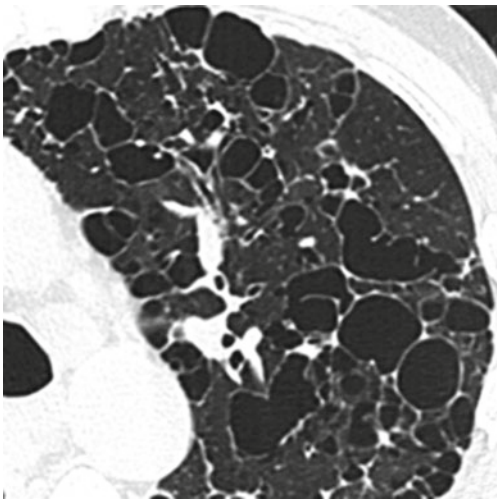
CYSTIC PATTERN

Definition

Cystic pattern is present when multiple roundish, well-defined, air-containing spaces ("holes") are variably scattered throughout the pulmonary parenchyma. The "holes" appear black on HRCT and white on pathological specimens.
These "holes in the lung" may be due to dilatation of bronchial structures, abnormal distension of alveolar spaces, focal destruction of lung parenchyma, or late stage of even cavitation of solid lesions. In elderly patients, lung cysts have also been reported in asymptomatic nonsmoking individuals, raising the possibility that they may represent part of the aging process.

Holes in the lung





The cystic pattern should not be confused with the dark lung pattern. In both models, the elementary lesions are hypodense on HRCT, but, in the cystic pattern, these lesions are focal and not diffuse and their density is that of pure air containing units, as black as the ambient air outside the chest or inside the trachea.

Sometimes, sporadic cysts may be present as ancillary signs in patients with other main signs belonging to other patterns, e.g., subacute hypersensitivity pneumonitis (HP) and desquamative interstitial pneumonia (DIP) (please refer to chapter "Alveolar Pattern").

The possible HRCT signs are:

- Thin-walled or not-walled cysts
- Thick-walled cysts
- Cysts with irregular shape
- Cysts with regular shape
- Bunch of grapes sign
- Incidental lung cyst

The prevalent distribution of the cysts together with the presence of nonparenchymal signs may be helpful for the diagnosis of a specific disease (please see the Table at the end of this Chapter).

Gupta N (2015) Diffuse cystic lung disease. Part I. Am J Respir Crit Care Med 191(12):1354

Gupta N (2015) Diffuse cystic lung disease. Part II. Am J Respir Crit Care Med 192(1):17

Raoof S (2016). Cystic Lung Diseases: Algorithmic Approach. Chest;150(4):945

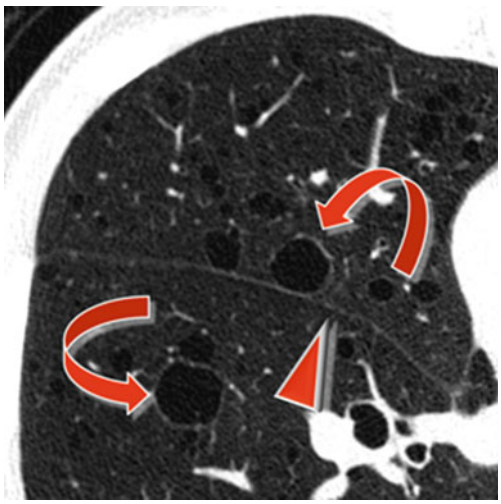
CYSTIC SIGNS

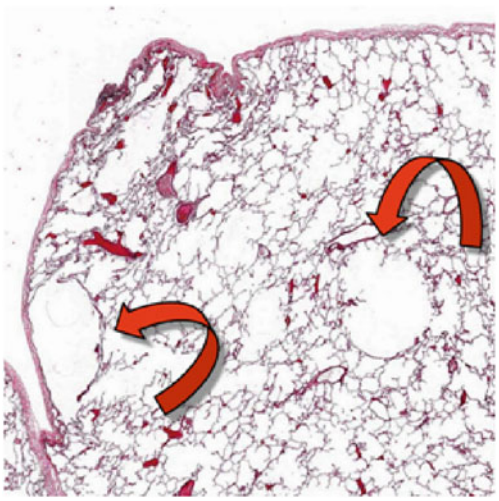
Thin-Walled Cysts or Not-Walled Cysts

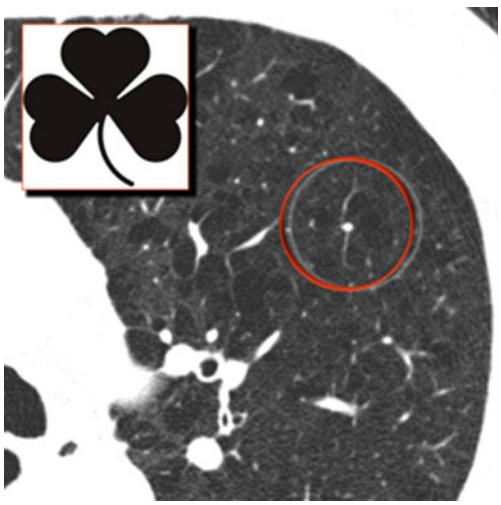
On HRCT thin-walled cysts (☟) present a white encircling rim of a thickness similar to the fissure (►). These types of cysts are often secondary to check-valve mechanisms in the context of a normal parenchyma (e.g., LAM) (☟).

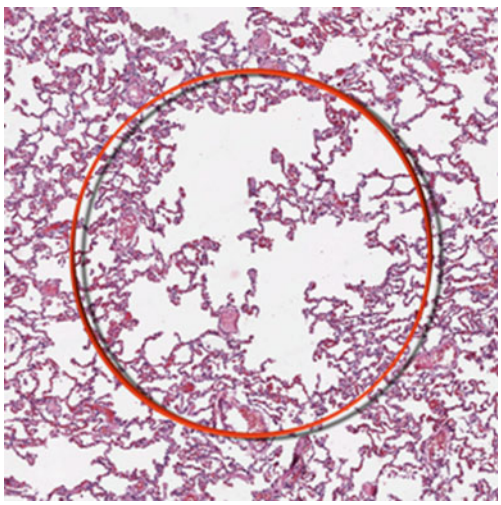
Not-walled cysts appear as roundish black holes with invisible walls, surrounded by normal lung parenchyma. Sometimes a central nodular or branching opacity representing the centrilobular artery is seen (O). From time to time this type of black hole may present a clover aspect (O). These types of cysts often are the result of local destruction of lung parenchyma (e.g., emphysema) (O).

☯ Bubble-like cysts, cysts with thin (or no) wall









🚹 Diseases having cysts with thin (or no) wall:

- *Emphysema*, *centrilobular* (images above O): it is the prototype of cystic diseases without wall; however, it may display thin-walled cysts and, occasionally, it can hardly be differentiated from LAM. In these cases, the upper lobe predominance is a key for the differential diagnosis. Paraseptal emphysema is often visible also in the subpleural space in single layer. The anamnesis of smoking habit is also crucial for the diagnosis.
- *Lymphangioleiomyomatosis (LAM)* (images above ☟): the disease typically involves young women in reproductive age, and the cysts are characteristically thin-walled and round in shape ("lacy" appearance). The most useful sign to differentiate LAM from LCH is the distribution of the cysts. Unlike in LCH, cysts are diffused throughout the lungs and they may involve the juxtaphrenic recesses.

- *Langerhans Cell Histiocytosis (LCH), end-stage disease*: in this phase of disease the cysts may present a thin wall similarly to LAM; however, they are bizarre in shape and predominate in the lung apices, with relative sparing of the lung bases. Crucial is also the anamnesis of smoking habits.
- *Lymphocytic Interstitial Pneumonia (LIP)*: cysts are scattered with normal intervening lung parenchyma. Ground-glass opacities and nodules are often associated. The disease typically occurs in patients with collagen vascular disorders, in particular Sjögren's syndrome.
- *Birt-Hogg-Dubè (BHD)*: unlike most cystic diseases, in BHD there are just a few scattered cysts with lower and medial zone predominance. Cysts are often larger than those in LAM and LCH. Subpleural lentiform cysts may involve the fissures, more frequently than in other cystic diseases. BHD is a very rare condition that is associated with renal cell carcinomas and skin fibrofolliculomas.
- *Light-Chain Deposition Disease* (*LCDD*): HRCT findings can vary from diffuse multiple small (<2 cm), round cysts in a diffuse distribution (mimicking LAM) to large cystic spaces. The associated nodules are irregular, multiple, and can be bilateral or unilateral. Patchy areas of consolidation can also be seen. Crucial for the diagnosis is the clinical history of lymphoproliferative disorders.

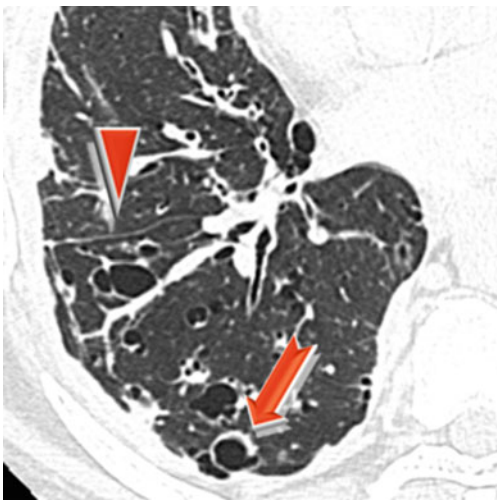
In the end stage of several diseases the wall may appear thin.

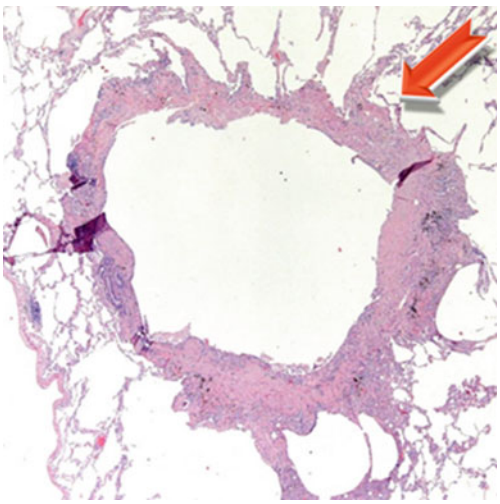
Cosgrove GP (2007) Challenges in pulmonary fibrosis. 3: cystic lung disease. Thorax 62(9):820

Thick-Walled Cysts

On HRCT, empirically, the wall of a cyst is defined as thick (➡) when its thickness is greater than a normal fissure (►). Thick-walled cysts may be secondary to check-valve mechanisms or due to excavation of nodules. Thick-walled cysts with irregular shape and contour are often due to fusion of several lesions or fibrotic traction phenomena (e.g., in LCH), please see the images below (➡).

Cysts with thick walls





Diseases having Cysts with thick walls:

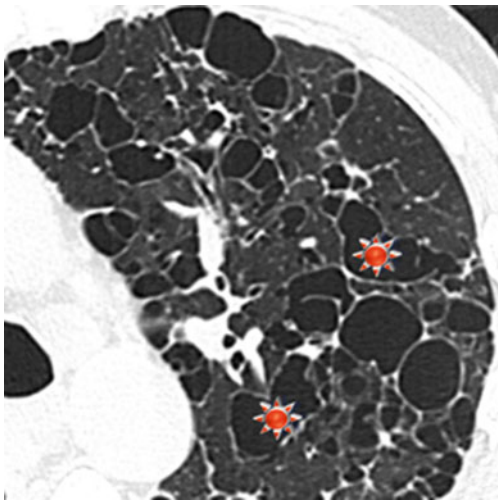
- *LCH* (Figures above): the combination of nodules, cavitating nodules, and thick-walled cysts (➡) in a smoker should allow a confident and accurate diagnosis of LCH to be made on CT. The lesions are diffusely distributed, with a predominance in the lung apices and relative sparing of the lung bases. Another helpful clue is the sparing of the medial tips of the middle lobe and lingula. The cysts can have bizarre shapes and unequal sizes also due to confluence phenomena.
- *Metastases*, *cystic*: associated with random cavitating nodules. The cysts are not confluent. History of primary squamous cell carcinoma, adenocarcinoma, or sarcoma.
- *Laryngotracheobronchial papillomatosis*: sporadic thick-walled cysts associated with random, often cavitating macronodules and a history of tracheobronchial papillomatosis.
- *Bronchiectases*, *cystic*: unlike in other diseases, the cysts appear clustered close to bronchial tree.

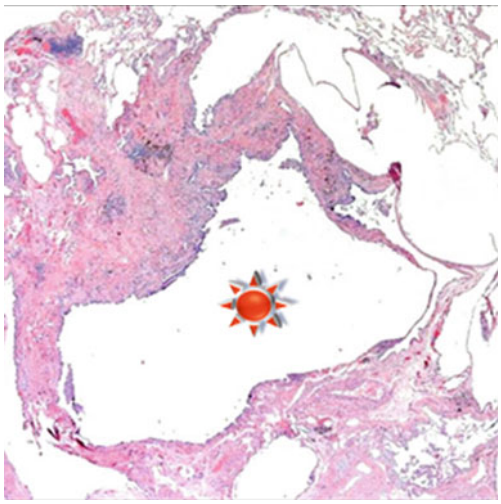
Cysts with Irregular Shape

Beddy P (2011) A practical approach to cystic lung disease on HRCT. Insights Imaging 2(1):1

Bizarre shape is often associated with parenchymal distortion. Cysts with irregular shape are frequently the result of fusion of several lesions and/or fibrotic phenomena (e.g., in LCH, please see the images below ✸)

Bizarre cysts





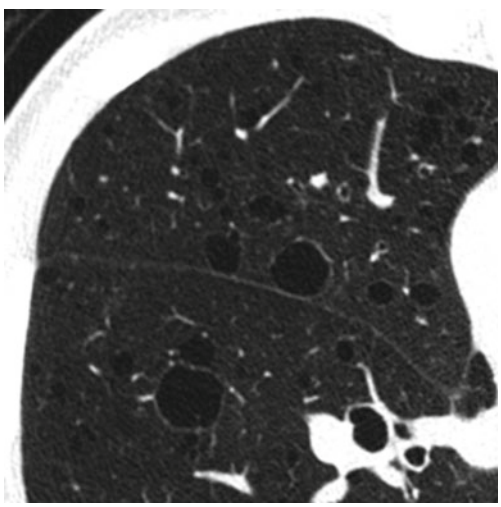
Diseases having Cysts with irregular shape:

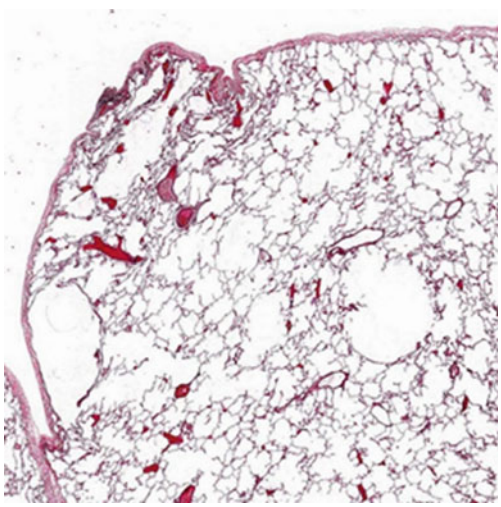
- *Langerhans Cell Histiocytosis* (Figures above): pulmonary involvement develops most commonly in young patients, between the ages of 20 and 40 years, almost all of whom are cigarette smokers. Most cysts are bizarre in shape, irregular, with a tendency to confluence (✸). Upper and middle lungs predominance, with sparing of the costophrenic angles and lung bases, is typical; nodular and cystic patterns may coexist.
- *Emphysema*: severe forms appear as extensive areas of parenchymal destruction, although the structure of the secondary lobule can still be recognized.

Cysts with Regular Shape

Cantin L (2010) Multiple cystlike lung lesions in the adult. AJR Am J Roentgenol 194(1):W1–W11

Cysts with regular shape (rounded or oval) are usually secondary to check-valve mechanisms in the context of a normal parenchyma.





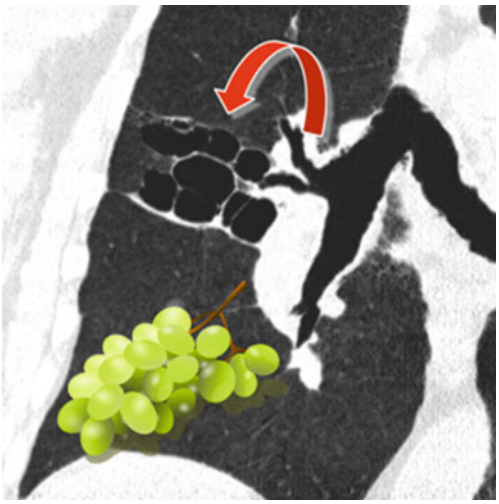
All cystic diseases. Rarely in LCH.

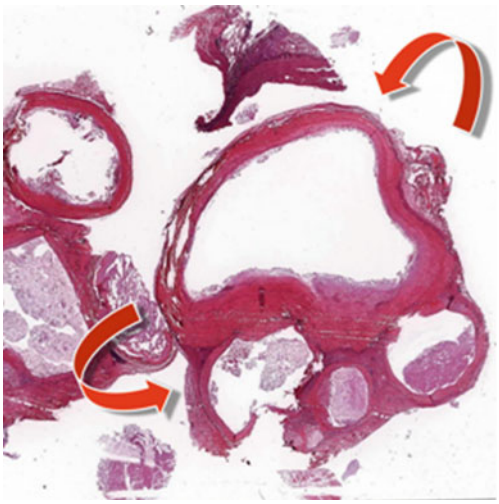
Cordier JF (2011) Multiple cystic lung diseases. Eur Respir Mon 54:46

Bunch of Grapes Sign

The cysts are arranged in grapelike clusters (), often around a stem (the bronchovascular pedicle). Usually, these lesions have thick walls; their diameter may be not uniform. Clustered cysts refer to cystic bronchiectases.
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.

Clustered cysts, cystic bronchiectases





Evaluation of the cranio-caudal distribution is important because it often provides valuable clues to a specific diagnosis. Use of coronal and sagittal reformatted images can be helpful in establishing an apical or basal gradient.

Diseases with cystic bronchiectases:

- *Cystic Fibrosis (CF)*: extensive cystic and cylindrical bronchiectases predominate in the upper lobes.
- *Allergic Bronchopulmonary Aspergillosis (ABPA)*: cystic or varicoid bronchiectases with a central or proximal upper lobe predominance. A "finger-in-glove" sign can be seen that corresponds to mucoid bronchial impaction (please also refer to finger-in-glove sign in the "Case-Based Glossary with Tips and Tricks").
- *Mounier-Kuhn (tracheobronchomegaly)*: is characterized by the coexistence of a dilatation of the trachea and main bronchi with often severe (cystic) bronchiectases. The syndrome is likely due to a congenital deficiency of elastic fibers in the membrane of the trachea and central bronchi. More peripheral bronchiectases are also secondary to recurrent infections of the lower respiratory tract.
- *Williams-Campbell syndrome*: it is a rare form of diffuse congenital bronchiectasis, not associated with ectasia of the trachea and main bronchi. Cystic bronchiectasis is sometimes misinterpreted as a parenchymal cystic lung disease because of the unusual mid-order location.

Honeycombing is a peculiar sign appearing as a cluster of small black holes of variable size (from 2 mm to 1 cm) and shape separated by thick walls. It is a key sign of advanced fibrotic conditions and associated with other fibrosing signs (please refer to chapter "Fibrosing Pattern").

Milliron B (2015) Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. Radiographics 35(4):1011

Incidental Lung Cysts

A solitary or small number of apparently incidental lung cysts may of course be a very early manifestation of any of the disease processes described in the Table below. However, it is important to remember that sporadic cysts or single cyst in an asymptomatic patient could be the residual manifestation of a previous infection (i.e., a persistent pneumatocele). In elderly patients, lung cysts have also been reported in asymptomatic nonsmoking individuals, raising the possibility that they may represent part of the aging process

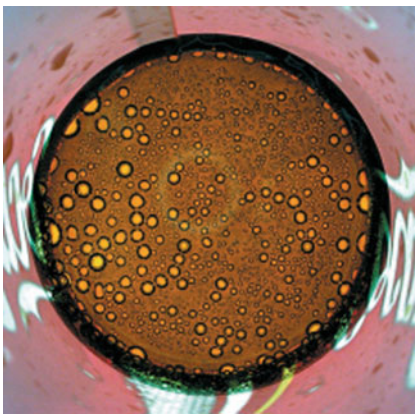
Copley SJ (2009) Lung morphology in the elderly: comparative CT study of subjects over 75 years old versus those under 55 years old. Radiology 251(2):566

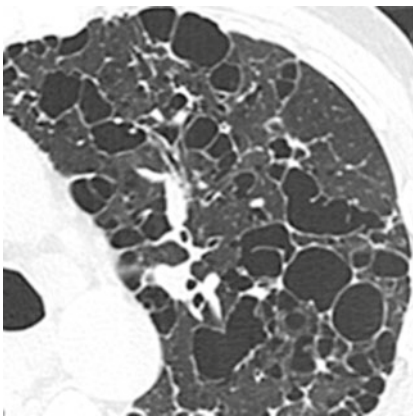
Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Cystic disease
Thin-walled cysts, few in number and variable in size; the cysts may be rounded or lenticular in shape	Lower and medial zone predominance, often subpleural in location	Absent	Pneumothorax, renal tumors, often multiple and bilateral	**Birt-Hogg-Dubè (BHD)**
Bunch of grapes sign, bronchial wall thickening	Upper predominance in CF and ABPA. Central bronchiectases in Mounier-Kuhn's and Williams-Campbell syndrome	Varicoid and cylindrical bronchiectasis, tree-in-bud sign, finger-in-glove sign, air-fluid levels, air trapping, consolidations	Tracheobronchomegaly in Mounier-Kuhn syndrome, lymph nodes enlargement	**Cystic bronchiectasis**
Bunch of grapes sign, bronchial wall thickening	Upper zone predominance	Varicoid and cylindrical bronchiectases, tree-in-bud sign, finger-in-glove sign, air-fluid levels, air trapping, consolidations	Lymph nodes enlargement, pulmonary arterial hypertension	**Cystic fibrosis (CF)**
Not-walled and thin-walled cysts in upper lobes, fibrosing pattern in the lower lobes	Upper and lower lobes	Thickening of bronchial walls	Lymph nodes enlargement, pulmonary arterial hypertension in the advanced stages of disease	**Combined Pulmonary Fibrosis Emphysema (CPFE)**

Key signs	Distribution	Ancillary signs	Non-parenchymal signs	Cystic disease
Not-walled and thin-walled cysts	Upper zone predominance	Thickening of bronchial walls, increased lung volumes	Lymph nodes enlargement, bronchial diverticula, saber-sheath trachea, pulmonary arterial hypertension	**Emphysema, centrilobular and paraseptal**
Rounded thin-walled cysts with "lacy" appearance	Bilateral uniform distribution without any lobar predominance	Possible patchy areas of ground-glass opacity with septal thickening	Pneumothorax, pericardial or pleural effusions, lymphadenopathy, renal angiomyolipomas	**Lymphangioleiomyomatosis (LAM)**
Thick-walled cysts	Basal zone predominance	Scattered bilateral nodules and macronodules, often cavitated, possible atelectasis and consolidations	Polypoid formations in the trachea and major bronchi	**Laryngotracheobronchial (LTB) papillomatosis**
Thick-walled cysts, bizarre shaped	Upper and middle zone predominance	Small solid centrilobular nodules with sharp margins and irregular contours, also cavitated. DIP-like and RB reaction	Pneumothorax, lymph nodes enlargement, bone lytic lesions	**Langerhans cell histiocytosis (LCH), advanced**
Thin-walled cysts, often large and with regular shape, usually few in number	Bilateral and often subpleural	GGO and centrilobular nodules	Possible recurrent pneumothorax, lymph nodes enlargement	**Lymphocytic Interstitial Pneumonia (LIP)**
Thick- or thin-walled cysts of various size	Peripheral, random bilateral distribution	Nodules, often cavitated	Possible pneumothorax, lymph nodes enlargement, possible bone lytic lesions	**Metastases, cystic**

Cystic Diseases

Radiology	**Maurizio Zompatori** **Domenico Attinà**	





G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_12

Definition

The syndrome was reported for the first time in 1977 by Birt, Hogg, and Dubè who described small papular skin lesions distributed on the scalp, forehead, face, and neck in 15 out of 70 members of the same family. Histologic examination of the lesions reveals fibrofolliculomas, trichodiscomas, and acrochordons. Birt–Hogg–Dubè syndrome is a rare autosomal dominant genodermatosis caused by a mutation in the FLCN gene, which encodes for tumor suppressor protein, folliculin. Mutation predisposes to the development of cutaneous hamartomas (particularly fibrofolliculomas), cystic lung lesions, pneumothorax, and renal tumors ranging from benign oncocytoma to renal cell cancer. Skin lesions, however, may be absent.

BHD, Hornstein–Knickenberg syndrome, fibrofolliculomas with trichodiscomas and acrochordons

Birt AR, Hogg GR, Dubé WJ (1977) Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 113(12):1674

Souza CA (2005) Birt-Hogg-Dubé syndrome: a rare cause of pulmonary cysts. AJR Am J Roentgenol 185(5):1237

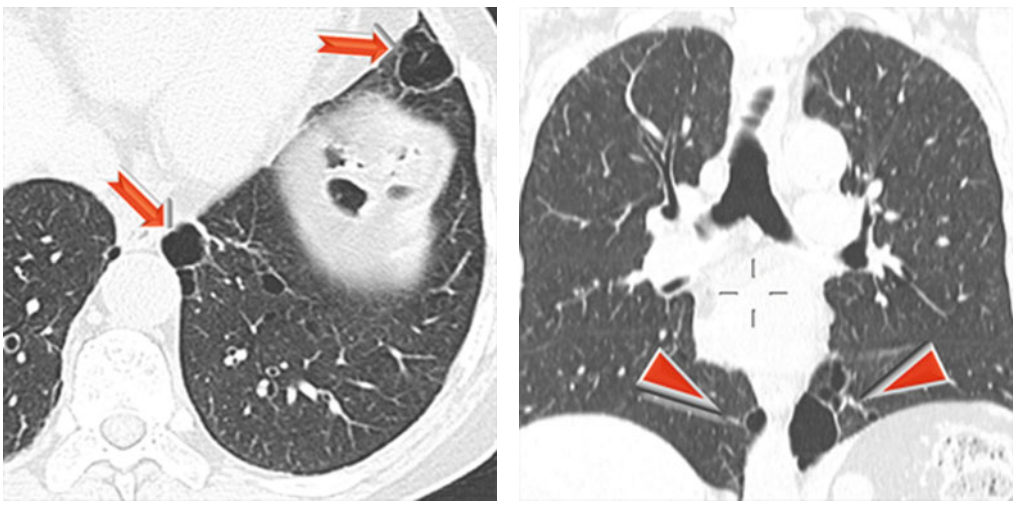
HIGH-RESOLUTION CT: HRCT

Key Signs

- Thin-walled, sometimes septated cysts, few in number, and variable in size (from a few millimeters to several centimeters) (➡); the cysts may be rounded or lenticular in shape.

Distribution

Lower and medial zone predominance, often subpleural in location (90 %) (►)



Cysts are often larger than those in LAM and LCH. Subpleural cysts, which may involve the fissures, are more frequent than in other cystic diseases.

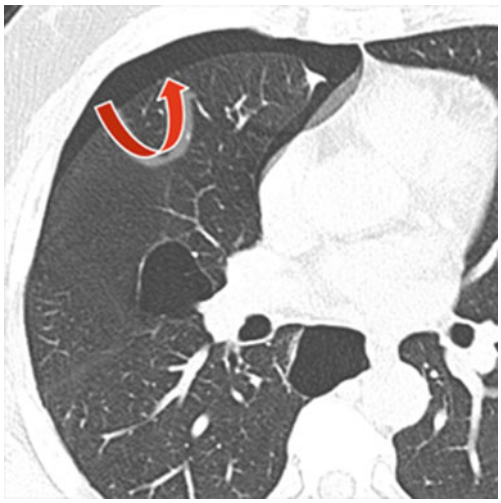
Agarwal PP (2011) Thoracic CT findings in Birt-Hogg-Dubè syndrome. AJR Am J Roentgenol 196:349

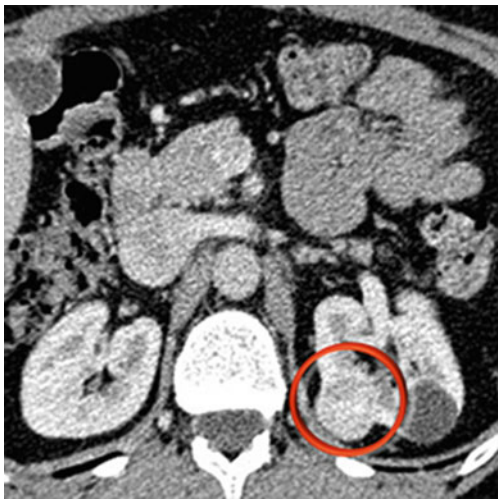
Ancillary Signs

- Absent

Non-parenchymal Signs

- Pneumothorax due to rupture of subpleural cysts (⇩)
- Renal tumors, often multiple and bilateral (O)





Patients aged 20–40 years frequently develop pneumothorax, usually without prior diagnosis of the underlying genetic syndrome, and may have isolated lung cysts without involvement of skin and/or kidney.

Renal tumors include hybrid chromophobe oncocytoma (50 %), chromophobe carcinomas (34 %), clear cell carcinomas (9 %), oncocytomas (5 %), and papillary renal cell cancers (2 %). Extrarenal neoplasm has been occasionally observed.

Menko FH (2009) Birt-Hogg-Dubé syndrome: diagnosis and management. Lancet Oncol 10(12):1199

Tomassetti S (2011) Pulmonary features of Birt-Hogg-Dubé syndrome: cystic lesions and pulmonary histiocytoma. Respir Med 105:768

Course and Complications

- Often recurrent pneumothorax

Dal Sasso AA (2015) Birt-Hogg-Dubé syndrome. State-of-the-art review with emphasis on pulmonary involvement. Respir Med 109(3):289

Definition

Bronchiectasis refers to an abnormal, permanent, and irreversible dilatation of the bronchial tree due to the destruction of the elastic and muscular components of bronchial walls. This condition represents the final common pathway of several respiratory and systemic diseases. Cystic bronchiectasis is the most severe manifestation of bronchial dilation. Smaller dilations with a cylindrical or varicose appearance may coexist. Bronchiectasis typically presents with chronic productive cough, recurrent chest infections, and hemoptysis (50 % of cases). The disease is more commonly encountered in middle aged and elderly.

☯ Clustered cysts

📖 Barker AF (2002) Bronchiectasis. N Engl J Med 346:1383

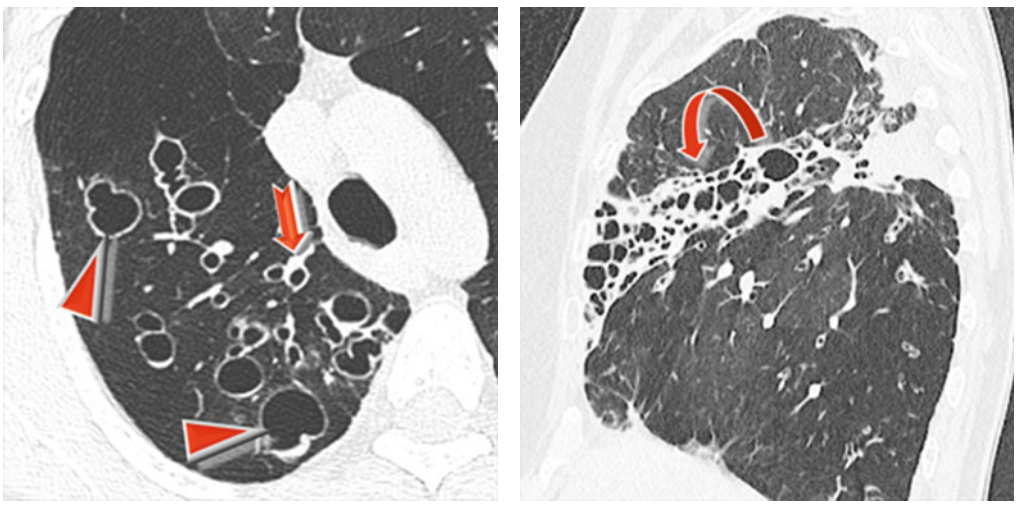
HIGH-RESOLUTION CT: HRCT

Key Signs

- Cystic bronchiectasis is arranged in grapelike clusters (►), often around a stem being the broncho-vascular pedicle (bunch of grapes sign).
- Bronchial wall thickening.

Distribution

Focal or diffuse, depending on the underlying disease. Upper predominance is common in cystic fibrosis (CF) and allergic bronchopulmonary aspergillosis (ABPA). Cartilage deficiency disorders (Mounier–Kuhn and Williams–Campbell syndrome) are characterized by central bronchiectases.



☝ Cystic or varicose bronchiectasis can be confused with parenchymal cystic disease, because dilated airways may show a cystic-like appearance on cross-sectional views. Assessment of adjacent sections on CT and multiplanar reconstructions should differentiate between these conditions.

📖 Hansell DM (1998) Bronchiectasis. Radiol Clin North Am 36:107

Cantin L (2009) Bronchiectasis AJR Am J Roentgenol 193:W158

Milliron B (2015) Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. Radiographics 35(4):1011

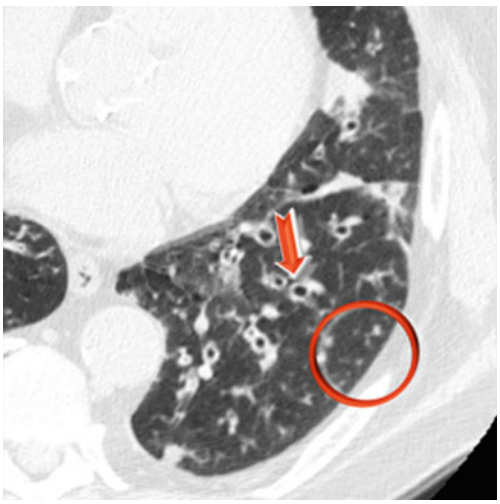
Ancillary Signs

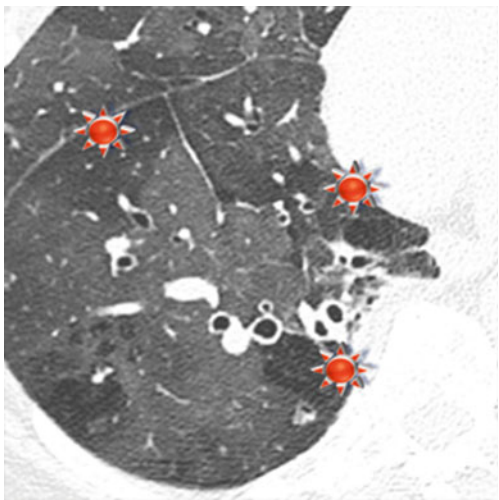
- Varicoid and cylindrical bronchiectasis (signet ring sign ➡)
- Mucus plugging within bronchi (finger in glove sign) (please also refer this sign in the "Case-Based Glossary with Tips and Tricks")
- Centrilobular nodules and tree-in-bud pattern related to cellular bronchiolitis O

- Air trapping due to obliterative bronchiolitis (✸)
- Air-fluid levels (mucus, pus, or blood)
- Inflammatory consolidations

Non-parenchymal Signs

- Enlarged mediastinal lymph nodes
- Dilated and dysmorphic appearance of the trachea (tracheomegaly) and the main bronchi in cases of Mounier–Kuhn syndrome





Pathophysiology consists in a vicious cycle which includes chronic inflammation and inability to clear mucoid secretions. A predisposed individual develops a robust inflammatory response to pulmonary infection or tissue injury. The inflammation that results is partially responsible for the structural damage to the airways. The structural abnormalities allow for mucus stasis, which favors continued chronic infection, and the vicious cycle persists.

McShane PJ (2013) Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 188:647

Course and Complications

- Recurrent infection, especially caused by *nontuberculous mycobacterial species, Pseudomonas aeruginosa* and *Haemophilus influenzae*, with frequent hospitalizations and increased risk of death, can occur.
- Cystic lesions may extend progressively especially in relation to the recurrence of inflammatory events and phenomena of scarring with retraction.
- Inclusions inside the cysts (mycetoma).

An intracystic macronodule/mass is often due to a mycetoma (particularly by *Aspergillus* colonization); please also refer to air crescent sign in the Case-based glossary. Rarely, the cause of intracystic macronodule/mass is neoplastic; however, only a mycetoma moves when the patient's position is changed. Sometimes, the cysts may be completely filled with material and assume a pseudo-nodular appearance.

McGuinness G (2002) CT of airways disease and bronchiectasis. Radiol Clin North Am 40:1

Definition

Cystic fibrosis (CF) is an autosomal recessive genetic disease which affects the exocrine function of the lungs, liver, pancreas, and small bowel resulting in progressive disability and multisystem failure. CF is more common in children and young adults of Caucasian origin. Mutation in the CF transmembrane regulator (CFTR) gene alters chloride passage across cell membranes. In the lungs it causes an abnormally low water content in the airway secretions, resulting in reduced clearance, mucus plugs, and increased incidence of airways infections. Although a few tens of mutations are responsible for most cases of CF, nearly 2000 CFTR gene mutations have been identified. These genotypic variants often cause a less severe disease and therefore in these patients CF is more likely to be detected in adulthood.

CF, Mucoviscidosis

O'Sullivan BP (2009) Cystic fibrosis. Lancet 373:1891

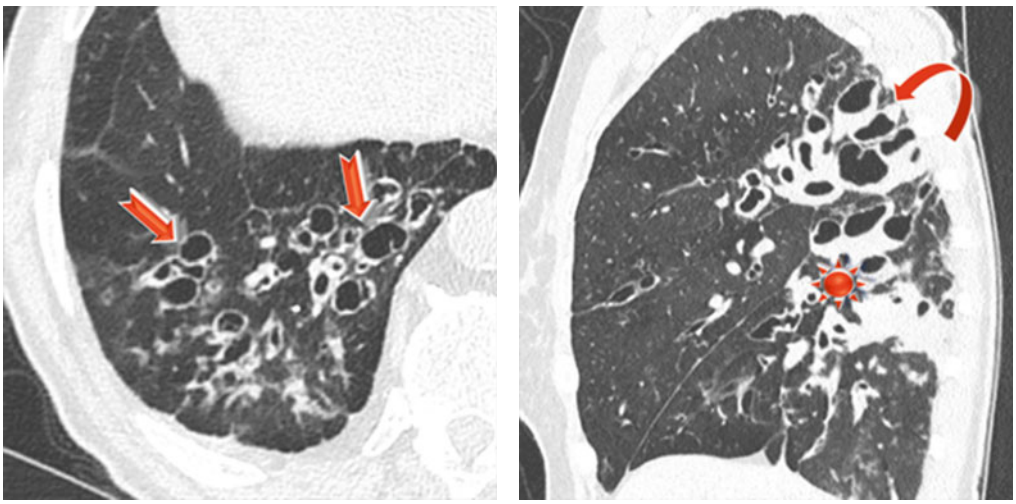
HIGH-RESOLUTION CT: HRCT

Key Signs

- Extensive cystic bronchiectases appearing as "clustered cysts" often found adjacent to the bronchial tree (bunch of grapes sign ➡)
- Cystic spaces within dense fibrotic and postinfectious conglomerates (✸)
- Air-fluid levels in the dilated cystic spaces ( )
- Bronchial wall and peribronchial interstitial thickening

Distribution

Upper lobe predominance of findings is seen in many but not all cases; a diffuse distribution is also a common finding.



Bronchiectasis begins as cylindrical and progresses through varicoid to cystic forms. It can be filled with air, mucus, or exudate (due to infection). Structural changes detected by HRCT scans often precede functional changes in children with CF.

The lungs of CF patients are frequently colonized with a variety of characteristic organisms such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus*, and *nontuberculous mycobacterial species*. Aspergillus may cause an asthmatic condition called allergic bronchopulmonary aspergillosis (ABPA), characterized by an exaggerated response of the immune system to the fungus spores, which lead, if not treated, to a more rapid functional impairment.

Dodd JD (2015) Imaging in cystic fibrosis and non-cystic fibrosis bronchiectasis. Semin Respir Crit Care Med 36:194

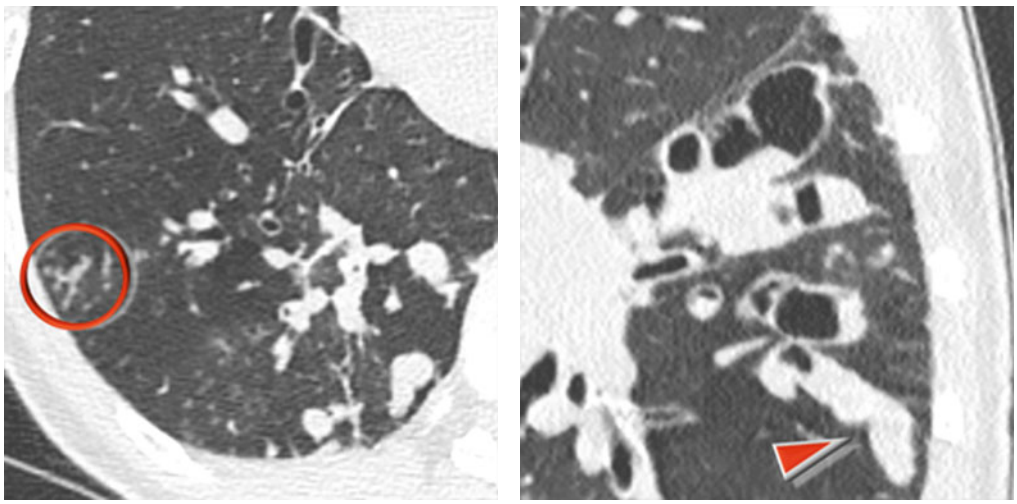
Mott LS (2012) Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax 67:509

Ancillary Signs

- Extensive cylindrical bronchiectasis
- A mosaic pattern of attenuation secondary to air trapping due to obstructed bronchi and bronchioles.
- Commonly seen tree-in-bud pattern (O) indicates the diffuse bronchiolitis that typically occurs in cystic fibrosis.
- Consolidations (infections).
- Mucus plugging within bronchi (finger in glove sign ►) (please refer to finger in glove sign in the "Case-Based Glossary with Tips and Tricks").

Non-parenchymal Signs

- Lymph node enlargement
- Chronic cor pulmonale in the advanced stages of disease



Hara AK (2009) Iterative reconstruction technique for reducing body radiation dose at CT: feasibility study. AJR Am J Roentgenol 193:764

Course and Complications

- Recurrent infectious bronchiolitis and lung function impairment.
- 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.
- Pulmonary arterial hypertension and chronic cor pulmonale.

As a result of the improvement of medical care and early detection, the average life expectancy of patients with CF has been steadily increasing and quality of life has improved. Several CF HRCT scoring systems have been developed to monitor the extension of lung damage, compare clinical severity, evaluate the effects of therapeutic interventions, and estimate prognosis.

Recent advances in the therapy of CF have improved the survival rate. Low-dose CT techniques should be considered to minimize radiation exposure, as these patients may have numerous CT for the long-term follow-up of lung disease. These techniques demonstrated the same accuracy to identify CF exacerbations as the high-dose techniques.

Ng MY (2014) Pulmonary complications of cystic fibrosis. Clin Radiol 69:e153

Helbich TH (1999) Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology 213:537

Definition

Combined pulmonary fibrosis and emphysema (CPFE) is a smoking-related interstitial lung disease characterized by the coexistence of emphysema with pulmonary fibrosis in the same patient. Pulmonary function tests reveal preserved lung volumes in contrast with severely impaired gas exchange and significant decreased PaO_2 on exercise. The unexpected subnormal lung volumes are usually attributed to the balanced effect of the restrictive defect of fibrosis and the hyperinflation of emphysema, and it may be responsible for the underrecognition of this syndrome. The incidence of CPFE remains unknown, but several case series suggest that this subgroup may comprise up to 35 % of patients with IPF.

CPFE

Cottin V (2005) Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 26:586

Jankowich MD (2012) Combined pulmonary fibrosis and emphysema syndrome. Chest 141:222

Cottin V (2013) The impact of emphysema in pulmonary fibrosis. Eur Resp Rev 22:153

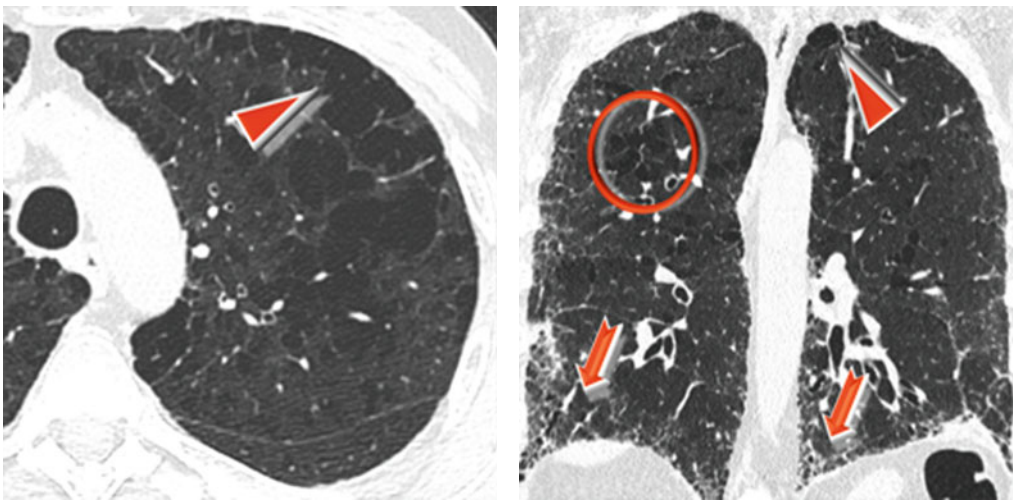
HIGH-RESOLUTION CT: HRCT

Key Signs

- In the upper lobes: classical features of emphysema including paraseptal (thin-walled cysts in the subpleural region ►) and less frequently centrilobular (black areas which may appear in the central portion of the secondary pulmonary lobule ○)
- In the lower lobes: fibrotic reticular opacities and traction bronchiectases with or without honeycombing (➡)

Distribution

Both lungs are almost always affected, not always symmetrically. Upper zones are affected by emphysematous changes, while in the lower zones, fibrotic alterations are prevalent.



Usual interstitial pneumonia (UIP) is the most common fibrotic pattern detected, but a variety of other patterns have been reported including nonspecific interstitial pneumonia (NSIP), airspace enlargement with fibrosis (AEF), respiratory bronchiolitis-associated interstitial lung disease (RBILD) with alveolar septal fibrosis, desquamative interstitial pneumonia (DIP) with extensive fibrosis, and unclassifiable smoking-related interstitial fibrosis (SRIF). However, it would seem that patients with a UIP pattern have a more rapid progression and a worse prognosis compared to the others.

Ciccarese F (2016) Combined pulmonary fibrosis and emphysema (CPFE): what radiologist should know. Radiol Med 121(7):564–72

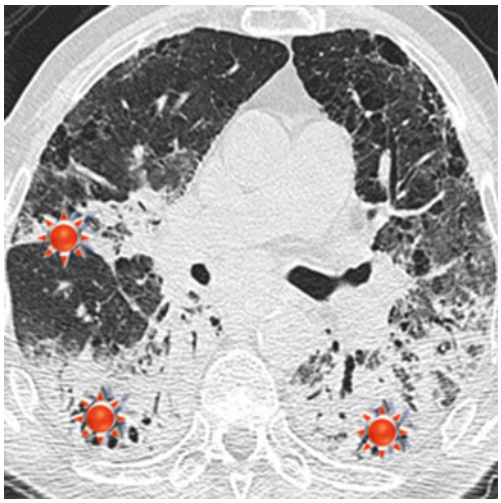
Jankowich MD (2008) Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration 75:411

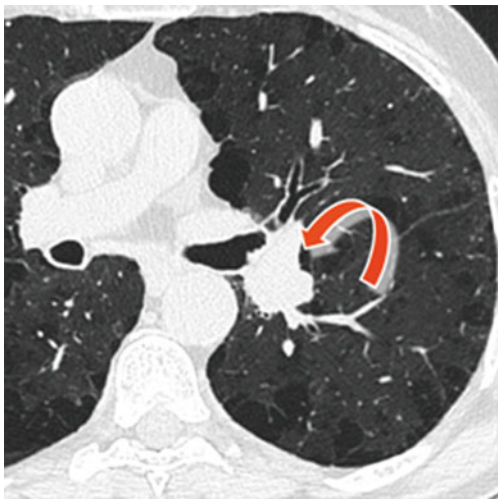
Ancillary Signs

- Relatively preserved lung volumes.
- Thickening of bronchial walls.
- Ground-glass attenuation areas and consolidations may be present in case of acute lung injury (✸).
- Nodules or masses are often due to associated lung cancer (☟).

Non-parenchymal Signs

- Pulmonary arterial hypertension is the most common complication, occurring in up to 50 % of patients.
- Mediastinal lymphadenopathies.





☝ CPFE has also been described within the context of smoker patients with ILDs associated with connective tissue diseases (CTDs), especially with rheumatoid arthritis or systemic sclerosis. Patients were younger, more frequently women, and tended to present with a less severe prognosis.

📖 Papiris SA (2013) Combined pulmonary fibrosis and emphysema. Expert Rev Respir 7:19

Cottin V (2011) Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum 63:295

Course and Complications

The natural course of CPFE seems to be different from the one of patients with classic emphysema or fibrosis: the majority of studies reveals a worse prognosis than emphysema, while it is still not clear whether CPFE has a worse or a better prognosis compared to pulmonary fibrosis. Median survival in reported series ranges from 2.1 to 8.5 years. Survival is linked to the development of complications such as pulmonary hypertension, acute lung injury, and lung cancer, which are associated with a worse clinical course and lower survival rates.

The reasons for the coexistence of pulmonary fibrosis and emphysema remain unknown. Their relationship may be due to a pure coincidence or to a common environmental insult (tobacco smoke) upon an unknown genetic predisposition. A recent hypothesis suggests that fibrosis and emphysema share common pathogenetic mechanisms of accelerated senescence via telomere length abnormalities.

📖 Lee CH (2011) The impact of combined pulmonary fibrosis and emphysema on mortality. Int J Tuberc Lung Dis 15:1111

Mejía M (2009) Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 136:10

Chilosi M (2013) Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema. Transl Res 162:156

Definition

Pulmonary emphysema is part of the chronic obstructive pulmonary disease (COPD) spectrum. It is defined as the abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of the alveolar wall and without obvious fibrosis. Emphysema traditionally affects more men than women, and it is predominantly a disease of middle to late life, owing to the cumulative effect of smoking and other environmental risk factors. Centrilobular and paraseptal emphysema appear as diffuse cystic disease and therefore will be discussed in this chapter.

Centroacinar and distal acinar emphysema

Litmanovich D (2009) CT of pulmonary emphysema – current status, challenges, and future directions. Eur Radiol 19(3):537

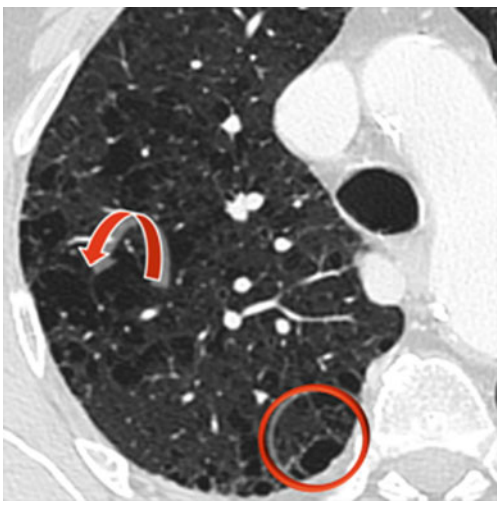
HIGH-RESOLUTION CT: HRCT

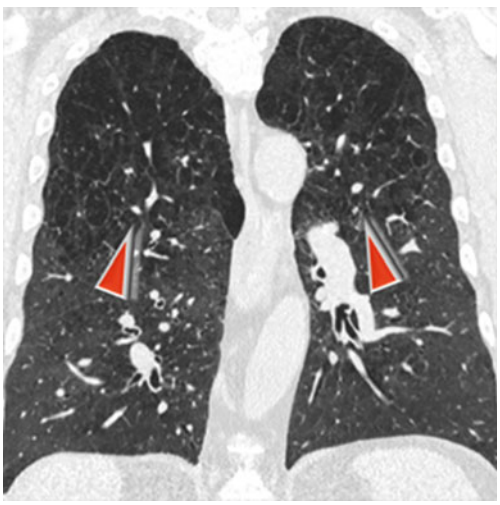
Key Signs

- Centrilobular emphysema appears as black areas often without wall in the central portion of the secondary pulmonary lobule, surrounding the central bronchovascular bundle (↬). Severe forms appear as extensive areas of parenchymal destruction, although the structure of the secondary lobule can still be recognized.
- Paraseptal emphysema appears as thin-walled cysts arranged in a single layer, in the subpleural region, and adjacent to the septal lines (O). If the diameter of the cysts is greater than 1 cm, the terms “bullae” and “bullous emphysema” are used.

Distribution

Lesions are predominantly located in the upper zones of each lobe: apical and posterior segments of the upper lobes and superior segment of the lower lobes (►). With the progression of emphysema, the elementary lesions tend to merge, extending to the whole lobule, and occupy larger and larger areas of parenchyma.





In patients with centrilobular emphysema, signs of paraseptal emphysema often coexist. Some patients with pulmonary emphysema in the upper lungs are reported to have simultaneous pulmonary fibrosis in the lower lung field, a condition known as combined pulmonary fibrosis and emphysema Combined Pulmonary Fibrosis and Emphysema (CPFE). Also refer to Combined Pulmonary Fibrosis and Emphysema (CPFE).

Takahashi M (2008) Imaging of pulmonary emphysema: a pictorial review. Int J Chron Obstruct Pulmon Dis 3(2):193

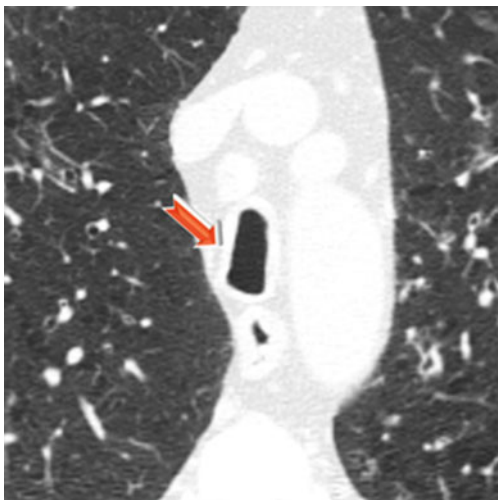
Jankowich MD (2012) Combined pulmonary fibrosis and emphysema syndrome: a review. Chest 141(1):222

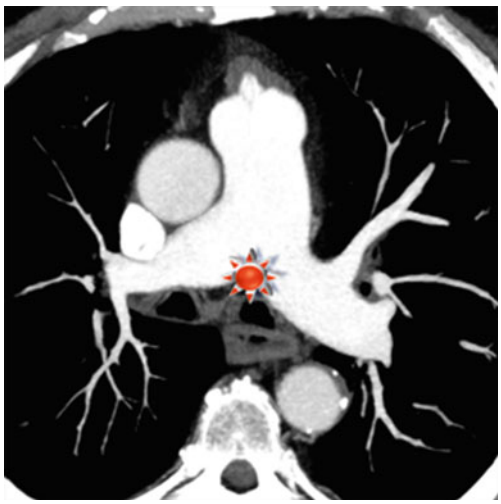
Ancillary Signs

- Increased lung volumes
- Thickening of bronchial walls

Non-parenchymal Signs

- Mediastinal lymphadenopathies
- Bronchial diverticula along the central bronchial surfaces of smokers
- Saber-sheath trachea (➡)
- Pulmonary arterial hypertension (✸) (diameter of the main pulmonary artery >28 mm)





Course and Complications

- Acute exacerbations (infection or pulmonary edema)
- Chronic respiratory failure, associated with pulmonary arterial hypertension in severe cases

Patients with emphysema have an increased susceptibility to respiratory infections. Acute exacerbations are associated with impaired quality of life, a more rapid decline in lung function, and higher mortality.

Han MK (2011) Chronic obstructive pulmonary disease exacerbations in the COPD Gene study: associated radiologic phenotypes. Radiology 261(1):274

Patients with bullous emphysema have an increased incidence of bronchogenic carcinoma. Since tumors tend to grow along the intervening normal lung, bizarre shapes are often observed.

Maki D (2006) Computed tomography appearances of bronchogenic carcinoma associated with bullous lung disease. J Comput Assist Tomogr 30(3):447

Definition

Lymphangioleiomyomatosis (LAM) is a rare multisystemic disorder characterized by proliferation of abnormal smooth muscle-like cells (LAM cells) in the walls of airways, venules, and along the axial lymphatic system, leading to progressive cystic lung destruction. Extrapulmonary lymphadenopathy and cystic masses of the axial lymphatics (termed lymphangioleiomyomas) can result in abdominal and pelvic lymphatic obstruction. LAM almost exclusively affects young women of childbearing age (20–40 years). LAM can arise sporadically or in association with tuberous sclerosis complex (TSC). Both TSC–LAM and sporadic LAM are associated with mutations in the TSC1/2 genes, resulting in constitutive activation of the kinase mammalian target of rapamycin (mTOR).

☯ LAM

📖 Johnson SR (2006) Lymphangioleiomyomatosis. Eur Respir J 27(5):1056

Moss J (2001) Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med 164(4):669

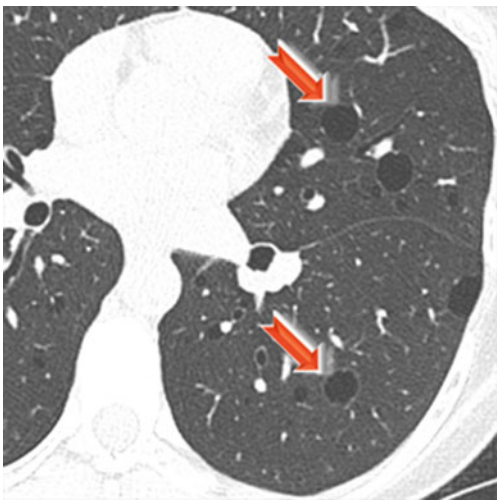
HIGH-RESOLUTION CT: HRCT

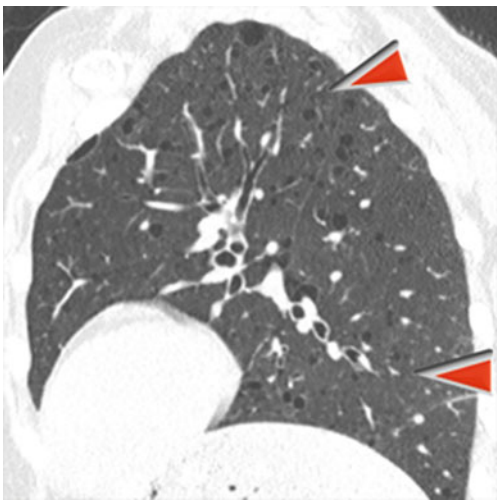
Key Signs

- Rounded thin-walled cysts (range from 2 to 60 mm in diameter), surrounded by relatively normal lung parenchyma (➡). No vessels are identifiable within the cysts.
- Lesions are uniform in shape, tending to give an overall homogeneous, "lacy" appearance.

Distribution

Bilateral uniform distribution, without any lobar predominance (►). There is no sparing of the costophrenic angles. Lung volumes are normal or increased in the advanced form.





The cystic changes have been postulated to be the result of the constrictive effect of bundles of LAM cells on airways, leading to airflow obstruction and air trapping. An alternative or coexisting mechanism might be the metalloproteinase-mediated destruction of elastic tissue in the pulmonary interstitium.

📖 Tobino K (2015) Computed tomographic features of lymphangioleiomyomatosis: evaluation in 138 patients. Eur J Radiol 84:534

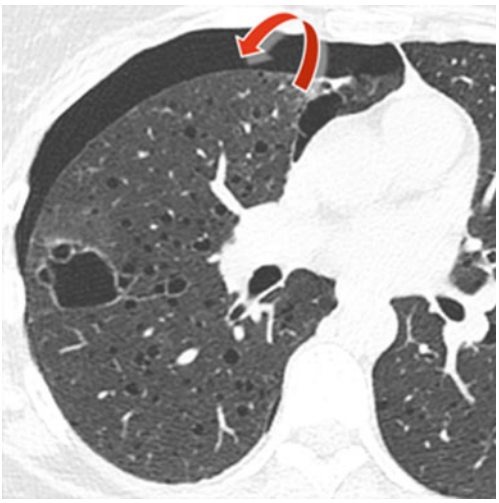
Harari S (2011) Lymphangioleiomyomatosis: what do we know and what are we looking for? Eur Respir Rev 20:34

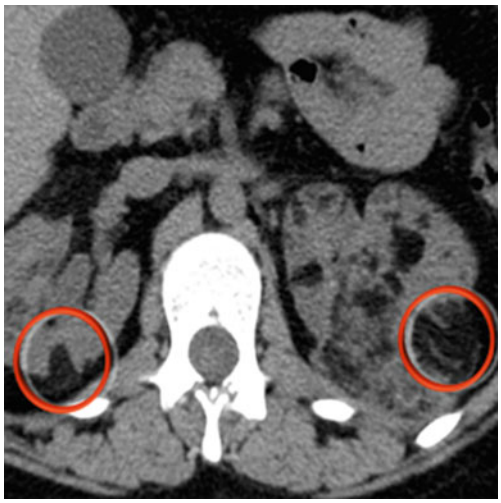
Ancillary Signs

- Patchy areas of ground-glass opacity with septal thickening (parenchymal hemorrhages and edema due to occlusion of small veins).
- Nodules are very rare and represent micronodular pneumocyte hyperplasia.

Non-parenchymal Signs

- Pneumothorax (50 %)
- Chylous pericardial or pleural effusions (obstruction of lymphatics)
- Thoracic and abdominal lymphadenopathy (40 %)
- Thoracic duct enlargement
- Lymphangioleiomyomas in the thorax and abdomen
- Renal angiomyolipomas (50 %) and increased frequency of meningioma
- Chylous ascites





Pneumothorax is often the first manifestation and recurrences are common. Other presenting symptoms are dyspnea (70 %), cough, hemoptysis, and chylous pleural effusions.

Johnson SR (2010) European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J 35:14

Abbott GF (2005) From the archives of the AFIP: lymphangioleiomyomatosis: radiologic-pathologic correlation. Radiographics 25:803

Maruyama H (2001) Pathogenesis of multifocal micronodular pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous sclerosis and association with tuberous sclerosis genes TSC1 and TSC2. Pathol Int 51(8):585

Course and Complications

- As the disease progresses, the cysts increase in size and number but maintain their characteristic thin wall and rounded shape.
- Progressive deterioration in respiratory function is particularly marked in pregnancy or with administration of estrogens; therefore, contraceptive pill or other forms of hormone replacement should be avoided.

To date, there is no effective therapy for LAM, but there are case studies and clinical trials that showed disease stabilization by progesterone and oophorectomy in a small number of patients. In the advanced stage of the disease, lung transplantation is still considered the best therapy, although the disease may recur in the transplanted lung. The recent finding of abnormalities in the TSC genes has led to trials of mTOR inhibitors including sirolimus in patients with LAM and angiomyolipoma.

Mavroudi M (2013) Lymphangioleiomyomatosis: current and future. J Thorac Dis 5(1):74

Davies DM (2008) Sirolimus therapy in tuberous sclerosis or sporadic lymphangioleiomyomatosis. N Engl J Med 358:200

Definition

LCH is a fibroinflammatory interstitial lung disease, characterized by proliferation and infiltration of several organs by Langerhans cells (LCs), an immature stage in development of dendritic cells with function of antigen-presenting cells. In the early stages, the morphologic features of LCH consist of peribronchiolar nodules, but as the lesions evolve, the cellular elements are gradually replaced by fibrotic scars. Perifibrotic airspace enlargement along with bronchiolar mural destruction and lumen dilatation cause formation of cysts. LCH occurs predominantly in young adult smokers, with a peak incidence between 20 and 40 years of age, without gender predilection.

LCH, pulmonary Langerhans cell histiocytosis, PLCH, histiocytosis X, pulmonary eosinophilic granuloma, Letterer–Siwe disease, Hand–Schüller–Christian disease

Nair A (2014) High-resolution computed tomography features of smoking-related interstitial lung disease. Semin Ultrasound CT MR 35(1):59

Wei P (2014) Pulmonary Langerhans cell histiocytosis: case series and literature review. Medicine (Baltimore) 93(23):e141

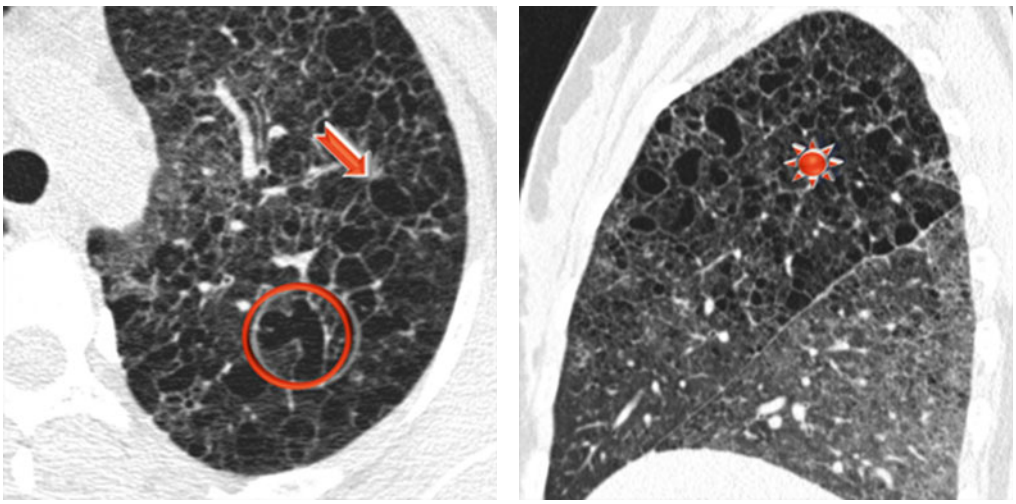
HIGH-RESOLUTION CT: HRCT

Key Signs

- Irregular thick-walled and thin-walled cysts (➡).
- Most cysts are less than 10 mm in diameter but there may be larger, bizarre-shaped cysts, with a tendency to confluence (⭕).

Distribution

Upper and middle lung predominance with sparing of the costophrenic angles and lung bases (✸)



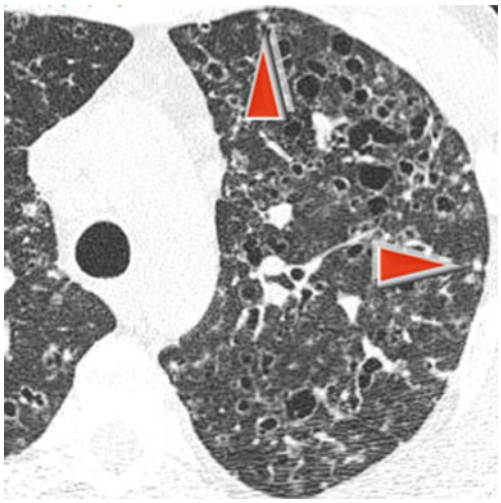
Tazi A (2006) Adult pulmonary Langerhans cell histiocytosis. Eur Respir J 27(6):1272

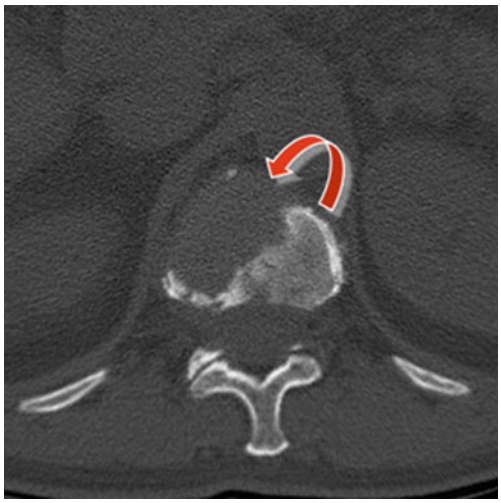
Ancillary Signs

- Small solid centrilobular nodules with sharp margins and irregular contours, also cavitated (►) (image courtesy by Riccardo Panzavolta, Rovigo, Italy).
- A DIP-like reaction and respiratory bronchiolitis are also common, reflecting incidence in the smoking population.
- Mosaic attenuation and air trapping may be due to bronchial obstruction.

Non-parenchymal Signs

- Pneumothorax occurs in 10–20 % of patients and may occasionally be the presenting manifestation.
- Lymphadenopathy and pleural effusions are occasionally seen.
- Bone lytic lesions. (🦴)





Nodular and cystic patterns may coexist. The appearance of new nodules later in the disease (when cystic change is established) indicates disease progression, but is a rare finding.

LCH, in addition to the lungs, can also involve the bone, pituitary gland (diabetes insipidus), thyroid, skin, lymph nodes, and liver. LCH patients may also be at increased risk of developing a malignancy. Lymphoma, particularly Hodgkin's disease, and multiple myeloma have been reported in association with LCH before, after, or at the time of diagnosis.

Egeler RM (1998) The relationship of Langerhans cell histiocytosis to acute leukemia, and other solid tumors. Hematol Oncol Clin North Am 12:369

Course and Complications

- Most patients regress with steroid therapy and smoking cessation.
- Progression to end-stage pulmonary fibrosis may occur in approximately 10 % of cases. Fibrotic lesions may mimic UIP, but show a bronchiolocentric distribution and retain their stellate shape.

Approximately 70 % of patients have low diffusing capacity to carbon monoxide (DL_{co}). Reduction in DL_{co} may occur in isolation or accompany restrictive, obstructive, or mixed abnormality. A restrictive pattern is more frequently observed in earlier stages of disease, while an obstructive pattern is more common as disease progresses and is the predominant pattern in advanced disease.

Castoldi MC (2014) Pulmonary Langerhans cell histiocytosis: the many faces of presentation at initial CT scan. Insights Imaging 5:483

Suri HS (2012) Pulmonary Langerhans cell histiocytosis. Orphanet J Rare Dis 19:7

Definition

Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative disorder characterized by diffuse interstitial infiltration of the lung by lymphocytic and plasma cell components. LIP is usually encountered in association with connective tissue diseases, particularly Sjögren's syndrome and rheumatoid arthritis, or may result from human immunodeficiency virus (HIV) infection or other immunodeficiency syndromes. It is more common in women, presenting between the fourth and seventh decades. Clinical presentation of LIP is nonspecific and includes dyspnea, cough, fever, and weight loss in the majority of patients. Additional clinical features may be related to the underlying systemic disease.

LIP, lymphoid interstitial pneumonia

Swigris JJ (2002) Lymphoid interstitial pneumonia: a narrative review. Chest 122:2150

Cha SI (2006) Lymphoid interstitial pneumonia: clinical features, associations and prognosis. Eur Respir J 28(2):364

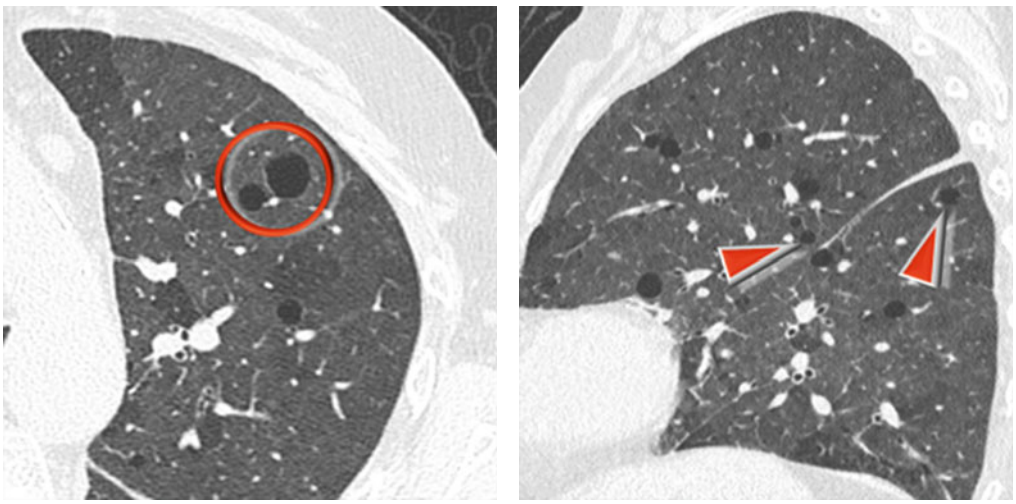
HIGH-RESOLUTION CT: HRCT

Key Signs

- Thin-walled cysts, often large and with regular shape, usually few in number. The cysts may be the sole manifestation of the disease (O).

Distribution

The lesions are almost always bilateral. The cysts are often subpleural or perivascular in location (►).



The diagnosis of LIP should be considered in a patient with lung cysts and an immunological abnormality. A few scattered cysts in a patient with Sjögren's syndrome are very likely due to LIP.

Cysts formation in LIP appears to arise from peribronchiolar lymphoid infiltration resulting in bronchiolar stenosis or occlusion with distal cyst formation from small airway obstruction.

Cha SI (2006) Lymphoid interstitial pneumonia: clinical features, associations and prognosis. Eur Respir J 28 364

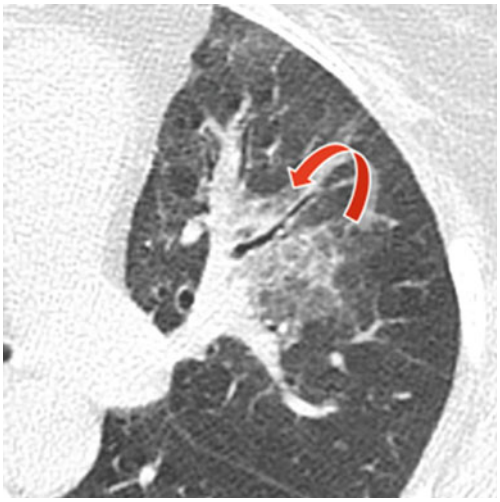
Tian X (2012) Lymphocytic interstitial pneumonia and other benign lymphoid disorders. Semin Respir Crit Care Med 33:450

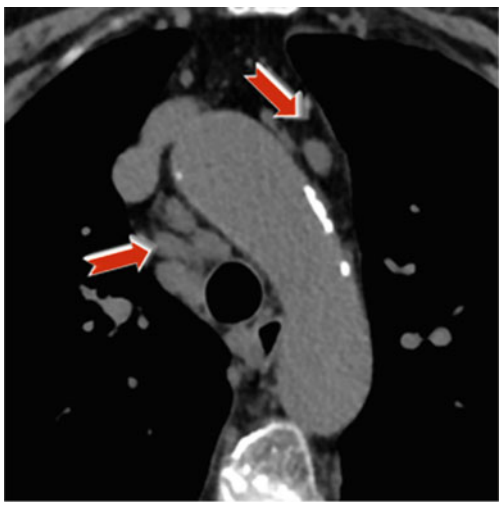
Ancillary Signs

- Ground-glass opacity ( ) and centrilobular nodules are also frequently seen.
- Interlobular septal thickening.
- Focal consolidation and thickening of the bronchovascular bundles.

Non-parenchymal Signs

- In some patients cystic changes may predispose to recurrent pneumothorax.
- Mediastinal and hilar lymphadenopathies are present in the majority of patients (➡).





In some classification schemes, LIP has been considered a preneoplastic condition with a high likelihood of progression to lymphoma; however, immunohistochemical and molecular analyses indicate that malignant transformation is unusual.

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

Silva IS (2006) Diffuse lung cysts in lymphoid interstitial pneumonia: high-resolution CT and pathologic findings. J Thorac Imaging 21:241

Course and Complications

- The clinical course of LIP is variable. It is often stable for months and in some patients may resolve spontaneously.
- It may progress to pulmonary fibrosis, respiratory failure, and death despite therapy.

Treatment of LIP partly depends on the nature of the underlying disorder. Corticosteroids are commonly employed, especially for patients with idiopathic LIP who experience progression of lung disease. Other immunosuppressive agents and single or multidrug antiretroviral therapy have also been used in human immunodeficiency virus patients.

Honda O (1999) Differential diagnosis of lymphocytic interstitial pneumonia and malignant lymphoma on high-resolution CT. AJR Am J Roentgenol 173:71–74

Definition

Laryngotracheobronchial (LTB) papillomatosis is a rare benign disease of childhood, even more rarely seen in adults, caused by infection of the upper respiratory tract with the human papillomavirus (HPV), resulting in the formation of papillomas. It is typically restricted to the larynx but can also invade the tracheobronchial tree (from 2 to 5 % of patients) and the pulmonary parenchyma. Small airway or alveolar involvement occurs in less than 1 %. HPV infection occurs most frequently at the time of birth, when the child passes through an infected birth canal. However, infection can also occur later in life, possibly by sexual transmission. Although the papillomas represent growth of new tissue, tracheolaryngeal papillomatosis is most frequently categorized as a nonneoplastic disease.

LTB papillomatosis, juvenile laryngotracheal papillomatosis, laryngeal papillomatosis, tracheobronchial papillomatosis, respiratory tract papillomatosis, recurrent respiratory papillomatosis

Kim EY (2012) Histologically benign but clinically malignant neoplasms in the thorax: CT-pathological overview. Clin Radiol 67:1115

Marchiori E (2008) Laryngotracheobronchial papillomatosis: findings on computed tomography scans of the chest. J Bras Pneumol 34:1084

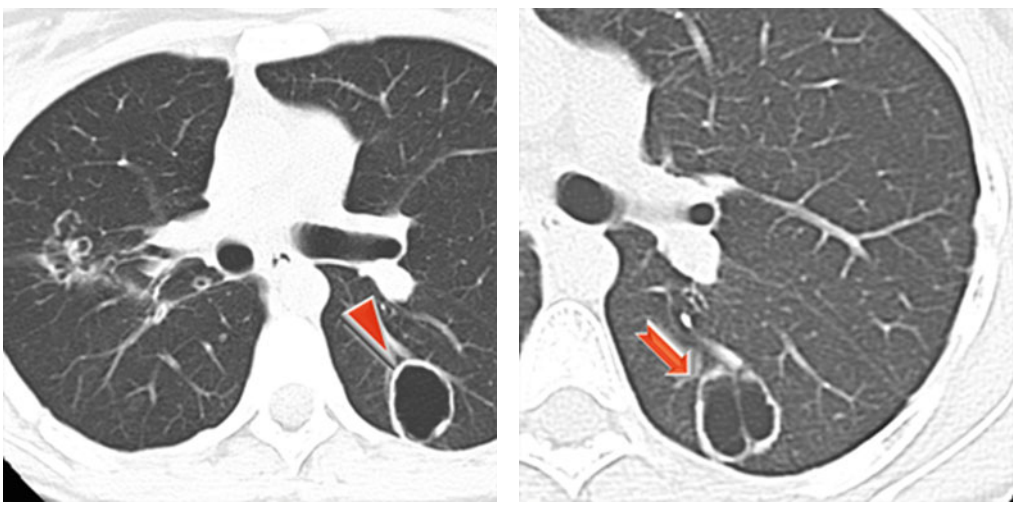
HIGH-RESOLUTION CT: HRCT

Key Signs

- Thick-walled cysts also with irregular internal walls (►)
- Cavitated lesions with irregular internal borders and walls of various thicknesses.
- Cavities may have a multilobulated aspect (➡) and a tendency toward confluence.

Distribution

The lesions are predominantly located in the basal and posterior lung regions.



Patients undergo frequent surveillance bronchoscopy because recurrent therapy is typically required. Antiviral and laser treatment may be used for management; however, recurrence of the papillomas is common.

Obusez EC (2014) Computed tomography correlation of airway disease with bronchoscopy: part I – nonneoplastic large airway diseases. Curr Probl Diagn Radiol 43(5):268

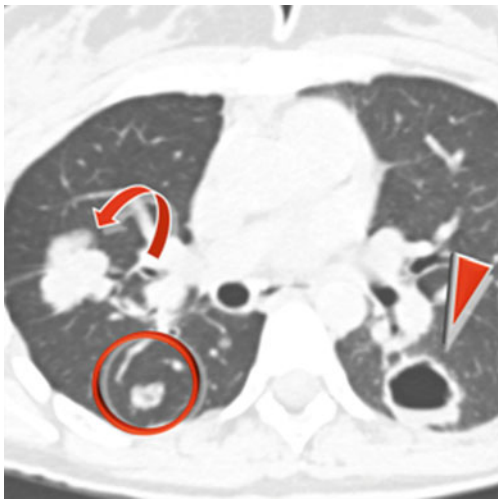
Ancillary Signs

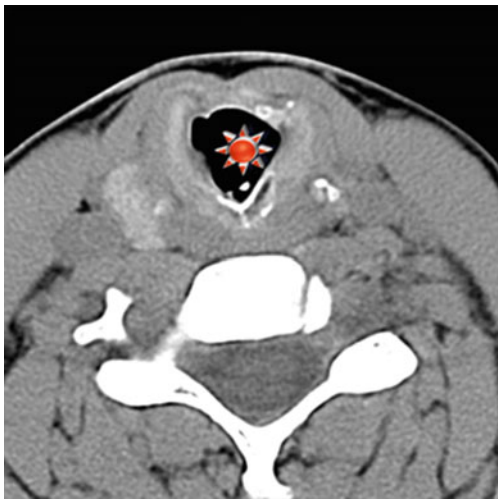
- Scattered bilateral nodules and macronodules (O), often cavitated
- Atelectasis
- Consolidations
- Air trapping

Non-parenchymal Signs

Polypoid formations in the trachea and major bronchi (✸)

The cavitated nodules can be air-filled or, when infected, they can present an air-fluid level (please see the figure below ►).





Acar T (2015) Computed tomography findings of tracheobronchial system diseases: a pictorial essay. Jpn J Radiol 33(2):51

Course and Complications

- Malignant degeneration to squamous cell carcinoma is reported in 1–10 % of all cases (please see the figure above ↳).
- Mycetoma (please also refer to air crescent sign in the "Case-Based Glossary with Tips and Tricks")

HPV types 16 and 18 have most often been associated with malignant transformation. Any new or enlarging nodule identified radiographically should be evaluated further to exclude malignancy.

Prince JSI (2002) Nonneoplastic lesions of the tracheobronchial wall: radiologic findings with bronchoscopic correlation. Radiographics 22:S215

Definition

Cystic pulmonary metastases are atypical morphological form of pulmonary metastases where lesions manifest as distinct cystic lesions. It is slightly different from the cavitating pulmonary metastases because the lesions are extremely thin-walled. Reports include so-called benign metastasizing leiomyoma, endometrial stromal sarcoma, colorectal cancer, soft tissue sarcomas, and fibrous histiocytic tumors of the skin. In contrast, metastatic tumors of squamous cell origin are more likely to cavitate than tumors of other origins, suggesting a common pathogenesis for cavitation among these tumors. Therefore, the common and seemingly unimportant finding of bullous change in the lungs assumes much greater significance in patients who have a known malignancy of any type.

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

Vourtsi A, Gouliamos A, Moulopoulos L et al (2001) CT appearance of solitary and multiple cystic and cavitary lung lesions. Eur Radiol 11:612

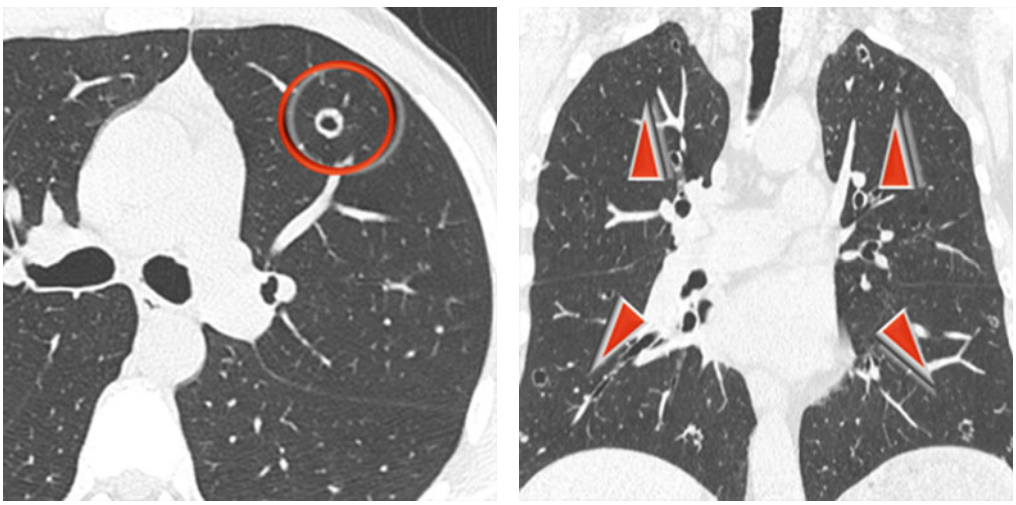
HIGH-RESOLUTION CT: HRCT

Key Signs

- Multiple thick-walled (O) or thin-walled cysts of various size (►), surrounded by normal lung parenchyma

Distribution

Peripheral, random bilateral distribution (►)



The mechanism of thin-walled cystic lesion development is presumed to be a check-valve effect secondary to the infiltration of malignant cells into the wall of small airways.

Seaman DM (2011) Diffuse cystic lung disease at high-resolution CT. AJR Am J Roentgenol 196:1305

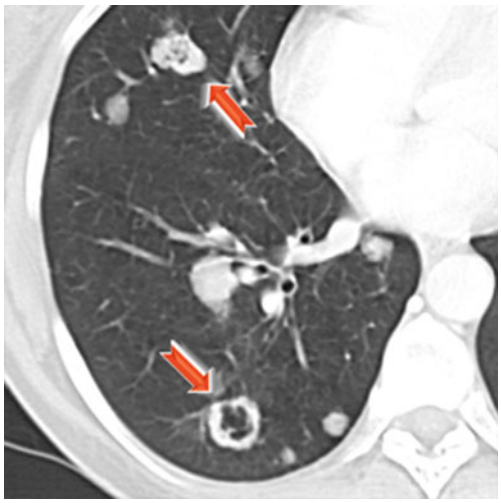
Traweek T (1990) Cystic pulmonary metastatic sarcoma. Cancer 65(8):1805–11

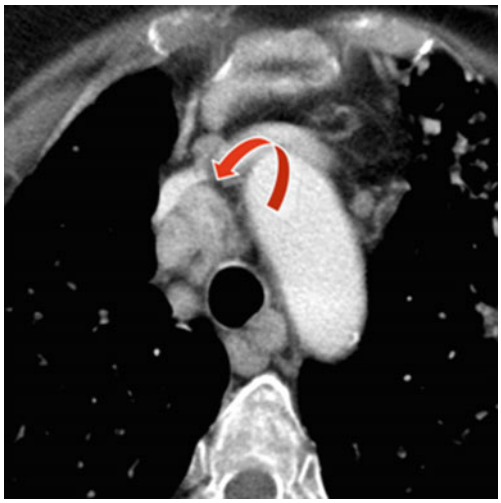
Ancillary Signs

- Nodules and cavitary lesions with thick and irregular walls often coexist (➡)

Non-parenchymal Signs

- Lymph node enlargement (⇩)
- Pneumothorax
- Possible bone lytic lesions due to hematogenous metastases





When accompanied by multiple pulmonary nodules, lesions can be easily identified as possible metastases from an unidentified primary tumor. Otherwise, when pulmonary nodules are absent and primary tumor is unknown, neoplastic etiology may not be readily suspected.

Aboualfa K (2011) Benign metastasizing leiomyoma presenting as cystic lung disease: a diagnostic pitfall. Histopathology 59:796

Hasegawa S (1999) Pulmonary cysts as the sole metastatic manifestation of soft tissue sarcoma: case report and consideration of the pathogenesis. Chest 116:263

Course and Complications

- Morphologic changes consist of thickening of the wall, increasing circumferential involvement, development of a solid component, or progression in a completely solid lesion.

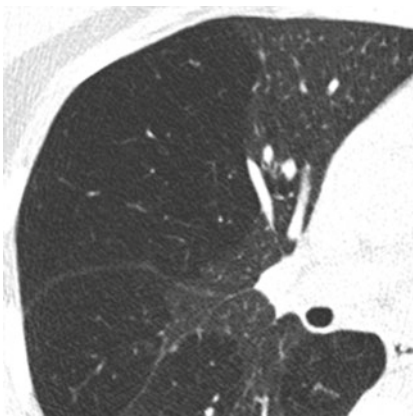
The definitive treatment for pulmonary metastases from extrathoracic malignancies is surgical resection (pulmonary metastasectomy). Surgery is performed if the primary tumor is controlled, if no extrathoracic lesions are present, if it is technically resectable, and if general and functional risks are tolerable. Alternative options available include stereotactic radiosurgery and thermal ablation procedures, typically performed with CT guidance.

Simion NI (2011) Cystic appearance: an uncommon feature of pulmonary metastasis of colorectal origin. BMJ Case Rep 13;2011

Murakami A (2014) Cystic, nodular and cavitary metastases to the lungs in a patient with endometrial stromal sarcoma of the uterus. Intern Med 53:1001

Dark Lung Pattern

Radiology	**Giorgia Dalpiaz**
Pathology	**Alessandra Cancellieri**



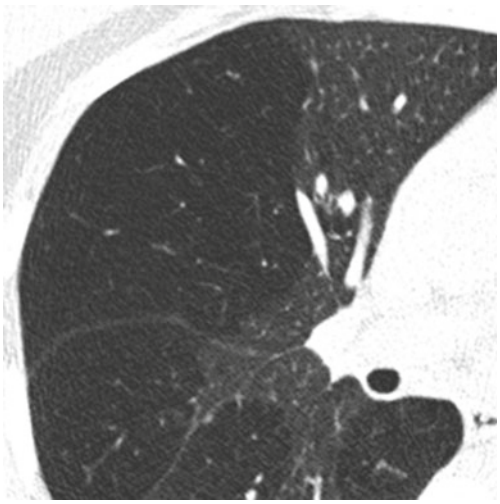
G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_13

DARK LUNG PATTERN

Definition

A dark lung pattern is present when variable portions of pulmonary parenchyma show reduced attenuation to the X-rays, and then are darker than normal. The size and number of the vessels within the pathologic dark areas are smaller than in the non-pathologic white areas.
Unlike the cystic pattern, here the basic abnormality is not pure black, but rather a dark gray. The dark areas basically depend on a reduction of blood flow, either due to a reduced vascular flow (vascular dark lung) or to a hypoxic vasoconstriction from a bronchiolar disease (bronchiolar dark lung).

☯ Mosaic oligoemia/perfusion



☝ The non-pathologic "white" areas are also defined "pseudo-GGO". When the "mosaic" is otherwise given by patchy areas of ground-glass opacity (GGO), size and number of the vessels within different areas should be equal.

✓ The prevalent distribution of the signs together with the presence or absence air trapping and non-parenchymal signs may be helpful for the diagnosis of a specific disease (see the Tables at the end of this Chapter).

📖 Castañer E (2009) CT diagnosis of chronic pulmonary thromboembolism. Radiographics 29(1):31

Hansell DM (2008) Fleischner society: glossary of terms for thoracic imaging. Radiology 246(3):697

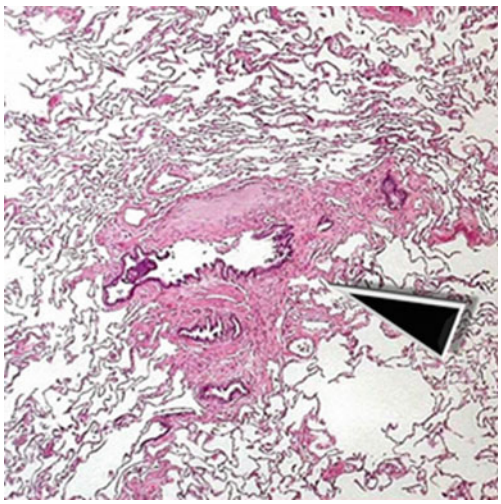
Kligerman SJ (2015) Mosaic attenuation: etiology, methods of differentiation, and pitfalls. Radiographics 35(5):1360

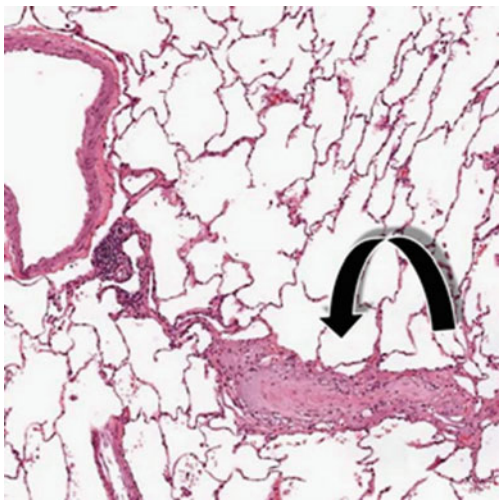
Maffessanti M, Dalpiaz G (2011) Dark lung pattern. In: Leslie KO, Wick MR (eds) Practical pulmonary pathology. A diagnostic approach. Churchill Livingstone (Elsevier), Philadelphia

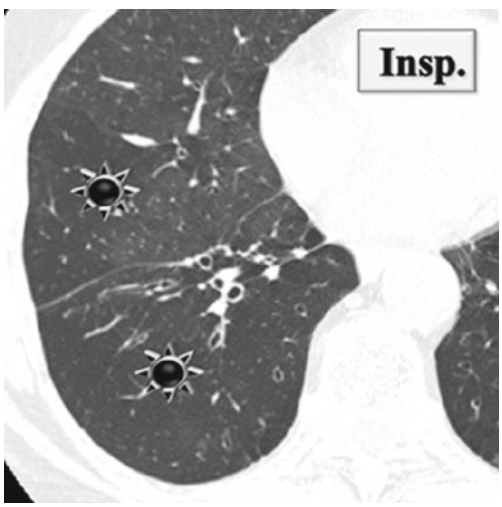
SUBSET BRONCHIOLAR

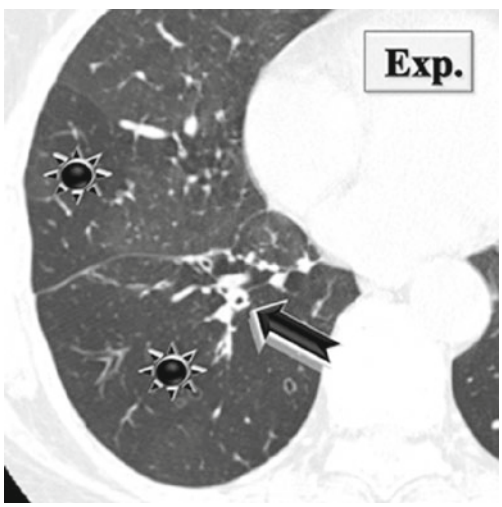
In patients with dark lung pattern from bronchiolar diseases, the dark areas (✸) result as a consequence of bronchiolar narrowing (►) or obstruction (🡻) with subsequent hypoxic vasoconstriction and variable air trapping.
Air trapping is a key HRCT sign of bronchiolar lung pattern, and it refers to retention of excess gas ("air") in a part of the lung, especially during expiration as a result of obstruction. Air trapping is seen as dark parenchymal areas which remain dark or appear even darker on end-expiration CT scans (✸, compare the HRCT images below) (please also refer to air trapping in the "Case-Based Glossary with Tips and Tricks"). The dark lung areas may present anatomic extension (maybe lobular), often with well-defined margins.

Smooth thickening of bronchial walls and cylindrical or cystic bronchiectases may coexist. Some collapse of the bronchial lumen is possible during expiration (➡).









Diseases with Bronchiolar Dark lung:

- *Constrictive bronchiolitis (CB)* (all images above): it is the prototype disease of bronchiolar dark lung pattern. The dark areas are quite well defined; often the bronchi inside them show thickening of their walls or luminal modifications, and vessels inside the white areas are enlarged but with regular course.

- *Diffuse Idiopathic Pulmonary NeuroEndocrine Cell Hyperplasia (DIPNECH)*: dark lung areas with air trapping associated with small solid nodules with random distribution is highly suggestive for DIPNECH.
- *Swyer-James Syndrome (SJS)*: the affected lung (or a part of it) shows overdistention of the alveoli in conjunction with reduced arterial flow. It is often unilateral. Bronchiectases (saccular or cylindrical) may be present.
- *Emphysema*, *panlobular*: widespread areas of abnormally low attenuation (dark lung) without visible walls. The caliber of the vessels in the involved areas is decreased, due to overinflation of the air space. The disease is predominantly located in the lower lobes.

☝ Air trapping may be the key for differentiating bronchiolar versus vascular disease; however, according to some authors, some of the subjects with pulmonary thromboembolism may exhibit expiratory air trapping.

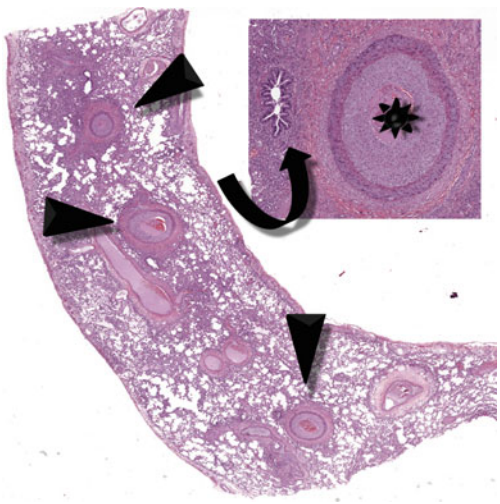
SUBSET VASCULAR

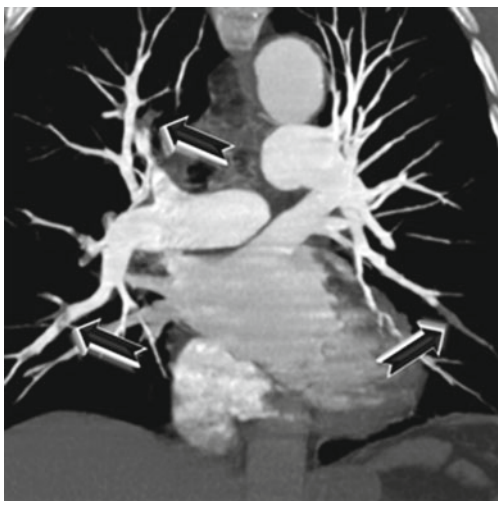
In patients with dark lung pattern from vascular diseases, the dark areas result from hypoperfusion as a consequence of an occlusive vascular disorder (►). As highlighted in the inset, arteriolar lumen (✸) is reduced by intimal proliferation due to organizing thromboembolic disease; the associated bronchiole is unaffected (↻).

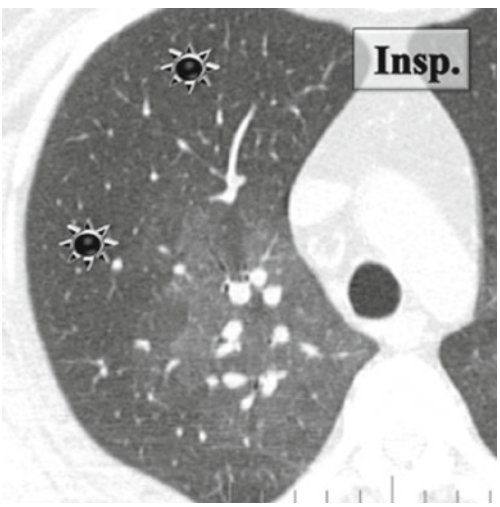
Contrast-enhanced CT shows direct signs of thromboembolism: totally or partially occlusive thrombi (➡), eccentric calcified thrombi, bands, webs, post-stenotic dilatation.

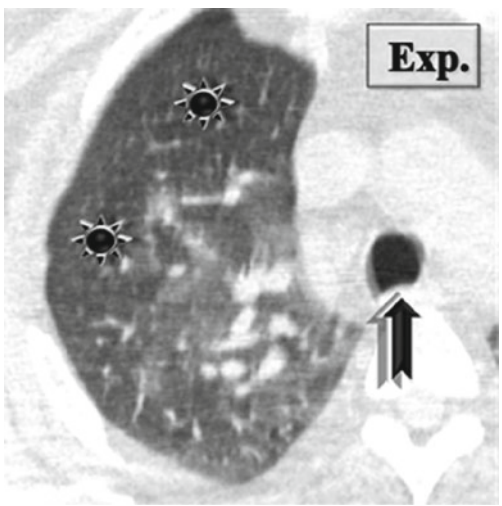
On HRCT, the hypoperfused pathologic areas appear dark (✸). On the contrary, the nonpathologic areas appear white due to hyperperfusion simulating ground-glass opacity.

In post-expiration, both dark and white areas appear even whiter and a variable volume loss is also visible (compare the HRCT images below). The margins of the black areas may be ill defined, with normal bronchi within them and enlarged and often tortuous vessels in the white areas.









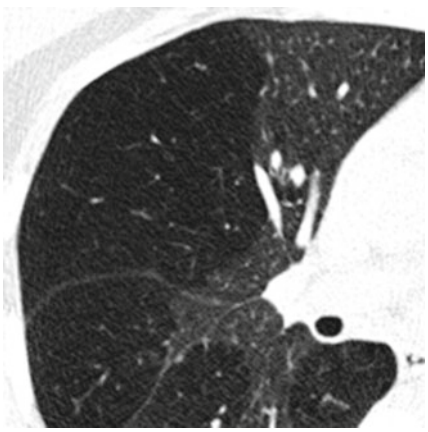
☝ Bowing of the posterior wall of the trachea (➡) signifies good expiratory effort.

Key signs	Distribution	Ancillary signs	Non-parenchymal Signs	Bronchiolar dark lung diseases
Patchy dark lung areas with air trapping	Generally bilateral, asymmetrical	Bronchial wall thickening, dilatation of the small bronchioles	Lymph nodes enlargement	**Constrictive bronchiolitis (CB)**
Patchy dark lung areas with air trapping, multiple random solid nodules	Bilateral nodules with peripheral location, mainly basal	Bronchial wall thickening, mild bronchiectases	Lymph nodes enlargement	**Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)**
Widespread areas of dark lung	Predominantly in the lower lobes	Bronchial wall thickening, mild bronchiectases	Lymph nodes enlargement, saber-sheath trachea, pulmonary arterial hypertension	**Emphysema, panlobular**
Areas of dark lung	May predominate in one lung or lobe, especially in the lower ones	Bronchiectases	Lymph nodes enlargement	**Swyer-James syndrome (SJS)**

Key signs	Distribution	Ancillary signs	Nonparenchymal signs	Vascular dark pattern
Patchy dark lung areas	Generally lower lobes are more affected	Parenchymal scars	With contrast-enhanced CT: thromboembolism, pulmonary arterial hypertension	**Chronic pulmonary thromboembolism (CPTE)**

Dark Lung Diseases

Radiology	**Maurizio Zompatori** **Domenico Attinà**	



G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_14

Definition

Constrictive bronchiolitis (CB) refers to an irreversible destructive process characterized by inflammation and concentric fibrosis in the bronchiolar submucosal layer, associated with luminal occlusion and resulting in extrinsic compression and obliteration of the airway. CB is limited to the bronchioles and does not extend into the alveoli. The causes of CB include toxic fumes, oral toxins, respiratory infections (Mycoplasma), drugs, connective tissue diseases (particularly rheumatoid arthritis), and organ transplantation. CB is the most common form of chronic rejection in patients with lung transplants, occurring in up to 50 % of patients, especially after graft-versus-host reaction. CB is also seen as a manifestation of graft-versus-host disease in 10 % of people who have received allogeneic bone marrow transplants. Imaging findings in patients with this form of bronchiolitis are identical to those found with CB after lung transplantation.

Obliterative bronchiolitis, bronchiolitis obliterans

Kang EY (2009) Bronchiolitis: classification, computed tomographic and histopathologic features, and radiologic approach. J Comput Assist Tomogr 33:32

Leung AN (1998) Bronchiolitis obliterans after lung transplantation: detection using expiratory HRCT. Chest 113:365

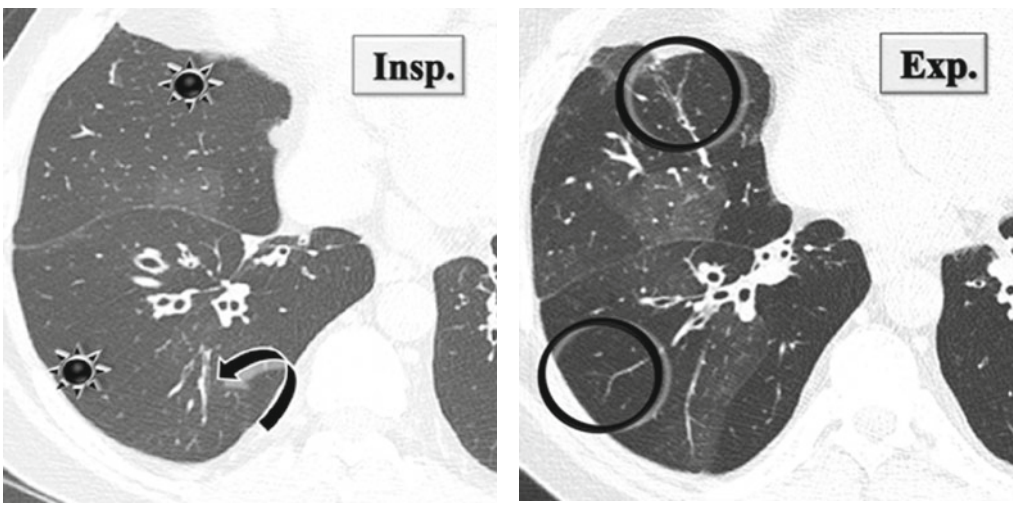
HIGH-RESOLUTION CT: HRCT

Key Signs

- Sharply defined, areas of decreased lung attenuation (dark lung areas ✸) associated with vessels of decreased caliber (↘) (mosaic oligemia).
- Air trapping is seen as dark parenchymal areas which remain dark or appear darker on end-expiration CT scans (○) (please compare the HRCT images below).
- Lung volume is normal or increased.

Distribution

Generally bilateral, asymmetrical. Patchy lobular, segmental, or larger confluent areas accentuated on expiratory scans. In some secondary forms of localized CB, such as postinfectious 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.



Paired inspiratory and expiratory thin-section CT can help distinguish CB from vascular obstructive lung disease. In CB, at the expiration state, dark areas remain as dark as in inspiration state, or get even darker, often with minimal decrease in volume.

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).

CB should not be confused with both bronchiolitis obliterans organizing pneumonia (BOOP), in which inflammation involves also alveoli and causes consolidations, and proliferative bronchiolitis with intraluminal polyps, which is a steroid-reversible lesion limited to the bronchiolar lumen which results obliterated.

Epler GR (2007) Constrictive bronchiolitis obliterans: the fibrotic airway disorder. Expert Rev Respir Med 1:139

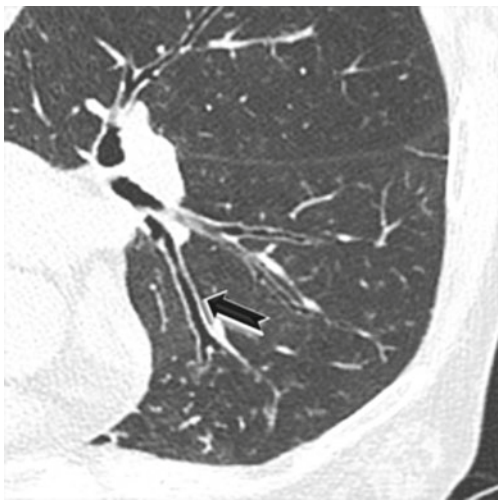
Pipavath SJ (2005) Radiologic and pathologic features of bronchiolitis. AJR Am J Roentgenol 185:354

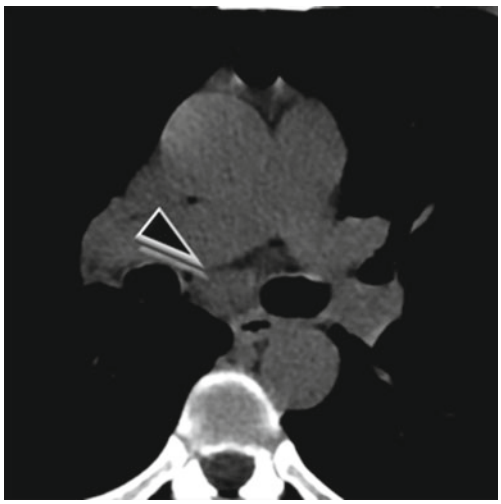
Ancillary Signs

- Thickening of the bronchiolar walls (➡) and dilatation of the small bronchioles
- Mucus plugs

Non-parenchymal Signs

- Lymph nodes enlargement (►)





Hansell DM (1997) Obliterative bronchiolitis: individual CT signs of small airways disease and functional correlation. Radiology 203:721

Lynch JP 3rd, Weigt SS, DerHovanessian A et al (2012) Obliterative (constrictive) bronchiolitis. Semin Respir Crit Care Med 33:509

Course and Complications

- Prognosis is variable, ranging from slowly progressive to rapidly deteriorating disease.
- Most patients deteriorate inexorably, ultimately dying of respiratory failure within months to years. In some patients the disease stabilizes after an initial decline.
- Secondary bacterial infections may accelerate the course of disease.

Pulmonary function tests traditionally show airway irreversible obstruction with no response to bronchodilator inhalation. The extent of air trapping on expiratory CT provides the best correlation with indexes of physiologic impairment.

Bankier AA (2001) Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. Radiology 218:533

Definition

Chronic pulmonary thromboembolism (CTPE) is a consequence of incomplete resolution of acute pulmonary thromboembolism. The failure of complete clot lysis occurs in 4–5 % of patients with pulmonary embolism. Unresolved thrombi form endothelialized fibrotic obstructions of the pulmonary vascular bed. Vascular stenosis and increased vascular resistance may lead to severe pulmonary hypertension (CTEPH) and cor pulmonale. In the majority of patients, months or even years (the so-called honeymoon period) may pass before clinically significant CTEPH manifests. The most common presenting symptom is indolent but progressive shortness of breath with normal pulmonary functional tests. Patients with CTEPH become symptomatic only when at least 60 % of the pulmonary arterial bed is obstructed.

CPTE, CPE

Wittram C (2004) CT angiography of pulmonary embolism: diagnostic criteria and causes of misdiagnosis. Radiographics 24:1219

Guérin L (2014) Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Haemost 2;112:598

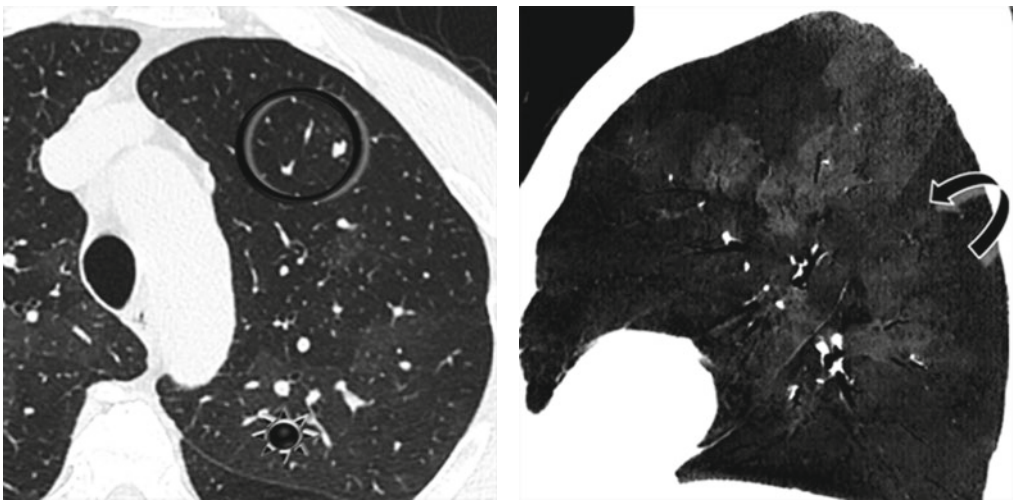
HIGH-RESOLUTION CT: HRCT

Key Signs

- Patchy regions of decreased attenuation (dark lung ○) and increased attenuation (white lung ✸) because of irregular perfusion (mosaic oligemia).

Distribution

Patchy, generally lower lobes are more affected.



Oligemia distal to occluded vessels causes a redistribution of blood away from the affected areas. Hypoperfused areas are of low attenuation (dark lung), while the increased attenuation areas (white lung) have larger and more prominent arteries.

Please note that the sagittal image is obtained from an algorithm defined minIP (Minimum intensity projection). It is useful both for defining the distribution of mosaic oligemia and for easy visibility of mosaic pattern.

Wittram C (2006) Acute and chronic pulmonary emboli: angiography-CT correlation. AJR Am J Roentgenol 186:S421

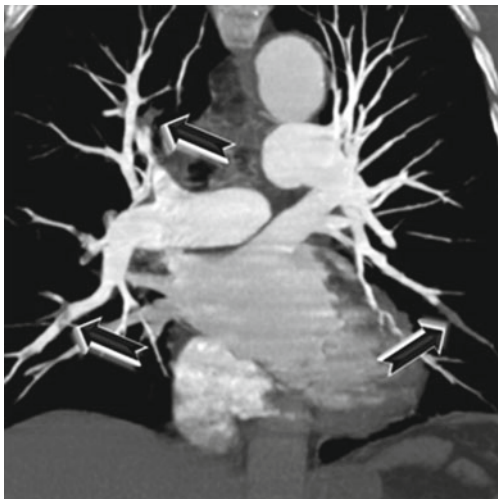
Castañer E (2009) CT diagnosis of chronic pulmonary thromboembolism. Radiographics 29:31

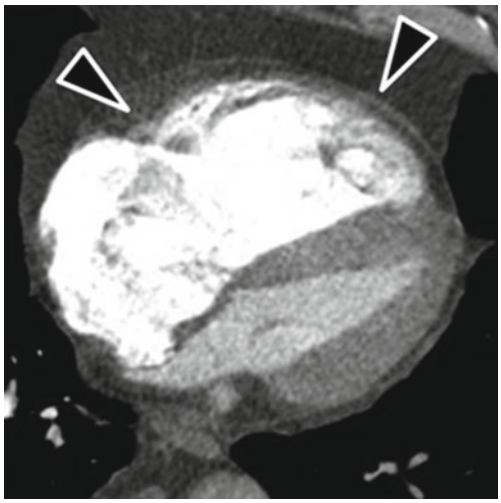
Ancillary Signs

- Parenchymal scars from prior pulmonary infarctions (peripheral bands or nodules, cavities or irregular lines)
- With contrast-enhanced CT: direct pulmonary artery signs of thromboembolism (totally or partially occlusive thrombi (➡), eccentric calcified thrombi, bands, webs, post-stenotic dilatation)

Non-parenchymal Signs

- Enlargement of main pulmonary arteries, right ventricular enlargement (►), and hypertrophy (pulmonary arterial hypertension)
- With contrast-enhanced CT: enlargement of bronchial and nonbronchial systemic arteries (systemic collateral supply)





Primary pulmonary artery sarcoma is an uncommon but fatal tumor, which is often mistaken for a chronic pulmonary embolism. The enhancement after the administration of contrast and the high metabolic activity of the neoplastic lesion allow to distinguish between these two pathologies.

Wijesuriya S (2013) Chronic pulmonary emboli and radiologic mimics on CT pulmonary angiography: a diagnostic challenge. Chest 143:1460

Guérin L (2014) Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. Thromb Haemost 112:598

Course and Complications

- The clinical course of CTPE reflects the progressive increase in the pulmonary vascular resistance which characterizes this condition.
- Progressive pulmonary hypertension, right ventricular dysfunction, and death ensue if the condition is left untreated.

Pulmonary endarterectomy is the treatment of choice for patients with CTEPH as it is a potentially curative option. Proximal organized thrombi represent the ideal indication, while more distal obstructions may prevent a successful procedure. After an effective intervention patient response is usually dramatic, with a decrease in pulmonary vascular resistance and decreased dyspnea. The mortality rate from the procedure, however, is high (4–8 %).

Mayer E (2011) Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. J Thorac Cardiovasc Surg 141:702

Jenkins D, (2012) State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management. Eur Respir Rev 21:32

Definition

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an under-recognized disease characterized by proliferation of neuroendocrine cells in the bronchial wall and symptomatic airflow obstruction due to bronchiolitis obliterans. It is considered a preinvasive lesion for lung carcinoid tumors. Most patients are female, typically between 50 and 70 years of age, and usually present with insidious-onset respiratory symptoms such as nonproductive cough and long-standing dyspnea due to the obstructive syndrome, that can be mistaken for asthma. Some patients are completely asymptomatic and are diagnosed incidentally during the workup of other conditions, like cancer.

☯ DIPNECH

📖 Benson RE (2013) Spectrum of pulmonary neuroendocrine proliferations and neoplasms. Radiographics 33:1631

Trisolini R (2016) DIPNECH: association between histopathology and clinical presentation. Lung 194(2):243

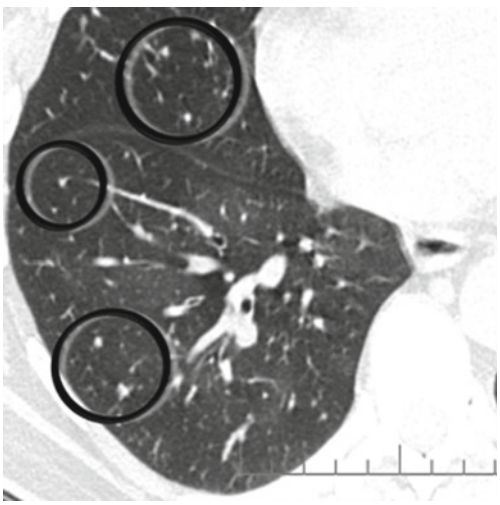
HIGH-RESOLUTION CT: HRCT

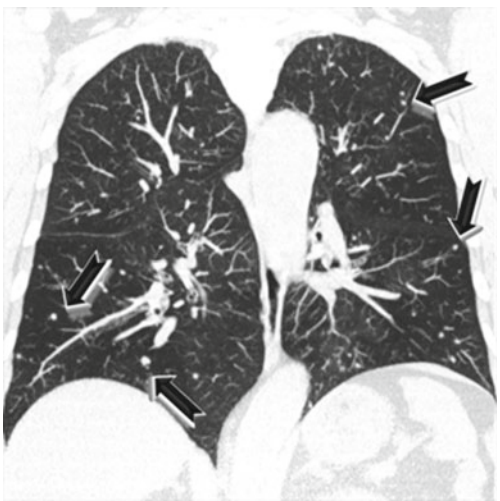
Key Signs

- Mosaic oligemia (dark lung) with air trapping due to small airways obstruction (O).
- Multiple small random solid rounded nodules. According to their size, nodules correspond to either tumorlets (<5 mm ➡) or carcinoid tumors (>5 mm ➪).

Distribution

Lesions are almost always bilateral. DIPNECH-associated carcinoid tumors are almost invariably in a peripheral location, distal to the segmental bronchi.





☝ Diagnosis is more difficult in asymptomatic patients, especially those undergoing CT for cancer follow-up, in which nodules must not be mistaken for diffuse lung metastases.

✓ Minimum intensity projection (MinIP) reformations may be useful for detection of subtle mosaic perfusion. Additional expiration CT should always be performed to detect air-trapping, which may be the only and indirect sign of small airway obstruction.

📖 Davies SJ (2007) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognized spectrum of disease. Thorax 62:248

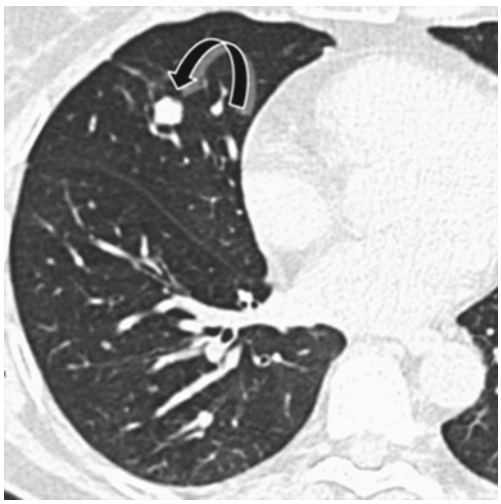
Chassagnon G (2015) DIPNECH: when to suggest this diagnosis on CT. Clin Radiol 70:317

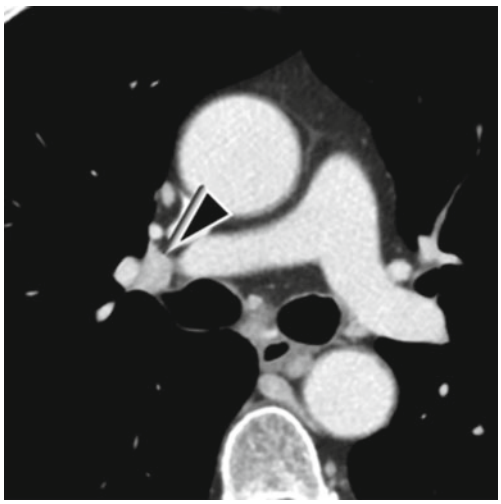
Ancillary Signs

- Bronchial wall thickening, due to the proliferation of the neuroendocrine cells in the bronchial wall
- Mild bronchiectasis and mucoid impactions, secondary to the constrictive obliterative bronchiolitis

Non-parenchymal Signs

- Metastatic spread has been reported in up to 27 % of patients with carcinoids, usually in the mediastinal or hilar lymph nodes (►) but also in the adrenal glands.





Pulmonary neuroendocrine cells (PNECs), also known as Kulchitsky-type cells, play a part in paracrine regulation of lung development during fetal life. In adulthood PNECs act as airway chemoreceptors, inducing local vasoconstriction by secreting serotonin in response to hypoxemia.

Gorshtein A (2012) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia and the associated lung neuroendocrine tumors: clinical experience with a rare entity. Cancer 118:612

Benson RE (2013) Spectrum of pulmonary neuroendocrine proliferations and neoplasms. RadioGraphics 33:1631

Course and Complications

- The disease have generally a slow progression, remaining stable over several years, but with the potential to metastasize in locoregional lymph nodes and rarely to extrathoracic sites.

^{68}Gallium-labeled somatostatin analogue peptides have been recently employed for the evaluation of neuroendocrine tumors of the lung, with encouraging results. Directly binding to somatostatin receptors on the tumor cell surface, they provide a good visualization of well-differentiated carcinoid and metastases. Several different somatostatin analogues (DOTA-TOC, DOTA-TATE, DOTA-NOC) have been described.

Foran PJ (2015) Imaging appearances of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. Clin Imaging 39:243

Prasad V (2015) Somatostatin receptor PET/CT in restaging of typical and atypical lung carcinoids. EJNMMI Res 5:53

Definition

Panlobular emphysema is characterized by uniform, nonselective destruction of the entire acinus distal to the respiratory bronchioles, from its center to its periphery. The pathogenesis relates to a protease-antiprotease imbalance in the lung, due to decreased functional activity of protease inhibitors in the interstitium and alveolar lining fluid. Autosomal recessive alpha-1-antitrypsin (AAT) deficiency is thought to be the major cause (exacerbated by smoking). AAT neutralizes neutrophil elastase which is carried by leukocytes in the blood and gradually destroys the lung when it is not inactivated by this inhibitor. The resultant lung destruction is extremely uniform throughout both individual lobules and the lung as a whole but is slighty more prominent in the lower lobes because of greater blood flow.

Other etiologies, including intravenous injection of methylphenidate (Ritalin lung) or Swyer-James syndrome, have been reported.

☯ Panacinar emphysema

📖 Takahashi M (2008) Imaging of pulmonary emphysema: a pictorial review. Int J Chron Obstruct Pulmon Dis 3(2):193

Foster WL Jr (1993) The emphysemas: radiologic-pathologic correlations. Radiographics 13(2):311

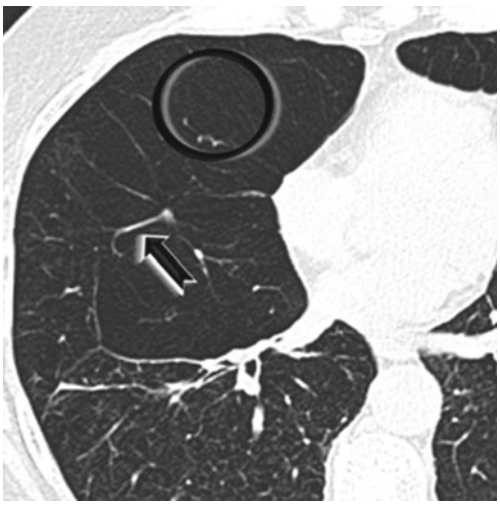
HIGH-RESOLUTION CT: HRCT

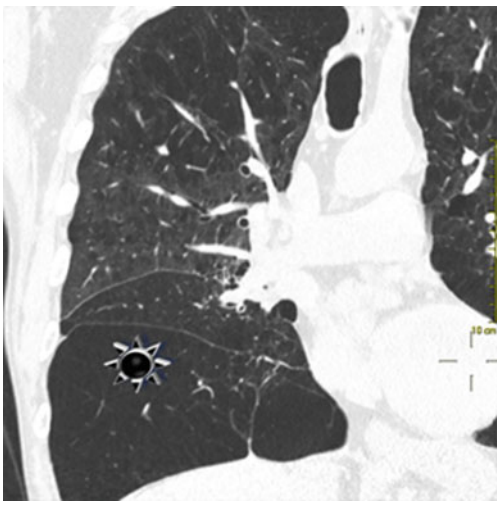
Key Signs

- Widespread areas of abnormally low attenuation (dark lung) (○). The caliber of the vessels in the involved areas is decreased (➡), due to overinflation of the air space.

Distribution

The disease is predominantly located in the lower lobes; distribution is uniform across all parts of the secondary pulmonary lobule (✸).





☝ Diffuse panlobular emphysema, not associated with focal areas of destruction or bullae, may be difficult to distinguish from diffuse small airways obstruction and air trapping due to constrictive bronchiolitis.

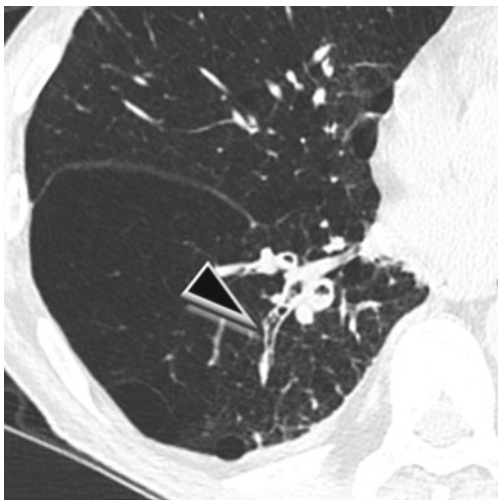
📖 Litmanovich D (2009) CT of pulmonary emphysema-current status, challenges, and future directions. Eur Radiol 19:537

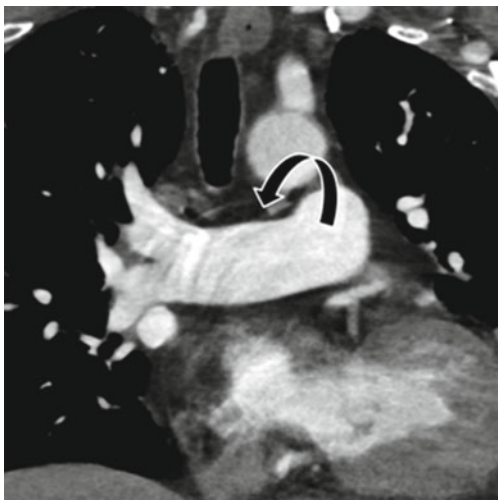
Ancillary Signs

- Increased lung volumes, pruning of small vascular branches
- Thickening of bronchial walls (►)
- Bronchiectases

Non-parenchymal Signs

- Mediastinal lymphadenopathies
- Saber-sheath trachea
- Pulmonary arterial hypertension (☟)





About 40 % of patients with alpha-1-antitrypsin deficiency shows bronchiectases or bronchial wall thickening. Patients with this deficiency are more susceptible to airways injury during infections compared to normal patients, because of the same imbalance in protease-antiprotease that causes emphysema.

Shaker SB (2004) Alpha1-antitrypsin deficiency. 7: computed tomographic imaging in alpha1-antitrypsin deficiency. Thorax 59(11):986

Course and Complications

- As severity increases, paucity of peripheral vessels increases and the lungs appear homogeneously reduced in attenuation

Several CT techniques are now available to detect and accurately quantify emphysema. Quantitative assessment is most often based on the percentage of lung voxels below a specific threshold (density mask technique). The results correlate significantly better than chest radiography with functional impairment and pathological score. Quantitative CT has been used in patient selection for surgical treatment of pulmonary emphysema and in pharmacotherapeutical trials.

Sverzellati N (2014) Physiologic and quantitative computed tomography differences between centrilobular and panlobular emphysema in COPD. Chronic Obstr Pulm Dis (Miami) 1(1):125

Bankier AA (2002) CT quantification of pulmonary emphysema: assessment of lung structure and function. Crit Rev Comput Tomogr 43(6):399

Definition

Swyer-James (MacLeod's) syndrome (SJS) is a rare lung condition characterized by often predominantly, unilateral lung hyperlucency and air trapping. The condition is a post-infectious form of bronchiolitis obliterans and typically follows a viral respiratory infection in infancy or childhood. Adenovirus infection is considered the most usual epidemiology. In SJS, the involved lung or portion of the lung does not grow normally and is slightly smaller than the opposite lung: in particular, peripheral branches of the pulmonary vessels do not develop, and vasculature is arrested at the stage at which the infection occurred. Patients respond well to management with bronchodilators, even though this is not primarily a bronchial abnormality.

SJS, SJMS, Swyer James MacLeod syndrome, MacLeod syndrome, Bret syndrome, Janus syndrome, hyperlucent lung syndrome

Sen HS (2014) Adult diagnosis of Swyer-James-Macleod syndrome: retrospective analysis of four cases. Respir Care 59:e51

da Silva PS (2012) Swyer-James-MacLeod syndrome in a surgically treated child: a case report and brief literature review. J Pediatr Surg 47:e17

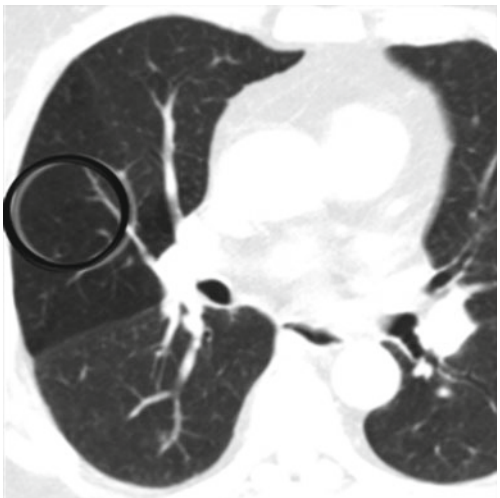
HIGH-RESOLUTION CT: HRCT

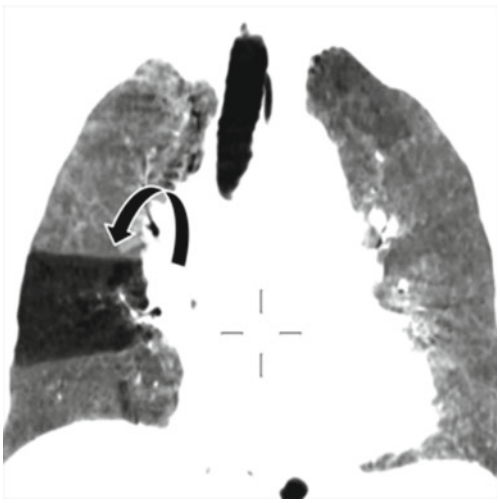
Key Signs

- The affected lung (or a part of it) shows a low attenuation (dark lung ○) caused by overdistention of the alveoli in conjunction with diminished arterial flow.

Distribution

The lesions may predominate in one lung or lobe, especially in the lower one ().





Air trapping in dark lung regions should be confirmed by a lack of change in volume on expiratory CT scans. The size of the majority of the affected lobes is smaller although occasionally they can be normal.

Moore AD (1992) Swyer-James syndrome: CT findings in eight patients. AJR Am J Roentgenol 158:1211

Dalpiaz G (1999) Swyer-James syndrome: assessment of a case with high resolution and volumetric computerized tomography. Radiol Med 98(1–2):96

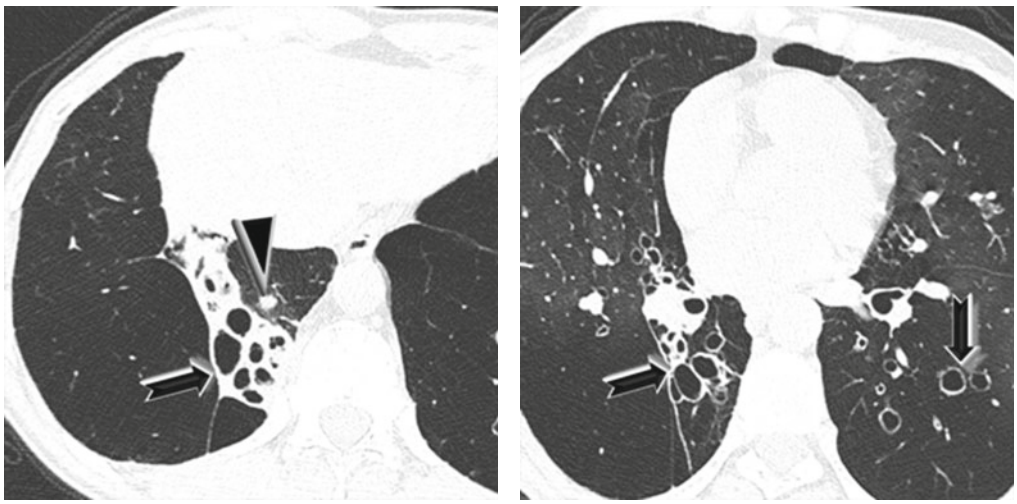
The disparity in size between the two lungs may represent a hypoplastic pulmonary artery or congenital hypoplasia of the lung. A comparison with a previous set of radiographs helps with the differential diagnosis. A history of severe lung infection also helps in making the diagnosis.

Ancillary Signs

- Bronchiectases (saccular or cylindrical) may be present (➡), although this is not a universal finding.
- Small focal opacities (►) due to chronic infections or residual scars from previous pneumonia.

Non-parenchymal Signs

- Lymph nodes enlargement



SJS is usually asymptomatic and is often detected as an incidental finding on a chest radiograph. Symptomatic children usually present with productive cough, dyspnea, hemoptysis, and recurrent pulmonary infections. The severity of symptoms is influenced mainly by the presence of saccular bronchiectases.

Tutar O (2012) Adult diagnosis of Swyer-James-Macleod syndrome. BMJ Case Rep 10:2012

Bernardi F (1999) Swyer-James syndrome: bronchoalveolar lavage findings in two patients. Eur Respir J 8:654

Course and Complications

- Minor symptoms or completely asymptomatic until adulthood
- Recurrent episodes of pulmonary infection and progression of bronchiectases

Wojcicki KM (2015) An uncommon obliterative lung disease: Swyer-James-MacLeod syndrome. Intern Emerg Med 10:881

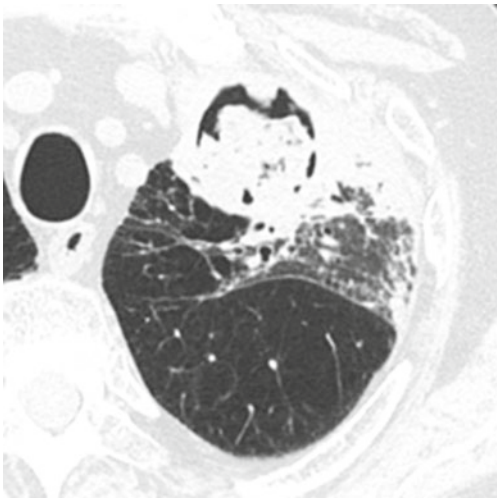
Case-Based Glossary with Tips and Tricks

Clinical features	**Marco Patelli**
Radiology	**Giorgia Dalpiaz** **Marta Fiscaletti** **Marco Piolanti**
Pathology	**Alessandra Cancellieri**

G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2_15

AIR CRESCENT SIGN

Meniscus or cap sign



Clinical History

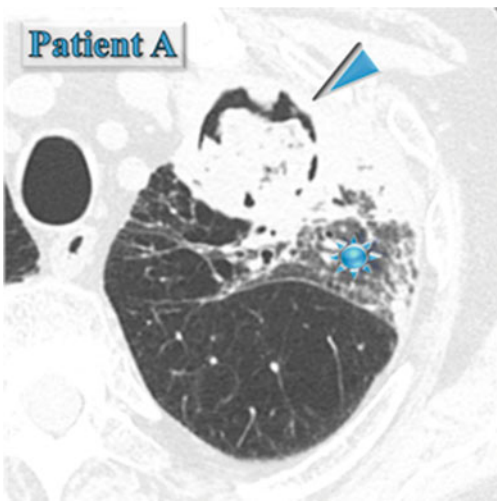
(Patient A) Male in his 70s with fever, cough, and hemoptysis: immunocompromised patient with neutropenia.

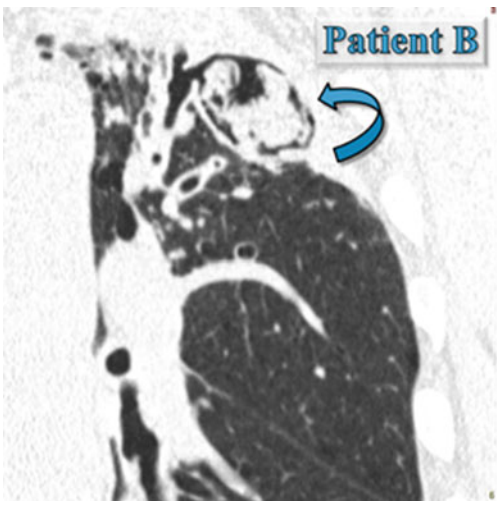
(Patient B) Male in his 70s, he underwent coronary artery bypass due to ischemic heart disease. No dyspnea, immunocompetent, BPCO, and persistent productive cough.

HRCT

(Patient A) In the left upper lobe, axial HRCT image shows rounded area of consolidation surrounded by a very thin black area (air crescent sign) (►). An area of ground-glass opacity (GGO) also coexists in the same lobe (✸).

(Patient B) In the left upper lobe, coronal HRCT image shows cystic bronchiectases with intracavitary material surrounded by a crescent-shaped thin black area (air crescent sign) (↷).





Causes of Air Crescent Sign

Common
Angioinvasive aspergillosis
Mycetoma (also defined aspergilloma)

Rare
Abscess
Cavitary neoplasm
Granulomatosis with polyangiitis (Wegener granulomatosis)
Hematoma
Hydatid cyst
Pneumocystis jiroveci pneumonia
Tuberculosis (TB)

Tips and Tricks

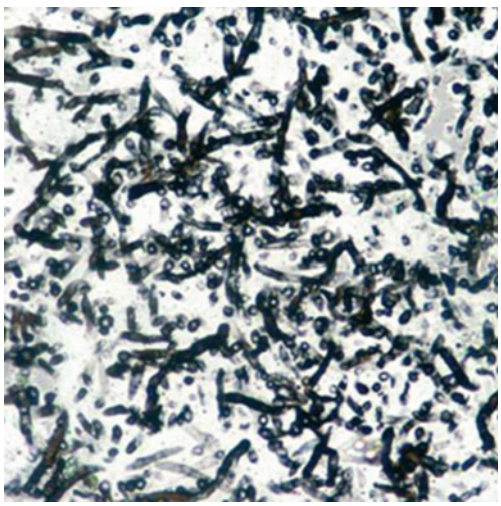
- Please pay attention to the state of the patient immunocompetence and if there was a preexisting cystic or cavitary lung disease in a previous CT. As a matter of fact, *invasive aspergillosis* should be suspected in any patient with neutropenia who develops a fever and presents the air crescent sign inside a consolidation or mass (Patient A). On the contrary, the air crescent sign of *mycetoma*, also referred to as the Monad sign, is seen in an immunocompetent host with preexisting cystic or cavitary lung disease, usually from tuberculosis or sarcoidosis (Patient B).
- *Mycetoma* is usually located in the upper lobes. Lower lobes and multifocal distribution should increase the suspicion of a different diagnosis.

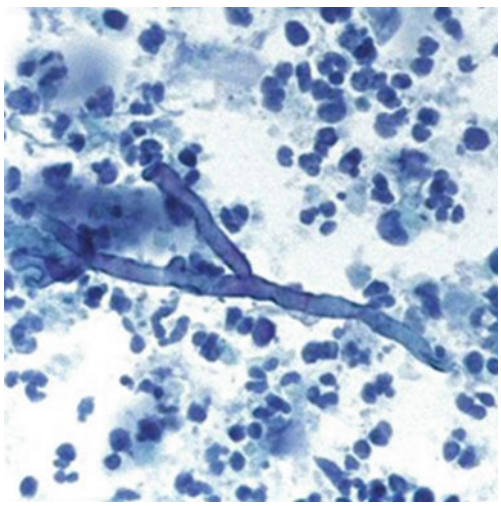
Management and Diagnosis

Both patients were positive for serum biomarker galactomannan together with the presence of *Aspergillus* in the bronchoalveolar lavage (BAL) (septate hyphae branching at 45° on a necrotic background; see the images below).

Final diagnosis of Patient A: angioinvasive aspergillosis

Final diagnosis of Patient B: mycetoma





Pearls

- *Air crescent sign* is recognized as a crescent-shaped or circumferential area of radiolucency within a parenchymal consolidation or nodular opacity. This sign is often seen in two types of *Aspergillus infection*: *angioinvasive* and *mycetoma*.
- *Pathogenesis* of air crescent sign in *angioinvasive Aspergillus infection.* It is caused by parenchymal cavitation, which typically occurs 2 weeks after the detection of the initial radiographic abnormality. The nodules are composed of infected hemorrhagic and infarcted lung tissue. As the neutrophil count recovers and the patient mounts an immune response, peripheral reabsorption of necrotic tissue causes the retraction of the infarcted center, and air fills the space in between. This creates an air crescent within the nodules and is a good prognostic finding because it marks the recovery phase of the infection. This sign is seen in approximately 50 % of patients. *Angioinvasive Aspergillus* infection is often fatal.
- *Pathogenesis* of air crescent sign in *mycetoma (aspergilloma)*. It is caused by the presence of a fungus ball inside a cavity separated from the wall of the cavity by an airspace of variable size. Air crescent sign in *mycetoma*, also referred to as the Monad sign, was first described in 1954 by Pesle and Monod. It is seen in an immunocompetent host with preexisting cystic or cavitary lung disease, usually from tuberculosis or sarcoidosis. The radiographic appearance is often that of a gravity-dependent mass within a preexisting cavity.

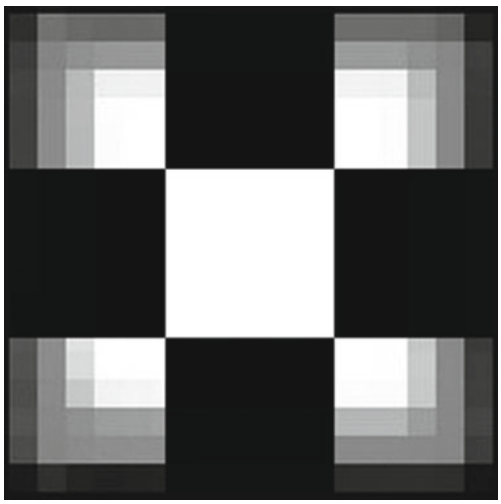
Hansell DM (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

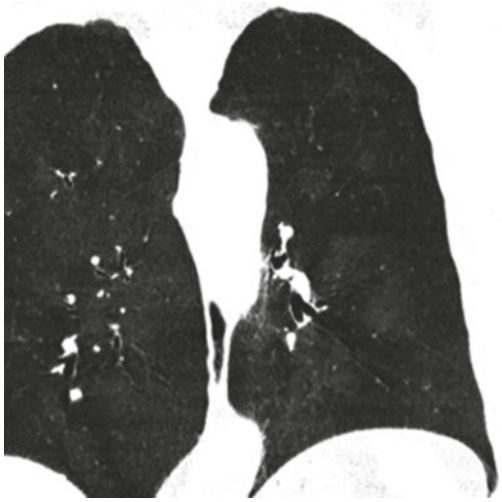
Nitschke A (2013) Monod sign. J Thorac Imaging 28:W120

Franquet T (2001) Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics 21(4):825

AIR TRAPPING

Gas trapping



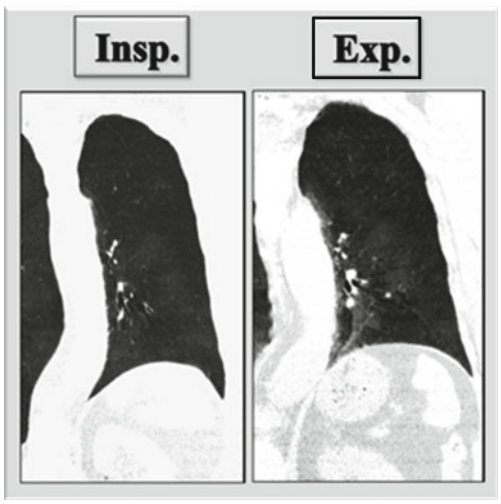


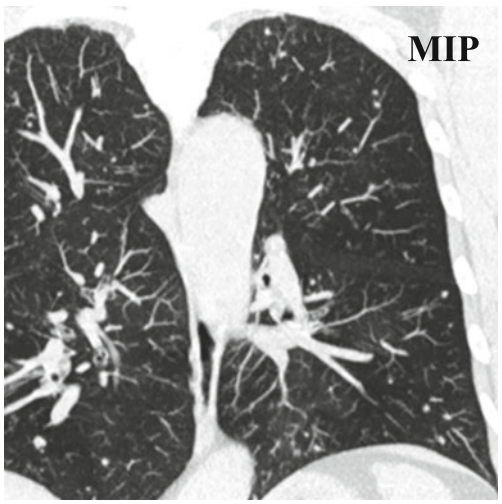
Clinical History

Female in her 60s, ex-smoker. Bronchial asthma from 15 years, on continuous therapy during the last 3 years. Clinical reevaluation for worsening cough shows bronchial obstruction, not reversible.

HRCT

Coronal inspiratory (Insp.) and expiratory (Exp.) CT images with minimum intensity projection (MinIP) algorithm show patchy areas of black and white aspect due to air trapping. Coronal CT image with maximum intensity projection (MIP) shows small solid nodules with random distribution.





Causes of Air Trapping

With Bronchiectasis
Constrictive bronchiolitis (CB)
Congenital conditions (cystic fibrosis, primary ciliary dyskinesia, Swyer–James Syndrome – SJS, Williams–Campbell syndrome)
Infection (atypical mycobacteria, tuberculosis, ABPA)

With Interstitial Lung Disease
Constrictive bronchiolitis (CB), DIPNECH, sarcoidosis, hypersensitivity pneumonitis (HP), and collagen vascular disease (CVD)

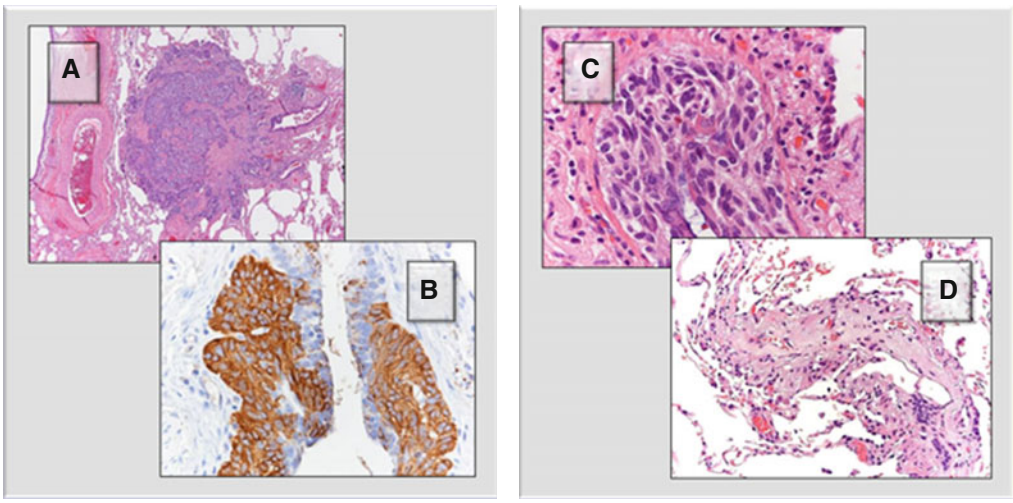
Tips and Tricks

- In our patient air trapping is not associated with bronchiectasis but with interstitial lung disease (nodules) displaying solid density and random distribution. The presence of random nodules rules out the diagnosis of sarcoidosis or hypersensitivity pneumonitis.
- The coexistence of patchy areas of air trapping with solid random nodules supports the diagnosis of constrictive bronchiolitis in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH).

Management and Diagnosis

The patient underwent a surgical lung biopsy. Nodules (A) are composed of a proliferation of neuroendocrine cells, as demonstrated by the positivity with anti-chromogranin antiserum (B). The neuroendocrine proliferation can also consist in a linear growth within the airway wall (C). As a result, fibrosis of the bronchioles can ensue, both in the form of stenosis and complete obliteration of the lumen (D).

Final diagnosis: diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)



Pearls

- *Air trapping* is the retention of air in the lung distal to an obstruction (usually partial). Air trapping is seen on expiration CT scans as parenchymal areas with less than normal increase in attenuation and lack of volume reduction. Comparison between inspiratory and expiratory CT scans can be helpful when air trapping is subtle or diffuse.
- *Pathogenesis.* Small-airway disease results from different causes (please see the table above).
- *DIPNECH*, when associated with bronchiolar fibrosis, is also known as *Aguayo–Miller syndrome* after the name of the authors who first published a clinical series of six cases in 1992. The majority of patients presenting with DIPNECH are middle-aged females with symptoms of cough and dyspnea, obstructive abnormalities on pulmonary function testing, and radiographic imaging showing pulmonary nodules, air trapping, and mild bronchiectases. In general, the clinical course remains stable; however, progression to respiratory failure does occur. Long-term follow-up and treatment remain unclear. Transbronchial biopsy in search of a specific etiology is often a first step. If this remains negative, then a video-assisted thoracoscopic surgical biopsy may be necessary. Please also refer to DIPNECH in the Dark Lung Diseases chapter.

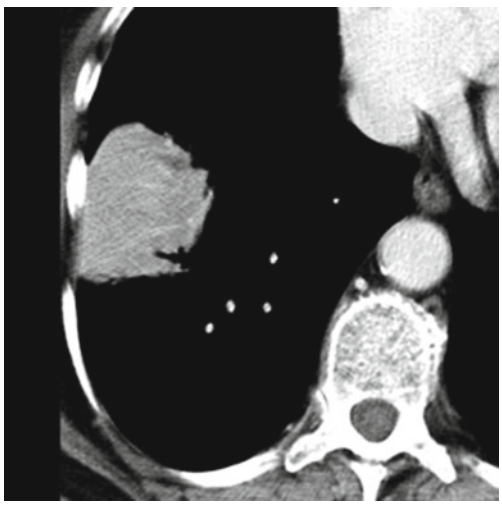
Hansell DM (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697

Kligerman SJ (2015) Mosaic attenuation: etiology, methods of differentiation, and pitfalls. Radiographics 35(5):1360

Nassar AA (2011) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: a systematic overview. Am J Respir Crit Care Med 184(1):8

ANGIOGRAM SIGN

Lightning sign (n.d.e.)

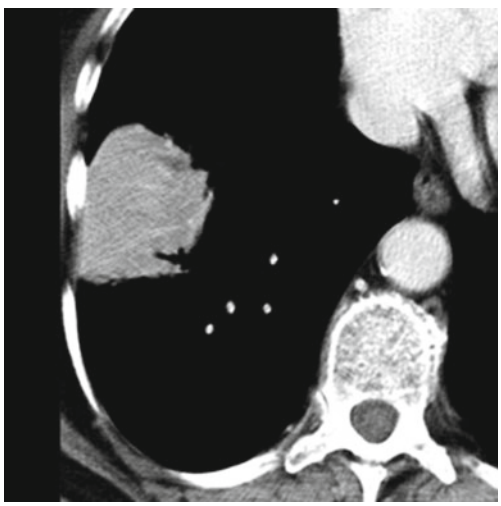


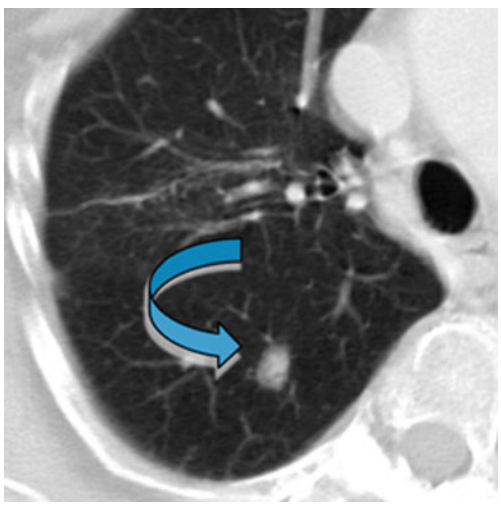
Clinical History

Woman in her 70s, previous smoker with dry cough, asthenia, and chest right pain for 6 months. Recent diagnosis of autoimmune disease. The chest radiography shows consolidation not responsive to medical treatment ("non-resolving pneumonia").

CT

In the lower right lobe, CT shows consolidation with visibility of patent white vessels crossing the lesion (angiogram sign). In the upper right lobe, a parenchymal nodule is also visible ( ).





Causes of Angiogram Sign

Common Disease Adenocarcinoma Pneumonia
Rare Disease Lipoid pneumonia Lymphoma Metastasis of gastrointestinal adenocarcinomas Obstructive pneumonitis due to central lung tumors

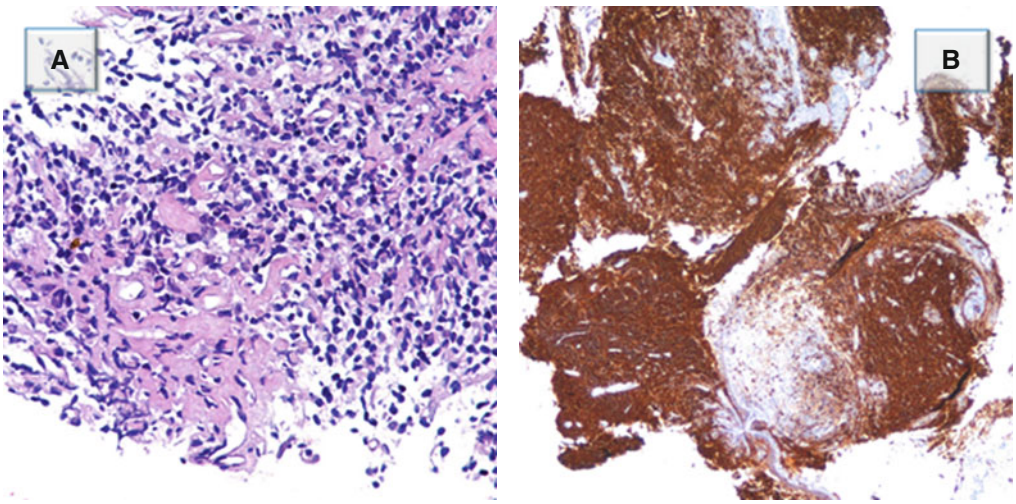
Tips and Tricks

- Please note that the consolidation presents a mass-like aspect without bronchogram sign. The vessels inside the lesion (angiogram sign) appear thinned and stretched. This feature suggests the presence of material that occupies the alveoli with mass effect.
- In our case the mass-like consolidation with angiogram sign is associated with a nodule. These imaging features are nonspecific and may resemble a variety of benign and malignant chest disorders including adenocarcinoma. However, the diagnosis of pulmonary MALT lymphoma should be considered in patient with the imaging features described above and with a history of autoimmune disorder.

Management and Diagnosis

The bronchoscopy showed endobronchial vegetation into the proximal tract of the lower right bronchial pyramid. Pathologic analysis showed fragments of a diffuse proliferation composed of small centrocyte-like lymphocytes (Figure A). The proliferating lymphocytes are CD20 positive, a feature consistent with B-cell derivation (Figure B) (Courtesy of S. Damiani, Bellaria Hospital, University of Bologna).

Diagnosis: low-grade B-cell pulmonary lymphoma MALT



Pearls

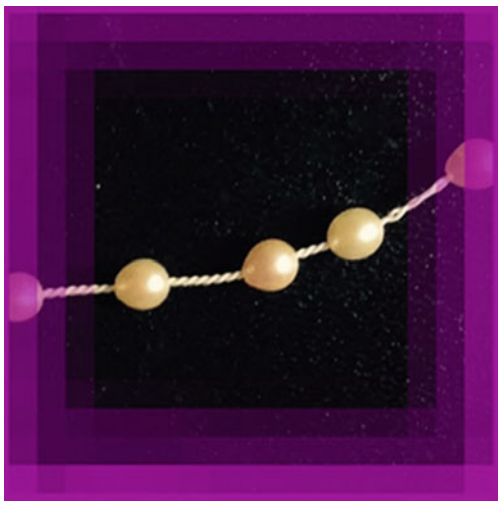
Angiogram sign refers to the visualization of pulmonary vessels within an consolidation, on contrast-enhanced CT scanning. The vessels are prominently seen against a background of a relatively low-attenuation lesion. It has been initially described in 1990 by Im as a specific sign of lobar bronchoiolo-alveolar carcinoma. In the following years, this sign has been reported to be present in several different benign and malignant diseases (please see the table).

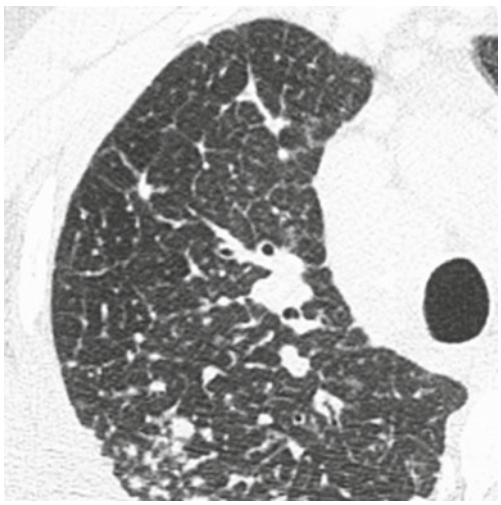
- *Pathogenesis.* The vessels are prominently seen due to the variable low-attenuation density of the consolidation. CT low-attenuating lung consolidations with angiogram sign after intravenous contrast material administration may be due to the presence in the airspace of fat (lipoid pneumonia), mucus (obstructive pneumonia with abundant accumulation of secretions), necrosis (necrotizing pneumonia), or mucin (primary or metastatic mucinous adenocarcinoma) (please also refer to the Cheerio sign in this chapter).
- *Pulmonary MALToma* does not present pathognomonic imaging features. The commonest radiological manifestations are pulmonary mass, or mass-like area of consolidation and multiple pulmonary nodules. Common associated features include air bronchograms, positive angiogram sign on contrast-enhanced CT, and halo of ground-glass opacity (halo sign). Please also refer to MALToma in the Alveolar Diseases chapter.

Im JG (1990) Lobar bronchioloalveolar carcinoma: “angiogram sign” on CT scans. Radiology 176(3):749

BEADED SEPTUM SIGN

Beaded appearance, nodular septal thickening



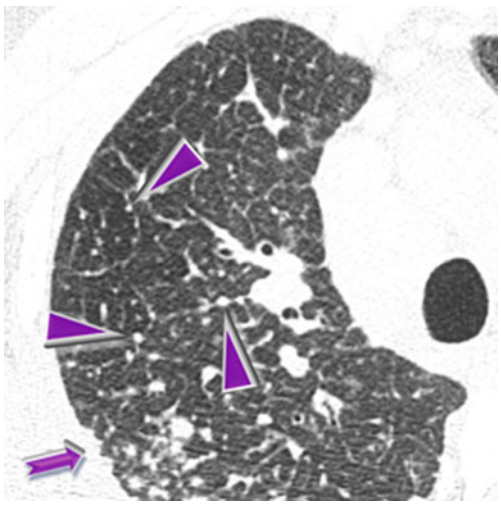


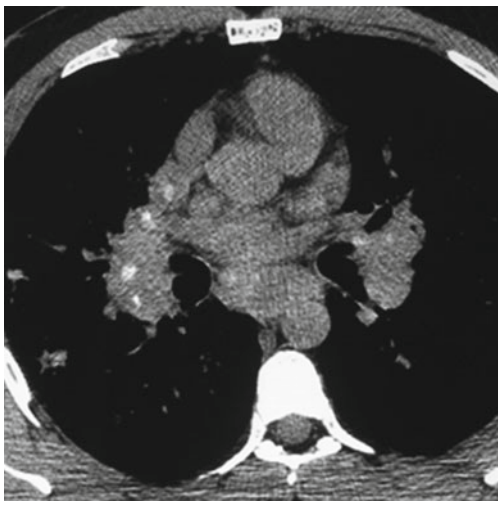
Clinical History

Man in his 20s with cough, dyspnea, and restrictive ventilatory defect at pulmonary function tests. The chest radiography shows multiple micronodules predominant in the upper and middle zone.

HRCT

HRCT at the level of the right upper lobe shows diffuse nodular thickening of the interlobular septa (beaded septum sign ►) and subpleural micronodules (➡). Axial unenhanced CT (mediastinal window) shows bilateral hilar and subcarinal calcified lymph node enlargement.





Causes of Beaded Septum Sign

Common
Lymphangitic carcinomatosis (LC)
Rare
Amyloidosis
Lymphoproliferative disease (lymphoma, leukemia)
Sarcoidosis

Tips and Tricks

- Small and dense nodules beaded some septa (see above, left) but also the subpleural space with the so-called perilymphatic distribution ("avid of pleura"). This pattern is most typical of sarcoidosis, lymphangitic spread of carcinoma or other neoplasms, and lymphoproliferative disease.

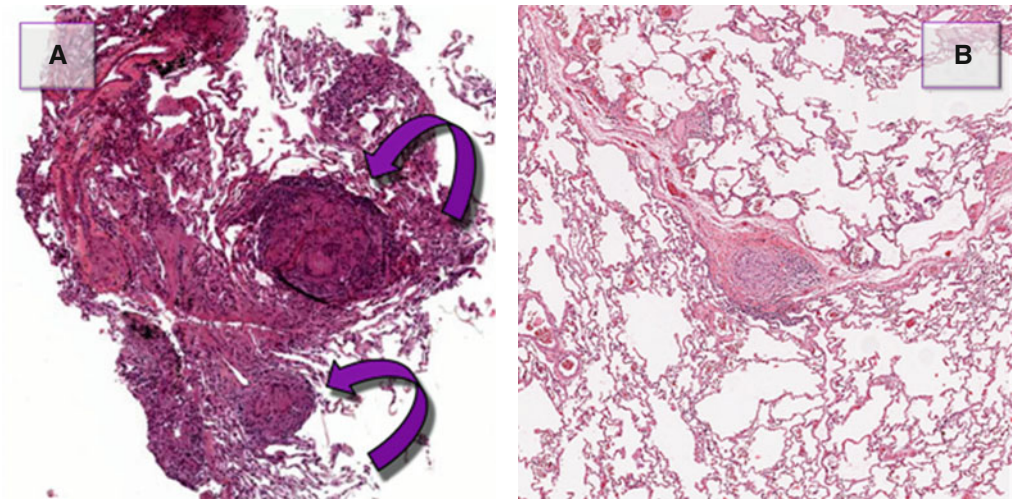
- Note that a grouping of small subpleural nodules adjacent to the costal margins coexists. They are due to agglomerates of nodules and arranged linearly along the pleural surfaces, thus mimicking focal thickening (pseudoplaques ➡). Pseudoplaques are thought to be most commonly seen in association with granulomatous disease and in particular with sarcoidosis.
- The distribution of the enlarged lymph nodes is a key sign for diagnosis of some diseases. Bilateral hilar lymph node enlargement may be a feature of infection (particularly fungal or mycobacterial infection) or malignancy (e.g., lymphoma), but sarcoidosis is the most common cause of bilateral lymph node enlargement.
- Calcifications are often present in chronic sarcoidosis.
- In our case the beaded septum sign, together with perilymphatic micronodules, pseudoplaques, and the symmetric lymphadenopathy with punctate calcifications are highly suggestive of sarcoidosis.

Management and Diagnosis

Transbronchial biopsy (TBB) can easily show non-necrotizing, well-formed granulomas, due to their centrilobular distribution (Figure A ↘).

Transbronchial needle aspiration (TBNA) from mediastinal lymph nodes can also provide granulomas with similar features (please also refer to TBB and TBNA in the chapter Clinical Approach to DLD).

Final diagnosis: sarcoidosis



Pearls

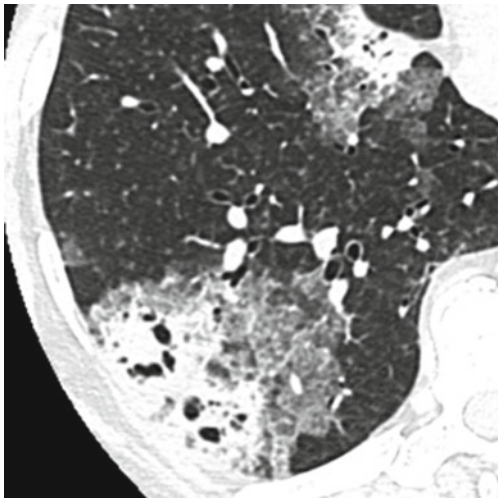
- *Beaded septum sign* consists of nodular thickening of interlobular septa reminiscent of a row of beads (Please see Figure B and Septal Pattern, subset Nodular). The beaded septum sign was initially described as a sign of lymphangitic spread of cancer, although thoracic sarcoidosis in the literature has been known as a "great mimicker" and can manifest with various pattern on HRCT, like nodular septal thickening simulating lymphangitic carcinomatosis.
- *Sarcoidosis, septal.* Beaded septum sign often is an ancillary sign. It may be a predominant radiologic feature in only 15–20 % of patients with sarcoidosis. Other atypical manifestations of sarcoidosis, such as mass-like or alveolar opacities, honeycomb-like cysts, miliary opacities, mosaic attenuation, tracheobronchial involvement, and pleural disease, and complications such as aspergillomas may also be seen. The most common pattern in sarcoidosis, which helps to make a diagnosis, is the presence of micronodules with a perilymphatic distribution (avid of pleura) and bilateral, symmetric hilar lymph node enlargement.

Andreu J (2004) Septal thickening: HRCT findings and differential diagnosis. Curr Probl Diagn Radiol 33:226

Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestation at high-resolution CT with pathologic correlation. Radiographics 30:1567–1586

BUBBLE-LIKE LUCENCIES

Bubbly consolidation, pseudocavitations

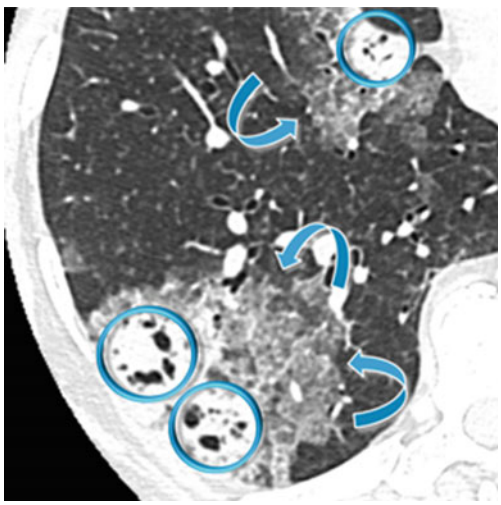


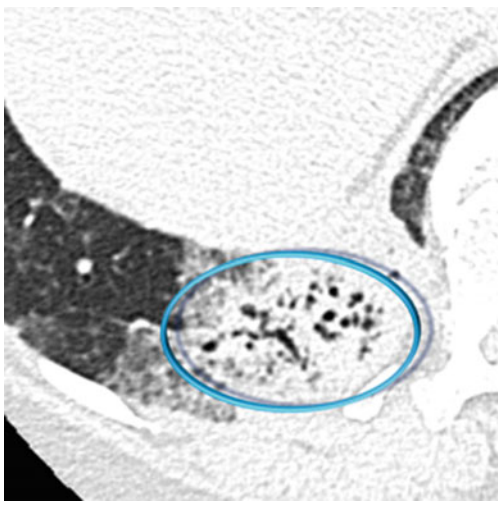
Clinical History

Female in her 60s with asthenia, chronic dyspnea, arthralgia, and low-grade fever for about 2 months. Chest X-ray shows bilateral patchy consolidations. The picture remains unchanged after antibiotic therapy ("non-resolving pneumonia").

HRCT

Patchy bilateral lung disease with alveolar pattern in the form of peripheral consolidations. All lesions show multiple bubble-like hyperlucencies (O) and surrounding ground-glass opacity (halo sign ⇘).





Causes of Bubble-Like Lucencies

Neoplastic Adenocarcinoma, primary or metastatic BALT lymphoma
Nonneoplastic Infection (e.g., TB), organizing pneumonia (OP), and pulmonary infarction

Tips and Tricks

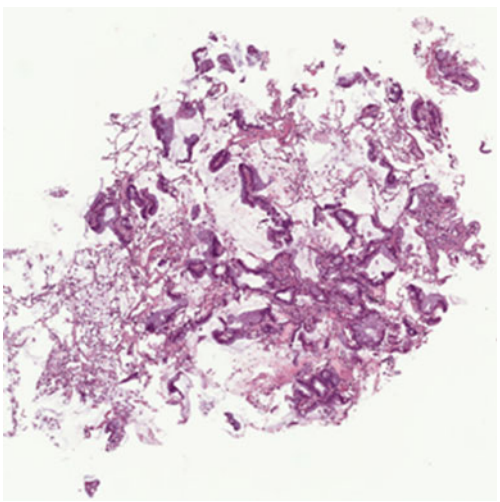
- The presence of hyperlucencies within a consolidation or within a subsolid nodule should not always be considered as a synonym of necrosis or cavitation. Small, rounded, or oval hyperlucencies, similar to bubbles (bubble-like lucencies), may be the expression of ectatic bronchioles (O); in this last case, therefore, they are pseudocavitations.

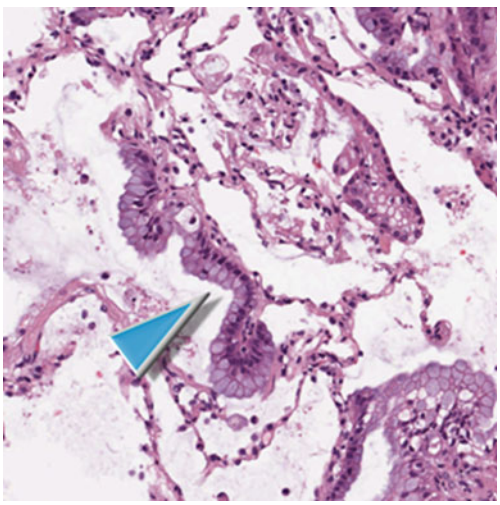
- The association between persistent opacities ("non-resolving pneumonia") with bubble-like hyperlucencies and extended halo sign (☟) is suggestive of primary pulmonary adenocarcinoma, more frequently of the mucinous type.
- Infectious disease (mainly, secondary tuberculosis), pulmonary infarction, organizing pneumonia (OP), and BALT lymphoma are other possible etiologies, more rarely encountered.

Management and Diagnosis

The patient underwent bronchoscopy. Bronchoalveolar lavage (BAL) showed increased lymphocyte and neutrophil count, absence of malignancy, and negative bacteriological examination and culture for mycobacteria. Histologic sampling by transbronchial biopsy (TBB, images below) revealed the presence of a small focus of adenocarcinoma; neoplastic cells grow along the alveolar septa (lepidic growth ►). They show a fence-like arrangement in a fence and show abundant intracytoplasmic mucin, with positive TTF-1 expression.

Final diagnosis: primary mucinous adenocarcinoma of the lung





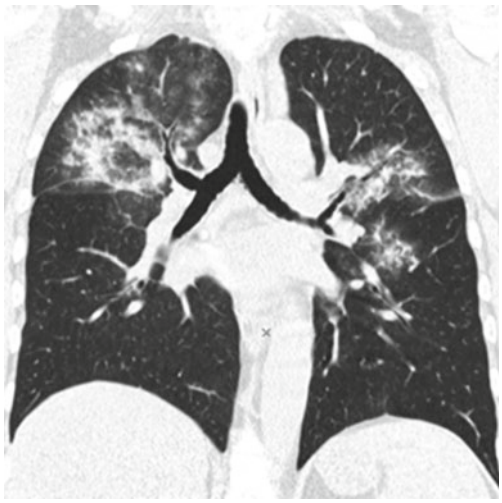
Pearls

- *Bubble-like lucencies* are small lucencies inside both nodules and consolidations. The origin of these pseudocavitations has been clarified by histopathological studies in patients with adenocarcinoma, in particular with the in situ mucinous adenocarcinoma (previously known as mucinous bronchoalveolar carcinoma or BAC).
- *Pathogenesis*. Bubble-like lucencies (pseudocavitation) can be formed by a valve mechanism by bronchiolar obstruction or by desmoplastic bronchiolar traction or paracicatricial emphysema. Also, lucency can result from spared pulmonary lobules.
- *Lepidic growth* is defined as cancer cells which proliferate respecting the microscopic structure of pulmonary alveoli and papering them like butterflies (Lepidoptera) on a fence.
- *Mucinous adenocarcinomas* of the lung often manifest as diffuse lung involvement (multilobar and bilateral), showing patchy and extensive consolidations (pneumonia-like), often with bubble-like lucencies and possible halo sign. It also may display air bronchograms and the CT-angiogram sign, or it may be also associated with nodules, prevalently subsolid. It carries a worse prognosis than non-mucinous variants (survival by about 30 % at 5 years versus 70 %). Please also refer to adenocarcinoma in the Alveolar Diseases chapter.

📖 Gaeta M (1999) Radiolucencies in bronchioloalveolar carcinoma: CT-pathologic correlation. Eur Radiol 9:55

BUTTERFLY SIGN

Bat's wing/angel wing opacities

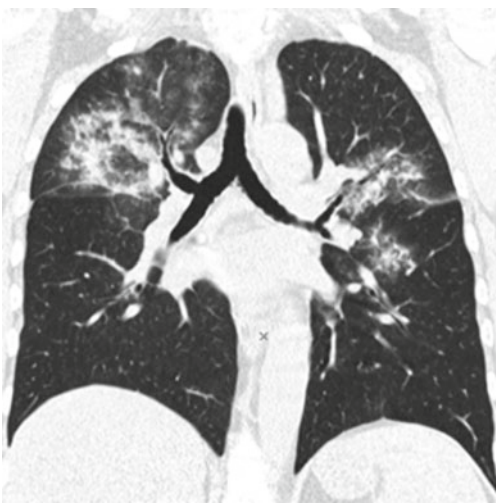


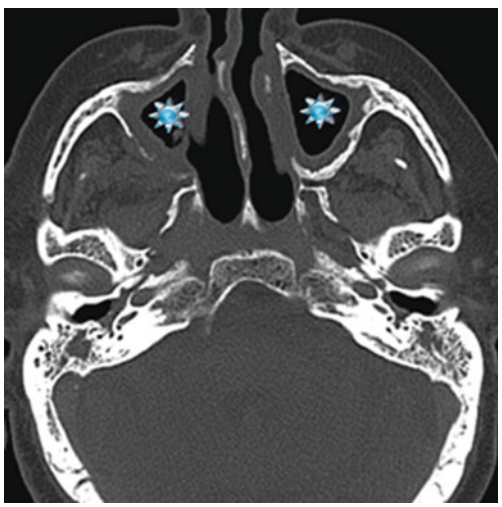
Clinical History

Woman in her 50s turned to the emergency room for sudden onset of hemoptysis and *acute* respiratory distress. The patient had also been suffering from low-grade fever and diffuse arthralgia for several months. At admission a chest radiography was performed, followed by a pulmonary HRCT study. A sinonasal CT was later performed due to upper airway symptoms.

CT

HRCT shows bilateral pulmonary involvement in the form of extensive ground-glass opacities. Distribution is central: note the presence of "subpleural sparing" (butterfly pulmonary opacities). CT scan of the paranasal sinuses shows bilateral maxillary sinus mucosal thickening (✸).





Causes of Butterfly Pulmonary Opacities

Acute Hydrostatic pulmonary edema, diffuse alveolar hemorrhage, *pneumocystis* pneumonia, viral pneumonia, and aspiration or inhalation pneumonia
Chronic Pulmonary alveolar proteinosis (PAP), adenocarcinoma, lipoid pneumonia (LP), "alveolar" sarcoidosis, and lymphoma/leukemia

Tips and Tricks

- Diffuse parenchymal opacification, either with GGO or consolidations, constitute the alveolar pattern, which encompasses a wide range of diagnostic hypotheses. Consequently, it is very useful to consider the "time" factor: distinguishing *acute* from *chronic* opacification is very helpful in reducing the differential diagnoses (please see the tables at the end of Alveolar Pattern).
- Bat's wing distribution with *acute* symptoms primarily refers to a hydrostatic pulmonary edema. However, other acute lung diseases may show this distribution, such as diffuse alveolar hemorrhage (DAH), pneumonia, or inhalation/aspiration pneumonia.
- The presence of Bat's wing or butterfly pulmonary opacities without pleural effusion, and of other signs of pulmonary venous hypertension, makes the hypothesis of hydrostatic pulmonary edema unlikely.
- Bat's wing opacities in a patient with hemoptysis, *acute* respiratory distress, and signs of sinus inflammation support the final diagnosis of granulomatosis with polyangiitis (Wegener's granulomatosis).

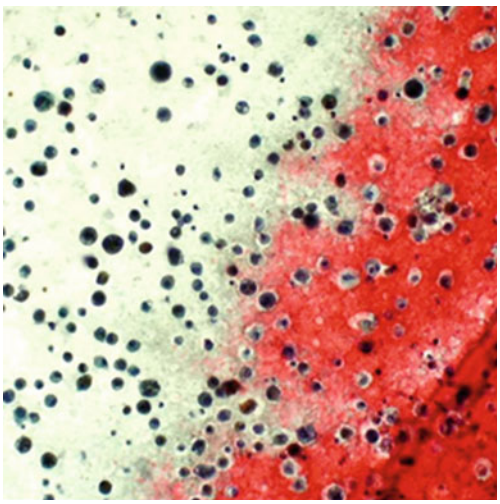
Management and Diagnosis

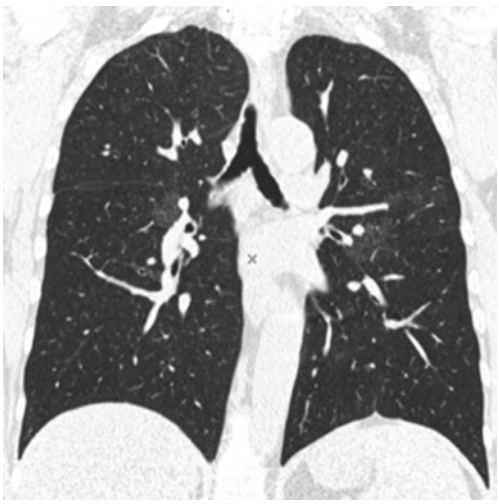
Laboratory tests showed iron deficiency anemia and hematuria (pulmonary renal syndrome).

Bronchoscopy ruled out the presence of bronchial lesions, and the bronchoalveolar lavage (BAL) showed hemosiderin-laden macrophages on a background of red blood cells (please see the image below). Laboratory tests were positive for antibodies c-ANCA and negative for other antibodies.

Final diagnosis: granulomatosis with polyangiitis (Wegener's granulomatosis)

Follow-up: complete resolution of the opacities (see the coronal HRCT image below).





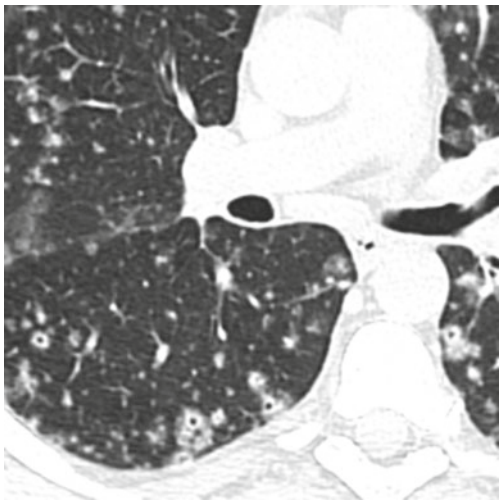
Pearls

- *Butterfly or Bat's wing sign* refers to the presence of bilateral parenchymal opacities, with perihilar distribution and sparing of the periphery of the lungs. It is classically described in the chest X-ray but is best appreciated on CT.
- *Pathogenesis.* It is not clearly established and there are various hypotheses. The most shared is that of a propulsive effect of the respiratory cycle: the effect is more pronounced at the periphery determining a flow of fluids toward the hilum. Otherwise the contractile properties of the alveolar septa may boost edema toward the hilum. One other hypothesis is that of an increase in hydraulic conductivity centrally with the over hydration of the tissues.
- *Granulomatosis with polyangiitis (Wegener's granulomatosis)* is a systemic granulomatous necrotizing vasculitis. It is characterized by diffuse systemic involvement of the microcirculation: precapillary arterioles, capillaries, and capillary venules. DAH occurs in approximately 10 % of patients. According to the Chapel Hill classification of 2012, Wegener's granulomatosis belongs to the systemic "small vessels vasculitis," along with microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss).

Jennette JC (2013) Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol 17:603

CHEERIO SIGN

Tarallucci sign (n.d.e.)

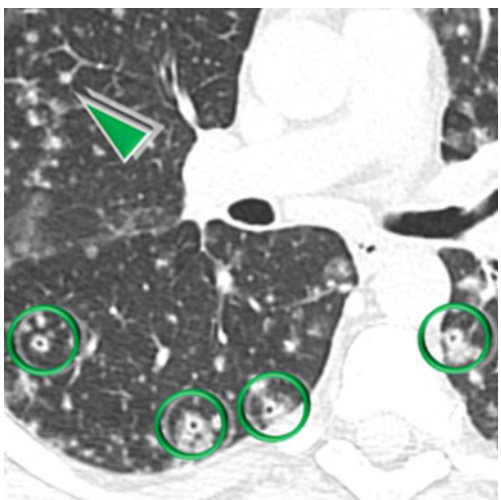


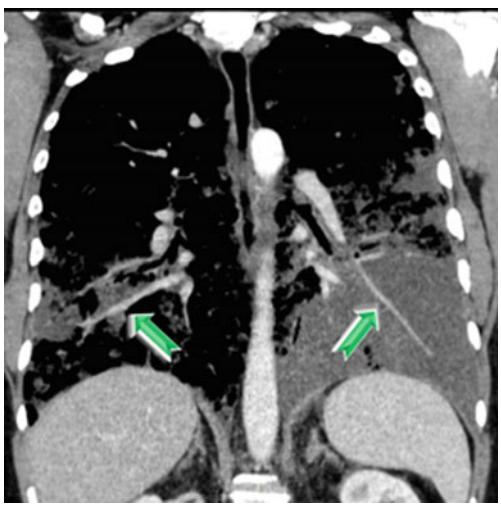
Clinical History

Man in his 50s with weight loss, chronic dyspnea on exertion, no fever. The chest X-ray shows multiple nodules throughout both lungs and consolidations in the lower lobes, not responsive to medical treatment.

HRCT

Axial HRCT shows multiple nodules containing central lucencies (Cheerio sign) (O). Some nodules are feeding vessels (►). Coronal contrast-enhanced CT image shows normally enhancing pulmonary vessels within basal consolidations (➡).





Causes of Cheerio Sign

Neoplastic Adenocarcinoma, primary or metastatic Langerhans cell histiocytosis (LCH) Lymphoma Sarcoma Squamous cell carcinoma
Nonneoplastic Infection (fungal or mycobacterial) Rheumatoid arthritis (RA) and granulomatosis with polyangiitis (former Wegener's granulomatosis, often macronodules)

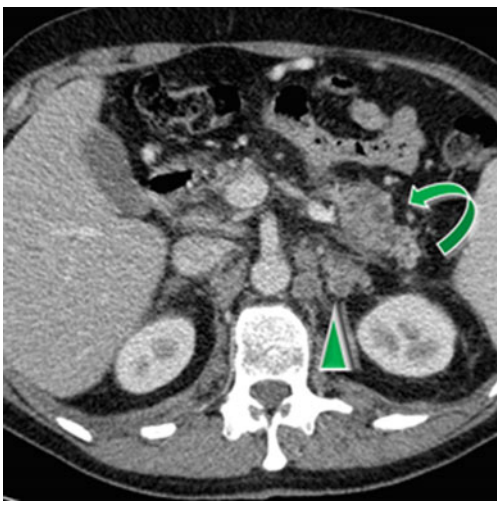
Tips and Tricks

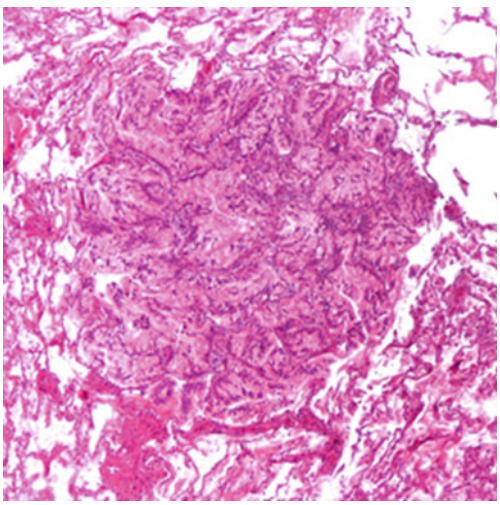
- In case of a diffuse nodular pattern, it is useful to identify the fissure and the pleural surface to define the distribution of the nodules (random, perilymphatic, or centrilobular). If only few nodules touch the pleura (indifferent to the pleura), as in this case, their distribution is random. Random nodules are expression of hematogenous spread of disease, supported by the "feeding vessel" site of some of them (►).
- The second step involves the evaluation of the morphological characteristics of the nodules. They are solid and have different size due to *poussées of hematogenous* spread. Some of them have a central lucency (like a Tarallucci or Cheerios) due to possible necrosis or bronchiolar ectasia (O); some of them and also some non-Cheerio nodules have halo sign that can be an expression of perinodular bleeding, neoplastic infiltration, or inflammation.
- The CT scans after intravenous contrast material administration show normally enhancing pulmonary vessels within lung parenchyma consolidation (angiogram sign) (➡). The vessels appear normal in the right lower lobe and are thinned and stretched in the left lower lobe (compare their caliber!). This latter feature suggests the presence of material that occupies the alveoli with mass effect. The consolidations are low-attenuating in comparison with the chest wall musculature. The low density cannot be secondary to ischemia since the vessels are patent, but it is due to the presence of hypodense material which occupies the alveoli (necrosis, mucin, and fat) (please also refer to the Angiogram sign in this chapter).

Management and Diagnosis

A total-body CT, performed to define the general clinical condition, demonstrates a partially cystic solid mass in the pancreatic tail (☟) with a adrenal metastasis (►). The lung biopsy showed (see Figure below, right), a small nodule of neoplastic glands with prominent mucinous differentiation TTF1 negative. The fine needle aspiration (FNA) of lateral cervical lymph detects metastasis from pancreatic mucinous adenocarcinoma.

Final diagnosis: metastatic pancreatic mucinous adenocarcinoma





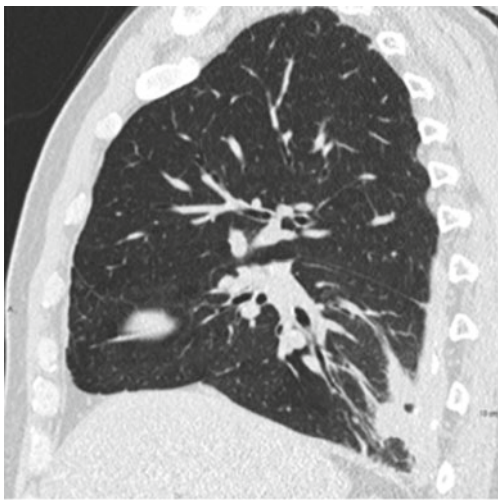
Pearls

- *Cheerio sign* is defined by a nodule with a central lucency seen on CT, similar to the ring-shaped "Cheerios breakfast cereal" and to Italian "Tarallucci". The sign was first described in 1993 by Sandra Reed in low-grade adenocarcinoma of the lung. Many subsequent reports have shown that other diseases may be responsible for the "Cheerio sign" such as the Langerhans cell histiocytosis (LCH), metastatic gastrointestinal adenocarcinoma, mycobacterial/fungal infections, and necrobiotic rheumatoid nodules.
- *Pathogenesis.* The Cheerio appearance is determined by the proliferation of either neoplastic cells or nonmalignant cells around a patent airway. Any cell proliferation surrounding other types of central radiolucencies, such as pseudocavitation, cavitation, alveoli, or multiple thin-walled cysts, can also produce appearances similar to Cheerios.

Chou SH (2013) Cheerio sign. J Thorac Imaging 28(1):W4

COMET TAIL SIGN

Crab nippers sign, parachute sign

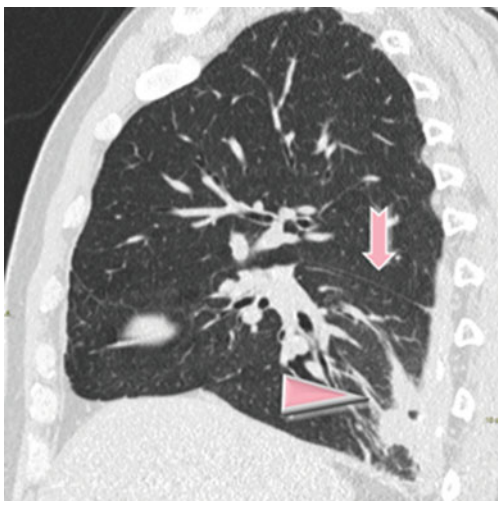


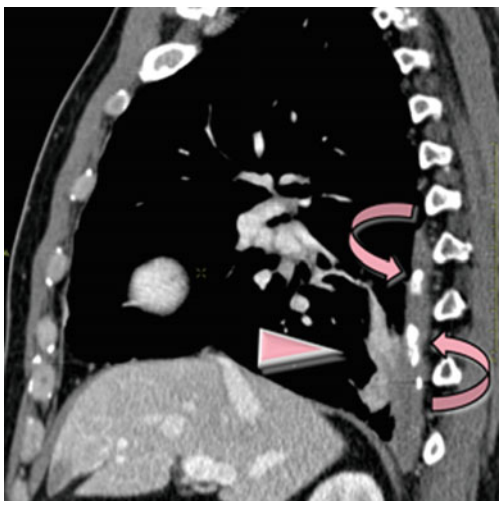
Clinical History

Male patient in his 70s, asymptomatic, with past exposure to asbestos. Chest X-ray showed multiple bilateral pleural plaques and a right basal nodule. The patient underwent a chest CT with contrast medium.

CT

MPR sagittal images show in the right lower lobe a subpleural oval parenchymal lobulated opacity connected to the ipsilateral hilum by curvilinear bands (►). It is also adherent to a pleural plaque with some linear calcifications, the latter well visible in the image with mediastinal window (⇘).





Causes of Comet Tail Sign

Common Asbestosis
Rare Congestive heart failure, pulmonary infarct, Dressler syndrome, parapneumonic effusion, tuberculous effusion, nonspecific pleurisy, uremic pleurisy, trauma, malignancies, and sarcoidosis

Tips and Tricks

- The peripheral parenchymal lesion has oval lobulated morphology and is strictly adhering to a pleural plaque, which shows in its context some minute hyperdense calcifications. The contrast enhancement of the nodule is homogenous.

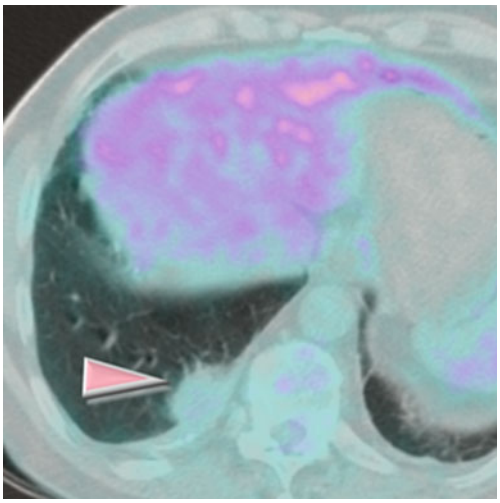
- In the sagittal reconstruction, the pulmonary vessels and bronchial branches afferent to the lesion appear as curved strands extending from the lesion to the hilum. They appear like the tail of a comet, while the nucleus is represented by the lesion, hence the term comet tail sign.
- Note the presence of volume loss of the involved lobe (that is revealed by the downward displacement of the fissure ➡).
- The past history of exposure to asbestos together with CT pictures suggests the diagnosis of asbestosis with rounded atelectasis.

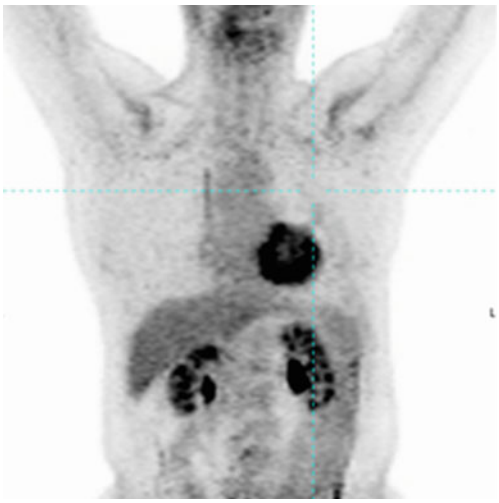
Management and Diagnosis

In the light of the CT findings and to avoid the use of invasive procedures, a PET/CT scan has been performed, which showed no areas of tracer uptake, nor at the level of the pulmonary lesion (►) or in the pleural lesions or mediastinal lymph nodes.

The patient was sent to radiological follow-up, which showed a stationary picture, even 5 years later.

Final diagnosis: rounded atelectasis in asbestos-related disease





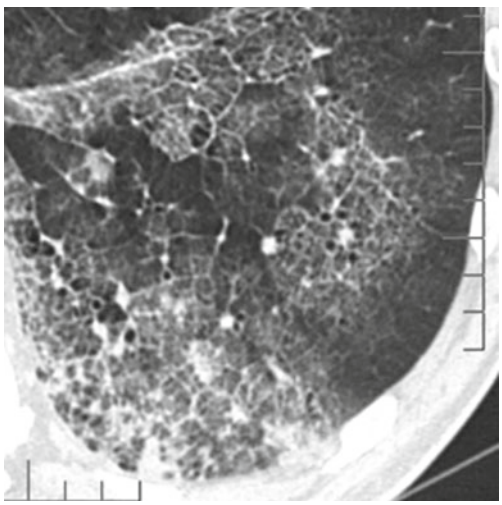
Pearls

- *Comet tail sign* is a finding that can be seen on CT scans of the chest. It consists of a curvilinear opacity that extends from a subpleural "mass" toward the ipsilateral hilum. The comet tail sign is produced by the distortion of vessels and bronchi leading to an adjacent area of round atelectasis, which is the mass. The bronchovascular bundles resemble a comet tail. It has also been defined in several ways in literature: parachute sign and crab nippers sign. This sign has a high specificity (90 %) for rounded atelectasis, which is more frequent in men. Also, rounded atelectasis has been variously defined: Blesovsky syndrome, "folded" lung, atelectatic pseudotumor, and shrinking pleuritis with atelectasis.
- At *PET/CT*, rounded atelectasis is not avid, since it is metabolically non-active. PET/CT may be useful to confirm the diagnosis, without resorting to invasive biopsy investigations. However, some malignancies, like pulmonary adenocarcinoma in situ (former BAC), carcinoid, and metastatic renal cell carcinoma, may show no uptake. Furthermore, there are reports of mild positivity at PET, possibly due to associated inflammation.
- *Curiosity*. The comet tail of rounded atelectasis is not the only comet tail in radiology. There is the comet tail sign in sonography. It is a reverberation artifact generated by calcific, crystalline, or other highly reflective interfaces.

📖 Sobocińska M (2014) Rounded atelectasis of the lung: a pictorial review. Pol J Radiol 79:203

CRAZY PAVING

Palladian sign

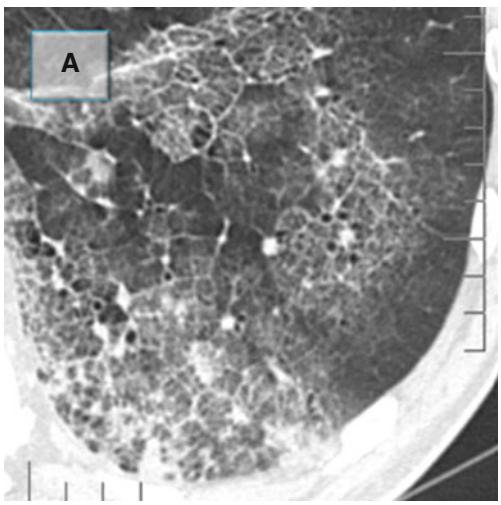


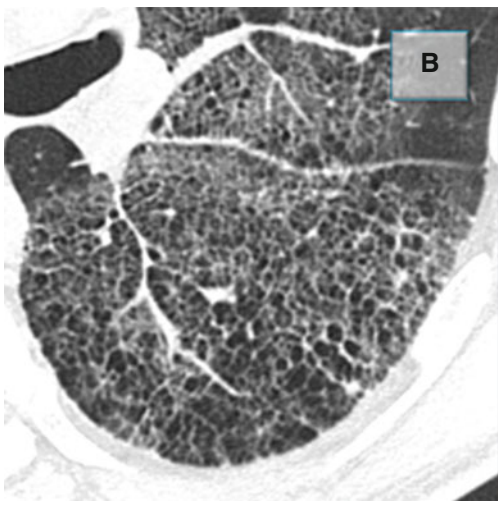
Clinical History

Man in his 40s, smoker (20 pack/year), no environmental or occupational exposures. Chronic clinical history (exertional dyspnea for several months with productive cough). The chest radiograph showed bilateral parenchymal consolidations. The chest X-ray picture was unchanged after medical treatment ("non-resolving pneumonia"). HRCT was then performed.

HRCT

In the left lower lobe, extended areas of ground-glass opacity with superimposed interlobular septal thickening and intralobular lines (crazy paving) are visible (Figure A). Cranially in the same lobe, diffuse ground-glass opacities coexisting with multiple small cysts are present (Figure B).





Causes of Crazy Paving

Acute
Pulmonary edema, infection, diffuse alveolar hemorrhage (DAH), acute interstitial pneumonia (AIP), acute respiratory distress syndrome (ARDS), drug-induced pneumonitis, and DAD superimposed on UIP

Subacute/Chronic
Pulmonary alveolar proteinosis (PAP, the most frequent), lipoid pneumonia (LP), chronic eosinophilic pneumonia (CEP), organizing pneumonia (OP), sarcoidosis (alveolar), tuberculosis, primitive pulmonary neoplasms (adenocarcinoma, MALT lymphoma), nonspecific interstitial pneumonia (NSIP), and radiation pneumonitis

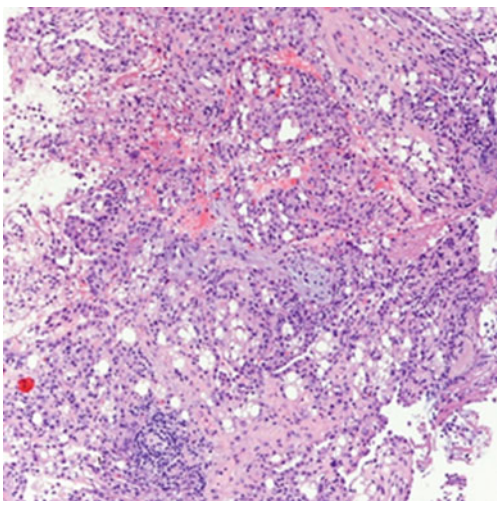
Tips and Tricks

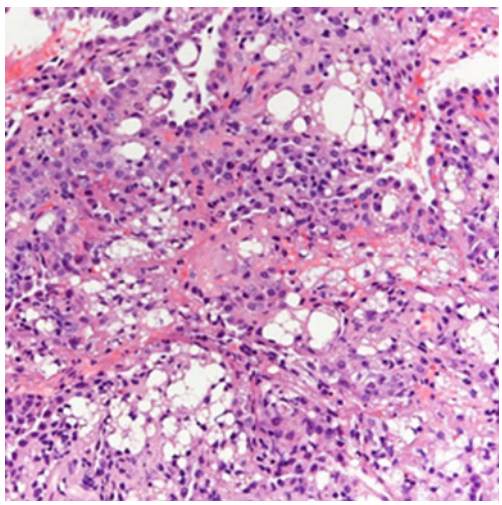
- Crazy paving may be present in many diseases. To narrow the differential diagnosis, first of all, is necessary to evaluate whether the process is *acute* or *subacute/chronic* (please see the table above).
- Our patient presents *chronic* symptoms together with signs of fibrosis consisting of a little volume loss, distortion of the architecture, and also a festooned course of the fissure. Small cysts coexist, which probably have mixed origin (honeycombing and traction bronchiolectasis, Figure B).
- Crazy-paving sign in association with a fibrotic pattern considerably narrows the range of diagnostic possibilities, as well as the subacute course. The HRCT findings may be attributable to an interstitial pneumonia (NSIP-type) or to an exogenous lipoid pneumonia.

Management and Diagnosis

Pulmonary function tests (restrictive) and arterial blood gas analysis (mild hypoxemia) result nonspecifically. Transbronchial biopsy (TBB) was performed, revealing chronic interstitial infiltrate, including lipid-laden macrophages; alveolar septa result thickened, with hyperplasia of type II pneumocytes (please see the images below). Only after obtaining a new medical history, the patient referred the long-term use of nasal lubricating oils, used to relieve the symptoms induced by the chronic use of cocaine.

Final diagnosis: exogenous lipoid pneumonia





Pearls

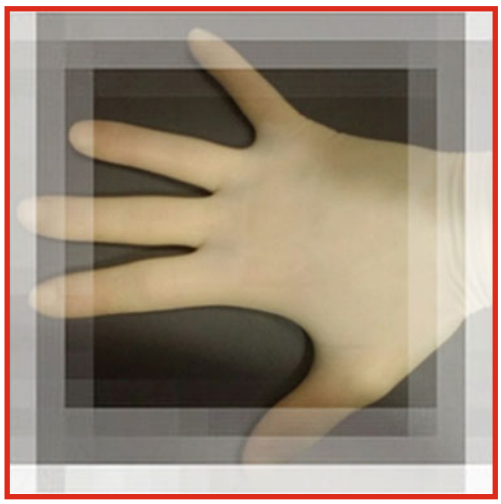
- *Crazy paving* refers to the appearance of ground-glass opacity with superimposed interlobular septal thickening and intralobular reticular thickening, seen on HRCT.
- *Pathogenesis.* Ground-glass opacity (GGO) is created by different materials (inflammatory, proteinaceous, neoplastic, etc.) partially filling the alveoli. Also it may be the expression of the thickening of the alveolar walls and of the interstitium. The "linear" component may be due to the smooth interlobular septal thickening and/or to thickening of the intralobular interstitium and/or also to deposition of material along the peripheral walls of the lobules. Therefore, the pathogenesis of the crazy paving is variable: it may be due to alveolar filling processes (airspace disease), to an interstitial disease, or to a combination of the two.
- *Exogenous lipoid pneumonia* is an inflammatory disease caused by the inhalation or aspiration of fats or oils, especially mineral oils. Patients at risk are those with swallowing dysfunction and those who use lubricating oils for endotracheal and nasogastric tubes or nasal sprays to contrast the dryness of mucous membranes. Also at risk are patients with chronic constipation with prolonged use of laxatives.

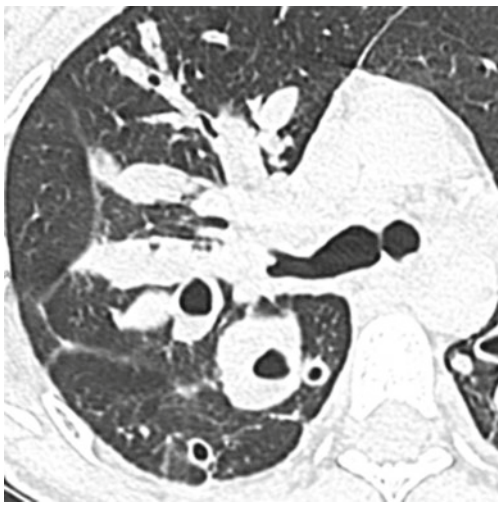
Rossi SE (2003) "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics. 23(6):1509

Laurent F (1999) Exogenous lipoid pneumonia: HRCT, MR, and pathologic findings. Eur Radiol 9:1190

FINGER-IN-GLOVE SIGN

Rabbit ear appearance, mickey mouse appearance, toothpaste-shaped opacities, Y-shaped opacities, V-shaped opacities, and hand-in-glove sign



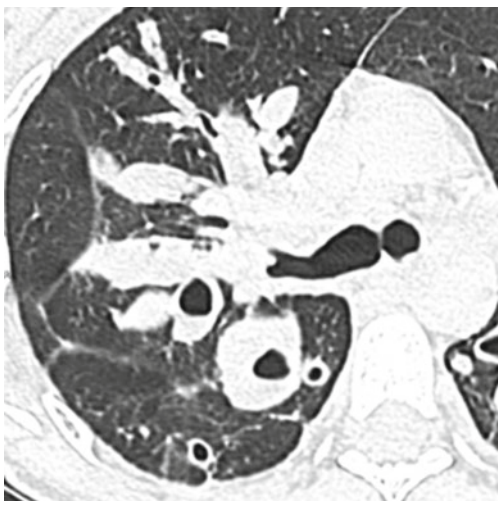


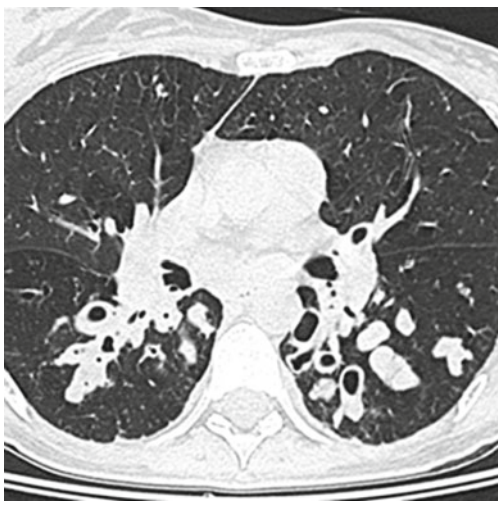
Clinical History

Woman in her 30s with recurrent allergic bronchial asthma exacerbations, bilateral bronchiectases diagnosed when she was 22 year-old, expectoration of dark mucous plugs and hemoptysis.

HRCT

Bilateral extensive central bronchiectases filled with mucus and fluid.





Causes of Finger-in-Glove Sign

Nonobstructive Allergic bronchopulmonary aspergillosis (ABPA) Cystic fibrosis (CF)
Obstructive Broncholithiasis Congenital segmental bronchial atresia Foreign body Neoplasms, benign: hamartoma and lipoma Neoplasms, malignant: carcinoma and carcinoid TB

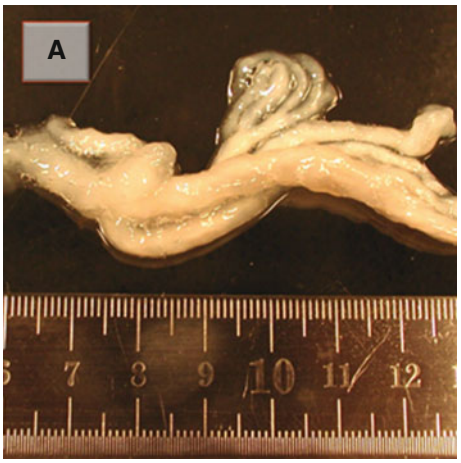
Tips and Tricks

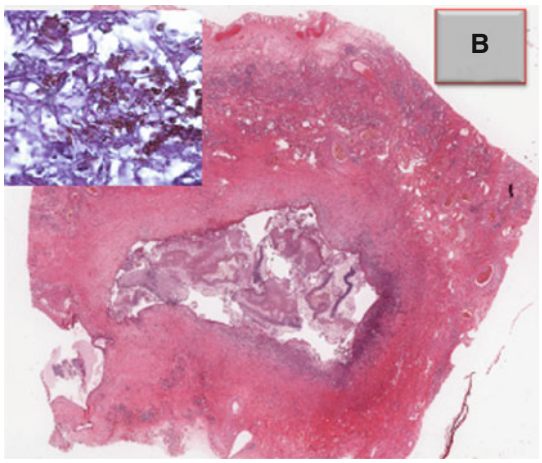
- The bilateral and extensive distribution of the finger-in-glove sign is suggestive for nonobstructive nature. Both in allergic bronchopulmonary aspergillosis (ABPA) and in cystic fibrosis (CF), bronchiectases involve central airways with upper-mid-lung predominance.
- The presence of bilateral and extensive finger-in-glove sign in a patient with history of asthma is suggestive of ABPA.
- Caveat! At the periphery of the lung, bronchiectases with mucoid impaction may assume a nodular-like appearance.

Management

The patient underwent fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) which showed mucoid impaction (Figures A) and saprophytic proliferation of *Aspergillus* organisms (Figure B, inset).

Final diagnosis: allergic bronchopulmonary aspergillosis (ABPA)





Pearls

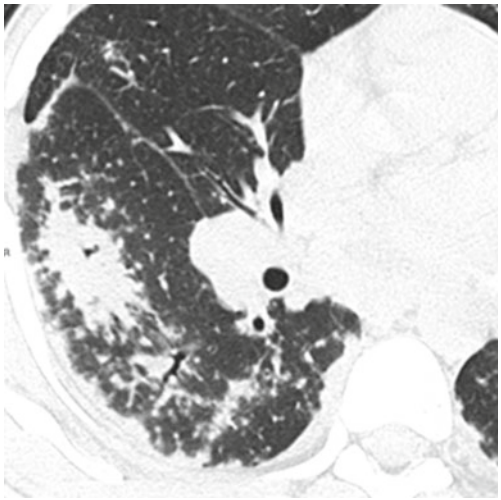
- *Finger-in-glove sign* can be seen on either chest radiograph or chest CT and refers to branching tubular or fingerlike opacities which often originate from the hila and are directed peripherally.
- *Pathogenesis*. The fingerlike opacities extending out from the hila represent dilated bronchi filled with mucus (mucoid impaction) (please see Figure B).
- *Pulmonary aspergillosis* can be subdivided into five categories: 1. aspergilloma, 2. hypersensitivity reaction (ABPA), 3. semi-invasive (chronic necrotizing) aspergillosis, 4. airway-invasive aspergillosis, and 5. angioinvasive aspergillosis.
- *ABPA*, first described in 1952 by Hinson et al., is most often seen in patients with asthma. The mucoid impaction is caused by saprophytic proliferation of *Aspergillus* organisms within the dilated and thickened bronchi (Figure B).
- The HRCT scan may be useful in the diagnosis of ABPA in asthmatic patients because the combination of centrilobular nodules often seen as branching opacities (tree-in-bud pattern), central bronchiectases in three or more lobes, and mucoid impaction is highly suggestive of ABPA. In approximately 25 % of patients with mucoid impactions, HRCT scan with mediastinal window may show high-attenuation mucus secondary to the deposition of calcium salts.
- CT may be helpful, moreover, for differentiating mucoid impactions from other causes of branching opacities (e.g., arteriovenous malformations) as well as for indicating a particular disease process or processes.

Nguyen ET (2003) The gloved finger sign. Radiology 227:453

Martinez S (2008) Mucoid impactions: finger-in-glove sign and other CT and radiographic features. Radiographics 28(5):1369

GALAXY SIGN

Sarcoid galaxy sign

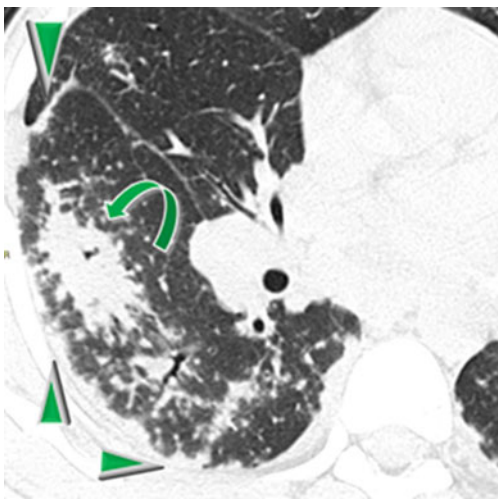


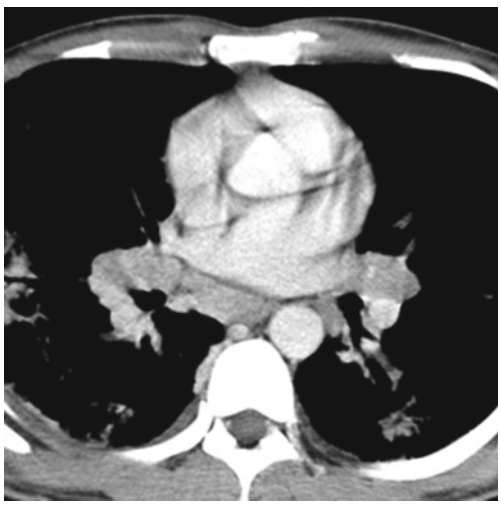
Clinical History

Man in his 30s underwent chest X-ray for low-grade fever which showed a nodule in the right lung. The patient received a broad-spectrum antibiotic therapy, but the lesion appeared unchanged at control X-ray performed 1 month later. HRCT and contrast-enhanced CT were then performed.

CT

HRCT shows a macronodule in the right lower lobe with peripheral nodular margination consistent with the galaxy sign (↬). Numerous confluent nodules along the costal pleura and the fissure also coexist (►). Contrast-enhanced CT shows lymphadenopathy at hilar and subcarinal level.





Causes of Galaxy Sign

- Sarcoidosis
- Tuberculosis (TB)

Tips and Tricks

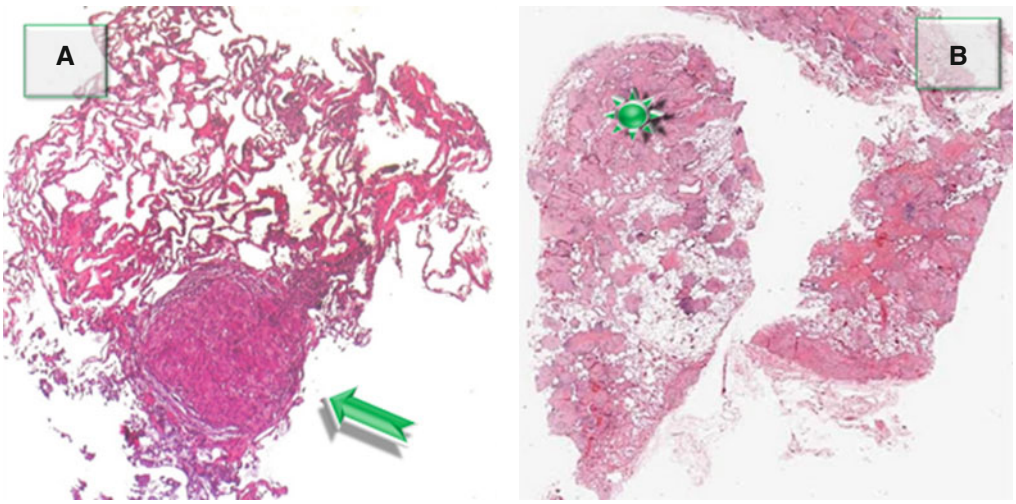
- The solid macronodule has irregularly micronodular margins and satellite micronodules. These features are defined as galaxy sign, described in sarcoidosis and active tuberculosis. For the differential diagnosis, it is mandatory to find out the associated lesions. Please carefully look at the periphery of the lung and note the presence of numerous nodules along the costal pleura and the fissure (►) ("avid of pleura"). This perilymphatic nodules are typically present in sarcoidosis and not in TB.
- Please note that coalescent costal small nodules mimic the appearance of a pleural plaque (►). This feature is defined "pseudoplaques" and is associated with sarcoidosis, silicosis, and coal-worker's pneumoconiosis (CWP).

- Contrast-enhanced CT with mediastinal window shows slightly enlarged lymph nodes in the hilar and subcarinal stations.
- The presence of the galaxy sign with micronodules "avid of pleura", pseudoplaques, and coexistence of bilateral nodal enlargement suggests the diagnosis of sarcoidosis.

Management and Diagnosis

The patient underwent transbronchial biopsy (TBB): bronchiolar wall with a non-necrotizing granuloma with well-defined margins (Figure A ➡); minimal inflammation coexists. Microorganisms were not found.

Final diagnosis: sarcoidosis



Pearls

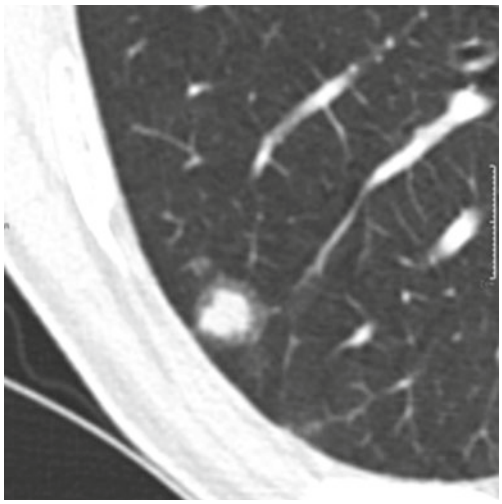
- *Galaxy sign* consists of confluent nodules with multiple small peripheral nodules emanating from the margins of the central nodule (see Figure B ✸). It was initially described as the "sarcoid galaxy", by Nakatsu et al. in 2002. In 2005, Heo et al. described the presence of the same sign in a series of patients with active tuberculosis, and they named it "clusters of small nodules". Please also refer to Galaxy sign in the Nodular Pattern.
- *Pathogenesis*. The galaxy sign results from the coalescence of granulomas, creating the appearance of a nodule. Granulomas become less concentrated at the periphery of the lesion, justifying the irregularity and micronodularity of the margins and the satellite micronodules.
- *Sarcoidosis*. Bilateral hilar lymph node enlargement is the most common finding, followed by interstitial lung disease. At HRCT, the most typical findings of pulmonary involvement are micronodules with a perilymphatic distribution and bilateral hilar lymph nodes. Multifocality of the galaxy sign supports the diagnosis of sarcoidosis.
- *TB* can also present with a galaxy sign in the upper lobes and the superior segments of the lower lobes. A single isolated focus of the galaxy sign supports the diagnosis of TB. Associated findings can be very helpful as well: necrotic nodules or consolidation and tree-in-bud opacities.
- *Mimicker: neoplasm*. The irregular margins should not be mistaken for the spiculated contour of lung carcinoma. The presence of symmetric mediastinal lymphadenopathies suggests sarcoidosis.
- *Mimicker: silicosis and coall workers pneumoconiosis (CWP)*. The fibrotic stage of these pneumoconioses may resemble the galaxy sign. Signs of fibrosis such as architectural distortion, bronchiectases, and paracicatricial emphysematous destruction are crucial for the differential diagnosis.

Nakatsu M (2002) Large coalescent parenchymal nodules in pulmonary sarcoidosis: "sarcoid galaxy" sign. AJR Am J Roentgenol 178:1389

Criado E (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiographics 30(6):1567

Aikins A (2012) Galaxy sign. J Thorac Imaging 27(6):W164

HALO SIGN

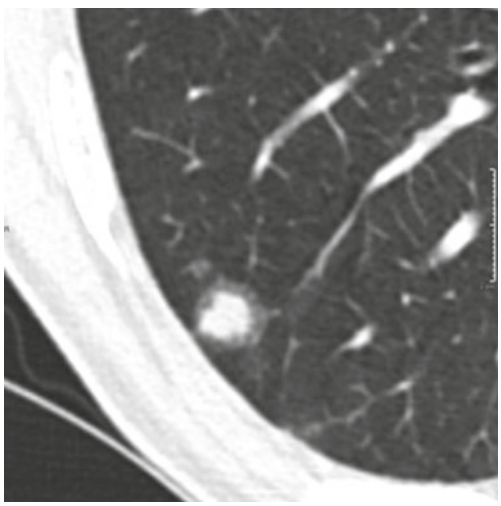


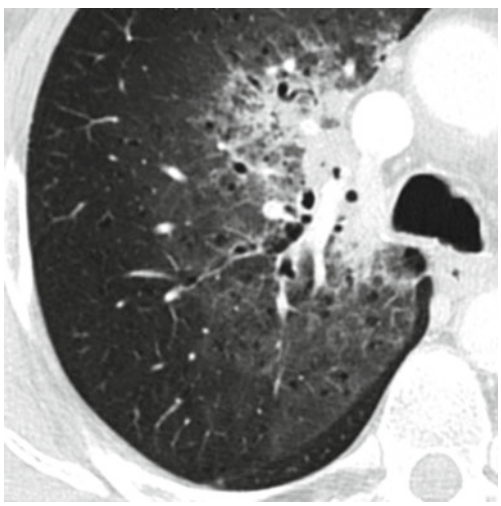
Clinical History

An immunocompetent man in his 70s underwent chest X-ray for weight loss and low-grade fever. Chest X-ray showed a small nodule in the right lung.

HRCT

CT showed a nodule with halo sign, together with a concomitant parahilar soft density tissue with extended halo of ground-glass opacity. A total-body contrast-enhanced CT after 1 month of medical therapy showed a thoracic unchanged picture ("non-resolving lesions") but also a pancreatic lesion (please see the contrast enhancement abdominal CT image below ○).





Causes of Halo Sign

Infection
Fungi, viruses, bacteria, mycobacteria, and parasites

Noninfectious diseases
Granulomatosis with Polyangiitis (GPA), formerly defined Wegener Granulomatosis (WG), organizing pneumonia (OP), eosinophilic diseases, amyloidosis, amiodarone-induced toxicity, and endometriosis

Neoplasms
Adenocarcinoma; lymphoproliferative diseases; hemorrhagic metastasis of angiosarcoma, choriocarcinoma, melanoma, osteosarcoma, and renal cell carcinoma; nonhemorrhagic metastases of adenocarcinoma of the digestive tract, pancreas, and lung; Kaposi's sarcoma; and primary angiosarcoma

Tips and Tricks

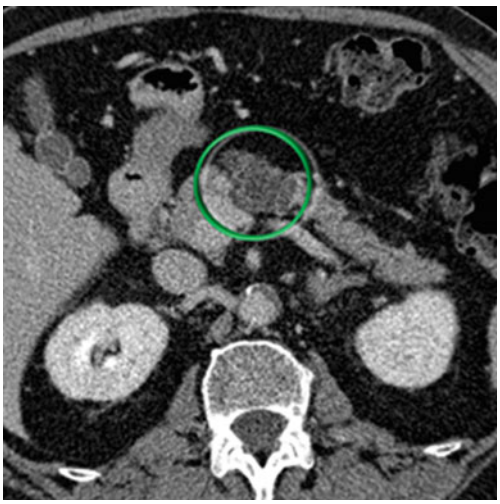
- Although nonspecific, the halo sign is important because the clinical setting and associated radiological features may give a clue to the differential diagnosis.
- In an immunocompromised patient, the halo sign suggests infection, Kaposi's sarcoma, or a lymphoproliferative disorder. If the patient is neutropenic, it strongly suggests angioinvasive aspergillosis.
- In immunocompetent patients, primary lung adenocarcinoma is the most frequent cause of halo sign. On the contrary, metastatic adenocarcinoma from other size rarely presents with halo sign. In both neoplastic conditions, the halo reflects histopathologically a lepidic growth pattern.
- In our immunocompetent patient, the neoplastic nature of the lung lesions is suggested by a concomitant, likely malignant, focal pancreatic lesion (please see the abdominal CT below).

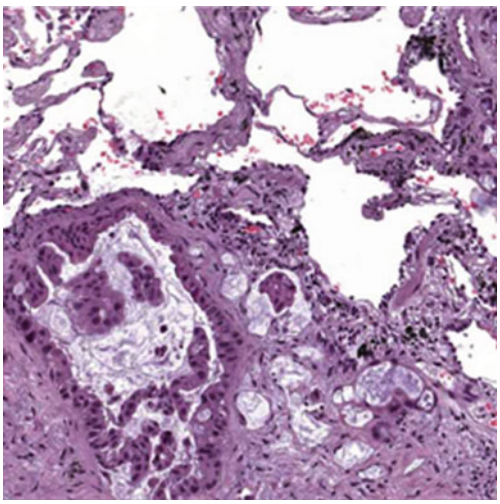
Management and Diagnosis

Abdominal contrast-enhanced CT showed a focal hypodense pancreatic lesion suspect for cystic neoplasm (O). Pancreasectomy showed a mucinous adenocarcinoma.

Transbronchial biopsy (TBB): mucinous adenocarcinoma, showing positivity with ck7 and ck20 and negativity with TTF1, consisting in metastasis from pancreatic adenocarcinoma.

Final diagnosis: pulmonary metastatic pancreatic mucinous cystadenocarcinoma





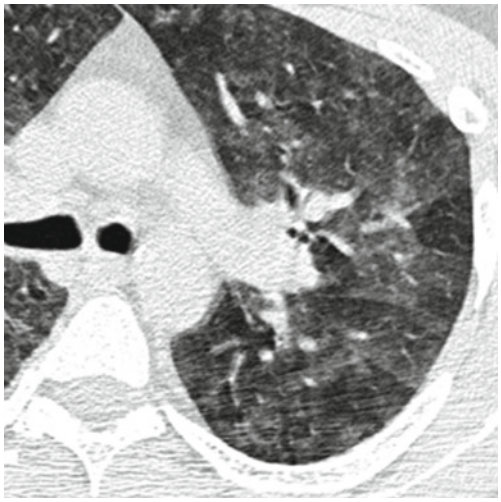
Pearls

- *Halo sign* is defined as a ground-glass opacity which circumferentially surrounds a pulmonary nodule or mass. The sign was originally described by Kuhlman in association with invasive pulmonary aspergillosis, but, actually, many infective, inflammatory, and neoplastic diseases may present with this pattern (see the table).
- *Pathogenesis.* The halo sign is more frequently associated with hemorrhagic nodules, although it may be the expression of neoplastic or inflammatory infiltration. In the so-called hemorrhagic nodules, the halo is the expression of perinodular hemorrhage, which is produced by various mechanisms: infarction, broncho-arterial fistula, spillage from neovascularization, or vasculitis.
- *Metastases from adenocarcinoma.* It is known from histopathologic studies that metastases from adenocarcinoma may spread into the lung along intact alveolar walls (lepidic growth), in a fashion similar to primary adenocarcinoma (former BAC). In another pattern of growth, tumor cells fill the alveolar spaces in a manner analogous to that of exudative pneumonia (airspace pattern). Four CT features were used to classify lesions as airspace metastases: (a) airspace nodules, (b) parenchymal consolidation containing air bronchogram and/or showing angiogram sign, (c) focal or extensive ground-glass opacities, and (d) nodule(s) with a "halo" sign.

Parrón M (2008) The halo sign in computed tomography images: differential diagnosis and correlation with pathology findings. Arch Bronconeumol 44(7):386

HEAD-CHEESE SIGN

Hog's head-cheese sign, mixed (infiltrative and obstructive) disease

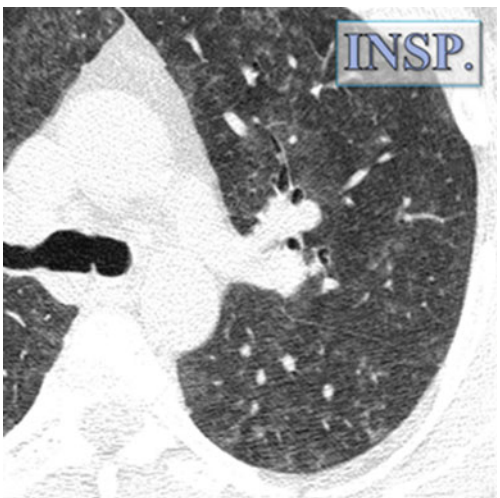


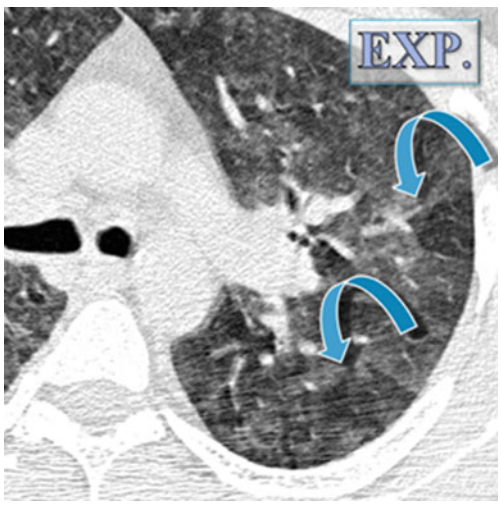
Clinical History

Male patient in his 40s. Minimal exertional dyspnea from a few months with occasional flaring up. Thoracic chest X-ray negative.

HRCT

The selected CT images through the mid-lung zones reveal a patchy pattern of a mixed density appearing as juxtaposition of regions of low, normal, and high attenuation (ground-glass opacity). It is defined "head-cheese sign". Low-density lobular areas due to air trapping are more visible on expiratory CT (↬).





Causes of Head-Cheese Sign

Common Hypersensitivity pneumonia (HP)
Rare Atypical infection with bronchiolitis (e.g., *Mycoplasma pneumoniae*) Smoking-related interstitial lung disease (RB-ILD, DIP) Sarcoidosis

Tips and Tricks

- In the presence of mixed density, it is mandatory to perform an expiratory chest CT to find out the coexistence of air trapping, which appears as darker areas on expiratory CT. In our patient, note that some dark areas present a polygonal morphology with lobular size suggesting small-airway obstruction as a component of the disease.

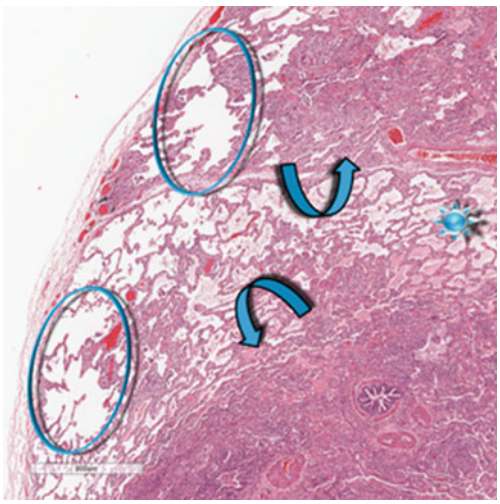
- Look at the images carefully and note that there are also, although difficult to recognize, some diffuse centrilobular subsolid nodules (snowflake nodules). This associated sign suggests primarily a diagnosis of subacute hypersensitivity pneumonitis (HP). CT differential diagnosis with RB-ILD may be challenging due to a similar pattern; however, the latter is a smoking-related disease and, as a consequence, wall thickening and centrilobular emphysema coexist.
- Integrating clinical findings and laboratory tests may indicate the most likely diagnosis in the setting of the head-cheese sign.

Management and Diagnosis

Further anamnesis revealed that the patient was a pigeon fancier. Laboratory findings revealed serum-precipitating antibodies against pigeons.

A second HRTC after removal of the birds and steroid therapy was performed, which showed a clear clinical and radiologic improvement.

Final diagnosis: hypersensitivity pneumonitis (HP)



Pearls

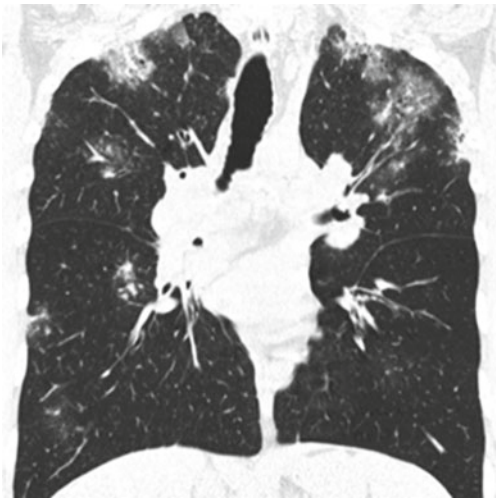
- *Head-cheese sign* is characterized by the juxtaposition of lobular regions of low, normal, and high attenuation. Head cheese, believe it or not, is not a cheese and is often not made of head. It is actually a type of terrine, with bits of meat scavenged from various parts of various animals (including the head) usually from calves or pigs. It has a heterogeneous mosaic pattern, ranging from light to dark.
- *Pathogenesis.* The head-cheese sign is indicative of a mixed infiltrative and obstructive process. The ground-glass opacity and consolidation component represent the infiltrative portion of the underlying disease (figure above ✸☟). Low attenuation lobules reflect obstructive small-airway disease with resultant air trapping and vasoconstriction from localized hypoxia (O). Please also refer to head-cheese sign in the Alveolar Pattern.
- *Hypersensitivity pneumonitis (HP)* is the prototype disease showing the head-cheese sign. It is classified into acute, subacute, and chronic; however, there are actually many overlaps between these phases. In particular, HRCT does not allow to discern an acute from a subacute form. Findings are centrilobular GG nodules, patchy or diffuse GGO, mosaic pattern, and the head-cheese sign. Rarely, acute HP may present as ARDS with DAD. From a histopathological point of view, HPs are heterogeneous and can be characterized by various alterations such as cellular bronchiolitis, organizing pneumonia, or nonspecific interstitial pneumonia with ill-defined granulomas.
- Chung et al. showed that well-defined bronchovascular nodules and nodules along the pleural surface helped distinguish sarcoidosis from HP.

Chong BJ (2014) Headcheese sign. J Thorac Imaging 29(1):W13

Chung MH (2001) Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. J Thorac Imaging 16(2):69

REVERSED BAT WING SIGN

Reversed butterfly sign, reversed pulmonary edema, and photographic negative of pulmonary edema

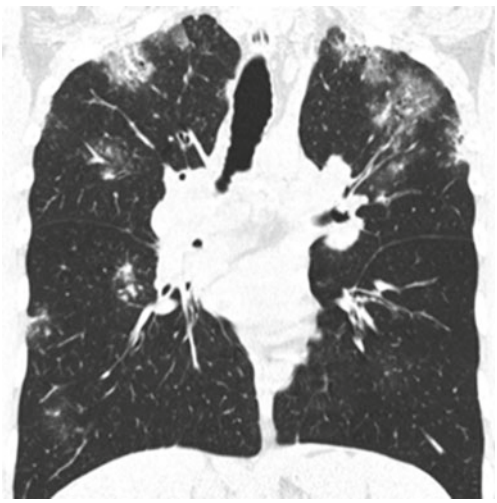


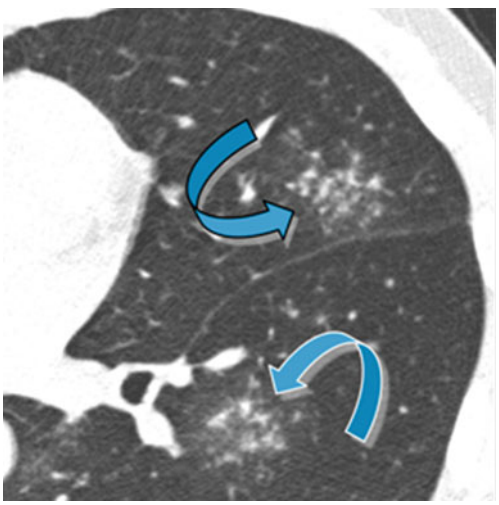
Clinical History

Male in his 30s with mild fever and cough. Chest X-ray shows consolidations in the upper lobes and bilateral, symmetrical hilar enlargement.

HRCT

Coronal HRCT image confirms the presence of bilateral airspace disease with predilection for the peripheral upper lobes of the lungs. Close-up of axial image shows two rounded areas of clustered nodules (↘).





Causes of Reversed Batwing Sign

Common Chronic eosinophilic pneumonia (CEP) and organizing pneumonia (OP)
Rare Sarcoidosis, alveolar Contusions Infarcts

Tips and Tricks

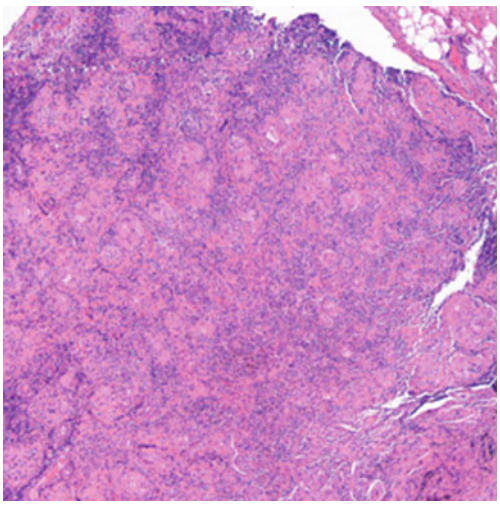
- The disorders presenting with peripheral pulmonary consolidations can be remembered by the easy mnemonic AEIOU (Alveolar sarcoidosis, Eosinophilic pneumonia, Infarcts, OP, contUsions). This acronym was firstly suggested by Jannette Collins (please see the reference in the next page).

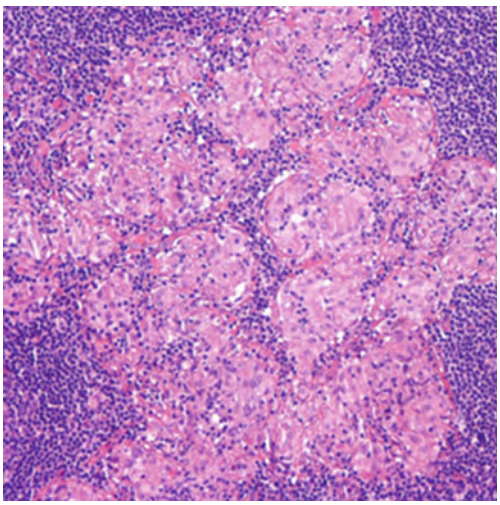
- In our patient the lesions mainly involve the upper lung zones. This location is more frequent in CEP and in "alveolar" sarcoidosis. It is possible in OP but not typical for infarcts or contusions.
- In the close-up axial image, please note the presence of two rounded clusters of multiple tiny nodules (the so-called sarcoid cluster sign ↳); the latter may be associated both with sarcoidosis and tuberculosis.
- A careful visualization of coronal CT image reveals a convex aspect of the hila suggesting a pathological involvement. Enlarged lymph nodes are also visible in the subcarinal region.
- Mediastinal and symmetrical hilar lymphadenopathy together with "sarcoid cluster sign" and peripheral (Reversed bat wing sign) nonexcavated consolidations in the upper lobes provide clues to the diagnosis of sarcoidosis.

Management and Diagnosis

Surgical biopsy of carinal mediastinal lymph nodes shows non-necrotizing microgranulomatous inflammation (please see the images below). Special stain for micobacteria (Ziehl-Neelsen) was negative.

Final diagnosis: sarcoidosis





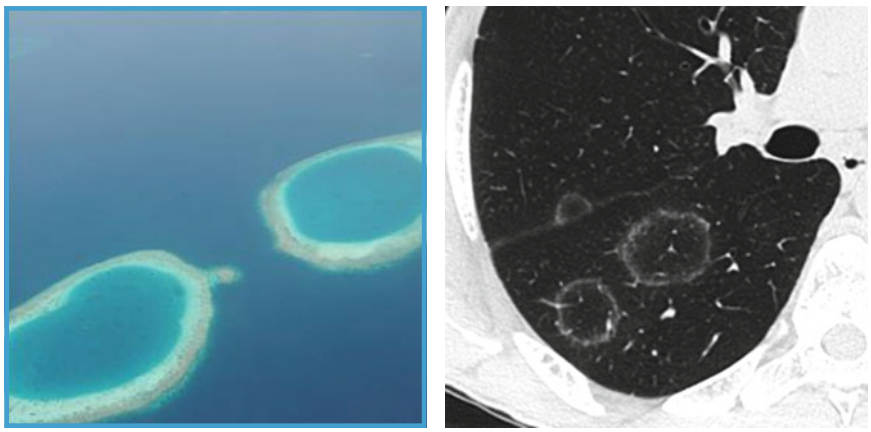
Pearls

- *Reversed bat wing sign* is a radiographic sign characterized by bilateral peripheral opacities sparing the perihilar region.
- *Sarcoid cluster sign* corresponds to rounded or long clusters of multiple small nodules in the pulmonary parenchyma which are close to each other but not confluent. It may be seen in both pulmonary sarcoidosis and pulmonary tuberculosis.
- *Alveolar sarcoidosis*. The so-called "acinar" or "alveolar" form of sarcoidosis is a definition derived from conventional radiology and refers to sarcoidosis mimicking an alveolar pattern. "Alveolar" sarcoidosis is seen in 10–20 % of patients with sarcoidosis. HRCT shows bilateral patchy alveolar consolidations, which may show air bronchograms or ground-glass opacities. It is usually bilateral and symmetric and involves the middle and upper zones of the lungs. Associated CT findings of nodules in a perilymphatic distribution and mediastinal and hilar lymphadenopathy provide clues to the correct diagnosis.
- *CEP and OP*. The classic radiographic and chest CT scan finding is peripheral, nonsegmental, homogeneous alveolar opacities, often with air bronchograms. Areas of ground-glass attenuation are common. In CEP the lesions involve mainly the middle and upper lung zones. On the contrary in OP, the lesions may be prevalent in the lower zones.
- *Infarcts*. Only 15 % or less of thromboemboli cause pulmonary infarction. It is unknown why some emboli cause infarction and others do not, but it is likely due to compromise of both the pulmonary and bronchial arterial circulation. Pulmonary infarction results in airspace opacities that may be multifocal and predominantly peripheral in the lower lung zones.
- *Contusions*. Pulmonary contusions result in the leakage of blood and edema fluid into the interstitial and alveolar spaces. On CT, contusions present as areas of consolidation, ground-glass opacification, or both which tend to be peripheral, nonsegmental, and geographic in distribution.

Collins J, Stern E (2015) Chest Radiology: The Essentials. 3rd edition, Wolters Kluwer

REVERSED HALO SIGN

Atoll sign

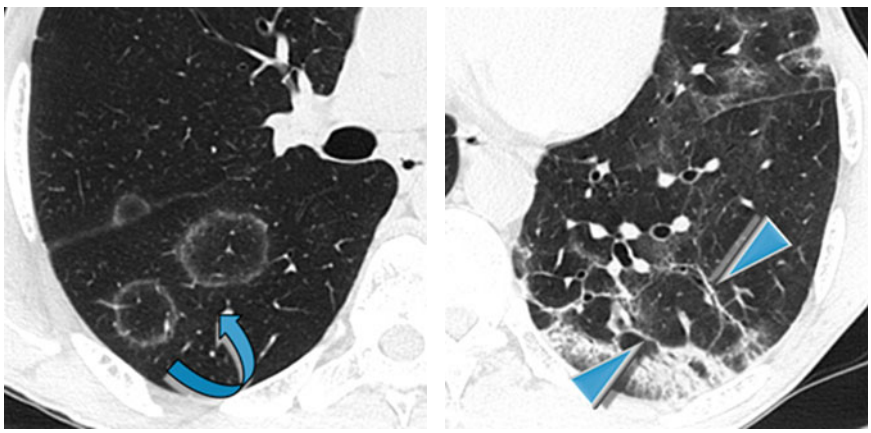


Clinical History

Male in his 50s presents with cough and low-grade fever for about a month. Chest X-ray showed small parenchymal opacities, basal and bilateral. The lesions did not regress after a cycle of broad-spectrum antibiotics ("non-resolving pneumonia").

HRCT

In the right lower lobe, multiple GGOs, rounded, one of them conformed to "semicircle," with a denser peripheral ring (atoll sign) are present (↷). In the left basal lobes, there are peripheral consolidations and thin arcade-like opacities (the so-called perilobular sign) (►).



Causes of Atoll Sign

Infection Fungal pneumonia (pneumocystosis, paracoccidioidomycosis, histoplasmosis, mucormycosis, angio-invasive aspergillosis), bacterial infection (TB, bacterial pneumonia), and virus infection (H1N1)
Noninfectious and Nonneoplastic Cryptogenic organizing pneumonia (COP, the more frequent) and secondary OP, chronic eosinophilic pneumonia (CEP), nonspecific interstitial pneumonia (NSIP), sarcoidosis, granulomatosis with polyangiitis (Wegener), lymphoid interstitial pneumonia (LIP), acute fibrinous organizing pneumonia (AFOP), hypersensitivity pneumonia (HP), exogenous lipoid pneumonia, post-embolic infarction, radiotherapy, and percutaneous RF ablation
Neoplastic Lymphomatoid granulomatosis, lung adenocarcinoma, and metastases

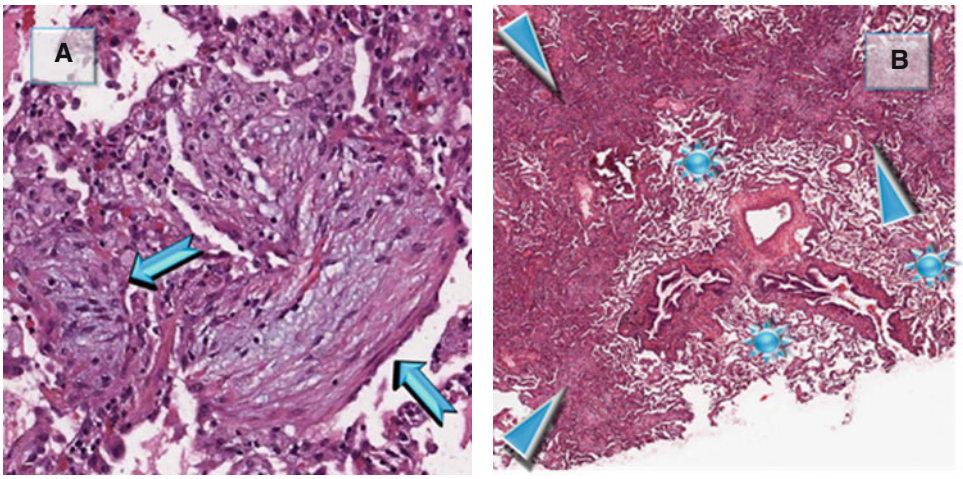
Tips and Tricks

- The reversed halo sign/atoll sign is a nonspecific sign. To narrow the differential diagnosis, the evaluation must include clinical data and other radiological findings: first of all, it is necessary to rule out clinical signs and symptoms of infection. In severely immunocompromised patients, it should be considered expression of opportunistic invasive fungal infection, until proven otherwise. In AIDS patients it may be caused by *Pneumocystis jirovecii* infection.
- In neoplastic patients it may be the expression of secondary lesions, but also of an OP following chemotherapy or radiotherapy.
- In our patient, the concomitant presence of "chronic" peripheral ground-glass opacities and consolidations, mostly of thin arcade-like opacities (⇳), suggests the diagnosis of COP, while other diagnoses result less likely.

Management and Diagnosis

Serological testing for a connective tissue disorder and infection was negative. A drug history was ruled out. Bronchoalveolar lavage (BAL) excluded the possibility of organisms or neoplastic cells. Transbronchial biopsy (TBB) showed plugs of fibroblastic tissue within bronchioles and surrounding alveoli (please see Figure A ➡).

Final diagnosis: cryptogenic organizing pneumonia (COP)



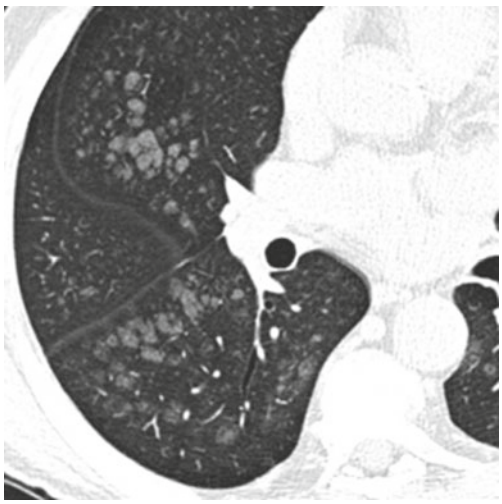
Pearls

- *Reversed halo sign.* According to the glossary of the Fleischer society, reversed halo sign is defined as a focal rounded area of ground-glass opacity surrounded by a more or less complete ring of consolidation. This sign was at first described in 1996 by Voloudaki et al. who reported this finding in two cases of bronchiolitis obliterans with organizing pneumonia (BOOP – now defined OP). The definition of *atoll sign* was at first coined by Zompatori et al. in 1999, in a case report of a patient with BOOP. Still in 1999, Marlow et al. used the term "fairy ring" to describe the atoll sign in a case of sarcoidosis. In organizing pneumonia (OP, Figure B above), the central ground-glass opacity corresponded histopathologically to the area of alveolar septal inflammation and cellular debris (✸) and the ring-shaped or crescentic peripheral airspace consolidation, to the area of organizing pneumonia (►). Reversed halo sign was initially considered highly specific for OP, where it is present in about 20 % of the cases. Later, the presence of this sign has been described in several different diseases (please see table above).

📖 Maturu VN (2014) Reversed halo sign: a systematic review. Respir Care 59(9):1440.

SNOWFLAKE SIGN

Snowflake nodules, fluffy nodules, nodular GGO, ill-defined nodules, and airspace nodules

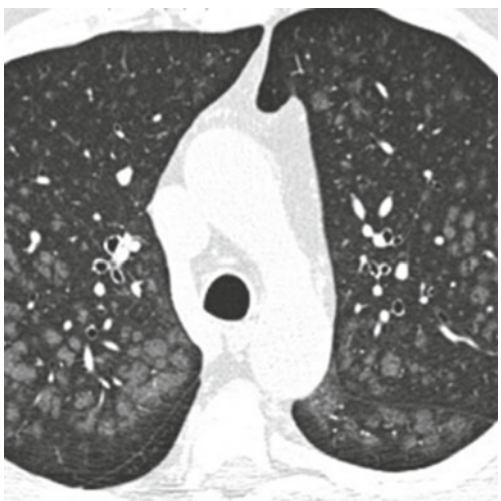


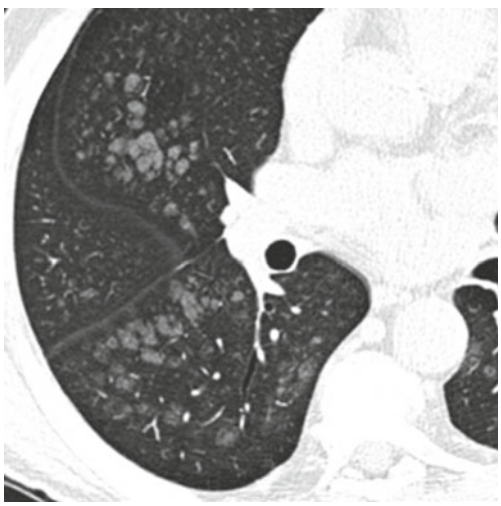
Clinical History

Male in his 50s, never smoker, not allergy sufferer. Kidney transplant at age of 40 years after a 7 year dialysis for postinfectious severe renal failure. Slowly progressive dyspnea and functional limitation exercise. Lung function was normal except for a reduced mild DLCO and mild hypocapnia.

HRCT

CT images show bilateral fluffy snowflake nodules. Some nodules are confluent involving whole lobules. (Images courtesy of Gaetano Rea, Naples, Italy)





Causes of Snowflake Sign

Common
Hypersensitivity pneumonitis (HP), subacute
Respiratory bronchiolitis–interstitial lung disease (RB-ILD)
Rare
Follicular bronchiolitis (FB)
Hemorrhage
Hot tub lung (HTL)
"Metastatic" pulmonary calcification (MPC)
Pulmonary capillary hemangiomatosis (PCH)

Tips and Tricks

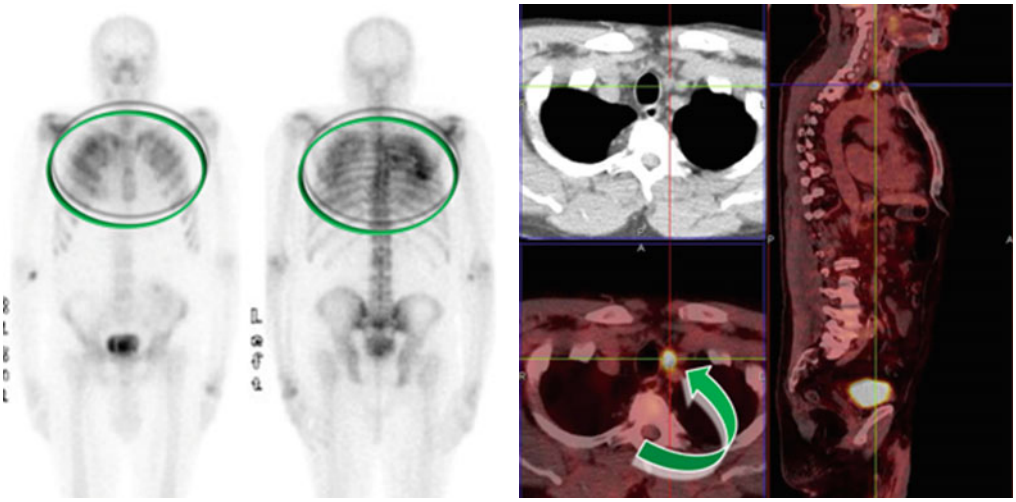
- Note as the nodules stop at a certain distance from the pleural surfaces ("pavid of the pleura"). So a centrilobular distribution can be assumed.
- To reduce the number of differential diagnoses look at the cranio-caudal distribution of the nodules. The prevalent distribution in the upper-medium lobes, as present in our patient, is often present in the RB-ILD, in the "metastatic" pulmonary calcification and in the subacute HP.
- The size of the nodules is another helping parameter. Tiny centrilobular nodules may be visible in RB-ILD. Tiny nodules are randomly distributed in HTL.
- The presence or absence of associated signs may be crucial. Lobular air trapping is often associated with subacute HP. The association with moderate centrilobular emphysema is suggestive of RB-ILD. Calcification in the vessels of the chest wall is suggestive for "metastatic" pulmonary calcification. Main pulmonary arterial enlargement due to pulmonary arterial hypertension turns to pulmonary capillary hemangiomatosis (PCH).
- Last but not least, think about the anamnesis: allergy in HP, heavy smoker (RB-ILD), hemoptysis (hemorrhage), and conditions that directly or indirectly result in hypercalcemia, e.g., chronic renal failure ("metastatic" pulmonary calcification).

Management and Diagnosis

Neck ultrasonography showed a left solid nodule due to possible parathyroid origin. Parathyroid hormone (PTH) blood test: 220 pg/ml (normal values 15–69),

Skeletal scintigraphy showed a widespread increased activity at the third and top of both lung fields (O). The total-body PET/CT shows intense metabolic activity area in correspondence of the left paratracheal region (SUV max 37 ↳). No evidence of further metabolic hyperactivity areas at the level of other body segments was present. At surgery, a poorly differentiated parathyroid carcinoma, infiltrating the outer capsule, was observed.

Final diagnosis: "metastatic" pulmonary calcification due to parathyroid carcinoma



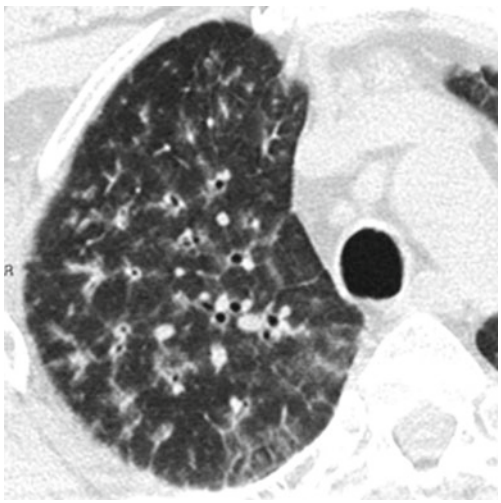
Pearls

- The *snowflakes sign* refers to nodules appearing with subsolid density (nodular ground-glass opacities) like snowflakes.
- *Pathogenesis.* The appearance of low-density CT nodules is due to the partial alveolar filling or minimum interstitial peribronchiolar thickening. Both the pathogenic mechanisms are inferior to CT spatial resolution, and then the final common effect is low-density lesions.
- *Metastatic pulmonary calcification (MPC)* is a metabolic lung condition, rare cause of centrilobular snowflake nodules, sometimes calcified. This entity is secondary to the deposition of calcium in the normal lung parenchyma. The word metastatic is put in brackets because it is a misnomer (nde).
- *Causes of MPC.* It occurs in association with conditions that directly or indirectly result in hypercalcemia, e.g., chronic renal insufficiency, primary or secondary hyperparathyroidism, vitamin D toxicity, intravenous therapy of calcium, multiple myeloma, and massive osteolytic metastasis.

Belém LC (2014) Metastatic pulmonary calcification: state-of-the-art review focused on imaging findings. Respir Med 108(5):668

TREE-IN-BUD SIGN, BRONCHIOLAR

Centrilobular branching opacities, budding tree, V- or Y-shaped branching pattern, and jacks

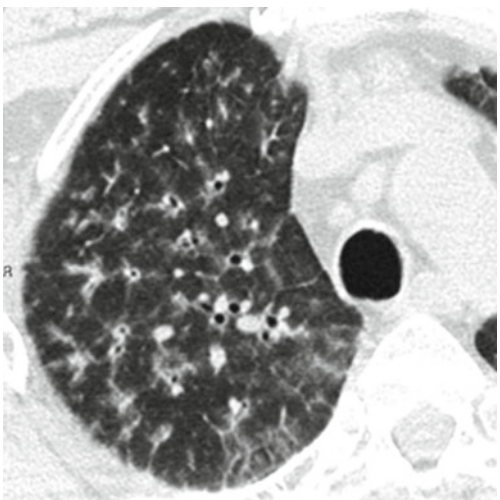


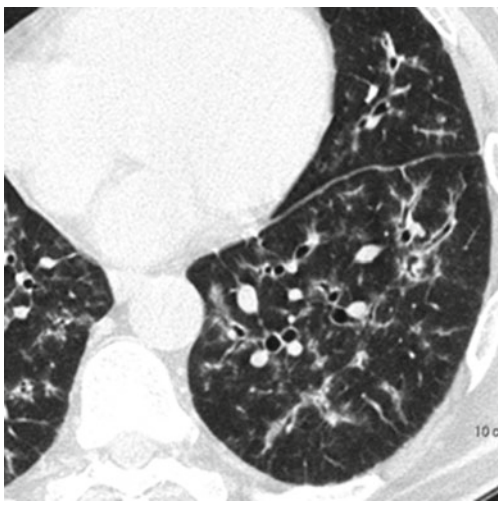
Clinical History

A 65-year-old retired man, nonsmoker. Two-day history of acute shortness of breath without fever.

HRCT

Bilateral widespread tree-in-bud sign with ill-defined margins and uniform distribution in all lobes together with thickening of the bronchial wall.





Causes of Bronchiolar Tree in Bud

Infections Bacterial (*Mycobacterium TB*, *non-TB Mycobacterium* and *Staphylococcus aureus*, *Haemophilus influenzae*) Fungal (*Aspergillus*) Viral (*Respiratory syncytial virus*, *Cytomegalovirus*)
Congenital Cystic fibrosis (CF)
Immunologic Disorders Allergic bronchopulmonary aspergillosis (ABPA)

Connective Tissue Disorders Rheumatoid arthritis (RA) and Sjögren syndrome
Neoplasms Endobronchial spread of adenocarcinoma
Other Causes Aspiration, inhalation (toxic fumes and gases), and diffuse panbronchiolitis

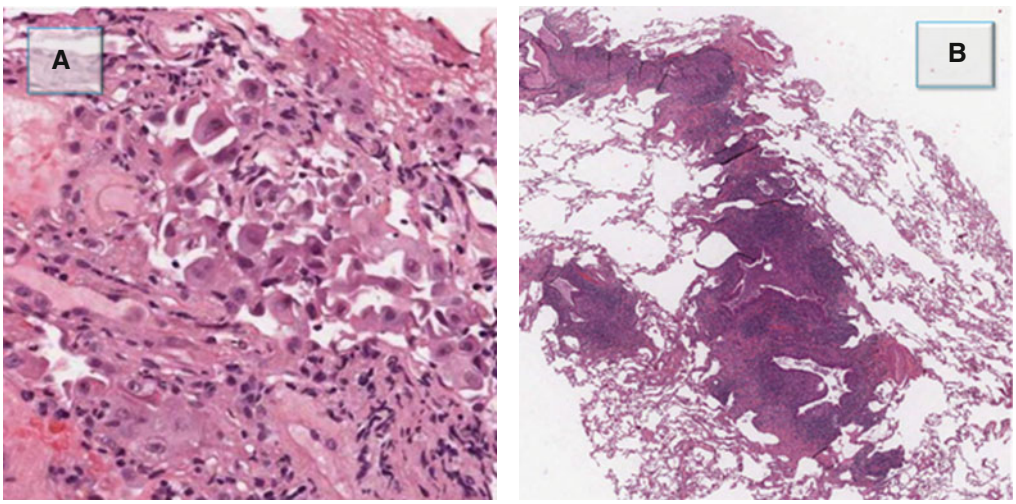
Tips and Tricks

- The identification of the tree-in-bud sign should urge you to determine its location together with clinical history. Gravity-dependent distribution and esophageal abnormality or hiatal hernia with tree-in-bud opacities were associated with aspiration. Upper lung predominance is commonly encountered in patients with cystic fibrosis.
- Please look for further imaging findings (e.g., cavitated consolidation or nodules and necrotic lymphadenopathy support the diagnosis of infection). In our patient the thickening of the bronchial wall is not specific but supports the airway involvement.
- Widespread tree-in-bud sign with ill-defined margins, together with acute shortness of breath, supports the diagnosis of inhalation of toxic fumes and gases or infection.
- Scrutinize patient history, including appropriate exposure history, as this may aid in determining the most likely diagnosis. In our patient the acute and rapid onset of shortness of breath without fever supports the diagnosis of inhalation of toxic fumes and gases. Only after a second anamnesis, the patient admits that he had weeded in the garden some days before the onset of symptoms using a high dose of forbidden herbicide.

Management and Diagnosis

Transbronchial biopsy (TBB) performed after a week shows organizing DAD (please see Figure A).

Final diagnosis: acute inhalation of toxic fumes



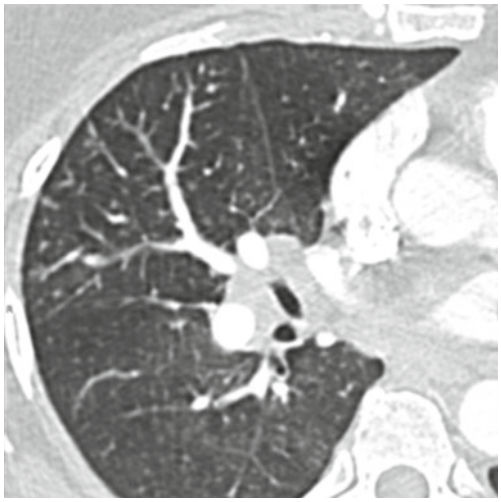
Pearls

- *Tree in bud* (also referred to as branching opacities, budding tree or children's toy jacks, see above, Figure B) is referred to a centrilobular branching opacity whose appearance resembles a budding tree. The branching opacities end with small nodular opacities usually well recognizable at the periphery of the lungs. It is not visible on chest X-ray.

Rossi SE (2005) Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 25:789

TREE IN BUD: VASCULAR

TIB, centrilobular branching opacities, budding tree, V- or Y-shaped branching pattern, and jacks

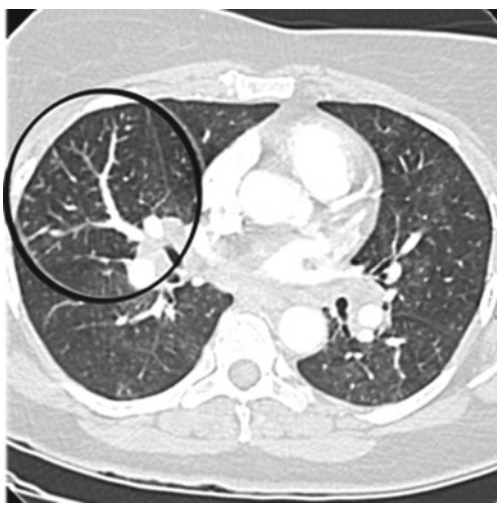


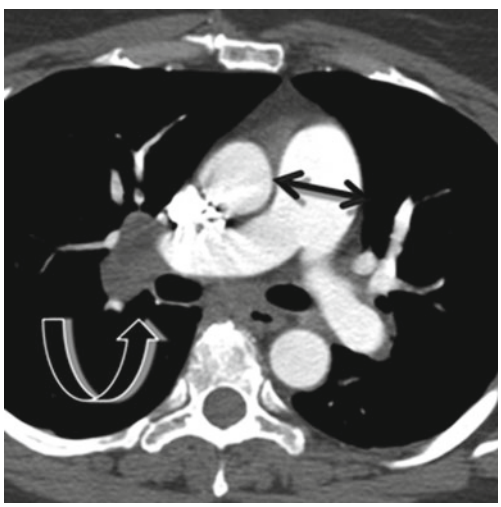
Clinical History

Female in her 50s, nonsmoker, with cough for about 1 month, mild dyspnea, fatigue, and weight loss. For the sudden worsening of dyspnea, associated with hypoxemia and hypercapnia, a CT angiography was performed to rule out a pulmonary thromboembolism.

CT

Image with lung window shows in the right middle lobe an area of clustered peripheral vascular branching opacities: the small vessels are ectatic with small nodules at their ends, similar to gems (O). This finding corresponds to the so-called vascular tree in bud. Contrast-enhanced CT shows no intraluminal arterial filling defects related to pulmonary thromboembolism. However, it reveals mediastinal and hilar enlarged lymph nodes (☟). Ectasia of the common arterial trunk is also visible (⬌).





Causes of Vascular Tree in Bud

Neoplastic Extrapulmonary primary malignancies (breast, liver, renal, stomach, prostate, and ovarian cancers)
Nonneoplastic Cellulose and talc granulomatosis

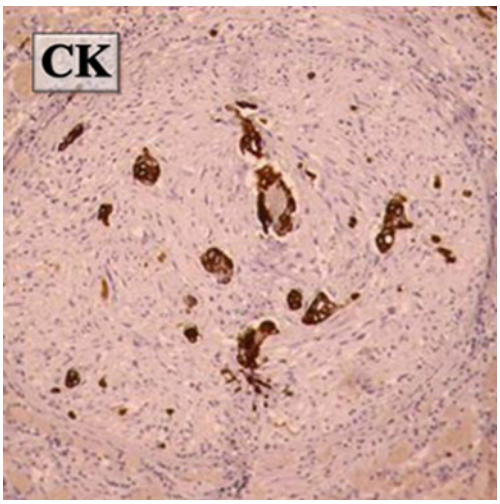
Tips and Tricks

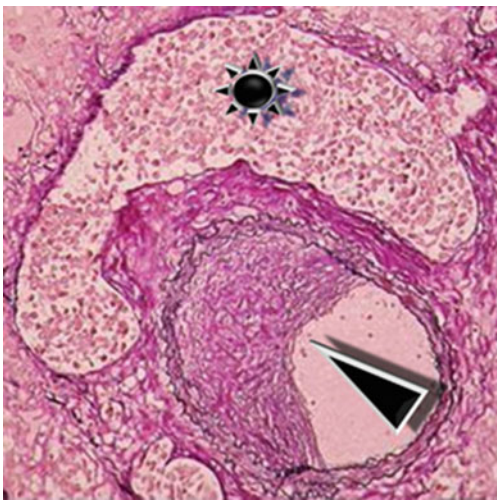
- The common pulmonary artery is considered enlarged when it is larger than the adjacent ascending aorta. This comparison, however, can be misleading in the presence of a concomitant aortic ectasia. This occurrence is not uncommon in the elderly. Quantitatively, the common arterial trunk should be considered as dilated when its size is > 2.9 cm. This value has a sensitivity of 87 % and a specificity of 89 % for the diagnosis of pulmonary hypertension.
- The association of vascular tree-in-bud pattern with lymphadenopathies and signs of pulmonary hypertension should raise the suspicion of neoplastic thrombotic microangiopathy.

Management and Diagnosis

Echocardiogram confirmed pulmonary arterial hypertension. The patient was transferred to the ICU for the worsening of dyspnea and hypoxemia. PET/CT revealed the presence of an ovarian hypermetabolic mass and enlarged abdominal and thoracic lymph nodes. About a month later, the patient died from cardiorespiratory arrest. Postmortem examination revealed thrombosis of a pulmonary arteriole with foci of neoplastic cells resulting positive for cytokeratin (*CK*). Arteriolar eccentric intimal hyperplasia (►) associated with neoplastic lymphangitis was present (✸). These findings confirm the radiological suspicion of neoplastic thrombotic microangiopathy. The ovarian mass turns out to be a carcinoma with positivity for cytokeratin (CK). Images courtesy of Pathology Department of S. Orsola Hospital (Bologna) and Pneumology Unit of Arco (Trento) – Italy.

Final diagnosis: pulmonary tumor thrombotic microangiopathy





Pearls

- *Tree in bud* is referred to a centrilobular branching opacity whose appearance resembles a budding tree. The branching opacities end with small nodular opacities usually well recognizable at the periphery of the lungs. Tree in bud is often due to bronchiolar disease (please see also bronchiolar Tree-in-bud sign in this chapter), rarely due to peripheral pulmonary vascular disease responsible of the so-called vascular tree in bud.
- *Vascular tree in bud* is rare and often due to neoplastic conditions such as adenocarcinoma.
- *Pathogenesis*. The neoplastic vascular TIB is secondary to neoplastic thrombosis with or without microangiopathy.

- *Pulmonary tumor thrombotic microangiopathy* is a distinct and rare variant of neoplastic pulmonary thrombosis, found in 3.3 % of the autopsies of patients with extra-thoracic malignancy, especially adenocarcinomas. It is characterized by neoplastic thrombosis of the centrilobular arterioles and intimal fibrocellular hyperplasia induced by the tumor. These changes increase vascular resistance resulting in severe pulmonary arterial hypertension. Patients present with cough and progressive dyspnea and may develop a fatal acute right heart failure.
- Another kind of vascular TIB is the cellulose and talc granulomatosis, secondary to i.v. injection of drugs prepared for oral administration.

Rossi SE (2005) Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 25:789

Franquet T (2002) Thrombotic microangiopathy of pulmonary tumors: a vascular cause of tree-in-bud pattern on CT. AJR Am J Roentgenol 179:897

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We are all inclined to be quick with the verdict that 'things do not look like that'. We have a curious habit of thinking that nature must always look like the pictures we are accustomed to. We are all inclined to accept conventional forms or colours as the only correct ones. Children sometimes think that stars must be star-shaped, though naturally they are not. The people who insist that in a picture the sky must be blue, and the grass green, are not very different from these children. They get indignant if they see other colours in a picture, but if we try to forget all we have heard about green grass and blue skies, and look at the world as if we had just arrived from another planet on a voyage of discovery and were seeing it for the first time, we may find that things are apt to have the most surprising colours.

Sir Ernst Gombrich – The Story of Art – 16th Edition – London

Davos in Summer, 1925 - Ernst Ludwig Kirchner

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.

The number in bold indicates the detailed explanation of the disease/sign.

G. Dalpiaz, A. Cancellieri (eds.), *Atlas of Diffuse Lung Diseases*,
DOI 10.1007/978-3-319-42752-2

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