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BRIEF REPORT

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# Bronchiolitis obliterans organizing pneumonia (BOOP) with suspected liver graft-versus-host disease after allogeneic bone marrow transplantation

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**Abstract** We report on a patient with chronic myelogenous leukemia who developed bronchiolitis obliterans organizing pneumonia (BOOP) after allogeneic bone marrow transplantation (BMT). A 19-year-old Japanese male complained of dry cough and dyspnea 7 months after BMT. The chest X-ray and computed tomography revealed patchy infiltrates bilaterally. Lung function test, lung biopsy and bronchoalveolar lavage were consistent with the diagnosis of BOOP. The patient also suffered from suspected graft-versus-host disease (GVHD) of the liver, after discontinuation of cyclosporine. Furthermore, prednisolone proved effective against the BOOP and the liver dysfunction. These findings indicate that BOOP is a possible pulmonary manifestation of chronic GVHD, and that immunological mechanisms may have effected the onset of BOOP after BMT in this case.

**Keywords** Allogeneic bone marrow transplantation · Bronchiolitis obliterans organizing pneumonia · Graft-versus-host disease · Immunological reaction

**Abbreviations** *ALP* Alkaline phosphatase · *BMT* Bone marrow transplantation · *BO* Bronchiolitis obliterans · *BOOP* Bronchiolitis obliterans organizing pneumonia · *CML* Chronic myelogenous leukemia · *GVHD* Graft-versus-host disease

## Introduction

Infectious and non-infectious pulmonary complications are relatively common after allogeneic bone marrow transplantation (BMT) [8]. It is suggested that chronic graft-versus-host disease (GVHD) and late-onset non-infectious pulmonary complications, such as diffuse alveolar damage, interstitial pneumonia and bronchiolitis obliterans (BO) are connected [7]. Moreover, bronchiolitis obliterans organizing pneumonia (BOOP) has previously been reported following BMT [1, 5, 6, 9]. Although histologic findings of BO and BOOP share several similarities, their clinical features are quite different. BO is characterized by obstructive airway disease. The chest X-ray shows no findings or hyperinflation. The disease responds moderately to steroids and usually shows a progressive course. In contrast, BOOP is characterized by restrictive impairments; BOOP chest X-rays show patchy areas of consolidation; steroids treatment generally improve the clinical and radiological findings. We report on a patient who developed BOOP in coincidence with suspected GVHD of the liver after allogeneic BMT, however, the etiology of BOOP and its relationship with GVHD remain unclear.

## Materials and methods

A 19-year-old male with chronic myelogenous leukemia (CML) in its second chronic phase was transferred to our hospital for BMT in August 1997. After one course of chemotherapy, he received an allogeneic bone-marrow transplant from his HLA-identical sister in November. The conditioning regimen consisted of fractionated total body irradiation (from days –8 to –5; 3 Gy/day), etoposide (on day –4; 1600 mg/m$^2$ per day), and cyclophosphamide (on days

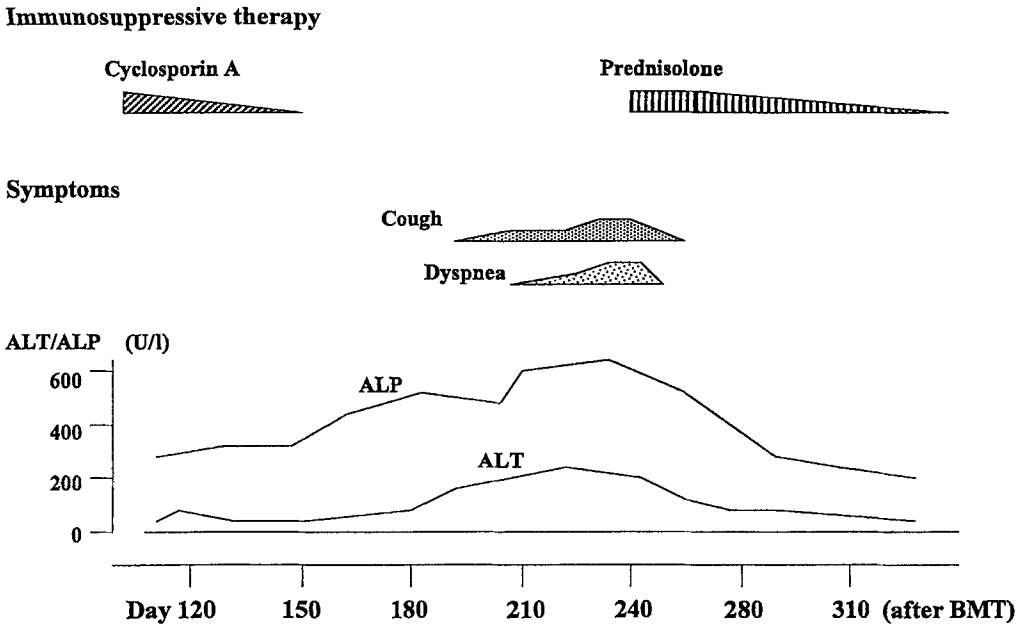


**Fig. 1** Clinical course

–3 and –2; 2250 mg/m$^2$ per day). The patient received methotrexate (on day 1; 15 mg/m$^2$ per day, and on days 3 and 6; 10 mg/m$^2$ per day) and Cyclosporin A (CsA) (3 mg/kg administered daily as a continuous infusion) in order to prevent GVHD. The engraftment of bone marrow was favorable. He was discharged on day 98 without acute GVHD in February 1998.

CsA was tapered and stopped on day 150, although aminotransferase levels gradually rose. The patient complained of a non-productive cough and low-grade fever on day 150. Although he was treated with antibiotics, he had to be rehospitalized on day 239 for progressive dyspnea. On admission, the serum aspartate aminotransferase (AST) level had increased to 83 U/l, that of alanine aminotransferase (ALT) to 141 U/l, and that of alkaline phosphatase (ALP) to 575 U/l (Fig. 1). The chest X-ray with air bronchogram revealed multiple patchy infiltrates. High resolution computed tomography (CT) of the lung also demonstrated bilateral nodular patchy inclusions (Fig. 2 a). Lung function tests showed a moderate, restrictive impairment (VC 2.13 l/min, 47.9 % of expected value and $FEV_1$ 2.91 l/min, 96.3 %). Carbon monoxide diffusion capacity was 21.06 ml/mm Hg per s (58.1 % of expected value). Analysis of arterial blood gas showed a slight hypoxemia. Transbronchial lung biopsy and bronchoalveolar lavage (BAL) were performed on day 245. Pathological findings showed interstitial fibrosis with lymphocyte infiltration and intraluminal fibrosis with of plugs of inflammatory cells, fibroblasts, and connective tissue (Fig. 3). The most conspicuous cells were foamy macrophages occupying free alveolar air spaces. Cytology of BAL fluid revealed a high lymphocyte count (36.0 %), and the CD4/CD8 ratio was 0.04, using flowcytometry analysis. Examination of BAL fluid including cultures for bacteria, fungi and PCR for cytomegalovirus were negative. From these findings, the lung lesion was diagnosed as BOOP.

The patient received prednisolone at a dose of 1 mg/kg daily from day 248. Clinical symptoms disappeared, and the chest X-ray improved within few days. The lung CT also showed improvement of the patchy lesions on day 13 after prednisolone treatment (Fig. 2 b). The patient was discharged on day 276 without symptoms. Around day 280, the serum AST- and ALT levels improved to 25 U/l and 40 U/l, respectively. He is now doing well without immunosuppressive therapy after a follow-up period of 28 months after BMT.

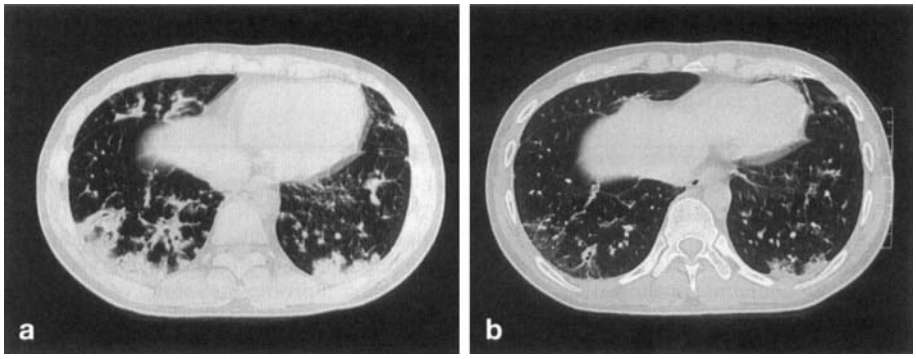


**Fig. 2** **a** The chest CT scan indicates bilateral patchy infiltrates with peribronchial thickening on day 240 (pre-treatment with prednisolone). **b** Abnormal shadow apparently improved on day 260 (post-treatment)

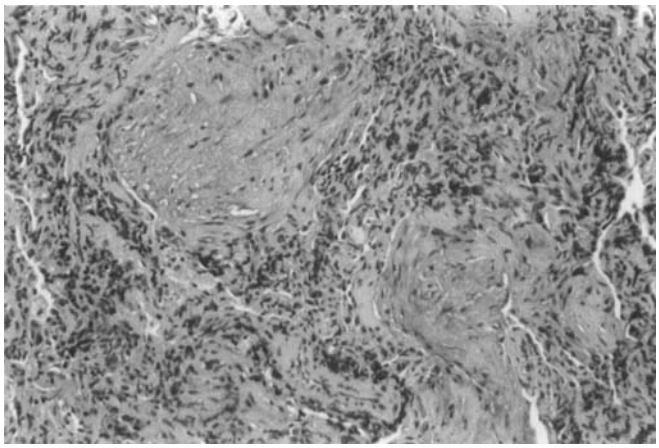

**Fig. 3** Microscopic photograph of the lung biopsy. Alveolar ducts were filled with granulation with foamy macrophages. Interstitial fibrosis was also visible

## Discussion

We describe here a patient who developed BOOP with suspected chronic GVHD of the liver following allogeneic BMT. BOOP has been reported by Epler et al. [3] in 1985 and is a clinicopathologic syndrome distinct from bronchiolitis obliterans (BO). BO and BOOP are characterized by granulation tissue plugs within the lumens of small airways, with scarring and occasional obstruction of these airways. However, in BOOP, the granulation tissue extends into the alveolar ducts and the alveoli. In the present case, the histological findings were consistent with these characteristics of BOOP.

Despite these similar histologic findings, their clinical manifestations are very different. Patients with BO have wheezing and an obstructive lung function test. The response to steroids is usually poor. Patients with BOOP, however, reveal dyspnea, and late inspiratory crackles are present on physical examination. Treated with steroids, the therapeutic outcome is excellent, and prognosis is generally good.

There are several reports of BOOP after allogeneic BMT since Chien J et al. [1] described the first case report in 1990. Thirman et al. state that BOOP may be an under-recognized complication of allogeneic BMT and confused with an infectious process [9]. Therefore, it is possible that there has been some confusion about the differences between BOOP and BO in the previous reports. Although it is difficult to determine the true incidence of this complication after allogeneic BMT, the literature states it to be 1.7% of late-onset pulmonary complications [7].

The definite etiology of BOOP can not be clarified, since it has been reported in various conditions, such as drug-induced pneumonitis, interstitial pneumonia of collagen diseases, chronic infectious pneumonia, and radiation pneumonitis [2]. The pathogenesis of BOOP after allogeneic BMT may be more complicated because of the influence of drugs and/or radiation used as a conditioning regimen and the abnormality of immunity. One possibility of pathogenesis underlying BOOP after BMT may be an activation of cell-mediated immunity.

The relationship between BOOP and GVHD after BMT is still controversial. BOOP in connection with GVHD following BMT has been reported [5, 9]. In contrast, there was no evidence of GVHD in three children with BOOP in a paper that was reported by Mathew et al [6]. Moreover, Kanda et al. have described a patient who developed BOOP after syngeneic BMT [4]. It is of interest that liver dysfunction and BOOP began after CsA was discontinued and responded well to prednisolone in this case. Although the pathologic diagnosis of liver dysfunction was not obtained, it was suspected of being a GVHD-induced phenomenon because the deterioration of serum aminotransferase was observed together with the discontinuation of CsA. Therefore, immune-mediated mechanisms may affect the onset of BOOP as well as liver dysfunction. In general, the reconstitution of host immunity and the reduction of immunosuppression by the withdrawal of CsA lead to an increased immunocompetence. It is suggested that the host's cell-mediated response caused by foreign pathogens, such as virus or bacteria, may play an important role in the occurrence of BOOP following allogeneic BMT.

In summary, our patient developed BOOP coinciding with suspected chronic GVHD of the liver after allogeneic BMT, soon after CsA was discontinued. On the basis of clinical findings, we hypothesized that the activation of cell-mediated immunity may have contributed to the onset of BOOP in this case. Furthermore, we recommend that these patients should be reported in order to accumulate sufficient information to clarify the pathogenesis of BOOP following BMT.

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