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Case report

Pure red cell aplasia (PRCA) and post-transplant lymphoproliferative disorder (PTLD) constitute rare complications after allogeneic hematopoietic stem cell transplantation (AlloHSCT). The incidence of EBV-PTLD is above 1%, but it may increase in patients with well-known risk factors such as EBV seronegativity at the time of transplantation, T-cell depletion of donor grafts, HLA mismatch and use of antithymocyte globulin (ATG) for prophylaxis of graft versus host disease. The risk factors for PRCA were defined and they include: 1) elevated post-transplant anti-donor isohemagglutinin titers, 2) reduced-intensity conditioning before transplant, 3) the presence of anti-A agglutinin and 4) ciclosporin for graft versus host disease (GVHD) prophylaxis and 5) transplant from sibling donor. The anti-CD20 monoclonal antibody rituximab remains the first line treatment for PTLD following AlloHSCT, but its efficacy in PRCA is limited. Reduction of immunosuppression is also strongly advised. This is the first report on an adult patient who simultaneously developed PRCA and PTLD after ABO-mismatched AlloHSCT. The early introduction of rituximab resulted in prompt resolution of clinical symptoms with subsequent full recovery.

Key words: allogeneic hematopoietic stem cell transplantation, pure red cell aplasia, post-transplant lymphoproliferative disorder, rituximab.

Rituximab is highly effective for pure red cell aplasia and post-transplant lymphoproliferative disorder after unrelated hematopoietic stem cell transplantation

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) includes lymphoid proliferation that is the consequence of immunosuppression in a recipient of a solid organ or stem cell allograft. The pathologic spectrum of PTLD is heterogeneous, ranging from Epstein-Barr virus (EBV)-driven infectious mononucleosis-type to EBV-negative proliferations resembling B or less frequently T-cell lymphomas [1]. Currently, rituximab, an anti-CD20 monoclonal antibody, remains a first line therapeutic option for patients with PTLD following AlloHSCT. Additionally, when it is possible, rapid reduction of immunosuppression should be strongly advised [2].

Pure red cell aplasia after ABO-mismatched AlloHSCT is associated with recipient's anti-A or anti-B isohemagglutinin directed against A or/and B antigens on donor erythroid precursor cells. PRCA occurs in about 20% of patients transplanted with ABO blood group incompatibility [3]. PRCA may resolve spontaneously, but it usually requires several weeks or months and multiple red blood cell (RBC) transfusion are associated with iron overload with subsequent organ damage [4].

Herein we present a male patient who developed PRCA and PTLD after AlloHSCT and rapidly responded to rituximab.

Case presentation

A 34-year male patient was diagnosed with myelodysplastic syndrome-refractory cytopenia with multilineage dysplasia (MDS-RCMD) in April 2010. He was treated with corticosteroids (CS) and erythropoietin (EPO), but this therapy failed. He remained transfusion dependent. A fully matched unrelated donor was found and the patient was scheduled for a transplant procedure. The conditioning regimen consisted of treosulfan, fludarabine and rabbit ATG (total doses: 81 000 mg, 250 mg and 1100 mg, respectively). GVHD prophylaxis consisted of ciclosporin and methotrexate. There was major and minor ABO blood group incompatibility between recipient (blood group A Rh-positive) and donor (blood group B Rh-positive). Anti-B isohemagglutinin titers before transplant were 1 : 128 (IgM) and 1 : 64 (IgG). No pre-transplant procedures regarding ABO blood incompatibility were performed. Serological examination revealed past infections with CMV and EBV in donor and recipient. The source of stem cells was peripheral blood and the total number of transplanted nuclear cells was 4.11×10^8/kg including 6.46×10^6/kg CD34+ cells and 12.1×10^7/kg CD3+ cells. Complete neutrophil and platelet engraftments were

demonstrated on day +16, but moderate anemia was still present. Reticulocyte count was below the lower limit. Marrow assessment performed on day + 30 after AlloHSCT showed normal myeloid and megakaryocytic cells, but the number of erythroid precursors was markedly decreased. There was complete donor chimerism by STR (short tandem repeats). No symptoms of GVHD were noted. The patient remained transfusion dependent. Two weeks later he was admitted to our department due to a fever and general weakness. On physical examination progressive cervical enlargement of lymph nodes was observed. Wide spectrum antibiotics were introduced with no effect. Cytomegalovirus (CMV) and parvovirus B19 were excluded whereas PCR test revealed 19 200 copies/μl of EBV. Anemia was still present. Anti-B isohemagglutinin titers after transplant were 1 : 64 (IgM) and 1 : 32 (IgG). As EBV-driven PTLD was suspected, the immunosuppression was promptly stopped. Histological examination of the lymph node was not done due to bad patient's condition overall, but flow cytometry of a peripheral blood specimen detected a monoclonal population of B cells expressing CD20. Despite RI, the progressive lymphadenopathy was still observed. Chest X-ray and abdominal ultrasonography were normal. Rituximab at weekly doses of 375 mg/m^2 was administered twice with good tolerance. Prompt resolution of clinical symptoms and significant regression of cervical lymphadenopathy were demonstrated. The patient was discharged from our hospital although anemia was still present. Two weeks later, a marked increase in reticulocyte count was noted with hemoglobin increase. The patient became transfusion independent. The anti-donor isohemagglutinin titers were undetectable and the donor's blood group conversion was observed. Currently, 8 months later, the patient is alive with no features of PRCA and PTLD with full donor chimerism. EBV-DNAaemia is negative.

Discussion

EBV-PTLD has become a growing problem in allograft recipients due to the increasing number of transplantations. Most cases of PTLD develop in the first year after transplant or even later. The incidence of EBV-PTLD after AlloHSCT is above 1%, but it may significantly increase up to 20% in patients with well-known risk factors such as EBV seronegativity at the time of transplantation, T-cell depletion of donor grafts, HLA mismatch and use of ATG for prophylaxis of graft versus host disease [5]. The most frequent clinical manifestation of PTLD is fever and cervical lymphadenopathy. The diagnosis is usually based on histological findings and we can distinguish the following forms: early benign lesions, polymorphic and monomorphic PTLD and classical Hodgkin lymphoma PTLD [6]. According to the ECIL (European Conference on Infections in Leukemia) the diagnosis of EBV-associated PTLD was divided into: 1) proven EBV-PTLD (histological evidence of tissue infiltration by monoclonal lymphoid cells and detection of EBV gene products), 2) probable EBV-PTLD (usually marked lymphadenopathy with an increased number of EBV copies in blood but without an established diagnosis) and 3) EBV-DNAemia (the presence of EBV-DNA in the blood) [2].

Currently, the anti-CD20 monoclonal antibody rituximab remains the first line treatment in patients with PTLD after AlloHSCT [2]. A recently published review showed that rituximab was found to be effective in about 63% of patients when used in monotherapy or in combined treatment [7]. It should be mentioned that rituximab causes prolonged B-cell depletion lasting up to 12 months and therefore its use may lead to severe infectious complications [8]. A summary of current management in PTLD was recently presented by Gil *et al*. [9].

PRCA after major ABO-incompatible transplant results from the presence of host-derived B lymphocytes which produce isohemagglutinins directed against erythroid cells of donor origin. Several risk factors of post-transplant PRCA development were defined and they included: 1) elevated post-transplant anti-donor isohemagglutinin titers, 2) reduced-intensity conditioning before transplant, 3) the presence of anti-A agglutinin, 4) ciclosporin for graft versus host disease (GVHD) prophylaxis, and 5) transplant from sibling donor [3, 4, 10, 11]. The treatment of PRCA includes several therapeutic approaches. Plasmapheresis and immuno-adsorption remain the first-line therapeutic option in a majority of ABO-mismatched PRCA cases [12]. Rituximab was found to be effective in single patients although the mechanism of its efficacy remains unclear. It is postulated that opsonization of B-cells by antibody may be responsible for an early rapid phase of response. An additional mechanism is associated with the suppression of autoreactive B-cells producing autoantibodies and it allows the maintenance of remission [13, 14].

It is unlikely that the drop of agglutinin titers demonstrated after rituximab was responsible for PRCA recovery in our patient. They were relatively low, both before and after transplantation. Some authors share the view that the correlation between pre-transplant hemagglutinin titers and the occurrence of PRCA remains controversial [15].

To our best knowledge this is the first report on an adult patient who simultaneously developed PRCA and PTLD after AlloHSCT and promptly responded to rituximab. Zhu *et al*. [16] presented a case of a 5-year-old girl with chronic myeloid leukemia who developed PRCA and PTLD after HLA-identical unrelated cord blood transplantation. The clinical symptoms of PTLD resolved after rituximab at four standard lymphoma doses with a subsequent decline in anti-donor agglutinin titers and PRCA recovery. Unfortunately, the patient died due to CMV pneumonitis two months later. Both presented cases demonstrated several risk factors of development of PTLD and PRCA in the transplant period.

Regarding these two reported patients we may conclude that: 1) early recognition of high EBV load after transplant with symptoms of PTLD may enable rapid treatment with anti-CD20 antibody, and 2) rituximab may offer rapid and complete recovery from overt PTLD and PRCA with some caution regarding infectious complications.

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