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Imaging of Pneumonias and Other Thoracic Complications After Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Hematopoietic stem cell transplantation (HSCT) is used in the treatment of various oncologic and hematologic diseases. After HSCT, patients are immunocompromised and are at risk for a wide variety of infectious and noninfectious complications. CT is routinely used when pulmonary complications are suspected after HSCT. In this article, we review the CT appearance of pulmonary complications that occur in the post-transplantation period with special emphasis on opportunistic infections, many of which are life-threatening.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a procedure used in the treatment of various oncologic and hematologic diseases including hematologic malignancies, some solid organ malignancies, anemias, and congenital immunodeficiency syndromes. HSCT involves ablation of bone marrow with either high-dose chemotherapy or total body radiation therapy and transfusion of pluripotent stem cells to repopulate bone marrow and restore hematopoiesis.[1] The term HSCT is favored over bone marrow transplantation because of the different potential sources of stem cells, which include bone marrow, peripheral blood, and fetal cord blood.[2] In autologous stem cell transplantation, the patient's own stem cells are used, whereas in allogeneic stem cell transplantation, the stem cells used are typically from a human leukocyte antigen-matched donor.

The poststem cell transplantation period may be divided into 3 phases: the pre-engraftment or neutropenic phase (0-30 days), the early post-transplantation phase (30-100 days), and the late post-transplantation phase (beyond 100 days). During the pre-engraftment phase, which spans the period between stem cell transfusion and marrow engraftment and/or restoration of hematopoiesis, the immune system is severely compromised; patients are pancytopenic and severely neutropenic.[1] Although profound neutropenia resolves by the early post-transplantation phase, lymphopenia continues, resulting in continued cellular and humoral immunodeficiency.[1] Lymphocyte levels subsequently normalize although recovery of humoral immunity lags behind.[1] Immune function gradually recovers throughout the first year after transplantation.[3]

Familiarity with the time course of immune system recovery after HSCT helps in the understanding and prediction of post-transplantation complications (Fig 1). After HSCT, patients are at risk for a multitude of pulmonary complications: infectious (Table 1) and noninfectious. Chest CT is valuable in the evaluation of patients with suspected pulmonary complications. In this article, we review CT imaging of pulmonary complications that occur after HSCT with an emphasis on opportunistic infections.

Neutropenic Phase

In the neutropenic phase, patients are at severe risk for bacterial and fungal infections. The presence of a nodule around 1 cm or greater or multiple nodules of 1 cm or larger are associated with invasive fungal pneumonias.[4] These may be associated with several associated signs: the CT halo sign, reversed halo sign, hypodense sign, and the air-crescent sign, which are discussed below.[5] Fungal infections in neutropenic patients are most commonly due to *Aspergillus, Mucor*, and *Candida* species (Table 2).[6-8]

Aspergillosis

Aspergillus is found within the normal environmental flora in the soil; organisms usually enter the body after inhalation of spores. Humans are routinely exposed to *Aspergillus*, but invasive *Aspergillus* infection almost exclusively only occurs in highly immunocompromised patients. Invasive aspergillosis is a leading cause of infection-related death in patients with acute leukemia and in HSCT recipients.[9] In a review of 960 patients with invasive aspergillosis, the most frequent underlying disease was hematologic malignancy ($n = 464$,

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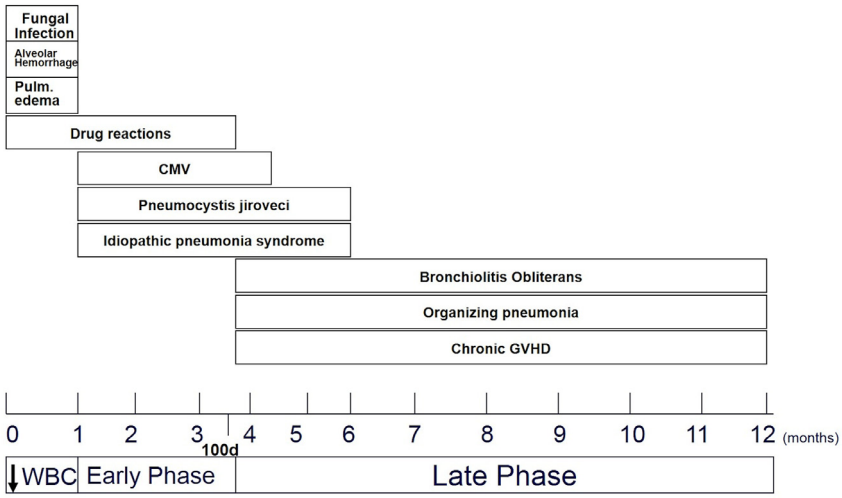

FIG 1. Graph illustrates time course of pulmonary complications after HSCT. CMV = cytomegalovirus, GVHD = graft versus host disease. Adapted from reference 3.

TABLE 1
CT findings in pulmonary infections after bone marrow transplantation

HRCT finding	Fungal	Bacterial	RSV	CMV	*P* value
Nodules					
Small (<1 cm)	38%	50%	43%	50%	>0.05
Large (≥1 cm)	62%	19%	10%	14%	<0.006
Tree-in-bud	14%	12%	10%	9%	>0.05
Ground glass opacities	10%	35%	23%	68%	>0.05
Airspace disease	52%	69%	33%	32%	>0.05
Bronchial thickening	14%	19%	37%	14%	>0.05
CT halo sign	48%	8%	10%	5%	<0.004

CMV = cytomegalovirus; RSV = respiratory syncytial virus.
Adapted from reference 4.

TABLE 2
CT patterns of disease in fungal pneumonia. Data from references 22-26

CT finding	Aspergillosis	Mucormycosis	Candidiasis
Nodules (<3 cm)	71%-84%	57%-79%	88%-95%
Tree-in-bud opacities	13%-29%	13%	5%-41%
Consolidation	29%-84%	38%-71%	50%-65%
CT halo sign	21%-37%	25%-38%	32%-33%
Cavitation	16%-17%	13%-25%	4%-6%

48.3%), with acute myelogenous leukemia being the most common diagnosis.[10] A total of 268 patients (27.9%) had received a HSCT.[10] *Aspergillus* fumigatus is the most common species to cause invasive infection.[10] Other less common but clinically important species include *Aspergillus flavus*, Aspergillus niger, and *Aspergillus terreus*.[10]

Invasive aspergillosis is characterized by tissue invasion and may be divided into angioinvasive aspergillosis (AIA) and airway-invasive aspergillosis. Angioinvasive infection is the more common of the two. The hallmark of AIA is invasion and occlusion of small to medium pulmonary arteries by fungal hyphae and subsequent hemorrhagic infarction.[6] A hemorrhagic infarct caused by invasive fungal infection characteristically manifests on CT as a nodular opacity surrounded by a halo of ground glass (CT halo sign; Fig 2A and B). Though not specific for invasive aspergillosis, the CT halo sign is strongly suggestive of AIA in neutropenic patients. It is considered an early sign of invasive aspergillosis, present in more than 90% of patients at presentation but if imaging is performed 1 week later, only a fifth of patients will still show it (Fig 3).[11,12] Lung lesions in aspergillosis usually present during the first 2 weeks of infection.[7] Direct detection of occlusion of a vessel leading to a parenchymal lesion by high-resolution multidetector CT angiography has been shown to be a potential early sign in the diagnosis of AIA and may be identified even earlier than the CT halo sign.[13] In some cases, retraction of infarcted lung with leukocyte-mediated resorption of necrotic tissue at the periphery leads to a sequestrum of dead tissue.[7] As air fills the space between retracted infarcted tissue and surrounding parenchyma, the air-crescent sign can be seen.[14] The air-crescent sign is visualized as a crescent-shaped lucency within a nodule or area of consolidation. Because the air-crescent sign is dependent on leukocyte function, it occurs during bone marrow recovery,[14] and therefore the development of this sign is thought to indicate that the infection is improving (Fig 4). The air-crescent sign is thus seen, later in the course of disease and typically not present at presentation (Fig 3).[11]

The hypodense sign, a central low attenuation region within a lung nodule or within an area of consolidation, is a supplementary tool in the diagnosis of AIA[15] (Fig 5). It has been reported in 30.2% of immunocompromised patients with AIA while it usually does not occur in immunocompromised patient with viral or bacterial pneumonia.[15] The mean time between the appearance of the first CT findings of AIA (large nodule or consolidation ± positive CT halo sign) and the hypodense sign is 7.8 days.[15]

Another sign, the reversed halo sign, when observed in immunosuppressed patients, should be considered an indication of invasive fungal infection until proven otherwise.[16,17] The reversed halo sign is a focal round ground-glass opacity surrounded by a crescent or ring of consolidation (Fig 6).[16,17] This sign is more common with mucormycosis, but can also be seen in AIA.[18]

Airway-invasive aspergillosis occurs in up to 10% of cases of invasive aspergillosis and is characterized by the invasion of airways rather than blood vessels.[6] Histologically, airway-invasive aspergillosis is characterized by the presence of organisms deep to the basement membrane of the airway.[19] Airway-invasive aspergillosis may manifest as acute tracheobronchitis, bronchiolitis, or bronchopneumonia[6] (Fig 7). CT findings are not specific and may include tracheal and bronchial wall thickening (Fig 8), centrilobular or tree-in-bud nodules, peribronchovascular consolidation, and lobar consolidation.[6,19]

Mucormycosis

Mucormycosis is a life-threatening infection caused by fungi in the order of Mucorales. *Mucoraceae* species are ubiquitous, usually found in soil and decaying matter. Among organisms responsible for causing mucormycosis, Rhizopus species are the most common followed by Mucor.[20] Based on site of disease, mucormycosis is classified into 1 of 6 forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous.[21] Pulmonary infection is the second

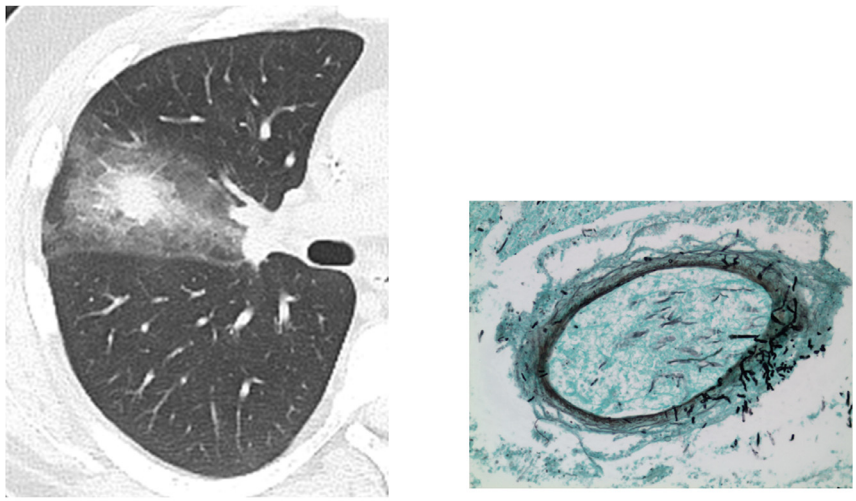

FIG 2. Angioinvasive aspergillosis in a 28-year-old man with acute myeloid leukemia (AML) and neutropenic fever. (A) CT shows the CT halo sign, a nodular opacity surrounded by a halo of ground-glass. The CT halo sign is strongly suggestive of angioinvasive aspergillosis in neutropenic patients. (B) Grocott's methenamine silver (GMS) stain in a different patient highlighting elastic fibers in the blood vessel wall as well as fungal elements, morphologically consistent with *Aspergillus* spp. Note invasion of *Aspergillus* organisms into the vessel. Color version of figure is available online.

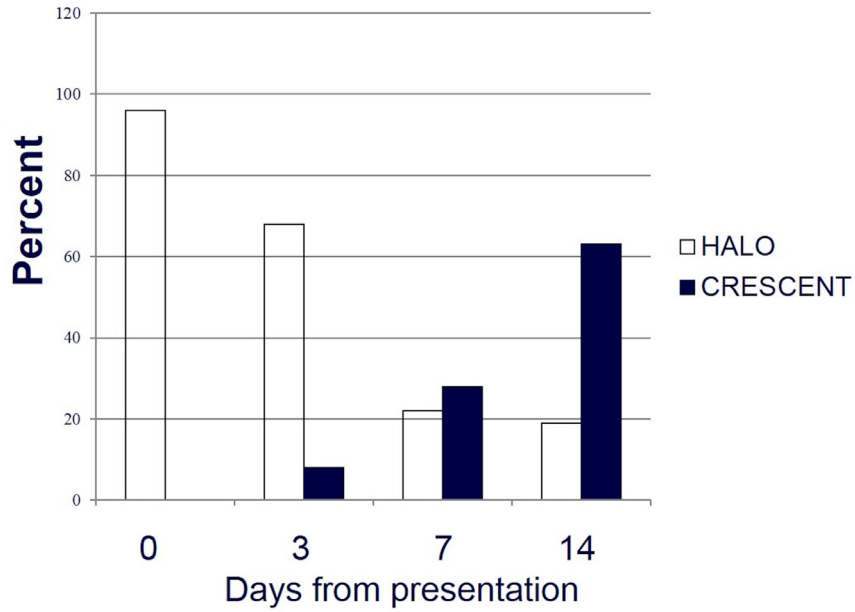

FIG 3. Graph depicting the time course of the CT halo and air-crescent signs in invasive pulmonary aspergillosis. The CT halo sign is considered an early sign, present in more than 90% of patients at presentation and gradually decreasing to about a third by day 7. The air-crescent sign is a late sign. Not typically present at presentation, it is seen in about a third of patients by day 7 and 60% of patients 2 weeks after presentation. Color version of figure is available online.

most common manifestation of mucormycosis infection (after rhinocerebral disease) and occurs after inhalation of fungal spores or via hematogenous spread from a distant focus of infection.[6] Mucormycosis infections usually occur in neutropenic patients. Patients with uncontrolled diabetes or ketoacidosis are also at risk for infection.[20] As with *Aspergillus, mucoraceae* can invade blood vessels, leading to tissue infarction and necrosis.

In a series of 32 patients with pulmonary mucormycosis, the most common radiographic manifestation was lobar or multilobar consolidation, seen in 66%.[22] Cavitary disease occurred in 41% of cases.[22] Masses, either solitary or multiple, were present in 25% and nodules, solitary or multiple, were present in 16%.[22] The air-crescent sign was seen in 13%.[22] In a review of CT findings of pulmonary mucormycosis, multiple nodules with the associated CT halo sign and less commonly central necrosis were the most common manifestation, followed by a single focus of wedge-shaped or mass-like consolidation[23] (Fig 9). The CT halo sign was seen with 78% of nodules. Other findings seen with pulmonary mucormycosis include pulmonary artery pseudoaneurysms and invasion of contiguous structures such as the chest wall, spine, aorta, pericardium, and diaphragm.[22,23]

It is important to distinguish between mucormycosis and aspergillosis since voriconazole, the preferred antifungal therapy for invasive pulmonary aspergillosis is ineffective in mucormycosis.[24] Distinguishing between the two based on CT findings alone is difficult. Features that favor mucormycosis over aspergillosis include the presence of multiple nodules (>10) and, to a lesser degree, the presence of pleural effusions.[24] Additionally, the reversed halo sign

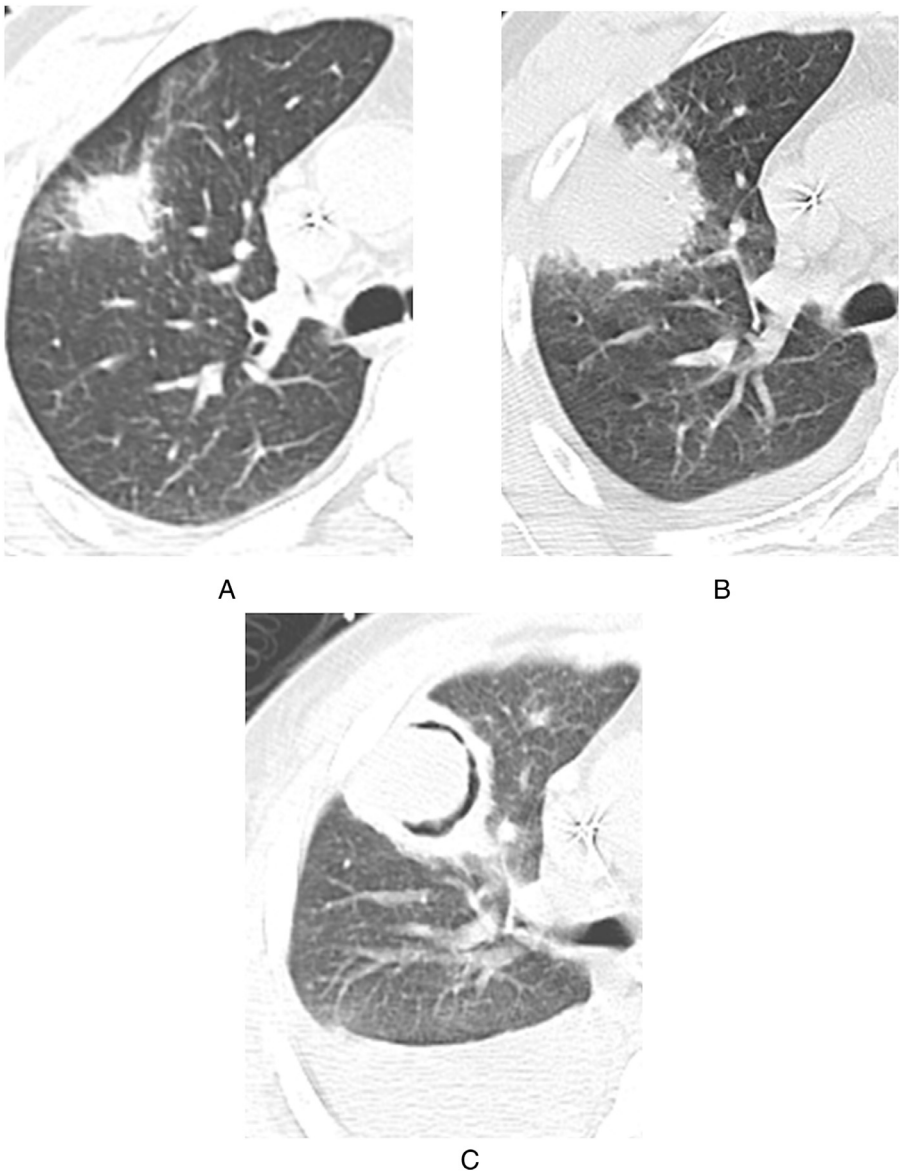

FIG 4. Evolution of angioinvasive aspergillosis. CT at presentation (A) shows a nodular opacity in the right upper lobe. Two weeks later (B), the nodular opacity has enlarged. Invasive fungal nodules in neutropenic patients may enlarge during the first 2 weeks of treatment. (C) CT done 3 weeks later (5 weeks after presentation) shows the air-crescent sign.

is more common with mucormycosis than aspergillosis.[18] Underlying diabetes mellitus or the presence of sinusitis also favors mucormycosis.[21,24]

Candidiasis

Candidiasis is caused by infection with *Candida* species, most commonly *Candida albicans. Candida*, like *Aspergillus* and *Mucoraceae*, are ubiquitous fungi. Risk factors for the development of *Candida pneumonia* include acquired immune deficiency syndrome, hematologic malignancies, chemotherapy-induced neutropenia, and HSCT.[25]

Candida are commensal organisms of mucocutaneous surfaces including mucous membranes of the respiratory and gastrointestinal tracts. *Candida* species enter the lungs via 1 of 2 methods: aspiration of contaminated oropharyngeal secretions or from hematogenous dissemination.[25-27] Owing to the mechanisms of pulmonary infection, *Candida* species may cause 2 forms of pulmonary infection—in cases of hematogenous spread, miliary and larger nodules are seen, whereas in cases of aspiration, a bronchopneumonia pattern predominates.[26]

The most common CT findings of pulmonary candidiasis in HSCT patients are multiple bilateral nodular opacities often associated with areas of consolidation (Fig 10).[25] In a review of 17 patients with pulmonary candidiasis, multiple nodules were identified in 88% of patients.[25] Nodules ranged from 3 to 30 mm were the only finding in 24% and were the predominant finding in 65%.[25] Nodules were frequently associated with other abnormalities such as ground-glass opacities, airspace consolidation, and tree in bud opacities.[25] The CT halo sign was present in 29% of all cases.[25] Airspace consolidation was present in 65% of patients and was the predominant feature in 35%.[25]

A study comparing the chest CT findings of pulmonary invasive aspergillosis and candidiasis in immunosuppressed patients showed that both groups manifested with similar findings.[26] Nodules were the most common feature in both diseases. Centrilobular nodules were more common in aspergillosis than candidiasis (96% vs 52%) while random nodules were more common in candidiasis than aspergillosis (48% vs 4%). Consolidation was more common in aspergillosis (84% vs 50%). Presence of the CT halo sign, cavitation, and ground-glass opacities was similar in both groups and was not helpful in the differentiating between them.

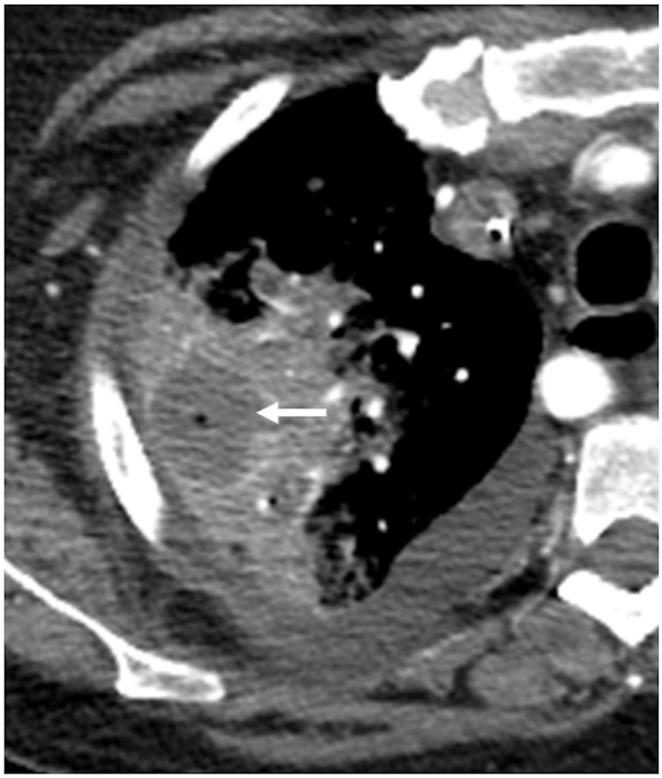

FIG 5. Hypodense sign in a 54-year-old woman with AML and neutropenic fever. CT shows mass-like consolidation in the right upper lobe with a central rounded area of low attenuation (arrow). *Aspergillus* organisms were isolated. AML = acute myeloid leukemia.

Noninfectious

Noninfectious complications that occur during the neutropenic phase include pulmonary edema, diffuse alveolar hemorrhage (DAH), drug toxicity, idiopathic pneumonia syndrome (IPS), and engraftment syndrome (periengraftment respiratory distress syndrome, aka PERDS).[2]

Pulmonary edema is the most common noninfectious complication in the first weeks after HSCT.[2] Edema can be hydrostatic or due to increased capillary permeability.[2] Imaging findings include interlobular septal thickening, ground-glass opacities, and pleural effusions (Fig 11).

DAH occurs early, with a median time to onset of 12-19 days after HSCT.[28] The pathogenesis of DAH in HSCT recipients is not well known. Imaging findings include variable degrees of ground-glass opacities and consolidation (Fig 12). Intralobular and interlobular septal thickening may be present. Pleural effusions are uncommon.[2]

Numerous drugs have been implicated as causes of pulmonary toxicity. Common cytotoxic drugs include bleomycin, busulfan, and methotrexate. Whole body irradiation, in addition to causing lung toxicity, can potentiate the effects of cytotoxic drugs. Cytotoxic drugs may cause a varied pattern of injury including increased permeability edema, hypersensitivity pneumonitis, diffuse alveolar damage, eosinophilic pneumonia, organizing pneumonia (OP), and other interstitial pneumonias.[29] CT Findings correlate with the type of injury, most commonly presenting ground-glass opacities and consolidation, with reticular opacities usually developing at a later stage.[3]

IPS is defined as an idiopathic syndrome of pneumopathy after HSCT, with widespread alveolar injury and in which infectious etiologies and cardiac dysfunction, acute renal failure, or iatrogenic fluid overload have been excluded.[28] It is a diagnosis of exclusion. Median time of onset is 19 days after HSCT.[28] Imaging findings are nonspecific and may include lobar, multilobar, or diffuse airspace or reticular opacities.[2]

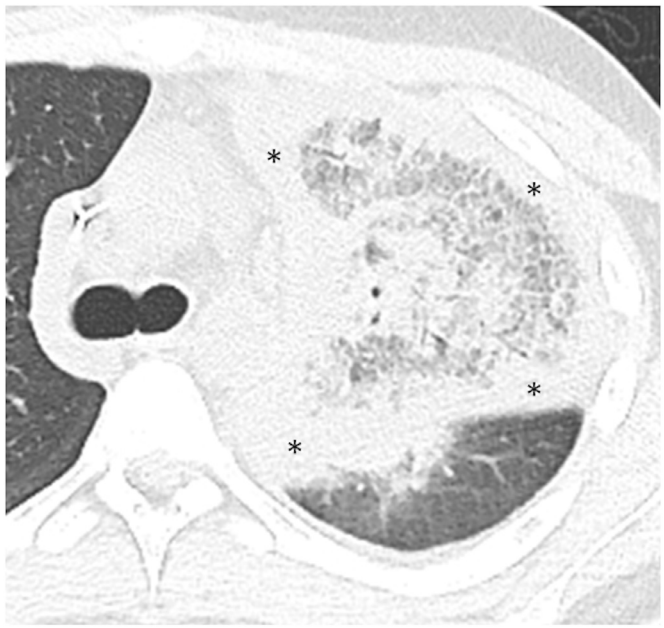

FIG 6. Reversed halo sign in an 18-year-old man with acute lymphoblastic leukemia (ALL) and neutropenic fever. CT shows ground-glass opacities surrounded by a ring of consolidation (asterisks) in the left upper lobe. Mucor organisms were isolated. The reversed halo sign is more common with mucormycosis than angioinvasive aspergillosis.

Engraftment syndrome is a subset of IPS and occurs within 5 days of engraftment, usually 7-21 days after transplantation.[2,28] CT findings may be indistinguishable from edema and hemorrhage and include ground-glass opacities, perihilar consolidation, and pleural effusions.[2]

Early Post-Transplantation Phase

In the second phase after transplantation, which extends from 30 to 100 days after transplantation, the predominant infectious risk is viral, most notably cytomegalovirus (CMV).[1,3,29] *Pneumocystis jiroveci* pneumonia (PJP) also occurs but is less frequent due to effective prophylaxis.

CMV

CMV infection is usually caused by reactivation of the latent virus during a period of immunosuppression. In transplant recipients, the most common CT findings in CMV pneumonia are small nodules (1-5 mm), parenchymal consolidation, and ground-glass opacities (Fig 13).[30] Pleural effusions are also relatively common while reticular opacities are less common. Masses or mass-like areas of consolidation are uncommon for CMV in transplant recipients but are common in AIDS patients with CMV pneumonia.[30] Diagnosis of CMV infection is based on identification of nuclear or cytoplasmic CMV inclusion bodies in BAL or lung tissue samples.

Other viral infections, including respiratory syncytial virus, influenza, parainfluenza, adenovirus, and herpes simplex virus, occur with increased prevalence in HSCT patients. The predominant abnormalities in viral pneumonias are small poorly defined nodules and bilateral patchy ground-glass opacities and airspace consolidation.[31-33]

PJP

PJP is seen primarily in patients who are unable to tolerate prophylaxis.[3] The characteristic CT abnormality in Pneumocystis pneumonia is ground-glass attenuation. Ground-glass opacities may be

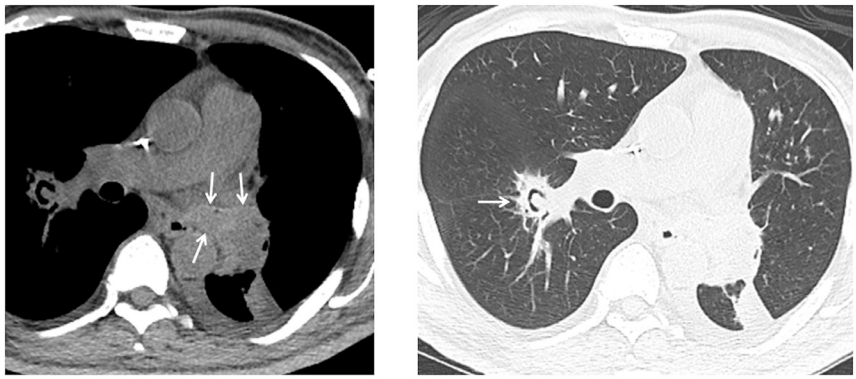

FIG 7. Airway-invasive and angioinvasive aspergillosis in a 46-year-old man with AML. (A) CT image on soft tissue windows reveals debris filling the left bronchi (arrows) consistent with airway-invasive disease. (B) CT image on lung windows shows the air-crescent sign (arrow), a sign of angioinvasive disease. AML = acute myeloid leukemia.

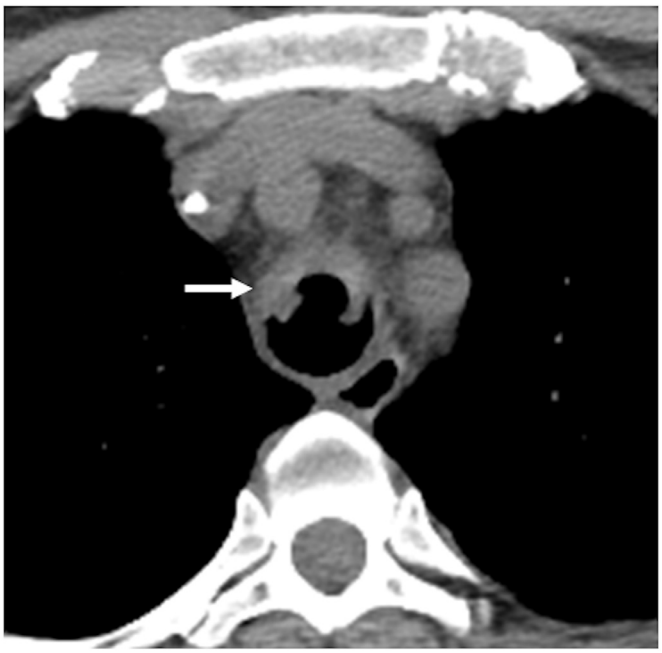

FIG 8. *Aspergillus* tracheitis in a 35-year-old woman with ALL and cough, fever, and dysphonia. CT shows tracheal wall thickening and endoluminal material (arrow). Bronchoscopy revealed severe tracheitis with destruction of cartilage and airway wall and associated pseudomembrane formation. Cultures revealed *Aspergillus* terreus.

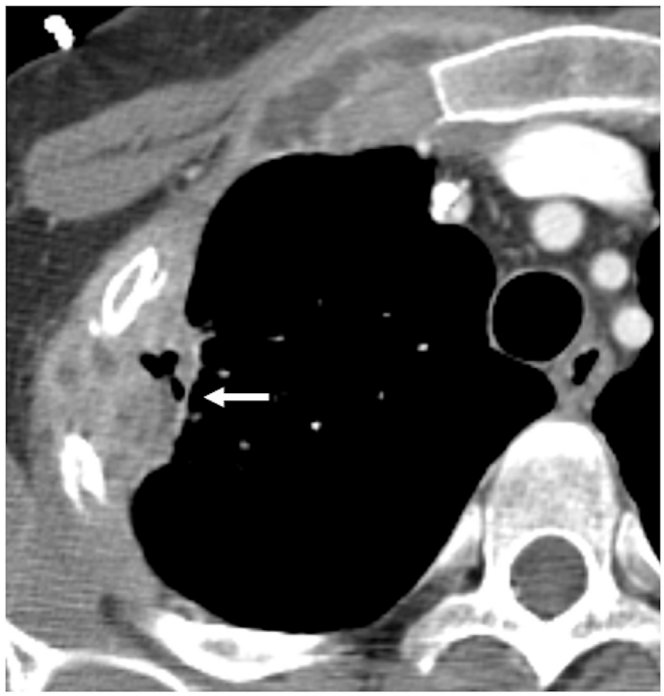

FIG 9. Pulmonary mucormycosis in a 25-year-old woman with AML. CT shows mass-like consolidation in the right upper lobe associated with chest wall invasion (arrow). AML = acute myeloid leukemia.

diffuse, perihilar predominant, or may show a mosaic pattern (Fig 14).[3]

Noninfectious

Noninfectious pulmonary complications that occur in the early post-transplant phase include IPS, acute graft versus host disease (GVHD), and acute radiation pneumonitis.[2] IPS, described above, can have a delayed onset and manifest in the early post-transplant phase.[2] GVHD represents an immune reaction of donor T lymphocytes against the host tissues; because it is a result of human leukocyte antigen disparities, it does not occur in cases of autologous HSCT.[2] The lungs are not commonly affected in acute GVHD.[2] CT findings, which include diffuse interstitial and alveolar opacities, may be indistinguishable from pulmonary edema.[2] Acute radiation pneumonitis, which may be seen in patients who have undergone radiation therapy for mediastinal lymphoma prior to undergoing HSCT, manifests as symmetric ground-glass opacities and consolidation in the paramediastinal regions.[2] It may appear 6 weeks to 6 months after radiation.

Late Post-Transplantation Phase

In the late post-transplantation phase (>100 days after HSCT), immune function has largely recovered. As a result, pulmonary complications encountered during this time period are primarily noninfectious. The most common late complication is chronic GVHD. Post-transplant lymphoproliferative disorder (PTLD) is a less common complication.

Chronic GVHD

Chronic GVHD occurs solely in allogeneic transplant recipients and its pulmonary manifestations are quite common.[2] Unlike acute GVHD, which is mediated primarily by mature donor T cells,[34] chronic GVHD is a more complex immune reaction caused by donor-

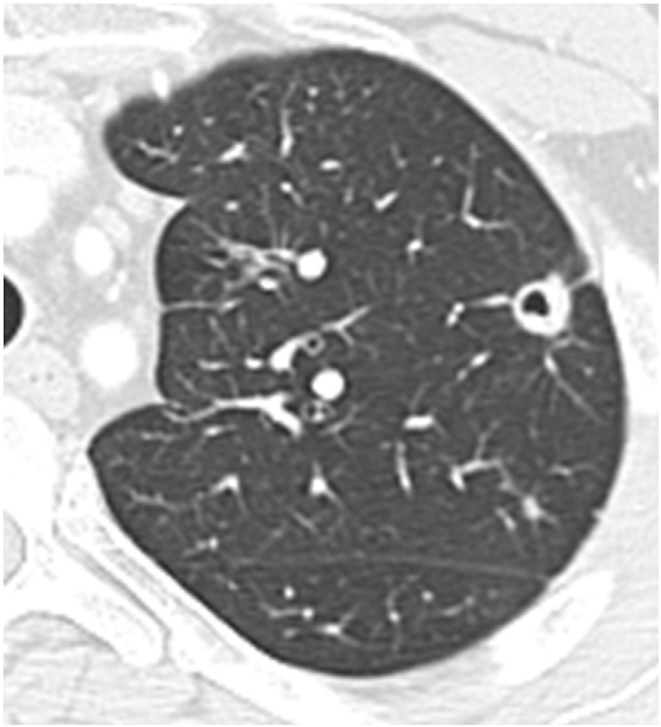

FIG 10. Pulmonary candidiasis. CT shows a cavitary nodule in the left upper lobe. Additional smaller pulmonary nodules were also present. The most common CT findings of pulmonary candidiasis in HSCT patients are multiple bilateral nodular opacities often associated with areas of consolidation.

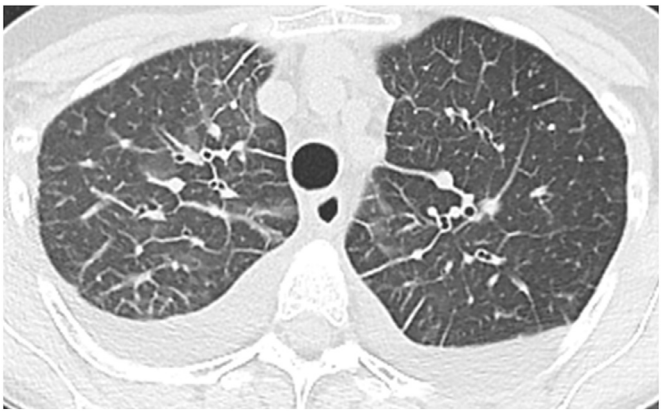

FIG 11. Interstitial pulmonary edema in a patient 10 days after HSCT. CT shows interlobular septal thickening, mild ground-glass opacities, and small pleural effusions.

derived effector T cells and B cells. Histologically this results in infiltration of the perivascular zones and alveolar septa by mononuclear cells and ongoing lymphocyte mediated injury to the large and small airways. This results in an inflammatory lymphocytic bronchiolitis, which may lead to bronchiolitis obliterans (BO) or to epithelial damage and patchy interstitial mononuclear cell infiltrate which may lead to OP.[35]

BO has an incidence of 2%-30% and most commonly occurs between 7 and 15 months after transplantation.[28] BO is characterized histologically by small airway constrictive bronchiolitis. Constrictive bronchiolitis manifests on CT with a mosaic pattern, ie, hyperlucent, hypovascular areas of lung (as a result of air-trapping) interspersed with normal lung (Fig 15). Expiratory CT imaging can confirm air-trapping.

OP is not unique to GVHD, as it is an inflammatory response of the lung to various lung insults. The incidence of OP after HSCT is much

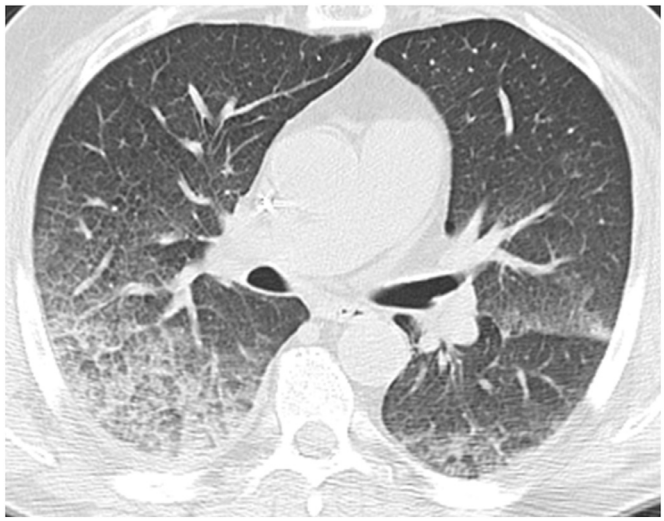

FIG 12. Diffuse alveolar hemorrhage 14 days after HSCT. CT shows bilateral ground-glass opacities, worse on the right. Bronchoalveolar lavage revealed hemorrhagic fluid and hemosiderin-laden macrophages were seen on cytologic analysis.

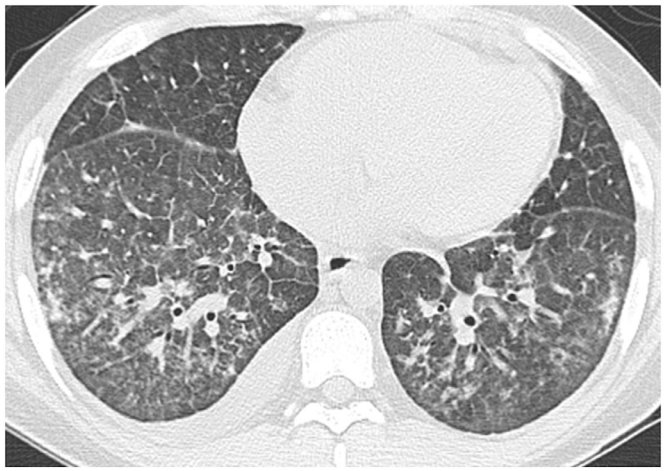

FIG 13. CMV pneumonia in an 18-year-old man with ALL who presented with fever, nausea, and vomiting 80 days post-HSCT. CT shows small nodular opacities, mild diffuse ground-glass opacities, and mild interlobular septal thickening. There is a small right pleural effusion. CMW = cytomegalovirus.

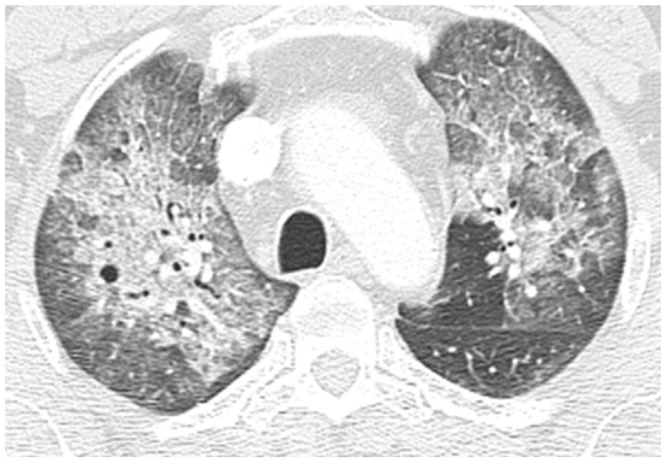

FIG 14. Pneumocystis jiroveci pneumonia in a 63-year-old man with refractory chronic lymphocytic leukemia (CLL) and neutropenic fever. CT shows diffuse ground-glass opacities. The characteristic CT abnormality in Pneumocystis pneumonia is ground-glass attenuation.

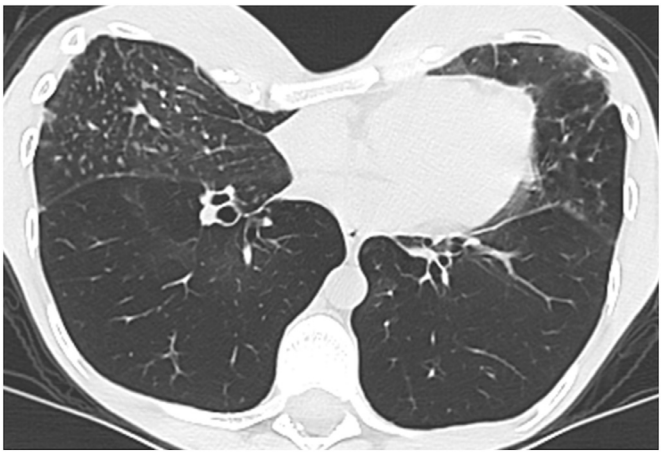

FIG 15. Bronchiolitis obliterans in a 24-year-old woman with T-cell lymphoma who developed dyspnea on exertion 2 years after allogeneic HSCT. CT shows marked lucency in the lower lobes and associated small size of the pulmonary vessels as a result of air-trapping. Centrilobular nodularity in the right middle lobe represents superimposed pneumonia. Pulmonary function tests revealed new onset airflow obstruction. Findings were consistent with bronchiolitis obliterans, a delayed manifestation of graft versus host disease of the lung.

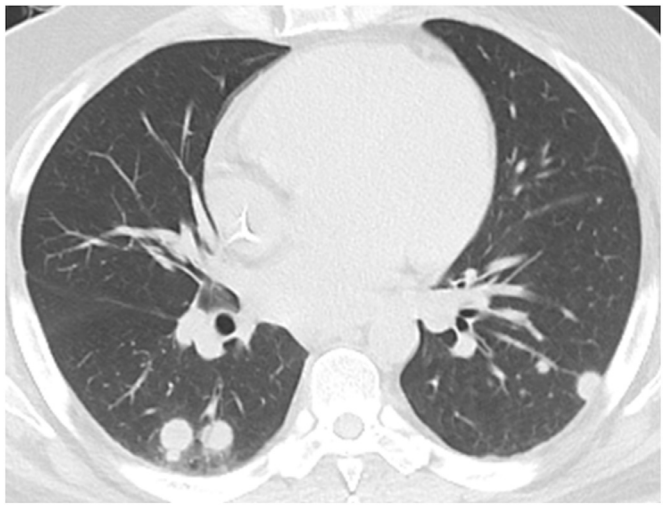

FIG 17. Post-transplant lymphoproliferative disorder. CT done 89 days after HSCT in a 44-year-old man with mycosis fungoides shows multiple bilateral pulmonary nodules. Biopsy revealed diffuse large B-cell lymphoma, EBV-positive, consistent with post-transplant lymphoproliferative disorder.

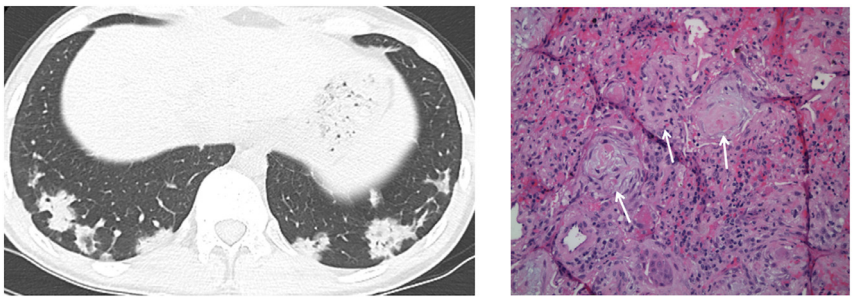

FIG 16. Organizing pneumonia. (A) CT in a 21-year-old man with ALL, 103 days post-HSCT, shows peripheral predominant consolidative opacities, proven to represent organizing pneumonia. Typical CT findings of organizing pneumonia are patchy consolidative opacities that predominate in the subpleural or peribronchovascular regions. (B) High-power photomicrograph (hematoxylin and eosin stain) from lung biopsy in a different patient shows nodular fibroblast plugs characteristic of organizing pneumonia. Color version of figure is available online.

lower than that of BO. OP has a median onset of 3 months after HSCT.[28] It is characterized histologically by plugs of granulation tissue within the distal airways and alveoli.[2] Typical CT findings are patchy consolidation that predominates in the peripheral or peribronchovascular regions (Fig 16).[36,37] The areas of consolidation frequently have well-circumscribed margins. OP may also manifest on CT with the reversed halo sign. Although the sign was first described in OP, its presence in immunosuppressed patients is highly suggestive of invasive fungal pneumonia.[17,18]

Treatment of BO and OP rely primarily on corticosteroids and other broadly immune suppressive agents.[34] As a result, the treated patients are at risk for developing superimposed infections.

PTLD

PTLD disorder is a rare but potentially fatal complication that can occur in the late post-transplantation phase after allogeneic HSCT. PTLD likely results from Epstein-Barr virus stimulation of B lymphocytes in the setting of a pharmacologically suppressed host T-cell system.[29] Abnormalities range from plasma cell hyperplasia through premalignant polymorphic B-cell proliferation to malignant monoclonal lymphoma.[38] Its incidence is 1% and the majority of PTLD cases occur within 1 year after transplantation.[39] On CT, PTLD may manifest with multiple pulmonary nodules with mediastinal and hilar lymphadenopathy (Fig 17).[40] Pleural or chest wall masses may also be seen.[38] Definitive diagnosis requires biopsy.

Conclusion

Various pulmonary complications may occur after HSCT. The differential diagnosis includes both infectious and noninfectious etiologies. Awareness of the time course after HSCT and recognition of common patterns of disease allow the differential diagnosis to be narrowed and, in some cases, suggest a specific diagnosis. This is of utmost importance in cases of invasive fungal infections, which can be rapidly fatal if not recognized at onset.

Supplementary materials

Supplementary data associated with this article can be found in the online version at doi:10.1067/j.cpradiol.2018.07.006.

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