BACKGROUND: Bone marrow transplantation with minor ABO incompatibility may be followed by moderate delayed hemolysis of the recipient’s red cells by donor-derived ABO antibodies. This reaction may be more severe after transplantation of peripheral blood progenitor cells (PBPCs).

CASE REPORT: A 16-year-old boy underwent an allogeneic PBPC transplant from his HLA-mismatched mother as treatment for acute myeloblastic leukemia that had proved resistant to induction chemotherapy. Transfusion of the unmanipulated PBPCs proceeded without any complication, despite the difference in ABO blood group (donor, O Rh-positive; recipient, A Rh-positive). On Day 7, a rapid drop in hemoglobin to 4 g per dL was observed, which was attributed to a massive hemolysis. All the recipient’s group A red cells were destroyed within 36 hours. This delayed and rapidly progressive hemolytic anemia was not associated with the transfusion of the donor’s plasma. Rather, the anti-A titer increased in parallel with marrow recovery, which suggested an active synthesis of these antibodies by immunocompetent cells from the donor against the recipient’s red cells. The mother’s anti-A titer was retrospectively found to be 2048. Her unusually high titer is probably due to prior sensitization during pregnancies. On Day 12, the patient developed grade IV graft-versus-host disease, which proved resistant to all treatments instituted and led to his death on Day 35.

CONCLUSION: PBPC transplantation with minor ABO incompatibility may be associated with significant risk of massive delayed hemolysis.

Delayed massive immune hemolysis mediated by minor ABO incompatibility after allogeneic peripheral blood progenitor cell transplantation

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Bone marrow transplantation can be carried out successfully between donors and recipients who have ABO incompatibilities, provided that measures are taken to avoid acute hemolytic reactions after the transfusion of incompatible red cells (RBCs).1,2 There are two types of ABO incompatibility. One type, referred to as minor, may involve hemolysis after the destruction of a proportion of the patient’s RBCs by the anti-A or anti-B present in the small quantity of plasma contained in the graft. The other type, referred to as major, involves the systemic presence in the recipient of ABO antibodies against the RBC antigens of the donor. These antibodies will mediate severe acute hemolytic reactions if the incompatible RBCs are not removed from the graft.

We present a case of massive delayed hemolysis of the recipient’s RBCs by donor-derived ABO antibodies after peripheral blood progenitor cell (PBPC) transplant with minor ABO incompatibility. This hemolysis was probably due to recall immunity in relation to previous pregnancies of the donor, in the context of an extremely precocious recovery of donor-derived white cells, which is a result of the very rapid hematopoietic engraftment associated with PBPCs and the use of granulocyte-colony-stimulating factor (G-CSF).

ABBREVIATIONS: ara-C = arabinoside-cytosine; G-CSF = granulocyte-colony-stimulating factor; GVHD = graft-versus-host disease; PBPC(s) = peripheral blood progenitor cell(s); RBC(s) = red cell(s).

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CASE REPORT

A 16-year-old boy was diagnosed with acute myeloblastic leukemia M1 according to the FAB classification, with trisomy 8, in the context of back pain as well as multiple febrile episodes that were resistant to antibiotics. He had no other particular antecedent medical problem. He underwent a first course of induction chemotherapy with mitoxantrone, arabinoside-cytosine (ara-C), and etoposide, which resulted in failure, with persistence of 16-percent blast cells in the bone marrow. A second line of treatment based on amsacrine and intermediate-dose ara-C was then administered, but the patient again did not reach a complete remission. In light of this refractory leukemia, an allogeneic transplant was proposed as the therapeutic solution of last resort, in full awareness that it represented only a 10-percent chance of cure. The preparative regimen consisted of ara-C, cyclophosphamide, and an 8-Gy single dose of total body irradiation, with intrathecal administration of methotrexate. Infection prophylaxis was based on trimethoprim/cotrimoxazole, ciprofloxacin, fluconazole, and ganciclovir before transplant, followed by acyclovir after transplant, as well as polyvalent immunoglobulins. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A alone.

The donor was the patient’s mother, who had a major HLA mismatch at the D locus, as well as a different ABO group (donor, O Rh-positive; recipient, A Rh-positive). It should be noted that she had undergone four pregnancies and had received one RBC transfusion. To carry out the transplant, the donor’s marrow was stimulated with G–CSF (10 µg/kg) for 5 days and PBPCs were collected by cytophesis on 2 consecutive days. Erythropoietin, 600 U per kg twice a week, was also given for 3 weeks before and 3 weeks after the transplant, to proceed in parallel with the collection of autologous RBC concentrates for use in the recipient as needed. The return of the unmanipulated PBPCs (12.23 × 10^6 CD34+ cells/kg) proceeded without complication, and, in particular, no acute hemolytic reaction was engendered on Day 0 or Day 1. From that time on, the patient received only filtered and irradiated O Rh-positive platelet concentrates resuspended in group A plasma.

The patient was provided with 5 µg per kg of G–CSF from Day 1 through Day 12 and with 200 U per kg of erythropoietin from Day 1 through Day 33. Neutrophil recovery was prompt, with 0.5 × 10^9 polymorphonuclear neutrophils per L achieved on Day 9 and 2 × 10^9 on Day 10. The platelets never attained a value of 20 × 10^9 per L, as their recovery was hampered by the severe gastrointestinal bleeding observed later. As for the RBC lineage, early signs of recovery were noted by Day 10, with a reticulocyte count of 1 percent, which attained a maximum value of 14 percent on Day 20 before returning to aplastic values thereafter. However, the patient never became independent of transfusion, first because of hemolysis and then because of the gastrointestinal bleeding (see below).

The posttransplant course was first complicated by Staphylococcus epidermidis bacteremia on Day 3. Then, the hemoglobin dropped dramatically from 8.5 g per dL on Day 6 to 4 g per dL on Day 8, without any evidence of bleeding (Fig. 1). The drop in hemoglobin occurred concomitantly with hematopoietic recovery, which was also accompanied by a major increase in serum bilirubin (556 µmol/L on Day 8) and lactate dehydrogenase (1218 IU/L on Day 9), a complete disappearance of haptoglobin, and a positive direct antiglobulin test. Renal function was maintained. The group A RBCs from the recipient were accordingly destroyed within 36 hours. The recipient was group A until Day 6, showed a mixed-field population with very few group A RBCs among group O cells on Day 7, and was group O from Day 8 on (Table 1). The anti-A titer in the recipient was 0 on Day 6, 4 on Day 7, and 128 on Day 8. Consequently, there was no agglutination of group A RBCs in the presence of the patient’s serum until after Day 6, when there was weak agglutination on Day 7 and 2-agglutination from Day 8 on. The patient was treated with RBC transfusions, corticosteroids, and four sessions of plasmapheresis. This allowed the hemolysis to resolve rapidly after all the patient’s group A RBCs had been destroyed.

In the same period (i.e., Day 6–12), the patient developed acute GVHD, which attained an overall maximum grade of IV on Day 12, including grade III skin GVHD, grade IV hepatic GVHD, and grade IV gastrointestinal GVHD, the latter of which was responsible for massive uncontrollable bleeding that compromised survival. Aggressive therapy in-

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**Fig. 1.** Evolution of hematologic and hemolytic measures in the patient between Day 0 and Day 14 after transplant.
This situation is of concern only when the plasma antibody titer of the donor is such that it is likely to induce GVHD or prejudice the prognosis for survival.1,2 In fact, this type of incompatibility does not engender transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome after marrow transplantation.5 The literature like- phylaxis incorporating methotrexate prevented the syn- drome 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ate hemolysis immediately after their infusion. All these factors may have contributed to the massive hemolysis that developed in our patient.

Our observation confirms the potential hemolytic risk of using a graft of PBPCs with a minor ABO incompatibility. Two additional considerations may have accentuated the phenomenon in our patient: 1) a gestational sensitization and 2) a high lymphocyte content in the graft. This type of hemolytic reaction could be minimized by the inclusion of methotrexate in the program of GVHD prophylaxis, as well as by the elimination of B-lymphocytes from the graft—for instance, through CD34 selection.

REFERENCES