Update on Rare Idiopathic Interstitial Pneumonias and Rare Histologic Patterns

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Context.—In 2013, the revised American Thoracic Society and European Respiratory Society classification of idiopathic interstitial pneumonias (IIPs) described 2 rare IIPs and 2 rare histologic patterns. Because of the rarity of the disease, there is limited evidence related to the histology. Because the rare histologic patterns are provisional criteria, no unanimous consensus on histologic diagnostic criteria has yet been reached.

Objective.—To review the histologic features for rare IIPs and rare histologic patterns, and to provide diagnostic aids and discuss the differential diagnosis.

Data Sources.—Published peer-reviewed literature and the authors’ personal experience.

Conclusions.—Following the publication of the international consensus classification, evidence regarding rare IIPs and rare histologic patterns has accumulated to some extent, although to date the amount remains insufficient and further evidence is required. Because the diagnosis is sometimes challenging, a multidisciplinary approach represents the gold standard in reaching an accurate diagnosis for these rare disorders.

The classification of idiopathic interstitial pneumonias (IIPs) was revised by the American Thoracic Society and European Respiratory Society (ATS/ERS) in 2013.¹ The updated classification described 2 rare IIPs: lymphoid interstitial pneumonia (LIP) and pleuroparenchymal fibroelastosis (PPFE). The classification also described the provisional criteria of 2 rare histologic patterns: acute fibrinous and organizing pneumonia (AFOP) and bronchiolocentric patterns of interstitial pneumonia (BPIP). Because of the rarity of the diseases, not many reports have been published, and those that were published comprised small series. Because the rare histologic patterns are provisional criteria, no unanimous consensus on histologic diagnostic criteria has yet been reached. For the above-mentioned reasons, the histologic diagnosis is sometimes challenging. This review is designed to provide an overview of the histologic features, the differential diagnosis, and updates in this area.

IDIOPATHIC LYMPHOID INTERSTITIAL PNEUMONIA

Clinical and Radiologic Features

Lymphoid interstitial pneumonia was first proposed by Liebow and Carrington² in 1969 for lung pathology of diffuse infiltration of lymphocytes in alveolar walls. It has been argued that LIP should be included in lymphoproliferative disorders rather than in interstitial pneumonia.³

After the 2002 ATS/ERS consensus classification, stricter diagnostic criteria were adopted.¹ Nodular shadows have been excluded from the LIP pattern, many of which are now considered diffuse lymphoid hyperplasia or nodular lymphoid hyperplasia. Immunoglobulin G4 (IgG4)–related disease and lymphoproliferative disorders, such as multicentric Castleman disease, are also excluded from the LIP pattern, and many cases previously considered as LIP are now considered cellular nonspecific interstitial pneumonia (NSIP).³⁻⁹

Histologic Features

The histologic features of the LIP pattern are summarized in Table 1.

Low magnification reveals diffuse distribution of lymphocytic infiltration without chronic dense fibrotic changes (Figure 1, A and B). Although a cystic lesion may sometimes be detected on high-resolution CT (HRCT),⁵,¹⁰ it is rare to discover the cyst histologically. Unlike a honeycomb change, the cysts are sporadically distributed (Figure 1, C). The most characteristic feature of LIP is an extensive infiltration of the alveolar septum by lymphocytes, macrophages, and plasma cells without atypia, resulting in a widening of the septum (Figure 1, D). Focal alveolar...
Major histologic features are frequently observed histologic findings and clinical information. In challenging cases, the final diagnosis requires a multidimensional approach, including immunohistochemistry, flow cytometry, gene rearrangement, fluorescence in situ hybridization, polymerase chain reaction, radiologic assessment, and clinical information.

Minor histologic features are not frequently but sometimes observed in this histologic pattern.

Eosinophilic exudate in the alveolar space
Focal alveolar wall destruction
Extensive lymphoplasmacytic infiltration
Nonnecrotizing granuloma
Lymphoid follicle with or without germinal center
Chronic dense fibrotic changes
Severe architectural distortion
Distribution along lymphatic routes
Cyst formation
Lack of neoplastic condition
Lack of necrotizing granuloma

Table 1. Histologic Features of the Lymphoid Interstitial Pneumonia–like Pattern

| Major histologic features? | Diffuse and alveolar septal distribution |
|---------------------------|----------------------------------------|
|                          | Extensive lymphoplasmacytic infiltration |
|                          | Focal alveolar wall destruction          |
|                          | Eosinophilic exudate in the alveolar space |

Minor histologic features?

Lymphoid follicle with or without germinal center
Nonnecrotizing granuloma
Cyst formation

Table 2. Differential Diagnosis of Lymphoid Interstitial Pneumonia–like Pattern

| Differential Diagnosis |
|------------------------|
| Idiopathic             |
| Malignant lymphoma (especially marginal-zone B-cell lymphoma) |
| Collagen vascular disease (especially Sjögren syndrome) |
| Human immunodeficiency virus infection |
| Diffuse lymphoid hyperplasia/nodular lymphoid hyperplasia |
| Cellular nonspecific interstitial pneumonia pattern |
| Multicentric Castleman disease |
| IgG4-related disease |

Another common differential diagnosis is collagen vascular disease, especially Sjögren syndrome. Because it is histologically impossible to differentiate most LIP patterns seen in Sjögren syndrome from the idiopathic condition, it is critical to check clinical information, such as autoantibodies, Sicca syndrome, and so forth. Rheumatoid arthritis and Sjögren syndrome are frequently accompanied by small airway disease, especially follicular bronchiolitis, and may be a clue with respect to differentiation.

HIV infection can manifest with an LIP pattern, especially in children. Some cases of LIP associated with HIV tend to demonstrate more nodular accumulation of lymphocytes, resembling lymphoma (Figure 1, H).

Diffuse lymphoid hyperplasia/nodular lymphoid hyperplasia is classically the accumulation of lymphoid follicles, so its definition differs somewhat from LIP; however, some patients demonstrate overlapping histology with diffuse alveolar or interstitial infiltration of lymphocytes and lymphoid follicles.

The differential aspect is theoretically the degree of lymphoplasmacytic infiltration, although there is no consensus regarding the borderline. One possible differential histologic finding is organizing pneumonia (OP), either Masson type or incorporated type, because the NSIP pattern is often accompanied by OP. Another possible differential histological finding is the color of the lesion at low magnification, because the LIP pattern demonstrates a more blue or purple picture than NSIP does.

As previously mentioned, many former LIP cases are now reconsidered as a cellular NSIP pattern. The distinction between cellular NSIP and LIP is sometimes problematic. The differential aspect is theoretically the degree of lymphoplasmacytic infiltration, although there is no consensus regarding the borderline. One possible differential histologic finding is organizing pneumonia (OP), either Masson type or incorporated type, because the NSIP pattern is often accompanied by OP. Another possible differential histological finding is the color of the lesion at low magnification, because the LIP pattern demonstrates a more blue or purple picture than NSIP does.

Multicentric Castleman disease, which was previously classified as LIP, is now considered to be related to hyper-interleukin 6. At first glance the histology of multicentric Castleman disease resembles that of LIP, although inflammatory cell infiltration is composed mainly of plasma cells. In multicentric Castleman disease these plasma cells are distributed along the “lymphatic route,” such as the area around the bronchovascular bundle, vein, and interlobular septum, whereas in LIP they are mainly distributed along alveolar septal walls. The lymphoid follicle in multicentric Castleman disease is usually atrophic with a small germinal center.
center and is surrounded by a layered lymphocyte with an onion ring pattern. If large-sized lymphoid follicles exist, one must consider the possibility of IgG4-related disease. In such cases, immunostaining of IgG4 or IgG4/IgG ratio helps the diagnosis. Evaluating the serum interleukin 6 or IgG4 level also helps the diagnosis.29

Communication among clinicians, pulmonary radiologists, and pulmonary pathologists is important regarding the diagnosis of this rare condition, as was also emphasized in recent reports.1,20

Update on LIP

There has been little progression of knowledge because of the rarity of this disease. Most of the recent literature describing LIP consists of reports of a single case.

The American Thoracic Society/European Respiratory Society (ATS/ERS) Project Team proposed a concept of interstitial pneumonia with autoimmune features, which includes a group of patients who have characteristics of connective tissue disease but do not satisfy the diagnostic criteria of connective tissue disease.22 The concept of interstitial pneumonia with autoimmune features consists of 3 domains, of which the morphologic domain contains the histologic pattern of LIP. Albeit only in a small number of cases, interstitial pneumonia with autoimmune features manifesting as an LIP pattern has been reported (Figure 1, I).22

An immunocompromised host often develops Epstein-Barr virus–related lymphoproliferative disorders. van Zyl-Smit et al23 investigated 32 HIV-related LIP patients and reported that the frequency of positive Epstein-Barr virus LMP-1 antigen staining was similar in definite LIP and non-LIP patients, although all cases were evaluated by transbronchial biopsy. In their report, the infiltrating lymphocytes were composed mainly of B cells and CD8+ T cells.

IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS

Clinical and Radiologic Features

In 1992, Amitani et al24 reported in a Japanese article a case series of 13 patients with idiopathic upper lobe–predominant pulmonary fibrosis, which currently is designated pleuroparenchymal fibroelastosis (PPFE).25 After the original report, Frankel et al25 reported the same pathology in an English-language journal in 2004 and used the term

Figure 1. Lymphoid interstitial pneumonia (LIP)–like pattern. A and B, LIP-like pattern seen in Sjögren syndrome. A, Diffuse distribution of lymphocytic infiltration. B, Minimal architectural destruction. C and D, LIP-like pattern seen in Sjögren syndrome. C, Cystic changes (arrowheads). The cysts are sporadically distributed. D, The alveolar septum shows widening with infiltration of lymphocytes or plasma cells without atypia. E, Idiopathic LIP. The chronic fibrosis and structural distortion are seen in the end stage of the LIP pattern. F and G, LIP-like pattern seen in Sjögren syndrome. F, Eosinophilic exudate in the alveolar space. G, Nonnecrotizing granulomas. H, LIP-like pattern seen in human immunodeficiency virus infection. Nodular accumulation of lymphocytes is characteristic. I, LIP pattern seen in interstitial pneumonia with autoimmune features. This patient demonstrates high titer of antinuclear antibody but does not satisfy the diagnostic criteria of connective tissue disease (hematoxylin-eosin, original magnifications ×10 [A, C, E, H, and I], ×100 [B and F], ×400 [D], and ×200 [G]).
PPFE for the first time. Idiopathic PPFE is a chronic interstitial pneumonia, and the estimated period without symptoms is relatively long (several years). A history of pneumothorax is common. Pulmonary surfactant protein D (SP-D), a serum marker of interstitial pneumonia, may show a high value.27

Chest x-ray shows a prominent volume loss of the upper lung zone, with elevation of the hilum, whereas HRCT is characterized by a predominant shadow in the upper lobe, with delta-shaped consolidation beneath the pleura. In about half of the cases, PPFE is seen in the upper lung area and the usual interstitial pneumonia pattern is simultaneously seen in the lower lung area.3,28 There is no effective treatment for PPFE at present.1,27,29

**Histologic Features**

First, it is important to confirm the biopsy site, because the upper lung zone sometimes cannot be biopsied because of pleural adhesion. The histology sometimes differs between the upper and lower lung area. If the histologic and clinical diagnoses are not consistent, a multidisciplinary discussion is necessary.20

The histologic features of the PPFE-like pattern are summarized in Table 3.

A low-power view reveals a patchy, chronic fibrotic process. The fibrosis is mainly seen beneath the pleura and along the interlobular septum (Figure 2, A).26 Some patients demonstrate fibrous band-like thickening of the pleura. In the parenchymal fibrotic areas, the respiratory bronchiole often shows dilatation or cystic change in a traction-like manner. The cyst is covered by bronchiolar epithelium, and occasionally giant cells (Figure 2, B and C). Small airway disease is common, although mostly with a mild, nonspecific fibrotic process.

### Table 3. Histologic Features of the Pleuroparenchymal Fibroelastosis–like Pattern

| Major histologic features          | Subpleural or paraseptal distribution |
|------------------------------------|---------------------------------------|
| Patchy distribution of chronic fibrosis | Layered fibroelastosis                 |
| Collapse of alveoli                | Abrupt change from fibrotic area to the residual normal parenchyma |
| Cystic change (bronchioloectasis and/or interstitial emphysema) |

| Minor histologic features          |
|------------------------------------|
| Collagenous band-like thickening of the pleura |
| Lymphocytic infiltration           |
| Lymphoid follicle with or without germinal center |
| Small airway disease               |

| Rare histologic findings           |
|------------------------------------|
| Smooth muscle hyperplasia          |
| Fibroblastic focus                 |
| Masson-type organizing pneumonia   |
| Nonnecrotizing granuloma           |

| Negative histologic findings       |
|------------------------------------|
| Lack of honeycomb change          |
| Lack of necrotizing granuloma      |
| Lack of acute or subacute change   |

**Differential Diagnosis**

A PPFE-like pattern has been reported for several conditions. The differential diagnosis of the PPFE-like pattern is summarized in Table 4.

| Idiopathic                           |
|--------------------------------------|
| Apical cap fibrosis                  |
| Usual interstitial pneumonia pattern fibrosis |
| Chronic hypersensitivity pneumonitis  |
| Pneumoconiosis                       |
| Graft-versus-host disease             |
| Drug toxicity                        |
| Scar stage of radiation pneumonia    |
| Fibrotic stage of sarcoidosis        |
| Old mycobacterium tuberculosis       |
| Collagen vascular disease            |

On medium-power view the collapse of alveoli is observed, and deposition of elastic fibers together with collagenous fibers (so-called obliterative fibrosis) is seen in the alveolar space (Figure 2, D and E). Elastic van Gieson staining highlights a layered accumulation of elastic fibers (Figure 2, F). Upon elastic van Gieson staining, airspace collapse is prominent, but rupture of elastic fibers is inconspicuous, and the lung architecture is relatively preserved. The transition from the fibrotic area to the residual normal parenchyma is abrupt (Figure 2, D). In many cases inflammatory cell infiltration is inconspicuous, although an occasional lymphoid aggregate is apparent. Acute or subacute change, such as OP and type 2 pneumocyte hyperplasia, is not a feature. Histologic findings indicating poor prognosis have not been identified thus far.20

#### Differential Diagnosis

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|--------------------------------------|
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| Usual interstitial pneumonia pattern fibrosis |
| Chronic hypersensitivity pneumonitis  |
| Pneumoconiosis                       |
| Graft-versus-host disease             |
| Drug toxicity                        |
| Scar stage of radiation pneumonia    |
| Fibrotic stage of sarcoidosis        |
| Old mycobacterium tuberculosis       |
| Collagen vascular disease            |

| References: Travis et al,1 Kokosi et al,9 Reddy et al,25 Frankel et al,26 Lagstein,32 and Hashisako et al.55 |

**References:** Travis et al,1 Kokosi et al,9 Reddy et al,25 Frankel et al,26 Lagstein,32 and Hashisako et al.55
As alluded to above, we often observe that the upper lung area shows a PPFE pattern, while at the same time the lower lung area shows a UIP pattern. Some reports described a PPFE pattern in the upper lobe and an NSIP pattern in the lower lobe. In these discordant cases there is no consensus regarding how to classify the fibrosis. However, it is important to note that IPF with PPFE has a worse prognosis than IPF by itself. When only the lower lobe is biopsied, nonclassifiable fibrosis or a UIP-like pattern is seen in the biopsy, whereas PPFE pattern histology may not be
observed. In these cases, there is a discrepancy between CT findings and pathology; therefore, we need to make the diagnosis by using a multidisciplinary approach.\textsuperscript{20,37}

Chronic hypersensitivity pneumonitis (CHP) demonstrates various histologic patterns, including PPFE-like histology (Figure 2, G).\textsuperscript{30} Nonnecrotizing granulomas are the hallmark of hypersensitivity pneumonitis (Figure 2, H). Because small airway disease and lymphocytic infiltration around the small airway are also features of CHP, the distinction between idiopathic PPFE and CHP in cases lacking granuloma can be difficult. In reaching the diagnosis, it is helpful to refer to information on avian serum-related antibodies, exposure to avian antigens, and clinical improvement with antigen avoidance.\textsuperscript{38–40}

Several papers reported that a PPFE pattern occurs in chronic graft-versus-host disease after bone marrow transplantation.\textsuperscript{31} In addition, constrictive bronchiolitis has been reported in PPFE patients after bone marrow transplantation (Figure 2, I and J).\textsuperscript{32,43} Considering these facts, small airway obstruction is hypothesized to be a pathogenetic factor in PPFE.\textsuperscript{38}

A PPFE-like pattern has also been reported in pneumoniosis, such as asbestosis.\textsuperscript{26,44} A deposition of mixed dust helps to differentiate pneumoniosis from idiopathic PPFE (Figure 2, K through M).

In addition, it has been reported that PPFE patterns occur after chemotherapy\textsuperscript{35} or radiotherapy.\textsuperscript{26}

**Table 5. Histologic Features of Acute Fibrinous and Organizing Pneumonia--like Pattern\textsuperscript{a}**

| Major histologic features | \begin{itemize}
| Accumulation of fibrin inside the alveolar space
| Associated with organizing pneumonia (either Masson type or incorporated type)
| Type 2 pneumocyte hyperplasia
| Edematous alveolar septum widening
| \end{itemize}
| Minor histologic features | \begin{itemize}
| Patchy distribution
| Alveolar hemorrhage (not extensive)
| Alveolar space exudate
| Rare histologic findings | Infiltration of neutrophils and/or eosinophils
| Negative histologic findings | Lack of hyaline membranes
| Lack of chronic fibrosis and/or severe architectural modification
| Lack of severe eosinophilic infiltration
| Lack of vasculitis and/or capillaritis
| Lack of infection, especially Pneumocystis jirovecii
| \end{itemize}

\textsuperscript{a} References: Travis et al,\textsuperscript{1,3} Kokosi et al,\textsuperscript{9} Beasley et al,\textsuperscript{30} Hughes and Beasley,\textsuperscript{34} Hashisako et al.\textsuperscript{35}

**Update on PPFE**

Pleuroparenchymal fibroelastosis was previously thought to be a rare condition, but in recent years its increased prevalence has become much more apparent. Nakatani et al.\textsuperscript{46} reported that 12 of 205 consecutive ILD patients (5.9%) received a diagnosis of PPFE. Oda et al.\textsuperscript{47} retrospectively reviewed 110 cases of IPF and identified 9 cases (8.2%) with an accompanying PPFE pattern in the upper lobe. They also revealed that IPF with PPFE demonstrated a worse prognosis than IPF alone. Because surgical lung biopsies are mainly taken from the lower lobe, PPFE may have been underrecognized.\textsuperscript{28}

Hirota et al.\textsuperscript{47} examined 4 patients who had undergone surgical lung biopsy twice, or who had undergone surgical lung biopsy and had been autopsied. They compared the pathology and hypothesized that interstitial inflammation or OP may be one of the early phases of PPFE.

Camus et al.\textsuperscript{45} reported on 6 patients with PPFE after chemotherapy including cyclophosphamide and bis-chloroethyl nitrosourea. They pointed out the possibility of PPFE development due to chemotherapy.

Currently there is no consensus on diagnostic criteria for PPFE. Rosenberg and Rosenberg\textsuperscript{46} proposed the following diagnostic criteria: multilobar subpleural and/or centrilobular fibrous interstitial pneumonia characterized by an extensive (>80%) proliferation of elastic fibers in nonatelectatic lung, along with absent to mild chronic inflammation and absent or rare granulomas.\textsuperscript{48} However, clinical evidence regarding PPFE remains insufficient and much more data need to be accumulated.

Recent molecular biologic techniques revealed that telomerase mutations lead to short telomere lengths and pulmonary fibrosis. Telomere abnormalities are the common mutation found in familial pulmonary fibrosis. Newton et al.\textsuperscript{49} reported that about 10% of PPFE patients also have a telomere abnormality.

**ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA**

**Clinical and Radiologic Features**

Acute fibrinous and organizing pneumonia was first described by Beasley et al\textsuperscript{50} as a variant of diffuse alveolar damage (DAD). The histologic pattern of AFOP does not meet the classic histologic criteria for DAD, OP, or eosinophilic pneumonia. This condition occurs in various disorders, such as idiopathic disease, collagen vascular disease, infection, and drug toxicity.\textsuperscript{31–35} There is an acute onset with symptoms of dyspnea, fever, and cough. The clinical course is similar to that of DAD.\textsuperscript{50,54} The radiologic features of AFOP are not well understood.\textsuperscript{3,9}

**Histologic Features**

The histologic features of AFOP are summarized in Table 5.

Similar to the OP pattern, the distribution is typically patchy. Because AFOP is an acute to subacute condition, fibrosis or severe architectural modification is basically inconspicuous (Figure 3, A). The most characteristic finding of AFOP is accumulation of fibrin inside the alveolar space, known as the “fibrin ball” (Figure 3, B). Masson-type OP has been observed within the alveolar space and is associated with the fibrin to a varying extent (Figure 3, C). In the intervening alveolar septa, edematous interstitial widening is seen, with mild to moderate inflammatory cell infiltration. Although it is minimal or focal, a myxoid fibroelastic change in the alveolar septum, usually seen in DAD, is common. Type 2 pneumocyte hyperplasia is frequently observed. It is important to note that classic hyaline membranes, the hallmark of DAD, are not identified in AFOP. Eosinophils are inconspicuous even if they are seen.\textsuperscript{50,54,55}

**Differential Diagnosis**

The differential diagnosis of AFOP is summarized in Table 6.
The AFOP-like pattern is a relatively universal tissue reaction in acute lung injury and is recognized in various diseases. Diffuse alveolar damage is the most important histologic pattern to distinguish. Originally AFOP was proposed as a subtype of DAD because the histologies of AFOP and DAD have common characteristics. In autopsy cases, DAD pattern sometimes shows intra-alveolar fibrin (Figure 3, D). From this perspective it is very difficult to make a diagnosis of AFOP in a transbronchial lung biopsy or needle biopsy. Architectural distortion is not a feature of AFOP, and if it is observed, the organizing phase of the DAD pattern should be considered in the differential diagnosis.

The OP pattern is also a condition that requires differentiation from AFOP. Moreover, the OP pattern is an interstitial pneumonia of a subacute nature, and often experience fibrin is admixed in Masson-type OP (Figure 3, E). The distinction between AFOP and OP is sometimes arbitrary because there is no consensus about the borderline between them.

In infection, especially Pneumocystis jirovecii, eosinophilic exudates are pooled in the alveolar space, resembling the “fibrin ball” of AFOP (Figure 3, F and G). If AFOP-like histology is seen, it is important to exclude infections by

Table 6. Differential Diagnosis of Acute Fibrinous and Organizing Pneumonia

| Differential Diagnosis                                      |
|-------------------------------------------------------------|
| Idiopathic                                                  |
| Diffuse alveolar damage pattern, especially organizing phase|
| Organizing pneumonia pattern                                |
| Eosinophilic pneumonia                                      |
| Infection (especially Pneumocystis jirovecii)               |
| Acute onset of hypersensitivity pneumonitis                 |
| Organizing phase of granulomatosis with polyangiitis        |
| Aspiration pneumonia                                        |
| Radiation pneumonia                                         |
| Drug toxicity                                               |

References: Travis et al,1 Kokosi et al,9 Beasley et al,50 Hughes and Beasley,54 Hashisako et al.55
periodic acid–Schiff staining and/or Grocott methenamine silver staining.58

Differential diagnosis from eosinophilic pneumonia is considered relatively easy because in eosinophilic pneumonia many eosinophils can be observed. As is often the case for acute lung injury, treatment may be performed before biopsy. In this case, there may be situations whereby eosinophils become inconspicuous because of steroids, making the diagnosis difficult. The presence of eosinophilic debris, a feature of eosinophilic pneumonia, could be helpful in the differential diagnosis (Figure 3, H).54

Acute fibrinous and organizing pneumonia–like patterns have also been reported in acute onset of hypersensitivity pneumonitis. In these cases, granulomatous histiocytic accumulation is mingled with fibrin.59

Granulomatosis with polyangiitis occasionally shows fibrin balls in the alveolar space. In granulomatosis with polyangiitis, a necrotizing vasculitis is a hallmark of granulomatosi with polyangiitis and helps to distinguish granulomatosis with polyangiitis from AFOP (Figure 3, I).

**Update on AFOP**

Since the revised ATS/ERS IIP classification in 2013, new evidence regarding AFOP has been reported. Regarding etiology, Feinstein et al60 investigated 10 cases of surgical lung biopsy–proven AFOP and reported that AFOP can be related to prior chemotherapy and history of cancer.

Regarding the clinical course, Nishino et al61 investigated 26 cases of surgical lung biopsy–proven OP and reported that intra-alveolar fibrin is related to recurrence. In another report with similar results, Onishi et al62 investigated 75 cases of small biopsy–proven OP and reported that high fibrin deposition was associated with relapse.

Radiologic features of AFOP are not well understood. Dai et al63 investigated 20 cases of small biopsy–proven AFOP. They reported that AFOP demonstrated lobar consolidation on HRCT and responded well to steroids.

**BRONCHIOLOCENTRIC PATTERNS OF INTERSTITIAL PNEUMONIA**

**Clinical and Radiologic Features**

Several authors previously described bronchiolocentric fibroinflammatory changes, such as idiopathic bronchiolocentric interstitial pneumonia, centrilobular fibrosis, airway-centered interstitial fibrosis, peribronchiolar metaplasia, and bronchiolitis interstitial pneumonia.64–68 These patterns seem to belong to the same spectrum but differ in detail in each series. In 2013, the ATS/ERS committee on IIPs proposed rare histologic patterns termed bronchiolocentric patterns of interstitial pneumonia as provisional classifications.1 Patients with BPIP are more likely to be women and nonsmokers, with cough and dyspnea being the most common presenting symptoms.64 On HRCT, more than half of the cases demonstrate lower lobe predominance, with ground-glass opacity along bronchovascular bundles. Mosaic attenuation and centrilobular nodules are sometimes seen.64

The prognosis varies depending on the study, but this is considered to be due to the different entry criteria of the studies.

**Histologic Features**

As mentioned above, this condition has been reported by various authors, and there is no consensus regarding the histologic diagnostic criteria. The histologic features of BPIP are summarized in Table 7.

At low magnification, the most characteristic feature of BPIP is multiple foci of bronchiolocentric fibroinflammatory changes (Figure 4, A). Identification of the airway-centered disease may seem easy, but some specimens are difficult to distinguish from perivenular fibrosis. Another important fact is that the areas adjacent to a large membranous bronchule may be a peripheral zone and not a central zone of a secondary lobule. Using elastic van Gieson staining helps to identify airway-centered lesions.

Several types of histology have been reported for bronchiolocentric lesions.64–68 Various degrees of fibrosis are seen in BPIP. The fibrosis is often composed mainly of collagen fibers (Figure 4, B), although in smokers it may be smooth muscle. As fibrosis progresses, the fibrotic change incorporates with interlobular septa or pleura (Figure 4, C). In the end stage, cases with honeycomb change or emphysematous cysts have also been reported (Figure 4, D).64

There are also cases in which inflammatory cell infiltration is accentuated around the bronchiole. The degree of inflammatory cell infiltration varies, and the infiltrating cells are mainly lymphocytes.64 Lymphoid follicles are relatively rare, in which case one must consider the possibility of collagen vascular disease.70

Peribronchiolar metaplasia, also referred to as Lamber-tosis, is a frequent finding in BPIP. Peribronchiolar metaplasia is characterized by the ciliated bronchiolar epithelium of the airways extending around the small airway (Figure 4, E and F). Peribronchiolar metaplasia shows mild interstitial fibrosis, and the degree of inflammatory cell infiltration varies.71

It has been reported that fibroblastic foci and OP are seen in BPIP. The fibroblastic focus is also an indicator of poor

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Table 7. Histologic Features of Bronchiolocentric Pattern of Interstitial Pneumonia

| Major histologic features | Bronchiolocentric chronic fibrosis (various degrees) |
|---------------------------|------------------------------------------------------|
|                           | Bronchiolocentric lymphocytic infiltration (various degrees) |
|                           | Peribronchiolar metaplasia |
| Minor histologic features | Organizing pneumonia (either Masson type or incorporated type) |
|                           | Fibroblastic focus |
|                           | Emphysematous change |
|                           | Giant cells (not many) |
| Rare histologic findings  | Honeycomb change |
|                           | Subpleural and paraseptal distribution |
|                           | Lymphoid follicle with or without germinal center |
|                           | Fibroelastosis |
|                           | Nonnecrotizing granuloma |
| Negative histologic findings | Lack of many granuloma |
|                           | Lack of severe dust deposition associated with pneumoconiosis |
|                           | Lack of severe smoker macrophage and/or Langerhans cells |

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*a References: Churg et al,64 Fukushima et al,65 Mark and Ruan-chiura,66 Yousem and Dacic,67 de Carvalho et al,68 and Kuranishi et al.69*
prognosis in BPIP. Mark and Ruangchira-urai reported on 31 cases of the coexistence of bronchiolitis and interstitial pneumonia, among which OP was seen in 58%. In the real world, the distinction between fibroblastic focus and OP is sometimes difficult.

**Figure 4.** Bronchiolocentric pattern of interstitial pneumonia (BPIP). A and B, Idiopathic BPIP. A, Multiple foci of bronchiolocentric fibroinflammatory changes are seen. B, Fibrosis and mild lymphocytic infiltration are seen around the small airway. C, Idiopathic BPIP. The fibrotic change incorporates with interlobular septa or pleura. D, Idiopathic BPIP. Bronchiolocentric fibrosis coexists with emphysematous change. Smoking-related disease, especially the scarring stage of pulmonary Langerhans cell histiocytosis, needs to be considered in the differential diagnosis. E and F, Idiopathic BPIP with peribronchiolar metaplasia (PBM). E, Bronchiolocentric PBM is conspicuous. F, The ciliated bronchiolar epithelium extends around the small airway into the adjacent alveoli. G and H, Usual interstitial pneumonia (UIP) pattern fibrosis looks like BPIP. G, The chronic fibrosis shows a patchy and micronodular pattern. H, Elastic van Gieson staining highlights the pleura and the septum of secondary lobules (green lines). The chronic fibrosis is basically distributed around the green line. The true small airways (arrows) show little fibrotic change. This histology is interpreted as UIP pattern. I, Hypersensitivity pneumonitis. Bronchiolocentric distribution of chronic inflammation is seen. High magnification reveals multiple foci of poorly formed nonnecrotizing granuloma and lymphocytic infiltration (inset) (hematoxylin-eosin, original magnifications ×10 [A, C, D, E, G and I], ×100 [B and I, inset], and ×40 [F]; original magnification ×10 [H]).

**Table 8. Differential Diagnosis of Bronchiolocentric Pattern of Interstitial Pneumonia**

| Diagnosis                              | Idiopathic                           | Usual interstitial pneumonia pattern fibrosis | Chronic hypersensitivity pneumonitis | Collagen vascular disease | Respiratory bronchiolitis | Inhalation/environmental exposures | Microaspiration | Scar of postinfection |
|----------------------------------------|---------------------------------------|-----------------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------------------|----------------|---------------------|

* References: Churg et al,64 Fukuoka et al,65 Mark and Ruangchira-urai,66 Yousem and Dacic,67 de Carvalho et al,68 and Kuranishi et al.69

**Differential Diagnosis**

The differential diagnosis of BPIP is summarized in Table 8. The early phase of the UIP pattern sometimes demonstrates a micronodular pattern. In early UIP, fibrosis might start from the perivascular area, and the distribution resembles a bronchiolocentric pattern (Figure 4, G). Using elastic van Gieson staining helps to identify the distribution of the fibrosis (Figure 4, H). It is important to distinguish UIP pattern fibrosis from BPIP because they may follow a different clinical course.

Chronic hypersensitivity pneumonitis is also a representative disease showing a BPIP-like histology. In previous reports of CHP, about 12% to 27% show BPIP-like histology.72-74 Characteristic features of CHP are poorly formed nonnecrotizing granulomas and interstitial multinucleated giant cells (Figure 4, I). Although granuloma is a feature of hypersensitivity pneumonitis, one third of the cases have no granuloma.74-75 Multidisciplinary discussion may help to diagnose CHP, as could information regarding
avian serum–related antibodies, exposure to avian antigens, and clinical improvement with antigen avoidance.29,40,76

Collagen vascular disease, such as Sjögren syndrome, has also been reported to show BPIP pattern fibrosis, especially peribronchiolar metaplasia.11 Bronchiolocentric patterns of interstitial pneumonia have been reported in systemic sclerosis, the mechanism for which is thought to be aspiration.77

Smoking-related change also shows bronchiolocentric processes, such as respiratory bronchiolitis. In heavy smokers there are cases whereby fibrosis is superimposed on respiratory bronchiolitis. When pigmented macrophages are prominent around the terminal bronchiole, respiratory bronchiolitis needs to be considered in the differential diagnosis.78

Inhalation/environmental exposures, such as mixed-dust pneumoconiosis or asbestosis, also demonstrate BPIP-like histology. Prominent dust deposition, dust macules, and presence of asbestos bodies can exclude the idiopathic form of BPIP. Prussian blue staining is sometimes helpful for identifying asbestos bodies and other iron-coated particles.

Several authors reported the association between microaspiration and airway lesions.79 Unlike classic aspiration pneumonia, it is difficult to distinguish microaspiration from BPIP because identification of aspirated substances may be difficult. A recent report related to IPF stated that airway-centered fibroblastic foci may be related to microaspiration.80

Update on Bronchiolocentric Patterns of Interstitial Pneumonia

Kuranishi et al89 investigated 68 cases of BPIP and reported that hypersensitivity pneumonitits and gastro-esophageal reflux disease are the most common etiologies. In their study, the median survival of BPIP was approximately 10 years, and histologic findings of organizing tissue in the small airways, fibroblastic foci, and microscopic honeycombing predict worse survival. Most of the patients demonstrate small airway inflammation and peribronchiolar metaplasia. A total of 50% of patients showed fibroblastic foci, whereas OP was seen in 37%. Interestingly, microscopic honeycomb change was also seen in 30% of cases. Pradere et al83 reported on 5 cases of airway-centered fibroelastosis. All patients previously received a diagnosis of asthma and were nonsmoker women. The authors hypothesized an idiopathic or asthma-associated condition.

Regarding treatment of BPIP, clarithromycin was reported to be effective in 1 study.82

CONCLUSIONS

Since the 2013 ATS/ERS classification was proposed, there have been many published reports related to rare IIPs and rare histologic patterns, although more evidence is needed to elucidate the pathologic features. The diagnosis of rare interstitial lung disease is sometimes challenging, and the differential diagnoses are various. Multidisciplinary discussion is helpful in augmenting the accuracy of the diagnosis.

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