⌘ Alveolar Diseases

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Acute Interstitial Pneumonia

Definition

Acute interstitial pneumonia (AIP) is a rare and rapidly progressive form of lung damage that arises abruptly in apparently healthy individuals. The disease has no known cause and is classified among the idiopathic interstitial pneumonias

Hamman-Rich syndrome, fulminant interstitial pneumonia

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

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

DEMOGRAPHICS

Etiology and pathogenesis

Although the etiology and pathogenesis are unknown, the lung damage is thought to be caused by the release of toxic oxygen species and proteases by polymorphonuclear neutrophils

Epidemiology

Mean age at onset is 50 years. Both sexes are equally affected and there is no correlation with tobacco smoking

Risk factors

There are no known risk factors

CLINICAL FEATURES

History

The onset is acute and the most common presenting symptoms are cough (100%), dyspnea (80-100%) and fever. Patients often report a prodromal flu-like illness (joint and muscle pain, fever, chills and malaise)

Physical findings

Physical examination reveals tachypnea and peripheral cyanosis. In 50% of cases fine rales can be heard throughout the lung fields

Pulmonary function tests

All patients have reduced D_LCO and a restrictive pattern. Moderate to severe hypoxemia, at times refractory to oxygen therapy, rapidly ensues. Rapid progression to respiratory failure similar to acute respiratory distress syndrome (ARDS) is common

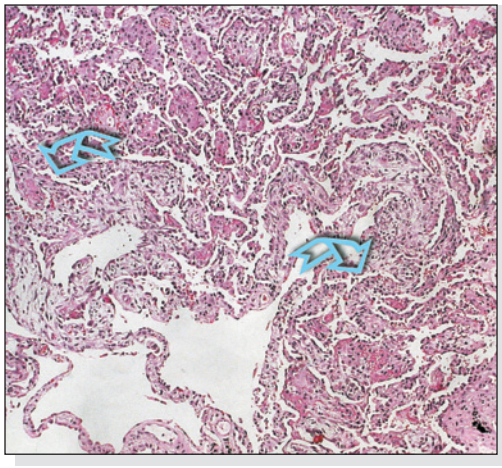
Vourlekis JS. Acute interstitial pneumonitis. Case series and review of the literature. Medicine 2000, 79: 369

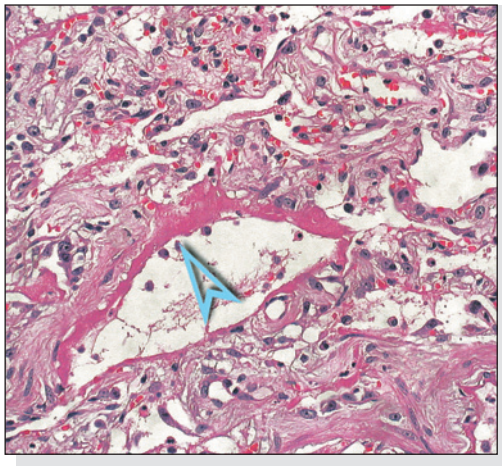
PATHOLOGY

Basic lesions

The histologic features of AIP are those of diffuse alveolar damage (DAD):

- Acute (exudative) phase, rarely biopsied: hyaline membranes, an expression of acute epithelial damage, line the alveolar walls. The alveolar septa show edema and varying amounts of acute and chronic inflammatory infiltrate. Thromboses of small and medium-size arterioles are common
- Organizing (proliferative) phase: proliferation of myofibroblasts that migrate from the interstitium to the alveolar spaces: the hyaline membranes (➢) are resorbed and organized within the alveolar septa, which become thickened (↯). Proliferation of hyperplastic type II pneumocytes restores the alveolar epithelium
- Chronic (fibrotic) phase: dense fibrosis with possible distortion of lung architecture





Distribution

Diffuse (alveoli and alveolar septa)

Differentials

Histopathologic differential diagnoses:

- DAD associated with infections: granulomas, viral inclusions, necrotic foci, abscesses; identification of the microorganism with special stains
- DAD superimposed on UIP (accelerated UIP): associated with the characteristic UIP pattern
- DAD due to other causes: not idiopathic but secondary to other causes (shock, trauma, physical or chemical causes, etc.)
- OP: predominantly intraalveolar foci of fibroblastic organization, intense inflammatory infiltrate, bronchiolar involvement (not constant)

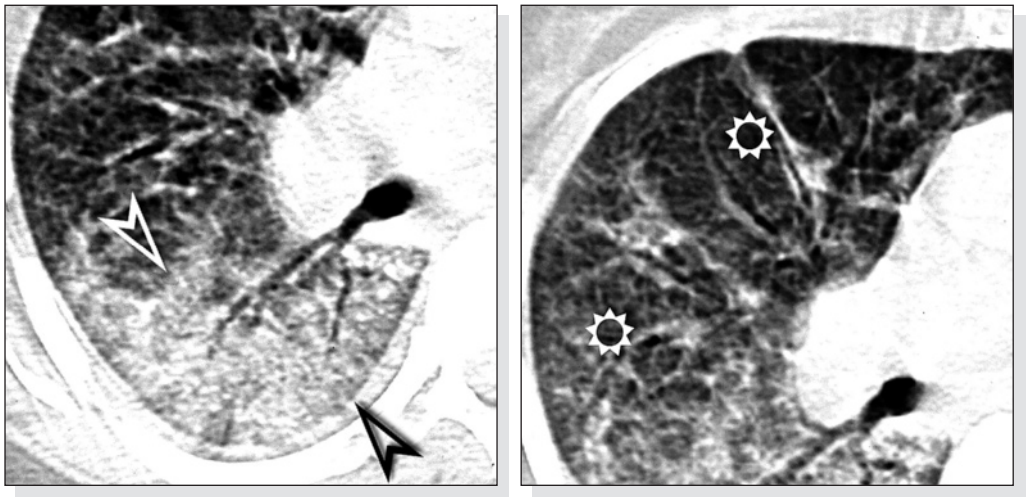
Katzenstein AL. Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 1986, 10: 256

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs, typical of the early stage (1-7 days):

- Parenchymal consolidation (≥)
- Ground-glass opacities (☼)



Akira M. Computed tomography and pathologic findings in fulminant forms of idiopathic interstitial pneumonia. J Thorac Imaging 1999, 14: 76

Distribution

Diffuse or patchy, generally bilateral and symmetrical

Lesions may predominate in the peripheral and lower regions of the lung

Variable

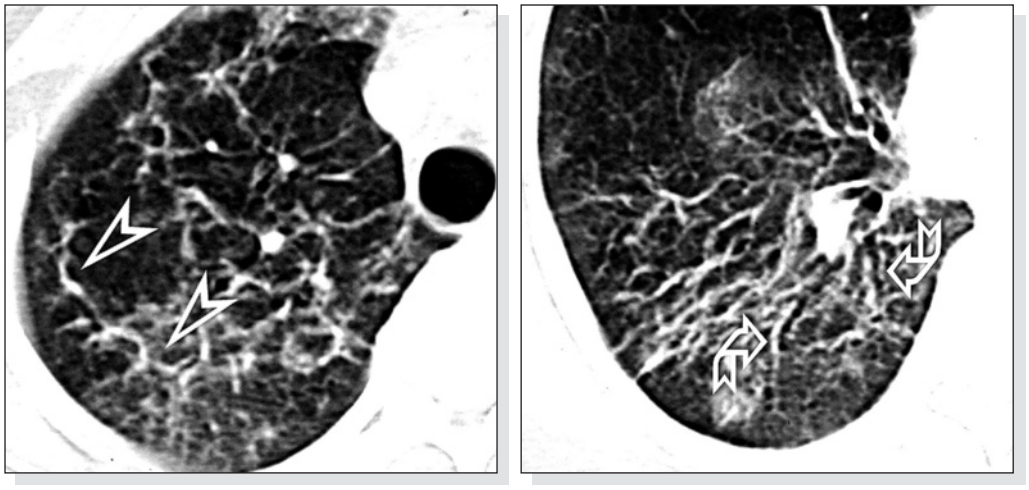
Lung volume is normal or reduced

Primack SL. Acute interstitial pneumonia: radiographic and CT findings in nine patients. Radiology 1993, 188: 817

Other signs

Transition to the proliferative fibrotic stage may manifest with:

- Reticular pattern (≫) with distortion of parenchymal architecture
- Traction bronchiectasis (↳) and mild honeycombing



Ichikado K. Acute interstitial pneumonia: high-resolution CT findings correlated with pathology. AJR Am J Roentgenol 1997, 168: 333

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

Differentials

Radiological differential diagnoses:

- Atypical pneumonias in immunocompetent subjects and opportunistic pneumonias in immunodepressed subjects: the differential diagnosis cannot be made clinically and requires surgical biopsy
- OP: the peripheral and/or peribronchial consolidations tend to be triangular or polygonal in shape; accelerated forms exhibit patterns similar to those of AIP
- DAH: the consolidation tends to be centrally distributed and absent in the subpleural regions
- PE: more distinctly gravitational and hilar-parahilar, with smooth thickening of the septal and peripheral interstitium

Ichikado K. A case of acute interstitial pneumonia indistinguishable from bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia: high-resolution CT findings and pathologic correlation. Radiat Med 1998, 16: 367

Mihara N. Can acute interstitial pneumonia be differentiated from bronchiolitis obliterans organizing pneumonia by high-resolution CT? Radiat Med 2000, 18: 299

COURSE and COMPLICATIONS

Associated diseases

There are no known associated diseases

Clinical course

The disease tends to progress to respiratory failure requiring mechanical ventilation. The mortality rate is 50% mostly within 1-2 months of presentation. Those who recover may develop chronic interstitial lung diseaselesions that progress to fibrosis

Radiological course

In survivors, the alveolar opacities tend to regress, whereas the more-or-less extensive irregular reticular changes and honeycombing may persist indefinitely

LABORATORY FINDINGS

Peripheral neutrophilic leukocytosis is a common finding. Increased serum creatinine levels and reduced hematocrit are considered unfavorable prognostic factors

CLINICAL DIAGNOSIS

Acute clinical onset with severe and refractory respiratory failure associated with a radiological picture of diffuse, bilateral, air-space opacification should suggest a diagnosis of AIP, in the absence of any possible cause

INVASIVE DIAGNOSIS

The large number of differential diagnoses, the poor prognosis and the need to institute high-dose immunosuppressive therapy all call for a definitive diagnosis that can only be obtained by surgical lung biopsy. Transbronchial lung biopsy is of no diagnostic value, however, it can significantly narrow the differential diagnosis

Bronchoalveolar lavage

BAL fluid reveals an increased total cell count, signs of alveolar hemorrhage by the finding of red blood cells and hemosiderin-laden macrophages, increased levels of polymorphonuclear neutrophils (>50%) and occasionally lymphocytes. The cytologic preparations of BAL fluid should also examined for reactive type II pneumocytes (the atypia of these cells may be severe enough to mimic carcinoma), as well as fragments of hyaline membranes

In intensive care units, BAL is particularly useful for differentiating AIP from: 1. diffuse alveolar hemorrhage (bloody fluid, erythrocytes and hemosiderin-laden macrophages); 2. acute eosinophilic pneumonia (marked increase in eosinophils); 3. drug-induced pulmonary toxicity (CD8+ lymphocytosis and foamy macrophages); 4. fast-growing neoplasms (cancer cells); 5. infections with associated acute lung injury (direct visualization or positive quantitative culture of the causative microorganism); 6. cryptogenic organizing pneumonia (CD8+ lymphocytosis, neutrophils and foamy macrophages)

Bonaccorsi A. Acute interstitial pneumonia: report of a series. Eur Respir J 2003, 21: 187

Pesci A. Bronchoalveolar lavage in intensive care units. Monaldi Arch Chest Dis 2004, 61: 39

Adult Respiratory Distress Syndrome

Definition

Adult respiratory distress syndrome (ARDS) is a form of severe acute respiratory failure characterized by severe hypoxia (PaO_2/FiO_2 ratio <200), pulmonary capillary wedge pressure <18 mmHg and diffuse lung opacities on chest radiograph. A trigger mechanism can always be identified (sepsis, trauma, surgery, burns, infections, drugs, etc.)

Non-cardiogenic pulmonary edema, edema due to membrane damage, shock lung

DEMOGRAPHICS

Etiology and pathogenesis

The edema is caused by disruption of the alveolocapillary barrier: the alveoli become engulfed with protein-rich fluid, blood cells and cellular debris; the loss of surfactant leads to atelectasis. This early exudative stage may be followed by a organizing phase with fibroblast proliferation in the alveolar spaces and interstitium, and type II cell hyperplasia

The pathogenesis of lung injury is complex and linked to inflammatory phenomena involving cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha), granulocyte macrophage colony stimulating factor (GM-CSF), chemokynes (IL-8) and inflammatory mediators (leukotriene B4). These in turn recruit polymorphonuclear neutrophils, which become activated and release toxic oxygen species and proteases capable of damaging the epithelial and endothelial cells

Epidemiology

The reported incidence of ARDS varies from 1.5% to 13.5% per year

Risk factors

The main risk factors are sepsis, gastric content aspiration, severe trauma, multiple transfusions, near drowning, acute pancreatitis, prolonged hypotension, severe bacterial pneumonia, and disseminated intravascular coagulation. The presence of multiple risk factors increases the likelihood of developing ARDS

CLINICAL FEATURES

History

The signs and symptoms of ARDS may develop insidiously 8-48 hours after the initiating event, or acutely immediately after the event. The main symptoms are rapidly progressive dyspnea, dry cough, chest pain and agitation. The presence of mild or massive hemoptysis indicates full-blown ARDS

Physical findings

Patients present with marked dyspnea, tachypnea, cyanosis and agitation; auscultation of the lung reveals bilateral rales. Pulmonary hypertension with right-sided cardiac failure (jugular venous distension, tender hepatomegaly, peripheral edema) is often associated

Pulmonary function tests

Lung function testing reveals low D_LCO, functional residual capacity, and decreased lung compliance. Patients typically have severe hypoxia refractory to oxygen supplementation, mechanical ventilation with positive end expiratory pressure (PEEP) or other resuscitation procedures. The severity of functional impairment does not correlate with prognosis

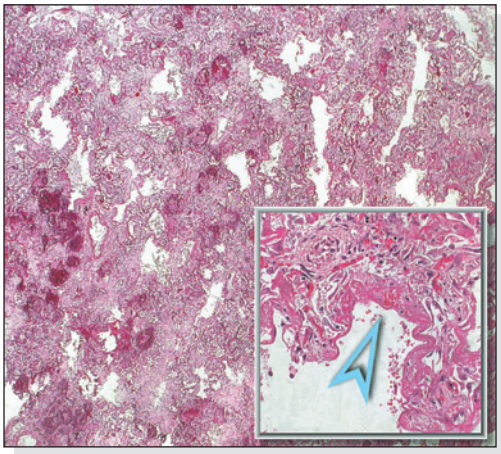
Ware LB. The acute respiratory distress syndrome. N Engl J Med 2000, 342: 1334

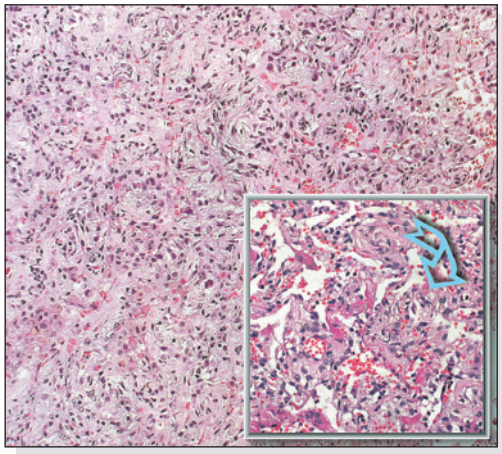
PATHOLOGY

Basic lesions

ARDS is the clinical syndrome associated with the histologic picture of diffuse alveolar damage (DAD) secondary to various diseases conditions. The process is characterized by different histologic changes depending on the stage of disease:

- In the acute (exudative) phase there is a predominance of hyaline membranes. These are sheets of eosinophilic material made up of necrotic type I pneumocytes and plasma proteins that line the alveolar surfaces (➢). These are also associated with interstitial edema and microthromboses
- In the organizing (proliferative) phase there is a proliferation of type II pneumocytes, fibroblasts and myofibroblasts. The latter migrate from the interstitium to the intraalveolar exudate turning it into granulation tissue (↳), which may eventually be completely reabsorbed with complete healing of the lesions or progress towards fibrosis
- In the chronic (fibrotic) phase there is deposition of dense fibrous tissue which causes remodeling of the lung architecture





Distribution

Diffuse (alveoli and alveolar septa)

Differentials

Histopathologic differential diagnoses:

- DAD associated with infections: granulomas, viral inclusions, necrotic foci, abscesses; demonstration of the microorganism with special stains
- DAD superimposed on UIP (accelerated UIP): the characteristic UIP pattern appears, that is, spatially and temporally heterogeneous fibrosis originating from the subpleural regions, with fibroblastic foci at the interface with normal parenchyma
- OP: predominantly intraalveolar foci of fibroblastic organization, intense inflammatory infiltrate, bronchiolar involvement (not constant)

A possible variant of DAD, acute fibrinous and organizing pneumonia (AFOP), has recently been reported, which is histologically characterized by intraalveolar fibrin accumulation in the form of "fibrin balls" without the classic hyaline membranes and associated with foci of organizing pneumonia in the bronchioles and alveolar ducts

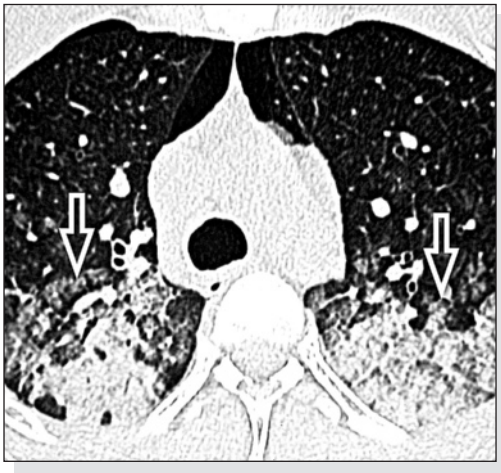
Beasley MB. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. Arch Pathol Lab Med 2002, 126: 1064

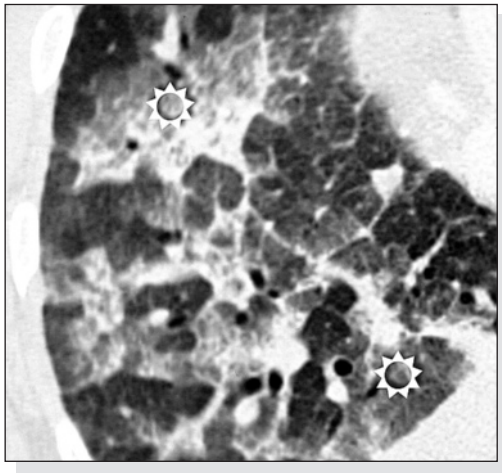
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation with air bronchogram (⇨)
- Ground-glass opacities associated with air bronchogram (☼)





Goodman LR. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. Radiology 1999, 213: 545

Distribution

Bilateral and patchy, prevalently symmetrical in ARDS due to extrapulmonary causes, and asymmetrical in ARDS due to a primary pulmonary cause

Diffuse, although the opacities tend to become more uniform and dense in the dependent areas, especially in ARDS due to extrapulmonary causes

Diffuse, although consolidation is more extensive at the lung bases

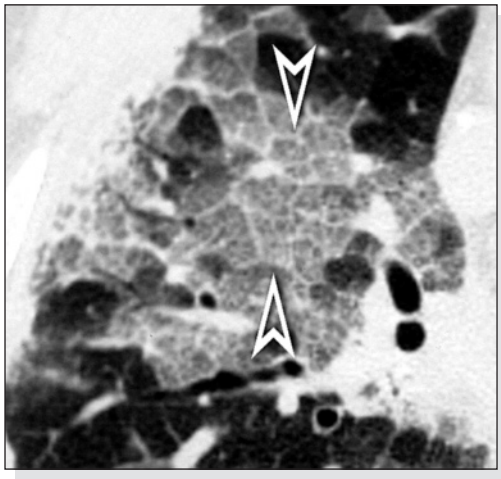
The degree of opacification tends to increase in the more dependent regions as a result of the parenchyma progressively collapsing under the weight of the dense lung above

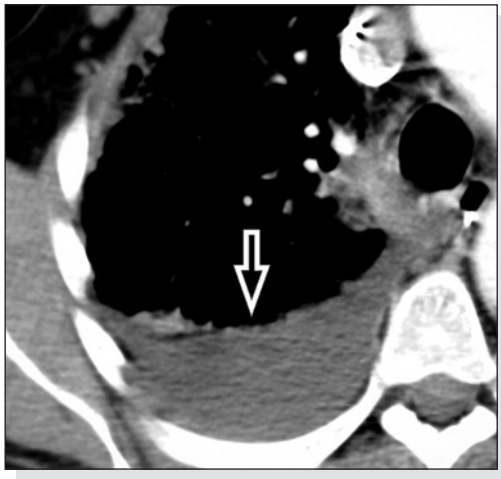
Lung volume may be reduced

Other signs

Other non-constant radiological signs:

- Regular reticular pattern due to septal thickening
- Association of reticular pattern and ground-glass attenuation (≥)(crazy paving)
- Pleural effusion (moderate)(⇨)





Desai SR. Acute respiratory distress syndrome: imaging of the injured lung. Clin Radiol 2002, 57: 8

Differentials

Radiological differential diagnoses:

- AIP: the radiological pattern may be identical since AIP is an idiopathic form of ARDS
- PE: the opacities are more uniform, frankly gravitational and without air bronchogram. A reticular pattern is almost always present, and cardiomegaly and pleural effusion are common
- Fluid overload: increase in the diameter of the superior vena cava (due to increased volume of circulating blood) and thickening of the chest wall soft tissues

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

Ketai LH. A new view of pulmonary edema and acute respiratory distress syndrome. J Thorac Imaging 1998, 13: 147

COURSE and COMPLICATIONS

Associated diseases

Patients requiring mechanical ventilation have a higher risk of developing the typical complications of ARDS (ventilator-associated pneumonia, multiple organ failure) or complications associated with treatment (barotraumas with pneumothorax, pneumomediastinum and chest wall emphysema)

Clinical course

Prognosis is poor and the disease may be fatal in 35-40% of cases. Ninety percent of deaths occur within the first 2 weeks of onset of the symptoms. The presence of infections or multiorgan failure has negative prognostic implications. Survivors may recover normal pulmonary function or in some cases experience pulmonary fibrosis

Radiological course

Depending on the clinical course, the following radiological patterns may be observed:

- Progressive regression of opacities with complete healing of lesions
- Regression of the alveolar opacities with persisting reticular pattern and distortion of lung parenchyma anteriorly
- Progressive increase in opacities with appearance of linear opacities and remodeling of the lung architecture (fibrosis) and formation of paradoxical hyperlucencies due to vascular obstruction

Desai SR. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology 1999, 210: 29

LABORATORY FINDINGS

Neutrophilic leukocytosis in the peripheral blood is a common finding, and hematological changes ascribable to disseminated intravascular coagulation (DIC) are relatively common

CLINICAL DIAGNOSIS

The diagnosis is made on the basis of the clinical picture (acute onset in the absence of left cardiac failure and with apparent predisposing condition), radiological pattern (bilateral opacities at chest radiograph) and functional findings (PaO_2/FiO_2 <200; pulmonary capillary wedge pressure <18 mmHg)

INVASIVE DIAGNOSIS

Surgical lung biopsy is rarely required. Transbronchial lung biopsy is of no diagnostic value, however, it can significantly narrow the differential diagnosis

Bronchoalveolar lavage

In early ARDS, the BAL fluid shows a marked increase in neutrophils, whereas in late ARDS lymphocytes and eosinophils predominate. The finding of a high number of neutrophils in late stage ARDS indicates a negative prognosis. The cytologic preparations of BAL fluid should also examined for reactive type II pneumocytes (the atypia of these cells may be severe enough to mimic carcinoma), as well as fragments of hyaline membranes. Increased concentrations of toxic oxygen species, proteases and cytokines/chemokines (TNF-alpha, IL-1 and IL-8) have been found in the supernatant

In intensive care units, BAL is particularly useful for differentiating ARDS from: 1. diffuse alveolar hemorrhage (bloody fluid, erythrocytes and hemosiderin-laden macrophages); 2. acute eosinophilic pneumonia (marked increase in eosinophils); 3. drug-induced pulmonary toxicity (CD8+ lymphocytosis and foamy macrophages); 4. fast-growing neoplasms (cancer cells); 5. infections with associated acute lung injury (direct visualization or positive quantitative culture of the causative microorganism); 6. cryptogenic organizing pneumonia (CD8+ lymphocytosis, neutrophils and foamy macrophages)

Nakos G. Bronchoalveolar lavage fluid characteristics of early intermediate and late phases of ARDS. Alterations in leukocytes, proteins, PAF and surfactant components. Intensive Care Med 1998, 24: 296

BronchioloAlveolar Carcinoma

Definition

Bronchioloalveolar carcinoma (BAC) is a primary lung tumor that may present in a focal (more frequent) or diffuse form, both at onset and during the course of the disease. This chapter will cover only the diffuse form

Alveolar carcinoma, pulmonary adenomatosis

DEMOGRAPHICS

Etiology and pathogenesis

BAC is thought to originate from a bronchiolar stem cell capable of differentiating into different cell types. The multifocal form may result from a single lesion spreading through the airways or the synchronous growth of independent neoplastic clones. A viral etiology (retrovirus) has also been suggested based on the morphological similarity of BAC to jaagsiekte (a contagious viral disease in sheep)

Epidemiology

BAC accounts for 1-9% of all primary lung tumors. Age at diagnosis ranges from 50 to 70 years, and there is no racial or gender predilection

Risk factors

BAC features may be seen in old focal or diffuse scar lesions

CLINICAL FEATURES

History

In the diffuse form of BAC the most common symptoms (often present 6 months to 1 year before diagnosis) are cough (50-70%), sputum production (20-50%), bronchorrhea >100 ml/day (5-25%), chest pain (30-50%), dyspnea (25-50%), hemoptysis (10-25%) and weight loss (25%)

Physical findings

Physical examination reveals localized or diffuse rales and at times signs of pleural effusion

Pulmonary function tests

Lung function tests are often normal. There may be a restrictive ventilatory defect with reduced D_LCO and hypoxemia, which may be severe due to a physiologic shunt

Bronchorrhea is indicative of diffuse disease and may be so massive as to cause hypovolemia and prerenal failure with hyponatremia

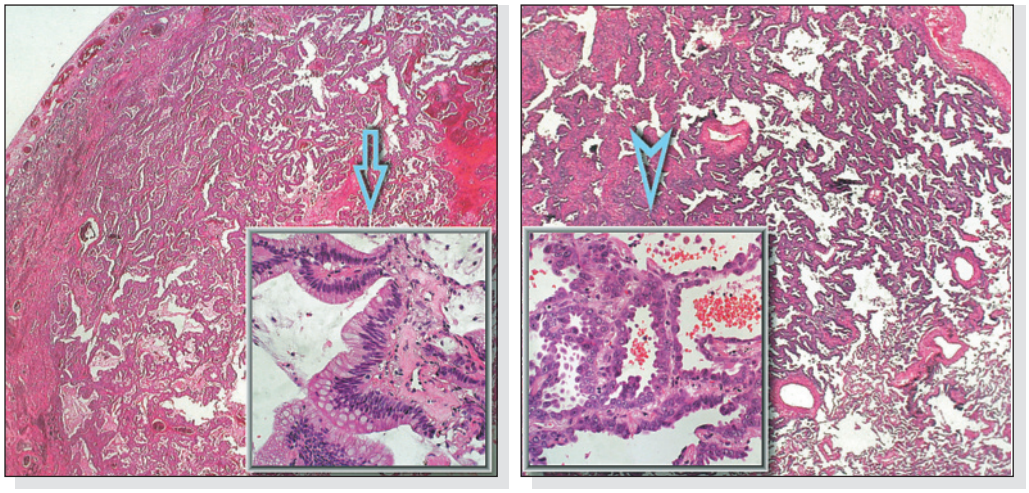
Harpole DH. Alveolar cell carcinoma of the lung: a retrospective analysis of 205 patients. Ann Thorac Surg 1988, 46: 502

PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Adenocarcinoma with tumor cells growing along the alveolar walls (lepidic growth pattern). By definition there is no stromal, vascular or pleural invasion
- Septa and interstitium may be thickened by fibrosis or chronic inflammatory infiltrate
- Tumor cells may or may not secrete mucous and, based on their prevalence, bronchioloalveolar carcinomas are classified into mucinous (⇨), non-mucinous (≻) and mixed



Mucinous BAC consists of columnar cells with round basal nuclei and abundant clear cytoplasm rich in mucin that often form micropapillae. In this variant, which may present as a solitary nodule, multiple nodules or alveolar consolidation (diffuse pneumonitis variant), dissemination often occurs through the airways with the formation of satellite nodules and rapid development of diffuse intrathoracic disease

Non-mucinous BAC may exhibit the two distinct cell types of the distal lobule: one is similar to Clara cells, with cuboid or cylindrical eosinophilic cytoplasm with apical projections and PAS-positive granules; the other is similar to type II pneumocytes, and consists of squamoid cells with round nuclei and finely vacuolated or even foamy cytoplasm. The nuclei of either of these cell types may show eosinophilic inclusions surrounded by a clear halo. Dissemination through the airways is rare in this variant

Mixed or indeterminate BAC consists of a mixture of mucinous and non-mucinous cells or indeterminate cells which grow along the alveolar walls without invading the stroma

Non-mucinous BAC is often associated with central alveolar collapse leading to fibrosis. The fibrosis should not be mistaken for the scars seen at the center of peripheral adenocarcinomas (scar cancer)

Distribution

Diffuse along the alveolar septa

It is not uncommon to find foci of adenocarcinoma with stromal invasion associated with features of bronchioloalveolar growth; consequently, the histopathologic diagnosis of a "pure" BAC requires extensive sampling to exclude the presence of stromal invasion

A four-point grading system for stromal invasion has recently been proposed which has prognostic implications. Invasion is absent in BAC (grade 0) and present to varying degrees in adenocarcinoma (grades 1, 2, 3)

Brambilla E. The new World Health Organization classification of lung tumours. Eur Respir J 2001, 18: 1059

Sakurai H. Grade of stromal invasion in small adenocarcinoma of the lung: histopathological minimal invasion and prognosis. Am J Surg Pathol 2004, 28: 198

Differentials

Histopathologic differential diagnoses:

- Atypical adenomatous hyperplasia: the lesion is smaller than 5 mm, the cells are arranged in a single layer, and cytological atypia is not prominent
- Bronchiolar metaplasia (lambertosis): the lesion is centrilobular and originates from the bronchiole. There may be an identifiable connection with clearly benign epithelium. The cells are often ciliated and show no evidence of malignancy or nuclear inclusions
- Type II pneumocyte hyperplasia: the cellular monotony and lepidic growth pattern typical of BAC are absent, and the transition to normal epithelium is gradual
- Clara cell, papillary and alveolar adenomas: small, well-circumscribed lesions without cytologic atypia
- Sclerosing hemangioma: papillary, well-circumscribed lesion with areas of recent and old hemorrhage and sclerosis
- Metastases: infiltration of the septa, marked atypia, history of neoplasm

Although both primary and metastatic adenocarcinomas (e.g. of the colon and pancreas) may exhibit bronchioloalveolar-type (lepidic) growth patterns at the periphery, they also show stromal, vascular (hematic or lymphatic) or pleural invasion

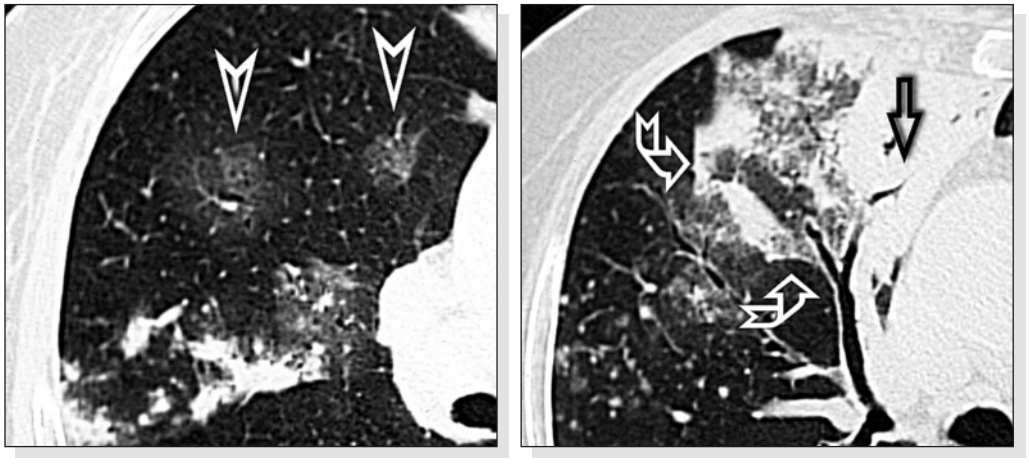
Travis WD. Histopathologic typing of lung and pleural tumours: World Health Organization International Histological Classification of Tumours, 3rd ed. Springer, 1999

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Multiple areas of parenchymal consolidation (↳)
- Ground-glass opacities with irregular hazy contours (➢)
- Air bronchogram within the lesions giving the appearance of a leafless tree (⇨)



Adler B. High-resolution CT of bronchioloalveolar carcinoma. AJR Am J Roentgenol 1992, 159: 275

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

✓ One of the parenchymal opacities usually predominates in terms of density or extension

Distribution

Unilateral or bilateral, usually asymmetrical, often patchy

Peripheral and subpleural (50%)

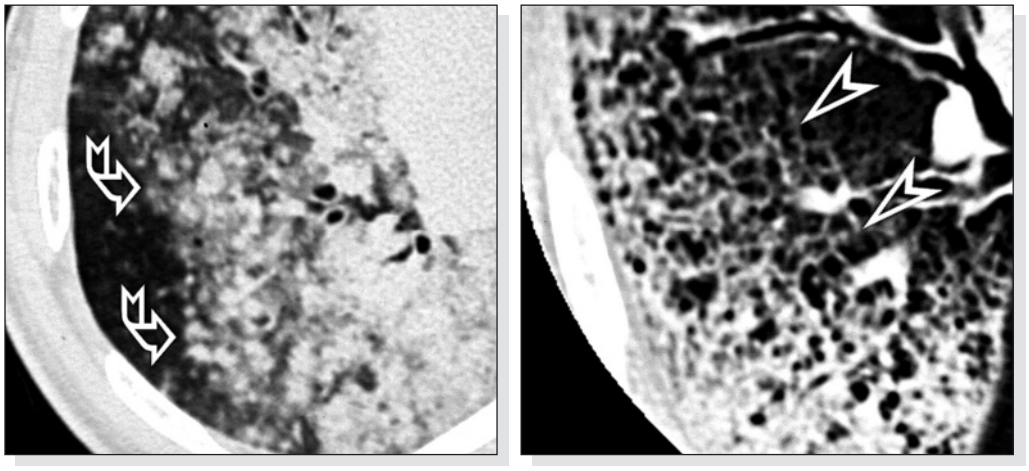
Basal (50%)

Other signs

Lung volume is normal, although bulging of the fissural border may be noted in extensive lobar consolidation

Other radiological characteristics:

- Nodules with hazy margins (↳) or true large opacities (● Large rounded opacities: BAC)
- Internal hyperlucencies appearing as pseudocavitations or pseudocysts
- Low-attenuating parenchymal consolidation with enhancing vessels after administration of contrast material (angiogram sign)
- Linear bands of septal thickening associated with the ground-glass opacity (crazy paving) (➢)
- Adenopathy, pleural effusion, calcifications (of the mucoid matrix)



Im JG. Lobar bronchioloalveolar carcinoma: "angiogram sign" on CT scans. Radiology 1990, 176: 749

Recent research suggests that a pattern of well-defined nodules, once thought to be possible in BAC, is instead due to hematogenous spread of components of classical adenocarcinoma

The pseudocavitary hyperlucencies are related to bronchiolar obstruction, even though true cavitations may also occur (rarely)

Gaeta M. Radiolucencies and cavitation in bronchioloalveolar carcinoma: CT-pathologic correlation. Eur Radiol 1999, 9: 55

Differentials

All diseases characterized by chronic parenchymal consolidation enter the differential diagnoses:

- Slowly resolving infections: the clinical history and the regression of the opacities in subsequent radiograms are the key to the diagnosis
- OP: the peripheral and/or peribronchial areas of consolidation tend to be triangular or polygonal in shape
- PAP: bilateral, symmetrical, more extensive in the axial plane; widespread crazy paving
- CEP: the areas of consolidation are more distinctly subpleural and prevail in the upper lung fields
- MALToma: differentiation may be impossible, except for a slower progression; the differential diagnosis is based on the biopsy findings
- Exogenous lipoid pneumonia: clinical history, at times negative density at CT

Aquino SL. Distinction of consolidative bronchioloalveolar carcinoma from pneumonia: do CT criteria work? AJR Am J Roentgenol 1998, 171: 359

COURSE and COMPLICATIONS

Associated diseases

Superimposed acute bacterial diffuse or localized pneumonia

Clinical course

The clinical progression of the diffuse form of BAC is very rapid, with death sometimes occurring within weeks of diagnosis. The most frequent causes of death are respiratory failure, pulmonary embolism, cardiac tamponade, pneumothorax and pneumonia

Radiological course

The existing areas of consolidation become more compact and homogeneous, and new areas of consolidation appear, even contralaterally, as a result of bronchogenic spread, in a relentless progression

LABORATORY FINDINGS

About half of patients show increased serum carcinoembryonic antigen levels, whereas a smaller proportion have increased amylasemia and CA 19-9. Patients with bronchorrhea may have elevated azotemia due to prerenal failure and electrolyte disturbances

CLINICAL DIAGNOSIS

In an appropriate clinical and radiological setting, the repeated finding of well-differentiated cancer cells in the sputum is considered diagnostic (25-50% of cases)

INVASIVE DIAGNOSIS

In some cases, the diagnosis requires a histological sample which may be obtained by transbronchial or transthoracic lung biopsy. However, the diagnostic certainty of a “pure” BAC requires extensive samples and therefore surgical lung biopsy

Bronchoalveolar lavage

Analysis of the BAL fluid often reveals the presence of well-differentiated neoplastic alveolar cells, although this finding is not sufficient for differentiating BAC from a primary or metastatic adenocarcinoma

The cytologic preparations of BAL fluid during AIP or ARDS may show reactive type II pneumocytes with consistent atypia

Sprigmeyer SC. Bronchioloalveolar cell carcinoma diagnosed by bronchoalveolar lavage. Chest 1983, 83: 278

Constructive Bronchiolitis

Definition

Bronchiolitis refers to a heterogeneous group of diseases characterized by non-specific inflammation of the small airways. This chapter, devoted to the forms in which the dominant histopathologic change is a narrowing of the distal bronchioles, will mainly cover idiopathic constrictive bronchiolitis (CB)

☯ Bronchiolitis obliterans

✓ Various diseases may have histological changes of CB and the corresponding clinical and radiological presentations:

- Healed infections (e.g. adenovirus, respiratory syncytial virus, mycoplasma, influenza)
- Collagen vascular diseases (e.g. rheumatoid arthritis)
- Exposure to toxic fumes
- Damage induced by Sauropus androgynus, a vegetable of the Euphorbiaceae family taken for weight reduction purposes
- Lung, heart-lung and allogenic bone marrow transplant (graft versus host disease - GVHD)
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Bronchial asthma
- Sarcoidosis
- HP

DEMOGRAPHICS

Etiology and pathogenesis

The causative agent and pathogenesis are unknown

Epidemiology

Idiopathic CB is a rare clinical-pathological syndrome seen in middle-aged adults, and more commonly in females. It accounts for 4% of all obstructive pulmonary diseases

Risk factors

There are no known risk factors, not even cigarette smoking

CLINICAL FEATURES

History

The main symptoms are dyspnea, dry cough and rarely wheezing. Systemic symptoms such as malaise and asthenia may also be noted. The symptoms may be present for several months before diagnosis

Physical findings

Chest physical examination is generally unhelpful, although there have been rare reports of wheezes, rales and ronchi

Pulmonary function tests

Typically there is an irreversible obstructive ventilatory pattern. The obstruction is often severe and accompanied by a reduced D_LCO

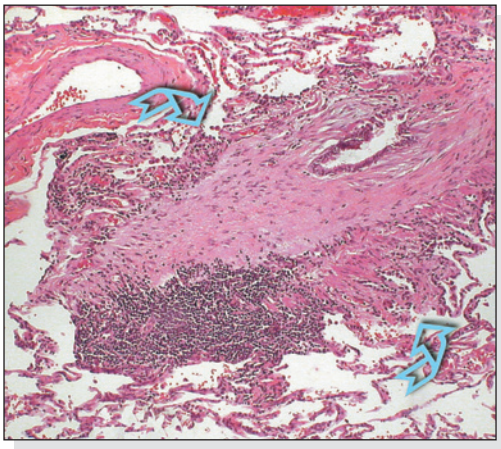
📖 Kraft M. Cryptogenic constrictive bronchiolitis. A clinicopathologic study. Am Rev Respir Dis. 1993, 148: 1093

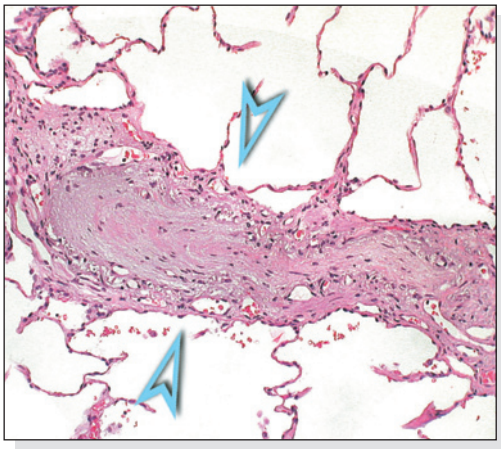
PATHOLOGY

Basic lesions

CB usually presents as an isolated lesion of the bronchioles, with only minimal, if any, changes to the surrounding parenchyma. The basic lesions include:

- Narrowing and distortion of the lumen of the small airways due to submucosal or adventitial fibrosis (↳). In the more severe cases the lumen may be completely obliterated (≻)
- Hypertrophy of the bronchiolar wall smooth muscle
- Bronchiolar ectasia with mucostasis
- Bronchiolar metaplasia of the alveolar epithelium (“bronchiolization” or “lambertosis”)





Distribution

Centrilobular

Differentials

Histopathologic differential diagnoses:

- Normal lung: the bronchiole and accompanying branch of the pulmonary artery have similar diameters, and no fibrosis is present in the bronchiolar wall
- LCH: peribronchiolar nodules and cysts consisting of fibrous tissue with inflammatory cells such as Langerhans' cells and eosinophils
- RB: pigmented macrophages in the peribronchiolar alveolar spaces associated with slight changes in the bronchiolar wall
- OP: the lumen of the distal respiratory bronchioles is obliterated by plugs of granulation tissue

Colby TV. Bronchiolitis. Pathologic considerations. Am J Clin Pathol 1998, 109: 101

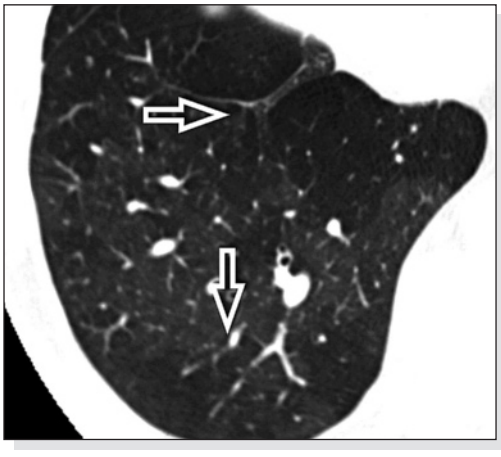
The bronchiole and accompanying branch of the pulmonary artery have a similar diameter and are uniformly distributed in the peripheral parenchyma. Any variation to this condition suggests small airways disease. In addition, the normal bronchiole has a layer of loose connective tissue beneath the epithelium. In patients with small airways disease fibrous tissue is deposited in this area

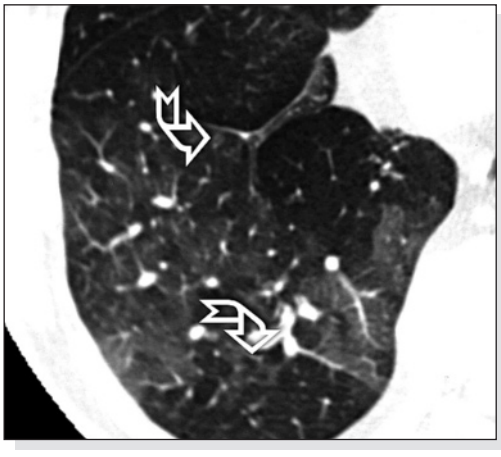
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Well-defined patchy areas of reduced parenchymal density (⇨), which stand out on a background of normal lung
- Paucity (reduction in number and diameter) of vascular structures within the pathological areas without distortion of the lobular architecture (mosaic pattern)
- Expiratory air-trapping (↳)





In about one third of cases the diseased areas are visible on expiratory scans only

The hypoperfusion results from reflex vasoconstriction in the areas of the lung which are less ventilated due to bronchiolar narrowing. The narrowing also produces air-trapping in these areas which is well-depicted on expiratory CT scans

Hansell DM. HRCT of obliterative bronchiolitis and other small airways diseases. Semin Roentgenol 2001, 36: 51

Stern EJ. Small-airway diseases of the lungs: findings at expiratory CT. AJR Am J Roentgenol 1994, 163: 37

Distribution

Generally bilateral, asymmetrical and patchy

In some secondary forms of localized CB, such as post-infectious CB in Swyer-James syndrome (MacLeod), the lesions may predominate in one lung or lobe

In contrast, severe and extensive disease (rare) may have an almost uniform distribution similar to emphysema

Swyer-James syndrome is the effect of post-infectious CB usually due to viral infections contracted in early infancy. Damage to the bronchioles leads to incomplete development of the distal respiratory structures and to the formation of bronchiectasis proximally. Pulmonary vascularity is consequently reduced

Variable

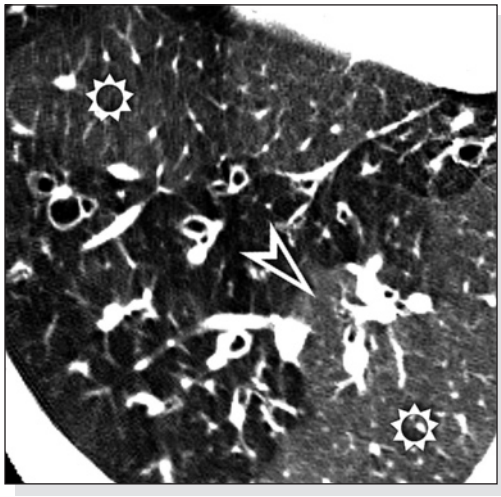
Variable

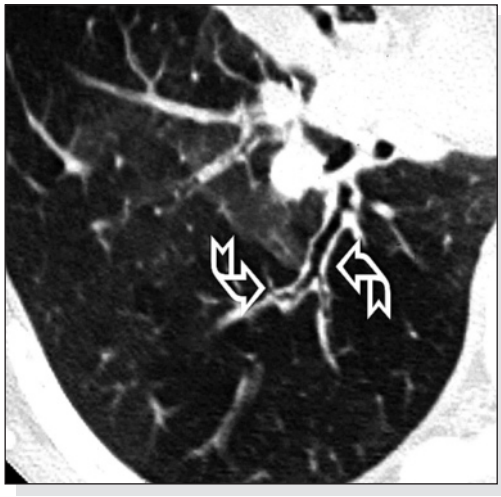
Lung volume is normal or increased, except in Swyer-James syndrome in which the volume of the affected areas is reduced

Other signs

Other radiological signs:

- Increased density of the normally ventilated areas (☼) where the vessels are enlarged (≽) due to hyperperfusion, at times to the point of simulating disease (pseudo-ground-glass opacity)
- Direct signs of airway disease (bronchial wall thickening (↳), bronchiolectasis, etc.)





A number of diseases, such as extrinsic allergic alveolitis, and airway infections (mycoplasma) may show an alternation of areas of three different levels of density (head-cheese pattern): true ground-glass opacities, areas of normally ventilated parenchyma, and hyperlucent areas due to air-trapping

Waitches GM. High-resolution CT of peripheral airways diseases. Radiol Clin North Am 2002, 40: 21

Differentials

Radiological differential diagnoses:

- Chronic pulmonary thromboembolism: the vessels within the areas of oligemia are reduced in number and diameter, but there is no expiratory air-trapping. The central pulmonary arteries may be dilated due to chronic arterial hypertension
- Diseases responsible for patchy ground-glass opacities: the pulmonary vessels are equally well-depicted and have similar diameters both in the hypodense and hyperdense areas. There is no expiratory air-trapping
- Panlobular emphysema: the hyperlucency is diffuse rather than patchy and bilaterally symmetrical with lower lobe predominance. In addition, there is distortion with straightening and rigidity of the vascular markings
- Postobstructive emphysema: the hyperlucency is uniform rather than patchy even if the affected area is limited. The cause of the obstruction can usually be identified

Overall, HRCT is able to differentiate CB from other causes of mosaic perfusion in more than 70% of cases

Copley SJ. Thin-section CT in obstructive pulmonary disease: discriminatory value. Radiology 2002, 223: 812

Worthy SA. Mosaic attenuation pattern on thin-section CT scans of the lung: differentiation among infiltrative lung, airway, and vascular diseases as a cause. Radiology 1997, 205: 465

COURSE and COMPLICATIONS

Associated diseases

Recurrent bronchiolar superinfections, with clinically obrious flare-ups

Clinical course

Clinical course varies from rapid evolution to long periods of stability. There is no definitely effective treatment.

Radiological course

Radiological course is variable. Among the secondary forms of CB, those due to rheumatoid arthritis, graft versus host disease in bone marrow transplant, and chronic rejection in lung transplant are progressive and have a poor response to therapy. The microgranulomatous forms (sarcoidosis, HP) may regress completely or partially with regression of the disease

LABORATORY FINDINGS

Laboratory findings are usually non-specific and unhelpful for diagnosis

CLINICAL DIAGNOSIS

Idiopathic CB should be suspected in the presence of an irreversible obstructive ventilatory defect without a previous history or clinical findings of associated diseases. The diagnostic suspicion can be confirmed by HRCT in the majority of cases

INVASIVE DIAGNOSIS

Transbronchial lung biopsy is rarely diagnostic and surgical lung biopsy may become indispensable for reaching a diagnosis in doubtful cases, in cases with possible multifactorial etiology or when considering a lung transplant

Bronchoalveolar lavage

The BAL fluid shows marked neutrophilia (>25%) and an increase in neutrophil products such as collagenase and myeloperoxidase. BAL neutrophilia tends to decrease in patients responding to treatment

Dorinsky PM. Adult bronchiolitis. Evaluation by bronchoalveolar lavage and response to prednisone therapy. Chest 1985, 88: 58

Chronic Eosinophilic Pneumonia

Definition

Chronic eosinophilic pneumonia (CEP) is an idiopathic condition characterized by an abnormal accumulation of eosinophils in the lungs. The clinical course lasts more than 3 months

DEMOGRAPHICS

Etiology and pathogenesis

The etiology is unknown, although there have been occasional reports of association with aspergillus infection, rheumatoid arthritis, and cutaneous vasculitis. The frequent association with atopy and elevated IgE levels suggests a Gell and Coombs type I immune reaction mechanism. The lungs of these patients contain a high number of activated eosinophils that produce eosinophil cationic protein (ECP) and an increase in activated helper lymphocytes (CD4+) that produce interleukins (IL): IL-5, IL-6 and IL-10

Epidemiology

The disease is rare and the true prevalence and incidence are unknown. Women are more frequently affected (2:1), with a peak incidence between 20 and 50 years of age. There have been rare reports of familial cases

Risk factors

Atopy, allergen immunotherapy

CLINICAL FEATURES

History

The onset of disease is insidious, with symptoms being present for at least 2-3 months before diagnosis. The most common symptoms are: cough (80-90%), fever as high as 40°C (80-90%), dyspnea, weight loss, night sweats and malaise. Asthma accompanies or precedes the illness in about 50% of cases. Hemoptysis, chest pain and myalgia are rarely noted

Physical findings

Chest physical examination is non-specific, with wheezes, rales and signs of pulmonary consolidation

Pulmonary function tests

These often reveal a restrictive or mixed ventilatory pattern with reduced D_LCO. In the acute phases there may be severe hypoxemia. After remission, an obstructive ventilatory defect is common at times associated with irreversible small airways obstruction

Allen JN. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994, 150: 1423

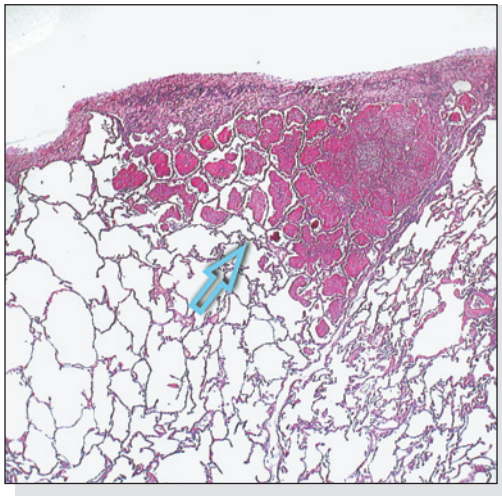
Naughton M. Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. Chest 1993, 103: 162

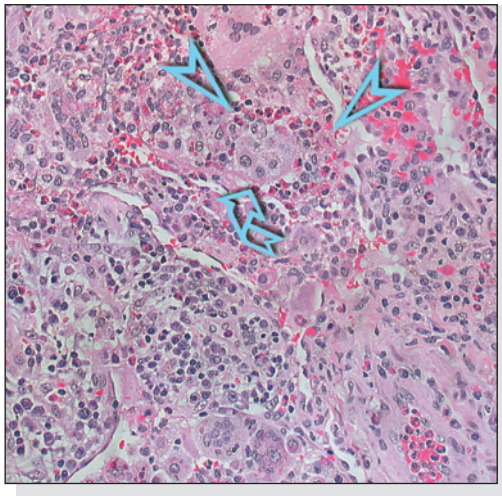
PATHOLOGY

Basic lesions

CEP is characterized by:

- Aggregates of eosinophils (➢) and macrophages (↳) filling the air spaces (⇨)
- Type II pneumocyte hyperplasia
- Increased interstitial eosinophils





The intraalveolar aggregates of eosinophils often contain necrotic foci (eosinophilic abscesses). Macrophages and pneumocytes typically have dense eosinophilic cytoplasm. There may be numerous foci of intraalveolar fibroblastic organization as in OP, and interstitial lymphoplasmacellular infiltrate. Giant cells and mild non-necrotizing vasculitis of arterioles and venules may also be present

Distribution

Diffuse intraalveolar

Differentials

Histopathologic differential diagnoses:

- DIP: eosinophils are rare in the alveolar spaces, and there is a predominance of macrophages. Type II pneumocyte hyperplasia is less prominent, and there is no necrosis within the intra-alveolar aggregates
- LCH: stellate scars and small cysts with Langerhans' cells. Eosinophils are fewer and interstitial
- Churg-Strauss syndrome: necrotizing granulomas rich in eosinophils ("red" necrosis). Necrotizing vasculitis is also present
- Wegener's granulomatosis, eosinophilic variant: patchy necrosis containing neutrophils ("blue" necrosis) and intense vasculitis. The eosinophilic infiltrate is interstitial and mixed with granulomatous inflammation

Jederlinic PJ. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine 1988, 67: 154

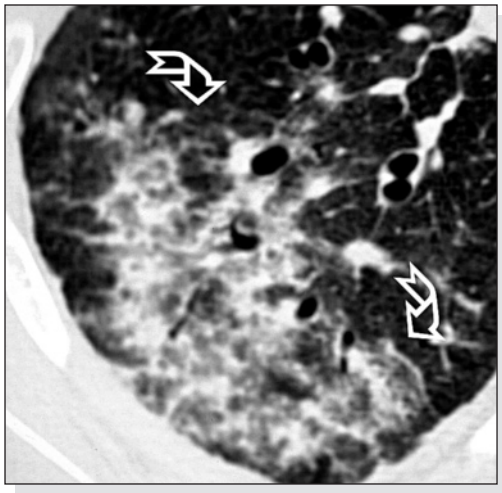
Olopade CO. Chronic eosinophilic pneumonia and idiopathic bronchiolitis obliterans organizing pneumonia: comparison of eosinophil number and degranulation by immunofluorescence staining for eosinophil-derived major basic protein. Mayo Clin Proc 1995, 70 : 137

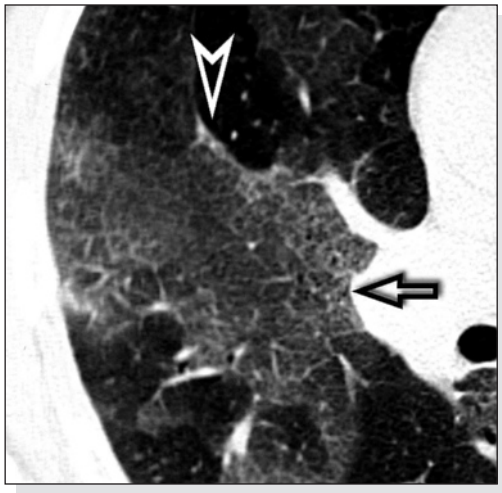
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Multiple areas of consolidation (↳) with non-segmental distribution
- Ground-glass opacities (≻)
- Patchy ground-glass opacities associated with smooth septal thickening (crazy paving)(⇨)





Distribution

Unilateral or bilateral, patchy

Peripheral, subpleural

Often predominant in the upper or central lung regions

✓ The classical appearance has been described as photographic negative of the "butterfly" or "batwing" pattern seen in alveolar edema

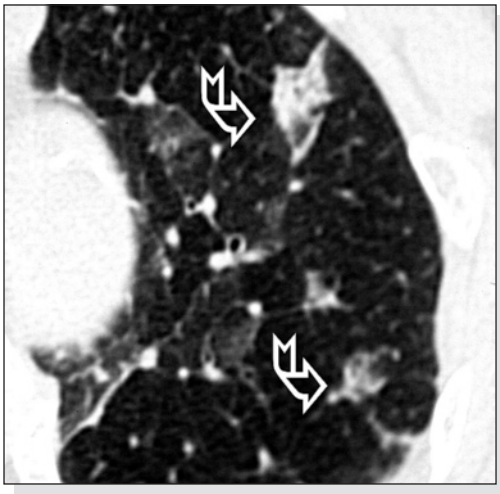
Johkoh T. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. Radiology 2000, 216: 773

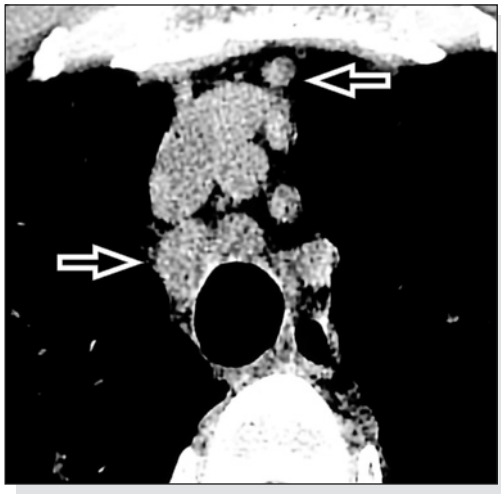
Other signs

Lung volume is preserved

Other radiological signs:

- Nodular opacities with hazy contours (↳)(20%)
- Areas of atelectasis
- Mediastinal adenopathy (⇨)
- Pleural effusion (rare)





Jederlinic PJ. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine 1988, 67: 154

Mayo JR. Chronic eosinophilic pneumonia: CT findings in six cases. AJR Am J Roentgenol 1989, 153: 727

Differentials

Radiological differential diagnoses:

- OP: the lesions are not only confined to the lung periphery, but are also bronchocentric and predominate in the lower lobes. In addition, a macronodular appearance or a pattern of round opacities is frequent. There may be patchy air-trapping. Septal thickening or parenchymal bands are uncommon
- Slowly-resolving bacterial infections: distribution is different from that typically seen in CEP, and the clinical findings are not suggestive of CEP
- Churg-Strauss syndrome: the areas of consolidation may have a random distribution and be migratory. The differential diagnosis is nonetheless difficult
- Drug toxicity (amiodarone-induced lung disease): the areas of parenchymal consolidation are often hyperdense and tend to be located in the lower lobes. Hyperdensity of the liver and spleen and at times of the myocardium may be present

Arakawa H. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. AJR Am J Roentgenol 2001, 176: 1053

Bain GA. Pulmonary eosinophilia. Eur J Radiol 1996, 23: 3

Worthy SA. Churg-Strauss syndrome: the spectrum of pulmonary CT findings in 17 patients. AJR Am J Roentgenol 1998, 170: 297

COURSE and COMPLICATIONS

Associated diseases

Asthma is present in almost 50% of patients

Clinical course

Response to steroid treatment is generally dramatic with improvement of symptoms within 24 hours and clinical and radiological remission within 3 weeks. Progression to diffuse lung fibrosis is rare. The disease tends to recur frequently after discontinuation of steroid treatment (75%)

☝ Steroid treatment failure should prompt reconsideration of the diagnosis of CEP

Radiological course

During regression, consolidation tends to disappear centrifugally and may be temporarily followed by subpleural curvilinear bands. If the disease is left untreated, the opacities may progressively increase in number and even migrate

📖 Ebara H. Chronic eosinophilic pneumonia: evolution of chest radiograms and CT features. J Comput Assist Tomogr 1994, 18: 737

LABORATORY FINDINGS

In 85% of patients, peripheral eosinophilia is present (10-40% of white blood cells or more than 500 eosinophils/mmc). Erythrocyte sedimentation rate (ESR) may exceed 100 mm/hour. There may be hypochromic anemia, thrombocytosis and elevated IgE levels

✓ Persistence of peripheral eosinophilia >1500 cells/mmc for more than 6 months should suggest a diagnosis of hypereosinophilic syndrome

CLINICAL DIAGNOSIS

The association of characteristic clinical, laboratory and radiological findings are required for diagnosis

☝ In addition to CEP, a number of other conditions can cause pulmonary eosinophilia (see the table "Eosinophilic lung diseases" at the end of this chapter). Differential diagnosis among these diseases is complex. However, the following criteria apply: 1. normal total IgE levels in a patient with eosinophilic pneumonia rule out allergic bronchopulmonary aspergillosis and helminth infestation; 2. asthma is usually present in subjects with allergic bronchopulmonary aspergillosis, in 50% of CEP cases and is a characteristic feature of Churg-Strauss syndrome; 3. atopy is unusual in eosinophilic pneumonia due to drug toxicity, helminth infestation, and acute eosinophilic pneumonia

INVASIVE DIAGNOSIS

Transbronchial lung biopsy and/or BAL, is indicated if the clinical, radiological and laboratory findings are uncharacteristic and in particular, in the absence of peripheral eosinophilia

☝ If a biopsy is performed, this should be done under radiological guidance as areas of consolidation may rapidly migrate from one zone to another within the lungs

The biopsy should be performed before steroid treatment, since steroids can drastically reduce the number of intraalveolar and interstitial eosinophils

Bronchoalveolar lavage

The BAL fluid is characterized by eosinophilia >25-40%. The eosinophils often appear degranulated. The finding of degenerating alveolar macrophages is frequent. Significantly high concentrations of ECP may be found in the supernatant

The highest proportion of eosinophils in BAL fluid are found in association with CEP and Churg-Strauss syndrome

📖 Allen JN. Diagnostic significance of increased bronchoalveolar lavage fluid eosinophils. Am Rev Respir Dis 1990, 142: 642

Olivieri D. Eosinophilic alveolitis in immunologic interstitial lung disorders. Lung 1990, 168 Suppl: 964

TABLE

On the following page is a table which presents:

- Eosinophilic lung diseases

EOSINOPHILIC LUNG DISEASES

CEP	Condition characterized by bilateral peripheral airspace consolidations with fever, dyspnea, weight loss and malaise of several weeks duration. Usually there is eosinophilia and high serum levels of IgE
Parasitic infections	Many parasite infestations may cause eosinophilic pneumonia, including Ascaris lumbricoides, Strongyloides stercoralis, Toxocara canis, etc
Hypereosinophilic syndrome	A condition in which mature eosinophils infiltrate different organs; the heart and nervous system are most frequently involved, whereas the lung is affected in 30-40% of cases. Usually there is peripheral eosinophilia >1500 cells/mmc for more than 6 months
Churg-Strauss syndrome	This is a small vessel systemic vasculitides that may affect various organs. The most typical features are asthma, rhinosinusitis and peripheral eosinophilia. Pulmonary infiltrates are present in about two thirds of patients
Drug-toxicity	Many drugs can cause eosinophilic pneumonia, including anti-infectious, anti-inflammatory, cytotoxic agents, and L-tryptophan
Allergic bronchopulmonary aspergillosis	A clinical syndrome seen in patients with chronic asthma who develop hypersensitivity to fungal antigens, and in particular to Aspergillus fumigatus. About one third of patients may exhibit eosinophilic pulmonary infiltrates
Acute idiopathic eosinophilic pneumonia	Lung disease characterized by acute (<7 days) respiratory failure often requiring mechanical ventilation. There is no blood eosinophilia

DAH in Wegener's granulomatosis

Definition

Systemic vasculitides are diseases characterized by an inflammatory process of the vessel wall. The forms most frequently presenting with pulmonary involvement are Wegener's granulomatosis, Churg-Strauss allergic angiitis and granulomatosis, and microscopic polyangiitis

This chapter will deal with Wegener's granulomatosis as a representative example, and in particular with its diffuse lung involvement in the form of diffuse alveolar hemorrhage (DAH) (see the table entitled "Vasculitides syndromes associated with DAH" at the end of the chapter)

Diffuse Alveolar Hemorrhage

Travis WD. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 1990, 14: 1112

Travis WD. Vasculitis of the lung. Pathology 1996, 4: 23

The anatomical and radiological manifestations of Wegener's granulomatosis are not limited to DAH, but also include large nodules or masses (● Large rounded opacities: Wegener's granulomatosis)

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis are unknown, although various causative agents and pathogenetic mechanisms have been implicated in the development of Wegener's granulomatosis. These include genetic predisposition, infectious agents, autoantibodies, (in particular anti-neutrophil cytoplasmic antibodies C-ANCA), immune complex deposition, and involvement of cell-mediated immunity. The etiology is most likely to be multifactorial

Epidemiology

The prevalence is about 1.5-3 cases per 100,000 people. The disease primarily affects adults between 30 and 50 years of age, without sex predilection. DAH is present in approximately 5% of cases at presentation

Risk factors

Spring months, pregnancy, silica exposure, allergic syndrome (cutaneous, drug-induced, reaction to insect bites). Advanced age and renal involvement at onset are negative prognostic factors

CLINICAL FEATURES

History

Onset is usually abrupt with dyspnea, cough, and hemoptysis (which may however be absent in up to one third of patients with DAH). Patients may report symptoms secondary to upper airway involvement (50-75% of cases), as well as symptoms ascribable to involvement of other organs (kidney in 75-85% of cases, polyneuritis in 20-35%, eye in 10-15%, skin in 10-15%, and muscles and joints in 30%)

Physical findings

If DAH is present, physical examination of the chest reveals fine diffuse rales or signs of pulmonary consolidation. There may be physical signs of the underlying systemic vasculitis in other organs

Pulmonary function tests

DAH causes an increase in D_LCO due to the abundance of hemoglobin in the airspaces. Hypoxemia, moderate to severe, is frequent

In the follow-up, D_LCO monitoring may reveal disease recurrence

DAH in Wegener's granulomatosis needs to be differentiated from other forms of vasculitis with capillaritis (see the table entitled "Vasculitis syndromes associated with DAH" at the end of the chapter) as well as from other conditions responsible for DAH, such as lung damage induced by drugs (penicillamine, nitrofurantoin, propylthiouracil) (⌘ Drug toxicity) or toxic inhalation (trimellitic anhydride, cocaine, paraquat, pesticides, isocyanates)

Imoto EM. Pulmonary capillaritis and hemorrhage. A clue to the diagnosis of systemic necrotizing vasculitis. Chest 1989, 96: 927

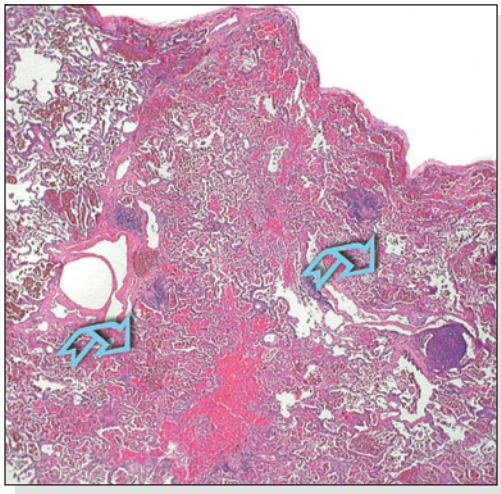
Langford CA. Wegener's granulomatosis. Thorax 1999, 54: 629

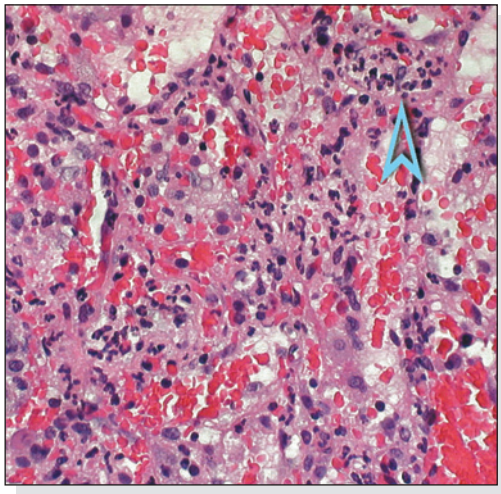
PATHOLOGY

Basic lesions

DAH in Wegener's granulomatosis presents as:

- Intraalveolar accumulation of red blood cells and hemosiderin-laden macrophages (↳). This may be associated with capillaritis, consisting of an intense neutrophilic infiltrate around the capillaries of the alveolar septa (➢), as well as foci of organizing pneumonia (OP)
- In chronic hemorrhage there is also fibrous septal thickening and the presence of hemosiderin-laden septal and intraalveolar macrophages





✓ Capillaritis is often a focal and transient process: its presence may therefore depend on the timing of the biopsy

☝ The characteristic lesions of Wegener's granulomatosis should be sought in the interstitium: these may be primary or secondary

The primary lesions are necrosis, vasculitis and background granulomatous inflammation. Necrosis may present in the form of both neutrophil microabscesses and extensive patchy ("geographic") basophilic ("blue") areas due to the prevalence of neutrophils. Vasculitis may affect the arteries, veins or capillaries. The lesion is often focal and all types of inflammatory cells are implicated. Granulomatous inflammation may be expressed both by giant cells, sparse or in small groups, and by palisading histiocytes around the necrotic foci

Secondary lesions, bronchial or parenchymal, include alveolar hemorrhage, OP, lymphoid hyperplasia, endogenous lipoid pneumonia, acute, chronic and follicular bronchiolitis, tissue eosinophilia. Secondary lesions sometimes dominate the morphological pattern

Distribution

Diffuse intraalveolar

The finding of "endogenous pneumoconiosis" is frequent during chronic hemorrhage

It consists of hemosiderin deposition in the vessel walls with fragmentation of the elastic lamina and consequent giant cell granulomatous reaction (not to be mistaken for Wegener's granulomatous inflammation)

Differentials

Histopathologic differential diagnoses:

- Traumatic hemorrhage (biopsy-related): this is the most common cause of intraalveolar bleeding. The macrophages show no hemosiderin or erythrophagocytosis and the red blood cells are not mixed with fibrin. Capillaritis is absent
- Neutrophilic margination: the neutrophils within the lumen of capillaries may adhere to the vessel walls and simulate capillaritis
- Microscopic polyangiitis (MPA): absence of granulomas
- Churg-Strauss syndrome: prominent eosinophilic infiltrate ("red" necrosis)
- Idiopathic pulmonary hemosiderosis: capillaritis is uncommon, but differentiation requires clinical and radiological data
- Other pulmonary hemorrhagic syndromes (diffuse pulmonary hemorrhage due to anti-basal membrane antibodies, systemic lupus erythematosus (SLE), idiopathic glomerulonephritis, drugs, Henoch-Schönlein purpura, IgA disease, cryglobulinemia, pulmonary-renal syndrome): differentiation is based on clinical-serological data, immunofluorescence and electron microscopy findings. The characteristic lesions of Wegener's granulomatosis are absent
- Hemorrhagic DAD (due to crack, cocaine): presence of acute-phase hyaline membranes, and marked hyperplasia of type II pneumocytes
- Infectious hemorrhagic pneumonia: the neutrophils are predominantly intraalveolar and peribronchial
- DIP and RB-ILD, smoker's lung: the macrophages contain finely dispersed granules of pigment which are negative or weakly positive for iron, whereas the granules in chronic hemorrhage are coarse and strongly positive for iron

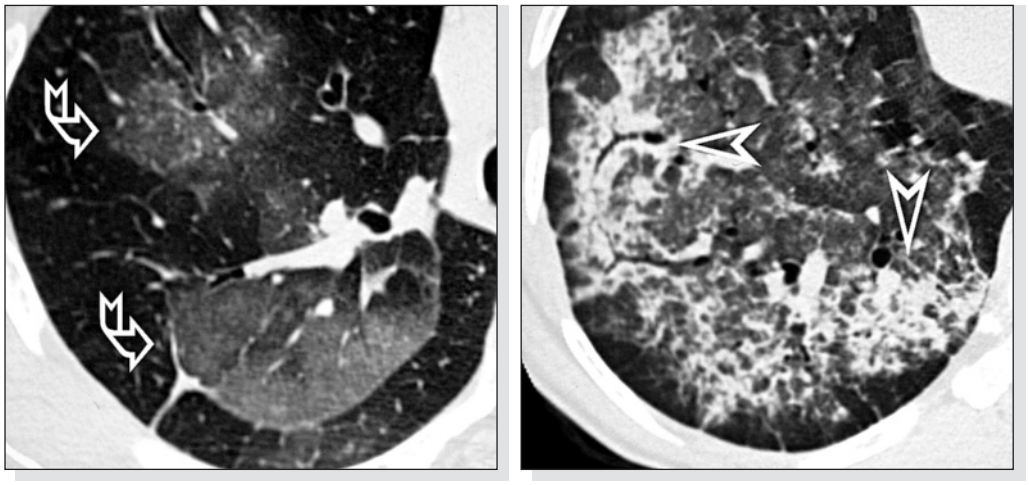
Travis WD. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 1990, 14: 1112

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Areas of ground-glass attenuation (↳)
- Multiple areas of parenchymal consolidation (➢)



Parenchymal consolidation may reflect alveolar hemorrhage, edema or superimposed infections (favored by pharmacological immunosuppression). At times there are true peripheral wedge-shaped opacities due to tissue infarction in connection with the pulmonary vessels

Hansell DM. Small-vessel diseases of the lung: CT-pathologic correlates. Radiology 2002, 225: 639

Primack SL. Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. AJR Am J Roentgenol 1995, 164: 295

Distribution

Bilateral (even though unilateral predominance is also possible), diffuse or patchy

Diffuse, at times predominant in the parahilar region ("butterfly" or "batwing" pattern) with absence in the subpleural regions

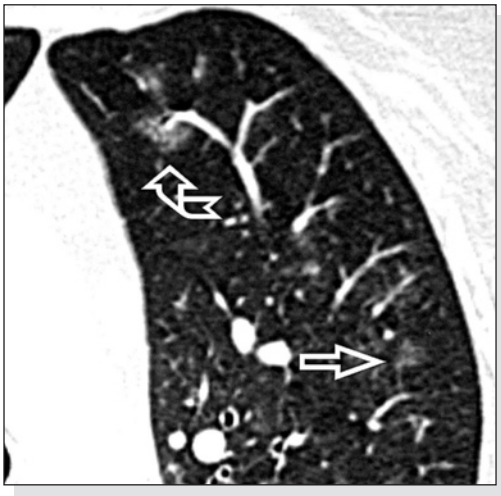
Variable; when diffuse, the lung apices and costophrenic sinuses are relatively unaffected

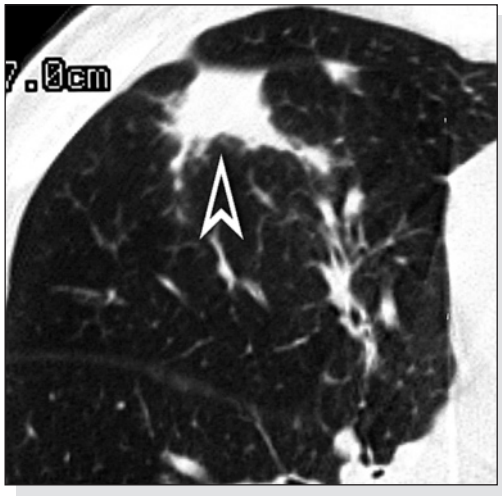
Lung volume is normal

Other signs

Other radiological signs:

- Scattered low-density nodules (⇨) (nodular ground-glass pattern), at times in connection with the small vessels (↳)
- Smooth septal thickening and crazy paving
- Round opacities with diameter varying between 1 and 4 cm, usually bilateral (75%), often cavitated and with irregular thick walls
- Macronodules (➢) and masses with ill-defined borders
- Hilar or mediastinal adenopathy (2-15%)
- Smooth or irregular tracheal stenosis with wall thickening and possible calcifications
- Pleural effusion (less than 10%)





In some cases the round opacities and masses are the dominant or exclusive sign of disease (● Large rounded opacities: Wegener's granulomatosis)

Tracheal stenosis tends to involve the subglottic cervical trachea; diffuse stenosis involving the central bronchi with lobar atelectasis or the entire lung is rare

Maguire R. Unusual radiographic features of Wegener's granulomatosis. AJR Am J Roentgenol 1978, 130: 233

Maskell GF. Computed tomography of the lung in Wegener's granulomatosis. Clin Radiol 1993, 48: 377

Stein MG. Computed tomography of diffuse tracheal stenosis in Wegener granulomatosis. J Comput Assist Tomogr 1986, 10: 868

Differentials

The radiological differential diagnoses are:

- Other vasculitis syndromes, hemorrhage collagen vascular diseases and immune diseases: the differential diagnosis is based on the clinical and laboratory findings, although the presence of nodules and masses with a tendency to cavitate is less common
- PE: pleural effusion (common), widening of the vascular pedicle, possible cardiomegaly, absence of macronodules or masses
- Infectious pneumonias: the pattern is often indistinguishable, especially in immunodepressed patients. Ground-glass attenuation in perihilar regions or in the upper lobes prevails in PCP, and thick/thin-walled cysts are possible

Specks U. Granulomatous vasculitis. Wegener's granulomatosis and Churg-Strauss syndrome. Rheum Dis Clin North Am 1990, 16: 377

COURSE and COMPLICATIONS

Associated diseases

An association with immune-mediated diseases such as Hashimoto's thyroiditis and CREST syndrome has been described

Clinical course

The clinical course of DAH is often dramatic and may be fatal if the disease is not promptly treated. Pulmonary interstitial fibrosis or progressive broncho-obstructive disease have been reported in patients with repeated episodes of DAH

Radiological course

Hemorrhagic alveolar consolidations typically evolve rapidly, even within days. During the resolution phase, a reticular pattern may be present which may persist in the case of relapsing hemorrhage

LABORATORY FINDINGS

A typical finding is the rapid development of anemia. Non-specific findings include: leukocytosis, thrombocytosis, and elevated ESR. Renal involvement produces changes in renal function indices (azotemia, creatinemia), and in urinalysis (red blood cells, proteinuria, cell casts). More than 90% of patients with active disease and pulmonary-renal involvement have C-ANCA (directed against proteinase) in the serum

The role of C-ANCA in the diagnosis of Wegener's granulomatosis is well-established, and according to some studies, C-ANCA might also be useful in monitoring the disease. However, the possibility of false positives should be kept in mind. These may occur both with other forms of vasculitis and with non-vasculitic diseases (tuberculosis, HIV infection, endocarditis, nasal septal perforation, monoclonal gammopathy, neoplastic disease, drug-toxicity, polyneuritis). A negative C-ANCA test undoubtedly has a strong negative predictive value (90%)

CLINICAL DIAGNOSIS

In the appropriate clinical setting, positive serum C-ANCA and anti-proteinase-3 antibodies are considered to be strongly suggestive of Wegener's granulomatosis. Histologic confirmation should nonetheless be sought, with demonstration of necrotizing vasculitis at the affected sites (kidney, lung, skin, etc.)

INVASIVE DIAGNOSIS

Surgical lung biopsy is the method of choice for a definitive diagnosis. Transbronchial lung biopsy does not provide diagnostic material

Bronchoalveolar lavage

BAL may reveal the presence of DAH in patients without hemoptysis or significant anemia. The BAL fluid is hemorrhagic and the cytological analysis reveals hemosiderin-laden macrophages. C-ANCA may be assayed in the supernatant, but the prognostic significance of the titer is unknown

BAL is useful in differentiating disease recurrence from opportunistic infection or drug toxicity in the event that new pulmonary infiltrates appear in the follow-up

Hoffman GS. Bronchoalveolar lavage analysis in Wegener's granulomatosis. A method to study disease pathogenesis. Am Rev Respir Dis 1991, 143: 401

VASCULITIDES SYNDROMES ASSOCIATED WITH DAH

- Wegener's granulomatosis
- Churg-Strauss allergic angiitis and granulomatosis
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Bechet's disease
- Mixed cryoglobulinemia
- Collagen vascular diseases: Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), polymyositis
- Antiphospholipid antibody syndrome
- Goodpasture's syndrome
- Isolated pulmonary capillaritis

Desquamative Interstitial Pneumonia

Definition

Desquamative interstitial pneumonia (DIP) is a discrete clinical and pathologic entity characterized by abnormal and uniform accumulation of intraalveolar macrophages. A rare disease, it is classified among the idiopathic interstitial pneumonias

Alveolar macrophage pneumonia

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

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

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis are unknown. Similarities with RB-ILD (● RB-ILD) suggest that the two entities represent the extremes of a spectrum of diseases caused by cigarette smoking. The cells which accumulate in the alveolar spaces are now known to be alveolar macrophages attracted to the site by chemotactic stimuli (probably cigarette smoke antigens) rather than sloughed epithelial cells

Epidemiology

The disease tends to affect smokers in their 4th or 5th decades of life, and is more common in men than in women by a ratio of 2:1

Risk factors

Cigarette smoking

CLINICAL FEATURES

History

DIP develops insidiously with dyspnea (87%) and cough (43%) over a course of weeks or months before diagnosis. Chest pain may be observed, albeit rarely (17%)

Physical findings

Bibasilar fine rales may be heard. About 25% of patients have digital clubbing

Pulmonary function tests

The earliest functional alteration is reduced D_LCO (35%) on a background of a mild restrictive ventilatory defect (30%)
Lung volumes may be normal (20%)

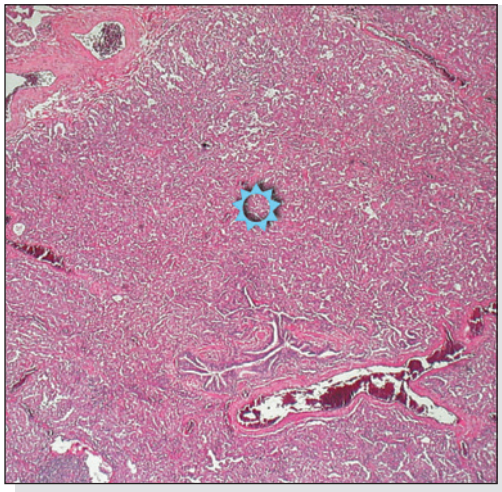
Rju JH. Desquamative interstitial pneumonia and respiratory bronchiolitis - associated interstitial lung disease. Chest 2005, 127:178

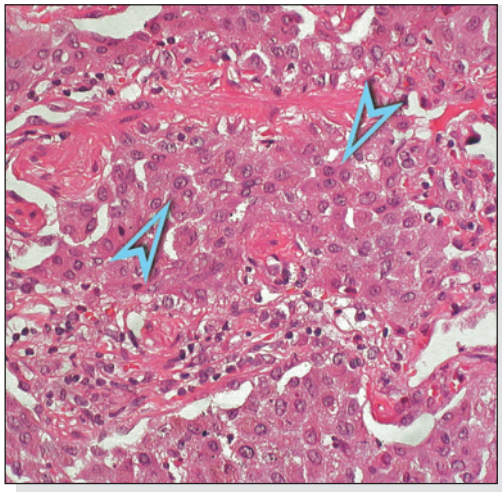
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Extensive accumulation of macrophages in the alveolar spaces (☼). The alveolar septa may be slightly thickened by fibrosis and mild lymphoplasmacellular infiltrate with rare eosinophils
- The intraalveolar macrophages have dense eosinophilic cytoplasm (➢) containig particles of golden-brown pigment. They tend to form monotonous aggregates. Necrosis, fibrin, intraalveolar organization and intense interstitial infiltrate are usually absent





✓ **Distribution Differentials**

Pulmonary architecture is basically preserved

Diffuse intraalveolar

Histopathologic differential diagnoses:

- DIP-like reaction: associated with other conditions such as drug- or asbestos-induced disease, eosinophilic pneumonia, infections or simply as a consequence of smoking
- RB-ILD: the proliferation is not diffuse but bronchiolocentric with sparing of the alveoli
- NSIP: septal thickening due to inflammation and fibrosis are more pronounced and there is less involvement of the alveolar spaces
- LCH: centrilobular nodules with stellate margins associated with cysts, and interstitial infiltrate consisting of eosinophils and Langerhans' cells

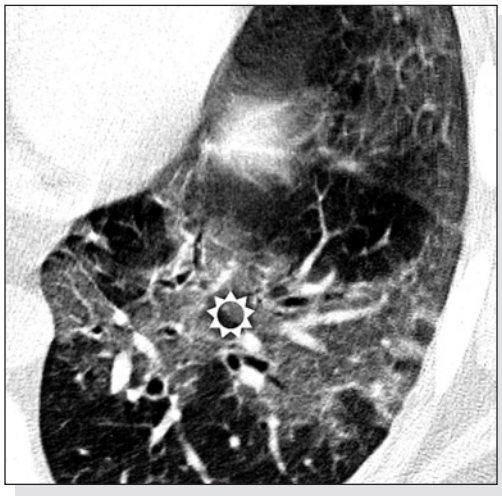
American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277

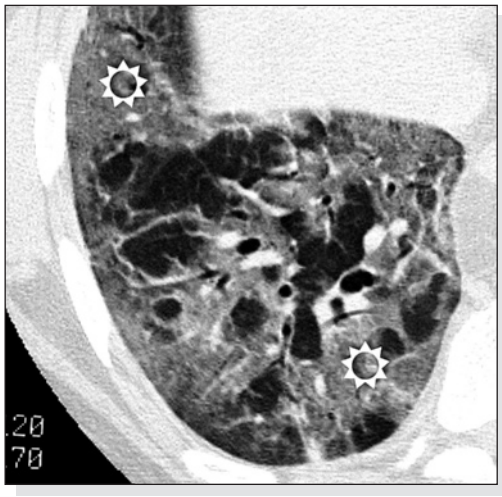
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Patchy ground-glass opacities (☼)





Distribution

Bilateral, generally symmetrical

Diffuse, at times predominant in the peripheral and subpleural regions

Basal

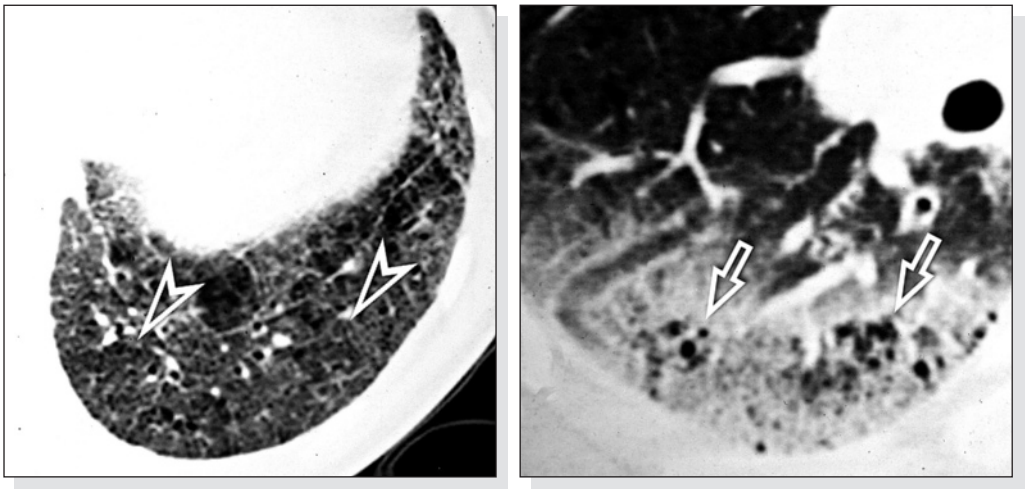
Lung volume is normal or slightly reduced

Hartman TE. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology 1993, 187: 787

Other signs

Other non-constant signs:

- Basal reticular opacities (≽)
- Moderate distortion of the pulmonary architecture and traction bronchiectasis
- Small air-filled cysts within the areas of ground-glass attenuation (⇨)



The cysts, which are due to dilatation of the alveolar ducts and respiratory bronchioles, are smaller than those seen in UIP; in addition, there is no fibrotic distortion!

Lee KH. The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. J Comput Assist Tomogr 2002, 26: 5

Differentials

The main radiological differential diagnoses are:

- NSIP: more evident reticular changes, bronchiectasis and traction bronchiolectasis
- PCP: acute onset in immunodepressed subjects, frequent localization in the middle-upper regions
- HP: the patchy areas of ground-glass attenuation are more randomly distributed. Centrilobular nodules are often associated

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

COURSE and COMPLICATIONS

Associated diseases

The disease may be associated with other smoke-induced lung diseases such as respiratory bronchiolitis and centrilobular emphysema

Clinical course

The majority of patients demonstrate a stable clinical course with favorable prognosis. However, there have been sporadic reports of progression of disease with death (26-32%) despite smoking cessation and corticosteroid treatment

Radiological course

The lesions may become stable or even regress after smoking cessation. The small air-filled cysts within the areas of ground-glass attenuation may disappear spontaneously

LABORATORY FINDINGS

Laboratory findings are usually unremarkable

CLINICAL DIAGNOSIS

In smokers with chronic dyspnea, dry cough, restrictive ventilatory pattern and reduced D_LCO, the HRCT pattern can raise the suspicion of DIP. The diagnosis, however, requires histological confirmation by surgical lung biopsy. The differential diagnosis will mainly consider the other idiopathic interstitial pneumonias, in particular NSIP (□ NSIP) and RB-ILD (● RB-ILD)

INVASIVE DIAGNOSIS

Surgical lung biopsy is mandatory for a definite diagnosis. The usefulness of BAL and transbronchial lung biopsy is limited to the exclusion of infectious or neoplastic diseases

Bronchoalveolar lavage

BAL typically shows increased numbers of alveolar macrophages with yellow, golden, brown or black inclusions (which are also seen in healthy smokers). The absence of these cells makes a diagnosis of DIP highly unlikely. There may be increases in neutrophils, eosinophils and, at times, lymphocytes

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

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

Amiodarone-induced lung disease

Definition

A number of drugs can cause lung injury, which is expressed by different histopathological patterns (see the table "Drug-induced lung injury: histopathologic patterns" at the end of this chapter). This chapter covers amiodarone-induced lung disease as a representative example of drug-induced alveolar damage

It should nonetheless be noted that the same drug may cause different types of lung injury, even in sequence. For example, amiodarone itself may also cause OP (⌘ OP) or chronic interstitial pneumonia (☐ Drug toxicity) or diffuse alveolar damage (DAD) such as AIP (⌘ AIP) and ARDS (⌘ ARDS)

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

DEMOGRAPHICS

Etiology and pathogenesis

The lung injury induced by amiodarone is thought to result in part from a direct toxic effect (altered phospholipid turnover, toxic oxygen species) and in part from an immune reaction (hypersensitivity pneumonitis). Inhibition of phospholipid degeneration within the lysosomes is responsible for the characteristic "foamy" appearance of the alveolar macrophages

Epidemiology

Amiodarone causes pulmonary toxicity in 5-10% of patients treated with the drug

Risk factors

A higher risk of pulmonary toxicity is associated with: 1. daily dose (maintenance therapy) ≥400 mg; 2. duration of treatment longer than 2 months: 3. age over 60 years; 4. pre-existing lung disease; 5. surgery (thoracic and non-thoracic); 6. angiographic investigations. There is no correlation between duration of treatment or cumulative dose and the extent of lung damage

CLINICAL FEATURES

History

The onset of disease is insidious, with dry cough and dyspnea arising within months of starting therapy. Systemic symptoms such as low-grade fever, weight loss and weakness are also common. In one third of patients the onset is acute and mimics a pulmonary infection

Physical findings

Patients are tachypneic, and chest auscultation reveals fine diffuse rales and at times pleural rubs. Digital clubbing has not been reported

Pulmonary function tests

Pulmonary function tests reveal a restrictive ventilatory defect with decreased D_LCO. Hypoxemia is present in all patients

Martin WJ 2nd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part I). Chest 1988, 93: 1067

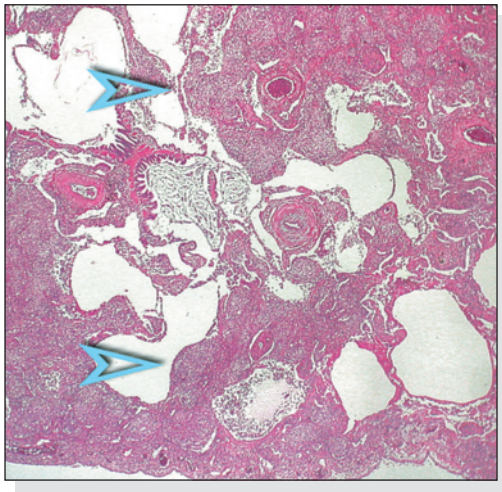
Martin WJ 2nd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part 2). Chest 1988, 93: 1242

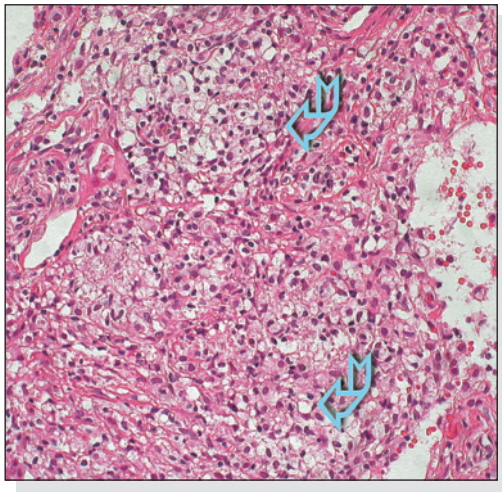
PATHOLOGY

Basic lesions

The most common lesion associated with amiodarone-induced pulmonary toxicity is the following:

- Chronic interstitial pneumonia with lymphoid hyperplasia and accumulation of foamy macrophages (↳) with finely vacuolated cytoplasm predominantly in the alveolar spaces, but also in the interstitium (➢)





At low magnification the histologic appearance is similar DIP

Non-specific inflammatory pleural infiltrate, with or without effusion, may be observed

In addition to chronic interstitial pneumonia, amiodarone may occasionally produce OP and DAD patterns with the presence of foamy macrophages

The presence of foamy macrophages is not confined to amiodarone-induced pneumonia, as they can also be observed in other conditions associated with airway obstruction

Distribution

Alveolar and, to a lesser extent, septal

Differentials

Histopathologic differential diagnoses:

- Obstructive pneumonia: there is obstruction of large or small airways
- Diffuse panbronchiolitis (DPB) and DPB-like pattern (e.g. associated with idiopathic inflammatory bowel disease): centrilobular lesions with cellular bronchiolitis containing numerous foamy macrophages in the alveolar spaces, but mostly in the pulmonary interstitium
- Erdheim-Chester disease: interstitial infiltrate of foamy macrophages along the lymphatic routes associated with fibrosis
- TB and mycobacteriosis: presence of numerous mycobacteria in immunodepressed patients
- NSIP: interstitial fibrosis and inflammation are more pronounced

Bedrossian CW. Amiodarone pulmonary toxicity: cytopathology, ultrastructure, and immunocytochemistry. Ann Diagn Pathol 1997, 1: 47

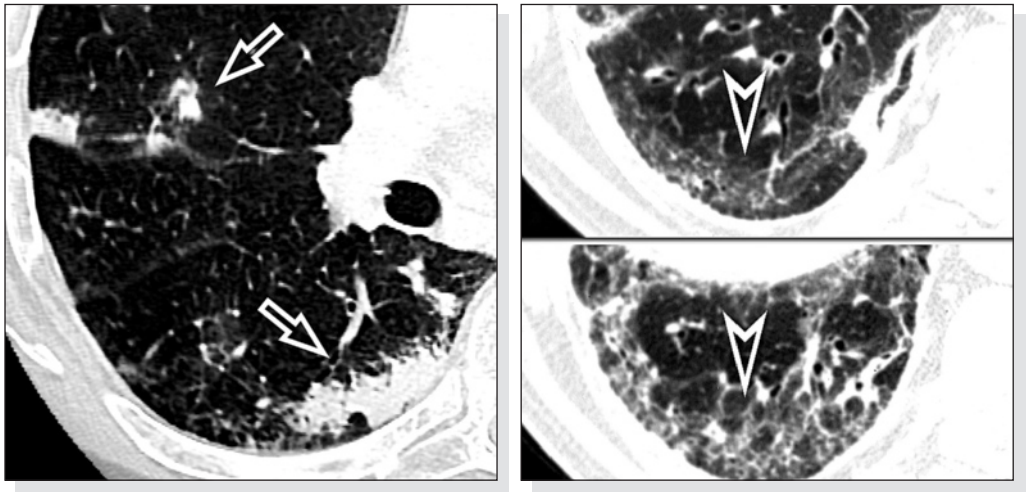
Ott MC. Pulmonary toxicity in patients receiving low-dose amiodarone. Chest 2003, 123: 646

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (⇨) often hyperdense compared to muscle (80-180 HU)
- Patchy ground-glass opacities (≫)



These findings correspond to NSIP possibly associated with OP: the two patterns may coexist in the same patient. The hyperdensity of the lesions is due to the accumulation of amiodarone (which contains iodine) in the macrophages and type II pneumocytes. In some patients, the consolidation appears as a single pneumonia-like opacity or as a solitary pseudoneoplastic mass

Kuhlman JE. Amiodarone pulmonary toxicity: CT findings in symptomatic patients. Radiology 1990, 177: 121

Padley SP. High-resolution computed tomography of drug-induced lung disease. Clin Radiol 1992, 46: 232

Polverosi R. [Thoracic radiography and high resolution computerized tomography in the diagnosis of pulmonary disorders caused by amiodarone]. Radiol Med 1996, 92: 58. Italian

Distribution

Bilateral and asymmetrical, patchy

Predominantly peripheral

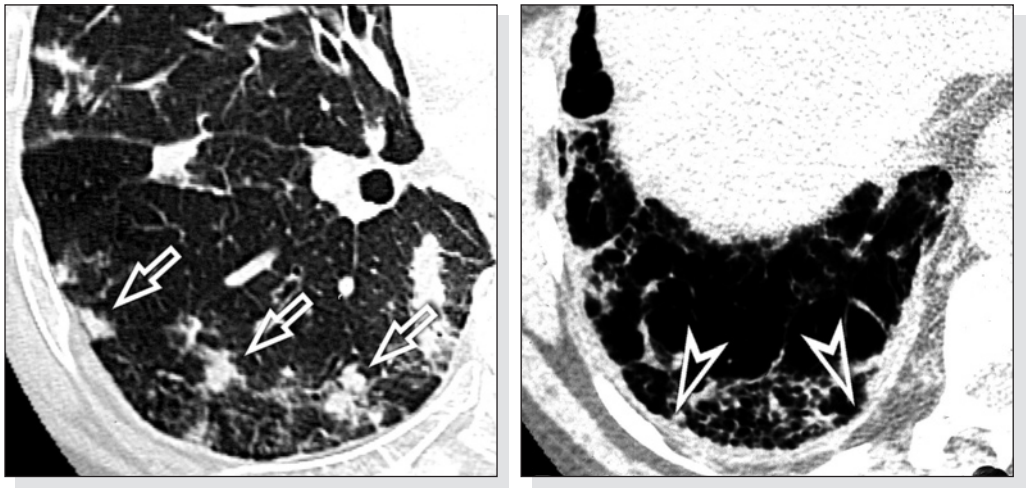
Predominantly basal

Lung volume is normal or reduced

Other signs

Other radiological signs:

- Reticular opacities and micronodules (⇨)
- Hyperdense pleural thickening (➢)
- Pleural effusion
- Hyperdense liver and spleen (80%) and heart (20%)



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

Differentials

The presence of hyperdensities within the areas of consolidation needs to be differentiated from:

- Amyloidosis: possible presence of more pronounced hyperdensities due to calcifications within the areas of consolidation and, above all, nodules

The radiological differential diagnoses also include other conditions responsible for consolidation with subacute or acute clinical courses:

- Slow-healing infections: the differential diagnosis is made on the basis of the clinical and bronchological findings
- CEP: the areas of consolidation are located in the upper lung regions and are always peripheral ("photographic negative" of the butterfly or batwing edema pattern)
- OP: the pattern is similar
- Churg-Strauss syndrome: the differential diagnosis is challenging. The areas of consolidation may be not only peripheral but also randomly distributed and migratory
- BAC and MALToma: the diagnosis is based on bronchoscopy and biopsy

Leung AN. Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. Radiology. 1993, 188: 209

COURSE and COMPLICATIONS

Associated diseases

Amiodarone is used to treat cardiopathic patients affected by supraventricular arrhythmias unresponsive to conventional therapy

Clinical course

Discontinuation of the drug and administration of corticosteroids have proven to be very effective. Recurrences have been reported following interruption of steroid treatment. Amiodarone-induced lung disease has a mortality rate below 10% which increases to 50% in cases complicated by ARDS

Radiological course

The areas of parenchymal consolidation resolve with steroid therapy and only in a small minority of patients do they progress to fibrosis

Ellis SJ. Drug-induced lung disease: high-resolution CT findings. AJR Am J Roentgenol 2000, 175: 1019

LABORATORY FINDINGS

The laboratory findings are non-specific: leukocytosis, > lactate dehydrogenase (LDH), > ESR. The serum levels of amiodarone are not predictive of lung damage. It has been suggested that serum concentrations of the glycoprotein KL-6 may predict lung damage

CLINICAL DIAGNOSIS

Amiodarone-induced lung disease is a diagnosis of exclusion made on the basis of the clinical, radiological and, where possible, BAL findings

INVASIVE DIAGNOSIS

In the appropriate clinical setting, surgical lung biopsy is unnecessary, in part because the findings would not be specific. Transbronchial lung biopsy may be useful in identifying OP pattern

Bronchoalveolar lavage

A common BAL pattern in patients receiving amiodarone, whether or not they have lung disease, is the presence of numerous "foamy" macrophages. In addition to this, patients with lung disease also have an increase in lymphocytes, neutrophils and eosinophils (mixed alveolitis). The lymphocytes are predominantly of the CD8+ subset. These findings may assist in the diagnosis, although they have no prognostic significance

The BAL finding of mixed alveolitis in a patient with amiodarone-induced lung damage is similar to that seen in HP, idiopathic OP and at times NSIP. BAL may be of value in ruling out infection or malignancy

Coudert B. Amiodarone pneumonitis. Bronchoalveolar lavage findings in 15 patients and review of the literature. Chest 1992, 102: 1005

The table entitled "Drug-induced lung injury: BAL findings" at the end of this chapter summarizes the main BAL features encountered in lung disease induced by various drugs

TABLES

On the following pages are two detailed tables which present:

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

DRUG-INDUCED LUNG INJURY: HISTOPATHOLOGIC PATTERNS

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

DRUG-INDUCED LUNG INJURY: BAL FINDINGS

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

Hypersensitivity Pneumonitis

Definition

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

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

Etiology and pathogenesis

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

Gell and Coombs type III and type IV immune reactions lie at the basis of the immunopathogenesis of the disease. The acute form seems to be related to heavy exposure to antigens and working conditions (environmental antigen concentration, duration and frequency of exposure, type of work)

Epidemiology

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

Risk factors

The disease is more common in non-smokers

CLINICAL FEATURES

History

Symptoms of the acute form are cough, dyspnea, fever, chills, malaise and myalgia. A careful clinical history may reveal massive exposure to an inciting antigen and a temporal relationship between exposure and onset of symptoms (4-12 hours)

Physical findings

Patients present with tachypnea, and auscultation of the lungs may be normal or reveal fine diffuse rales. Wheezes and stridors are rarely heard

Pulmonary function tests

Patients typically have a restrictive ventilatory defect with reduced D_LCO or, in rare cases, an obstructive pattern. Mild hypoxemia at rest is common

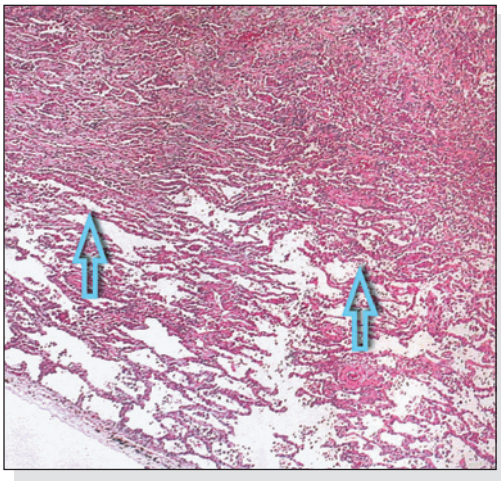
Patel AM. Hypersensitivity pneumonitis: current concepts and future questions. J Allergy Clin Immunol 2001, 108: 661

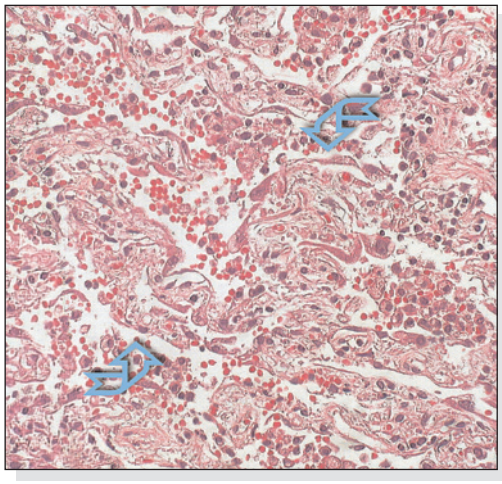
PATHOLOGY

Basic lesions

In the acute stage, the histologic pattern is characterized by:

- Neutrophilic infiltrate in the alveolar spaces and respiratory bronchioles (acute bronchiolitis)
- Extensive foci of organizing pneumonia (⇨)
- Acute or organizing DAD (↳) with hyaline membranes and necrosis in severe cases





✓ Additional findings:

- Interstitial granulomatous pneumonia characterized by cellular bronchiolitis with diffuse interstitial lymphoplasmacellular infiltrates. Small poorly-formed non-necrotizing granulomas are also present

Ancillary findings:

- Giant cells containing refractile crystals
- Foci of obstructive pneumonia with foamy macrophages histiocytes in the alveolar spaces

Distribution Centrilobular

Seal RM. The pathology of the acute and chronic stages of farmer's lung. Thorax 1968, 23: 469

Tasaka S. Fatal diffuse alveolar damage from bird fancier's lung. Respiration 1997, 64: 307

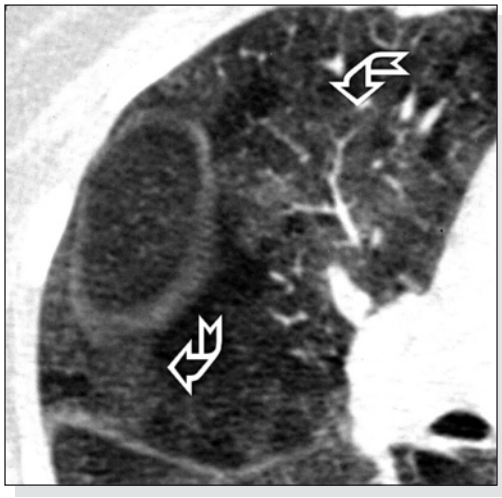
Differentials Histopathologic differential diagnoses:

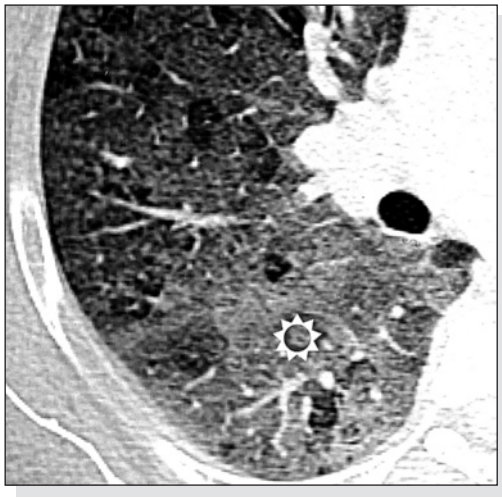
- NSIP: diffuse rather than bronchiolocentric lesions; granulomas and foci of organizing pneumonia may be present, but they are not characteristic
- DAD: the process is diffuse rather than bronchiolocentric, and there is marked hyperplasia of type II pneumocytes
- OP: less intense interstitial infiltrate and absence of granulomas

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions Basic radiological signs:

- Ground-glass opacities (↳)
- Parenchymal consolidation (☼)





Distribution Bilateral and patchy; rarely homogeneous

Random

Variable but more commonly basal

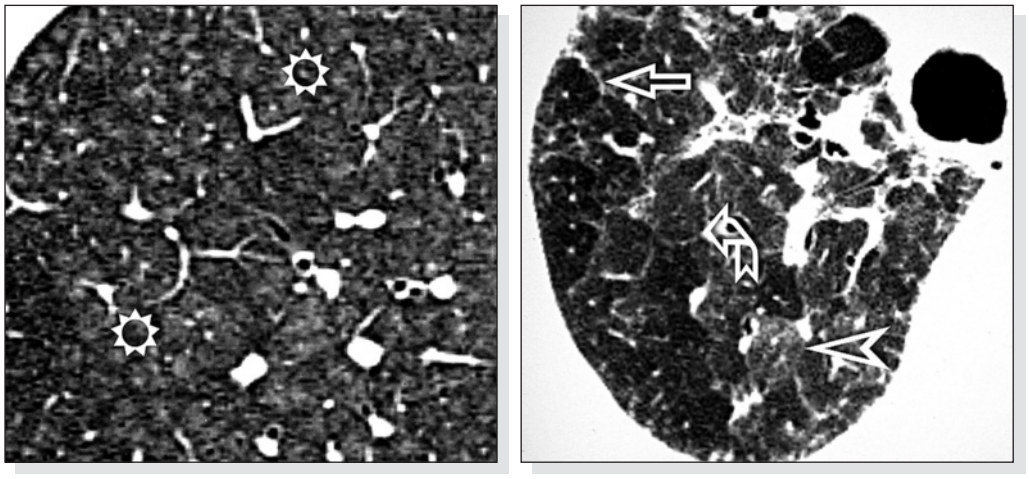
Lung volume is normal

Silver SF. Hypersensitivity pneumonitis: evaluation with CT. Radiology 1989, 173: 441

Other signs

Other radiological features:

- Low-density poorly-defined centrilobular nodules 1-5 mm in diameter (☼)
- Mediastinal adenopathy
- Mosaic oligemia with air-trapping (⇨), possibly associated with areas of normal parenchyma (↳) alternating with areas of ground-glass attenuation (≫) (head-cheese pattern)



Cormier Y. High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. Eur Respir J 2000, 16: 56

Differentials

Radiological differential diagnoses:

If the ground-glass attenuation prevails:

- PCP: in immunodepressed patients only. Ground-glass attenuation is present in the parahilar regions and in the upper lobes in patients treated with aerosol pentamidine. Thin- or thick-walled cysts may be seen

If consolidation prevails:

- AIP: reticular pattern associated with consolidation, parenchymal distortion, traction bronchiectasis and limited honeycombing
- OP: the peripheral and/or peribronchial consolidation tends to be triangular or polygonal in shape. The accelerated form tends to have an AIP-like appearance

Herraez I. Hypersensitivity pneumonitis producing a BOOP-like reaction: HRCT/pathologic correlation. J Thorac Imaging 2002, 17: 81

Remy-Jardin M. Computed tomography assessment of ground-glass opacity: semiology and significance. J Thorac Imaging 1993, 8: 249

COURSE and COMPLICATIONS

Associated diseases

About one quarter of patients with HP have non-specific bronchial hyperreactivity to methacholine

Clinical course

If the patient avoids exposure to the antigen, single acute episodes may resolve spontaneously within days. The pulmonary function tests and radiological alterations return to normal within weeks: only D_LCO takes longer to normalize. The disease may recur with re-exposure. If areas of fibrosis, or honeycombing at HRCT, develop, the disease may become irreversible

✓ "Bird fancier's lung" has a worse prognosis than "Farmer's lung"

Radiological course

If exposure continues, the disease progresses to the subacute form (● HP, subacute) and may eventually become chronic (□ HP, chronic)

LABORATORY FINDINGS

The presence of serum precipitating antibodies against the offending antigen is a characteristic feature. There may also be a slight increase in inflammatory indices (ESR and C-reactive protein - CRP), as well as a significant increase in quantitative immunoglobulins which return to normal once the acute phase is over. Some patients may also test positive for rheumatoid factor and circulating immune complexes

CLINICAL DIAGNOSIS

The disease is diagnosed on the basis of a history of exposure to an offending antigen with onset of compatible clinical, radiographical or physiological findings within 4-12 hours. Other diagnostic criteria include clinical improvement after removal from exposure and recurrence on re-exposure. There is little agreement regarding the usefulness of inhalation challenge to the offending antigen

INVASIVE DIAGNOSIS

In cases where the inciting antigen cannot be identified or in the presence of conflicting clinical, radiological and functional findings, fiberoptic bronchoscopy with BAL and transbronchial lung biopsy are indicated. Surgical lung biopsy is only required if these prove inconclusive

Bronchoalveolar lavage

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

Similar patterns (CD8+ lymphocytic alveolitis, foamy macrophages, and mastocytes) may also be seen in drug-induced lung disease (⌘ Drug toxicity), in OP (⌘ OP), and in NSIP (☐ NSIP)

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

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

Atypical mycobacteriosis

Definition

Pulmonary infections characterized by endobronchial spread may be caused by a variety of pathogens, including mycobacteria other than Mycobacterium (M.) tuberculosis, commonly referred to as non-tuberculous mycobacteria (NTM). This chapter will cover these forms. The radiological hallmark of endobronchial spread is known as the tree-in-bud pattern (see the table entitled "Diseases with radiological tree-in-bud pattern" at the end of the chapter)

DEMOGRAPHICS

Etiology and pathogenesis

The main causative agents are M. avium-intracellulare, M. Kansasii, M. fortuitum, and M. chelonei, traditionally classified into 4 groups based on pigment production and growth rate: photochromogens, scotochromogens, nonchromogens and fast-growers. These mycobacteria are ubiquitous and infection generally occurs through environmental contamination rather than human-to-human transmission

Epidemiology

A North-American surveillance study from the pre-AIDS era (early 1980s) reported that 65% of mycobacterial isolates were M. tuberculosis, 21% were M. avium-intracellulare (MAI) (nonphotochromogen), 6.5% M. fortuitum and M. chelonei (fast-growing), 3.5% M. Kansasii (photochromogen) and 2.3% M. scrofulaceum (scotochromogen). The overall incidence of NTM disease was 1.78 cases per 100,000 with variations due to geographical differences in the mycobacterial habitats

The advent of AIDS has brought about an increase in the incidence of M. avium-intracellulare infection. Atypical mycobacteriosis is more common in white males over 50 years of age, and rare in children

Risk factors

Immunodepressed states such as AIDS or conditions such as alcoholism, rheumatoid arthritis, gastric resection, organ transplant and diabetes mellitus facilitate infection by atypical mycobacteria. Most patients have co-existing lung diseases such as chronic obstructive bronchitis, bronchiectasis, cystic fibrosis, lung cancer, silicosis, lipoid pneumonia, or a history of tuberculosis

A form of diffuse interstitial granulomatous pneumonia has been described in immunocompetent subjects who had inhaled aerosolized water contaminated with MAI (hot tub lung). These cases exhibit small granulomas with or without necrosis that involve the bronchiolar wall and at times the lumen

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

CLINICAL FEATURES

History

The clinical pulmonary manifestations are those of tuberculosis (TB). Immunocompetent subjects with atypical mycobacteriosis due to MAI present with cough, low-grade fever, malaise and, at times, hemoptysis. Systemic symptoms are rare in immunocompetent individuals but frequent in HIV+ subjects, in whom pulmonary involvement is, however, rare

Physical findings

The physical examination is often unremarkable. Bronchiolar crackles may occasionally be heard

Pulmonary function tests

Mycobacterial infections predominantly affect the upper lobes. Because these have limited functional importance, lung function impairment tends to be mild, and possible alterations should therefore be ascribed to the underlying disease

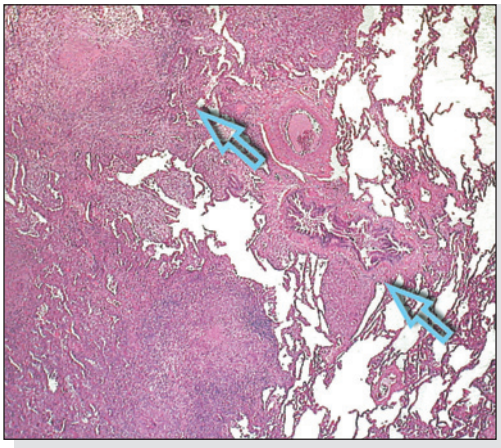
Griffith DE. Nontuberculous mycobacteria. Curr Opin Pulm Med 1997, 3: 139

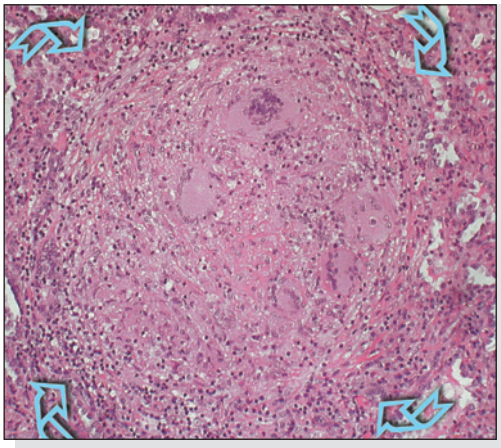
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Epithelioid necrotizing granulomas (↳) with Langhans' type giant cells, distributed along the airways (⇨)(bronchi, bronchioles, and alveolar ducts). The caseating necrosis is less extensive in atypical mycobacteriosis compared to the typical form
- In AIDS patients, well-formed granulomas are often absent and the infiltrate consists of foamy macrophages with cytoplasm filled with numerous mycobacteria





Distribution

Along the airways

✓

It is almost impossible to distinguish between tuberculous and non-tuberculous mycobacteria on the basis of morphology alone: the differential diagnosis requires special stains (PAS), and cultures or molecular biology assays

Differentials

Histopathologic differential diagnoses:

- Sarcoidosis: small non-necrotizing granulomas. The search for mycobacteria by any method, is negative
- Fungal infections: presence of mycetes
- Wegener's granulomatosis (endobronchial): necrosis is patchy ("geographic") and "blue" as it is rich in neutrophilic debris. The infiltrate is more intense and granulomas are not associated with marked fibrosis
- HP: poorly-formed granulomas associated with intense interstitial lymphoplasmacellular infiltrate. Presence of giant cells containing needle-shaped clefts, and absence of necrosis

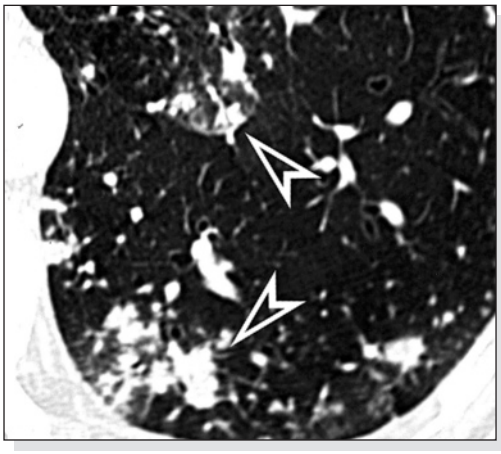
Fujita J. Pathological and radiological changes in resected lung specimens in Mycobacterium avium intracellulare complex disease. Eur Respir J 1999, 13: 535

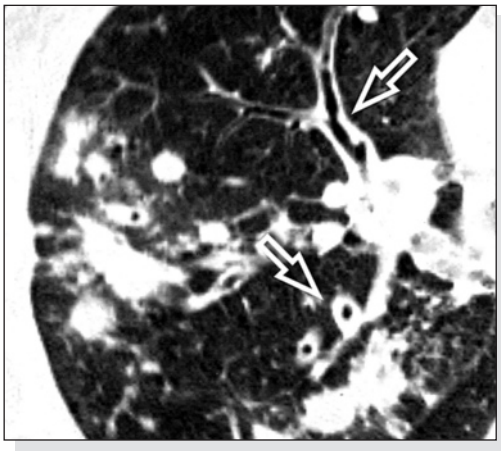
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Mycobacteriosis, classic form (70% of cases):

- Poorly-defined centrilobular nodules, often clustered into "rosettes" (➢)
- Branching opacities with tree-in-bud appearance
- Bronchial wall thickening (⇨) with or without bronchiectasis
- Multiple areas of consolidation of acinar or lobular size; cavitation is common





In addition to the classic presentation (70%), which strongly resembles that of tuberculosis with endobronchial spread, there is another less frequent presentation (non-classic, 30%) typical of elderly women (80%) and characterized by bronchiectasis and bronchiolectasis, centrilobular nodules and patchy mosaic hypoperfusion (Lady Windermere syndrome). More rarely, mycobacterial infection may give rise to pneumonia-like areas of consolidation or centrilobular nodular ground-glass opacities due to the extrinsic allergic alveolitis produced by the mycobacterial infection

Erasmus JJ. Pulmonary nontuberculous mycobacterial infection: radiologic manifestations. Radiographics 1999, 19: 1487

Reich JM. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. Chest 1992, 101: 1605

Distribution

Unilateral or bilateral, patchy

Variable but more prominent in the peripheral areas and usually showing a clear connection with the bronchi

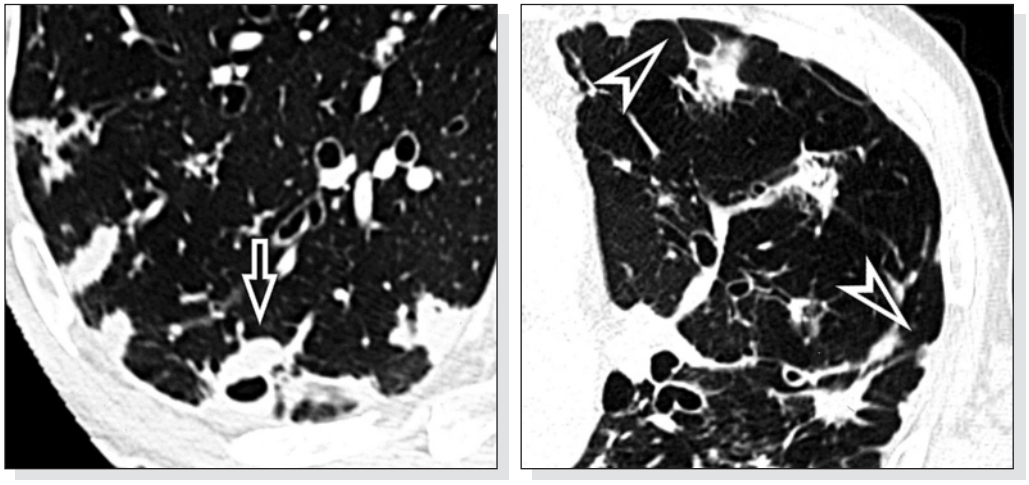
In the classic form, decreasing craniocaudal severity of lesions originating from an apical focus; in non classic forms, predominance of lesions in the middle lobe and lingula

Overall lung volume is preserved, although retraction in correspondence with the areas of consolidation is common

Other signs

Other possible radiological manifestations:

- Cavitating consolidations (⇨), particularly in the dorsal regions as in post-primary TB
- Retraction along the pleural borders adjacent to the areas of consolidation (≻)
- Pleural effusion associated with mediastinal and hilar adenopathy (rare)
- Superimposed hematogenous miliary form



Levin DL. Radiology of pulmonary Mycobacterium avium-intracellulare complex. Clin Chest Med 2002, 23: 603

Miller WT Jr. Spectrum of pulmonary nontuberculous mycobacterial infection. Radiology 1994, 191: 343

Differentials

The radiological differential diagnoses include:

- Diseases producing a tree-in-bud pattern (see the table at the end of this chapter)
- Mycosis: uncommon in immunocompetent individuals; in immunodepressed subjects the invasive forms show nodules or cavitating masses frequently associated with a perilesional halo sign
- Branching micrometastases within the vessels (beaded vessel sign)

Goo JM. CT of tuberculosis and nontuberculous mycobacterial infections. Radiol Clin North Am 2002, 40: 73

Worthy SA. Small airway diseases. Radiol Clin North Am 1998, 36: 163

COURSE and COMPLICATIONS

Associated diseases

Obstructive chronic bronchitis, bronchiectasis, cystic fibrosis, history of tuberculosis, lung cancer, silicosis, lipoid pneumonia

Clinical course

If left untreated, NTM infections follow a variable course depending on the underlying lung disease. Even after healing of the parenchymal lesions, an active bronchial infection may persist, which becomes a constant source of infection. The advent of new treatments relying on macrolides and rifabutin has markedly improved the prognosis of these patients

Radiological course

If the disease regresses, the opacities will disappear progressively. If it progresses, the bronchiectasis, which are generally more pronounced than in TB, tend to worsen, above all in the forms due to MAI infection

LABORATORY FINDINGS

Sputum microbiology and culture can identify the colonizing or pathogenic mycobacterium. The culture, staining and detection techniques used for atypical mycobacteria are very similar to those used for tuberculosis. The advent of genetic probes will enable a faster and more specific diagnosis, whereas laboratory tests are not specific

CLINICAL DIAGNOSIS

In immunocompetent individuals, the diagnosis is based on radiological criteria (cavitating lung disease in the absence of other identifiable causes and/or tree-in-bud pattern) and microbiological findings (detection of the mycobacterium in at least 3 sputum samples). The differential diagnosis mainly includes the other forms of infectious necrotizing granulomatosis, such as tuberculosis and fungal infections

☝ Isolation of the microorganism (even on repeated occasions) in the absence of pulmonary cavitations indicates colonization rather than infection. These patients should not be treated but instead, closely monitored

INVASIVE DIAGNOSIS

Transbronchial lung biopsy can provide material for the direct detection of the microbic agent or for microbiological culture. Surgical lung biopsy to confirm the diagnosis is rarely required

Bronchoalveolar lavage

BAL may be used in the event that sputum is unavailable. The search for atypical mycobacteria in the BAL fluid must be carried out with extreme care (in particular for M. avium-intracellulare) as often the germs are only present inside the alveolar macrophages. These may have a Gaucher-like appearance due to the massive number of germs distending their cytoplasm

DISEASES WITH TREE-IN-BUD PATTERN

The radiological pattern known as tree-in-bud may be found in different diseases characterized by the presence of distended centrilobular bronchioles with a mucous- or pus-filled lumen and often inflammation of the peribronchiolar airspaces. These include:

- TB with endobronchial spread
- Atypical mycobacteriosis
- Infectious bronchopneumonia and bronchiolitis
- CF
- Bronchiectasis of any cause
- Asian panbronchiolitis
- Allergic bronchopulmonary aspergillosis (ABPA)
- BAC

Mucosa-Associated Lymphatic Tissue lymphoma

Definition

Mucosa-associated lymphatic tissue lymphoma (MALToma) is an extranodal pulmonary B-cell lymphoma with a low grade of malignancy. The cells arise from the marginal zone (centrocyte-like cells) of the normal or hyperplastic bronchus-associated lymphoid tissue (BALT)

MALT lymphoma, BALT lymphoma, marginal zone B-cell lymphoma

These tumors express CD19, 20, 22 and 79a, are negative for CD5, CD 23 and CD10 and do not present bcl-1 and bcl-2 gene rearrangements

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis of the disease are unknown. It is thought, however, that certain stimuli (cigarette smoking, infections, asbestos exposure, various collagen vascular diseases) are capable of provoking BALT hyperplasia with subsequent malignant transformation

In contrast to other pulmonary lymphomas, no association with Epstein-Barr virus has been described for MALToma

Epidemiology

MALToma primarily affects adults in their fifth decade of life, without gender predilection. It is the most common primary pulmonary lymphoma (60-80%)

Risk factors

Collagen vascular diseases such as RA, Sjögren's syndrome and SLE. Hepatitis C virus infection

CLINICAL FEATURES

History

Half of the patients are asymptomatic. When present, the most common symptoms are cough and dyspnea, whereas pleural pain and hemoptysis are rare. Systemic symptoms such as fever, night sweats or weight loss are encountered in 20-40% of cases

Physical findings

In the presence of a large lymphomatous mass, physical examination may reveal lung consolidation. Pleural effusion is uncommon (10%)

Pulmonary function tests

Most patients have normal lung function tests, although a restrictive or obstructive defect may be present

The presence of systemic symptoms is indicative of extrapulmonary involvement, in which case the prognosis is worse (5 year survival rate of 55%)

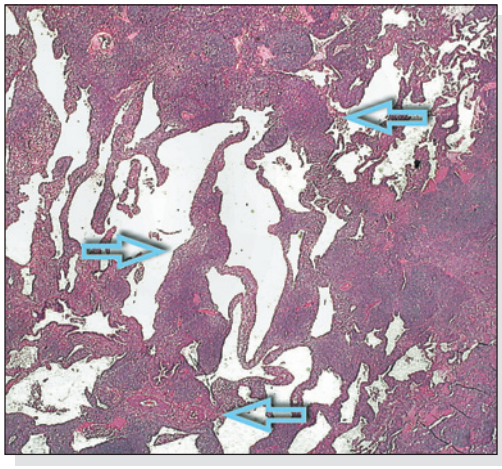
Koss MN. Pulmonary lymphoid disorders. Semin Diagn Pathol 1995, 12: 158

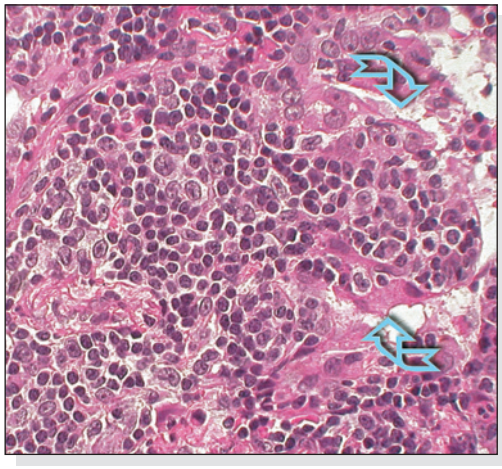
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Dense and monotonous lymphoid infiltrate, forming cuffs or micronodules along the lymphatic vessels (⇨)
- Lymphoepithelial complexes of neoplastic lymphocytes within the bronchial and bronchiolar epithelium (↳)





The neoplastic population is composed of different cell types in varying proportions: 1. small lymphocytes with round nuclei; 2. "monocytoid" lymphocytes with slightly larger and more irregular nuclei and abundant, pale cytoplasm; 3. lymphocytes with plasmocytoid appearance and plasma cells; 4. occasional large "transformed" lymphocytes, with round vesicular nucleolated nuclei and abundant cytoplasm. This pattern is often associated with a non-neoplastic (polyclonal) reactive lymphoplasmacellular infiltrate and, in 70% of cases, with numerous germinal centers. Amyloid deposits, bands of dense fibrosis and granulomas may also be present. Although non-specific, lymphoepithelial complexes are a characteristic feature of MALT lymphomas. Infiltration of the pleura and bronchial cartilage is rare but, when present, is strongly suggestive of lymphoma

Many cases now interpreted as MALT lymphomas were previously classified as pseudolymphomas or LIP (● LIP) depending on whether the lesions were localized or diffuse

Distribution

Along the lymphatics. In macronodular lesions, lung architecture is effaced in the center of the nodule and lymphatic distribution can therefore only be identified at the periphery

Differentials

Histopathologic differential diagnoses:

- LIP, diffuse lymphoid hyperplasia, pseudolymphoma: the lymphocyte population is heterogeneous and polyclonal. Absence of dense monotypic lymphocytic infiltrate around the germinal centers and in the septa, which is typical of lymphomas. Infiltration of the pleura and the bronchial cartilage is rare, as is the presence of lymphoepithelial complexes
- Chronic lymphocitic leukemia: although neoplastic infiltrates which are histologically indistinguishable from those of MALToma, may be present along the lymphatics lymphoepithelial complexes rare

Begueret H. Primary lung small B-cell lymphoma versus lymphoid hyperplasia: evaluation of diagnostic criteria in 26 cases. Am J Surg Pathol 2002, 26: 76

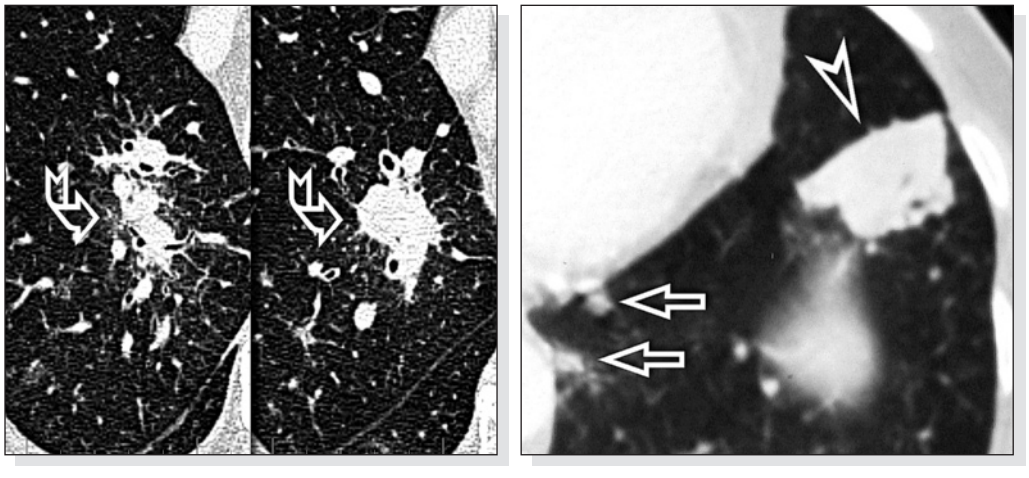
Kurtin PJ. Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. Am J Surg Pathol 2001, 25: 997

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (60%) with air bronchogram (↳)(50-90%); the bronchi appear stretched and narrowed
- Masses with variable diameter up to several centimeters (➢)
- Nodules with hazy margins (⇨) due to airspace filling (60%)



The above HRCT signs are frequently seen in combination

Distribution

Frequently bilateral (60%), but also unilateral, diffuse, or patchy with involvement of extensive areas (80%)

Tendency towards peribronchial distribution

Variable

Lung volume is normal

Kinsely BL. Pulmonary mucosa-associated lymphoid tissue lymphoma: CT and pathologic findings. AJR Am J Roentgenol 1999, 172: 1321

Lee DK. B-cell lymphoma of bronchus-associated lymphoid tissue (BALT): CT features in 10 patients. J Comput Assist Tomogr 2000, 24: 30

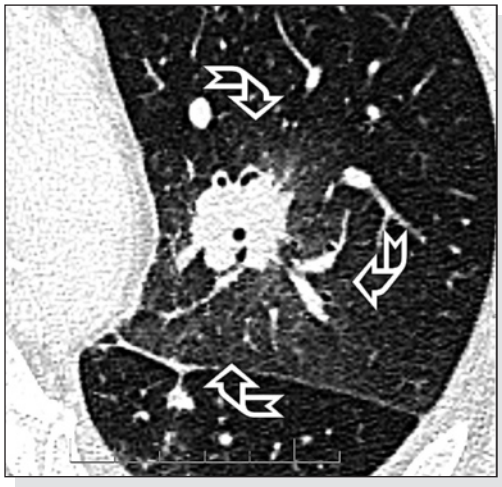
Other signs

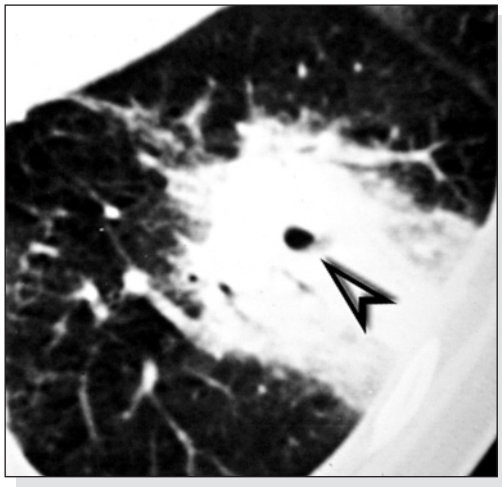
Common:

- Perinodular halo sign (↳)
- Air alveologram and small cysts (⩾) within the consolidation (due to bronchiolar dilatation)
- Angiogram sign after contrast material administration
- Bronchial wall thickening, luminal stenosis or signs of fibrosis with bronchiectasis (50%)

Uncommon:

- Pleural effusion (10-25%) generally associated with the parenchymal lesions
- Hilar and mediastinal adenopathy (10%)
- Lymphangitis-like septal thickening





King LJ. Pulmonary MALT lymphoma: imaging findings in 24 cases. Eur Radiol 2000, 10: 1932

Rodallec M. Imaging of MALT lymphomas. Eur Radiol 2002, 12: 348

Differentials

Radiological differential diagnoses:

- OP: the consolidations are basal and peripheral, at times migratory, and respond readily to steroid treatment
- BAC: the differential diagnosis is histological; however, the form with endobronchial spread tends to progress more rapidly
- Metastases: consolidation is present in a limited number of cases (hemorrhagic metastases, or metastases from angiosarcoma or choriocarcinoma)
- Angioinvasive mycosis: associated nodules or masses with a tendency to cavitate
- Lymphomatoid granulomatosis: nodules or masses without air bronchogram and with a tendency to coalesce; consolidation is rare

COURSE and COMPLICATIONS

Associated diseases

Pleural effusion (10%), lymphadenopathy (5%). In some subjects, the disease may manifest with signs and symptoms in other regions, such as the upper respiratory tract or the stomach (33%). The signs of lung involvement may appear later. Besides the above-mentioned elements, an association with LCH and sarcoidosis has been described in a small number of instances

Clinical course

If appropriately treated, patients with low-grade pulmonary B-cell lymphoma have a good prognosis (84% survival at 5 years). Progression of the disease into a high-grade lymphoma is rare

Radiological course

Progression of the lesions is very slow: they can initially appear months, or even years, before diagnosis

LABORATORY FINDINGS

If plasmcytoid differentiation develops, monoclonal gammopathy, usually IgM, may be detected in the peripheral blood. Free light chains may be detected in the urine, including Bence-Jones protein. The leucocyte count is generally normal, although lymphocytosis can be detected in a small number of cases. In the case of pleural effusion, the exudate will contain predominantly B lymphocytes

CLINICAL DIAGNOSIS

Normally, diagnosis neccesitates invasive techniques

INVASIVE DIAGNOSIS

Diagnosis can be based on histologic-immunohistochemical analysis of pulmonary tissue obtained by transbronchial biopsy or surgery, or, more rarely, based upon typification of lymphocytes in the BAL or pleural fluid

Bronchoalveolar lavage

The BAL results are pathognomonic where cytofluorometry demonstrates an increase in the B lymphocyte population (>5%) with monoclonal aspects (k or λ light chains). In this case, use of the polymerase chain reaction (PCR), can allow analysis of the gene re-arrangement of the tumor cells

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

Cryptogenic Organizing Pneumonia (COP)

Definition

Cryptogenic organizing pneumonia (COP) is a disease entity classified among the idiopathic interstitial pneumonias, which presents clinically with pneumonia-like features

Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

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

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

An identical histological and radiological pattern (BOOP-reaction pattern) may be seen in a number of diseases where the lung responds non-specifically to different noxae (see the table entitled "BOOP-reaction pattern" at the end of this chapter)

Katzenstein AL. Katzenstein and Askin's surgical pathology of non-neoplastic lung disease. WB Saunders, 1997

DEMOGRAPHICS

Etiology and pathogenesis

The etiology and pathogenesis of idiopathic COP is unknown. The disease is thought to result from alveolar epithelium injury due to an unknown cause, capable of triggering angiogenesis and exaggerated reparative response by the fibroblasts

Epidemiology

Mean age at onset varies from 50 to 60 years. The two sexes are equally affected, with a prevalence in non-smokers (2:1). The incidence of COP on hospital admissions is 6-7 per 100,000

Risk factors

There are no known specific risk factors

CLINICAL FEATURES

History

At the time of diagnosis, 75% of patients report symptoms of less than 2 months duration. The most common presentation is that of a community-acquired pneumonia, at times preceded by a flu-like illness. The most frequent symptoms are cough and dyspnea upon exertion at times associated with mucous production. Systemic symptoms are also frequent and include weight loss (57%), chills, sweats, intermittent fever and myalgia

Physical findings

Localized or diffuse fine rales are noted in 74% of patients. Digital clubbing is absent

Pulmonary function tests

The most common findings are a restrictive ventilatory defect (mild to moderate) and reduced D_LCO. An obstructive ventilatory defect is present in a minority of patients (20%), usually smokers. More than 80% of affected individuals have mild resting hypoxemia

The main clinical differential diagnoses are infectious pneumonia and CEP (⌘ CEP)

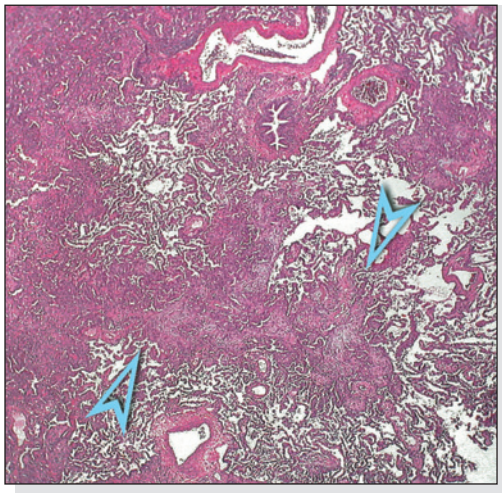
Nagai S. Bronchiolitis obliterans with organizing pneumonia. Curr Opin Pulm Med 1996, 2: 419

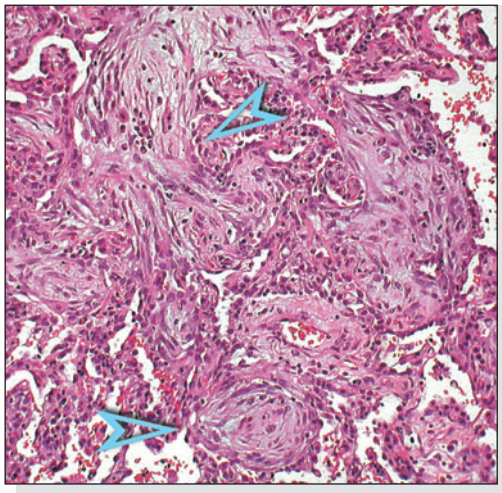
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- "Polyps" of loose connective tissue (≥) within the terminal or respiratory bronchioles (bronchiolitis obliterans, BO), in the alveolar ducts and surrounding alveoli (organizing pneumonia, OP)
- The alveolar septa are often distended by a more-or-less intense chronic inflammatory infiltrate of lymphocytes, histiocytes and plasma cells, and are sometimes lined by hyperplastic type II pneumocytes
- Intense infiltrate of foamy macrophages and other changes typical of obstructive pneumonia





Because the bronchiolar component may be lacking, there is a tendency to replace the acronym BOOP with OP. However, the term BOOP remains commonly used

The disease process involves multiple temporally uniform foci (the connective tissue is young and at the same stage of maturation throughout). Lung architecture is preserved

On hematoxylin-and-eosin stain, the "polyps" appear as pale serpiginous plugs reproducing the shape of the airways in which they form. These plugs consist of fibroblasts arranged parallel to one another and immersed in a mucopolysaccharide-rich matrix containing inflammatory cells

As the disease progresses the "polyps" become covered by bronchiolar or alveolar epithelium and incorporated within the septa, resulting in the healing of the lesions

Distribution

Bronchiolar and peribronchiolar

Differentials

Histopathologic differential diagnoses:

- Infections: suppurative or granulomatous inflammation, presence of necrosis. Identification of the infectious agent
- Obstructive pneumonia: predominance of foamy macrophages in the inflammatory infiltrate
- Organizing DAD: the process is diffuse rather than patchy, the fibrosis is interstitial with uniformly distended and edematous septa. The septal infiltrate is less intense and hyperplasia of type II pneumocytes is more pronounced. In addition, a bronchiolar component is absent
- Wegener's granulomatosis (BOOP-like variant): vasculitis and necrosis with an infiltrate often rich in eosinophils are present
- HP: poorly-formed granulomas, very intense inflammatory infiltrate
- CEP: intense eosinophilic infiltrate in the interstitium and alveoli
- UIP: subpleural fibrosis with fibroblastic foci at the edges of the fibrotic areas; temporal heterogeneity and remodeling with honeycombing. There is no bronchiolar involvement

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

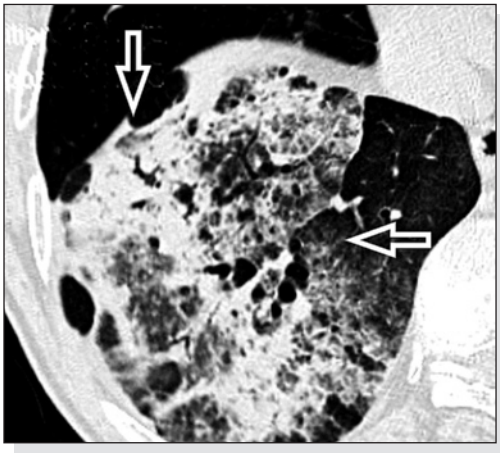
Colby TV. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. Chest 1992, 102: 38S

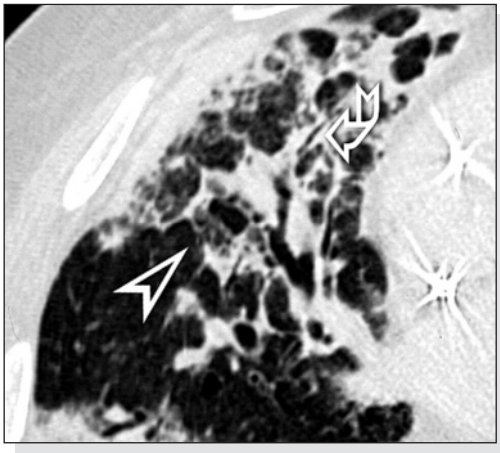
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Patchy areas of consolidation (⇨), often triangular (➢) or polygonal in shape, with hazy borders (80%)
- Ground-glass opacities with patchy (60%) or perilobular distribution (↳)
- Air bronchogram within the areas of consolidation, at times mild bronchiectasis





The ground-glass pattern is the dominant feature in immunodepressed subjects, and may be associated with the presence of inflammatory nodules

Johkoh T. Perilobular pulmonary opacities: high-resolution CT findings and pathologic correlation. J Thorac Imaging 1999, 14: 172

Muller NL. Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 1990, 154: 983

Distribution

Usually bilateral (although unilateral is also possible), characteristically patchy

Peripheral subpleural, although also peribronchial

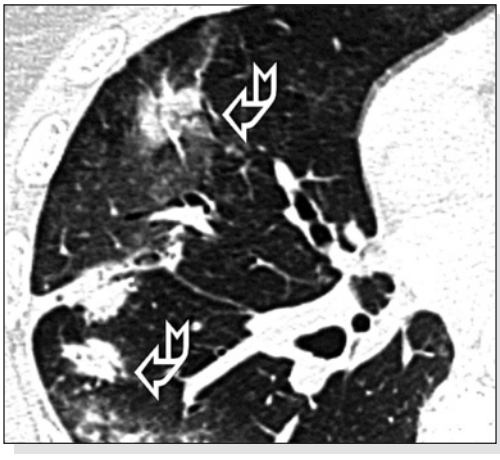
Prevalently basal

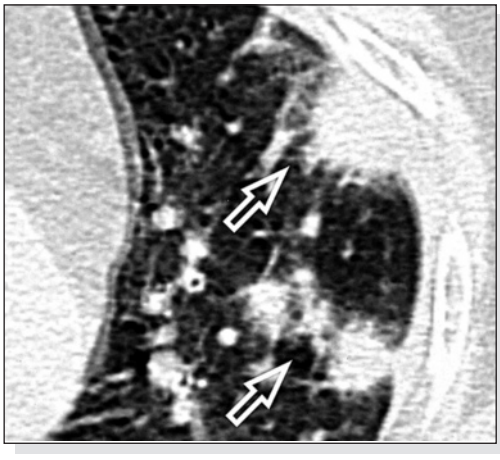
Lung volume is normal

Other signs

Other radiological signs:

- Centrilobular, often peribronchial (↳)(50%), nodules with ill-defined borders
- Bronchial wall thickening and cylindrical bronchiectasis within the areas of consolidation
- One or more large nodules or masses (⇨)(● Large rounded opacities: Organising Pneumonia)
- Moderate pleural effusion





Lee KS. Cryptogenic organizing pneumonia: CT findings in 43 patients. AJR Am J Roentgenol 1994, 162: 543

Differentials

The differential diagnoses of the typical pattern (patchy consolidation and ground-glass attenuation) include:

- Slow-resolving bacterial infections: clinical history and regression of the opacities at follow-up are the key to the diagnosis
- BAC: the radiological pattern may be similar
- TB: the differential diagnosis is based on bronchological studies especially in elderly, diabetic, debilitated or mildly immunodepressed patients
- Sarcoidosis: associated subpleural nodules, hilar and mediastinal adenopathy
- CEP: consolidation predominates in the upper lung fields and has strictly subpleural distribution

In contrast, the differential diagnosis of the pattern seen in immunodepressed patients (ground-glass opacities and nodules) includes:

- Opportunistic infections: the differential diagnosis is based on the biopsy

Arakawa H. Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: high-resolution CT findings in 81 patients. AJR Am J Roentgenol 2001, 176: 1053

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

COURSE and COMPLICATIONS

Associated diseases

The various diseases that result in the development of a BOOP-like pattern (see the table "BOOP-reaction pattern" at the end of this chapter)

Clinical course

Two thirds of subjects treated with corticosteroids make a full recovery: most patients recover within several weeks or months and some respond dramatically with improvements appearing even within 1 or 2 weeks. Only a minority of patients, however, experience spontaneous remission and about half of those treated relapse when treatment is reduced or discontinued

One third of patients have persistent disease which rarely, however, progresses to respiratory failure or death. On the other hand, rare hyperacute forms are possible which rapidly lead to death (accelerated BOOP)

Radiological course

The opacities may resolve spontaneously and then form elsewhere, usually more cranially and at times in the contralateral lung (migratory opacities). Left untreated, the disease may progress to permanent damage with fibrosis and bronchiectasis

LABORATORY FINDINGS

Common findings include elevated ESR, often more than 100 mm in one hour (70-80%), and raised CRP. Leukocytosis is present in 50% of cases. Autoantibodies are usually absent or the titer is low

CLINICAL DIAGNOSIS

A definitive diagnosis cannot be made on the basis of the clinical features alone. The HRCT findings will enable the correct diagnosis to be included among the first three in 50% of cases and, in the appropriate clinical setting, can provide the diagnosis in 80% of cases

BOOP-pattern should be considered in patients with areas of parenchymal consolidation labeled as pneumonia, which persist or migrate after antibiotic therapy

INVASIVE DIAGNOSIS

In the presence of a characteristic clinical-radiological setting, transbronchial lung biopsy alone may be sufficient for histological confirmation, with BAL providing further support for the diagnosis. The diagnosis of COP is, however, a diagnosis of exclusion made only after ruling out all the other conditions characterized by a BOOP-reaction pattern

If biopsy is needed, it should be performed under radiological guidance since the areas of consolidation may rapidly migrate from one zone to another within the lungs

Bronchoalveolar lavage

The BAL fluid is characterized by elevated total cell count, with a reduction in the percentage of macrophages and an increase in lymphocytes (>40%), neutrophils and eosinophils (mixed alveolitis pattern). The CD4/CD8 ratio is reduced. Foamy macrophages are typically present and mast cells and plasma cells are increased

A mixed alveolitis pattern (increased CD8+ lymphocytes, neutrophils and at times eosinophils) is not specific to COP, and may also be observed in HP (⌘ HP, acute), NSIP (☐ NSIP) and drug-induced lung disease (⌘ Drug toxicity)

Costabel U. Bronchiolitis obliterans organizing pneumonia (BOOP): the cytological and immunocytological profile of bronchoalveolar lavage. Eur Respir J 1992, 5: 791

Pesci A. Mast cells in bronchiolitis obliterans organizing pneumonia. Mast cell hyperplasia and evidence for extracellular release of tryptase. Chest 1996, 110: 383

TABLE

On the following page is a table providing further information on the:

- BOOP-reaction pattern

BOOP-REACTION PATTERN

The histological pattern known as "BOOP-reaction pattern" occurs when the lung responds non-specifically to different noxae. As a result, it is seen in varying extents and severity in a number of diseases

BOOP as a disease:	• COP • RA • Toxic respiratory agents • Drugs and medications • Other collagen vascular diseases • Viral and bacterial infections • Radiotherapy
BOOP as an associated reaction in the course of:	• Malignancies • Infectious granulomas • Vasculitides • Pulmonary infarction
BOOP as a minor reaction accompanying:	• HP • NSIP • LCH • Allogeneic bone marrow transplant • Lung transplant

Pulmonary Alveolar Proteinosis

Definition

Pulmonary alveolar proteinosis (PAP) is a chronic disease of unknown etiology characterized by the accumulation of amorphous PAS-positive lipoproteinaceous material in the alveoli

DEMOGRAPHICS

Etiology and pathogenesis

The etiology of the disease is unknown, although similar histopathologic findings have been reported in acute silicosis, exposure to dusts containing aluminium, titanium or silicon, Pneumocystis carinii (jiroveci) infection, hematologic malignancies and immunosuppressive disorders. The pathogenesis of the disease is related to changes in the production or degradation of surfactant resulting from altered macrophage function and/or diminished production or inhibition (neutralizing antibodies) of the cytokine granulocyte-macrophage colony stimulating factor (GM-CSF)

Epidemiology

The disease is rare and its incidence is unknown. It primarily affects subjects aged 20 to 50 years, with a predominance of males (2:1), without racial or geographic predilection

Risk factors

Exposure to mineral dusts and cigarette smoking

CLINICAL FEATURES

History

Approximately one third of patients are asymptomatic. The main symptoms at onset are progressive exertional dyspnea, and less frequently productive cough with expectoration of gelatinous material, low-grade fever, fatigue, hemoptysis, chest pain and weight loss

Physical findings

Breath sounds are often normal, although fine rales may be heard in about 50% of patients. Digital clubbing is rare, as is cyanosis

Pulmonary function tests

The most common physiologic alteration is a restrictive ventilatory defect associated with a reduction in D_LCO. Hypoxemia at rest is present in only one third of patients, whereas oxygen desaturation with exercise is seen in over half

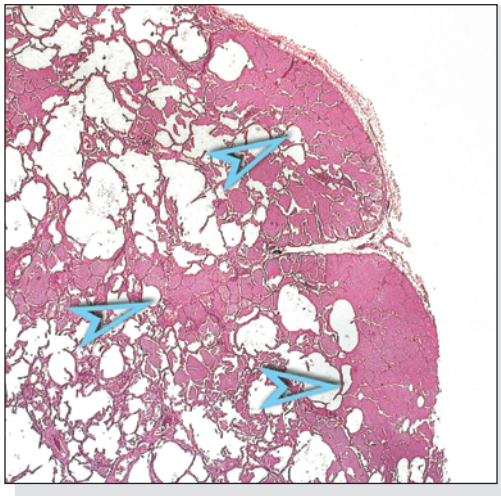
Shah PL. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax 2000, 55: 67

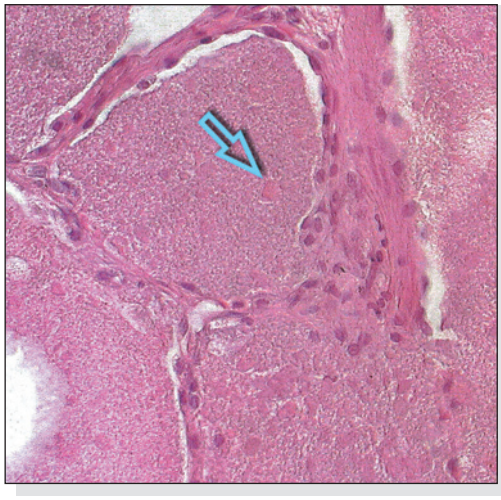
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Alveolar spaces filled with granular eosinophilic PAS-positive material (➢) containing needle-like cholesterol clefts, eosinophilic globules (⇨), scattered macrophages, and cellular debris
- Minimal interstitial involvement consisting of slight septal thickening





Distribution

Diffuse in the alveolar spaces, sometimes extending to the bronchi and alveolar ducts

The lesions are more numerous in the peripheral and subpleural regions, but may also affect the peribronchial airspaces. These features often make it possible to diagnose the disease with transbronchial biopsy

In alveolar proteinosis secondary to infection and in long-standing disease, marked interstitial alterations may be seen, which are due to intense inflammatory infiltrate and septal fibrosis, respectively

Differentials

Histopathologic differential diagnoses:

- PE: the material is neither granular, nor PAS-positive; macrophages and cholesterol clefts are lacking
- Infections: demonstration of the infectious agent in PCP
- DAD: in the exudative phase, presence of fibrin in the form of hyaline membranes associated with hyperplasia of type II pneumocytes; in the proliferative phase, foci of fibroblastic organization

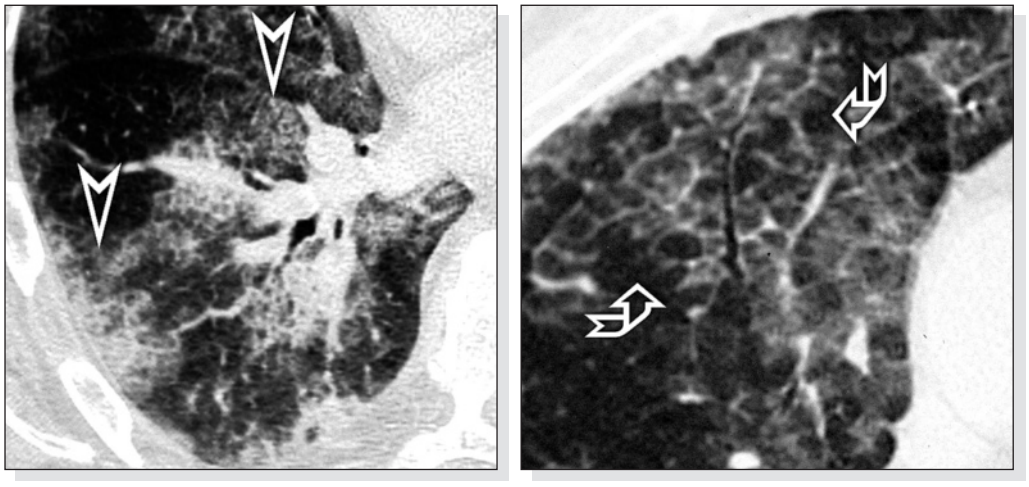
Seymour JF. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002, 166: 215

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Ground-glass opacities (≥)
- Patchy ground-glass opacities associated with smooth septal thickening (↳)(crazy paving)



Reticular septal thickening is exclusively seen within the areas of ground-glass attenuation

Holbert JM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 2001, 176: 1287

Murch CR. Computed tomography appearances of pulmonary alveolar proteinosis. Clin Radiol 1989, 40: 240

Distribution

Bilateral, patchy and sharply demarcated from normal lobules or groups of lobules

Variable, without clear predilections

Variable

Lung volume is normal

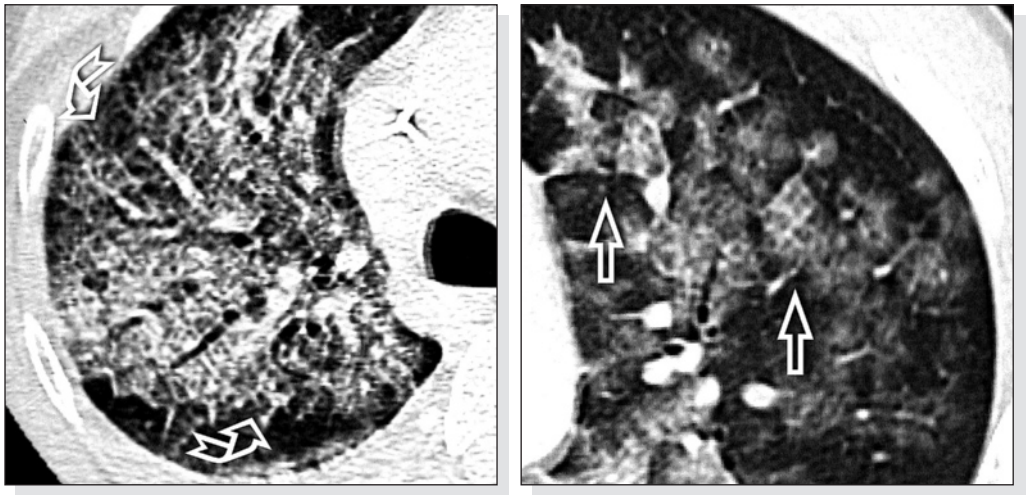
Lee KN. Pulmonary alveolar proteinosis: high-resolution CT, chest radiographic, and functional correlations. Chest 1997, 111: 989

Wang BM. Diagnosing pulmonary alveolar proteinosis. A review and an update. Chest 1997, 111: 460

Other signs

Other radiological signs:

- Diffuse (↳) or focal (⇨) areas of parenchymal consolidation



Parenchymal consolidation may be caused both by the underlying disease and by supervening opportunistic infection. The latter is suspected when the consolidation is focal

Godwin JD. Pulmonary alveolar proteinosis: CT findings. Radiology 1988, 169: 609

Differentials

The differential diagnosis includes all chronic consolidative diseases exhibiting a crazy paving pattern:

- BAC: crazy paving is not the dominant feature, and is associated with hazy nodules. Lesion distribution is asymmetrical, often peripheral and basal, and pleural effusion and adenopathy may be present
- Slow-resolving bacterial pneumonia: frank areas of consolidation predominate and crazy paving is rare
- Lipoid pneumonia: negative density at CT
- CEP: peripheral distribution in the middle and upper regions. Crazy paving is not a constant feature and, when present, has limited extension. Ill-defined nodular opacities and mediastinal adenopathy may be associated

Johkoh T. Crazy-paving appearance at thin-section CT: spectrum of disease and pathologic findings. Radiology 1999, 211: 155

Zompatori M. [Crazy paving]. Radiol Med 1999, 98: 432. Italian

COURSE and COMPLICATIONS

Associated diseases

Hematological malignancies are associated in 8% of cases (acute myeloblastic leukemia, chronic myelocytic leukemia, paraproteinemia). Secondary alveolar proteinosis has also been described in AIDS, dermatomyositis and pulmonary tuberculosis

Clinical course

Left untreated, the disease proves fatal in about 25% of patients with death due to respiratory failure or pulmonary superinfections. Spontaneous recovery may occur in 20-30% of cases, whereas progression to fibrosis is rare. In 15% of cases, the disease may become complicated by opportunistic infections (Nocardia, Aspergillus, Cryptococcus, Histoplasma, Mucor, Mycobacterium, Pneumocystis, Cytomegalovirus)

Radiological course

In patients treated with repeated therapeutic bronchial lavage, follow-up radiology demonstrates regression or improvement of the opacities, which may, however, recur. Progression to fibrosis is rare. Transient alveolar opacities noted immediately after therapeutic bronchial lavage may be due to the procedure itself

Clague HW. Pulmonary interstitial fibrosis associated with alveolar proteinosis. Thorax 1983, 38: 865

LABORATORY FINDINGS

Serum levels of LDH are typically increased. Less common findings include polycytemia and hypergammaglobulinemia, as well as elevated serum levels of surfactant proteins A and D (SP-A and SP-D)

Elevated levels of SP-A and SP-D are not specific and may also be observed in idiopathic pulmonary fibrosis

CLINICAL DIAGNOSIS

Alveolar proteinosis is suspected on the basis of the clinical and radiological setting and in particular in the presence of extensive crazy paving visualized by HRCT. In patients with a productive cough, the diagnosis can be confirmed by the detection of PAS-positive macrophages and lamellar bodies in the sputum. More often, the diagnosis is provided by bronchoscopy with BAL and transbronchial biopsy. The possibility of diagnosing idiopathic alveolar proteinosis based on the presence of serum antibodies against GM-CSF has recently been reported

Kitamura T. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000, 162: 658

INVASIVE DIAGNOSIS

Surgical lung biopsy is rarely required

Bronchoalveolar lavage

The BAL fluid is strongly opaque or "milky". Total cell count is reduced and there are large acellular eosinophilic bodies in a background of amorphous granular eosinophilic material. The proteinaceous component typically stains positive for PAS and negative for Alcian blue. The macrophages are engulfed by PAS-positive material. There are elevated levels of SP-A. Finally, electron microscopy reveals the presence of concentric layers of laminated structures (lamellar bodies). These findings are diagnostic

Milleron BJ. Bronchoalveolar lavage cell data in alveolar proteinosis. Am Rev Respir Dis 1991, 144: 1330

Pneumocystis Carinii Pneumonia

Definition

Pneumocystis carinii (recently renamed Pneumocystis jiroveci) pneumonia (PCP) is a clinically significant lung infection, found only in immunosuppressed subjects

Pneumocystosis

DEMOGRAPHICS

Etiology and pathogenesis

The mode of transmission of the infectious agent is unknown. Some studies have suggested an exogenous infection transmitted through inhalation, whereas others have implicated a reactivation of a latent infection acquired during childhood

Infection is undoubtedly favored by the subject's immunosuppressed state and in particular by CD4+ T-cell deficiency (circulating CD4+ count below 200/mm^3) and impairment of the bactericide action of alveolar macrophages and neutrophils

Epidemiology

Prior to advent of highly active antiretroviral therapy (HAART), 15% of HIV+ patients receiving prophylactic treatment and 45% of those not on prophylaxis developed PCP. PCP is decreasing in frequency due to use of prophylaxis and HAART

Risk factors

Immunodeficiency: HIV+, post-transplant immunosuppression, lymphatic system malignancies, and immunosuppressive treatments

CLINICAL FEATURES

History

Onset is generally insidious. In patients with full-blown AIDS, however, the disease may manifest abruptly with fever and hypoxemia. The most common symptom is dyspnea (95%) often associated with dry cough (90%). Less frequent symptoms include chills, malaise, weight loss and chest pain. Sputum production may be present in 25% of patients, whereas hemoptysis is unusual. About 7% of patients are asymptomatic

Physical findings

Patients have fever (84%) and tachypnea (62%). The most common finding on chest auscultation is fine rales heterogeneously distributed throughout the lung fields. At times ronchi and wheezes are heard. Chest examination is normal in 50% of cases. Patients may have splenomegaly and skin lesions. Digital clubbing is rare

Pulmonary function tests

Most patients have reduced D_LCO (<70% of the predicted value) with increased alveolar-arterial oxygen gradient. A finding of normal D_LCO and alveolar-arterial oxygen gradient has a strong negative predictive value for PCP

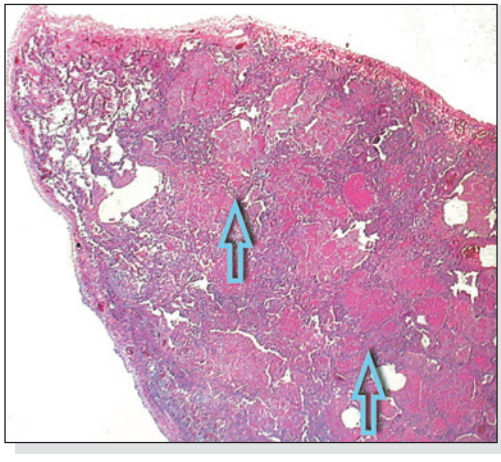
Santamauro JT. Pneumocystis carinii pneumonia. Med Clin North Am 1997, 81: 299

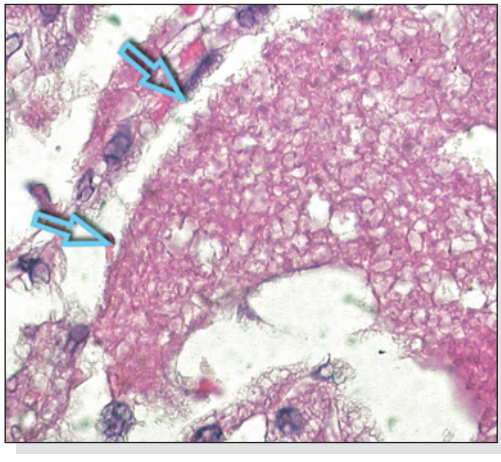
PATHOLOGY

Basic lesions

The histopathologic features are the following:

- Colonies of Pneumocystis carinii consisting of intraalveolar eosinophilic masses with a foamy appearance as they are made up of tiny cysts approximately the size of a red blood cell (⇨). At the center of these cysts is a small gray-blue spot that is poorly appreciable upon hematoxylin-and-eosin stain but clearly evident with silver stains (methenamine silver). The walls of the microcysts are PAS-positive
- Sparse inflammatory elements are commonly observed in the interstitium associated with hyperplasia of type II pneumocytes





Other possible histopathologic patterns include: 1. DAD with hyaline membranes; 2. non-specific cellular, granulomatous or desquamative interstitial pneumonia; 3. intraalveolar hemorrhage; 4. fibrosis and micro-calcification; 5. alveolar proteinosis-like pattern. Colonies of Pneumocystis may also be found in the context of a normal lung

Distribution

Intraalveolar

Differentials

Histopathologic differential diagnoses:

- Intraalveolar fibrin or edema: the intraalveolar material is not foamy and is negative upon PAS and silver stainings
- PAP: the intraalveolar material is not foamy and is negative upon silver stainings. Although PAS may be positive, it does not selectively stain the microcyst walls

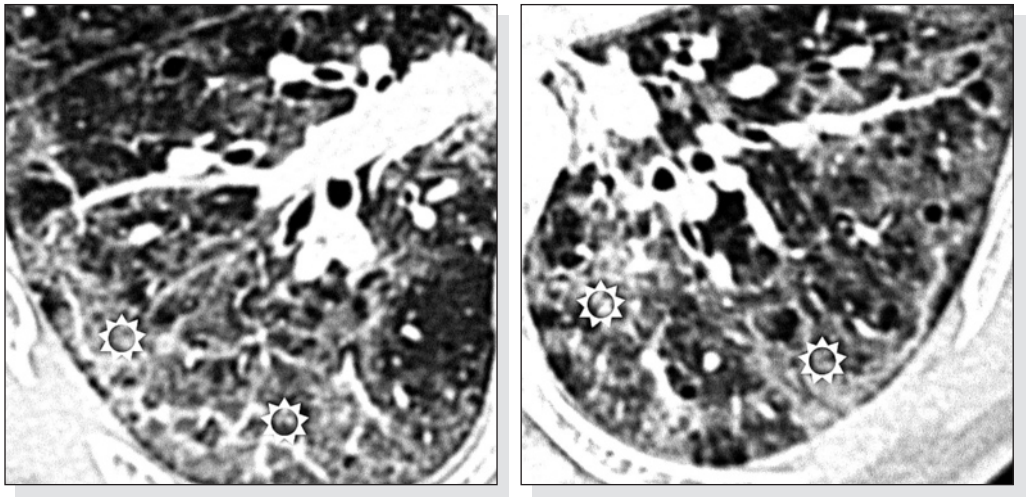
Travis WD. Atypical pathologic manifestations of Pneumocystis carinii pneumonia in the acquired immune deficiency syndrome. Review of 123 lung biopsies from 76 patients with emphasis on cysts, vascular invasion, vasculitis, and granulomas. Am J Surg Pathol 1990, 14: 615

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- More or less extensive ground-glass opacities (☼)
- Associated parenchymal consolidation



Kuhlman JE. Pneumocystis carinii pneumonia: spectrum of parenchymal CT findings. Radiology 1990, 175: 711

Distribution

Bilateral and asymmetrical, diffuse or patchy

Often central and parahilar

Middle-upper lung regions

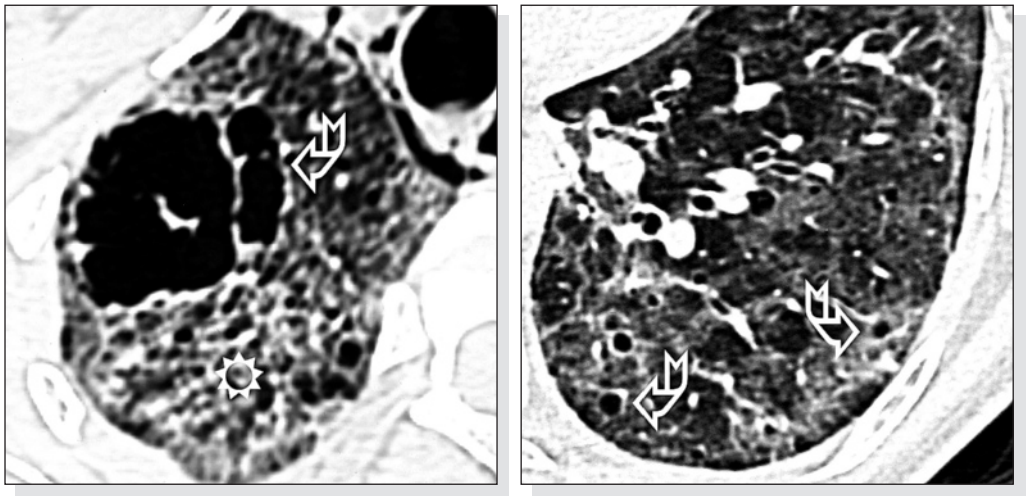
The lesions tend to predominate in the upper lobes in subjects receiving aerosol pentamidine

Lung volume is normal, or moderately reduced in the more extensive forms

Other signs

Other radiological signs:

- Cysts (↳) within the ground-glass opacities (35% of cases)
- Reticular opacities (☼) due to smooth interlobular septal thickening possibly associated with ground-glass density with resulting crazy paving pattern
- Small diffuse or parahilar nodules with ill-defined borders (due to granulomatous reaction); more rarely large nodules or true masses (pneumocystomas) may be seen
- Mediastinal or hilar adenopathy
- Pleural effusion (about 5% of cases)
- At times signs of infectious bronchiolitis with tree-in-bud pattern, bronchial wall thickening, and bronchiectasis



The cysts, which are often arranged in clusters in the upper lobes, have thick walls and bizarre shapes. At times the cysts are septated and may become very large

A reticular pattern associated with ground-glass attenuation is often seen in the subacute phase of the disease. This is the result of interstitial organization of the intraalveolar exudate

Moskovic E. High resolution computed tomography of Pneumocystis carinii pneumonia in AIDS. Clin Radiol 1990, 42: 239

Differentials

The differential diagnosis includes other diseases characterized by acute alveolar pattern:

- Viral infections: the radiological patterns may be similar, but the cysts are absent
- DAH: the longitudinal distribution is variable. In Wegener's disease large round cavitating opacities may be present
- PE: predominantly basal distribution, and frequent cardiomegaly and pleural effusion

COURSE and COMPLICATIONS

Associated diseases

Infections in other organs, in particular due to Cytomegalovirus, or neoplastic disease (Kaposi's sarcoma or lymphomas). Pneumothorax due to rupture of a cyst into the pleural space in 5-10% of cases

The appearance of severe dyspnea in a patient with PCP should raise the suspicion of pneumothorax

Feurestein IM. Thin-walled cavities, cysts, and pneumothorax in Pneumocystis carinii pneumonia: further observations with histopathologic correlation. Radiology 1990, 174: 697

Clinical course

PCP is a severe infection which may be fatal if overlooked. If promptly treated, on the other hand, it has a favorable prognosis (50-95% survival). In 50-75% of AIDS patients, the disease will relapse unless appropriate chemoprophylaxis has been instituted

Radiological course

If treatment is effective the radiological consolidative changes may resolve completely. A minority of cases show persistence of mild fibrosis in the form of retracting strands. The cysts may even persist for weeks or months after the pneumonia has resolved, and in this case they have thin walls

In cases not responding to therapy, the consolidative changes may progress to a clinical and radiological pattern of ARDS (⌘ ARDS)

Chow C. Lung cysts associated with Pneumocystis carinii pneumonia: radiographic characteristics, natural history, and complications. AJR Am J Roentgenol 1993, 161: 527

LABORATORY FINDINGS

Most patients have moderate leukocytosis with lymphopenia. In 50% of cases, the CD4/CD8 ratio is reduced (often the absolute count of CD4+ T-cells is <200/mm^3). Elevated serum levels of LDH are common (90%), as are high serum levels of angiotensin-converting enzyme (ACE). Recent studies showed undetectable plasma levels of S-adenosylmethionine in PCP patients

The finding of elevated LDH levels is a negative prognostic factor

LDH has been suggested to be an index of pneumonia extension more than a marker of PCP infection

CLINICAL DIAGNOSIS

Although the clinical and radiological setting may often be strongly suggestive of PCP, the presence of Pneumocystis carinii (jiroveci) in the respiratory specimens should always be demonstrated (first in induced sputum)

The sensitivity of HRCT is close to 100% and its specificity is greater than 80%, with good interobserver agreement

The negative predictive value of HRCT is so high that a negative scan allows a diagnosis of PCP to be confidently ruled out. HRCT has replaced gallium scintigraphy

INVASIVE DIAGNOSIS

Given the high diagnostic yield of induced sputum and BAL, histological confirmation, which is mostly obtained by transbronchial lung biopsy, is rarely required. When performing a biopsy, the high risk of post-biopsy bleeding due to the typical thrombocytopenia found in HIV+ subjects should be borne in mind

Bronchoalveolar lavage

BAL is recommended if sputum induction is non-diagnostic. A characteristic BAL finding is “foamy exudate”: the “foamy” effect is due to the presence of empty cysts within the pathological secretions. This exudate, which can be seen with May-Grunwald-Giemsa or Papanicolau stains, is diagnostic of PCP even without special stains. Sporozoites may be observed inside, and free trophozoites outside the cysts

The diagnostic yield of BAL in HIV+ subjects in 97-100%, which drops to 62% in those on pentamidine prophylaxis. Increased levels of interleukin-8 or the presence of cysts in the BAL fluid have been reported to be negative prognostic factors

Golden JA. Bronchoalveolar lavage as the exclusive diagnostic modality for Pneumocystis carinii pneumonia. A prospective study among patients with acquired immunodeficiency syndrome. Chest 1986, 90: 18

Pulmonary Edema

Definition

Pulmonary edema (PE) refers to the accumulation of extravascular fluid in the alveoli

Cardiogenic, hemodynamic edema

DEMOGRAPHICS

Etiology and pathogenesis

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

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

Epidemiology

PE is a frequent cause of admission to hospital

Risk factors

These include liver cirrhosis, kidney failure, heart disease, valvulopathy

CLINICAL FEATURES

History

The onset of symptoms is often acute and dramatic. Patients present with orthopnea and are in an obvious state of respiratory distress (use of accessory respiratory muscles). Peripheral and central cyanosis, tachycardia, pallor, cold clammy skin, anxiety and often elevated systemic pressure are all common findings. In the more severe cases, the patients have productive cough with expectoration of pink frothy sputum up to frank hemoptysis. Patients often have a long history of orthopnea and/or paroxysmal nocturnal dyspnea

Physical findings

The physical examination reveals indirect signs of increased venous return such as jugular venous distention, tender hepatosplenomegaly and peripheral edema. Examination of the lung is characterized by fine diffuse inspiratory rales and expiratory wheezees. In patients with valvular dysfunction, a gallop rhythm may be noted on cardiac auscultation. In the end stages of disease, loss of consciousness and cardiocirculatory failure occur

Pulmonary function tests

Lung function testing is rarely performed in patients with full-blown PE. Nonetheless, the findings will include a reduction in compliance, vital capacity and total lung capacity, and an acute increase in pulmonary resistance and closing volume

Bronchial hyperreactivity has been reported in some patients. Severe hypoxemia and normocapnia or hypercapnia are also encountered

The differential diagnosis of PE includes fulminant pneumonia, acute asthma, acute exacerbation of COPD and acute hemorrhagic alveolitis

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

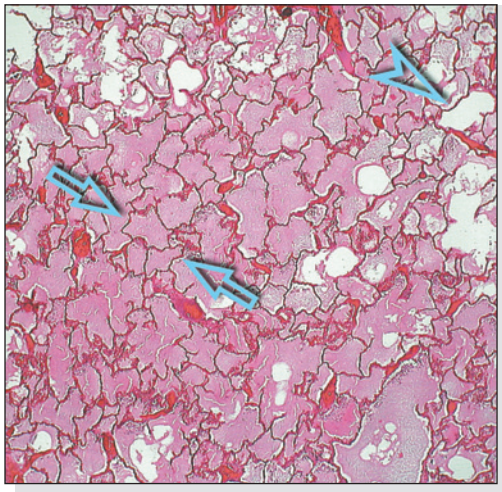
Gropper MA. Acute cardiogenic pulmonary edema. Clin Chest Med 1994, 15: 501

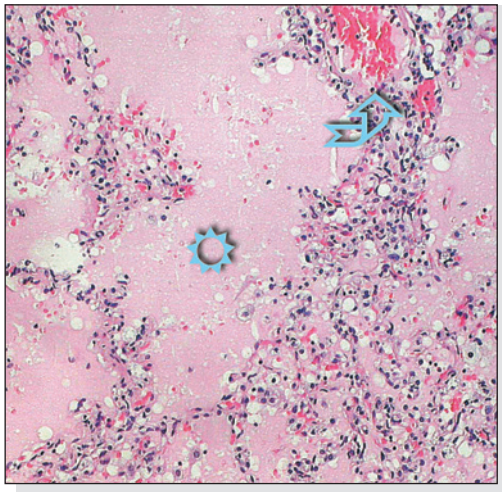
PATHOLOGY

Basic lesions

The histopathologic features of PE are the following:

- Accumulation of intraalveolar fluid (⇨): the lungs are heavier than normal, with frothy fluid oozing out of the cut surface of the lung and bronchi, either spontaneously or following compression
- The alveolar spaces appear overdistended and often optically empty (≻) as their content is easily lost during tissue processing
- Less frequently, slightly eosinophilic granular and proteinaceous material may be seen within the alveolar spaces (☼)
- Interstitial edema associated with congested capillaries in the intraalveolar septa (↯)





Distribution

Intraalveolar

Differentials

Histopathologic differential diagnoses:

- Normal parenchyma: normal lung weight and optically empty alveoli; there is no edema in the pulmonary interstitium
- DAD: the edema is associated with the presence of hyaline membranes
- PAP: the alveoli are filled with granular and PAS-positive material

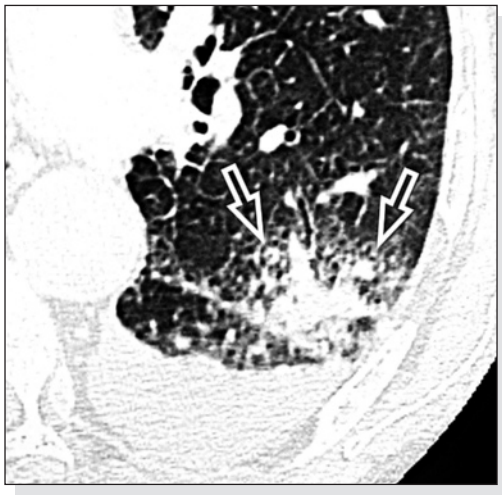
Colby TV. Pulmonary histology for the surgical pathologist. Am J Surg Pathol 1988, 12: 223

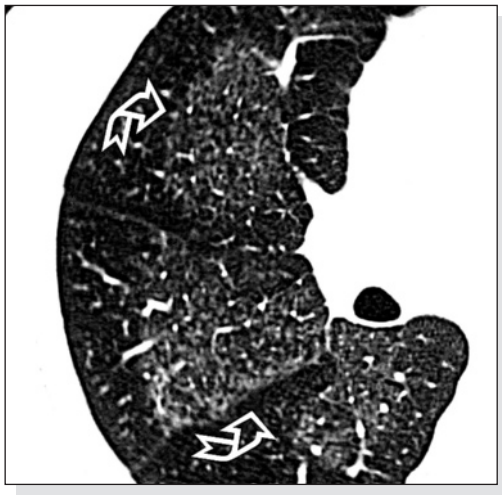
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - H R C T

Basic lesions

Basic radiological signs:

- Parenchymal consolidation (⇨)
- Associated ground-glass (↳)
- Limited or absent air bronchogram





Distribution

Bilateral, symmetrical

The edema may be unilateral, as in patients in protracted lateral decubitus, or asymmetric and bizarre-shaped, as in patients with regional emphysema (because edema does not form in the affected area)

In patients with acute pulmonary thromboembolism, hemodynamic edema due to hyperperfusion may develop in the otherwise unaffected areas

Predominantly subpleural and gravitational, although also diffuse

Peripheral edema is more characteristic of cardiogenic edema because the movement of the fluid towards the hilum (mediated by the lymphatics) is hindered by the elevated central venous pressure. Instead, a hilar distribution is more typical of hypervolemic edema since the central pressures are relatively normal

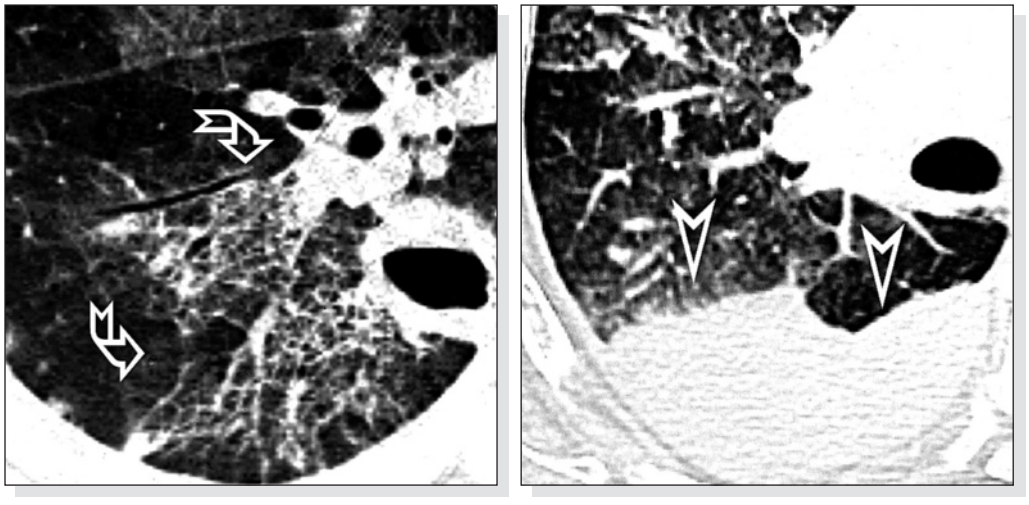
Predominantly basal

Lung volume is slightly reduced

Other signs

Other radiological characteristics:

- Smooth reticular pattern (↳), prevalent in the initial stages of disease (☐ PE, interstitial)
- Subpleural thickening and pleural effusion (➢)
- Cardiomegaly



An increase in the thickness of the chest wall may reflect an accumulation of fluid in the "third space", whereas a widening of the vascular pedicle indicates an increase in the blood volume circulating in the venous district

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

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

Differentials

The differential diagnoses include the various causes of acute parenchymal consolidation:

- ARDS: patchy opacities with air bronchogram without clear gravitational predominance. There is no reticular pattern or pleural effusion, and the vascular pedicle and heart volume are normal
- AIP: there are no cardiovascular signs of hemodynamic edema
- Acute eosinophilic pneumonia: the appearance is similar to lesional edema (AIP associated with DAD or ARDS)
- HP: patchy distribution, with associated hazy centrilobular nodules, and mosaic pattern with air-trapping
- DAH: "butterfly" or "batwing" pattern with perihilar distribution and sparing of the subpleural regions. Cardiomegaly is absent
- PCP: crazy paving, thick-walled cysts, and distribution in the middle-upper lung regions

Desai SR. Acute respiratory distress syndrome: imaging of the injured lung. Clin Radiol 2002, 57: 8

Primack SL. Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. AJR Am J Roentgenol 1995, 164: 295

COURSE and COMPLICATIONS

Associated diseases

Various valvular and non-valvular heart diseases may also be present

Clinical course

Alveolar PE is a dramatic condition that may become life-threatening if not treated promptly

Radiological course

Acute onset and rapid regression with treatment are characteristic features of this form of edema, and may assist in the differential diagnosis

There may be a time lag between the regression of edema and pleural effusion and the return to normal of the pulmonary capillary wedge pressure

LABORATORY FINDINGS

Laboratory findings are useful for ruling out infection or anemia which may act as precipitating factors. Normal cardiac enzymes allow exclusion of an underlying myocardial infarction, and renal function indices enable detection of concurrent renal failure

Brain natriuretic peptide (BNP) levels are increased in PE and therefore can be helpful in differentiating between cardiogenic and lesional PE

CLINICAL DIAGNOSIS

The diagnosis is clinical and may be aided by instrumental investigations such as BNP serum levels, chest radiographs, electrocardiogram and echocardiography

INVASIVE DIAGNOSIS

Bronchoalveolar lavage

There is no indication to perform BAL in PE. The small amount of data available in the literature suggests that the BAL findings are similar to those seen in hemorrhagic alveolitis

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