Case report

Passenger lymphocyte syndrome in liver transplantation

Denise M. Brunetta a,b,*, Lilian M. de Albuquerque a, Andressa H. de Morais Batista b, Lhais Hellen O. Santos b, Dirk Schreen a, Clébia A. de Lima a, Denissa F.G. Mesquita a, Luciana Maria de B. Carlos b, José Huygens P. Garcia a

a Universidade Federal do Ceará (UFC), Fortaleza, CE, Brazil
b Centro de Hematologia e Hemoterapia do Ceará (HEMOCE), Fortaleza, CE, Brazil

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Introduction

Due to the limited availability of organ donors and the growing number of patients awaiting orthotopic liver transplantation (OLT), non-ABO identical transplantation is often performed, in an attempt to lower the morbidity and mortality rates of transplant lists.1 Minor ABO incompatibility is described as the presence of naturally occurring ABO antibodies against the recipient red blood cells (RBCs) of the donor. Donor viable, immunocompetent lymphocytes present within the graft (known as passenger lymphocytes) are transferred and can produce antibodies against RBCs if they are stimulated shortly after transplant by recipient or transfused red cell antigens.2,3 Passenger lymphocyte syndrome (PLS) can also occur due to the transfer of lymphocytes that produce other anti-RBC antibodies.4,5

PLS is associated with different types of transplants. In solid organ transplants, the incidence of PLS is lowest in kidney, followed by liver and heart-lung transplants.6 PLS can also occur in allogeneic hematopoietic stem cell transplantation.7

Biochemical PLS, indicated by a derangement of the laboratory parameters of hemolysis, is relatively common in liver transplantation, affecting up to 37% of the patients undergoing minor ABO incompatible OLT.8 Therefore PLS is not an uncommon cause of anemia in non-ABO identical OLT, but often goes undiagnosed. The aim of this article is to describe two cases of PLS in liver transplantation and provide a literature review of this complication.

Case report 1

A 57-year-old man with diabetes, hypertension and coronary heart disease was diagnosed with alcoholic liver cirrhosis in October 2013. He presented with severe and frequent episodes of hepatic encephalopathy and hemorrhagic events. OLT was
performed using the piggyback technique in September 2014. His MELD score was 16. The donor was ABO group O+ and the recipient was A+. The patient received four A+ RBC units. Immunosuppression consisted of hydrocortisone, tacrolimus and mycophenolic acid. He was discharged from the hospital eight days after the transplantation, with hemoglobin (Hb) concentration of 8.52 g/dL.

Four days later, he was readmitted to the hospital because of anemic syndrome. His exams showed: Hb of 5.03 g/dL, positive direct antiglobulin test (DAT – IgG1+, C3d2+), reticulocytosis of 393 × 10^9/L, lactate dehydrogenase (LDH) of 544 U/L (normal value <460 U/L) and total bilirubin of 1.24 mg/dL. Laboratory coagulation values (platelet count, partial thromboplastin time, prothrombin time) were all within the normal ranges. Ultrasound screening was performed and there was no evidence of intra-abdominal bleeding. An ABO discrepancy was found and anti-A1 antibodies were detected in the eluate and in the serum, with titration of A+. The patient received four leukoreduced RBC units (two of A2 blood type and two of O blood type) according to the protocol for transfusion of liver transplant recipients in our institution and his clinical condition improved. He was discharged five days later with stable Hb and asymptomatic.

**Case report 2**

A 13-year-old girl was diagnosed with acute liver failure, Child C (12) with FELD 32 in August 2015. She underwent OLT with no excessive bleeding or other complications. The recipient blood type was B+ and donor blood type was O+. Immunosuppression consisted of hydrocortisone, tacrolimus and mycophenolic acid. The patient was discharged from the hospital eight days after surgery. On Day 11 post-transplant her Hb concentration was 9.54 g/dL.

On day 13, she was readmitted because of a sudden decrease in Hb concentration. Her exams showed: Hb of 5.8 g/dL, positive DAT (IgG2+), reticulocytosis of 240.19 × 10^9/L (normal value <89.0 × 10^9/L), LDH of 798 U/L (normal value <460 U/L), total bilirubin of 2.51 mg/dL, indirect bilirubin of 1.55 mg/dL with no evidence of bleeding in abdominal ultrasound. Spherocytes and erythroblasts were noted on the peripheral smear (Figure 1). An ABO discrepancy was found and anti-B antibodies were detected in serum and eluate. The patient received folic acid and hydration with improvement of clinical condition and hemoglobin levels after three days. She was discharged after seven days. The post-transplant reevaluation on Day 26 showed an Hb concentration of 11.1 g/dL.

**Discussion**

Liver transplantation can be associated with many hematological abnormalities. Graft-versus-host disease, post-transplant lymphoproliferative malignancies, thrombotic microangiopathy, hemophagocytic syndrome induced by infections and PLS are among the hematological complications of liver transplantation. Since anemia can occur in more than 50% of liver transplant recipients, the differential diagnosis of anemia and jaundice also includes inferior vena cava and hepatic vein thrombosis, portal vein thrombosis, hepatic artery thrombosis and stenosis, biliary complications, and infections or sepsis.

PLS is a well-known syndrome of immune hemolysis following allogeneic hematopoietic stem cell or solid organ transplantations, such as kidney liver and heart-lung transplants. Patients of A, B or AB blood groups may receive organs from ABO-compatible, but non-identical donors. These minor ABO incompatible transplantations occur more frequently in: (a) the use of allografts from live donors, (b) acute liver failure, (c) urgent re-transplants and (d) AB blood group patients. PLS is more frequent with donor O and recipient A.

Both of our patients had PLS due to minor ABO incompatibility (donors O and recipients A and B).
The frequency of PLS after minor ABO incompatibility
organ transplantation depends on the lymphoid mass
transplanted\(^\text{14}\) with lymphocytes accounting for almost 4% of
the liver mass.\(^\text{16}\) The incidence of PLS is about 13.5%\(^\text{13}\) in
kidney and 70% in heart and in lung transplants.\(^\text{17}\) Ramsey
et al. described an incidence of 37% of PLS in liver transplan-
tation in a retrospective analysis of 1000 patients.\(^\text{8}\) Another
recent retrospective study at a transplant center in Spain
detected 12 PLS in a total of 1217OLT.\(^\text{18}\) Ten patients of 56
OLT with minor ABO incompatibility developed PLS (17.9%)
and two patients of 147 cases with minor Rh incompatibil-
ity developed the syndrome (1.40%).\(^\text{18}\) On the other hand, in
a prospective analysis of eleven ABO or RhD mismatched liver
transplantations, EIAnsary et al. found only two PLS with anti-
bodies directed against ABO or RhD in the serum or eluate.\(^\text{19}\)
Although, a positive DAT was encountered in six of the eleven
patients.\(^\text{19}\)

The PLS may be considered a type of graft-versus-host
disease, according to Audet et al.,\(^\text{20}\) where donor immuno-
competent memory B lymphocytes escape from immune
surveillance of the immunosuppressed recipient and are stimu-
lated to produce antibodies directed against RBC antigens
(or of transfused RBC), causing hemolysis. The importance of
donor-derived memory B lymphocytes within the trans-
planted organ is highlighted by two case series,\(^\text{21,22}\) as
hemolysis was observed in more than one organ recipient
from the same donor.

The PLS usually has a sudden onset\(^\text{14}\) of between four
days\(^\text{1}\) and three weeks after transplantation,\(^\text{2}\) and the clinical
presentation of PLS ranges from mild and compensated
hemolysis to severe and possibly fatal anemia with kidney
failure.\(^\text{18,21}\) The patient of Case Report 1 was diagnosed with
PLS on the 12th day and of Case Report 2, on the 15th day after
OLT. They had significant decreases in Hb concentration with
altered hemolysis screen and no evidence of bleeding to justify
the anemia.

Besides a decrease in Hb concentration, laboratory abnor-
malities in PLS include alterations in hemolysis markers
such as increased indirect bilirubin and LDH, decreased haptoglo-
bin, in addition to the presence of a positive DAT.\(^\text{15,21}\) Both
patients described herein had anemic symptoms with
very mild jaundice, hardly noticed at physical examination,
although indirect bilirubin was increased. They also had the
other abnormalities found in PLS such as reticulocytosis, ele-
vated LDH and positive DAT (one IgG and C3d; the other IgG).

The presence of an antibody with a known specificity
against a host RBC antigen in the serum and/or in the eluate
is necessary for diagnosis.\(^\text{22}\) Both our patients had ABO
discrepancies in blood tests and there were antibodies against
ABO antigens in the eluate (anti-A1 in the first case and anti-
B in the second case). Although most cases of PLS are due
to ABO incompatibility, other antibodies against red cell an-
gens such as Rh,\(^\text{23}\) Kell,\(^\text{4,20,24}\) Kidd\(^\text{2}\) and Duffy\(^\text{20}\) have been
mentioned.

The disease is often self-limiting, usually resolving within
three months, because the passenger lymphocytes do not
engraft and there is a finite time during which the viable lym-
phocytes can proliferate.\(^\text{2,6}\) However, Fung et al. described
a severe case of PLS after OLT that only resolved with splenec-
tomy almost one year after the diagnosis.\(^\text{23}\)

Treatment is supportive and consists of simple transfu-
sions with blood products of donor blood group and, in severe
cases, erythrocytapheresis can be performed\(^\text{25}\) to remove
incompatible recipient-origin red blood cells and, conse-
quently, the amount of the target antigen.\(^\text{7}\) Rituximab has also
been used with reported success.\(^\text{25}\) Steroids have not been
shown to be of benefit in treating hemolysis in this setting.\(^\text{21}\)
Both our patients improved within a few days with supportive
therapy and the maintenance of the same dose of prednisone
they were already using. The patient in Case Report 1 was
elderly with coronary heart disease and his Hb decreased to
5.03 g/dL so he received four RBC units matched to the liver
donor. The patient of Case Report 2 did not receive RBC trans-
fusions.

As anemia is a frequent finding in patients undergoing OLT,
the transplantation team must always consider PLS in patients
with abrupt decreases of Hb concentrations and no sign of
bleeding, particularly if the recipient received an organ from
a minor ABO incompatibility donor, or if the donor was tested
positive in RBC antibody screening. Furthermore, these two
cases illustrate well that PLS is usually a self-limiting con-
dition and the change in the immunosuppressive scheme is
not always required, since it may increase the risk of infec-
tive complications that are already common in transplanted
patients. Perhaps a more aggressive treatment is only justified
in hemolysis with renal repercussion, in the patients where
it is not possible to maintain safe levels of hemoglobin only
with transfusions or in those with hemolysis persisting for
periods longer than two weeks, during which time PLS usually
resolves.

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