Pleuroparenchymal Fibroelastosis as a Series of Airway Complications Associated with Chronic Graft-versus-host Disease following Allogeneic Bone Marrow Transplantation

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Abstract

We herein report the case of a 31-year-old woman who presented with bilateral upper lobe volume loss and pleural irregularities with hilar retraction. She had undergone allogeneic bone marrow transplantation (BMT) for the treatment of acute lymphoblastic leukemia nine years earlier. A surgical lung biopsy showed pleural thickening and subpleural alveolar collapse and fibrosis, consistent with a diagnosis of pleuroparenchymal fibroelastosis (PFPE). Antecedent sicca syndrome and the absence of other causes of fibroelastosis suggested that these abnormalities were associated with chronic graft-versus-host disease (cGVHD). PFPE as a late, noninfectious complication is rare; however, the present case suggests a new class of BMT-related pulmonary complications associated with cGVHD.

Key words: allogeneic bone marrow transplantation, bronchiolitis obliterans, pleuroparenchymal fibroelastosis, chronic graft-versus-host disease, idiopathic pulmonary upper lobe fibrosis


Introduction

Bone marrow transplantation (BMT) can lead to a variety of pulmonary complications (1, 2). Late-onset, noninfectious pulmonary complications are considered a manifestation of chronic graft-versus-host disease (cGVHD) and remain a significant cause of morbidity and mortality (3).

Bronchiolitis obliterans (BO) is the most common form of late-onset, noninfectious pulmonary complications (4-6). Recently, other rare pulmonary complications that have led to the development of small chronic pneumothoraces or pleuroparenchymal fibroelastosis (PFPE) in patients with BMT have been reported (7, 8). Although BO may be related to cGVHD, the pathophysiological role of cGVHD in other pulmonary complications is not fully understood (3, 5).

In this report, we demonstrate unusual pleuroparenchymal abnormalities as late-onset, noninfectious pulmonary complications indicating a relationship with cGVHD following allogeneic BMT.

Case Report

A 31-year-old woman presented with a complaint of progressive dyspnea on exertion and a nonproductive cough lasting for six months. She had no history of smoking or bronchial asthma. Nine years previously, she had undergone conventional-intensity allogeneic BMT from an unrelated donor for the treatment of T-cell acute lymphoblastic leukemia in a second complete remission. The transplantation was uncomplicated; however, she had developed oral and ophthalmic sicca syndrome over the last six years.

Laboratory tests revealed the following results: KL-6=323 IU/mL (normal <500 IU/mL), SP-A=28.9 ng/mL (normal <43.8 ng/mL), SP-D=163 ng/mL (normal <110 ng/mL) and a normal blood cell count and C-reactive protein level. No anti-SS-A or SS-B antibodies were detected.

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dicted), a FEV1/Forced vital capacity ratio (FEV1%) of...

Histopathologically, BO is characterized by peribronchiolar fibrosis that leads to luminal narrowing and eventual obliteration (5). In previous reports of secondary PPFE, obliteration and fibroblastic plugging have been recognized in the terminal bronchioles and alveolar ducts (8). The present patient exhibited similar findings, albeit with more peripheral lesions than usual BO. In both the present and previous reports, BO was confirmed in all reported cases using histopathological examinations, which differs from the findings for idiopathic pleuroparenchymal fibroelastosis in the Japanese literature (10). Coexisting BO is a different pattern from reported idiopathic PPFE or IPUF and, although speculative, is a promoting factor of secondary PPFE in BMT patients.

The spontaneous pneumothoraces and peripheral obliteration changes observed in the present case may have interacted with each other, possibly through a peripheral check valve mechanism (7). Progressive subpleural fibrosis and elastin deposition are attributed to pneumothorax secondary to obliteration, and these recurrent processes of rupture and healing of the visceral pleura may develop into PPFE. The pleural thickening observed in the present case was mild;

Figure 1. Chest radiography showing bilateral upper lung volume loss with pleural thickening (A). High-resolution chest computed tomography showing bilateral pleural irregularities extending into the interlobular fissures with mild bronchiectasis (B).

The patient subsequently developed repeated small, bilateral pneumothoraces (Fig. 3A-C), and the upper lobe volume loss gradually deteriorated despite the use of systemic and inhaled corticosteroids.

Discussion

We herein report a case of pleuroparenchymal fibroelastosis followed by BMT, focusing on a new entity of pulmonary complications associated with cGVHD. Recently, unique radiologic and histopathologic patterns of pleuroparenchymal abnormalities in patients with BMT demonstrating pleural and subpleural parenchymal fibrosis with an upper lobe predominance have been reported (7, 8). These abnormalities are characterized by chronic, small, spontaneous pneumothoraces and are histopathologically consistent with PPFE, which was first described as an idiopathic disease (9). The histopathologic features of idiopathic PPFE are similar to those of idiopathic pulmonary upper lobe fibrosis (IPUF), as previously described in the Japanese literature (10). Although there are some differences in clinical features among reports (9-11), idiopathic PPFE and IPUF are essentially the same spectrum of disease.

In the present case, the patient had no history of autoimmune disease or asbestos or drug exposure (12) known to induce such pleuroparenchymal lesions, and no chronic infectious complications were found in the lung specimens. Although possible causes include thoracic irradiation for pre-BMT, the pulmonary lesion was associated with cGVHD followed by sicca syndrome. The diagnosis of sicca syndrome was established based on the presence of mild sialadenitis on a lip biopsy, keratoconjunctivitis on a Schirmer test and ocular surface staining. Sialadenitis does not meet the criteria of Sjögren syndrome.

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however, disease progression can cause pleural thickening and become more compatible with PPFE.

We thus consider BO, recurrent pneumothorax and PPFE to be a series of airway diseases associated with cGVHD. Increased peripheral obliteration causes recurrent pneumothorax and eventually PPFE; however, such small lesions take a long time for disease progression. Both the present case and previous reports appear to support a 3- to 24-month presentation time of BO (3, 5, 6). In contrast, the presentation time for pneumothorax and PPFE ranges from two to 16 years (7, 8, 13).

With respect to the BO, systemic and inhaled corticosteroids (3) were administered in this case; however, there was no clinical efficacy. Although the PPFE demonstrated a poor clinical outcome (8, 10, 11), the therapeutic approach is not established for either idiopathic or secondary PPFE. It is clear that late-onset, noninfectious pulmonary complications are a cause of transplantation-related morbidity and mortality. With the increasing number of cases of BMT and the ability to effectively control infectious complications, the

Figure 2. Surgical lung biopsy specimen demonstrating mild pleural thickening and subpleural alveolar collapse as well as fibrosis with abrupt transitions between the areas of fibrosis and the unaffected lung [A: Hematoxylin and Eosin (H&E) staining, original magnification ×40; B: elastic stain, original magnification ×40]. Patchy fibrotic lesions in the normal parenchyma (C; H&E staining, original magnification ×40) and partial fibrous obliteration in the terminal bronchiole [D; H&E staining, original magnification ×40, E (*): elastic stain, original magnification ×100]. Intra-alveolar lymphocytic infiltration with foamy macrophages was also observed [F (**); H&E staining, original magnification ×100].

Figure 3. Chest radiography performed three months after the surgical lung biopsy showing bilateral pneumothoraces (A). Small pneumothorax repeated at seven months (B) and 19 months (C), respectively.
late-onset, noninfectious complications of cGVHD will become more common and long-term follow-up is urgently needed. Additional reports and studies are required to determine the importance of this rare pattern of pulmonary complications following BMT.

The authors state that they have no Conflict of Interest (COI).

References