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PICTORIAL ESSAY

High-resolution computed tomography of chest complications in patients treated with hematopoietic stem cell transplantation

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Abstract Hematopoietic stem cell transplantation (HSCT) has become a standard method for treating patients with hematological malignancies. Preconditioning chemotherapeutic drugs, total body irradiation (TBI), or chronic graft-versus-host disease (GVHD) can cause several chest complications after HSCT. Because immunosuppression is marked after HSCT, it takes at least 1 year for the immune system to recover completely. Therefore, several infectious and noninfectious complications may occur within the year after HSCT. HSCT-specific complications occur in a characteristic temporal sequence associated with the period following HSCT. During the neutropenic phase, bacterial pneumonia, fungal infection, pulmonary edema, and diffuse alveolar hemorrhage may occur. During the early phase, pneumocystis pneumonia, cytomegalovirus pneumonia, engraftment syndrome, and idiopathic pneumonia syndrome are the common complications. During the late phase, constrictive bronchiolitis and organizing pneumonia may occur probably associated with chronic GVHD. Although high-resolution CT findings lack specificity, the frequency and likelihood of occurrence of certain complications in certain phases and sometimes characteristic features (such as a CT halo sign for fungal infection) facilitate early detection of a life-threatening complication.

Key words Hematopoietic stem cell transplantation · Chest complication · High-resolution computed tomography · Graft-versus-host disease

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Introduction

Hematopoietic stem cell transplantation (HSCT), including bone marrow transplantation, peripheral blood stem cell transplantation, and cord blood stem cell transplantation, is composed of intensive myeloablative chemotherapy, total body irradiation (TBI) to eradicate malignant cells, and infusion of the donor's hematopoietic stem cells to compensate for the hematopoiesis. Preconditioning chemotherapeutic drugs, radiation effects, and a graft-versus-host disease (GVHD) can cause several chest complications after HSCT. HSCT includes autologous transplantation, which uses hematopoietic stem cells of the patient, and allogeneic transplantation, which uses cells from a human leukocyte antigen-consistent donor. With allogeneic transplantation, GVHD may occur because donor T lymphocytes attack the organs of the recipient by recognizing the organs of the patient as a foreign body. In contrast, GVHD basically does not occur in patients with autologous transplantation. Therefore, chest complications occur less frequently with autologous transplantations than with allogeneic ones.

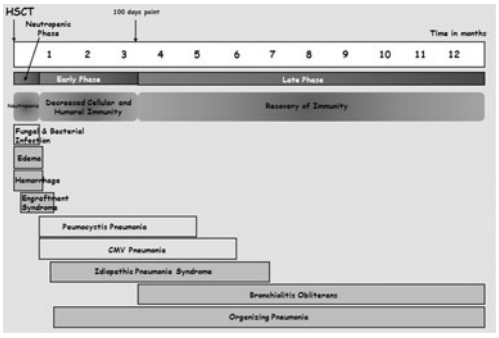

Fig. 1. Time that chest complications occurred after hematopoietic stem cell transplantation (HSCT). Pulmonary complications often occur in a characteristic temporal sequence

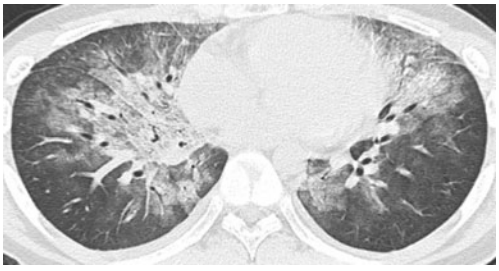

Fig. 2. A 16-year-old boy with bacterial pneumonia. HRCT image shows extensive ground-glass opacity (GGO) in the bilateral lungs, which resembles pulmonary edema. The absence of cardiomegaly or enlargement of pulmonary veins might be the differential points from pulmonary edema. This feature is rarely seen in immunocompetent patients

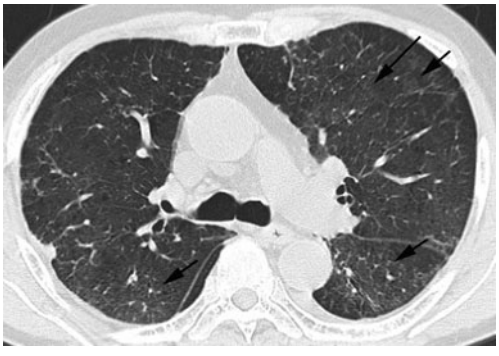

Fig. 3. A 74-year-old man had bacterial pneumonia. HRCT image shows minimal GGO (*arrows*) in the bilateral lungs. This tiny feature is probably caused by a minimal exudative reaction in patients with neutropenia

Although pulmonary complications caused by acute GVHD are rare,[1] those associated with chronic GVHD are relatively common, such as constrictive bronchiolitis and organizing pneumonia.

Immunosuppression is marked after HSCT, and it takes a long time for the immune system to recover completely. It takes 2–4 weeks for neutrophils to recover and a couple of months for lymphocytes to recover. It has been reported to take 6–12 months for cellular and humoral immunity to recover completely.[2] HSCT-specific complications occur in a characteristic temporal sequence associated with the period following HSCT[3] and the immune status of patients (Fig. 1).

Complications during the neutropenic phase (2–3 weeks after HSCT)

Noninfectious disease accounts for more than 50% of all complications.[2,4] Pulmonary edema and diffuse alveolar hemorrhage are especially common. Although any infectious disease may occur, bacterial pneumonia and fungal infections are more likely. Invasive aspergillosis is a particularly life-threatening entity during this phase.[2]

Bacterial pneumonia

Gram-negative and Gram-positive organisms presumably from the gastrointestinal tract or oral mucosa are the predominant causative bacteria for pneumonia. The frequent high-resolution computed tomography (HRCT) finding of bacterial pneumonia includes airspace consolidation or extensive ground-glass opacity (GGO) (Fig. 2) with centrilobular opacities. Tiny findings with minimal GGO may be seen due to diminution of the inflammatory change in the immunocompromised host caused by neutropenia and minimal exudative reaction (Fig. 3).[5]

Fungal infection

The most common pathogen in fungal infections is *Aspergillus*. Invasive pulmonary aspergillosis (IPA) includes angioinvasive and airway-invasive aspergillosis (angio-IPA, airway-IPA). Angio-IPA shows two characteristic CT findings: CT halo and the air crescent sign (Fig. 4). CT-halo sign, which is an early sign after infection, represents a hemorrhagic infarction in which the nodule corresponds to a necrotic center, and the GGO to hemorrhage is now regarded as a nonspecific finding.[6] The air crescent sign is observed 2–3 weeks after infection at the period when neutropenia has recovered and represents the cavitation of nodules. This sign is associated with a good prognosis.[7] Pathological and CT findings of airway-IPA correspond to bronchiolitis and bronchopneumonia (Fig. 5).

Pulmonary edema

Cardiac or renal dysfunction, increased capillary hydrostatic pressure, and increased capillary permeability due

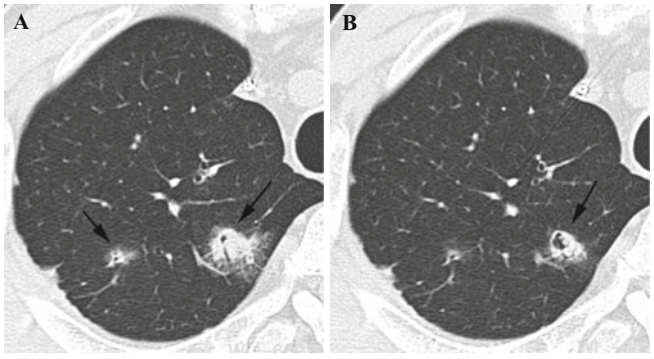

Fig. 4. A 51-year-old man had angioinvasive pulmonary aspergillosis (angio-IPA). **A** HRCT image shows multiple nodules with a halo of GGO (*arrows*) in the right lung field, with a typical CT halo sign. **B** HRCT image obtained 2 weeks later shows a cavitary nodule (*arrow*) in the right upper lobe, which corresponds to the nodule with the CT halo sign in **A**

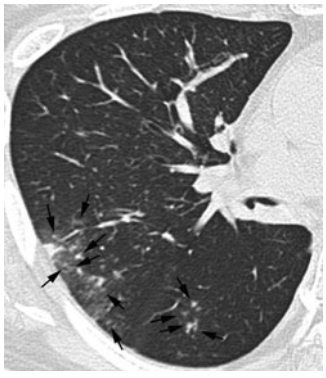

Fig. 5. A 32-year-old woman had airway-invasive pulmonary aspergillosis (airway-IPA). HRCT image shows multiple small nodules with a centrilobular distribution (*arrows*), indicating endobronchial spread of the lesions

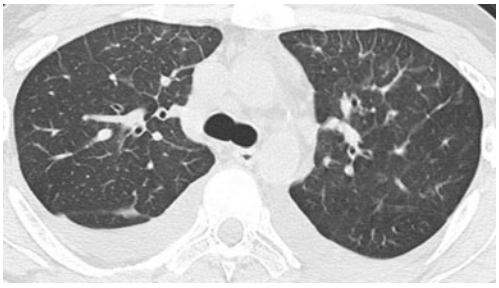

Fig. 6. An 18-year-old man had pulmonary edema. HRCT image shows enlarged pulmonary vessels, marked interlobular septal thickening, and bilateral pleural effusion, which indicates interstitial pulmonary edema

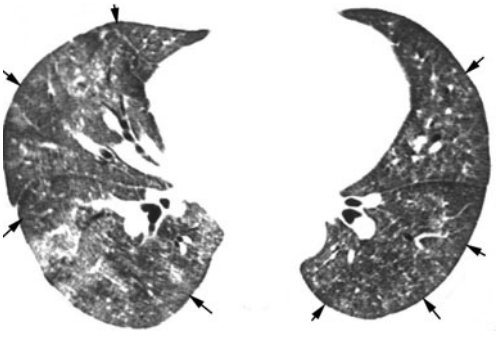

Fig. 7. A 37-year-old woman had diffuse alveolar hemorrhage. HRCT image shows bilateral, extensive GGO with subpleural sparing (*arrows*). Note that centrilobular opacities are also seen in the bilateral lungs. A combination of GGO and nodules may make it difficult to differentiate diffuse alveolar hemorrhage from cytomegalovirus (CMV) pneumonia. The diagnosis of diffuse alveolar hemorrhage was confirmed by bronchoalveolar lavage

to intensive chemotherapy and TBI may result in pulmonary edema.[1,8] The frequent HRCT findings are indistinguishable from those of any other etiology and include enlarged pulmonary vessels, interlobular septal thickening, and GGO involving mainly the peribronchovascular, central, or dependent lung regions (Fig. 6).[3]

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage occurs more often in autologous HSCT recipients than in allogeneic HSCT recipients and is usually associated with a high mortality rate (70%–100%).[8] The reported frequency of this entity varies and has been reported as approximately 5% in a study with a large number of patients.[9] The risk factors of this entity have been noted as microangiopathy due to conditioning chemotherapy and TBI, neutrophil infiltration during the granulocyte recovery phase, and GVHD.[3] HRCT findings consist of extensive bilateral GGO with or without intralobular reticulation (crazy-paving pattern), subpleural sparing and centrilobular opacities, which show perivascular accentuation of hemorrhage (Fig. 7).[3]

Complications during the early phase (2–3 weeks and 100 days after HSCT)

During the early phase, the neutrophil count returns to normal, but the cell-mediated and humoral immunity is still impaired. It is important to consider *Pneumocystis jiroveci* pneumonia (PCP) and cytomegalovirus (CMV) pneumonia as infectious complications, with engraftment syndrome and idiopathic pneumonia syndrome as noninfectious complications.

Pneumocystis jiroveci pneumonia

Characteristic pathological findings include intraalveolar macrophages or a mixture of inflammatory infiltrates

(Fig. 8A). As chest radiography may be normal at the time of the initial examination, HRCT is needed for early detection of PCP. On HRCT, widespread GGO, distributed typically at the perihilar regions, is a frequent and characteristic finding (Figs. 8B, 9).[8,10] Extensive GGO is usually observed with sparing of adjacent secondary pulmonary lobules (geographic or mosaic pattern) (Figs. 8B, 9).[3,10] Centrilobular opacities are rarely seen.

Cytomegalovirus pneumonia

Cytomegalovirus infection occurs in 70% of recipients, approximately one-third of whom develop CMV pneumonia.[3] The characteristic HRCT findings of CMV pneumonia include patchy or widespread GGO, airspace consolidation, and centrilobular or randomly distributed nodules (Figs. 10, 11).[11,12] Nodules with the CT halo sign are sometimes observed and correspond to the hemorrhagic nodules.[3,6] Lesions tend to be distributed in the lower zone (Fig. 10B).

Engraftment syndrome

Engraftment syndrome shows capillary leakage that results in interstitial pulmonary edema. Patients usually complain of fever and skin rashes. Engraftment syndrome usually occurs around 7 days after HSCT at the time of neutrophil engraftment and is associated with overproduction of cytokines. It occurs most frequently after autologous HSCT in 7%–11% of recipients. HRCT findings are similar to those of interstitial pulmonary edema (Fig. 12).[8]

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) is defined as diffuse lung injury occurring after HSCT in the absence of active lower respiratory tract infection or other noninfectious causes.[13] IPS has been reported to occur in 5%–25% of allogeneic HSCT recipients.[14] The cause of

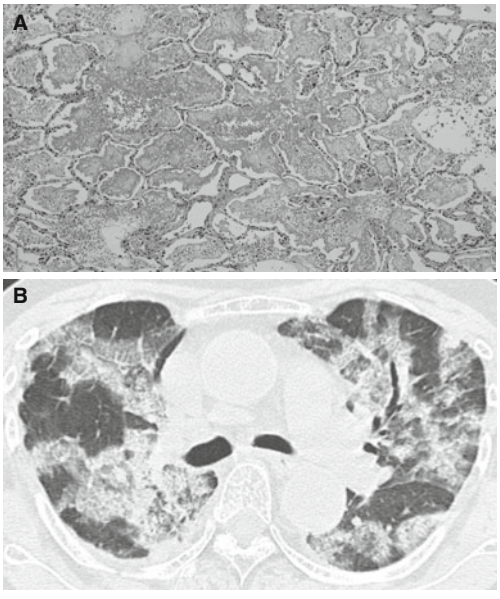

Fig. 8. A 55-year-old woman had *Pneumocystis jiroveci* pneumonia. **A** Pathological specimen obtained at autopsy shows foamy intraalveolar exudates in the alveoli and minimal thickening of alveolar walls. **B** HRCT image shows extensive GGO with a characteristic mosaic pattern in the bilateral lungs. Note that reticular opacities can be seen within GGO (crazy-paving pattern)

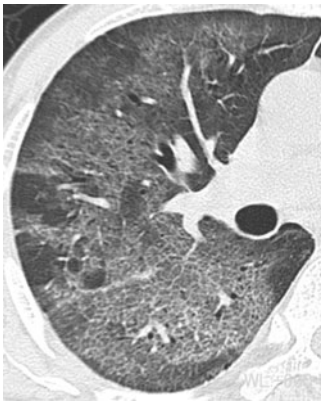

Fig. 9. A 45-year-old man had *Pneumocystis jiroveci* pneumonia. HRCT image shows bilateral GGO with sparing of adjacent secondary lobules, showing a mosaic pattern. Note that the crazy-paving pattern is also seen

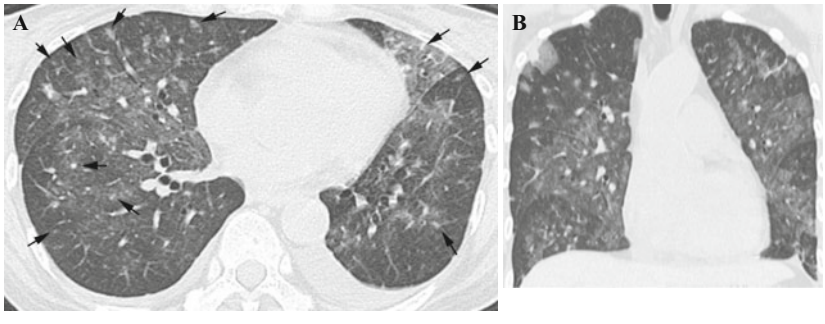

Fig. 10. A 48-year-old woman had CMV pneumonia. **A** HRCT image shows multiple nodules with or without the halo sign (*arrows*) superimposed on extensive GGO. **B** Thin-section coronal image shows the distribution of lesions in relatively inner and lower zones

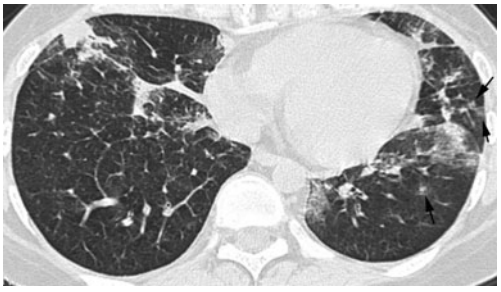

Fig. 11. A 27-year-old woman had CMV pneumonia. HRCT image shows airspace consolidation, GGO, and multiple nodules with the halo sign (*arrows*) in bilateral lung fields. This combination—consolidation, GGO, nodules—is a characteristic finding of CMV pneumonia

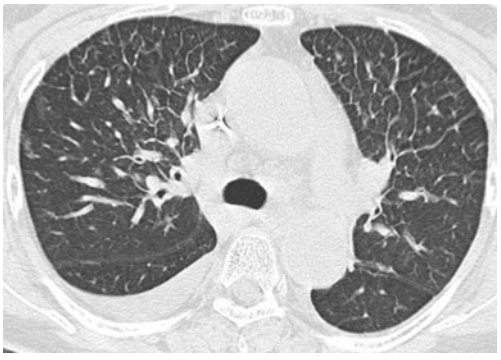

Fig. 12. A 52-year-old woman had engraftment syndrome. HRCT image shows smooth thickening of interlobular septa distributed extensively in the bilateral lungs. Note that enlargement of pulmonary vessels is not so evident, which is the point differentiating it from cardiogenic pulmonary edema. However, it is slightly difficult to differentiate this finding from that of pulmonary edema (shown in Fig. 6)

IPS has been speculated to be preconditioning chemotherapy, TBI, or GVHD.[14] The mortality rate remains >70%. The main histological pattern includes diffuse alveolar damage and lymphocytic bronchitis/bronchiolitis with cellular interstitial pneumonia[15] (Fig. 13A). A frequent HRCT finding is airspace consolidation or GGO in the bilateral lungs with basilar or dorsal predominance (Figs. 13B, 14).

Complications during the late phase (100 days to 1 year after HSCT)

During the late phase, noninfectious complications, including organizing pneumonia (OP) and constrictive bronchiolitis, occur more frequently than infectious diseases because the immune status of HSCT recipients has usually recovered. It is estimated that OP and constrictive bronchiolitis are caused by chronic GVHD.

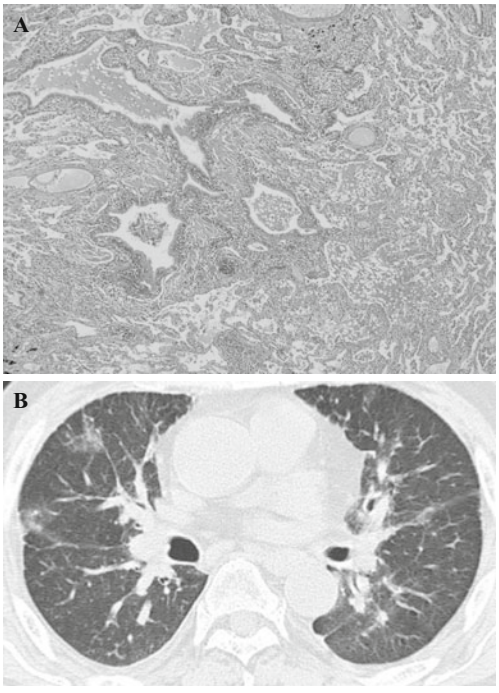

Fig. 13. A 55-year-old man had idiopathic pneumonia syndrome. **A** Pathological specimen from a surgical lung biopsy shows marked lymphocytic infiltration into the alveoli and alveolar septa, which corresponds to cellular interstitial pneumonia. It also shows lymphocytic infiltration around the bronchial wall, which corresponds to lymphocytic bronchiolitis. This feature seems to correspond to the lymphocytic bronchitis/bronchiolitis with cellular interstitial pneumonia described by Yousem.[15] **B** HRCT image shows patchy GGO distributed in the subpleural area or along the bronchus

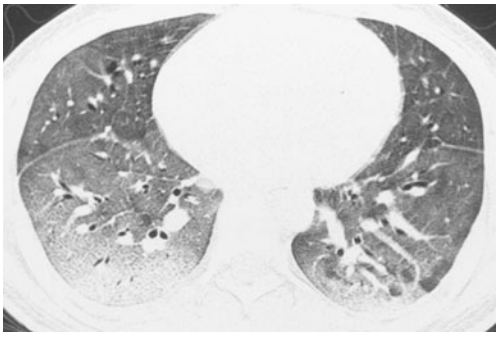

Fig. 14. A 27-year-old man had idiopathic pneumonia syndrome. HRCT image shows extensive GGO with predominance in the dorsal lung area, which is almost identical to the HRCT findings of acute respiratory distress syndrome or acute interstitial pneumonia. This patient was diagnosed as having idiopathic pneumonia syndrome (IPS) because of the negative findings for other infectious or noninfectious causes confirmed by bronchoalveolar lavage

Constrictive bronchiolitis

Constrictive bronchiolitis is a chronic inflammatory and fibroproliferative process centered on the terminal and

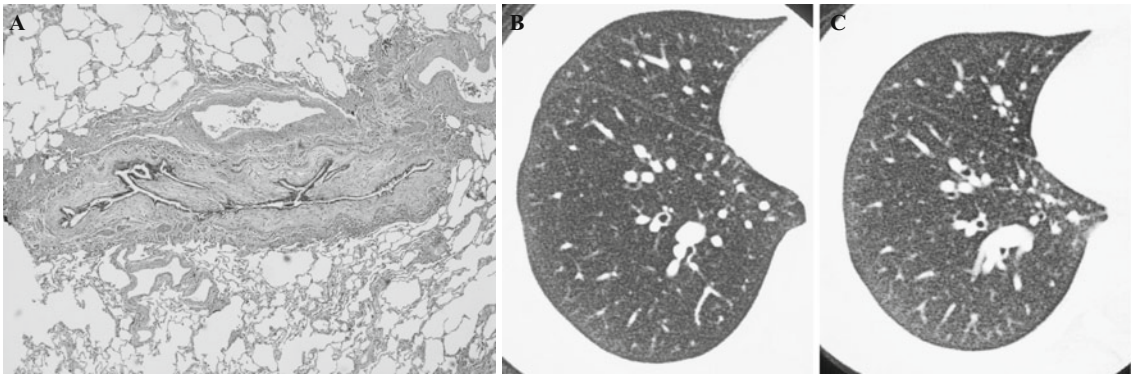

Fig. 15. A 30-year-old woman had constrictive bronchiolitis. **A** Pathological specimen obtained by surgical lung biopsy shows concentric narrowing of the bronchiolar lumen by submucosal fibrosis. **B**, **C** HRCT images show little increase in lung attenuation from inspiratory (**B**) to expiratory (**C**) status, which shows the existence of air trapping

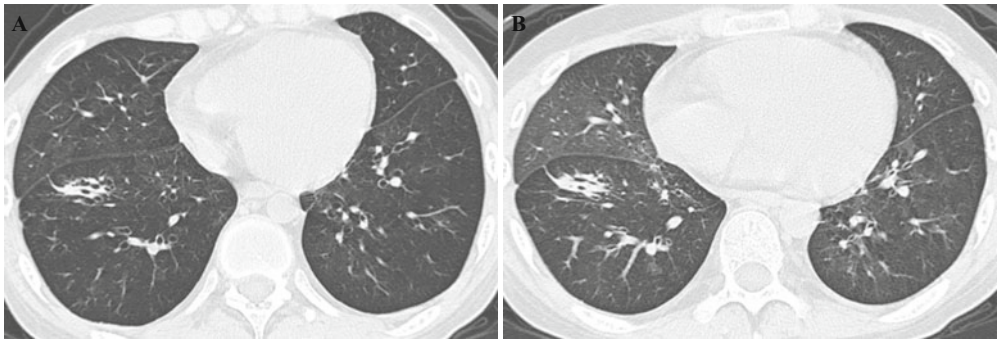

Fig. 16. A 21-year-old man had constrictive bronchiolitis. HRCT images show the existence of air trapping from inspiratory (**A**) to expiratory (**B**) status. Also note the existence of a mosaic pattern in the bilateral lungs and slight dilatation of bronchi during inspiration (**A**)

respiratory bronchioles, leading to stenosis or scarring of the bronchioles (Fig. 15).[3,4] The incidence of this entity has been reported as 2%–14% in allogeneic recipients who survive more than 3 months. The causes of constrictive bronchiolitis remain unclear. The entity is associated with a high mortality rate; therefore, early detection and appropriate immunosuppressive therapy are essential. Characteristic HRCT findings include the mosaic pattern of lung attenuation, bronchial dilatation, and the existence of air trapping on expiratory CT[1] (Fig. 16).

Organizing pneumonia

Organizing pneumonia occurs in up to 10% of HSCT recipients and usually appears 1–13 months after HSCT. Pathologically, OP is characterized by edematous granulation tissue polyps in the lumen of alveolar ducts and bronchioles in association with a variable degree of interstitial inflammation and fibrosis (Fig. 17A). On HRCT, airspace consolidation along the bronchovascular bundle or in the subpleural area is a frequent finding. However, GGO tends to be more frequently and independently observed in immunocompromised patients (Figs. 17B, 18).[2,3]

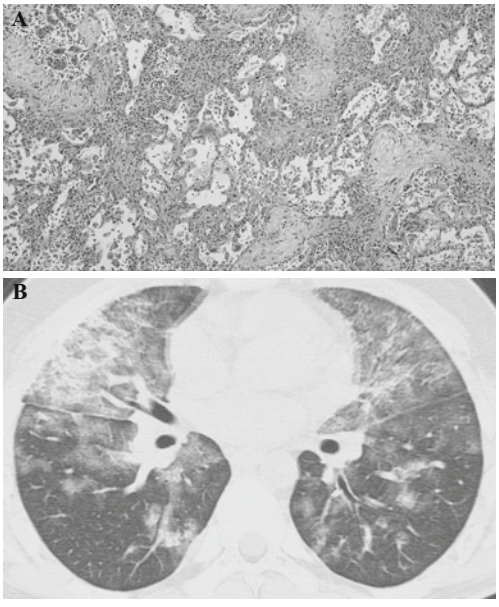

Fig. 17. A 16-year-old boy had organizing pneumonia (OP). **A** Pathological specimen from a surgical lung biopsy shows edematous granulation tissue polyps in the alveolar and bronchiolar lumens with minimal thickening of the alveolar wall. **B** HRCT image shows extensive GGO and minimal airspace consolidation in the bilateral lungs. GGO tends to be more frequently and independently observed in immunocompromised patients with OP

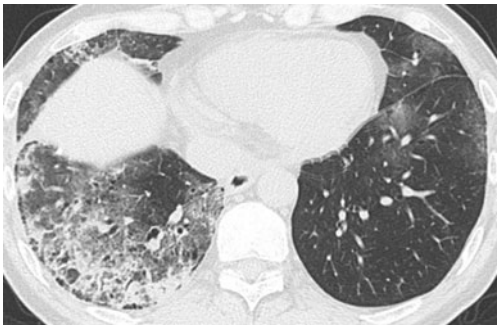

Fig. 18. A 51-year-old man had organizing pneumonia. HRCT image shows a mixture of GGO and airspace consolidation in the bilateral lungs

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