

Interstitial lung diseases—can pathologists arrive at an etiology-based diagnosis? A critical update

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Abstract Interstitial lung diseases (ILD) encompass a group of diseases with a wide range of etiologies and a variety of tissue reactions within the lung. In many instances, a careful evaluation of the tissue reactions will result in a specific diagnosis or at least in a narrow range of differentials, which will assist the clinician to arrive at a definite diagnosis, when combining our interpretation with the clinical presentation of the patient and high-resolution computed tomography. In this review, we will exclude granulomatous pneumonias as well as vascular diseases (primary arterial pulmonary hypertension and vasculitis); however, pulmonary hypertension as a complication of interstitial processes will be mentioned. Few entities of pneumoconiosis presenting as an interstitial process will be included, whereas those with granulomatous reactions will be excluded. Drug reactions will be touched on within interstitial pneumonias, but will not be a major focus. In contrast to the present-day preferred descriptive pattern recognition, it is the author's strong belief that pathologists should always try to dig out the etiology from a tissue specimen and not being satisfied with just a pattern description. It is the difference of sorting tissue reactions into boxes by their main pattern, without recognizing minor or minute reactions, which sometimes will guide one to the correct etiology-oriented interpretation. In the author's personal perspective, tissue reactions can even be sorted by their timeliness, and therefore, ordered by the time of appearance, providing an insight into the pathogenesis and course of a disease. Also,

underlying immune mechanisms will be discussed briefly as far as they are essential to understand the disease.

Keywords Diffuse interstitial lung disease · Interstitial pneumonia · Autoimmune disease · Collagen vascular disease · Rare interstitial lung disease

Introduction into interstitial lung diseases and pneumonias

Interstitial lung diseases (ILD) are characterized by a diffuse infiltration of both lungs, usually evaluated by high-resolution computed tomography (HRCT) scan. The types of infiltrating cells are not predefined, so this can be inflammatory as well as tumor cells. Tumorous infiltration will be excluded, since there are too many entities, not only carcinomas but also lymphomas and certain sarcomas such as angiosarcomas. Therefore, our main focus will be on interstitial pneumonias (IP).

Historic remarks on interstitial pneumonia classification

Many classifications on IP have been published over the last four decades, and our understanding of these processes has improved stepwise and resulted in a refined schema, which can be used to sort these diseases accordingly. However, there are still many problems, making the use of this classification problematic to pathologists, not specifically dealing with lung pathology.

Originally, Liebow [1] proposed a classification based on morphological descriptions, with the following entities: usual interstitial pneumonia (UIP), bronchiolitis obliterans–interstitial pneumonia (BIP), diffuse alveolar damage (DAD, also acute interstitial pneumonia [AIP], clinically corresponding to

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acute respiratory distress syndrome [ARDS]), lymphocytic interstitial pneumonia (LIP), desquamative interstitial pneumonia (DIP), and giant cell interstitial pneumonia (GIP). Katzenstein's updates from 1993 and 1998 [2, 3] were the next major step, adding nonspecific interstitial pneumonia (NSIP) to the list of UIP, DIP, BIP, and AIP/DAD and removing LIP and GIP because an etiology could be assigned to them. Later on, Muller and Colby showed a radiologic–pathologic correlation and used the previously created name bronchiolitis obliterans-organizing pneumonia (BOOP) [4, 5] instead of BIP.

When these entities were combined with clinical data, it was apparent that there was a major difference between UIP and the “rest”: Patients with UIP had a worse prognosis and most of them died within 5 years after diagnosis [6]. Another intention to separate idiopathic interstitial pneumonias (IIP) from those with known cause was to provide prognostic and therapeutic information to the clinicians: No response of patients with UIP/idiopathic pulmonary fibrosis (IPF) towards corticosteroids and immunosuppressive drugs and dismal prognosis, whereas responsiveness of patients with NSIP to corticosteroids and immunosuppressive drugs and a better prognosis.

The next step happened, when UIP and the fibrosing variant of NSIP were compared to each other, showing that the initial difference vanished especially when evaluated for 10 years survival [6]. Then, IP were classified into idiopathic and those with known etiology: DIP and respiratory bronchiolitis with or without interstitial lung disease (RBILD) were excluded from idiopathic because, in both entities, cigarette smoking was identified as the main cause of the disorder. LIP was also skipped, probably because of a clearly defined etiology in almost all cases, either lymphoma, allergic, or autoimmune diseases. GIP was skipped, since it either is induced by hard metal inhalation or viral infection (measles, respiratory syncytial virus [RSV], and others) [7, 8].

What makes the present-day classification complicated is the combination of radiology, pathology, and pulmonology, resulting in provisional diagnoses or divergent names for pathology and clinics. In addition, the final diagnosis needs to be discussed between clinicians, radiologists and pathologists. This also changed the general view: Many clinicians suppose they are the only ones being able to make the diagnosis of IPF, and pathologists in the classification committee have accepted it.

There are examples which support such a perspective: Organizing pneumonia (OP) has a wide variety of etiologic causes, and the idiopathic form cryptogenic organizing pneumonia (COP) needs exclusion of all other causes, which on several occasions can be done by pathologists, but in other cases only by combining morphology with clinical information. Furthermore, radiology has gained a

major impact on the diagnosis of ILD, which resulted in decreasing numbers of patients for whom a pathologic diagnosis is required. It cannot be neglected that pathologists have also contributed to this situation: There are colleagues who are happy to make the diagnosis of, e.g., UIP and do not further look for features which would allow the differentiation between UIP/IPF versus other causes of UIP, e.g., collagen vascular diseases (CVD).

Based on recommendations from a joint committee established by the European Respiratory Society (ERS) and American Thoracic Society (ATS) pathologists, radiologists, and pulmonologists proposed a new classification and also a diagnostic algorithm for ILD [9, 10] (Table 1; Fig. 1).

In this review, I will discuss IIP following the schema shown in Fig. 1. When discussing IP with known etiology, I will group these diseases according to their etiologic basis. Therefore, some of the morphologic patterns of idiopathic IP will be recapitulated. Finally, ILD with various etiologies will be discussed at the end of this review. Granulomatous pneumonias including extrinsic allergic alveolitis/hypersensitivity pneumonia (EAA/HP) will be excluded because this alone would fill a review on its own. However, in some of the diseases to be discussed, granulomas do appear and, therefore, will be explained briefly.

This review is based on the personal experience of the author being responsible for the diagnostic workup at the Medical University of Graz, but also acting as a consultant for many central European hospitals, which allowed me to set up a huge lung and pleura biobank. In addition, several published articles and reviews in this area including published classifications by the ATS/ERS joint committees on ILD are critically reviewed.

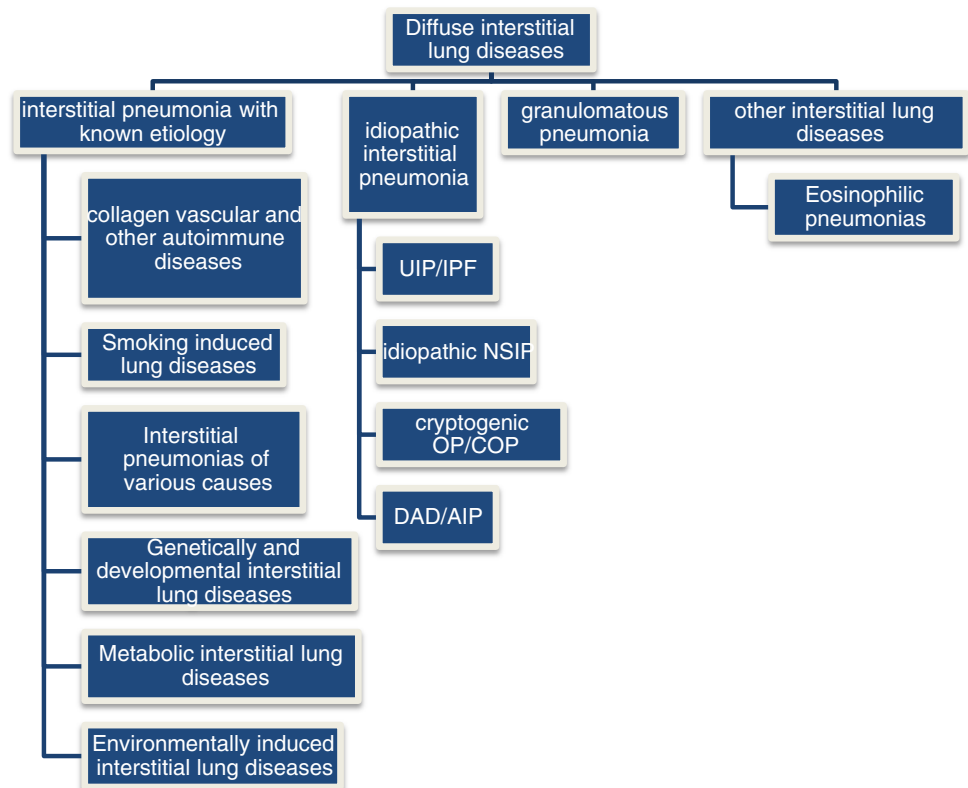
Usual interstitial pneumonia/idiopathic pulmonary fibrosis

UIP/IPF is a chronic progressive fibrosing disease of the lung, which leads to death of the patient usually within 5–10 years after the diagnosis is made. It affects predominantly patients in their fourth to fifth decade of life; however, lesions may occur much earlier and remain undetected until

Table 1 CRP diagnoses and their morphologic counterparts

Clinico-radiologic-pathologic (CRP) diagnosis of idiopathic interstitial pneumonias	Morphologic pattern
Idiopathic pulmonary fibrosis (IPF)	Usual interstitial pneumonia (UIP)
Idiopathic nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia (NSIP)
Cryptogenic organizing pneumonia (COP)	Organizing pneumonia (OP)
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)

Fig. 1 Diagnostic algorithm for idiopathic ILD, excluding some of the diseases with known etiology (modified from [9])



they will cause impaired lung function by their increasing number—UIP/IPF is seen more often in younger-aged patients, probably due to increased awareness. Characteristically, lesions are found in both lower lobes with a predominance of subpleural regions. The involvement of both lobes is most often symmetrical. By HRCT, different features can be seen: fibrotic and scar lesions, ground glass areas, and honeycombing. Cystic lesions, consolidations, and scars are found on gross cut surface. The pleura usually show multiple retractions, giving the surface a cobblestone appearance, but pleuritis is not seen. The histological hallmarks are fibroblastic foci, scars and diffuse fibrosis, honeycomb areas, and uninvolved areas in between (Figs. 2 and 27; Suppl. Fig. 28).

The cause and the etiology of IPF/UIP are not well understood. There is a working hypothesis, which can explain some of the features. The disease starts with an as yet unidentified epithelial injury causing apoptosis of pneumocytes [11–14]. Inflammatory signals released by the dying pneumocytes cause transformation and proliferation of fibroblasts and myofibroblasts in a myxoid stroma and repair [15] (so-called fibroblastic focus). Genetic abnormalities may underlie these apoptotic responses: In the recent years, research in familial forms of IPF has highlighted the importance of surfactant apoproteins in maintaining homeostasis between injury and repair and that mutations in the surfactant apoprotein C gene might be causally related to the development of familial IPF [16]. In these familial IPF, mutations in

genes encoding surfactant apoprotein C and A2 increases endoplasmic stress reactions in pneumocytes type II, and in addition, mutations in the telomerase genes TERT and TERC are responsible for telomere shortening, probably decreasing the pool of peripheral lung stem cells and thus impairing repair and regeneration [17]. This later defects are also found in sporadic IPF cases. Therefore, inhalation of any kind of toxic material from the environment might cause an overwhelming oxygen stress reaction leading to increased apoptosis of pneumocytes and impaired regeneration [18]. This fits quite well into the epidemiology of IPF patients: The majority are smokers, and some have a history of environmental dust exposure [19, 20]. There is also evidence of epithelial–mesenchymal transition (EMT) of pneumocytes into myofibroblasts (Fig. 3), and also scattered bone marrow-derived mesenchymal stem cells seem to move into these foci [21–23]. These foci undergo maturation with collagen deposition, and finally, the process results in fibrosis of alveolar septa and bronchiolar walls [13]. This in turn causes obstruction of the terminal airways resulting in cystic destruction of the remaining peripheral lobules, giving rise to honeycombing and remodeling of the lung parenchyma [14, 24, 25]. The process develops stepwise, which means there are lung lobules not affected yet looking normal, whereas others are destroyed or even completely lost to fibrosis and scarring. This is meant by the term “timely heterogeneity.” In the author’s experience, a diagnosis of UIP/IPF can be established in some cases even without clinical information

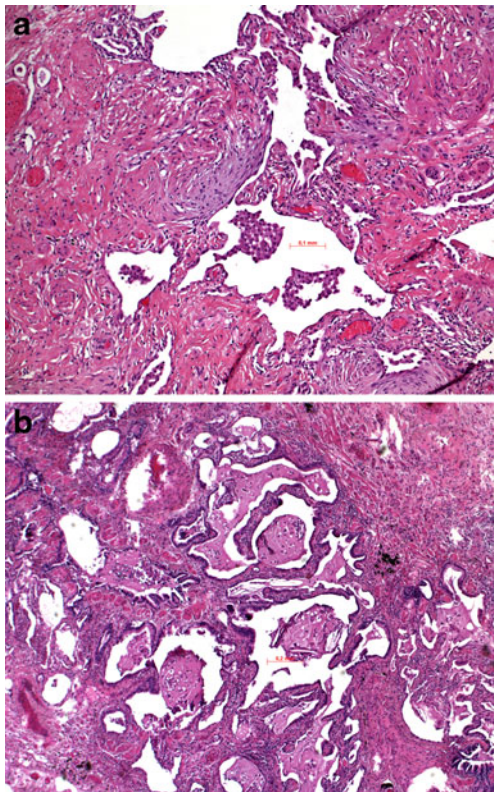


Fig. 2 **a** Fibroblastic foci and **b** cystic remodeling of lung lobules (microscopic equivalent of honeycombing). Note the transformation of epithelia into a bronchiolar type. H&E; bar, 0.1 and 0.2 mm

when the following features are given: fibroblastic foci, timely heterogeneity (involved and uninvolved peripheral lobules), cystic and fibrotic destruction resulting in honeycombing, and most importantly, the absence of inflammatory infiltrates in areas of fibroblastic foci, absence of granulomas, or features of other interstitial inflammation.

Let us briefly characterize the main morphologic features, since this still causes confusion and misunderstanding:

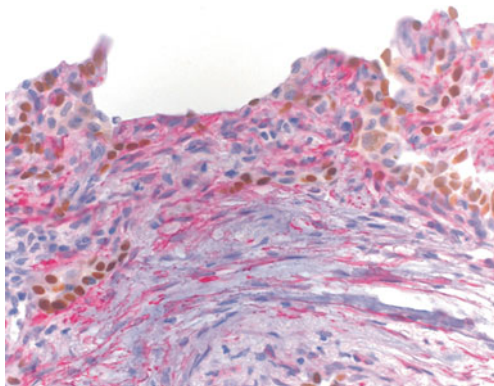


Fig. 3 EMT in a fibroblastic focus: Immunohistochemistry using double stain for TTF1 (brown, nuclear) and smooth muscle actin (red, cytoplasmic) in the same cells. Magnification, $\times 200$

The *fibroblastic focus* lies within the walls of alveolar and interlobular septa, as well as bronchioles. They do not project into the alveolar lumen. In early stages, they are composed of myofibroblasts and fibroblasts in an immature myxoid matrix. This matrix will stain for immature collagen and reticulin fibers. The overlying surface is either denuded (no pneumocytes) or can show pneumocyte regeneration with a lot of reactive changes of the nuclei, even epithelial giant cells can be present (Figs. 2 and 27a). When the focus gets older, mature collagen appears and the cells look more like fibrocytes. The overlying epithelium looks reactive and usually has a type II or bronchiolar cell appearance.

The *honeycomb lesion* was originally defined by radiologists as a single or multicystic lesion within a fibrotic lung area [26]. Given the differences in resolution between HRCT and histology, there is a substantial difference in size between the two. Pathologically, a so-called honeycomb lesion is a cystic lung lesion involving a secondary lobule. This lobule has lost most of the peripheral alveoli, shows a cystic central area composed of bronchioles and centroacinar structures, covered by a cuboidal and cylindrical epithelium, resembling bronchiolar epithelium and transformed pneumocytes type II (Figs. 2b and 4). In some cases, a pseudostratified squamous-looking epithelium can be present. The cyst walls are fibrotic and often merge with scarred lung tissue or large fibrotic areas involving sometimes a subsegment of the lung. Within the lumen, mucus can accumulate, and in late stage, this can be the starting point for secondary infection and bronchopneumonia, causing death of the patient. I prefer the term lobular cystic lung remodeling, instead of honeycombing, because of the size differences between HRCT and microscopy (Suppl. Fig. 28).

The areas of *fibrosis* and *scarring* and the uninvolved lung tissue (heterogeneity) do not need an explanation. But what about inflammation? From what we understand presently, IPF/UIP is not an immune-driven or classic

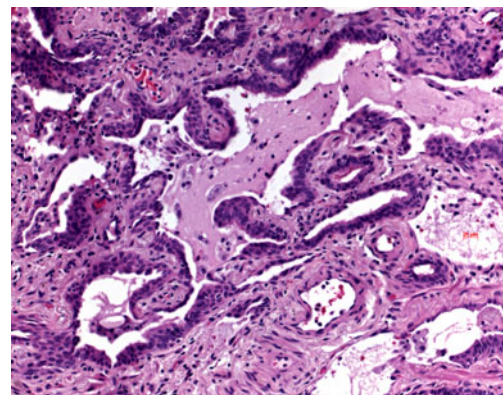


Fig. 4 Cystic remodeling of lobules, the histologic correlate to CT scan of honeycombing; bar, 20 μm ; compare the size of the cystic lesion to a CT lesion

inflammatory disease. Therefore, we do not expect inflammatory cells within the fibroblastic foci. If lymphocytes appear in numbers (>10 /HPF) within a fibroblast focus, this should raise the possibility of an underlying immune reaction. The appearance of granulocytes within these foci should prompt the search of remnants of hyaline membranes because this may represent organizing DAD.

Modes of handling diagnosis

The ATS/ERS recommends that a panel of experts composed of pulmonologists, radiologists, and pathologists (clinical–radiological–pathological [CRP]) should make the diagnosis of IPF. The clinical presentation and course, the HRCT picture, and the pathologic pattern of UIP should be combined. Five categories of confidence of IPF diagnosis can be reached:

- Definite IPF, when UIP with a classical HRCT and typical clinical presentation is present,
- Probable IPF, when one of the classical features is not present (e.g., no definite UIP or no definite HRCT scan),
- Possible IPF, if several features from CT and histology are not conclusive,
- Probable not IPF, when CT and pathology show features not compatible with IPF,
- Definite not IPF, if there are features of other interstitial diseases [10].

In some cases, the diagnosis of IPF can be based on clinical and CT findings alone. Whenever pathologic evaluation is involved, a diagnosis of UIP is mandatory for the diagnosis of IPF.

Acute exacerbation of UIP/IPF is clinically characterized by rapid worsening of the patient's symptoms, with severe hypoxia most often requiring mechanical ventilation and oxygen supply. Many patients will die under this condition. Histologically, two types of acute exacerbations can be seen when examining autopsy cases: secondary infection with infectious pneumonia in the background of UIP or multiple fibroblastic foci and severe fibrosis leaving not much lung parenchyma for ventilation. In these latter cases, there is usually severe lung edema present. If a viral infection is present, the histological pattern is DAD [27] overlaying UIP; if bacterial or fungal infection causes exacerbation, a purulent bronchopneumonia is found.

Besides, in IPF, a UIP pattern can occur in many other diseases, such as autoimmune diseases, allergic diseases, toxic inhalation, drug-induced pneumonias, and many more. This still causes a lot of confusion because the term UIP is not used uniformly: Some authors use UIP strictly in the sense of IPF, others do not care about etiology and simply diagnose UIP as a pattern, and a third group discerns UIP

and UIP-like tissue reactions. The same happens with clinicians: Most think that a UIP diagnosis already means IPF and are confused to learn that UIP can present in chronic EAA as well as drug reactions for example. We will discuss these later on.

Nonspecific interstitial pneumonia (NSIP)

NSIP is a diffuse IP, characterized by loose lymphocytic, macrophagocytic, and histiocytic cell infiltration within alveolar septa combined with mild fibrosis. There is no timely heterogeneity, meaning that the lesions seem to have appeared at the same time. Hyperplasia of the bronchus-associated lymphoid tissue (BALT) is usually not present [28, 29]. The lung architecture is preserved in contrast to UIP, and cystic destruction is absent. Two forms are discerned, which in some cases might represent timely sequences of the disease: the cellular and fibrotic types (Figs. 5 and 6). Both behave differently; the cellular type has a better prognosis, whereas the fibrotic variant is more close to UIP [6]. In the etiologic background, NSIP is most often associated with autoimmune diseases, especially with CVD [30–34]. An association with drug-induced pneumonia and also with allergic diseases such as EAA/HP has also been reported [35, 36]. Only those cases without an identifiable etiology are labeled as idiopathic NSIP. However, the morphologic pattern is identical; therefore, in most instances, idiopathic NSIP remains a clinical diagnosis. Clinically, NSIP shows diffuse infiltrations, corresponding to ground glass opacities on HRCT. Symptoms as in the other ILD are quite unspecific. Many patients with NSIP will respond to corticosteroid and/or immunosuppressive drug treatment, and also spontaneous resolution of the disease has been reported [37, 38].

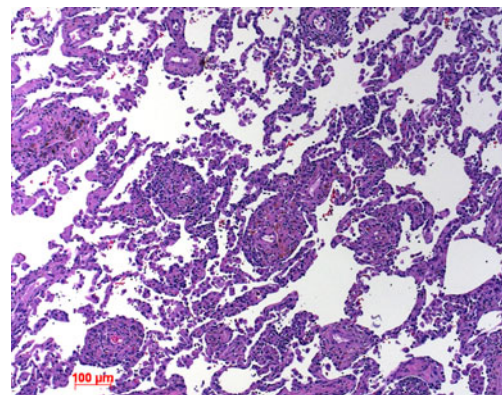


Fig. 5 Cellular NSIP; note the well-preserved lung architecture, only the alveolar septa are widened by the inflammatory infiltrate. H&E; bar, 100 μ m

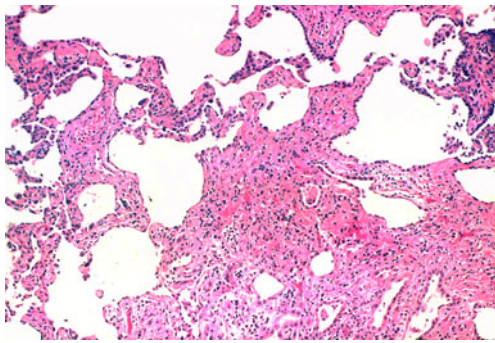


Fig. 6 Fibrotic NSIP; even in this fibrotic lesion, the architecture with the alveolar walls can be discerned. H&E; magnification, $\times 100$

So what makes this diagnosis?

- The lung architecture is preserved. On low power, the alveolar walls, interlobular septa, and primary as well as secondary lobules can be outlined (draw lines along alveolar walls on a digitized photograph, this helps in understanding).
- Diffuse infiltrates composed of lymphocytes, macrophages, and histiocytic cells, usually a few plasma cells.
- If fibrosis is present, this usually causes no distortion of the lung architecture.
- Fibrosis is diffuse, not merging with scars. Inflammatory infiltrates in cases of fibrosing NSIP are usually scarce.
- Non-necrotizing granulomas can be present in certain cases (EAA), however, should not be encountered in idiopathic NSIP.
- Hyperplasia of BALT is absent.

Cryptogenic organizing pneumonia

COP is a diagnosis of exclusion, based on the morphology of OP (formerly BOOP). On HRCT, OP/COP shows a pattern with combinations of ground glass opacities and consolidations and the almost diagnostic tree-in-bud pattern, sometimes also reticulonodular pattern [39]. In rare cases, the consolidation can mimic a tumor [40]. Histologically, the hallmark of OP is an intra-alveolar granulation tissue, the so-called Masson body (Figs. 7 and 27). It consists of proliferating fibroblasts and myofibroblasts with inflammatory cells like neutrophils, lymphocytes, histiocytes, and macrophages. Few hemosiderin-laden macrophages are often present. The granulation tissue can start from the wall of bronchi, bronchioli, and alveoli. There is usually a defect of the epithelial layer and also the basal lamina. Fibroblasts and myofibroblasts grow into the defect; however, in contrast to normal repair, the granulation tissue does not stop but continuously grows into the airspaces, filling these completely or incompletely. In later stages, pneumocytes will grow over these granulation tissue plugs and, therefore, a slit-like airspace can be formed (Fig. 8) [40]. The amount of inflammatory cells

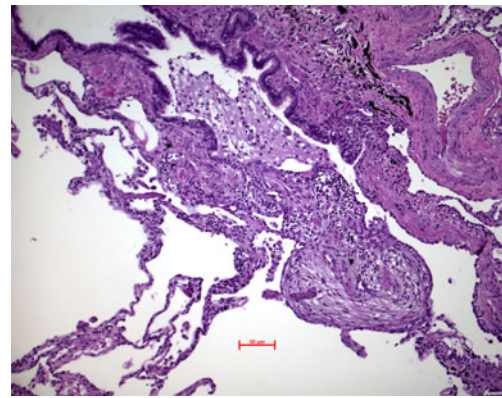


Fig. 7 Granulation tissue within an alveolus, so-called Masson body (OP). Note the inflammatory infiltrate and also a blood vessel within the granulation tissue. H&E; bar, 50 μm

within the granulation tissue depends on the cause of OP. The morphologic pattern of OP has a very wide range of etiologies. It can occur as a post-infectious process, in inactive or resolving stages of autoimmune disease/CVD and vasculitis, in toxin inhalation, in drug-induced lung diseases, in chronic inflammatory bowel diseases, or idiopathic, which is COP [41–44]. In some cases of OP, the etiologic cause can be determined, for example, by viral inclusion bodies in post-viral OP (Fig. 9) or by endothelial cell reactions in drug-induced OP. In some cases, an additional pathologic tissue reaction besides OP can also point to the underlying etiology.

So what are the diagnostic features?

- Granulation tissue growing into bronchi, bronchioles and alveoli, usually with remnants of inflammatory cells.
- Fibrotic occlusion of whole lobules or remaining slit-like spaces covered by pneumocytes.
- A mixture of inflammatory cells within these granulation tissue plugs depending on the cause of previous damage.

If looking for the etiology, one should also closely investigate the small blood vessels and the regenerating pneumocytes: Viral inclusion bodies might be still visible, scattered neutrophilic granulocytes can be found in the granulation

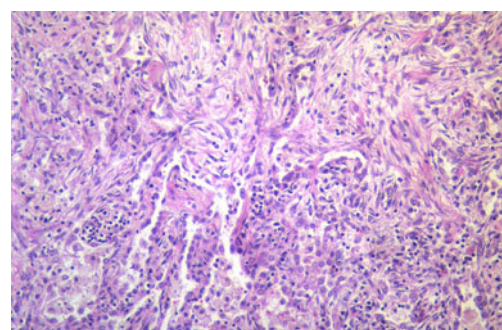


Fig. 8 Late stage of OP: granulation tissue plugs are covered by regenerating epithelium, a slit-like space of the original alveolus remained. H&E; magnification, $\times 200$

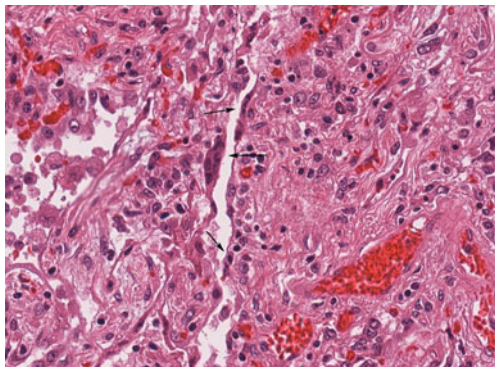


Fig. 9 DAD in viral infection; besides hyaline membranes, there are scattered atypical pneumocytes with viral inclusion bodies (arrows). H&E; magnification, $\times 400$

tissue in cases of bacterial or fungal infection, and eosinophils might be seen pointing to a previous drug-induced pneumonia. In virus-induced pneumonias, another feature can be found, even after several months: single transformed pneumocytes showing atypical nuclei and a homogeneously stained smudged chromatin pattern (Suppl. Fig. 29). In drug-induced and metabolic as well as in autoimmune diseases, the vascular walls can show various structural changes, making an etiology-based diagnosis probable: Eccentric vasculopathy with scattered lymphocytes and without endothelial damage might point to deposition of idiotype–anti-idiotype immune complexes (without complement activation; Fig. 15; Suppl. Fig. 30), endothelial damage with fibrosis and repair can point towards drug-induced damage (Suppl. Fig. 29).

COP as a CRP diagnosis is a diagnosis of exclusion: If all possibly underlying diseases are excluded, COP can be diagnosed. This has some importance, since COP responds well to corticosteroid treatment.

Diffuse alveolar damage

Clinically, AIP (also ARDS) is characterized by acute onset of severe hypoxia, with the radiological appearance of white lung. Histologically, there is edema and fibrinous exudate, widened edematous alveolar septa. Later on, hyaline membranes are formed (DAD). Inflammatory infiltrates are usually scarce. Depending on the cause of DAD, neutrophilic and/or eosinophilic granulocytes can be found in bacterial, toxic, or drug-induced DAD or scattered lymphocytes are seen in viral and rickettsial infections [45, 46] (Fig. 9). Inflammatory infiltrates may be even absent such as in various kinds of shock. Rarely, cases of “idiopathic AIP” have been reported. Probably, some of these cases represent cases of undiagnosed systemic lupus erythematosus (SLE) or drug toxicity. In the author’s experience, in all cases sent for consultation and primarily labeled as idiopathic DAD, an etiology could finally be established. So it might be

questioned, if idiopathic DAD does exist. Hamman and Rich described an IP with fulminant course, leading to death in their six cases within 6 months. In the authors’ description, there was no hyaline membrane mentioned, but a proliferation of fibroblasts. Since the tissues from these cases were all lost, this disease cannot be reconstructed and remains an enigma [47].

The sequence of events in DAD is largely dependent on the cause: Toxic metabolites of drugs or released collagenase and elastase from necrotizing pancreatitis will cause endothelial damage, followed by leakage of the small peripheral blood vessels. This causes edema, followed by pneumocyte cell death (hypoxia). Serum proteins will pass into the alveolar lumina, coagulate there, and by the breathing movements are compressed into hyaline membranes. In case of airborne disease, e.g., infection or inhaled toxins, pneumocytes type I die followed by type II. The basement membrane is either preserved or destroyed (especially in viral infection). This again causes leakage of capillaries, edema with/without bleeding, protein extravasation into the alveoli, and finally, formation of hyaline membranes.

The lethality of DAD is still high despite improvements which have been made in the past decade. In some cases, the progression of the disease might be blocked by antiprotease treatment [48]. In more recent time, extracorporeal oxygenation or nitric oxide treatment has shown some benefit. If the patient survives the acute phase, DAD will be organized, which is essentially an OP-type of lesion, but is most often labeled as organizing DAD: Granulation tissue grows into the alveoli and hyaline membranes are incorporated into the plugs. They can be demonstrated several weeks after the initial injury. If a tissue biopsy or an autopsy specimen is available early on in the course of the disease, the etiology might be elucidated. In viral infection, inclusion bodies can be seen, later followed by atypical proliferation and transformation of pneumocytes type II. In contrast to atypical pneumocyte hyperplasia (AAH), these atypical cells are single, do not form a continuous layer along the alveolar wall, and usually show bizarre nuclei and nucleoli. Rickettsial infection results in less pronounced proliferation of pneumocytes. In shock- and drug-induced DAD, the endothelia will undergo apoptosis and necrosis, and fibrin cloths might be seen in capillaries. In these cases, the alveolar septa are widened and edematous. Inflammatory cells are scarce or absent. In later stages of drug-induced pneumonia, scattered eosinophils are encountered—their function being completely unknown in these cases.

What are the characteristics of DAD?

- Edematous fluid accumulation in alveoli and in the interstitium (depending on the time course),
- Fibrin cloths in alveoli with/without hyaline membranes,

- Scarce inflammatory infiltrates (neutrophils and/or lymphocytes, etiology-dependent),
- Minor diagnostic but etiologically important features are damage of pneumocytes, endothelial cells, fibrin thrombi in small blood vessels, and regeneration±atypia.

Lymphocytic interstitial pneumonia

LIP almost vanished from the literature in the last 5 years. The major problem is the separation from NSIP. When NSIP was described, it was never clearly separated from LIP [49]. When comparing my own cases and reports from the literature, it becomes evident that differences do exist: In LIP, the lymphocytic and plasmocytic infiltration is dense, hyperplasia of the BALT is common, and within lymph follicles, germinal centers are usually present [49]. The infiltration in LIP is more diffuse, architectural distortion is common, and scarring does occur. Histiocytic and monocytic cellular infiltrations are much less pronounced compared to NSIP. Lymphoepithelial lesions do occur similar to lymphomas, in some entities aggressively infiltrating and destroying the epithelium and in other cases no epithelial disruption does occur. In contrast to NSIP, the architecture of the peripheral lung is remodeled, especially in later stages (Figs. 10 and 11). The organization phase is often characterized by OP.

Within the etiologic spectrum, similar diseases are found as in NSIP: autoimmune diseases especially CVD, allergic diseases such as EAA (acute and subacute), allergic drug reactions, and in children, different types of immunodeficiency (T cell defect, NK cell defect). The most important differential diagnosis, however, are extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT/BALT) type and lymphomatoid granulomatosis type I. In all cases, the clonality has to be evaluated and a lymphoma needs to be excluded by proof of multiclonality. Also, it is important to exclude posttransplant lymphoproliferative disease [50], which can present in a similar pattern (large lymphoid cells usually Epstein–Barr virus-positive).

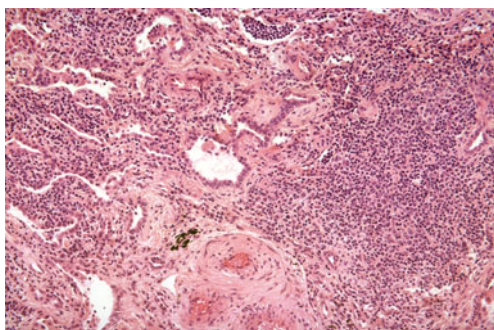


Fig. 10 LIP, lymphoepithelial lesion, here in a case of SjS; note the aggressive lymphocytic infiltration with destruction of the epithelium. H&E; magnification, $\times 200$

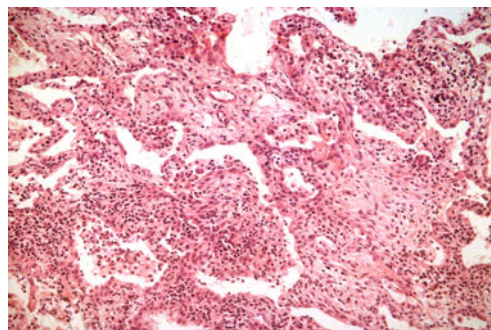


Fig. 11 LIP, late stage with destruction of the lung architecture. Here in a case of immunodeficiency in a 3-year-old child. H&E; magnification, $\times 100$

However, it should be taken into account that some of the autoimmune diseases have a high propensity of developing non-Hodgkin lymphomas later in the course [51]. Within the autoimmune diseases, Sjögren's disease (SjS) most often presents with the LIP pattern [33, 52].

What are the characteristics of LIP?

- Diffuse dense lymphoplasmocytic infiltrates in alveolar septa and bronchial/bronchiolar walls. In some cases, the lymphocytic infiltration can form concentric rows encasing capillaries and venules;
- Hyperplasia of BALT with well-formed follicular centers;
- Focal fibrosis and scarring with distortion of the peripheral lung architecture;
- Lymphoepithelial lesions;
- Eccentric sclerosis of vessels walls with narrowing of lumina. This is usually a sign of deposition of immune complexes in the vessel walls and should prompt the search for diseases associated with the production of autoantibodies, such as SjS and systemic sclerosis (SSc).

Autoimmune disease-related interstitial pneumonias

In autoimmune-induced ILD, many different factors come together: A wide variety of immune reactions can cause a wide variety of tissue reactions, for example, circulating autoantibodies either capable or devoid of complement activation, circulating immune complexes including large insoluble immune complexes formed by idiotypic–anti-idiotypic antibody networks, activation of coagulation, metabolism of proinflammatory substances, involvement of different types of leukocytes, and not the least, drugs given for the relieve of symptoms. These drugs themselves can cause toxic or inflammatory side effects.

Each of the different diseases will induce a different reaction pattern, and this pattern will be modified during the course of the disease. Therefore, we cannot expect a single reaction or pattern, but a complex picture composed

of new and old lesions, resolving lesions, and acute exacerbations of the disease. It will always be of help to know the mechanisms and underlying pathogenesis of each disease to interpret the histological picture in its presented form.

Since we have already extensively discussed the different IP, we will focus now on the modifications induced by the autoimmune diseases.

Rheumatoid lung disease

IP in rheumatoid arthritis (rhA) is not uncommon; however, it is often complicated by additional drug reactions, which can look like rhA-induced pneumonia. Most often, NSIP is associated with this disease [34, 53], but these reported studies have in common a selection bias: they looked up the incidence of rhA in cases presenting with NSIP. The diversity of reaction patterns is much better reflected in studies looking up patients with rhA and lung involvement [54]. UIP was more common in this study. In our own experience (Stacher et al., submitted), most often, a mixture of reaction patterns occurred, such as UIP combined with dense lymphocytic infiltrates or LIP and UIP combined with OP or NSIP. If features of DAD occur, one should discuss drug reactions with the clinicians because many immunosuppressive drugs given in rhA and other CVD can cause DAD [45, 46, 55, 56]. Not uncommonly, granulomas are present too. These are most often foreign body-type granulomas with giant cells, sometimes classical rheumatoid granulomas with palisading histiocytes, and rarely epithelioid cell granulomas [55]. In classical rheumatoid granulomas, it is essential to exclude infectious organisms, since patients receiving immunosuppressive drugs like methotrexate and leflunomide are prone to acquire infections [56–58] (Figs. 12 and 13). This is even more important with the new “biologicals.”

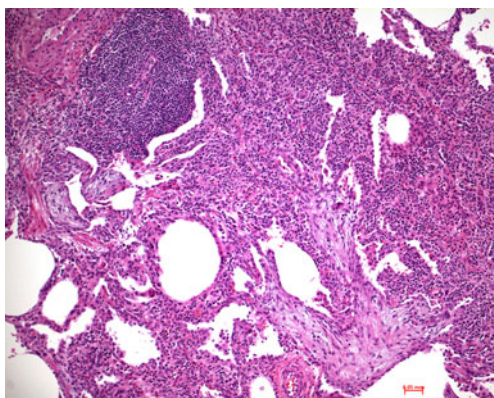


Fig. 12 rhA with a combination of IP patterns: UIP and LIP in this case. Note the fibroblastic foci; in contrast to IPF, the lymphocytic infiltration is mixed with the myofibroblast proliferation. H&E; bar, 0.05 mm

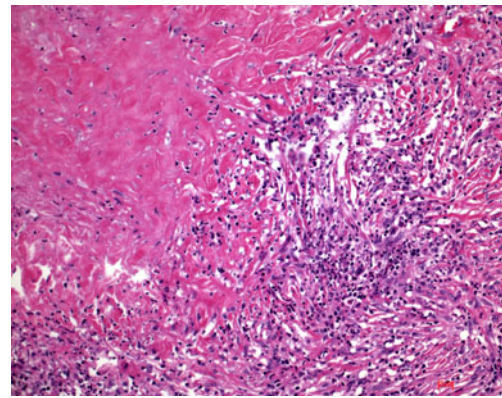


Fig. 13 rhA with lung involvement; here formation of a histiocytic granuloma, similar what is found in affected joints; polarized light helps to highlight remnants of collagen fibers within the necrotic center. H&E; bar, 20 μ m

The etiology of rhA is still an enigma. Genetic variants for several immune regulators such as Toll receptors and interleukins may form the basis for the susceptibility to adversely react against antigens and immune complexes trapped in cartilages and by that induce an inflammatory reaction, resulting in cartilage damage [59, 60]. Regulatory T cells either deficient or functionally impaired might also play an important role in rhA. In addition to the genetic basis for the disease, the autoimmune reaction might be triggered by streptococcal infections, and in that respect, probably mimicry of proteins of the organism might come into play.

Systemic lupus erythematosus

In acute lupus manifestation, which is more often autopsied and rarely seen as surgical material, hemorrhagic pneumonia, infarcts, or DAD or all mixed are found [61–63]. Most probably, the extent of any of these reactions depend on the extent of intravascular death of neutrophils attacked by lupus autoantibodies: low numbers of dying neutrophils might release less toxic enzymes and, therefore, cause focal endothelial cell death, interstitial edema, proteins leaking out into alveolar spaces, and finally, DAD with hyaline membrane formation. In case of massive neutrophilic cell death, there might be massive leakage of vessel walls and hemorrhage will occur. In later stages, DAD will be organized, so OP is another feature found in systemic lupus. Since the disease affects the coagulation cascade, lung infarction is a common feature of SLE. I personally have seen, in addition, perivascular amyloidosis in a classical active SLE case. The occurrence of pulmonary hypertension is less well understood [64, 65].

The etiology of SLE is also not well understood. Autoantibodies directed against granulocytic enzymes have been shown to be secondary effects and not the cause of SLE. In a

recent study in familial forms of SLE, a null mutation in the DNASE1L3 gene has been found. This finding confirms the critical role of impaired clearance of degraded DNA in SLE as a probable cause [66], a finding also seen in adult SLE [67]. However, given the wide range of autoantibodies found in SLE, there might be much more autoimmune mechanisms involved than anticipated [68, 69].

Systemic sclerosis

SSc usually presents with a mixture of tissue reactions, dependent on the immune phenomena present at the time of biopsy. Most often, a UIP or NSIP pattern is found, accompanied by lymphocytic infiltration of LIP type and a hyperplasia of BALT (Suppl. Fig. 31). Germinal centers are less common compared to Sjögren's syndrome. Ill-formed granulomas composed of histiocytic and/or epithelioid cells can be seen (Fig. 14). The distribution pattern of the IP is irregular, involving peripheral as well as midzone areas of the lung. This is clinically helpful in separating it from UIP/IPF. Another feature helpful in the diagnosis is a vasculopathy. Medium- and small-sized arteries show a thickening of the intima and media. Within the thickened vessel wall, there is a myxoid change of the matrix. A few lymphocytes can be seen, however, no endothelial necrosis or any other sign of vasculitis. These changes can possibly be best interpreted as a consequence of immune complex deposition (Fig. 15). Functionally, these vascular changes will cause pulmonary hypertension, which is common in SSc [70, 71].

Genetic studies provided some new insights into SSc. Interleukins, especially IL-8, has an impact on lung fibrosis in SSc patients [72]. Also, transforming growth factor-beta (TGF- β) and connective tissue growth factor (CTGF) received attention as essential factors in the pathogenesis of SSc. CTGF mRNA expression was observed in the fibrotic lesions, serum CTGF concentrations were significantly elevated, and correlated with skin sclerosis and lung fibrosis. In an animal model, TGF- β

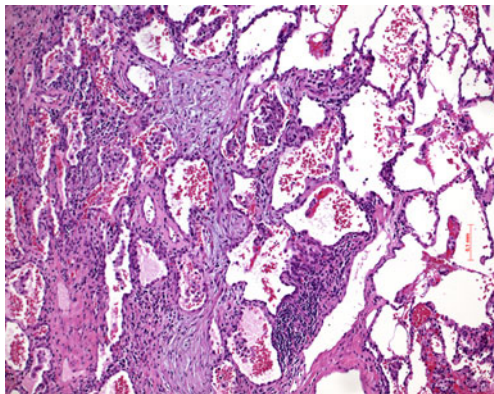


Fig. 14 Mixed UIP and NSIP pattern in a case of SSc. H&E; bar, 0.1 mm

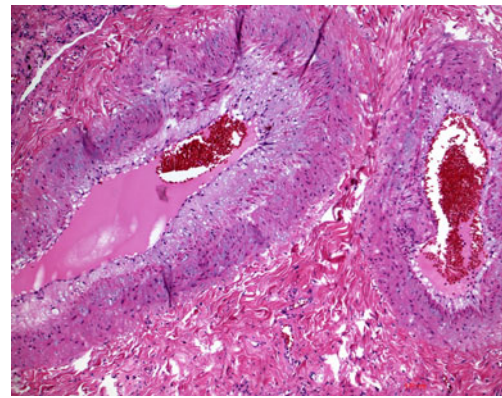


Fig. 15 Vasculopathy in SSc; note the eccentric thickening of the arterial wall and pseudomyxoid changes. H&E; magnification, $\times 100$

induced subcutaneous fibrosis and subsequent CTGF application caused persistent fibrosis. Based on these data, the authors of this study hypothesized that TGF- β induces fibrosis in the early stage, whereas CTGF acts to maintain tissue fibrosis [73]. In another study, fibrillin has been investigated. It has been demonstrated that caveolin-1 and fibrillin-1 influence storage and regulation of TGF- β and other cytokines and fibrillin-1 mutations might be responsible for a congenital form of scleroderma called stiff skin syndrome [74, 75]. In addition to tissue-resident fibroblasts, bone marrow-derived fibroblasts and endothelial and epithelial cells undergoing EMT are also under the control of fibrillin. Gain-of-function and loss-of-function abnormalities of these mediators may account for the characteristic activated phenotype of SSc fibroblasts [75]. The impaired expression of the nuclear orphan receptor PPAR- γ in SSc seems to play an important role in causing uncontrolled progression of fibrosis through impaired control of fibroblast activation and differentiation [76].

Dermatomyositis/polyserositis

Dermatomyositis rarely affects the lung. If lung involvement is present, various forms and combinations of pneumonias can occur. UIP and NSIP are the most common alterations; however, histiocytic and ill-formed epithelioid cell granulomas can be encountered in some cases in my personal experience. Lymphocytic infiltrates are quite common, most often exceeding what is seen in NSIP and better matched by LIP. Vasculopathy is rare. The serosa is usually involved too; however, this is also common in other CVD. Polyserositis in contrast to the other CVD cannot be diagnosed on tissues, since these serosal infiltrations are unspecific and occur in a multitude of diseases.

Sjögren's disease

SjS is another multisystemic collagen vascular or autoimmune disease. It affects predominantly the mucosa of salivary and

lacrimal glands, but can also similarly affect the lung. The main finding is an aggressive lymphocytic infiltration into the epithelial lining of bronchi and bronchioles and a diffuse infiltration of the alveolar walls (LIP). In the bronchi/bronchioles, lymphoepithelial lesions occur, similar to what is seen in marginal zone lymphomas. The epithelial layer is disrupted, which later on is repaired and can present as OP (Fig. 10). The lymphocytic infiltration is polyclonal and composed of T and B lymphocytes. Lymphollicles are well formed and will show activated germinal centers. Other types of IP can be associated to LIP, even UIP can occur, usually in the form of UIP–LIP mixed pattern.

As in SSc, interleukins play an important role in SjS too. IL-12 overexpressing transgenic mice developed bronchial and alveolar abnormalities such as lymphocytic infiltrates around the bronchi, cell proliferation in the alveolar septa, and increased interstitial and alveolar macrophages, strikingly similar to those found in the lungs of Sjögren's patients. There were also fourfold higher numbers of natural killer cells. A new mouse model highlights the role of IL-12 in the initiation of Sjögren's syndrome [77]. Rangel-Moreno studied the hyperplasia of BALT in patients with pulmonary involvement in rHA and Sjögren's syndrome. Increased expression of CXCL13 and CCL21, as well as B cell-activating factor of the TNF family (BAFF), ICOS ligand, and lymphotoxin, correlated with BALT hyperplasia. The presence of BALT hyperplasia correlated also with tissue damage in the lungs of these patients [78]. In a recent investigation, genes related to one of the major symptoms of Sjögren's syndrome have been identified, namely, the immunological attack of salivary and lacrimal glands resulting in the loss of acinar cell tissue and function, leading to stomatitis sicca and keratoconjunctivitis sicca. One gene lying on chromosome 1 (autoimmune exocrinopathy 2 [Aec2]) and the second on chromosome 3 (autoimmune exocrinopathy 1 [Aec1]) have been shown to be necessary and sufficient to replicate SjS-like disease in C57BL/6 mice. Aec2 lies distal to the centromere. This chromosomal region contains several sets of genes known to correlate with various immunopathological features of SjS. One gene in particular, tumor necrosis factor (ligand) superfamily member 4 (or Ox40 ligand), encoding a product whose biological functions correlate with both physiological homeostasis and immune regulations, could be a potential candidate SjS susceptibility gene [79]. Although many open questions remain, this mouse model opens the way to better understand this autoimmune disease and also will serve to study the mechanisms, which are responsible for the common development into MALT lymphomas.

Mixed collagen vascular diseases

Mixed CVD cannot be diagnosed with certainty. The combination of features of two different CVD makes it almost impossible to come up with an etiologic suggestion or

proposal. Depending on the features of the single CVD, morphologic mixtures can be found. For example, mixed Sjögren–lupus CVD can either have dominant features of SjS or systemic lupus [80]. However, general features suggestive of CVD are usually present: a combination of different features of IP with lymphocytic infiltrations, hemorrhage, etc.

So when to think about lung affected by autoimmune diseases?

- Any combination of IP;
- Any kind of IP with a high proportion of lymphocytes;
- Any combination of an IP with other inflammatory reactions not fitting within IPs, such as a combination of UIP/NSIP or LIP with epithelioid or histiocytic granulomas;
- Any kind of IP with unusual vasculopathy (not sclerosis!) and/or alveolar hemorrhage.

Goodpasture's syndrome

Goodpasture's syndrome is an autoimmune disease not related to CVD. The cause has been identified recently: By mimicry against bacterial proteins, cross-reacting autoantibodies are formed, which bind to the α -3 chain of collagen IV causing disruption and hemorrhage by complement activation (most often the alternate pathway) [81, 82]. There are still unexplained features such as why collagen IV in glomerular, alveolar, and alveolar capillary basement membranes is attacked, but not those in other organs. The major finding is alveolar hemorrhage without infiltrating leukocytes. Later on, macrophages with hemosiderin can be seen within alveoli and septa (Fig. 16). Depending on the duration of the disease, the final result is septal fibrosis [83].

Other autoimmune diseases affecting the lung

IP can be encountered in Behcet disease and Kikuchi disease, whereas in Whipple's disease, granulomatous

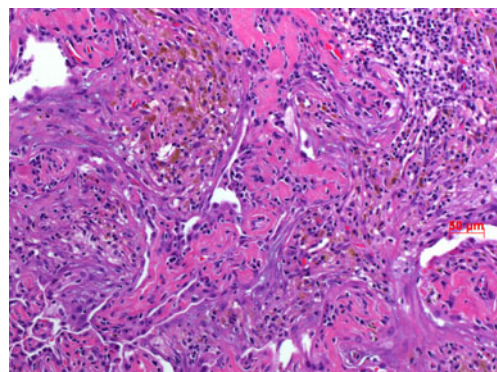


Fig. 16 Older lesion in a case of Goodpasture's disease showing hemosiderin-laden macrophages and recent hemorrhage. In addition, lymphocytic and histiocytic inflammatory infiltrates are seen. H&E; bar, 50 μ m

pneumonia with histiocytes and macrophages is the prominent feature, similar to what is seen in the small bowel [84].

IgG4-related sclerosis is an autoimmune disease involving many organs such as the pancreas, mediastinum, and retroperitoneal space. Hypergammaglobulinemia and deposition of IgG4 is seen in affected tissues. In the lung, the disease usually presents with extensive lymphoplasmocytic infiltration (Suppl. Fig. 32), very often simulating inflammatory pseudotumor (plasmocytic variant); however, in this disease, increased numbers of IgG4-positive plasma cells are found (≥ 25 % of IgG-positive cells), not seen in inflammatory pseudotumor (myofibroblastic tumor) [85]. This inflammation typically results in sclerosis of the lung tissue [86].

Phospholipid autoantibody-mediated lung disease is another rare disease not only affecting the lung but also other organs [87]. In the affected lung, the major finding is alveolar hemorrhage or hemorrhagic pneumonia and DAD (Suppl. Fig. 33), followed by an OP in a later stage. The cause is unknown, and the morphologic findings are not specific. The disease needs the proof of phospholipid autoantibodies in the serum.

Airway-centered interstitial fibrosis

Airway-centered interstitial fibrosis (ACIF) is a new, recently described ILD mainly affecting patients with a history of environmental exposure to toxic or allergic substances. Also, cocaine abuse was found in one [88]. The morphology is characterized by fibrosis along the small bronchi extending into the peripheral lung following a lobular distribution. In some cases, fibroblastic foci can occur, however, always associated with this distribution pattern. Cystic lung remodeling is absent; instead, a whole lobule or subsegment is destroyed by fibrosis. Metaplastic epithelium is common in the affected lobules and also hyperplasia of smooth muscle cells (muscular cirrhosis; Fig. 17). The disease rapidly

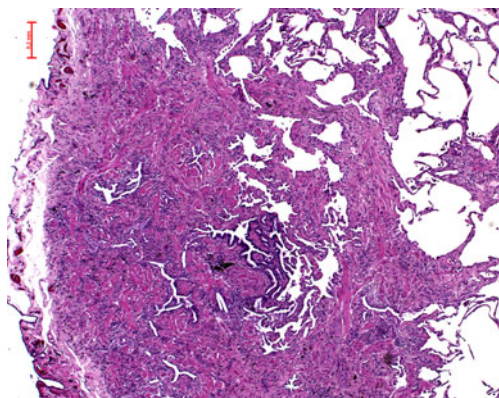


Fig. 17 Typical distribution pattern of fibrosis and muscular cirrhosis in a case of ACIF. The involvement is strictly confined to a lobular structure and follows the bronchial tree from the larger bronchus to the small bronchioles. H&E; bar, 0.2 mm

progresses, and in the reported series, almost half of the patients died of disease. Corticosteroid treatment was effective in some patients.

Smoking-induced interstitial lung diseases

Here, we will focus on several diseases with quite different morphological features, but all of them related to cigarette smoke exposure, most often in young-aged heavy smokers. Combinations of these diseases are currently more often seen, probably due to the increased use of HRCT followed by lung biopsy because of the wide variety of differential diagnosis, even including malignant disease.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LHCH, histiocytosis X, eosinophilic granuloma) is caused by excessive inhalation of tobacco smoke. It occurs predominantly in young-aged people. It has been postulated that tobacco plant antigens still present within tobacco smoke (incomplete combustion) might cause this accumulation and proliferation of Langerhans cells, which are part of the antigen-presenting reticulum cell population [89–91]. So the continuous exposure of Langerhans cells to plant proteins in susceptible persons might cause proliferation of these cells to keep with the increasing amount of antigens. Langerhans cells proliferate within bronchial mucosa as well as in the peripheral lung. In bronchi, this proliferation causes necrosis of the mucosa, occlusion of the lumen, and finally, scar tissue [92] (Fig. 18; Suppl. Fig. 34). Langerhans cell proliferation is accompanied by an infiltration of eosinophils, hence the old name eosinophilic granuloma. These eosinophils are attracted by cytokines such as interleukin 4 secreted by the Langerhans cells [93]. Eosinophilic granulocytes might also act

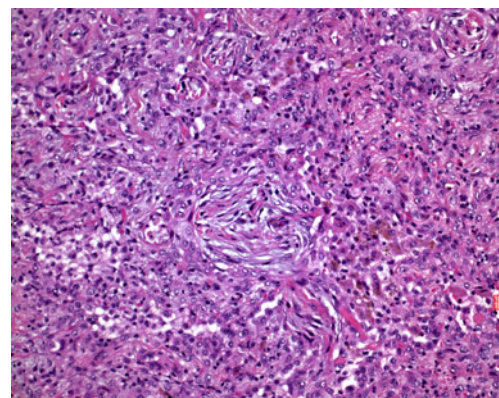


Fig. 18 LHCH; note the complete destruction of the bronchial wall (center) by the proliferation of Langerhans cells and infiltrating eosinophils. Remnants of smooth muscle cells can be seen. The pulmonary artery is nearby. H&E; bar, 50 μ m

cytotoxic in cooperation with Langerhans cells releasing eosinophilic basic proteins and destroy the epithelium. The granulomas undergo regression especially in patients with smoking cessation. The resulting scar has a star-like appearance and is surrounded by bronchiolectasis and emphysema blebs. On CT scan, this results in a characteristic picture (starry sky). An underlying genetic abnormality has recently been identified [94–96]. Mutations in the BRAF oncogene has resulted that LHCH is now regarded as a tumor. However, several issues remain to be solved before this view can be accepted: Lung cases are most often induced by smoking and, in many patients, will undergo regression in case of smoking cessation, which is unlikely in a tumor [91]. BRAF mutations were not found in all cases. On the other hand, there exists a tumorous form, characterized by a multiorgan involvement, seen in children and young adults and not related to smoking. So probably, we might be confronted with two different diseases. So far, the reactive form cannot be discerned from the tumor form other than by involvement of at least two organ systems [97, 98]. Further investigations hopefully will increase our knowledge about this disease. In the differential diagnosis, LHCH has to be separated from other histiocytosis or reticulum cell proliferations by their positive staining for CD1a and langerin [99, 100], whereas the positivity for S100 protein is not specific.

Respiratory bronchiolitis–interstitial lung disease

RBILD is a common disease in heavy smokers. RB can be seen in many cigarette smokers with lung carcinoma, if the lung tissue adjacent to the tumor is sampled and investigated. RB can also be seen combined with LHCH [101]. An accumulation of alveolar macrophages within the respiratory bronchioles and the adjacent centrilobular region of the lung lobules characterize RBILD. The macrophages usually contain dirty brownish-yellow fine granular pigment (Fig. 19). Ultrastructurally, this pigment represents phagolysosomes filled with tobacco waste

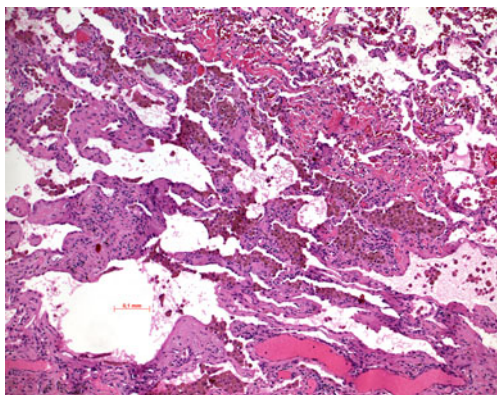


Fig. 19 RBILD; recognize the accumulation of pigmented smokers macrophages in the bronchioles and the adjacent centrilobular region. H&E; bar, 0.1 mm

[102–104]. Functionally, this macrophage accumulation obstructs the terminal bronchioles and impairs airflow, resulting in distension of alveoli and eventually rupture of septa. Some authors use the diagnosis of RB only in those cases, where no other pathology is present, others this author included follow the morphology and accept RB diagnosis also in heavy smokers with lung carcinoma in whom RB is also present. The argument is that RB is a disease of smokers, and there is no good argument why smokers are not allowed to have more than one disease, e.g., RB, carcinoma, LHCH. However, this results in different statistical figures: If RB diagnosis is only accepted presenting as a singular disease, it is rare; if diagnosed by its morphological features regardless of other smoking induced diseases, it is a common disease, present in many patients with lung cancer. RB and RBILD in my opinion are subsequent stages of the same disease. In the early stages, accumulation of alveolar macrophages is concentrated within bronchioles. If tobacco smoke exposure goes on, more and more areas of the centroacinar region of alveoli are occupied by these cells, resulting in radiological ground glass opacities, now clinically called RBILD.

Desquamative interstitial pneumonia

The term DIP was created by Liebow in 1965 [105], long before immunohistochemistry was invented. Liebow misinterpreted the cells accumulating within the alveoli as pneumocytes type II, therefore the term desquamative. By immunohistochemistry, these cells were identified as macrophages [92, 106, 107]. Therefore, the name macrophagocytic pneumonia would have been more appropriate. By definition, DIP is characterized by an accumulation of pigmented smoker macrophages within alveoli, completely obscuring the peripheral airspaces. No infiltration of bronchioles is present (Suppl. Fig. 35). Fibrosis of alveolar septa, if present, is mild. DIP can radiologically simulate a tumor with ground glass opacity, not uncommonly misdiagnosed as adenocarcinoma in situ [101].

Smoking-induced interstitial fibrosis/respiratory bronchiolitis-associated interstitial lung disease

Smoking-induced interstitial fibrosis (SRIF) and RB-associated ILD might represent the same diseases characterized by RB and a paucicellular eosinophilic collagenous thickening of alveolar septa with a subpleural distribution [108, 109]. In some areas, the disease resembles fibrotic NSIP, but the typical association with tobacco smoking points to this underlying etiology. In looking up several cases of RB, we also recognized similar reactions as described by S. Yousem and A.L. Katzenstein, but in addition, also cases showing fibroblastic foci associated with emphysema blebs and fibrosis (Fig. 20). In these cases, also RB could be seen in different areas. In contrast to UIP, there were no honeycomb lesions and

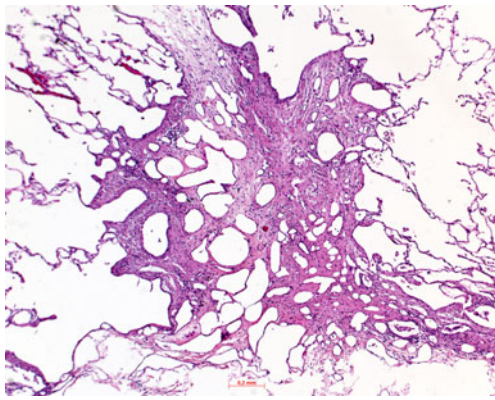


Fig. 20 SRIF and RB in a patient with clinical severe COPD; here, an area with emphysema and fibroblastic focus is shown. H&E; bar, 0.2 mm

almost all lobules showed changes of centrilobular emphysema. Some of these patients were clinically diagnosed as having chronic obstructive pulmonary disease (COPD); in others, the lesions were found incidentally because of pneumothorax. So this might represent another form of smoking-induced lung fibrosis, probably resulting from the release of toxic enzymes from macrophages and subsequent alveolar septa destruction and repair.

Interstitial pneumonias with a wide variety of causes—from infection to toxic inhalation

Acute interstitial pneumonia/diffuse alveolar damage

Many different agents can cause AIP/DAD. Classical ones are viral infections, but toxic inhalation, drug reactions, and all variants of shock reactions will also present with this morphologic picture. The features have been described above, so we need to focus only on specific changes pointing to a specific etiology. In viral infection, the most characteristic feature is the viral inclusion body, which can present either as nice large inclusion bodies (cytomegalovirus [CMV], respiratory syncytial virus [RSV]) or by red-violet-stained nucleic acids forming ill-defined speckles in nuclei and/or cytoplasm (adenovirus) [27]. Typically, the infected cell shows enlargement, an atypical large bizarre nucleus, and an accentuated nuclear membrane due to increased nucleic acid traffic induced by the virus. These cellular features can last for several months. In contrast to preneoplastic lesions in viral infection, the atypical cells are single cells being grouped together with otherwise normal-looking pneumocytes.

Giant cell interstitial pneumonia (see also under pneumoconiosis)

GIP has a quite narrow etiologic spectrum either being caused by hard metal dust or by viral infection. The

former will be discussed later. Several viruses can cause GIP, the classical one being measles virus. However, in contrast to pneumoconiosis in infections, the giant cells are mixed epithelial as well as macrophagocytic. The epithelial giant cells (Hecht cells) are transformed pneumocytes type II in whom nuclear division was not followed by cell division, giving rise to multinucleation [110]. The additional features are identical to DAD as described above. Especially within the epithelial cells, viral inclusion bodies can be found (Suppl. Fig. 36). Besides measles, RSV can also present, with this picture predominantly in children [111].

Organizing pneumonia

We have already described OP under the idiopathic ILDs, so we have only to focus on other causes of OP. OP can have a great variety of causes. In many cases, this is a post-infectious organization of a purulent bacterial bronchopneumonia, when for several reasons the exudate could not be completely degraded and, therefore, has to be organized by granulation tissue. Also, in viral infections, organizing DAD is morphologically identical to OP, as discussed previously. In other cases, OP is a form of organization of an autoimmune disease, usually in the inactive phase. The resolution phase of toxic inhalation is usually in the form of OP, and drug-induced lung toxicity is also often organized the same way (Suppl. Fig. 29).

Genetically and developmentally related interstitial lung diseases

Chronic pneumonia of infancy

Originally, surfactant-related IP with alveolar proteinosis were included into chronic pneumonia of infancy (CPI); however, since the different causes of alveolar proteinosis were discovered, it has been excluded. Therefore, CPI has been reduced to those pediatric interstitial diseases with unknown cause. It is now quite rare. CPI is characterized by an infiltration of lymphocytes and macrophages/histiocytes in the alveolar septa, accumulation of debris within the alveoli, and hyperplasia of type II pneumocytes (Suppl. Fig. 37), all causing thickening of the septa and impaired gas exchange. CPI predominantly occurs in newborn or small children [112, 113]. In many instances, a careful investigation of the biopsies might uncover underlying infectious diseases, such as Wilson–Mikity syndrome and infections caused by respirotropic viruses, Chlamydiae, or uroplasm [114]; another cause might be gastroesophageal reflux [115]. In rare instances, a metabolic disease,

interstitial glycogenesis, might be the cause of CPI [116, 117]. However, it should be taken into account that, although the clinical symptoms in affected children are severe, the density of the inflammatory cells is much less compared to pneumonias in adults.

Surfactant-related interstitial pneumonias—alveolar proteinosis

Alveolar proteinosis occurs in two forms, either as a genetically inherited disease or as an acquired disease of adults [118–122]. It is characterized by an accumulation of surfactant lipids and proteins within the alveoli, in severe cases completely obstructing the peripheral parenchyma and causing severe dyspnea. Morphologically, there is eosinophilic material within the alveoli sometimes mixed with debris and, in some cases, accompanied by an inflammatory infiltration of the alveolar walls.

In the inherited form, the underlying genetic defect is either a mutation in the surfactant apoprotein genes B or C or a mutation in the transporter protein gene ABCA3 [123, 124]. This results in the production of immature surfactant or an accumulation of surfactant within giant lamellar bodies. This material is secreted but does not function as mature surfactant. The result is alveolar collapse, followed by apoptosis of pneumocytes, infiltration of inflammatory cells (lymphocytes, macrophages), and sometimes also formation of hyaline membranes or fibrin cloths within alveoli. The histological picture simulates but never completely imitates IRDS (Suppl. Fig. 38).

In the acquired form (predominantly adults), different defects of the degradation cascade of surfactant do occur. The most common is a deficiency of granulocyte macrophage colony-stimulating factor (GM-CSF) caused by autoantibodies against this protein [118, 120, 121, 125]. GM-CSF is necessary for the uptake and subsequent degradation of surfactant by alveolar macrophages. The hallmark is an accumulation of surfactant material within alveoli. There is usually no inflammatory infiltrate present (Fig. 21a). The diagnosis can be even easily made by bronchoalveolar lavage (BAL): the recovered fluid looks milky. In later stages, the disease can get chronic. In addition to the accumulation of surfactant lipids and proteins, there is a diffuse interstitial fibrosis, which can cause death of the patient (Fig. 21b). Sometimes, alveolar proteinosis can be induced by tuberculosis, acute silicosis, and other diseases; the mechanisms in these are still unclear.

Although some authors prefer to include idiopathic neuroendocrine hyperplasia of infancy (INHI) into pediatric ILD, I do not follow this line because INHI does not present with diffuse interstitial infiltrations but rather with an increase of neuroendocrine cells within bronchi and

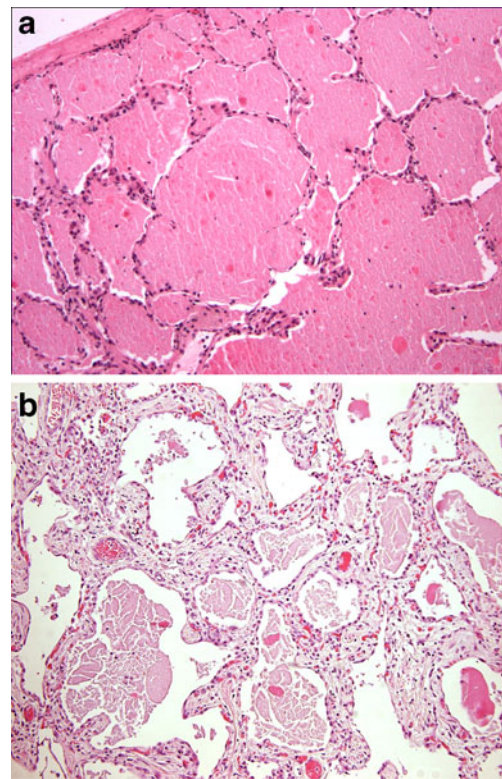


Fig. 21 Alveolar lipoproteinosis in an adult (a) with proven autoantibodies for GMCSF and in a 19-year-old male patient (b) with severe fibrosis of alveolar septa; he died after many recurrences of alveolar lipoproteinosis. H&E; magnification, $\times 100$

bronchioles and less pronounced neuroendocrine bodies in the periphery [126].

Idiopathic pulmonary hemosiderosis

Idiopathic pulmonary hemosiderosis is an interstitial disease usually found in children, but also young adults. The characteristic clinical feature is recurrent alveolar hemorrhage and morphologically diffuse lymphocytic and histiocytic/macrophage infiltrations in both lungs. The etiology is largely unknown. Many patients develop iron deficiency anemia due to recurrent bleeding. There is usually a high mortality rate. A degradation of elastic fibers followed by an incrustation by iron-containing proteins (Prussian blue-positive) can be seen on histologic examination and is a diagnostic feature. Usually, foreign body giant cells are found in the areas of ongoing destruction of the elastic fibers ingesting the fibers together with the iron coat [127] (Suppl. Fig. 39). In later stages, interstitial fibrosis results. Vasculitis, granulomatous inflammation, or immunoglobulin deposits are absent. Corticosteroids alone or in combination with other immunosuppressive agents may be effective for either exacerbations or maintenance therapy of idiopathic pulmonary hemosiderosis [128].

Lymphangioliomyomatosis

Lymphangioliomyomatosis (LAM) is an inherited disease, based on the dysfunction of TSC genes. TSC1 coding for hamartin and TSC2 coding for tuberin are both required for controlling the expression and regulation of mTOR and the mTOR complexes TORC1/2. Both proteins form a complex, which activates cAMP kinase, which subsequently inactivates mTOR. In LAM, TSC2 is more often mutated than TSC1 [129–132]. Tuberin is thus not functional and does not form heterodimers with hamartin, and TORC1/2 is constantly activated. TSC mutation can be a germline mutation as in tuberous sclerosis syndrome or mutated somatically, called by some authors as “form fruste” [133]. The second allele is most often mutated somatically. The type of mutation also dictates the extent of syndromes and tumors associated with this mutation. Patients carrying the germline mutation present with genetic instability causing several somatic mutations and, therefore, in addition to LAM, can present with different other benign tumors. Previously, lung transplantation was one of the few choices of treatment; since the discovery of the function of both TSC proteins, a clinical trial with anti-mTOR therapy has been started and seems to be effective [134–136]. Interestingly, in rare cases, with lung transplantation, a recurrence of the disease occurred from circulating LAM cells, repopulating the transplanted lungs [137–141].

LAM is characterized by a proliferation of immature myoblasts in the periphery of the lung and in lymph nodes. In addition, perivascular epithelioid cells (PEC) also proliferate (probably derived from pericytic stem cells). The proportion of myoblasts and PEC can vary considerably: In some cases of LAM, PEC are numerous, in other cases scarce. The cells together form microscopic nodules in the bronchiolar mucosa, along lymphatics and arteries, and in alveolar septa, causing lymphatic obstruction and rupture (chylothorax) and also bronchial obstruction and cystic lung destruction. These myoblasts show immature myofilaments, are not ordered in parallel as normal smooth muscle cells, and also have a more epithelioid appearance. Nuclei are round and larger than in regular smooth muscle cells. Most importantly, these cells proliferate in locations where no muscle cell proliferation occurs (Suppl. Fig. 40). By immunohistochemistry, the myoblasts express smooth muscle actin, and a few also desmin, whereas the PEC express HMB45 [133, 142].

Hermansky–Pudlak syndrome

Hermansky–Pudlak syndrome is an autosomal recessive disease, which results in the inability of several cells to form intracellular vesicles. This can affect the ability to

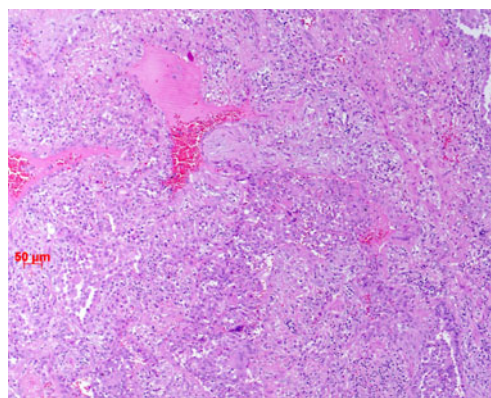


Fig. 22 Hermansky–Pudlak syndrome in a child. Note the accumulation of foamy macrophage giant cells within alveoli, proliferation of pneumocytes type II, many fibroblastic foci, and severe fibrosis. H&E; bar, 50 μ m

form melanosomes (resulting in albinism), platelet granules (inducing bleeding diathesis), and also phagolysosomes in macrophages and lamellar bodies in type II pneumocytes [143]. To date, seven forms are known, but only two of them (types I and IV) constantly affect the lung, causing phagocytosis defects with accumulation of macrophages, lamellar body defects in type II pneumocytes with disturbed surfactant release and macrophage foam cell changes, inflammation, and finally, lung fibrosis [144–147]. The characteristic morphologic changes are hyperplasia of pneumocytes type II, giant lamellar bodies (large PAS-positive cytoplasmic granules), accumulation of foamy macrophages within the alveoli, lymphocytic interstitial infiltration and lung fibrosis, sometimes as OP with intra-alveolar granulation tissue, and also as interstitial fibrosis with myofibroblastic foci, identical to those in UIP (Fig. 22; Suppl. Fig. 41). Even both types of fibrosis OP and UIP can be present concomitantly in one patient. In contrast to UIP/IPF, honeycomb lesions are scarce, and usually, the lung is diffusely involved, leaving not much uninvolved tissue in between (no timely heterogeneity). In contrast to UIP/IPF, the involvement of the lung is not symmetric, fibrosis can occur peripherally as well as centrally, and is always patchy. Ultrastructurally, there are no well-formed lamellar bodies within pneumocytes type II. Within macrophages, lysosomes are enlarged and irregularly contoured, while phagolysosomes are absent (no fusion of lysosomes with phagosomes).

Erdheim–Chester disease

Erdheim–Chester disease is a rare systemic histiocytosis (non-Langerhans dendritic cells) that may present with pulmonary symptoms. The condition seems to be nonfamilial and

typically affects middle-aged adults. Radiographic and pathologic changes in the long bones are diagnostic, but may mimic multisystemic LHCH [148, 149]. Patients often present with extraskeletal manifestations. Advanced pulmonary lesions are associated with extensive fibrosis that may lead to cardiorespiratory failure [150]. In rare instances, there are diffuse dense infiltrations by histiocytes accompanied by lymphocytes and plasma cells. These histiocytes are negative for Langerhans cell markers (CD1a, langerin) and markers for follicular and interdigitating dendritic cells (CD35, CD83), but can be positive for S100 protein (much less intensive staining compare to interdigitating dendritic cells) and are usually positive for CD68, CD163, and lysozyme (Suppl. Fig. 42). Mutation within the BRAF gene has been found in few cases (personal communication). Histiocytes can express PDGFR α and PDGFR β , which might be used as therapeutic targets.

Diffuse panbronchiolitis

Diffuse panbronchiolitis (DPB) was first described in patients from Southeast Asia. It is characterized by an accumulation of macrophages within bronchioles and a lymphocytic infiltration within the bronchiolar walls. Hyperplasia of BALT does occur and follicle centers might be present, usually related to recurrent infections [151]. In contrast to LIP, the infiltration is always concentrated along bronchi and bronchioles. DPB might be difficult to separate from other forms of bronchiolitis. However, there are some features which are of help: In DPB, the obstructive lesions are confined to the respiratory bronchioli; chronic parasinusitis is common; follicular bronchiolitis is a common finding [152] (Fig. 23). The cause is a phenotypic variation in the HLA system involving HLA-B54, HLA-A11, and HLA-DRB5*010/020 [153], which leads to susceptibility to otherwise nonpathogenic bacterial infection in immunocompetent children. Children with this HLA type need to be treated with erythromycin every time a respiratory tract infection occurs. In nontreated children, the disease will cause secondary

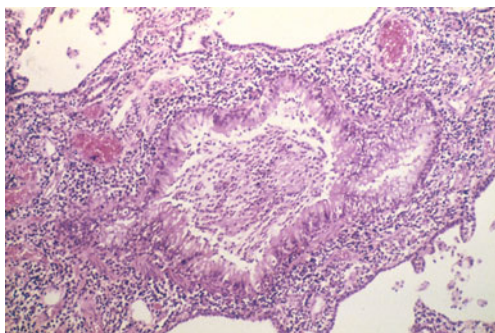


Fig. 23 DPB in a 5-year-old child. The characteristic features are a follicular bronchiolitis and BALT hyperplasia. H&E; magnification, $\times 150$

destruction of the peripheral lung with cyst formation and fibrosis. Initially, DPB was mainly identified in children of Asian descent; however, this disease has also been diagnosed in Caucasians [154]. But it should be mentioned that the diagnosis should be confirmed by morphologic analysis because of similarity with other forms of bronchiolitis, seen by HRCT [103, 155].

Metabolic-induced interstitial lung disease

Amyloidosis

Amyloidosis is a metabolic disease characterized by the deposition of amyloid in lung tissues. Amyloidosis is presently regarded as a protein misfolding disease [156, 157]. Normally, four proteins are folded into a complex with the help of chaperones. Many different forms of amyloid proteins have been identified. Misfolding can occur in several different compositions of amyloid [158]. Most common are amyloid A and P; however, microglobulin 2β , transthyretin, and others can also be seen in pulmonary amyloidosis. The reason for amyloid deposition can be a tumor; one of the best-known examples is plasmocytoma. In this case, amyloid is formed out of immunoglobulins secreted by the tumor cells. Chronic inflammation such as CVD can also cause amyloid deposition [159, 160]. Amyloid deposition can occur as a tumor-like deposit, either along the bronchial tree or within the lung periphery (nodular form), or it can be diffuse perivascular and interstitial (Suppl. Fig. 43). Amyloid stains red by eosin stain, orange by the Congo red stain, or can be demonstrated by immunohistochemistry using specific antibodies for the different components [161]. If a Congo red stain is applied, the tissue section should be examined under polarized light, where the stain exhibits a green birefringence. Amyloid deposits very often will cause a tissue reaction with foreign body giant cells forming granulomas, and also calcification and metaplastic bone formation can occur. The major differential diagnosis to amyloidosis is IgG4-mediated fibrosis and hyalinosis; however, the dense lymphoplasmocytic infiltrations will lead to the correct diagnosis.

Disturbed calcium metabolism

We will not discuss tracheobronchopathia chondroosteoplastica because this is a localized process in the trachea and large bronchi. Although pulmonary ossification would also qualify to be included into metabolic diseases, it is usually a very focal disease and thus does not fit into diffuse interstitial diseases. However, diffuse metabolic calcification and microlithiasis are diffuse interstitial processes and fall herein.

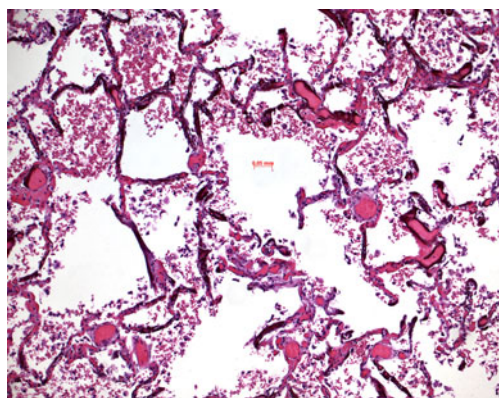


Fig. 24 Metastatic pulmonary calcification in a patient with secondary hyperparathyroidism (renal failure and hyperplasia of two parathyroid glands and clinical hypercalcemia). Note the sponge-like calcium deposits within the alveolar walls, almost outlining the septa. H&E; bar, 0.05 mm

Metabolic/metastatic pulmonary calcification

Diffuse calcification of alveolar septa can occur in patients with hyperparathyroidism and hypercalcemia [162–165]. Most often, the kidneys and the stomach, which functionally are also involved in ion exchange, can be affected. In the lungs, calcium deposits are seen along the alveolar septa, forming a network completely outlining the septa (Fig. 24). There is no inflammatory reaction towards the calcium deposits in contrast to microlithiasis. Treatment needs to be focused on the underlying disease; no specific treatment for the calcification does exist.

Microlithiasis

Microlithiasis is a diffuse lung disease characterized by a deposition of microliths in alveolar septa and lumina with a foreign body giant cell reaction (Fig. 25). The giant cells phagocytose the microliths. Large foreign body cell granulomas can be formed. The microliths usually show a center which can be calcified. The etiology was unknown until recently: first, familial cases were described [166], and finally, a candidate gene, SLC34A2, that encodes a type IIb sodium phosphate cotransporter was found to be mutated in all six patients being investigated. SLC34A2 is specifically expressed in type II pneumocytes, and the mutation abolishes the normal protein function [167, 168]. There exist no specific therapy; in severe cases, lung transplantation can be considered [169, 170]. Microlithiasis should be clearly separated from lung tissue with alveoliths, i.e.,

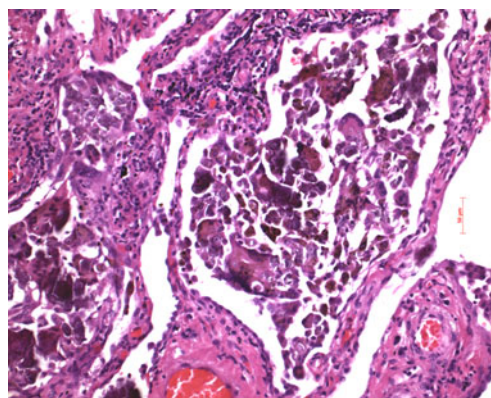


Fig. 25 Microlithiasis; note the lamellated bodies within alveoli and alveolar septa, accompanied by a macrophage reaction with many foreign body giant cells. H&E; bar, 50 μ m

concentric lamellae of proteins around a crystalline center, lying within alveolar lumina without any tissue reaction.

Eosinophilic pneumonias

Eosinophilic lung diseases all together are rare. LHCH has already been discussed. We will not discuss bronchial asthma, although it can present with severe eosinophilic infiltrations along the bronchi and bronchioles, but much less in the alveoli. We also exclude Churg–Strauss syndrome because it would require a discussion of systemic vasculitis. Allergic bronchopulmonary mycosis (formerly allergic bronchopulmonary aspergillosis) is not in our focus, since the majority of cases present as a specific form of bronchitis (mucoid impaction) and less frequently as bronchocentric granulomatosis. There are rare forms of allergic bronchopulmonary mycosis presenting as eosinophilic pneumonia, however, not showing any specific feature other than the forms discussed below.

Eosinophilia is most often induced by the release of interleukins 4 and 5 [171, 172]. It can vary quite remarkably in the different diseases, less pronounced in LHCH, whereas massive in eosinophilic pneumonias. By BAL, a tentative diagnosis can be made: eosinophil counts in BAL usually are between 5 and 20 % in LHCH, whereas in the eosinophilic pneumonias, it usually exceeds 30 %. In parasitic diseases, sometimes the parasites (larvae) might be seen in BAL.

Acute eosinophilic pneumonia

Acute eosinophilic pneumonia (AEP) is characterized by an acute onset with dyspnea and diffuse infiltrations by

eosinophils in both lungs. Blood eosinophilia can be present, especially in Loeffler's syndrome and in parasitic infections. On histology, the alveoli and the alveolar and bronchiolar walls are stuffed by eosinophils and macrophages. Etiologically, parasitic infection or hypersensitivity reaction for drugs is the cause; however, an idiopathic form also does exist. An infection by helminthes will usually cause mild symptoms, whereas in filarial infections (tropic eosinophilia), the symptoms can be severe (high fever, cough, wheezing, peripheral eosinophilia; Suppl. Fig. 44) [173, 174]. In very rare cases, an allergic reaction for fragments of fungi can present with AEP (allergic bronchopulmonary mycosis).

Many drugs can cause eosinophilia and pneumonia such as beclomethasone, bleomycin, carbamazepine, chlorpromazine, chlorpropamide, cromolyn, dilantin, gold salts, non-steroidal anti-inflammatory drugs, naproxen, nitrofurantoin, penicillin, phenothiazine, propylthiouracil, phenylbutazone, sulfonamide, tetracycline, and clarithromycin, so a proper investigation of treatment protocols is advised (more details are found on www.pneumotox.com).

Loeffler's syndrome is a self-limiting condition, resolving usually within 1 month. On CT scan, migratory pulmonary infiltrates can be seen, accompanied by a peripheral blood eosinophilia. In some cases, specific causes such as chronic eosinophilic leukemia can be identified; however, in other cases, no underlying etiology can be identified.

In acute idiopathic eosinophilic pneumonia, there is acute febrile illness usually of 1 week duration, with myalgia, chest pain, and hypoxemic respiratory failure. On CT scan, alveolar and interstitial infiltrates are seen; in BAL, eosinophils increase over 25 %, however, there is no blood eosinophilia. Patients rapidly respond to steroid therapy. No cause can be identified.

Chronic eosinophilic pneumonia

Chronic eosinophilic pneumonia is a serious disease that requires a specific treatment. Most often affected are middle-aged patients, sometimes also young atopic women (Suppl. Fig. 45). The disease starts with an insidious onset with progressive respiratory symptoms. A history of asthma is present in 50–60 % of cases. Some cases can be attributed to drug toxicity (ampicillin, bleomycin, nitrofurantoin, penicillin, streptomycin, tetracycline, and others); in others, hypersensitivity to fungi has been shown. Some cases represent chronic infection with parasites. Single cases have been described where chronic eosinophilic pneumonia was associated with cocaine or nickel carbonyl vapor inhalation. The characteristic histologic picture shows dense eosinophilic infiltrations accompanied by macrophages and lymphocytes. There

can be eosinophilic abscesses. Fibroblast proliferations can be seen focally, which finally results in interstitial fibrosis.

Hyper eosinophilic syndrome

Hyper eosinophilic syndrome is a rare disease of unknown cause [175]. It is characterized by increased eosinophilic infiltrations in multiple organs (mainly in the heart and central nervous system, rarely in the lungs). Fatal cases have been reported mainly caused by restrictive cardiomyopathy.

Environmentally induced diffuse interstitial lung diseases (excluding conventional pneumoconiosis)

Giant cell interstitial pneumonia

There are two forms of GIP, one caused by infection such as measles virus (see above), while the other form caused by inhalation of hard metal dust. Hard metal is an alloy composed of cobalt, chromium, tungsten, titanium, and a variety of other metals. In experiments, it has been shown that cobalt is the most toxic compound within this alloy, can easily dissolve out, and will subsequently induce giant cell formation of macrophages [176–178] (Fig. 26). Following the deposition of metal dust the disease starts with respiratory bronchiolitis; giant cells loaded with compound from this alloy are formed early on. The macrophage accumulation spreads further to the periphery, and finally macrophages and giant cells can be found in alveoli, septa, and peribronchiolar. Also DAD can be seen in some cases. The disease can present with acute illness, shortness of breath, and severe hypoxia. If the patient survives the acute onset, peribronchial/peribronchiolar fibrosis and fibrosis of alveolar septa results [178–180]. Large scars are usually absent.

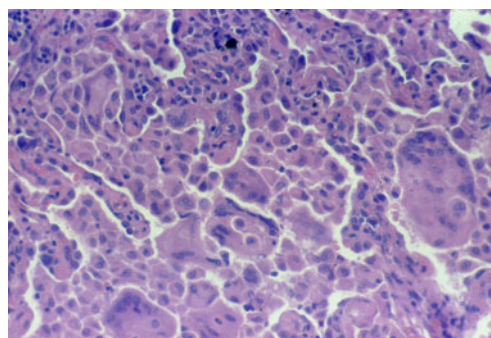


Fig. 26 GIP in hard metal disease. Note the accumulation of foreign body giant cells containing a dirty brown-black material, in this case identified as tungsten and titanium. Many other components of the hard metal (cobalt, nickel, and chromium) alloy can dissolve easily and are, therefore, dissolved by fixation and embedding procedures, so mainly tungsten and titanium compounds remain and can be detected by energy-dispersive X-ray spectroscopy. H&E; magnification, $\times 400$

Asbestosis

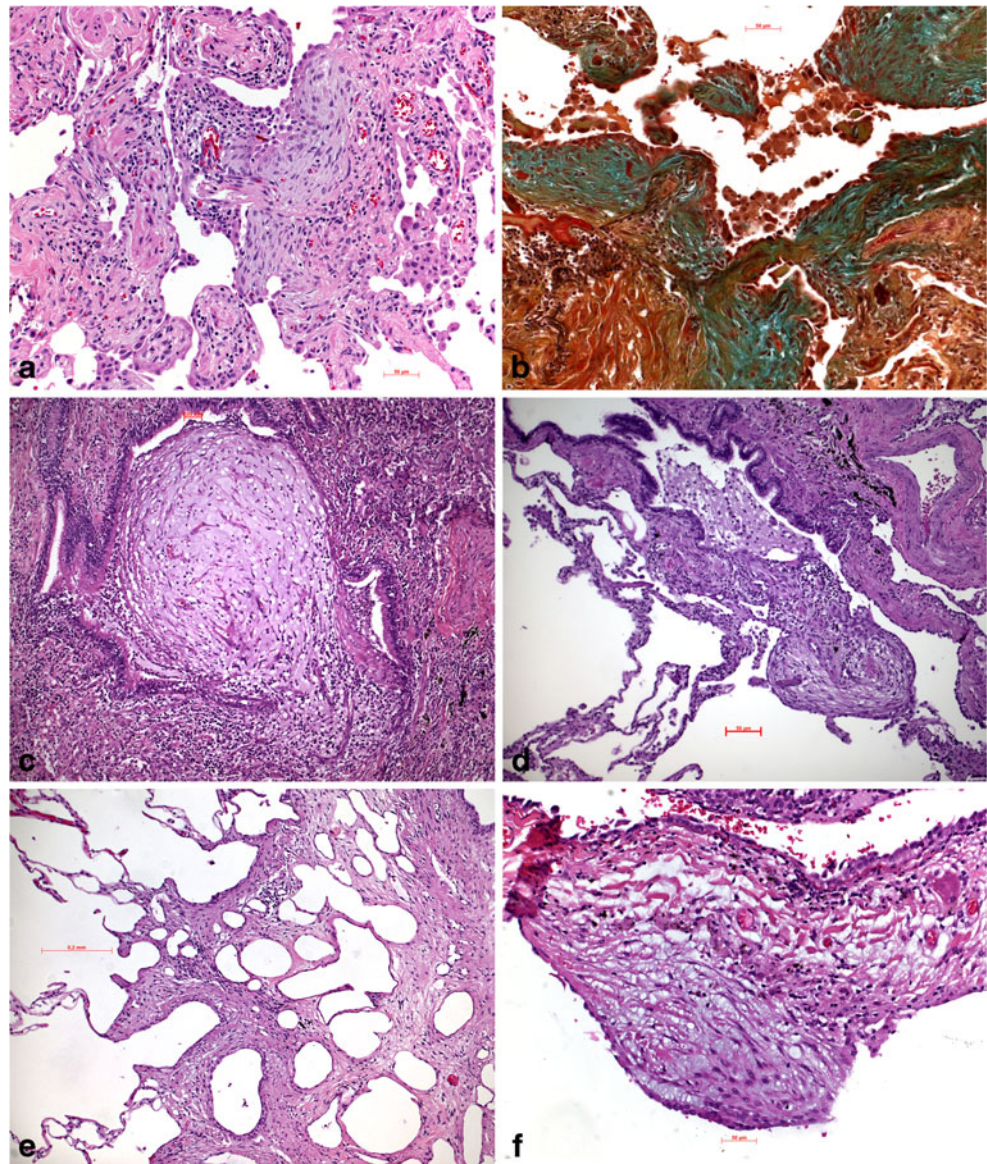
Asbestosis is another diffuse fibrosing lung disease, which can present with UIP or OP morphology. In the early phase, it starts with bronchiolitis and peribronchiolar pneumonia. Later on, fibrosis with UIP morphology can be the predominant feature. In contrast to UIP/IPF, the fibrosis is focal, asymmetric in distribution, and early on can involve central portions of the lung. The diagnostic clue is the demonstration of asbestos bodies together with lung fibrosis.

Drug-induced interstitial lung diseases

Drug-induced ILD present with a variety of tissue reaction, most of them already discussed in previous chapters.

A common presentation is DAD as an acute reaction, often followed by organizing DAD, where hyaline membranes can still be recognized, and finally, ending as OP and lung fibrosis. Other drugs induce NSIP-like tissue reactions. The major problem in interpreting drug reaction in the lung is our limited understanding of drug metabolism. Some drugs will induce toxic injury of endothelial cells, thus the blood barrier is leaking, and proteins can enter the interstitium and finally the alveolar lumen. Here, these proteins will form complexes and, by the action of respiration, hyaline membranes will form. In addition, the exudate from the capillaries will cause a transient edema and this is followed by hypoxia affecting the pneumocytes. This damage will contribute to DAD development. Later on, OP can result. Other drugs act on the immune system, forming

Fig. 27 Comparison of different types of fibroblast/myofibroblast proliferations; **a**, **b** fibroblastic focus in UIP by H&E and Movat stains; by Movat stain, the immature collagen fibers are stained *green*, whereas mature collagen (usually collagen 1) stains *yellow*. **c** Early granulation tissue in OP, here bronchiolitis obliterans, **d** later stage of OP; note the proliferating immature blood vessels, quite characteristic in these early phase OP. Different types of fibrosis in emphysema-associated lung fibrosis: **e** scarring with entrapped emphysema blebs and **f** fibroblastic focus within the wall of an emphysema bleb. Magnification; bars, 50, 50, 50, 50, 200, and 50 μm , respectively



immune complexes either because immunogenic by itself or by complexing with endogenous proteins like a hapten. In these cases, an NSIP or LIP pattern can result. In these cases, scattered eosinophils are regularly found. Granulomas are rarely formed, usually pointing to an underlying immune mechanism. Since our understanding is so limited and no systematic experimental investigation has been performed, we still need to rely on databases, summarizing all described drug reactions in a systematic way (www.pneumotox.com) (Fig. 27 and Suppl. Fig. 28) [45, 181–187].

Conflict of interest I declare that I have no conflict of interest.

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