Obliterative Bronchiolitis

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Abstract: Obliterative bronchiolitis (OB) is a clinical syndrome marked by progressive dyspnea and cough with the absence of parenchymal lung disease on radiographic studies. Pulmonary function testing reveals an obstructive ventilatory defect that is typically not reversed by inhaled bronchodilator. Transbronchial biopsies are insufficiently sensitive to achieve diagnosis, and in most cases, clinical, physiological, and radiological data obviate the need for the increased risk associated with open lung biopsy. This diagnosis has been documented in a variety of exposures, including fumes from flavoring plants, smoke from burn pits, and environmental sulfur gas. Among lung transplant recipients, bronchiolitis obliterans syndrome, a disorder with clinical and histopathological similarity to OB, represents the leading cause of long-term allograft dysfunction and mortality. After hematopoietic stem cell transplantation, chronic graft versus host disease of the lung manifests most frequently with similar clinical and pathological features. In all circumstances, immunologic and nonimmunologic mechanisms are thought to lead to airflow epithelial dysfunction, which results in progressive airflow obstruction and debility. Augmentation of immunosuppression is occasionally effective in slowing or reversing the progression of disease though a significant number of patients will be nonresponders. Other immunomodulatory methods have been attempted in each circumstance where this pathology has been identified. Unfortunately, OB is poorly understood and often results in sufficient progression of disease to warrant evaluation for lung transplantation (or retransplantation). Here, we review what is known regarding pathophysiology and discuss clinical, pathological, radiological, and therapeutic factors associated with the spectrum of OB-related disease with a particular focus on lung transplantation.

Obliterative bronchiolitis (OB) refers to a rare but serious condition resulting in progressive and irreversible airway obstruction. This syndrome is the result of injury to the respiratory and terminal bronchioles from a wide variety of potential causes.1 Here, we provide a general overview of OB and then focus on the syndrome in two transplant populations where its development has major implications on long-term survival. In lung transplant recipients, bronchiolitis obliterans syndrome (BOS) is the major cause of death after the first year of transplantation and is a form of allograft rejection.2 An analogous syndrome develops in 5% to 10% of human stem cell transplant (HSCT) recipients and is associated with major morbidity and mortality.3

Much confusion exists among clinicians regarding the similar terminologies used for vastly different pulmonary conditions. The conditions most often confused are OB and an entity previously named bronchiolitis obliterans organizing pneumonia, now referred to as cryptogenic organizing pneumonia.45 Obliterative bronchiolitis is primarily a syndrome of progressive air trapping due to involvement of small airways without parenchymal involvement. Bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia is significantly more common and manifests as parenchymal disease with alveolar consolidation and intraluminal polyps in the respiratory bronchioles.4 Table 1 contrasts many of the clinical, pathologic, and radiologic characteristics of clinical syndromes, which are often confused due to their nomenclature. Much of this confusion is the result of the terms being used to denote a clinical syndrome by clinicians and as a histopathologic finding by pathologists.

PATHOGENESIS

Overview

The pathogenesis of OB remains poorly understood in all its manifestations. Ultimately, injury to the respiratory epithelium and subepithelium results in dysregulation of epithelial repair and development of disease. Injury results in denudation of the epithelium and loss of basal progenitor cells.6 This is followed by an inflammatory infiltrate and the development of an abnormal cytokine response profile.7 Epithelial-mesenchymal transition may occur, resulting in excessive accumulation of fibroblasts and resultant fibroproliferation.8 Several divergent inflammatory mechanisms have been invoked in attempting to explain the disease, particularly in lung transplantation. Further, the pathways which lead to the histopathological finding of constrictive bronchiolitis, airway distortion, and subepithelial fibrosis in circumstances of toxin exposure, autoimmunity, and transplant related alloimmunity may share some immunological commonality. In one model of rodent diacetyl exposure, the posited mechanism involved damage to membrane proteins which compromised epithelial integrity and led to migration...
### TABLE 1. Differential diagnosis for and comparisons of bronchiolitis syndromes

<table>
<thead>
<tr>
<th>OB COP/BOOP</th>
<th>DPB</th>
<th>RB-ILD/DIP</th>
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<tbody>
<tr>
<td><strong>CT imaging</strong></td>
<td>Diastolic bronchioles, centrilobular nodules, mosaic attenuation, bronchiolar dilation, bronchiectasis and ground glass opacities.</td>
<td>Bronchial wall thickening with associated centrilobular nodules and ground glass opacities.</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Centrilobular nodules, mosaic attenuation, bronchiolar dilation, bronchiectasis and ground glass opacities.</td>
<td>Bronchial wall thickening with associated centrilobular nodules and ground glass opacities.</td>
</tr>
<tr>
<td><strong>PFT changes</strong></td>
<td>Concentric narrowing of bronchial lumen resulting in luminal obliteration.</td>
<td>Mixed, impaired gas exchange.</td>
</tr>
<tr>
<td><strong>BAL findings</strong></td>
<td>Neutrophilia, increased macrophages, decreased CD4/CD8 ratio.</td>
<td>Neutrophilia, increased macrophages, decreased CD4/CD8 ratio.</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Poor.</td>
<td>Mixed response to treatments.</td>
</tr>
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BOOP indicates bronchiolitis obliterans organizing pneumonia; COP, cryptogenic organizing pneumonia; DPB, diffuse panbronchiolitis; RB-ILD, respiratory bronchiolitis-interstitial lung disease; DIP, desquamative interstitial pneumonia.
of fibroblast precursors from the ulcerated airway wall into the lumen. This process of trigger leading to epithelial injury with resultant inflammation and fibroproliferation is thought to underpin the development of OB in all its forms, though a comprehensive step-by-step sequence has yet to be clearly elucidated.

**Fibrotic Pathways**

Exposure to diacetyl, a key component of artificial butter flavoring, has been associated with an increased risk of developing OB in workers at a microwave-popcorn production plant.10 Indeed, diacetyl exposure has been shown in a murine model to result in the development of epithelial injury, peribronchial lymphocytic inflammation, and fibrohistiocytic lesions in the terminal bronchioles in a manner consistent with OB.11

Similarly, exposure to 2,3-pentanedione (an alternative component of artificial butter flavoring) is associated with airway epithelial toxicity and histopathological changes similar to OB.12 After exposure to this compound in a rat model, analysis of fibrotic airways showed significant up-regulation of transforming growth factor-β (TGF-β) and downstream genes implicated in fibrosis. Further, genes coding for peptidases and peptidase inhibitors were significantly altered, demonstrating changes consistent with airway remodeling.13 In vitro models of mechanical airway injury, TGF-β has been shown to increase in a dose-dependent fashion and enhance downstream modulators of fibrosis.14 These data support the notion that nontransplant OB is mediated through common fibrotic pathways.

The clinical impact of BOS, established above, has prompted a substantial amount of effort to identify the molecular underpinnings of disease in an attempt to develop effective therapy. As a result, this represents the best understanding of the pathophysiology of OB-spectrum diseases. Here, we will attempt to describe a variety of key inflammatory pathways to introduce the modern understanding of disease development.

In an extrapolation of the findings illustrated in OB, blood samples were obtained from 51 lung transplant recipients to assess for serologic evidence of altered fibrotic pathways. Indeed, patients with clinical evidence of BOS have more circulating fibrocytes and fewer circulating epithelial progenitors when compared to those without evidence of disease.15,16 Further, BOS has been associated in multiple studies with bronchial epithelial to mesenchymal transition (EMT), a process that has been shown to be accentuated both by TGF-β and by modulators of TGF-β activity.17-19 For example, in a laboratory model of human lung epithelial injury, the administration of TNF-α and TGF-β significantly enhanced features of EMT and treatment of injured epithelium with TGF-β in the presence of an activated macrophage-like cell line resulted in accentuated changes in cell phenotype when compared to treatment with TGF-β alone.20

Clinically, acquisition of *Pseudomonas aeruginosa* has been shown to increase the risk of BOS. In primary bronchial epithelial cells collected from recipients of lung transplantation, the coculturing of *Pseudomonas*-activated monocyes with primary bronchial epithelial cells significantly accentuated TGF-β1-driven EMT, a finding which demonstrates that through activation of monocytic cells, *Pseudomonas* can affect changes in cellular fibrotic pathways.21 These findings demonstrate that complex cytokine and cellular processes upregulate the fibrotic pathways associated with BOS.

**Lymphocyte Pathways**

The role of lymphocytes in the development of BOS is also complex. For example, in a murine model of tracheal transplantation into mismatched mice, provision of either anti-CD4+ or anti-CD8+ antibody treatments partially reduced the histopathologic development of obstructive airways disease, whereas combined therapy against both anti-CD4+ and anti-CD8+ cells resulted in further interruption of disease development, demonstrating that both of these types of T cells have a role in the pathogenesis of obstructive airway disease.22 Similarly, in a separate model of lung transplantation using fully mismatched mice, allospecific CD8+ T cells were detected in airway allografts shortly after transplantation. Interestingly, an influx of similar CD8+ effector cells was identified in the allograft once obstructive airways disease had developed. Antibody-mediated depletion of CD8+ T cells resulted in decreased luminal obliteration and fibrosis in this setting.23

Th17 cells provide a major source of IL-17A. Upregulation of both IL-17A and Th17 cells have been associated with the development of BOS. In a murine model of lung transplantation, depletion of CD4+ T cells has been shown to lead to significantly decreased frequency of IL-17A+ lymphocytes. This was found to be protective against acute rejection and BOS.24 In contrast to Th17 cells, the absence of Th17 cells has been shown to increase the risk of BOS.25 Although few clinical studies have used the awareness of regulatory T cells, it is known that depletion of this cell type results in counterproductive effects of some transplant immunotherapy.26

**Antibody-Mediated Pathways**

Antibodies to graft antigens are strongly linked to the development of BOS in lung transplantation. In several reviews, HLA locus mismatch and development of donor-specific anti-HLA antibodies (DSA) have been described as significant independent predictors of the development of BOS after lung transplantation.27-31 Further, both decreased incidence of BOS and increased survival have been associated with clearance of DSA.32 These data suggest a role for the presence of DSA in the development of the chronic inflammatory state which precedes BOS.

Although antibody-mediated rejection (AMR) of lung allografts has long been suspected, proving its existence has been relatively complex. Recently, a series of 21 patients with
clinical and histologic evidence of acute antibody-mediated lung allograft rejection was described. Each of these patients had identification of DSA, and the simultaneous demonstration of endothelial deposition of the complement split product C4d on transbronchial lung biopsy. Fifteen of these patients survived the incident hospitalization associated with the AMR episode, one of whom had previously been diagnosed with BOS. Of the 14 patients without previously identified BOS, AMR was associated with the development of subsequent chronic allograft dysfunction in 13 patients.33

In recent years, there has been emerging recognition of the role of autoimmunity in the development of chronic allograft dysfunction. Processes associated with allograft injury may lead to exposure of intercalated self-antigens which lead to cellular and antibody-mediated immune responses.7 In lung tissue, this pattern has been associated with collagen V and k-α 1 tubulin. Presence of antibodies against these epithelial cell antigens has been associated with the development of BOS.34 Identification of DSA precedes development of these antiepithelial antibodies, and their presence increases the risk of BOS after transplantation.35,36

Summary

In this section, we have attempted to delineate some of the suspected mechanisms of OB-spectrum disease development. Epithelial injury is thought to expose targets for humoral, cellular, and innate immunologic activation. This injury may take the form of infectious or environmental damage, though other mechanisms (such as ischemia-reperfusion injury after lung transplantation) likely contribute. Antibody and lymphocyte mediated immune responses initiate damage and fibrotic pathways (including EMT) are activated. It is nearly certain that these responses are intertwined, though the details of their relationship are, as yet, incompletely defined. Regardless, it seems clear that a multifaceted process of inflammation and resultant fibrotic transition occurs, resulting in airflow limitation and development of disease. Although much of the pathophysiologic knowledge arises from lung transplant pathology, the overlap between disease in nontransplant, solid organ transplant and HSCT settings is unclear. Some pathophysiologic links exist but further work is needed to clarify the relationship.

NONTRANSPLANT OB

Overview

Table 2 summarizes the many possible causes of OB. This is an important and underrecognized disease in the general pulmonary population. Disease may follow infectious, pharmacologic, and environmental exposures as well as autoimmune disease, such as rheumatoid arthritis. Clinically, most patients present with progressive dyspnea and cough, which are often misdiagnosed as asthma or emphysema. There is frequent progression to significant debility before the correct diagnosis is achieved.

Imaging

Most commonly, chest radiographs in OB are relatively normal though hyperinflation and peripheral attenuation of vascular markings may become obvious in advanced disease. High-resolution CT scanning, preferably with inspiratory and expiratory views, reveals mildly dilated airways, thickened bronchial walls and signs of patchy air trapping which manifest as a pattern of mosaic attenuation (areas of hyperlucent lung alternating with areas of increased lung density).37

Obliterative bronchiolitis is also suggested by the absence of associated ground glass opacities (commonly seen in hypersensitivity pneumonitis), the absence of tree-in-bud opacities (commonly seen in infectious bronchiolitis) and the absence of centrilobular nodules (commonly seen in respiratory bronchiolitis interstitial lung disease).

Pulmonary Function Testing

Spirometry in OB typically demonstrates an obstructive ventilatory defect with a progressive decline in the forced expiratory volume over 1 second (FEV1) and a decrease in the ratio of FEV1 to forced vital capacity (FVC).37-39 In addition, decline in small airways forced expiratory flow (FEF25-75) occurs and may be an early indicator of developing airflow obstruction. Response to inhaled bronchodilators is generally poor but some patients may have mild spirometric improvement. Body plethysmography reveals air trapping and elevated residual volume. Diffusing capacity for carbon monoxide is typically reduced in advanced disease although it may remain normal in the early stages of illness. Impairment of gas exchange and hypoxemia, initially with exertion and then at rest, occur as the obstructive ventilatory defect worsens.

Histopathology

Obliterative bronchiolitis can be classified as either “constrictive,” representing circumferential fibrosis compressing the bronchiolar lumen, or “proliferative,” representing histologic proliferation of fibroelastic polyoid tissue in the bronchiolar lumen. In constrictive disease, histologic evaluation demonstrates peribronchiolar cellular infiltrates which progress to airway distortion and ultimately subepithelial fibrosis. Trichrome staining identifies fibrosis in bronchiolar muscle.40,41 In proliferative disease, an intraluminal bud called a “Masson body” fills the airway lumen, leading to bronchiolar plugging and extension through the conducting airways.4 A butterfly wing-like appearance may be microscopically observed.42 Organizing pneumonia is more commonly associated with proliferative disease. Table 1 reviews the histopathologic differences between OB and related diagnoses.

Obliterative lesions are localized from the small bronchi to membranous bronchiole. Intermittent distribution is seen in constrictive disease, whereas destructive/proliferative disease is associated with continuous obliteration of the bronchiolar lumen.43-45 The diagnosis is usually made based on clinical findings, imaging, and pulmonary function testing with a rare need for histologic evidence of disease. Owing to lesion heterogeneity and distribution, surgical lung biopsy is superior to transbronchial approaches in the rare circumstances, where there is sufficient diagnostic uncertainty to warrant biopsy.

Treatment

There is no uniformly accepted treatment protocol for patients with OB. Many patients are tried on corticosteroids or other immunosuppressants based on anecdotal evidence of improvement.38 These medications have significant toxicity and may complicate optimization for lung transplantation. Macrolides have been used with some success in lung transplant-related BOS which results in some use in OB, though evidence for this practice is scant. Routine vaccination against
pneumococcus and influenza are recommended as in other chronic lung diseases.

Although some patients stabilize after an initial decline, disease typically progresses to respiratory failure with or without cor pulmonale. Patients with hypoxemia should be treated with oxygen. As the obstructive defect progresses, gram-negative airway colonization may occur, resulting in complex antimicrobial management needs. Ultimately, many patients require transplantation, which remains the ultimate treatment for OB in appropriate patients.46

LUNG TRANSPLANTATION

Introduction

After lung transplantation, the term BOS describes a late complication involving persistent decline in spirometrically measured FEV1 that is not associated with another known and potentially reversible cause of allograft dysfunction. This phenomenon shares some histopathological overlap with OB and affects up to 50% of lung transplant recipients who survive at least 5 years after transplantation, making it the most commonly recognized noninfectious form of chronic lung allograft dysfunction (CLAD). It has a highly variable clinical course and is the leading cause of death beyond the first posttransplant year, responsible for 40% of deaths after lung transplantation.7,46,47 Survival is worse in patients who develop early-onset BOS or have higher grades at disease onset.57 Median survival after BOS diagnosis has been reported as 2.5 years with a 74% mortality within 5 years of diagnosis.31

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Bronchiolitis obliterans syndrome was initially described in 1984 when a number of early heart-lung transplant recipients were noted to have developed airway disease 3 years after transplantation. Pathological evaluation of these allografts revealed OB.48 In 1993, the International Society for Heart and Lung Transplantation (ISHLT) published the results of a working group on CLAD. This group formally
standardized the term BOS and established a severity grading system based on the FEV1.49

In 2002, the ISHLT released a new consensus on the definition of BOS designed to improve sensitivity to early changes in lung function, which represent potential targets for intervention. To accomplish this, subtle changes in FEV1 were separated out, and the FEF25–75 was incorporated to identify a “possible BOS” classification. The “baseline” FEV1 was defined as the average of the 2 highest posttransplant measurements obtained on separate visits at least 3 weeks apart. Bronchiolitis obliterans syndrome was divided into 4 subcategories which were defined as follows: BOS 0 represented an FEV1 greater than 90% of baseline and FEF25–75 greater than 75% of baseline; BOS 0-p represented an FEV1 of 81% to 90% of baseline and/or FEF25–75 75% or less of baseline; BOS 1 represented an FEV1 of 66% to 80% of baseline; BOS 2 represented an FEV1 of 51% to 65% of baseline; and BOS 3 represented an FEV1 of 50% or less of baseline.70 Importantly, other identifiable causes of allograft dysfunction (acute respiratory infection, and so on) should be excluded before the diagnosis of BOS can be made. This scheme continues to be the classification system used to describe the degree of allograft dysfunction present in the period after lung transplantation.

Intrinsic Risk Factors

Early studies have established a relationship between the presence of recipient genetic polymorphisms and the risk of BOS. Identified mutations involve a wide array of functions, ranging from toll-like receptors to cytokine regulators and innate immune responses. The strength and causality of these genetic relationships is poorly established and remains an area of active research.51

Numerous cellular and cytokine-related factors have been identified as predictors of BOS. For example, the presence of greater degrees of neutrophilia in bronchoalveolar lavage (BAL) fluid has been associated with a marked increase in the risk of developing BOS.52 In another study, increased serum levels of KL-6 (a MUC1 mucin which is sensitive for inflammatory pulmonary disorders) were shown to significantly correlate with decline in FEV1 after lung transplantation.53 Continued investigations into possible predictive factors will be necessary to attempt earlier identification and treatment of at-risk patients.

Allograft Injury

Primary graft dysfunction after lung transplantation represents the development of acute lung injury in the immediate posttransplant period. The mechanism of this disease is thought to be a nonimmune development of ischemia-reperfusion injury associated with the mechanical procedure of transplantation. Indeed, this phenomenon has been observed in canine autotransplantation, even in the setting of technically uncomplicated surgery.54,55 Primary graft dysfunction of all levels of severity has been associated with a significantly increased risk of BOS in a manner independent of other risk factors.56 The mechanism for this association is imperfectly understood but may represent the relationship between allograft injury, antigen exposure and inflammatory response described above.

Episodes of acute cellular rejection have consistently been identified as the strongest risk factors for the development of BOS.2,57–59 Conventionally, cellular rejection is identified by perivascular lymphocytic infiltrates on histopathologic examination. However, peribronchial lymphocytic infiltrates are also seen in some cases of acute cellular rejection. In recipients of lung transplantation, there is an increased risk of BOS associated with higher grades of lymphocytic bronchiolitis.60,61 The relationship between acute rejection and the development of BOS, however, is not limited to severe rejection episodes. In a series of 228 lung transplant recipients, an episode of “minimal acute cellular rejection” (the lowest severity of biopsy-proven rejection) persisted as a distinct risk factor for BOS even when controlled for other known risk factors.62

Gastroesophageal reflux has long been associated with various forms of lung disease presumably through reflux-mediated injury. This association extends to BOS in recipients of lung transplantation, leading some centers to aggressively treat evidence of reflux with pharmacological and surgical measures.2,63 Among lung transplant recipients with pH probe-diagnosed gastroesophageal reflux, annual decline in FEV1 was noted to be significantly worse than controls, although those who received surgical fundoplication had clinically and statistically significant improvements in peak FEV1 up to 1 year after surgery when compared to those who did not.64

Microbiological and Environmental Factors

Tissue damage and antigenic exposure, thought to be participatory in the development of BOS, is commonly associated with infection. Cytomegalovirus (CMV) has been strongly associated with development of BOS after lung transplantation.7,65,66 Among 231 lung transplant recipients, 21% of patients had evidence of CMV pneumonitis within 6 months of transplant. This finding was strongly associated with a higher incidence of BOS and posttransplant death and persisted despite treatment with ganciclovir.66 This has led to widespread use of early CMV prophylaxis and aggressive treatment of CMV viremia after lung transplantation. Indeed, extension of prophylaxis through a decrement in prednisone dose to less than 0.1 mg/kg per day has been associated with decreased incidence of both CMV complications and BOS after lung transplantation.67

Both cumulative exposure to aerosolized particulate matter (pollution) and proximity of a patient’s home to major roadways have been significantly associated with development of BOS.68,69 Additionally, community-acquired respiratory viruses have been associated with an increased risk of BOS. Acquisition of a community-acquired respiratory virus has been associated with both a significant increase of developing advanced BOS and a worsened mortality.70,71 Many patients who undergo lung transplantation (such as those with cystic fibrosis) have colonization of their native lungs with pathogenic microorganisms. After transplantation, these organisms can recolonize the lower airways of the allograft, a phenomenon that is associated with increased incidence of BOS.63,72 Together, these findings suggest microbiological and environmental factors may increase risk of BOS development.

Treatment—Steroids and Standard Immunosuppression

Considering the complex immunologic processes involved in the development of BOS, it is unsurprising that no specific
therapeutic approach has been uniformly adopted as a “standard of care.” Although the optimal immunosuppression regimen after transplantation is uncertain, lower cumulative exposure to immunosuppressant drugs is associated with increased incidence of BOS.7,60,72 Therefore, careful attention to maintenance immunosuppression is a key component of prevention.

The role of induction immunosuppression is unclear. In an analysis of the United Network for Organ Sharing database, induction immunosuppression was associated with improved graft and patient outcomes for kidney, liver, and lung transplantation.74 Induction immunosuppression carries increased risks of infection and has the potential to increase the risk of malignancies associated with immunosuppression. Further, other analyses of lung transplant recipients have failed to demonstrate strong survival benefits associated with this therapy.57 As a result, significant variability in lung transplant center induction practice exists, and overall use of induction immunosuppression has significantly decreased in recent years.75

The 2014 ISHLT/European Respiratory Society consensus guidelines on the management of BOS list augmentation of immunosuppression (styled as a 3-day course of daily doses of 1000 mg of intravenous methylprednisolone) as a primary approach to rejection episodes, including minimal acute cellular rejection. Although there is a clear relationship between rejection episodes and the development of BOS, the evidence supporting the use of high doses of steroids to abrogate this association is weak. Therefore, this recommendation comes with the recognition that short time side effects may increase but justifies tolerance of this reality through the hope of decreasing the likelihood of life-threatening allograft rejection. High doses of corticosteroids, however, are not recommended for the long-term management of BOS given the poor evidence and the more significant potential deleterious effects associated with prolonged use.47

Treatment—Alternative Pharmacology

Retrospective data have demonstrated significant improvements in FEV1 after initiation of macrolide antibiotics, particularly among patients with a high degree of neutrophilia in BAL fluid.76,77 In a separate study, azithromycin administration was associated with a survival advantage in patients with BOS and demonstrated a more pronounced effect when treatment was initiated during BOS stage 1.78 In a double-blind, randomized, controlled trial of azithromycin for the prevention of BOS, administration of 250 mg of azithromycin thrice weekly was associated with significant improvements in BOS-free survival with improved FEV1 and decreased airway neutrophilia.79 The proper duration of therapy is not established and provides an area of necessary further investigation. In a pilot study of the use of montelukast in BOS, patients started on treatment immediately after diagnosis experienced a significantly reduced rate of decline in lung function as compared to a retrospectively selected control cohort.80 This represents another potential therapeutic intervention for BOS and warrants larger-scale analyses.

Pirfenidone, an inhibitor of fibroblast proliferation, has been recently approved for the treatment of idiopathic pulmonary fibrosis in the United States. In a rodent model of tracheal transplantation, administration of pirfenidone was associated with less epithelial cell injury and less luminal fibrosis when compared with untreated controls. Of note, pirfenidone treated animals also exhibited decreased plasma TGF-β levels and local TGF-β expression based on immunohistochemistry.81

Treatment—Nonpharmacologic

Extracorporeal photopheresis (ECP) involves the procedure of removing a portion of the patient’s blood volume from which the leukocyte-enriched buffy coat is extracted and exposed to ultraviolet light in the presence of 8-methoxypsoralen. This leads to binding of DNA, cell-surface molecules and cytoplasmic components in exposed leukocytes and results in leukocyte dysfunction. Although further evidence is needed, this therapy has been associated with a reduction in the rate of decline in lung function in patients with BOS after lung transplantation, a response that may be variable depending on the phenotype of the patient’s allograft dysfunction.82-84

Radiation induced lymphocyte depletion (in the form of total lymphoid irradiation [TLI]) was used in Hodgkin lymphoma before cytotoxic chemotherapy became widely available. This therapy has also been utilized to induce T-cell depletion and immunosuppression in solid organ transplant recipients.85 In the largest series, examining the use of TLI in 37 patients with BOS, therapy was both well tolerated and associated with significant improvements in the rate of decline in FEV1.86 Given the relative paucity of data regarding TLI, further studies will be useful in defining the propriety role of this treatment in the prevention of CLAD.

Finally, in the absence of effective relief of BOS, patients should be referred for consideration of retransplantation. Retransplantation represents a complex, controversial intervention with poor outcomes and high cost. Although outcomes still lag behind recipients of initial transplants, they have improved. Among 205 recipients of retransplantation between 2001 and 2006, the risk of death was significantly lower than it had been among patients retransplanted between 1990 and 2000. However, the risk of death was significantly higher than that experienced among patients undergoing initial transplant during the more modern period.87 Therefore, consideration of retransplantation should be undertaken in a multidisciplinary fashion with a careful consideration of patient-specific factors likely to affect outcome.

Phenotypes of CLAD

Because the primary focus of this article is the spectrum of diseases associated with the histopathologic appearance of OB, BOS has been discussed at greatest length. It is important to recognize, however, that other forms of CLAD have been described. The restrictive allograft syndrome has been recently described as a progressive decline in lung function with proportional decreases in both FVC and FEV1.88 Allograft biopsies demonstrate pleuroparenchymal fibroelastosis with or without diffuse alveolar damage, though several patients also had lesions consistent with concomitant OB.89 Disease progression follows a “stair step” pattern with frequent exacerbations and intermittent stability, though survival associated with this syndrome is worse than that observed in patients with BOS.88,90 Although little is known about the underlying pathophysiology of, or risk factors for, this disease, the same pathologic findings have been found in a small number of patients after hematopoietic stem cell transplantation and in a number of patients for whom no cause was identified.91
HEMATOPOIETIC STEM CELL TRANSPLANT

Introduction

Hematopoietic stem cell transplant is an increasingly utilized treatment for hematologic malignancies, aplastic anemia, and rare immunodeficiency disorders, offering approximately half of all recipients’ long-term disease-free survival.92,93 The high rate of transplant-related mortality initially limited use of this intervention; however, evolution of transplant medicine over the past 3 decades has significantly reduced the short-term mortality, allowing more patients to live long enough to experience late complications.94 Chronic graft-versus-host disease (cGVHD) is the most common late complication of HSCT and is manifested in the lungs as BOS in a manner clinically and pathologically similar to that seen in the BOS phenotype of CLAD, described above.

Bronchiolitis obliterans syndrome occurs in 2% to 4% of all HSCT recipients.95 Greater than 80% of cases of BOS after HSCT occur within 18 months of transplant, and 5-year survival among affected patients may be as low as 10%.95-100

In 2005, a National Institutes of Health-sponsored consensus committee proposed a unified set of diagnostic criteria for BOS to include either biopsy proven disease or GVHD in 1 organ other than the lung plus all of the following: FEV1/FVC ratio less than 0.7 with FEV1 less than 75% predicted; evidence of air trapping, airway thickening, or bronchiectasis on high-resolution CT or residual volume greater than 120%, and absence of infection in the respiratory tract.101

Risk Factors

Development of cGVHD in an extrapulmonary site is a significant risk for BOS with a more than two-fold increase in incidence when extrapulmonary involvement is identified. Up to 97% of patients with BOS have identifiable disease in other organs.92,93,94,95 Additionally, acute GVHD portends a high risk for subsequent development of chronic disease.96,99,102

Before HSCT, all patients undergo a conditioning regimen of myeloablative chemotherapy to create a hospitable bone marrow environment for engraftment. As many chemotherapeutic agents carry significant risk of adverse pulmonary effects, the regimen selected for this purpose poses a risk for the development of subsequent disease. Specifically, in several series, busulfan-based regimens have been associated with the development of BOS after HSCT.102-104 This effect may be the result of direct epithelial toxicity causing antigenic exposure and subsequent donor alloreactivity. In contradistinction, the use of antithymocyte globulin as part of the conditioning regimen has been demonstrated to be protective against the development of BOS.102

After conditioning, patients are infused with donor cells. These cells were conventionally acquired directly from bone marrow, although pheresis-driven acquisition of peripheral blood stem cells has become increasingly common. Use of peripheral blood stem cell has been identified as an independent risk factor for BOS (93, 102, 103).

Unsurprisingly, the degree of mismatch between donor and recipient does appear to play a significant role, with a higher BOS rate at 2 years among recipients from a matched-unrelated or mismatched donor (40%) than those with a matched-related donor (20%).105 This relationship persists regardless of the method of stem cell acquisition.105 In conjunction with the multiple reports of a decreased incidence of BOS in patients who receive T cell-depleted transplants, this suggests a strong role for alloantigen recognition in HSCT-associated complications.106-108

Female sex of both recipient and donor has been shown across multiple studies to confer a significant risk for BOS.92,95,96,102,104 The putative mechanism for this may involve endocrinologic factors or the complex immunological effect of conception and pregnancy, although it remains poorly understood. Patients younger than 20 years, those with an abnormal FEV1 before transplantation, those who develop respiratory infections within the first 100 days after transplant and those with an ABO-incompatible donor all have a higher risk for developing BOS as well.99,102,104

Treatment—Steroids and Standard Immunosuppression

Unfortunately, the treatment of long-term pulmonary complications in HSCT has lagged behind advances in transplant protocols. There are currently no randomized trials evaluating optimal treatments for BOS, and treatment is based largely on data from small cohorts and retrospective clinical trials.

Post-HSCT prophylaxis for GVHD is a complex topic with relatively poor standardization. In a large meta-analysis, regimens containing tacrolimus or antithymocyte globulin in combination with methotrexate and/or cyclosporine were associated with decreased incidence of BOS when compared to methotrexate or cyclosporine monotherapy.109 Few studies have evaluated the role of mycophenolate or sirolimus-containing regimens.

Both the American Society for Bone Marrow Transplant and the British Society for Bone Marrow Transplant recommend corticosteroids as first line treatment for cGVHD at a dose of 1 mg/kg per day alone or in combination with a calcineurin inhibitor.110-112 There is no standardized approach to steroid taper. The expected response to first line treatments ranges from 20% to 40%, and clinical improvement after first line treatment is associated with significant improvements in survival.99,112

Treatment—Alternative Pharmacology

The combination of budesonide/formoterol inhalational therapy has been associated with a significant improvement in FEV1 sustained over 1 year after treatment initiation.113 Azithromycin, used with the above-noted success after lung transplantation, has not been clearly demonstrated to confer the same benefit after HSCT although its relatively favorable side effect profile and efficacy in other circumstances promotes its continued use in this setting.114,115 The combined use of the inhaled corticosteroid fluticasone, the macrolide azithromycin, and the leukotriene inhibitor montelukast was associated with more rapid weaning from systemic corticosteroids despite preservation of FEV1 in a small, retrospective, case-control study.116
The TNF-α inhibitor etanercept and ECP have both been demonstrated to have some success in achieving systemic corticosteroid reduction and disease stabilization, although these are considered second-line therapy in most centers.117-123 Identification of antibodies activating the platelet-derived growth factor receptor pathway led to the use of the tyrosine kinase inhibitor imatinib in a small study of patients with treatment refractory, fibrotic GVHD. Six months after treatment initiation, 15 of 19 patients had achieved either complete or partial remission, a response that persisted in 14 of those patients through 17 months of follow-up.124 Multiple other immunomodulators, including rituximab and thalidomide, have been studied in BOS with disappointing results.125-127

Treatment—Nonpharmacologic

As in lung transplantation, ECP has been tried in the therapy of GVHD after HSCT. In 1 study of 95 patients, those randomized to ECP experienced a significant increase in the likelihood of decrease in steroid dose as well as a decrease in cutaneous involvement of disease.119 It is not clear whether these findings extend to improvement in pulmonary function, and further studies are necessary to clarify the role of ECP in BOS after HSCT.

Finally, in patients with advanced BOS, lung transplantation may be considered as a therapeutic option. This has been controversial owing to the presence of recent malignancy as a relative contraindication to lung transplantation. Further, there is concern that the immunologic processes underlying the development of BOS after HSCT may be equally pathological and poorly responsive after lung transplantation. In 1 series of 7 patients who underwent lung transplant a median of 18 months after the diagnosis of BOS, median survival was 24 months, significantly less than that reported among the general population of lung transplant recipients.128 In a more recent review of the reported literature, 84 recipients of lung transplantation after HSCT were described by Soubani et al.129 The median time between HSCT and lung transplant was 52 months. Three years after lung transplantation, survival was 71% with 30% of patients developing BOS and only 2 patients experienced a relapse of their hematologic malignancy. This suggests better outcomes than initially reported and raises the prospect of lung transplantation as a means to improve outcomes in appropriately selected patients with advanced BOS after HSCT.

CONCLUSIONS

Obliterative bronchiolitis is likely the pathologic consequence of a series of elaborate immunological and nonimmunological processes. This disease is the complex result of a poorly understood progression toward airway epithelial dysfunction. Obliterative bronchiolitis in nontransplant populations may be the result of autoimmune disease or inhatalional exposure but an etiologic agent is not always determined. A spectrum of related disease plays a significant role in the outcomes of patients who undergo lung transplantation and hematopoietic stem cell transplantation. Regardless of the cause, this pathology is associated with significant disease burden and poor responsiveness to treatment. Ongoing investigations are necessary to help elucidate the best approach to preventing this epithelial dysfunction and improving the lives of affected patients.

REFERENCES


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