Topical Review

Bronchiolitis obliterans following heart–lung and lung transplantation

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Introduction

The success of heart–lung and lung transplantation has given hope to patients with various end stage lung diseases (1–5). Since the first successful heart–lung transplantation was performed at Stanford in 1981 (1), more than 300 heart–lung, single and double-lung transplants are performed each year in more than 250 centres around the world (3). With the advancement in technical skills, improved management of severe infections and early rejections, more and more transplants are performed successfully and early results are constantly improving (5,6). Recent reports suggest that the 1 yr survival in some centres following single lung and heart–lung transplantation may reach 90% and 75% respectively (5–7). The major obstacle for continuous survival and a morbidity-free life is the development of bronchiolitis obliterans, an unexplained, often non-reversible condition unresponsive to therapy and in most cases fatal (9). Since its first description by Burke in 1984 (10), it has been a continuous challenge for any lung transplant team world-wide.

Definition

Bronchiolitis obliterans (BO) is an inflammatory process involving small airways, leading to plugging and destruction of bronchioles while causing a rapidly progressive often non-reversible obstructive airway disease.

Incidence

The incidence of BO after lung transplantation varies from centre to centre and from one report to another. It is quite difficult to estimate the true incidence of BO as there is large variability in early death rates, mean follow-up periods and differences in reports (% of total cases vs. % of long term survivors) and even in terminology (Chronic rejection vs. BO). It is quite natural that newer programs with only a short follow-up period report low incidence of BO while those with longer follow-up have higher rates of BO.

Table 1 gives a summary of recent reports. Overall incidence can be estimated to be between 30–50% of those who survive more than 6 months following the procedure (5–15).

Early reports have suggested that single lung transplantation has less frequent BO than heart–lung recipients (16). However, as follow-up has become longer and experience enlarged, it seems that the differences are not that significant (7). Similarly, some centres have suggested that patients with cystic fibrosis have lower incidence of BO following transplantation as compared to patients with pulmonary hypertension (17), but again, looking at the large series of CF patients from Harefield (12) with a longer follow-up there is an incidence of 17, 23 and 48% at 1, 2, and 3 yr following transplantation respectively. In the pediatric population the incidence of BO can be as high as 80% of patients (18).

Timing of BO

Reports from early autopsies have shown that BO can occur as early as 2 months post transplantation (10). Most cases, however, appear between 6–18 months after the transplant. Figure 1 shows timing of occurrence of BO at Stanford which peaks between 7 and 12 months after the transplant. Later occurrence is not infrequent and BO has occurred in a patient 7 yr post heart–lung transplantation without any prior evidence of pulmonary function abnormality. (Theodore, personal communication.)
Table 1  Incidence of BO after heart–lung transplantation

<table>
<thead>
<tr>
<th>Centre</th>
<th>No. of Transplants</th>
<th>Years</th>
<th>Type</th>
<th>Incidence (%)</th>
<th>Ref No.</th>
</tr>
</thead>
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<td>81–89</td>
<td>H/L</td>
<td>40</td>
<td>6</td>
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<tr>
<td>Minnesota</td>
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<td>88–91</td>
<td>H/L</td>
<td>22</td>
<td>11</td>
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<td>84–89</td>
<td>H/L</td>
<td>48</td>
<td>12</td>
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<td>86–90</td>
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<td>82–91</td>
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<td>20–49</td>
<td>15</td>
</tr>
<tr>
<td>Toronto</td>
<td>90</td>
<td>83–91</td>
<td>DL/SL</td>
<td>14–20</td>
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</tbody>
</table>

Fig. 1 Timing of obliterative bronchiolitis after transplantation – Stanford experience.

Clinical Manifestations

The clinical onset of BO is often insidious with mild symptomatology which may include mild cough, sometimes associated with minimal sputum production, and exertional dyspnoea. In some cases a 'viral syndrome' of upper respiratory tract infection may precede the development of the full blown picture. Later on, a rapidly progressive obstructive airways disease occurs with the development of dyspnoea, hypoxemia and recurrent bronchitis often with purulent sputum production. Unlike typical obstructive airway disease such as emphysema or chronic bronchitis, the clinical course of BO is rapid with deterioration of the lung function from practically normal to an end stage within several months (9,13).

Pulmonary Function

Serial pulmonary function measurements which are performed routinely in lung transplant patients reveal a dramatic decline in flow rates, initially involving the small airways with decline of the FEF_{25-75} or FEF_{40} and later on, a constant decline in FEV_{1} to levels below 30% predicted. Figures 2 and 3 show a typical case of BO occurring in a 17-year-old heart–lung recipient 8 months following a successful transplant. Note the rapid downhill course following an 'upper respiratory tract infection' and ending with retransplantation. Hypoxemia commonly follows the flow rate decline with hypocarbia and widened A–a gradient. In contrast
to classic forms of COPD, lung volumes are not increased and a reduction in lung volumes is common, thus creating a mixed obstructive and restrictive pattern. Diffusion capacity is usually decreased even after correction for volume, probably due to the interstitial fibrosis associated with the airways disease.

In the single lung transplant, moderate restriction could be seen prior to the development of BO due to the effect of the remaining lung. However, when BO develops the obstructive pattern is prominent

Imaging Features

Chest films are often normal in most cases with BO (20). When disease progresses some parenchymal changes can be observed which include either nodular, linear or diffuse alveolar opacities (20,21). These changes are not specific for BO and are indistinguishable from other post-transplant complications that should be excluded. High resolution CT can show bronchial dilatation mainly in the lower lobes (22). Ventilation-perfusion abnormalities are common (23) but are non-specific.

Diagnosis

The diagnosis of BO can be made by either the clinical or pathological picture. Clinically, the development of rapidly progressive obstructive airway disease following transplantation which is not due to infection or acute rejection and does not resolve within 6-8 weeks is highly suggestive of BO. As acute rejection may also manifest with small airway obstruction a trial of pulse steroids is always indicated. However, if no response is observed and transbronchial lung biopsy does not show rejection (24) the diagnosis of BO is highly probable. Pathologically, BO can be diagnosed by transbronchial biopsy. However, as the disease is patchy in nature, the yield of TBB is quite low and diagnosis is frequently missed (25). Nevertheless, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy should always be performed to rule out rejection and acute infection as a cause of pulmonary function deterioration. If TBB is negative, however, BO should be suspected if the physiological picture is compatible. Open lung biopsy can easily make the diagnosis but this may jeopardize the option of retransplantation when lung function further decreases. Therefore, the diagnosis should be based mainly on the physiological picture.

Pathology (Plate 1)

The initial pathological changes include inflammation of the terminal and respiratory bronchioles. This is manifested by lymphocytic and plasma cell infiltration around the bronchioles. Further early changes include denuding and ulceration of the ciliated respiratory epithelium with sloughing of necrotic debris into the lumen. Later on, fibroblasts grow into the area, creating intraluminal plugs of myxoid tissue with concentric sheets of matured collagen, enveloping the central necrotic material, thus creating onion shaped plugs. This process creates a rigid bronchiole which may be filled with debris (19,26).

Subsequently, proximal bronchiectasis develops and is often filled with bacteria and necrotic debris due to recurrent infection.

Early changes could be misinterpreted as BO and include bronchiolitis obliterans organizing pneumonia (BOOP) associated with acute infection or rejection. Unlike BO, these pathological changes usually resolve without permanent damage.

Etiology

Although much has been written on the possible etiological factors and pathogenesis of BO, to date no definite answers exist as to the basic mechanism by which BO develops nor the means to treat or prevent it.

The Chronic Rejection Theory

Acute rejection of lung allograft is a common complication in the early postoperative period. Both the Pittsburgh group (27) and Papworth group (28) have shown good correlation between multiple early rejection episodes and late occurrence of BO. However, BO has been seen in patients without evidence of early rejection. The Pittsburgh group have studied extensively the properties of bronchoalveolar lavage lymphocytes alloreactivity on the occurrence of BO. They have found good correlation between donor-specific proliferative response of BAL lymphocytes to acute and chronic rejection (29,30). However, a positive reaction was seen in some patients without rejection as well. Positive correlation between a greater HLA mismatch and BO was noted in an early report from Stanford (31) but was not repeated by other centres. HLA-class II antigen expression is increased in epithelium as well as endothelium of patients with BO, suggesting again increased antigenic stimuli as a cause of rejection. This phenomenon, however, is not specific (32,33).

Further studies show evidence of accumulation of CD8 lymphocytes around bronchioles affected by BO.
Plate I  Lung biopsy of a patient with BO. Note the onion shaped fibrotic plug in a terminal bronchiole (a) and lymphocytic infiltration next to the fibrotic bronchiole (b).
again suggesting an immunologic mechanism, i.e. rejection (34).

Graft-versus-host disease following bone marrow allograft transplantation is considered a classic immunologic rejection. One of the important manifestations of this syndrome is the development of obstructive airway disease which is identical to BO following lung transplantation (35). This further suggests a rejection mechanism although the exact pathogenesis in both clinical settings is still unknown.

Against the chronic rejection theory are several facts: Despite early reports, patients with BO do not respond to augmented immunosuppression and most of them succumb to fatal end-stage lung disease or require retransplantation. Moreover, in many patients the course is not chronic at all and a rapid course occurs after an 8–12 month period of normal lung function. Furthermore, no correlation was found between level of immunosuppression and BO. In addition, cases with no evidence of early rejection may develop BO eventually.

**The Infection Theory**

Infections are common following lung transplantation and therefore it is not surprising that some investigators believe they are the cause of airway damage and BO. It is well known that adenovirus can cause bronchiolitis in children (36) and BO in the non-transplant population (37). Viral infections have been associated with rejection of transplanted kidneys and cytomegalovirus (CMV) infection is commonly associated with lung as well as heart and renal acute rejection. Infection with *Pneumocystis carinii* as well as bacterial infection have been associated with increased rate of BO (38). Recently, evidence has been accumulating in favour of the role of CMV infection in the development of BO. The Pittsburgh group have shown that CMV positive recipients had a much higher incidence of BO than CMV negative patients although this has not reached statistical significance (15,39,40). Patients with proven CMV pneumonitis had significantly more BO and worse prognosis in general. It was assumed that CMV antigen can induce proliferation of lymphocytes which accelerate rejection (41). Correlation of OB and CMV infection was not clearly supported by data by Scott *et al.* from Papworth (27). Moreover, prophylactic therapy with Gancyclovir has not yet been shown to reduce occurrence of BO. It is important to remember that 70–80% of all donors and recipients are CMV positive and it is extremely difficult to isolate this factor as the sole cause of BO.

At Stanford, BO was noted in one case following a documented adenovirus infection (42), and the rapid course of BO seen in some cases resembles an infection episode.

Many researchers favour a combined theory: an infection (viral/CMV) that up-regulates expression of MHC-II antigens at the epithelium or endothelium. This is followed by T-cell activation and an inflammatory process which is targeted on the bronchioles and subsequently results in fibrosis (40,41,43).

**Other Theories**

Some reports associate gastric content aspiration as a cause of BO. This is supported by evidence of increased esophageal reflux and slow gastric emptying secondary to vagal nerve injury or cyclosporin therapy (44).

Other theories include direct cyclosporin toxicity on the lungs which seems less likely as BO is not associated with other solid organ transplants.

The reduction of mucociliary clearance which is a common sequel of lung transplantation can also increase risk of infection/inflammation at the bronchiolar level and contribute to late fibrosis.

Another possibility is ischemic damage to the transplanted lung occurring either immediately at the time of transplantation or later as a result of lack of bronchial circulation (5).

**Therapy and Management**

Once the diagnosis of BO is established, a trial of enhanced immunosuppression is usually indicated. However, despite early reports on arrest of the lung function deterioration with augmentation of therapy (increased steroid dose) (42,45), the accumulating experience suggests that BO cannot be reversed in most cases. The goal of therapy should therefore be reduction of further airways damage by control of recurrent infections. The bronchiectasis which commonly occurs in these patients is frequently infected with Gram-negative bacteria (*Pseudomonas* sp) and requires frequent antibiotic therapy (46).

**Retransplantation**

When lung function further deteriorates and reaches end-stage, the possibility of retransplantation is always considered and poses a serious dilemma. On one hand, the responsibility towards the transplanted patient in whom the initial attempt failed, and the great effort invested, favours retransplantation. On the other hand, results of retransplantation in most centers are poor, probably due to the condition of the candidate, the redo procedure, and the recurrent infections.
Moreover, in view of organ shortage, a new candidate has a much higher chance to benefit from a transplant than a redo procedure. Another problem yet to be solved is what kind of a transplant should be done – a single lung or a double/heart-lung? The fibrosis favours single lung, but many patients are chronically infected in both lungs and a double heart-lung transplantation should therefore be preferred.

Prognosis and Outcome

Theodore et al. (47) reported a group of 12 patients with post-transplant BO with poor lung function who were able to survive up to 36 months after diagnosis of BO. Initially, these patients were not hypoxemic and could maintain a fair quality of life. In most BO cases, however, lung function deteriorates within several months and death or retransplantation follows.

Future aspects of research to prevent or decrease the incidence of this devastating complication include a search for better immunosuppressive agents, better control or prevention of viral/CMV infections and perhaps better ways to improve arterial circulation to the lung.

In conclusion, BO is still the most frustrating complication of lung transplantation arising in about 40% of all recipients. Despite extensive research, pathogenesis of this syndrome is still obscure and once disease has occurred the prognosis is extremely poor. After recent successes in technical and early post-operative management of patients with lung transplantation, BO remains the major threat to long-term survival and is still awaiting a major breakthrough.

References


