Reticular Diseases

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Amyloidosis

Definition

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

Chronic inflammatory disease or plasma cell dyscrasia

CLINICAL FEATURES

History

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

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

Physical findings

Diffuse fine bilateral rales

Pulmonary function tests

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

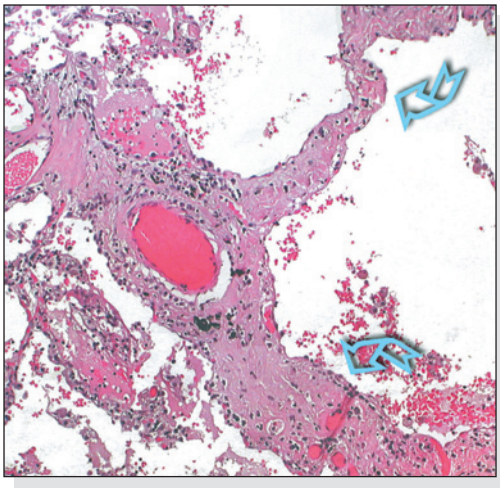
Gillmore JD. Amyloidosis and the respiratory tract. Thorax 1999, 54: 444

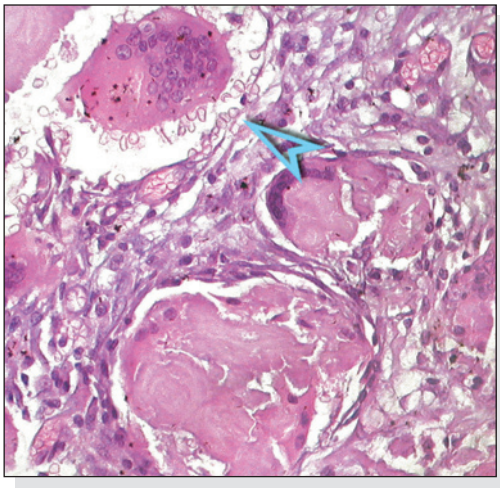
PATHOLOGY

Basic lesions

Diffuse interstitial amyloidosis presents in the form of:

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





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

Distribution

In the interstitium of the alveolar and perivascular septa

Differentials

Histopathologic differential diagnoses:

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

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

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

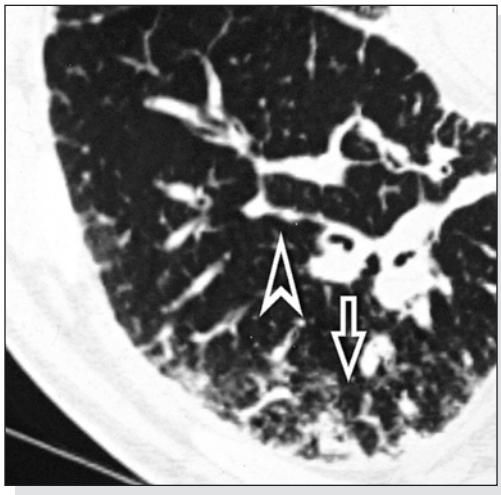
Sumiya M. Diffuse interstitial pulmonary amyloidosis in rheumatoid arthritis. J Rheumatol 1996, 23: 933

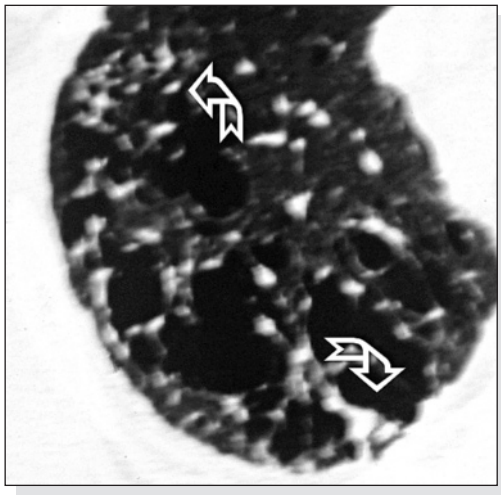
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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





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

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

Distribution

Bilateral, patchy

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

Dorsal subpleural

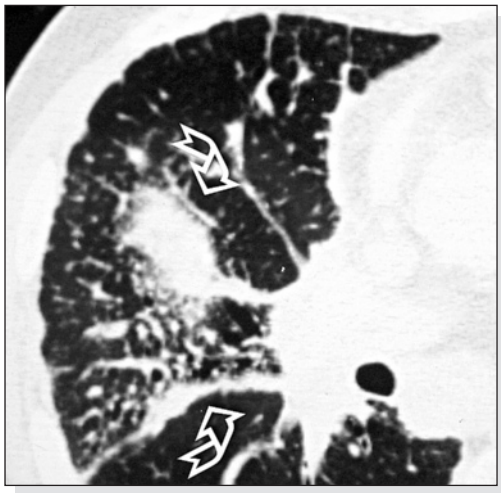
Middle and basal zones

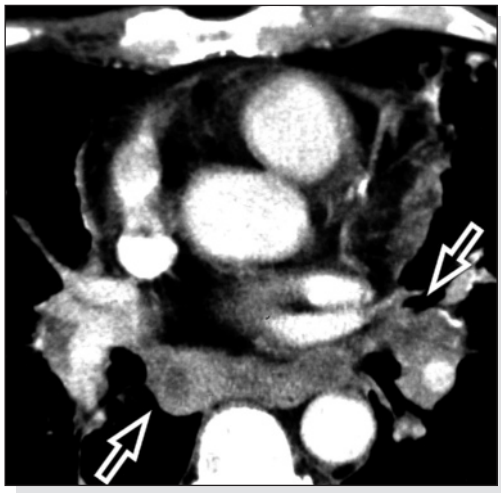
Lung volume is normal

Other signs

Other characteristics:

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





Differentials

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

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

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

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

COURSE and COMPLICATIONS

Associated diseases

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

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

Asbestos-induced pneumoconiosis

Definition

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

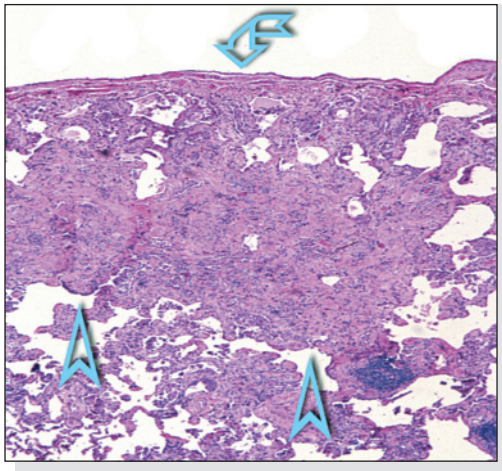
The earliest functional changes include reduced D_LCO and hypoxemia with exercise. A restrictive pattern is observed in a later stage. The presence of airway obstruction is generally due to cigarette smoking

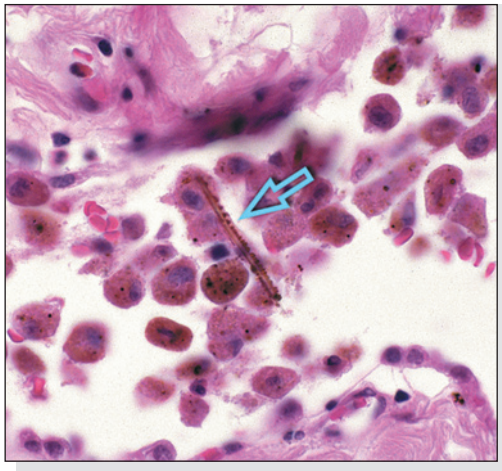
Mossman BT. Asbestos-related diseases. N Engl J Med 1989, 320: 1721

PATHOLOGY

Basic lesions

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





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

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

Distribution

Initially peribronchiolar and subpleural, then progressively diffuse

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

Differentials

Histopathologic differential diagnoses:

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

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

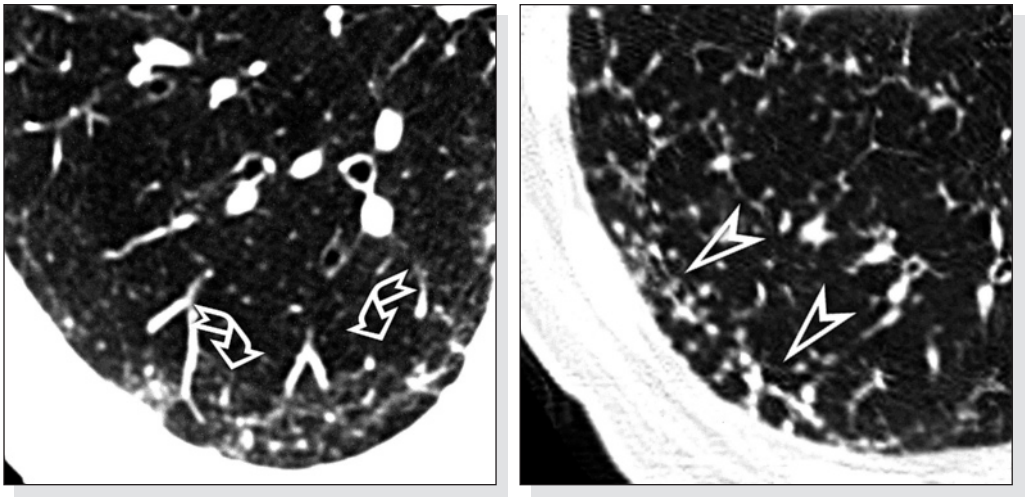
Mossman BT. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 1998, 157: 1666

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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



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

Distribution

Bilateral and symmetrical

Peripheral, dorsal

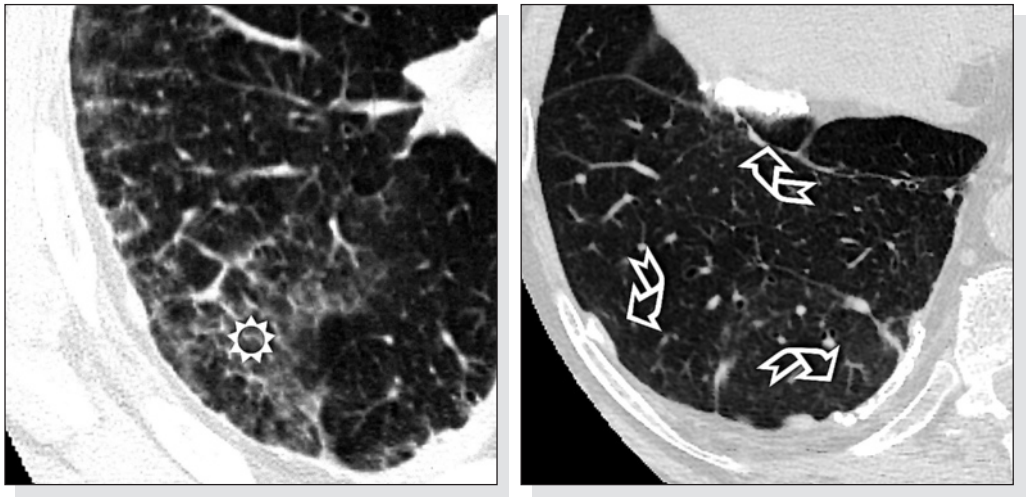
Prevalently basal

Initially normal, lung volume becomes progressively reduced

Other signs

Other radiological characteristics:

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



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

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

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

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

Differentials

The signs described may be present in other fibrosing diseases:

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

COURSE and COMPLICATIONS

Associated diseases

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

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

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

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

The presence of pleural plaques is a hallmark of asbestos exposure

INVASIVE DIAGNOSIS

In doubtful cases a surgical lung biopsy should be performed

Bronchoalveolar lavage

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

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

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

Scleroderma

Definition

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

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

Progressive Systemic Sclerosis (PSS)

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

Almost 50% of patients present diffuse fine bibasilar rales

Pulmonary function tests

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

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

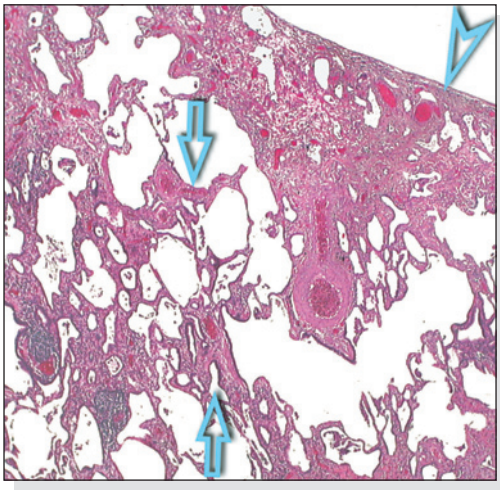
Lamblin C. Interstitial lung diseases in collagen vascular diseases. Eur Respir J Suppl 2001, 32: 69s

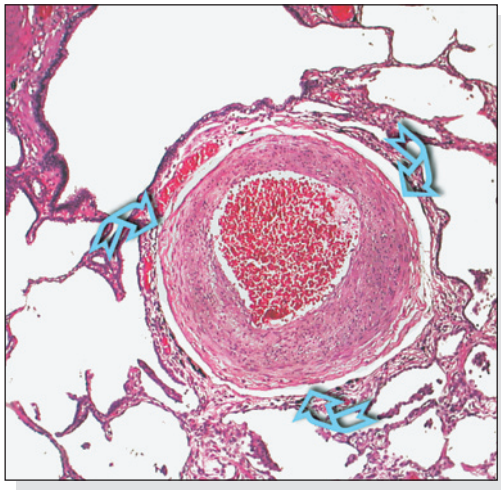
PATHOLOGY

Basic lesions

In the early phase scleroderma presents with:

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





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

Distribution

Diffuse interstitial and subpleural

Differentials

Histopathologic differential diagnoses:

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

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

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

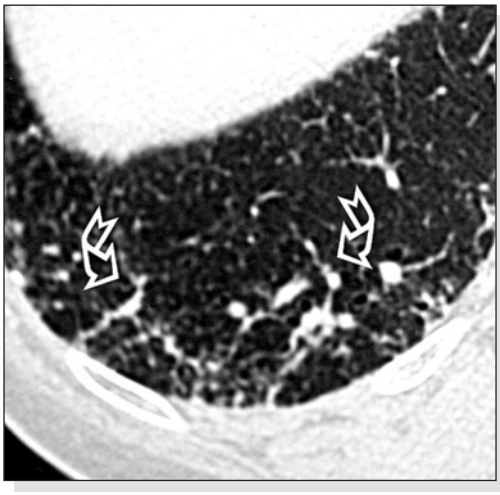
Yousem SA. The pulmonary pathologic manifestations of the CREST syndrome. Hum Pathol 1990, 21: 467

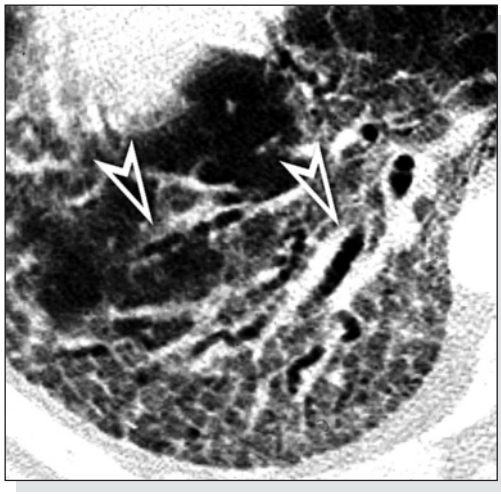
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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





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

Distribution

Bilateral, diffuse

Peripheral, subpleural, dorsal

Basal

Lung volume is slightly reduced

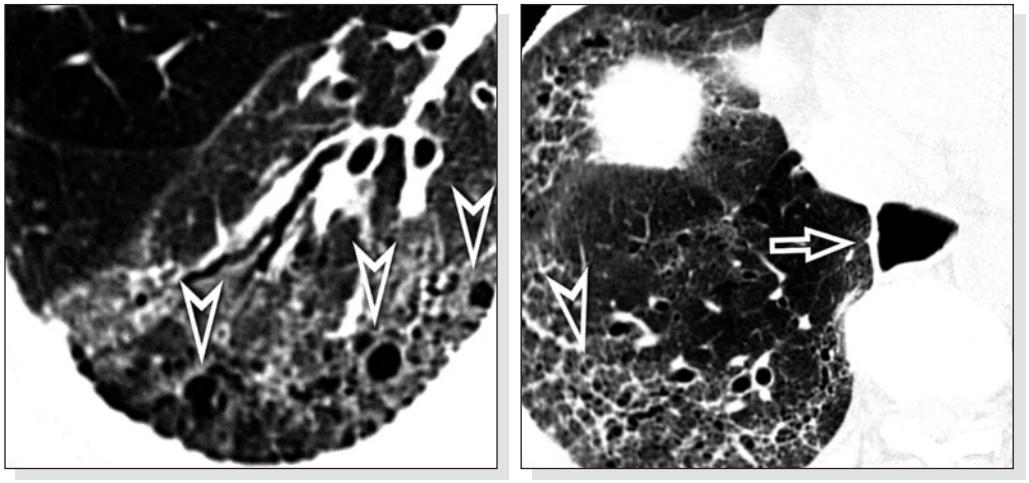
Gamsu G. Radiographic manifestations of thoracic involvement by collagen vascular diseases. J Thorac Imaging 1992, 7: 1

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

Other signs

Other characteristics:

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



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

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

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

Differentials

Radiological differential diagnoses are:

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

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

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

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

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

COURSE and COMPLICATIONS

Associated diseases

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

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

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

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

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

Methotrexate-induced lung disease

Definition

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

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

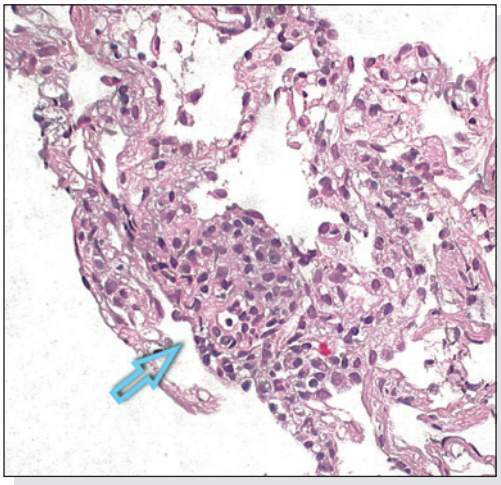
Most patients do not have functional deficits. In rare cases there is a restrictive deficit with a decrease on D_LCO and at times hypoxemia. It has been shown that pulmonary function tests are unable to predict lung involvement caused by methotrexate

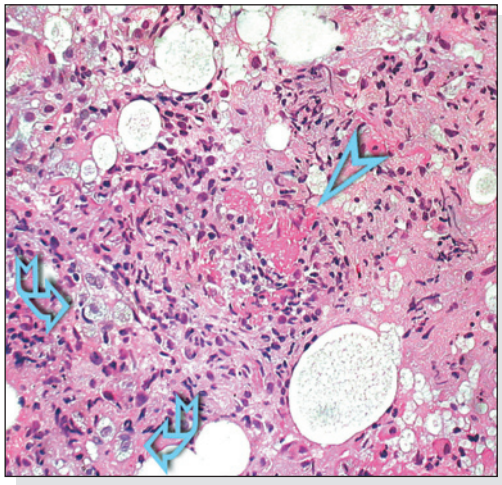
PATHOLOGY

Basic lesions

These include:

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





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

Distribution

Diffuse interstitial

Differentials

Histopathologic differential diagnoses:

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

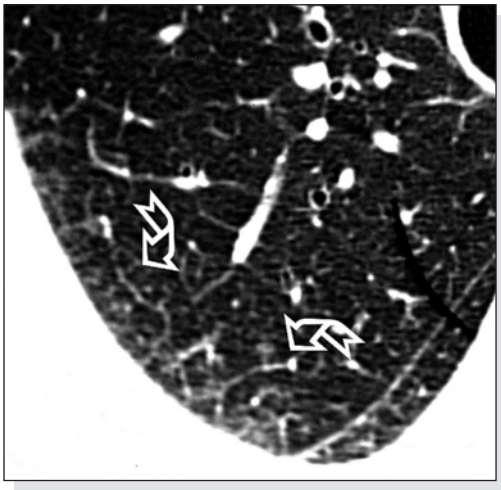
Imokawa S. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J 2000, 15: 373

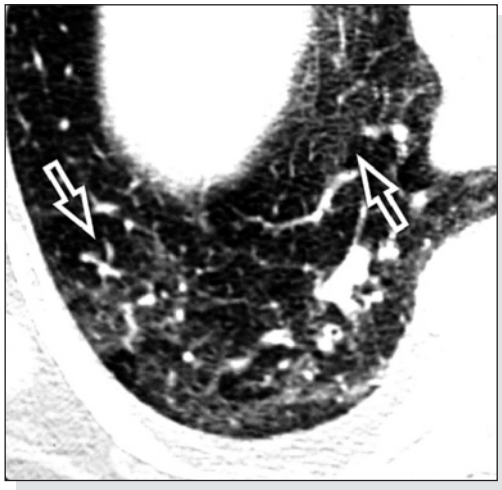
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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





Distribution Bilateral, patchy

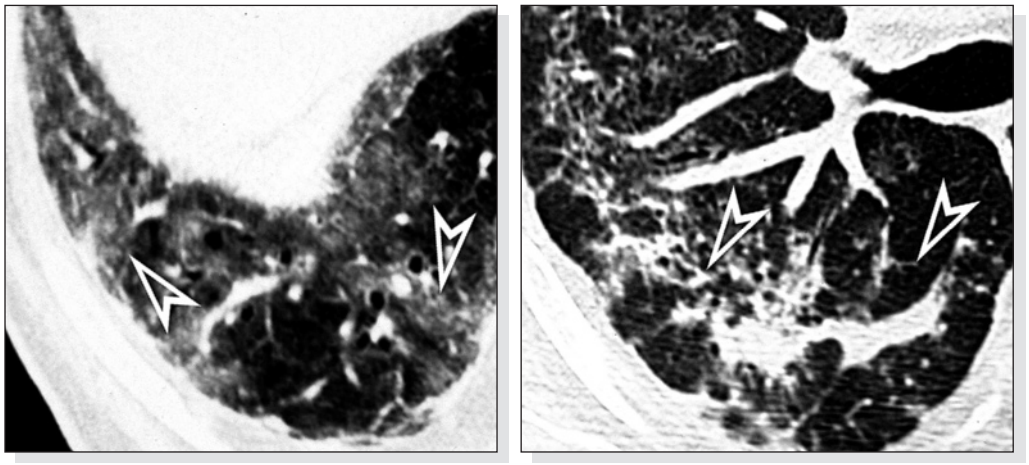
Variable

Variable

Lung volume is normal or slightly reduced

Other signs Other radiological characteristics:

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



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

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

Differentials Radiological differential diagnoses include:

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

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

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

COURSE and COMPLICATIONS

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

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

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

LABORATORY FINDINGS

Peripheral eosinophilia may be seen (40-65%)

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

DRUG TOXICITY TABLES

On the following pages are two detailed tables which present:

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

DRUG-INDUCED LUNG DAMAGE: HISTOPATHOLOGIC PATTERNS

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

DRUG-INDUCED LUNG DAMAGE: BAL FINDINGS

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

Hypersensitivity Pneumonitis

Definition

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

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

Etiology and pathogenesis

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

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

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

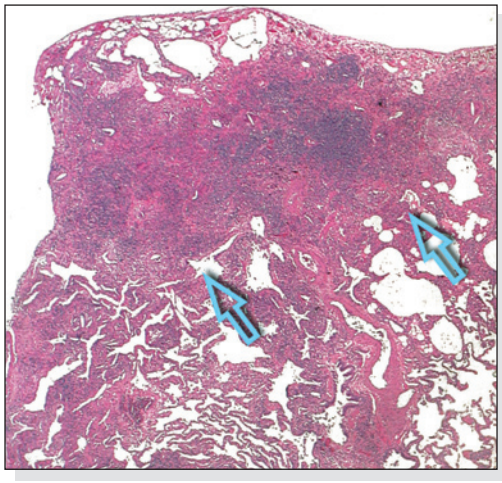
Patel AM. Hypersensitivity pneumonitis: current concepts and future questions. J Allergy Clin Immunol 2001, 108: 661

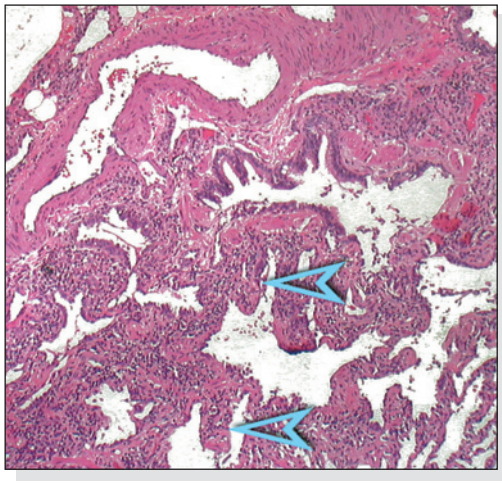
PATHOLOGY

Basic lesions

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

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





Distribution

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

Differentials

Histopathologic differential diagnoses:

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

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

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

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

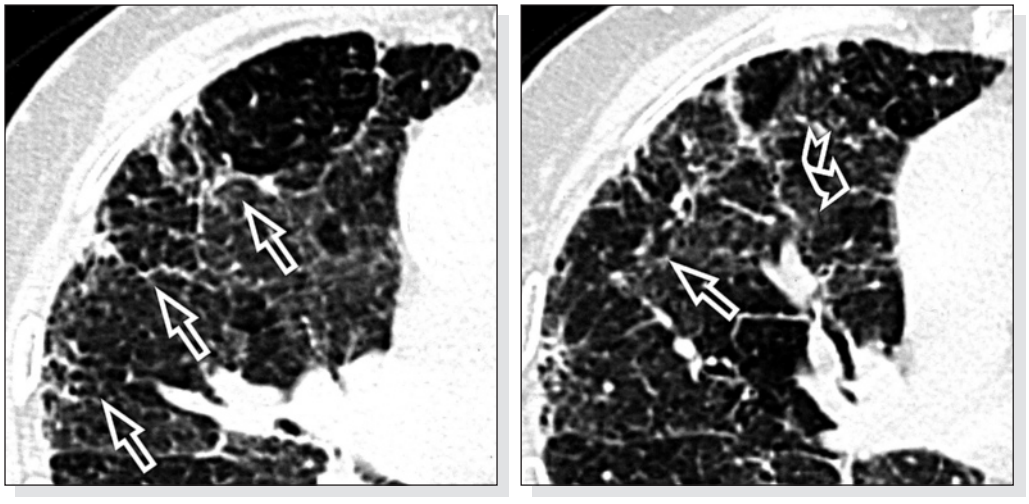
Katzenstein AL. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994, 18: 136

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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



Distribution

Bilateral, patchy

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

Variable

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

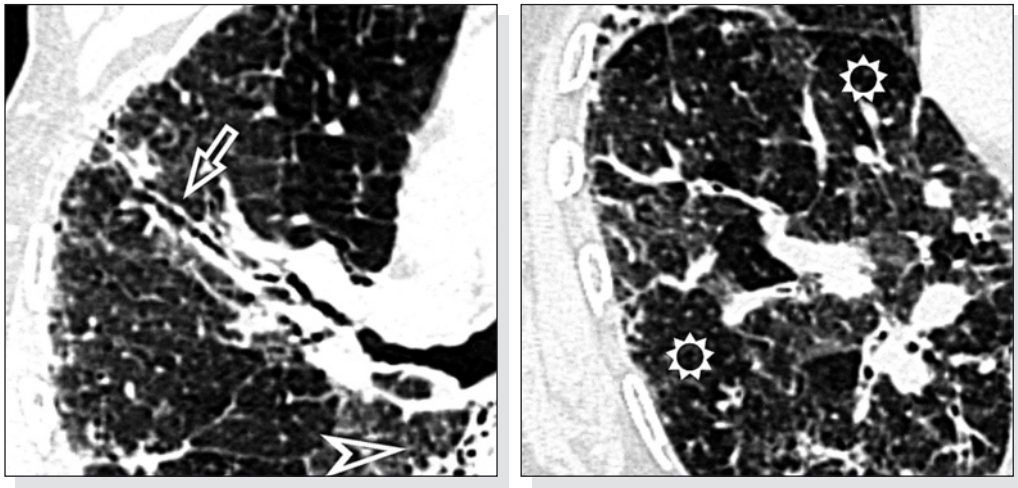
Buschman DL. Chronic hypersensitivity pneumonitis: use of CT in diagnosis. AJR Am J Roentgenol 1992, 159: 957

Lung volume is reduced

Other signs

Other characteristics:

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



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

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

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

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

Differentials

Radiological differential diagnoses:

If the alterations are prevalently in the lung bases:

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

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

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

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

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

COURSE and COMPLICATIONS

Associated diseases

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

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

Clinical course

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

Radiological course

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

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

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

LABORATORY FINDINGS

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

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

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

Lymphangitic Carcinomatosis

Definition

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

Primary neoplasm

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

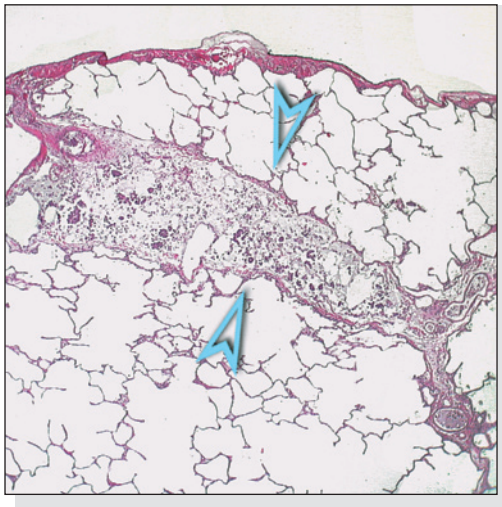
There is a restrictive ventilatory defect with reduced compliance and D_LCO. A rapid respiratory failure, complicated by tumor emboli, leads to hypoxemia and pulmonary arterial hypertension

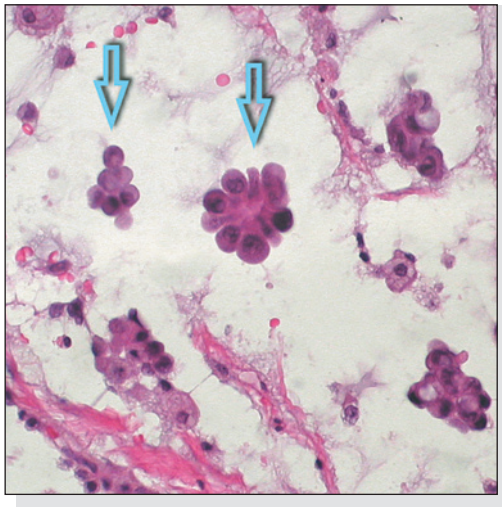
Soares FA. Pulmonary tumor embolism to arterial vessels and carcinomatous lymphangitis. A comparative clinicopathological study. Arch Pathol Lab Med 1993, 117: 827

PATHOLOGY

Basic lesions

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





Distribution

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

Differentials

Histopathologic differential diagnoses:

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

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

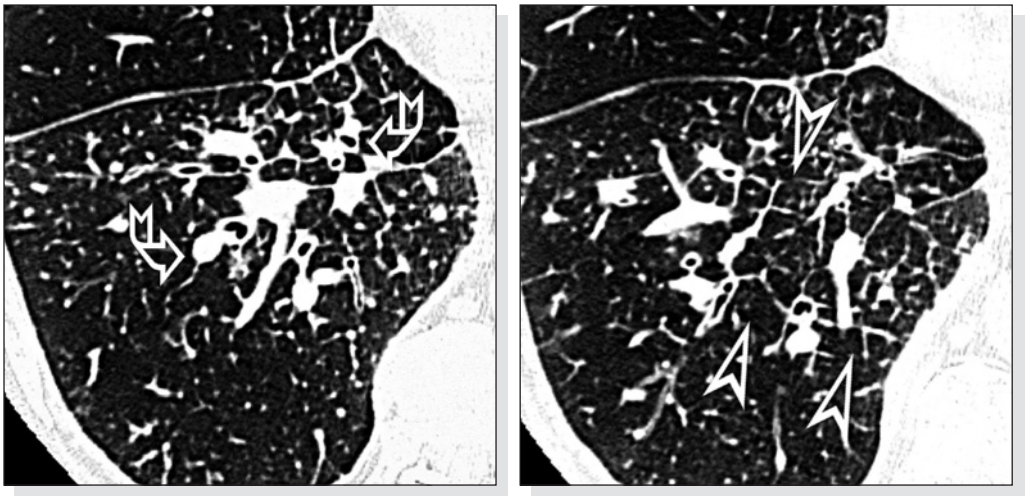
Sweeney S. Vasculitis carcinomatosa occurring in association with adenocarcinoma of the stomach. Ann Diagn Pathol 1998, 2: 247

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

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

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



Nodular reticular pattern, beaded appearance

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

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

Distribution

Monolateral, more rarely bilateral, patchy

Variable

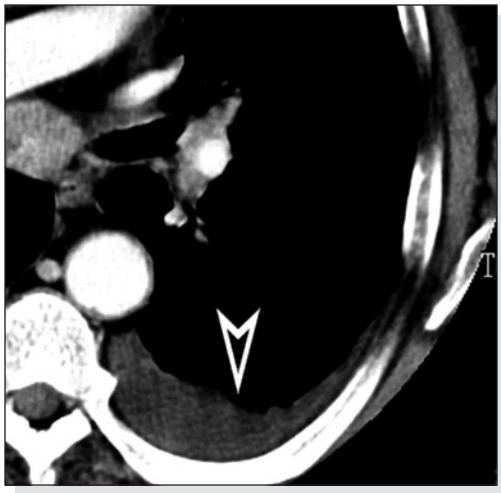
Variable

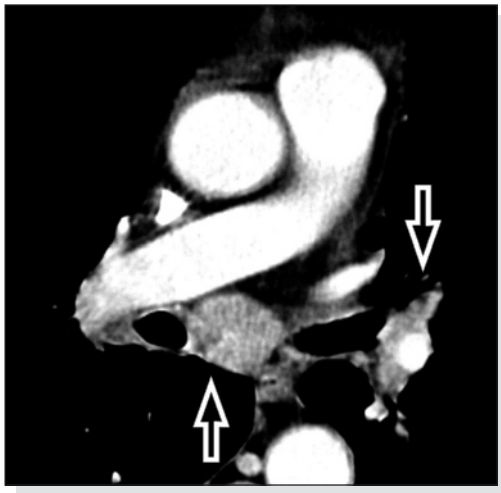
Lung volume is normal

Other signs

Other non-constant characteristics:

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





Differentials

Radiological differential diagnoses:

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

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

COURSE and COMPLICATIONS

Associated diseases

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

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

Non-Specific Interstitial Pneumonia

Definition

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

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

None are known

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

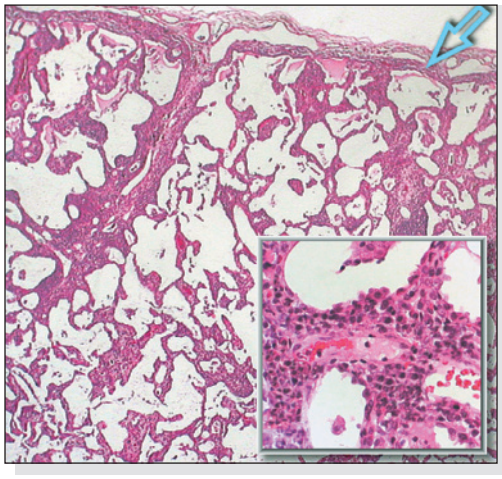
All patients have reduced D_LCO, and there is a concurrent restrictive defect in 90 percent of cases. A minority of patients also have a mild obstructive syndrome, whereas two thirds show exertional hypoxemia

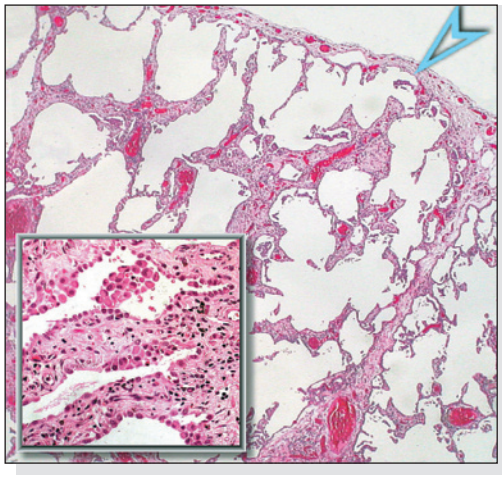
PATHOLOGY

Basic lesions

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

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





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

Distribution

Diffuse interstitial

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

Differentials

Histopathologic differential diagnoses:

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

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

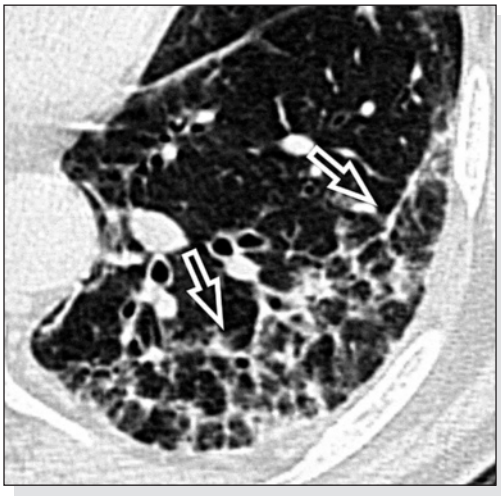
Travis WD. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000, 24: 19

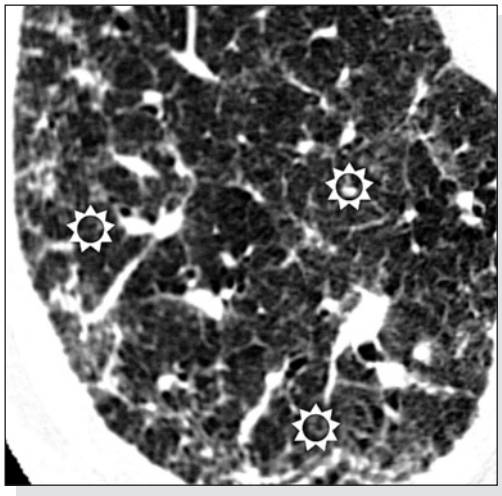
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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





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

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

Distribution

Bilateral, symmetrical, often patchy

Peripheral, although also central; less commonly diffuse

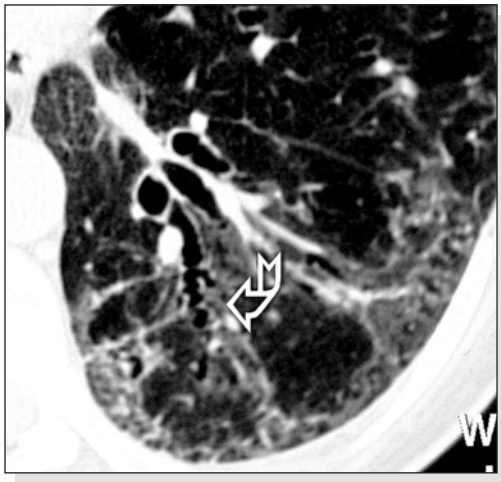
Basal

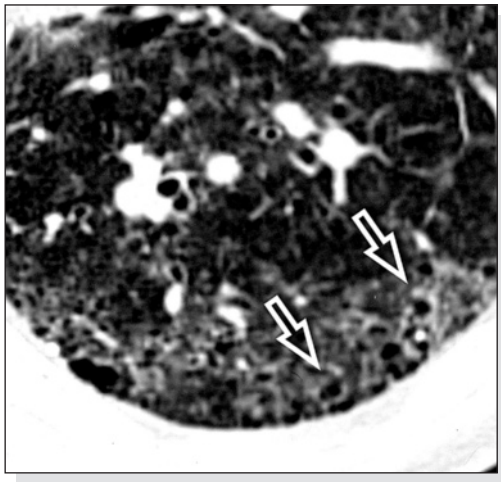
Lung volume is normal or slightly reduced

Other signs

Other non-constant characteristics:

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





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

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

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

Differentials

Radiological differential diagnoses:

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

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

COURSE and COMPLICATIONS

Associated diseases

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

Clinical course

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

Radiological course

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

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

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

Pulmonary Edema

Definition

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

Cardiogenic, hemodynamic edema

DEMOGRAPHICS

Etiology and pathogenesis

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

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

Epidemiology

Pulmonary edema is a frequent cause of admission to the hospital

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

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

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

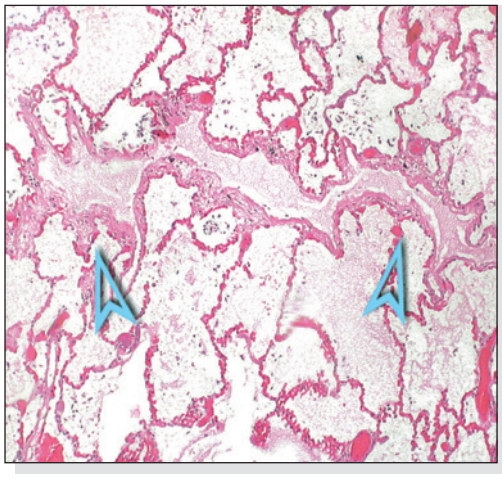
Gandhi SK. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001, 344: 17

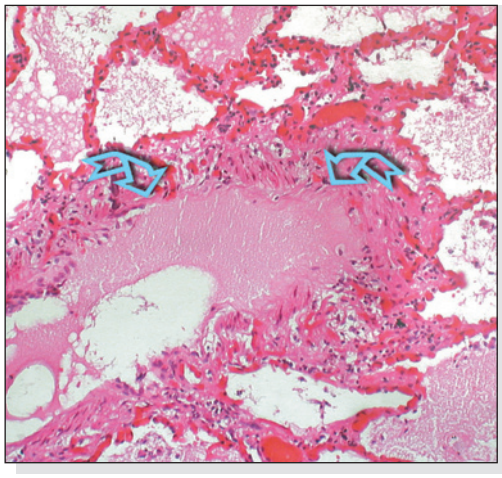
Gropper MA. Acute cardiogenic pulmonary edema. Clin Chest Med 1994, 15: 501

PATHOLOGY

Basic lesions

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





Distribution

Interlobular, perivascular, peribronchial and subpleural interstitium

Differentials

Histopathologic differential diagnoses:

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

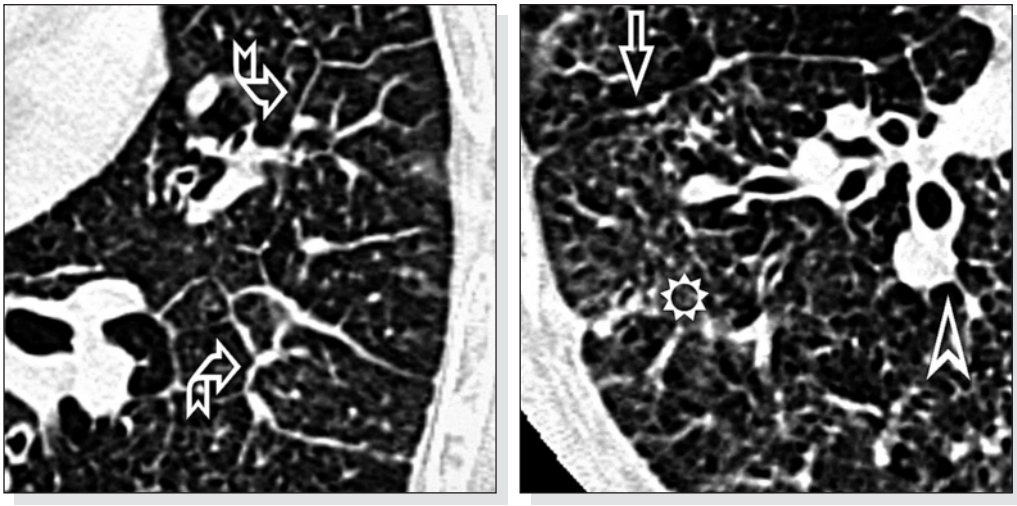
Colby TV. Pulmonary histology for the surgical pathologist. Am J Surg Pathol 1988, 12: 223

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

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



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

Distribution

Bilateral, diffuse

Central, peribronchovascular in parahilar and dependent regions

Basal, gravity-dependent

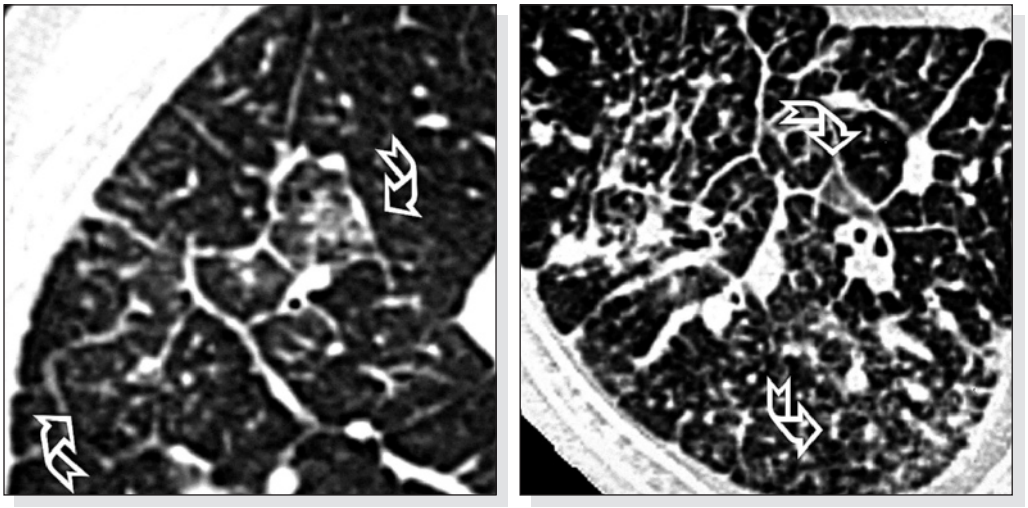
Lung volume is normal

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

Other signs

Other characteristics:

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



Differentials

The main radiological differential diagnosis is:

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

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

COURSE and COMPLICATIONS

Associated diseases

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

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

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

CLINICAL DIAGNOSIS

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

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

INVASIVE DIAGNOSIS

Bronchoalveolar lavage

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

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

Sarcoidosis

Definition

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

DEMOGRAPHICS

Etiology and pathogenesis

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

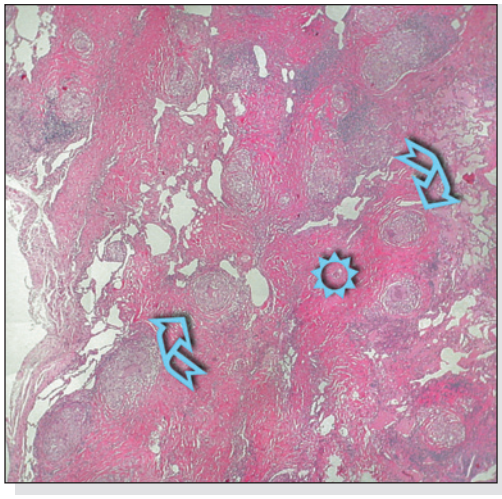
A more or less serious restrictive syndrome may be present in relation to the extent of fibrosis, and reduction in D_LCO. Patients present with hypoxemia on exertion and in the more severe cases even at rest

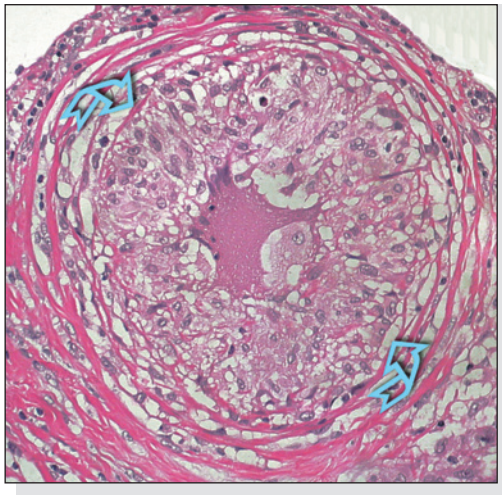
Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Am J Respir Crit Care Med 1999, 160: 736

PATHOLOGY

Basic lesions

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





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

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

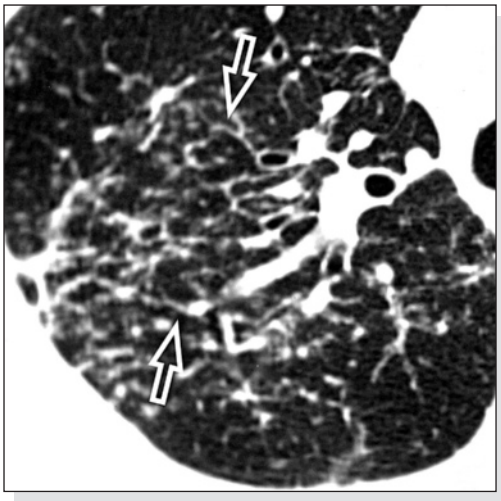
Differentials Histopathologic differential diagnoses:

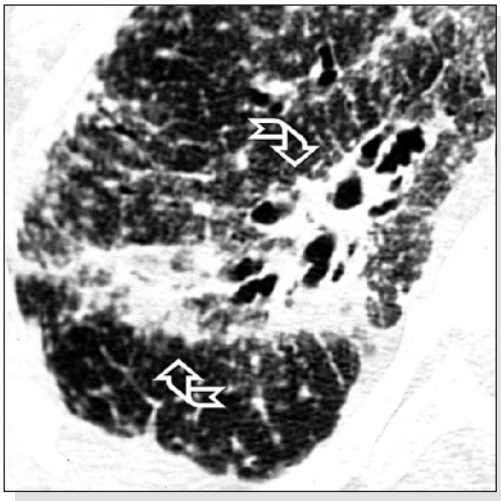
- NSIP: alveolar septa are uniformly thickened without a prevalently lymphatic distribution, while granulomas are rare
  The interstitial inflammatory infiltrate is more abundant
- HP: lesions are centrilobular, there is intense lymphoplasmacellular inflammation, and granulomas are poorly formed
- UIP: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

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions Basic radiological signs:

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





Distribution Bilateral, patchy

Predominantly central, especially dorsal

Upper lung regions

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

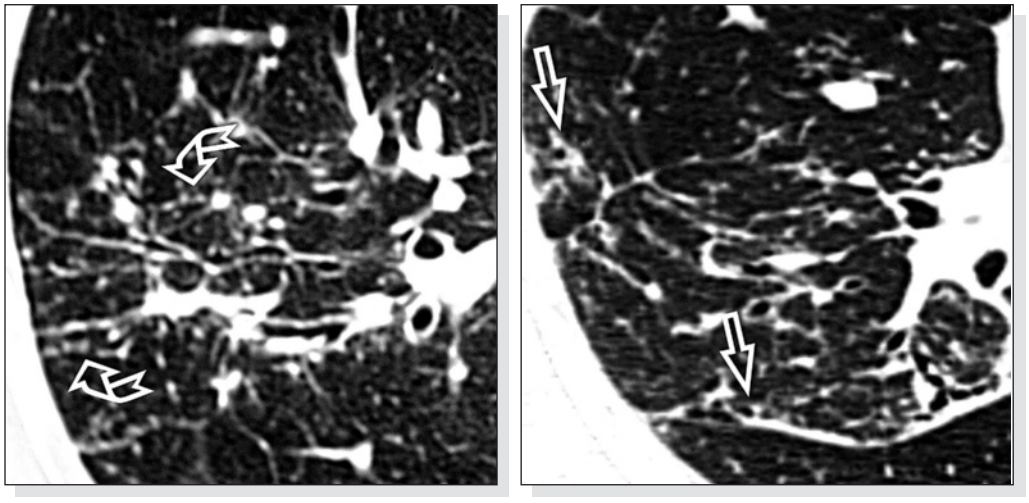
Abehsera M. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol 2000, 174: 1751

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

Other signs

Other radiological characteristics:

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



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

Differentials

Radiological differential diagnoses:

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

COURSE and COMPLICATIONS

Associated diseases

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

The presence of hemoptysis is sufficient cause for suspecting aspergillus superinfection

Clinical course

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

Radiological course

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

Usual Interstitial Pneumonia

Definition

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

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

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

DEMOGRAPHICS

Etiology and pathogenesis

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

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

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

Epidemiology

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

Risk factors

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

CLINICAL FEATURES

History

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

Physical findings

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

Pulmonary function tests

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

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

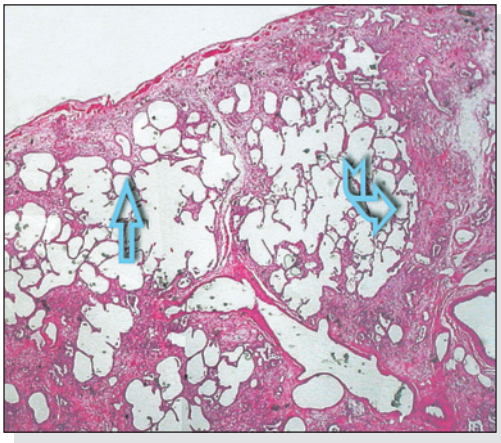
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

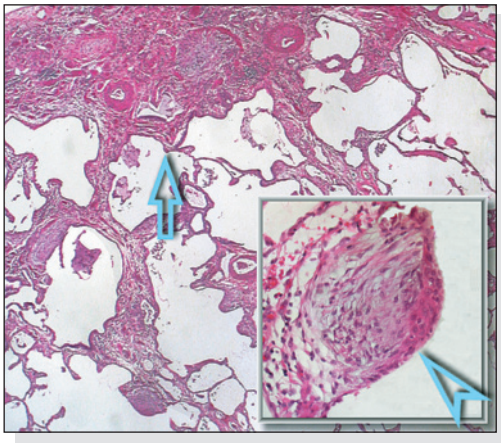
PATHOLOGY

Basic lesions

The lesions in early UIP are:

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





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

Distribution

Subpleural and paraseptal

Differentials

Histopathologic differential diagnoses:

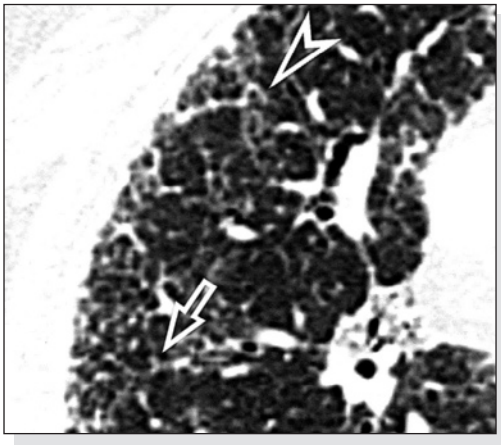
- NSIP: lesions are spatially and temporally homogeneous, lacking fibroblastic foci
- HP: peribronchiolar distribution, presence of granulomas and a more intense inflammatory interstitial infiltrate
- LCH: centrilobular stellate nodules containing a mixed infiltrate with Langerhans' cells and often eosinophils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

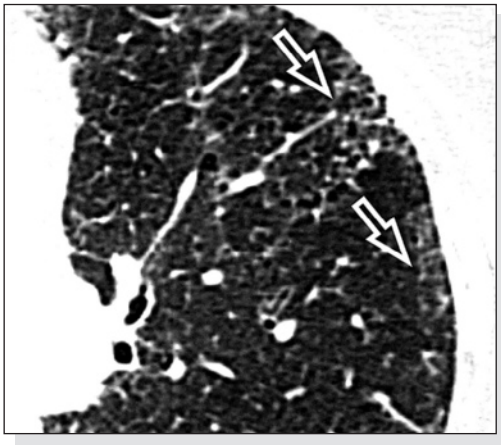
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

The HRCT pattern commonly shows irregular reticulation:

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





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

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

Distribution

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

Preferentially peripheral (subpleural), predominantly dorsal

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

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

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

Lung volume is normal or only slightly reduced in this phase

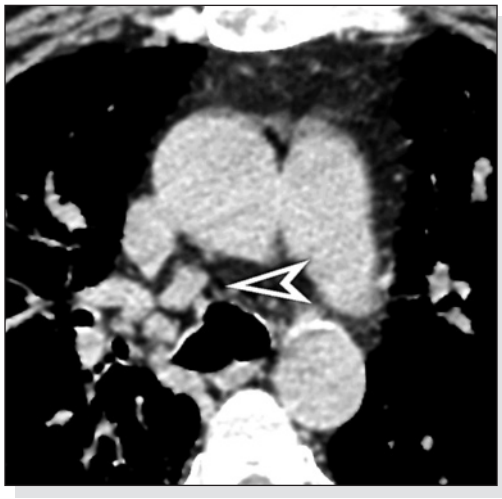
McAdams HP. The alphabet soup revisited: the chronic interstitial pneumonias in the 1990s. Radiographics 1996, 16: 1009

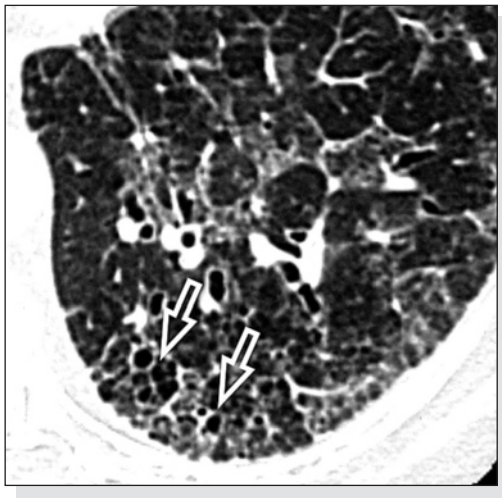
Johkoh T. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology 1999, 211: 555

Other signs

Other radiological characteristics:

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





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

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

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

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

Differentials

Radiological differential diagnoses:

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

COURSE and COMPLICATIONS

Associated diseases

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

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

Clinical course

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

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

Radiological course

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

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

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

LABORATORY FINDINGS

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

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

CLINICAL DIAGNOSIS

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

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

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

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

INVASIVE DIAGNOSIS

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

Bronchoalveolar lavage

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

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

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

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