1083-8791/07/1307-0001$32.00/0
doi:10.1016/j.bbmt.2007.05.001

ASBMT
American Society for Blood and Marrow Transplantation

Bronchiolitis Obliterans Syndrome (BOS), Bronchiolitis Obliterans Organizing Pneumonia (BOOP), and Other Late-Onset Noninfectious Pulmonary Complications following Allogeneic Hematopoietic Stem Cell Transplantation

Satoshi Yoshihara,[1] *Gregory Yanik*,[2] *Kenneth R. Cooke*,[2] *Shin Mineishi*[1]

[1]Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; and [2]Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, Michigan

Correspondence and reprint requests: Shin Mineishi, MD, Blood and Marrow Transplant Program, University of Michigan, 5303 Cancer Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109 (email: smineish@umich.edu).

Received January 31, 2007; accepted May 1, 2007

ABSTRACT

Pulmonary dysfunction is a significant complication following allogeneic hematopoietic stem cell transplantation (HSCT), and is associated with significant morbidity and mortality. Effective antimicrobial prophylaxis and treatment strategies have increased the incidence of noninfectious lung injury, which can occur in the early posttransplant period or in the months and years that follow. Late-onset noninfectious pulmonary complications are frequently encountered, but diagnostic criteria and terminology for these disorders can be confusing and therapeutic approaches are suboptimal. As a consequence, inaccurate diagnosis of these conditions may hamper the appropriate data collection, enrollment into clinical trials, and appropriate patient care. The purpose of this review is to clarify the pathogenesis and diagnostic criteria of representative conditions, such as bronchiolitis obliterans syndrome and bronchiolitis obliterans organizing pneumonia, and to discuss the appropriate diagnostic strategies and treatment options.

KEY WORDS

Bronchiolitis obliterans syndrome (BOS) • Bronchiolitis obliterans organizing pneumonia (BOOP) • Late-onset noninfectious pulmonary complications • Allogeneic • Pathogenesis • Diagnostic criteria

INTRODUCTION

Allogeneic hematopoietic bone marrow transplantation (allo-HSCT) is a curative treatment option for a variety of malignant and nonmalignant disorders. However, a number of complications associated with the occurrence of either acute or chronic graft versus host disease (aGVHD, cGVHD) have limited the utility of this procedure. In particular, pulmonary complications occur in 25%-50% of allo-HSCT recipients, and can account for approximately 50% of transplant related deaths [1-6]. In nearly 50% of cases, no infectious organisms are identified in the lungs of affected individuals. Both an acute and a subacute pattern of lung injury have been recognized in this context (Figure 1). Noninfectious, acute lung injury has been defined as idiopathic pneumonia syndrome (IPS). IPS occurs with in the first 120 days after HSCT and typically has a rapidly progressing fulminant course resulting in death in 60% to 80% of patients. By contrast, subacute lung injury is associated with a later onset, typically >6 months posttransplant, and the clinical course tends to be more insidious and protracted (Figure 1). This review will focus on 2 common subacute or late-onset pulmonary complications, namely bronchiolitis obliterans syndrome (BOS), and bronchiolitis obliterans with organizing pneumonia (BOOP).

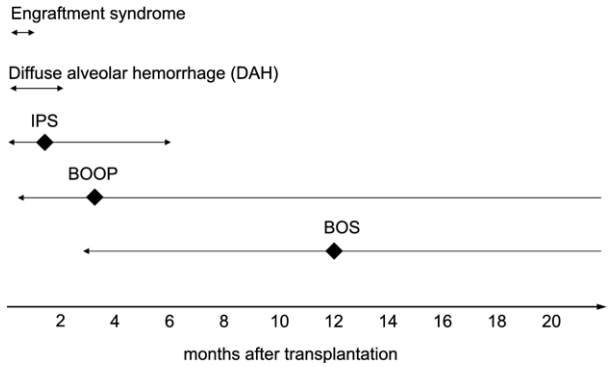

Figure 1. Schematic diagram of the time of occurrence of IPS, BOOP, and BOS.

BOS

"Bronchiolitis obliterans" describes a histologic pattern of small airway inflammation that includes fibrogenic deposition in small airways or bronchioles. Bronchioles consist of terminal bronchioles and respiratory bronchioles, and serve as the bridge between conducting airways and alveoli. BO is synonymous with the term "constrictive bronchiolitis," and is manifested clinically by the presence of airflow obstruction and recognized histologically by submucosal bronchiolar fibrosis, along with luminal narrowing and obliteration. BOS is a clinical term defined by pulmonary function changes rather than histology [7-10]. BOS is defined as an irreversible decline in forced expiratory volume in 1 second (FEV1) of at least 20% from baseline, and is graded using the International Society for Heart and Lung Transplantation (ISHLT) criteria [11]. Although BO and BOS may include different patient cohorts, indicated by the fact that some patients with positive histologic findings of BO do not have pulmonary function changes seen in BOS, these 2 entities are believed to greatly overlap, and the terms tend to be used interchangeably [9,11].

PATHOGENESIS

The pathogenesis of BOS after HSCT has not been well defined. However, the heterogeneous histopathologic findings and clinical course suggest that the development of BOS is a multifactorial process involving both alloimmunologic and nonalloimmunologic reactions. Because the occurrence of BOS has been closely associated with cGVHD, it has been hypothesized that BOS is mediated, at least in part, by alloimmunologic injury to host bronchiolar epithelial cells [12]. Unlike IPS, elevations of pro-inflammatory cytokine levels within the serum and broncho-alveolar lavage (BAL) compartment of affected subjects have not been well documented in humans or animal models [13-21]. Murine models have suggested, however, that lymphocytes and associated chemokines and cytokines, including tumor necrosis factor alpha (TNFα), may be important contributors to the development of the chronic inflammatory process that characterizes BOS after lung transplantation [13,14,22,23]. The pathogenesis of disease is believed to primarily involve the interplay between immune effector cells (monocytes, lymphocytes, neutrophils) that have been recruited to the lung and cells resident to the pulmonary vascular endothelium and interstitium. This complex process results in the loss of type I pulmonary epithelial cells, proliferation of type II cells, the recruitment and proliferation of endothelial cells, and the deposition of the extracellular matrix. In response to this pattern of injury, cytokines released from these effector cells and lung cells (macrophages, alveolar epithelial, and vascular endothelial cells) can stimulate fibroblast proliferation and increase the synthesis of collagen and extracellular matrix proteins. Ultimately, this leads to enhanced deposition of collagen and granulation tissue in and around bronchial structures, and eventually complete obliteration of small airways (Figure 2) [12].

Clinical data suggest that nonalloimmunologic inflammatory conditions such as viral infections, recurrent aspiration, and conditioning chemoradiotherapy may also play a role in the pathogenesis of BOS after HSCT. A recent report indicated that respiratory tract infections with some community respiratory viruses (parainfluenza virus and respiratory syncytial virus) were associated with late airflow decline [15]. BOS after autologous transplantation and decreased risk of BOS after reduced intensity conditioning support a contribution to tissue damage from chemoradiotherapy that is part of HSCT conditioning regimens [16,17], as has been observed with IPS [18].

INCIDENCE AND RISK FACTORS

Because of the lack of defined diagnostic criteria, the reported incidence of BOS following allo-HSCT varies widely from 1.7% to 26% [8,19-21,24]. As noted above, the development of BOS in both pediatric and adult populations is closely associated with the occurrence of cGVHD. Other potential risk factors that have been identified include the use of methotrexate for aGVH prophylaxis [8], decreased serum IgG levels [19], the prior occurrence of acute GVHD [25], older recipient age, older donor age [26], lower pretransplant FEV1/forced vital capacity (FVC) ratio, respiratory viral infections within the first 100 days posttransplant [20], busulfan-based conditioning regimen, peripheral blood stem cell transplantation, female donor to male recipient, a prior episode of interstitial pneumonitis [24], and the intensity of HSCT conditioning [17].

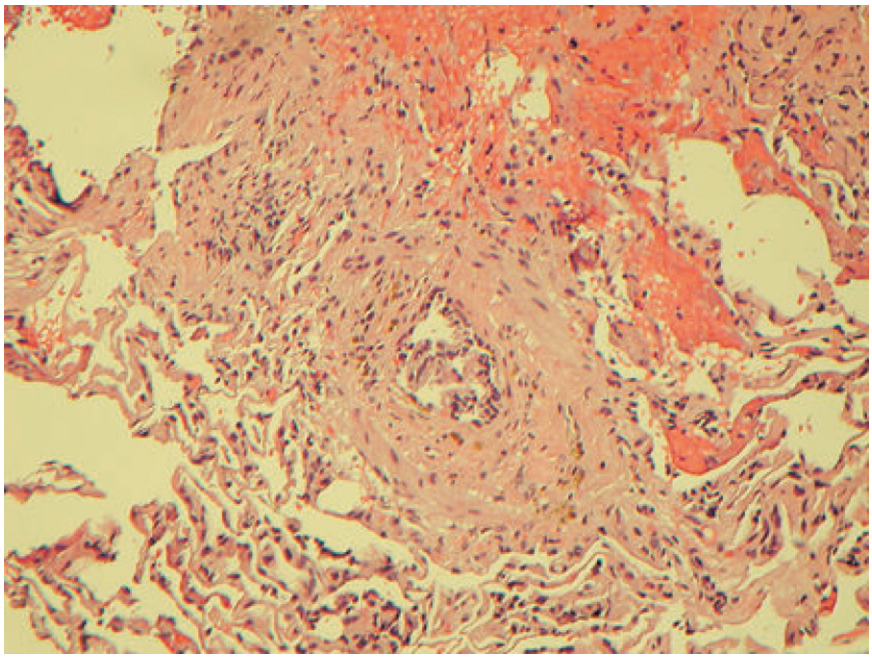

Figure 2. Histology of BO. Characterized by concentric obstruction of the small airways and relative sparing of alveolar space.

CLINICAL PRESENTATION

The onset of BOS varies from 3 months to >10 years, with a median onset approximately 1 year post-HSCT [10,21,24,27,28]. Common symptoms include progressive dyspnea, nonproductive cough, and wheezing. Unlike BOOP, fever is usually absent in BOS. Many patients remain asymptomatic for long periods, despite having evidence of moderate to severe airway obstruction on pulmonary function tests. In this context, and because >33% of patients with cGVHD develop signs of airflow obstruction [20], close observation should be a part of the follow-up plans in these patients.

DIAGNOSIS

Pulmonary Function Testing (PFT)

Airflow obstruction is the hallmark of BOS. A decrease in forced expiratory volume in 1 second (FEV1) and diminished FEV1/FVC ratio are observed. Total lung capacity is not usually affected (Table 1). Lung diffusion capacity for carbon monoxide (DLCO) is often decreased; however, this is a nonspecific finding that may be seen in many patients following HSCT irrespective of airflow obstruction [29].

For patients undergoing allogeneic lung transplantation, ISHLT diagnostic criteria for BOS include a >20% decline in FEV1 values when compared with the postoperative baseline [30]. Recently, the introduction of forced expiratory flow rates (FEF25-75) has been added to these diagnostic criteria [31]. In comparison to FEV1, the FEF25-75 may be a more sensitive indicator of early airflow obstruction in BOS following allogeneic lung transplant [32].

In several studies, airflow obstruction has been defined as a decrease of the FEV1/FVC ratio to <0.7 and FEV1 to <80% of the predicted value [21,27]. Chien et al. [20] recently proposed new criteria, in which patients were defined as having airflow obstruction if the annualized rate of predicted FEV1 decline

Table 1. *Comparison of Clinical Presentations of BOS and BOOP*

	BOS	BOOP
Symptom	Progressive dyspnea	Fever
	Non productive cough	Nonproductive cough
	Wheezing	Dyspnea (usually mild)
Physical exam.	Wheezing	Rales
Lab data	Non specific	Elevated level of CRP
		Increased neutrophil
PFT	Obstructive lung disease	Restrictive lung disease
FEV1/FVC	Decreased	Normal
TLC	Normal	Decreased
DL_{CO}	Decreased	Decreased
Radiology		
CT scan	Air trapping (expiration phase)	Consolidation
	Mosaic perfusion	Ground glass opacity
	Bronchiectasis	Nodules
	Bronchial wall thickening	
	Centrilobular nodules	

PFT indicates pulmonary function test; BOS, bronchiolitis obliterans syndrome; BOOP, bronchiolitis obliterans organizing pneumoria.

was >5% per year and the lowest documented posttransplant FEV1/FVC ratio was <0.8. Using these criteria, the investigators showed that development of airflow decline by day 100 posttransplant was associated with an increased risk for airflow obstruction at 1 year, but was not with an increase in mortality risk [33]. By contrast, patients with the fastest rate of decline between day 100 and 1 year had the highest mortality risk.

Radiographic Findings

Chest X-rays are often normal in patients with BOS, although hyperinflation has been described [27]. The role of high-resolution computed tomography (HRCT) or thin-section CT in the diagnosis of BOS has been explored in lung transplant recipients [26,34-36]. Characteristic findings of BOS include air trapping, mosaic perfusion, bronchial dilatation (bronchiectasis), and bronchial wall thickening. Air trapping may be demonstrated on HRCT during expiration, and had the highest sensitivity for the development of BOS in lung transplant recipients (Figure 3) [34].

BRONCHOSCOPY AND LUNG BIOPSY

Bronchoscopy with BAL in patients with BOS is usually nonspecific, showing neutrophilic and/or lymphocytic inflammation [37], but is essential to help rule out infectious causes of pulmonary dysfunction. Although lung biopsy is the only way to definitively diagnose BO, it is infrequently performed in the settings of BOS after HSCT. Although transbronchial lung biopsies (TBLB) can be routinely performed with minimal risk of hemorrhage and pneumothorax, the sensitivity of such testing is suboptimal. In 1 recent report, only 15% to 40% of patients with BOS could be provided with histologic confirmation with this procedure [38]. The low sensitivity of the procedure is likely related to the patchy nature of BO and because of the small quantity of bronchiolar material obtained. Surgical lung biopsy by video-assisted thorocoscopic surgery (VATS) is useful; however, it is often avoided because of the surgical risks present in this population.

Because histologic confirmation can be obtained in only a limited number of patients, BOS following HSCT is usually a clinical diagnosis that is made based upon clinical symptoms, PFT results, and radiologic findings. Respiratory infections and BOOP should be ruled out with imaging and other appropriate procedures.

TREATMENT OF BOS

Based on the premise that BOS results from an alloimmunologic reaction, augmentation of immunosuppression has been widely used as the initial line of treatment. The use of corticosteroids with prednisone at 1-1.5 mg/kg/day over 4-6 weeks [9] or pulsed corticosteroid dosing with methylprednisolone (10 mg/kg/day + 3 days every month up to 6 cycles) has been reported [39]. A recent report suggested that inhaled

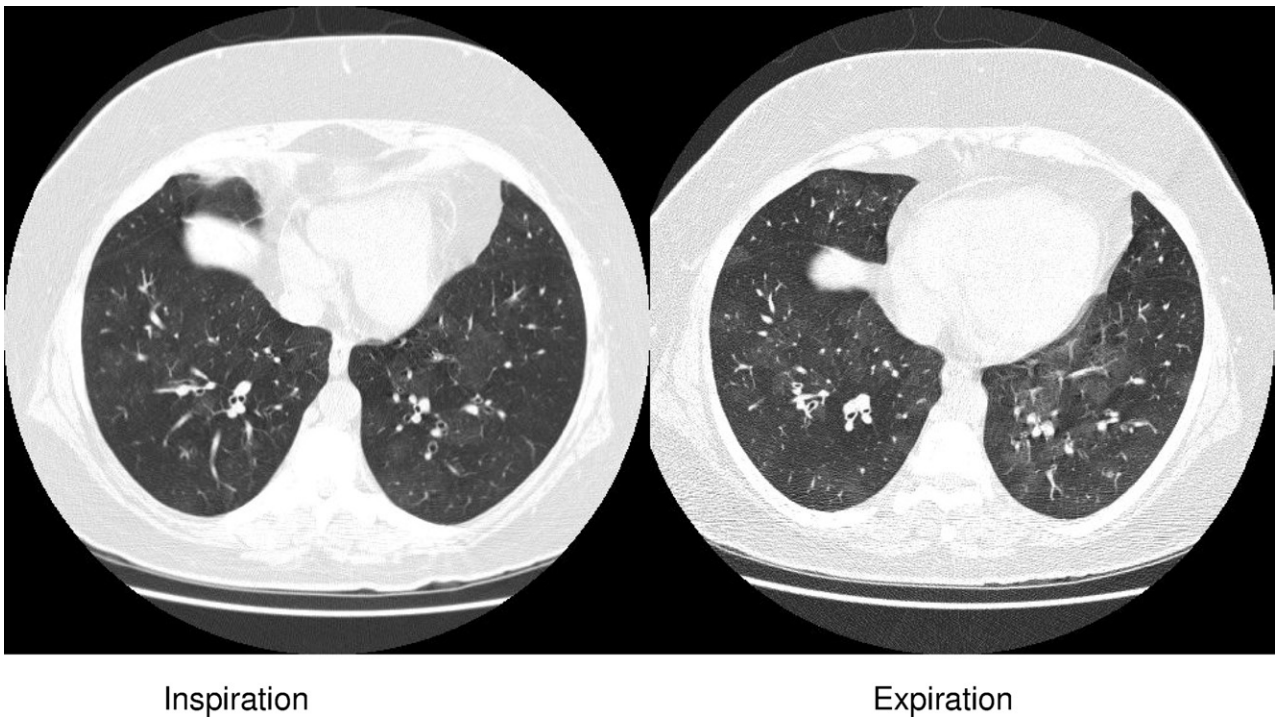

Figure 3. CT scan of BOS. Mosaic pattern of air trapping is clearly shown in expiratory phase.

cyclosporine may be effective both in the prevention and treatment of BOS after lung transplantation [40,41], but this strategy has not been investigated in HSCT recipients. The role of azithromycin has also been explored in the setting of lung transplantation [42,43]. Recently, the efficacy of azithromycin (500 mg every day for 3days, followed by 250 mg 3 times a week for 12 weeks) has been reported in the treatment of a small number of patients with BOS after HSCT [44]. Azithromycin has been shown to have anitiinflammatory effects, particularly with respect to IL-8 and airway neutrophilia, and these properties may contribute to beneficial effects observed in BOS [45]. Given the potential role of inflammatory cytokines, the use of TNFα neutralizing agents has also been reported, and may represent a novel therapy for the management of BOS. Yanik et al. [46] reported the potential efficacy of etanercept, human TNFα neutralizing agent, in the treatment of IPS and have found that this molecule may be useful for subacute lung injury as well [47]. Larger prospective trials in each setting are ongoing. Fullmer et al. [48] reported a case of BOS following HSCT in a pediatric patient that was successfully treated with infliximab, a monoclonal antibody for human TNFα. Other interventions including the long-term administration of intravenous immunoglobulin has failed to show the effect on preventing the development of BOS [49]. Extracorporeal photochemotherapy (ECP), which has been shown to be a promising treatment for cGVHD [50,51], has been used with some success for BOS following lung transplantation [52]. However, only a few case reports are available that examine the effectiveness of this therapy for BOS after HSCT [53,54]. Because of the poor response to traditional therapies, lung transplantation has been increasingly reported as a possible therapeutic option for end-stage BOS after HSCT [55-60].

PROGNOSIS

Despite treatment with augmented immunosuppression, the prognosis for patients with BOS remains poor. Improvement of lung function once significant impairment has occurred can be obtained in only a minority of the patients. Mortality remains high, varying from 14% to 100% (mean 61%) [61]. In the majority of cases, death is attributed to progressive respiratory failure and opportunistic pulmonary infections. Clark et al. [27] reported that a 3-year mortality rate of 65% in the patients with BOS accompanying cGVHD. Rapid decline in FEV1 [27,33], resistance to first-line therapy [21], earlier onset (earlier than 6 months or 200 days) [17,21] are all factors reported to be associated with a worse prognosis.

BOOP

BOOP is a disorder involving bronchioles, alveolar ducts, and alveoli, the lumen of which become filled with buds of granulation tissue consisting of fibroblasts and an associated matrix of loose connective tissue. The bronchiolitis in BOOP is of the proliferative type, and generally includes mild inflammation of the bronchiolar walls. In contrast to BO, there is no prominent bronchiolar wall fibrosis or bronchiolar distortion [62]. The intraluminal lesions and consequent organizing pneumonia are the most significant histopathologic findings in BOOP. Recently, idiopathic BOOP has been termed cryptogenic organizing pneumonia (COP) to avoid confusion with the BO nomenclature [63].

PATHOGENESIS

Although the pathogenesis of BOOP following HSCT is poorly understood, involvement of an alloimmunologic reaction has been again been considered. In animal studies, BOOP develops following infection with reovirus, and a significant role for T cells and Th1-derived cytokines, including interferon-α, was implicated in the development of disease [64]. A case reported following syngeneic bone marrow transplantation suggests that BOOP is not always the result of an allogeneic immune response [65]. In other non-HSCT settings BOOP has been seen in association with infection, drugs, radiation therapy, and a number of connective tissue disorders [62].

INCIDENCE AND RISK FACTORS

Patients with BOOP following HSCT have been described in several reports [62,65-73]. Freudenberger et al. [74] recently reported a case-control study of histologic BOOP. Of 5340 patients who received alloHSCT, 49 cases (0.9%) of histologic BOOP were identified. An association between aGVHD and cGVHD and the subsequent development of BOOP was noted. Patients with BOOP were more likely to have acute cutaneous GVHD and cGVHD involving the gut and oral cavity. In other reports, 3 of 179 (1.6%) patients receiving matched sibling donor HSCT [72] and 4 of 39 (10.3%) patients who received unrelated donor HSCT developed BOOP [75].

CLINICAL PRESENTATION

The onset of BOOP has been reported to vary from 5 to >2800 days posttransplant, with a median occurrence by day 108 post-HSCT [74] Following HSCT, BOOP has a similar clinical presentation to that seen with idiopathic BOOP (a.k.a. COP). Fever,

nonproductive cough, and dyspnea are all typically noted. On physical examination, rales are common, but wheezing is generally absent. Elevations in serum levels of C-reactive protein have been seen in conjunction with a moderate leukocytosis and neutrophilia.

DIAGNOSIS

PFT

PFTs typically reveal a mild to moderate restrictive defect, the degree of which depends on the extent of the pulmonary inflammation. DLCO is commonly decreased, and in contrast with BOS, airflow obstruction is usually absent.

Radiology

The radiologic findings in idiopathic BOOP include diffuse, "fluffy" consolidations, ground glass opacity, and nodules (Figure 4). Consolidation is often migratory [76,77]. Lee et al. [78] reported the CT findings in 43 patients with biopsy-proven idiopathic BOOP. The most common pattern was consolidation, present alone or as part of a mixed pattern in 79% of cases. The consolidation had a predominantly subpleural and/or peribronchovascular distribution. Ground-glass opacity and nodules were seen in 60% and 30%, respectively. Of note, BOOP in immunocompromised patients (following HSCT, with leukemia, or myelodysplastic syndrome) showed different radiographic patterns from that in immunocompetent patients. Less areas of consolidation (45% versus 91%), greater ground-glass involvement (73% versus 56%) and more frequent pulmonary nodules (55% versus 22%) are seen in this group. Dodd et al. [79] recently reported the HRCT findings of 4 patients with BOOP following HSCT. All patients showed consolidation and significant ground-glass opacifications.

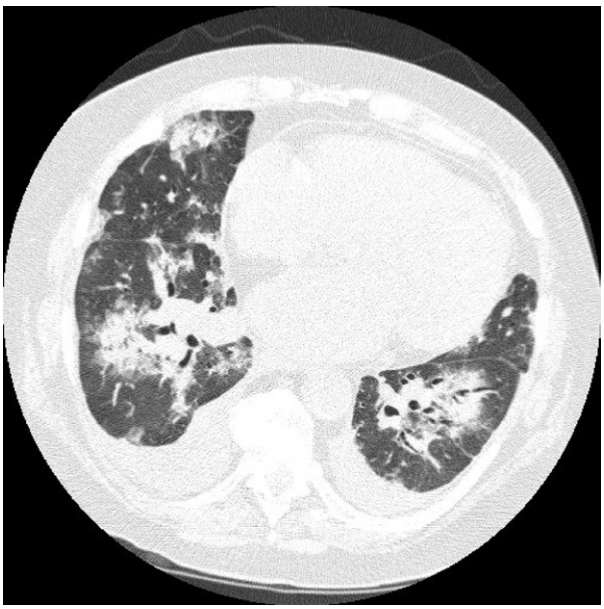

Figure 4. CT scan of BOOP. Consolidation/nodules are shown.

Bronchoscopy and Lung Biopsy

Bronchoscopy and BAL are useful in ruling out pulmonary infection and establishing the diagnosis of BOOP (Figure 5). BAL fluid reveals lymphocytosis, with a decreased CD4/CD8 ratio. Despite the usefulness of BAL, histologic confirmation is still believed to be necessary for a diagnosis of BOOP. Unlike BO, BOOP usually can be sufficiently diagnosed with TBLB by demonstrating organizing pneumonia. VATS is required in the cases with atypical features or in whom the diagnosis cannot be made with TBLB [80].

TREATMENT AND PROGNOSIS

Although there is no standardized treatment protocol for BOOP after HSCT, corticosteroid is the mainstay of therapy. In the treatment of idiopathic BOOP, prolonged treatment (prednisone 1 mg/kg for 1-3 months, 40 mg for 3 months, followed by 10-20 mg for a total of 1 year) was proposed to avoid relapses [81]. The rate of relapse in idiopathic BOOP varies from 9% to 58%, although relapses may not necessarily affect long-term outcome [80]. Based on this fact, the use of lower corticosteroid dosages with a shorter duration of treatment (prednisone 0.75 mg/kg for 4 weeks, 0.5 mg/kg for 4 weeks, 10 mg for 6 weeks, 5 mg for 6 weeks) has been proposed [82]. The role of macrolides has also been explored also in the treatment in BOOP [73].

Freudenberger et al. [74] reported that BOOP after HSCT resolved in 57% and remained stable in 21% of cases. BOOP progressed in 22% of patients despite corticosteroids, with the majority of these patients (16% of total) dying from respiratory failure. Although the overall prognosis of idiopathic BOOP is good, with mortality rates 5% to 15%, the prognosis of BOOP after HSCT still remains to be defined, and is potentially lower [69,75].

OTHER COMPLICATIONS

Pulmonary veno-occlusive disease (PVOD) is a rare complication observed following both auto- and allo-HSCT that results in pulmonary hypertension [83-88]. The pathologic hallmark of PVOD is the extensive and diffuse occlusion of pulmonary veins by fibrous tissue [89]. In addition to HSCT recipients, PVOD has been reported in patients who received chemotherapy [90] and in patients with an associated

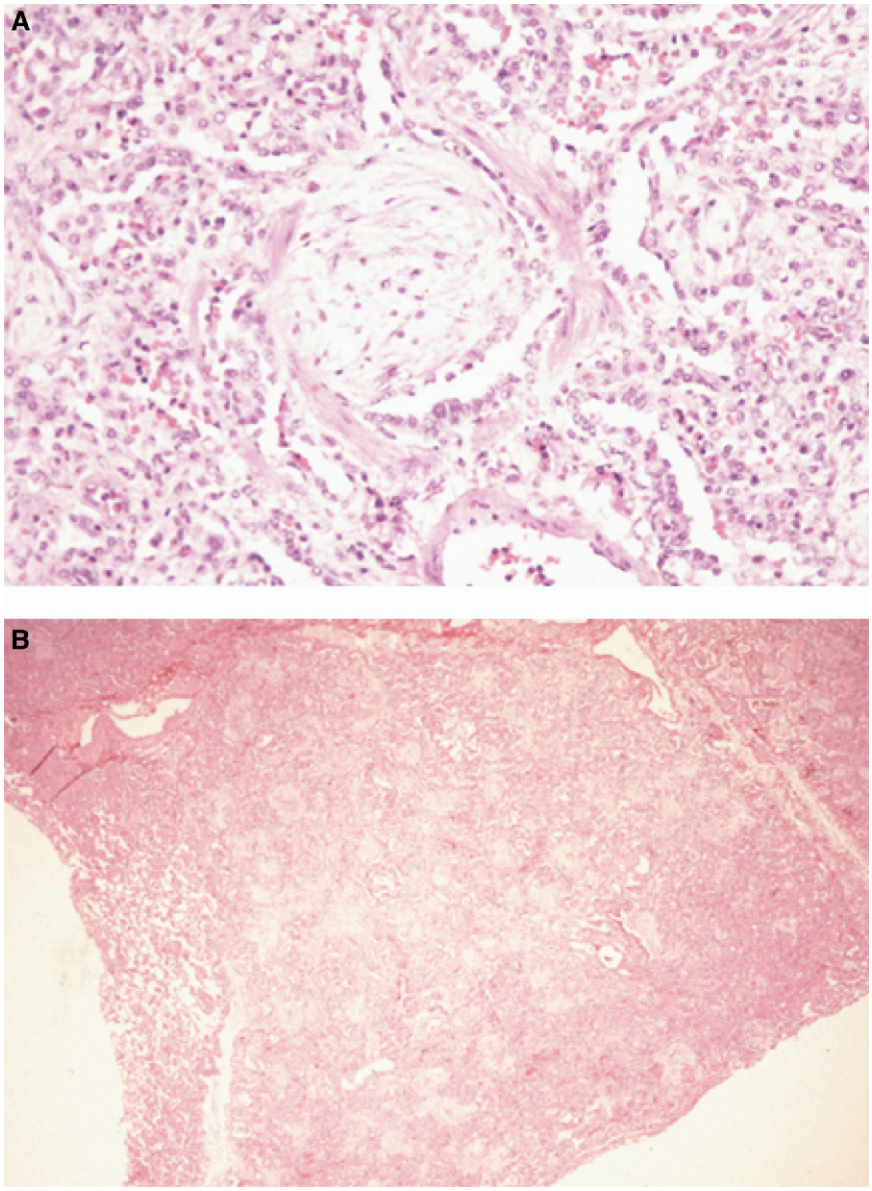

Figure 5. Histology of BOOP. Alveolar space is occupied by organizing pneumonia.

viral illness [91]. Autoimmune destruction of pulmonary venules has not been commonly observed in those patients, and only a minority of patients with PVOD have associated autoimmune disorders [92]. These findings suggest that PVOD after HSCT is a result of tissue injury from HSCT conditioning and/or infection. The onset of PVOD varies from a month to a year after HSCT. Most patients with PVOD present with nonspecific complaints such as dyspnea on exertion and fatigue. The physical examination and radiologic findings are consistent with pulmonary hypertension. Right heart catheterization shows elevated pulmonary artery pressure with normal pulmonary artery wedge pressure. The triad of severe pulmonary hypertension, radiographic evidence of pulmonary edema, and a normal pulmonary artery occlusion pressure is thought to be diagnostic of PVOD. However, many patients with PVOD do not have this triad. Surgical lung biopsy is the only way for a definitive diagnosis, and thus should be considered to confirm the clinical suspicion of PVOD [89]. Most reported cases of PVOD after HSCT were treated with high-dose corticosteroids, with minimal effectiveness, and the prognosis of PVOD remains poor.

Pulmonary cytolytic thrombi (PCT) is a recently recognized rare noninfectious pulmonary complication seen almost exclusively in pediatric patients post allo-HSCT [93-97]. PCT appears as pulmonary thrombi in small to medium distal pulmonary vessels, consisting predominantly of monocytes of both donor and recipient origin, and associated with hemorrhagic pulmonary infarction [94,97]. The onset ranges between 8 and 343 days (median 72 days) after HSCT. PCT presents with fever, cough, chest pain, respira-

tory distress. Chest CT scans may reveal multiple small peripheral or subpleural nodules and opacities of varying size. The majority of cases had active aGVHD or cGVHD. Woodard et al. [93] reported that 9 of 13 patients with PCT were alive with a median follow-up of 1.5 years. Several patients showed clinical improvement and radiologic resolution of their pulmonary nodules after immunosuppressive therapy was administered.

As noted earlier, acute noninfectious interstitial pneumonitis (IP) occurring within 120 days after HSCT is termed IPS. In the majority of cases, affected patients also exhibit signs of aGVHD. In contrast, it has been reported that patients develop progressive IP much later (11 months to 8 years) after HSCT in association with severe cGVHD, especially scleroderma tous skin GVHD [75,98,99]. This late onset progressive IP presents with dyspnea, and cough and PFT results commonly show a severe restrictive pattern. Pneumothorax may occur secondary to severe pulmonary fibrosis. The prognosis is poor because of respiratory failure despite augmented immunosuppression.

SUMMARY

Both BOS and BOOP are potential "late" pulmonary complications that may occur following allo-HSCT. Importantly, BOS and BOOP each represents distinct clinical entity, and should not to be used interchangeably, although such usage is common. The 2 disorders are clearly distinct with respect to histopathologic findings, radiographic and functional characteristics, and most importantly, response to therapy. BOOP following allo-HSCT is responsive to steroids (and in other settings may resolve spontaneously), whereas BOS is not. Although diagnostic methods and treatment strategies for pulmonary infections have improved significantly over the last decade, options in the treatment of noninfectious lung injury remain limited.

Because the onset and progression of both BOS and BOOP can be insidious, pulmonary function testing should be performed every 3 to 4 months for the first 2 years posttransplant, particularly in patients with cGVHD. A significant drop in pulmonary function should prompt a workup in which careful physical examination, radiographic analysis, and BAL are considered. The appropriate use of defined diagnostic criteria for each condition, in combination with early diagnosis and well-designed prospective clinical trials, is required to make progress in outcomes in these conditions.

ACKNOWLEDGMENTS

Dr. Cooke is an Amy Strelzer-Manasevit Scholar of the National Marrow Donor Program, a Fellow of the Robert Wood Johnson Harold Amos Medical Faculty Development Program, a Clinical Scholar of the Leukemia and Lymphoma Society, and the recipient of a Clinical Scientist in Translational Research Award from the Burroughs Wellcome Fund.

REFERENCES

1. Clark JG, Madtes DK, Martin TR, Hackman RC, Farrand AL, Crawford SW. Idiopathic pneumonia after bone marrow transplantation: cytokine activation and lipopolysaccharide amplification in the bronchoalveolar compartment. *Crit Care Med*. 1999;27:1800-1806.
2. Crawford SW, Hackman RC. Clinical course of idiopathic pneumonia after bone marrow transplantation. *Am Rev Respir Dis*. 1993;147:1393-1400.
3. Weiner RS, Bortin MM, Gale RP, et al. Interstitial pneumonitis after bone marrow transplantation. Assessment of risk factors. *Ann Intern Med*. 1986;104:168-175.
4. Quabeck K. The lung as a critical organ in marrow transplantation. *Bone Marrow Transplant*. 1994;14(Suppl 4):S19-S28.
5. Crawford SW, Longton G, Storb R. Acute graft-versus-host disease and the risks for idiopathic pneumonia after marrow transplantation for severe aplastic anemia. *Bone Marrow Transplant*. 1993;12:225-231.
6. Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW. Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. *Transplantation*. 1997; 63:1079-1086.
7. Ralph DD, Springmeyer SC, Sullivan KM, Hackman RC, Storb R, Thomas ED. Rapidly progressive air-flow obstruction in marrow transplant recipients. Possible association between obliterative bronchiolitis and chronic graft-versus-host disease. *Am Rev Respir Dis*. 1984;129:641-644.
8. Clark JG, Schwartz DA, Flournoy N, Sullivan KM, Crawford SW, Thomas ED. Risk factors for airflow obstruction in recipients of bone marrow transplants. *Ann Intern Med*. 1987;107: 648-656.
9. Crawford SW, Clark JG. Bronchiolitis associated with bone marrow transplantation. *Clin Chest Med*. 1993;14:741-749.
10. Curtis DJ, Smale A, Thien F, Schwarer AP, Szer J. Chronic airflow obstruction in long-term survivors of allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1995;16:169-173.
11. Chan CK, Hyland RH, Hutcheon MA, et al. Small-airways disease in recipients of allogeneic bone marrow transplants. An analysis of 11 cases and a review of the literature. *Medicine (Baltimore)*. 1987;66:327-340.
12. Cooke KR, Ferrara JLM. The pathophysiology of lung Injury after hematopoietic stem cell transplantation. In: James LM, Ferrra KRC, Deeg HJ, eds. *Graft-vs-Host Disease*. 3rd edition New York: Marcel-Dekker; 2005:329-367.
13. Belperio JA, Keane MP, Burdick MD, et al. Critical role for the chemokine MCP-1/CCR2 in the pathogenesis of bronchiolitis obliterans syndrome. *J Clin Invest*. 2001;108:547-556.
14. Aris RM, Walsh S, Chalermskulrat W, Hathwar V, Neuringer IP. Growth factor upregulation during obliterative bronchiolitis in the mouse model. *Am J Respir Crit Care Med*. 2002;166: 417-422.
15. Erard V, Chien JW, Kim HW, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the

role of community respiratory viruses. *J Infect Dis*. 2006; 193:1619-1625.
16. Paz HL, Crilley P, Patchefsky A, Schiffman RL, Brodsky I. Bronchiolitis obliterans after autologous bone marrow transplantation. *Chest*. 1992;101:775-778.
17. Yoshihara S, Tateishi U, Ando T, et al. Lower incidence of Bronchiolitis obliterans in allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning compared with myeloablative conditioning. *Bone Marrow Transplant*. 2005;35:1195-1200.
18. Fukuda T, Hackman RC, Guthrie KA, et al. Risks and outcomes of idiopathic pneumonia syndrome after nonmyeloablative and conventional conditioning regimens for allogeneic hematopoietic stem cell transplantation. *Blood*. 2003;102:2777-2785.
19. Holland HK, Wingard JR, Beschorner WE, Saral R, Santos GW. Bronchiolitis obliterans in bone marrow transplantation and its relationship to chronic graft-v-host disease and low serum IgG. *Blood*. 1988;72:621-627.
20. Chien JW, Martin PJ, Gooley TA, et al. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med*. 2003;168:208-214.
21. Dudek AZ, Mahaseth H, DeFor TE, Weisdorf DJ. Bronchiolitis obliterans in chronic graft-versus-host disease: analysis of risk factors and treatment outcomes. *Biol Blood Marrow Transplant*. 2003;9:657-666.
22. Boehler A, Bai XH, Liu M, et al. Upregulation of T-helper 1 cytokines and chemokine expression in post-transplant airway obliteration. *Am J Respir Crit Care Med*. 1999;159:1910-1917.
23. Neuringer IP, Walsh SP, Mannon RB, Gabriel S, Aris RM. Enhanced T cell cytokine gene expression in mouse airway obliterative bronchiolitis. *Transplantation*. 2000;69:399-405.
24. Santo Tomas LH, Loberiza FR, Jr., Klein JP, et al. Risk factors for bronchiolitis obliterans in allogeneic hematopoietic stem-cell transplantation for leukemia. *Chest.* 2005;128:153-161.
25. Schwarer AP, Hughes JM, Trotman-Dickenson B, Krausz T, Goldman JM. A chronic pulmonary syndrome associated with graft-versus-host disease after allogeneic marrow transplantation. *Transplantation*. 1992;54:1002-1008.
26. Worthy SA, Park CS, Kim JS, Muller NL. Bronchiolitis obliterans after lung transplantation: high-resolution CT findings in 15 patients. *AJR Am J Roentgenol*. 1997;169:673-677.
27. Clark JG, Crawford SW, Madtes DK, Sullivan KM. Obstructive lung disease after allogeneic marrow transplantation. Clinical presentation and course. *Ann Intern Med*. 1989;111:368-376.
28. Philit F, Wiesendanger T, Archimbaud E, Mornex JF, Brune J, Cordier JF. Post-transplant obstructive lung disease ("bronchiolitis obliterans"): a clinical comparative study of bone marrow and lung transplant patients. *Eur Respir J*. 1995;8:551-558.
29. Marras TK, Chan CK, Lipton JH, Messner HA, Szalai JP, Laupacis A. Long-term pulmonary function abnormalities and survival after allogeneic marrow transplantation. *Bone Marrow Transplant*. 2004;33:509-517.
30. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 1993;12:713-716.
31. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant*. 2002;21:297-310.
32. Reynaud-Gaubert M, Thomas P, Badier M, Cau P, Giudicelli R, Fuentes P. Early detection of airway involvement in obliterative bronchiolitis after lung transplantation. Functional and bronchoalveolar lavage cell findings. *Am J Respir Crit Care Med*. 2000;161:1924-1929.
33. Chien JW, Martin PJ, Flowers ME, Nichols WG, Clark JG. Implications of early airflow decline after myeloablative allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2004; 33:759-764.
34. Leung AN, Fisher K, Valentine V, et al. Bronchiolitis obliterans after lung transplantation: detection using expiratory HRCT. *Chest*. 1998;113:365-370.
35. Bankier AA, Van Muylem A, Knoop C, Estenne M, Gevenois PA. Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. *Radiology*. 2001;218: 533-539.
36. Siegel MJ, Bhalla S, Gutierrez FR, Hildebolt C, Sweet S. Post-lung transplantation bronchiolitis obliterans syndrome: usefulness of expiratory thin-section CT for diagnosis. *Radiology*. 2001;220:455-462.
37. St John RC, Gadek JE, Tutschka PJ, Kapoor N, Dorinsky PM. Analysis of airflow obstruction by bronchoalveolar lavage following bone marrow transplantation. Implications for pathogenesis and treatment. *Chest*. 1990;98:600-607.
38. Chan A, Allen R. Bronchiolitis obliterans: an update. *Curr Opin Pulm Med*. 2004;10:133-141.
39. Ratjen F, Rjabko O, Kremens B. High-dose corticosteroid therapy for bronchiolitis obliterans after bone marrow transplantation in children. *Bone Marrow Transplant*. 2005;36:135-138.
40. Iacono AT, Corcoran TE, Griffith BP, et al. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. *Eur Respir J*. 2004;23:384-390.
41. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med*. 2006;354:141-150.
42. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med*. 2003;168:121-125.
43. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. *Transplantation*. 2004;77:1465-1467.
44. Khalid M, Al Saghir A, Saleemi S, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J*. 2005;25:490-493.
45. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med*. 2006;174:566-570.
46. Yanik G, Hellerstedt B, Custer J, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2002;8:395-400.
47. Yanik G, Uberti J, Ferrara JL, et al. Etanercept for sub-acute lung injury following allogeneic stem cell transplantation. *Blood.* 2003;102:(Suppl):471a.
48. Fullmer JJ, Fan LL, Dishop MK, Rodgers C, Krance R. Successful treatment of bronchiolitis obliterans in a bone marrow transplant patient with tumor necrosis factor-alpha blockade. *Pediatrics*. 2005;116:767-770.
49. Sullivan KM, Storek J, Kopecky KJ, et al. A controlled trial of long-term administration of intravenous immunoglobulin to

prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. *Biol Blood Marrow Transplant*. 1996;2:44-53.
50. Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. *Blood*. 2006;107:3074-3080.
51. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood*. 1998; 92:3098-3104.
52. O'Hagan AR, Stillwell PC, Arroliga A, Koo A. Photopheresis in the treatment of refractory bronchiolitis obliterans complicating lung transplantation. *Chest*. 1999;115:1459-1462.
53. Ilhan O, Arat M, Arslan O, et al. Extracorporeal photoimmunotherapy for the treatment of steroid refractory progressive chronic graft-versus-host disease. *Transfus Apher Sci*. 2004;30: 185-187.
54. Oyan B, Koc Y, Emri S, Kansu E. Improvement of chronic pulmonary graft-vs-host disease manifesting as bronchiolitis obliterans organizing pneumonia following extracorporeal photopheresis. *Med Oncol*. 2006;23:125-129.
55. Calhoon JH, Levine S, Anzueto A, Bryan CL, Trinkle JK. Lung transplantation in a patient with a prior bone marrow transplant. *Chest*. 1992;102:948.
56. Gascoigne A, Corris P. Lung transplants in patients with prior bone marrow transplants. *Chest*. 1994;105:327.
57. Boas SR, Noyes BE, Kurland G, Armitage J, Orenstein D. Pediatric lung transplantation for graft-versus-host disease following bone marrow transplantation. *Chest*. 1994;105:1584-1586.
58. Rabitsch W, Deviatko E, Keil F, et al. Successful lung transplantation for bronchiolitis obliterans after allogeneic marrow transplantation. *Transplantation*. 2001;71:1341-1343.
59. Heath JA, Kurland G, Spray TL, et al. Lung transplantation after allogeneic marrow transplantation in pediatric patients: the Memorial Sloan-Kettering experience. *Transplantation*. 2001;72:1986-1990.
60. Sano Y, Date H, Nagahiro I, Aoe M, Shimizu N. Living-donor lobar lung transplantation for bronchiolitis obliterans after bone marrow transplantation. *Ann Thorac Surg*. 2005;79:1051-1052.
61. Afessa B, Litzow MR, Tefferi A. Bronchiolitis obliterans and other late onset non-infectious pulmonary complications in hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28:425-434.
62. Cordier JF. Bronchiolitis obliterans organizing pneumonia. *Semin Respir Crit Care Med*. 2000;21:135-146.
63. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med.* 2002;165:277-304.
64. Majeski EI, Paintlia MK, Lopez AD, Harley RA, London SD, London L. Respiratory reovirus 1/L induction of intraluminal fibrosis, a model of bronchiolitis obliterans organizing pneumonia, is dependent on T lymphocytes. *Am J Pathol*. 2003;163: 1467-1479.
65. Kanda Y, Takahashi T, Imai Y, et al. Bronchiolitis obliterans organizing pneumonia after syngeneic bone marrow transplantation for acute lymphoblastic leukemia. *Bone Marrow Transplant*. 1997;19:1251-1253.
66. Thirman MJ, Devine SM, O'Toole K, et al. Bronchiolitis obliterans organizing pneumonia as a complication of allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1992;10:307-311.
67. Mathew P, Bozeman P, Krance RA, Brenner MK, Heslop HE. Bronchiolitis obliterans organizing pneumonia (BOOP) in children after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1994;13:221-223.
68. Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. *Hum Pathol*. 1995;26:668-675.
69. Alasaly K, Muller N, Ostrow DN, Champion P, FitzGerald JM. Cryptogenic organizing pneumonia. A report of 25 cases and a review of the literature. *Medicine (Baltimore)*. 1995;74: 201-211.
70. Kleinau I, Perez-Canto A, Schmid HJ, et al. Bronchiolitis obliterans organizing pneumonia and chronic graft-versus-host disease in a child after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1997;19:841-844.
71. Baron FA, Hermanne JP, Dowlati A, et al. Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. 1998;21:951-954.
72. Palmas A, Tefferi A, Myers JL, et al. Late-onset noninfectious pulmonary complications after allogeneic bone marrow transplantation. *Br J Haematol*. 1998;100:680-687.
73. Ishii T, Manabe A, Ebihara Y, et al. Improvement in bronchiolitis obliterans organizing pneumonia in a child after allogeneic bone marrow transplantation by a combination of oral prednisolone and low dose erythromycin. *Bone Marrow Transplant*. 2000;26:907-910.
74. Freudenberger TD, Madtes DK, Curtis JR, Cummings P, Storer BE, Hackman RC. Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. *Blood*. 2003;102:3822-3828.
75. Patriarca F, Skert C, Sperotto A, et al. Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. *Bone Marrow Transplant*. 2004;33:751-758.
76. Miyagawa Y, Nagata N, Shigematsu N. Clinicopathological study of migratory lung infiltrates. *Thorax*. 1991;46:233-238.
77. Izumi T, Kitaichi M, Nishimura K, Nagai S. Bronchiolitis obliterans organizing pneumonia. Clinical features and differential diagnosis. *Chest*. 1992;102:715-719.
78. Lee KS, Kullnig P, Hartman TE, Muller NL. Cryptogenic organizing pneumonia: CT findings in 43 patients. *AJR Am J Roentgenol*. 1994;162:543-546.
79. Dodd JD, Muller NL. Bronchiolitis obliterans organizing pneumonia after bone marrow transplantation: high-resolution computed tomography findings in 4 patients. *J Comput Assist Tomogr*. 2005;29:540-543.
80. Wells AU. Cryptogenic organizing pneumonia. *Semin Respir Crit Care Med*. 2001;22:449-460.
81. Epler GR. Bronchiolitis obliterans organizing pneumonia. *Semin Respir Infect*. 1995;10:65-77.
82. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. The Groupe d'Etudes

et de Recherche sur les Maladles "Orphelines" Pulmonaires (GERM"O"P). *Am J Respir Crit Care Med* 2000;162:571-577.
83. Troussard X, Bernaudin JF, Cordonnier C, et al. Pulmonary veno-occlusive disease after bone marrow transplantation. *Thorax*. 1984;39:956-957.
84. Hackman RC, Madtes DK, Petersen FB, Clark JG. Pulmonary venoocclusive disease following bone marrow transplantation. *Transplantation*. 1989;47:989-992.
85. Kuga T, Kohda K, Hirayama Y, et al. Pulmonary veno-occlusive disease accompanied by microangiopathic hemolytic anemia 1 year after a second bone marrow transplantation for acute lymphoblastic leukemia. *Int J Hematol*. 1996;64:143-150.
86. Williams LM, Fussell S, Veith RW, Nelson S, Mason CM. Pulmonary veno-occlusive disease in an adult following bone marrow transplantation. Case report and review of the literature. *Chest*. 1996;109:1388-1391.
87. Trobaugh-Lotrario AD, Greffe B, Deterding R, Deutsch G, Quinones R. Pulmonary veno-occlusive disease after autologous bone marrow transplant in a child with stage IV neuroblastoma: case report and literature review. *J Pediatr Hematol Oncol*. 2003;25:405-409.
88. Mukai M, Kondo M, Bohgaki T, Notoya A, Kohno M. Pulmonary veno-occlusive disease following allogeneic peripheral blood stem cell transplantation for chronic myeloid leukaemia. *Br J Haematol*. 2003;123:1.
89. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med*. 2000;162:1964-1973.
90. Doll DC, Yarbro JW. Vascular toxicity associated with antineoplastic agents. *Semin Oncol*. 1992;19:580-596.
91. McDonnell PJ, Summer WR, Hutchins GM. Pulmonary veno-occlusive disease. Morphological changes suggesting a viral cause. *JAMA*. 1981;246:667-671.
92. Sanderson JE, Spiro SG, Hendry AT, Turner-Warwick M. A case of pulmonary veno-occlusive disease respondong to treatment with azathioprine. *Thorax*. 1977;32:140-148.
93. Woodard JP, Gulbahce E, Shreve M, et al. Pulmonary cytolytic thrombi: a newly recognized complication of stem cell transplantation. *Bone Marrow Transplant*. 2000;25:293-300.
94. Gulbahce HE, Manivel JC, Jessurun J. Pulmonary cytolytic thrombi: a previously unrecognized complication of bone marrow transplantation. *Am J Surg Pathol*. 2000;24:1147-1152.
95. Morales IJ, Anderson PM, Tazelaar HD, Wylam ME. Pulmonary cytolytic thrombi: unusual complication of hematopoietic stem cell transplantation. *J Pediatr Hematol Oncol*. 2003;25:89-92.
96. Gulbahce HE, Pambuccian SE, Jessurun J, et al. Pulmonary nodular lesions in bone marrow transplant recipients: impact of histologic diagnosis on patient management and prognosis. *Am J Clin Pathol*. 2004;121:205-210.
97. Peters A, Manivel JC, Dolan M, Gulbahce HE, Baker KS, Verneris MR. Pulmonary cytolytic thrombi after allogeneic hematopoietic cell transplantation: a further histologic description. *Biol Blood Marrow Transplant*. 2005;11:484-485.
98. Griese M, Rampf U, Hofmann D, Fuhrer M, Reinhardt D, Bender-Gotze C. Pulmonary complications after bone marrow transplantation in children: twenty-four years of experience in a single pediatric center. *Pediatr Pulmonol*. 2000;30:393-401.
99. Wolff D, Reichenberger F, Steiner B, et al. Progressive interstitial fibrosis of the lung in sclerodermoid chronic graft-versus-host disease. *Bone Marrow Transplant*. 2002;29:357-360.