Anaphylactic Reactions to IgA: A Difficult Transfusion Problem

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ABSTRACT

Miller, William V., Holland, Paul V., Sugarbaker, Everett, Strober, Warren, and Waldmann, Thomas A.: Anaphylactic reactions to IgA: A difficult transfusion problem. Amer. J. Clin. Path. 54: 618–621, 1970. A woman with isolated IgA deficiency and a history of carcinoma of the colon experienced severe reactions to blood products containing IgA. The reactions were characterized by abdominal pain, vomiting, diarrhea, generalized flushing, and edema. The patient had no detectable IgA in serum and secretions; she had anti-IgA as demonstrated by agglutination of IgA-coated erythrocytes, rapid IgA catabolism, and radioimmunoelectrophoresis. She was transfused without incident using autologous plasma obtained by preoperative plasmapheresis, and using IgA-deficient whole blood during two surgical procedures. Frozen, deglycerolized erythrocytes could be used to replace lost erythrocyte mass, but only if transfused slowly.

Several investigators recently have reported anaphylactoid transfusion reactions in patients with antibodies to the immunoglobulin IgA. These severe reactions are characterized by flushing, abdominal pain with emesis and diarrhea, chills, fever, and, occasionally, edema and bronchospasm. Once identified, patients with anti-IgA antibodies must be transfused with blood products free of IgA. This presents special problems for the blood bank. The following is a report of such a patient and the means used to deal with transfusion problems which arose during her care.

Report of a Case

In December 1968, a 60-year-old woman was admitted to the Clinical Center, National Institutes of Health, for treatment of a decubitus ulcer of the sacral area. In 1954, a carcinoma of the sigmoid colon was removed; a year later a local recurrence was treated by abdominal–perineal resection. She was given eight units of whole blood on three occasions during a 5-week period, all without incident. She had never received a transfusion before and was not transfused again until the present admission. Tumor reappeared in the perineal wound 10 months after the abdominal–perineal resection; this was excised and the perineal wound subsequently irradiated. In May 1968 the patient's perineal scar was biopsied because of suspected recurrence; although no carcinoma was identified, the wound failed to heal. A progressively erosive ulcer formed, exposing a necrotic sacrum. The patient was admitted for radical excision and pedicle grafting. Preoperative transfusion was attempted,
but following the administration of only 30 ml. of whole blood, she experienced nausea, chills, severe abdominal cramps, and then emesis and diarrhea. Moderate hypertension (160/90 mm. Hg) was followed by moderate hypotension (70/40 mm. Hg), transient loss of consciousness, and generalized flushing. The patient remained afebrile throughout the reaction and she recovered within a few hours.

Laboratory examinations of the patient's serum revealed no erythrocyte incompatibility, leukoagglutinins, lymphocytotoxic antibodies, or antibodies to Gm or InV antigens. The direct antiglobulin test was negative at this time.

In order to find a blood product to support surgery involving potentially major blood loss, we attempted transfusions with concentrated erythrocytes, carefully washed erythrocytes, cell-free plasma, and Plasma Protein Fraction (Plasmanate). In each case, the patient reacted to the material and the infusion was discontinued. However, autotransfusion of her ACD-preserved whole blood and plasma was well tolerated. At this time no IgA could be detected in her serum by immunoelution or by radial immunodiffusion. Aliquots of blood from two donors with no detectable IgA were subsequently transfused without incident. Frozen, deglycerolized erythrocytes could also be slowly transfused without incident, but more rapid infusion resulted in a mild reaction. Albumin preparations were not given because IgA was found in them by radial immunodiffusion.

Prior to her operative procedures, 1,500 ml. of the patient's plasma were collected by plasmapheresis and stored at −30 C. During and after two operative procedures, one of the units of IgA deficient whole blood, the patient's plasma, and frozen deglycerolized erythrocytes from random donors were given without incident.

During the patient's postoperative course, she developed irregular blood group antibodies to the Kell (K), rh'(c), and rhw (Cw) antigens. At 10 weeks, she developed icteric hepatitis with Australia antigen in her serum. After a month the hepatitis resolved and the Australia antigen was no longer detectable. One month after the last transfusion her direct antiglobulin test became positive; it was still positive 8 months later; this evidently had no clinical significance since her hemoglobin has been stable in the normal range.

**Serologic Findings**

No IgA was detectable in the patient's serum, saliva, or stools by radial immunodiffusion or by immunoelution. Her IgG level was 700 mg. per 100 ml. (normal = 1,200 ± 200 mg. per 100 ml.), her IgM was 50 mg. per 100 ml. (normal = 160 ± 60 mg. per 100 ml.), and her IgE was 500 ng. per ml. (normal). Antibodies to IgA were demonstrated by agglutination of erythrocytes coated with an incomplete IgA antibody having HI specificity and by radioimmunoelution, but not by simple double diffusion technics. To further evaluate the significance of the anti-IgA, 10 microcuries (10 μg.) of 125I-labeled IgA were injected intravenously. The patient did not experience a reaction with this minute quantity but the labeled IgA was cleared very rapidly (T½ of a few minutes compared with 5.8 days in normal persons) from her circulation, confirming the specificity of the antibody and demonstrating its ability to shorten the survival of IgA.

The C'la fixation and transfer test of Borsos and Rapp² was used to determine the immunoglobulin class of the anti-IgA. The patient's anti-IgA, when mixed with IgA-coated erythrocytes, fixed complement without the use of enhancing antisera, indicating that the anti-IgA antibody was of the IgM class. Additional complement fixation was obtained with the use of anti-IgG-enhancing antibody, indicating that the
patient's IgA was also composed of molecules in the IgG class. Radioimmunoelectrophoresis provided additional evidence that the anti-IgA was also present in the IgG immunoglobulin class.

Tests of immunologic function in this patient showed an active humoral and cellular immune response despite the isolated IgA deficiency. The patient was capable of making antibody to erythrocytic antigens, had a positive skin test to the delayed-type antigen, dinitrochlorobenzene (DNCB), and had a 1.5 cm. wheal and flare with pseudopods in response to intradermally-injected antibody to IgE (normal reaction). In addition, the patient's lymphocytes underwent a normal blastic transformation upon stimulation with phytohemagglutinin. Studies of chromosomes from peripheral blood cells were normal. Studies of sera from the patient's four siblings revealed that all had normal levels of IgG, IgM, and IgA.

Discussion

Reactions to transfused IgA and accelerated clearance of IgA in patients with anti-IgA antibodies have been described. The anti-IgA antibodies may be formed by two groups of people: IgA-deficient patients who form an antibody with specificity against virtually all IgA proteins, and those with normal IgA levels who make antibodies against specific IgA proteins. Isolated IgA deficiency has been associated with ataxia telangiectasia, partial deletion of chromosome 18, connective tissue diseases, and gastrointestinal disorders characterized by diarrhea and malabsorption. Several patients with IgA deficiency have had gastrointestinal neoplasia; this association may be important in regard to our patient. In addition, as many as one of 700 apparently healthy people have isolated IgA deficiency.

The pattern of this patient's reactions to IgA was quite similar to those described in other patients. The severe gastrointestinal effects and the marked flushing help distinguish this reaction from those due to leukocyte incompatibility, since the latter has not been associated with these symptoms. The pathophysiologic mechanism through which the response to infused IgA is mediated is not clear, but in one report complement levels fell during a reaction, suggesting that complement may trigger activation of the kinin system or release of other biologically active substances. In our patient, the clinical picture suggested release of serotonin, but one 24 hr. urine measurement after a reaction was not elevated.

Few of the previously reported patients with anti-IgA have required transfusion. Our patient experienced severe reactions with transfusions of whole blood, concentrated erythrocytes, cell-free plasma, and Plasma Protein Fraction, presumably due to their IgA content. Even erythrocytes washed with 3 to 5 liters of physiologic saline solution (to a final effluent protein concentration with an optical density of less than 0.08 units) resulted in a reaction. On the other hand, erythrocytes which were glycerolized, frozen, thawed, and washed were well tolerated if transfused slowly, but the reason these were accepted and washed cells were not is obscure. The experience of Vyas and associates, who used the cytoglomerator to glycerolize, deglycerolize, and wash the cells to remove IgA, suggests that the actual freezing process is unimportant.

The patient was successfully transfused with blood from two IgA-deficient donors. A number of donors have low levels of IgA, but only about one in 700 has no detectable IgA. Since this problem will probably be recognized more frequently, a central registry of such rare donors should be established. Until then, patients with reactions due to anti-IgA who require transfusion may be given deglycerolized
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erythrocytes to replace lost erythrocyte mass and autologous plasma for volume replacement. They should be encouraged to put their own blood or plasma, or both, in frozen storage, and they should certainly wear some identification, such as the bracelets used to warn physicians of other types of hypersensitivity.

Addendum

Since submitting this manuscript for publication, the authors have learned that Dr. G. N. Vyas, University of California School of Medicine, San Francisco, has initiated a registry of donors who have no detectable IgA. As of December 1969, 38 such donors were registered.

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References


