Immune Hemolysis Associated With Transplantation

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Immune hemolysis is one of the adverse effects that can occur following hematopoietic cell or solid organ transplantation. Understanding the clinical settings and the various causes of immune hemolysis is necessary for prompt diagnosis and appropriate management. One of the important causes is the passenger lymphocyte syndrome, which occurs following minor ABO blood group incompatibility between donor and recipient. Hemolysis in this syndrome is often modest in severity but may be severe and even life-threatening. Major ABO blood group incompatibility is also associated with hemolysis, although this is relatively unusual and generally not severe. Autoimmune hemolytic anemia is a relatively common late complication of allogeneic transplantation and carries significant risk of mortality. Also, alloantibodies may be produced by engrafted cells of the donor's immune system or by residual cells of the patient's immune system following hematopoietic cell transplantation. Hemolysis may occur after solid organ transplantation, particularly as part of the passenger lymphocyte syndrome.
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I mmune hemolysis is one of the adverse effects that can occur following hematopoietic cell or solid organ transplantation. Understanding the clinical settings and the various causes of immune hemolysis is necessary for prompt diagnosis and appropriate management.

Table 1 lists the most frequent causes of hemolysis following hematopoietic cell transplantation (HCT). This review encompasses those that have an immune etiology, although it should be noted that there are a number of non-immune causes that must be considered. The clinical setting often provides an important clue to the diagnosis, as in the passenger lymphocyte syndrome, described below. However, a major pitfall is that hemolytic syndromes often begin abruptly and unexpectedly, and the acute onset sometimes results in a delay in diagnosis while more common post-transplant problems such as graft-versus-host disease (GVHD) and veno-occlusive disease of the liver are inappropriately considered as reasons for elevated bilirubin and anemia. Delay in instituting appropriate therapy may result in unnecessary morbidity.

Minor ABO Blood Group Incompatible Hematopoietic Stem Cell Transplants

Passenger Lymphocyte Syndrome

A well-recognized syndrome of immune hemolysis following HCT has become known as the passenger lymphocyte syndrome.[1–5] This syndrome occurs in some patients who are transplanted with hematopoietic stem cells from a minor ABO blood group mismatched donor. Occasionally, mismatches of other blood groups result in similar, although milder, hemolysis. The syndrome has been attributed to proliferation and antibody production by "passenger" lymphocytes, which are infused with the stem cell product. A typical case is illustrated in Fig 1 and clinical and laboratory data regarding six patients described by Hows et al[2] are listed in Table 2. (In one patient, the passenger lymphocyte syndrome was caused by minor Rh incompatibility.)

Predisposing Clinical Factors

Several factors may increase the risk of development of passenger lymphocyte syndrome[6,7]: the use of cyclosporine alone in the absence of an antiproliferative agent such as methotrexate for post-transplant GVHD prophylaxis,[1,2,6] the use of peripheral blood as a source of the hematopoietic stem cells,[7–9] the use of a reduced-intensity pretransplant preparative regimen,[10] utilization of a nongenotypically human leu-

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Table 1 The Differential Diagnosis of Hemolysis Following Hematopoietic Stem Cell Transplantation

Minor ABO blood group incompatibility
  Passenger lymphocyte syndrome
  Antibody in the donor marrow product
Major ABO blood group incompatibility
  Immediate hemolysis of RBCs in donor stem cell product
  Early posttransplant hemolysis of RBC in donor stem cell product caused by rebound of isohemagglutinins after
    transplantation in patients treated with plasma exchange prior to transplantation
  Delayed hemolysis of RBCs produced by the newly engrafted marrow caused by residual isohemagglutinins
Red cell alloantibodies of blood groups other than ABO
  Alloantibodies produced by engrafted cells of the donor's immune system
  Alloantibodies produced by residual cells of the patient's immune system
Autoimmune hemolytic anemia
Passive transfer of antibody
  Plasma transfusion
  Platelet transfusion
  Intravenous immunoglobulin
  Other causes of passive transfer of antibody, eg, packed RBCs, intravenous anti-D, and antilymphocyte globulin
Drug-induced hemolylic anemia
Microangiopathic hemolytic anemia
Miscellaneous additional causes of hemolysis following bone marrow transplantation
  Infusion of cryopreserved stem cell products
  Infusion of dimethylsulphoxide (DMSO) and free plasma hemoglobin
Clostridium perfringens septicemia
Hemolysis associated with hemodialysis

kocyte antigen (HLA)-matched donor, and, possibly, a female donor.[1] No instances of the passenger lymphocyte syndrome have been reported after umbilical cord blood HCT.

Clinical Findings

Immune hemolysis generally begins near the end of the first week or during the second week post-transplant. Hemolysis is usually abrupt in onset and may be severe, with a rapidly

Figure 1 Minor ABO-mismatched bone marrow transplant (BMT) (donor group O, recipient B). Flow chart shows hematologic and biochemical evidence for hemolysis. Fourteen units of packed group O RBCs were required to maintain the hemoglobin between day 10 and day 19 post-BMT. Note that hemoglobin, LDH, and total bilirubin levels were normal for the first 5 days post-BMT. During the hemolytic episode, no incompatible isohemagglutinins were infused; RBCs transfused were washed group O, and platelets were group B or washed and resuspended in fresh AB plasma. Reprinted from Hows J, Beddow K, Gordon Smith E, et al: Donor-derived red blood cell antibodies and immune hemolysis after allogeneic bone marrow transplantation. Blood 1986;67:177-181.

dropping hemoglobin level, signs of intravascular hemolysis (hemoglobinemia and hemoglobinuria),[2,6,11,12] and renal failure.[6,11,13,14] Less severe cases are characterized by a falling hemoglobin level, an increase in serum bilirubin and lactate dehydrogenase (LDH), and decreased serum haptoglobin.

Hemolysis usually persists for 5 to 10 days and then subsides as the patient's residual incompatible red blood cells (RBCs) are destroyed and then replaced by transfused group O RBCs and/or by RBCs of donor type produced by cells derived from the engrafted stem cells. Also, antibody production gradually decreases as the passenger lymphocytes, which are not engrafted, reach the end of their life span.
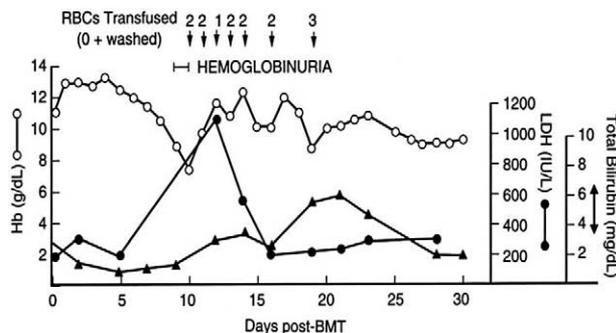
Serologic Findings

Typical serologic findings are displayed in Table 3. The direct antiglobulin test (DAT) is positive using anti-IgG and/or anti-C3, and the relevant serum antibody is demonstrable in the patient's serum and eluate. The specificity of the antibody will be one that can be produced by cells of the donor against antigens on the RBCs of the patient.

Generally, serologic findings are evident at the onset of hemolysis. However, in a minority of patients, signs of hemolysis may precede by 1 or 2 days the ability to detect the expected antibody.[1,12,15]

The passenger lymphocyte syndrome is most likely to occur when the donor is group O and the patient group A, perhaps related to the fact that IgG anti-A and anti-B are far more common in group O than in B or A subjects.[16] Pretransplant anti-A and anti-B titers in the donor do not appear to be helpful in predicting which patients will develop the passenger lymphocyte syndrome or the severity of hemolysis.[2]

Table 2 Clinical and Laboratory Data Regarding Six Patients Who Received Bone Marrow Transplants From a Minor ABO-Incompatible Donor and Who Developed Hemolytic Anemia in the Post-transplant Period

Case No.	ABO Group and Rh Type		Details of Hemolysis and RBC Transfusion Requirement
	D	R	
1	O+	A−	Severe intravascular hemolysis; hemoglobinuria; maximum hemolysis day +15; treated with plasma exchange; 9 units RBCs required day +10 to +15
2	O+	A+	Moderate hemolysis, maximum day +16; 6 units RBCs required day +16 to +22
3	O+	B+	Severe hemolysis; hemoglobinuria; maximum day +10; 14 units RBCs required day +10 to +19
4	O+	A+	Moderate hemolysis, maximum day +10; 7 units RBCs required day +9 to +18
5	B+	AB+	Moderate hemolysis; maximum day +12; 6 units RBCs required day +11 to +14
6	A−	A+	Moderate hemolysis, maximum day +13; 5 units RBCs required day +9 to +16

Abbreviations: D, donor; R, recipient.
Reprinted from Petz LD: Immunohematologic problems unique to bone marrow transplantation. In Garratty G (ed): Red Cell Antigens and Antibodies. Arlington, VA: American Association of Blood Banks, 1986:195–229.

Antibodies Other Than Those of the ABO Blood Group System Produced by Passenger Lymphocytes

Antibodies other than anti-A and anti-B have been reported to cause the passenger lymphocyte syndrome, but they are unusual and generally do not cause severe hemolysis. Antibodies that have been reported are anti-D and -E, anti-s, anti-Jk[b], and anti-Jk[a].[1] Cases of non-ABO immune hemolysis frequently involve donors and recipients with no prior evidence of alloantibodies, thus making it impossible to predict which patients are at risk.

Source of Antibody Causing Hemolysis

The syndrome has been attributed to production of antibody by rapidly proliferating "passenger" lymphocytes transfused with the donor stem cell product; antibodies persist until the culpable lymphocytes reach the end of their life span. Detailed serologic studies indicate that the relevant serum antibody is not present in the immediate post-transplant period but is first detectable at about the time hemolysis becomes evident.[2–4] Therefore, passive transfer during infusion of the donor's plasma with the stem cell product cannot account for the presence of the antibody. Also, antibody production and hemolysis generally occur before clinical evidence of engraftment while pancytopenia caused by the pretransplant preparative regimen is present and prior to immune reconstitution of the patient.

Patients With Massive Hemolysis

Of particular concern are the reports of massive hemolysis after minor ABO-incompatible marrow or peripheral blood stem cell allotransplantation[6,8,11–13,15] leading to renal insufficiency[6,10,12,13] and even fatal multisystem organ failure.[13]

Striking hemolysis in seven patients transplanted with minor ABO-incompatible marrow grafts from matched unrelated donors was accompanied by renal failure severe enough to require hemodialysis in four.[6] The course of one of these three patients is illustrated in Fig 2. Transfusion requirements in three of the patients with massive hemolysis (Table 4) were far greater than could be accounted for by lysis of the patients' ABO-incompatible erythrocytes. The patients' RBC volumes on day 5 ranged from 1,592 to 2,039 mL, whereas

Table 3 Serologic Investigation of Patients Presenting With Immune Hemolysis

Case No.	Maximum Hemolysis Day Post-BMT	ABO Group Rh Type		DAT Positive for:	Day Post-BMT DAT First Positive	Antibody in Eluate	Antibody in Serum	Day Post-BMT Serum Antibody Last Detected
		D	R					
1	+15	O+	A−	C3	+18	ND	Anti-A	+38*
2	+16	O+	A+	C3	+15	ND	Anti-A	+24*
3	+10	O+	B+	IgG+ C3	+10	Anti-B	Anti-B	+42*
4	+10	O+	A+	C3	+4	Anti-A	Anti-A	+30*
5	+12	B+	AB+	C3	+9	Anti-A	Anti-A	+42*
6	+13	A−	A+	IgG	+13	Anti-D	Anti-D	+70†

Abbreviations: BMT, bone marrow transplant; DAT, direct antiglobulin test; D, donor; R, recipient; ND, not done.
*Serum antibody not detectable in subsequent followup.
†Anti-D titer 256; later samples not tested.
Reprinted from Hows J, Beddow K, Gordon Smith E, et al: Donor-derived red blood cell antibodies and immune hemolysis after allogeneic bone marrow transplantation. Blood 1986;67:177–181.
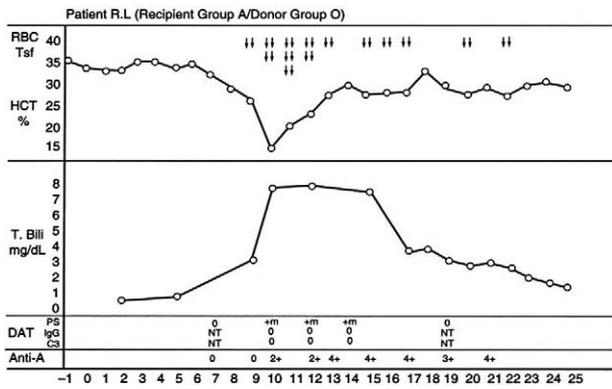
Figure 2 Flow chart of index group patient not receiving pretransplant exchange transfusion showing transfusion requirements with biochemical and serologic evidence for hemolysis; RBC Tsf, RBC transfusions (arrows); DAT, direct antiglobulin reagent; PS, polyspecific (anti-IgG + C3); IgG, anti-IgG reagent; C3, anti-C3; 4+, cells agglutinated in one clump; 3+, cells agglutinated in three to six very large clumps; 2+ cells agglutinated in many medium clumps; 1+, cells agglutinated in numerous tiny clumps, very cloudy background; +m, very tiny agglutinates only seen microscopically; O, no agglutinates detected; NT, not tested; ↓, transfusion. Reprinted from Gajewski JL, Petz LD, Calhoun L, et al: Hemolysis of transfused group O red blood cells in minor ABO-incompatible unrelated-donor bone marrow transplants in patients receiving cyclosporine without posttransplant methotrexate. Blood 1992;79:3076-3085.

the volume of RBCs transfused for each patient was 4,680 mL (26 units of RBCs at 180 mL/U). All of the units of transfused RBCs were group O and were saline-washed. Since none of the patients demonstrated any signs of bleeding, the conclusion was that large volumes of transfused group O RBCs were hemolyzed in addition to the patients' own RBCs.

Bystander Hemolysis

Since the only RBC antibodies detected in these patients were anti-A and anti-B, yet group O RBCs were also hemolyzed, hemolysis of antigen-negative RBCs occurred. We refer to this as "bystander immune hemolysis," defined as immune hemolysis of cells that are intrinsically negative for the antigen against which the relevant antibody is directed.[1,6,17]

Transplant physicians have been cautious in acceptance of the concept of bystander immune hemolysis in some patients with the passenger lymphocyte syndrome, but there have been an increasing number of reports of massive hemolysis that is far more extensive than can be explained on the basis of hemolysis of the patient's own RBCs. Accordingly, bystander immune hemolysis has been discussed frequently in the recent medical literature.[9,15]

Additional Reports of Severe Hemolysis

Numerous additional reports of severe hemolysis due to the passenger lymphocyte syndrome have been published.[1] Greeno et al[12] reported a patient with hemolysis of her entire group A RBC population between days 8 and 11. By day 11, the circulating RBCs were completely group O but she continued to require transfusion of 2 units of group O RBCs every 2 to 3 days for an additional 10 days for a total of 16 units of RBCs (about 2,800 mL of RBCs). Tiplady et al[15] reported a 28-year-old man with lymphoblastic lymphoma who received granulocyte colony-stimulating factor (G-CSF)–mobilized stem cells from his HLA-identical sister. The recipient's blood group was A Rh D-positive and the donor's group was O Rh D-positive. From day 9 to day 13 he received 17 units of group O blood (approximately 3 L of RBCs) at a time when his calculated RBC volume was 1 L. By day 26 a further 8 units of blood had been transfused, bringing the total to 28. The excessive transfusion requirements led the investigators to speculate that hemolysis of compatible blood was occurring, as only anti-A and anti-B were found in the patient's serum. They noted that bystander hemolysis is a very rare, albeit clinically serious complication of HCT. Worel et al[9] described four patients who developed the passenger lymphocyte syndrome, one of whom received 40 units of RBCs during the first 30 days following transplantation of a minor ABO incompatible transplant using peripheral blood stem cells and a nonmyeloablative conditioning regimen. The patient ultimately died of multi-organ failure on day 35. The extent of hemolysis suggested bystander hemolysis in addition to immune hemolysis due to ABO incompatibility.

Table 4 Transfusion Requirements of Group O RBCs in Three Patients Transplanted With Bone Marrow From Unrelated Minor ABO-Incompatible Donors

Patient	Patient's RBC Volume Day +5 (mL)	Volume of RBCs Transfused Day +5 to +20 (mL)	Baseline Transfusion Requirement* Day +5 to +20 (mL)	Excess Transfusion Requirement† Day +5 to +20 (mL)
1	2,039	4,680	1,733	908
2	1,592	4,680	1,353	1,735
3	1,635	4,680	1,389	1,656

*Baseline transfusion requirement was determined by measuring the transfusion requirements during days +5 to +20 in 61 marrow transplant patients in whom the donor and recipient were ABO identical. This value was 0.85 times the RBC volume on day +5.

†Excess transfusion requirement is defined as the volume of group O RBCs required above the sum of the baseline transfusion requirement and the patient's volume of (ABO incompatible) RBCs on day +5. Thus, even if all of the patient's ABO-incompatible RBCs were hemolyzed and there is, in addition, a baseline transfusion requirement, an average of almost 1.5 liters additional group O RBCs needed to be transfused. Therefore, not only were the patient's ABO-incompatible RBCs hemolyzed, but transfused group O RBCs must have been hemolyzed as well.

Reprinted from Petz LD: The expanding boundaries of transfusion medicine. In Nance SJ (ed): Clinical and Basic Science Aspects of Immunohematology. Arlington, VA: American Association of Blood Banks, 1991:73–113.

Bolan et al[7] reported massive immune hemolysis in three of 10 consecutive patients undergoing HLA-identical, related-donor peripheral blood stem cell transplants with minor ABO incompatibility. Nonablative conditioning had been given in nine patients, including two with hemolysis. Cyclosporine alone was used as prophylaxis against GVHD. Catastrophic hemolysis of 78% of the circulating RBC mass led to anoxic death in the first case they observed (Fig 3). In their second patient, the authors calculated that hemolysis of more than 80% of the patient's estimated RBC mass had occurred during a 36-hour period. In their third patient, the volume of RBCs transfused between days 5 and 11 was equivalent to the patient's entire estimated RBC volume. The patient also required "numerous" additional RBC transfusions, the need for which was attributed to the development of pulmonary hemorrhage on day 13 and thrombotic microangiopathy on day 26. Haas et al[18] reported a group A_1 patient who was transplanted with T-cell–depleted bone marrow from a group O donor. The patient developed a positive DAT and anti-A_1 was found in the serum. On day 6, the patient developed life-threatening intravascular hemolysis, with the hemoglobin dropping from 11.8 to 3.8 g/dL in 6 hours.

Management of Patients Receiving Hematopoietic Cell Transplants from Minor ABO Incompatible Donors

Volume Reduction of Marrow Products to Prevent Hemolytic Transfusion Reaction

Since the volume of a bone marrow product for a transplant recipient may be 700 mL or greater, anti-A and anti-B in the
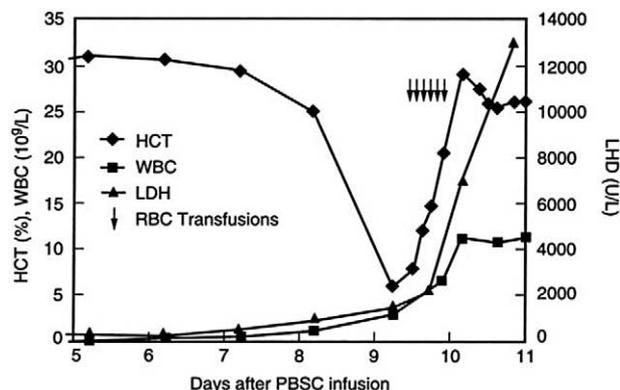

Figure 3 Course of severe hemolysis in a patient. On days 8 and 9 after transplantation, fever, hemodynamic instability, and renal insufficiency occurred; hematocrit dropped precipitously and LDH doubled. Although the hematocrit responded to transfusions with group O RBCs, cardiopulmonary arrest occurred, renal failure ensued, neurologic function did not recover; and the patient died on day 16. Serologic testing revealed that donor-type anti-A isohemagglutinins were the cause of massive immune hemolysis. Reprinted from Bolan CD, Childs RW, Procter JL, Barrett AJ, Leitman SF: Massive immune haemolysis after allogeneic peripheral blood stem cell transplantation with minor ABO incompatibility. Br J Haematol 2001;112:787-795.

donor plasma may cause an acute hemolytic transfusion reaction. One option is to measure the anti-A and/or anti-B titer on each marrow donor when there is a minor ABO incompatibility with the intended recipient. If the titer of the relevant antibody is greater than 256, one should consider plasma reduction of the marrow product. The decision is reached on the basis of the height of the anti-A or anti-B titer, the adequacy of the marrow harvest, and the knowledge that some stem cells will be lost during manipulation of the marrow. Studies in bone marrow transplant recipients have indicated that transfusion of ABO incompatible RBCs to patients with anti-A or anti-B titers of ≤16 produced no evident hemolysis.[19] Thus, in calculating the amount of plasma reduction that might be appropriate for a given product, reducing the volume of plasma to be transfused so that the post-transfusion anti-A or anti-B titer will be less than 16 should make serious hemolysis unlikely.

Pretransplant RBC Exchange Transfusion

Hemolysis caused by passive transfer of antibody in bone marrow products may be minimized by performing pretransplant RBC exchange transfusions using red cells of the donor's type. However, since significant hemolysis caused by antibodies in the donor marrow is rare and can be prevented more easily by plasma reduction of the donor marrow product when high-titer antibodies are detected in the donor, routinely subjecting patients to such an extensive procedure as exchange transfusion to avoid hemolysis by passive transfer of antibody is not appropriate. In contrast, Worel et al[9] recommend prophylactic RBC exchange, especially for patients who receive a peripheral blood stem cell graft in combination with a GVHD prophylaxis regimen without methotrexate.

Since pretransplant anti-A and anti-B titers do not appear to predict the incidence or severity of hemolysis following minor ABO-mismatched transplants,[2] selection of patients to undergo pretransplant exchange transfusion on the basis of these titers would not seem indicated.

Monitoring the Recipient for Development of the Passenger Lymphocyte Syndrome

Since hemolysis resulting from the passenger lymphocyte syndrome usually has its onset between days 3 and 15 post-transplant, routine monitoring of all patients receiving a minor ABO-mismatched hematopoietic stem cell transplant is indicated, for the presence of hemolysis and for donor-derived antibodies during this period. Usually, the syndrome is readily detected by the presence of signs of hemolysis, a positive DAT, and the relevant antibody (usually anti-A or anti-B) in the patient's serum and in a RBC eluate.

Management of Patients With the Passenger Lymphocyte Syndrome

In most instances, hemolysis caused by the passenger lymphocyte syndrome may be managed by transfusion of compatible RBCs, the empirical use of corticosteroids,

avoidance of ABO-incompatible plasma products, and maintenance of adequate renal perfusion. Such supportive care is generally adequate since hemolysis will be self-limiting because newly formed RBCs produced by the donor marrow will not be affected by the donor-derived antibody.

For massive hemolysis, exchange transfusion can be considered, to replace the patient's antigen-positive erythrocytes with group O RBCs. This therapeutic maneuver has been used and perhaps is an effective means of preventing the renal failure that has resulted from hemolysis in some patients.[6] Plasma exchange transfusion also should decrease the concentration of the causative antibody.

Selection of Blood Products

The appropriate selection of blood products for patients receiving a minor ABO-incompatible HCT are indicated in Table 5.[20] It is generally most practical to transfuse group O RBCs from the beginning of the preparative regimen. Although packed RBCs will contain anti-A and/or anti-B that are reactive with the patient's RBCs, hemolysis caused by transfusion of plasma in RBCs is rare so that using washed RBCs is generally unnecessary. (In those unusual cases in which the donor is group A or B and the recipient is group AB, the donor's type RBCs may be used instead of group O.)

Platelets and other plasma-containing products of recipient type are generally used to avoid the transfusion of anti-A and/or anti-B reactive against RBCs of the patient, even though passive transfusion of such antibodies in plasma products is only infrequently an important contributing factor. When the patient has converted to donor group RBCs, ABO-matched platelets would be preferable since they are generally recommended for platelet transfusions.

Major ABO Blood Group Incompatible Hematopoietic Cell Transplants

Immune Hemolysis of RBCs in the Stem Cell Product

Since the volume of RBCs in a bone marrow product may be equal or greater than in a unit of RBCs, the potential exists for an immediate hemolytic transfusion reaction due to ABO incompatibility. This may be prevented by removal of the RBCs from the donor marrow or by removal of allohemagglutinins from the recipient.

Hemolysis of RBCs Produced by the Newly Engrafted Marrow Caused by Persistence of ABO Antibodies

Although ABO antibodies usually become undetectable during the second month following major ABO-incompatible HCT,[21] this is not always the case. Indeed, Van Tol et al[22] reported that IgG of recipient origin persisted in 15 of 18 informative recipients (83%) for several years after bone marrow transplant.

Prolonged persistence of ABO antibodies may result in hemolysis of RBCs produced by the newly engrafted marrow. Anti-A or anti-B persisted for longer than 120 days post-transplant in nine of 58 evaluable patients receiving a major ABO-incompatible marrow transplant.[23] Five patients developed overt hemolysis at a time when ABO antibodies were still detectable but had decreased to a low titer (≤4). Hemolysis started on day 37 to 105 (median, day 65), persisted for 10 to 94 days (median, 36 days), and was manifested by a drop in hemoglobin of 1.5 to 4 g/dL (median, 2.5 g/dL), increases in bilirubin and LDH, and decreases in serum hap-

Table 5 ABO-Incompatible Bone Marrow Transplantation (from preparative regimen until engraftment)

Recipient	Donor	RBCs	Platelets: First Choice	Platelets: Second Choice*	FFP*
Major incompatible					
O	A	O	A	AB, B, O	A, AB
O	B	O	B	AB, A, O	B, AB
A	AB	A	AB	A, B, O	AB
B	AB	B	AB	B, A, O	AB
O	AB	O	AB	A, B, O	AB
Minor incompatible					
A	O	O	A	AB, B, O	A, AB
B	O	O	B	AB, A, O	B, AB
AB	O	O	AB	A, B, O	AB
AB	A	A	AB	A, B, O	AB
AB	B	B	AB	B, A, O	AB
Major and minor incompatible					
A	B	O	AB	A, B, O	AB
B	A	O	AB	B, A, O	AB

NOTE. Engraftment occurs when forward and reverse types are of donor and the DAT is negative.

*Avoid high titer ABO antibodies

toglobin. Additional cases have been reported by Lopez et al[24] and Biggs et al.[25] However, transient hemolysis of RBCs produced by the newly engrafted marrow caused by persistent ABO antibodies seems to be observed infrequently. Neither Gmur et al[26] nor Bar et al[27] identified episodes of hemolysis in their reports of 15 and 30 evaluable patients, respectively, who were transplanted with major ABO-incompatible marrows.

Management of Patients Receiving a Hematopoietic Cell Transplant From a Major ABO-Incompatible Donor

Prevention of Acute Hemolysis

Two general principles are used to prevent acute hemolysis resulting from transfusion of incompatible RBCs at the time of donor marrow infusion. RBCs can be removed from donor marrow products or ABO antibodies removed from the patient. In an analogous fashion, the RBC content of peripheral blood stem cell products may be minimized prior to cryopreservation. Additionally, RBCs are often removed from cord bloods prior to cryopreservation, but this procedure was developed primarily to satisfy the need to have a small volume for storage of the thousands of samples that are collected in cord blood banks.

Treatment of Delayed Hemolysis

Management of this rather uncommon complication of major ABO-incompatible transplants has only required supportive management with transfusion of group O RBCs.

Selection of Blood Products

From the onset of the preparative regimen, it is advisable to use group O RBCs when transfusion is necessary, although the recipient type RBCs may be used for group A or B patients in those unusual cases in which the donor is group AB (Table 5). Ultimately, when the patient's ABO antibodies become undetectable, RBCs of the donor's type may be transfused.

It is reasonable to minimize the administration of plasma that contains ABO antibodies that will react with RBCs of donor type. This is best accomplished by providing platelet products that are of donor type. If such platelets are not available, volume reduction of the platelets may be performed, although the amount of antibody in the platelet products is usually not a significant factor in causation of hemolysis. The use of washed RBCs or washed platelets as a means of minimizing plasma administration is generally unnecessary.

Autoimmune Hemolytic Anemia Following Hematopoietic Cell Transplantation

Another cause of hemolysis following HCT is autoimmune hemolytic anemia (AIHA). Hemolysis is thought to be due to antibodies produced by the donor's immune system against antigens on RBCs of donor origin, thereby qualifying these episodes of hemolytic anemia as AIHA. However, the source of the autoantibodies has not been documented definitively by immunoglobulin allotyping.

AIHA is a relatively common complication of HCT and has considerable morbidity and mortality as reported by O'Brien et al.[28] Between January 1995 to July 2001, 439 consecutive patients, less than 18 years, underwent allogeneic HCT (303 from unrelated donors, 136 from related donors). Nineteen patients developed AIHA. All 19 cases occurred following unrelated donor transplants ($P = .02$), giving a cumulative incidence of AIHA in this population of 6% (95% confidence interval, 4% to 8%) at 1 year post HCT. Median time of onset for AIHA was 4 months from HCT (range, 1.2 to 28.8 months). Multiple regression analysis (adjusting for age, HLA matching, stem cell source [cord blood v bone marrow), T-cell depletion, differences in conditioning regimens, acute GVHD, ABO matching, recipient cytomegalovirus status) found the only significant independent prognostic factor was pretransplant diagnosis. Patients with a metabolic storage disorder were 4.2 times more likely to develop AIHA posttransplant and patients with other nonmalignant disorders, 1.9 times more likely when compared to patients with a malignancy ($P = .01$ and $P = .07$, respectively). Mortality was high: 10 of 19 (52%) patients died, three (16%) as a direct consequence of hemolysis. Fifty percent of the deaths were related to fungal or viral infection occurring while on aggressive immunosuppressive therapy for hemolysis. Survival at 1 and 3 years post-HCT was less for patients with AIHA when compared with those without (32% v 69% and 28% v 57%, respectively). AIHA was severe and refractory in many patients despite a variety of treatment strategies, including cortiscosteroids, intravenous immunoglobulin, rituximab (n = 3), cyclophosphamide (n = 1), mycophenolate mofetil (n = 2), splenectomy (n = 1), and plasma exchange (n = 2). AIHA thus is a relatively common late complication of pediatric allogeneic HCT and carries significant risk of mortality. Patients transplanted for nonmalignant diseases, particularly metabolic, appear to be at greatest risk.

Drobyski et al[29] reported seven adults who developed AIHA among 236 patients who received T-cell–depleted marrow grafts. The onset of AIHA was at a median of 10 months (range, 7 to 25 months) post-transplant and occurred in 5% of all patients who survived at least 6 months. Six patients had a warm-reacting autoantibody, while one patient had a cold-reacting antibody. In the series reported by Chen et al,[30] nine of 293 patients (3.1%) developed AIHA after marrow transplantation. Three of the nine patients had matched unrelated donors and the other six had matched sibling donors; some of the marrow products were T-cell–depleted. Four patients developed AIHA with cold antibodies and five with warm antibodies. Cold antibody AIHA had an earlier onset beginning 2 to 8 months post-transplant, whereas AIHA associated with warm antibodies developed 6 to 18 months post-transplant. In both series the hemolysis was resistant to treatment and the overall prognosis was poor, although none of the patients died as a direct result of hemolysis but rather from associated problems such as sepsis and GVHD. A number of additional case reports of post-transplant AIHA have been published.[1] Although most cases have

been of the warm antibody type, cold agglutinin syndrome has also been described.[31–33] Several cases of AIHA have been reported after cord blood transplants,[34,35] including two patients with Evans' syndrome.[36,37]

RBC Alloantibodies of Blood Groups Other Than ABO Produced by Engrafted Cells of the Donor's Immune System or by Residual Cells of the Patient's Immune System Following Hematopoietic Cell Transplantation

Either complete chimerism or mixed chimerism may exist after HCT. Thus, RBC antibodies may be derived from cells of the immune system of the donor, the recipient, or both. Donor-derived alloantibodies produced as part of the passenger lymphocyte syndrome are produced by donor-derived lymphocytes that temporarily proliferate. The syndrome resolves after the passenger lymphocytes, which are not engrafted, reach the end of their life span. Hemolysis has its onset within the first few weeks after bone marrow transplant and is transient. In contrast, other patients develop donor-derived alloantibodies that are produced by the immune system of the donor long after transplant, presumably by engrafted cells of the donor's immune system. In still other patients, residual cells of the transplant recipient's immune system produce RBC antibodies.

Alloantibodies Produced by Engrafted Cells of the Donor's Immune System

Numerous reports of alloantibodies produced by cells of the donor have been reported, as might be expected when there is immune stimulation of the engrafted marrow as by RBC transfusion.[1] In seven of 12 patients[38] who developed non-ABO RBC alloantibodies after bone marrow transplant, the antibodies were first detected after day 45 to 330. A 32-year-old white man with chronic myeloid leukemia, never transfused, received G-CSF–mobilized peripheral blood progenitor cells from his HLA-identical sister; the patient was 0 Rh-K-Jk(a-) and the donor was 0 Rh-K-Jk(a+).[39] Pretransplant alloantibody screening was negative in the patient. In the donor, anti-E was detected before donation, together with anti-Jk^a and anti-Di^b 4, 9, and 12 months after donation, likely triggered by RBC transfusion 2 months before cell harvest. In the patient, anti-Jk^a was detected on day 25, and later anti-E and anti-Di^b as well. In both, a Di^a/Di^a genotype was identified. The rapid development of antibodies in the recipient despite intensive immunosuppression suggests their production by the donor cells primed by the RBC transfusion before hematopoietic cell harvest, although their production by the residual host cells cannot be unequivocally excluded. Esteve et al[40] reported a 16-year-old boy who was group O, Rh-positive (phenotype ccDEe) transplanted with marrow

from a group A, Rh-negative donor who had had four pregnancies and whose serum contained anti-D and anti-C. Seven months post-transplant, anti-D was detected in the patient's serum, which was well characterized as being of IgM immunoglobulin class. The antibody persisted for about 10 months but disappeared 1 month after cyclosporine was discontinued as GVHD prophylaxis. The patient did not develop anti-C, possibly due to the lack of an immunizing stimulus because his RBCs did not bear the C antigen. The long follow-up period without appearance of an IgG component suggested a defect in the immunoglobulin isotype switching mechanism. Heim et al[41] reported a 22-year-old man, blood group O, Rh-positive (R$_2$r), who received bone marrow from his blood group A$_1$, Rh-negative (rr) HLA-identical sister for treatment of acute lymphocytic leukemia. Three months after transplantation, the patient was found to be a mixed chimera with 0.5% of the RBCs still of the host's type. Four months after transplantation, three different Rh antibodies (anti-D, anti-E, and –G) were detected. It was evident that the engrafted marrow had produced these antibodies and, since the patient had received only Rh-negative RBC transfusions, it appears that he had become immunized to his original RBCs.

Alloantibodies Produced by Residual Cells of the Patient's Immune System

Von Tol et al[22] reported that IgG of recipient origin persisted in 15 of 18 informative recipients (83%) for several years after bone marrow transplantation. This may occur despite the fact that the circulating B cells appeared to be entirely of donor origin at that time. Other investigators have reported similar results.[42,43] Petz et al[44] reported that RBC antibodies persisting more than 6 months after transplantation served as the basis of diagnosing mixed chimerism in seven patients. In two, immunoglobulin allotyping also indicated mixed chimerism, whereas in the other five, immunoglobulin allotyping either was uninformative or was not performed. Anti-A or anti-B were present in six patients and caused a positive DAT without hemolysis in two, a positive DAT with transient hemolytic anemia in one, and a delayed onset of erythropoiesis in three. Other instances of alloantibodies produced by residual cells of the patient have been reported by Girelli et al,[45] Moore et al,[46] and Izumi et al.[47]

Incidence of RBC Antibody Formation Following Hematopoietic Cell Transplantation

The incidence of RBC antibody production following HCT appears to be low. Abou-Ellela et al[48] reported that only four of 193 patients (2.1%) developed RBC alloantibodies from the date of admission until the date of hospital discharge (48.5 ± 14.9 days for autologous HCT and 58.7 ± 25.9 days for allogeneic HCT). Three patients each had one RBC antibody and one patient had two antibodies. The specificities were anti-E (2 antibodies), anti-Jk^a, anti-M, and anti-Lu14. The RBC antibody formation rate was 0.1% per unit of RBCs transfused. The authors did not comment on the source of the antibodies. Bar et al[49] reported that none of 230 patients

developed irregular antibodies following boen marrow transplantation.

Immune Hemolysis Associated With Solid Organ Transplantation

The Passenger Lymphocyte Syndrome

The passenger lymphocyte syndrome, with clinical and laboratory findings very similar to that found after HCT, has been reported on numerous occasions following transplantation of kidney, liver, lung, heart, heart-lung, spleen, pancreas, and pancreas-spleen. Ramsey, in a 1991 review,[50] found that among minor ABO-incompatible transplants, 61% of cases involved group O donors and group A recipients, 22% involved group O donors and group B recipients, and 17% involved group AB patients receiving non-AB organs.

Hemolytic anemia after organ transplantation is more frequently encountered in proportion to the lymphoid mass transplanted.[51,52] Ramsey[50] found that the frequencies of antibodies and hemolysis were lowest in kidney transplant patients (17% and 9%, respectively), intermediate in liver transplant patients (40% and 29%), and highest in heart-lung transplant patients (70% for both). Borka et al[53] reported that hemolysis attributed to the passenger lymphocyte syndrome developed in 22 of 237 (9%) who received a minor incompatible renal transplant. Salerno et al[54] reported that in heart-lung transplantation, the incidence of hemolysis from donor-derived anti-ABO antibodies is as high as 70%. Five of nine (56%) patients receiving an ABO minor mismatched liver transplant reported by Triulzi et al[55] developed donor-derived antibody and hemolysis. It is remarkable that the few lymphocytes transplanted with some donor organs are able to proliferate sufficiently to produce adequate quantities of antibody to cause hemolysis of the recipient's RBCs within a few weeks of transplantation. Antibody may be produced even when the donor organs have been copiously perfused with preservative solution and, just before transplantation, with saline.

Serologic Findings

Hemolysis is usually abrupt in onset. Ramsey[50] reported that a positive DAT, serum antibodies, and hemolysis have generally been found at the same time. However, in some instances, serologic abnormalities do not occur before the onset of hemolysis, so that the most informative laboratory findings are a sudden drop in hemoglobin and hematocrit without evidence of a significant source of bleeding. These findings are associated with an elevation of the serum bilirubin and LDH. The DAT and serum antibody tests, if not immediately positive, will become so during the ensuing 1 to 2 days. Hemolysis caused by Rh antibodies has more commonly been reported after solid organ transplantation than after HCT. Specificity has most often been anti-D, but anti-c and anti-e have also been noted.[1] The onset of hemolysis is generally between 3 and 24 days, regardless of whether the antibodies are in the ABO or Rh blood group systems. The findings of the DAT in 43 minor ABO-incompatible transplants revealed that 36 patients had IgG on their RBCs, 35 had complement, and 28 had both.[50]

Clinical Features

Hemolysis is characteristically acute and, although many cases are mild and self-limited, RBC transfusion is often required. Ramsey[50] reported the median number of units transfused in 18 renal transplant patients was 6.5, with a range of 1 to 18. In seven liver transplant patients, the range was 2 to 11 units and four heart-lung patients received 16 to 24 units. In some instances, more severe hemolysis has occurred with resultant renal failure requiring dialysis.

In contrast to HCT, where the patient's RBCs are replaced by those produced by the donor marrow, incompatible red cells continue to be produced by the solid organ transplant

Table 6 Blood Selection for Recipients of ABO-Mismatched Organs

Recipient ABO	Donor ABO	Red Blood Cells	Fresh-Frozen Plasma No. 1 Platelets*	No. 2 Platelets†
O	A	O	A, AB	B, O
	B	O	B, AB	A, O
	AB	O	AB	A, B, O
A	O	A, O	A, AB	B, O
	B	A, O	AB	B, A, O
	AB	A, O	AB	A, B, O
B	O	B, O	B, AB	A, O
	A	B, O	AB	A, B, O
	AB	B, O	AB	B, A, O
AB	O	AB, A, B, O	AB	A, B, O
	A	AB, A	AB	A, B, O
	B	AB, B	AB	B, A, O

*No. 1 = Preferred ABO choice for platelets.
†No. 2 = Alternative ABO choice for platelets, in order of preference, if preferred ABO is not available.
Reprinted from Petz LD, Calhoun L: Preparation for blood and blood product replacement. In Busuttil RW, Klintmalm GB (ed): Transplantation of the liver. Philadelphia: WB Saunders, 1996:442–448.

recipient. Nevertheless, hemolysis is generally short-lived, evidently because the lymphocytes transferred with the donor organ are able to proliferate only temporarily and are not permanently engrafted. In kidney transplant patients, the final positive DATs were seen 2 to 13 weeks after operation (median, 5), and the last reactive serum specimens were at 3 to 23 weeks (median, 5.5). In liver transplant patients, the reactive DAT or serum was last detected 10 to 50 days after surgery (median, 20).[50]

Management

Anticipation of the passenger lymphocyte syndrome is important. Unfortunately, the titer of antibody in the donor is not reliable as a means of prediction of the occurrence of antibody or hemolysis in the postoperative period.

Appropriately selected blood products must be used throughout in all organ transplants (Table 6).[56] RBC components for transfusion must be ABO-identical or compatible with recipient serum regardless of the organ donor's type. However, when donor and recipient are of different ABO blood groups, special attention is given to the selection of plasma and platelet components. These should be ABO-compatible with both recipient RBCs and donor organ tissue cells to avoid transfusing antibody that might contribute to RBC hemolysis. Cryoprecipitate can be given without regard to ABO type because this product contains only a small volume of plasma.

Since most cases of the passenger lymphocyte syndrome are the result of a minor ABO blood group incompatibility between donor and recipient, such patients should be monitored carefully between approximately days 3 and 15, as for marrow transplant recipients.

Hemolysis can generally be managed by transfusion of group O RBCs, avoidance of ABO-incompatible plasma products, and maintenance of adequate renal perfusion. Corticosteroids are often used empirically. In patients with more severe hemolysis, plasma exchange may be used to decrease antibody titer. Also, RBC exchange may be used to decrease the volume of circulating incompatible RBCs. Jenkins et al[57] have recommended that if more than 2 units of RBCs need to be transfused within the first 24 hours after the onset of hemolysis, RBC exchange should be considered. Subsequent transfusions should be of group O RBCs until anti-recipient antibody has disappeared.

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