Case Report
Successful treatment of polymorphic post-transplant lymphoproliferative disorder after allo-HSCT with reduction of immunosuppression

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Abstract: Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening complication for recipients of solid organ transplantation (SOT) and allogeneic hematopoietic stem cell transplantation (allo-HSCT). In SOT recipients, who previously have a normal immune system that has been immunosuppressed, reduction of immunosuppression (RI) shows favorable outcome. However, in HSCT recipients, who have been profoundly immunosuppressed and for whom the tempo of immune reconstitution cannot be fast enough to eliminate the lymphoproliferative process, RI is ineffective in most patients. Therefore, cases of tumor regression via RI alone are rare in the setting of HSCT. We present a case of 26-year-old female developing a polymorphic B-cell PTLD 4 months after receiving allo-HSCT for T cell lymphoblastic lymphoma. RI alone led to regression of the nasopharyngeal tumor, and no sign or evidence of graft-versus-host disease (GVHD) after RI was observed. The general condition of this patient was quite well just before we submitted our draft. To our knowledge, this is the first case that tumor of PTLD regressed upon RI alone with a favorable prognosis and without any evidence of GVHD and relapse of PTLD after RI therapy in the setting of HSCT, which justify the possible advantage of RI alone for low-risk patients.

Keywords: Post-transplant lymphoproliferative disorder, hematopoietic stem cell transplantation, reduction of immunosuppression, T cell lymphoblastic lymphoma

Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a life-threatening disease which consists of a heterogeneous group of diseases ranging from polyclonal hyperplasia to aggressive lymphoma in recipients of solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT) [1]. According to the WHO classification, PTLD comprises four major categories: early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma. Risk factors for the development of a PTLD after HSCT include the degree of HLA mismatch between donor and recipient, manipulation of the graft to deplete T cells, and the degree and duration of immunosuppression used to prevent and treat graft-versus-host disease (GVHD) [1]. Approximately 1% of patients undergoing allo-HSCT could develop PTLD, and the incidence rate can increase to high levels among patients with risk factors [2]. The pathogenesis of PTLD in most patients is thought to be sustained by Epstein-Barr virus (EBV)-driven B-lymphocyte proliferation in the setting of immunosuppression, in which EBV-specific T-cell-mediated immunity is impaired, although EBV-negative cases of PTLD have also been described [1, 3, 4]. Current modalities for treatment of EBV-positive PTLD include reduction of immunosuppression (RI), chemotherapy, anti-CD20 monoclonal antibody (rituximab), antiviral drugs, and infusion of EBV-specific cytotoxic T lymphocytes (CTLs). However, no standard treatment had been established to date.

RI is a primary treatment for PTLD in recipients of SOT whose immune system is previously normal [5]. In contrast, for HSCT recipients whose immune system has been previously destroyed by the conditioning regimen, RI therapy fails to bring about favorable results. Cases of tumor
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regression through RI therapy alone are rare in the setting of HSCT. Here we present a case of 26-year-old female who developed a polymorphic PTLD 4 months after receiving allo-HSCT for T cell lymphoblastic lymphoma. Upon RI alone, her PTLD lesions regressed and her general condition was well just before we submitted our draft. To our knowledge, this is the first description that PTLD after HSCT regressed with a better prognosis and without any evidence of GVHD and relapse of PTLD following RI therapy.

Case report

A 26-year-old woman, complaining of cough, chest tightness, and chest pain, was admitted to our hospital on October 23, 2009. She also complained of night sweats and weight loss. Her chest X-ray revealed a mediastinal mass and bilateral pleural effusion. CT scan showed a huge mass in the anterior-superior mediastinum, pericardial invasion, and bilateral pleural effusion. CT-guided mediastinal mass biopsy and immunohistochemistry staining revealed homogeneous small tumor cells with Syn negative, CD3 positive, CD20 negative, CD99 positive, Ki-67 positive, TDT positive, CK negative, and PAX-5 negative. A diagnosis of T-lymphoblastic lymphoma at stage IVB (Binet stage) was made.

A CHOP regimen of decreased dose was given considering the high risk of tumor lysis syndrome on October 30, 2009. Subsequently, Hyper-CAVD, HD-MTX+Ara-C, then a second Hyper CAVD, MTX alone and a third Hyper CAVD chemotherapy were given. Despite no signs of central nervous systematic infiltration, three prophylactic chemotherapies were intrathecally performed during the series of systematic chemotherapy. Complete remission was achieved after the 6th chemotherapy. Then in order to make time for transplantation, maintenance chemotherapy of low dosage was started with methotrexate.

Nine months after the initial diagnosis, unrelated donor peripheral blood stem cell transplantation (PBSCT) was performed for this patient. Donor was searched from China Marrow Donor Program. High resolution HLA typing showed B, C, DQB1 matched and A, DRB1 mismatch. The conditioning regimen consisted of 10 Gy total body irradiation in 2 fractions with shielding of the lungs (7.5 Gy), cyclophosphamide 60 mg/kg/day for 2 days and Anti-thymocyte globulin 2.5 mg/kg/day for 4 days. GVHD prophylaxis consisted of cyclosporin A, MTX and MMF (mycophenolate mofetil). The dose of infused CD34 positive cells was $1.7 \times 10^6$/kg. Although no severe early complications were noted, the patient experienced sore throat, epigastric pain and intermittent diarrhea. A combination of antibiotics, G-CSF and intermittent platelet and red blood cell transfusions were used during severe neutropenia.
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Granulocyte and thrombocyte engraftment were achieved on the 11th and 34th day, respectively.

She was noted to have systemic skin rashes on the 27th day post transplantation. Skin biopsy confirmed the diagnosis of acute skin GVHD (grading 3, staging II). Methylprednisolone 80 mg/day was administrated intravenously, and steadily tapered until discontinuation when the signs of acute GVHD disappeared.

During the 5th month after HSCT, she gradually felt pharyngeal foreign body sensation and pharyngeal discomfort. 18F-FDG PET/CT performed on December 1, 2009 revealed a metabolically active soft tissue mass on the right side of the nasopharyngeal posterior wall (Figure 1A). She was admitted again to hospital due to suspicion of being involved into PTLD or relapse of lymphoma on December 6, 2009. Therefore, we adjusted the dosage of cyclosporine to 50 mg/day. Nasopharyngeal mass biopsy was performed, and histopathology revealed that the lamina propria of nasopharyngeal mucosal tissues was diffusely infiltrated by atypical lymphocytes. Immunohistochemical analysis showed that the vast majority of atypical lymphocytes were positive for CD45RO, CD3, CD20, and EBER (Figure 2). Scattered lymphocytes were positive for CD5, CD38, CD99, CD138, TIA-1, and Ki-67 (focal exceeding 50%). All these cells were negative for CD10, CD1a, TDT, Granzyme B, and CK. Polymorphic PTLD was confirmed. Thus cyclosporine was steadily tapered till stopped. CT scan performed on January 27, 2010 demonstrated the disappearance of the nasopharyngeal mass (Figure 1B). No evidence of GVHD and signs of her lymphoma were detected after RI therapy. And she was still alive just before we submitted our manuscript.

Figure 2. Pathological findings. (A) The hematoxylin and eosin (HE)-stained biopsy specimen revealed he lamina propria of nasopharyngeal mucosal tissues was diffusely infiltrated by small, medium, large atypical lymphocytes (×400); (B and C) Immunohistochemistry for the lymphocyte markers CD3Ab (B, ×400) and CD20Ab (C, ×400) shows the cell phenotype of the large scattered atypical cells; (D) In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) showed many positive cells (×100).
Discussion

PTLD is a relatively uncommon but life-threatening complication following HSCT. PTLD after HSCT usually appeared as disseminated disease with early and rapid organ dysfunction resulting in a fulminant clinical course with poor outcomes. For this reason, PTLD could be fatal if not treated at an early stage [6]. Nevertheless, several treatments for EBV PTLD have been developed, including RI, chemotherapy, antiviral drugs, anti-CD20 monoclonal antibody (rituximab), donor leukocyte infusion (DLI), and infusion of EBV-specific CTLs. The optimal treatment is controversial since no randomized trial for PTLD has been performed [7, 8].

More than 90 percent of adults are infected with EBV virus, and EBV-specific cytotoxic T-cells control EBV infection with the virus lurking in memory B cells, leading to the lifelong asymptomatic virus persistence throughout life [9]. However, in the setting of immunosuppression in recipients of either SOT or HSCT, the situation could change, resulting in viral reactivation and proliferation of EBV-infected B-lymphocytes and the development of PTLD [10]. Thus we can either target the infected B cells with monoclonal antibodies or chemotheraphy, or boost the immune response to EBV by RI, DLI or infusing CTLs. Here we mainly focus on the RI therapy. In PTLD patients of SOT, RI has been proved to be effective, and is currently the fundamental therapy [5]. However, in PTLD patients after HSCT, who has been profoundly immunosuppressed and the tempo of immune reconstitution cannot be fast enough to eliminate the lymphoproliferative process [5, 11], RI therapy alone is therefore ineffective in most patients. Despite the mounting evidence of the efficacy of this approach in treating PTLD, it also carries the risk of inducing or exacerbating graft rejection and GVHD. Thus clinicians should carefully modulate the intensity of immunosuppression and closely monitor the function of allografts [12].

Here in our present case, the nasopharyngeal tumor regressed upon RI therapy alone, and the general condition of this patient is quite well without any evidence of GVHD after RI therapy. Although cases of regression of PTLD upon RI therapy have been described previously [13-16], nearly all the prognosis was poor. To our knowledge, this is the first description that the tumor of PTLD regressed upon RI alone with favorable prognosis and without any evidence of GVHD and relapse of PTLD after RI therapy in the setting of HSCT.

With the advent of more effective treatment options, the morbidity and mortality of PTLD in HSCT recipients decreased sharply. Perhaps the most controversial question with PTLD is not only how but also when to treat. For HSCT recipients, four major risk factors have been well defined: (1) T-cell depletion (in vivo or in vitro); (2) unrelated or ≥2 HLA-antigen mismatched related donor; (3) use of antithymocyte globulin; and (4) the degree and duration of immunosuppression used to prevent and treat graft-versus-host disease [1, 2]. The cumulative incidence rates of PTLD can increase with the number of risk factors [2]. Based on the number of risk factors of PTLD, HSCT recipients can be classified into the low risk group (≤2 factors) and the high risk group (≥3 risk factors). For the high risk patients, we’d better reserve preemptive treatments based on the combination of EBV DNA and T cell reconstitution [17], and choose aggressive treatments if these high risk patients were further diagnosed with PTLD. For the low risk group, the incidence rate of PTLD is approximately 1% [2], and there is no need to perform preemptive strategies [17].

The next question is how to treat the PTLD patients out of the low-risk groups. If the general condition of a patient is not life-threatening and the patient has a low risk of developing or exacerbating GVHD, we should first consider RI therapy to restore immune function. If a significant response is not achieved with reduction of immunosuppression or the general condition of the patient continues to deteriorate, we should perform more aggressive treatment options [18]. However, in the early stage after HSCT, the RI therapy alone may not be effective enough to restore the immune system against EBV, as patient’s immune system may have not been reconstituted completely [5]. This can be evidenced by the fact that incidence rates for PTLD peak at 2-3 months after allo-HSCT, and then decline sharply with increasing time since transplantation [2]. Thus, it is reasonable to monitor immune reconstitution to decide whether to perform further therapy or remain the RI therapy alone. Ideally, we should measure EBV-specific immunity directly. Unfor-
 fortunately, EBV-specific immunity assay is not routinely available commercially. However, we can simply use flow cytometry to evaluate T cell reconstitution, which is illustrated in Austen’s study [17]. If T cell immunity has recovered, there is a chance to eradicate PTLD spontaneously simply by reduction of immunosuppression alone. If T cell reconstitution is poor and the disease progresses, additional strategies are needed. As in our patient, considering her relatively mild clinical symptom, we performed RI therapy alone and the patient’s nasopharyngeal mass regressed. And if we had conducted flow cytometry to evaluate the T cell reconstitution, it can better justify why we didn’t perform addition strategies. With this strategy, we could avoid overtreatment and the related risk of complications in low-risk patients [19]. However, this is just a strategy, and further prospective clinical studies are needed to check the real value of this strategy.

In conclusion, the strategies of managing PTLD are varied, and we still lack the standard criteria for how to treat PTLD. RI therapy alone shows favorable clinical efficacy in our patient. Monitoring T cell reconstitution of PTLD patients out of low-risk groups could offer us reasonable evidence, which helps us to decide whether to perform further therapy or remain the RI therapy alone.

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Disclosure of conflict of interest

None.

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