Introduction

Advances in the management of patients in terms of the diagnosis and treatment of hematologic malignancies and treatment-related complications, especially infectious complications, have increased survival time. However, more than half of the patients treated for hematologic malignancies will develop a pulmonary complication during their follow-up, infectious pneumonia remaining the most common diagnosis that should be considered first in regard to its potential severity. Otherwise, new complications that may involve different organs, including the lungs, have been increasingly reported. Currently, over a quarter of lung infiltrates occurring in the context of hematological diseases are due to noninfectious causes [1]. Thus, lung physicians may be increasingly confronted with these lung disorders. Various noninfectious pulmonary complications have been described in the different hematological malignancies; however, these complications are most often studied in the context of allogeneic hematopoietic stem cell transplantation (HSCT). In this chapter, we will briefly review the lung diseases associated with various hematological malignancies before focusing on noninfectious pulmonary complications following allogeneic HSCT.

Pulmonary Manifestations of Hematological Malignancies

Given the wide spectrum of lung diseases that can occur in the context of hematological malignancies, the diagnostic process must be rigorous. In addition to the many pathogens potentially involved, a wide range of noninfectious causes should be considered. The pulmonary location of the hematological disorder should be considered depending on the underlying disease. Some hematological diseases, such as lymphoma, can progress in the lung, unlike others, such as myeloma, for which lung involvement is very rare. Pulmonary cardiogenic or noncardiogenic edema is frequent and can be due to hyperhydration required before chemotherapy, cardiotoxicity secondary to use of anthracyclines or increased capillary permeability from drugs such as all-trans-retinoid acid or cytosine arabinoside. Intra-alveolar hemorrhage is common in patients with thrombocytopenia or allogeneic HSCT. Many drugs frequently used for the treatment of hematological disorders may cause lung damage (Pneumotox.com); these drugs include Bleomycin, Busulfan, Chlorambucil, Cyclophosphamide, Cytosine, Fludarabine, Rituximab, Dasatinib and others (Table 32.1). Radiotherapy may cause radiation pneumonitis. Drug treatments can cause entirely different clinical patterns depending on the target organ in the respiratory system (lung, airways and pleura) [2].

Different other “immunological” causes of pneumonitis may occur in the course of several hematological malignancies (Table 32.2). For example, sarcoid-like granulomatosis may be associated with lymphoma, eosinophilic pneumonia may occur in the course of a myelodysplastic syndrome and pulmonary graft-versus host disease (GVHD) may be a complication following allogeneic HSCT. The medical history of the patient, including the clinical history of lung involvement and the type of underlying malignancy, the lung CT scan and the bronchoalveolar lavage (BAL), should be used when making a diagnosis. A lung biopsy, when possible, would rule out infection and would reinforce or even confirm a diagnostic
hypothesis. However, it is rarely performed in this context because it is associated with significant mortality and morbidity and results in a definitive diagnosis in only 60% of cases [3]. Furthermore, new biological tools including polymerase chain reaction for many pathogens and antigen for Aspergillus are used on both respiratory samples and sera greatly help to diagnose an infection [4]. Finally, the overall diagnostic approach of lung infiltrates in patients treated for a hematological malignancy must take into account the possible overlapping of different infectious and/or noninfectious causes.

### Pulmonary Manifestations of Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT is used as a curative treatment in various tumoral and non-tumoral diseases. The patient's abnormal hematopoietic tissue is replaced with healthy stem cells.

The transplanted stem cells can be derived from bone marrow, peripheral blood or umbilical cord blood harvested from a related donor or a compatible unrelated donor. Before the transplantation procedure is performed, the host is prepared with a special conditioning regimen that usually involves fractionated total body irradiation and cytotoxic chemotherapy to prevent graft rejection and to eradicate any residual tumor cells. Until recently, the conditioning regimen was “myeloablative,” leaving the patient severely neutropenic for several weeks. Over the past few years, nonmyeloablative transplants have been developed based on the graft-versus leukemia/lymphoma principle, thereby eradicating residual tumor cells. The conditioning regimen for these transplants is attenuated, depressing only the host immune response and thus limiting the neutropenic period to just a few days. This means that allogeneic HSCT can now be extended to older and frailer patients with comorbidities who have had long-term treatment in the past, which has increased the number of allogeneic HSCT procedures performed. The major complications that occur after allogeneic HSCT are infections or the consequences of the immune reactions of GVHD, which can be either acute or chronic depending on the clinical features [5]. For unknown reasons, unlike the skin, gastrointestinal tract and liver, the lungs have not been identified as a target of acute GVHD in humans. In contrast, lung involvement is common in chronic GVHD that may be either restricted to a single organ or tissue or widespread. Chronic GVHD is characterized by tissue destruction resulting in fibrosis and is associated with a process in which donor T cells recognize peptides presented by the major histocompatibility complex on antigen-presenting cells of the host. GVHD targets epithelial cells of various organs with an incidence that depends on various factors and most commonly occurs during unrelated transplantations and peripheral stem cell transplantations. Treatment of GVHD requires the maintenance or enhancement of immunosuppressive therapy. The prognosis of GVHD is primarily related to the severity of the initial response to corticosteroids. The occurrence of chronic GVHD affects the morbidity, mortality and the quality of life of patients [6].

### Table 32.1 Main drugs used for the management of patients with hematological malignancies known to induce lung toxicities [2]

| Antibiotic chemotherapeutic agents | Bleomycin, Mitomycin C |
| Alkylation agents | Busulfan, Cyclophosphamide, Chlorambucil, Melphalan, Ifosfamide, Procarbazine |
| Antimetabolites | Methotrexate, 6-mercaptopurine, Cytosine arabinoside, Fludarabine |
| Nitrosamines | Bischloroethyl nitrosourea (BCNU), Chlorotetracyclohexyl nitrosourea (CCNU), Methyl-CCNU |
| Tubulin-acting agents | Vinblastine, Etoposide |
| Other chemotherapeutic agents | All-trans retinoic-acid (ATRA), Imatinib mesylate, Dasatinib, Bortezomib |
| Immunomodulatory agents | Interferons, anti-Interleukin-2, TNF alpha inhibitors, Sirolimus, Temsirolimus |
| Monoclonal antibodies | Rituximab, Gemtuzumab ozogamicin, Alemtuzumab |
| Miscellaneous | Blood transfusion, GM-CSF, G-CSF |

### Table 32.2 Nonspecific noninfectious pulmonary complications reported in hematological malignancies

| Hematological malignancies | Pulmonary complications |
| Acute leukemia | Organizing pneumonia [60], Sweet’s syndrome [61], Alveolar proteinosis [62] |
| Lymphoma/chronic lymphocytic leukemia | Sarcoid-like granulomatosis [63, 64], Langerhans histiocytosis [65], Lung cancer [66, 67] |
| Myeloma | Amyloidosis [68], Venous thromboembolism [69] |
| Waldenstöm’s macroglobulinemia | Intra-alveolar hemorrhage [70], Pulmonary edema [70], Amyloidosis [68, 70], Lung cancer [71] |
| Myelodysplastic/myeloproliferative disorders | Extramedullary hematopoiesis [72], Sweet’s syndrome [72], Diffuse infiltrative lung disease in the context of autoimmune disorders [72], Eosinophilic pneumonia [72], Alveolar proteinosis [72], Organizing pneumonia [72], Pulmonary hypertension [73] |
chronic pulmonary graft versus host disease

chronic lung GVHD has been identified, the diagnosis of which is based on histopathological observations performed during lung biopsies showing bronchiolitis obliterans (BO). Although BO is the only condition attributed to pulmonary GVHD [5], other clinico-histological lung conditions are known to be associated with GVHD, such as organizing pneumonia (OP, formerly named bronchiolitis obliterans organizing pneumonia, BOOP) [5, 7]. Other noninfectious diffuse infiltrative lung diseases have been described and may also be associated with GVHD [8]. Although less frequent than BO, these diseases are often ignored, and their incidences may be underestimated.

bronchiolitis obliterans

Bronchiolitis obliterans (BO) is the main non-infectious late pulmonary complication in allogeneic HSCT recipients. This serious and potentially fatal complication typically develops in the first 2 years following transplant but also can occur several years later [9, 10]. The incidence of BO is difficult to assess; according to several retrospective studies, it varies from 2 to 26 % [11–16]. This disparity is mainly due to the lack of consensus regarding the diagnostic criteria. The most recent study, which was based on the largest number of patients, reported a prevalence of 5.5 % [15]. The incidence increased to 14 % in the subpopulation of patients who developed extrathoracic chronic GVHD [15]. Over a period of 3 years, we conducted a prospective cohort study that included a systematic follow-up of lung function for all of the consecutive patients who underwent an allogeneic HSCT in our center. Out of the 243 enrolled patients scheduled to be engrafted, 202 were included at Day 100, with an 18-month cumulative incidence of BO estimated at 12.9 % (Study NCT01219972 ALLOPULM clinical trials, analysis in progress; [17]).

Numerous risk factors for BO have been proposed in various retrospective studies, including age of the donor or recipient, type of transplant, degree of HLA incompatibility, presence of gastroesophageal reflux, gammaglobulin levels, type of GVHD prophylaxis, type of conditioning regimen, underlying blood disorder, tobacco use or acute GVHD, with conflicting results [8]. The only association reported in all of the studies was the occurrence of extrathoracic chronic GVHD at the time of BO diagnosis. One objective of our ALLOPULM study was to prospectively identify the events occurring within 3 months after transplantation that are associated with the subsequent occurrence of BO. Using multivariate analysis, we showed that a history of smoking, the occurrence of pulmonary infection, and pre-existing abnormal pre-transplant pulmonary function were associated with BO development [17].

physiopathology of bronchiolitis obliterans

The exact pathogenesis of BO is still unknown. Epidemiological studies have shown an association between the development of BO and the presence of active chronic GVHD, which led to the hypothesis that BO is, in fact, chronic GVHD of the lung [18]. The most important mechanism contributing to BO would then result from the immunemediated attack of airway epithelial cells by donor T cells. As opposed to acute GVHD, chronic GVHD also involves B-cell stimulation, autoantibody synthesis and systemic fibrosis [19]. Mouse models of chronic GVHD involve three disease mechanisms: autoantibody synthesis, pro-fibrotic processes and defective thymic function. Thymic damage leads to a decrease in TReg cell number and function and defective negative selection of T cells [19].

The recent development of an animal model of BO caused by allogeneic HSCT has revealed new pathophysiological pathways [20]: the peribronchiolar inflammatory infiltrate is mainly composed of CD4 lymphocytes, Clara cells that regenerate bronchiolar epithelium may be targets and a large number of cytokines are produced during the process [20]. More recently, the peribronchiolar deposition of alloantibodies was demonstrated in the same animal model, as was the role of mature B cells from the donor in the development of BO [21].

Some authors found that BO could be triggered by lower respiratory tract infections. In fact, it has been demonstrated that patients who present with respiratory syncytial or parainfluenza virus infection have an increased risk of developing BO in the year following HSCT [22]. The presence of a respiratory tract infection may lead to airway inflammation that causes an inappropriate alloimmune reaction.

diagnosis of bronchiolitis obliterans

The definitive diagnosis of BO is pathologic. The National Institutes of Health Consensus proposed some histopathological criteria for BO based on a limited amount of original data [23]. The Pathology Working Group Report retained the presence of unequivocal dense eosinophilic scarring of the bronchioles resulting in some degree of luminal narrowing as a diagnostic (Fig. 32.1b). Inflammation is common but variable and insufficient for diagnosis [23]. In fact, Yousem et al. and Yokoi et al. published small pathological series in allogeneic HSCT recipients with chronic GVHD and lung involvement [24, 25] and reported different small airway abnormalities in this setting. Yousem et al. described two types of bronchiolar affections: lymphocytic bronchiolitis and cicatricial BO. Lymphocytic bronchiolitis is characterized by peribronchiolar/bronchiolar lymphocytic and plasmocellular infiltrate. Airway inflammation is predominantly lymphocytic and plasmocellular. Cicatricial BO is characterized by the obliteration of the airway lumen by dense fibrous tissue. The authors proposed that cicatricial BO is the...
late-stage of lymphocytic bronchiolitis [24]. The pathologic description of Yokoi et al. comes from eight autopsy cases. Small airway lesions varied from early inflammatory changes to late scarring in each case. The inflammatory lesions were usually mild and mostly lymphoplasmacytic, except in three patients with predominant neutrophilic infiltrates. In all cases, inflammatory and scarring stages were present simultaneously [25]. Although the gold standard for diagnosis of BO is the demonstration of bronchiolar lesions upon histological evaluation of a lung specimen, it is not current practice to obtain a lung biopsy. Transbronchial biopsies have poor sensitivity, and surgical lung biopsies are invasive and usually reserved for cases of confusing diagnosis. Thus, BO is usually diagnosed as a new fixed airflow obstruction demonstrated by pulmonary function testing (PFT). BO syndrome (BOS) is diagnosed based on clinical, functional and radiological evaluation of the patient.

BOS clinically manifests as dyspnea at rest or on exertion, dry cough or wheezing. In a significant proportion of cases, it is asymptomatic and revealed by screening PFT. Clinical diagnoses of BOS are based on new-onset airflow obstruction identified by spirometry. Because BOS initial symptoms are nonspecific and spirometric findings are not sensitive, most patients are diagnosed when they have severe airflow obstruction. PFT is not sensitive, as BOS is a distal airway disease, and bronchiolar obstruction needs to be widespread before FEV1 declines [26].

The currently used definition is that of the National Institute of Health (NIH) consensus guidelines for chronic GVHD, published in 2005: a 1-s forced expiratory volume (FEV1) value <75 % of that predicted and a FEV1/forced vital capacity (FVC) ratio <70 %, together with the exclusion of an infection and the presence of an extrathoracic sign of GVHD [5] (Table 32.3). However, some patients do not meet this functional criterion; despite the presence of BOS, the FEV1/FVC ratio may remain normal (>70 %). In fact, because BOS is a disease of the small airway, distal airway obstruction may lead to air trapping, thereby increasing the residual volume (RV). Consequently, the FVC declines concomitantly with the FEV1, and the FEV1/FVC ratio stays over 70 % [27]. NIH-BOS criteria include signs of air trapping, observed either by PFT (RV >120 %) or high-resolution computed tomodensitometry (HRCT) (Table 32.3). Recently, modification of these guidelines has been proposed [18]. To minimize the dynamic collapse of airways during the forced expiratory maneuver, Chien et al. proposed the use of slow vital capacity (SVC) instead of FVC for the diagnosis of airflow obstruction. They also suggested that patients with annual FEV1 declines >5 % (from pre-transplant PFT) be considered at high risk of developing BOS and that an annual FEV1 decline >10 % (from pre-transplant PFT) be considered a diagnostic criterion for early BOS, even for a FEV1 >75 % of the predicted value [18]. Finally, two groups of patients may be diagnosed with BOS: one with a classical obstructive ventilatory defect and one with a normal FEV1/FVC ratio [18, 27]. The prognoses of both patients are similar [27]. Future studies should focus on the early detection of BOS. Chien et al. found that allogeneic HSCT recipients with annual FEV1 declines >5 %, even with FEV1/FVC ratios >80 %, have higher risks of nonrelapse mortality; this suggests that early airflow decline can be used as an indicator of early BOS [28]. This finding should prompt systematic

Fig. 32.1 Lung computed tomography (CT) scan (a) and lung biopsy (b) from a patient who was diagnosed with bronchiolitis obliterans 12 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows a mosaic pattern (a). The histological analysis shows a bronchiolar wall thickened by inflammatory fibrosis located between the epithelium and the smooth muscle. The airway lumen is narrowed (HES x 100) (b)
serial PFT after transplant, with careful attention to patients who develop airflow decline over time.

In addition to PFT, HRCT should be performed. In the case of BOS, it may reveal a mosaic pattern suggestive of air trapping (Fig. 32.1a) that can be accentuated on expiratory cuts. It can also reveal bronchial thickening, bronchiectasis or bronchiolar nodules with a tree-in-bud pattern [5, 29]. Otherwise, HRCT is needed in the initial evaluation of symptomatic patients to eliminate other causes of respiratory symptoms, such as infectious or inflammatory pneumonitis. Its value in the follow-up of a patient diagnosed with BOS is limited unless new respiratory symptoms develop. Finally, a bronchoscopic exam should be performed to rule out infection in the presence of infiltrates at the HRCT. In the case of normal imaging studies, nasal aspirates, sputum stains and cultures are considered sufficient to rule out viral, bacterial or fungal disease [5].

BOS may also occur after lung transplantation as the result of a chronic graft rejection. Philit et al. have shown very similar clinical, imaging and functional features both in lung transplant and allogeneic HSCT recipients [30]. Thus, the studies in each of these situations contribute to a better understanding of both conditions.

**Management of Bronchiolitis Obliterans Syndrome**

BOS is a potentially fatal complication. Despite advances in the management of allogeneic HSCT recipients, the survival and treatment of patients with BOS have not improved over the last two decades. The overall survival rates at 2 and 5 years after allogeneic HSCT are respectively 45 and 15 % in patients who develop BOS [26]. The natural history of BOS is variable. Classically, PFT declines with time, and patients develop infectious complications, which can lead to respiratory insufficiency and, eventually, death. Some patients remain stable after the development of airway obstruction, and a minority (20 %) will respond to treatment [31]. Actual management is based on case series and expert opinion. Based on the assumption that BOS is a manifestation of chronic GVHD, current practice involves optimizing or reintroducing immunosuppressive therapy upon a diagnosis of BOS. Some reports suggest that high-dose systemic corticosteroids (1–2 mg/kg) can improve or at least stabilize the FEV1. If BOS develops upon tapering the immunosuppressive therapy, clinicians usually reintroduce the tapered drug in combination with corticosteroids. Some case reports/series suggest other immunosuppressive therapies, such as TNF-receptor blockade, imatinib and extracorporeal photophoresis (ECP), may be efficacious [26]. These therapeutic options need to be studied further. Converging data suggest the ineffectiveness of rituximab for BOS treatment [32, 33].

It is well known that long-term exposure to corticosteroids, even at low doses, leads to significant complications. To minimize the morbidity associated with this treatment, considering the low efficacy of steroids in this setting, some authors have suggested alternative agents with anti-inflammatory properties. The use of topical steroid treatment is supported by two retrospective studies. We reported decreases in dyspnea and improvements in FEV1 in seven patients with new-onset airflow obstruction treated with combined inhaled therapy (budesonide-formeterol) [34]. Bashoura et al. reported stabilization or improvement in FEV1 in 16/17 BOS patients treated 3–6 months with high-dose fluticasone [35]. A recent study suggests bronchodilator responsiveness in BOS patients [36]. This information may support the inhaled combination therapy, including a long-acting bronchodilator and a corticosteroid, over an inhaled corticosteroid alone. The efficacy of azithromycin in the treatment of BOS following allogeneic HSCT is controversial [37, 38]. Finally, the efficacy of montelukast as a corticosteroid-sparing agent in the treatment of chronic GVHD had been suggested in a pilot study [39]. These three agents are actually under study in BOS patients following HSCT, either alone or in combination [40].

**Table 32.3** Consensus Criteria for diagnosis of bronchiolitis obliterans/bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation

| 2005 NIH Consensus Criteria [5] | Proposed modified Consensus Criteria [17] |
|--------------------------------|------------------------------------------|
| **All the following should be met:** | **All the following should be met:** |
| 1. **FEV1 < 75 % of predicted normal and FEV1/FVC <70 %**. | 1. **FEV1 < 75 % of predicted normal.** |
| 2. Either signs of air trapping by PFT (RV >120 % of predicted normal) or signs of air trapping, small airway thickening or bronchiectasis by in- and expiratory HRCT or pathological confirmation of constrictive bronchiolitis. | 2. **FEV1/VC <0.7.** |
| 3. **Absence of active respiratory tract infection.** | 3. **Evidence of air trapping on HRCT or RV >120 % of predicted normal.** |
| 4. In case of lacking histological proof of BO, at least one other distinct manifestation of cGVHD in an additional organ system is required. | 4. **Absence of active respiratory tract infection.** |
| 5. Presence of active cGVHD in another organ than the lung. | 5. **Presence of active cGVHD in another organ than the lung.** |
| 6. Decrease of the FEV1 by at least 10 % since pretransplant. | 6. **Decrease of the FEV1 by at least 10 % since pretransplant.** |
| 7. Use of slow vital capacity for calculation of the FEV1/VC ratio. | 7. **Use of slow vital capacity for calculation of the FEV1/VC ratio.** |

*FEV1 Forced expiratory volume in 1 s, FVC forced vital capacity, PFT pulmonary function testing, RV residual volume, HRCT high resolution computed tomography, BO bronchiolitis obliterans, cGVHD chronic graft-versus host disease*
Non Infectious Infiltrative Lung Diseases

Non infectious infiltrative lung diseases (ILDs) occurring late after allogeneic HSCT are not uncommon, representing 12 % to more than 60 % of late-onset non-infectious pulmonary complications in large retrospective studies, including OP [41, 42]. In the largest retrospective studies, ILDs after allogeneic HSCT are mostly described as OP, interstitial pneumonia or idiopathic pneumonia syndrome (IPS) [41, 43, 44]. Whereas OP has been well described in a large study [7], limited data are available on other forms of infiltrative lung diseases following allogeneic HSCT.

Idiopathic Pneumonia Syndrome

Idiopathic pneumonia syndrome (IPS) was first defined in 1993 by an NIH expert committee as diffuse alveolar opacities following allogeneic HSCT after lower respiratory tract infection or cardiac failure was excluded. This definition was recently updated to include new microbiological diagnostic tools for the exclusion of infection, especially for newly described pathogens (Table 32.4) [45]. Thus, this syndrome regroups different clinical entities that can be classified according to the primitively attempted lung compartment: parenchyma (acute interstitial pneunonitis (AIP), acute respiratory distress syndrome (ARDS), OP, iatrogenic lung injury) or pulmonary blood vessels (engraftment syndrome, capillary leak syndrome, diffuse alveolar hemorrhage). IPS is thought to result from a variety of lung insults, including the toxic effects of HSCT conditioning regimens, immunologic cell-mediated injury, inflammatory cytokines, and occult pulmonary infections [45]. Peri-engraftment respiratory distress syndrome (PERDS) occurring within 5 days of engraftment after allogeneic HSCT represents a clinical subset of IPS that should be identified because of its specific clinical characteristics and because its responsiveness to corticosteroids can lead to a good prognosis [45]. PERDS is the result of non-cardiogenic pulmonary edema with or without concurrent pleural effusions in the context of a diffuse capillary leak syndrome and dysfunction of other organs, such as the liver, kidney, skin or gut [45, 46].

The incidence of IPS may vary according to the time following allogeneic HSCT and the type of conditioning regimen, with a historical reported incidence of 3–15 % after myeloablative conditioning, which may be lower (but with a similar severity) after nonmyeloablative conditioning [47]. Although time from allogeneic HSCT is not a diagnostic criterion of this syndrome, IPS occurs early in the course of HSCT (median time: 3–7 weeks after HSCT), with a historical high mortality rate (60–80 %, depending on the study, and up to 90 % in case of respiratory failure requiring mechanical ventilation). Proposed risk factors of IPS include total body irradiation-based myeloablative conditioning regimens, older recipient age, myelodysplastic syndrome, acute leukemia as an underlying disease and acute GVHD [45]. However, the association between IPS and acute GVHD is inconstant in humans, although a causal relationship between the two disorders has been proposed [45].

Therapeutic strategies for IPS include supportive care measures, broad-spectrum antimicrobial agents and intravenous corticosteroids. However, new treatments are needed due to the lack of efficacy of the currently applied strategies. Etanercept, a neutralizing agent of TNF-α, is currently being evaluated for this indication and has yielded encouraging results that should be confirmed [48]. In fact, new insights in the classification of IPS that include very different entities would likely lead to better propositions of treatments.

Organizing Pneumonia

Organizing pneumonia (OP) is a distinct entity of diffuse ILD defined histopathologically by intra-alveolar connective tissue plugs of granulation tissue consisting of intermixed myofibroblasts and connective tissue that fill the lumens of the distal airways and extending into the alveolar ducts in association with chronic interstitial inflammation [49] (Fig. 32.2b). OP can occur in many different contexts: post-infection; following environmental, professional or toxic exposure; iatrogenically (due to medications, chemotherapy...

Table 32.4 Diagnostic criteria of idiopathic pneumonia syndrome occurring after hematopoietic stem cell transplantation [42]

1. Evidence of widespread alveolar injury
   - Multilobar radiologic infiltrates (chest X-ray, computed tomography)
   - Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
   - Evidence of abnormal pulmonary physiology
     - Increased alveolar to arterial oxygen difference
     - New or increased restrictive pulmonary function test abnormality
2. Absence of active lower respiratory tract infection
   - Negativity of exhaustive microbiological assessments of BAL fluid and non-invasive samples (serum, nasal swab, sputum)
   - Bacteriology, virology, mycology and parasitology
   - Culture, cytology, direct fluorescence, serology and polymerase chain reaction
   - Transbronchial biopsy if condition of the patient permits
3. Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction

Conditions routinely included under the classification of idiopathic pneumonia syndrome

Pulmonary parenchyma
- Acute interstitial pneumonia
- Acute respiratory distress syndrome
- Organizing pneumonia
- Delayed pulmonary toxicity syndrome

Vascular endothelium
- Peri-engraftment respiratory distress syndrome
- Noncardiogenic capillary leak syndrome
- Diffuse alveolar hemorrhage
or radiotherapy); or associated with connective tissue diseases, other chronic inflammatory diseases, solid cancers, hematological malignancy, lung transplantation or allogeneic HSCT. When no specific cause is found, OP is referred to as cryptogenic (COP). For more clarity, the terminology “Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)” has been progressively abandoned because the major histological process is OP, whereas bronchiolar lesions are a minor and inconstant process \[49\]. The change in terminology is particularly relevant in the context of allogeneic HSCT to avoid confusion with BO, for which the clinical presentation and prognosis are very different.

In a case control study, Freudenberger et al. described 49 cases of biopsy-proven OP following allogeneic HSCT and compared them to control subjects from a computerized database of all patients who received an allogeneic transplant \[7\]. They identified a strong association between OP and previous signs of acute and chronic GVHD, suggesting a causal link between both entities \[5, 7\]. Other authors have also associated post-allogeneic HSCT OP with the presence of HLA B35 antigen \[50\]. The time from HSCT to OP onset ranged from a few days to more than 7 years, with a median time of 108 days. In 22 % of these cases, a tapering of immunosuppressive treatments preceded the respiratory signs. The clinical presentation was similar to that of COP, mimicking unresolved or subacute infectious pneumonia with unspecified symptoms (fever, dyspnea and cough) and physical signs (crackles). Radiological signs consisted of alveolar, nodular or interstitial opacities with a focal, multifocal or more diffuse extension that is indicative of the diagnosis when the topography of the lesions is peripheral or peribronchovascular \[7, 51, 52\] (Fig. 32.2a). Unlike COP, opacities were rarely migratory \[7\].

Freudenberger et al. found normal PFT in 38 % of the patients with post-allogeneic HSCT OP, whereas 43 % had a restrictive pattern, 11 % had an obstructive ventilatory defect and 8 % had both. In addition, a decrease in the carbon monoxide diffusion capacity was noted in 64 % of the cases \[7\]. The histological features of post-allogeneic HSCT OP were similar to the histological pattern of COP. In Freudenberger’s study, almost 80 % of the patients were treated with steroids, with improvement or stabilization in most cases. However, 22 % of the patients progressed, despite a treatment with high-dose corticosteroids, leading to death due to respiratory failure in most cases \[7\].

**Other Infiltrative Lung Diseases**

In addition to OP, other ILDs are generally poorly described and are usually referred to IPS if diagnosed early after allogeneic HSCT or interstitial pneumonitis without more precision in these studies. In most cases, ILDs are associated with a history of extrathoracic acute and/or chronic GVHD and usually occur following the tapering of immunosuppressive therapy, mostly within the first 2 years after allogeneic HSCT \[53\]. These findings raise the hypothesis of pulmonary patterns of chronic GVHD. Very few data regarding lung histological patterns of ILD post-allogeneic HSCT are available because lung biopsies are rarely performed in this setting. However, diffuse alveolar damage, lymphoid interstitial pneumonia, nonspecific interstitial pneumonitis (Fig. 32.3) and eosinophilic pneumonia have been previously identified \[24, 53–57\]. Due to the difficulties of achieving lung biopsies in these patients and the current lack of impact of lung biopsy results on the management of patients in a noninfectious context, we reviewed 40 cases of ILD post-allogeneic HSCT and described their

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**Fig. 32.2** Lung computed tomography (CT) scan (a) and lung biopsy (b) from a patient who was diagnosed with organizing pneumonia 8 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows an alveolar condensation (a). On lung biopsy, all the alveolar spaces are filled by fibroblast plugs (HES x 100) (b)
clinical characteristics and outcomes as it is usually done for idiopathic ILD [53]. The median time from allogeneic HSCT to ILD was 11.1 months (IQR, 9.1–19.2 months). The clinical presentation was unspecific, with cough (productive or not), variable levels of dyspnea and fever in half of the cases. As for IPS, infection had to be ruled out to retain the diagnosis of ILD. Radiological signs of ILD were variable in extent and ranged from localized to more or less diffuse (Fig. 32.3) [53]. BAL fluid analysis typically showed lymphocytic or both lymphocytic and neutrophilic alveolitis. In some cases, BAL can show an eosinophilic alveolitis that allows the diagnosis of eosinophilic pneumonia [55]. Pulmonary function tests usually showed a restrictive ventilatory defect associated with an alteration in the carbon monoxide diffusion capacity. PFT could also reveal an obstructive lung disease, isolated or not, suggestive of an overlap or a continuum between ILD and BOS [53].

High-dose steroids were usually administered as the first-line therapy and were often associated with a reinforcement of other immunosuppressive drugs. The survival rate was estimated to be 61 % at 24 months from ILD diagnosis. The main cause of death was respiratory failure [53]. Because late fibrosis often remains inaccessible to conventional therapies, early identification and treatment of ILD are essential for prognosis. For this purpose, ILD should be suspected in every atypical, subacute or unresolved case of infectious pneumonia, especially in the presence of extrathoracic chronic GVHD.

GVHD sometimes has features resembling autoimmune disorders, such as scleroderma, Sjögren syndrome, lupus erythematosus, mixed connective tissue disease, polymyositis ANCA-positive vasculitis, or primary biliary cirrhosis. A spectrum of pulmonary manifestations occurring in patients with a well-defined connective tissue disease (CTD) after allogeneic HSCT similar to idiopathic CTD has been reported [54]. Therefore, nonspecific interstitial pneumonia and lymphoid pneumonia have been reported in the course of Sjögren-like disorders diagnosed on both clinical and biological characteristic features [54]. The incidence of these CTDs that may arise very late after allogeneic HSCT remains unknown, and they are most likely overlooked [54]. Several pathologic mechanisms have been proposed for these autoimmune manifestations, such as genetic predisposition, thymic deficiency, the expression of an abnormal B-cell and/or T-cell reconstitution or donor-related pathogenic clone transfer [58, 59]. The prognoses for these ILDs occurring in post-allogeneic HSCT connective tissue disorders are poor with very high mortality rates despite the usual administration of high dose steroids [54]. Considering therapeutic protocols similar to those used in CTD (e.g., cyclophosphamide, anti-CD20 monoclonal antibodies or TNFR blockers) might be interesting in addition or as an alternative to the more classical steroid therapy.

Conclusion

A wide spectrum of lung diseases can be observed in patients treated for hematological malignancies. In addition to infectious causes, various inflammatory conditions may be encountered similar to those observed in other contexts. In the context of allogeneic HSCT, these pulmonary complications are often attributed to GVHD. However, pulmonary GVHD is not a clinical diagnosis; rather, it is
only the concept of a pathophysiological process. The elucidation of specific clinical, radiological and histopathological pulmonary entities is necessary to adapt patient care and to improve prognosis.

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