

# Fibrosing Alveolitis in Hematologic Malignancy Patients Undergoing Hematopoietic Cell Transplantation

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## Case Presentation

A 20-year-old man patient with *de novo* acute myelogenous leukemia (AML) was induced into complete remission with chemotherapy consisting of idarubicin and cytarabine. After consolidation with high-dose cytarabine, he later received conditioning with cyclophosphamide 60 mg/kg/day intravenously for 2 days and fractionated total body irradiation (TBI) 1,200 cGy followed by allogeneic hematopoietic cell transplant (HSCT) using a HLA-identical sibling donor. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and short-course methotrexate. His clinical course was uncomplicated, but after withdrawal of immunosuppression he developed extensive chronic GVHD involving skin and liver. This complication was controlled with the re-institution of tacrolimus.

Surveillance pulmonary function testing completed 180 days after HSCT showed evidence of mild reductions in forced expiratory volume in 1 s ( $FEV_1$ ) with preservation of forced vital capacity (FVC). Follow-up study revealed significant and rapid worsening of obstructive lung disease (OLD) despite resolution of hepatic and skin GVHD and continued prophylaxis against viral, fungal and *Pneumocystis* infections using acyclovir, fluconazole and trimethoprim-sulfamethoxazole, respectively. Reductions in pulmonary function ultimately were associated with shortness of breath and dyspnea with exertion. Subsequent workup revealed ground-glass opacities with air trapping on chest computed tomography (CT) scan and evidence of progressive AFO on pulmonary function testing based on reduction of  $FEV_1$  (50% of predicted normal), a ratio of  $FEV_1$  to FVC of 0.64 and a residual volume of 1.52 L (157% of predicted normal). Bronchoalveolar lavage was negative for infection. Video-assisted thoracoscopic biopsy of the lungs

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revealed changes consistent with bronchiolitis obliterans with early fibrosis. The patient continued to receive tacrolimus, and ultimately a course of oral prednisone (2 mg/kg/day) and etanercept 50 mg subcutaneous once weekly was initiated. Clinical symptoms resolved and pulmonary function improved. He remains in complete remission regarding the AML.

## 42.1 Introduction

Fibrosing alveolitis (FA) is a progressive and often fatal disorder characterized by sequential acute lung injury with subsequent scarring and end-stage lung disease. Historically, idiopathic pulmonary fibrosis (IPF) encompassed a heterogeneous group of histologic and clinical entities arising in an idiopathic setting [1]. Patients with hematologic malignancies treated with chemotherapy, radiation or HSCT, such as the patient described above, commonly develop a wide variety of late and chronic pulmonary dysfunction states [2]. These complications share many of the clinical and pathologic features described in typical idiopathic FA.

This spectrum of pulmonary toxicity observed during FA can be simplified by considering the time of diagnosis in relation to institution of therapy, whether the radiographic abnormalities are focal or diffuse, and by underlying histopathology. In addition, there are individual patient factors that should be considered when formulating a differential diagnosis. These include:

- Radiotherapy delivered to the chest wall or as part of total body irradiation (TBI)
- Exposure to pulmonary- or cardio-toxic chemotherapeutic agents
- Current or prior immunosuppressant therapy
- History of high-dose chemotherapy exposure prior to autologous or allogeneic HSCT
- History of opportunistic pulmonary infection (fungal or otherwise)

In the case described herein, the patient was exposed to radiation therapy in preparation for HSCT and received an allogeneic graft from his HLA-matched sibling. While his early posttransplant course was uncomplicated, he developed chronic GVHD of the

skin and liver lung after immunosuppression was tapered. The widespread and appropriate use of prophylactic antibiotics has shifted the spectrum of pulmonary dysfunction in HSCT recipients from infectious to noninfectious etiologies. This chapter will address the chronic lung complications that lead to pulmonary fibrosis and persistent organ dysfunction in each context with specific focus on hematologic malignancy patients treated using HSCT.

## 42.2 Fibrosing Alveolitis Secondary to Pulmonary Infections

In patients with hematologic malignancies, severe lung infections frequently lead to the development of acute respiratory distress syndrome (ARDS). Bacterial infections predominate (see Table 42.1) and arise because of severe immune suppression inherent to these disorders and their treatments. The pathology of ARDS involves severe alveolar epithelial cell damage, hyaline membrane formation, and festinate myofibroblast proliferation and fibrosis in the intra-alveolar spaces. Affected HSCT recipients who deteriorate and require intubation and mechanical ventilation for ARDS experience a high mortality. In one series, overall intensive care unit (ICU) mortality was 74% [3]. In recent years, advancements in supportive care have resulted in significant improvement in survival [4]. However, long-term survivors continue to have residual lung dysfunction that may progress over time. In one series, autopsy evaluation revealed pulmonary fibrosis in 55% of such patients, underscoring the importance of dysregulated reparative mechanisms in the lung after an acute insult [5]. Factors influencing progression to the fibro-proliferative phase of ARDS versus resolution and reconstitution of the normal parenchymal architecture are poorly understood. Abnormal repair and remodeling may be profoundly affected by both environmental and genetic factors. In this context, mechanical ventilation may affect the macromolecules that constitute the extracellular matrix (collagen, elastin, fibronectin, laminin, proteoglycan and glycosaminoglycans) and impact the biomechanical balance within the lung parenchyma.

Fungal infections also may follow a chronic course of prolonged inflammation with focal or diffuse

**Table 42.1** Timing of likely infections among allogeneic hematopoietic cell transplant (HCT) recipients receiving antimicrobial prophylaxis

	Pre-engraftment: <3 weeks after HCT	Immediate post-HCT: 3 weeks-3 months after HCT	Late post-HCT: >3 months after HCT
Risk factors	Mucositis Organ dysfunction Neutropenia and other immune defects	Acute GVHD and its therapy  Mucocutaneous damage Cellular immune dysfunction Immune modulating viruses	Chronic GVHD and its therapy  Mucocutaneous damage Cellular and humoral immune dysfunction Hyposplenism and decreased opsonization Decrease in reticuloendothelial function
Infecting			
Bacterial species	Many gram-positive spp. including coagulase-negative staphylococci, <i>Staphylococcus aureus</i> , viridans streptococci  Many gram-negative spp. including <i>Legionella</i> spp, <i>Pseudomonas aeruginosa</i> , Enterobacteriaceae, <i>Stenotrophomonas maltophilia</i>	<i>Listeria monocytogenes</i> <i>Legionella pneumophila</i>	Encapsulated organisms, e.g., <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i>
Fungal species	<i>Candida</i> sp.	<i>Candida</i> sp. <i>Aspergillus</i> sp. <i>Pneumocystis jiroveci</i>	<i>Aspergillus</i> sp <i>Pneumocystis jiroveci</i>
Viral species	Herpes simplex	Respiratory viruses, CMV, HHV6, HHV7	CMV, HHV6, HHV7, VZV, Bk adenovirus, JC virus, EBV
Parasitic species		Toxoplasmosis	

HCT hematopoietic cell transplant, GVHD graft-versus-host disease, HHV6 and HHV7 human herpes virus 6 and 7, CMV cytomegalovirus, JC virus John Cunningham virus

scarring ultimately resulting in significant pulmonary dysfunction. Invasive aspergillosis (IA) occurs frequently in hematologic malignancy patients, particularly after an allogeneic HSCT, presenting classically as angio-invasive or airway-invasive disease. Angio-invasive IA is characterized histologically by invasion and occlusion of small to medium-sized pulmonary arteries by fungal hyphae. This effect leads to the formation of necrotic hemorrhagic nodules or pleural-based, wedge-shaped hemorrhagic infarcts. The “halo sign” (nodules surrounded by areas of ground-glass attenuation) on chest CT scan strongly suggests a diagnosis of IA [6].

Airway-invasive aspergillosis is characterized by the presence of organisms in the basement membrane

of the bronchioles and within the airway lumen. Positive yield from respiratory samples such as sputa examination or broncho-alveolar lavage (BAL) is more likely in this subtype of IA than in the angio-invasive variety. Clinical manifestations of acute airway-invasive aspergillosis include: acute tracheobronchitis, exudative bronchiolitis and bronchopneumonia. Using high-resolution CT, the associated bronchiolitis is characterized by the presence of peri-bronchial consolidation, centri-lobular micro-nodules, and branching linear or nodular areas of ground-glass attenuation having a “tree-in-bud” appearance [7]. This form of airway-invasive aspergillosis can be associated with pseudo-membranous necrotizing tracheal involvement that can cause pneumo-mediastinum and has a high

mortality [8]. Airway-invasive aspergillosis can also follow a chronic course known as chronic necrotizing aspergillosis. This condition is characterized by an indolent, granulomatous cavitary infection that may mimic reactivation of tuberculosis radiographically [9]. Mortality is lower compared with the other forms of IA and often is related to the underlying disease of the patient.

### 42.3 Fibrosing Alveolitis Secondary to Noninfectious Etiologies

Hematologic malignancy patients treated with chemotherapy or chest wall radiation therapy, or those who proceed to receive a HSCT may develop a wide variety inflammatory noninfectious lung disorders that ultimately may lead to pulmonary fibrosis.

#### 42.3.1 Radiation Therapy

Radiation-induced lung injury first was described in 1898, soon after the development of roentgenograms [10]. In 1925 the distinction between two separate types of radiation-induced lung injury, radiation pneumonitis and radiation fibrosis, was made [11]. An entire chapter from Drs. Gallego and Rello in this book is dedicated to radiation-related lung injury. Radiation-induced lung injury results from the combination of direct cytotoxicity upon normal lung tissue and, perhaps more importantly, the development of fibrosis triggered by radiation-induced cellular signal transduction. The cytotoxic effect is largely a consequence of DNA damage and death in normal lung epithelial cells. The development of fibrosis that can compromise lung function is mediated by a number of different cytokines. Clinically, the most extensively studied radiation-induced cytokine is transforming growth factor beta 1 (TGF- $\beta$ ), which can induce fibroblast collagen deposition. A normal plasma TGF- $\beta$  concentration at the conclusion of a clinical course of radiotherapy has been observed to be a predictor for the risk of

pneumonitis [12]. Other proinflammatory cytokines, including, but not limited to, interleukin IL-6, tumor necrosis factor-alpha TNF $\alpha$  and IL-1, are upregulated immediately after irradiation. Increased IL-6 plasma concentrations correlate with an increased risk of radiation-induced lung injury [13, 14]. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor ( $\beta$ FGF) are upregulated in animal models of lung irradiation injury and antedate the development of fibrosis [15]. Factors affecting the development of radiation-induced lung disease are numerous and are included in Table 42.2 [16–19]; all have been reported to raise the risk of radiation pneumonitis.

Radiographic and bronchoscopic findings are non-specific, and the diffusion capacity for carbon monoxide (DL) typically is depressed in patients with radiation-induced lung damage. Long-term glucocorticoids may be effective in the treatment of radiation-associated lung injury in which COP is the leading pulmonary involvement; however, symptoms and radiographic abnormalities, as well as immunologically mediated lymphocytic alveolitis frequently recur with discontinuation of therapy [20, 21]. Early studies suggested that pentoxifylline may have a role

**Table 42.2** Factors affecting the development of radiation-induced lung disease [16–19]

- Method of irradiation such as conformal radiation therapy or specialized techniques including intensity-modulated radiation therapy and stereotactic body radiation therapy
- Volume of lung tissue irradiated
- Radiation dosage and time-dose factor administered
- Use of concurrent chemotherapy
- Prior thoracic irradiation
- Volume loss due to lung collapse
- Younger patient age
- Smoking history
- Poor pretreatment clinical performance status
- Reduced pretreatment lung function
- Chronic obstructive pulmonary disease
- Female gender
- Endocrine therapy for breast cancer
- Glucocorticoid withdrawal during radiotherapy

in the treatment of radiation-induced fibrosis involving the skin and subcutaneous tissues as this agent also inhibits experimental bleomycin-induced pulmonary fibrosis in rats, likely via its anti-TNF $\alpha$  effects [22]. Pentoxifylline showed a significant protective effect for both early and late lung radiotoxicity. Amifostine is a pro-drug that is de-phosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. This drug can reduce the toxic effects of chemotherapy by acting as a scavenger of free radicals generated in tissues exposed to radiation. Early evidence suggests that amifostine may decrease radiation-induced pulmonary injury without diminishing the therapeutic effect [23, 24]. Captopril and other ACE inhibitors also have been shown to reduce radiation-induced lung fibrosis in rats [25], but there are no published data in humans.

Improvements in the perfusion and ventilation of radiation-injured lung tissue may be expected from 3 to 18 months after radiation therapy. Beyond 18 months, however, further significant improvement appears unusual [26, 27].

### 42.3.2 Chemotherapy

Patients with hematologic diseases are exposed to a host of traditional and newer chemotherapeutic agents that can cause lung injury at an incidence that ranges from less than 5% to as high as 60% [28, 29]. The

increased complexity of multi-modality treatments and high-dose protocols designed to augment antineoplastic efficacy, particularly in the context of HSCT, has increased the incidence of pulmonary complications. The diagnosis of drug-induced respiratory disease often is complex because: (1) 1 patients may be exposed to several pneumo-toxic drugs concurrently or in sequence due to earlier treatment failure; (2) 2 time to onset of pulmonary toxicity may be delayed, making it difficult to ascertain which agent is responsible for the pulmonary reaction; (3) 3 the combination of drugs to treat malignant hematologic conditions may lead to unexpected drug interactions, producing enhanced toxicity compared with the toxicity of each agent considered separately; and (4) 4 radiation therapy to the chest or TBI. Other factors that play a role in the development of pulmonary toxicity include advanced age, current smoking, abrupt withdrawal of corticosteroids and the use of HSCT (allogeneic vs autologous). Changes in blood neutrophil counts, thrombocytopenia, coagulation deficits, volume overload or left ventricular dysfunction also can influence the spectrum and severity of pulmonary drug toxicity. In addition to overt pulmonary toxicity, subclinical drug-induced lung dysfunction often occurs in the form of reduced DLCO and lung volumes or changes in cell populations in BAL fluid. Upon cessation of exposure to the agent, most of these changes reverse slowly in a few weeks or months.

Drug-induced lung injury can manifest in several patterns (Table 42.3). Nonspecific interstitial pneumonia (NSIP) is a common pattern of pulmonary injury to

**Table 42.3** Lung toxicities associated with chemotherapeutic agents

Pattern of toxicity	Drug
Nonspecific interstitial pneumonia	Methotrexate, azathioprine, chlorambucil, cyclophosphamide, procarbazine, and rarely, vinca alkaloids
Pulmonary infiltrates and eosinophilia	Fludarabine, rarely: interferons, inhaled or parenteral pentamidine and radiographic contrast media
Organizing pneumonia	Bleomycin
Diffuse alveolar damage (DAD)	BCNU, lomustine, CCNU, bleomycin, busulfan, chlorambucil, cyclophosphamide, melphalan, procarbazine, vinblastine
Diffuse pulmonary fibrosis	BCNU, lomustine, CCNU, bleomycin, busulfan, chlorambucil, cyclophosphamide, melphalan, vinca alkaloids, radiation therapy
Granulomatosis	Bleomycin
Pulmonary nodules	Bleomycin, cyclophosphamide, vinblastine, rarely fludarabine

chemotherapeutic agents. Drugs causing the syndrome include methotrexate (accounting for the majority of cases), azathioprine, chlorambucil, cyclophosphamide, procarbazine and, rarely, vinca alkaloids. The onset of this condition is unpredictable; symptoms may develop a few days to years after exposure. The clinical picture includes increasing dyspnea, dry cough, high fevers and rash. The severity of illness can vary from mild to progressive respiratory failure, and associated radiographic findings may range from bilateral (usually symmetrical) interstitial or alveolar opacities to extensive consolidation with air bronchograms and volume loss [30–32]. Pleural effusions and mediastinal lymph node enlargement have been reported in patients with methotrexate-induced lung injury [33, 34]. BAL fluid usually shows lymphocyte predominance. A low ratio of CD4 to CD8 lymphocytes is suggestive, but not specific, for drug-induced lung disease. Other BAL findings include neutrophilia or a combined pattern of lymphocytosis with neutrophilia or eosinophilia [35]. Appropriate stains, cultures and molecular techniques in BAL fluid should be performed to exclude opportunistic infections. A lung biopsy may be required in selected cases. Histopathologic features include interstitial inflammation and pulmonary granulomas. Fibrosis can be present, but is generally not the dominant histopathologic feature. Alveolar edema or hemorrhage may be found as a manifestation of severe methotrexate pneumonitis [34]. High-dose corticosteroids may be indicated with more advanced disease, as drug-induced NSIP can lead to mortality if it is not treated promptly, but in milder cases, symptoms can subside after simple drug withdrawal [36]. Although rechallenge with the drug may be safe, it is not generally recommended [37].

Eosinophilic pneumonia (EP) is an unusual and unpredictable pattern of response to chemotherapeutic agents as opposed to that described following the use of some antibiotics. EP in patients with hematologic malignancies can result from treatment with fludarabine and, rarely, interferons, inhaled or parenteral pentamidine, and radiographic contrast media [33]. Although methotrexate and procarbazine pneumonitis can often be associated with peripheral eosinophilia, BAL and histopathologic features are not those of EPs. Typically, the syndrome of EP develops during or shortly after termination of treatment. A history of an allergic disorder, or repeated courses of treatment with the specific drug, may predict for a higher risk.

The diseases could manifest as acute pneumonia and progress to respiratory failure [38, 39]. Radiographic findings of EP include alveolar infiltrates and the classic pattern of “photographic negative” pulmonary edema [40]. It also could cause faint ground-glass opacities, or Kerley’s “B” lines (dense and diffuse). EP is diagnosed by the presence of increased percentages or numbers of eosinophils in blood, BAL, or lung tissue. A lung biopsy is rarely required, but discontinuance of the offending drug is essential. Corticosteroid drug therapy is suggested in cases with severe involvement. The prognosis for this condition usually is good.

Chemotherapy-induced organizing pneumonia (OP) may manifest with chest pain, dyspnea and diffuse radiographic abnormalities with [41] or without acute respiratory failure [42], or may be discovered incidentally on chest imaging [36]. Nodular OP typically is seen in patients exposed to chemotherapy who develop round-shaped foci that localize mainly in lung bases, may abut the pleura and simulate metastatic nodules [43–45]. Nonspecific findings are retrieved from BAL, such as increases in the percentage of lymphocytes, neutrophils or eosinophils. Open lung biopsy guided by the results of CT scan is the procedure of choice. The nodules correspond to sterile aggregates of mononuclear cells. Histology reveals interstitial inflammation, superimposed on the dominant background of alveolar and ductal fibrosis. Lung nodules with the histopathologic features of cryptogenic organizing pneumonia or of localized fibrosis can be observed after treatment with bleomycin, cyclophosphamide, vinblastine and, rarely, fludarabine [46–49]. Drug discontinuation and, if required, corticosteroid therapy usually are followed by improvement in most cases. Organizing pneumonia (formerly BOOP) can be seen following HSCT and is described in detail later in the chapter.

Diffuse alveolar damage (DAD) is a serious form of pulmonary pathology that may develop in the context of drug-related lung injury. Single chemotherapeutic agents (e.g., BCNU or other nitrosoureas, bleomycin, busulfan, chlorambucil, cyclophosphamide, melphalan, procarbazine, vinblastine) or multiagent cytostatic chemotherapy have been reported to cause this lung toxicity [50]. Some regimens may be associated with a greater likelihood of DAD than others even if they differ in one agent only. For instance, in patients with de novo-treated Hodgkin’s lymphoma, the substitution of gemcitabine for dacarbazine, e.g., ABVG

rather than ABVD (doxorubicin, bleomycin, vinblastine and gemcitabine instead of dacarbazine), was associated with a 42% incidence rate of pulmonary toxicity [51]. Likewise, the substitution of gemcitabine for etoposide in the dose-escalated BEACOPP regimen (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone and gemcitabine rather than etoposide) significantly escalated the likelihood of pulmonary toxicity [52–54]. Concurrent administration of radiation therapy to the chest or use of TBI, supplemental oxygen and possibly colony-stimulating factors (CSFs) may increase the risk of DAD.

Time to onset of DAD can vary from shortly after the first administration of the offending drug to much later into the treatment course [55]. Restrictive lung function patterns and hypoxemia are typical. DLCO abnormalities often precede clinical symptoms. The clinical evolution of drug-induced DAD varies from an isolated decrease in DLCO [56, 57] or evidence of fibrosis in trans-bronchial or pulmonary biopsies [58, 59] as the only manifestation of toxicity to bilateral, interstitial and alveolar infiltrates [57, 60]. Severe cases progress to an ARDS picture and death [61].

High-resolution CT scanning may show ground-glass opacities and intra-lobular septal thickening, and the extent of changes correlates with clinical severity [62]. Dysplastic pneumocytes may be retrieved by BAL [63, 64]. A lung biopsy is reserved for patients with an atypical presentation or for those who do not improve with empirical antibiotic and corticosteroid treatment [65]. The main histopathologic feature of DAD is consistent with hyaline membranes and fibrin deposits lining the alveolar border, dysplasia of type II cells, free alveolar fibrin, cells and debris in alveolar spaces and various stages of interstitial edema, inflammation and organization [66]. DAD may be reversible after discontinuation of drugs or after the addition of corticosteroids, or both [67]. The usual doses of oral corticosteroids may not prevent the condition from developing, but higher doses are reported to reduce the incidence [68].

The high incidence, severity and unpredictability of DAD associated with chemotherapy suggest that it is reasonable to discontinue such treatment once the DLCO has decreased 50% compared with pre-therapy values. Although smaller decrements in DLCO do not equate to toxicity and should not lead to withdrawal of chemotherapy, a precipitous decrease in the DLCO

indicates impending toxicity [69]. When radiation therapy is planned after the administration of chemotherapeutic agents, it is advisable to wait for any chemotherapy-induced decrease in the DLCO to stabilize or show a trend toward improvement before starting radiation.

Finally, drug-induced pulmonary fibrosis may develop in patients receiving cytotoxic agents, such as bleomycin, busulfan, BCNU, lomustine, CCNU chlorambucil, cyclophosphamide, melphalan, vinca alkaloids, radiation therapy and TBI [70]. This entity more often is diagnosed months or years after termination of treatment. Early signs of this disease are basilar or diffuse streaky opacities and volume loss. This condition can progress to honeycombing and fibrotic changes; reversal of this toxicity and the response to corticosteroids are unpredictable and often unsatisfying. Histologic exam can demonstrate the characteristic dysplasia of type II pneumocytes that reflects exposure to alkylating agents and radiation therapy. In a few patients, especially children treated for hematologic malignancies, pleural or pulmonary fibrosis may develop [71]. This process results in thoracic deformity, encasement of the lungs and severely restricts lung physiology. An accelerated variant of pulmonary fibrosis, acute interstitial pneumonia (formerly termed the Hamman and Rich syndrome), has been described after treatment with chlorambucil and methotrexate [72–74]. The prognosis of this condition is poor despite drug withdrawal and institution of high-dose corticosteroids.

### **42.3.3 Chronic Pulmonary Dysfunction After Hematopoietic Cell Transplantation**

As seen in the patient description at the start of this chapter, a decline in lung function long has been identified as a significant complication in the months to years that follow allogeneic HSCT. A clinical pearl from Dr. Bergeron in this book also very nicely describes this type of pulmonary involvement. Noninfectious conditions now represent the major pulmonary causes of morbidity and mortality after HSCT. Idiopathic pneumonia syndrome (IPS), discussed in another chapter in this book, remains one of the more common and serious pulmonary complications occurring within

months after HSCT. Although graft-versus-host reactions may play an etiologic role, the major contributing factor is conditioning-related toxicity. Among lung conditions that are more closely associated with GVHD, both bronchiolitis obliterans (BrOb) (onset months to years after HSCT) and bronchiolitis obliterans with organizing pneumonia (COP) may lead to FA. The term COP should not be used interchangeably with bronchiolitis obliterans (BO) to describe a patient with chronic lung dysfunction after HSCT, although such usage unfortunately is widespread. The two disorders differ with respect to histopathology, pulmonary function characteristics and, most importantly, response to therapy. BrOb is an inexorably progressive condition, whereas COP behaves similarly to idiopathic COP seen in other populations. COP after HSCT usually is quite responsive to corticosteroids and in other settings may resolve spontaneously, whereas BrOb is not [75, 76]. Organizing pneumonia also is associated with restrictive (rather than obstructive) changes on pulmonary function testing (Table 42.4).

In allogeneic HSCT recipients, the disparity in match between the donor graft and the recipient for the human leukocyte antigens (HLAs) mediate both GVHD and graft rejection (host-versus-graft reaction). The presence of alloreactive injury to the lung attributed to GVHD is poorly defined and remains debated. In the skin, liver and intestine, GVHD produces a characteristic T-lymphocyte-mediated

epithelial destruction. There are few data to support such a defined lesion with the exception of lymphocytic pneumonitis [77]. A variety of pulmonary complications have been described as manifestations of GVHD, but these associations are based primarily on the simultaneous occurrence of pulmonary abnormalities, the absence of an infectious agent and nonspecific histopathologic lesions in the setting of established GVHD in other organs. Nevertheless, both acute and late-onset lung injury syndromes have shown a clinical association with GVHD, including IPS, engraftment syndrome, diffuse alveolar hemorrhage, BrOb and COP [78]. Several murine models also demonstrate pathologic lung changes in the setting of GVHD, thus supporting a mechanistic relationship between GVHD and lung injury.

OLD and chronic AFO are the most common non-infectious late pulmonary complications of allogeneic HSCT. These entities are manifested on pulmonary function testing by a diminished FEV1 or FEV1/FVC. The incidence of these syndromes ranges from 6% to 32%, depending upon the definition of AFO applied in each study [79, 80]. Typically, the presentation occurs beyond the third month after HSCT [81]. Among patients who develop chronic GVHD, new-onset AFO may develop in up to one third of the patients. In a study of 11 cases the underlying process accounting for AFO was BrOb in 70% [82]. Histologically, this process demonstrates fibrous obliteration of the lumen

**Table 42.4** Clinical factors present in obstructive versus restrictive lung disease

Clinical Factor	Obstructive lung disease	Restrictive lung disease
Onset	Late (3–12 months after HCT)	Early (within 3 months after HSCT)
Symptoms	Dyspnea, nonproductive cough	Dyspnea, nonproductive cough
Physical exam	Wheezing	Crackles
PFTs	Obstructive physiology	Restrictive physiology
FEV <sub>1</sub> /FVC	Decreased	Normal
TLC	Normal	Decreased
DLco	Decreased	Decreased
CT scan findings	Air trapping Bronchial wall thickening Centrilobular nodules	Patchy consolidation Organizing pneumonia Ground-glass opacities
Chronic GVHD	Strong association	Variable, association with organizing pneumonia

*PFTs* pulmonary function tests, *FEV1/FVC* forced expiratory volume in 1 s/forced vital capacity, *TLC* total lung capacity, *DLco* diffusion capacity for carbon monoxide



of respiratory and membranous bronchioles. In the absence of histopathologic evidence, new onset AFO after allogeneic HSCT often is referred to as “bronchiolitis obliterans syndrome” (BOS). In addition to chronic GVHD, risk factors for the development of AFO include increasing recipient age, pre-transplant reduction in the ratio FEV<sub>1</sub>/FVC, low serum immunoglobulin levels, use of methotrexate and a history of respiratory viral infection within the first 100 days [79]. The onset typically is insidious with presenting symptoms including dry cough (60–100%), dyspnea (50–70%) and wheezing (40%), but fever is uncommon [79, 82, 83]. The chest radiograph is usually normal, but high-resolution CT scans often demonstrate evidence of expiratory air trapping, hypo-attenuation and bronchial dilation [80, 84–86]. Demonstrating persistent AFO using pulmonary function testing and exclusion of other causes of AFO such as asthma, tobacco-related emphysema, and viral or bacterial respiratory infection establish the diagnosis. Except for its utility in excluding an infectious etiology, BAL is usually nonspecific [87], and transbronchial biopsies typically are nondiagnostic due to the patchy nature of this small airway process and the limited size of samples obtained. Surgical lung biopsy is rarely indicated.

The etiology of new onset AFO after HSCT is unknown. Those recognized causes in otherwise normal hosts rarely include recurrent aspiration, viral infection (influenza, adenovirus, measles) and bacterial infection (*Mycoplasma* sp.) [88]. Immunologic mechanisms inducing bronchial epithelial injury are suggested by the strong association between chronic GVHD and new onset AFO. Indeed, the lung epithelium may be the target of immune-mediated injury induced by donor cytotoxic T cells in chronic GVHD [89]. Thus, BrOb after HSCT may represent a manifestation of GVHD in the lung.

Disease progression is variable; however, the syndrome is associated with significantly increased mortality rates, and improvement in lung function is uncommon. Many patients develop a progressive decline in lung function resulting in respiratory failure [79, 80]. There are no prospective studies of the treatment of new onset AFO after HSCT. OLD in the presence of chronic GVHD is managed primarily by controlling GVHD. Various immunosuppressive agents have been reported to result in stabilization of lung function in 30–50%, but improvement in only

8–30% [37, 51]. In the hope that early recognition and treatment may improve outcome, routine spirometry among patients with chronic GVHD is encouraged to detect the insidious onset of this process.

Restrictive lung disease (RLD) is defined by reductions in FVC, total lung capacity (TLC) and DLCO as measured by standard pulmonary function tests (PFTs). In RLD, the ratio FEV<sub>1</sub>/FVC is maintained near 100% [90, 91]. RLD is common after HSCT. Significant decreases in FVC or TLC have been reported in as many as 25–45% of allogeneic HSCT recipients by day 100. A decline in TLC or FVC after HSCT (even if the absolute values for each measurement remained within the normal range) has been associated with an increase in nonrelapse mortality. TBI-containing conditioning regimens and the presence of acute GVHD have been associated with RLD, in addition to obstructive lung disease [92–94]; however, the impact of age on the development of RLD is less clear. Early reports suggested that the incidence of RLD is lower in children compared to adults and that the incidence increases with advancing recipient age [95]. More recent studies have revealed significant RLD in children receiving HSCT [96]. Organizing pneumonia after HSCT falls under the RLD pattern on liver function tests and recently was shown to be associated with prior acute and chronic GVHD. Organizing pneumonia has been described in case reports as occurring after both allogeneic and syngeneic HSCT; these data suggest an association of the lung lesion with chronic GVHD and intestinal ulcerations. In addition, corticosteroid therapy appeared beneficial in the resolution of the lesion. In a recent case control study, Freudenberger et al. reviewed 49 cases of histologic COP [97]. The clinical features of COP in this population were similar to idiopathic and other etiologies with an association between acute and chronic GVHD and the subsequent development of COP. Affected patients were more likely to have skin involvement with acute GVHD and chronic GVHD affecting the gut and oral mucosa. The causes of COP following HSCT remain enigmatic, but possible etiologies include direct allo-immunologic reactions, atypical infection or atypical manifestations of IPS. Regardless, the clinical presentations and responses of COP are similar to other cases of idiopathic COP.

The published literature contains a paucity of therapeutic trials for chronic lung injury after HSCT. A study by Payne and colleagues showed that the use of

cyclosporine and methotrexate as GVHD prophylaxis prevented the development of OLD when compared to historic controls receiving prednisone and methotrexate [98], but results of prospective, randomized trials in this setting are not available. Three recently published case series have exploited the antiinflammatory effects of azithromycin to treat OLD in both allogeneic HSCT and lung allograft recipients. Each study suggested a beneficial effect of this drug on pulmonary function when administered for 12 or more weeks [99–101]. The potential role for TNF $\alpha$  in the pathogenesis of both OLD and RLD suggests that agents such as etanercept may have promise, and several studies have demonstrated a potential benefit of this drug in some HSCT patients with chronic lung injury [102, 103].

The immunologic mechanisms responsible for chronic, fibrotic pulmonary dysfunction after HSCT remain poorly defined, in large part because of the lack of correlative data obtained from afflicted HSCT recipients and the paucity of suitable SCT animal models for either RLD or OLD. Chronic pulmonary disease following allogeneic HSCT likely involves an initial insult to lung parenchyma followed by an ongoing inflammatory process involving the interplay between recruited donor-derived immune cells and the resident cells of the pulmonary vascular endothelium and interstitium. Mechanistic insights into OLD following HSCT have been derived from studies of lung allograft rejection. Data generated from both humans and mice support the hypothesis that the development of BrOb in this scenario involves the secretion of inflammatory cytokines and chemokines, along with interactions between APCs and activated lymphocytes [104, 105].

A tri-phasic model of chronic noninfectious lung injury after HSCT has been proposed [106]. In phase I, an acute pneumonitis develops as a consequence of an allogeneic immune response, resulting in the sequential influx of lymphocytes, macrophages and neutrophils into an inflamed pulmonary parenchyma. In phase II, a persistent inflammatory signal, in the setting of dysregulated repair mechanisms, promotes the transition from acute to chronic injury. If the inciting injurious stimulus predominantly involves bronchiolar epithelial cells, phase II is associated with the concentric infiltration of lymphocytes and collagen deposition in the peri-bronchiolar areas resulting in the development of chronic bronchiolitis. If, however, the alveolar epithelium is the primary target, leukocyte recruitment and matrix deposition are confined primarily to the

interstitial space. As chronic inflammation proceeds to phase III, lung fibroblasts increase dramatically in number and contribute to the enhanced deposition of collagen and granulation tissue in and around bronchial structures, ultimately resulting in complete obliteration of small airways and fixed OLD. By contrast, fibroblast proliferation and intra-septal collagen deposition during phase III ultimately result in interstitial thickening, septal fibrosis, significant volume loss and severe RLD.

Clinical and experimental data suggest that the progression to a chronic, pro-fibrotic form of pulmonary toxicity involves the secretion of cytokines and chemokines [107–109], and in this context, TNF $\alpha$  may be a central factor in the proposed tri-phasic model of disease. Evidence for a role of TNF $\alpha$  in the transition from acute to chronic lung injury comes from studies using targeted over-expression of TNF $\alpha$  in the lungs of rodents [110]. In these models, early lung histopathology includes a lymphocytic infiltrate similar to that seen in experimental IPS models [111, 112], whereas the histologic changes associated with more prolonged exposure to TNF $\alpha$  show both interstitial and peribronchial inflammation that closely resemble changes seen at later time points after HSCT [107, 113].

## 42.4 Conclusion

FA is characterized by sequential acute lung injury that can culminate in scarring and end-stage lung disease. Despite the high success rate in treating hematologic malignancies with or without using HSCT, this sequence of events continues to be a significant contributor to nonrelapse morbidity and mortality in patients with hematologic malignancies because of either the disease itself or as a result of treatment modalities employed. The pathophysiologic mechanisms contributing to the initiation and progression of disease remain poorly defined. To this end, current treatment options remain suboptimal and primarily limited to supportive care measures and antiinflammatory agents, such as corticosteroids or other immunosuppressant therapy. Further research is necessary (in the form of clinical trials and pre-clinical models) to improve our understanding of fibrosing alveolitis and related disorders and to ultimately design and implement targeted therapeutic strategies.

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