THORAX

Editorials

BOOP and COP

Pathological descriptions of rare lung diseases often precede their clinical recognition and classification. The confusion this can cause is well illustrated in the story of OB, COP, and BOOP, which came about in the following way.

In the first place pathologists described some characteristic patterns of response to insult in the lungs: bronchiolitis with or without obliteration was one and intra-alveolar inflammation and fibrosis was another. The former was described as a common feature in infections and was found with bronchitis and bronchiectasis but occasionally occurred in isolation.¹ The latter pattern was usually seen in the context of organising infectious pneumonia, and occasionally the changes extended into the airways.^{1,2} Then three papers were published by clinicians and these pathological features became clinical diagnoses. The first two were essentially clinical descriptions of rare patterns of disease that were labelled according to the predominant histological abnormality. Geddes *et al*³ described an airway disease and called it obliterative bronchiolitis (OB), while Davison *et al*⁴ described an alveolar disease and called it cryptogenic organising pneumonitis (COP). The third paper did not describe a clinical syndrome but started from the histology. Epler *et al*⁵ looked through 2000 reports of open lung biopsies in Boston spanning 30 years and pulled out those that contained the words bronchiolitis obliterans, 94 in all. Fifty of these had no underlying cause and because the dominant pathological changes were in fact those of organising pneumonia they were described under the title of obliterative bronchiolitis organising pneumonia (BOOP). This histological pattern was essentially the same as that described by Davison in the paper on COP and had originally been described by Liebow and Carrington as bronchiolitis interstitial pneumonia.⁶

Partly because the paper on BOOP appeared in the prestigious *New England Journal of Medicine*, partly because it still has the largest number of patients, and partly because BOOP is fun to pronounce, the name has stuck even though the first two letters refer to a minor and potentially misleading part of the disorder.

If all the patients in the three reports of OB, COP, and BOOP are considered together two quite different groups emerge. Patients in the first (OB) have *small airway disease* with normal alveoli and hypertranslucent lung fields without infiltrates and show little, if any, response to treatment. OB occurs in association with rheumatoid arthritis, in graft versus host disease in bone marrow transplantation, after viral infection, and as part of rejection in lung transplantation. Patients in the second group (BOOP) have an *alveolar disease* with granulation tissue that extends variably into the airways. These patients have infiltrates on the chest radiograph and, in general, a good response to corticosteroids. This second group, which accounts for the bulk of the patients of Epler *et al*, is commoner than the first, has been the subject of many recent papers, and is discussed in more detail below.

Pathology

The original description of COP⁴ emphasises buds of connective tissue in air spaces, indicating organisation of persistent exudate by fibroblasts and capillaries from the alveolar walls. Inflammatory cells that cluster in the centre of the buds include lymphocytes and plasma cells as well as a few neutrophils and eosinophils. The connective tissue extends into the alveolar ducts and occasionally into respiratory bronchioles. There is a minor amount of interstitial inflammation and fibrosis. The reported findings in COP are almost identical to those described as BOOP by Epler *et al*.⁵

Subsequent reports have used these pathological features for diagnosis and so are largely repetitive. An interesting range of other features, however, has been mentioned. Cordier *et al*,⁷ in a review of 16 patients,

Cryptogenic organising pneumonitis, with buds of granulation tissue occupying most of the alveoli. The appearances are those of organising pneumonia, compatible, in the absence of infection and in association with characteristic clinical features, with cryptogenic organising pneumonitis. Reproduced from Corrin²⁵ by courtesy of Churchill Livingstone.

Table 1 Clinical abnormalities in bronchiolitis obliterans organising pneumonia (BOOP)

Reference n:	Davison ⁴ 8	Epler ⁵ 50	Bellomo ⁹ 6	Cordier ⁷ 16	Miyagawa ⁸ 6
	% with abnormality				
Cough	88	75	100	56	83
Fever	25	33	33	—	83
Breathlessness	88	50	83	88	50
Weight loss	75	—	33	63	—
Crackles	75	68	100	17	—
Erythrocyte sedimentation rate increased	100	—	100	100	100
Chest radiograph:					
Local	—	10	33	25	—
Multiple	100%	69	33	44	100
Diffuse	50	10	33	—	—
Steroid response	100	—	100	—	83

confirmed the predominantly alveolar distribution of the abnormalities. All patients showed some degree of interstitial inflammation and fibrosis but this was intense in only two patients. In three cases multinucleate giant cells were found. Miyagawa *et al*⁸ reported 11 patients with fleeting infiltrates on the chest radiograph and divided them into six with the above features but no eosinophils and five with eosinophils in the biopsy material. These latter patients had peripheral blood eosinophilia and fall clearly into a different clinical group of cases of pulmonary eosinophilia. Although the small airways were relatively unaffected in this eosinophilic group, pathologically the alveoli had many features in common with those of BOOP/COP, albeit with a greater predominance of eosinophils. In all of these reports the blood vessels were spared and there was no evidence of infecting microorganisms.

The pathological features of BOOP are essentially those of organising pneumonia and are therefore in no way specific. They may be found with viral and other organising infections, allergic alveolitis, irradiation pneumonitis, and drug reactions. In the idiopathic group overlap and diagnostic difficulty may also occur with Wegener's granulomatosis, and eosinophilic pneumonia when vasculitis and eosinophilia are the distinguishing characteristics.

Table 2 Associations of bronchiolitis obliterans organising pneumonia (BOOP), excluding infections

	Reference
Collagen vascular disease	
Rheumatoid arthritis	10
Polymyositis	11
Dermatomyositis	11
Chronic thyroiditis	12
Wegener's granulomatosis	13
Drugs	
Gold	14
Amiodarone	15
Cephalosporin	16
Acebutalol	15
Sulphasalazine	17
Sulindac	18
Cocaine	19
Aspiration	20
Irradiation	21
Ulcerative colitis	22
AIDS	23
(Infection)*	
(Extrinsic allergic alveolitis)*	

*The pathological changes of BOOP may be found, though the clinical picture usually differs.

Clinical features

The classical clinical presentation as described by Davison is of a subacute influenza like illness, with cough, malaise, fever, and dyspnoea and with chest radiographic abnormalities and no response to antibiotics. Other reports have emphasised a wider spectrum of both symptoms and radiographic changes. These are summarised in table 1.

Three points emerge from a comparison of the reports summarised in the table. The first is that the clinical spectrum cannot be completely defined when the condition requires histology for diagnosis. Transbronchial biopsy specimens are too small to be reliable and as only the more severe cases come to open lung biopsy the milder cases may remain undiagnosed. This is well brought out by Cordier's subgroup with localised disease that was removed to exclude neoplasm. If these patients had been given a short course of corticosteroids or possibly if they had been observed for a little longer the condition would have resolved and therefore never have been diagnosed. There may be many such patients and this clinical group remains undefined. The second issue is the range of radiographic abnormalities. Although peripheral fleeting shadows similar to pulmonary eosinophilia are characteristic it is now clear that localised disease may occur as well as diffuse changes. The localised and peripheral shadows are described as alveolar infiltrates whereas the diffuse changes have an interstitial appearance, and these changes appear more resistant to corticosteroid treatment. Whether these diffuse interstitial changes are the result of fibrosis from previous acute episodes is not clear, but this appears unlikely. A few shadows have cavitated and in a few patients pleural effusions have developed. The third point concerns the serological findings. Almost all patients have had a raised erythrocyte sedimentation rate and some have had autoantibodies. No reports have mentioned anti-neutrophil cytoplasmic antibodies.

Aetiology and differential diagnosis

There is some confusion about whether the label of BOOP should be used when the cause is known or whether it should be confined to cryptogenic cases, as suggested by the label COP. The above clinical, radiological, and pathological features have now been described in association with many different events (table 2). The fact that the same pattern occurs as a result of infections, drugs, and connective tissue disorders confirms that BOOP is not a single clinicopathological entity but rather one way in which the lung mounts an inflammatory response to a range of different insults. The term BOOP is probably best restricted to those cases of unknown cause.

The idiopathic cases are likely to prove no more

homogeneous than those with known cause. Some may be caused by an external antigen, inhaled or ingested, that has not been identified, whereas others may represent a response to a host antigen. Not surprisingly therefore there appears to be overlap with other idiopathic conditions, such as Wegener's granulomatosis and pulmonary eosinophilia. Presumably the same cause (for example, a drug) may provoke predominantly eosinophilic inflammation in one individual and a predominantly granulomatous or vasculitic response in another. BOOP appears to be another variant of such reactions.

Clinical decisions

The usual clinical problem is that posed by a patient with a pneumonic illness that fails to respond to empirical antibiotic treatment. The questions are then how far to investigate and whether to start corticosteroids in a patient who may still have an untreated infection. The results of serological investigations are not conclusive, though the presence of antinuclear antibodies or rheumatoid factor may be a clue and the absence of antibodies to organisms that cause pneumonia is a useful negative finding. Radiographic findings are not diagnostic and, although fleeting peripheral shadows are relatively characteristic and seldom occur in infectious pneumonia, the radiographic patterns are too varied and imprecise to make this distinction. Computed tomography may provide interesting pictures,²⁴ but cannot confirm or refute the diagnosis.

The central issue is whether to obtain biopsy material and if so how. Bronchoalveolar lavage has been performed in some patients but too wide a range of cell counts have been reported to be of any diagnostic value. The only exception to this might be the finding of a high eosinophil count in the lavage fluid, which would suggest an eosinophilic infiltrate even without peripheral blood eosinophilia. Nevertheless, lavage for bacteriological examination is strongly recommended. Sterile lavage fluid is mandatory for excluding infection if empirical corticosteroid treatment is intended. Transbronchial biopsy specimens are worth taking at the same time, though the diagnostic rate may be low. Sufficient material for diagnosis may, however, be obtained, especially if multiple sections are cut. Open lung biopsy provides a better specimen but at greater cost to the patient. When the clinical picture is typical and infection has been excluded some clinicians may be confident enough of the diagnosis to give a therapeutic trial of steroids. If, however, there are unusual features—for example, cavitation, haemoptysis, or suspicion of neoplasm—empirical treatment is risky and has the added disadvantage of modifying the histological features.

Once the diagnosis is secure and a response to corticosteroid treatment has been obtained, the steroid dose may be reduced over months and in most patients may be stopped altogether after 6–12 months. More rapid withdrawal may lead to relapse, and in a few patients progression or a chronic relapsing course despite treatment may suggest a systemic disorder with a vasculitic component. Such cases should be further investigated for the possibility of systemic vasculitis and immunosuppressive drugs considered.

Summary

BOOP and COP are essentially the same condition and represent one of many ways in which the lung may respond to an inflammatory stimulus. Some underlying causes of BOOP have been identified but in many cases no cause can be found. The clinical and radiological features are of a pneumonic illness that responds to corticosteroids rather than antibiotics, but as milder cases are being identified the clinical spectrum is widening. Most cases can be confidently diagnosed only by open lung biopsy, but bacteriological lavage and transbronchial biopsy followed by a trial of steroids may sometimes be considered.

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