

## Passenger Lymphocytic Syndrome following orthoptic diseased donor liver transplantation

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Passenger lymphocytic syndrome (PLS) is a complication of solid organ and stem cell transplant where minor ABO incompatibility between the donor and the recipient (most commonly A recipient, O donor) causes a complement mediated haemolysis of the recipient's red blood cells (RBC). Immunocompetent donor B lymphocytes are transferred passively with the graft and generate antibodies that will bind to recipient's RBCs causing haemolysis.

We report a case of a 58-year-old gentleman who underwent an orthoptic diseased donor liver transplantation with a minor ABO incompatibility (donor O positive, recipient A positive) who subsequently developed PLS following A positive blood transfusions intra operatively and in the immediate post-operative period. He developed features of acute haemolysis attributable to PLS. He made a good recovery with supportive measures and subsequent O positive blood transfusion.

PLS should be suspected in a patient with a minor ABO incompatibility with drop in haemoglobin (Hb) without evidence of active bleeding. The direct agglutination test (DAT) may not be always positive. High degree of suspicion and supportive measures can make a complete recovery in this group of patients.

**Keywords:** Passenger lymphocytic syndrome (PLS); liver transplantation; haemolysis

### Case Report

A 58-year-old gentleman, non-alcoholic and non-smoker with type 2 diabetes mellitus for 10 years was diagnosed to have chronic liver cell disease (CLCD) 3 years ago, secondary to non-alcoholic steato hepatitis (NASH). He gradually progressed into a decompensated state needing a liver transplantation. CLCD was complicated with portal hypertension and portal gastropathy with grade I varices, grade II hepatic encephalopathy and an episode of spontaneous bacterial peritonitis. At the time of transplant, the MELD score was 28.

On examination, he was 90kg (BMI - 30kg/m<sup>2</sup>) with no other significant clinical findings. All

pre-operative investigations were normal. Pre-op baseline direct agglutination test (DAT) was negative. The patient's blood group was A positive and the transplanted liver was O positive. He had not received any previous blood transfusions.

He underwent an orthoptic deceased donor liver transplantation under general anaesthesia. He had a 5.3 litre blood loss in theatre and received 10 units of A positive blood (3000ml), 9 packs of A positive platelets, 50 units of cryoprecipitate and 2000mls of fresh frozen plasma (FFP) and was started on i.v. piperacillin tazobactam and teicoplanin intra-operatively. He was admitted to the intensive care unit for post-operative management. The patient was closely monitored for features of haemolytic anaemia in the post-operative period.

Post operatively the patient had a well-functioning liver graft with initial rise of transaminases followed by an incremental reduction. IV piperacillin tazobactam and teicoplanin and an immunosuppression regimen of prednisolone and tacrolimus were continued. On post-operative day 2, the haemoglobin (Hb) decreased from 8.3g/dl to 6.1g/dl. The platelet

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count was 18,000/mm<sup>3</sup>. Haemodynamic parameters remained stable with insignificant drain output. Bleeding was excluded clinically and ultrasonically. 1 unit of A positive blood and 9 units of A positive platelets were transfused. However, the post transfusion Hb remained at 6.7g/dl. Furthermore, an indirect hyperbilirubinaemia, high reticulocyte count of 9.5% and a rising LDH of 882 U/L were noted (Table 1). DAT was repeatedly negative. A multidisciplinary decision was made to transfuse O positive blood and A positive platelets. He was discharged from ICU on post op day 5. There was no further evidence of haemolysis. DAT was repeated every other day until discharge and up to post op day 7-8.

**Table 1: Patient's serologic results**

Post op day	0	1	2	3
Hb (g/dl)	11	10.3	6.3	6.7
Bilirubin (mg/dl)	162	111	82	152
Indirect Bilirubin(mg/dl)	72	45	37	100
Retic Count %				9.5
LDH (U/L)			882	

### Discussion

Sokol et al<sup>1</sup> described three types of immune mediated haemolytic conditions following organ transplantation – autoimmune haemolytic anaemia, PLS and major blood group mismatch. PLS is a rare entity where the donor B lymphocytes known as ‘Passenger lymphocytes’ produce antibodies against recipient’s red blood cells by a primary or a secondary immune response<sup>1</sup>. PLS is also a type of graft versus host disease according to Audel et al.<sup>2</sup> It was first described in the 1980’s in patients who had mismatched renal allografts.<sup>2</sup> PLS usually occurs following a minor ABO incompatibility, where, naturally occurring ABO antibodies act against the recipient’s RBCs. Immunocompetent lymphocytes, present within the graft or ‘passenger lymphocytes’ are passively transferred to the recipient in the donor organ forming antibodies resulting in complement mediated RBC destruction in the recipient causing haemolysis.<sup>2</sup> These antibodies act against the ABO or the Rh system of the recipient. Rarely PLS occurs secondary to non-ABO/Rh antibodies especially in donors who are previously sensitized by previous RBC transfusion or pregnancy.<sup>2</sup> PLS usually occurs with a minor mismatch when an ‘O’ type donor allograft is

transplanted into an A type recipient as in this case. Non-ABO identical liver transplants are done more frequently now due to limited availability of organs. Therefore, it is important to be aware of PLS to be able to diagnose and treat early.

The volume of lymphoid tissue transplanted with the allograft may play a key role in the incidence of antibody formation and haemolysis and determines the severity of haemolysis.<sup>3</sup> The highest incidence is seen with heart and lung transplants followed by liver and kidney. Ramsey et al described 37% of PLS in liver transplants.<sup>3</sup> There were many other studies that found comparable results. According to Triulzi et al<sup>4</sup>, five out of nine who had liver transplants showed biochemical evidence of haemolysis with elevated transaminases, low haptoglobin levels, unconjugated hyperbilirubinemia and high reticulocyte count. However, direct agglutination test (DAT) was positive only in a few studies. In our patient, DAT was repeatedly negative. A possible reason is that most commonly PLS occurs due to ABO incompatibility but other antibodies against RBCs such as Rh, Kell, Kidd and Duffy may also be responsible. Our patient had A positive blood transfused during intra and post-operative periods due to lack of experience.

PLS usually occurs from day 4 to 3 weeks post-transplant period and rarely afterwards. Clinical presentation ranges from mild compensated haemolysis to severe fatal anaemia with renal failure. PLS should be suspected when a sudden reduction in Hb occurs with no bleeding in patients who had a ABO mismatched liver transplantation. This condition is usually self-limiting and resolves within 3 weeks as passenger lymphocytes do not engraft.<sup>3,4</sup> Therefore, there is a finite time of viability. However, if severe, it can cause disseminated intravascular coagulopathy, hypotension, acute kidney injury and multi organ failure.

Management is mainly supportive with transfusion of blood and blood products. Transfused RBCs should be of the donor’s ABO type.<sup>4,5</sup> This will replace RBCs that would not be haemolysed. Plasma products should be of recipient’s ABO type. Unfortunately, there are no reliable clinical features or tests that can predict the occurrence of haemolysis. If severe haemolysis develops, another option would be to increase immunosuppression. Anti-CD 20

monoclonal antibodies such as rituximab has a place in more refractory cases but there are no reported cases of rituximab usage in liver transplant.<sup>2</sup> Plasmapheresis and red cell exchange with donor ABO type RBCs has also been reported.<sup>5</sup> However, the efficacy of this treatment lacks data. There have been reported cases of splenectomy as a treatment measure.<sup>4</sup>

### Conclusion

Minor ABO incompatible organ transplants occur due to scarcity of donor organs. As such, PLS is a common complication and occurs in 30-40% of liver transplant recipients, both cadaveric and living. We should have a high index of suspicion in patients who present with jaundice and anaemia in the early transplant period, especially when they have received ABO mismatched organs. If suspected, testing for auto antibodies should be initiated. Currently, there is little evidence of a treatment strategy. However, blood transfusions that are matched to the organ donor's blood type and corticosteroid therapy<sup>2</sup> can have a favourable outcome as with our patient. Also, it is important to have an institutional policy for blood and blood product transfusion, especially for non- ABO identical liver transplants, due to scarce availability of organs.

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