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Inability of OKT3 to prevent donor-derived ABO hemolytic anemia in a kidney-pancreas transplant recipient

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Sir: Minor incompatibility for ABO antigens involves the presence on the recipient's red cells of A and/or B blood group antigens lacking in the donor. Such donor-recipient combinations may expose the recipient to the development of an ABO hemolytic anemia in the early post-transplant period [6, 7]. This anemia is due to the production by "passenger" donor B lymphocytes [2, 8] of allohemagglutinins directed against recipient ABO antigens.

The frequency of this complication reaches 70 % in heart-lung, 30 % in liver, and 10 % in heart and kidney transplants [7]. This is probably related to the number of B cells transferred with the graft. Minor ABO incompatibilities are, however, accepted for lung, liver, and heart transplantations because the poor vital prognosis without transplantation outweighs the risk of post-transplant hemolysis. For kidney [10] and combined kidney-pancreas transplantations, minor ABO mismatches are allowed if HLA compatibility is considered to be favorable.

ABO hemolytic anemia has been observed with immunosuppressive regimens consisting of polyclonal antithymocyte/lymphocyte globulins, azathioprine, and cyclosporin A [2, 7] but not, to our knowledge, in patients receiving the OKT3 monoclonal antibody. Furthermore, it has been suggested that the addition of OKT3 to the immunosuppressive regimen might even prevent this complication [7, 9]. Herein, we report on a kidney-pancreas transplant recipient who developed a severe ABO hemolytic anemia during prophylactic OKT3 therapy.

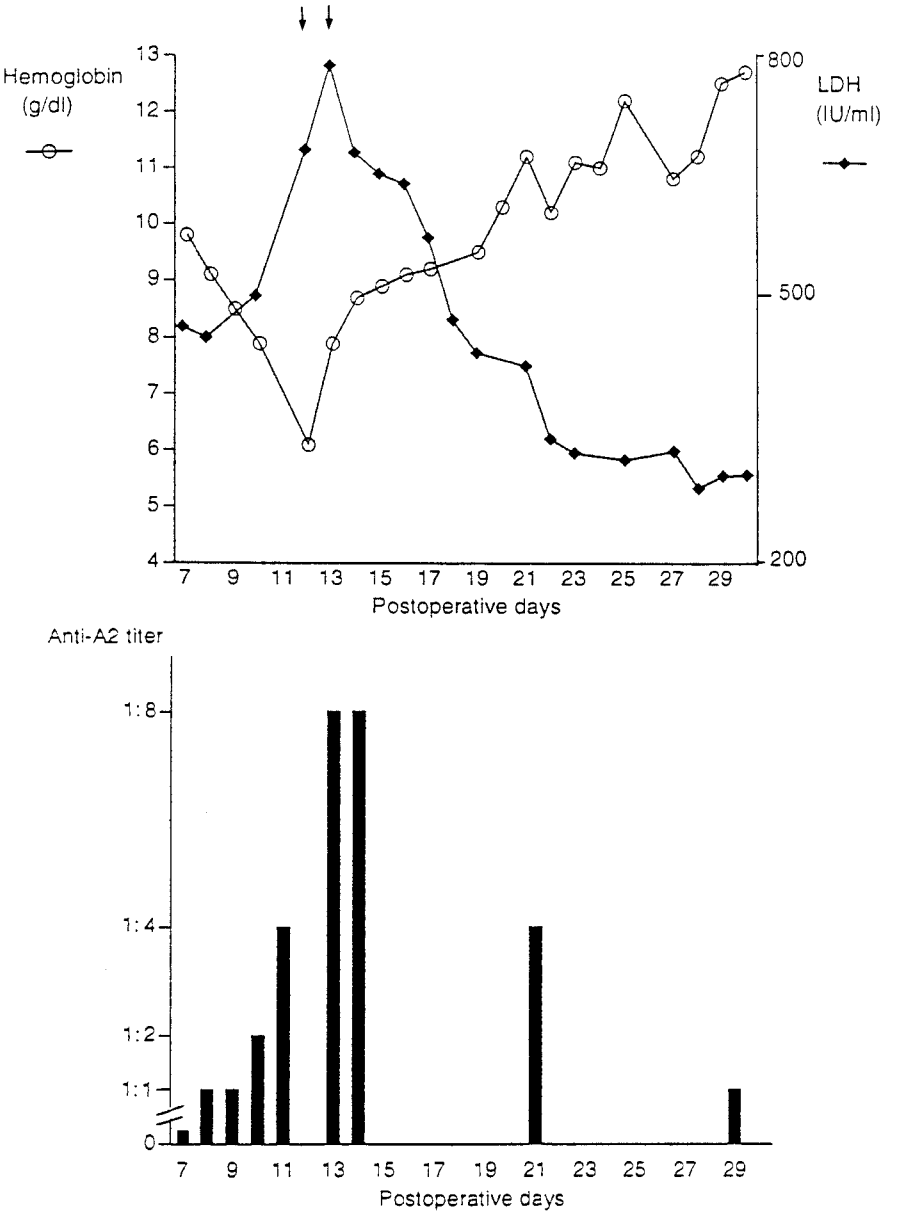

Fig. 1 Time-course of immunosuppressive medications (OKT3, 10 mg/day; azathioprine, 2 mg/kg per day; prednisone, 0.4 mg/kg per day; cyclosporin A, 6 mg/kg per day) and of serum hemoglobin, LDH, and anti-A2 antibody titers. *Arrows* indicate RBC transfusions

A 43-year-old patient underwent a kidney-pancreas transplantation for end-stage diabetic nephropathy in February 1991. His blood group was A2B, Rh-positive. The donor was a 26-year-old woman with B, Rh-positive blood who died of in-

tracerebral hemorrhage. HLA serological typing demonstrated HLA-DR identity and HLA-A and B disparity between the donor and the recipient. Immunosuppression consisted of OKT3 (10 mg/day), azathioprine (2 mg/kg per day), and steroids, with initiation of cyclosporin A on postoperative day (POD) 9 (Fig. 1). During OKT3 therapy, circulating CD3+ cells were lower than 50/mm^3 and OKT3 serum levels were higher than 800 ng/ml. The patient received two units of A, Rh-positive packed red blood cells (RBCs) on the day of transplantation and an additional four units of AB, Rh-positive RBCs in the course of the following 6 days. On POD 12, laboratory studies revealed a hemolytic anemia [hemoglobin 6.1 g/dl, LDH 782 IU/l (normal < 300 IU/l), haptoglobin 11 mg/dl (normal 25–180 mg/dl), total bilirubin 1.8 mg/dl]. The direct antiglobulin test (direct Coombs test), which detects immunoglobulins present on the red cell membrane, was positive with anti-IgG antihuman globulins up to a dilution of 1 : 4. Isotypic analysis demonstrated that the antibodies present on RBCs were mainly IgG1, with a minor IgG2 component. Antibodies eluted from the patient's RBCs, as well as those detected in plasma, showed anti-A2 specificity. The time-course and the titers of the serum anti-A2 antibodies are shown in Fig. 1. They first appeared on POD 8, reached maximal titers on POD 13, and disappeared after POD 29 (Fig. 1). The determination of the specificity of the anti-RBC antibodies allowed for efficient control of the anemia with four units of compatible packed RBCs. Three years after transplantation, the patient has well-functioning kidney and pancreas grafts.

The present case appears to be the second observation of ABO hemolytic anemia among more than 2000 combined kidney-pancreas transplantations [3]. Whether this low incidence reflects the rarity of this complication in these patients or underestimates the actual frequency is unclear.

What is most interesting about the present observation is the development of ABO hemolytic anemia during prophylactic OKT3 therapy. Hemolysis occurred despite adequate OKT3 therapy, as indicated by persistently low numbers of circulating CD3+ cells and high OKT3 serum levels. In addition, the patient received azathioprine, which is known to inhibit B cell antibody production. Indeed, ABO hemolytic anemia most often developed when azathioprine was absent from the immunosuppressive regimen [6, 7]. It is, therefore, possible that the release of B-cell growth factors following the first OKT3 injections [1, 4] played a role in triggering pathogenic antibody production. In addition, the potent immunosuppressive properties of OKT3 might have favored the persistence of donor lymphocytes in this patient. Along this line, significant chimerism has been demonstrated by genomic HLA tipping in a heart-lung transplant recipient with prolonged, donor-derived hemolysis [5]. Whatever the explanation, our observation indicates the possible occurrence of ABO hemolytic anemia in spite of OKT3 therapy.

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