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Bronchiolitis obliterans—current concepts

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Summary

We review current concepts about the clinical manifestations, diagnosis and treatment of patients with bronchiolitis obliterans (BO) with emphasis on clinical/pathological correlations and recent developments. BO is a relatively rare disease, but its incidence is probably higher than generally believed and is continuously rising, partly because of better recognition, but also because of increased exposure to industrial fumes, and its occurrence in lung transplantation. BO is characterized histologically by varying degrees of obliteration of the lumen of the respiratory bronchioles by organizing connective tissue often extending into the alveoli ('proliferative' BO with organizing pneumonia—BOOP) or by more extensive fibrosis and scarring of the more proximal, conductive bronchioles ('constrictive' BO). Diverse clinical conditions have been associated with the development of BO, notably viral and mycoplasma infection, toxic fume exposure and immune reactions in the setting of a collagen vascular disease, drug reaction or organ transplantation. The clinical course and features of BO may vary considerably according to the aetiology, histological pattern and stage of the disease. The most common presentation is that of a progressive dry cough and dyspnea, associated with diffuse patchy interstitial lung infiltrates on chest X-ray. In the more advanced cases, lung function tests show either restrictive or obstructive defects, depending on the extent of alveolar involvement, and hypoxemia without CO_2 retention. The diagnosis is often possible on clinical grounds, however, in a seriously ill patient uncertainty should be resolved by tissue diagnosis, preferably by open lung biopsy. Treatment is based on symptomatic therapy. The use of corticosteroids is controversial, but common. Patients with BOOP are exceptional, in that there may be no underlying condition ('idiopathic' BOOP or cryptogenic organizing pneumonia—COP), a restrictive ventilatory defect is usual and the response to corticosteroids often remarkable.

Introduction

Bronchiolitis obliterans (synonyms: obliterative bronchiolitis, obstructing bronchiolitis) is a relatively rare disease whose precise prevalence is unknown. In a study of its incidence 50 years ago, Ladue found only one case of bronchiolitis obliterans (BO) in over 42 000 autopsies.[1] Hardy *et al.* found 7 cases in almost 3000 pediatric autopsies in the only other published work on the prevalence of BO, but suggested that its true incidence was probably higher.[2] This is very likely so, since BO represents a non-specific stereotyped histopathological response of the lung to injury and many cases may go clinically unrecognized, due either to the local nature of the process, to its masquerading within the symptomatology of another pulmonary disease, or to its resolution. The first and classic study of BO was published by Lange in 1901,[3] although Gosink refers to a report by Reynauld in France in 1835 as the first description of the disease.[4] In 1977, Geddes and colleagues[5] have added rheumatoid arthritis to the

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recognized categories of BO associated with infections, inhalation of irritant fumes or unknown cause,[1] and more recently, important associations of BO with several drugs and with bone marrow or heart-lung transplantation have been reported and studied.[6] Two papers in the early eighties by Davison and by Grinblatt *et al.* [7,8] have drawn attention to patients with intra-alveolar organization of cryptogenic etiology. Following Epler's study,[9] this pattern is now accepted as an independent clinopathological entity termed either cryptogenic organizing pneumonia (COP) or BO organizing pneumonia (BOOP), which is distinct from obliteration of proximal bronchioles leading to an obstructive defect and termed 'constrictive' bronchiolitis.[4] We present a review of these two intriguing syndromes, focusing on new insights.

Histological features

Most of the pathological changes in BO occur at or beyond the conductive bronchioles, and essentially show partial or complete obliteration of the bronchiolar lumen either by polyps of organizing connective tissue ('proliferative' BO) or by fibrosis and scarring ('constrictive' bronchiolitis)[6] (Figures 1 and 2). These two patterns are quite distinct, in that proliferative BO is characterized by a more distal involvment (often extending into respiratory bronchioles and alveoli), a restrictive defect and potential reversibility which is mainly related to the inflammatory component. 'Constrictive' BO, on the other hand, affects mainly proximal bronchioles with an obstructive defect which is largely irreversible due to established fibrosis. This difference between the two syndromes will be fully discussed in the following sections. Proliferative ('classic') BO, is characterized by intraluminal polyps of myxoid connective tissue

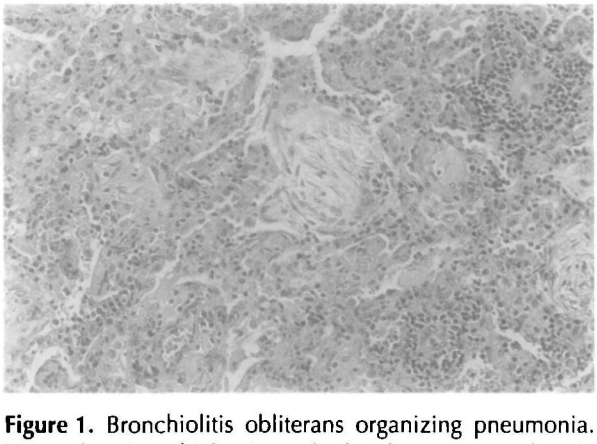

Figure 1. Bronchiolitis obliterans organizing pneumonia. Lung showing thickening of alveolar septae, chronic inflammation and obliteration of bronchiolar lumen by loose connective tissue. Open lung biopsy. Hematoxylin-eosin stain, ×150.

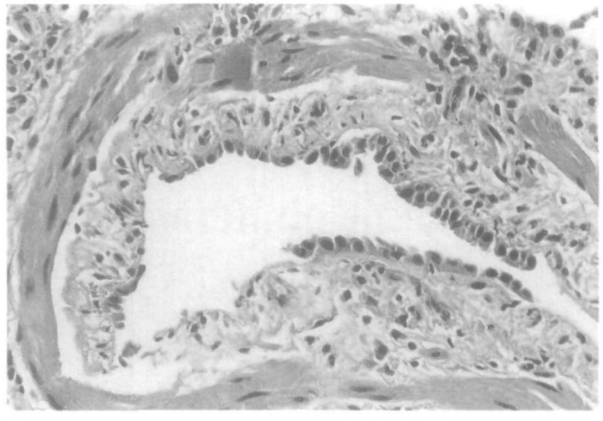

Figure 2. Post-transplant bronchiolitis obliterans. Submucosal fibrosis and mild inflammatory infiltrate narrow the lumen of a bronchiole. Transbronchial biopsy. Hematoxylin-eosin stain, ×600. (Courtesy of Joanne L. Wright, MD Vancouver; by permission.)

partially filling the bronchioles, and often involves the respiratory rather than the more proximal bronchioles. These changes are usually accompanied by organizing pneumonia–a distal extension of granulation tissue plugs (or buds) into alveolar ducts and alveolar spaces, termed BO and organizing pneumonia (BOOP).[7–9] These plugs are formed by fibroblasts embedded in loose connective tissue and by chronic inflammatory cells, particularly foamy macrophages. Other notable features include an interstitial infiltrate (mainly lymphocytes and plasma cells) of varied intensity, a maintained lung architecture and the absence of honeycombing or extensive interstitial fibrosis.[10] Since the polyps are often quite inconspicuous relative to the size of the airway lumen and a rather distal as well as patchy pattern of involvement is commonly seen, airflow is not usually significantly obstructed. In contrast, constrictive BO shows many conductive (membranous) bronchioles which are partially or entirely obliterated by fibrous tissue in the submucosa and adventitia causing scarring and concentric narrowing of the lumen.[2,4,10] Other important elements are chronic bronchiolar and peribronchiolar inflammatory infiltrate of variable density, and marked bronchiolar ectasia with stasis of mucous and macrophages forming mucous plugs within the lumen. Smooth muscle hypertrophy and necrosis of bronchiolar epithelium may also be seen. Thus, in constrictive BO a spectrum of changes may be encountered, ranging from bronchiolar inflammation and minimal scarring (more prominent in the early stages) to considerable submucosal fibrosis which encroaches upon the bronchiolar lumen, often reducing it dramatically and irreversibly (in advanced disease). In some atypical cases larger airways may also be involved, sometimes resulting in unilateral atelectasis.[12] In both proliferative and constrictive BO, a patchy distribution is common,

and the extent of involvement is best clarified by a fairly large biopsy specimen, step sectioning and elastic tissue stains.[5,6,11] Since the underlying conditions associated with both types of BO are quite similar, constrictive bronchiolitis may represent a more chronic and established response to stimuli which were more intense and severe, causing a more diffuse and protracted bronchiolar damage.[13–16] Overall, the histological features of BO are quite distinctive, and tissue should be obtained and used to confirm the diagnosis and guide therapy in all cases where the diagnosis is not already highly suggested by the combination of history, course and positive and negative ancillary findings.

Aetiology

The etiology of BO is diverse, reflecting the fact that the distinct histologic findings of BO represent a nonspecific 'final common pathway' of tissue reactions at the level of the small airways, to many possible noxious mechanisms in a variety of clinical contexts. Perhaps the most complete aetiological classification is that of Hardy *et al.* According to this and other reports, one may classify the aetiology of BO as follows.

Postinfectious BO

The infection is most often viral and many viruses have been implicated, including adenovirus, rhinovirus, coronavirus, respiratory syncytial virus, influenza and parainfluenza, measles, mumps, cytomegalovirus and varicella-zoster.[2,13,17–21] Recently, the human immunodeficiency virus (HIV) was also demonstrated to cause BOOP, in the absence of other infectious agents.[22] In addition, BO may commonly follow infections with *Mycoplasma pneumoniae*, and has also been reported in association with varied other infectious agents including β-haemolytic streptococci, *S. pneumoniae, Haemophilus influenzae, B. pertussis, Serratia, Legionella, Coxiella burnetti, Pneumocystis carinii, Nocardia* and *Cryptococcus*.[23] Thus, the most frequent cause of BO in children is a viral infection, although bronchopulmonary dysplasia in premature infants and infections in cystic fibrosis patients are also notable causes in that age group.[2] Apparently, organizing slowly resolving viral (or other) infections, clinically inseparable from idiopathic BOOP pattern, exist side-by-side with cases of healed infections due to similar agents, which are however associated with the development of constrictive BO.[6,10] A valid distinction usually requires tissue diagnosis.

Toxic fume BO

Inhalation of nitrogen dioxide, sulphur dioxide, ammonia, chlorine, phosgene, chloropicrin, trichloroethylene, hydrogen sulphide and fluoride, cadmium, talcum powder, zinc chloride and stearate, phosphorus pentachloride, nickel and iron carbonyl, ozone, thionyl chloride and thermal injury have all been linked to the appearance of BO.[14–16,24–28] Toxic fume exposure constitutes a significant occupational hazard in both agricultural and, especially, industrial workers, and may occur in many different settings, e.g. chemical manufacturing, fuel handling, welding, sewage work, firemen and others exposed to burning materials, silo filling, etc.[14] Different mechanisms are involved, but most cause tissue injury by acting as a strong acid, a strong base or an oxidant. Injuries due to nitrous fumes are most common, but in many injuries are induced by a combination of two or more noxious gases.[24] Both histological forms of BO may be encountered after toxic fume exposure, which appears to be a frequent cause of BO in adults.[29]. However, only a small percentage of patients exposed to irritant fumes develop marked constrictive bronchiolitis with the possibility of remaining severely disabled.[27]

BO associated with connective tissue disease, drugs or organ transplantation ('immune' BO)

Rheumatoid arthritis (RA) in particular, but virtually all connective tissue disorders, including Sjögren's syndrome, scleroderma, polymyositis and dermatomyositis, lupus erythematosus, essential mixed cryoglobulinemia and vasculitis have been associated, albeit rarely, with the development of both forms of BO.[6,13,14,30–33] Drugs such as penicillamine, gold, sulphasalazine and methotrexate have also been implicated,[34–36] although conclusive proof of an association is lacking. Altogether, BO is more likely to be an uncommon manifestation of RA than an adverse effect of the drugs used in its treatment, as suggested by occasional cases of BO in early RA or even antedating its appearance.[6,37] BOOP has been described as a result of drug toxicity for a number of other medications, including bleomycin, cyclophosphamide, mitomycin C, amiodarone and acebutolol, as well as following paraquat poisoning, cocaine smoking and radiation.[38,39] More recently, BO has emerged as a major complication of heart-lung transplantation, but may also occur after single lung transplants. It had developed in up to 50% of recipients in early series, occurring three months or more after the transplant, with a mortality rate of at least 50%.[40–42] BO in these patients is believed to result from a prolonged rejection reaction, with the

possible contribution of infectious agents, to which these patients are particularly susceptible,[6,43,44] Bone marrow transplant recipients with chronic graft-versus-host disease (GVHD) may also develop progressive dyspnea and airflow obstruction due to BO, occurring in about 10%.[45] This is not limited to patients undergoing allogeneic bone marrow transplantation, but can also follow autologous transplants.[46] Multifactorial pathogenesis and constrictive histology characterize these cases, often implying irreversibility and poor response to therapy. Finally, extrinsic allergic alveolitis (hypersensitivity pneumonitis) may also be associated either with BOOP or with constrictive bronchiolitis in the more protracted cases.[47]

Idiopathic BO

This is usually associated with organizing pneumonia (BOOP), (synonym: cryptogenic organizing pneumonitis), and constitutes a recently studied entity in which no underlying disorder or apparent cause can be detected.[7–10,48–49] The term BOOP refers to the extension of granulation tissue within the lumen of small airways into the alveoli, mimicking an organizing pneumonia rather than an obstructive small airway disease. Thus, idiopathic BOOP appears to have a very distinctive clinical pattern which will be discussed below, but its exact histological appearance may also accompany BO of the localized, 'immune' and postinfectious patterns.[6,13] In contrast with BOOP, constrictive BO which is primary or idiopathic is very rare.

Localized lesions with BO

This type of focal BO is usually asymptomatic and discovered during lung biopsy for incidental radiographic findings, investigated to exclude lung tumors, or as minor findings in patients with other lung diseases such as Wegener's granulomatosis, sarcoidosis, pneumoconioses or lung abscess.[6,50] These lesions, which are often located distal to obstruction or at the periphery of pulmonary nodules, are thought to be the residue of previous pneumonias, though no confirmation exists on this point.[13] Their histological appearance, not surprisingly, is that of a BOOP pattern.

In addition, miscellaneous diseases and conditions have been associated with BO. These include organizing adult respiratory distress syndrome (ARDS), alveolar proteinosis, malignancies (malignant histiocytosis, myelodysplastic syndrome, etc.), myasthenia gravis, inflammatory bowel disease, and aspirations of several types including amniotic fluid, prune pit, poppy-seed oil and gastro-oesophageal reflux.[4,6,49]

Thus, clinically important BO appears to be a rare but distinct pattern of pathophysiological reactivity of the lung to a variety of noxious stimuli, whether infectious, physical or immunological in nature, occurring predominantly at the level of the small bronchioles and resulting in either a BOOP or a constrictive BO type of clinicopathologic syndrome.

Pathogenesis

Transplant bronchiolitis is a highly specific entity, but has been extensively studied, and may give clues to understanding the pathogenesis of BO in general. An enhanced expression of MHC class II antigens on bronchiolar epithelium was demonstrated in these patients,[51–53] associated with cytotoxic T lymphocyte infilatration,[53,54], which are not found in patients without rejection or BO. Thus, aberrant (non-lymphoid) MHC class II expression might be the primary event in other types of bronchiolitis as well, resulting from local cytokine production (especially interferon-τ) in response to varied infections and other stimuli.[54,55] This may lead to autoantigen presentation, T-cell activation, and a vicious cycle of inflammation and fibrosis at the distal airspaces designated as BO, in analogy to some 'autoimmune' diseases such as scleroderma or primary biliary cirrhosis, where considerable evidence supports similar mechanisms leading to both inflammation, fibrosis and target organ dysfunction.[55] In other cases, however, it can be postulated on the basis of several intriguing models that denudation of alveolar epithelial cells following injury (toxic inhalation, etc.) is the initial event.[56] This is followed by inappropriate production of growth factors (e.g. platelet-derived growth factor) and monocyte/macrophage chemotactic factors (e.g. MCP-1) by the alveolar epithelial cells, culminating in a cycle of unsuppressed fibroblast proliferation and excessive collagen synthesis and deposition, accompanied and supported by an activated inflammatory infiltrate.[57] Further studies are clearly needed to elucidate the pathogenesis of both transplant and non-transplant BO.

Diagnosis

BO is usually suspected on the basis of the medical history, physical examination, chest X-rays and arterial blood gas analysis.[2] Other useful diagnostic procedures include lung function tests, a ventilation/perfusion lung scan and bronchoalveolar lavage (BAL). However, histological examination of either a transbronchial lung biopsy or an open-lung biopsy specimen, interpreted in the context of the clinical information, is the most rewarding diagnostic method, though it need not be applied in every case.

The medical history and examination may reveal the aetiological factors, such as a history of a recent infection, fume exposure or a collagen disease. However, these maybe obscure, as in idiopathic BO.[2,13,48] Both the clinical course and features of BO depend upon its aetiology. Thus, the disease appears in an acute form in cases of HCl or SO_2 inhalation and after viral infections, is delayed in cases of NO_2 inhalation, and insidious in idiopathic and 'immune' BO.[15,25,31,45] In toxic fume BO, the illness characteristically evolves in three phases.[29] At first, the patient may either be asymptomatic or present with a combination of cough and dyspnea, possibly associated with cyanosis and sometimes (at higher concentrations of exposure) even pulmonary oedema. This acute phase is followed by an apparent improvement which may last from several days to 2–6 weeks. Then the third phase of florid BO appears, in which the features are similar regardless of aetiology, and include progressive dyspnea, dry cough, chest pain and hypoxemia.[58] The development of respiratory distress a few days after inhalation of irritant fumes which was followed by a period of latency is so characteristic that BO should immediately be suspected.[59] While little is known about factors associated with an adverse outcome in postinfectious BO (which may however include extremes of age and a previous lung pathology), the severity of BO caused by inhalation of irritant gases depends on a number of factors: temperature, solubility, concentration and pH of the offending substance; duration of exposure; respiratory rate; use of respiratory protective apparel; number of bronchioles involved; and the presence of underlying disease.[29] As for idiopathic BO (BOOP), this typically occurs in the sixth decade and starts insidiously, sometimes following or resembling a flu-like illness, with associated non-productive cough and mild dyspnea which progressively worsen over several weeks or months. Fever (usually low grade), weight loss (approximately 3 kg) and malaise are often present.[7–9,49] The clinical manifestations depend on the phase of the disease at the time of its detection and may be misdiagnosed, especially in its chronic phase. Among the many possibilities, organizing infections, hypersensitivity pneumonitis, eosinophilic pneumonia and idiopathic interstitial pneumoniae such as usual interstitial pneumonitis (UIP) should be especially considered in the differential diagnosis.[60] However, the typical clinical features which are present for <2 months in 75% of the patients, combined with suggestive radiological findings should alert the physician to the possibility of idiopathic BO.[61] This has to be confirmed by tissue diagnosis (as well as by negative serological and microbiological data), in patients who show no response to a course of antibiotics or a gradual resolution.[6,60] The presenting symptoms of BO associated with connective tissue diseases are non-specific, and quite similar to those of the idiopathic form.[31,34] When a patient with RA being treated with penicillamine develops increasing dyspnea with no extrapulmonary reason, the drug should be stopped and an open lung biopsy considered, especially when pulmonary function studies reveal airflow obstruction, since constrictive bronchiolitis is a serious possibility.[14] Post-transplantation BO usually begins within 4–12 months of surgery, and is characterized by dyspnea and a relentlessly progressive deterioration of respiratory function due to irreversible obstructive pulmonary changes.[40,41] Thus, BO should be considered in the differential diagnosis of any new and progressive respiratory symptoms in a patient with a predisposing condition or a suggestive history; however, it may also develop with no relation to any identifiable factor, such as in the idiopathic cases.

The physical examination is variable and non-specific. It may either be normal, or reveal inspiratory crackles (often localized), decreased intensity of breath sounds, rales, ronchi and wheezing which is typically unresponsive to bronchodilators and accompanied by fever, raised ESR and leukocytosis.[2,14] In BOOP, however, clubbing and wheezes are rarely present, dry rales (Velcro) are found in 75% of patients, and over 25% may have no relevant physical findings.[8,49] In patients with constrictive BO, on the other hand, wheezing is the most common auscultatory finding, and is characteristically persistent, increasing during episodes of airway infection, to which these patients are prone.[4] Chest X-ray findings are also varied in relation to the etiological groups as well as within each category. In idiopathic BOOP, chest radiography shows an unusual and rather typical pattern with diffuse patchy 'ground glass' densities progressing bilaterally in most cases.[4,8,60] Other recognized radiographic patterns include a solitary pulmonary involvement resembling pneumonia and a diffuse interstitial lung disease presentation suggestive of UIP.[49] Hyperinflation is seldom recognized, but the alveolar infiltrates may be peripheral or migratory.[62,63] A normal chest radiograph is rare. In toxic fume exposure, the early X-rays often reveal a pattern of ARDS—diffuse alveolar or ground-glass opacities uniformly distributed throughout both lungs, while in the late stages it may appear normal (in mild cases), or show marked hyperinflation or multiple diffusely occurring nodular opacities of various sizes, which may even become confluent (in severe cases). Other possible changes include atelectases, bullae, and linear densities[4,12,28] (Figure 3). In postinfectious BO, the chest X-ray is most frequently normal or demonstrates a diffuse nodular or reticulonodular pattern, reflecting considerable interstitial fibrosis and

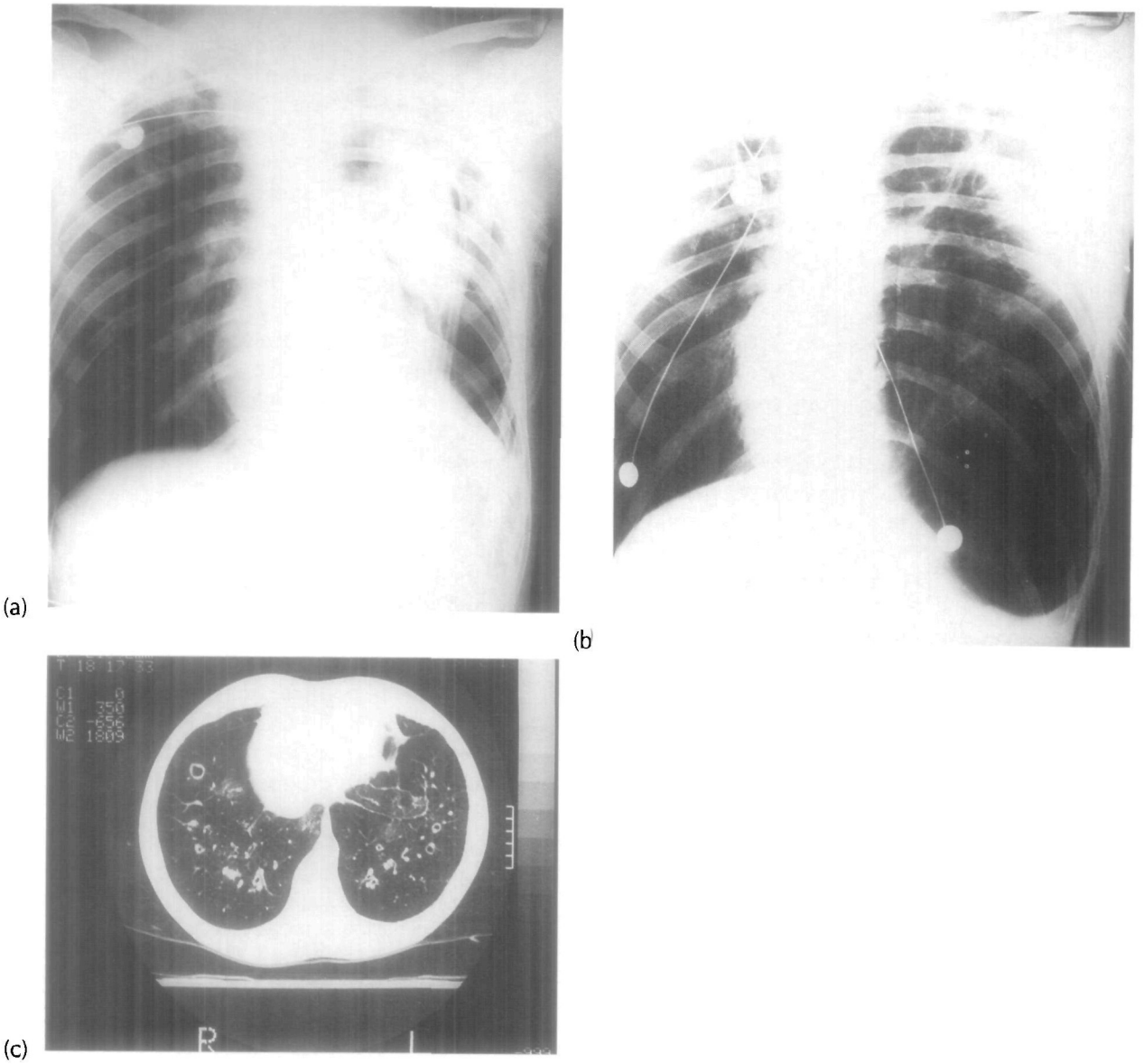

Figure 3. Chest X-rays (**a**, **b**) and CAT scan (**c**) of patients with BO due to toxic fume inhalation. **a** Left upper lobe atelectasis. **b** Left lower lobe giant bullae pushing the heart to the right side. **c** Bilateral hyperinflation of lungs with multiple bilateral bronchiectasis.

scarring.[2] Diffuse hyperinflation is rare here, but the changes characteristic of BOOP may also be encountered. In 'immune' BO, chest X-ray is normal or shows hyperinflated lungs, possibly with the changes seen in BOOP or with coarse reticulonodular opacities, especially in survivors of organ transplantation.[40]

Additional diagnostic studies include ventilation/perfusion lung scan, which show matched areas of absent or decreased air and blood flow often revealing a mottled distribution of defects even in patients with minimally abnormal chest X-rays.[2] The post-transplantation BO patients have been called 'blue puffers' because of hypoxemia and hypocarbia,[40] and this is indeed the typical pattern of the arterial blood gases in most cases. For example, arterial hypoxemia is an almost universal abnormality in patients with BOOP: most show a $P(A\text{-}a)O_2$ gradient >20 mmHg at rest, and in the others a similar finding could be induced by exercise.[60] After SO_2 inhalation, even asymptomatic patients often exhibit this blood gas pattern for at least six weeks.[25] Lung function tests may show obstructive (in the more severe cases, in correlation with a marked fibrosis on biopsy), restrictive or mixed patterns.[13,48] Usually, the one-second forced expiratory volume (FEV_1) and flow rates are reduced, functional residual capacity (FRC) increases and total lung capacity (TLC) is normal. Following SO_2 inhalation, this impairment is maximal one week after exposure, persisting thereafter for about three months. Four years later, a 'reversible' airway obstruction with a residual restrictive defect may still remain.[25,26] After inhaling toxic fumes, only a few patients show restriction, while the majority present with an

obstructive pattern.[64] The pattern is usually a mixed one in drug-associated BO, while in post-viral BO, tests of lung function are often normal.[34–36,60] Severe obstruction, which may be irreversible, can often be found in BO associated with RA or organ transplantation, corresponding to a pattern of constrictive bronchiolitis on histopathology.[6] However, in idiopathic BOOP, an obstructive pattern was uncommon (excepting smokers) and physiological studies tend to show restriction with a reduced TLC and impaired gas exchange: a reduced single breath diffusing capacity (Dco) was the most common abnormal finding, found in over 70% of the patients.[8,9] In approximately 20% of the patients, pulmonary function tests are within normal limits.

Bronchoscopy is not helpful, since the pathology of BO is distal to the examined airways, but recent studies suggest that bronchoalveolar lavage (BAL) may both exclude other causes of airway disease and positively support the diagnosis of BO by demonstrating a large percentage of lymphocytes in the BAL fluid (>25% of the cells), as well as increased recovery of eosinophils and neutrophils, and identification of their enzymic products.[60,65] Computerized tomography (CT) of the lung may indirectly support the diagnosis by demonstrating lung hyperinflation or bronchiectasis in severe cases (Figure 3c), while in BOOP it commonly shows a distinctive pattern of patchy peripheral airspace consolidation, and is considerably more sensitive than plain chest X-rays.[66] The CT scan can be used as a guide for selection of optimal biopsy sites, and is also useful in excluding other diseases. Recently, it has been suggested that high-resolution CT may further help the differentiation between interstitial and air space abnormalities.[60] Nevertheless, many of the above findings are not specific for BO,[2] and cases with an unequivocal diagnosis should always be considered for a lung biopsy to confirm the diagnosis and evaluate its possible response to treatment. While transbronchial biopsy may provide sufficient information in some cases,[67] open-lung biopsy remains the gold standard of diagnosis in BO, and many studies strongly suggest its superiority over the transbronchial approach.[6,68]

In summary, even though no single test is specific for the diagnosis, and each may show considerable variability according to the aetiology and stage of BO, it is often the combination of the history, chest X-ray findings and pulmonary function tests which, taken together, may be highly suggestive of the diagnosis of BO, leaving the decision as to the need to obtain tissue diagnosis in the hands of the clinician.

Complications and prognosis

Certain types of fume inhalation are characterized by the rapid progression of BO from the acute phase to chronic obstructive pulmonary disease (COPD). In other cases, the course may be slowly deteriorating, static, or the patient may recover completely. Many cases do, however, progress to COPD.[8,25,28] The prognosis is generally good in post-infectious, idiopathic, drug-induced or localized BO, and moderate to poor in BO caused by inhalation of toxic fumes or associated with RA or organ transplantation.[23,34,40] Even following clinical and radiographic improvement, patients may relapse and should therefore be followed for several months. The presence and degree of airflow obstruction, and most importantly the identification of constrictive bronchiolitis (as opposed to BOOP pattern) in biopsy specimens are potent predictors of adverse prognosis.[6] However, even when they exist, early detection and intervention may prove beneficial, especially when contributing factors can be identified and treated. For example, early biopsies and aggressive management of episodes of acute rejection have reduced the incidence of post-transplant BO to <10%, improving the overall survival of these patients.[69] Nevertheless, death may occur with each of the aetiological variants of the disease,[17,45,58] and may be caused during the acute phase by fulminant pulmonary oedema or subsequently by pulmonary fibrosis or secondary complications. Even patients with the usually steroid-responsive COP syndrome show a mortality of 5%.[60] Besides sequelae related to the original insult (e.g. airway hyperreactivity and bronchiectasis after SO_2 inhalation) and the development of obstructive airway disease, BO may also be followed by chronic atelectasis, unilateral hyperlucent lung and lung infections. Patients with constrictive bronchiolitis are especially prone to recurrent airway inflammation and infection.[6] Lung bullae, spontaneous pneumothorax, and bronchopleural fistula may also occur (Figure 3).[2,25–28]

Management

The management of BO is essentially symptomatic and supportive, and makes use of bronchodilators, antibiotics, and if necessary, oxygen and artificial ventilation. The effectiveness of steroids in the prevention and treatment of BO is controversial and often difficult to predict, especially in the absence of a lung biopsy.[4,13] Experimental studies have shown that steroids inhibit fibroblastic response in the early phase of the disease.[70] On the other hand, in the presence of denuded respiratory epithelium, steroid treatment may predispose to lung infections.[71] Steroids have been found to have dramatic healing effects in patients with NO_2 inhalation, post-infectious BO and eosinophilic pneumonitis.[14,28] In cases of NO_2 injury, steroid treatment should be

initiated as early as possible and continued for eight weeks.[16] The delayed complications of SO_2 exposure also appear to respond well to steroids,[72] although there is no general agreement about this.[73] If it is decided to use steroids in fume-induced BO, they should be started at the first sign of the disease.[59] The recommended dose is 200 mg × 6/day of hydrocortisone or 60–100 mg/day of prednisone for a few days.[24,29] Steroids may help to relieve bronchiolar spasm, which may occur during the first 24–48 h after fume inhalation. The effectiveness of prolonged steroid therapy needs to be monitored by lung function tests, and the drugs should be gradually discontinued if no objective improvement is noted over a period of several weeks. The use of steroids in paediatric patients should probably be restricted to severe cases of post-viral BO.[2] Steroids appear to be ineffective in BO associated with RA or gold, yet they are often administered, since other therapeutic modalities are scarce.[33] Most idiopathic cases of BOOP (COP) respond well to steroids, but this is not invariable and early diagnosis is crucial for a good response to this treatment.[7,8] The recommended dose is in the range of 1 mg/kg of prednisone for about three months, tapered over one year. Clearing is generally slow, with response occurring over weeks to months, but relapse is frequent if treatment courses are too short.[4] Complete recovery has been observed in over 65% of patients.[60] Post-transplantation BO responds to steroid therapy only in the early phase of the disease,[40,41] and therapy should focus on earlier detection of rejection and augmented immunosuppression using a combination of drugs.[5] Full-blown BO is an end-stage bilateral lung disease. Patients with this condition are therefore candidates for heart-lung transplantation, despite the possible occurrence of BO after the operation.[41] Burke *et al.*[41] point out that in well-selected patients the risk:benefit ratio is probably favourable. However, the irreversibility of the bronchiolar lesions may be difficult to assess during the first phase of the disease, and an unpredictable improvement may still occur in some cases with time.[27,41] Colchicine, which has important anti-fibrotic and immunomodulatory effects has not been used in BO to our knowledge, but is a relatively safe drug and should be considered and studied as an adjunct to the treatment of BO in analogy to its experimental use in conditions incorporating fibrosis and inflammation.[75]

In conclusion, BO is a distinct clinicopathological syndrome which is relatively rare but intriguing. It is the result of a primarily fibrotic response of the lung to diverse types of injuries at the level of the distal airspaces which are usually of infectious, chemical, immune or idiopathic aetiology and not specific to one disease. In many cases with a histological pattern of constrictive BO, a severe and debilitating illness ensues which may not be responsive to corticosteroids, and may necessitate a heart-lung transplantation in selected cases. In contrast, a histologically distinct pattern of proliferative BO termed BOOP or COP in the idiopathic cases usually resolves with steroid treatment and carries a much better prognosis.

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