Case Report

Bronchiolitis Obliterans Following Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Bronchiolitis obliterans (BO), characterized by progressive and irreversible respiratory failure, is one of rare complications associated with graft-versus-hostdisease (GvHD) following allogeneic hematopoietic stem cell (HSC) transplantation. We reported here a 15-year-old male patient who was first diagnosed with acute lymphoblastic leukemia and subsequently underwent matched related HSC transplantation. Five months post-transplant, he developed persistent cough, hypoxemia and worsening dyspenia complicated by grade I GVHD with skin stage II. His multidetector—row computed tomography scan was highly suggestive of OB. Considerable clinical improvement were once achieved with the augmented immunosuppressive agents including corticosteroids and methotrexate, however, he eventually died of heart failure followed by chronic pulmonary heart disease 9 months post-transplant. The possible risk factors and the management of OB in this case are discussed.

INTRODUCTION

Bronchiolitis obliterans (BO), an inflammatory / fibroproliferative process that results in airway obstruction, was first described in 1901 in patients with progressive dyspnea and nowadays referred to as a late complication in allograft recipients undergoing lung, heart-lung, and bone marrow transplantation (BMT). It is still under recognized and carries high morbidity and mortality [1-3]. Herein we reported a case of a 15-year-old boy who developed BO following matched related hematopoietic stem cell (HSC) transplantation. He died of heart failure resulted from chronic pulmonary heart disease despite the clinical improvement of bronchiolitis and airway obstruction following the use of systemic corticosteroids and methotrexate.

CASE REPORT

A 15-year-old boy was admitted on January 2006 with complaints of pallor and fever. A diagnosis of philadelphia chromosome (Ph) / bcr-abl negative B-cell precursor acute lymphoblastic leukemia was made after hematologic investigation. Remission induction consisted of Vincristine (2 mg) IV days 1, 8, 15, 22. Daunorubicin 60 mg IV push days 1, 8,

15. Methylprednisolone 60 mg/day PO divided TID days 1 – 28. Complete remission was attained in March 2006. He received three more courses of chemotherapy consisting of cyclophosphamide/ vincristine/daunomycin/prednisone/methotrexate in May 2006, cyclophosphamide/vincristine/ aclacinomycin /prednisone/ cytarabin in June 2006 and /vincristine/prednisone/cytarabin/ L-asparaginase for consolidation in July 2006. The total cumulative dose of antracyclines was 300 mg/m2. In addition, he experienced intrathecal injection of methotrexate (MTX, 10mg), cytarabin (Ara-c, 25mg) plus dexamethasone (DXM, 5mg) as a CNS prophylactic regimen during each interval between chemotherapy cycles. Subsequently he underwent matched, related HSC transplantation. The donor was an HLA-matched sister. Conditioning regimen consisted of busulfan (1 mg/kg, day –5 to –3) and cyclophosphamide (2 g/m², day –2 to –1). Cyclosporin A (an initial dose of 3 mg/kg/day given as a continuous infusion and then adjusted to maintain serum levels between 150 to 250 ng/ml) and short course of methotrexate were administered as immunosuppressive therapy for graft-versus-host disease (GVHD) prophylaxis. His course was complicated by acute respiratory tract infection, mumps, grade I GVHD with skin involvement (according to NIH consensus criteria, see Figure 1),

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Figure 1 This boy developed stage II skin involvement with grade I chronic graft versus host disease (GVHD) in spite of receiving prophylaxis with cyclosporin A. He presented with a lichenoid eruption resembling lichen planus.

for which he was treated with Cefoperaxone Sodium / Sulbactam Sodium, intravenous immunoglobulin (IVIg), and Cyclosporin A. Four months after HSC transplantation, he developed skin GVHD II with manifestation of dryness, itching rash, peeling or shedding, and also blood in the urine. He was then hospitalized for 5 days and was therefore treated with Cyclosporin A, Basiliximab (an anti-CD25 antibody) and Mesnaum. During and after this illness, persistent and productive cough without fever and haemoptysis was noted, which was evaluated five months post-transplant. Chest radiograph was unremarkable, and a multidetector—row computed tomography (MDCT) scan of the chest showed no bronchiectasis or air trapping. He was then given a 2-week trial of antibiotic and bronchodilators, with no improvement in his symptoms. Seven months after transplantation, an increase in cough with hypoxemia, dyspenia and worsening fatigue was noted and bilateral medium moist rales were detected on physical examination. Special stains and cultures for bacterial and fungal resulted from sputum were negative, unfortunately, neither a bronchoalveolar lavage nor a transbroncial biopsy was performed without the family's consent, and moreover the Pulmonary Function Test (PFT) was not available at that moment. MDCT scan showed bronchial dilatation, bronchitis shadows, hyperlucency and mediastinal emphysema, indicating airflow obstruction (Figure 2a). He was then started empirically on Methylprednisolone (intravenously, 80 mg, twice daily, then 60mg, twice daily, then tapered to 40mg twice daily.) and methotrexate (intravenously, 10 mg, once weekly). With this therapy, he improved clinically, with an increase in his performance status (ECOG) and resolution of his cough, rales on examination, and a repeated MDCT scan showed obvious improvement in the bilateral infiltrates and airflow obstruction (Figure 2b). Unfortunately 9 months post-transplant, he died of refractory heart failure, which might due to chronic obstructive pulmonary heart disease. A conventional autopsy could not be performed without the explicit consent of the parents.

DISCUSSION

Bronchiolitis obliterans (BO) is a late-onset noninfectious pulmonary complication following allogeneic HSC transplantation, and characterized by progressive obstruction of the small airway leading to hyperinflation with areas of atelectasis, impaired mobilization of secretions, development of bronchiectasis, and the fibrosing process.

According to its rarity [4,5] and so far missing prospective, randomized and controlled trials, case reports about successful

treatment of BO might be still of interest for us. Generally, the clinical manifestations of BO are the persistence of respiratory symptoms (cough and wheeze) and signs (tachypnea, crackles, and wheezes on auscultation) beyond the expected time frame after pulmonary injury, and the severity various from asymptomatic to fulminant and fatal [6,7].

A definitive diagnosis of BO required histological examination of lung biopsy. However, diagnostic yield of lung biopsy remains suboptimal [8,9], although the safety and efficacy of lung biopsy for pulmonary infiltrates in patients with hematologic malignancy have been stated recently [10]. Its clinical correlate, bronchiolitis obliterans syndrome (BOS), defined as a fall in FEV1 of greater than 20% from baseline determined by the average of two measurements made at least 3 weeks apart [11]. Implementation of increasingly sensitive criteria for identifying early decline in pulmonary function may allow the prediction of BOS. As such, a potential-BOS stage (BOS 0-p), defined by a 10 to 19% decrease in FEV1 and/or by a 25% or greater decrease in forced expiratory flow, midexpiratory phase (FEF25–75%), from baseline was added to the original staging system in 2001[12].

Nevertheless, a rapid presumptive clinical diagnosis that allows identification of patients is needed. The inclusive criteria has been suggested to be as follows: The patients must develop breathlessness and bronchodilator nonresponsive airflow limitation with moderate to severe chronic graft versus host disease 100 days post-transplantation and thickened or dilated small airways with mosaic attenuation are determined by the radiological examination, such as a clear chest radiograph or a high-resolution computed tomography (HRCT) scan [9]. In the case presented here, a 15-year-old male patient developed persistent cough, hypoxemia and worsening dyspenia complicated by grade I GVHD with skin involvement five months post-transplant, and his MDCT scan showed bilateral bronchiolitis and airflow obstruction. According to the clinical inclusive criteria for BO as stated previously, the timing and nature of his clinical symptoms combined with MDCT changes were characteristic for BO.

Many potential risk factors associated with the development of post-transplant BO have been identified [3-5,8,11,13,14], among which are some highlighted in this case, including male recipient with female donor, a busulfan-based conditioning
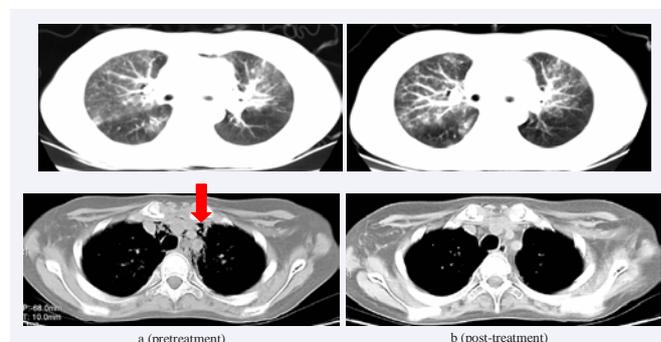

a (pretreatment)   b (post-treatment)

Figure 2 **Representative MDCT scans of pretreatment (a) and post-treatment (b).** The right side (a) showed bronchial dilatation, patchy and stripe shadows, hyperlucency and mediastinal emphysema (red straight arrow), indicating airflow obstruction before the treatment, while the left side (b) showed obvious improvement in the bilateral infiltrates and airflow obstruction.

regimen, methotrexate (MTX) regimen for GvHD prophylaxis, peripheral blood stem-cell transplantation, and also the most common identified risk factor – GvHD. Although the pathophysiology of post-transplant BO is not yet well understood, its strong association with these risk factors is highly suggestive of an alloimmune response triggered by donor T-lymphocytes, which is characterised histopathologically by a predominantly lymphocytic bronchiolar and peribronchiolar inflammatory infiltrate [4,9,15]. Further studies revealed that the inflammatory response of BO is provoked and perpetuated by vast arrays of cytokine and chemokine networks, which consists of TNF-α, interleukin-2 (IL-2), interferon λ, interleukin-8 (IL-8), RANTES (regulated on activation, normal T-cell expressed and secreted), platelet-derived growth factor (PDGF), transforming growth factor, and fibroblast growth factor [16-19]. Thereafter, the repeated or persistent process of inflammation results in an augmented fibroblastic response leading to peribronchiolar fibrosis and obliteration of the airways. In this context, BO is defined as a manifestation of allograft rejection [20].

In the light of the alloimmune nature of BO, combined immunosuppressive treatment may provide an opportunity for reducing pulmonary complications and improving survival [21,22]. However, therapeutic interventions in patients are somehow disappointing. The patient presented here died from heart failure resulted from chronic pulmonary heart disease despite the clinical improvement of both brochiolitis and airway obstruction following the use of systemic corticosteroids and methotrexate. Thus, further investigations on new therapeutic options are required. Since TNF-α seems to play a central role in the inflammatory reaction and enhanced fibroblast proliferation, the commercial anti-TNF-α antibodies (infliximab, etanercept, and adalimumab) have been studied on the treatment of BO. Significantly reduced inflammation, fibrosis, and luminal obstruction with TNF-α blockage have been shown with the animal models of BO and of GVHD with acute lung injury [17,23-25], and moreover, a successful treatment with the use of infliximab has been achieved in a bone marrow transplant patient after failed corticosteroid therapy [6]. Other clinical trials on both lung transplantation and allogeneic HSC transplantation provided the evidence that azithromycin may be promising in the treatment of BO post-transplant [26-28], which led to the new insights with the identification of at least two different phenotypes of BOS: azithromycin-responsive phenotype (the so-called neutrophilic reversible allograft/airways dysfunction (NRAD), and azithromycin-unresponsive phenotype (the fibroproliferative form of BOS or classical obliterative bronchiolitis) [29]. The therapeutic value of azithromycin may due to the inhibition of interleukin-8 release by human alveolar macrophages or by an increase in the apoptosis of neutrophils [30]. There are also evidences that extracorporeal photopheresis can be an effective method of treatment of any inflammatory disorder that is T-cell dependent, including BOS [31,32].

In particular, given the pathophysiological process of BO from lymphocytic bronchiolitis to subepithelial fibrosis, the timing of therapy is likely to be critical for the clinical response. It is reported that azithromycin treatment initiated before the development of BOS stage 2 significantly reduced the risk of death [33]. Moreover, azithromycin prophylaxis might attenuate local

and systemic inflammation, which resulted in the prevention of BOS [34]. Thus, BO should be considered when patients post-transplant present early respiratory symptoms, which might trigger a good clinical response.

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