

# Lung in chronic autoimmune diseases and hypersensitivity – how to separate these from idiopathic pulmonary fibrosis

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## Research article

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# Abstract

## Background

Lung involvement in autoimmune disease (AID) is not uncommon, and may precede other organ manifestations. The histologic pattern is variable and difficult to interpret. Another problem was recently encountered: chronicity presenting with fibrosing pneumonia. This resulted that patients with chronic AID and usual interstitial pneumonia (UIP) were excluded from antifibrotic therapy. Creating a new category of UIP with autoimmune features (IPAF) for patients with AID enabled treatment for these patients. This however raised the opinion, that a pathological investigation for the underlying disease is not necessary.

## Results

We retrospectively evaluated 66 cases of AID, 31 cases of hypersensitivity pneumonias (HP), and 10 clinically confirmed usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF) cases. 12 additional cases could not be assigned into any of these categories. Acute AID presented with lymphocytic interstitial pneumonia, immune complex deposition, cytotoxicity for specific cell compartments, and alveolar hemorrhage. Subacute patterns most often presented with organizing pneumonia, whereas chronic pattern most often presented as UIP. Granulomas were present in some patients. UIP pattern was the most common presentation in chronic AID and HP, whereas NSIP was rather rare.

## Conclusion

The most important, statistically significant feature differentiating chronic AID or HP, from UIP/IPF are lymphocytic infiltrations into myofibroblastic foci. Other features such as granulomas, Langhans giant cells, and protein deposits were significantly associated with AID and HP, but were not encountered in all cases. This study demonstrated that the morphological analysis can uncover the possible etiology in many cases, and a more specific diagnosis can be provided to the clinicians.

## Background

Autoimmune diseases (AID) are heterogenous, some of them affecting joints, others involving blood vessels, and some with quite unspecific clinical symptoms [1–3]. They all have in common a deregulation of the immune system resulting in auto-aggression against normal tissues[4–8]. In some diseases, a clinical diagnosis is usually straight-forward as they present with a typical clinical picture: e.g. of skin affection in lupus erythematosus (LE), joint inflammation in rheumatoid arthritis (RA), or glomerular disease in systemic LE or granulomatosis with polyangiitis/Wegener's granulomatosis (GPA). Most of these AIDs can affect the lung. In a minority of cases lung involvement can precede the classical symptoms delaying or impeding the diagnosis[9]. This can result in an undetected and untreated

pulmonary disease, which might progress into chronic AID. Hypersensitivity pneumonia (HP) in the acute stage is easily diagnosed, clinically by an exposure anamnesis and typical undulating symptoms associated with exposure to the allergen, and morphologically by loose peripherally concentrated epithelioid cell granulomas combined with lymphocytic interstitial pneumonia (LIP) dominated by CD8<sup>+</sup>Tcells. Due to increased sensitivity of CT scan and awareness of fibrosing pneumonia more biopsies are performed, which results in an increasing detection of chronic AID and HP presenting with lung fibrosis.

Subacute and chronic AID and HP in lung can present with three classic patterns: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), and organizing pneumonia (OP). Rarely unspecific fibrosis of the lung is seen in this setting[1, 10–15]. UIP is the typical pattern of idiopathic pulmonary fibrosis (IPF), a deadly fibrosing pneumonia with incompletely understood etiology. Some underlying mechanisms have been reported, which might be correlated to morphologic features: continuous toxic injury by tobacco smoke toxins inducing apoptosis of pneumocytes,, repair by myofibroblasts, and regeneration, during which some epithelial cells differentiate into senescent cells[16–19]. Factors associated with aging are mutations of telomere maintenance genes[20–22] (hTERT, telomerase), affecting the regenerative capacity, regulators of homeostasis and inflammation[23–25] (surfactant apoprotein genes), contributing to prolonged inflammation, and MUC5B[26, 27]. Mutation in the promoter of MUC5B might be responsible for a reduced mucociliary clearance and probably also disrupts regeneration in the peripheral lung parenchyma[28]. Senescent cells release inflammatory cytokines, stimulate the proliferation of myofibroblasts, and prolong the repair process, finally resulting in fibrosis. What patterns in IPF might be expected from these underlying mechanisms? Toxic injury caused by tobacco smoke products will cause apoptosis of pneumocytes, a denuded basal lamina, and a proliferation of myofibroblasts – inflammatory cells likely will be absent, and only be seen in cystic remodeled areas, due to bacterial colonization. The proliferation of the myofibroblasts is driven by the senescent cells [19].

What about UIP in AID and HP? An UIP pattern has been reported in chronic AID and chronic HP. These chronic stages often clinically cannot be attributed to a specific AID, and a new term, interstitial pneumonia with autoimmune features (IPAF) has been created[29]. In chronic HP the causing allergen can often no longer be identified. Senescence seems to play also a role in these immune diseases[19]. If UIP in IPF can be differentiated from UIP in chronic AID and HP has not been evaluated in larger studies, but it might be of therapeutic and prognostic relevance[1, 12, 14, 30–32]. There are divergent reports about survival of chronic AID or HP with UIP pattern versus IPF [14, 31–35]. In both AID and HP immune cells play a major role by inducing injury to the peripheral lung. As both diseases are, similar to IPF, stepwise progressing, additional features enabling a more detailed and etiology-based diagnosis should be reported. Here we aimed to analyze the different patterns of chronic AID and HP in a retrospective series, and compare this to IPF, to identify features which might allow an etiology-based diagnosis. We believe, a more detailed pathological report over just an UIP pattern report will help in a better stratification of patients and concise discussion within the multidisciplinary team[36].

## Methods

Out of 103 cases with autoimmune diseases and 148 cases of chronic HP, 78 cases of AID and 31 cases of HP were retrieved from lung tissue archive of the Institute of Pathology, Medical University of Graz. A total of 119 tissues samples from patients with immune diseases and IPF were selected, for which a clinical diagnosis and clinical response was received either before or after the pathological report was issued. These cases were predominantly consultation cases submitted to one of the authors. All 10 IPF cases came from one institution and were clinically verified (see Suppl. Table 1 for patient characteristics and clinical data).

Table 1

Classification of cases and presence of different patterns, including combinations thereof; abbreviations: AID = autoimmune disease, HP = hypersensitivity pneumonia, RA = rheumatoid arthritis, SSc = systemic sclerosis, SLE = systemic Lupus erythematosus, IPF = idiopathic pulmonary fibrosis,, UIP = usual interstitial pneumonia, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, BALT = bronchus associated lymphoid tissue

<b>Diagnosis</b>	<b>Number of cases</b>
acute, subacute, and chronic AID	66
subacute or chronic HP	31
IPF	10
Unclassified with respect to AID/HP/IPF	12
Combinations of patterns in AID	
UIP only	26
UIP and OP	2
UIP and LIP	16
NSIP cellular	3
NSIP fibrosing	1
OP only	5
OP and LIP	6
LIP only (acute AID)	6
unspecific fibrosis	2
BALT Hyperplasia only	1
Combinations of patterns in HP	
UIP only	22
UIP and LIP	12
LIP only acute HP	4
OP and LIP, subacute HP	5
Specified AID	
RA	12
SSc	11
Sjo	4

Diagnosis	Number of cases
SLE	5
Dermatomyositis	1
Behcet	1
Raynaud	1
Good Pasture	1
Anti-phospholipid antibody syndrome	2
AID versus HP	9, including 1 case each with OP, ACIF, and unspecific fibrosis
AID versus IPF	3

## Definition of patterns

UIP was defined by the presence of myofibroblastic foci, fibrosis, cystic remodeling of lung lobules, uninvolved normal lung parenchyma, and peripheral accentuation (temporal and spatial heterogeneity). NSIP pattern was defined by uniform widening of alveolar septa by a mixed lymphocytic and histiocytic infiltration (cellular NSIP) without remodeling, or fibrosis of alveolar septa with residual inflammatory infiltrates (fibrosing NSIP) again without remodeling. Organizing pneumonia (OP) was defined by intraalveolar granulation tissue with newly formed capillaries and inflammatory infiltrates predominantly macrophages, but sometimes with residual granulocytes. LIP, a dominant pattern in immune disorders, is characterized by a diffuse monomorphic infiltration of lymphocytes and plasma cells, with a few scattered immunoblasts, with or without follicular hyperplasia of BALT (bronchus associated lymphoid tissue). In contrast to cellular NSIP, cells of the innate immune system are scarce or absent in LIP. Other features of AID and HP are histiocytic or epitheloid granulomas, amyloid or immune complex deposition with/without complement activation, isolated BALT hyperplasia, lymphocytic bronchitis/bronchiolitis, follicular bronchiolitis, and hemorrhage, often mixed in different proportions. Amyloid was defined by a positive Congo red stain with green birefringency, and in addition by immunohistochemistry for amyloid A or P. Immune complex deposition was verified by a positive immunohistochemical reactions for IGG and activation of complement components 1q, 3c, and 5–9 complex.

The tissues were obtained either by video-assisted thoracoscopic or cryobiopsies. Hematoxylin and Eosin (H&E) stained slides were available in all cases. In several cases immunohistochemistry (IHC) for lymphocyte subtypes was performed, using antibodies for CD3, CD4, CD8, CD20, and rarely for FOXP3 (regulatory T cells). All cases were re-evaluated by HP and ES. The presence or absence of the following patterns were recorded for each case: myofibroblastic foci, cystic remodeling of the peripheral lung lobules, spatial and temporal heterogeneity, fibrosis, lymphocytic infiltrates (including LIP), lymphocytes infiltrating the myofibroblastic foci, hyperplasia of bronchus associated lymphoid tissue (BALT),

histiocytic and/or epithelioid granulomas, isolated Langhans giant cells, amyloid deposition, immune complex deposition, complement activation, vasculitis, hemorrhage, vasculopathy (myxoid changes of the intima with few scattered lymphocytes), vascular sclerosis, neutrophils, eosinophils. Additional features not generally associated with fibrosing pneumonias were also recorded (e.g., bronchial and/or bronchiolar inflammation and pleuritis).

For statistical analysis cases were classified as AID, HP, and IPF. The program Kaleidagraph (Synergy Software, v4.5) was used. A significance was stated, if the p-value was  $\leq 0.05$ .

## Results

### Study cohort

There were altogether 66 cases with acute, subacute, and chronic AID, 31 cases of subacute or chronic HP, and 10 confirmed UIP/IPF cases. 12 cases could not be assigned into any of these categories (Table 1; more detailed data for each patient are given in Supplementary Table 1.).

### Histological Findings in autoimmune disease

In 44 cases an UIP pattern was seen, in two cases combined with OP; in 16 cases UIP was combined with LIP pattern. In 12 cases LIP without UIP was found, in six cases combined with OP (within this group there were acute AIDs); OP alone was seen in 5 cases, in two cases unspecific interstitial fibrosis was seen. In four cases NSIP, one fibrosing, and three cellular were seen. In one case only BAL hyperplasia was found (Table 1).

Out of these 66 cases of AID a more specific diagnosis could be established: RA in 12, systemic sclerosis SSc in 11, SLE in 5, Sjogren's disease in 4 cases, and one case each for Behcet disease, Raynaud's syndrome (secondary form), dermatomyositis, and Good Pasture syndrome. In 26 cases AID was clinically confirmed, but without a more specific diagnosis. In one of the cases a combination of SSc and SLE was discussed and in another case either Sjogren's disease or RA was discussed as a possible diagnosis. There were two cases with an antiphospholipid antibody syndrome. In both a diagnosis of an AID was suggested, and as both presented with alveolar hemorrhage, systemic vasculitis or LE was suggested.

### Findings in hypersensitivity pneumonia

In 22 of 31 cases of HP an UIP pattern was seen, which was combined with LIP in 12 cases. Four cases presented with LIP only (acute or recurrent HP), in 5 cases LIP was combined with OP; in 9 cases a differential diagnosis of either AID or HP was rendered, three of them presented with OP, airway centered interstitial fibrosis (ACIF), or unspecific interstitial fibrosis, respectively (Table 1).

### Differences of AID versus HP by Immunohistochemistry

In cases of HP and AID, where a sufficient number of lymphocytes could be evaluated, a predominance of CD8 + lymphocytes were seen in HP, whereas in AID CD20<sup>+</sup>Bcells, CD4<sup>+</sup>, and CD8<sup>+</sup>Tcells were present; whereas scattered FOXP3<sup>+</sup> regulatory Tcells were seen in HP, these were scarce in AID (Table 2).

Table 2

Features, which are helpful for the differentiation of chronic autoimmune disease and hypersensitivity pneumonia from idiopathic pulmonary fibrosis (presence of feature/pattern = 1, absence = 0); \* denotes which of the entities are statistically compared.

Features	AID	HP	IPF	significance
Lymphocytes in myofibroblastic foci	Yes* (1)  0.91 ± 0.28	Yes (1)	No* (0)  0.16 ± 0.38	*P < 0.0001
Lymphocytes in myofibroblastic foci	Yes* (1)	Yes* (1)		*P = 0.92
Granulomas or giant cells	Yes* (1)	Yes (1)	No* (0)	*P = 0.028
Granulomas or giant cells	Yes* (1)  0.66 ± 0.47	Yes* (1)  0.28 ± 0.45		*p < 0.001
Hyperplasia of BALT	Yes*  0.48 ± 0.50	Yes**  0.32 ± 0.47	No*  0.0	*AID vs IPF p = 0.001; **HP vs IPF p = 0.023  AID vs HP p = 0.09
Amyloid or immune complex deposition	Yes*	No*	No	*AID vs HP p = 0.004
Predominance of CD8 lymphocytes	no	yes	no	
Mixed lymphocytic infiltrations (CD4, CD8, CD20)	yes	no	no	

## Findings in IPF

All ten cases of IPF showed the typical UIP pattern without pronounced inflammation (Table 2). In 3 additional cases a differential diagnosis of either AID or IPF was rendered - these were cryobiopsy derived tissue samples.

*Different patterns in AID, HP, and IPF ( see Tables 2 and 3)*

Table 3

A: Features seen in autoimmune diseases. The more morphologic features are combined, the better the diagnosis can be specified.

Patterns present	Chronic Rheumatoid arthritis	Chronic SLE	Chronic SSc	Chronic Dermatomyositis	Chronic Sjögren	Chronic HP
UIP pattern	yes	no	yes	yes	no	yes
NSIP pattern	yes	no	yes	yes	no	yes
OP pattern	yes	yes	yes	yes	yes	yes
Unspecific Fibrosis	yes	yes	no	yes	yes	no
Lymphocytic infiltrations or LIP	yes	yes	yes	yes	yes	yes
Giant cells	yes	no	no	yes	no	yes
Lymphoid hyperplasia	yes	no	yes	yes	yes	yes
Epithelioid or histiocytic cell granulomas	yes	no	no	yes	no	yes
alveolitis						
Amyloid deposition	yes	no	yes	yes	yes	no
Immune complex deposition	yes	yes	yes	yes	no	no
Complement activation	yes	yes	no	no	?	no
Vasculitis						
Vasculopathy	no	yes	yes	no	no	no
Vascular sclerosis	no	no	yes	no	no	no
Alveolar hemorrhage, fresh and old	no	yes	no	no	yes	no
Neutrophils	yes	yes	yes	yes	no	no
Eosinophils	yes/no	no	no	yes	no	yes
Bronchiolitis and/or specific forms thereof	yes	no	yes	yes	yes	yes
LE phenomenon	no	yes	no	no	no	no

Table 3

B: Combinations of features which might allow a more specific diagnosis for certain chronic AIDs

<b>Chronic RA</b>	<b>UIP, LIP, granulomas, amyloid, CD4/CD8/CD20 present</b>
Chronic SLE	arterial thrombosis, hemorrhage, pleuritis, immune complex deposition
Chronic SSc	UIP, LIP, hyperplasia of BALT, vasculopathy
Chronic/subacute Sjögren	LIP, OP, lymphoepithelial lesions, CD8 + dominance
Behcet disease and other rheumatoid diseases	Fibrosis, granulomas, amyloid deposition, lymphocytic infiltrations

The presence of lymphocytes infiltrating myofibroblastic foci in AID (Fig. 1) was statistically significant different from IPF ( $p < 0.0001$ , Table 2), whereas no significant difference was seen when AID was compared to HP ( $p = 0.92$ ). Next, we compared the presence of histiocytic/epithelioid cell granulomas and/or Langhans giant cells in AID versus IPF (Fig. 2), which also showed a significant difference ( $p = 0.028$ ), as granulomas were absent in all IPF cases (Table 2); however, granulomas were present in a minority of AIDs. Granulomas were more often found in HP compared to AID, therefore the presence of Langhans cells or granulomas (Fig. 3) favor HP over AID ( $p < 0.001$ ). Isolated histiocytic giant cells were more common in HP compared to AID. The presence of hyperplasia of BALT (Fig. 4) was in favor of AID or HP ( $p = 0.001$  and  $p = 0.023$ , respectively) when compared to IPF, whereas no significance was seen when AID and HP were compared ( $p = 0.09$ ; Table 2). There was no deposition of amyloid or autoimmune complexes (Fig. 5) in IPF. When the presence or absence of deposits was compared between AID and HP, this was significant ( $p = 0.004$ ), because deposits were not seen in HP (Table 2). However, only a small number of AID cases presented with deposits, which explains the p-value. Other features such as chronic bronchitis/bronchiolitis, vasculitis, hemorrhage, and degenerative changes of the intima (vasculopathy) were seen in few cases, therefore due to the small numbers, a statistical analysis was not performed.

In more than half of the cases a more specific diagnosis of AID could be suggested to the clinicians (Table 3AB). Examples were cases of RA presenting with combinations of UIP, LIP, granulomas, and amyloid deposits (Fig. 5, 6). A combination of arterial thrombosis, immune complex deposits, and hemorrhage, sometimes combined with pleuritis pointed to SLE (Fig. 7). In acute juvenile SLE an LE phenomenon could be seen in pleuritis (Fig. 7). An LIP pattern combined with OP and lymphoepithelial lesions with predominant CD8<sup>+</sup> T cells favored Sjögren's disease (Fig. 8). Finally, UIP combined with LIP, hyperplasia of BALT, and myxoid changes of the intima of pulmonary arteries was suggestive of SSc (Fig. 9). Good Pasture disease could be suggested due to alveolar hemorrhage, fibrosis, and the proof of linear deposits of immunoglobulin at the basal membrane of alveolar septa and capillaries combined with complement activation. A pathological diagnosis of anti-phospholipid syndrome and secondary Raynaud's syndrome was not possible; in Behcet disease a rheumatoid disorder was suggested because of large fibrotic areas, few ill-formed epithelioid cell granulomas, amyloid, and scattered lymphocytic infiltration (Fig. 10).

## Discussion

Sorting fibrosing pneumonias into UIP, NSIP, and OP are usually performed in pathological laboratories. The pattern report is further discussed in a multidisciplinary team composed of clinicians, radiologists, and pathologists, proposed by international guidelines[37, 38]. These recommendations suggested not to perform biopsies, when clinical and radiological features were in favor of UIP/IPF. But, new studies showed that radiologic features of UIP are not specific enough to make a diagnosis of IPF. Wright et al evaluated 23 cases, and found that features of peribronchiolar metaplasia and giant cells or granulomas were in favor of HP and excluded IPF – features which can only be evaluated in biopsies[39]. One third of their cases could even not be solved by a multidisciplinary team discussion. Similarly Churg pointed to other features favoring HP over IPF, such as upper-lobe predominance, giant cells or granulomas, and peribronchiolar metaplasia[40]. Not much reports have focused on AID /connective tissue diseases, although patterns seen in chronic AID are very similar to IPF[40]. Even genetic alterations of surfactant and telomerase genes have been reported in AID similar to IPF[41, 42]. Whereas an NSIP pattern almost exclusively is associated with AID or HP, an UIP pattern has a wider range of differentials. Positive anti-nuclear antibodies (ANA) are not always present in chronic AID, and CT scans might also not always discriminate IPF from AID[43]. If chronic AID with UIP pattern has a better overall survival remains uncertain.

In this study we demonstrated, that a pathological analysis of patterns in addition to UIP, NSIP, or OP can add more information about the underlying etiology. Lymphocytes infiltrating myofibroblastic foci are indicators of an immune disease, either AID or HP. Other combinations of UIP with granulomas and/or histiocytic giant cells, hyperplasia of BALT, and protein deposits are also characteristic for immune disorders. Based on these findings the pathological report can exclude IPF without knowing radiologic and clinical data. The issued report can further strengthen the discussion in a multidisciplinary team to narrow down the differential diagnosis, by including distribution patterns, clinical presentation and laboratory data.

Even more, by including specific patterns in some of the AIDs the pathologic report can provide suggestions for one of the AIDs, as we have shown in roughly 40% of these cases (Table 3). RA with lung involvement can present with LIP in the acute form, but with UIP or NSIP in the chronic and subacute form, often combined with LIP in the former. Granulomas are seen especially in seropositive forms of RA. In chronic RA deposition of immune complexes as well as amyloid is common. Very large idiotypic-antiidiotypic immune complexes with granulomatous reaction are most often encountered in RA less in SLE[6, 44, 45]. Therefore, if a combination of these patterns is seen in a biopsy RA can be suggested. Subacute or chronic SLE in the authors experience rarely present with UIP, but often a combination of OP, unspecific fibrosis, thrombosis, and deposition of immune complexes is seen. In SLE these antigen-antibody complexes usually activate complement, which can be proven by IHC. SSc is known for its high numbers of autoantibodies and circulating immune complexes. In our cases an UIP pattern with hyperplasia of BALT, and vasculopathy of the pulmonary arteries, e.g. a concentric deposition of myxoid material and scattered lymphocytes within the intima of pulmonary arteries was commonly seen and did

allow the suggestion of SSc. Sjögren's disease is characterized by an aggressive lymphocytic infiltration of the mucosa of salivary and lacrimal glands, and also a similar infiltration of the mucosa of bronchi and bronchioles, mimicking lymphoepithelial lesions as seen in MALT lymphomas. A combination of OP and LIP with a CD8<sup>+</sup> Tcell infiltration (in our cases) and lymphoepithelial lesions are suggestive for Sjögren's disease.

Chronic HP can in some instances be differentiated from AID. Protein deposits either immune complexes or amyloid help to rule out HP, whereas scattered giant cells and ill-formed granulomas favor HP. In contrast to other reports, we could not see any significant difference between AID and HP with respect to BALT hyperplasia[46]. NSIP and OP patterns were relatively rare in our cases. NSIP and an isolated OP pattern in all cases were associated with AIDs, similar to previous reports[47]. However, OP pattern was combined with UIP in some cases, and more important LIP was present in several cases with an immune-based etiology.

Since several years cryobiopsies are preferred over open lung biopsies in diagnosing interstitial lung diseases, including fibrosing pneumonias. These biopsies are useful in all cases, where a clinical and radiological diagnosis already favors IPF, AID or HP. However, in those cases with unusual clinical and radiological pattern videothoroscopic biopsy is superior and should be considered if the cryobiopsy is not diagnostic. The distribution of patterns as described above can be very focal, involving different lung segments or even lobes. This is also seen on CT scans, where honeycombing might be seen focally, while ground glass opacities are present in other foci. A larger piece of tissue will increase the likelihood of sampling all these different patterns.

## Conclusion

Here we have shown that a pathological analysis can provide more than just diagnosing IPAF, which does not even include chronic HP. In our diagnostic workup we should try to be as specific as possible, and dig for the underlying etiology. In some cases, we might be able to even discern chronic HP from AID. This might provide additional clues for treatment. Even in those cases, where the pathological report can only exclude IPF this would enable clinicians to investigate additional treatment options.

A multidisciplinary team discussion is recommended by international guidelines[48]. In the view of the authors a biopsy should be performed not only in cases, where CT scan findings are inconclusive[38]. Lynch recommended a re-review of IPF cases on a regular basis, as the diagnosis might change. However, a pathological analysis can provide much more information and might early on help clinicians to better stratify their patients. In our consultation praxis we have seen cases, initially diagnosed as IPF by CT scan and clinical presentation, which later on turned into chronic AID.

## Declarations

Ethics approval and consent to participate: A consent was not required as the patient data were anonymized. The study was approved by the Ethical Committee of the Medical University of Graz (EK 24-135 ex 11/12).

Helmut Popper can submit the manuscript in behalf of all authors

All data are provided in the method and result section.

The authors declare no conflict of interest associated with this study.

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HP and ESP analyzed the cases and designed the study. LB analyzed some cases. FR and AN provided several cases, and FR did a clinical follow-up study for the IPF cases. HP wrote the draft manuscript, and all authors contributed to the final version.

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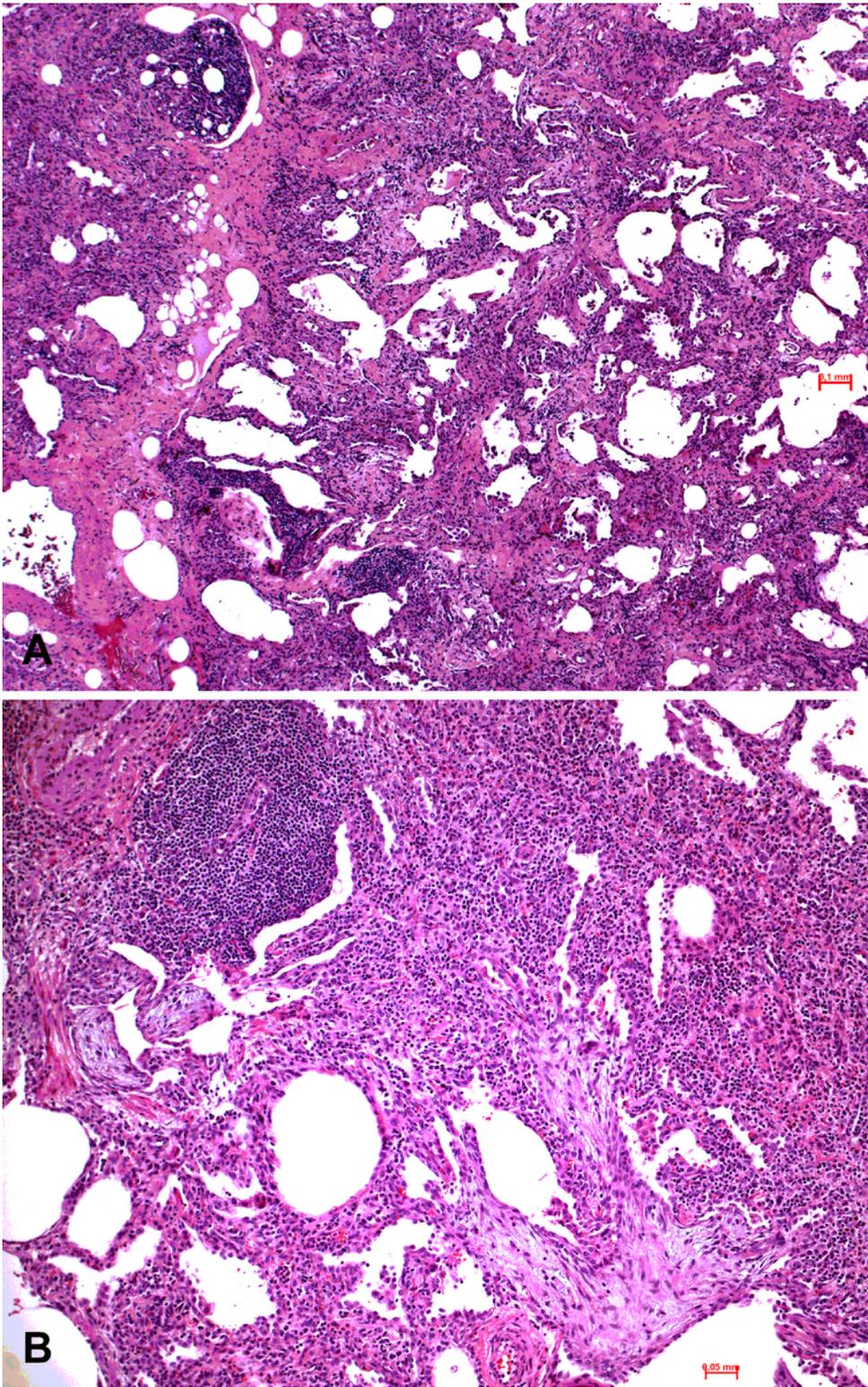
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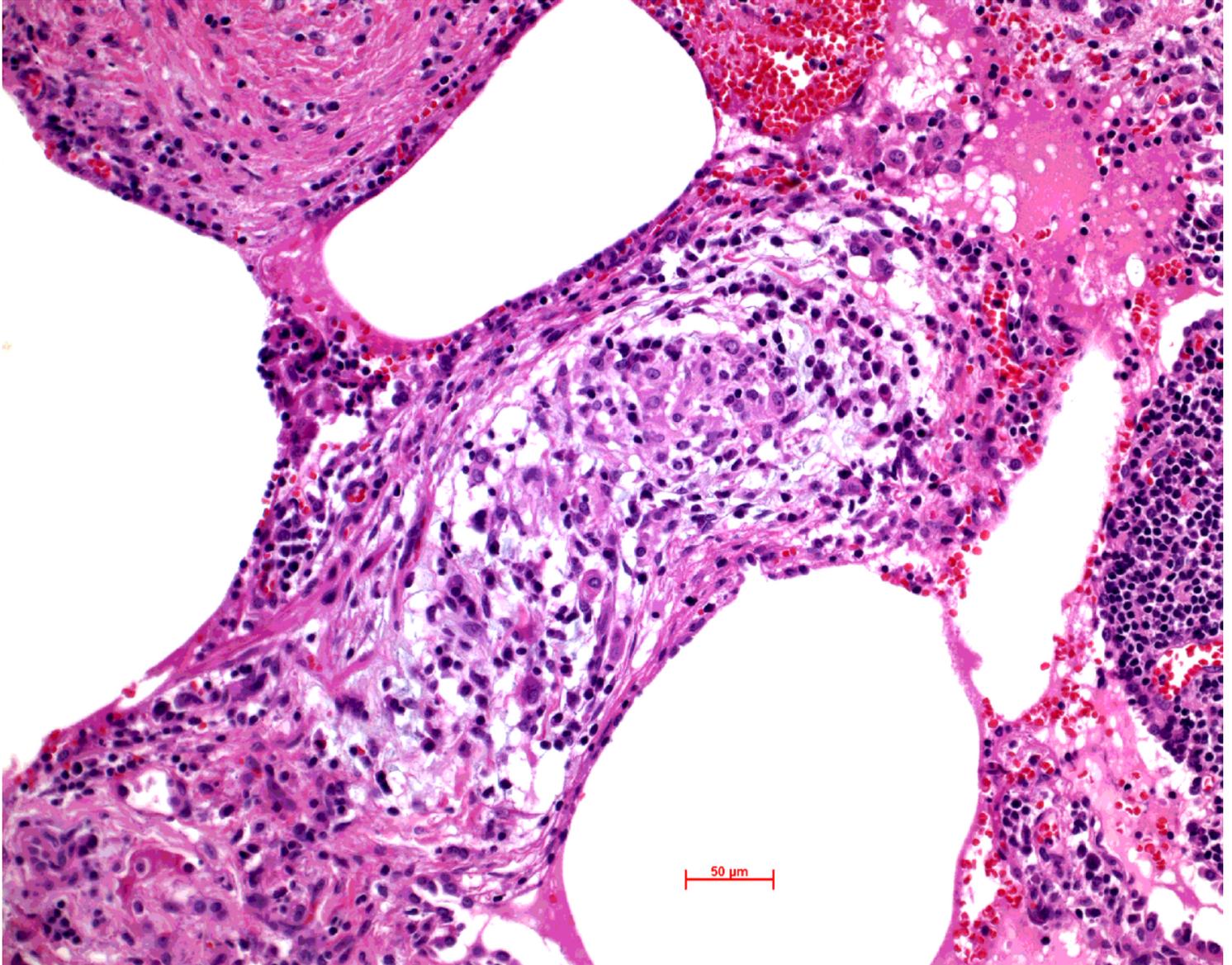
## Figures



**Figure 1**

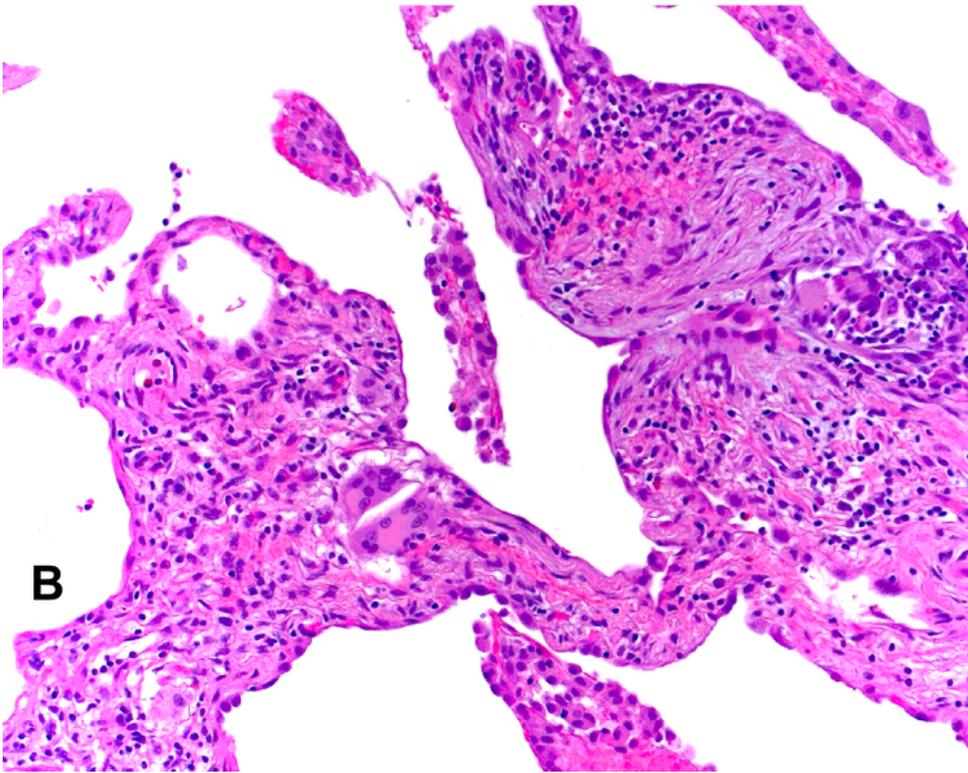
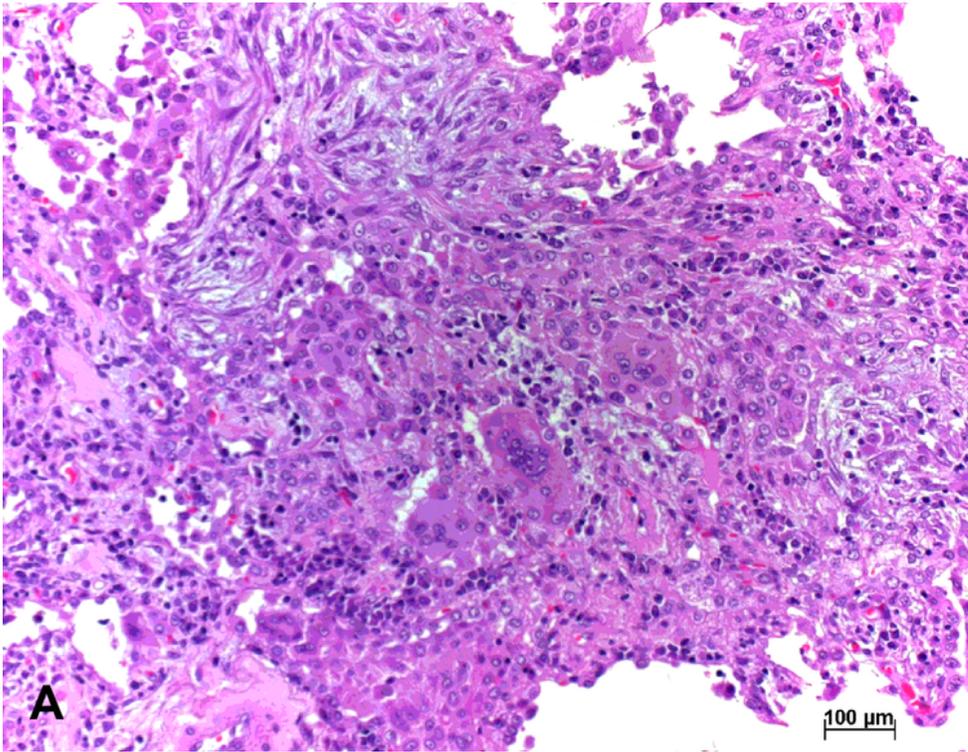
Two cases of chronic autoimmune disease are shown, in both the diagnosis of rheumatoid arthritis with lung involvement was finally made. A) Case one shows an overview with UIP pattern (fibrosis, myofibroblastic foci, cystic remodeling of lung lobules), but in addition dense lymphocytic infiltrations and hyperplasia of BALT. B) Case two shows the intimate association of lymphocytes with

myofibroblastic foci, a significant feature pointing to a chronic immune disorder with UIP pattern. H&E, bars 100, 50  $\mu$ m.



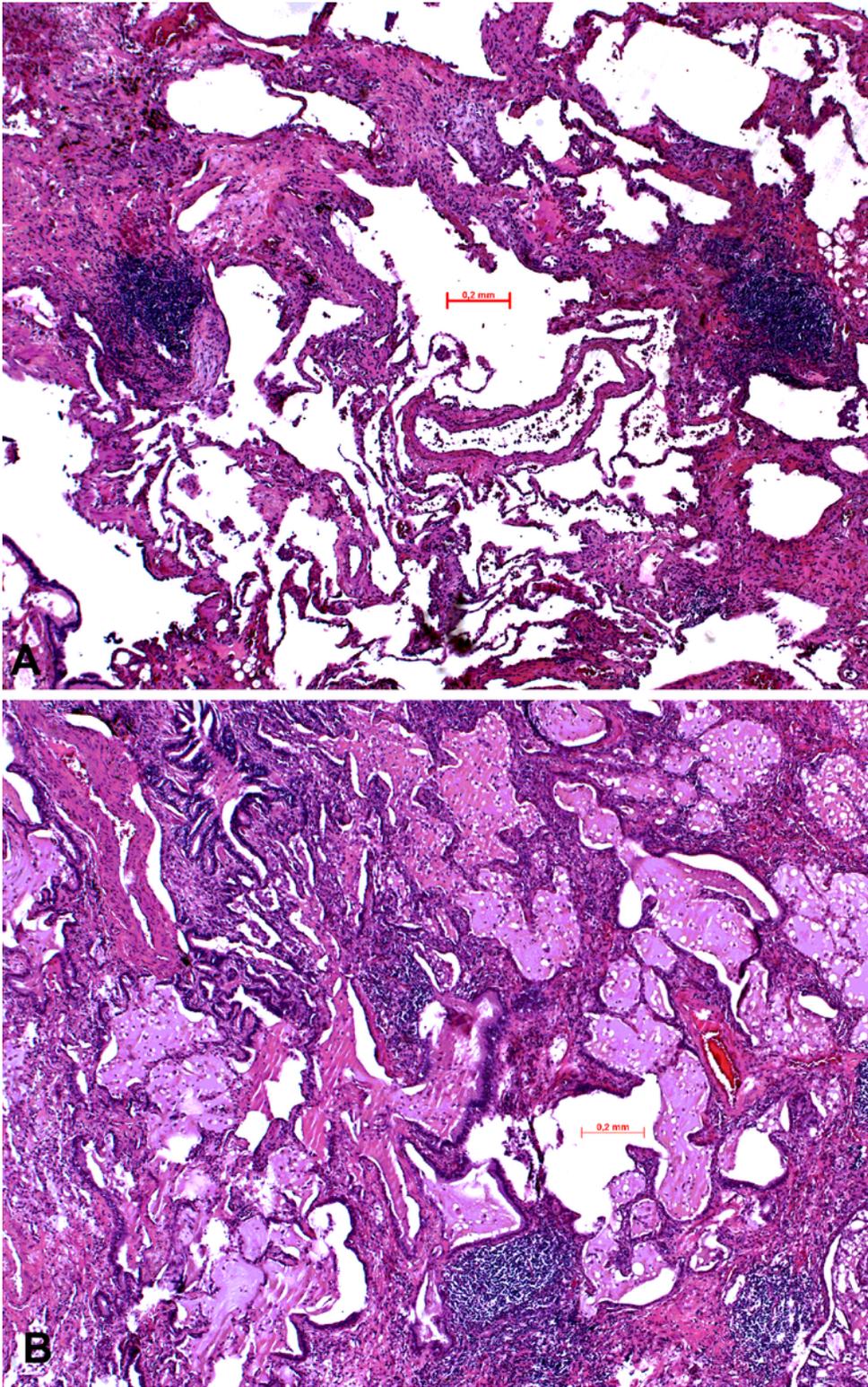
**Figure 2**

Epithelioid cell granuloma seen in another case of rheumatoid arthritis with lung involvement. This granuloma was an additional pattern together with UIP and dense lymphocytic infiltration. H&E, bar 50  $\mu$ m.



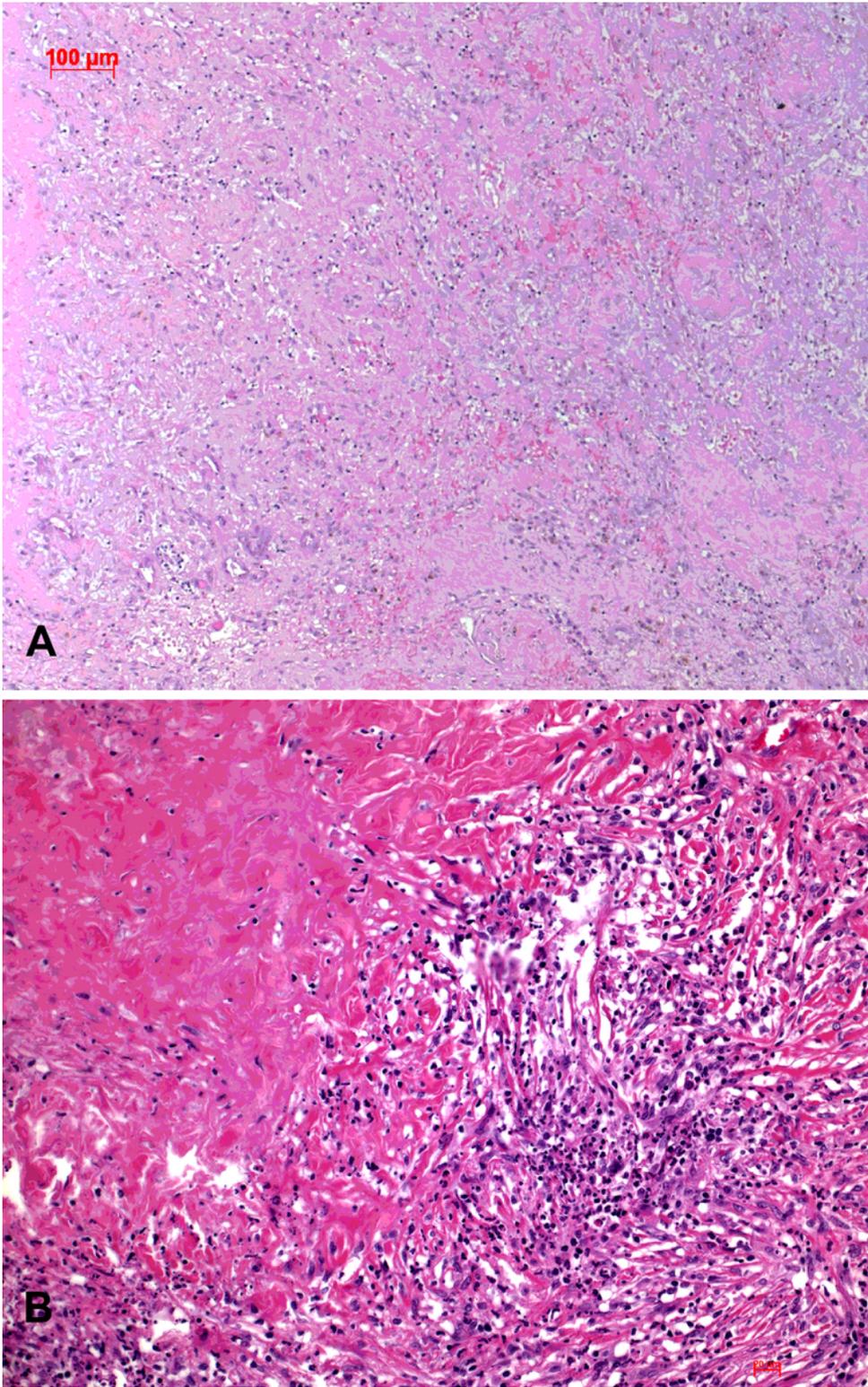
**Figure 3**

A, B: Giant cells of Langhans and foreign body type in two cases of chronic HP associated with a UIP pattern. H&E, bar 100 μm and x200.



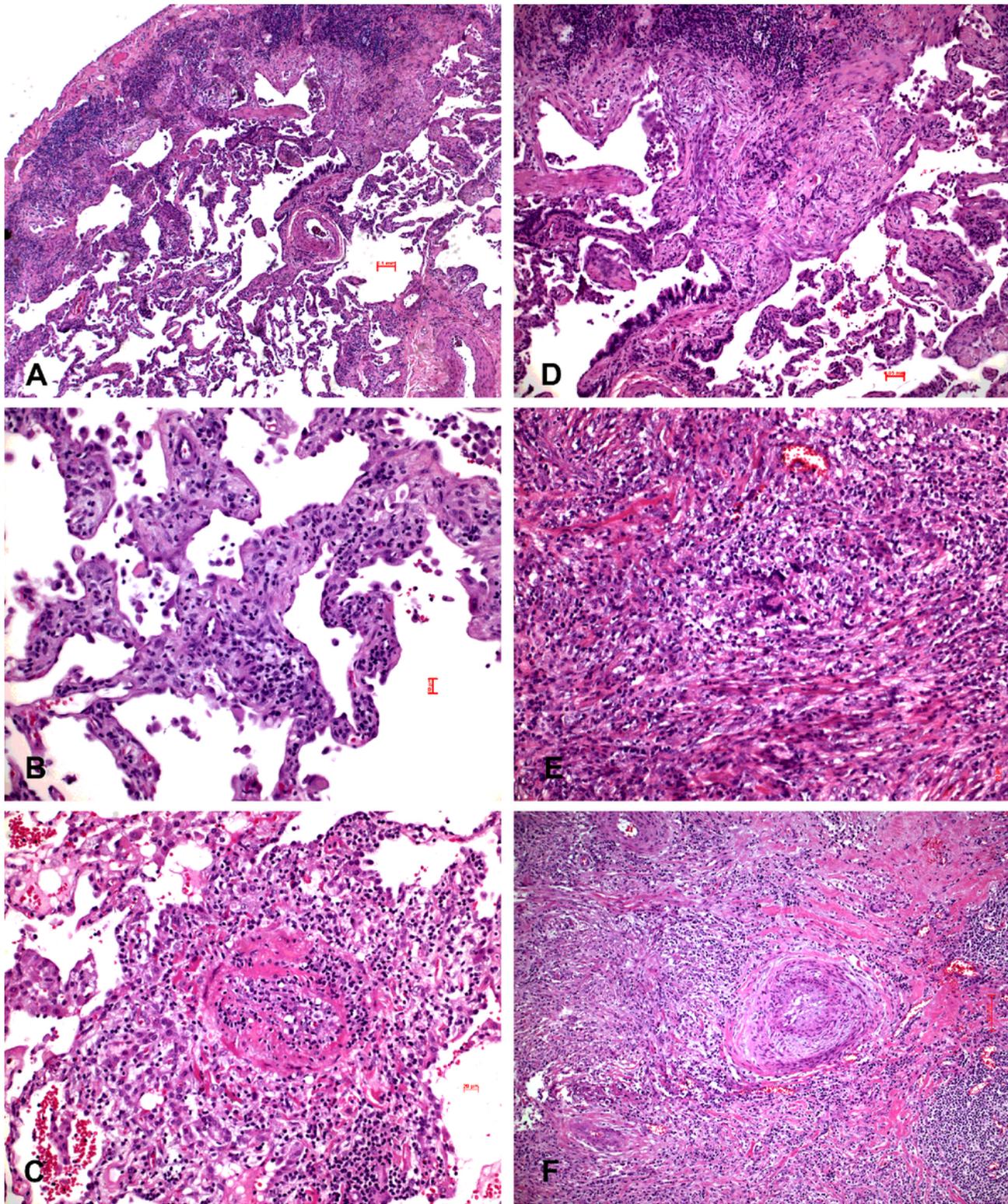
**Figure 4**

Hyperplasia of the bronchus associated lymphoid tissue in two cases of systemic sclerosis with UIP pattern. In A) myofibroblastic foci in addition to lymph follicles associated with bronchovascular bundles are seen; in B) cystic remodeling of lung lobules with mucostasis is seen. H&E, bars 200  $\mu$ m.



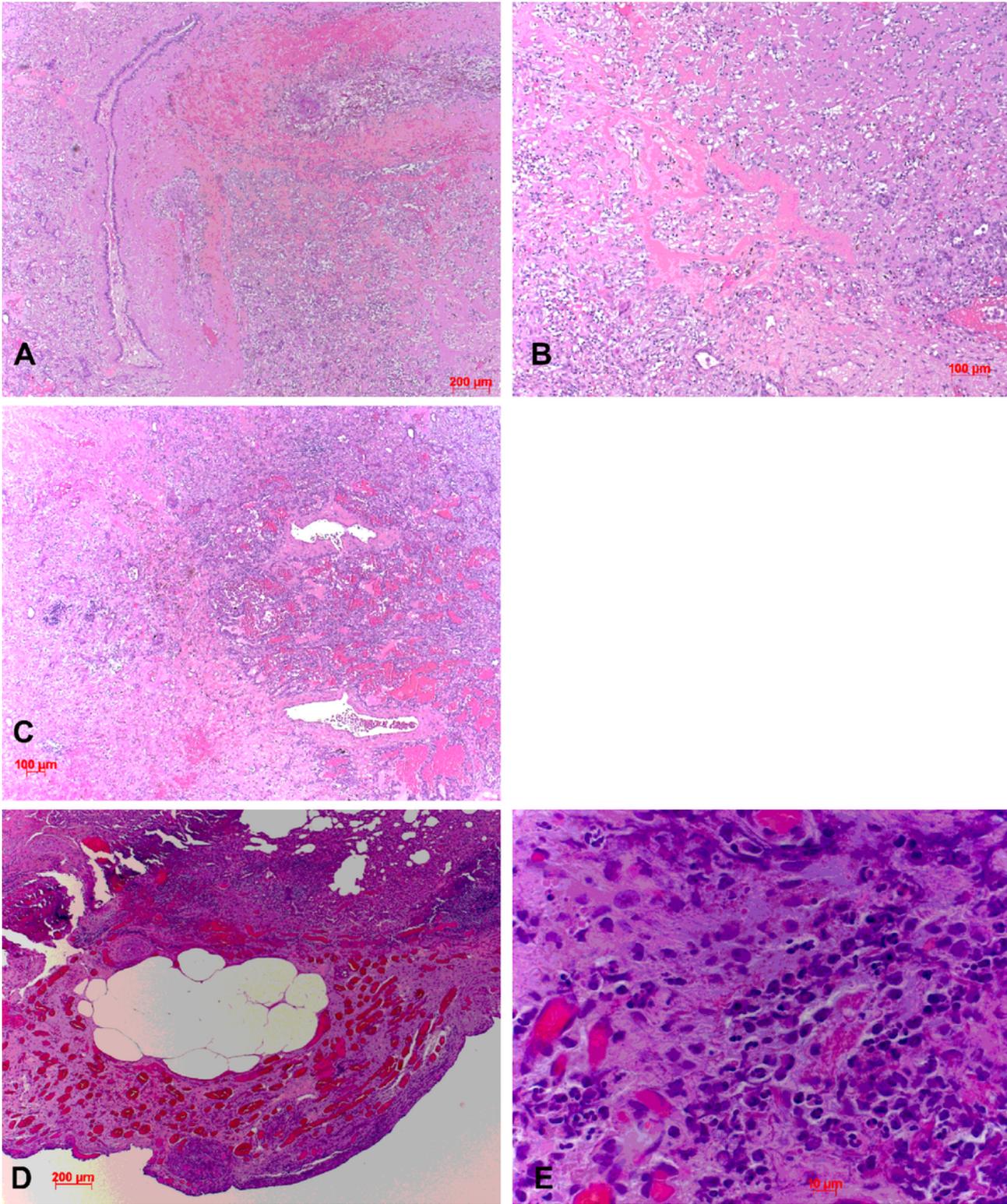
**Figure 5**

Deposition of eosinophilic material; in A) the deposit consisted of immune complexes (IGG) with complement activation in a case of systemic LE; in B) this was proven to be amyloid by Congo red stain and immunohistochemical analysis in a case of rheumatoid arthritis. H&E, bars 100, 20 μm.



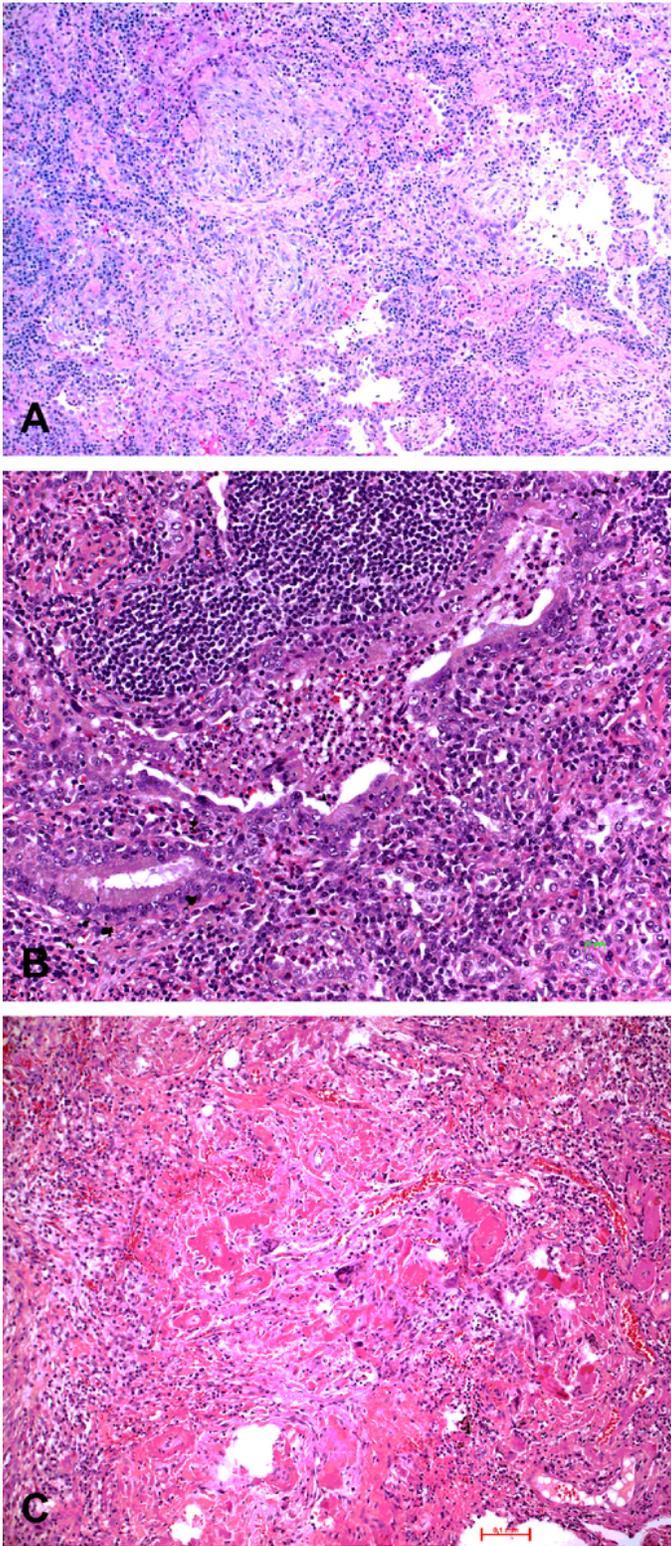
**Figure 6**

Rheumatoid arthritis with lung involvement, two cases are illustrated; Case 1 shows dense lymphoid infiltrations (A, B), myofibroblastic foci, cystic remodeling (A), histiocytic cells and early deposition of eosinophilic material (C); Case 2 showed an UIP pattern combined with dense lymphocytic infiltration (D), scattered histiocytic giant cells (E), and myofibroblastic focus combined with giant cells and BALP hyperplasia (F). H&E, bars 100, 50, 20 $\mu$ m.



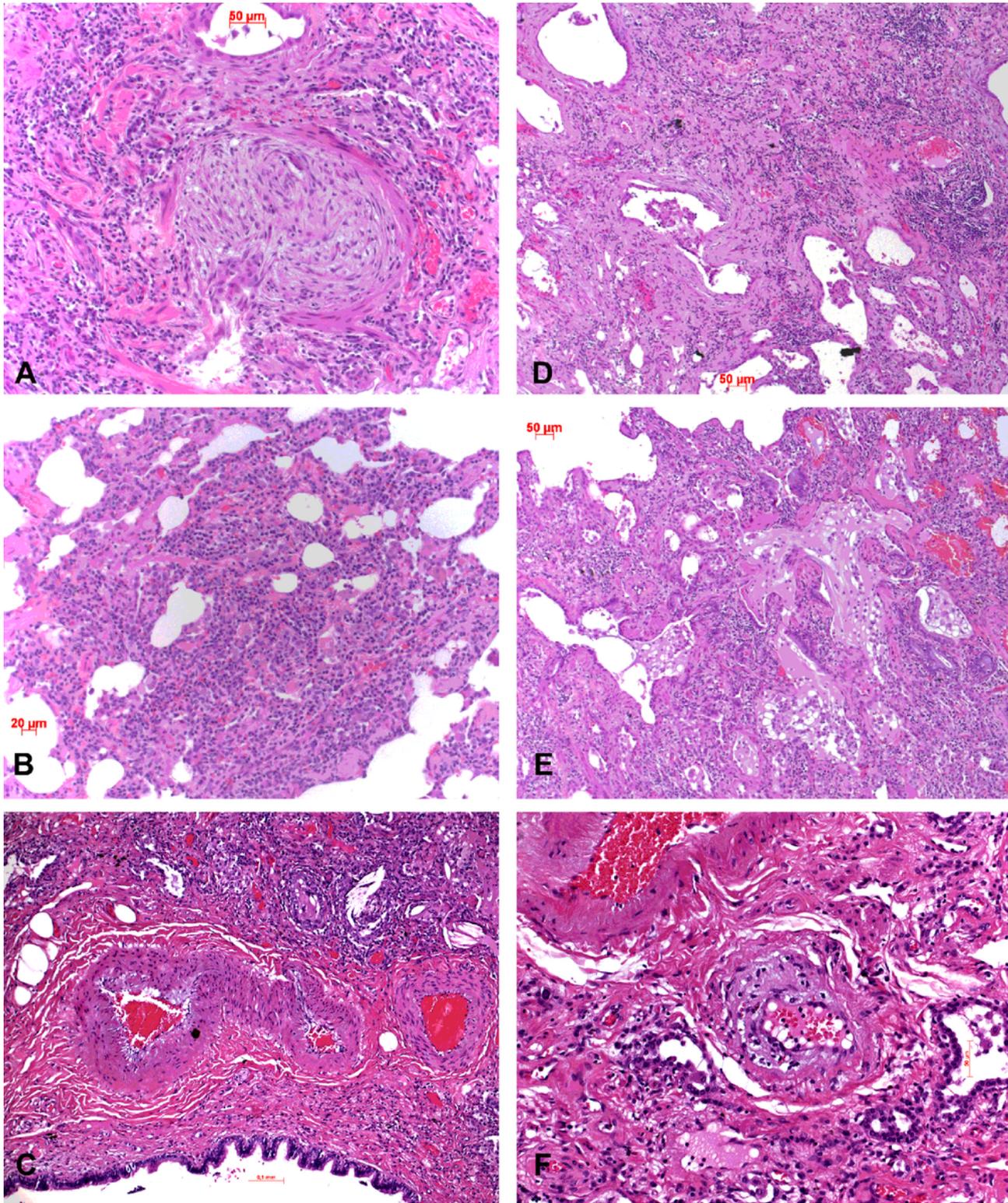
**Figure 7**

SLE, two cases; Case 1 (A-C) shows arterial thrombosis in organization (A), eosinophilic deposits mimicking amyloid and unspecific fibrosis (B), and fibrosis focally OP with hemorrhage (C); in Case 2 there was florid pleuritis with focally mild lymphocytic infiltration within the lung parenchyma (D); on high magnification of the pleuritis an LE phenomenon could be seen (E). H&E, bars 200, 100, 10 $\mu$ m.



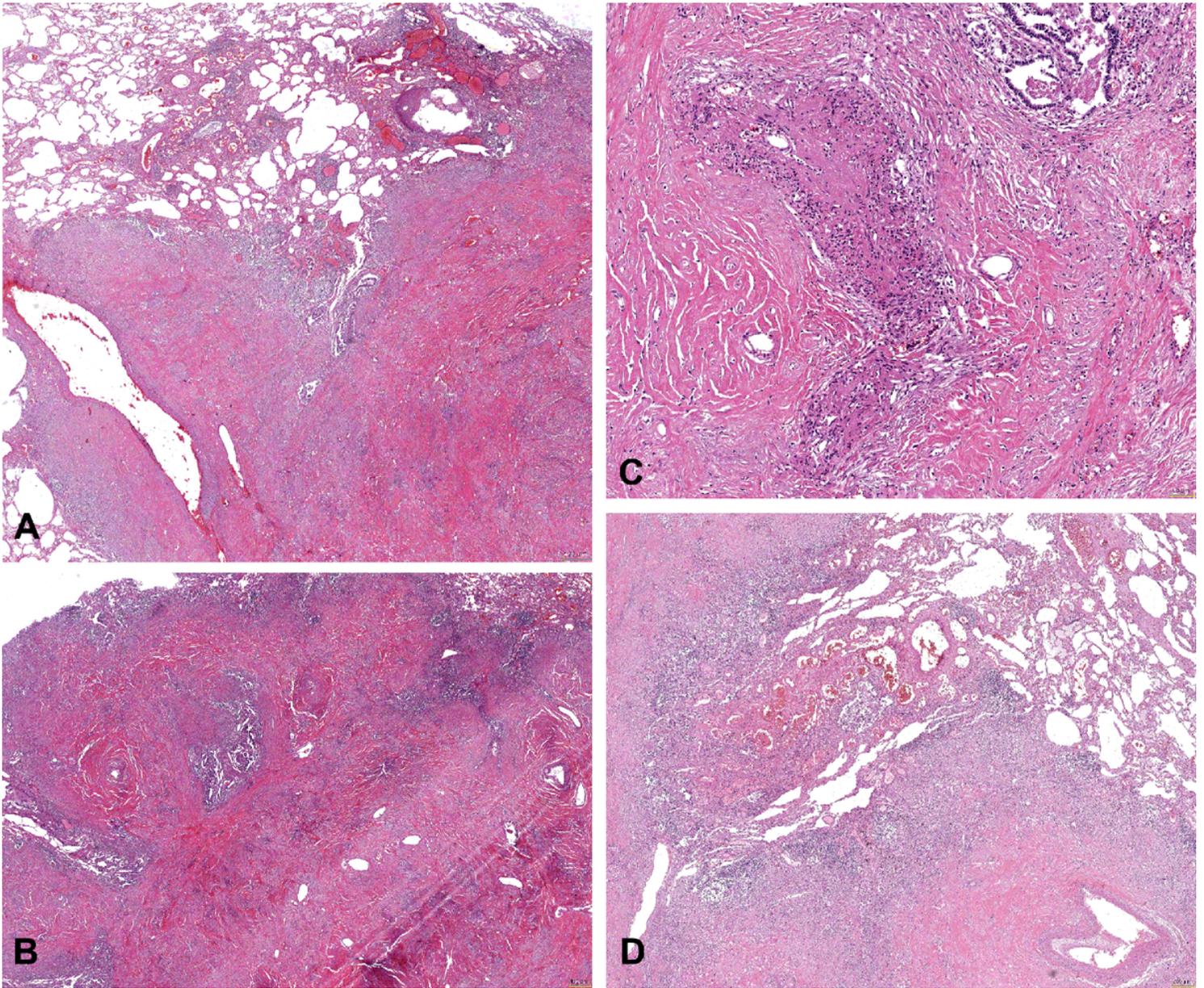
**Figure 8**

Sjogren's disease, illustrated with 2 cases; in (A) organizing pneumonia and dense lymphocytic infiltrations are seen, focally (B) showing a lymphoepithelial lesion; in case 2 an area with eosinophilic deposits is seen, a few giant cells, and fibrosis; dense lymphocytic infiltrations were present in other areas. H&E, bars 100 and 20 $\mu$ m.



**Figure 9**

Systemic sclerosis illustrated by two cases; in both cases an UIP pattern was present with myofibroblastic foci and remodeling (A, B, D, E), in case 2 already mucostasis (E); in case 1 myxoid changes of the intima was seen in a middle-sized pulmonary artery, whereas in case 2 a small artery was involved. H&E, bars 100, 50, 20μm.



**Figure 10**

Behcet disease; extensive fibrosis is seen in (A), eosinophilic deposits in (B, C) mimicking amyloid; in (C) there is an area of necrosis with an ill-formed histiocytic granuloma; in (D) focal dense lymphocytic infiltrations are seen, myxoid changes of a large pulmonary artery and eosinophilic deposits. H&E, bars 400, 200, 50 $\mu$ m.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Suppl.Table1.docx](#)