Noninfectious Pulmonary Complications after Hematopoietic Stem Cell Transplantation: Practical Approach to Imaging Diagnosis[1]

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Hematopoietic stem cell transplantation (HSCT) is a widely available treatment for a variety of malignant and nonmalignant disorders. The treatment outcome is affected by the type of transplant and is limited by complications secondary to immunosuppression and treatment-related toxicity. Pulmonary complications are very common and follow a predictable timeline that reflects the immunologic status of the patient in the peritransplant period. Until recently, pulmonary complications were largely attributed to infectious causes. However, advances in diagnosis and treatment have led to a shift, and noninfectious complications have emerged as a major cause of morbidity and mortality in this population. With the increasing number of centers that perform HSCT, knowledge of posttransplant noninfectious pulmonary complications has become increasingly relevant. The basic principles of and indications for HSCT are described, and a timeline for the clinical, radiologic, and pathologic manifestations of noninfectious pulmonary complications is presented. Emphasis is given to high-resolution computed tomographic findings and the role of imaging in management of complications. A practical approach is provided to guide imaging interpretation and diagnosis of noninfectious pulmonary complications after HSCT.

Abbreviations: ALS = air-leak syndrome, BAL = bronchoalveolar lavage, DAH = diffuse alveolar hemorrhage, GVHD = graft versus host disease, H-E = hematoxylin-eosin, HRCT= high-resolution CT, HSCT = hematopoietic stem cell transplantation, IPS = idiopathic pneumonia syndrome, PAP = pulmonary alveolar proteinosis, PERDS = periengraftment respiratory distress syndrome, PTLD = posttransplant lymphoproliferative disorder, PVOD = pulmonary venoocclusive disease

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- List the primary noninfectious pulmonary complications after HSCT.
- Identify findings of noninfectious pulmonary complications after HSCT at high-resolution CT.
- Classify noninfectious pulmonary complications according to a timeline of their expected occurrence after HSCT.

See www.rsna.org/education/search/RG.

TEACHING POINTS

See last page

Introduction

Hematopoietic stem cell transplantation (HSCT) is a well-established treatment for various oncologic and hematologic diseases. Different types of HSCT are available and may directly affect patient outcome. In particular, the origin of the stem cells to be transplanted is an important factor in the type and severity of transplant-related complications. Pulmonary complications are common in HSCT recipients and are a leading cause of morbidity and mortality. Although pulmonary infections are widely recognized and well described in the literature, little emphasis has been given to common noninfectious complications, which are important determinants of patient outcome.

We describe the basic principles of and indications for HSCT and review a timeline for the clinical, radiologic, and pathologic manifestations of the main noninfectious pulmonary complications after HSCT. Emphasis is given to high-resolution computed tomographic (HRCT) findings, and a practical approach is described to assist radiologists with imaging interpretation and diagnosis of these complications.

Principles of HSCT

HSCT has been used with increasing frequency as a curative treatment for various malignant and nonmalignant disorders and aims to restore the hematopoietic or immune function of the recipient.

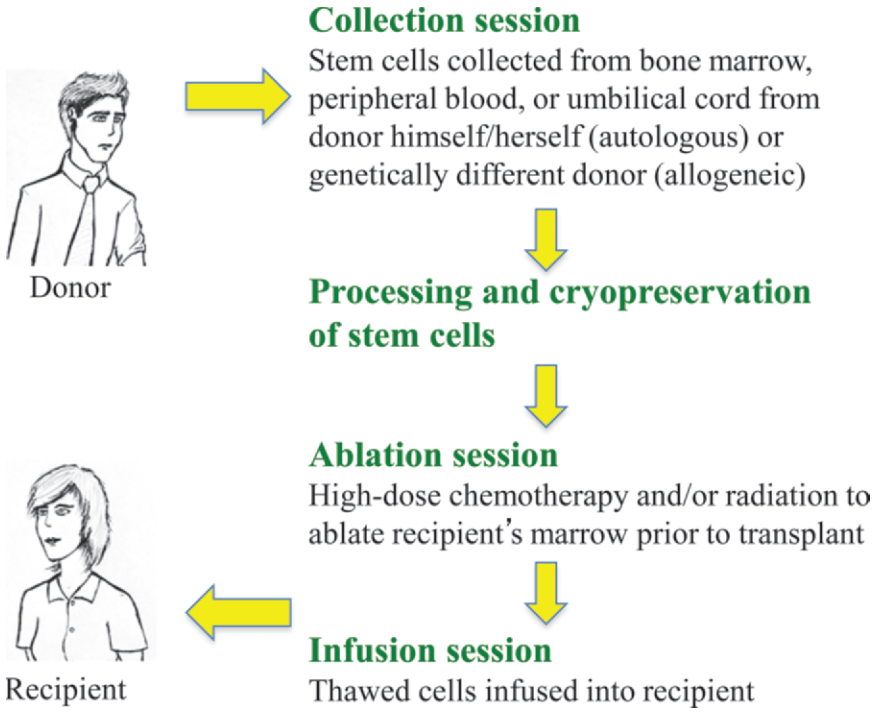


Figure 1. Diagram describes the principles and types of HSCT.

Indications for HSCT include hematologic malignancies; some solid-organ tumors, such as breast, kidney, and ovarian tumors; aplastic anemia; congenital immunodeficiency syndromes; thalassemia; sickle cell anemia; and, less commonly, amyloidosis and genetic disorders. More recently, HSCT has been increasingly used to treat immunologic disorders, including multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis (1,2).

HSCT has replaced the term *bone marrow transplantation* because it more accurately reflects the different potential sources of stem cells, which include bone marrow, peripheral blood, and fetal cord blood (Fig 1). After collection, the stem cells are processed, concentrated, and prepared for cryopreservation. At transplant, they are thawed and infused into the recipient through a central venous catheter (1).

Autologous HSCT involves stem cells collected from the recipient's bone marrow, blood, or umbilical cord that are treated in vitro and retransplanted into the patient. In contrast, allogeneic transplantation is performed with cells obtained from a suitable but genetically different donor with compatible human leukocyte antigens. Because of the genetic differences with allogeneic transplants, there is increased risk for an immunologic reaction between the host and graft and a need for more intense and prolonged immunosuppressive treatment. Less commonly, stem cells may be obtained from a genetically identical donor or identical twin (syngeneic transplantation).

Before transplant, the recipient undergoes preparative regimens (conditioning or myeloablative) that consist of high-dose chemotherapy with or without total-body radiation to ablate the bone marrow; eradicate malignant cells in case of malignancy; and, in recipients of allogeneic HSCT, cause immunosuppression and prevent rejection of donor stem cells.

Complications of HSCT

The success of HSCT is in great part limited by complications secondary to immunosuppression, treatment-related toxicity, and immunologic interactions between the host and graft (in cases of allogeneic transplant). Pulmonary complications are common, affecting approximately 40%–60% of recipients, and contribute significantly to morbidity and mortality. According to some studies, pulmonary complications account for 50% of all deaths in this population (1,3–6), and patients with pulmonary complications have a higher mortality rate than those without such complications.

Historically, pulmonary complications have been largely attributed to infectious causes. More recently, however, there has been a shift in the etiology of pulmonary complications, and noninfectious lung injury has emerged as a major cause of morbidity and mortality. This change is due to a relative decrease in infection with the use of broad-spectrum antimicrobial agents for prophylaxis and treatment. Although infectious complications are more common in patients with allogeneic HSCT because of the need for posttransplant immunosuppressant therapy to prevent or treat graft versus

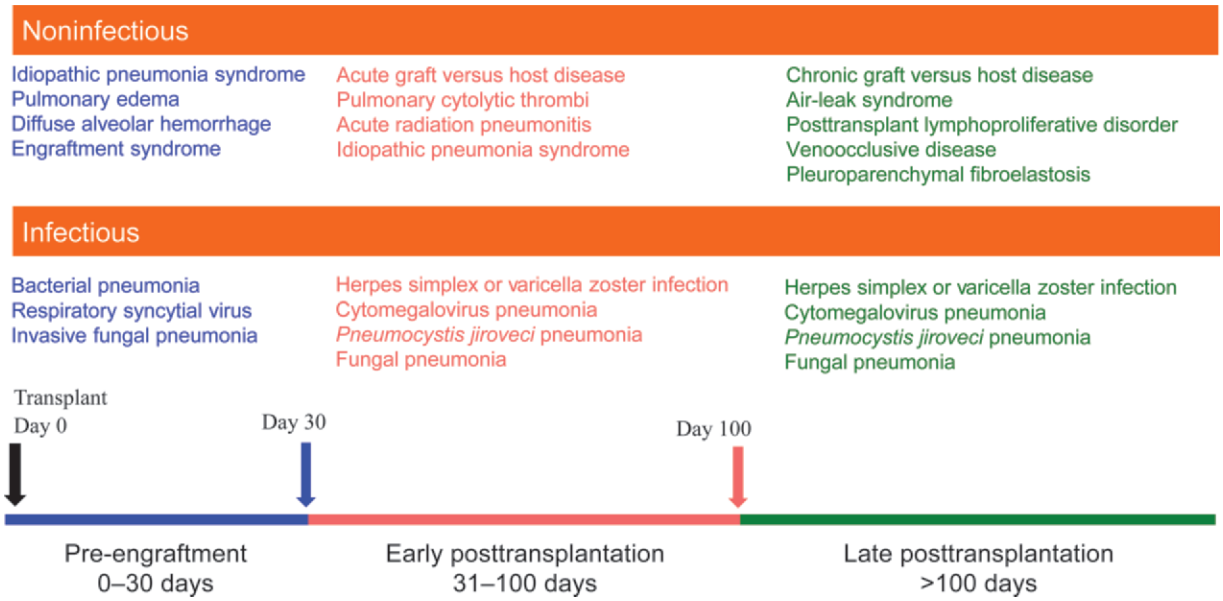


Figure 2. Diagram depicts the timeline of infectious and noninfectious pulmonary complications after HSCT.

host disease (GVHD), noninfectious complications occur with a similar overall frequency in allogeneic and autologous HSCT (1,5).

In contrast to pulmonary infections, which can be confirmed by identification of pathogens in laboratory studies, definitive diagnosis of noninfectious complications is difficult. This is due to several factors, including overlap of clinical syndromes; comorbidities; coexistence of infectious and noninfectious diseases; and risks associated with invasive diagnostic procedures, particularly in the early posttransplant period when patients are thrombocytopenic. Histopathologic diagnosis, considered the standard of reference, is rarely obtained. These factors emphasize the importance of imaging studies and the role of radiologists in diagnosis of these complications. Familiarity with the types of noninfectious complications, the specific timeline during which they may occur, and the patient's clinical scenario is paramount to make a presumptive diagnosis and affect clinical care. Moreover, with the steady increase in the number of centers that perform HSCT and provide posttransplant care, knowledge of pulmonary complications after HSCT has become increasingly relevant.

Timeline of Complications

Pulmonary complications, both infectious and noninfectious, follow a predictable timeline after HSCT. This is because of the increased risk for specific types of lung injury related to the patient's immunologic status and treatment-related toxicity in the peritransplant period. Many of these complications occur secondary to the conditioning regimens used before transplant. After transplant, the degree and duration of immunosuppression is influenced by the marrow function recovery time and immune reconstitution, as well as the type of transplant (autologous or allogeneic). In allogeneic HSCT, chronic GVHD is an important factor in the duration and severity of immunosuppression because it often requires prolonged treatment with immunosuppressants (7). In addition, pulmonary complications may occur as a result of specific therapies used for HSCT recipients, such as blood transfusion and drug-induced lung toxicity.

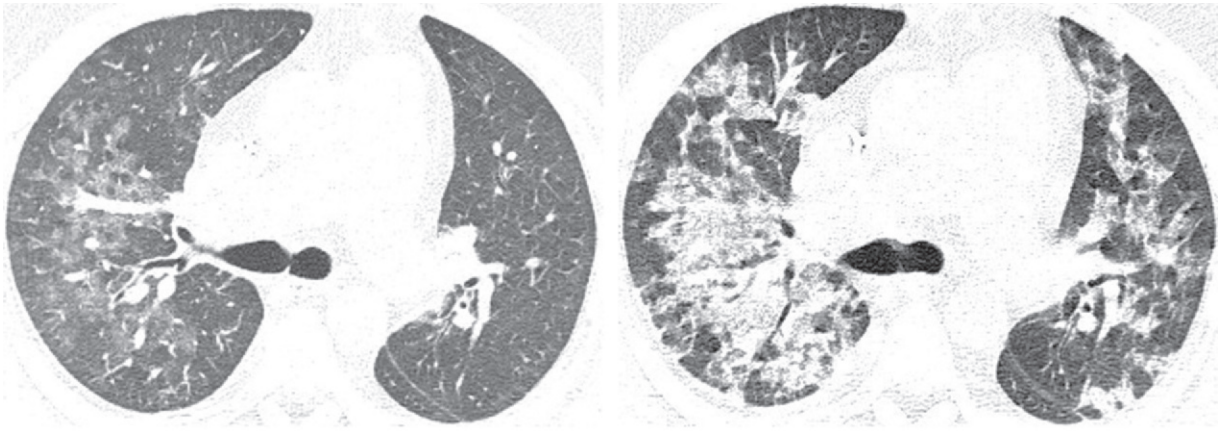
Similar to infectious complications, noninfectious complications can be classified as occurring in either the early or late posttransplant period, depending on their time of onset after HSCT (Fig 2) (1).

Early Pulmonary Complications

Early pulmonary complications occur in the first 100 days after transplant. Although some overlap occurs, the early complication period is subdivided into the neutropenic, or pre-engraftment, period (within 30 days of transplant) and the early posttransplant period (30–100 days after transplant) (1).

Neutropenic or Pre-Engraftment Period

The neutropenic period includes the first 30 days after transplant, when the transplanted marrow is not yet functioning and the patient remains neutropenic. During this period, the frequency of infectious and noninfectious pulmonary complications is similar. Idiopathic pneumonia syndrome (IPS) is a frequent early



a. b.

Figure 3. IPS in a 44-year-old man with acute respiratory failure 60 days after allogeneic HSCT for acute myeloid leukemia. **(a)** Axial HRCT image shows patchy ground-glass opacities in the right upper lobe. **(b)** Axial HRCT image obtained 2 days after **a** shows rapid progression of the ground-glass opacities toward consolidation in the right upper lobe. Note also the new patchy consolidations in the left upper lobe.

noninfectious complication with a complex definition and complex manifestations. Other noninfectious entities that may occur during this period include pulmonary edema, diffuse alveolar hemorrhage (DAH), and engraftment syndrome (periengraftment respiratory distress syndrome [PERDS]) (1,6).

Idiopathic Pneumonia Syndrome.—IPS is a severe complication of HSCT. The incidence of IPS is higher in allogeneic HSCT recipients who undergo myeloablative regimens; IPS occurs in 3%–15% of these patients. The median time of onset described in the literature is 20–42 days after transplant (range, 4–106 days) (8–10). Mortality is high (60%–80%) and usually occurs shortly after diagnosis. Although IPS may also affect autologous HSCT recipients, the incidence is lower in these patients, the onset is later, and the overall prognosis is better.

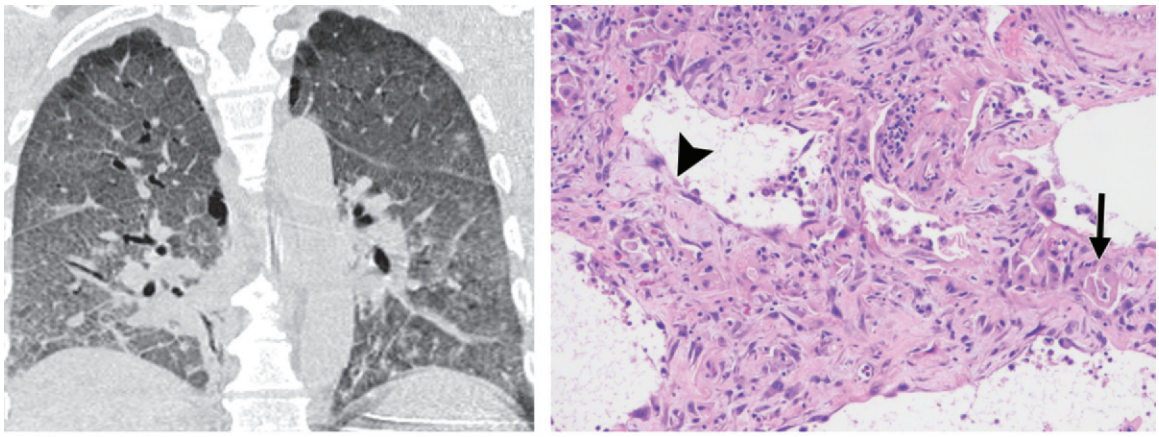
Recently, the American Thoracic Society has issued an official statement that defines IPS as a post-HSCT clinical syndrome that manifests with widespread alveolar injury and acute pulmonary dysfunction in the absence of infection, cardiac or renal disease, or an iatrogenic cause such as fluid overload (8). IPS is believed to result from a variety of lung insults, including direct toxicity from conditioning regimens, occult infection, and release of inflammatory cytokines, and possibly from immunologic factors (8,9,11–13). Disease entities included under the classification of IPS in the new statement include acute respiratory distress syndrome, noncardiogenic edema, capillary leak syndrome, delayed pulmonary toxicity syndrome, PERDS, DAH, and cryptogenic organizing pneumonia. For didactic purposes, some of these entities will be reviewed separately in this article and are classified according to their time of onset after transplant, an approach used in clinical practice.

Considering the wide spectrum of clinical syndromes and histologic patterns included under the classification of IPS, the clinical and imaging manifestations of IPS are nonspecific. However, patients invariably present with signs of rapidly progressive acute respiratory dysfunction often associated with cough and fever. Imaging studies demonstrate nonspecific findings of lobar, multilobar, or diffuse airspace or reticular opacities (Fig 3) that may be indistinguishable from findings of pulmonary infection. Because the definition of IPS is clinical, there is no definite histopathologic diagnosis. Furthermore, tissue biopsy is rarely obtained because of the elevated risk for lung biopsy complications in the early posttransplant period. However, two main nonspecific patterns may be seen in lung pathology specimens: diffuse alveolar damage and interstitial pneumonia (Fig 4).

Imaging findings of parenchymal opacities in a patient with rapidly progressive respiratory symptoms after recent HSCT in the absence of infection (confirmed with BAL) suggest a diagnosis of IPS. Distinguishing between infection and IPS is important because the treatment differs and may affect the prognosis. Treatment of IPS involves supportive care and intravenous corticosteroid therapy.

Pulmonary Edema.—Pulmonary edema is the most common noninfectious complication in the first weeks after HSCT, with a peak incidence in the 2nd to 3rd week after transplant. Pulmonary edema affects autologous and allogeneic transplant recipients equally. The etiology is multifactorial,

Teaching Point



a. b.

Figure 4. IPS in a 64-year-old man with flu-like symptoms 3 months after allogeneic HSCT for acute myeloid leukemia. **(a)** Coronal HRCT image shows a diffuse crazy-paving pattern. The patient underwent bronchoscopy, bronchoalveolar lavage (BAL), and open lung biopsy, which showed no evidence of infection or other acute complications. **(b)** Photomicrograph (original magnification, ×100; hematoxylin-eosin [H-E] stain) from the open lung biopsy shows thickened alveolar septa (arrowhead) with collapsed alveoli in the septa (arrow), findings consistent with the proliferative phase of diffuse alveolar damage. The patient died of progressive respiratory failure.

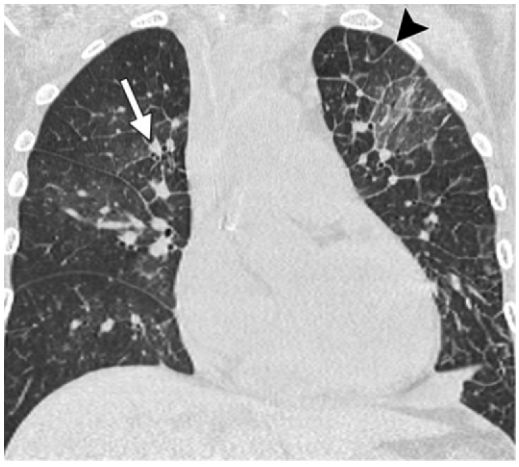


Figure 5. Pulmonary edema in a 56-year-old woman with shortness of breath 7 days after allogeneic HSCT for aplastic anemia. Coronal HRCT image shows enlarged pulmonary vessels (arrow), smooth interlobular septal thickening (arrowhead), and bilateral ground-glass opacities.

and pulmonary edema may be either hydrostatic or due to increased permeability. Causes of hydrostatic pulmonary edema include fluid overload, cardiac dysfunction secondary to chemotherapy, radiation therapy, and renal failure. Permeability edema may be caused by chemotherapy-induced lung toxicity, total-body radiation, or a transfusion reaction (1,3).

Clinical manifestations include sudden dyspnea, weight gain, and basal crackles. Imaging features are those typically described for pulmonary edema. At HRCT, findings of septal thickening, enlarged pulmonary vessels, bronchial wall thickening, and ground-glass opacities, along with cardiomegaly and pleural effusions, are very suggestive of hydrostatic pulmonary edema (Fig 5). Imaging findings of enlarged pulmonary vessels and dependent predominance of the abnormalities may be particularly helpful in the differential diagnosis of ground-glass opacities to distinguish hydrostatic pulmonary edema from other causes. During the appropriate posttransplant period, rapidly evolving characteristic imaging findings in patients with acute dyspnea suggest pulmonary edema (3,14).

Diffuse Alveolar Hemorrhage.—DAH occurs in the early post-HSCT period, with a median onset of 12–15 days after HSCT. The reported incidence varies from 5% to 30% (8,15). Although some studies have suggested a higher incidence in patients with autologous HSCT, others have reported a similar incidence in patients with allogeneic HSCT (1,16). Mortality is invariably high (60%–100% of cases within 3 weeks of diagnosis) despite treatment.

The pathogenesis of DAH in patients with HSCT is unknown. It is believed that, similar to IPS, DAH is part of the spectrum of post-HSCT acute lung injuries, with capillary bleeding induced by conditioning chemotherapy and radiation and possibly by occult infection (1,3). Interestingly, although thrombocytopenia is common, the platelet count of patients with DAH is not lower than that of patients without DAH, and platelet transfusion is not helpful.

Patients typically present with dyspnea and cough, with or without fever. Hemoptysis should

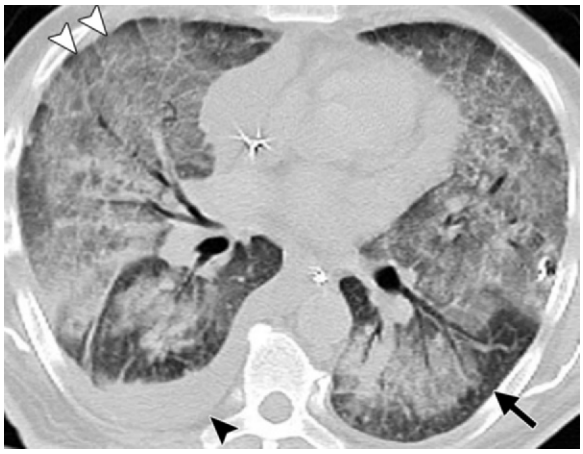


Figure 6. DAH in a 58-year-old man who developed respiratory failure 2 weeks after allogeneic HSCT for hairy cell leukemia. Axial HRCT image shows a diffuse crazy-paving pattern (white arrowheads), areas of consolidation, and a small right pleural effusion (black arrowhead). Note the typical subpleural sparing (arrow). The patient died within 1 week. Autopsy revealed severe diffuse alveolar damage in the proliferative phase, with intra-alveolar hemorrhage.

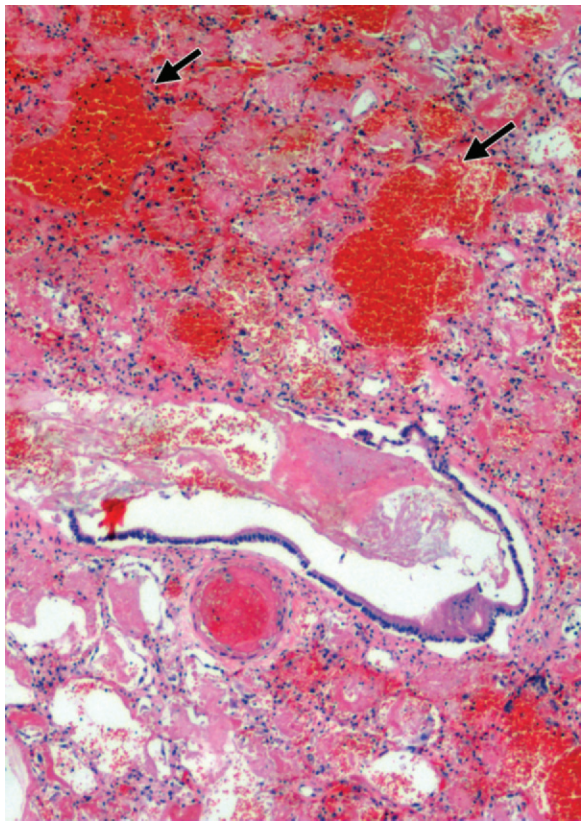


Figure 7. Photomicrograph (original magnification, ×40; H-E stain) of specimen from open lung biopsy shows DAH, with the alveolar spaces filled with extravasated red blood cells (arrows).

suggest the diagnosis of DAH but occurs in only 66% of cases, and frank hemoptysis is rare (8). Therefore, the absence of hemoptysis does not exclude DAH. Initial HRCT findings include airspace opacities with variable degrees of ground glass and consolidation. Ground-glass opacities may be the predominant finding. Over time, as the alveolar hemorrhage resolves, intra- and interlobular thickening develops and often leads to the "crazy-paving" pattern seen at imaging (Figs 6, 7). Although there may be a predominant dependent distribution similar to that seen with pulmonary edema, the heart size typically is normal, and pleural effusions are not present. The diagnostic criteria for DAH include multilobar pulmonary opacities seen at imaging and a progressively bloodier return at BAL in the absence of infection. A finding of more than 20% hemosiderin-laden macrophages in the BAL fluid is suggestive of DAH. However, this finding has low specificity and is commonly seen in patients with low platelets or pulmonary hypertension (8). Exclusion of associated infection with BAL is crucial because treatment of DAH involves steroid administration.

Engraftment Syndrome.—Engraftment syndrome, or PERDS, is characterized by diffuse capillary leak, cutaneous rash, and fever that occur during the engraftment of hematopoietic stem cells and neutrophil recovery.

Although the pathogenesis of engraftment syndrome is not completely understood, it appears to result from the release of proinflammatory cytokines during engraftment. It occurs within 5 days of engraftment, or 7–21 days after transplant (1,8), and is more common in patients with autologous HSCT. The predominant finding at HRCT is thickening of the interlobular septa, which often is associated with bilateral ground-glass opacities and perihilar or peribronchial consolidation and pleural effusions (Figs 8, 9). The imaging appearance of PERDS may be indistinguishable from that of pulmonary edema and may mimic that of acute respiratory distress syndrome when there are extensive ground-glass opacities. The absence of cardiac enlargement or other clinical findings of pulmonary edema and the presence of a skin rash and fever may be helpful for differentiation (3,14). Although histologic findings of PERDS have not been described, from a pathophysiologic point of view they likely range from interstitial edema and alveolar transudation to diffuse alveolar damage, depending on the degree of endothelial damage. The prognosis for patients with PERDS is generally good. PERDS may either resolve spontaneously or respond promptly to steroid treatment (1). However, when patients require mechanical ventilation (as for acute respiratory distress syndrome), high mortality has been noted (17).

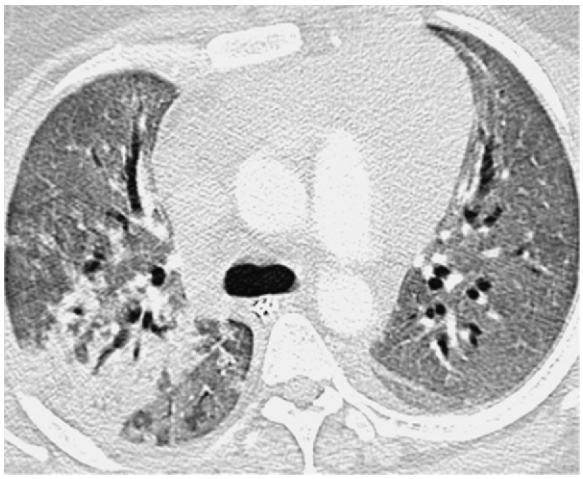


Figure 8. PERDS in a 30-year-old man 9 days after autologous HSCT for Hodgkin lymphoma. Axial HRCT image shows diffuse bilateral ground-glass opacities and peribronchial consolidation in the right upper lobe. The pulmonary arteries are not enlarged, a finding that helps distinguish engraftment syndrome from pulmonary edema.

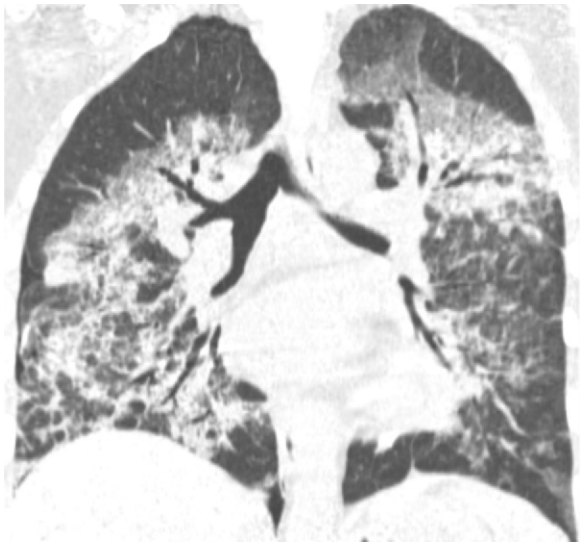


Figure 9. PERDS in a 27-year-old woman after HSCT. Coronal HRCT image shows bilateral peribronchial ground-glass opacities with a predominant perihilar and lower lobe distribution.

Early Posttransplant Period

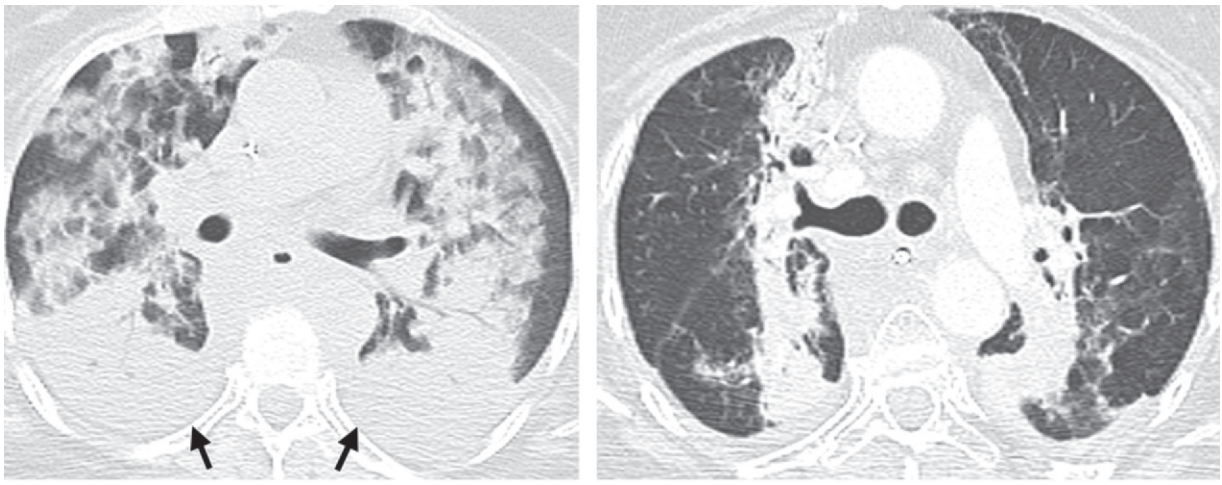
The early posttransplant period extends from 30 to 100 days after HSCT. During this phase, the neutrophil count is usually normal, but there is impaired cellular and humoral immunity. As a result of reconstitution of the immune system, the frequency of infectious complications decreases, and the spectrum of causative agents changes. Noninfectious pulmonary complications that may occur include acute GVHD, acute radiation pneumonitis, and, rarely, pulmonary cytolytic thrombi. IPS, although described earlier in this article, may have a more delayed onset and may manifest 30 days or more after HSCT. Some authors have described IPS as the most common noninfectious complication in the early posttransplant period and the most common cause of multilobar infiltrates 30–180 days after transplant (3,4,8).

Acute GVHD.—GVHD is a major cause of morbidity and mortality in patients after allogeneic HSCT and is caused by an immune reaction of the donor cells to the host tissues. Because GVHD is the result of human leukocyte antigen disparities, it does not occur with autologous transplant. GVHD has been reported in 20%–75% of allogeneic HSCT recipients and affects primarily the skin, liver, and gastrointestinal system. Although the lungs are not considered a classic target, a histologic spectrum of pulmonary GVHD has been described that ranges from acute injury to chronic irreversible damage (8,18). Acute pulmonary GVHD is rare. HRCT findings are nonspecific and may include diffuse interstitial and alveolar opacities that resemble pulmonary edema.

Acute Radiation Pneumonitis.—Acute radiation pneumonitis may occur in patients who received radiation therapy for mediastinal lymphoma before HSCT. Whole-body radiation as part of a conditioning regimen is not a cause of acute radiation pneumonitis seen at imaging.

Acute radiation pneumonitis may manifest 6 weeks to 6 months after radiation therapy termination, with a clinical syndrome similar to that of infection that includes fever, leukocytosis, and parenchymal infiltrates seen at chest radiography (1). HRCT demonstrates bilateral and often fairly symmetric ground-glass opacities and consolidation in a central distribution that is most severe in the mid and upper lung zones, corresponding to the irradiated area. A distinctive imaging feature of radiation pneumonitis is a well-demarcated border between the airspace opacities and the normal lung (Fig 10) (14). In the acute phase, the most common pattern of lung injury is diffuse alveolar damage. It typically progresses to radiation fibrosis, which is characterized at imaging by irreversible localized fibrotic changes with architectural distortion and bronchiectasis in the paramediastinal portions of the lungs (conforming to the radiation portal) (Fig 10b).

Pulmonary Cytolytic Thrombi.—Pulmonary cytolytic thrombi is a rare pulmonary complication that exclusively affects allogeneic HSCT recipients with acute or chronic GVHD. Although its pathogenesis is unknown, pulmonary cytolytic thrombi may be a manifestation of GVHD. It has



a. b.

Figure 10. Acute radiation pneumonitis in a 67-year-old woman who presented with fever and acute respiratory failure after HSCT for diffuse large B-cell non-Hodgkin lymphoma. She had received pretransplant radiation. **(a)** Axial HRCT image shows bilateral peribronchial consolidation and peripheral ground-glass opacities. Bilateral pleural effusions are seen (arrows). **(b)** Follow-up axial HRCT image obtained 2 months after **a** shows paramediastinal consolidation, with associated volume loss and marked parenchymal distortion due to radiation fibrosis. Note the sharp borders between the radiated and normal lung parenchyma.

been reported primarily in children, with a median onset of 72 days after HSCT.

Pulmonary cytolytic thrombi consists of intravascular thromboemboli associated with the infiltration of monocytes of donor and recipient origins in small and medium pulmonary vessels, surrounded by an area of alveolar hemorrhage or infarct. The thromboemboli are composed of necrotic basophilic debris, with an amorphous material suggestive of the products of cellular breakdown. HRCT findings consist of multiple bilateral pulmonary nodules and peripheral opacities that reflect lung infarcts. Symptoms are nonspecific and include fever, dyspnea, and chest pain (1,6).

The main differential diagnosis in these patients is infection, particularly invasive fungal infection, and infection must be excluded before treatment is instituted. Patients with pulmonary cytolytic thrombi usually respond well to an increase in immunosuppressive therapy, with radiologic resolution within weeks to months.

Late Pulmonary Complications

Late complications occur more than 100 days or 3 months after HSCT. During this period, noninfectious causes are more common than infectious complications (19). The most common late complication after HSCT is chronic GVHD, which manifests as bronchiolitis obliterans, organizing pneumonia, or nonclassifiable interstitial pneumonia. Other less common conditions include air-leak syndrome (ALS), posttransplant lymphoproliferative disorder (PTLD), pulmonary venoocclusive disease (PVOD), and pleuroparenchymal fibroelastosis, a clinicopathologic entity recently described in HSCT patients.

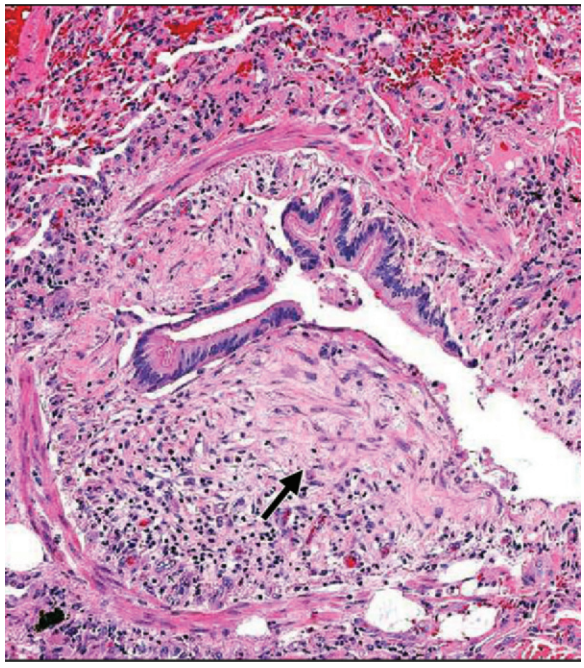


Figure 11. Bronchiolitis obliterans. Photomicrograph (original magnification, ×100; H-E stain) shows a bronchiole with subepithelial organizing fibrosis (arrow), a finding consistent with bronchiolitis obliterans.

Chronic GVHD

Chronic GVHD is the most common and most relevant complication in long-term survivors after HSCT. It occurs exclusively in patients with allogeneic HSCT as the result of an immune-mediated

Teaching Point

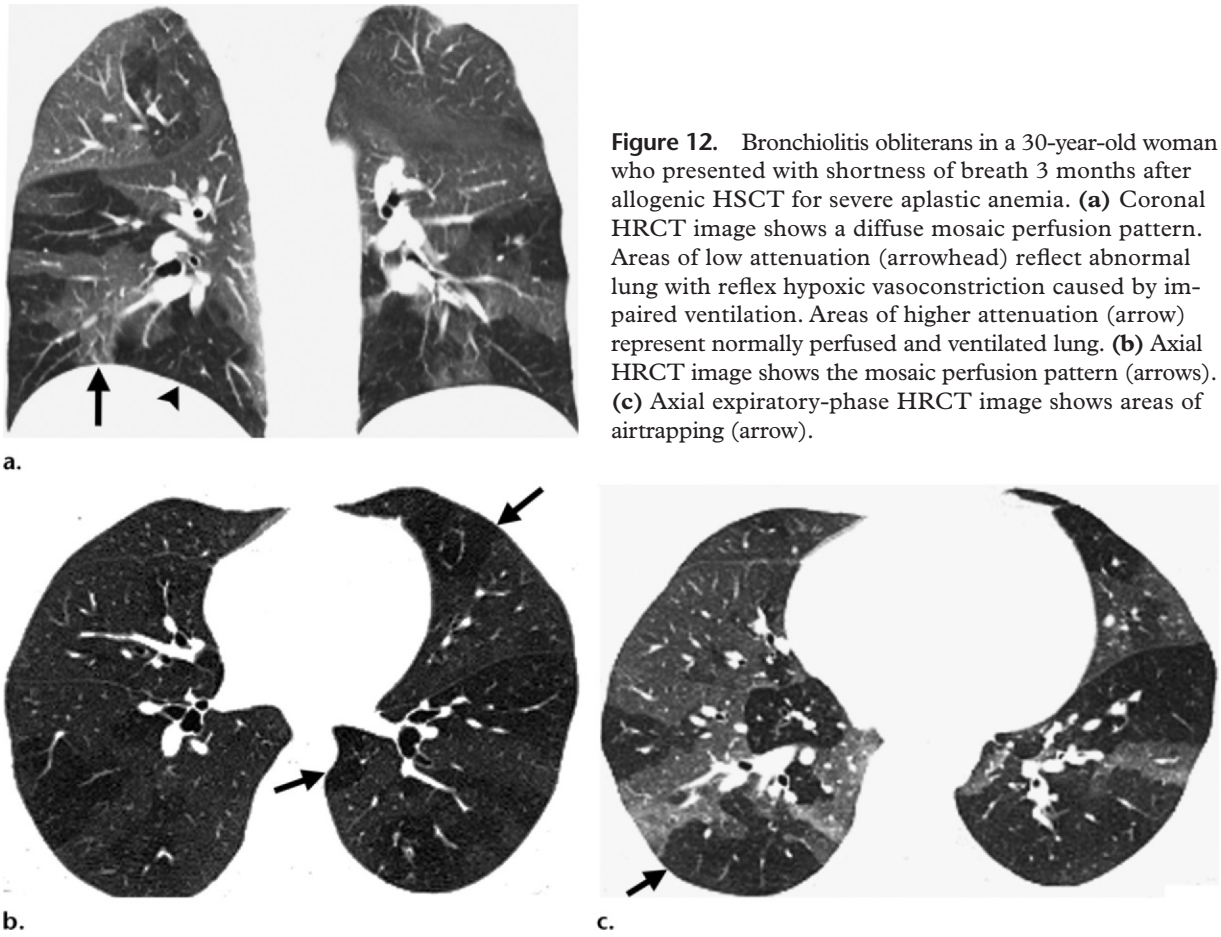


Figure 12. Bronchiolitis obliterans in a 30-year-old woman who presented with shortness of breath 3 months after allogenic HSCT for severe aplastic anemia. **(a)** Coronal HRCT image shows a diffuse mosaic perfusion pattern. Areas of low attenuation (arrowhead) reflect abnormal lung with reflex hypoxic vasoconstriction caused by impaired ventilation. Areas of higher attenuation (arrow) represent normally perfused and ventilated lung. **(b)** Axial HRCT image shows the mosaic perfusion pattern (arrows). **(c)** Axial expiratory-phase HRCT image shows areas of airtrapping (arrow).

reaction of the donor T lymphocytes against the host tissues. In contrast to the acute form of GVHD, chronic GVHD is relatively common in the lungs and may manifest as organizing pneumonia or bronchiolitis obliterans (20). Organizing pneumonia is a reversible process with a relatively favorable prognosis and an earlier occurrence, whereas bronchiolitis obliterans is an irreversible and often severe later complication (3,4,21). A recent study of late-onset pulmonary complications in patients with biopsy-proved chronic GVHD described an additional entity termed *nonclassifiable interstitial pneumonia* (21).

Bronchiolitis Obliterans

Bronchiolitis obliterans, or obliterative bronchiolitis, is the most common and most relevant late noninfectious pulmonary complication after HSCT. Its reported incidence varies from 2% to 48%, likely because of a lack of uniform classification (4). Most cases manifest within 6–12 months after transplant, although presentation as early as 3 months and as late as 10 years after transplant has been reported (8,22,23). Bronchiolitis obliterans is considered a manifestation of chronic GVHD in the lungs and therefore is a complication of allogeneic HSCT (4). Although bronchiolitis obliterans is not expected to occur after autologous HSCT, two fatal cases have been reported in the literature (24).

Histologically, bronchiolitis obliterans is characterized by constrictive bronchiolitis with submucosal bronchiolar fibrosis and luminal narrowing affecting the small airways (Fig 11). The pathogenesis, in most cases, may be related to immunomediated mechanisms secondary to GVHD (25).

Bronchiolitis obliterans is defined clinically by airflow obstruction. The term *bronchiolitis obliterans syndrome* describes a clinical syndrome characterized by an irreversible decline in forced expiratory volume in 1 second (FEV1) of at least 20% from the baseline (26,27). Patients with biopsy-proved bronchiolitis obliterans may not fulfill the clinical criteria for bronchiolitis obliterans syndrome on the basis of pulmonary function test results, whereas patients with a clinical diagnosis of bronchiolitis obliterans syndrome may not demonstrate the classic pathologic features. Nevertheless, these two terms are often used interchangeably in clinical practice (20,26,28).

Patients frequently present with an insidious onset of dry cough and progressive dyspnea (22,27,29,30). Fever is rare unless there is a superimposed infection due to underlying bronchiectasis (4). Early in the disease course, HRCT

may show normal findings or may demonstrate hyperinflation with subtle areas of decreased attenuation. Bronchiectasis is seen later in the course of the disease. The most characteristic HRCT manifestation of bronchiolitis obliterans is the mosaic perfusion pattern, a finding of areas of decreased attenuation and vascularity interspaced with areas of normal or increased attenuation (Fig 12a). The mosaic perfusion pattern is highly suggestive of bronchiolitis obliterans in this population, with 74%–91% sensitivity and 67%–94% specificity (21,31,32). The areas of decreased attenuation are accentuated on expiratory-phase images because of airtrapping (Fig 12b, 12c). In a recent study that assessed HRCT findings of bronchiolitis obliterans in patients after HSCT, the mosaic perfusion pattern was seen in all patients and showed a predominant peripheral distribution. Airtrapping was seen in 56% of cases (21). Therefore, it is strongly recommended that HRCT of HSCT recipients should include both inspiratory- and expiratory-phase image acquisition (14,23,33,34).

Although HRCT is the imaging modality of choice for these patients, spirometry remains the main tool for use in diagnosing and following cases of bronchiolitis obliterans. Lung biopsy is seldom performed for histologic confirmation because a confident presumptive diagnosis can be made on the basis of clinical, functional, and imaging findings. If histologic diagnosis is required, open or video-assisted thoracoscopic lung biopsy is indicated (22,23,35). The role of transbronchial biopsy is limited because of the patchy and peripheral nature of the disease and the limited amount of tissue provided.

Treatment includes corticosteroid and immunosuppressant therapies, but the overall response is poor (23,24,29,34,36,37). Although the disease course is variable, most patients have a slowly progressive worsening of respiratory function, with frequent episodes of acute exacerbation. Early recognition and treatment of superimposed infection is crucial to treatment. The overall mortality rate in post-HSCT bronchiolitis obliterans is 12%–27% at 5 years, and most patients die of a superimposed pulmonary infection (4,38).

Organizing Pneumonia

Organizing pneumonia is a common pattern of inflammatory response to various forms of pulmonary insult. It is a well-known late complication of HSCT, but its incidence is low (2%–10%) (34,37). The largest published series reported an incidence of 0.9% after allogeneic HSCT (38). Although it may occur in patients with either autologous or allogeneic HSCT, the frequency of organizing pneumonia is much higher in the latter population. The onset is usually 1–13 months after transplant (median, 3 months) (34,37,39,40). Because of the strong association between organizing pneumonia and chronic GVHD, rejection and immunomediated response are thought to be involved in the pathogenesis of organizing pneumonia. In patients with autologous HSCT, organizing pneumonia is believed to result from underlying infection or drug toxicity (30).

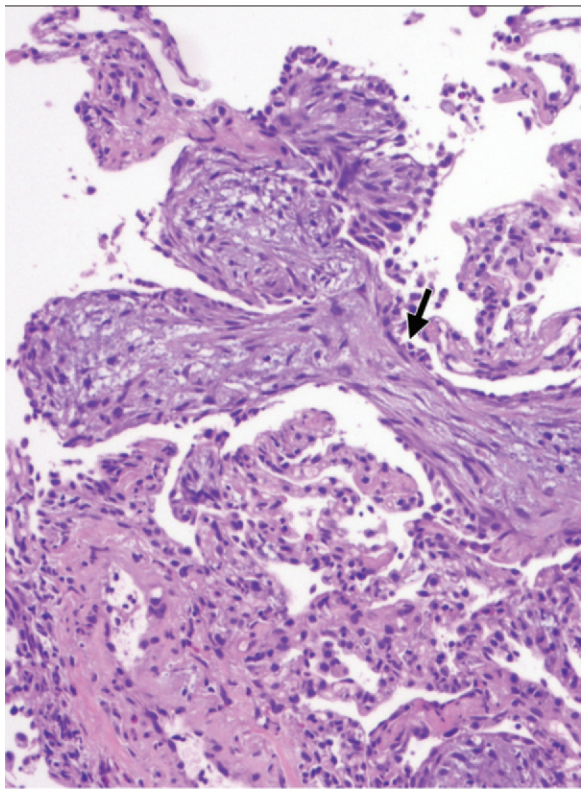


Figure 13. Organizing pneumonia. Photomicrograph (original magnification, ×100; H-E stain) from open lung biopsy shows findings of organizing pneumonia, with myofibroblastic plugs filling the distal airspaces (arrow).

Patients typically present with subacute signs and symptoms that include fever, nonproductive cough, and dyspnea (37,39,40). A diagnosis of organizing pneumonia should be considered in these patients, especially if there is no response to antibiotic therapy.

Histologically, organizing pneumonia is characterized by plugs of granulation tissue within the distal airways and alveoli associated with variable degrees of interstitial inflammation (Fig 13) (41). HRCT typically demonstrates patchy airspace consolidation with air bronchograms in a predominant peribronchial and peripheral distribution (Fig 14). The areas of consolidation tend to have relatively well-circumscribed margins and often contain dilated bronchi, a reversible finding (Fig 15). Ground-glass opacities and centrilobular nodules are also commonly seen (Fig 16) (14,42,43). In a study by Lee et al (44), organizing pneumonia

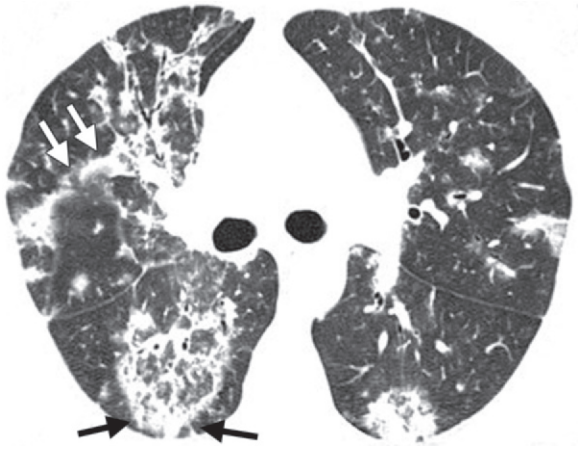
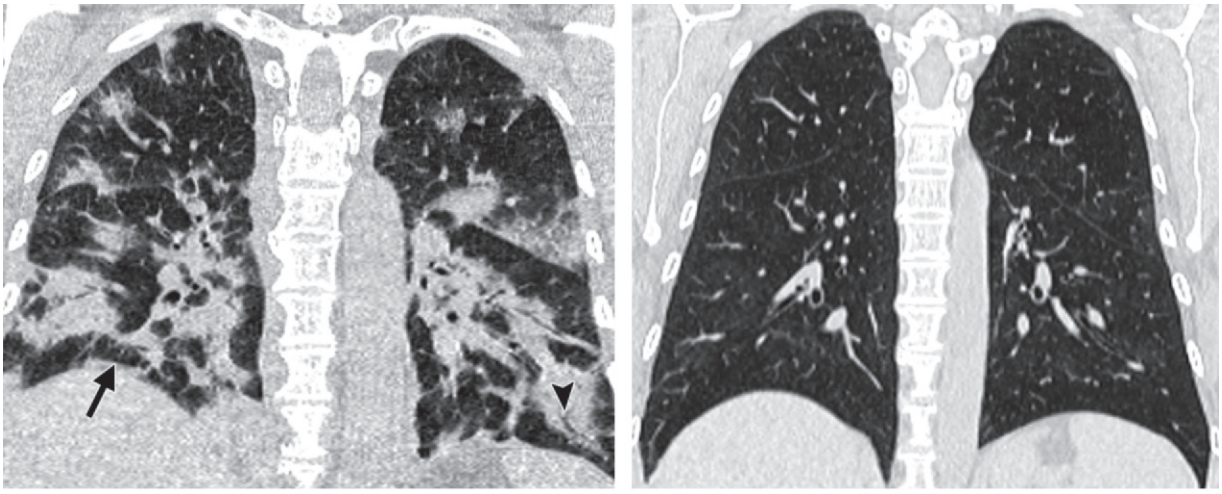


Figure 14. Organizing pneumonia in a 43-year-old man with chronic GVHD 9 months after allogenic HSCT for acute myeloid leukemia. Axial HRCT image shows patchy bilateral peribronchial and peripheral consolidation. Focal consolidation in the right lower lobe with central ground-glass attenuation ("reversed-halo" sign) (black arrows) is highly suggestive of organizing pneumonia. The elongated consolidation in a perilobular distribution seen in the right upper lobe (white arrows) is also very suggestive of this diagnosis.



a. b.

Figure 15. Organizing pneumonia in a 53-year-old woman who presented with fever and cough 5 months after allogeneic HSCT. BAL findings ruled out infection. **(a)** Coronal HRCT image shows patchy bilateral peribronchial and peripheral consolidation. Mildly dilated bronchi are seen in some of the areas of consolidation (arrowhead). Note the elongated perilobular consolidation in the right lower lobe (arrow). **(b)** Coronal HRCT image obtained 2 months after high-dose corticosteroid therapy shows complete resolution of the airspace disease.

in immunocompromised patients manifested more often with nodules (55% of patients) and ground-glass opacities (73%) than with consolidation (45%). Nevertheless, findings of consolidation, particularly with a perilobular or elongated distribution and the "reversed-halo" sign, are very suggestive of organizing pneumonia (Fig 14). Although pathology is the standard of reference for diagnosis, characteristic HRCT features in the appropriate clinical setting should allow confident presumptive diagnosis and preclude the need for biopsy. BAL plays an important role in these patients because it can help exclude infectious causes.

Teaching Point

Most patients respond favorably to steroid treatment, and in about 80% of patients, the findings resolve or remain stable. Radiographic resolution may take 1–3 months after the initiation of therapy (37,40,41). However, the prognosis for patients with HSCT-related organizing pneumonia is worse than for those with cryptogenic organizing pneumonia or other secondary forms of organizing pneumonia, with respiratory failure and death reported in 20% of cases (4,38).

Nonclassifiable Interstitial Pneumonia and Pulmonary Fibrosis

Long-term survivors after allogeneic HSCT may demonstrate CT findings of interstitial lung disease and fibrosis that are not classifiable as any other late-onset complication. These patients present with progressive dyspnea and cough and demonstrate a restrictive pattern with reduced diffusion capacity on pulmonary function tests, findings well described for chronic fibrotic lung diseases (4). The cause of such changes is likely multifactorial and remains speculative. Chronic GVHD is consistently seen in these patients,

which suggests a causal relationship. Indeed, data suggest that interstitial fibrosis may be another pulmonary manifestation of chronic GVHD. Other potential causes include drug toxicity, recurrent infection, and recurrent aspiration, particularly in patients with esophageal GVHD.

Song et al (21) have recently described a nonclassifiable form of interstitial pneumonia in HSCT recipients with pathologically proved extrapulmonary chronic GVHD. The diagnosis was determined by findings of a restrictive pattern at pulmonary function tests or interstitial changes at HRCT. All patients underwent lung biopsy, and histologic analysis demonstrated findings typical of pulmonary GVHD associated with subepithelial fibroblast proliferation. HRCT images obtained at presentation revealed ground-glass opacities, reticulation, and the crazy-paving pattern in a predominant peribronchial distribution, as well as traction bronchiectasis (Fig 17). Findings were randomly distributed in the upper and lower lung zones. All patients demonstrated progression of imaging findings at follow-up HRCT, including worsening bronchiectasis and honeycombing. Patients usually are treated with supportive care and may require oxygen therapy and antibiotics for acute exacerbations.

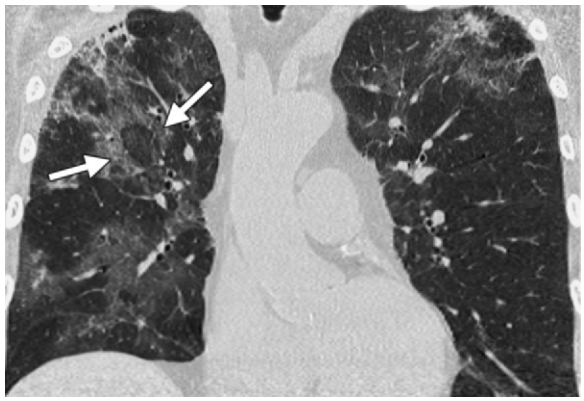


Figure 16. Organizing pneumonia in a 52-year-old man with chronic GVHD who presented with cough and fever 6 months after allogenic HSCT for severe aplastic anemia. Coronal HRCT image shows bilateral patchy ground-glass opacities with a peribronchial and peripheral distribution. Some areas are well demarcated and demonstrate a perilobular configuration (arrows).

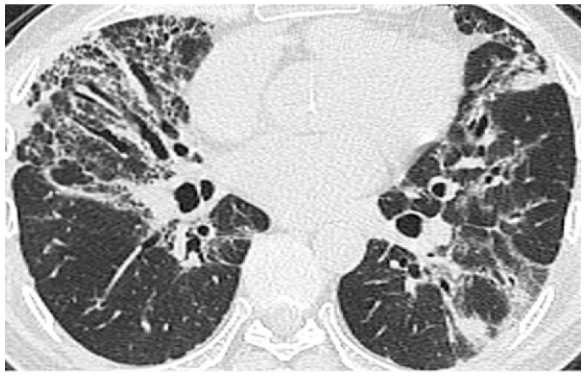


Figure 17. Nonclassifiable interstitial pneumonia and pulmonary fibrosis in a 59-year-old man after allogeneic HSCT for acute myeloid leukemia. The patient developed chronic GVHD of the lungs and mouth. Axial HRCT image shows increased reticulation, ground-glass opacities, and traction bronchiectasis in the right middle lobe, lingula, and lower lobes, findings compatible with chronic interstitial fibrosis.

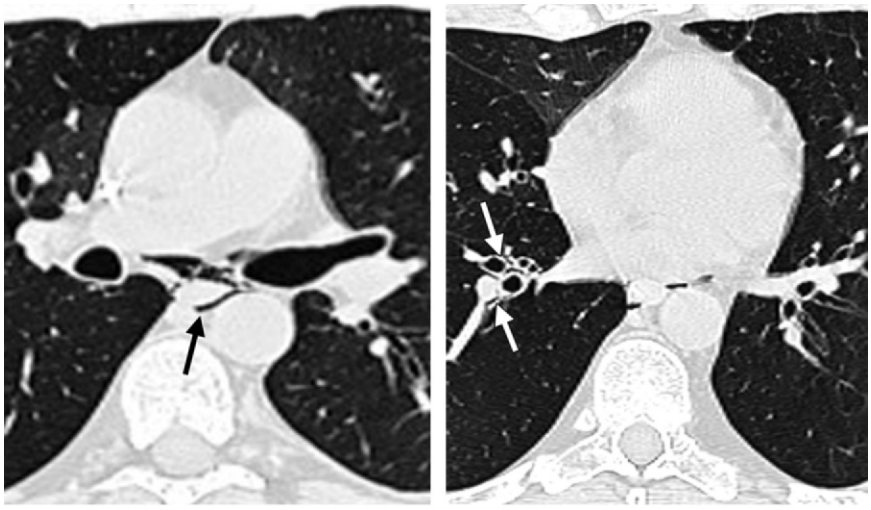
Air-Leak Syndrome

ALS refers to spontaneous pneumothorax, pneumomediastinum, subcutaneous emphysema, or pulmonary interstitial emphysema in HSCT recipients. Typically, ALS occurs as a late complication of allogeneic transplant in patients with chronic GVHD and bronchiolitis obliterans syndrome (25,45,46). ALS is rare, and its incidence is unknown. In the two largest retrospective studies, ALS was reported in 1.2% and 5.7% of patients (25,46).

In patients with bronchiolitis obliterans syndrome, ALS occurs as a result of increased intra-alveolar pressure that leads to alveolar rupture into the pulmonary interstitium (interstitial emphysema) and retrograde dissection of air along the bronchovascular sheaths toward the mediastinum and subcutaneous tissue (the Macklin effect). Rupture into the pleural space may occur, leading to pneumothorax. Other potential causes of air leak must be excluded, such as cough, vomiting, underlying emphysema, and infectious causes (ie, *Pneumocystis jiroveci* pneumonia [PCP] and aspergillosis).

ALS that manifests with pneumothorax and pneumomediastinum may be detected on chest radiographs; however, abnormalities may be subtle or absent, particularly when a supine patient position is used or radiographs are obtained with a suboptimal technique. Pulmonary interstitial emphysema is rarely seen on radiographs. Therefore, for patients who present with acute chest pain and dyspnea and have a normal chest radiograph, the possibility of ALS should be raised, and chest CT should be performed. At CT, air within the pleural space, mediastinum, and subcutaneous tissue is easily seen (Fig 18a). Findings of interstitial emphysema are more subtle and appear as linear lucencies along the bronchovascular bundles (Fig 18b). HRCT may demonstrate coexisting findings of bronchiolitis obliterans (25).

ALS that manifests with pneumothorax usually requires tube thoracostomy. Mediastinal, subcutaneous, and interstitial emphysema are treated conservatively with supportive care. Evidence suggests that patients with ALS have an overall poor prognosis, which may be due in part to underlying bronchiolitis obliterans (46).



a. b.

Figure 18. ALS in a 47-year-old man with chronic GVHD and bronchiolitis obliterans syndrome who presented with acute chest pain and shortness of breath 1 year after allogeneic HSCT for mantle cell lymphoma. **(a)** Coned-in axial HRCT image shows air anterior to the descending aorta and in the subcarinal region (arrow). **(b)** Coned-in axial HRCT image at a lower level shows air along the bronchovascular bundles in the right lower lobe (arrows), a finding compatible with interstitial emphysema.

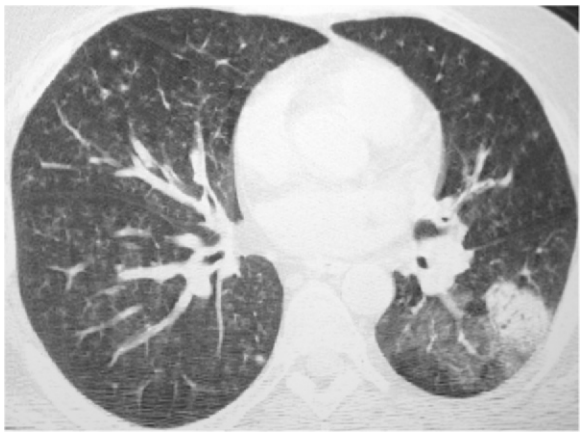


Figure 19. PTLD in a 31-year-old man 3 months after HSCT for acute lymphoid leukemia. Axial HRCT image shows a left lower lobe nodular opacity with mildly dilated bronchi within it and peripheral ground-glass opacities. Multiple tiny ill-defined nodules are seen throughout the lungs. The patient was treated with multiple antibiotics and antifungal drugs without response and died 1 month later. Autopsy findings revealed Epstein-Barr virus–related PTLD with extensive perivascular infiltrates in the lungs and associated hemorrhage. No infection was identified.

Posttransplant Lymphoproliferative Disorder

PTLD is a rare but serious complication of allogeneic HSCT, with an overall incidence of 1% (47). It typically occurs within 6 months of transplant and may occur as early as 30 days after transplant. In one study, the median onset was 72 days after transplant (48). Post-HSCT PTLD most commonly involves the lymph nodes, spleen, and liver (4). Pulmonary involvement occurs in approximately 20% of cases (49). The occurrence of PTLD is directly related to immunosuppression. Therefore, allogeneic HSCT recipients have an inherently higher risk for developing PTLD than do autologous HSCT recipients.

PTLD comprises a heterogeneous group of lymphoproliferative disorders that result from the abnormal proliferation of lymphocytes infected with Epstein-Barr virus originating from the donor. This uncontrolled proliferation is possible because of the impaired cytotoxic function of the host as the result of immunosuppression. Histologic subtypes vary from hyperplastic and indolent disease to aggressive lymphoma. B-cell non-Hodgkin lymphoma is the most common type of lymphoma associated with PTLD.

Features of pulmonary PTLD at HRCT include multiple nodules (Fig 19), often with mediastinal and hilar adenopathy (Fig 20) (14). Biopsy is required for definitive diagnosis (1). Two forms of post-HSCT PTLD have been described: early-onset, rapidly progressive, disseminated disease and, less commonly, localized relatively indolent disease (39). The overall outcome for HSCT recipients with PTLD is worse than that for recipients of a solid-organ transplant (49).

Pulmonary Venoocclusive Disease

PVOD is a rare complication of both autologous and allogeneic HSCT (50). The pathogenesis of

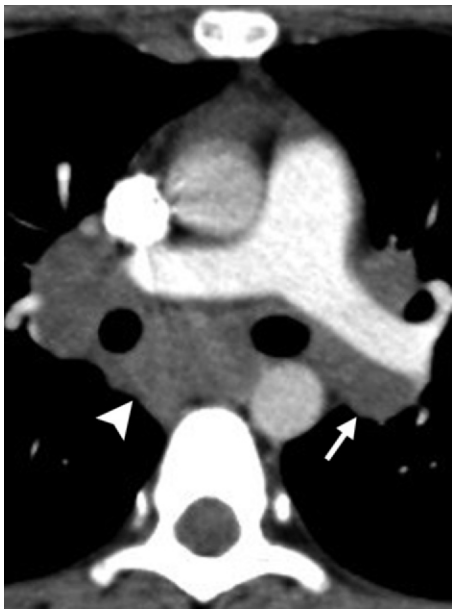
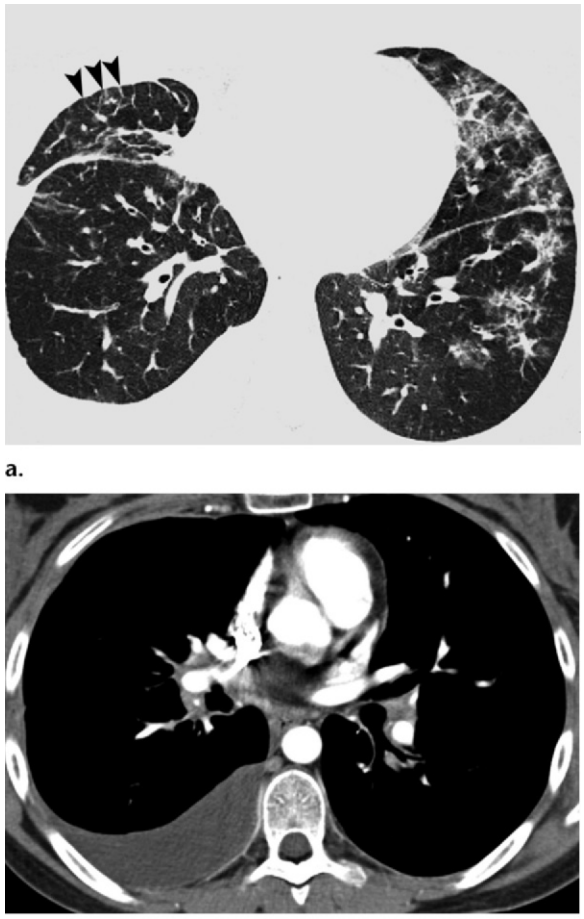


Figure 20. PTLD in an 18-year-old woman 4 months after allogeneic HSCT for severe aplastic anemia. Axial enhanced CT image obtained with mediastinal window settings shows enlarged subcarinal (arrowhead) and bilateral hilar (arrow) lymph nodes. The donor stem cells were proved to be infected with Epstein-Barr virus.



a.

b.

Figure 21. PVOD in a 33-year-old woman who presented with progressive shortness of breath and fatigue 1 month after allogeneic HSCT for non-Hodgkin lymphoma. **(a)** Axial CT image shows patchy ground-glass opacities and interlobular septal thickening (arrowheads). **(b)** Axial CT image obtained with mediastinal window settings shows dilatation of the right ventricular outflow tract and a small right-sided pleural effusion.

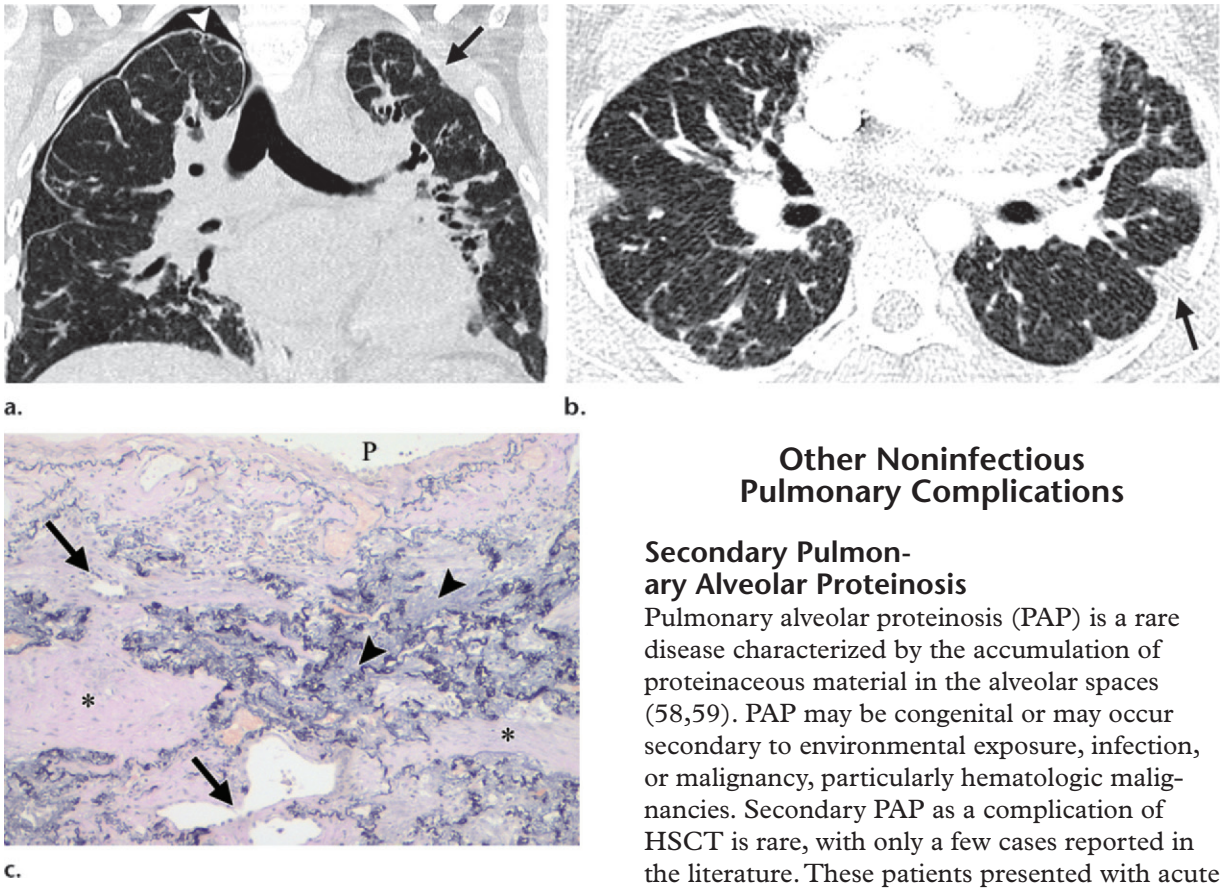
PVOD is not clearly understood, but some authors believe that it may result from endothelial injury caused by infection or drug toxicity (51). Histologically, PVOD is characterized by intimal proliferation and fibrous occlusion of venules and small veins that leads to vascular congestion, increased pulmonary capillary pressure, pulmonary arterial hypertension, and right-sided heart failure (4).

In HSCT recipients, PVOD typically manifests 2–6 months after transplant (8,52) with progressive dyspnea and fatigue resulting from pulmonary arterial hypertension. The triad of pulmonary hypertension, imaging findings of pulmonary edema, and normal pulmonary artery occlusion pressure is strongly suggestive of the diagnosis. HRCT findings include dilatation of the main pulmonary artery, right-sided cardiac chamber enlargement, centrilobular ground-glass opacities, and smooth interlobular septal thickening. Mediastinal lymph node enlargement is often seen (Fig 21) (53). Montani et al (53) have reported that the presence of two or three of these findings at HRCT has a sensitivity of 75% and a specificity of 84.6% for the diagnosis of PVOD. Definitive diagnosis requires a surgical lung biopsy, with an increased risk of complications (4). It has been suggested that HRCT findings with clinical and hemodynamic findings may be substituted when biopsy is contraindicated (50,51,54). The overall prognosis for PVOD is poor, and no specific treatment is available. As with other forms of PVOD, the use of vasodilators is dangerous because it can precipitate severe pulmonary edema and death (4).

Pleuroparenchymal Fibroelastosis

Pleuroparenchymal fibroelastosis is a rare recently described entity characterized by fibrotic thickening of the pleura and fibroelastosis of the subpleural parenchyma that affects predominantly the upper lobes. When first described in 2004 by Frankel et al (55), the term *idiopathic pleuroparenchymal fibroelastosis* was proposed because none of the four patients reported had an identifiable cause. More recently, a similar clinicopathologic entity was reported in HSCT and lung-transplant recipients (56). In a small series of four patients who had received an allogeneic transplant for hematologic diseases, all

Figure 22. Idiopathic pleuroparenchymal fibroelastosis in a 20-year-old woman who presented with progressive shortness of breath that led to respiratory failure. **(a)** Coronal HRCT image shows smooth thickening of the visceral pleura of the right lung and tiny subpleural blebs in the right apex (arrowhead). Also note the thickened pleura adjacent to the left upper lobe (arrow) and low lung volumes. **(b)** Follow-up axial HRCT image obtained after resolution of the right pneumothorax shows projections of thickened pleura into the underlying lung parenchyma (arrow). Note the increased reticulation and traction bronchiectasis in the periphery of the right lower lobe, a finding indicative of interstitial pulmonary fibrosis. **(c)** Photomicrograph (original magnification, ×100; elastic tissue stain [Verhoeff]) from wedge open lung biopsy of the upper lobe shows subpleural alveolar spaces completely obliterated by fibrosis (pink stain; ∗), and elastic tissue (gray stain; arrowheads). A few residual airspaces are seen (arrows). *P* = pleural surface.



patients presented with late-onset pulmonary complications that included recurrent pneumothorax. (57) Symptom onset occurred 2–16 years after transplant. Only one patient had a history of chronic GVHD. In all patients, chest CT demonstrated visceral pleural thickening or irregularity in the upper lung zones, findings identical to those described for the idiopathic form of the disease (Fig 22). Two patients had associated subpleural blebs, and one presented with interstitial fibrosis. The etiology of pleuroparenchymal fibroelastosis in HSCT recipients is speculative, and the authors suggested chemotherapy, radiation therapy, and chronic GVHD as potential causes. Despite the limitations of this small case series and the need for further studies to determine its clinical and prognostic relevance, pleuroparenchymal fibroelastosis should be included as a late-onset pulmonary complication after HSCT.

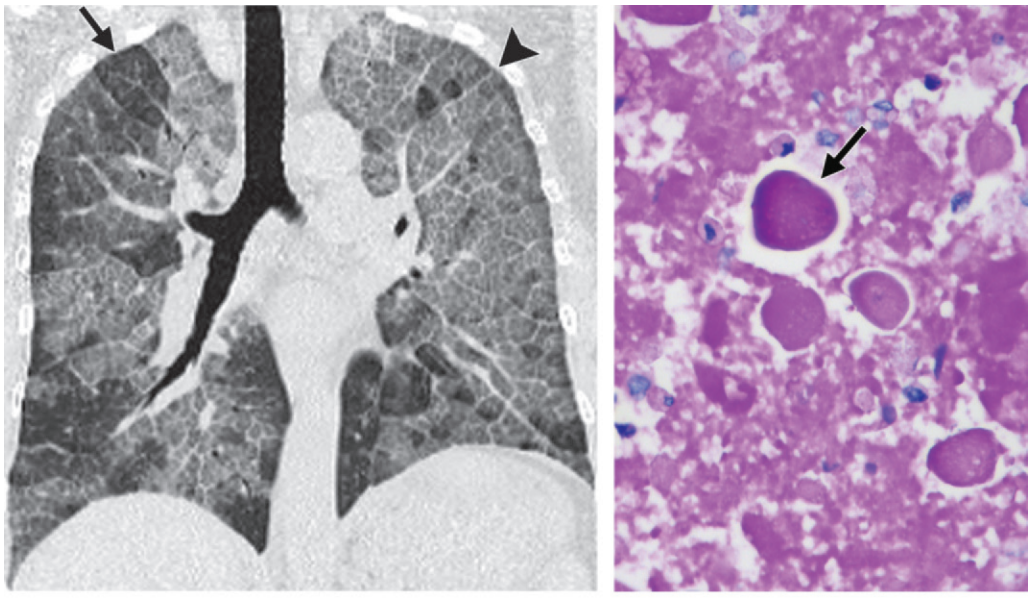
Other Noninfectious Pulmonary Complications

Secondary Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by the accumulation of proteinaceous material in the alveolar spaces (58,59). PAP may be congenital or may occur secondary to environmental exposure, infection, or malignancy, particularly hematologic malignancies. Secondary PAP as a complication of HSCT is rare, with only a few cases reported in the literature. These patients presented with acute respiratory failure and bilateral pulmonary infiltrates. However, respiratory failure was reversible in some of the cases (59,60).

A definitive diagnosis of PAP is obtained when periodic acid-Shiff stain–positive material is obtained from BAL. HRCT findings of PAP have been well described and consist of bilateral ground-glass opacities with superimposed smooth septal thickening (the crazy-paving pattern) in a perihilar and predominant lower lobe distribution (Fig 23) (27,28,61). However, no specific information is available regarding the post-HSCT HRCT appearance of PAP and whether it differs from that of other forms of the disease. The differential diagnoses for noninfectious causes of the crazy-paving imaging pattern seen in HSCT recipients are listed in Table 1 (49,60).

In contrast to patients with other forms of PAP, who have a relatively good prognosis with appropriate treatment, the prognosis for HSCT patients with secondary PAP is generally poor. The efficacy of sequential whole-lung lavage and



a. b.

Figure 23. PAP in a 30-year-old woman with leukemia and shortness of breath. **(a)** Coronal HRCT image shows diffuse ground-glass opacities with areas of geographic sparing (arrow) and prominent septal lines (arrowhead) creating the crazy-paving pattern. **(b)** Photomicrograph (original magnification, ×400; periodic acid–Schiff stain) of specimen from BAL shows positive-staining and diastase-resistant amorphous material (arrow).

Table 1: Differential Diagnosis of Noninfectious Causes of the Crazy-Paving Pattern after HSCT

IPS
Pulmonary edema
Drug toxicity
DAH
PERDS
Organizing pneumonia
Respiratory distress syndrome
PAP
Acute radiation pneumonitis
Nonclassifiable interstitial pneumonia and pulmonary fibrosis

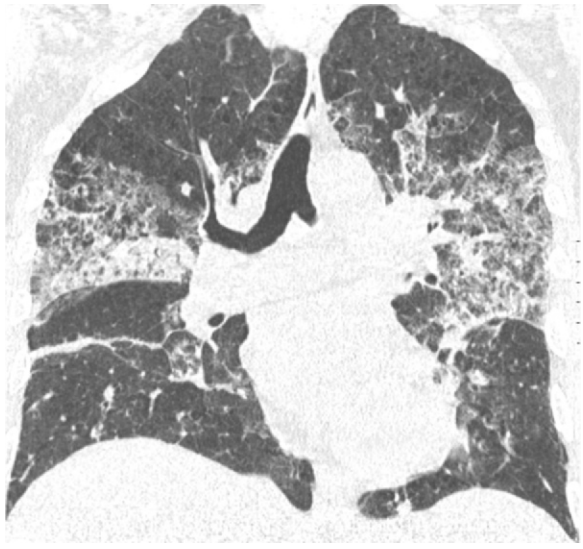
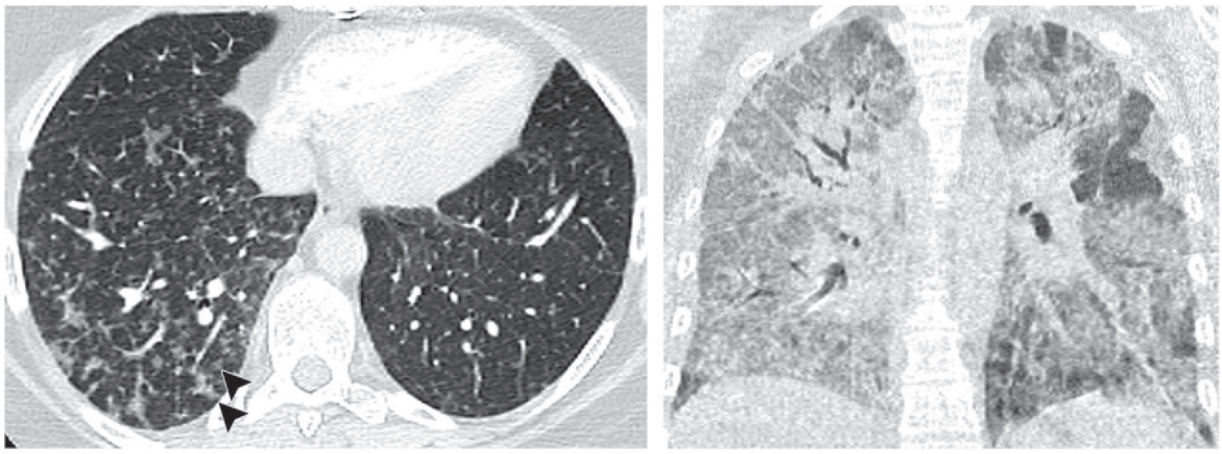


Figure 24. Transfusion-related acute lung injury in a 50-year-old man after HSCT for leukemia. Coronal HRCT image shows ground-glass opacities in a perihilar distribution. The heart and pulmonary vessels are normal in size, findings that help differentiate transfusion-related acute lung injury from cardiogenic pulmonary edema.

granulocyte-macrophage colony-stimulating factor therapy, well-established treatments for PAP, has not been studied in this population (4).

Transfusion-related Acute Lung Injury

Transfusion-related acute lung injury is a serious adverse reaction to transfusion of different blood products. A few cases have also been described after infusion of bone marrow cells during HSCT. Transfusion-related acute lung injury is characterized by noncardiogenic pulmonary edema, but its pathophysiology is poorly understood. Several theories have been proposed that include immune-mediated and nonimmune-mediated mechanisms. Both recipient and transfusion-product risk factors have been recognized (62). Transfusion-related acute lung injury typically manifests within 6 hours of transfusion as acute (often severe) hypoxemia, acute dyspnea, fever, and chills. Imaging findings are nonspecific and are indistinguishable from those of other causes of noncardiogenic pul-



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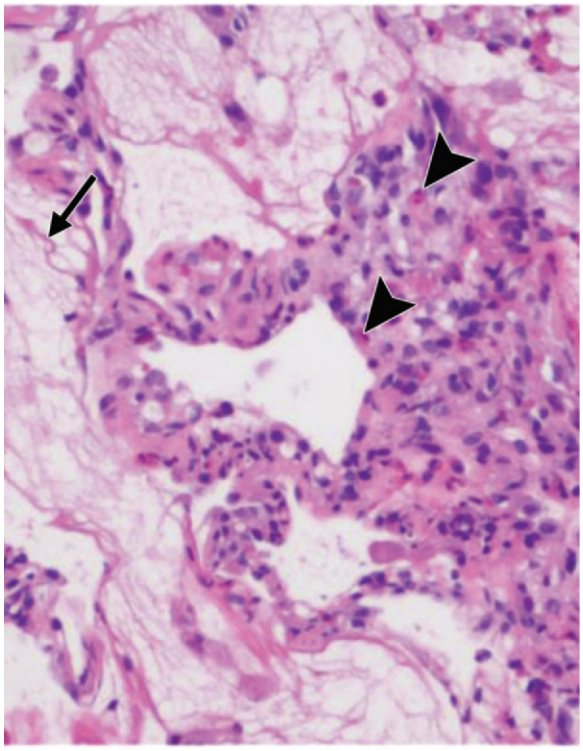

c.

Figure 25. Eosinophilic pneumonia due to bentuximab therapy lung toxicity in a 35-year-old woman who presented with respiratory failure 3 months after initiation of therapy after autologous HSCT for Hodgkin lymphoma. **(a)** Axial HRCT image shows patchy ground-glass opacities and nodules in the right lower lobe (arrowheads). **(b)** Coronal HRCT image obtained 1 week after **a** shows marked progression of the diffuse bilateral ground-glass opacities and interlobular septal thickening with the crazy-paving pattern. **(c)** Photomicrograph (original magnification; ×200; H-E stain) from transbronchial biopsy specimen shows fibrinous alveolar exudate (arrow) and eosinophils in the alveolar septa (arrowheads).

monary edema (Fig 24). Therefore, diagnosis requires a high index of suspicion and the exclusion of other entities with similar clinical and imaging findings, mainly fluid overload and diffuse alveolar damage secondary to other causes. Transfusion-related acute lung injury is the leading cause of transfusion-related mortality and is underdiagnosed. Management is supportive, and no specific treatment is available. Steroid and statin therapies have been suggested, but their use does not have sufficient support in the literature (42,62).

Drug Reactions

HSCT recipients are treated with various drugs at all phases of the transplant process, including chemotherapeutic agents during the conditioning period and immunosuppressants and antimicrobial agents. Hence, both allogeneic and autologous HSCT recipients are at high risk for developing drug-lung toxicity. The lung is one of the most susceptible organs, and several patterns of drug-induced lung reactions have been recognized. Clinical and imaging manifestations of drug toxicity are nonspecific and reflect the histologic pattern of reaction, which most commonly includes organizing pneumonia, hypersensitivity reaction, eosinophilic pneumonia (Fig 25), diffuse alveolar damage, and chronic interstitial fibrosis. HRCT findings are variable, and presumptive diagnosis requires a high index of suspicion, identification of a drug known to cause lung toxicity, and exclusion of other potential causes of lung disease, particularly infection (14,63).

Role of Pulmonary Imaging in HSCT

Treatment of patients with respiratory symptoms after HSCT is challenging. The disease signs and symptoms are nonspecific, and there is a wide spectrum of potential infectious and noninfectious causes. Particularly in the early posttransplant period, pulmonary disease is often multifactorial, with different processes, including polymicrobial infection, occurring at the same time. Furthermore, prompt diagnosis is important because it greatly affects patient

Table 2: Diagnostic Approach to Noninfectious Causes of Diffuse Infiltrates in the Early Phase (<100 Days) after HSCT

Features in Early Phase	Pulmonary Edema	DAH	PERDS	IPS	Acute Radiation Pneumonitis
Clinical presentation	Most common cause Improves rapidly	Bloody return at BAL	Systemic involvement (rash, fever)	Respiratory failure	Fever and leukocytosis in patients who underwent RT for mediastinal lymphoma
Transplant type	Autologous, allogeneic	Allogeneic	Autologous	Allogeneic	Autologous, allogeneic
Distinctive radiologic findings	Enlargement of pulmonary vessels (hydrostatic pulmonary edema) Diffuse GGO Septal thickening	Crazy-paving pattern Diffuse GGO No prominent pulmonary vessels	Diffuse GGO No prominent pulmonary vessels	Rapid confluent consolidation Diffuse GGO No prominent pulmonary vessels	Symmetric GGO and consolidation in upper and mid lung zones; sharp margins with normal parenchyma
Histopathologic findings	Edema	DAD	Edema or DAD	DAD	DAD
Prognosis	Good	Poor	Good	Poor	Good

Note.—DAD = diffuse alveolar damage, GGO = ground-glass opacities, RT = radiation therapy.

outcome. Treatment delays are associated with rapid deterioration and high mortality. A definite diagnosis is difficult to obtain because of the risks associated with invasive diagnostic procedures and the impracticality of waiting for lengthy laboratory results such as cultures. Sputum examination may occasionally be helpful in diagnosis of infection, but it often is unreliable because of contamination. BAL plays an important role in diagnosis of acute pulmonary complications but has limitations and may not be feasible for very sick patients. Although lung biopsy remains the standard of reference for diagnosis of many acute and chronic processes, it has an inherent risk of complications, particularly in this population (30). These factors emphasize the importance of imaging in patients with pulmonary complications after HSCT.

Chest radiography is the imaging modality of choice for initial assessment of patients with respiratory symptoms and febrile neutropenia after HSCT. However, radiographic findings are nonspecific and seldom provide a specific diagnosis. Studies have shown that chest radiographs are normal in 10%–15% of symptomatic patients with clinically proved lung disease after HSCT (37,64–67). Nonetheless, for patients with acute respiratory symptoms, chest radiography may confirm the presence and extent of pulmonary disease, and imaging findings, although nonspecific, may affect treatment and decision making. For patients with late pulmonary complications, chest radiography has limited value for diagnosis of chronic GVHD that manifests with bronchiolitis obliterans (23,68).

Chest CT, and in particular HRCT, is pivotal in the diagnostic assessment of HSCT recipients because it provides superior detection and characterization of parenchymal abnormalities (37,64,69). HRCT that includes expiratory-phase image acquisition when possible should be performed in patients with respiratory symptoms after HSCT, unless a definitive diagnosis is made or rapid clinical improvement occurs (34). The appearance and location of abnormalities at chest CT will also guide decisions about which invasive diagnostic procedures should be performed (34).

Teaching Point

Practical Approach to Diagnosis

Pulmonary complications in HSCT recipients follow a predictable timeline, a factor that helps guide radiologists toward the most likely diagnoses in a given period. Familiarity with the spectrum of early and late pulmonary complications after HSCT and the timing at which they are expected to occur is as important as knowledge of their imaging manifestations.

HRCT findings must be interpreted in light of the time since transplant, type of transplant (autologous or allogeneic), degree of immunosuppression, history of chronic GVHD, and symptom duration and severity. This approach helps narrow the differential diagnosis and allows radiologists to provide clinically relevant imaging interpretation, even with nonspecific

Table 3: Diagnostic Approach to the Most Common Causes of Noninfectious Pulmonary Complications in the Late Phase (>100 Days) after HSCT

Features in Late Phase	Bronchiolitis Obliterans	Organizing Pneumonia
Clinical presentation	No fever Dyspnea Cough	Fever Dyspnea Cough
Transplant type	Allogeneic	Allogeneic
Radiologic findings	No parenchymal infiltrates Mosaic perfusion pattern Airtrapping (at expiratory-phase CT) Bronchiectasis	Patchy circumscribed consolidation with dilated bronchi Ground-glass opacities Nodular opacities Reversed-halo sign
Pulmonary function test results	Obstructive pattern	Restrictive pattern
Histopathologic findings	Submucosal fibrosis and luminal narrowing in distal airways	Intraluminal granulation tissue in distal airways
Prognosis	Poor	Good

imaging findings. A practical approach to diagnosis of the main noninfectious complications after HSCT is provided in Tables 2 and 3.

Conclusion

The effective management of pulmonary infections after HSCT in the last decade has led to a relative rise in the frequency and an undisputed increase in the importance of noninfectious pulmonary complications after HSCT. Prompt diagnosis and treatment of such complications is paramount because it directly affects patient outcome. Radiologists play an essential role in the diagnosis of pulmonary diseases in this population, and radiologists must be familiar with the spectrum of infectious and noninfectious complications after HSCT. Although the imaging manifestations are nonspecific, clinical information combined with the time since transplant helps narrow the differential diagnosis and allows presumptive diagnosis in many cases. Imaging also plays an important role in determining the extent and evolution of disease and guiding treatment decisions.

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Noninfectious Pulmonary Complications after Hematopoietic Stem Cell Transplantation: Practical Approach to Imaging Diagnosis

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Pages 666–667
Pulmonary edema is the most common noninfectious complication in the first weeks after HSCT, with a peak incidence in the 2nd to 3rd week after transplant. Pulmonary edema affects autologous and allogeneic transplant recipients equally. The etiology is multifactorial, and pulmonary edema may be either hydrostatic or due to increased permeability.

Pages 670–671
Chronic GVHD is the most common and most relevant complication in long-term survivors after HSCT. It occurs exclusively in patients with allogeneic HSCT as the result of an immune-mediated reaction of the donor T lymphocytes against the host tissues. In contrast to the acute form of GVHD, chronic GVHD is relatively common in the lungs and may manifest as organizing pneumonia or bronchiolitis obliterans. Organizing pneumonia is a reversible process with a relatively favorable prognosis and an earlier occurrence, whereas bronchiolitis obliterans is an irreversible and often severe later complication.

Page 672
The most characteristic HRCT manifestation of bronchiolitis obliterans is the mosaic perfusion pattern, a finding of areas of decreased attenuation and vascularity interspaced with areas of normal or increased attenuation. The mosaic perfusion pattern is highly suggestive of bronchiolitis obliterans in this population, with 74%–91% sensitivity and 67%–94% specificity. The areas of decreased attenuation are accentuated on expiratory-phase images because of airtrapping.

Page 673
Although pathology is the standard of reference for diagnosis, characteristic HRCT features in the appropriate clinical setting should allow confident presumptive diagnosis and preclude the need for biopsy.

Page 680
HRCT that includes expiratory-phase image acquisition when possible should be performed in patients with respiratory symptoms after HSCT, unless a definitive diagnosis is made or rapid clinical improvement occurs.