The term “hematopoietic stem cell [HSC] transplantation” has replaced the previously used term “bone marrow transplantation” to reflect the broader range of donor stem cell sources that are now available [1]. HSC transplantation is being used with increasing frequency for treatment of leukemia, aplastic anemia, myeloma, and some forms of lymphoma and solid tumors. Although HSC transplantation is a well-established procedure, pulmonary infection and noninfectious...
pulmonary complications are common [1–3]. Noninfectious pulmonary complications include pulmonary edema, engraftment syndrome, alveolar hemorrhage, drug-induced lung injury, idiopathic pneumonia, obliterative bronchiolitis, cryptogenic organizing pneumonia, pulmonary venoocclusive disease, and posttransplantation lymphoproliferative disorder [2]. Most noninfectious causes of lung injury are attributed to treatment-related toxicities and are influenced by the myeloablative conditioning regimens used before transplantation, the degree of immunosuppression, and the interaction of the graft with the host. Therefore these causes tend to occur within specific time periods after transplantation.

The aim of this pictorial essay is to review the high-resolution CT and histologic features of various noninfectious pulmonary complications following HSC transplantation. Complications are grouped according to their time of presentation relative to the day of bone marrow transplantation (BMT) into early complications (≤ 100 days of BMT) and late complications (> 100 days of BMT). Early complications can be further subdivided into those that appear in the neutropenic phase (first 30 days of transplantation) or in the early phase (30–100 days of transplantation). During the early phase, the neutrophil count is normal but the cell-mediated and humoral immunity is decreased.

**Fig. 3.—** Diffuse alveolar hemorrhage in 46-year-old woman with non-Hodgkin’s lymphoma 3 weeks after allogeneic hematopoietic stem cell transplantation.
A. High-resolution CT scan obtained at level of carina shows diffuse ground-glass opacity in addition to septal thickening (crazy paving).
B. Photomicrograph of histopathologic specimen shows that macrophages containing hemosiderin are present within alveolar spaces (arrows). (H and E, ×100)

**Fig. 4.—** Vincristine sulfate–induced interstitial pneumonitis in 63-year-old man with myeloma.
A. High-resolution CT scan obtained at level of carina shows diffuse ground-glass attenuation in right lung and bilateral patchy areas of consolidation.
B. Photomicrograph of histopathologic section shows patchy expansion of interstitium by lymphocytic infiltrate, mild interstitial fibrosis, and reactive hyperplastic type 2 pneumocytes (arrows). (H and E, ×250)
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Early Complications
Neutropenic Phase

Pulmonary edema.—Pulmonary edema is one of the earliest complications after HSC transplantation. It is usually secondary to the large volumes of fluids (infused to minimize the toxicity of conditioning regimens) and to transfusion of blood products [2]. The high-resolution CT findings include enlarged pulmonary vessels, septal lines, peribronchial cuffing, ground-glass opacities, and small pleural effusions [4, 5] (Fig. 1). The ground-glass opacities tend to involve mainly the dependent lung regions.

Engraftment syndrome.—Engraftment syndrome is a noninfectious pulmonary complication that represents a form of diffuse capillary leak associated with lung injury and pulmonary edema. The syndrome occurs most frequently after autologous HSC transplantation, being reported in 7–11% of cases [2]. It is rarely seen after allogeneic transplantation. The median time of onset is 7 days after HSC transplantation [2]. Clinically, because it occurs with other noninfectious pulmonary complications, patients are febrile and may also present with skin rashes similar to those in acute graft-versus-host disease and hypoxia. Chest radiographic findings are nonspecific and range from normal to bilateral air-space opacification, diffuse vascular redistribution, and pleural effusions (Fig. 2). On CT, engraftment syndrome usually manifests as bilateral...
Fig. 7.—Acute graft-versus-host disease in 34-year-old man with cell-mediated lympholysis 5 weeks after hematopoietic stem cell transplantation. High-resolution CT scan obtained at level of inferior pulmonary veins shows small areas of consolidation (arrow) in association with discrete right pleural effusion.

Fig. 8.—Pleuropericardial effusion in 28-year-old woman after hematopoietic stem cell transplantation. High-resolution CT scan with mediastinal window setting shows presence of bilateral pleural and small pericardial effusions.

Fig. 9.—Pulmonary cytolytic thrombi in 11-year-old boy after hematopoietic stem cell transplantation for acute lymphoblastic leukemia.

A, CT scan shows discrete peripheral pulmonary nodules suggestive of opportunistic infection (arrows).

B, Photomicrograph of histopathologic specimen shows that nodules consist primarily of hemorrhagic infarcts (asterisk). Occlusive vascular lesions are present within, adjacent to, and away from hemorrhagic infarct (arrowheads). (H and E, ×40)

C, Photomicrograph of histopathologic specimen shows that intensely basophilic, tenacious, amorphous material occludes lumen of vessels (arrows). Few intact cells recognized as leukocytes (arrowheads) are also seen (inset). (H and E, ×400) (Courtesy of Gulbahce HE, Minneapolis, MN)
ground-glass opacification, air-space consolidation distributed at the hilar or peribronchial regions, and smooth thickening of interlobular septa [4, 5].

**Diffuse alveolar hemorrhage.**—Diffuse alveolar hemorrhage is a serious complication of HSC transplantation with a reported mortality rate of approximately 70–100% [6]. The overall incidence of diffuse alveolar hemorrhage is higher after autologous (20%) than allogeneic (10%) HSC transplantation. It typically occurs as a diffuse process in the first month after transplantation, often at the time of granulocyte recovery. Although its pathogenesis is not entirely understood, predisposing risk factors include intensive pretransplantation chemotherapy and total body and thoracic irradiation [2]. The high-resolution CT findings consist of extensive bilateral ground-glass opacities with or without superimposed intralobular linear opacities (crazy paving pattern) [4, 5] (Fig. 3).

**Drug-induced lung injury.**—Drug-induced lung disease occurs in up to 10% of patients after autologous or allogeneic HSC transplantation. A wide range of histologic reaction patterns can be seen, the most common being diffuse alveolar damage, hypersensitivity reaction, nonspecific interstitial pneumonia, and organizing pneumonia [7]. The high-resolution CT manifestations are nonspecific and reflect the histologic findings. High-resolution CT findings include bilateral ground-glass attenuation, poorly defined centrilobular nodules, peribronchial or subpleural areas of consolidation, and irregular linear opacities [4, 5] (Figs. 4 and 5).

**Early Phase**

**Idiopathic pneumonia syndrome.**—Idiopathic pneumonia syndrome is defined as diffuse lung injury occurring after HSC transplantation in the absence of active lower respiratory tract infection even in the presence of nonlobar radiographic infiltrates and physiologic changes consistent with pneumonia [8]. Thus, the diagnosis of idiopathic pneumonia syndrome is one of exclusion, which requires the elimination of potential infectious agents as a cause for the patient’s respiratory status. Idiopathic pneumonia is the most common cause for diffuse radiographic abnormalities between 30 and 180 days after HSC transplantation. Clinical symptoms include dyspnea, cough, and fever. The mortality rate of idiopathic pneumonia syndrome...
remains greater than 70%, and two-thirds of all deaths are associated with progressive respiratory failure [8]. The histologic features of idiopathic pneumonia syndrome range from a primarily interstitial reaction with diffuse or focal widening of the alveolar septa and interstitial spaces by mononuclear inflammatory cells and edema to diffuse alveolar damage with intraalveolar hyaline membranes, edema, and hemorrhage. Other associated patterns, such as organizing pneumonia and vascular damage, have also been described. High-resolution CT shows air-space consolidation with a basilar predominance (Fig. 6), a pattern consistent with noncardiogenic pulmonary edema [8]. Pleural effusions may be present.

**Acute graft-versus-host disease.**—Graft-versus-host disease is an immune reaction mediated by donor T-lymphocytes that recognize the recipient’s tissue as a foreign body. It may present as acute or chronic pulmonary complication after HSC transplantation. Acute graft-versus-host disease develops in 20–75% of patients [9]. The most commonly affected tissue systems are the skin, liver, and gastrointestinal system. Pulmonary involvement is rare. The median time of onset of respiratory symptoms is 5 months (range, 1–13 months). The reported radiologic manifestations include mild perihilar or diffuse interstitial fibrosis, cysts, and lung nodules (Fig. 7).

**Pleuropericardial effusion and hepatic venoocclusive disease.**—Pleuropericardial effusion has been reported in approximately 16% of patients in the first weeks after receiving HSC transplantation [9]. The most common noninfectious cause of pleural effusion is aggressive treatment with fluids, blood, and blood-product transfusion. The effusion is usually bilateral or right-sided and rarely related to an identifiable infectious source. Hepatic venoocclusive disease, an occasional complication in allogeneic HSC transplantation recipients, is characterized by jaundice, hepatic enlargement, right upper quadrant pain, and ascites [9]. Pleural effusion has been reported in up to 50% of HSC transplantation recipients with hepatic venoocclusive disease. Patients with venoocclusive disease and pleural effusions have either no or minimal respiratory symptoms. Hepatic venoocclusive disease usually precedes the development of pleural effusion (Fig. 8).

**Pulmonary cytolytic thrombi.**—A rare early pulmonary vascular complication consisting of endothelial swelling with arteriolar, venular, and capillary thrombi has been described after allogeneic HSC transplantation with acute graft-versus-host disease [10]. Active graft-versus-host disease shortly before or at the time of pulmonary cytolytic thrombi in all

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**Fig. 12.**—Organizing pneumonia after hematopoietic stem cell transplantation in 38-year-old man. 
**A**, High-resolution CT scan obtained at level of lower lung zones shows bilateral patchy areas of consolidation in predominantly peribronchial distribution. 
**B**, Photomicrograph of histopathologic specimen shows presence of fibroblastic tissue in lumina of peribronchial alveoli (arrows). (H and E, ×100)

**Fig. 13.**—Posttransplantation lymphoproliferative disease in 54-year-old man with multiple myeloma 2 months after allogeneic hematopoietic stem cell transplantation. CT scan shows multiple enlarged axillary and mediastinal lymph nodes.
patients is indicative of the presence of alloreactive donor cells and supports a causative association. Pathologically, it is characterized by intravascular formation of basophilic thrombi frequently accompanied by pulmonary infarcts [10]. The median time of onset of pulmonary cytolytic thrombi is 2 months after transplantation, although cases have been reported as early as 2 weeks. Although its pathogenesis is unknown, pulmonary cytolytic thrombi may be a manifestation of acute graft-versus-host disease. CT findings consist of multiple pulmonary nodules (Fig. 9). The main differential diagnosis is with pulmonary infection, a much more common cause of pulmonary nodules after HSC transplantation.

**Acute radiation pneumonitis.**—Whole-body irradiation used for bone marrow transplantation does not result in radiologically visible pneumonitis. However, radiation pneumonitis is commonly seen in patients who receive localized radiation therapy for control of mediastinal lymphoma before transplantation. Risk factors for radiation injury include total dose delivered, preexisting lung disease, and concurrent treatment with agents that sensitize the lung to radiation damage. Radiation pneumonitis presents 6 weeks to 6 months after completion of radiation therapy [4, 5]. In patients who progress to a clinically evident radiation pneumonitis, the radiographic findings range from normal to mild perivascular haziness. Over time, these initial lesions may develop into alveolar infiltrates. Clinically, patients present with fever and leukocytosis, making radiation injury a clinical syndrome difficult to distinguish from infection. A characteristic CT pattern consists of sharply marginated ground-glass opacities that do not follow an anatomic border [4, 5] (Fig. 10).

**Late Complications**

**Chronic Graft-Versus-Host Disease**

Chronic graft-versus-host disease is the most common nonrelapse problem affecting long-term survivors of allogeneic HSC transplantation. Pulmonary complications include bronchiolitis obliterans and cryptogenic organizing pneumonia.

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Fig. 14.—Radiation fibrosis in 48-year-old man after radiation therapy for lymphoma. 
**A.** Chest radiograph obtained 1 year after radiation therapy shows bilateral fibrotic changes in paramediastinal lung zone (arrows).  
**B.** CT scan confirms bilateral paramediastinal fibrosis in irradiation field (arrowheads).

Fig. 15.—Mediastinal lymph node calcification in 38-year-old man after radiation therapy for lymphoma. Close-up view of CT scan shows multiple calcified retrosternal lymph nodes (arrows). Patient had undergone radiation therapy for Hodgkin’s disease 3 years previously.
Bronchiolitis Obliterans

Bronchiolitis obliterans is an obstructive pulmonary disorder that affects the small airways and has been reported to occur in 2–14% of allogeneic HSC transplantation recipients who survive more than 3 months [9]. Presenting symptoms include progressive dyspnea accompanied by persistent cough and expiratory wheeze. Pulmonary function testing shows new obstructive lung defects defined by a forced expiratory volume in 1 sec (FEV₁) of less than 80% of that predicted or a decrease of FEV₁–forced vital capacity by 10% or more in less than 1 year. Obliterative bronchiolitis is associated with high mortality rate (60%) at 3 years after HSC transplantation [9]. Histologically, there is a predominantly constrictive bronchiolitis with destruction and narrowing of the bronchiolar lumen by fibrous tissue. High-resolution CT findings include areas of decreased attenuation and vascularity (mosaic perfusion), air trapping, and bronchial dilatation (Fig. 11).

Organizing Pneumonia

Organizing pneumonia is a well-known late manifestation of chronic graft-versus-host disease, occurring in up to 10% of patients with stem cell transplantation [9]. Risk
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Factors for cryptogenic organizing pneumonia include allogeneic HSC transplantation and graft-versus-host disease. CT findings consist of patchy consolidation frequently in a subpleural or peribronchial location, ground-glass opacities, and, occasionally, centrilobular nodules (Fig. 12).

Posttransplantation Malignancies

Posttransplantation malignancies in HSC transplantation patients are seven times more common than primary cancer in the general population. Posttransplantation malignancies include solid tumors, hematologic neoplasms, and posttransplantation lymphoproliferative disorder [2]. Posttransplantation lymphoproliferative disorder represents a heterogeneous group of Epstein-Barr virus–related lymphoid tumors that occur in the setting of ineffective T-cell function because of pharmacologic immunosuppression after solid-organ transplantation and HSC transplantation [2]. Posttransplantation lymphoproliferative disorder occurs in approximately 2% of HSC transplantation patients. The CT manifestations of posttransplantation lymphoproliferative disorder usually consist of multiple pulmonary nodules or hilar and mediastinal lymphadenopathy or both (Fig. 13).

Radiation Fibrosis

Radiation fibrosis typically occurs 6 months or more after radiation therapy. The high-resolution CT findings consist of a reticular pattern with associated traction bronchiecstasis limited to the radiation portal [2, 5] (Fig. 14).

Calcification of Mediastinal Lymph Nodes and Thymic Cysts

Calcification of lymph nodes and pretracheal soft-tissue disease may be seen after radiation therapy for Hodgkin’s disease [2]. Calcification of nonenlarged nodes in Hodgkin’s disease signifies a favorable response to therapy (Fig. 15). Thymic cysts, sometimes with a thin rim of calcification, may develop as an inflammatory response after radiation therapy for Hodgkin’s disease (Fig. 16); occasionally they enlarge and simulate recurrent tumor [2].

Summary

The diagnostic approach to noninfectious pulmonary complications in the HSC transplantation recipient remains a challenge for several reasons: the current increase in both the number of HSC transplantation recipients and their length of survival, the high frequency of lung disease in these patients, and the severity of these lung diseases. A combination of the clinical information and high-resolution CT findings, which are sometimes characteristic of several entities, may help the radiologist in forming a meaningful differential diagnosis of these disorders. Familiarity with the appearance of more typical pulmonary complications should improve diagnosis and patient care.

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