Differential Diagnosis of Bronchiolitis Obliterans Organizing Pneumonia*

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Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct entity among the spectrum of infiltrative lung diseases without apparent causes or associated diseases. While the disease concept of BOOP is based on the combination of clinical setting and pathologic findings, histopathologic features of BOOP (ie, bronchiolitis obliterans and organizing pneumonia) are not specific and are seen in various pulmonary diseases, including infectious and noninfectious diseases. Because of this, the term BOOP has caused some confusion and, to avoid this, the term idiopathic BOOP will be used. Idiopathic BOOP is an infiltrative lung disease with a subacute clinical course, and therefore, both acute and chronic pulmonary diseases must be considered in the differential diagnosis before a diagnosis of BOOP can be established. This review is based on the Kyoto symposium on BOOP between November 29 and December 1, 1990, personal study, and a review of the literature.

Pathologic Differential Diagnosis of BOOP in the Spectrum of Infiltrative Lung Diseases

The major histopathologic findings in BOOP are as follows: polypoid masses of granulation tissues in the lumen of small airways, alveolar ducts, and some alveoli, a variable degree of interstitial infiltration of mononuclear cells and accumulation of foamy macrophages in alveolar spaces in a patchy distribution, and preservation of background architecture of the lung (Figs 1 and 2).

Pulmonary disorders that have been encountered in the pathologic differential diagnosis of BOOP are shown in Table 1 and are discussed in detail.

Infectious Pulmonary Diseases

An infectious lung disease is important to exclude in the differential diagnosis, particularly for treatment. After clinical examinations, an open lung biopsy specimen may be necessary for diagnosis of the pulmonary disease and lung tissues submitted for both microbiologic and histopathologic examinations.

Findings such as a marked infiltration of polymorphonuclear leukocytes, granulomatous changes, and necrosis are suggestive of an infectious cause.

Mycoplasma pneumoniae infection may present an acute or subacute clinical course with diffuse bilateral small nodular shadows on chest roentgenograms and may also cause histopathologic changes similar to those in idiopathic BOOP, including bronchiolitis obliterans and reparative metaplastic epithelial changes. Viruses such as the adenovirus may cause obliterative changes of bronchioles but with airflow obstruction, and therefore, they differ clinically from BOOP. Legionella pneumophila is reported to cause a BOOP pattern.

Localized Organizing Pneumonia

Localized organizing pneumonia is a focal lesion roentgenographically that shows organization in the bronchioles and distal air spaces. Besides differing clinically from idiopathic BOOP, localized organizing pneumonia may show loss of background alveolar architecture with fibrosis and marked fibrotic and inflammatory lesions in the wall of bronchioles causing luminal stenosis (Fig 3).

Figure 1. A biopsy specimen of bronchiolitis obliterans organizing pneumonia (BOOP). Granulation tissues are formed in a respiratory bronchiole (asterisk) and a few alveolar ducts. These granulation tissues are continued into the wall of the bronchiole and alveolar ducts in a few places. Bronchial and alveolar walls show mild infiltration of lymphocytes and plasma cells (hematoxylin-eosin, original magnification 4X8).

Figure 2. Another biopsy specimen of BOOP. A respiratory bronchiole (asterisk) is filled with a granulation tissue that is continued into a portion of the bronchiolar wall. Many distal air spaces are filled with foamy cells (hematoxylin-eosin, original magnification 4X8).

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Table 1—Pathologic Differential Diagnosis of BOOP in the Spectrum of Infiltrative Lung Disease*

<table>
<thead>
<tr>
<th>Findings Negative for BOOP</th>
<th>Suspected Pulmonary Diseases</th>
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<tbody>
<tr>
<td>Honeycombing in the process of the diffuse infiltrative disease</td>
<td>Usual interstitial pneumonia (UIP), other types of interstitial pneumonias</td>
</tr>
<tr>
<td>Granulomatous lesion</td>
<td>UIP; organizing diffuse alveolar damage (organizing DAD), unclassified interstitial pneumonia (unclass IP), late fibrotic lesion of pulmonary eosinophilic granuloma, others</td>
</tr>
<tr>
<td>Marked infiltration of eosinophils</td>
<td>UIP; fibrotic stage of pulmonary eosinophilic granuloma</td>
</tr>
<tr>
<td>Heterogeneous fibrotic lesions in distribution and in progress</td>
<td>Infection including TB bacillus and virus, abscess, pulmonary infarction, lymphoproliferative disorder, Wegener’s granulomatosis (WG)</td>
</tr>
<tr>
<td>Marked cellular infiltration in pleura or interlobular septa</td>
<td>Lymphoproliferative disorder, eosinophilic pneumonia, WG</td>
</tr>
<tr>
<td>Marked nodular proliferation of lymphocytic cells</td>
<td>Lymphoproliferative disorder</td>
</tr>
<tr>
<td>Marked alveolar exudates</td>
<td>DAD including infectious cause, acute interstitial pneumonia (AIP), eosinophilic pneumonia, WG, lymphoproliferative disorder</td>
</tr>
<tr>
<td>Marked infiltration of polymorphonuclear leukocyte (PMN) neutrophils</td>
<td>Infection including TB bacilli and fungi, hypersensitivity pneumonitis, lymphoproliferative disorder, eosinophilic pneumonia, WG</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Eosinophilic pneumonia, WG</td>
</tr>
<tr>
<td>Localized lesion</td>
<td>Infection (mycoplasma)</td>
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</tbody>
</table>

*The histologic evaluation of biopsy specimens is usually made for those taken from the most involved areas of the lung for the diagnosis of BOOP. Apparent causes or associated diseases such as a collagen vascular disease should be excluded considering the clinical and follow-up information before the final diagnosis of BOOP (idiopathic BOOP).

**Usual Interstitial Pneumonia**

Usual interstitial pneumonia (UIP) or idiopathic pulmonary fibrosis (IPF) has a chronic progressive course that is usually not altered by treatment. Histologically, UIP shows a highly variegated structure often including the entire spectrum from normal alveolar walls to fibrotic, end-stage (honeycombing) lesions in the same tissue sample. UIP may show severe fibroelastic lesions protruding into the terminal air spaces remiscent of those in idiopathic BOOP and may be difficult to differentiate if the biopsy sample is very small (Fig 4).

However, in contrast to BOOP, UIP shows heterogeneous fibrotic lesions in spatial distribution and in progression, variable degrees of smooth muscle proliferation in fibrotic lesions and often honeycombing with or without mucin stasis being lined with mature epithelial cells. A pattern of peripheral acinar distribution is often identified in less fibrotic areas. In contrast, BOOP is more uniform in appearance with more prominent polypoid intraluminal lesions and architectural preservation.

**Diffuse Alveolar Damage**

Diffuse alveolar damage (DAD) is a common histologic reaction in severe acute lung injury and shows a relatively broad spectrum. In the organizing stage, DAD may show granulation tissue polyps in bronchioles and alveolar ducts. In contrast to BOOP, DAD usually also shows hyaline membranes and prominent hyaline exudates with or without organization (Fig 5) but when these features are dissipating, in the later phase of DAD, differential diagnosis on histologic features alone may be difficult. Clinical correlation is helpful.

**Unclassified Interstitial Pneumonia**

Some cases of interstitial pneumonia of unknown etiology cannot be put into any of the well-described categories and may be termed as unclassified interstitial pneumonia (unclass IP). Some of those show organization in the bronchioles and distal air spaces, as well as interstitial fibrosis causing loss of background alveolar architecture (Fig 6).

**Chronic Eosinophilic Pneumonia**

Chronic eosinophilic pneumonia has significant infiltrations of eosinophils in the peripheral air spaces and/or the pulmonary interstitium. Eosinophilic infiltrations are also seen in other types of pulmonary eosinophilia, including infectious etiologies. Chronic eosinophilic pneumonia is included in the differential diagnosis of BOOP because some cases of chronic eosinophilic pneumonia may not show marked eosinophilia either in examinations of blood or bronchoalveolar lavage fluid and there are true overlap cases of chronic eosinophilic pneumonia and idiopathic BOOP clinically, roentgenographically, and histologically. In addition, few focal tissue eosinophilia may be seen in cases of chronic eosinophilic pulmonary disease.

In chronic eosinophilic pneumonia, intra-alveolar exudates of fibrin, bronchiolitis obliterans, eosinophilic microabscesses with intra-alveolar necrosis, sarcoid-like granulomas, and organizing pneumonia are observed with considerable frequency (Figs 7 and 8). Eosinophils are numerous. In contrast, in idiopathic BOOP eosinophils are sparse.
Differentiation architecture infiltrates bronchiolitis alveolitis) isk) shows lin-eosin, subepithelial nodular B(center). matory BOOP (hematoxylin-eosin, A3..-. An elastic tissue stain of the specimen shown in Fig 4A. The pericinaiar dense fibrotic lesion shows aggregation and distortion of alveolar elastic frameworks. Fibroblastic lesions protrude into the distal air space (arrows), which is covered with epithelial lining cells. Some alveolar walls show fibrous thickening (Weigert’s elastic van Gieson’s method, original magnification 4X8).

(Scattered, small nonnecrotizing granulomas) (Fig 9).

In contrast to hypersensitivity pneumonitis, cases of BOOP do not show granuloma formation and the process is more patchy in distribution. Idiopathic BOOP is not related to particular seasons or environments as seen in farmer’s lung disease and summer-type hypersensitivity pneumonitis when developing the pulmonary disorder (unpublished observation by the author).

Wegener’s Granulomatosis

Wegener’s granulomatosis is a pulmonary necrotizing granulomatosis and angiitis of unknown etiology. This disease includes a broad spectrum of pathologic manifestations, including pulmonary hemorrhage, marked tissue eosinophilia, and a BOOP pattern (Fig 10). In contrast, cases of idiopathic BOOP do not show necrotizing granulomatous lesions or marked vasculitic features and do not have the systemic manifestations of Wegener’s granulomatosis.

Collagen Vascular Disease

Collagen vascular diseases are associated with a variety of noninfectious pulmonary lesions, including a BOOP pattern. By definition, these cases are excluded.
Some drugs may cause a BOOP pattern. When the clinical history or lymphocyte stimulation tests suggest a drug to be the causative agent of the pulmonary disorder, the case is excluded by definition from being idiopathic BOOP.

**Pulmonary Lesions due to Drugs**

Pulmonary lymphoma may show organizing exudates in the bronchioles and distal air spaces in adjacent areas to the main pulmonary lesion. In contrast to BOOP, pulmonary lymphoma due to drugs is often associated with a BOOP pattern.
differential diagnoses usually also show necrotizing lesions and/or marked hyaline exudates, as well as the obvious infiltration of atypical lymphoid cells, usually along interlobular septae, bronchiolevascular bundles, and visceral pleura (Fig 11).

**Pathologic Differential Diagnosis of BOOP in the Spectrum of Bronchiolitis Obliterans**

Two types of bronchiolitis obliterans can be identified, proliferative bronchiolitis obliterans and constrictive bronchiolitis. In the former type, bronchiolar lumens have polypoid masses of organizing exudates or granulation tissues. In constrictive bronchiolitis, bronchioles are obstructed or stenosed by peribronchiolar, mural, or subepithelial fibrosis, sometimes with complete occlusion. Constrictive bronchiolitis is usually associated with airflow obstruction.

BOOP shows proliferative bronchiolitis obliterans. The spectrum of pulmonary lesions showing either proliferative bronchiolitis obliterans or constrictive bronchiolitis are reviewed in the literature.**3,3,23-26**

**Summary**

The disease concept of idiopathic BOOP has emerged from a study of many open lung biopsy cases of diffuse...
infiltrative lung disease. The histopathologic features of idiopathic BOOP have several components: bronchiolitis obliterans, organizing pneumonia, accumulation of foamy cells in the peripheral air spaces, and interstitial infiltration of mononuclear cells. These pathologic findings are nonspecific and many conditions show such a BOOP pattern. Idiopathic BOOP has been discussed in the context of bronchiolitis obliterans, organizing pneumonia, and interstitial pneumonia. While clinically idiopathic BOOP has a relatively broad spectrum of manifestation, BOOP stands as a clinicopathologic disease entity among diffuse infiltrative lung diseases of unknown etiology.

REFERENCES

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