

Clinicopathological Case Conference of Haematological Medicine

Case 4:

Transfusion challenge in a solid organ transplant recipient

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Case presentation

- ▶ A 66 year-old male with primary sclerosing cholangitis received an orthotopic liver transplant (donor blood type O+, recipient blood type A+)
- ▶ 12 days post transplant
- ▶ Presented to Emergency with fatigue and dizziness

Clinical evaluations

- ▶ Patient denied symptoms of infection or bleeding.
- ▶ Vitals :Normal
- ▶ Physical exam was normal except for mild jaundice.
- ▶ Concern of graft rejections

further investigation

- Hb 5.3 g/dL (it was 11.3 g/dL 4 days prior), platelets 359,
- WCC : Normal
- INR 1.2, Fibrinogen : Normal
- Cr 0.75 mg/dL, total bilirubin 6.6 mg/dL: Increased
- Direct bilirubin 3.3 mg/dL: Increased
- AST 96 IU/L, ALT 128 IU/L, alkaline phosphatase 90 IU/L,
- LDH 785 IU/L: Increased
- Reticulocytes : Increased

Pre transplant

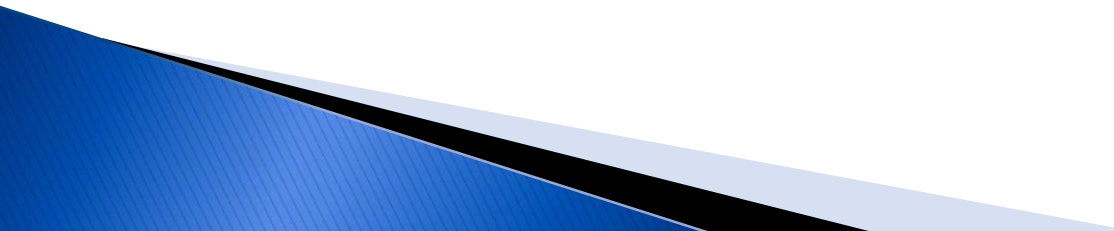
- ▶ Blood transfusion laboratory findings
- ▶ Received 2 unit RBC, compatible pre transplant

Recipient :Blood group A RhD positive

Donor : O RhD positive

Antibody screen: Negative

Haemolytic causes considered

- ▶ Acute or delayed haemolytic transfusion reactions
 - ▶ Autoimmune haemolysis
 - ▶ MAHA
 - ▶ Drug induced haemolysis
 - ▶ Steroid started
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Progress under renal team

- ▶ Despite multiple transfusions, haemoglobin continued to trend down over the next couple of days
- ▶ Repeat HB 4.4 g/dL

Haematology opinion sought

- ▶ Haematology was consulted
- ▶ Direct antiglobulin test: **Positive**
For IgG and anti-C3 with
- ▶ Elution study revealing : **Anti-A antibodies**
- ▶ Blood film: Evidence of haemolysis: NO MAHA

Diagnosis

Passenger Lymphocytes Syndrome

- ▶ Given the severity and timing of the HA in the setting of a minor ABO-incompatible liver transplantation (O into A),
- ▶ PLS was most likely the cause.
- ▶ After a week of supportive care and transfusions the patient's haemoglobin stabilized at 9.8 g/dL and he was discharged home with plan for close follow up
- ▶ Given O RhD positive bloods (donor type)

Suggested treatment approach



Treatment:

- Conservative if haemoglobin stable

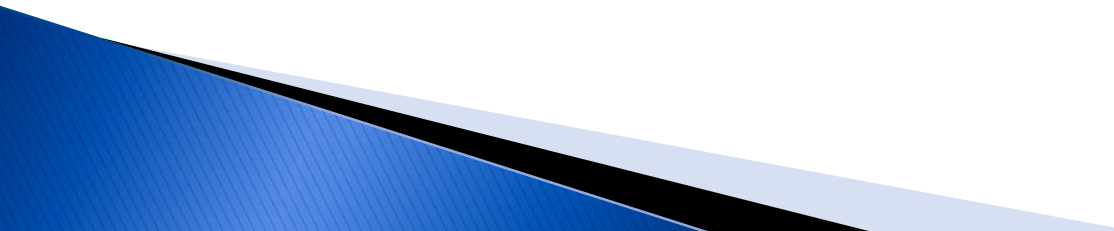
Transfusion support with **DONOR** blood group if required (e.g Hb < 8 and/or symptomatic anaemia)

- Increase steroids – prednisolone 1mg/ kg

If not resolving

- Stop CNI
 - Plasmapheresis / Rituximab
-

Discussions

- ▶ PLS is part of the differential diagnosis of HA after solid organ transplant, especially in the early setting (within 1-3 weeks),
 - ▶ With biochemical evidence (low haptoglobin, high transaminases, and unconjugated bilirubin) seen in 30-40% of these patients.
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Discussions

- ▶ Donor B-lymphocytes within the liver produce antibodies against the patient's red blood cells.
- ▶ While only a small subset of patients presents with severe anaemia, those who do, will require early diagnosis and transfusion for a favourable outcome

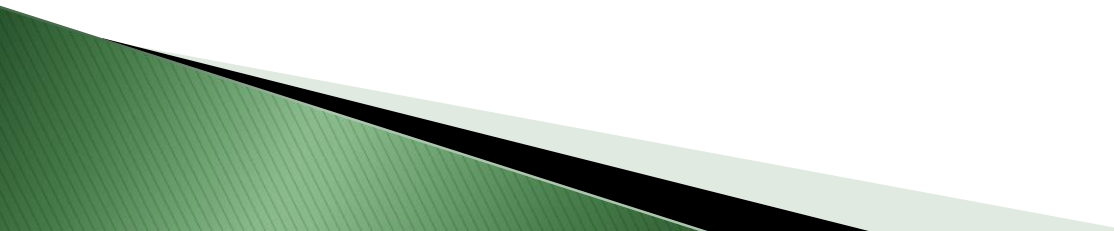
Discussions

- ▶ PLS is a cause of HA in recipients of minor ABO-incompatible solid organs.
- ▶ The diagnosis can be easily missed and only few patients require transfusion.
- ▶ However, clinicians should have a high index of suspicion for PLS in any recipient of an ABO organ mismatch presenting with haemolysis in the first 3 weeks following organ transplant

Passenger Lymphocyte Syndrome (PLS)

Definition


The PLS refers to the clinical phenomenon of alloimmune haemolysis resulting from the antibodies produced by viable donor B lymphocytes “passenger lymphocytes” in a primary or secondary immune response against the recipient’s red blood cell antigens



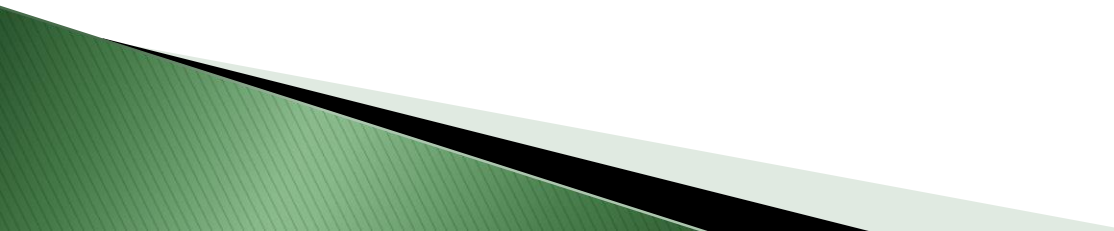
History

- ▶ The appearance of unexpected antibodies of A and B specificity in recipients of kidney allografts from ABO minor mismatched donors was first reported in the early 1980s.
- ▶ Then, more than 100 cases involving liver, kidney, pancreas, spleen, heart, lung, and heart-lung were published in 1991.

PLS can occur after

- ▶ Solid organ transplant
 - ▶ Stem cell transplant
 - ▶ Administration of B cell rich cellular therapeutic infusions
 - ▶ PLS most often seen in solid organ transplantation with minor ABO mismatch
 - ▶ Donor Group O / Recipient Group A,
 - ▶ Also reported with other blood group systems like Rh, K, Fy, Kidd
 - ▶ Donor lacks recipient's antigens
 - ▶ Donor can form antibodies against recipient's red blood cell antigens
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Pathophysiology

- ▶ PLS is heterogeneous
 - ▶ Donor B-lymphocytes are detected in recipients but antibody production is either delayed or is never detectable
 - ▶ Both donor B-lymphocytes and antibody are detected but haemolysis may not occur
 - ▶ The triggers for antibody production and haemolysis is still incompletely understood
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PLS – risk factors

Table 2: Risk factors for PLS

Risk factors

- Blood group O to A transfer
 - Possible sensitizing events: Pregnancy, blood transfusions
 - Cyclosporin use
 - Infection in the immediate posttransplantation period
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Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600

PLS - Solid organ transplantation

- ▶ PLS following solid organ transplantation has been reported to be;
- ▶ 09% for kidney transplants
- ▶ 29% for liver transplants
- ▶ 70% for heart-lung transplants

Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600

- ▶ These differences are likely to reflect the amount of lymphoid tissue implanted with the corresponding organ transplant

PLS – Worth anticipating

- ▶ Be vigilant about ABO and minor blood group incompatibilities
- ▶ Identify the risk factors
- ▶ Daily DAT starting 3 – 4 days post op aids early detection
- ▶ Use of donor-compatible RBCs prophylactically in the perioperative and immediate postoperative setting might reduce the development of graft associated immune haemolysis, but remains an untested hypothesis.

Fung et al. Transfusion 2004;44:1635-1639



References and good read

- ▶ *Nadarajah et al. American Journal of Transplantation 2013; 13: 1594–1600*
- ▶ *Maxime Audet et al. Clinical & Developmental Immunology 2008; ID 715769*
- ▶ *Fung et al. Transfusion 2004;44:1635-1639*
- ▶ *Gniadek et al. Transfusion 2017;57:1262–1266*