Immune Hemolytic Anemia After Renal Transplantation Secondary to ABO-Minor-Mismatch Between the Donor and Recipient1,2

James R. Gregoire3

J.R. Gregoire, Division of Nephrology, Mayo Clinic, Rochester, MN
(J. Am. Soc. Nephrol. 1993; 4:1122–1126)

ABSTRACT

A 52-yr-old man developed immune hemolytic anemia approximately 2 wk after receiving an ABO-

1 Received July 22, 1992. Accepted February 2, 1993.
2 Prepared under the guidance of Vicente Torres, MD, Consultant, Division of Nephrology, Mayo Clinic, Rochester, MN 55905.
3 Correspondence to Dr. J.R. Gregoire, E-16-A, Mayo Clinic, Rochester, MN 55905.
1046-6673/0405-1122$03.00/0
Journal of the American Society of Nephrology
Copyright © 1993 by the American Society of Nephrology

minor-mismatch renal transplant. When a Group O organ is transplanted into a non-O recipient or a non-
A-B organ is transplanted into a Group A-B recipient, hemolysis can occur and has been attributed to a form of graft-versus-host disease in which donor plasma cells carried along with the graft produce red blood cell antibodies. In this case, the diagnosis was confirmed when an antibody screen indicated that the organ recipient’s serum agglutinated panel red blood cells of the recipient’s ABO group. This type of hemolysis usually occurs 1 to 2 wk after transplantation, is limited in duration, and can be severe. If transfusion is required, blood of donor type should be used.

Key Words: Immune, anemia, ABO, transplantation, mismatch
A case of immune hemolytic anemia after renal transplantation is reported. An ABO-minor-mismatch between the donor and recipient was responsible for the hemolysis. We review the pathophysiology and management of this disorder.

CASE REPORT

A 52-yr-old white man with ESRD secondary to immunoglobulin A nephropathy was evaluated for his first renal transplantation. His past medical history was significant for hypertension, repair of an atrial septal defect with anomalous venous return in 1975, and laparoscopic cholecystectomy and umbilical herniorrhaphy in 1991. At the time of his heart surgery, he may have had a blood transfusion; however, he could not recall any other transfusions. He had been receiving erythropoietin since starting continuous ambulatory peritoneal dialysis in March 1991. Medications before transplantation were nifedipine (extended release), 60 mg twice daily, clonidine, 0.2 mg daily, 1.25-dihydroxy vitamin D, 0.25 μg daily, and a multivitamin, daily. On physical examination, the only abnormality noted was a Grade I/VI systolic ejection murmur. Laboratory values (with normal ranges) included hemoglobin, 12.4 g/dL (12.9 to 16.6 g/dL); hematocrit, 36.4% (38.6 to 48.0%); white blood cell count, 5.5 x 10⁹/L (4.1 x 10⁹ to 10.9 x 10⁹/L); platelets, 354 x 10⁹/L (184 x 10⁹ to 370 x 10⁹/L); creatinine, 8.6 mg/dL (0.8 to 1.2 mg/dL); and urica, 121 mg/dL (17 to 51 mg/dL). The direct antiglobulin test (direct Coomb's) and the antibody screen test (indirect Coomb's) were negative.

He received a one-haplotypic, living-related donor kidney from his brother in November 1991. A minor-ABO-mismatch existed: the recipient was A; rhesus positive and the donor was O; Rhesus positive. No transfusions were given intraoperatively or in the immediate postoperative period. He received triple-drug immunosuppression with cyclosporine, prednisone, and azathioprine. The hospital course was uncomplicated, and he was dismissed on posttransplantation Day 5.

On Day 6, he developed severe, diffuse lower abdominal pain with anuria, and he was readmitted. Medications were cyclosporine, 400 mg twice daily, prednisone, 40 mg daily, azathioprine, 150 mg daily, nifedipine (extended release), 60 mg twice daily, clonidine, 0.2 mg daily, trimethoprim-sulfamethoxazole double strength daily, acyclovir, 200 mg twice daily, nystatin suspension (100,000 U/mL), 5 mL four times a day, and ferrous sulfate, 325 mg daily. On physical examination, moderate to severe abdominal tenderness in both lower quadrants was present. Laboratory values included hemoglobin, 8.9 g/dL; white blood cell count, 8.5 x 10⁹/L; platelets, 312 x 10⁹/L; and creatinine, 2.4 mg/dL. A urinary leak was identified by a radionuclide (DTPA-hippuran) renal scan. The renal transplant was explored, and necrosis of the distal ureter was found. The necrotic portion was resected, an ureteroureterostomy to a native ureter was created, and an ureteral stent was placed. The urine output over the next 24 h was 1,715 mL; no further problems with urinary leak developed.

On posttransplantation Day 10, the hemoglobin was 8.4 g/dL. By Day 12, the hemoglobin had decreased to 5.1 g/dL, and he complained of fatigue. Other laboratory values included hematocrit, 14.4%; white blood cell count, 26.1 x 10⁹; platelets, 506 x 10⁹; reticulocytes, 8.9% (0.6 to 1.83%); total bilirubin, 2.9 mg/dL (0.1 to 1.1 mg/dL); direct bilirubin, 0.6 mg/dL (0 to 0.3 mg/dL); lactate dehydrogenase, 1,165 U/L (98 to 221 U/L); creatinine, 1.9 mg/dL; calcium, 7.6 mg/dL (8.9 to 10.1 mg/dL); phosphorus, 1.1 mg/dL (2.5 to 4.5 mg/dL); fibrinogen, 475 mg/dL (195 to 365 mg/dL); soluble fibrin monomer, negative; haptoglobin, <10.5 mg/dL (40 to 300 mg/dL); glucose-6-phosphate dehydrogenase level, 17.0 U/g of hemoglobin (8.6 to 18.6 U/g of hemoglobin); folate, 9.3 μg/L (2 to 20 μg/L); vitamin B-12, 241 ng/mL (191 to 770 ng/mL); and total complement, 102 U (25 to 110 U). The differential was segmented neutrophils, 80.5%; band forms, 7.0%; lymphocytes, 6.5%; monocytes, 2.5%; eosinophils, 1.5%; metamyelocytes, 0.5%; and myelocytes, 1.5%. A blood smear showed moderate polychromasia, moderate spherocytes, slight anisocytes, slight poikilocytes, slight microcytes, slight macrocytes, and slight red blood cell stippling. The presence of immunoglobulin G and complement on red blood cells was indicated by a positive (micro-positive) direct antiglobulin test and a positive anti-complement test, respectively.

The course of events is summarized in Figure 1. A hematology consult was obtained, and the clinical impression was immune-mediated hemolytic anemia. On Days 12 through 14, the patient received methyl-predisolone, 1.0 g/day iv. Over the next week,
he received a tapering dose of prednisone from 100 to 40 mg/day; thereafter, the prednisone dose was adjusted according to protocol. The trimethoprim-sulfamethoxazole was discontinued. On Day 12, he received 1 U of Group A (Type 1 or 2 not determined) rhesus-positive blood, and on Day 13, he received 4 U of group O rhesus-positive blood; these were the only transfusions he received. On Day 15, the antibody screen (indirect antiglobulin test) indicated the presence of antibody against panel A1, cells. An unsuccessful attempt was made to elute antibody for typing. On Day 15, the patient was started on folate, 2 mg/day po. When he was discharged from the hospital on Day 16 post–renal transplantation, the hemoglobin was 6.6 g/dL. On Day 30, the following laboratory values were obtained: hemoglobin, 9.5 g/dL; serum creatinine, 1.6 mg/dL; and corrected iothalamate clearance, 53 mL/min/1.73 m². During a follow-up evaluation on Day 93, no evidence of hemolysis was noted: hemoglobin, 12.2 mg/dL; hematocrit, 35.7%; direct and indirect antiglobulin tests, negative; reticulocytes, bilirubin, and lactate dehydrogenase, normal; and creatinine, 1.9 mg/dL. The blood smear showed only slight rouleaux formation.

DISCUSSION

Several cases of immune hemolytic anemia secondary to an ABO-minor-mismatch have occurred after transplantation of bone marrow and solid organs (1–7). ABO-minor-mismatch refers to the situation when a group O organ is transplanted into a non-O recipient or a non-AB organ is transplanted into a group AB recipient. According to the United States Renal Data System, 4% of group O cadaver kidneys went to non-O recipients in 1989 (8). The survival of ABO-minor-mismatched kidneys has been found to be both better (9) and worse (10) than ABO-matched kidneys.

Immune hemolytic anemia after the transplantation of an ABO-minor-mismatched kidney has been attributed to the production of red blood cell antibodies by donor plasma cells carried along with the graft. This condition is a form of graft-versus-host disease. Antibodies eluted from the recipient’s red blood cells have been shown to be of donor allotype (7). Presumably, the occurrence or severity of the hemolytic anemia is related in part to the amount of lymphatic tissue transplanted. The diagnosis is suggested in a patient with anemia after transplantation of an ABO-minor-mismatched kidney by either: (1) a positive direct antiglobulin test or (2) an antibody screen that shows that the recipient’s serum agglutinates panel red blood cells of the recipient’s ABO group. In our patient, the diagnosis was indicated by the positive antiglobulin test, the presence of an anti-A₁ antibody, and the blood smear, which showed polychromasia and spherocytes without evidence of red blood cell fragmentation in the setting of an ABO-minor-mismatch. In this case, the donor was group O rhesus positive and the recipient was group A₁ rhesus positive.

The frequency of immune hemolytic anemia after transplantation has been evaluated. In 1991, Ramsey summarized 46 reported cases of ABO antibody formation after renal transplantation (Table 1) (4). Of the 46 cases, hemolysis occurred in 33. Forty-eight percent of the cases reported were group O donor to group A recipient and 22% were O donor to B recipient. A few cases of O to AB, A to AB, and B to AB have been reported. The reports, which included ABO-minor-mismatch transplantations that did not develop hemolysis, were summarized. In 144 patients in whom antibodies were looked for, 24 (17%) developed antibodies, whereas in 165 patients in whom hemolysis was looked for, 15 (9%) developed hemolysis. The rates seen with renal transplantation were lower than for liver and heart-lung transplantations; again, this may relate to the quantity of lymphoid tissue transplanted with different organs.

Some evidence exists that the use of cyclosporine may promote the development of this condition (4–6). No more than three cases have been reported in patients whose immunosuppression did not include cyclosporine (4,5). Cyclosporine seems to selectively affect T helper cells and spare B cells (11). Some authors have proposed that selective sparing of B cells located within the transplanted kidney in patients receiving cyclosporine may somehow allow for the development of this syndrome (2,3,6).

Recently, a case of autoimmune hemolytic anemia in a patient with an ABO-compatible donor (both were O rhesus positive) was attributed to cyclosporine (12). Thirteen weeks after transplantation the

<table>
<thead>
<tr>
<th>Donor-Recipient ABO Blood Groups</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-A</td>
<td>22 (48)</td>
</tr>
<tr>
<td>O-B</td>
<td>10 (22)</td>
</tr>
<tr>
<td>O-AB</td>
<td>4 (9)</td>
</tr>
<tr>
<td>A-AB</td>
<td>2 (4)</td>
</tr>
<tr>
<td>B-AB</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Not given</td>
<td>8 (17)</td>
</tr>
<tr>
<td><strong>Patient Developed Hemolysis</strong></td>
<td>33 (72)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Transfusions</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient transfused</td>
<td>23 (50)</td>
</tr>
<tr>
<td>Patient not transfused</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Not specified</td>
<td>14 (30)</td>
</tr>
<tr>
<td><strong>Patient Required Hemodialysis</strong></td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Because of Hemolysis
Immune Hemolytic Anemia After Renal Transplantation

The patient developed anemia, hyperbilirubinemia, a positive direct antiglobulin test, and a blood smear that was reported to be consistent with autoimmune hemolysis. The patient required 12 U of blood. Azathioprine was substituted for cyclosporine 24 wk after transplantation, and the hemolysis then resolved. Although the specificity of the antibody covering the red blood cells could not be identified, the authors proposed that cyclosporine somehow allowed for the production or expression of an autoantibody by the recipient. If this is correct, then a similar mechanism may be playing a role in the apparent increased occurrence of hemolytic anemia in ABO-minor-mismatched patients receiving cyclosporine.

In renal transplantation, the typical presentation is onset of hemolysis 1 to 2 wk after transplantation (5). The hemolysis can be quite brisk but is generally self-limited (5). Of the 46 cases reviewed by Ramsey (Table 1), 23 received transfusions (range, 1 to 18 U), 9 did not receive transfusions, and in 14, transfusion requirements were not specified (4). Four patients required hemodialysis for acute renal failure due to hemolysis. Hemolysis was thought to contribute to the death of one patient, who developed disseminated intravascular coagulation with the hemolysis.

Other causes of hemolytic anemia should be considered in a patient with hemolysis after renal transplantation (Table 2). Cyclosporine has been associated with microangiopathic hemolytic anemia (13). Medications can precipitate hemolysis. This patient was taking trimethoprim-sulfamethoxazole, which was stopped when the hemolysis was noted. Sulfonamides can cause a hemolytic anemia, particularly in the setting of G6PD deficiency (14). Antithymocyte globulin has been reported to cause hemolytic anemia (15). This patient did not have a microangiopathic process or G6PD deficiency, and he did not receive antilymphocyte globulin. Severe hypophosphatemia can cause a nonimmune (direct antiglobulin test-negative) hemolysis. Our patient’s serum phosphorus level at the time of hemolysis was 1.1 mg/dL; hemolysis is seen at levels of 1.0 mg/dL or lower (16).

How should cases of immune hemolytic anemia in ABO-incompatible renal transplantation patients be managed? If transfusion is required, blood of donor type should be transfused (4). For example, a group A rhesus-positive recipient who develops hemolytic anemia after receiving a group O rhesus-positive kidney should receive compatible group O rhesus-positive blood. Some authors have advocated the discontinuation of cyclosporine (12), although several cases, including ours, have seen resolution of the hemolysis despite the continuation of cyclosporine (4,5). In protracted hemolysis, the discontinuation of cyclosporine may be required. Plasmapheresis has been used in some cases (4).

When an ABO-incompatible transplantation is performed, the patient should be observed for signs of hemolysis. It is unclear if screening with a daily hemoglobin level or hematocrit for the first 2 or 3 wk after transplantation is adequate or whether more specific screening, such as a direct antiglobulin test (6), should be performed. ABO-minor-mismatched transplants from living donors will likely continue to be performed. A change in the rate of occurrence of the syndrome may occur with the use of newer immunosuppressant agents.

**SUMMARY**

We report an additional case of immune hemolytic anemia that occurred in a renal transplantation patient with an ABO-minor-mismatch kidney. This condition is a form of graft-versus-host disease. Hemolysis, which can be severe, typically occurs 1 to 2 wk after transplantation. Cyclosporine may predispose patients to this disorder.

**REFERENCES**

6. Watzke H, Kovarik J, Gassner H: A permissive effect of cyclosporin on the development of isohaemaglutinins of graft origin in ABO-mis-

---

**TABLE 2. Causes of hemolytic anemia after renal transplantation**

<table>
<thead>
<tr>
<th>Graft-Versus-Host Hemolytic Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO antibody</td>
</tr>
<tr>
<td>Rh antibody</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
</tr>
</tbody>
</table>


