# Nodular Diseases

## Clinical features

**HP, subacute**
- Hypersensitivity Pneumonitis
- Extrinsic Allergic Alveolitis (EAA)

**LCH, early**
- Langerhans’ Cell Histiocytosis
- Pulmonary eosinophilic granuloma, pulmonary Langerhans’ cell granulomatosis, histiocytosis X

**LIP**
- Lymphocytic Interstitial Pneumonia

**Metastases**
- Respiratory Bronchiolitis-Interstitial Lung Disease
- Smoker’s bronchiolitis

**Sarcoidosis, granulomatous**
- Sarcoidosis

**Silicosis**
- Silica-induced pneumoconiosis

**TB, miliary**
- Miliary tuberculosis

## Clinical features

**Large rounded opacities**
- Aspergillosis
- Amyloidosis
- BronchioloAlveolar Carcinoma (BAC)
- High-grade primary lymphoma
- Kaposi’s sarcoma
- Metastases
- Organizing Pneumonia (OP)
- Rheumatoid Arthritis (RA)
- Sarcoidosis
- Septic emboli
- Tuberculomas
- Wegener’s granulomatosis
Hypersensitivity Pneumonitis

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

Extrinsic Allergic Alveolitis (EAA)

DEMOGRAPHICS

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

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

Non-smokers are more commonly affected.

CLINICAL FEATURES

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

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

Patterns include moderate-to-severe restrictive defects and mixed restrictive and obstructive defects. There is hypoxemia at rest and \( D_L \text{CO} \) is reduced in most cases.

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

PATHOLOGY

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

- Chronic interstitial pneumonitis with bronchiolocentric distribution (cellular bronchiolitis)
  The often intense infiltrate consists of lymphocytes and plasma cells
- Small, poorly-formed, non-necrotizing granulomas (>), mostly consisting of small aggregates of epithelioid histiocytes scattered in the peribronchiolar interstitium
- Foci of organizing pneumonia
Additional findings:
- Scattered multinucleated giant cells, often containing cholesterol crystals
- Obstructive pneumonia with foamy histiocytes in the air spaces

Bronchiolocentric

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127
Coleman A. Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 1988, 12: 514

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

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

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

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT

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

Distribution

Diffuse or patchy
Uniformly distributed
Variable with possible middle-lower predominance
Hansell DM. High-resolution computed tomography in extrinsic allergic alveolitis. Clin Radiol 1991, 43: 8
Lynch DA. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 1992, 159: 469
Remy-Jardin M. Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. Radiology 1993, 189: 111

Lung volume is normal

Other radiological findings:
- Air-trapping, often lobular, but also extensive (> ) mosaic appearance (common, up to 86%)
- Ground-glass ( ) + air-trapping ( ): head-cheese pattern

Chung MH. Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. J Thorac Imaging 2001, 16: 69
Hansell DM. Hypersensitivity pneumonitis: correlation of individual CT patterns with functional abnormalities. Radiology 1996, 199: 123
Small JH. Air-trapping in extrinsic allergic alveolitis on computed tomography. Clin Radiol 1996, 51: 684

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

**COURSE and COMPLICATIONS**

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

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

Removal from exposure to the inciting antigens is usually sufficient for complete remission, although corticosteroid treatment may be required. Recovery is slower than in the acute form (months). Continued exposure to the inciting antigens may lead to the development of the chronic form of the disease with diffuse pulmonary fibrosis ( □ HP, chronic)
The prognosis of “Bird fancier’s lung” is worse than that of “Farmer’s lung”. The appearance of digital clubbing is a negative prognostic factor.

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

LABORATORY FINDINGS

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

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

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

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

Costabel U. Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med 2001, 7: 255
Drent M. Bronchoalveolar lavage in extrinsic allergic alveolitis: effect of time elapsed since antigen exposure. Eur Respir J 1993, 6: 1276
Langerhans’ Cell Histioctytosis

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

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

DEMOGRAPHICS

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

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

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

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

CLINICAL FEATURES

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

They are generally normal.

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

PATHOLOGY

The histopathologic findings are the following:

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

The nodules vary in size and cellular composition and overtime progress from cellular lesions to foci of stellate fibrosis. The presence of Langerhans’ cells can be confirmed with immuno-cytochemistry (positive staining for S-100 and CD1a).
Smaller lesions are bronchiolocentric. The site of origin is often unidentifiable in advanced lesions.

**Histopathologic differential diagnoses:**

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

**HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT**

**Basic radiological signs:**

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

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

**Distribution**

- Bilateral and symmetrical
- Uniformly distributed
- Upper and middle lung zones: lesions are typically absent in the costophrenic angles
- Lung volume is normal or slightly increased

**Differentials**

- **Langerhans’ Cell Histiocytosis**

Colby TV. Histiocytosis X in the lung. Hum Pathol 1983, 14: 847
Travis WD. Pulmonary Langerhans’ cell granulomatosis (histiocytosis X). A clinicopathologic study of 48 cases. Am J Surg Pathol 1993, 17: 971

Giron J. Contribution of high resolution x-ray computed tomography to the diagnosis of pulmonary histiocytosis X. Apropos of 12 cases. Ann Radiol 1990, 33: 31
Grenier P. Chronic diffuse interstitial lung disease: diagnostic value of chest radiography and high-resolution CT. Radiology 1991, 179: 123

Moore AD. Pulmonary histiocytosis X: comparison of radiographic and CT findings. Radiology 1989, 172: 249
Other less frequent findings:
- Micronodules, possibly cavitating (25-30%)
- Thick-wall cysts (≥)
- Mosaic oligemia with air-trapping

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

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

**COURSE and COMPLICATIONS**

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

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

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

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

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

Laboratory findings are normal

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

CLINICAL DIAGNOSIS

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

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

INVASIVE DIAGNOSIS

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

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

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

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

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

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

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

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

DEMOGRAPHICS

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

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

There are no known risk factors.

CLINICAL FEATURES

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

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

The most common functional change is a restrictive defect and lowered DLCO.

PATHOLOGY

The histopathologic findings are the following:

- Intense interstitial infiltrate consisting of small lymphocytes and plasma cells in the alveolar septa or with a lymphatic distribution.
- Lymphoid follicles with germinal centers are often present, usually with a lymphatic distribution.
Lymphoid proliferation is polyclonal, often with a significant number of T-cells.

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

Peribronchiolar, lymphatic or diffuse.

Histopathologic differential diagnoses:

- MALToma, small lymphocytic lymphoma: dense monomorphic infiltrate with destruction of pulmonary architecture, and pleural, lymph node and cartilage infiltration. Lymphoid proliferation is monoclonal. Lymphoepithelial lesions are present in MALToma.

- Nodular lymphoid hyperplasia: lesions are localized and not diffuse, the lymphoid infiltrate is predominant around the airways and lymphatics with more numerous and prominent germinal centers.

- HP: less intense infiltrate, peribronchiolar distribution, poorly-formed granulomas, and cellular bronchiolitis.

- NSIP: the infiltrate is less dense and diffuse, while lymphoid follicles with germinal centers are rare.

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

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

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT

Basic radiological signs:

- Small centrilobular nodules with low density and ill-defined margins (>)

- Subpleural and perilobular nodules with well-defined margins and higher density (=) (86%)

Diffuse, uniform.

Uniformly distributed.

No predominance or middle-to-basal tendency.

Lung volume is normal.

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

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

**Differentials**

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

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

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

**COURSE and COMPLICATIONS**

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

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

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

A diagnosis of LIP cannot be made without using invasive procedures

INVASIVE DIAGNOSIS

A definitive diagnosis requires surgical lung biopsy

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

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

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

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

DEMOPGRAPHICS

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

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

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

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

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

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

CLINICAL FEATURES

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

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

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

Libshitz HI. Pulmonary metastases. Radiol Clin North Am 1982, 20: 437
The histopathologic findings are the following:

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

For example:

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

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

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

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

- Primary pulmonary neoplasm: in cases of known extrapulmonary malignancy, the pulmonary, possibly metastatic, lesion should be compared with the primary tumor. In the absence of a known primary tumor, immunohistochemistry, electron microscopy and molecular biology can be used to identify the origin of the metastases.

- Primary or secondary squamous-cell carcinoma: metastases from squamous-cell carcinoma (uterine cervix, head and neck) are relatively rare and in the presence of this histological type a primary pulmonary neoplasm is more likely.

HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT

Basic radiological signs:

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

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

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

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

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

Distribution

- Bilateral, often symmetrical, random
- Early predominance in subpleural regions
- Often at the lung bases
- Lung volume is normal
Other possible findings:
- Mediastinal adenopathy
- Lymphangitic carcinomatosis
- Primary thoracic neoplasm

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

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

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

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

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

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

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

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

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

Linder J. Bronchoalveolar lavage in the cytologic diagnosis of carcinoma of the lung. Acta Cytol 1987, 31: 796
Respiratory Bronchiolitis-Interstitial Lung Disease

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

Smoker’s bronchiolitis

**DEMOGRAPHICS**

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

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

Cigarette smoking

**CLINICAL FEATURES**

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

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

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

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

**PATHOLOGY**

The histopathologic findings are the following:

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

Histopathologic differential diagnoses:

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

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002, 165: 277
Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 1989, 64: 1373

HIGH-RESOLUTION COMPUTED TOMOGRAPHY – HRCT

Basic radiological signs:

- Low-density centrilobular micronodules (3-5 mm diameter) with ill-defined margins (’)
Other radiological findings:
- Patchy ground-glass in the middle and upper lung fields (85%)
- Bronchial wall thickening (94%)
- Centrilobular emphysema (50%)
- Intralobular reticular pattern (rare)

Holt RM. High resolution CT in respiratory bronchiolitis-associated interstitial lung disease. J Comput Assist Tomogr 1993, 17: 46
Park JS. Respiratory bronchiolitis-associated interstitial lung disease: radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 2002, 26: 13

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

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

COURSE and COMPLICATIONS
The disease may be associated with other smoking-related diseases, especially centrilobular emphysema. It is not clear whether RB-ILD is an early stage of desquamative interstitial pneumonia (DIP), which also affects smokers and with which RB-ILD has histopathologic similarities (36 DIP)

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

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

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

LABORATORY FINDINGS
Routine laboratory examinations are neither specific nor of diagnostic utility
CLINICAL DIAGNOSIS
In an appropriate clinical and radiological setting, a diagnosis of RB-ILD may be suspected in the presence of a history of cigarette smoking.

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

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

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

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

### DEMOGRAPHICS

The etiology of the disease remains unknown. It is thought that the pathogenesis of the disease involves the exposure of a genetically susceptible individual to specific antigens (propionobacteria and mycobacteria). This pathogenetic theory, suggesting conventional antigenic stimulation, is supported by the presence of activation and proliferation of helper T cell type 1 (Th1) and oligoclonality in TCR Vß repertoire.

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

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

### CLINICAL FEATURES

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

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

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

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

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

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

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

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

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

### PATHOLOGY

The histopathologic findings are the following:

- Multiple non-caseating giant-cell granulomas ( mỏi ) with a lymphatic distribution (along bronchovascular bundles, interlobular septa and subpleural connective tissue).
- The granulomas are discrete compact aggregates of epithelioid histiocytes, rare lymphocytes and multinucleated giant cells, sometimes with cytoplasmic inclusions (Schaumann bodies, asteroid bodies, Hamazaki-Wesenberg bodies). The granulomas often merge and tend to be surrounded by hyaline fibrosis.
Granulomas may occasionally exhibit focal coagulative necrosis or fibrinoid degeneration. The interstitial inflammatory infiltrate is mild. Granulomatous or lymphoplasmacellular vasculitis may be present.

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

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

Histopathologic differential diagnoses:

- **HP: the granulomas consist of small aggregates of epithelioid macrophages in the alveolar septa and in the peribronchiolar interstitium (poorly-formed granulomas) associated with intense inflammatory infiltrate**

- **Mycobacterial and fungal infections: randomly distributed necrotizing granulomas which may be bronchiolocentric, associated with inflammatory infiltrate. Positive staining for acid-fast bacilli and fungi**

- **Chronic berylliosis: histologically indistinguishable from sarcoidosis. History of exposure to beryllium**

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

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

**HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT**

Basic radiological signs:

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

Bilateral, patchy

Hilar-perihilar, dorsal and in the subpleural regions

Middle-upper lung fields (two thirds of cases)

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

Lung volume is normal
Less frequent manifestations:

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

The adenopathies are bilateral, symmetrical, not only hilar but also in the right paratracheal space, subcarinal space and aortopulmonary window. Adenopathies may contain "stippled" calcifications. Parenchymal consolidation and rounded opacities with galaxy signs are produced by the confluence of granulomas. Even the pseudoplaques are early aggregates of granulomas in the subpleural regions. The ground-glass pattern is produced by a multitude of small granulomas below the spatial resolution of HRCT. Granulomas situated in the small airways can cause lobular air-trapping or more significant mosaic oligemia.

Chiles C. Imaging features of thoracic sarcoidosis. Semin Roentgenol 2002; 37: 82
Gleeson PV. Evidence of expiratory CT scans of small-airway obstruction in sarcoidosis. AJR Am J Roentgenol 1996; 166: 1052
Johkoh T. CT findings in “pseudoalveolar” sarcoidosis. J Comput Assist Tomogr 1992; 16: 904
Nishimura K. Pulmonary sarcoidosis: correlation of CT and histopathologic findings. Radiology 1993; 189: 105

Radiological differential diagnoses:

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

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

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

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

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

LABORATORY FINDINGS

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

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

CLINICAL DIAGNOSIS

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

INVASIVE DIAGNOSIS

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

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

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

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

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

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

### DEMOGRAPHICS

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

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

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

### CLINICAL FEATURES

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

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

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

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

Spirometry can detect physiological abnormalities that may precede radiographic changes.

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

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

Balaan MR. Clinical aspects of coal workers’ pneumoconiosis and silicosis. Occup Med 1993, 8: 19.
The histopathologic findings are the following:

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

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

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

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

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

Histopathologic differential diagnoses:

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

Mossman BT. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 1998, 157: 1666.
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT

Basic radiological signs:
- Centrilobular (↑) and subpleural (→) nodules with a diameter variable up to several millimeters.

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

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

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

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

Upper and middle lung regions.

Lung volume is normal or increased.

Other characteristics:
- Pseudoplaques (↑): aggregates of nodules along the costal margins, which mimic pleural plaques (early).
- Mediastinal adenopathies (→)(15-40%): their “egg-shell” calcification is characteristic (late).

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

Remy-Jardin M. Subpleural micronodules in diffuse infiltrative lung diseases: evaluation with thin-section CT scans. Radiology 1990, 177: 133
Exposure to high concentrations of silica may cause progressive disease (accelerated silicosis) or even an acute form (silicoproteinosis). In accelerated silicosis, a reticular appearance is associated with nodular opacities. In acute silicosis the nodules are absent, and the HRCT appearance mimics the alveolar proteinosis.

Radiological differential diagnoses:

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

COURSE and COMPLICATIONS

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

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

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

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

LABORATORY FINDINGS

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

CLINICAL DIAGNOSIS

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

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

INVASIVE DIAGNOSIS

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

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

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

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

The term miliary tuberculosis encompasses all forms of progressive tuberculosis (TB) with hematogenous seeding. Although the lung is the preferred target organ (over 50% of patients), the disease may affect any other organ (e.g. spleen, liver, bone marrow, etc.)

**DEMOGRAPHICS**

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

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

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

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

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

**CLINICAL FEATURES**

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

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

Miliary TB produces a restrictive ventilatory defect with a marked deficiency in $D_\text{L}CO$.

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

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

The histopathologic findings are the following:

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

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

Random, sometimes peribronchiolar

Histopathologic differential diagnoses:

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

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

Cheung OY. Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 2003, 7: 127
Ikonomopoulos JA. Multiplex polymerase chain reaction for the detection of mycobacterial DNA in cases of tuberculosis and sarcoidosis. Mod Pathol 1999, 12: 854
HIGH-RESOLUTION COMPUTED TOMOGRAPHY - HRCT

Basic radiological signs:

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

Bilateral, symmetrical, diffuse

Uniformly distributed

Lung volume is normal

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

Other characteristics:

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

Hong SH. High resolution CT findings of miliary tuberculosis. J Comput Assist Tomogr 1998, 22: 220
Oh YW. High-resolution CT appearance of miliary tuberculosis. J Comput Assist Tomogr 1994, 18: 862
Ground-glass is recognizable in varying percentages. When extensive, it may be the expression of massive lung involvement and be a prelude to or accompany an acute respiratory failure.

Radiological differential diagnoses:

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

**COURSE and COMPLICATIONS**

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

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

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

**LABORATORY FINDINGS**

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

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

**CLINICAL DIAGNOSIS**

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

**INVASIVE DIAGNOSIS**

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

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

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

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

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

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

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

**ASPERGILLOSIS**

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

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

The acute invasive form is characterized by nodular infarct of the lung associated with angioinvasion by aspergillus hyphae. The necrotic lesions may cavitate or contain a fungus ball. The chronic necrotizing form is characterized by a combination of granulomatous inflammation, necrosis and fibrosis of varying degrees (☞). Often the fungal hyphae and spores (▷) cannot be detected with routine staining, and special stains and techniques are required (e.g. PAS, methenamine silver, immunofluorescence, tissue cultures, etc.)
Sarosi GA. Fungal diseases of the lung. 3rd ed. Lippincott William and Wilkins, 2000

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

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

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

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

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

AMYLOIDOSIS

Patients with nodular amyloidosis are usually asymptomatic and the lesions are often discovered as incidental findings on chest radiographs. Only one case with massive hemoptysis has been described. When multiple nodules are present, symptoms such as cough and hemoptysis occur. Physical lung examination and pulmonary function tests are generally normal and the prognosis is favorable.

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

Gillmore JD. Amyloidosis and the respiratory tract. Thorax 1999, 54: 444
In nodular amyloidosis the amyloid deposits consist of circumscribed masses of amorphous, eosinophilic and homogenous extracellular material, which replace the normal pulmonary architecture (○). Foci of osseous metaplasia or calcifications can be seen within these deposits, while lymphoplasmacellular infiltrates (△) and a multinucleated giant-cell reaction are common at the periphery. Amyloid is positive to Congo red staining, exhibiting a green birefringence in polarized light, and is fluorescent after thioflavin staining.

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

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

Urban BA. CT evaluation of amyloidosis: spectrum of disease. Radiographics 1993, 13: 1295
BRONCHIOLOALVEOLAR CARCINOMA (BAC)

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

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

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

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

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

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

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

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

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

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

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

The opacities, multiple with well-defined margins, usually have a spiculated appearance (†) and often are centered on the bronchi with an air-bronchogram sign. The diameter of the lesions may reach 5 cm. Cavitation is possible while calcifications are absent. Reticular opacities, parenchymal consolidations (†), mediastinal adenopathies and pleural effusion (common) may also be present. There is a tendency towards (†) central distribution but (†) without cranio-caudal predilection.

Eisner MD. The pulmonary manifestations of AIDS-related non-Hodgkin’s lymphoma. Chest 1996, 110: 729

Lee KS. Imaging of pulmonary lymphomas. AJR Am J Roentgenol 1997, 168: 339
KAPOSI'S SARCOMA

About one third of patients with Kaposi's sarcoma have clinically evident lung involvement. Kaposi's sarcoma may involve the lung parenchyma in either a nodular (25%) or interstitial pattern. The airways, the pleura and the intrathoracic lymph nodes may also be involved. Symptoms generally include dyspnea and cough, while hemoptysis and fever are less common. Clinical diagnosis is confirmed with fiberoptic bronchoscopy in cases where typical endobronchial lesions are present (bronchial and transbronchial lung biopsies have low diagnostic accuracy and cause significant hemorrhage in 30% of cases). In the remaining cases surgical lung biopsy is required. Diagnosis may also be suspected on the basis of the detection (PCR analysis) of the offending pathogen in BAL fluid (human herpes virus-8 – HHV8).

Miller RF. Bronchopulmonary Kaposi's sarcoma in patients with AIDS. Thorax 1992, 47: 721
Tamm M. Diagnosis of pulmonary Kaposi's sarcoma by detection of human herpes virus 8 in bronchoalveolar lavage. Am J Respir Crit Care Med 1998, 157: 458

The tumor is composed of hemorrhagic nodules distributed along the lymphatics which originates around vessels and then extends to the surrounding structures. Histologically it consists of a proliferation of spindle cells separated by interanastomosing vascular channels with extravased erythrocytes and hemosiderin deposits in the interstitium. The cytoplasm of the neoplastic cells contains characteristic PAS-positive eosinophilic globules. Also associated are varying degrees of chronic inflammatory infiltrate and vascular ectasia of the surrounding parenchyma.

Purdy LJ. Pulmonary Kaposi's sarcoma. Premortem histologic diagnosis. Am J Surg Pathol 1986, 10: 301

The nodules have hazy and irregular margins, often with a flame-like appearance and a diameter which can reach several centimeters. The non-cavitating and non-calcifying lesions tend to be broncho-centric in parahilar regions, especially at the lung bases. Other signs: peribronchial interstitial thickening, pleural effusion (35%), adenopathies (50%), consolidations and areas of ground-glass (30%).

Hartman TE. Diagnosis of thoracic complications in AIDS: accuracy of CT. AJR Am J Roentgenol 1994, 162: 547
METASTASES

Between 84% and 98% of multiple pulmonary coin lesions are metastatic. The primary neoplasm often originates in the testicles, ovaries, kidneys or breasts, or is a melanoma or sarcoma. Patients are generally asymptomatic, and symptoms of cough, hemoptysis (airways) and chest pain (pleura) are only occasionally observed in cases of tumor extension to the adjacent structures. In cases of numerous large lesions dyspnea may be present. Rarely and after the removal of the primary neoplasm (e.g. renal carcinoma or choriocarcinoma) cases of spontaneous remission have been reported.

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

While miliary nodules are common in metastases from melanomas, renal carcinomas and thyroid medullary carcinoma, “cannonball” metastases are typical of sarcomas (∇) and colo-rectal carcinomas (◻), as well as the above-mentioned renal carcinomas and melanomas. Histologically, the growth pattern of metastases can be classified in five groups: 1. lepidic growth (◻) (typical of bronchioloalveolar carcinoma) may be shared by various adenocarcinomas, especially colo-rectal adenocarcinoma; it is frequently necrotic and displays no anthracotic pigment in the areas of fibrosis; 2. interstitial growth with no involvement of the overlying alveolar epithelium is typical of low-grade malignant sarcomas (∇) (e.g. leiomyosarcomas, endometrial stromal sarcomas, etc.); 3. cavitation is frequent in metastases from carcinomas of the head and neck, cervix, bladder, colon and breast; 4. thin-walled cysts may be observed in sarcomas; 5. cavitation and cysts are seen in teratomas, lymphomas and melanomas.

Askin FB. Something old? Something new? Second primary or pulmonary metastasis in the patient with known extrathoracic carcinoma. Am J Clin Pathol 1993, 100: 4
The number of lesions is variable and their diameter may also vary within the same patient up to several centimeters. The opacities have regular and well-defined margins, but are sometimes hazy with a halo sign(๑) in choriocarcinomas and angiosarcomas. Cavitation (⇒) is possible in metastases from squamous-cell carcinomas of the head and neck, cervix or bladder, gastrointestinal adenocarcinomas and sarcomas. Calcifications are possible within the lesions from osteosarcoma, chondrosarcoma, thyroid papillary carcinoma, giant-cell bone tumors, synovial sarcomas, mucinous carcinomas of the gastrointestinal tract, breast and in treated metastases. The distribution is (○) peripheral (●) with a predilection for the lung bases. Mediastinal adenopathy (←), lymphangitic carcinomatosis (☐ LC) and primary pulmonary neoplasms (⊙) may also be present.

Diederich S. Helical CT of pulmonary nodules in patients with extrathoracic malignancy: CT-surgical correlation. AJR Am J Roentgenol 1999, 172: 353

Seo JB. Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 2001, 21: 403
ORGANIZING PNEUMONIA (OP)

Organizing pneumonia is a clinical condition which manifests in a cryptogenic form (OP) or secondary to various diseases, both infectious and non-infectious. The disease generally has a pneumonia-like appearance, but may also present large rounded pulmonary opacities. Seventy-five percent of patients have symptoms for at least 3 months prior to diagnosis. The clinical manifestations of disease onset are often similar to those of influenza.

Lohr RH. Organizing pneumonia. Features and prognosis of cryptogenic, secondary, and focal variants. Arch Intern Med 1997, 157: 1323

Early descriptions of the disease used the acronym BOOP to indicate the two components of the disease, i.e. bronchiolitis obliterans (BO) and organizing pneumonia (OP). Bronchioles, alveolar ducts and alveoli are filled with plugs of loose connective tissue containing fibroblasts and inflammatory cells in a mucopolysaccharide-rich matrix. The lesion is temporally uniform.

The radiological appearance is characterized by multiple opacities (from 2 to 8) with mixed well- and ill-defined irregular margins which may be spiculated and in contact with the pleura (38%). A reversed halo sign (atoll sign) may be also present. The diameter of the lesions vary from 1 to 5 cm. Bronchi can often be observed in the context of the lesions. Calcifications are absent. Lesions tend to be distributed peripherally without craniocaudal predilection. Consolidations, interlobular septal thickening, parenchymal bands and pleural thickening may be present.

Akira M. Bronchiolitis obliterans organizing pneumonia manifesting as multiple large nodules or masses. AJR Am J Roentgenol 1998, 170: 291

Zompatori M. Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign). A case report. Radiol Med 1999, 97: 308
RHEUMATOID ARTHRITIS (RA)

Rheumatoid nodules are the only pulmonary hallmark of this disease. Their precise prevalence is unknown, ranging from 0.5% at radiology to 32% at biopsy examination. They generally produce no symptoms, although they may be complicated by infection and/or cavitation with pneumothorax, pyopneumothorax, bronchopleural fistula and hemoptysis. Prognosis is usually favorable with spontaneous remission.

Yousem SA. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985, 131: 770

The nodules (—) are necrotic, surrounded by palisading histiocytes and possibly by a fibrous capsule (►), in subpleural and paraseptal regions. They may become infected and cavitate, or be the site of hemorrhage. The characteristic lesions of the disease can be seen in the surrounding parenchyma.

Yousem SA. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985, 131: 770

Isolated opacities up to several centimeters in diameter; the size may increase during the acute phases of the disease proportional to the antibody titre. The nodules are well-defined with lobulated margins (—). Cavitation (►) is common (50%), whereas calcifications are absent. Distribution is (►) peripheral, adjacent to the pleura and (●) without predilection along the craniocaudal axis. Associated tracheobronchial nodules may be observed.

Sarkar TK. Pulmonary necrobiotic nodule. J Rheumatol 1984, 11: 557

Walters MN. Pleuropulmonary necrobiotic rheumatoid nodules. A review and clinicopathological study of six patients. Med J Aust 1986, 144: 648
SARCOIDOSIS

Sarcoidosis presenting as solitary or multiple large nodules occurs in less than 5% of cases. In about 50% of cases the finding occurs incidentally on chest radiographs. Respiratory symptoms include dry cough, dyspnea and chest pain. If the opacities are cavitating, hemoptysis may be observed. Systemic symptoms such as weakness, fatigue, mild fever, polyarthralgia and weight loss may appear in 30% of cases. Less common symptoms include the involvement of extrapulmonary organs: skin (20%), eye (20%), CNS (5%) etc. Physical examination of the chest is generally normal. Diagnosis may be performed with transbronchial or surgical lung biopsy.

Costabel U. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999, 14: 735

Sarcoidosis rarely presents in the lungs as large nodules (\(\rightarrow\)) distributed predominantly along the airways and in subpleural regions. These larger lesions are formed by the coalescence of single, non-necrotizing, epithelioid granulomas (\(\rightarrow\)), with multinucleated giant cells often containing cytoplasmic inclusions and surrounded by fibrosis. The parenchyma between the lesions is normal or exhibits well-formed non-necrotizing epithelioid granulomas with a lymphatic distribution.

Abramowicz MJ. Tumour-like presentation of pulmonary sarcoidosis. Eur Respir J 1992, 5: 1286

The opacities of nodular sarcoidosis may be single or multiple, and the diameter may rise up to several centimeters. The lesions may have well-defined margins and irregular borders surrounded by multiple tiny satellite nodules (\(\rightarrow\)) (galaxy sign) or hazy margins and irregular borders and contain narrowed bronchi (\(\rightarrow\)), whereas calcifications are absent. A necrotizing variant may be observed. The distribution of the lesions (\(\rightarrow\)) tends to be bronchocentric (\(\rightarrow\)) with a predilection for the upper lung zones. Large opacities are usually associated with perilymphatic micronodules, and hilar and mediastinal adenopathies.

Muller NL. Ground-glass attenuation, nodules, alveolitis, and sarcoid granulomas. Radiology 1993, 189: 31

Nakatsu M. Large coalescent parenchymal nodules in pulmonary sarcoidosis: “sarcoid galaxy” sign. AJR Am J Roentgenol 2002, 178: 1389
SEPTIC EMBOLI

The main origin of septic emboli is septic deep venous thrombosis of the lower limbs or pelvis, with central venous lines, tricuspid endocarditis and intravenous drug use being less common. The most frequent complications include pulmonary abscess or septic pulmonary infarction, empyema (30%) and bronchopleural fistula (rare). The symptoms are the same as those of pulmonary embolism (e.g. dyspnea, chest pain and hemoptysis) accompanied by septicemia. Pulmonary hypertension with signs of right-sided heart failure may develop rapidly.

Libby LS. Pulmonary cavitation following pulmonary infarction. Medicine 1985, 64: 342

The pulmonary abscess consists of a cavitating lesion that at some time during its development contains purulent material. In the acute phase, pus and necrotic material are abundant at the center of the thin-walled cavity (arrow); in the chronic phase, the granulocytic infiltrate is substituted by lymphocytes, plasma cells and macrophages (►) and the cavity walls are thickened due to the presence of fibrosis (□) and granulation tissue.

Kumar V. Robbins. Basic Pathology. Elsevier Science, 2002

Rounded opacities (►) typically multiple with well-defined or hazy margins, size variable up to 3 cm and usually a peripheral vascular distribution (►). Cavitation (□) is common while calcifications are absent. The opacities tend to be distributed (►) peripherally with (◑) a predilection for the basal regions. Peripheral wedge-shaped pleural-based opacities due to parenchymal infarction, thereafter typically hypodense after contrast medium, may be found in association (50-70%)

Huang RM. Septic pulmonary emboli: CT-radiographic correlation. AJR Am J Roentgenol 1989, 153: 41
Kuhlman JE. Pulmonary septic emboli: diagnosis with CT. Radiology 1990, 174: 211
**Clinical features**

**Tuberculomas**

Tuberculoma may develop during a primary infection or when a secondary focus of tubercular reactivation becomes encapsulated. These lesions are often solitary and may be cavitating. Patients are almost always asymptomatic, thus tuberculoma is generally an incidental finding on chest radiographs. Diagnosis is difficult because bronchial washing, BAL and tissue culture assays are often negative. Surgical lung biopsy or transthoracic needle biopsy are therefore required.

Congregado Loscertales M. Usefulness of video-assisted thoracoscopy for the diagnosis of solitary pulmonary nodules. Arch Bronconeumol 2002, 38: 415

Histologically, the lesions share the features of tubercular infection. The solitary nodule has a necrotic (caseous) center, multinucleated giant cells with nuclei distributed peripherally in a horseshoe pattern (Langhans’ type cells) and surrounded by palisading histiocytes admixed with epithelioid cells and varying degrees of lymphocellular infiltrate. The capsule is usually thick and cavitiation is frequent.

American Thoracic Society and the Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000, 161: 1376

Opacities are most frequently solitary, but may be also multiple and bilateral. In the advanced phase, the tuberculomas are dense lesions with well-defined margins and characteristic central calcifications. In the early phase, the lesions display low density and a hyperdense rim after contrast medium, with possible cavitiation. In this phase the margins are well-defined although a halo sign may be present. The distribution of the lesions is relatively peripheral, possibly centered by a bronchus and often surrounded by satellite lesions (hazy micronodules, thick-walled bronchi, tree-in-bud opacities).

Lee JY. Pulmonary tuberculosis: CT and pathologic correlation. J Comput Assist Tomogr 2000, 24: 691

Gaeta M. Computed tomography halo sign in pulmonary nodules: frequency and diagnostic value. J Thorac Imaging 1999, 14: 109
WEGENER’S GRANULOMATOSIS

Symptoms of lower respiratory tract involvement in Wegener’s granulomatosis include cough (60-77%), hemoptysis (30-40%), dyspnea and chest pain. These may be associated with systemic symptoms, such as fever, anorexia, weight loss and malaise, as well as signs and symptoms of the involvement of other organs and/or systems (kidney in 75-85%, polyneuritis in 20-35%, ocular symptoms in 10-15%, skin alterations in 10-15%, alterations of the musculoskeletal system in 30%). Nodule cavitation can cause cough and hemoptysis. In cases of large pulmonary lesions the chest examination may reveal signs of consolidation. Positive staining for antineutrophil cytoplasmic antibodies (ANCA) and especially C-ANCA against the target antigen proteinase 3 is diagnostic in the appropriate clinical-radiological setting.

Hoffman GS. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992, 116: 488

Histologically, nodules represent areas of pulmonary consolidation with necrosis on an inflammatory background. The characteristic features are necrosis (both geographic and often basophilic due to the presence of numerous neutrophils, and in the form of microabscesses), vasculitis (which may involve arteries, veins or capillaries and is usually focal and eccentric to the vessel wall) and an inflammatory infiltrate (consisting of a mixture of neutrophils, lymphocytes, plasma cells, macrophages, eosinophils and giant cells). Intraalveolar hemorrhage, OP or tissue eosinophilia may be found in the surrounding lung and may be the dominant feature in some variants of the disease.

Katzenstein AL. Solitary lung lesions in Wegener’s granulomatosis. Pathologic findings and clinical significance in 25 cases. Am J Surg Pathol 1995, 19: 545

Scattered uni- or bilateral opacities, multiple in 85% of cases. The margins may be well-defined; the borders are irregular. The diameter may reach 10 cm. Cavitation is common, with thick and irregular walls. Calcifications are absent. The lesions may be distributed along the bronchovascular bundles peripherally but with no craniocaudal predilection. Ground-glass opacities and parenchymal consolidations are often present.

Aberle DR. Thoracic manifestations of Wegener granulomatosis: diagnosis and course. Radiology 1990, 174: 703