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Passenger Lymphocyte Syndrome: A Forgotten Cause of Postliver Transplant Jaundice and Anemia

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Abstract

A 48-year-old man with cirrhosis secondary to nonalcoholic steatohepatitis and chronic hepatitis C infection underwent a successful orthotopic liver transplant from a B+ donor without intraoperative complications. His postoperative course was complicated by hemolytic anemia, and he was ultimately diagnosed as having passenger lymphocyte syndrome.

Passenger lymphocyte syndrome is a complication of both solid-organ and stem cell transplants. It is caused by donor B lymphocyte production of antibodies causing a primary or secondary immune response to recipient erythrocytes. Most commonly, it is in the setting of minor ABO mismatches, such as with a group B liver transplanted into a group AB recipient. Typically, passenger lymphocyte syndrome presents as a mild, self-limiting hemolytic anemia. Laboratory findings are consistent with other forms of hemolytic anemia including decreased hemoglobin and haptoglobin, elevated reticulocyte count, and indirect hyperbilirubinemia

There is no definitive treatment for passenger lymphocyte syndrome or strong evidence to favor a particular treatment regimen. Passenger lymphocyte syndrome has been successfully treated with supportive care and blood transfusions matched to the liver donor. It is prudent that physicians caring for patients who receive ABO mismatched organs have a high index of clinical suspicion for passenger lymphocyte syndrome during the early postoperative period when posttransplant patients present with jaundice and anemia.

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Keywords

Transplant; Jaundice; Anemia

Introduction

Hyperbilirubinemia is a common phenomenon after a liver transplant. The differential diagnosis is broad and varies based on the timing of transplant. Early complications include inferior vena cava and hepatic vein thrombosis and stenosis (combined incidence < 1%, usually at the site of surgical anastomoses), portal vein thrombosis (1%-2%), hepatic artery thrombosis (4%-12%), hepatic artery stenosis (5%-11%), biliary leakage (5%), biliary strictures at site of anastomosis and elsewhere (5%-15%), and infections or sepsis.[1-4] Prompt recognition of abnormal hematologic parameters or aberrant findings on imaging are essential to ensure good outcomes. We present an under-recognized cause of jaundice in the early postoperative setting, as well as the pertinent diagnostic and therapeutic considerations.

Case Report

A 48-year-old AB+ man with a medical history of cirrhosis of the liver secondary to nonalcoholic steatohepatitis and chronic hepatitis C infection underwent a successful orthotopic liver transplant from a B+ donor without intraoperative complications. He received 13 units of A+ and 2 units of AB+ packed red blood cells (PRBC) intraoperatively. Immediately after transplant, the patient was started on immunosuppression that included basiliximab, mycophenolate mofetil, and prednisone. Cyclosporine was added on postoperative day (POD) 2. He was also started on pneumocystis and *cytomegalovirus* prophylaxis with trimethoprim-sulfamethoxazole and ganciclovir.

His postoperative course was initially uncomplicated with incremental improvements in bilirubin and transaminases. He received 2 units of AB+ PRBC on POD 1 for a hemoglobin of 75 g/L (7.5 g/dL). On POD 7, he developed a temperature of 38.6°C and several laboratory derangements including an increase in total bilirubin from 32.5 μmol/L (1.9 mg/dL) to 78.7 μmol/L (4.6 mg/dL), an increase in direct bilirubin from 17.1 μmol/L (1 mg/dL) to 54.7 μmol/L (3.2 mg/dL), and a decrease in hemoglobin from 86 g/L (8.6 g/dL) to 64 g/L (6.4 g/dL) (Figure 1). He subsequently received the transfusion of 2 units of AB+ PRBC and was placed on piperacillin-tazobactam for broad-spectrum coverage of enteric microbes. His repeat hemoglobin that afternoon was 78 g/L (7.8 mg/dL), and he was given another transfusion of 2 units of AB+ PRBCs. He had an inappropriate response with an increase in hemoglobin to 83 g/L (8.3 mg/dL) suggesting a continuing underlying process. An endoscopic retrograde cholangiopancreatography did not demonstrate a biliary obstruction or bile leak.

Further laboratory evaluations later in the day revealed a total bilirubin of 83.8 μmol/L (4.9 mg/dL), a reticulocyte count of 5.6%, haptoglobin < .06 g/dL (< 6 mg/dL), and positive results on a direct antiglobulin test. This was concerning hemolysis as the root of his anemia

and jaundice. Our suspicion for passenger lymphocyte syndrome (PLS) was heightened, and a hematology consultation was placed.

On POD 10, testing returned positive for the presence of anti-A1 antibodies that was confirmatory of PLS. He was subsequently started on 40 mg prednisone twice per day. On POD 12, he received 2 units of O+ PRBC for hemoglobin of 65 g/L (6.5 mg/dL) without any further evidence of hemolysis. He remained afebrile and had no further transfusion requirements through discharge on POD 13. His hemoglobin on the day of discharge was 80 g/L (8.0 mg/dL). An outpatient laboratory work-up 3 days later showed a hemoglobin of 94 g/L (9.4 mg/dL). On subsequent follow-up, his hemoglobin continued to improve, and 9 months after the transplant his hemoglobin was within normal limits. He remains on low-dose prednisone as part of his immunosuppression regimen.

Discussion

Passenger lymphocyte syndrome is a complication of both solid-organ and stem cell transplant. It is caused by donor B lymphocyte production of antibodies causing a primary or secondary immune response to recipient erythrocytes. Most commonly, it is in minor ABO mismatches, such as with a group B liver transplanted into a group AB recipient. The risk for developing PLS is greatest when the donor is group O and the recipient is group A, likely because group O individuals more frequently have IgG anti-A and anti-B.[5]

Although less common, there have also been reported cases with other blood group system mismatches, such as Rh, Kidd, and Lewis antigens.[5] Antibodies derived from donor lymphocytes typically do not appear until 7 to 14 days postoperatively and survive for 14 to 21 days after a liver transplant.[6] This is consistent with our case in which the patient did not manifest the signs and symptoms of PLS until 1 week after his initial transfusion.

Typically, PLS presents as a mild, self-limiting hemolytic anemia. Laboratory findings are consistent with other forms of hemolytic anemia including decreased hemoglobin and haptoglobin, elevated reticulocyte count, and indirect hyperbilirubinemia. Serious complications, such as disseminated intra-vascular coagulation and acute renal failure also have been reported.[7] The reported incidence of ABO mismatch antibody detection in liver transplant varies based on the source, with ranges from 30% to 40%[8] and reported hemolysis rates of 29%.[9]

There is no definitive treatment for PLS or strong evidence to favor a particular treatment regimen. As such, most current methodologies are derived from the sparse literature consisting of case reports and small case series. Passenger lymphocyte syndrome has been successfully treated with supportive care and blood transfusions. Importantly, it is recommended that transfused blood be identical to that of the liver donor when this entity is suspected. Alternatively, some authors recommend waiting until the development of specific antibodies confirms the diagnosis.[10] The use of corticosteroids is controversial and is supported only by case studies.[8] It is believed that corticosteroids induce remission of antibody production, thus quelling the effect of the donor-derived cells until their natural life cycle ends.[11]

There has been some success using rituximab, a monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells.[12,13] Presumably, destroying the passenger cells would prevent further production of antibodies to RBCs, thus halting hemolysis. Some authors have used plasmapheresis to remove the passenger lymphocyte-derived antibodies from circulation.[6,10,13] Other therapies reported include pretransplant red cell exchange and intravenous immunoglobulins. Red cell exchange with red cells of the donor's type avoids hemolysis by passive transfer of antibody.[14] The mechanism of intravenous immunoglobulins and is not fully understood, but may involve directly binding the donor-derived antibody, promoting its removal.

In conclusion, physicians caring for patients who receive ABO mismatched organs must have a high index of clinical suspicion for PLS during the early postoperative period when posttransplant patients present with jaundice and anemia. If suspected, testing for autoantibodies should be initiated. Currently, there is little evidence to support an advantageous treatment strategy. Based on our experience, blood transfusions that are matched to the organ donor's blood type and corticosteroid therapy can have a favorable outcome.

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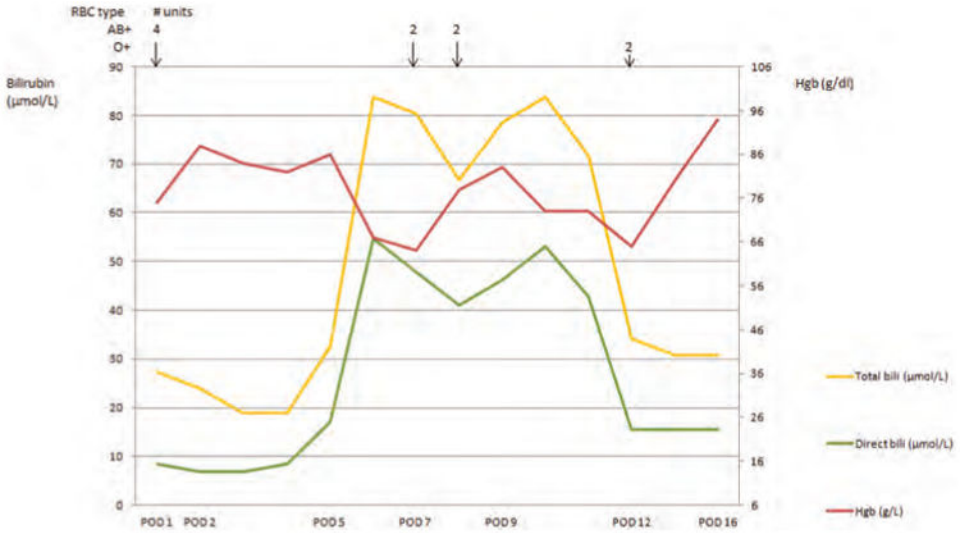

Figure 1. Progression of Bilirubin and Hemoglobin with Transfusions Over Time