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# Graft-Versus-Host Disease of the Lung after Allogeneic Hematopoietic Stem Cell Transplantation
## - A Report of Two Cases -

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Herein, we describe cases of pulmonary acute graft-versus-host disease (aGVHD) in two patients occurring after allogeneic hematopoietic stem cell transplantation (HSCT) due to precursor B-cell acute lymphoblastic leukemia in a 6-year-old patient and in acute myeloid leukemia in a 14-year-old boy. In both cases, chest CT revealed confluent ground-glass attenuation along the bronchovascular bundles, as well as some bronchial dilatation. Microscopically, in both cases we noted a characteristic bronchiolocentric pattern and bronchiolar epithelial changes, which included denudation of the bronchiolar epithelium, regenerating atypical cells, and wall thickening with subepithelial or transmural fibroblast proliferation, along with some lymphocytic infiltration. One patient died on day 86 after allogeneic HSCT due to sudden acute respiratory distress syndrome, and the other patient currently remains alive without active aGVHD. The authors' experiences in these two cases demonstrate that intense awareness of the pathologic findings of GVHD is mandatory after allogeneic HSCT.

**Key Words :** Graft-versus-host disease; Hematopoietic stem cell transplantation; Leukemia; Lung

Pulmonary complications occur in approximately 40 to 60% of patients after allogeneic hematopoietic stem cell transplantation (HSCT).[1,2] However, the widespread use of infection prophylaxis has substantially reduced the rates of infectious complications, and noninfectious complications are currently the principal pulmonary cause of morbidity and mortality in patients after HSCT.[3] Acute graft-versus-host disease (aGVHD) is a well-recognized life-threatening complication occurring after HSCT, and is independently associated with an increased incidence of post-HSCT alveolar hemorrhage.[4] The acute, noninfectious, and diffuse lung injury that occurs within the first 120 days after allogeneic HSCT is referred to as idiopathic pneumonia syndrome (IPS),[5] and GVHD may be an underlying cause of this condition.[6]

GVHD may be either acute or chronic; aGVHD accounts for two-thirds of GVHD patients, whereas cGVHD accounts for the remainder.[7] The organ systems affected predominantly by GVHD are the skin, liver, gastrointestinal tract, and lung.[8-12] Histologic findings of aGVHD in the skin, liver, and gastrointestinal tract have been relatively well-described, but this is not the case for the lung. Additionally, no report has yet been published detailing the histologic findings of GVHD in the bronchus and bronchiole of the lung following alllogeneic HSCT. Here, we report cases of pulmonary aGVHD in two patients after allogeneic HSCT, owing to precursor B-cell acute lymphoblastic leukemia (ALL) in a 6-year-old boy, and to acute myeloid leukemia (AML) in a 14-year-old boy.

## CASE REPORTS

### Case 1

A 6-year-old boy evidenced tachypnea during supportive management after the second allogeneic HSCT, which was performed 26 days previously for the treatment of second relapsed precursor B-cell ALL. He had been diagnosed 33 months previously with ALL. Chest CT revealed confluent ground-glass attenuation along the bronchovascular bundles and some bron-

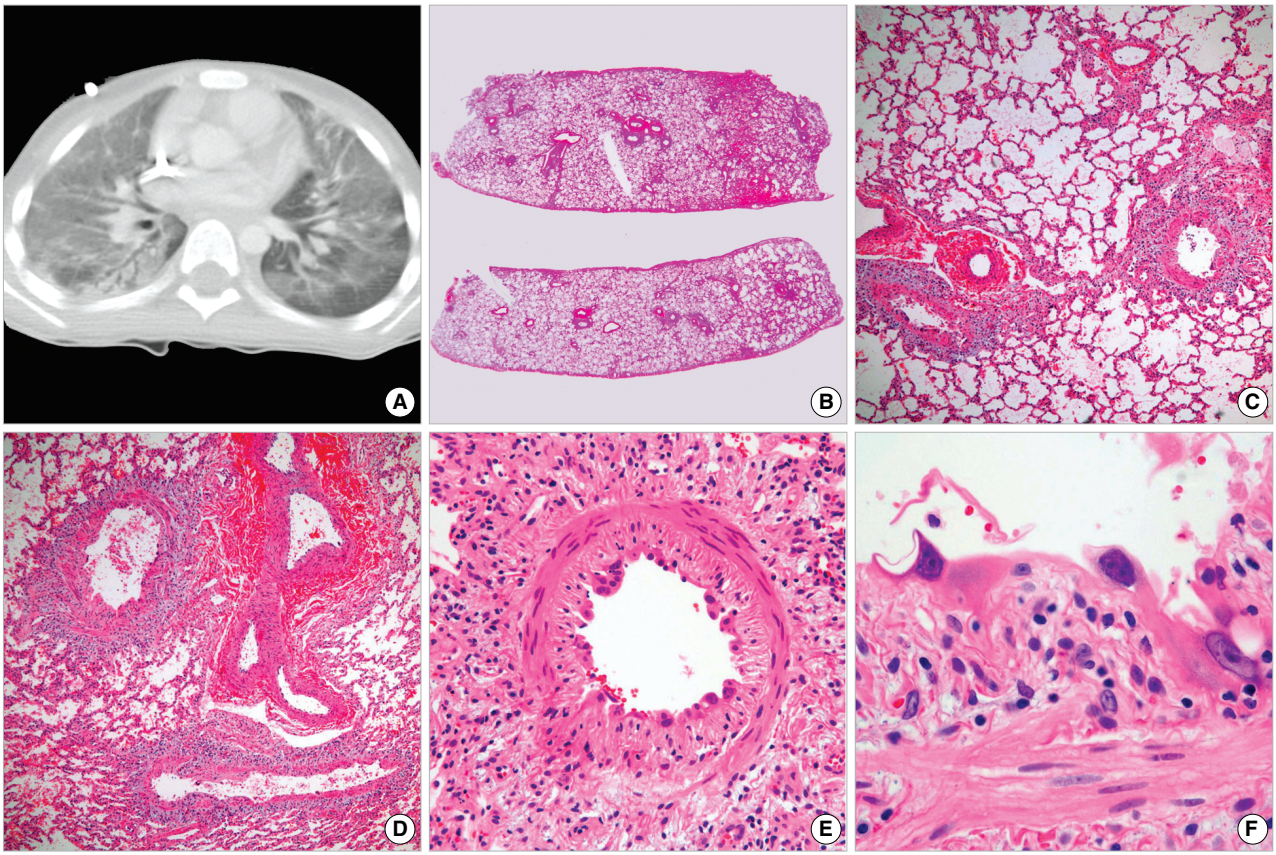


Fig. 1. (A) Chest CT image showing bilateral increased interstitial marking and confluent ground-glass opacity along bronchovascular bundles with focal patchy consolidation. (B) A bronchiolocentric lesion in scanning power view. (C) to (E) Bronchial wall thickening due to fibroblast proliferation with lymphocytic infiltration. (F) Denudated bronchiolar epithelium with regenerating atypical epithelial cells.

chial dilatation with focal patchy consolidation (Fig. 1A). A video-associated thoracostomy (VAT) resection of the right lower lobe of the lung was performed on day 28 after allogeneic HSCT.

The pathologic finding was of a bronchiolocentric lesion under scanning power view (Fig. 1B). Furthermore, bronchial wall thickening owing to fibroblast proliferation with lymphocytic infiltration (Fig. 1C-E), and denuded bronchiolar epithelium with regenerating atypical epithelial cells were also identified (Fig. 1F). Immunohistochemical staining for cytomegalovirus was negative. A palm skin rash was detected on day 7, diarrhea and fever occurred on day 11, and a trunk skin rash was noted on day 28 after allogeneic HSCT. Unfortunately, the patient died on day 86 after allogeneic HSCT as the result of sudden acute respiratory distress syndrome.

### Case 2

A 14-year-old boy visited the emergency room due to aggravating dyspnea that had persisted for 1 week. He was diagnosed with AML 14 months previously, and a second allogeneic HSCT was performed 105 days previously as the result of relapsed AML. A chest CT showed bilateral ground-glass opacity along the bronchovascular bundles with bronchial dilatation (Fig. 2A, B). VAT resection of the right lower lobe of the lung was performed.

Histologically, an airway-centered lesion was observed under scanning power view (Fig. 2C). Additionally, there was an epithelial sloughing or total epithelial loss in the bronchioles associated with subepithelial fibroblast proliferation (Fig. 2E-F), and diffuse interstitial widening due to lymphocytic infiltration and intraalveolar macrophages were observed with several foci of loose myxoid tissue (Fig. 2D). Immunohistochemical staining for cytomegalovirus was also negative. After immunosuppressive therapy, the patient's dyspnea was improved, and a third allogeneic HSCT was performed.

## DISCUSSION

GVHD is a mediated discrepancy in the match between the

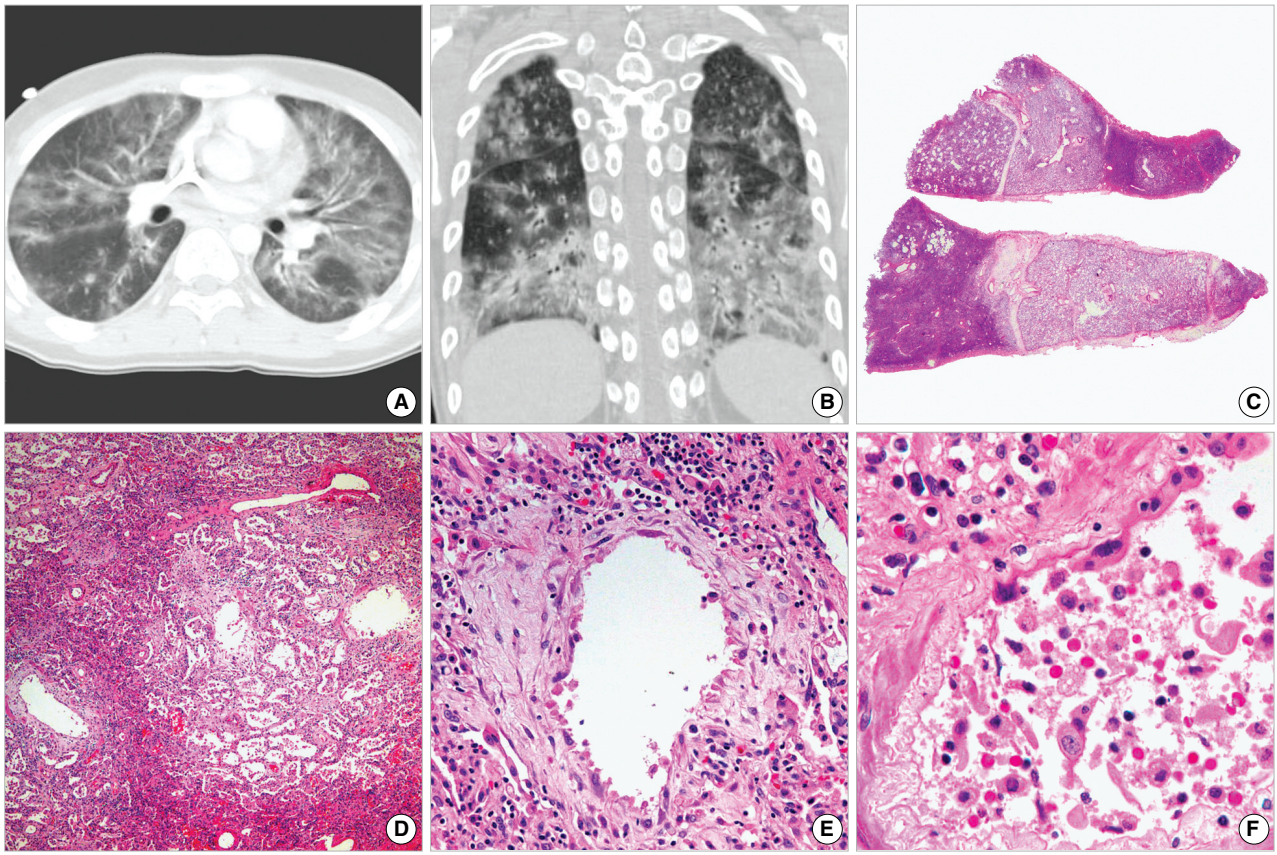


Fig. 2. (A) and (B) Chest CT image showing bilateral ground-glass opacity along bronchovascular bundles with bronchial dilatation. (C) Scanning power view image showing an airway-centered lesion. (D) Bronchial wall thickening due to fibroblast proliferation and diffuse interstitial widening due to lymphocytic infiltration. (E) and (F) Epithelial sloughing or totally epithelial loss in bronchioles associated with the proliferation of subepithelial fibroblasts.

human leukocyte antigens (HLAs) of a donor graft and the recipient.[13] A variety of pulmonary complications have been previously described as manifestations of GVHD. The lungs of cGVHD patients are frequently abnormal, but findings in aGVHD patients have been minimal.[14] In 1995, Yousem *et al*. studied the histological spectrum of "pulmonary GVHD" in 17 recipients of allogeneic HSCT.[15] They divided the observed morphological changes into four categories: diffuse alveolar damage, lymphocytic bronchitis/bronchiolitis with interstitial pneumonitis, bronchiolitis obliterans organizing pneumonia, and cicatricial bronchiolitis obliterans.[15] Patients with active lymphocytic bronchitis/bronchiolitis, cicatricial bronchiolitis obliterans, and diffuse alveolar damage have particularly poor outcomes.[15] Benesch *et al.* described the following pathologic findings of GVHD: lymphoplasmacellular infiltration of bronchioles with moderate extension of mononuclear infiltrates into alveolar septa, focal and incomplete bronchiolitis obliterans with intraluminal inflammatory granulation tissue, and interstitial and peribronchiolovascular infiltrates consisting predominantly of lymphocytes and histiocytes.[16]

The clinical manifestation of case 1 involved tachypnea and skin rash, which is similar to measles pneumonia. However, the most characteristic histologic finding of measles pneumonia is the presence of large multinucleated giant cells harboring eosinophilic, Feulgen-negative intranuclear and intracytoplasmic inclusions. Additionally, the radiologic finding of case 2 was bronchilolitis, which is similar to respiratory syncytial virus infection. The bronchial epithelium is usually sloughed, and necrotic debris fills the bronchial lumens in the respiratory syncytial virus infection; this is also found in cases of GVHD of the lung. However, the lymphoplasmacellular infiltration of bronchioles is not generally detected in respiratory syncytial virus infections. Therefore, an awareness of the difference between measles and respiratory syncytial viral infection of the lung and GVHD is important for the selection of appropriate treatment.

By definition, aGVHD occurs prior to day 100 after HSCT.[17]

According to the interval after allogeneic HSCT and the pathologic findings, case 1 is consistent with aGVHD and case 2 with a combined form of aGVHD and cGVHD. Chest CT images in the two patients revealed characteristic ground-glass attenuation along the bronchovascular bundles and some bronchial dilatation with focal patchy consolidation, and these results correlated well with the histologic findings. The pathologic findings of aGVHD in our two patients included epithelial necrosis and a subepithelial fibroblastic reaction with a bronchiolocentric pattern and some lymphocytic infiltration and/or interstitial widening, which are similar to the findings associated with aGVHD in the skin. The interstitial fibrosis with some lymphocytic infiltration observed in case 2 appears to have been a manifestation of cGVHD, and resembled scleroderma-like changes in the skin, which is suggestive of a close association between the occurrence of GVHD and the progression of IPS.

In conclusion, the pathologic findings of aGVHD are bronchiolocentric epithelial changes, characterized by epithelial necrosis, reparative fibroblast proliferation, and lymphocytic infiltration of the bronchial epithelium. On the other hand, the pathologic findings of cGVHD are interstitial pneumonitis, interstitial fibrosis, and lymphocytic infiltration. A keen awareness of these pathologic findings of GVHD is, therefore, necessary, because the early use of corticosteroids alters immune function.

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