

Case Report: Passenger Lymphocyte Syndrome

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Abstract

Passenger Lymphocyte Syndrome is an hemolytic syndrome that can occur after a ABO nonidentical transplant. Lymphocytes derived from the donors organ stimulate an imune response against receptors red blood cells antigens, which lead to hemolysis. Passenger Lymphocyte Syndrome is often self-limited, solving itself within 3 months. In cases of severe anemia, blood transfusion with the donos blood type is the ideal treatment. This article describes a case os Passenger Lymphocyte Syndrome occurred at Leforte Hospital, São Paulo, Brazil.

Keywords: Passenger Lymphocyte Syndrome; ABO Non-Identical Transplant; Haemolysis; Antibodies

Abbreviations: PLS: Passenger Lymphocyte Syndrome, GVHD: Graft-Versus-Host Disease, MELD: Model for End-Stage Liver Disease, UGIB: Upper Gastrointestinal Bleeding, Hb: Hemoglobin, LDH: Lactate Dehydrogenase, CMV: Cytomegalovirus, RBCC: Red Blood Cell Concentrate, DHL: Lactate Dehydrogenase, DAT: Direct Antiglobulin Test

Introduction

The performance of non-identical ABO transplants has become increasingly frequent in our midst given the recurrent shortage of organs for donation. Despite being a good alternative to attempt to reduce waiting time and mortality on the list, ABO incompatibility is not without its risks.

Passenger Lymphocyte Syndrome (PLS) is an example of a graft-versus-host disease (GVHD) [1], where lymphocytes from the donated organ are activated by receptor antigens and

trigger an immune reaction resulting in hemolysis [2,3]. It is most frequent in solid organ transplantation, mainly in heart-lung (70%), liver (29%), and kidney (9%) transplants, but it has been described in bone marrow transplants [4,5].

Its course is generally self-limited, beginning 3 to 24 days after transplantation [4] and resolving in up to 3 months [3]. The intensity of hemolysis varies according to the severity of the syndrome. When mild, therapeutic support is sufficient; moderate, blood transfusion and pharmacological management are recommended; and when severe, erythrocy-



-tpheresis may be necessary [3,6].

In this article, we will present a PLS case report, which occurred on the 14th postoperative day of a Liver-Kidney Transplant.

Methods

Written informed consent was obtained from the patient for publication of this case report.

Case Description

VL, 60-year-old man, type II diabetic for 10 years with diabetic nephropathy under conservative treatment for the past year; former smoker, diagnosed with alcoholic liver cirrhosis in 2019 after an episode of encephalopathy and an abstainer ever since, Model for End-Stage Liver Disease (MELD) 23. In 2020, he presented decompensation with ascites and three episodes of upper gastrointestinal bleeding (UGIB) requiring hospitalization and transfusion of at least 2 red blood cell concentrates in each episode.

He underwent a liver-kidney transplant: donor deceased in December 2020, piggy-back liver technique, left kidney with 2 arteries in the left iliac fossa, and Gregoir ureteral reimplantation. The deceased donor was O+ and the recipient AB+. The patient received 2 units of AB+ hemoconcentrates intraoperatively. Immunosuppression was performed with methylprednisolone 250 mg in the pre-surgical induction. On the 1st postoperative period, the patient was started on tacrolimus, 1 mg/kg/day, and mycophenolate sodium, 720 mg/day. He was discharged on the 7th postoperative day with a 7.7 g/dl hemoglobin (Hb) concentration.

He was readmitted to the hospital seven days after discharge due to hypotension, lowering of consciousness, and fever. Admission exams showed: Hb 3.2 g/dl, reticulocytosis 777,740/microL (4.6%), lactate dehydrogenase (LDH) 362 U/L (reference value <227 U/L); and a total bilirubin count of 3.17 mg/dL. Laboratory clotting values (platelet count, activated partial thromboplastin time, and prothrombin time) were all within the normal range. Doppler ultrasound of the abdomen showed no evidence of intra-abdominal bleeding and good graft perfusion.

At admission, suspension of mycophenolate sodium, search for cytomegalovirus (CMV) and parvovirus infections, blood

cultures, empirical antibiotic therapy with piperacillin-tazobactam and vancomycin, and three AB+ red blood cell concentrate (RBCC) were performed.

The patient remained in intensive care for 48 hours with an improvement of the clinical picture, transfusions, consequent control Hb: 5.4 mg/dl. Blood culture was positive for multi-sensitive *Enterococcus hirae*, so he was switched to ampicillin. Cytomegalovirus and parvovirus searches were both negative.

The Coombs test was positive and detected the presence of anti-A and anti-B antigens. The myelogram exhibited the hyperplasia of the erythrocyte series, hence establishing the Passenger Lymphocyte Syndrome diagnosis. The patient received two new O-type red cell concentrates and a dose of erythropoietin.

The Coombs test remained positive, with a decrease in anti-A and anti-B antibody counts. He was discharged on the 7th day of hospitalization, with Hb 7.5 d/dL and a re-introduction of mycophenolate. He was monitored by the team over the following months, without complications.

Discussion

Minor ABO incompatibility is described as the presence of preformed antibodies in the donor's plasma against the recipient's red cell antigens. For example, a group O organ transplanted into a group AB patient would be a case of minor ABO incompatibility, as the O blood type donor has anti-A and anti-B isohemagglutinins naturally present in their plasma [3]. This condition is a risk factor for the development of hemolysis after transplantation.

This antagonism between blood groups can lead to a hemolytic syndrome called Passenger Lymphocyte Syndrome (PLS). A 2015 retrospective study showed that 10 out of 156 patients who underwent liver transplantation with minor ABO incompatibility developed PLS [7]. The incidence of PLS is highest in heart/lung transplants (70%), followed by liver (37%) and kidneys (9%) [8]. In addition to these organs, PLS has been associated with pancreas and bone marrow transplants [5,8].

In this syndrome, B-lymphocytes transplanted with the organ ("passenger lymphocytes") produce an immune response against the recipient's red blood cells [3]. Host erythrocyte



antigens stimulate the donor's B-lymphocytes to produce antibodies against red blood cells, resulting in post-transplant hemolysis. Anti-A and anti-B antibodies are detectable in the recipient's plasma using the Coombs test. In addition to the ABO system, other antigens capable of stimulating the production of alloantibodies have been described, such as Rh [9], Jk [10], Kell [11], Fy [12], and HLA [13].

That said, one can assume that the amount of lymphoid tissue contained in the donated organ interferes with the frequency and degree of hemolysis, for the greater the number of Blymphocytes the more intense the production of antibodies. This is evidenced by the higher incidence of PLS in heart/lung transplants when compared to kidney transplants since the heart and lungs have a greater lymphoid tissue mass than the kidneys [8].

Some factors that may increase the risk of developing this syndrome are the use of peripheral blood as a source of hematopoietic stem cells; the use of cyclosporine in the absence of an antiproliferative agent, such as methotrexate, for post-transplant graft-versus-host reaction prophylaxis; and, possibly, a female donor [14].

Clinically, PLS has an acute onset between the 3rd and the 24th post-transplant day [3]. The most common laboratory findings are compatible with hemolysis, such as a rapid drop in hemoglobin levels, an increase in indirect bilirubin and lactate dehydrogenase (DHL), and a decrease in haptoglobin [3]. In more severe cases, hemoglobinemia, hemoglobinuria, and renal failure can be found [14]. The direct antiglobulin test (DAT) is generally positive, and the appearance of antibodies in the plasma is simultaneous with the appearance of hemolysis, with IgG being the most commonly detected antibody, followed by IgM and some complement proteins such as C3 [14,15].

Since donor lymphocytes can only proliferate temporarily, antibody production lasts only until the end of these cells' life cycle, thus hemolysis is generally self-limiting [14]. The antibodies are almost undetectable 3 months after the transplant [1].

In mild cases of PLS, management through therapeutic support has shown effectiveness [6]. However, some immunosuppressants, used in post-transplantation, such as cyclosporine and tacrolimus, can stimulate rapid proliferation

and dissemination of B-lymphocytes, playing an important etiological role in the syndrome [1]. If transfusion is needed, the red cell blood type must be compatible with the donor, since they will not be targeted by antibodies and therefore will not undergo hemolysis. As seen in the case above, the Coombs test revealed decreased anti-A and anti-B antibody counts after transfusion with type O blood. However, if transfusion of plasma products is necessary, those must be compatible with the recipient, in order to provide ABO antigens capable of neutralizing donor antibodies [15]. Romero et. al. described a case in which one patient received 6 blood bags incompatible with the donated organ and, for this reason, developed transfusion-associated hemolysis, while other patients who received blood compatible with the organ had limited hemolysis [7].

There is no specific pharmacological treatment for PLS, but some frequently used drugs, associated with improved hemolysis, are corticosteroids and monoclonal antibody CD20 (rituximab) [1]. For severe hemolysis, plasma exchange and transfusion with red blood cell exchange are among the recommended treatments [1,15].

Conclusion

Thus, in cases of post-transplant hemolytic anemia with minor ABO incompatibility and no evidence of bleeding, passenger lymphocyte syndrome (PLS) should be suspected. As seen in the report above, hemolysis can have important clinical consequences, so an early diagnosis is essential for the initiation of adequate treatment.

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