ARTICLE **SHORT COMMUNICATION**

Passenger Lymphocyte Syndrome the Standpoint of Transfusion Medicine: Short Communication

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Passenger lymphocyte syndrome (PLS) is a subtype of graft-versus-host disease. I is observed in patients within days to weeks (typically 10-14 days) after a minor ABO-mismatched solid organ or hematopoietic stem cell transplantation (HSCT) (1). While major ABO incompatibility is not a contraindication for stem cell transplantation, it remains a barrier to solid organ transplantation (2). Major ABO incompatibility refers to donor red blood cells (RBCs) that are incompatible with the recipient's plasma. In HSCT, major ABO incompatibility is associated with delayed engraftment, pure red cell aplasia, and, rarely, hemolysis (3). Minor ABO-incompatible donors are eligible for both HSCT and solid organ transplants. Minor ABO incompatibility occurs when the recipient's RBCs are incompatible with the donor's plasma, such as when a patient with ABO group B receives organs or hematopoietic stem cells from a patient with ABO group O. Bidirectional ABO incompatibility arises when both the donor and recipient have antibodies against each other's ABO blood groups, as seen when a patient with ABO group A receives organs from a donor with ABO group B (2).

PLS can lead to autoimmune hemolytic anemia due to the transfer of donor B-lymphocytes capable of producing antibodies throughout their survival. This anemia is typically mild and self-limiting (Figure 1). ABO and Rh antibodies are the most commonly identified antibodies in PLS patients, with ABO antibodies primarily causing hemolysis through complement fixation on RBC membranes. The risk of developing PLS depends on several factors, including antibody titers and antigen density. Homozygote expression of a red cell antigen in recipients leads to greater sensitization and hemolysis compared to heterozygote expression (1). Although cases of PLS were reported earlier, the term "passenger lymphocytes" was coined in 1981. PLS most commonly occurs following lung and heart transplants, followed by liver transplants. However, the incidence of PLS is decreasing due to immunosuppressive therapy and reduced donor lymphocyte dosage (4).

Close monitoring of patients using blood type and screen testing (T&S) and direct agglutination test (DAT) can serve as early indicators of PLS. The appearance of unexpected antibodies against the patient's ABO antigens in the serum indicates the activity of donor B-lymphocytes in the graft and is a crucial factor for diagnosis. Transfusion Medicine, also known as Blood Bank, establishes a baseline and follows up with patients post-transplant to detect these

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antibodies. The antibody testing involves T&S followed by DAT or direct Coombs' test. Only one blood draw is required for three different tests that detect ABO antigen/group, Rh (D-antigen), and non-ABO antibodies. ABO antigen/group testing consists of two components: front and back typing. Front typing tests the patient's RBCs for the presence of A-antigen, B-antigen, or both. Back typing involves testing the patient's plasma for the expected antibodies of the patient's ABO group (5). Patients with PLS exhibit unusual activity in their back types (Table 1 shows an example of a patient who developed PLS).

DAT is a test that detects the presence of attached antibodies on the surface of a patient's RBCs by adding antihuman globulin (AHG), which causes agglutination by binding to the antibodies attached to the RBC surface (5). A positive DAT in PLS patients also indicates in vivo hemolysis (Figure 2 illustrates the differences between direct Coombs' and indirect Coombs' tests).

Non-ABO antibodies, specifically antibodies directed against minor blood group antigens, are implicated in PLS patients (6). These antibodies primarily include Rh system (anti-D, anti-C, anti-E, and anti-V), Kell system (anti-K and anti-Kpb), Kidd system (anti-Jka), Lewis system (anti-Lea), and anti-M and anti-N (1). It is important to note whether the formation of non-ABO antibodies is de novo, resulting from the donor B-lymphocytes being exposed to new antigens, or if it is a passive transfer from the donor to the recipient. Therefore, screening the donor prior to transplantation is essential.

Patients with PLS typically present with signs and symptoms of hemolysis and should be evaluated and managed as with any other hemolytic anemia. The approach recommended by the American Society of Hematology involves investigating clinically suspicious cases through specific laboratory testing, such as RBC indices, reticulocyte count, unconjugated bilirubin, haptoglobin, and peripheral blood smear (7). To diagnose PLS, these tests must be combined with the patient's clinical history and transfusion medicine workup. Some cases may have a subclinical presentation, particularly if the patient experiences perioperative complications that can mask the hemolysis caused by PLS.

In the presence of ABO antibodies, patients should be transfused with "O" RBC units. In the case of antibodies against minor blood groups, RBC units that are negative for these specific antigens should be transfused. Plasma products should be ABO type compatible with the recipient. Other treatment options include fluid administration, immunosuppression with corticosteroids, rituximab (an anti-CD20 antibody therapy), and, to a lesser extent, alemtuzumab (an anti-CD52 antibody therapy), as well as intravenous immunoglobulin (to decrease the rate of antibody formation by B-lymphocytes) or plasma exchange (to remove antibodies formed in the recipient's plasma) (8).

In summary, the prognosis for PLS is generally favorable. It is crucial to initiate post-transplant surveillance immediately to facilitate early detection and proper management of these cases.

Figure 1. An example of PLS, the donor's ABO group is O, and recipient is A. Donor B-lymphocytes are transferred with the transplanted organ and start forming antibodies (Anti- A) against the recipient's ABO group, resulting in hemolytic anemia.

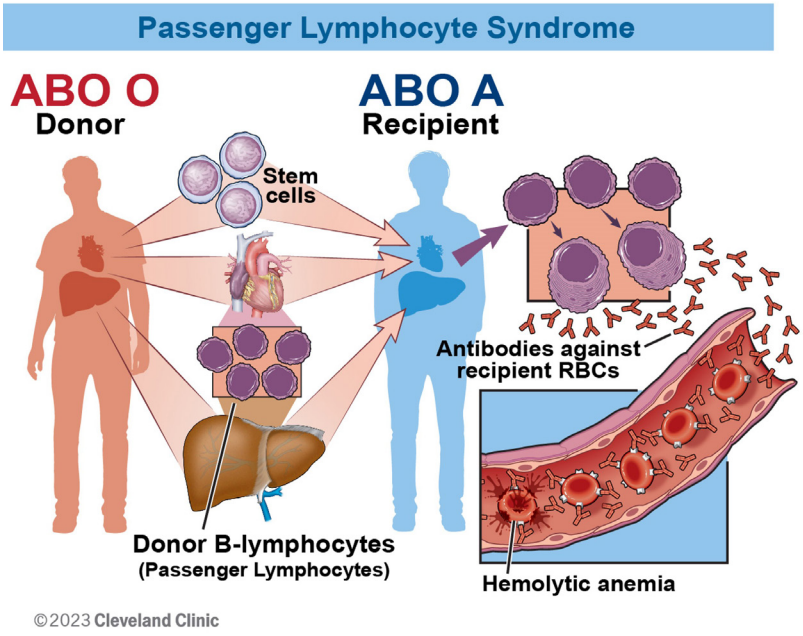

Figure 2. Direct Coombs test (top image). Indirect Coombs test (bottom image)

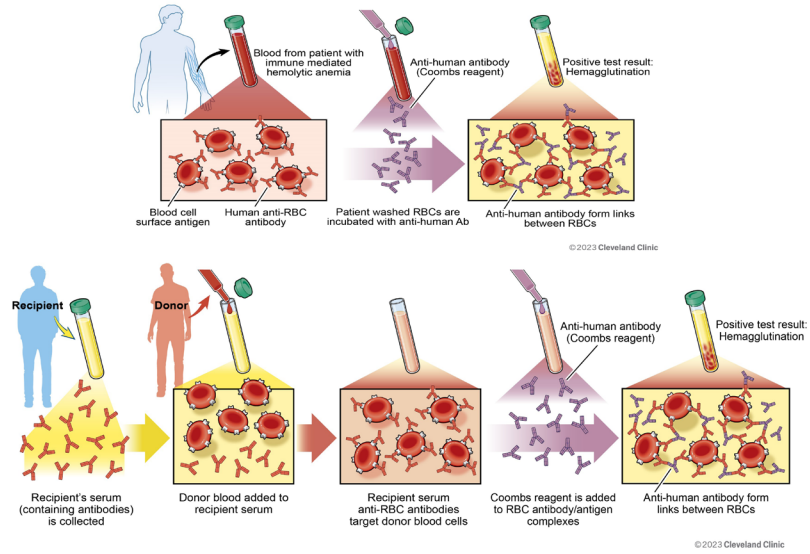

Table 1. Shows a patient with ABO group A pre and post HSCT transplant from ABO group O donor.

Front Type (detecting antigens on Patient's RBC)		Back Type (detecting antibodies in patient's serum expected for patient's ABO group		Transplant Status	ABO Blood Group
Anti-A	**Anti-B**	A1 RBC (Reagent cells)	B RBC (Reagent cells)		
4+ (positive)	0 (negative)	0	4+	Pre- transplant	**A**
4+ (positive)	0 (negative)	1+ (weak positivity)*	4+	Post- transplant	

* Antibodies formed by B- lymphocytes from the O-donor are detected in the serum of the patient indicating possible PLS.

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