


REVIEW

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Fibrosing pneumonia – how to diagnose, and how to recognize the etiology?



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Abstract

Background: Fibrosing pneumonias are a group of interstitial lung diseases with a different etiologic background and divergent prognosis. They are differentiated into usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia (OP). Some of these entities were initially described by A. Liebow.

Main: In the 90ties the main differences in survival lead to the separation of UIP/IPF as a disease with dismal outcome, from the prognostically better NSIP and OP. Later it was shown that fibrosing NSIP confers an almost identical worse prognosis. Under the heading of pulmonologists a classification was created, where the diagnosis has to be established by a multidisciplinary team, based on pattern recognition done by radiologists and pathologists. A clinical diagnosis has to be established based on the patterns: UIP pattern was the basis for IPF, NSIP pattern for the clinical diagnosis NSIP, and organizing pneumonia pattern for the diagnosis of cryptogenic organizing pneumonia. This created confusion, because the pattern UIP was taken almost as synonymous with idiopathic pulmonary fibrosis (IPF). Later on in many articles and classifications the role of the pathologic diagnosis was diminished, because pulmonologists based their diagnosis on CT-scan and clinical presentation. This resulted in less tissue biopsies but also delay and misinterpretation of diseases. Even new techniques in tissue biopsies such as cryobiopsy was regarded as unnecessary.

Conclusion: Tissue analysis in fibrosing pneumonias is still the gold standard in making a diagnosis and also evaluating the etiologic background. After an analysis the findings should be discussed in a multidisciplinary board to establish a final diagnosis and a treatment option for the patient.

Keywords: Interstitial lung disease, Usual interstitial pneumonia, Non-specific interstitial pneumonia, Organizing pneumonia, Autoimmune disease, Hypersensitivity pneumonia

Background

Fibrosing pneumonias have been discussed and classified several times during the last 60 years. Starting in 1969, A. Liebow created the first classification of fibrosing pneumonias, at that time under the heading of interstitial pneumonia (Liebow and Carrington 1969). At that time there was usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans organizing pneumonia and diffuse alveolar damage, lymphocytic interstitial pneumonia (LIP), and giant cell interstitial pneumonia (GIP). In the late 1990-ties two other proposals for classification

appeared: Katzenstein (Katzenstein and Fiorelli 1994; Katzenstein 1993) and Colby (Daniil et al. 1999; Nicholson et al. 2000). Katzenstein added nonspecific interstitial pneumonia (NSIP) to the classification, and the group around T. Colby added respiratory bronchiolitis, and compared the outcome of NSIP versus UIP. In the following years the American Thoracic Society and the European Respiratory Society created consensus panels, which formulated new classifications and sorted the entities in idiopathic and Interstitial Lung Disease (ILD) with known etiology. At present the newest classification appeared in 2013 and also additional publications sorted other ILD accordingly (Travis et al. 2013; Fischer et al. 2015). There are three entities regarded as idiopathic, UIP, NSIP, and cryptogenic organizing pneumonia, which latter

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correspond to organizing pneumonia by morphology. Other pneumonias with a known etiology are LIP, which correspond to an immune/autoimmune disease, DIP and RB-ILD, which are both smoking associated diseases in almost all cases, GIP being either associated with hard metal disease, or viral infection. Diffuse alveolar damage (DAD) is most often associated with viral infection, or drug induced lung disease, only very rare might be idiopathic. DAD also can be seen in toxic inhalation injury, for example induced by insecticides or pesticides. When DAD is resolved/resolving, it usually will

present as organizing pneumonia (also called organizing DAD).

It should be noted, that NSIP is often associated with immune diseases, either autoimmune, or hypersensitivity. However, there are still cases, for which no etiology can be assigned. In this review we will address the morphologic patterns for UIP, NSIP, and OP. In addition, we also will focus on morphologic features, which allow a more precise evaluation of the etiology of these patterns. Although the ATS/ERS recommendations now

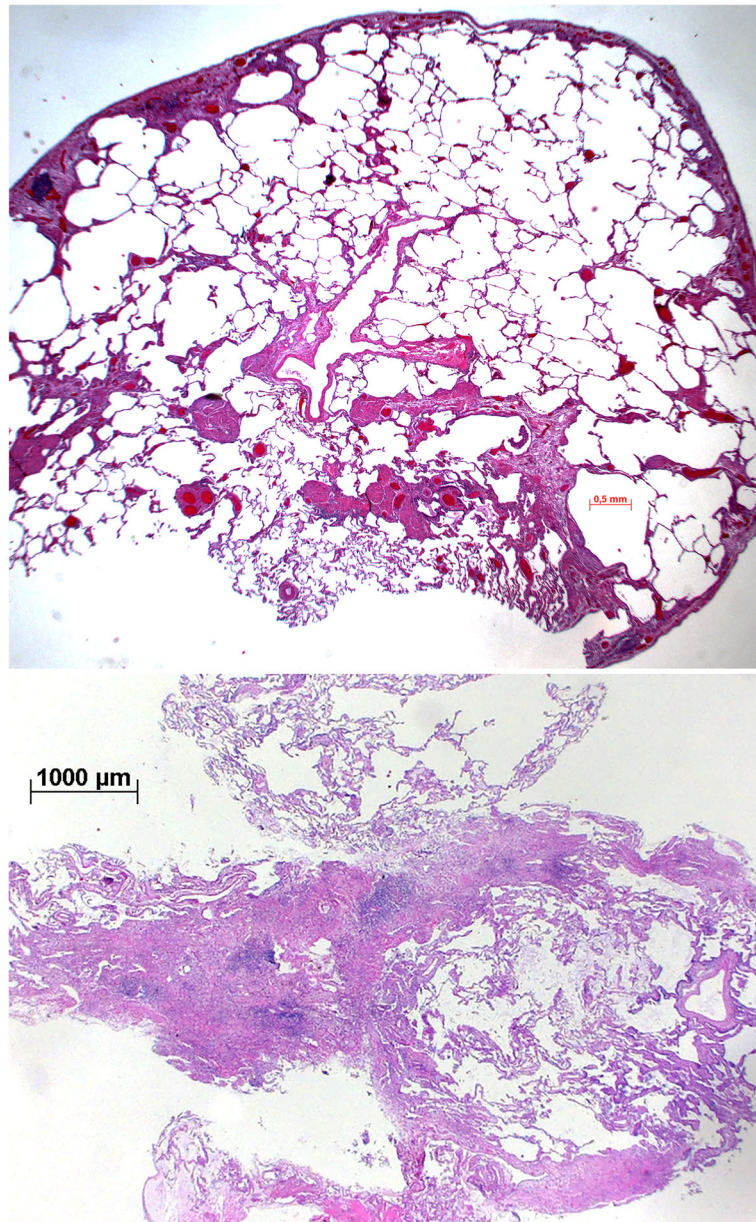


Fig. 1 Overview of UIP/IPF. The upper figure demonstrates the peripheral distribution of fibrosis. There is a lot normal lung visible. In the lower figure there is more fibrosis, also normal lung (heterogeneity), and lymphocyte aggregates around the cystic structures. H&E, bars 500 and 1000 μm

state, that CT scan might be sufficient to make the diagnosis of IPF, NSIP, and OP, in the authors experience this holds not true: In my consultation practice I had to correct several cases, which have been labeled by the radiologist as either UIP, or NSIP, or undefined fibrosis. The statement by ATS/ERS that cryobiopsies should not be done in IPF/UIP cases can also not be confirmed, as in a cooperation with a large Pulmonology Department we have not seen complications, and the tissue was in more that 90% suitable to make a definite diagnosis and guide the clinicians. The new guidelines propose clinical findings and CT scans as the most important methods to diagnose UIP/IPF and reduced histopathology for those cases, where the CT scan cannot provide a definitive pattern. In addition a consensus is now the gold standard instead of histopathology. This provoked a critical review about the role of pathology in the diagnosis of fibrosing pneumonias and their etiologic background.

Material and methods

The review is based on 296 cases from middle and northern Europe including my University serving local clinical departments. All these cases represent fibrosing pneumonias of one of the above-mentioned entities. A patient consent was not necessary, as no clinical data were used, except the final diagnosis. In addition, all cases were anonymized.

Hematoxylin and Eosin stained sections were most often sufficient, a Movat pentachrome stain was applied in selected cases. This stain allows the simultaneous detection of elastic fibers, mucus, old and young fibrosis

(green-turquoise for early fibrosis-immature collagen, yellow for old fibrosis-collagen 1) (Garvey et al. 1986).

Immunohistochemistry was done in some cases, using antibodies for CD3, CD4, CD8, CD20, and FOXP3, if necessary – i.e. in cases with a diffuse lymphocytic infiltration. For example in chronic hypersensitivity pneumonia there are very often areas with active disease, characterized by a predominance of CD8⁺ lymphocytes.

UIP pattern

In UIP some characteristic features should be present. On low power magnification the morphologic changes are peripheral accentuated often subpleural (Fig. 1). On medium power magnification a geographic distribution is typically found, i.e. there are areas of fibrosis and active disease, and areas of uninvolved, normal lung lobules (Fig. 2). On high power magnification a temporal heterogeneity is seen: there are myofibroblastic foci, old fibrosis, and remodeling of the lung with microcystic areas, or large cystic areas composed of several primary lobules (Fig. 3) – this is what the radiologist see as honeycombing. The cystic remodeled structures are due to the destruction by the myofibroblastic foci, which results in obstruction of bronchioles, destruction of alveolar septa, followed by repair. Myofibroblasts will stain positively for smooth muscle actin, but usually less intense compared to smooth muscle cells of bronchi and pulmonary blood vessels (Fig. 4). This might be sometimes used to separate myofibroblastic foci from other kind of fibrosis. In the literature the name fibroblastic focus is widely used; however, these are essential myofibroblasts,

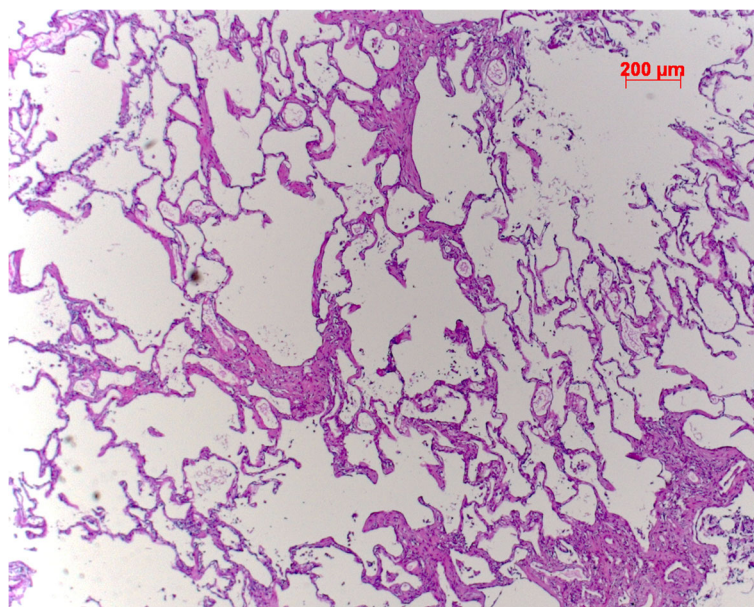


Fig. 2 In this case of UIP there are areas of fibrosis, few myofibroblastic foci, and normal lung. H&E, bar 200 μ m

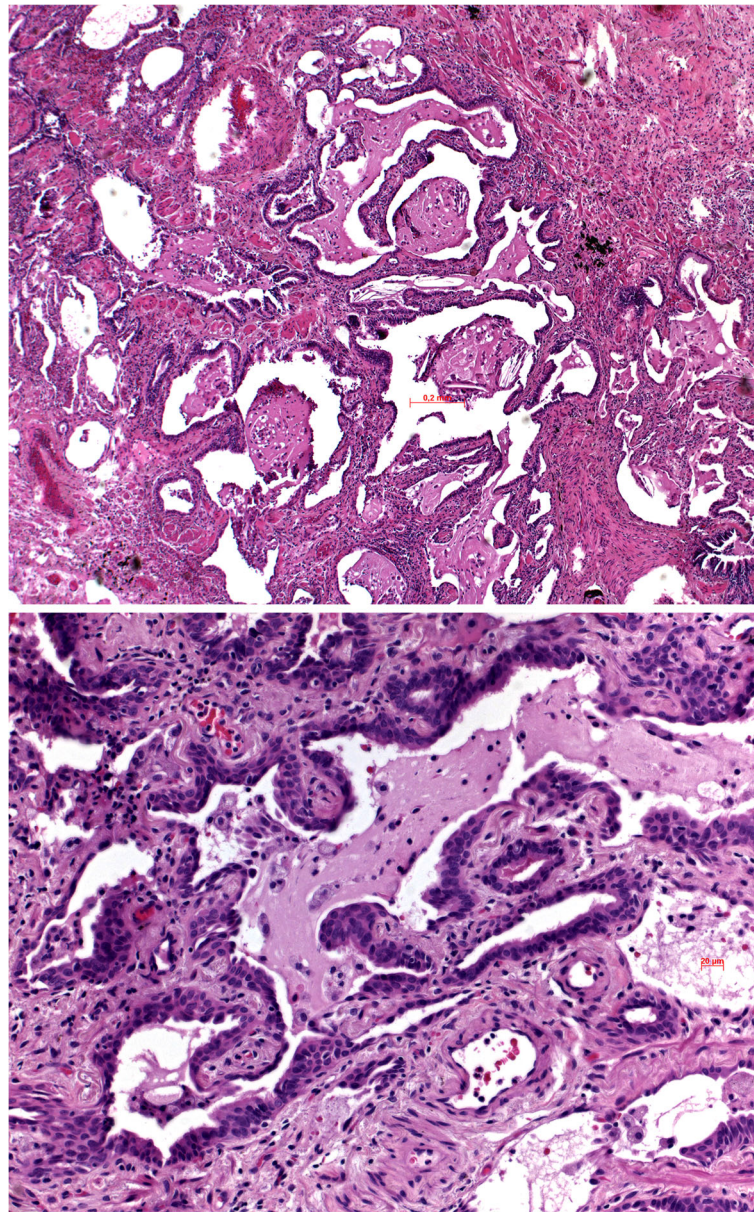


Fig. 3 Two cases of UIP with cystic remodeling, in the upper panel also fibrosis and mucus accumulation within the lumina. In the lower panel the epithelial metaplasia is illustrated with cuboidal cells of bronchiolar origin, replacing the pneumocytes. H&E, bars 200 and 20 μ m

which can be highlighted by a smooth muscle actin stain. The cells contain few myofilaments, and in addition can synthesize collagens.

These cystic structures are prone to mucostasis, colonization by infectious organisms, and therefore lymphocytes or granulocytes might accumulate in the wall of these cysts (Fig. 5). This most likely has nothing to do with the etiology of UIP, but rather a secondary effect. The development of lymph follicles in general and lymphocytic infiltrations into the myofibroblastic foci, however, might have some meaning with respect to the

underlying etiology (see below). UIP most important is not a diagnosis (Table 1), but rather a descriptive term. It includes different etiologies, which we discuss below.

What makes UIP an IPF?

Before we can discuss this question, we need to recall, what is known about the etiology of idiopathic pulmonary fibrosis (IPF). Although the etiology is still not clear, there are at least some aspects known: IPF is a disease of the elderly, presenting most often from the 5th decade on. It is seen predominantly in smokers. The disease

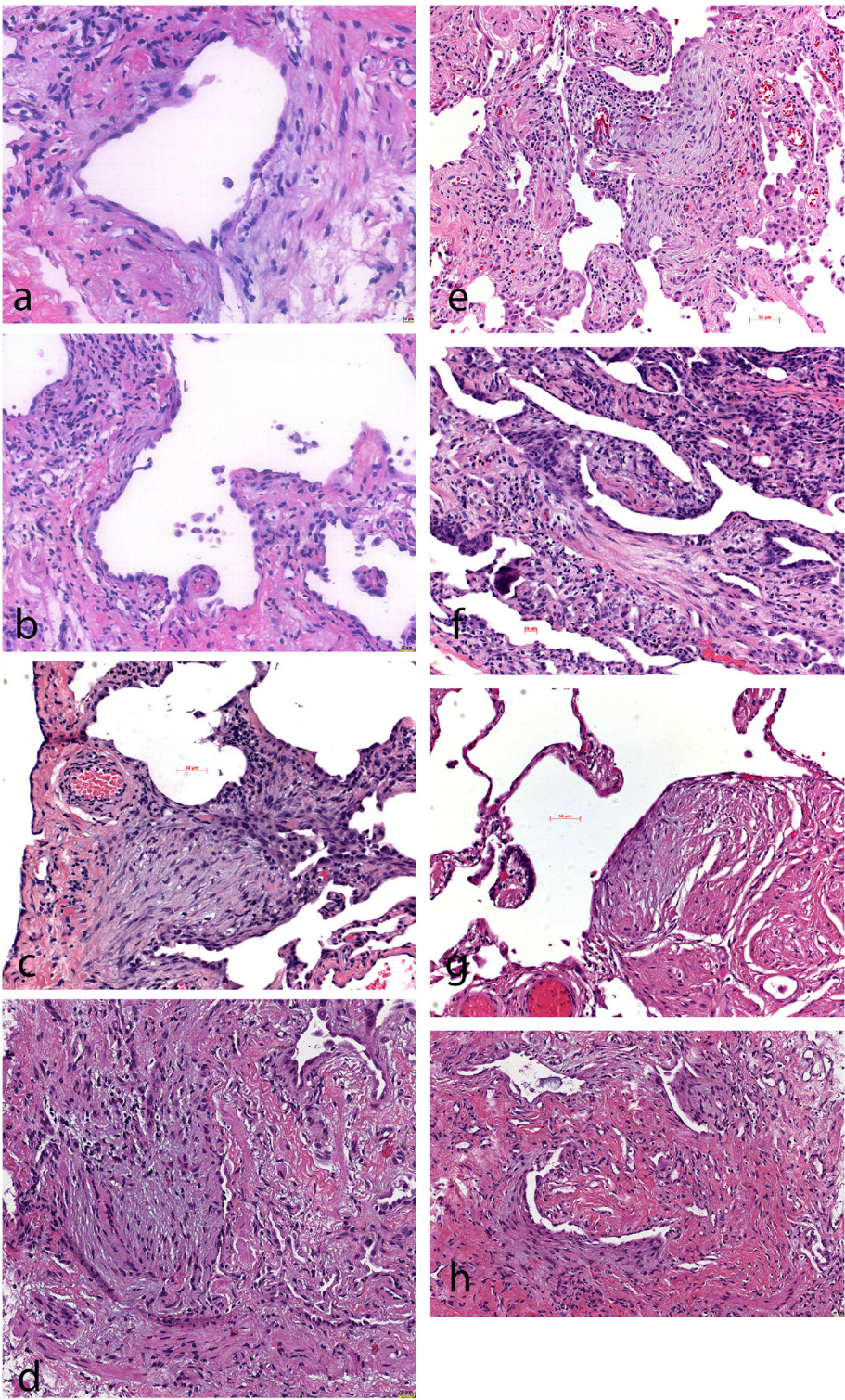


Fig. 4 Myofibroblastic foci at different age are shown; **a**), **b**), and **c**) young myofibroblastic foci with few cells (**a** and **b**) and abundant myxoid matrix, in **c**) more cellular lesion but still myxoid matrix; in **e**) and **f**) there is focal maturation of the myofibroblasts, characterized by an eosinophilic cytoplasm and collagen fibers; in **h**) young and old myofibroblastic foci are side by side. This nicely demonstrate the development of these lesions, where the myofibroblasts change their phenotype and slowly acquire a more fibroblastic one. H&E, bars 50, 20, and 10 μ m, respectively

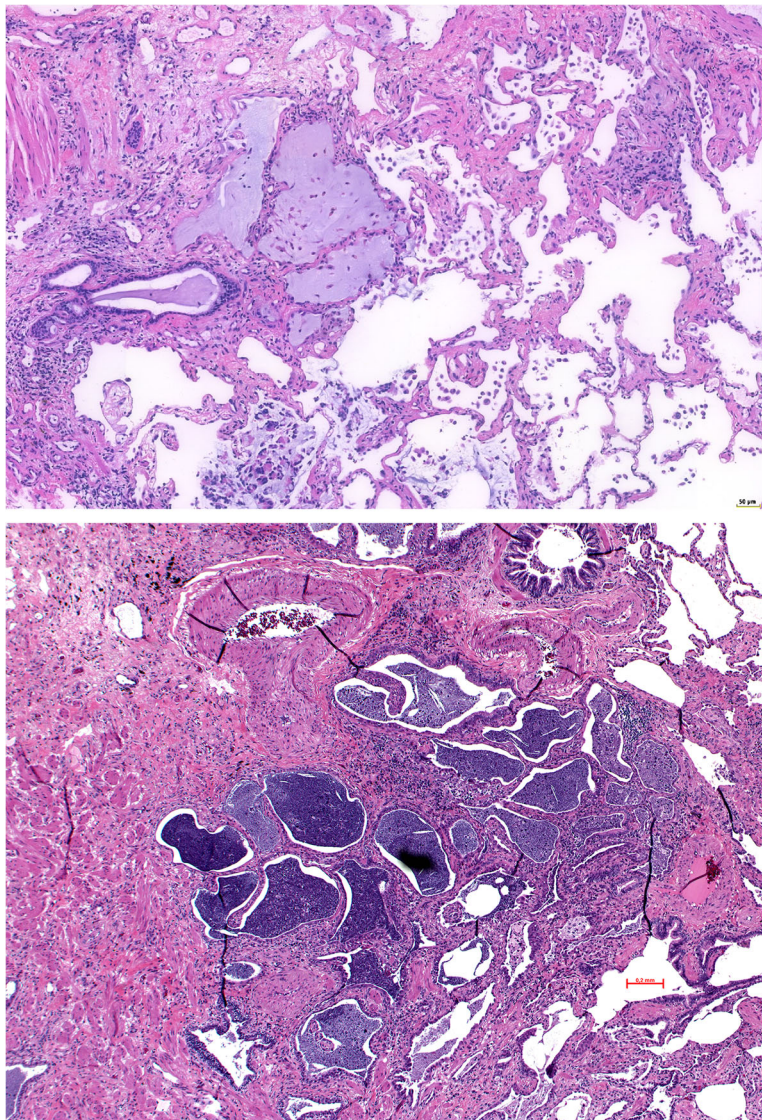


Fig. 5 Mucostasis, in the cystic structures in UIP; in the upper panel there is mucus accumulation with a few scattered macrophages; in the lower panel there is dense spissated mucus, macrophages and scattered neutrophils; this usually is a sign of bacterial colonization. There are also aggregates of lymphocytes around the cysts, which later on can progress into lymph follicles. H&E, bars 50 and 200 μm

Table 1 Criteria of UIP pattern

	Definite UIP	Probable UIP, at least two features should be present	Definite not UIP
Myofibroblastic foci scarce or abundant	yes	yes	Yes/no
Cystic remodeling with bronchiolar metaplasia	yes	Yes/no	no
Timely heterogeneity, i.e. normal alveolar septa	yes	Yes/no	No
Geographic heterogeneity, i.e. peripheral predominance	yes	Yes/no	No
Fibrosis, scar	yes	no	Yes/no

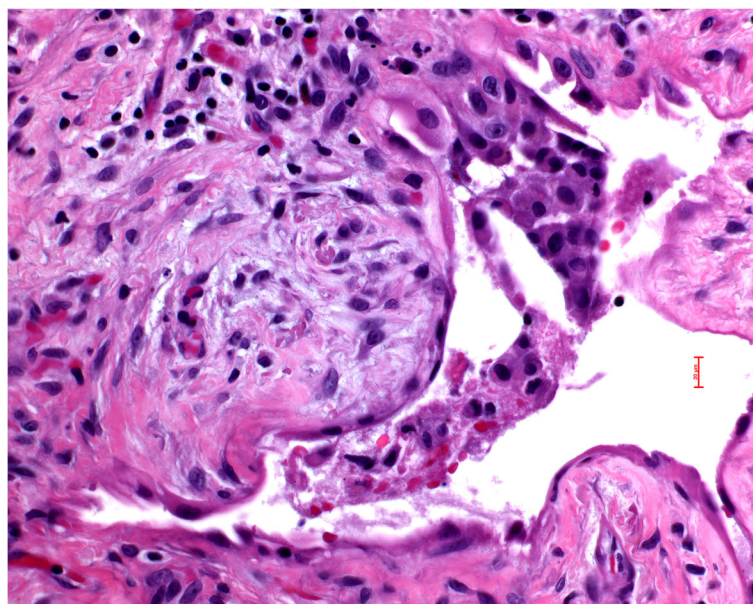


Fig. 6 Myofibroblastic focus with apoptosis of the pneumocytes; there is also a tiny focus where the surface is denuded. H&E, bar 20 μ m

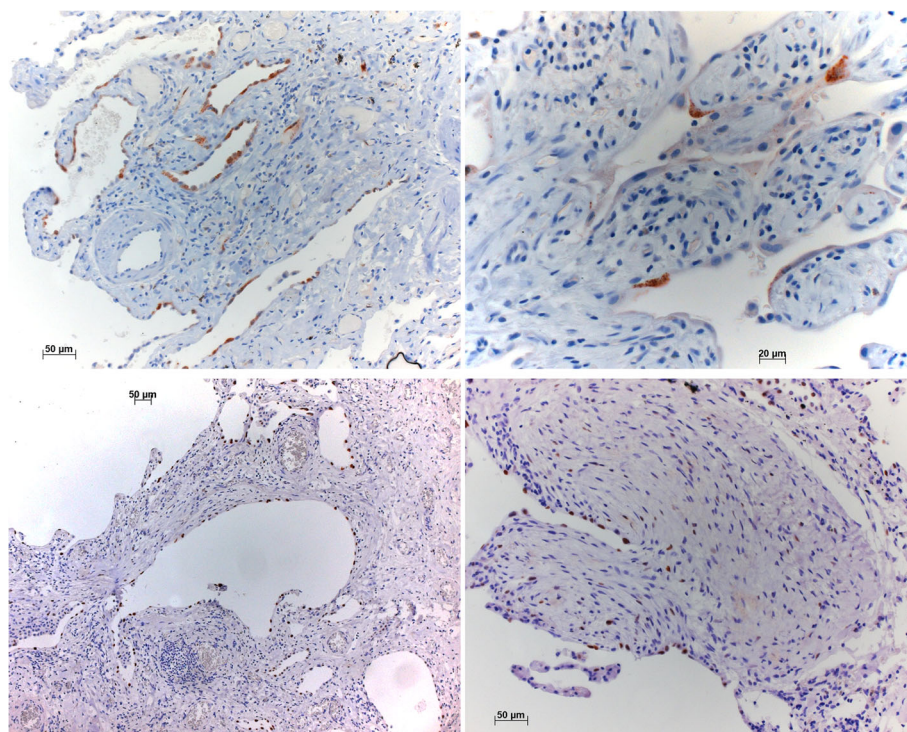


Fig. 7 Senescence in IPF, in the upper figures the senescent cells are stained by p16 (cytoplasmic), in the lower figures the cells are stained by p21 (nuclear). Both are surrogate markers for senescent cells. Bars 50 and 20 μ m, respectively

presents with a rapid downhill course, many patients will die within 3 years after diagnosis (Travis et al. 2013; du Bois and Wells 2001; Costabel and King 2001). Smoking induces injury in the peripheral lung, causing apoptosis of pneumocytes and bronchiolar epithelia (Fig. 6). Regeneration of these epithelia seems to be impaired, and some cells undergo senescence (Fig. 7) (Selman et al. 2010; Selman and Pardo 2014; Chilosi et al. 2013; Kuwano et al. 2016; Cardenes et al. 2018; Waters et al. 2018). Myfibroblasts start proliferating covering the denuded alveolar walls – this is a normal repair process. However, in contrast to normal, this repair does not stop (Fig. 8). The reason might be, that out of the pneumocytes senescent cells appear/transform, which induce an inflammatory environment by secreting inflammatory cytokines (Cardenes et al. 2018). These senescent cells probably very likely keep the repair ongoing. The myfibroblasts primarily produce and secrete immature matrix proteins like collagen (Katzenstein 1993), osteonectin, etc. (Fig. 9). Later on, the myfibroblasts either convert to or are replaced by fibroblasts, which produce collagen 1 and other more mature matrix proteins – fibrosis results (Fig. 4h). However, it should be mentioned, that myfibroblastic foci alone do not qualify for the diagnosis of UIP. These are repair processes, sometimes seen in smoking-related interstitial fibrosis, but in this disease associated with emphysema blebs.

Regeneration of pneumocytes is much reduced, because of aging-related dysfunction of the telomerase system, either with mutations of HTERT or telomerase (Alder et al. 2008; Cronkhite et al. 2008; Tsakiri et al. 2007). There are five different components (DKC1,

TERC, TERT, NOP10, NHP2), which encode components of the telomerase, or telomerase-associated factors, and TINF2, a telomeric protein (Kropski et al. 2014; Savage and Bertuch 2010). In the cystic remodeling areas cytokeratin 5-positive basal cells (CK5) from the small bronchi and bronchioles can be found, sometimes in early lesions completely outlining the cysts. In familial IPF other mutations have been identified, and subsequently also seen in sporadic IPF. Surfactant apoprotein C, A1 and A2 mutations were the first being described (Markart et al. 2007; van Moersel et al. 2010; Wang et al. 2009; Nathan et al. 2016). Mutations in these surfactant apoproteins caused stress reaction in endoplasmic reticulum, probably because of misfolded proteins (Zhong et al. 2011; Lawson et al. 2011). This might contribute or being closely associated with premature aging of pneumocytes. Other less well understood mutations or modifications are found in ABCA3 and MUC5B gene (promoter variant) (Young et al. 2008; Seibold et al. 2011). Autophagy has also been discussed as being involved downregulated in IPF (Kuwano et al. 2016; Araya et al. 2013). In contrast, we have shown, that autophagy is upregulated in IPF (Popper et al. 2019). Although, it would be expected, that autophagy is downregulated, because this would impair phagocytosis of cellular debris, which in turn would stimulate prolonged inflammation and repair, upregulation has also an important meaning: Areas of remodeling are under hypoxic stress. Autophagy will help to recycle cellular debris, use it for cell survival, and gain energy under hypoxic condition by

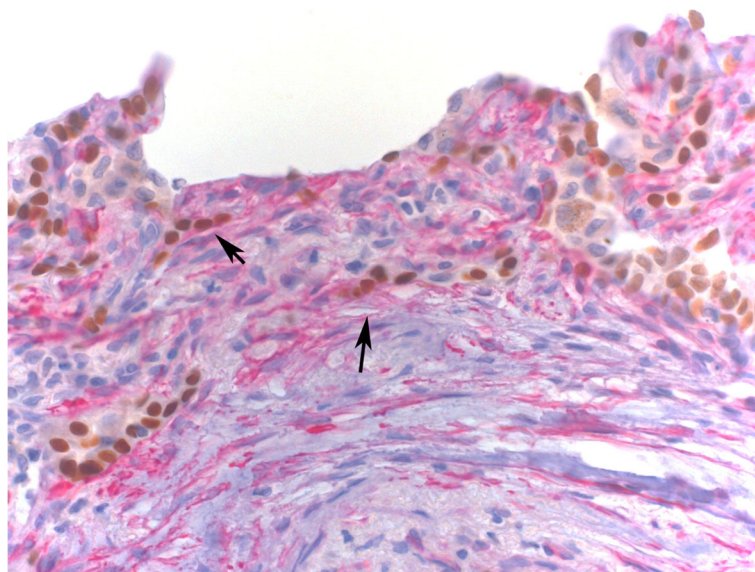


Fig. 8 UIP/IPF case, showing transition of epithelial or mesenchymal cells: TTF1 nuclear staining characterizes epithelial cells, whereas red filamentous staining for smooth muscle actin characterizes myfibroblasts. Arrows show cells coexpressing both markers. If these cells show epithelial-to-mesenchymal or mesenchymal-to-epithelial transition cannot be evaluated by morphology – both options might work. Magnification, X400

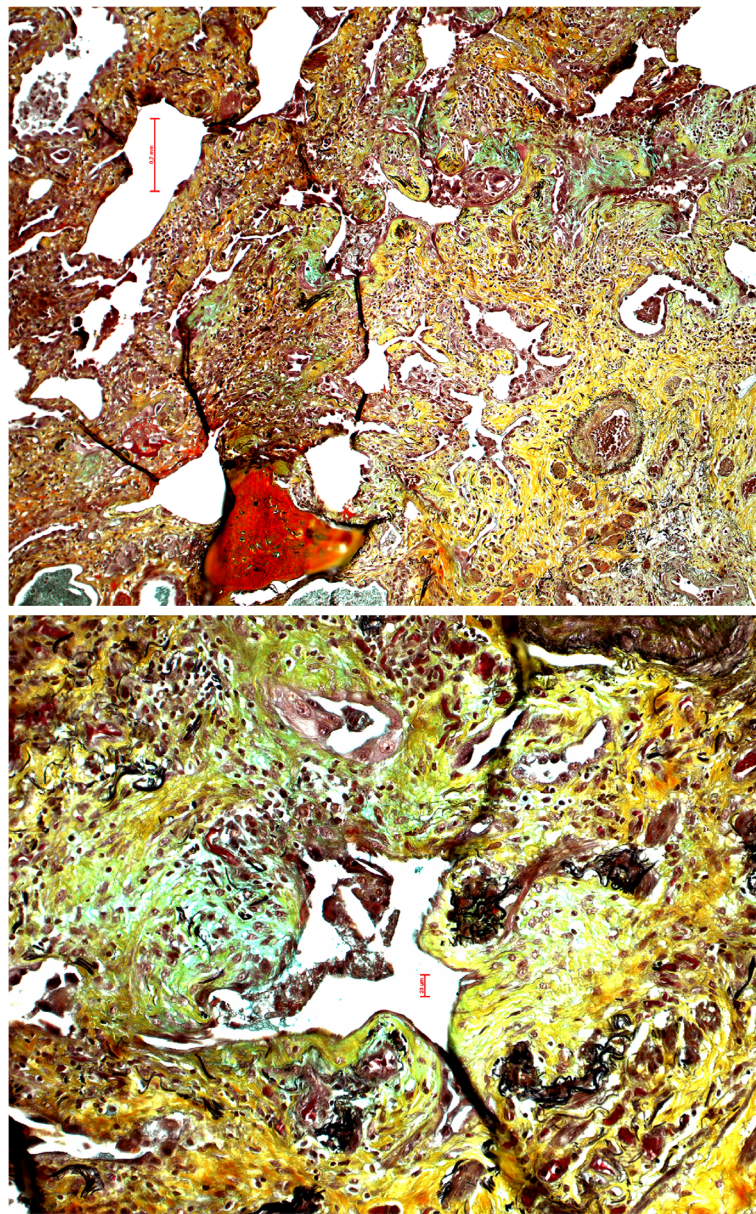


Fig. 9 Two different magnifications showing the changes of the matrix proteins in myofibroblastic foci: green for immature collagen (predominantly collagen III) and yellow mature collagen I. Movat stain, bars 200 and 20 μ m

upregulation of enzymes necessary for metabolism (for example lactate dehydrogenase) (Fig. 10).

What does that mean for morphology?

Granulocytes or lymphocytes do not play a role in the early lesion, i.e. the myofibroblastic focus and the dying pneumocytes. Macrophages are sufficient to remove the debris. So, if lymphocytes are seen within young myofibroblastic foci, most likely another etiology plays a role. If in addition to all the features of UIP a diffuse

lymphocytic infiltration and hyperplasia of the bronchus-associated lymphoid tissue does occur, IPF can be ruled out (Table 2) (Ozasa et al. 2018; Enomoto et al. 2014).

Here the lesion is very likely induced by an immune reaction (Figs. 11, 12 and 13). Another feature not consistent with IPF are granulomas. If these are seen in a UIP pattern, again an immune reaction has to be discussed. Granulomas, especially epithelioid cell granulomas are formed, if immune complexes cannot be

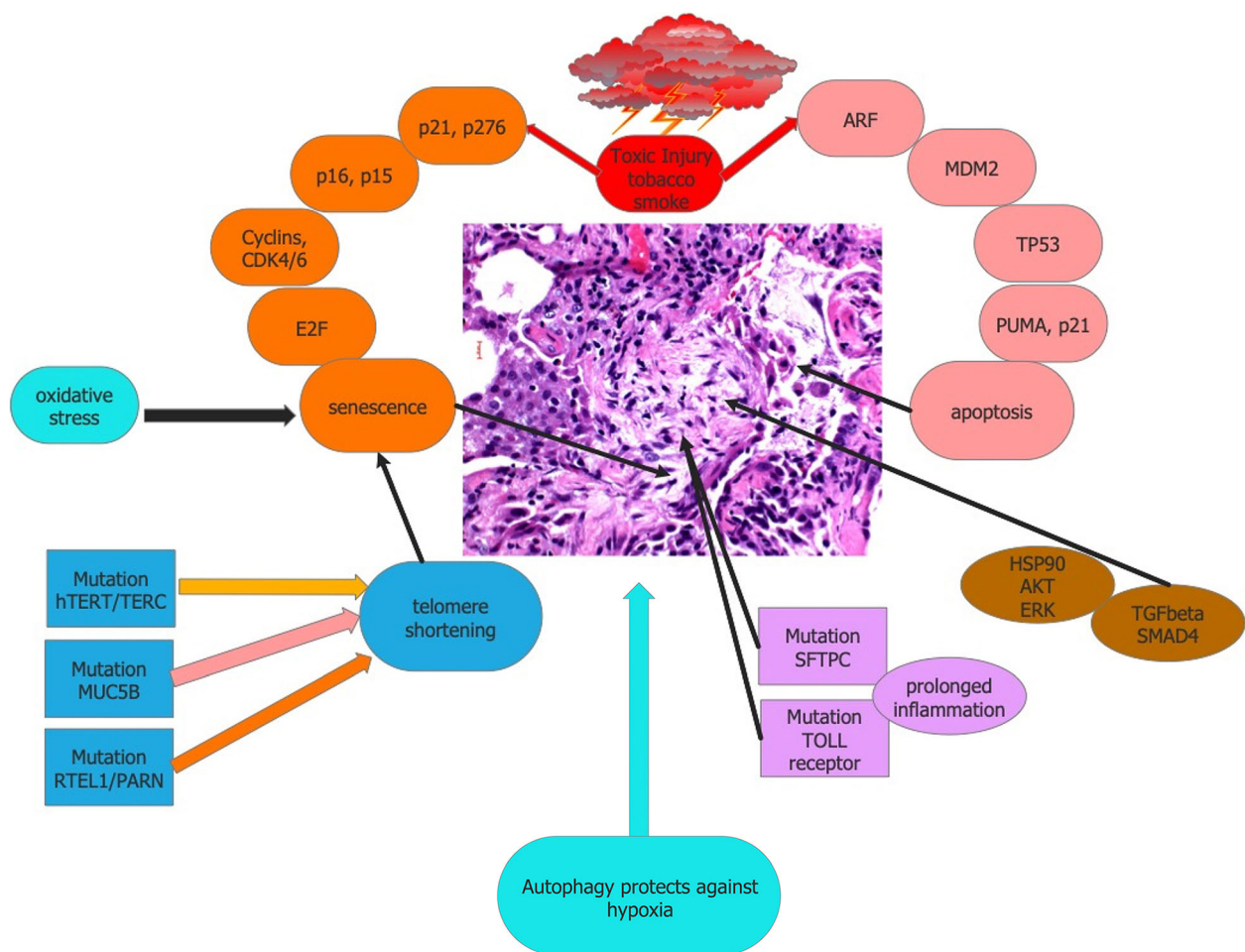


Fig. 10 Schematic diagram of the development of UIP/IPF. In familial and sporadic IPF an underlying gene defect induces apoptosis of pneumocytes, but in addition, some cells undergo senescence (in Fig. 7 these cells highlighted by p16 and p21 stains). Senescent cells release cytokines and growth factors, which induce proliferation of myofibroblasts. Later on, these cells undergo differentiation, become fibroblasts and turn immature collagen-III into mature collagen-I. There are still open questions, such as how much EMT and MET contributes to the continuation of the myofibroblast proliferation, what is the role of bone marrow derived stem cells? In chronic autoimmune and allergic diseases the causing factors are autoimmune mechanisms, deregulation of the immune system, by which probably cytotoxic lymphocytes induce apoptosis and necrosis of pneumocytes, followed by the same downstream inflammatory mechanisms, leading to fibrosis. Mutations of telomerase genes contribute to the senescence process, mutations in surfactant apoprotein genes and MUC5B might be involved in prolongation of the inflammatory status. Heat shock proteins seem to be involved in maintaining the myofibroblast proliferation

Table 2 Etiology in UIP pattern

	Myofibroblastic foci, cystic remodeling, timely heterogeneity	LIP pattern ± hyperplasia of BALT	Organizing pneumonia pattern	DAD pattern	Granulomas or giant cells	Lymphocytes, subtypes?
IPF	present	no	no	± in exacerbation	no	No
Chronic autoimmune disease	present	Yes/no	Yes/no	no	Yes/no	Mixed CD4/8 and CD20 population
Chronic hypersensitivity pneumonia	present	Yes/no peribronchial lymphocyte aggregates	yes	no	yes	Predominant CD8 population

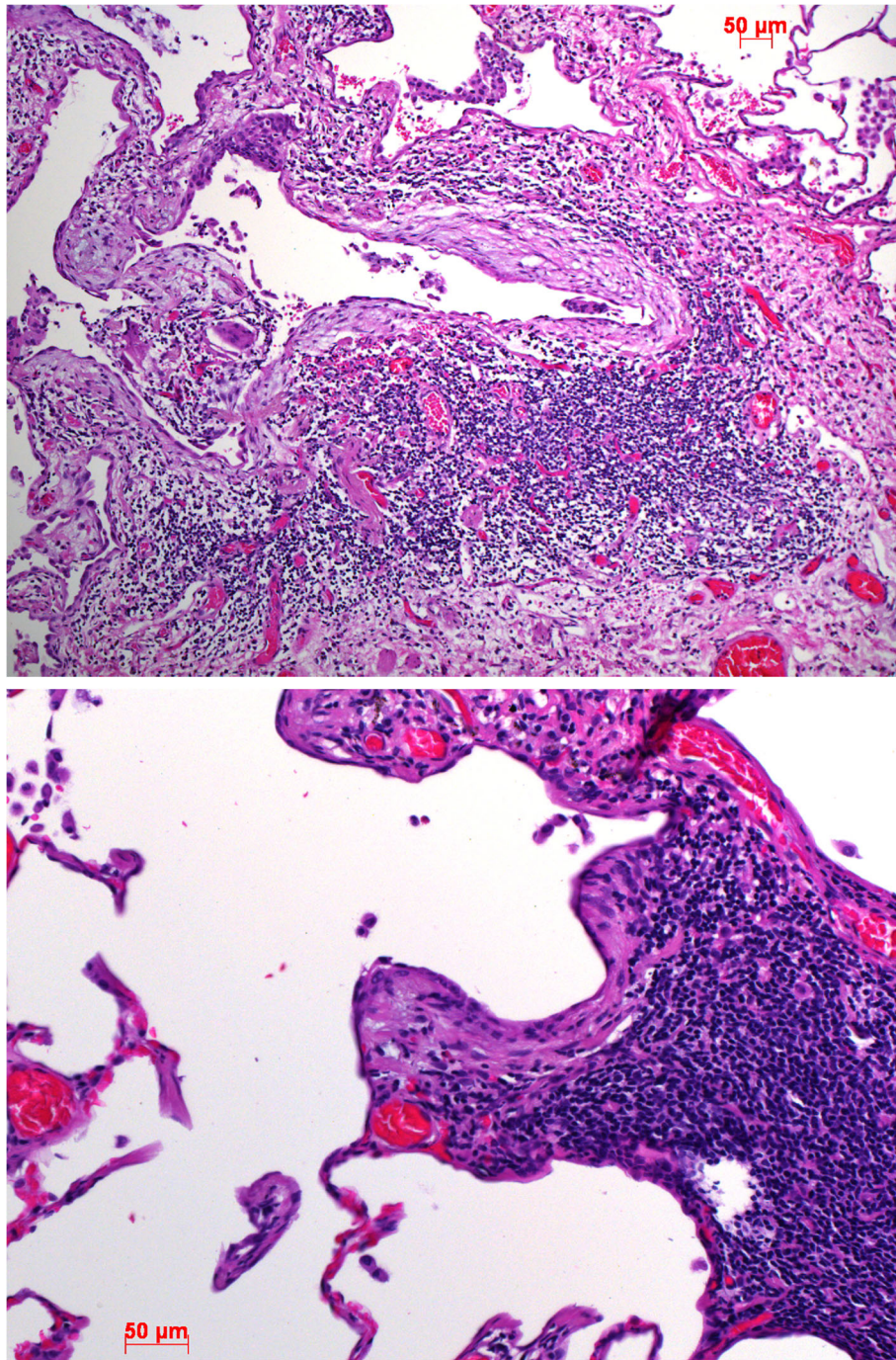


Fig. 11 Myofibroblastic foci in two cases of immune induced UIP/chronic autoimmune disease. Note the infiltration of lymphocytes in these young myofibroblastic foci. H&E, bars 50 μ m

removed/dissolved by leukocytes (Fig. 14). Therefore, macrophages undergo a differentiation into epithelioid cells, and others into giant cells, which start to degrade the immune complex. If the immune complex is part of an autoimmune disease or a hypersensitivity reaction

cannot be solved on morphology. However, there are some diseases, which regularly present with granulomas, such as hypersensitivity pneumonia (HP), rheumatoid arthritis (rA), and dermatomyositis (DMM). Others such as systemic lupus erythematosus (SLE), systemic

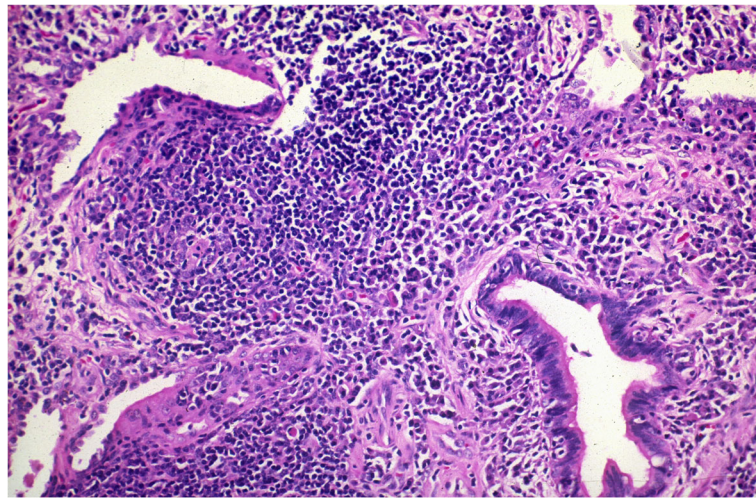


Fig. 12 Hyperplasia of the bronchus-associated lymphoid tissue (BALT hyperplasia), another sign of autoimmune diseases. H&E, X200

sclerosis (SSc), and polyserositis rarely will induce granuloma formation – most likely because they do create huge idiotypic-antiidiotypic immune complexes. In addition, SLE in my personal experience will rarely present with an UIP pattern.

If UIP pattern is present in an autoimmune disease, it is a sign of chronicity. In these cases, it might clinically be difficult to identify the underlying autoimmune disease. This might be a reason, why the ATS/ERS classification labelled this as IPAF. However, in my opinion in many cases a careful analysis of the tissue might provide additional features, which could help the clinician to assign a final etiologic diagnosis to the patient. Immune complex deposition, amyloid deposits, infarcts, hemorrhage, granulomas, hyperplasia of BALT system, LIP, these all will help to sort the spectrum of autoimmune diseases according to a probability schema Table 3.

In the ATS/ERS classification there are additional comments for uncertainties in the diagnosis of UIP. The recommendations therefore have added terms such as definite UIP, indeterminate UIP, probably UIP, alternate diagnosis (Raghu et al. 2018). This reflects in my opinion the fact, that biopsies are rarely done; this is also expressed in this statement: “for patients with newly detected ILD who have a high-resolution computed tomography scan pattern of UIP, strong recommendations were made against performing surgical lung biopsy, transbronchial lung biopsy, and lung cryobiopsy, and a conditional recommendation was made against performing BAL”.

In histopathological evaluations the diagnosis of indeterminate UIP is rarely made, but a probably UIP

diagnosis is sometimes necessary in cryobiopsy cases: for example myofibroblastic foci and cystic remodeling are present, but no normal lung parenchyma, and no fibrosis/scar. Here a pragmatic handling is recommended: If CT scan and clinical data are all in favor of UIP/IPF, no further biopsy is necessary. If the clinical history and the CT scan are not clear, an open lung biopsy might be necessary. An alternate pathological diagnosis does occur even in cases where the clinical and radiological diagnosis favor UIP/IPF. What is more common, is a question mark on the etiology: in some cases an UIP pattern is seen, but no additional features, which could direct one into either IPF or other UIP associated diseases. Again, if lymphocytic infiltrations are seen within myofibroblastic foci, this points to an immunological etiology, because lymphocytes are not involved in the initial injury in IPF.

NSIP pattern

In contrast to UIP, NSIP is uniform, there is no temporal heterogeneity. The peripheral lung structure is retained, which might be sometimes not easy to prove. There is some help: use a digitized slide and outline the alveolar septa with a pencil. By this action you will see, that the alveoli are still there, and no cysts have been formed.

NSIP comes in two versions, cellular and fibrotic. In cellular NSIP the alveolar septa are diffusely infiltrated by a mixture of lymphocytes, plasma cells, and histiocytes. In fibrotic NSIP the septa will show mild to moderate fibrosis and less inflammatory infiltrates (Fig. 20). After the initial description of

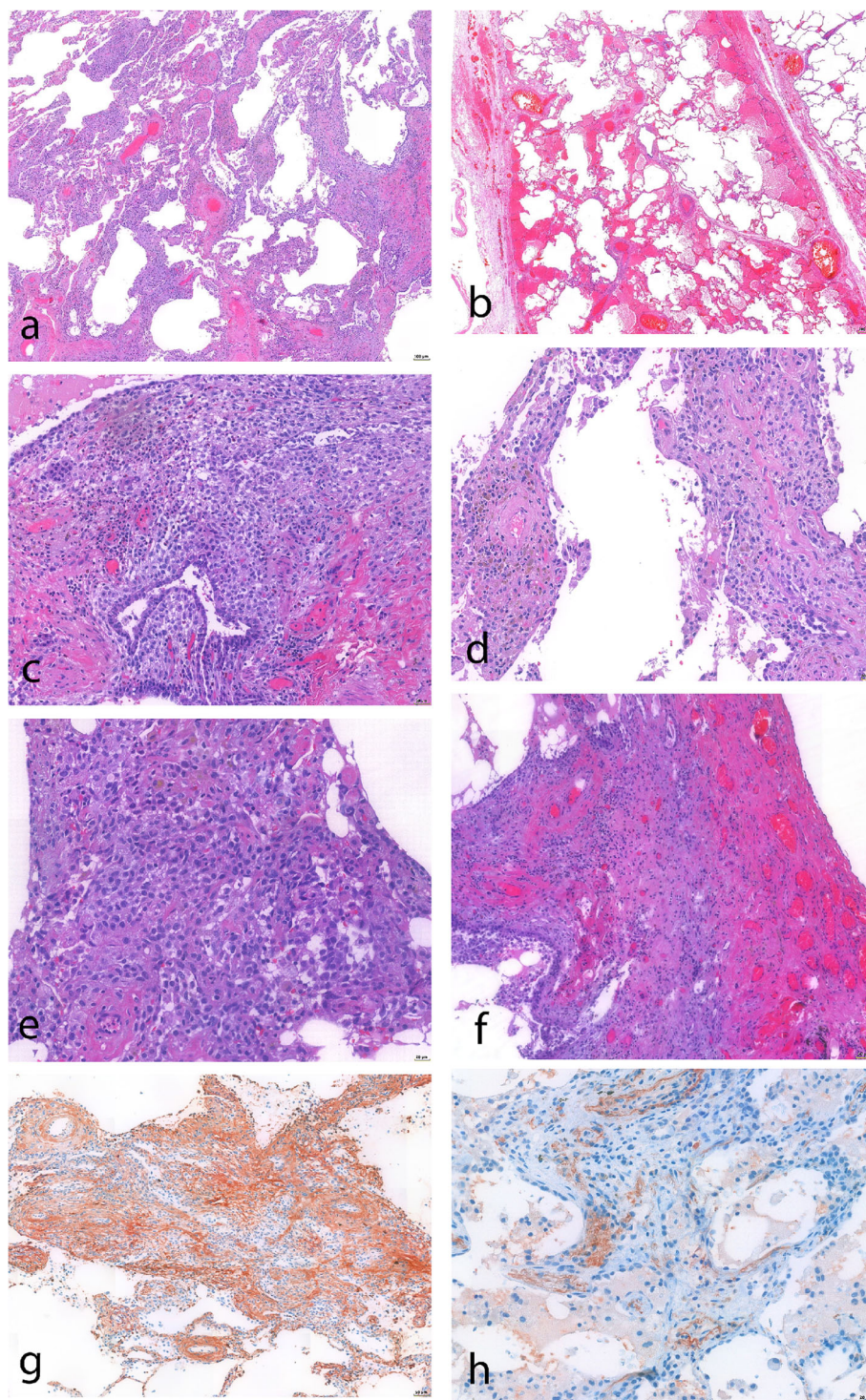


Fig. 13 Case of an autoimmune disease, probably SLE; **a** and **b** shows two different areas, one with LIP, the other with alveolar hemorrhage; in **c-e** there is a pattern which looks like LIP, but it could also be called NSIP; but as there is also BALT hyperplasia, which is uncommon in NSIP; in **e** and **f** there is fresh hemorrhage but also are siderin-laden macrophages; **g** and **h** shows deposition of immune complexes (**g**) and activation of the full complement cascade (**h**; C5–9 complex). H&E and immunohistochemistry for IGG and C5–9, bars 200, 100, 50, 20 μ m, respectively

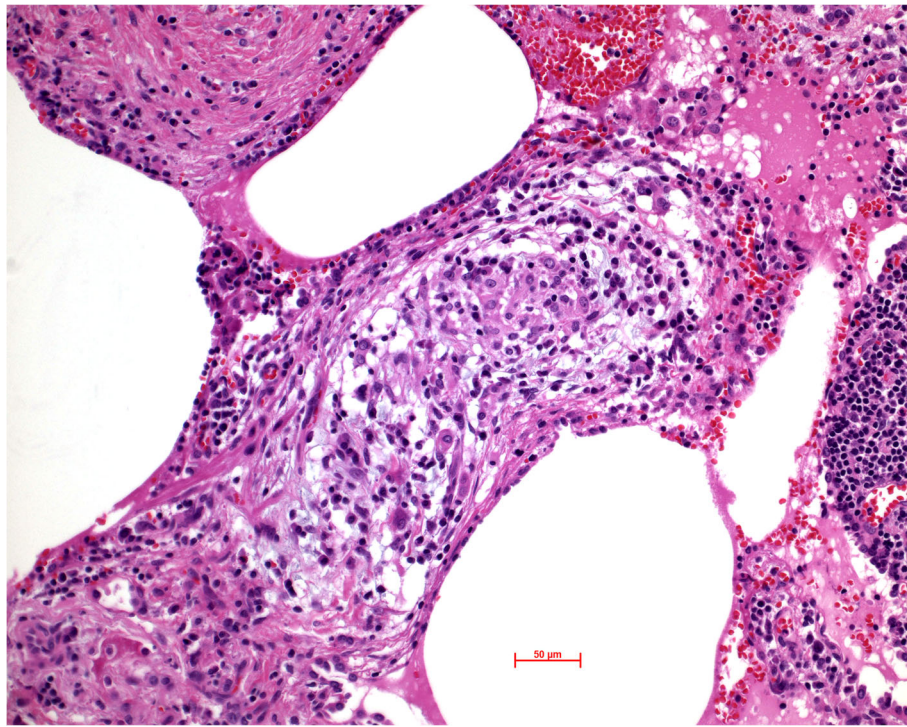


Fig. 14 Chronic rheumatoid arthritis, here with an epithelioid cell granuloma; the main differential diagnosis in such a case would be by hypersensitivity pneumonia; stains for CD markers on lymphocytes will help in such a differential diagnosis. H&E, bar 50 μ m

NSIP (Katzenstein and Fiorelli 1994), one could see a vanishing of LIP from the literature – everything was now published under the name NSIP. However, LIP was still there.

What differs NSIP from LIP? This was also never clearly differentiated.

In NSIP the infiltrate is mixed, composed of lymphocytes, plasma cells, histiocytes, and dendritic cells, whereas in LIP the infiltrate is much more uniform, composed of lymphocytes and plasma cells (Fig. 21). In addition, in LIP there is also a hyperplasia of BALT not present in NSIP. The prognosis of cellular

NSIP is usually good, whereas the prognosis of fibrotic NSIP is almost as worse as UIP (Kambouchner et al. 2014; Myers 2007).

The etiology of NSIP: There are different causes, autoimmune diseases, hypersensitivity and toxic reactions, and finally an idiopathic form (Cottin et al. 1998; Fujita et al. 2001; Kim et al. 2002; Bouros et al. 2002; Nicholson et al. 2002; Cottin et al. 2003; Arakawa et al. 2003; Tansey et al. 2004; Ohtani et al. 2005; Lee et al. 2005; Yoshinouchi et al. 2005). Some autoimmune diseases such as dermatomyositis, are preferentially seen with NSIP pattern, whereas others as rheumatoid arthritis are often associated with UIP. Toxic reactions are seen in several drug reactions, but also toxic dust inhalation.

Table 3 Features Combined features of some chronic autoimmune diseases

RhA: UIP pattern, LIP pattern, histiocytic or epithelioid cell granulomas, hyperplasia of BALT, amyloid deposition, mixed lymphocytes positive for CD4, CD8, and CD20. This will also help to exclude HP, which will present with predominant CD8+ cells. Rare or absent FOXP3 regulatory Tcells (Figs. 15 and 16).

SSc: UIP pattern, LIP pattern, no granulomas, hyperplasia of BALT, amyloid or immune complex deposition (Fig. 17)

SLE: hemorrhage, infarcts, immune complex deposits, NSIP or LIP pattern, OP (Fig. 18)

DMM: UIP pattern, NSIP pattern, granulomas (Fig. 19)

Organizing pneumonia

Organizing pneumonia (OP) was previously called bronchiolitis obliterans – organizing pneumonia, BOOP. Due to the fact, that bronchiolitis obliterans is rarely seen on transbronchial biopsy, the name was shortened to OP. Morphologically it is characterized by granulation tissue arising from the wall of bronchioles and alveolar walls. In contrast to the proliferation of myofibroblasts in UIP, there are newly formed

blood vessels in the granulation tissue. These granulation polyps also called Masson bodies protrude into the alveolar lumen. Usually there are mixed infiltrates visible, composed of macrophages, residual leukocytes or lymphocytes (Fig. 22). Sometimes the differentiation between myofibroblastic foci and granulation polyps can be difficult. In these cases, the other criteria for UIP should be looked up: cystic remodeling, fibrosis and scar, normal primary and secondary lung lobules. This will assist to sort the correct diagnosis.

Causes of OP

There exists a huge number of possible causes of OP. Cases of infectious pneumonias, if not solved can progress into OP. Other causes are inhalation of toxic material (including pesticides and herbicides), drug toxicity, aspiration, and distal to bronchial obstruction. OP can also present as a subacute reaction following autoimmune diseases (Fig. 23), eosinophilic lung disease, primary vasculitis, and some rare conditions such as lung involvement in chronic

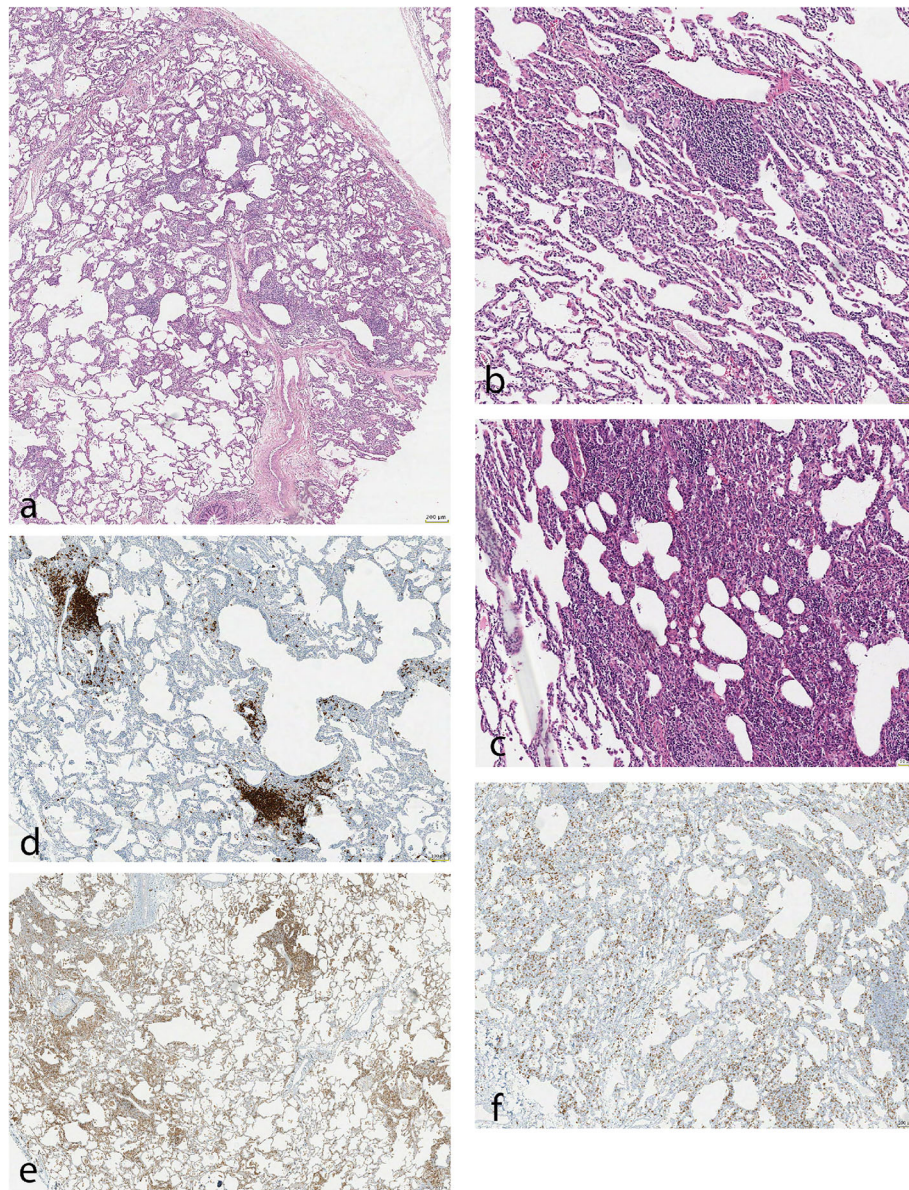


Fig. 15 rhA, acute form with LIP pattern; in this case the diagnosis of juvenile rhA was established. **a)** overview, **b** and **c)** LIP with hyperplasia of BALT; **d)** CD20 positive lymphocytes, **e)** lymphocytes positive for CD4, and **f)** CD8 positive lymphocytes. This immune reaction excluded hypersensitivity pneumonia. H&E and immunohistochemistry, bars 200, 100, and 50 μ m, respectively

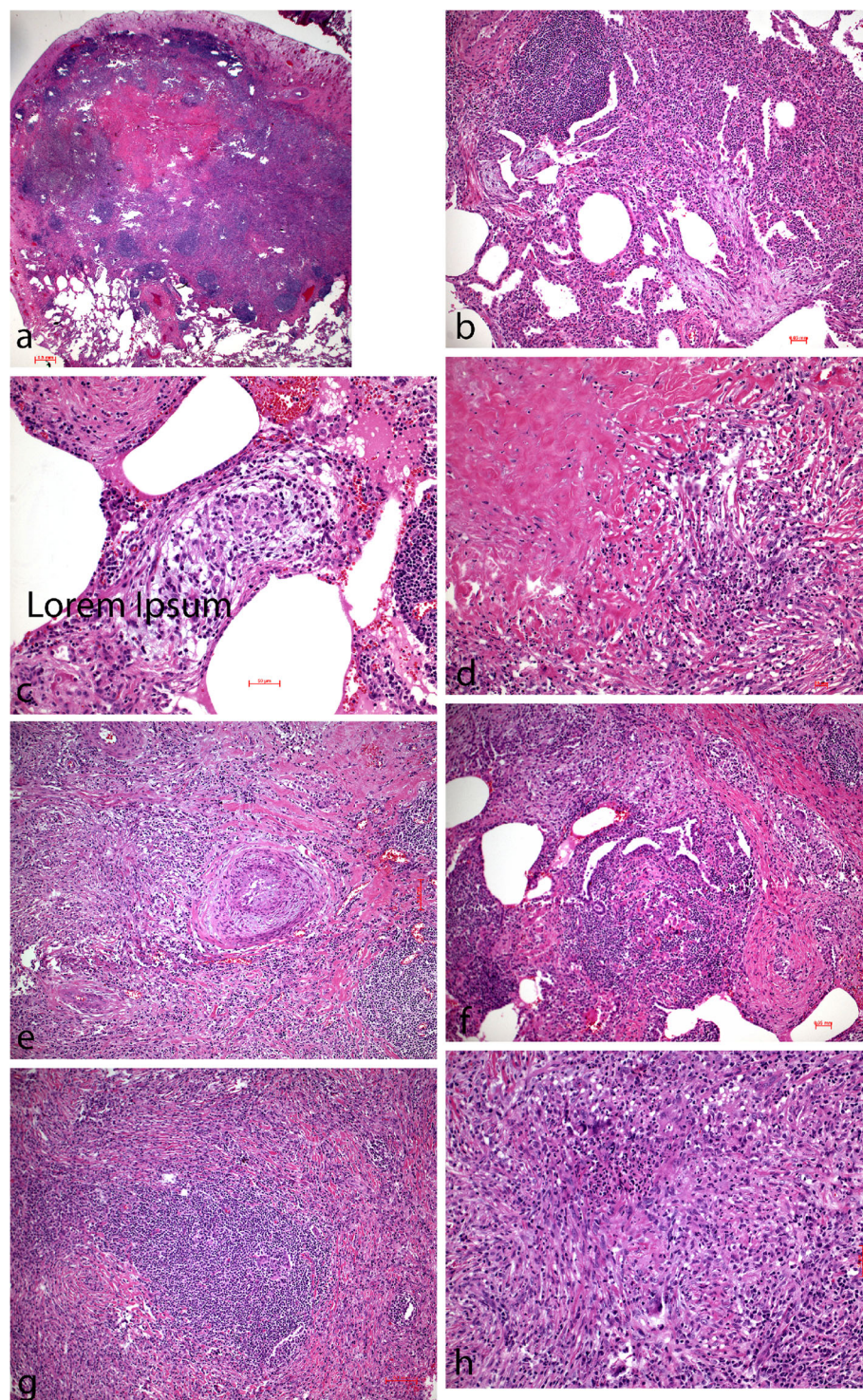


Fig. 16 Chronic rhA, **a)** overview, **b)** myofibroblastic foci with dense lymphocytic infiltration and lymph follicle, and cystic remodeling; **c)** loose epithelioid cell granuloma, **d)** amyloid deposit, **e)** dense lymphocytic infiltration and vasculopathy with severe narrowing of a pulmonary artery, **f)** cystic remodeling, loose granulomas with giant cells, lymphocytic accumulation, **g)** BALT hyperplasia, **h)** loose granulomas and focal necrobiosis with neutrophils. H&E, bars 500, 100, 50, and 20 μ m, respectively

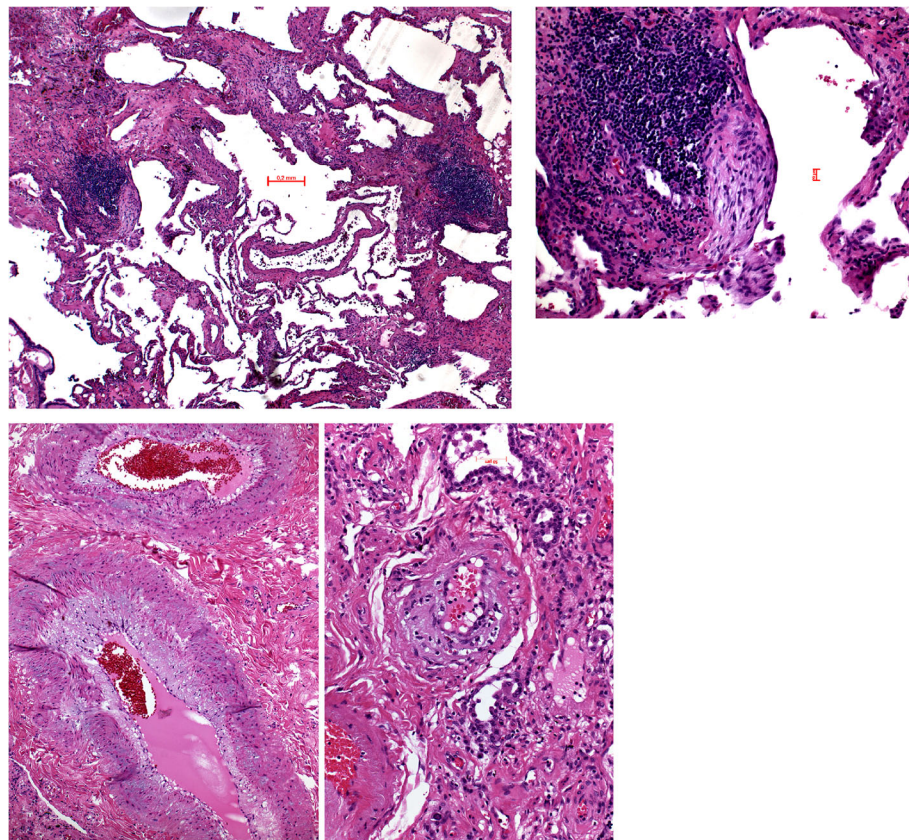


Fig. 17 Chronic systemic sclerosis (SSc); UIP pattern with myofibroblastic focus, fibrosis, cystic remodeling, but also hyperplasia of BALT. Note the dense lymphocytic infiltration into the myofibroblastic focus (top); at the bottom vasculopathy is seen with myxoid changes of the intima and narrowing of the arterial lumen. H&E, bars 200, 50, and 20 μ m

inflammatory bowel disease. If all these differential diagnoses have been excluded, idiopathic OP, called cryptogenic OP remains.

Autoimmune diseases

Finally, we will shortly comment on immune diseases, autoimmune as well as hypersensitivity diseases. Acute immune diseases will most often present as LIP (Fig. 15), however, subacute and chronic diseases can present either as OP, NSIP, or UIP. Prognostically there is not much difference if UIP is caused in the setting of IPF, or in the setting of autoimmune disease (Rampp et al. 2019). However, in NSIP the etiology seems to influence the prognosis: an underlying autoimmune disease has a better prognosis compared to idiopathic NSIP (Nunes et al. 2015).

How certain a diagnosis of chronic autoimmune disease can be made by morphology?

If a chronic autoimmune disease present with UIP pattern, there are usually several other features simultaneously present: granulomas, amyloid deposit, immune

complex deposit, alveolar hemorrhage, infarct, vasculitis/vasculopathy.

Hypersensitivity pneumonia (HP)

Similar to autoimmune diseases also HP can present as subacute or chronic disease. Clinically the diagnosis might be complicated, because the classic symptoms might no longer prevail. But morphology in many cases can pave the way to the diagnosis. In subacute disease HP will present with OP, but focally florid lesions often can be seen. Even in chronic HP (with UIP pattern) focally areas of active disease are seen (Fig. 24): there will be areas of BALT hyperplasia, LIP, granulomas or simply giant cells. In contrast to autoimmune disease pleuritis is absent.

Conclusions

Pathologists can arrive not only at a descriptive diagnosis, i.e. pattern description, but in some instances can direct clinicians to the etiology.

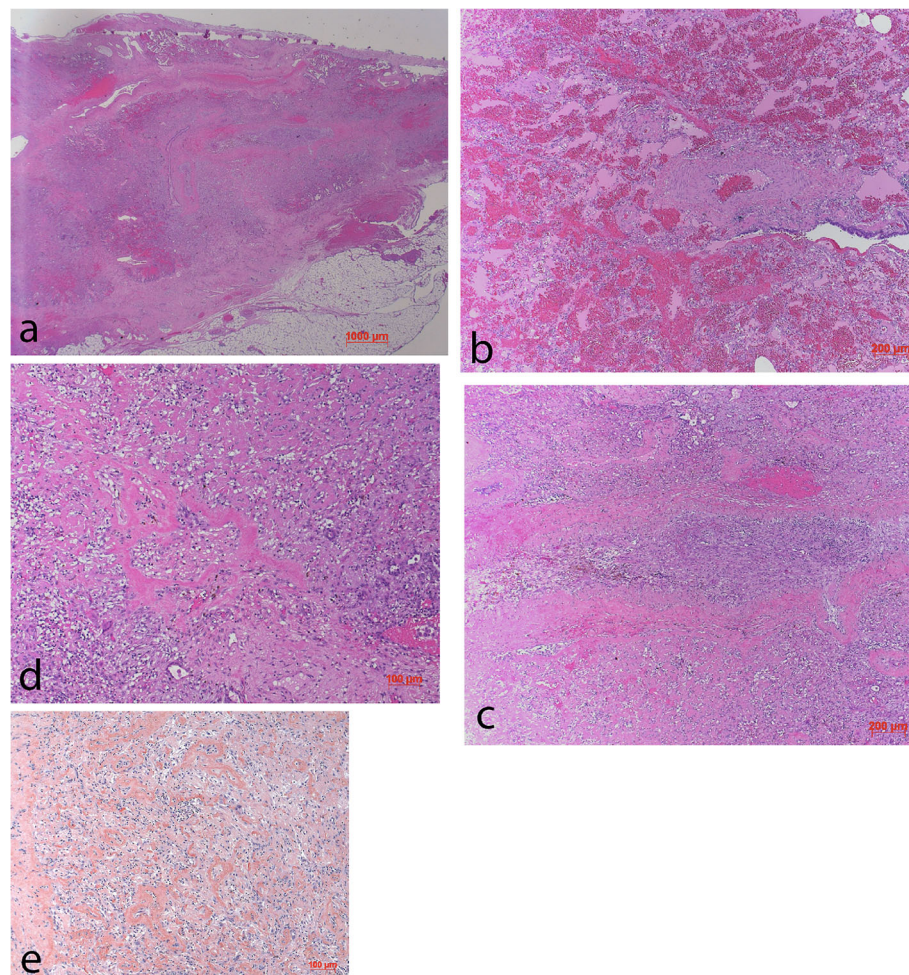


Fig. 18 SLE, **a)** overview, **b)** alveolar hemorrhage and vasculitis with thrombosis **(c)** and infarct; **d)** shows eosinophilic deposits simulating amyloid, but this corresponded to immune complexes **(e)**. H&E and immunohistochemistry for IgG, bars 1000, 200, and 100 μ m, respectively

Comments of multidisciplinary boards

In the recent consensus classification of ILD the ERS, ATS, JPS stated, that in most instances' histopathology is no longer required, only in unusual CT scan presentations a biopsy might be necessary. Cryobiopsy and BAL is not recommended. The diagnosis should be made by a board. There is a nice report on the results of such recommendations. During a meeting of pulmonologists, radiologists and pathologists each group had to analyze cases of proven IPF. When pulmonologists analyzed the cases there was a low k-value amongst them (0.11–0.56). The same applied to the radiologists. There was also a major discrepancy between clinicians in academic centers and community hospitals. When both groups merged, there was still no good correlation. When the pathologic diagnosis was disclosed, the k-value reached 0.92 (Flaherty et al. 2007). What does that mean, if pathology is no

longer the gold standard (Raghu et al. 2018)? In my personnel experience, there is a minority of IPF cases, which are correctly diagnosed by clinical and radiological data alone. Honeycombing is a feature, which is not seen in early UIP/IPF, whereas cystic remodeling in primary lung lobules can be seen in by histopathology. Myofibroblastic foci cannot be seen on CT scan. Fibrosis is not always a sign of IPF – many other diseases will cause fibrosis. Having the ability to see many consultation cases, there is a lot more to dig out of the morphology, than just UIP. This all escapes, if no more tissues are taken. On the other hand, pathologists have not done a good job by just handing over a description (UIP), instead of raising the question of the underlying etiology. So we have to learn and improve too!

Let me end with an important statement from Martin Tobin, former Editor-in-chief of the American Journal of Respiratory and Critical Care Medicine: "Controversy is

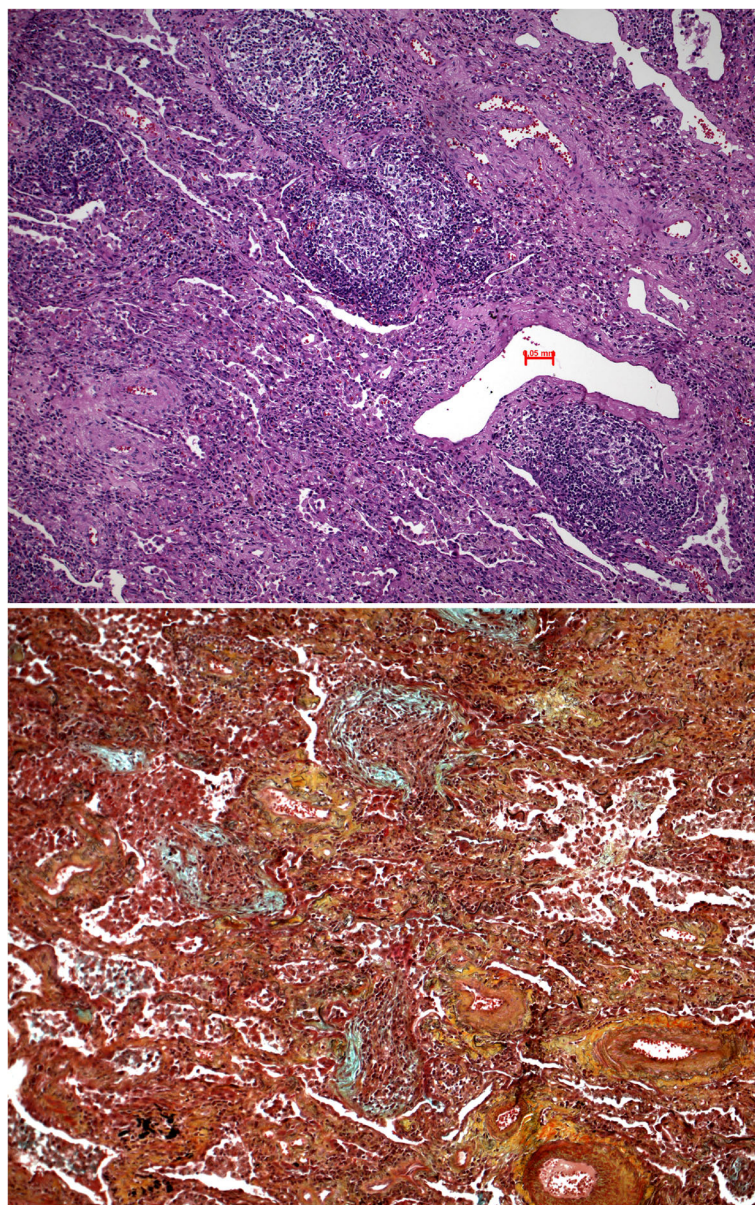


Fig. 19 Dermatomyositis, in this case the UIP pattern with myofibroblastic foci is not easily detected (upper panel), but these are highlighted by Movat stain (lower panel); there is fibrosis, cystic remodeling, but also BALT hyperplasia and sclerosis of pulmonary arteries. H&E and Movat stain, bars 50 μ m

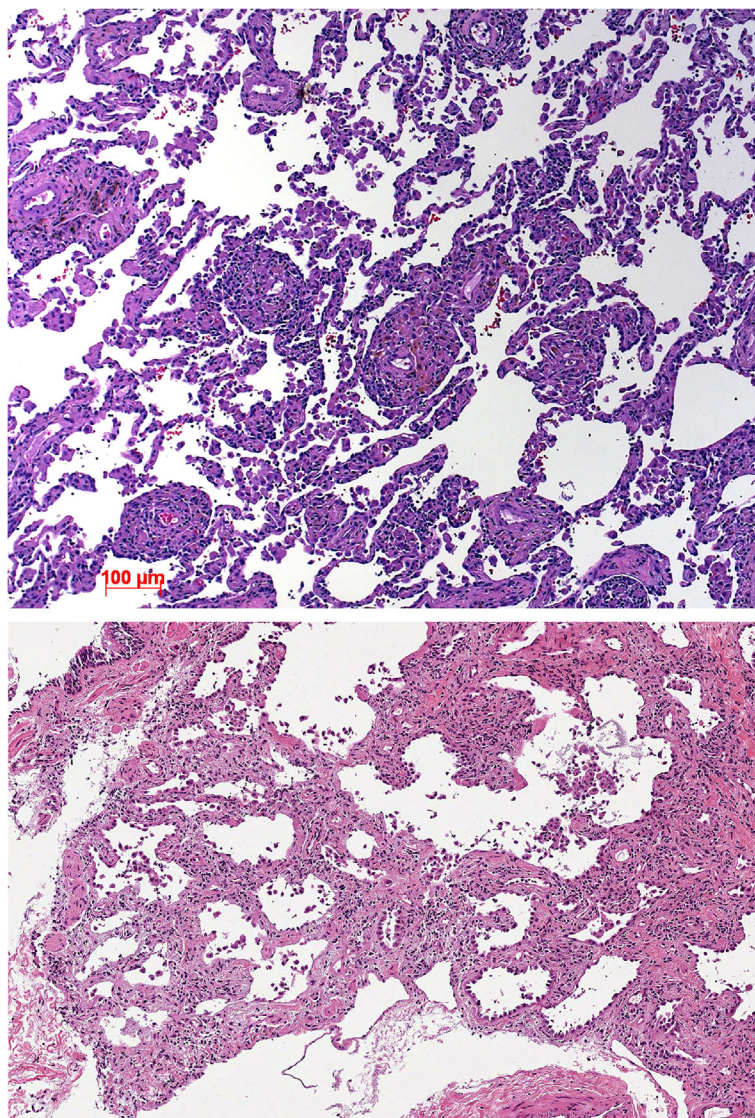


Fig. 20 NSIP, cellular upper, fibrotic lower panel; note the mixed infiltration by lymphocytes, plasma cells and histiocytes. H&E, bars 100 and 50 µm

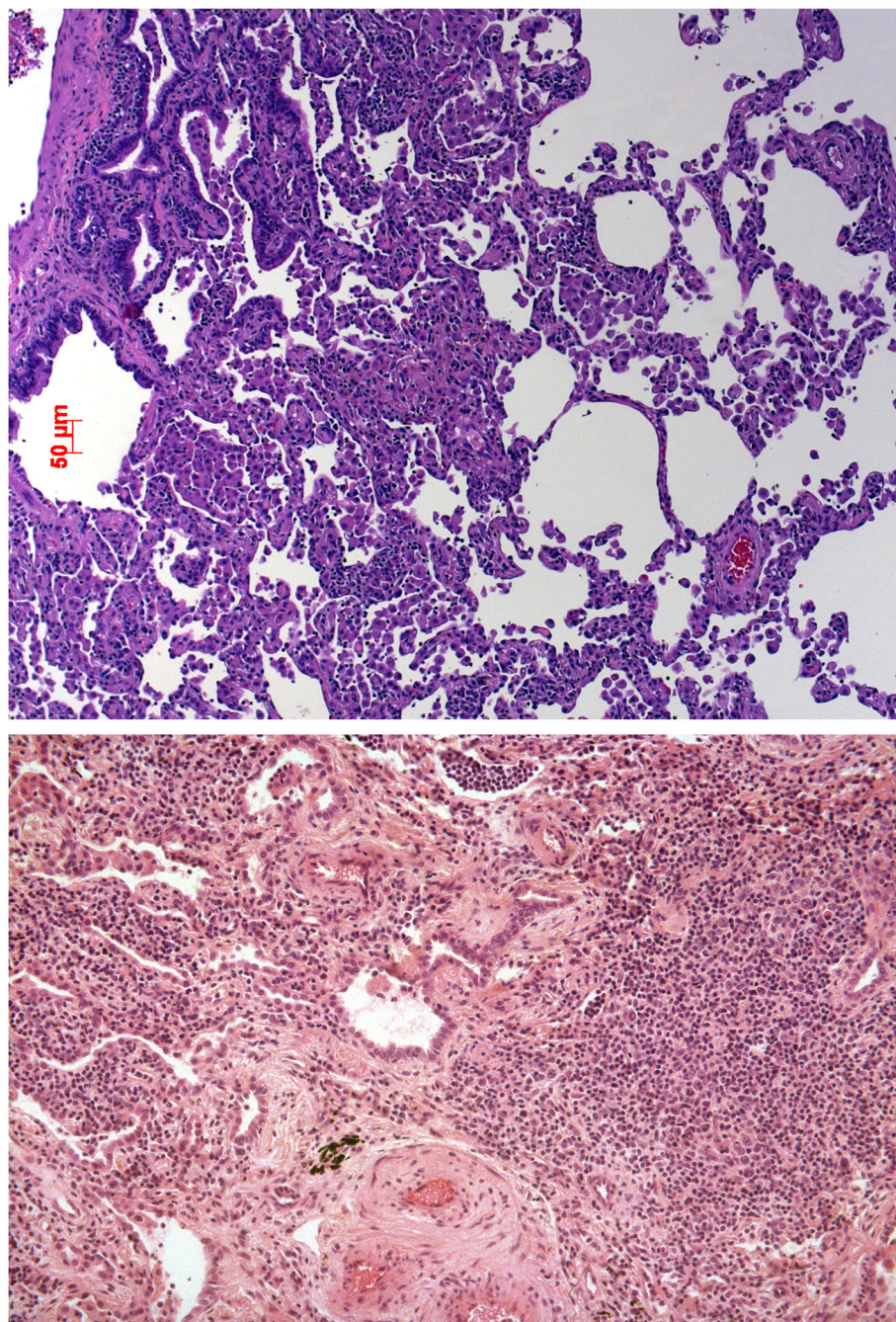


Fig. 21 NSIP upper versus LIP lower panel; whereas the infiltrating cells in cellular NSIP are mixed, the lymphocytic infiltration in LIP is monomorphic. H&E, bars 50 μ m

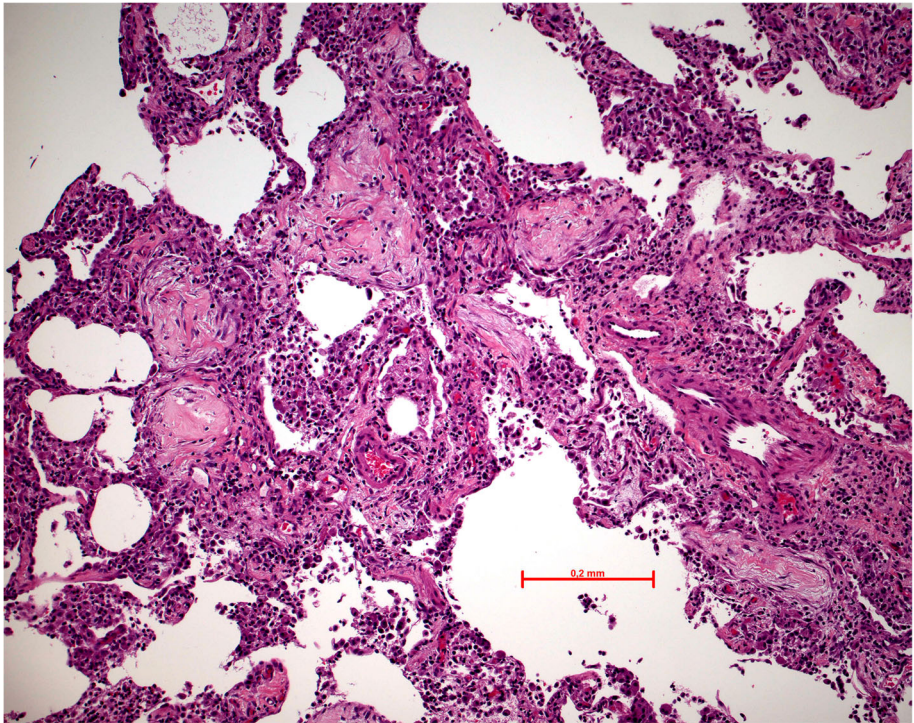


Fig. 22 Organizing pneumonia with many granulation polyps; note the newly formed blood vessels within these polyps. H&E, bar 200 μ m

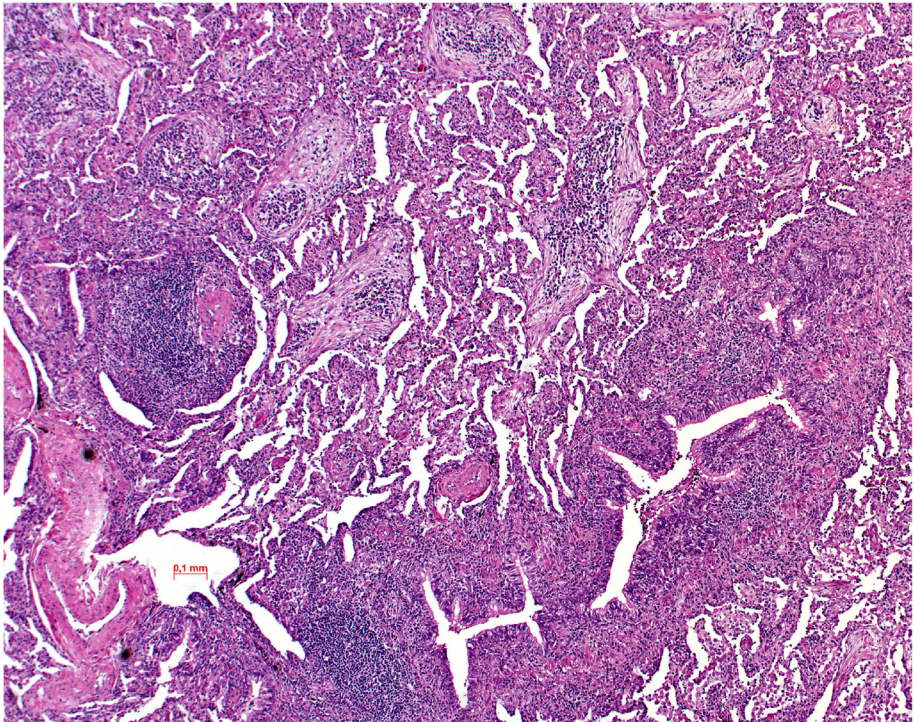


Fig. 23 OP in a case of autoimmune disease; note the combination of OP and LIP with BALT hyperplasia. H&E, bar 100 μ m

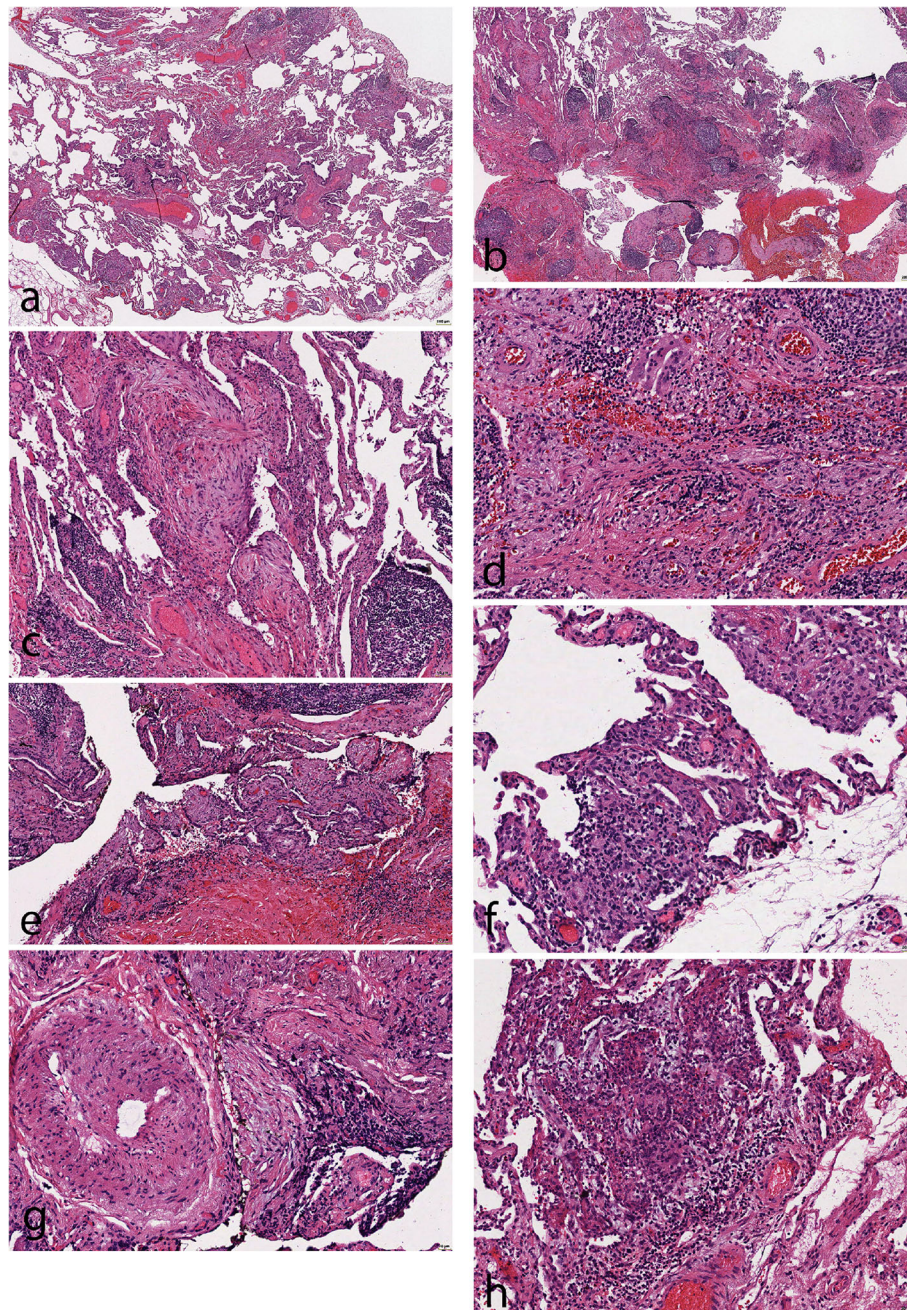


Fig. 24 Chronic hypersensitivity pneumonia, **a**) inflammatory infiltrates and cystic remodeling is seen, in **b**) BALT hyperplasia and fibrosis, in **c**) myofibroblastic foci and lymphocytic infiltrations, in **d**) fibrosis, lymphocytes and multinucleated giant cells; **e**) shows cystic remodeling and bronchiolar metaplasia, in **f** and **h**) ill formed granulomas and giant cells are seen; in **g**) massive sclerosis of a pulmonary artery next to an old myofibroblastic focus are found. H&E, bars 200, 100, 50, and 20 μ m, respectively

not a sign of confusion or a breakdown in the scientific process, but a sign of vibrancy and a motor for advance” (2003). What does that mean for consensus classification? I think all available data need to be discussed, and controversies upon the diagnosis need to be critically reviewed with these data. After such a critical review, a final diagnosis might be achieved for most cases, but cases with

contradictory findings in pathology, radiology, and clinics should kept open for close follow-up of the patient.

Abbreviations

UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; IPF: idiopathic pulmonary fibrosis; DIP: desquamative interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; GIP: giant cell interstitial pneumonia; ILD: Interstitial Lung

Disease; RB-ILD: respiratory bronchiolitis – ILD; DAD: diffuse alveolar damage; CD: cluster of differentiation; FOXP3: forkhead box P3; HTERT: human telomerase reverse transcriptase; DKC1: dyskerin pseudouridine synthase 1; TERC: telomerase RNA component; NOP10: NOP10 ribonucleoprotein; NHP2: NHP2 ribonucleoprotein; TINF2: TERF1 interacting nuclear factor 2; ABCA3: ATP binding cassette subfamily A member 3; MUC5B: mucin 5B, oligomeric mucus/gel-forming; HP: hypersensitivity pneumonia; rhA: rheumatoid arthritis; DMM: dermatomyositis; SLE: systemic lupus erythematosus; SSC: systemic sclerosis; IPAF: interstitial pneumonia with autoimmune features; BAL: bronchus associated lymphoid tissue; BOOP: bronchiolitis obliterans – organizing pneumonia

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Author's contributions

The author planned the review, selected the cases and figures. The author(s) read and approved the final manuscript.

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Consent for publication

A consent for publication was not necessary as no individual data from patients were used.

Competing interests

The author declares that he has no competing interests.

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