Thinking Through Pathology

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SECONDARY LOBULE

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

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

The main components of secondary lobule are:

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

Rule of thumb: no matter how they are cut, bronchioles and arterioles should have approximately comparable size (and – therefore – lumen diameter) and, often, shape. When arterioles and bronchioles are of different caliber, something is abnormal.
Within the lobule, a fine stromal network of intralobular septa make up the framework of the acini and, more specifically, of the anatomical units responsible for gas exchange: respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. The intralobular (alveolar) septa contain the smallest branches of arterioles and venules, as well as the capillary network.

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

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

- **Interlobular septa and septal structures** (Figure A below). At the periphery of lobule, the interlobular septa are arranged more or less regularly, parallel to each other and perpendicular to the pleural surface (▲). Venules can sometimes be seen as linear or arcuate structures (►). In healthy patients, a few septa are often visible in the lung periphery, but they tend to be inconspicuous; normal septa are most often seen in the apices.

- **Centrilobular region and centrilobular structures** (Figure A and Figure B below). Centrilobular arterioles and bronchioles measure approximately 1 mm in diameter. Arterioles can always be easily resolved on HRCT (▲). Pathologic thickened bronchioles are visible close to arterioles (▲). In healthy patients, bronchioles are not visible because the wall thickness measures approximately 0.15 mm; this is at the lower limit of thin-section CT resolution.

- **Intralobular interstitium (lobular parenchyma)**. Within the lobule, a fine stromal network of intralobular septa make up the framework of the acini and, more specifically, of the anatomical units responsible for gas exchange: respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli. The intralobular septa contain the capillary network which connects the arterial and venous system. In healthy patients, the intralobular interstitium is only partly visible on CT: the most peripheral millimeters of the subpleural lung are homogeneously black.

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

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

### DEFINING LESIONS: NEOPLASM

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

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

This modality of growth along the bronchovascular bundles, in the interlobular septa, and within the pleura is called carcinomatous lymphangitis (CL). Please also refer to carcinomatous lymphangitis in the chapter “Septal Diseases”.
A peculiar pattern of presentation frequently responsible for the so-called ground-glass opacity (GGO) in CT is due to a lepidic growth of the neoplasm along alveolar septa. Please also refer to Adenocarcinoma in the chapter “Alveolar Diseases”.

In the context of a malignancy, this can be due to the presence of mucus as in pneumonia-like pattern of invasive mucinous adenocarcinoma, formerly mucinous BAC, or to the presence of neoplastic cells. In these cases, ground-glass opacity (GGO) and consolidations are the radiological expression of the disease, and more often a mixed pattern, where the two aspects coexist, is present. Please also refer to Adenocarcinoma in the chapter “Alveolar Diseases”.
Some tumors preferentially grow along bronchial and bronchiolar walls eventually invading their lumen. Also, preinvasive conditions such as DIPNECH (diffuse idiopathic pulmonary neuroendocrine cell hyperplasia) can exhibit this pattern of growth. Expiratory HRCT shows patchy areas of black and white aspect due to air trapping. Some small solid nodules, consisting of tumorlets or typical carcinoids, also coexist. Please also refer to DIPNECH in the chapter “Dark Lung Diseases”.


DEFINING LESIONS: MIXTURE

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

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

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

Hyaline Membranes

Pulmonary Alveolar Proteinosis (PAP)

Diffuse Alveolar Hemorrhage (DAH)

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

Diffuse alveolar hemorrhage (DAH) is characterized by fibrin and hemosiderin-laden macrophages, which can be appreciated both on cytology in BAL fluid and at histology (Figure B). Capillaritis is often part of the picture; nevertheless, it represents a transient phenomenon and therefore it is not constantly seen.
Amyloid, whether nodular or interstitial, isolated finding or associated to chronic inflammation or low-grade lymphomas consists of the deposition of a homogeneous, acellular, pink material which can calcify or ossify (Figure A).

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

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

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

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

Atlas of Diffuse Lung Diseases

A B
NON-DEFINING LESIONS: INFLAMMATION

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

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

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

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

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

NON-DEFINING LESIONS: FIBROSIS

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

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

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

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

This fibrosis is quite homogeneous from the spatial point of view, so uniformly distributed throughout the lobule. The prototype is fibrosing NSIP (Figure B below).
The size of the process varies from the punctate fibrosis which is barely visible at low power (Minimal changes) because it is concentrically limited to the bronchiole, typically in constrictive bronchiolitis (Figure A) to more extended areas of eccentrically radiating stripes, often surrounding an irregularly ectatic bronchiole (typically, in Langerhans cell histiocytosis) (Figure B).

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

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

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

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

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

**ANATOMIC DISTRIBUTION**

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

This is the presentation of diseases arriving to the lung through the airways and/or developing just next to the bronchiole in the centrilobular area. A good example is the cellular bronchiolitis due to mycobacterial infection, consisting in centrilobular inflammatory nodules sparing the subpleural regions (〇). Note the focal ramified appearance (●), corresponding to the tree-in-bud sign at CT scan. Please also refer both to the Tree-in-bud, bronchiolar sign in the chapter “Alveolar Pattern” and in the “Case-Based Glossary with Tips and Tricks”.

**Bronchiolocentric**

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

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

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

Lymphatic

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

Septal

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

Angiocentric

- Thromboembolic disease (CTPE)
- Pulmonary tumor thrombotic microangiopathy (PTTM)
- Plexiform arteriopathy
Some diseases tend to involve the lobule at its periphery. The prototype disease is early usual interstitial pneumonia (UIP), with small scars in a peripheral subpleural (►) and paraseptal distribution. Please also refer to UIP in the chapter “Fibrosing Diseases”.

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

**Peripheral**
- UIP, early
- Perilobular opacities (OP)
The image shows a case of pleuroparenchymal fibroelastosis (PPFE), a rare disease consisting in elastotic tissue with a subpleural localization. The arrows (⇨) show a dilated bronchiole almost reaching the pleura (traction bronchiolectasis). Please also refer to PPFE in the chapter “Fibrosing Diseases”.

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

Pleural/Subpleural

- Pleuro-Pulmonary Fibro-Elastosis (PPFE)

Random

- Amyloidosis, nodular
- Churg–Strauss syndrome
- IgG4 syndrome
- Immunoglobulin deficiency
- Infection (e.g. miliary TB)
- Inflammatory bowel disease
- Neoplasm (e.g. metastases)
- Organizing Pneumonia (OP)
- Rheumatoid nodule
- Granulomatosis with Polyangiitis (GPA), formerly defined Wegener Granulomatosis (WG)
The alveolar septa are thickened, due to material growing inside them. Interstitial expansion by cells (cellular NSIP) or by fibrosis (fibrotic NSIP, figure below). Please also refer to NSIP in the chapter “Fibrosing Diseases”.

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

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

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

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

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

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

**Fibrosis**
- Aspiration, chronic
- Collagen Vascular Diseases (CVD)
- Drug reaction, chronic
- Hypersensitivity Pneumonitis (HP), chronic
- Infection, chronic
- Inhalation, chronic
- IPF (idiopathic UIP)
- Non-Specific Interstitial Pneumonia (NSIP), idiopathic
- Pneumoconioses
- Sarcoidosis, chronic
- Smoking-related ILD (DIP, chronic LCH)
An example of cellular infiltrate, consisting in inflammatory cells (lymphocytes and plasma cells) expanding the interstitium due to hypersensitivity pneumonitis (HP) is shown in the image below.

Cellular Infiltrate

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

Alveolar Filling

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

Alveolar Filling

- Acute Fibrinous and Organizing Pneumonia (AFOP)
- Alveolar microlithiasis
- Pulmonary alveolar proteinosis (PAP)
- Diffuse ossification
- Desquamative Interstitial Pneumonia (DIP)
- Pulmonary edema (PE)
- Eosinophilic pneumonia
- Diffuse alveolar hemorrhage (DAH)
- Infections (e.g., acute bacterial)
- Neoplasms
- OP, cryptogenic
A necrotic nodule due to a previous varicella infection is an example of a disease presenting with a nodular pattern (Figure below). Please also refer to chapter “Nodular Pattern”.


**ANCILLARY HISTOLOGIC FINDINGS**

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

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