Presentation and Diagnosis of Interstitial Lung Diseases

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Diffuse interstitial lung disease is a heterogeneous group of lung pathologies with similar clinical presentations. Radiologists and pathologists attempted to identify precise diagnostic criteria. Often, the pattern and distribution of the disease allow to narrow down the possible diagnoses, but the correlation with the clinical presentation is essential.

The main radiological patterns are:

- Nodular
- Septal
- Cystic
- Alveolar (ground-glass)
- Reticular
- Honeycombing

To recognize the radiological pattern of the disease, it is necessary to search and study on HRCT images the secondary pulmonary lobule (SPL) that is the smallest structural unit in the lung. It is a roughly polyhedral structure, 1–2 cm in size, lined by connective tissue septa; the lobules in the peripheral regions of the lung are larger and more regular in shape, becoming smaller and more irregular in the central portions. Each SPL is constituted by 3–15 acini and 30–50 alveoli and is fed by a small lobular bronchiole and a pulmonary artery branch. These structures run in parallel in the central portion of the lobule and are therefore described as centrilobular. In the peripheral region, the venous and lymphatic vessels are contained in the interlobular interstitium.

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The SPL is composed by three main elements:

– *The interlobular septa:* normally about 0.1 mm thick and therefore not visible on HRCT except in the peripheral region where they are slightly thicker and can barely be identified. The venous branches running within them have a caliber of about 0.5 mm and can, therefore, be visualized. Diseases affecting the venous or lymphatic systems of the lung will affect this region, e.g., "perilobular" patterns.
– *The centrilobular structures:* consist of the intralobular arterial and bronchial branches. In normal conditions, it is possible to identify the lobular artery (1 mm), the terminal artery (0.7 mm), and the acinar artery (0.5 mm). The bronchial branches contain air and cannot be visualized as their wall thickness is inferior to the lower limit of resolution on HRCT (0.15 mm). When the bronchiolar lumens become plugged with dense materials such as fluids, blood, or pus, the tracings of the intralobular branches become visible on HRCT as branched structures terminating in small nodules (tree-in-bud appearance).
– *The lobular parenchyma and acini:* not visible on HRCT under normal conditions. They include the functional units of the lung, i.e., the alveoli and the capillary bed with their supportive structures of connective tissue (intralobular interstitium). In some pathologies, e.g., inflammatory diseases, the involvement of the acinus appears as a small intralobular nodular opacity, about 0.6–1 mm in size.

Nodular Pattern

The nodular pattern is characterized by nodules less than 1 cm in size with variable characteristics and distribution, based on which it can subdivided into:

- Nodules in a random pattern (Fig. 9.1)
- Nodules in a miliary pattern (Figs. 9.1 and 9.2)
- Nodules in a centrilobular (or bronchovascular) pattern (Fig. 9.3)
- Nodules in a lymphatic or perilymphatic pattern (Fig. 9.4)

Nodules in a Random Pattern

They are usually secondary to pathologies with hematogenous dissemination (Table 9.1). Thus, they are:

- Diffuse (and never focal, as can occur in the bronchovascular pattern)
- More numerous in the periphery (within 2–3 cm from the pleura) and at the bases (where there is more blood flow)

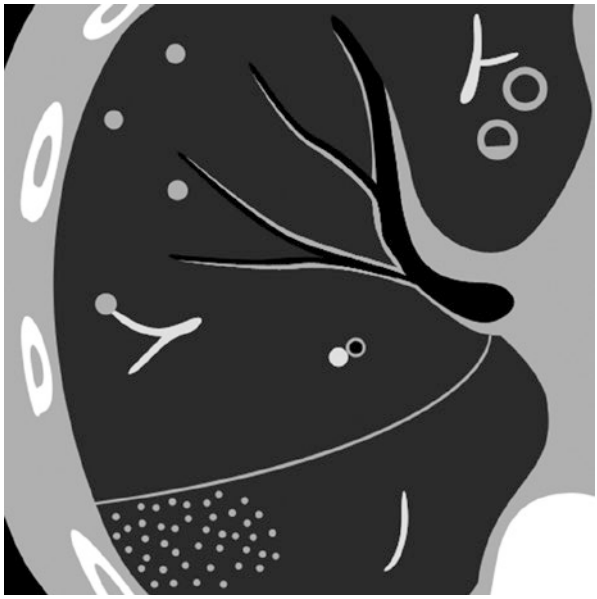

Fig. 9.1 Nodules in a random pattern

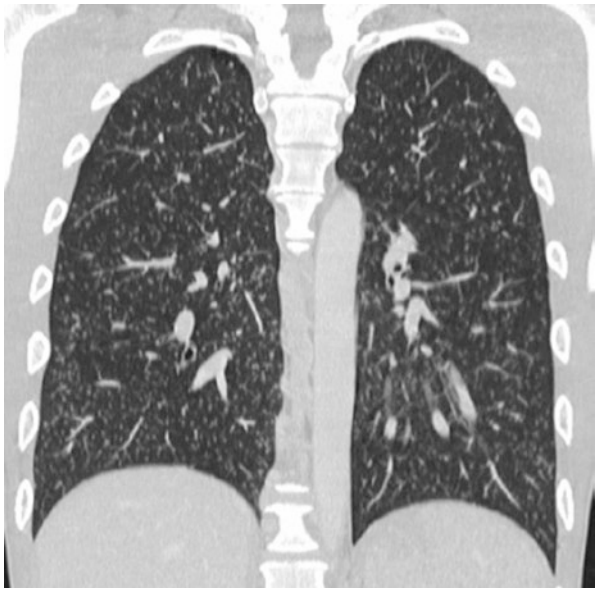

Fig. 9.2 Patient with miliary dissemination of tuberculosis

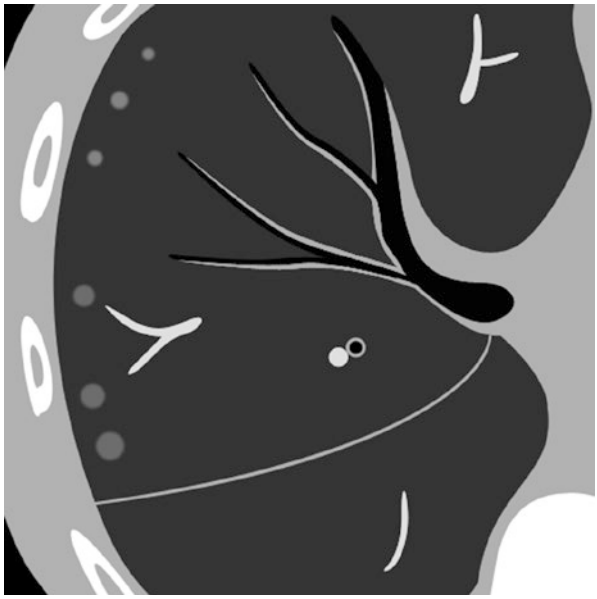

Fig. 9.3 Nodules in a centrilobular pattern

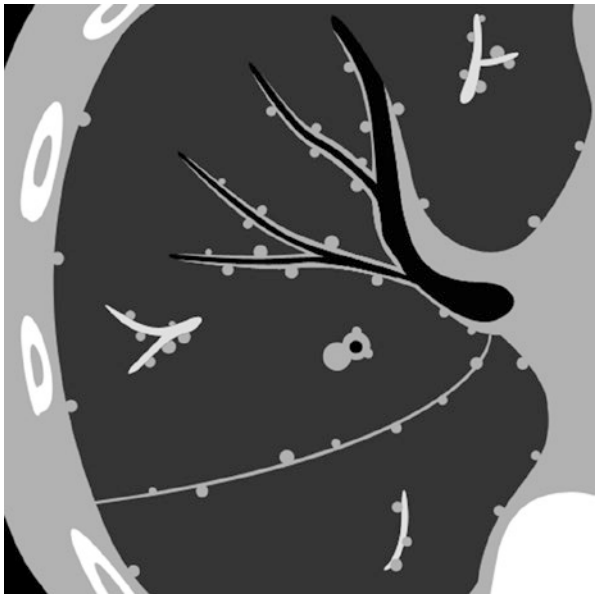

Fig. 9.4 Nodules in a lymphatic or perilymphatic pattern

Table 9.1 Differential diagnosis of nodules in a random pattern

Common	
Hematogenous metastases	Nodules of variable shape and size. The most common primary cancers are gastrointestinal, pulmonary, mammary or melanoma and sarcoma Calcified hematogenous metastases are most commonly secondary to chondrosarcoma and osteosarcoma or, especially when treated with chemotherapy, colon and ovarian cancer A halo of ground-glass attenuation can be appreciated if perilesional hemorrhage occurs Miliary metastases present as numerous nodules of the same size and are typically secondary to medullary thyroid, renal, head and neck, ovarian and testicular cancer and melanoma
Miliary infections	Mycobacterial, histoplasmosis, or viral infections
Septic emboli	Fever is associated. Cavitation usually occurs within 24 h (Fig. 9.1, upper part). It mostly occurs in patients with central lines, right-sided endocarditis, or in intravenous drug abusers
Intravascular talcosis	High-density pinpoint nodules due to the intravenous use of drugs mixed with talc
Less common	
Vasculitis	Nodules are due to hemosiderin-laden macrophages that accumulate after localized hemorrhages. On CT, they are seen as ground-glass opacities, in general with a centrilobular distribution

- Possibly associated to a feeding vessel, that is, an arterial vessel entering the nodule (Fig. 9.1, in the center)

If they are few in number, it may be difficult to distinguish this pattern from a centrilobular or perilymphatic one.

Nodules in a Miliary Pattern

They are secondary to pathologies with hematogenous dissemination (Tables 9.2 and 9.3) and have the following characteristics:

- Small nodules (<5 mm), too many to be counted (Fig. 9.1, lower part; Fig. 9.2);
- Random distribution within the SPL.

CXR may be negative due to their small size.

Dense or calcific nodules in a miliary pattern can be secondary to healed histoplasmosis, healed chickenpox, thyroid metastases after radioactive Iodine-131 treatment, talcosis, and pulmonary alveolar microlithiasis.

Table 9.2 Differential diagnosis of nodules in a miliary pattern

Common	
Primary or post-primary tuberculosis	Occurring mainly in immunocompromised patients. The sputum smear is usually negative, often needing a transbronchial biopsy for diagnosis
Atypical mycobacterial diseases	Nodules are often centrilobular but can occasionally be in a miliary pattern
Viral infections	Usually influenza and cytomegalovirus
Chickenpox and histoplasmosis	After healing, miliary calcified nodules may occur
Fungal infections	Can be observed when the infection disseminates in immunocompromised patients
Blastomycosis	Similar to tuberculosis
Metastases	Secondary to medullary thyroid, renal, head and neck, ovarian and testicular cancer, and melanoma
Less common	
Talcosis	Secondary to intravenous drug abuse
Pulmonary alveolar microlithiasis	Calcific nodules with subpleural sparing of the lung (black pleura sign)
Sarcoidosis and silicosis	Usually perilymphatic nodules but they can appear as miliary
Langerhans cell histiocytosis	Usually centrilobular nodules but they can appear as miliary
Hypersensitivity pneumonitis	
Bronchioloalveolar carcinoma	Ground-glass nodules, usually centrilobular, but in case of hematogenous dissemination they can be miliary and random

Table 9.3 Differential diagnosis between mycobacterial miliary nodules and metastases

	Mycobacterial nodules	Metastatic nodules
Appearance	<5 mm	Bigger and well-defined
Background ground-glass	Common	Rare
Location	Superior lobes	Inferior lobes

Nodules in a Centrilobular Pattern

These nodules are located in the bronchovascular core of the SPL and are a typical manifestation of bronchiolocentric or bronchiolar interstitial lung diseases (Table 9.4). They are:

- Located at least 5–10 mm from the pleural surface or the interlobar fissures or the SPL margins
- Generally of ground-glass density
- Associated to other signs of bronchiolar obstruction:
  - Tree-in-bud opacities: the bronchioles are dilated and plugged by dense contents (mucus, pus, or fluid) and peribronchial inflammation is present
  - Mosaic pattern: due to hyperinflation of some SPLs
- Common in bronchiectasis of any cause

Table 9.4 Differential diagnosis of nodules in a centrilobular pattern

Common	
Infectious bronchiolitis	Secondary to bacterial, viral, fungal, or mycobacterial infections; typical of tuberculosis with endobronchial spread
Respiratory bronchiolitis	Correlated to smoking (at least 2 years of smoking history) and characterized by pigmented macrophages within the respiratory bronchioles. There are centrilobular nodules with prevalent involvement of the superior lobes and progression to emphysema
Subacute hypersensitivity pneumonitis	Formation of granulomas in response to various types of antigens (farmer's lung or bird fancier's lung). There are centrilobular nodules that progress to thin-walled cysts and a prevalent involvement of the upper lobes with sparing of the inferior zones and costophrenic angles (typical aspect). A mosaic pattern can co-occur
Langerhans cell histiocytosis	Correlated to smoking, it is most likely due to an allergic response to some smoke components. Centrilobular nodules evolve into thin-walled cysts that can aggregate in bizarre shapes. There is prevalent involvement of the upper lobes and sparing of the inferior zones and costophrenic angles
Follicular bronchiolitis	Associated to hyperplasia of the Bronchus-Associated Lymphoid Tissue (BALT) in pathologies such as rheumatoid arthritis, Sjögren's, AIDS, infections, and hypersensitivity reactions. There are centrilobular nodules, subpleural nodules, thin-walled cysts, and ground-glass areas. It can be associated to interlobular septal thickening
Less common	
Aspiration	Usually secondary to chronic leguminous material aspiration. Characterized by centrilobular nodules in a gravity-dependent pattern
Bronchioloalveolar carcinoma	Early on, it can appear as centrilobular nodules
Vasculitis	Centrilobular nodules with ground-glass opacity due to the presence of hemosiderin-laden macrophages after localized hemorrhages
Pulmonary hypertension	Centrilobular nodules can be present in all forms of pulmonary hypertension. They are due to plexogenic arteriopathy in primary pulmonary arterial hypertension, to capillary dilatations in pulmonary veno-occlusive disease, and to capillary proliferation in pulmonary capillary hemangiomatosis
Kidney failure	Calcific nodules (calcified-cauliflower sign) can be seen in the most advanced stages of kidney failure
Laryngeal papillomatosis	Nodules can be seen in 1% of cases and are due to endobronchial seeding in the lung. The centrilobular nodules tend to cavitate forming cysts

Nodules in a Lymphatic or Perilymphatic Pattern

These are nodules located around the lymphatic vessels and the perilymphatic channels (Figs. 9.4 and 9.5; Table 9.5). Their characteristics are as follows:

- Well-defined nodules (2–5 mm)
- Axial distribution: in the peribronchovascular interstitium, from the hilum to the periphery

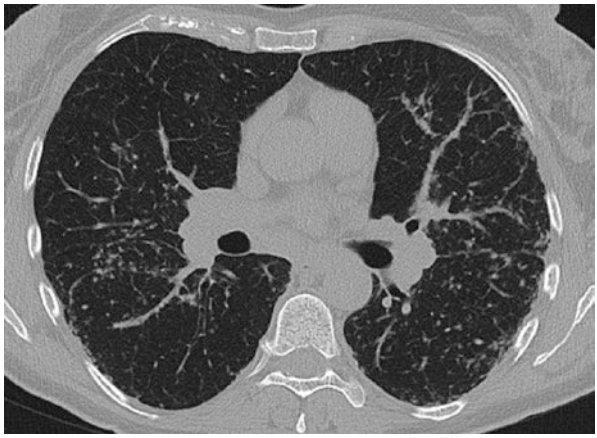

Fig. 9.5 Nodules in a perilymphatic pattern in a patient with sarcoidosis

Table 9.5 Differential diagnosis of nodules in a perilymphatic pattern

Common	
Sarcoidosis	Perilymphatic nodules in an axial distribution from the hilum, with hilar and mediastinal adenopathy. They can aggregate forming masses (alveolar sarcoids) which can contain calcifications, i.e., the typical galaxy sign, characterized by a central mass surrounded by small nodules. It progresses to fibrosis with a reticular pattern
Berylliosis	Same presentation as sarcoidosis but with a history of occupational exposure to beryllium
Round-shaped particles inhalation	Perilymphatic nodules in an axial distribution from the hilum, with hilar lymphadenopathy. They can aggregate forming masses in the dorsal regions. It progresses to fibrosis. It is more prevalent in the superior lobes, being more ventilated. The most typical forms are silicosis, coal worker's pneumoconiosis (typical hilar eggshell calcifications in 5% of cases), talcosis, and siderosis
Lymphangitic carcinomatosis	Perilymphatic nodules in a predominantly axial distribution (75%). Usually associated to adenocarcinoma. It differs from pneumoconiosis in that whole lobes or a whole lung are usually spared, the lung architecture is preserved (while it is distorted in sarcoidosis and silicosis), and pleural effusions can be present (never present in pneumoconiosis)
Less common	
Lymphocytic Interstitial Pneumonia (LIP)	Idiopathic or secondary to HIV infection, EBV infection, dysproteinemia, or Sjögren's syndrome. It appears as nodules in a perilymphatic pattern, thin-walled cysts (80% of cases), and ground-glass opacities (100% of cases)
Lymphoma	Non-Hodgkin (25% of cases) or Hodgkin (40% of cases) with lung involvement. Pulmonary nodules >1 cm in size, often with bronchogram
Miliary infections	CMV, tuberculous, or fungal infections. It appears as pulmonary micronodules, usually in a random or miliary pattern, but they can mimic a perilymphatic pattern
Follicular bronchiolitis	Nodules are more often in a centrilobular pattern, associated to subpleural nodules, thin-walled cysts, ground-glass areas, and interlobular septal thickening. It can mimic a perilymphatic pattern
Kaposi sarcoma	Occurs in AIDS-affected patients. Ill-defined nodules in a predominantly perihilar distribution
Amyloidosis	May present as perilymphatic nodules in a peripheral (subpleural) distribution, with nodular thickening of the peribronchovascular structures and septal thickening

HIV human immunodeficiency virus, *EBV* Epstein–Barr virus, *CMV* Cytomegalovirus

- Peripheral distribution: in the subpleural interstitium, in the interstitium of fissures and SPL contour
- Associated to involvement of mediastinal lymph nodes

Some diseases can start as a bronchovascular pattern (through inhalation) and then progress to a lymphatic pattern (through dissemination).

Differential Diagnosis of Nodular Patterns

The distinction of the nodular patterns depends mostly on the location, pattern, and appearance of the nodules (Table 9.6). The presence of accessory signs of airways obstruction, such as a mosaic pattern or tree-in-bud opacities, can help to distinguish the centrilobular pattern from the others, in which they rarely occur.

- *Tree-in-bud opacities (TIB):* They appear as quite defined centrilobular nodules (2–4 mm) from which linear opacities spread out in three or four V-shaped or Y-shaped branches (Fig. 9.6). They correlate to bronchiolar pathologies and are

Table 9.6 Differences between nodular patterns

	Random	Centrilobular	Perilymphatic
Etiology	Hematogenous	Aerogenous	Lymphogenous
Location	Inferior lobes (more blood flow)	Superior lobes (more ventilation)	Variable
Pattern	Random	In the center of SPL	Axial or peripheral perilymphatic
Appearance of nodules	Variable—a feeding vessel may be present	Ground-glass is suggestive	Denser and more well-defined
Signs of airways obstruction	Absent	Present	Absent

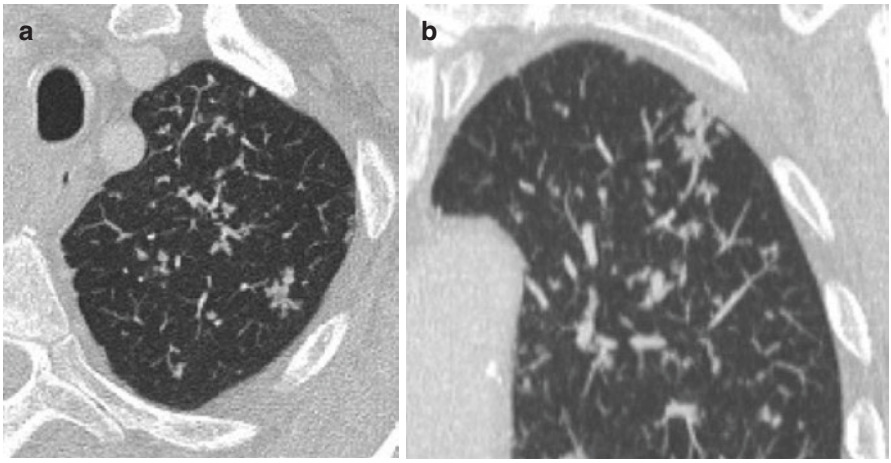

Fig. 9.6 Tree-in-bud opacities in a patient with tuberculosis: (**a**) axial view, (**b**) coronal view

caused by the dilation of the bronchiolar lumen, filled with mucus, pus, or fluid, and to the thickening of their walls. Rarely, they can be secondary to pathologies with hematogenous dissemination such as metastatic tumors or intravenous drug abuse, which can cause arteriolar dilation (Table 9.7).

- *Mosaic pattern:* There are areas of attenuation corresponding to the SPL (Fig. 9.7; Tables 9.8 and 9.9). It can be caused by:

Table 9.7 Differential diagnosis of tree-in-bud opacities (TIB)

Possible diagnoses when airways are normal	
Infectious bronchiolitis	Most frequent cause of TIB pattern. The bronchoalveolar lavage, performed when the cause is not immediately evident, is frequently positive for germs. The most frequent etiologies are: • Mycobacterium tuberculosis or atypical mycobacteria • Mycoplasma pneumoniae • Viral pneumonia, influenza • Other bacterial, viral, fungal etiologies • Diffuse panbronchiolitis: unknown etiology, can cause respiratory failure
Aspiration	TIB pattern in gravity-dependent regions: • Exogenous aspiration: in case of unconscious patients, alcoholism, swallowing disorders (posterior and basal lung segments in supine and standing patients, respectively) • Endogenous aspiration: aspiration of the contents in the M. tuberculosis cavitations (from apical cavitations to basal segments or contralateral lung)
Rare bronchial causes	Other rare causes of TIB with normal airways are: • Follicular bronchiolitis: typical centrilobular nodular pattern • Primary pulmonary lymphoma: similar to follicular bronchiolitis • Bronchioloalveolar carcinoma: typical presentation with ground-glass opacity and bronchogram • Asthma: late finding in severe asthmatic crisis
Vascular causes	Rare causes, characterized by absence of air-trapping and presence of enlarged pulmonary arteries: • Intravascular metastases from angiosarcoma, renal carcinoma, hepatic carcinoma; a characteristic finding is the 90° angle of the branches in the TIB pattern • Intravenous drug abuse: granulomatous reaction to injected substances
Possible diagnoses when bronchiectasis and proximal bronchial wall thickening are present (TIB pattern is seen in 25% of patients with bronchiectasis)	
Infectious bronchiolitis	Usually when secondary to M. avium complex. Prevalently located in the middle lobe and lingula
Cystic fibrosis, primary ciliary dyskinesia	Located in the superior lobes
Allergic bronchopulmonary aspergillosis	Located in the superior lobes
Common variable immunodeficiency	Secondary to recurrent bronchial infections

Fig. 9.7 Mosaic pattern

Table 9.8 Differences between mosaic patterns of different etiologies

	Bronchial	Vascular	Patchy ground-glass
Symptoms	Dyspnea, cough, wheezing	Dyspnea, no cough, or wheezing	Dyspnea, possible cough or wheezing
Pulmonary function tests	Obstructive pattern, DLCO normal	Normal pattern, DLCO significantly reduced	Restrictive pattern, DLCO variable
Caliber of vessels in regions with less attenuation (difficult to appreciate)	Reduced	Reduced	Normal
Air-trapping on CT during expiration	Prominent	None (except in acute pulmonary embolism due to reflex bronchoconstriction)	None

- Obstruction of the small airways: emphysematous areas due to air-trapping
- Vascular occlusive diseases: less vascularized areas. Usually, bronchoconstriction with air-trapping is also present in these regions as the lung attempts to maintain the ventilation-perfusion ratio within normal values
- Patchy lung diseases: ground-glass opacification of only some SPL
- Mixed: interstitial and small-airways disease

It can be observed in 60% of normal subjects during expiration (maximum 1 lobule per CT section, mainly in the superior and ventral lobes).

It can be difficult to recognize if almost all lobules are hyperextended.

Table 9.9 Differential diagnosis of mosaic pattern

Bronchogenic forms	
Bronchiolitis obliterans	A mosaic pattern is observed in 50% of cases. It can be cryptogenic, post-infectious (usually viral), toxic (from inhalation of fumes as in Silo-Filler's disease or from penicillamine), secondary to bone marrow and lung transplant (50% of cases), or to rheumatoid arthritis and chronic inflammatory bowel diseases
Acute/subacute hypersensitivity pneumonitis	Formation of granulomas in response to various types of antigens (farmer's lung or bird fancier's lung, hot tub lung). It is characterized by: • Centrilobular nodules of ground-glass density which evolve into thin-walled cysts (1–14 cysts) • Mosaic pattern, present in 85% of cases • Prevalent involvement of superior lobes and sparing of inferior zones and costophrenic angles (typical aspect)
Infectious bronchiolitis (viral)	Usually in viral forms. The typical aspect is the presence of centrilobular nodules, but a mosaic pattern can be associated
Normal aging-related changes in the lung	A mosaic pattern may be observed in 25% of older patients and is not correlated to smoking habits
Cystic fibrosis	Usually associated to bronchiectasis
False mosaic pattern	Artifact that can be observed when the lung window setting is too narrow
Bronchial asthma	A mosaic pattern is rare. It occurs in 3% of cases, especially in severe asthma
Panlobular emphysema	More commonly there are only regions with less attenuation; a mosaic pattern can be observed in the inferior lobes
Arterial forms	
Pulmonary arterial hypertension	• From vascular causes (75%): chronic thromboembolism, vasculitis, primary pulmonary hypertension, pulmonary veno-occlusive disease (PVOD), pulmonary capillary hemangiomatosis (PCH). In particular, the post-capillary forms (PVOD and PCH) have additional features: – Interlobular septal thickening – Pleural effusion – Mediastinal adenopathy • From cardiac causes (10%) • From pulmonary causes (5%)

Septal Pattern

It represents the interlobular septal thickening of the SPL and is seen as short lines in the periphery of the lung that arrive to the pleura. They can have different morphology: smooth, nodular, irregular.

The most common diagnoses are (Tables 9.10 and 9.11):

- Pulmonary edema: smooth (Figs. 9.8a and 9.9)
- Pulmonary fibrosis: irregular
- Lymphangitic carcinomatosis: smooth or nodular (Fig. 9.8b). It can be associated with the following:
  - Prevalently septal pattern with nodular and irregular thickening
  - Often entire lobes or the contralateral lung are spared
  - Hilar lymphadenopathy

Table 9.10 Differential diagnosis of septal pattern (acute forms)

Common	
Cardiogenic pulmonary edema	Prevalent involvement of gravity-dependent regions and association to effusion. The prevalence of crazy paving pattern is 10–20%
Pneumocystis pneumonia	Prevalent involvement of perihilar regions and superior lobes. It is associated to pneumatoceles (observed only in HIV patients)
Acute Interstitial Pneumonia (AIP), Acute Respiratory Distress Syndrome (ARDS), and Diffuse Alveolar Damage (DAD)	Cause of acute respiratory failure requiring mechanical ventilation (DAD is the histological presentation of AIP and ARDS). The radiological presentation is characterized prevalently by ground-glass opacities, but also crazy paving can be observed (30–66%)
Less common	
Diffuse alveolar hemorrhage	Characterized by different phases: • Hemorrhage in alveolar spaces resulting in consolidations or ground-glass • Removal of blood by macrophages, which migrate in the interstitium and in the septa (2–3 days), with crazy paving pattern (10–20%) • Removal of macrophages by the lymphatic system (7–14 days)
Acute eosinophilic pneumonia	Characterized by migrating ground-glass areas, less frequently by crazy paving (10–20%)

Table 9.11 Differential diagnosis of septal pattern (subacute and chronic forms)

Common	
Pulmonary Alveolar Proteinosis (PAP)	Diffuse crazy paving pattern. The clinical symptoms (cough and dyspnea) are typically less severe than the radiological presentation
Less common	
Non-Specific Interstitial Pneumonia (NSIP)	Idiopathic or secondary to scleroderma, rheumatoid arthritis, drug-induced lung disease It is characterized prevalently by ground-glass, reticular pattern, and traction bronchiectasis. There can also be a septal thickening more evident at the bases and at the periphery of the lung. Subpleural sparing of the lung in the dorsal regions is characteristic
Cryptogenic Organizing Pneumonia (COP)	Pathology characterized by granulomatous polypoid structures growing inside the bronchi. Different patterns can be observed: • Subpleural and peribronchial consolidations or ground-glass opacities (90%) with air bronchogram of variable shape and dimension (ranging from few centimeters to entire lobes), in a migrating pattern • Perilobular pattern: opacities or ground-glass at the periphery of the SPL that can mimic a septal pattern • Multiple or single opacities with the reversed halo sign, i.e., central ground-glass surrounded by consolidation, at least 2 mm • Ground-glass in peripheral zones, more common than crazy paving (10–20%)
Chronic eosinophilic pneumonia	The most frequent presentation is ground-glass opacity, but it can present as crazy paving in peripheral zones (10–20%)
Lymphangitic carcinomatosis	In general, it involves one or more lobes asymmetrically

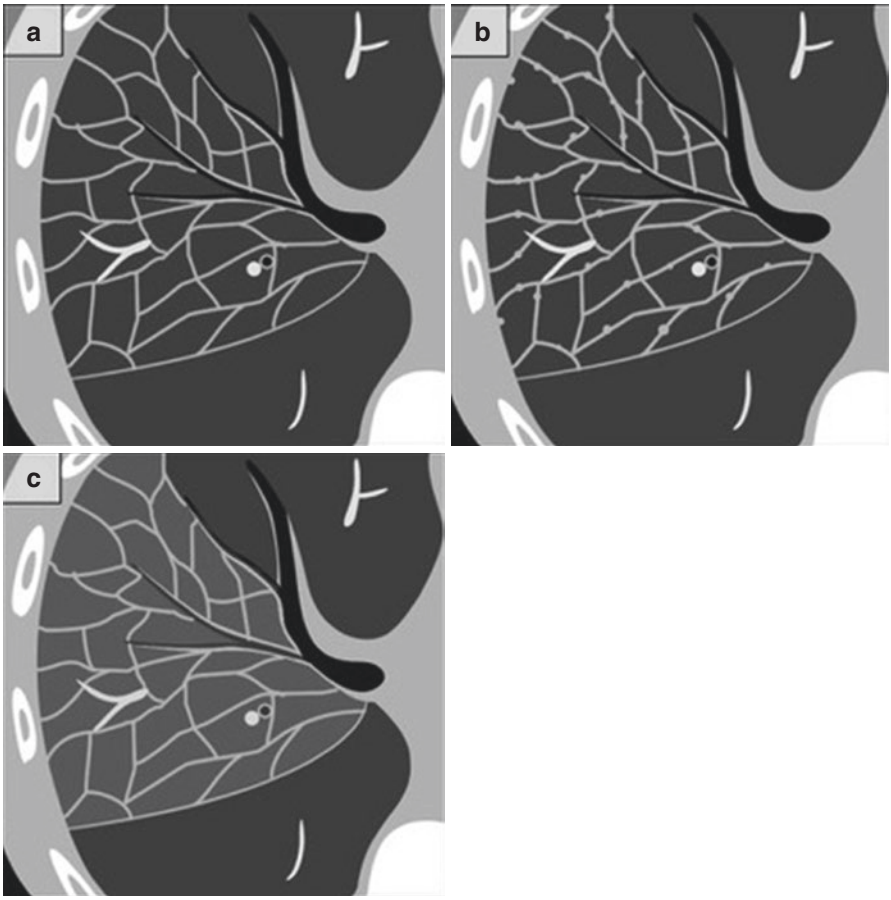

Fig. 9.8 Septal pattern: (**a**) Smooth septal thickening, (**b**) Nodular septal thickening, (**c**) Ground-glass with superimposed septal thickening, also called "crazy paving" pattern

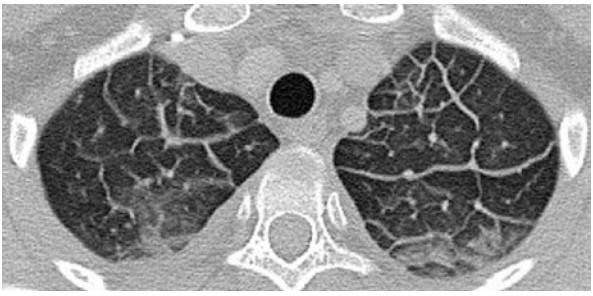

Fig. 9.9 Septal pattern with smooth septal thickening in a patient with non-cardiogenic pulmonary edema secondary to CHT

The septal pattern can be associated with ground-glass opacities, leading to the so-called crazy paving pattern (Fig. 9.8c). This was initially described in pulmonary alveolar proteinosis, where the ground-glass appearance is due to the partial alveolar filling with proteinaceous material, and the septal pattern is

due to the thickening of the SPL's septa or the accumulation of material at the periphery of the air spaces.

Cystic Pattern

It is characterized by air-filled or fluid-filled spaces with more or less defined walls. Superior lobes are more involved because the apical regions of the lung are subjected to greater gravity-induced stretching. All diseases causing a cystic pattern increase the risk of pneumothorax (Table 9.12).

Initially, pulmonary function tests show a restrictive pattern with reduction of lung diffusion for CO; later, they present an obstructive pattern.

Table 9.12 Differential diagnosis of cystic pattern

Common	
Pulmonary emphysema	Permanent enlargement of the distal air spaces up to the terminal bronchioles secondary to smoke, α1AT deficiency, intravenous drug abuse. It can be centrilobular, paraseptal, or panlobular
Langerhans cell histiocytosis	Centrilobular nodules that evolve into thin-walled cysts, which can aggregate in bizarre shapes. They spare the inferior zones and costophrenic angles. It correlates with smoke exposure and most likely is an allergic response to some smoke components (Fig. 9.10, on the left)
Pneumatoceles	Thin-walled transient cysts that usually resolve within months. The main causes are: • Staphylococcal pneumonia • Pneumocystis jirovecii pneumonia in AIDS-affected patients (30%) • Trauma
Less common	
Lymphangioleiomyomatosis (LAM)	Observed only in women. On CT, there are uniform cysts throughout the lung which slowly replace the parenchyma (Fig. 9.10, on the right). Possible complications are pneumothorax and chylothorax
Subacute hypersensitivity pneumonitis	Characterized by centrilobular nodules evolving into thin-walled cysts; usually 1–14 cysts are observed in 10% of cases
Lymphocytic Interstitial Pneumonia (LIP)	Can be idiopathic or secondary to infections (HIV, EBV), dysproteinemia, and Sjögren's syndrome. On CT, there are thin-walled cysts in 80% of cases, usually less than 20 in number, ground-glass appearance (100%), and nodules in a perilymphatic pattern
Desquamative Interstitial Pneumonia (DIP)	The etiology is unknown; it has a higher prevalence in heavy smokers. It is characterized by thin-walled cysts (80%) of usually small dimension in the lower lobes and ground-glass opacities
Idiopathic Pulmonary Fibrosis (IPF)	Presents with basal or peripheral honeycombing (multiple rows of cysts, 0.3–1 cm in dimension). It can mimic a cystic pattern
Laryngeal papillomatosis	Characterized by centrilobular nodules affecting gravity-dependent regions; they can evolve into cysts
Coccidioidomycosis	Fungal infection that is endemic in the southwestern regions of the USA (valley fever). In its late form, it presents as often single, thin-walled cysts in the superior lobes

α1AT Alpha-1 antitrypsin, *HIV* human immunodeficiency virus, *EBV* Epstein–Barr virus

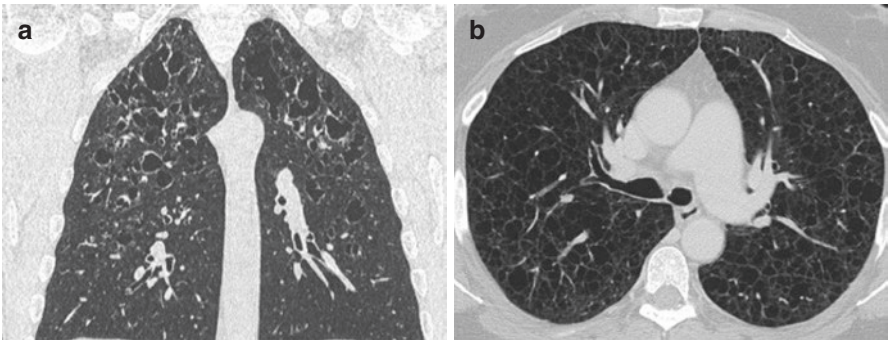

Fig. 9.10 Cystic pattern: (**a**) Langerhans cell granulomatosis. Characteristically dysmorphic thin-walled cysts. (**b**) Lymphangioleiomyomatosis

Alveolar Pattern: Ground-Glass Opacities

The alveolar patterns are ground-glass opacity and parenchymal consolidation.

The ground-glass opacities are characterized by an increased opacity of the lung parenchyma that does not obscure the underlying structures (Fig. 9.11). In the pulmonary consolidation, the bronchovascular structures are obscured.

Ground-glass opacities represent an acute process or an acute flare of a chronic disease (Table 9.13). The radiological presentation is due to:

- Partial filling of air spaces (edema, hemorrhage, pus)
- Interstitial thickening secondary to edema, inflammation, or fibrosis, usually associated to a reticular pattern or traction bronchiectasis
- Tumor growth preserving the parenchymal structures

Reticular Pattern

The reticular pattern is characterized by small and numerous intralobular linear opacities (Table 9.14). As the disease progresses, interlobular septal thickening and traction bronchiectasis are observed.

Honeycombing

It represents a fibrotic and severely damaged lung, characteristic of end-stage lung disease. It presents with multiple well-defined small cysts, from 3–10 mm in size up to 2.5 cm, uniform in size and clustered together. They are associated to traction bronchiectasis (Fig. 9.13).

The diagnosis is challenging as it usually represents an advanced stage of a lung disease and the biopsy is often non-conclusive (Table 9.15).

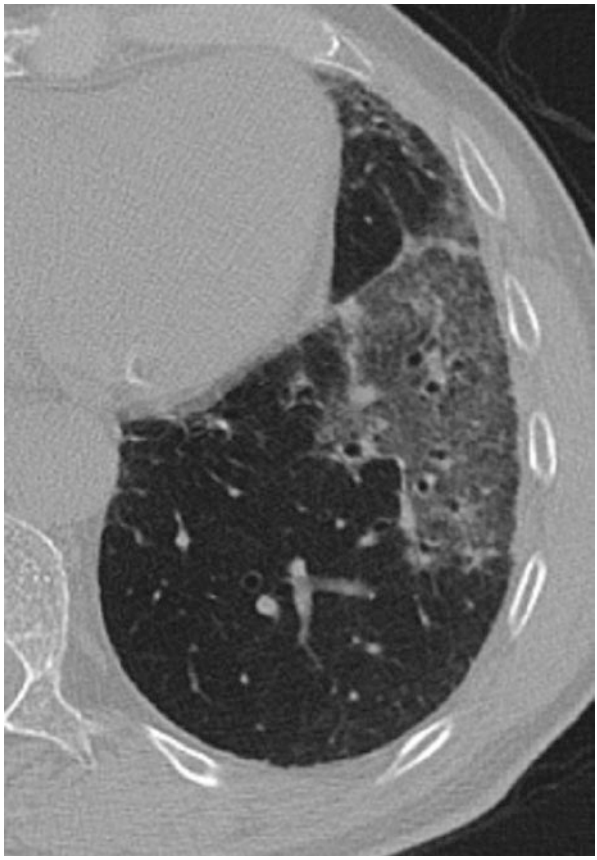

Fig. 9.11 Alveolar pattern. Ground-glass opacity in a patient with NSIP

Table 9.13 Differential diagnosis of alveolar pattern (ground-glass opacity)

Common	
Acute forms	
Atypical pneumonia	Occurs mostly in immunocompromised patients. The most common etiologic agents are P. jirovecii and viral infections (CMV)
Cardiogenic pulmonary edema	Ground-glass opacity with smooth septal thickening, mainly in gravity-dependent regions, associated to pleural effusion
Noncardiogenic pulmonary edema (ARDS)	Ground-glass areas in more than 50% of the lung
Diffuse alveolar hemorrhage	Lobular ground-glass associated to areas of consolidation
Hemorrhagic metastases	Usually secondary to renal cancer
Angioinvasive aspergillosis	Can be associated to ground-glass areas
Hypersensitivity pneumonitis	A mosaic pattern is present in 85% of cases but ground-glass can also be observed

(continued)

Table 9.13 (continued)

Acute eosinophilic pneumonia	Migrating ground-glass opacities with septal thickening and pleural effusion
Drug reaction	Can present in different ways: ARDS, hypersensitivity pneumonitis, pulmonary hemorrhage
Chronic forms	
Non-Specific Interstitial Pneumonia (NSIP)	Can be idiopathic or secondary to scleroderma, rheumatoid arthritis, or drug-induced lung disease It is prevalently characterized by ground-glass, a reticular pattern and traction bronchiectasis. Septal thickening can also be present, more evident at the bases and at the periphery of the lungs. There is subpleural sparing of the lung in the dorsal regions
Chronic eosinophilic pneumonia	Presents with consolidations (100%) and ground-glass appearance (90%) in the peripheral regions and in the upper lobes, with subpleural sparing of the lung
Desquamative Interstitial Pneumonia (DIP)	Of unknown etiology, is more prevalent in heavy smokers. It is characterized by thin-walled cysts (80%), usually in the lower lobes and small in dimension, and ground-glass opacities
Lymphocytic Interstitial Pneumonia (LIP)	Can be idiopathic or secondary to infections (HIV or EBV), dysproteinemia or Sjögren's syndrome. On CT, it appears as thin-walled cysts in 80% of cases, usually less than 20 in number, ground-glass appearance (100%), and nodules in a lymphatic pattern
Primary alveolar proteinosis	The typical presentation is crazy paving pattern, but ground-glass alone may also occur
Less common	
Bronchioloalveolar carcinoma	Focal ground-glass areas not well-defined from surrounding structures or ground-glass associated to solid tissue (part-solid nodule). Air bronchograms may be present
Atypical Adenomatous Hyperplasia (AAH)	Often a precancerous condition. It has a prevalence of 3–7% in the population (higher in elderly patients). It presents as spherical ground-glass opacities that are better delineated than those found in bronchioloalveolar carcinoma

CMV cytomegalovirus, *ARDS* acute respiratory distress syndrome, *HIV* human immunodeficiency virus, *EBV* Epstein–Barr virus

Table 9.14 Differential diagnosis of reticular pattern

Common	
Inferior lung fields	
Idiopathic Pulmonary Fibrosis (IPF)	Idiopathic pathology with a characteristic histopathologic pattern of Usual Interstitial Pneumonia (UIP). The pattern has temporal and spatial heterogeneity. It can be primary (IPF) or secondary to drugs such as chemotherapy, nitrofurantoin, and paraquat The typical radiological presentation is a reticular pattern more evident at the bases and in subpleural regions and traction bronchiectasis with pleural and bronchovascular distortion. It progresses to subpleural honeycombing (multiple rows of cysts, 2–25 mm in size)

Table 9.14 (continued)

Non-Specific Interstitial Pneumonia (NSIP)	Idiopathic or secondary to scleroderma, rheumatoid arthritis, polymyositis, or dermatomyositis. The pattern has temporal and spatial homogeneity The typical radiological presentation is ground-glass opacities that progress to a reticular pattern with septal thickening, which is more evident at the bases and periphery of the lungs. There is sparing of the subpleural lung in dorsal regions. Traction bronchiectasis can also be present, out of proportion to the reticular pattern (Fig. 9.12)
Superior lung fields	
Chronic hypersensitivity pneumonitis	Can mimic IPF and NSIP. It is characterized by a reticular pattern with small fibrous septa that extend from the centrilobular bronchiole to the periphery of the lobule. It has a prevalent involvement of middle portions of the lung in case of chronic exposure (bird fancier's lung); in case of intermittent exposure (farmer's lung), the involvement is more prevalent in the superior portions. Traction bronchiectasis can co-occur (20%)
Sarcoidosis	A reticular pattern may become evident in late stage disease (stage IV) at the level of perihilar regions and in the superior and middle portions of the lung, with distortions and bronchiectasis. The typical presentation is characterized by nodules in a perilymphatic pattern and perihilar and mediastinal adenopathy, which decreases as the fibrosis progresses
Less common	
Asbestosis	Prevalent involvement of the inferior lobes. Pleural plaques may be associated
Ankylosing spondylitis	Prevalent involvement of the superior lobes
Lymphangitic carcinomatosis	Usually presents with a septal pattern but can mimic a reticular one. It is characterized by an asymmetric involvement of one or more lobes

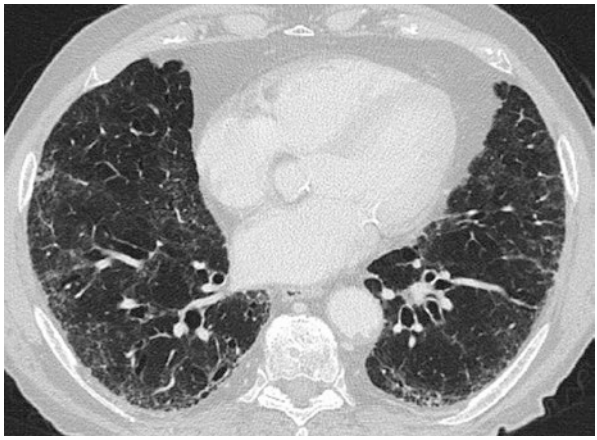

Fig. 9.12 Reticular pattern in a patient with NSIP

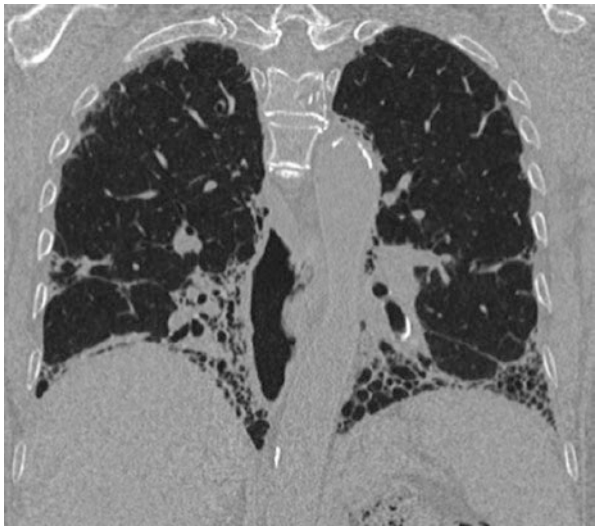

Fig. 9.13 Honeycombing in a patient with IPF

Table 9.15 Differential diagnosis of honeycombing

Common	
Inferior lung fields	
Idiopathic Pulmonary Fibrosis (IPF)	Always evolves into honeycombing
Non-Specific Interstitial Pneumonia (NSIP)	On CT it progresses to honeycombing only rarely but on histologic examination the so-called microscopic honeycombing is observed frequently
Asbestosis	Presents, similarly to IPF, the histological pattern of UIP. Its distinguishing features are pleural plaques (80%), fibrosis centered at the respiratory bronchiole (where the fibers deposit) and ramifying towards the pleura, peripheral hump- or wedge-shaped homogeneous opacities due to the obstruction of the respiratory bronchioles, lobular air-trapping (infrequent in IPF). Infrequently, it progresses to honeycombing
Superior lung fields	
Stage IV sarcoidosis	Can cause honeycombing prevalently in the superior lobes. Fibrous bands are present from the hilum along the bronchovascular bundles
Chronic hypersensitivity pneumonitis	Honeycombing can develop in the superior and middle regions, with relative basal sparing. Centrilobular nodules (not common in IPF) and lobular air-trapping (not common in IPF) can co-occur
Less common diagnoses	
Ionizing radiations	Secondary to thoracic radiotherapy
Diffuse alveolar damage (ARDS)	Occurs secondary to the fibrotic repair response to an acute damage and after the barotrauma occurring in the setting of positive-pressure ventilation

Suggested Readings

Hansell DM, et al. CT staging and monitoring of fibrotic interstitial lung diseases in clinical practice and treatment trials: a position paper from the Fleischner Society. Lancet Respir Med. 2015;3(6):483–96.

Dalpiaz G. Cancellieri A. Atlas of Diffuse Ling Diseases: A Multidisciplinary Approach. Editor: Springer 2017.

Mueller-Mang C, et al. What every radiologist should know about idiopathic interstitial pneumonia. Radiographics. 2007;27:595–615.

Nishino HM, et al. A practical approach to high-resolution CT of diffuse lung disease. Eur J Radiol. 2014;83(1):6–19.