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CASE REPORT

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Successful treatment of rapidly progressive interstitial pneumonia with autologous peripheral blood stem cell transplantation in a patient with dermatomyositis

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Abstract Aggressive autoimmune diseases are often treated by intensive immunosuppressive treatment such as high-dose methylprednisolone and intravenous cyclophosphamide. Autologous hematopoietic stem cell transplantation can facilitate high-dose immunosuppressive therapy (HDIT), which is myeloablative. We describe a 54-year-old female patient with rapidly progressive and refractory interstitial pneumonia due to dermatomyositis, which was successfully treated with high-dose cyclophosphamide and autologous blood stem cell transplantation. Following transplantation, dyspnea disappeared, and arterial blood gas analysis and respiratory function test showed marked improvement. This improvement was confirmed by diminished interstitial shadows on chest X-ray and computed tomography scans. Eighteen months after transplantation, the patient is doing well without symptoms and signs of interstitial pneumonia.

Keywords Autologous hematopoietic stem cell transplantation · Dermatomyositis · High-dose immunosuppressive therapy · Interstitial pneumonia

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Introduction

Dermatomyositis (DM) and polymyositis (PM) are conditions of presumed autoimmune etiology in which the skeletal muscle is damaged by inflammation and lymphocytic infiltration. The term polymyositis is used when the condition lacks skin involvement, and dermatomyositis is applied when polymyositis is associated with characteristic cutaneous manifestations [1].

Recently, increasing attention has been paid to rapidly progressive interstitial pneumonia as an important pulmonary manifestation of DM that can sometimes seriously influence the prognosis [2]. Especially, a subset of patients with DM, who have no muscular symptoms and/or show only slightly elevated levels of muscle-associated enzymes, have been reported to develop rapidly progressive interstitial pneumonia [3]. Interestingly, most of these patients are negative for antinuclear and anti- Jo-1 antibodies, and their treatment outcomes are poor. Interstitial pneumonia developing in these patients is refractory to corticosteroids and immunosuppressive drugs such as azathioprine and cyclophosphamide. Cyclosporin A (CsA) has emerged as a promising therapy for refractory interstitial pneumonia associated with DM, but its effect is limited [4]. Thus, it is widely accepted that interstitial pneumonia associated with DM is one of the fatal complications in aggressive autoimmune diseases, and a new therapeutic modality has been anticipated.

In recent years, based on animal studies and experiences in the treatment of hematological malignancy with coexisting autoimmune diseases, hematopoietic stem cell transplantation (HSCT) has been shown to be effective for the treatment of severe autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis [5]. Although theoretically allogeneic HSCT would be more effective to eliminate self-reactive lymphocytes and ameliorate active autoimmune diseases, autologous HSCT was tested initially for safety reasons.

We report herein high-dose immunosuppressive treatment (HDIT) supported by autologous peripheral blood stem cell transplantation (auto-PBSCT) for management of rapidly progressive and refractory interstitial pneumonia associated with DM.

Case report

A 54-year-old female patient was referred to us in January 2002 with a 2-week history of general fatigue, fever, and skin rashes on the extremities. Physical examination revealed rashes on the extensor surface of the finger joints (Gottron's sign) and elbows in addition to high fever (38°C). Pulmonary vesicular sounds were normal. Neither weakness nor pain of her proximal muscles was elicited on muscle strength testing. Laboratory data tests showed an elevated erythrocyte sedimentation rate (ESR) of 35 mm/1 h, a normal white blood cell (WBC) count of 5900 mm^{-3}, and an increased C-reactive protein (CRP) level of 2.97 mg/dl. Levels of muscle-associated enzymes on admission were slightly elevated; they were 188 U/l (normal: 45–163) for creatine phosphokinase, 7.2 IU/l (normal: 3–6) for aldolase, and 92 U/l (normal: 12–33) for glutamic oxaloacetic transaminase (GOT). The patient was negative for rheumatoid factor, antinuclear antibody, and anti-Jo-1 antibody. Her chest radiography showed patchy ground-glass opacity in the upper lobe of the left lung and in the lower lobes of both lungs, and chest computed tomography (CT) scans revealed patchy ground-glass opacity in the lower lobes of both lungs and consolidation and thickening of the bronchovascular bundle in the upper lobe of the left lung. Arterial blood gas and pulmonary function tests showed hypoxia with a decreased level of PaO_2 (66.2 mmHg), decreased vital capacity (VC) (2.00 l: 80.0% of the predicted value), and low diffusion capacity of the lung for carbon monoxide (DLCO) (8.85 ml/min mmHg: 69.7% of the predicted value). In addition, the disease activity of interstitial pneumonia was confirmed based on an increased level of KL-6 at 551 U/l (normal: <480 U/l). Infiltration of inflammatory cells was not detected by histological examination of biopsied muscle samples from the left deltoid muscle, while slight muscle atrophy was observed in the same samples. Skin biopsy samples were histologically consistent with dermatomyositis. A diagnosis of interstitial pneumonia due to DM without muscle weakness was made according to Bohan's criteria and Cosnes's criteria [1, 6]. Dermatomyositis occurring in the absence of myositis and specific antibodies has a known association with malignancy, but no pathological findings were obtained in the gastroenterology consultation conducted to explore the existence of an internal malignancy. A gynecologist was also consulted, but no pathological changes were observed in the vaginal smear. She was first treated with high-dose methylprednisolone (1000 mg/day × 3 days) and CsA (200 mg/day). Intravenous cyclophosphamide (IVCY) therapy (500 mg/m^2 body surface area) was also administrated 2 weeks later. Despite intensive immunosuppressive therapy, arterial blood gas analysis and pulmonary function tests did not show any improvement in hypoxia: values of PaO_2, VC, and DLCO were 58.3 mmHg, 1.32 l (50% of the predicted value), and 6.65 ml/min mmHg (50% of the predicted value), respectively.

The CT scans of the chest also revealed the worsening of interstitial pneumonia. The KL-6 level was also increased up to 3769 IU/l. Based on the progressive clinical course of the disease, which was refractory to the intensive immunosuppressive therapy, further intensified immunosuppression with auto-PBSCT was considered. After Institutional Review Board approval and informed consent were obtained, mobilization and collection of PBSC and auto-PBSCT were performed in June 2002 (Fig. 1).

Prior to this treatment, CsA was discontinued. To mobilize hematopoietic stem and progenitor cells into peripheral blood, she received high-dose cyclophosphamide (4.0 g/m^2), followed by the administration of granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg per day.

On the 9th day of G-CSF administration, leukapheresis was performed, and 4.9×10^6 $CD34^+$ cells/kg were collected. To purify hematopoietic stem/progenitor cells and eliminate self-reactive lymphocytes, immunological selection of $CD34^+$ cells was performed using the CliniMACS system (Miltenyi Biotec Inc., Auburn, Calif., USA). After positive selection of $CD34^+$ cells, the purity of $CD34^+$ cells in the product was 99.1% with contamination of 5.0×10^3 CD3+ cells/kg. After pretransplant conditioning with high-dose cyclophosphamide (50 mg/kg day × 4 days), the patient was infused with autologous $CD34^+$ cells (4.9×10^6 $CD34^+$ cells/kg). The G-CSF (5 μg/kg per day) was administrated until engraftment after transplantation. The early posttransplant clinical course was uneventful, and neutrophil and platelet engraftment (an absolute neutrophil count $>0.5\times10^9$ l and a platelet count $>50\times10^9$ l) were

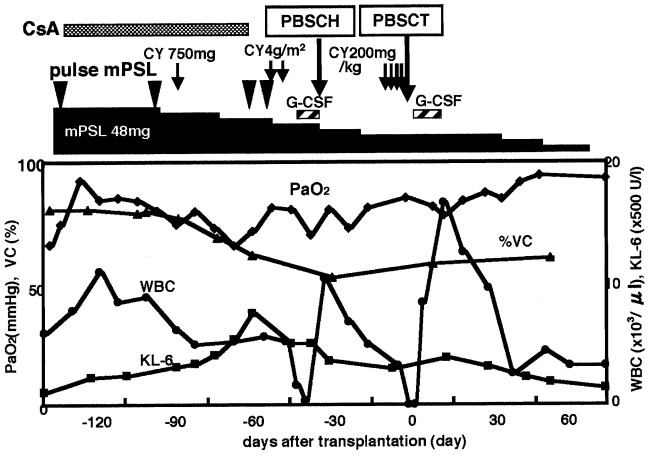

Fig. 1 Clinical course. *CsA* cyclosporin A, *pulse mPSL* pulse methylprednisolone therapy, *CY* cyclophosphamide, *PBSCH* peripheral blood stem cell harvest, *PaO_2* arterial partial pressure of O_2, *VC (%)* percent of predicted value of vital capacity

achieved on days 8 and 10, respectively. Cytomegalovirus antigenemia occurred on day 18, but it had been controlled by ganciclovir and cidofovir administrations. On day 25, blood gas analysis revealed marked improvement of hypoxia (PaO_2: 91 mmHg). Also on CT scans of the chest on day 112, interstitial pneumonia was resolved. The serum level of KL-6 also decreased (2200 IU/l). She was discharged on day 113. Unexpectedly, she was rehospitalized because of *Listeria* sepsis on day 120, but early administration of antibiotics was effective. To assess immunological recovery, we monitored reconstitution of lymphocyte subpopulations by flow cytometry (Fig. 2). Within 180 days, CD8-positive cells recovered first. However, CD4-positive and CD19-positive cells recovered slowly after day 180 (Fig. 2a). Similarly, CD4/CD45RA-positive and CD4/CD25-positive cells recovered slowly. In contrast, CD4/CD45RO-positive cells showed more rapid recovery (Fig. 2b).

One year after transplantation, the patient was in excellent clinical condition, and no signs of active interstitial pneumonia were observed. The pulmonary function tests performed in July 2003 (1 year after transplantation) showed significant improvement of VC (1.83 l: 74.1% of the predicted value). The serum level of KL-6 had normalized (425 IU/l).

Discussion

Our patient presented with a typical cutaneous change of DM without gross muscle involvement. Recently, a subset of DM patients who have no muscular symptoms and/or show only slightly elevated levels of muscle-associated enzymes, and are negative for antinuclear antibody and anti-Jo-1 antibody, have been reported to develop rapidly progressive interstitial pneumonia [2]. Treatment outcome is usually poor in most of these cases. Cyclosporin A (CsA) has emerged as a promising therapy for refractory interstitial pneumonia observed in such cases, but its effect is limited [4]. The present patient was also resistant to CsA as well as corticosteroid therapy, and additional IVCY therapy. Autologous HSCT has been applied to approximately 650 patients with aggressive autoimmune diseases such as systemic sclerosis and systemic lupus erythematosus to facilitate high-dose immunosuppression and eliminate self-reactive lymphocytes [5]. Accordingly, HSCT appears to be an effective therapy for resistant or refractory autoimmune diseases. Thus, several prospective randomized phase III trials are ongoing and have been finalized in systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus with the aim of assessing the efficacy and safety of this new treatment modality compared with conventional and other newly emerging therapies [5, 7].

However, there have been only five reported cases in which HDIT with auto-HSCT was employed for treatment of interstitial pneumonia due to PM/DM, and two cases had been reported in detail [7–9]. Both of these cases reported were anti-Jo-1-antibody-positive polymyositis with refractory interstitial pneumonia and myositis and were in remission after auto-HSCT. Thus, our patient appears to be the first case, which was successfully treated with auto-PBSCT for mangement of rapidly progressive interstitial pneumonia due to poor-risk DM characterized by weak muscle involvement and negativity for antinuclear and anti-Jo-1 antibodies. Again, since such DM patients show an extremely poor prognosis, HDIT and auto-PBSCT will be a favorable treatment for those patients. The rationale for HDIT with auto-PBSCT lies in the hypothesis that (1) an immunoablative regimen can eradicate autoreactive lymphocyte clones, (2) subsequently, there is a lack of persistence of the triggering environmental factor, and (3) a newly developed immune system from autologous stem cells might acquire tolerance toward the previously pathogenic antigens (immunological reconstruction) [5]. To avoid reinfusion of autoreactive lymphocytes, a CD34-enriched T cell-depleted stem cell graft was reinfused into our patient. As our patient's condition was complicated by prolonged cytomegalovirus (CMV) antigenemia and listeriosis, aggressive lymphocyte depletion may induce immunological insufficiency inducing opportunistic infections. We monitored the reconstitution of lymphocyte subsets by flow cytometry. Recovery of $CD4^+$ T cells was delayed compared to that previously reported after unmodified autografts [10].

There are many difficulties involved in evaluating the activity of interstitial pneumonia associated with PM/DM. KL-6 is a high molecular weight glycoprotein secreted by type II alveolar cells in the lung and levels of KL-6 in serum can be useful serum markers in the diagnosis of interstitial pneumonia and in monitoring

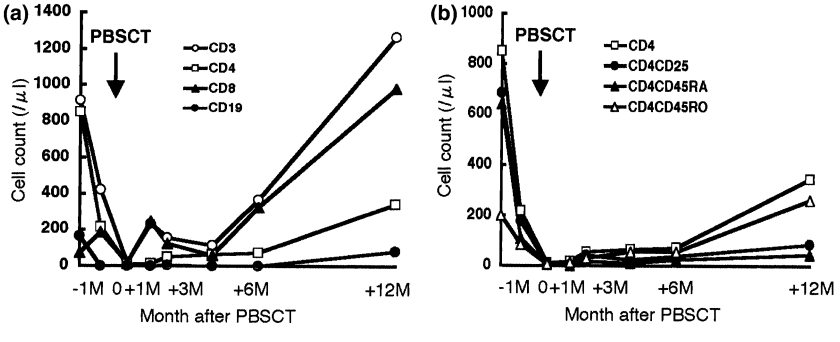

Fig. 2 Flow cytometric analysis of lymphocyte subpopulations. **a** Reconstitution of CD4-, CD8-, CD4-, and CD19-positive lymphocytes. **b** Reconstitution of CD4/CD25-, CD4/CD45RA-, and CD4/CD45RO-positive lymphocytes

disease activity [11]. Recently, it has been reported that the level of KL-6 in serum could be a useful marker to evaluate the severity of interstitial pneumonia associated with PM/DM [12, 13]. In these reports, levels of KL-6 in serum were inversely correlated with pulmonary functions, such as %DLCO and VC. Also in our case, there was an inverse correlation between KL-6 levels and pulmonary function (VC) and PaO_2. These results can confirm the usefulness of serum KL-6 in evaluating the activity of interstitial pneumonia associated with DM, and serum KL-6 may reflect the degree of the fibrotic process in interstitial pneumonia.

In summary, this case report indicates the efficacy of HDIT facilitated by auto-PBSCT for the treatment of rapidly progressive and refractory interstitial pneumonia associated with poor-risk DM. To assess the efficacy of this treatment modality, prospective clinical trials with more patients and longer follow-up are necessary.

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