Non-Infectious Bronchiolitis as an Early Pulmonary Complication of Hematopoietic Stem Cell Transplantation

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Abstract

Pulmonary complications occur in up to 60% of patients after hematopoietic stem cell transplantation (HSCT), causing significant morbidity and mortality. Among them, non-infectious bronchiolitis is considered a late complication in the form of bronchiolitis obliterans. We report a patient who developed non-infectious bronchiolitis within four weeks after undergoing HSCT for biphenotypic leukemia. Chest CT revealed centrilobular nodules that were reminiscent of diffuse panbronchiolitis, and lymphocytic bronchiolitis was confirmed by biopsy. Infection and bronchiolitis obliterans were ruled out, and the bronchiolitis resolved when leukemia relapsed. This case suggests that bronchiolitis may be another early, non-infectious pulmonary complication of HSCT.

Key words: bronchiolitis, hematopoietic stem cell transplantation, diffuse panbronchiolitis

(introduction)

Hematopoietic stem cell transplantation (HSCT) is used to treat hematological, neoplastic, autoimmune, and genetic diseases, often providing prolonged survival. However, complications are common in the lung; they occur in up to 60% of patients, and account for more than 30% of all transplantation-related deaths (1). They are classified as infectious or non-infectious, and a higher proportion of non-infectious complications have accounted for morbidity and mortality in recent years because the incidence of infection has diminished with effective prophylaxis. Several non-infectious pulmonary complications have been recognized: pulmonary edema, engraftment syndrome, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, veno-occlusive disease, organizing pneumonia, and bronchiolitis obliterans (BO) (1, 2). BO usually develops after the first 100 days post-transplant, and bronchiolitis other than BO have not been recognized as an early, non-infectious complication of HSCT. Here, we report a case of non-infectious bronchiolitis distinct from BO that developed within the first month of HSCT.

Case Report

A 19-year-old man developed dyspnea, impaired hemostasis, and arthralgia of the lower limbs. Blood tests revealed WBC 198,000/μL, Hb 5.1 g/dL, Plt 15,000/μL. He was admitted for suspected leukemia. Bone marrow aspiration revealed that 67% of nucleated cells were blasts, which were positive for CD10, CD13, CD14, CD19, CD20, CD22, CD33, CD34, HLA-DR, and myeloperoxidase, and a diagnosis of acute biphenotypic leukemia of B cell and myeloid lineage was made according to the European Group of Immunological Classification of Leukemias criteria (3). Two courses of chemotherapy consisting of 170 mg/day of cytarabine on days 1-7 and 20 mg/day of idarubicin on days 5-7 resulted in induction failure, as did two courses of high-dose cytarabine of 6,800 mg/day on days 1-4 and 12 mg/day of mitoxantrone on days 1-2. On-disease allogeneic peripheral blood stem cell transplantation from a completely HLA-

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matched sibling [HLA-A (31, 33), B (51, 58), and DR (0301, 0802)] was performed. Pre-transplant paranasal sinus radiograph, chest CT, and spirometry were normal. The conditioning regimen was 2 Gy of total body irradiation twice a day on days -6 to -4 for a total of 12 Gy, and 3,500 mg/day of cyclophosphamide on days -3 and -2. As prophylaxis against graft-versus-host disease (GVHD), he was given 170 mg/day of cyclosporine starting from day -1, and 17 mg of methotrexate on day 1 and 12 mg/day on days 3 and 6. Cefepime, vancomycin, micafungin, and acyclovir were given as prophylaxes against infection. CD34-positive peripheral blood stem cells were infused at a dose of 4.4×10^6 cells/kg. Engraftment was confirmed on day 23. On the same day, erythema of the palms and soles were noted, and grade 1 acute GVHD was diagnosed.

A fever of 37.6 degrees, purulent sputum, and dyspnea developed on day 24. On auscultation, lungs were clear. Serum fungal antigens for *Aspergillus*, *Cryptococcus*, and *Candida*, and the cytomegalovirus (CMV) pp65 antigenemia assay were negative. Chest radiograph showed diffuse nodular shadows in both lower lung fields, and sinus X-ray showed fluid in the maxillary sinuses. Bone marrow aspiration on day 30 revealed no blasts, confirming remission. Chest CT on day 32 revealed diffuse, bilateral centrilobular nodules with a predominance in the lower lung fields (Fig. 1A), and sinus CT showed fluid and mucosal thickening of the frontal, maxillary, ethmoidal, and sphenoid sinuses, together reminiscent of diffuse panbronchiolitis (DPB). Arterial blood gas showed pH 7.42, PaO₂ 75 Torr, and PaCO₂ 40 Torr while breathing ambient air. Pulmonary function tests showed declines in FEV₁, from 4.1 L to 2.4 L, and in FEV₁%, from 91% to 67%, and an increase in V50/V25, from 1.9 to 4.3, indicating significant airflow obstruction. %VC, %RV, %TLC, and RV/TLC all declined from 99% to 90%, from 132% to 80%, from 95% to 78%, and from 29% to 21%, respectively. Diffusing capacity was unchanged. Analysis of broncho-alveolar lavage fluid (BALF) showed total cell counts of 58×10^5 cells/ml with differential cell counts of 25% macrophages, 50% lymphocytes, and 25% eosinophils. Of the lymphocytes, 95% were CD3-positive T cells, and the CD4/8 ratio was 0.70. The peripheral blood white blood cell count was 6,500/μl, and the leukocyte differentials showed 42% neutrophils, 31% eosinophils, 18% monocytes, and 5% lymphocytes. Bacterial, mycobacterial, and fungal cultures of the BALF were negative, as were the polymerase chain reaction assays for *Aspergillus*, *Pneumocystis jiroveci*, CMV, respiratory syncytial virus, parainfluenza virus, and adenovirus, ruling out infection. Histological examination of trans-bronchial lung biopsy showed lymphocytic bronchitis and bronchiolitis with involvement of adjacent alveoli (Fig. 2). Very few eosinophils were seen. The infiltrating lymphocytes were CD8-positive T cells. The histological findings were not indicative of any infection or bronchiolitis obliterans.

Chest CT on day 46 showed that the lesions had regressed without any treatment (Fig. 1B). On the same day, leukemia cells were found in the peripheral blood, indicating disease relapse, and resolution of GVHD was also observed. The patient died of leukemia on day 64.

**Discussion**

We have described a case of non-infectious lymphocytic bronchiolitis that developed within a month of HSCT. Chest CT showed centrilobular nodules, pulmonary function tests showed airflow limitation without a decrease in diffusing capacity, and biopsy confirmed the presence of lymphocytic bronchiolitis. There was no evidence of infection, and the clinical picture was quite different from any of the well-
described non-infectious pulmonary complications of HSCT: pulmonary edema, peri-engraftment respiratory distress syndrome, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, veno-occlusive disease, organizing pneumonia, or BO (1, 2). The present case suggests that bronchiolitis may represent another early, non-infectious pulmonary complication of HSCT.

We do not consider the present case to be BO for three reasons. First, BO usually develops after the first 100 days after transplantation (4). Second, the typical CT findings of BO are air trapping, small airway thickening, or bronchiectasis, not centrilobular nodules (4). Third, biopsy findings did not show any fibrosis or eosinophilic scarring of the bronchioles resulting in narrowing of the lumen, suggestive of BO (5). It has been reported that airflow obstruction develops in the early stages after HSCT without any finding suggestive of BO (6). Therefore, it is possible that some cases of BO are sequelae of early bronchiolitis. Early bronchiolitis may have previously gone mostly unnoticed because of its mild clinical course.

The significance of an increase of eosinophils in the BAL fluid is unclear because only a few eosinophils were seen in biopsy specimens. This discrepancy is sometimes seen in diffuse lung diseases; however, what it indicates is not known. We consider that eosinophils had less of a role compared to lymphocytes based on the histological findings.

The chest CT finding of diffuse, centrilobular nodules with a lower lobe predominance together with clinical syndromes of purulent sputum, dyspnea, sinusitis, and airflow limitation was reminiscent of diffuse panbronchiolitis (DPB), a disease with chronic inflammation of the respiratory bronchioles most often seen in East Asians (7). However, it is clear he did not have DPB because there was no airflow obstruction and chest CT was normal before transplantation. It is possible that bronchiolitis and sinusitis share a common etiology, causing a sinobronchial syndrome, but infection was never ruled out. Therefore, the significance of sinusitis is unclear.

As a complication of HSCT, there have previously been several pathological descriptions of airway disease other than BO. Beschorner et al examined autopsy material from 59 patients with a mean survival of 48 days after receiving bone marrow transplants, and found that 15 had lymphocytic bronchitis (8). Yousem reviewed lung biopsy specimens and described lymphocytic bronchitis or bronchiolitis, distinct from BO, with cellular interstitial pneumonia as one of the manifestations of pulmonary GVHD (9). There have also been case reports of lymphocytic pneumonitis, but not bronchiolitis (10, 11). To our knowledge, this is the first clinical report on early, non-infectious, non-BO bronchiolitis complicating HSCT.

The pathogenesis of the well-recognized, early, non-infectious pulmonary complications have not yet been fully elucidated, but proposed mechanisms include conditioning-related toxicities, immune-mediated injury, and occult infection (1). The pathogenesis of non-infectious bronchiolitis remains obscure. Beschorner et al reported that the development of lymphocytic bronchitis was significantly correlated with the presence of GVHD (8), which is in agreement with the report of Yousem (9) and that using a rat model (12). On the other hand, some have suggested that lymphocytic bronchitis is unrelated to GVHD, using canine models (13). In the present case, because infection was effectively ruled out, and because the bronchiolitis was resolved without any treatment as leukemia relapsed and GVHD subsided, an immune-mediated injury in which the donor lymphocytes attack the recipient airway cells, may be the most plausible explanation.

In conclusion, the present case suggests that bronchiolitis may be considered a distinct form of early non-infectious pulmonary complication of HSCT.

References


