Passive Neonatal Thrombocytopenia
A Case Study of Factors Predicting the Response to IV IgG Therapy

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ABSTRACT

A term male infant was noted at birth to have petechiae over the face and trunk and a platelet count of $3 \times 10^9$ per L. Maternal immune thrombocytopenia (ITP) was suspected from the clinical data and confirmed by the presence of antiplatelet antibody (both in the mother and infant) detected by recently described flow cytometry method. Initial treatment with exchange transfusions, platelet transfusions, steroids, failed to correct thrombocytopenia and, hence, seven doses of high-dose gamma globulin (IV-IgG) were given intravascularly. Initiation of IV-IgG was followed by stabilization of platelet counts with marked reduction in the need for platelet transfusions. In this case of passive ITP, the therapeutic efficiency of high dose IV-IgG seems to depend upon maintaining a certain critical level of serum IgG (which in turn may depend upon the serum antiplatelet antibody titers).

Introduction

Passive neonatal immune thrombocytopenia (ITP), although transient, may result in increased morbidity and mortality from the risk of bleeding, especially intracranial, during the first week of life. The severity of thrombocytopenia and, hence, the clinical course of the condition, probably depends upon the avidity and titer of passively acquired IgG and the compensatory accelerated production of the platelets by the neonate's bone marrow. The clinical course was evaluated of a neonate with immune thrombocytopenia who was treated with exchange transfusions, platelet concentrates, and intravenous immunoglobulin therapy. Serial estimations of serum platelet antibody titers, serum total IgG levels and the platelet count in the peripheral blood were measured over the course of the acute illness. The possible relationship of these factors to therapeutic response is discussed.

Case History

Baby Boy S was born at term gestation, weighing 3640 grams, to a 30 years old Gravida 1 Para 0, blood group O positive mother by Caesarean section with APGAR scores of 8 and 9 at one and five minutes, respectively. The indications of the caesarean section...
were maternal pre-eclampsia with thrombocytopenia (4 × 10^9 per L) and fetal distress. Maternal history was negative for any drug ingestion or systemic autoimmune disease. Immune thrombocytopenia was suspected and later confirmed after the delivery.

Examination of the neonate was normal except for the petechiae over the face and trunk. Hemoglobin and white cell count and differential counts were normal. The initial platelet count was 3 × 10^9 per L. Since there was no evidence of intra-uterine infection, sepsis or asphyxia, immune thrombocytopenia secondary to transplacental transfer of anti platelet antibody from the mother was suspected. This was confirmed using flow cytometric analysis by demonstrating the presence of IgG anti platelet antibody in the serum samples of both the mother and infant.

The patient was discharged at 19 days of age with platelet count of 100 × 10^9 per L and Hb of 11 g (after packed red cell transfusion on day 18 for Hb of nine g). Platelet counts remained above 200 × 10^9 per L during the subsequent six months of follow-up of the infant. The effects of each therapeutic modality on total platelet counts, total serum IgG levels, and anti-platelet antibody titers (by flow cytometry) were monitored by serial blood sampling during the hospital stay.

**Methods**

Platelet counts were determined using the Coulter S Plus instrument† or by manual counting using phase microscopy when the automated count was less than 30 × 10^9 per L. Serum anti-platelet antibodies were measured using an indirect immunofluorescence assay performed as previously described using the Ortho Spectrum III flow cytometer. Serum IgG was measured using rate nephelometry.  

**Results**

**Platelet Counts**

The serial mean platelet counts were <7 × 10^9 per L on days 1 and 2; 7 × 10^9 per L on day 3; <7 × 10^9 per L on day 4; 14 × 10^9 per L on days 5 to 8; 7 × 10^9 per L on day 9; 5 × 10^9 per L on day 12; 45 × 10^9 on day 13; 100 × 10^9 per L on day 18; and >200 × 10^9 per L after the second month and throughout the follow up period.

**Serum IgG Levels**

The serum IgG levels varied from 1587 mg per dl to 2860 mg per dl during IV-IgG therapy. A significant correlation was observed between serum total IgG levels and serial platelet counts during the first 15 days of life (figure 1). The platelet counts remained >10 × 10^9 per L as long as serum IgG levels were >1800 mg per dl. On two occasions (days 6 and 12) when serum IgG levels dropped to 1800 mg per dl or less (1800 and 1140), the corresponding platelet counts were 10 × 10^9 per L, and 5 × 10^9 per L, respectively. Between days 16 and 19, the platelet counts were between 45 × 10^9 per L and 114 × 10^9 per L (mean 75,000), in spite of less than 1800 mg per dl of serum IgG levels (range 956 mg to 1950 mg per dl).

**Anti-Platelet Antibody Titers**

The mother's serum gave positive results up to 1:20 dilution for platelet antibody at the time of delivery. The baby's serum anti-platelet antibody titers were followed serially. The serum samples were positive for the antibody, neat and at dilution up to 1:20 from birth (cord blood) till 16 days of life. The titer began to drop at day 16 with positive test in 1:10 dilution. Beyond 19 days, no antibody was detected. On day 12, pre- and post IV-IgG blood samples showed interesting results. The pretransfusion sample showed a platelet count of 5 × 10^9 per L, serum IgG levels of 1140 mg per dl, and positive for platelet antibody in 1:20 dilution. Following IV-IgG, the platelet count rose to 50 × 10^9 per L.
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1. Exchange transfusions
2. Platelet transfusions
3. IV IgG transfusions (Solumedrol started on day 1 and tapered and discontinued by day 18)

(prior to platelet transfusion of any additional platelets), a serum IgG level of 2040 mg per dl, and a positive anti-platelet antibody in neat and 1/10 dilution only.

Discussion

Immune thrombocytopenia in the neonate may result from fetal-neonatal platelet destruction from the transplacentally passively transferred anti-platelet antibody. Maternal conditions resulting in such a transfer of platelet antibody include autoimmune diseases like systemic lupus erythematosus, ITP, and maternal fetal platelet antigen incompatibility. The nature and titer of antiplatelet antibody and efficient functioning of reticulo-endothelial system probably determine the clinical course in such a patient. Thus, the therapeutic modalities in these patients can be geared to either (1) decreasing the antibody titers by double volume exchange transfusions followed by platelet transfusions, (2) blocking antigen antibody reaction by steroids, or (3) blocking the receptors on the reticulo-endothelial (RE) system cells so that they may not recognize the sensitized platelets and eliminate them from the circulation rapidly.

Parenterally administered IgG probably acts in the latter manner by blocking the Fc receptors of RE cells. High doses of intravenous immunoglobulin G (IV-IgG) therapy have been successfully used in both adults and children with chronic ITP, neonatal isoimmune thrombocytopenia, immune thrombocytopenia associated with maternal ITP or autoimmune disease, and to prevent fetal and neonatal thrombocytopenia by treating
the mother with ITP prior to delivery.\textsuperscript{1,2,11,13} Furthermore, as shown by Sultan, et al.\textsuperscript{15} direct inhibition of platelet antibody may be produced by anti-idiotypic antibody concentrations of IV-IgG.

An equilibrium seems to exist between IgG in the serum, IgG bound to circulating cells (neutrophils, platelets, and red cells), and IgG bound to Fc receptors of the reticulo-endothelial cells.\textsuperscript{9} A rise or a fall in the plasma concentration of IgG results in a parallel rise or fall in the baseline amount of cell bound IgG and of IgG interacting with the Fc receptors of the RE cells. Consequently, there is no net change in the cell clearance. However, when the equilibrium is disrupted by a disproportionate rise in cell bound IgG occurring in certain immune cytopenic diseases, increased cell clearance results. Thus, one can logically assume that a high dose of IgG (i.e., 10 times normal endogenous production) may block the Fc receptors of RE cells and decrease the clearance of sensitized cells, either platelets, red cells, or neutrophils, as the case may be.\textsuperscript{9,11} In addition, since the interaction of immune complexes or monomeric IgG with the Fc receptors obeys the law of mass action, the relative concentrations of each are important. Furthermore, the anti-idiotypic inhibition of platelet antibody of IV-IgG also seems to be dose dependent.\textsuperscript{15} Thus, in our patient, the serial serum antiplatelet antibody titers and serum IgG levels. In our patient, the platelet count seemed to depend upon platelet antibody titers, serum IgG levels, and, understandably, the postnatal age of the patient. During the first four days of life, despite two exchange transfusions and removal of a large amount of anti-platelet antibody, the antibody titers still remained positive at 1:20 dilution samples: platelet counts were \( <7 \times 10^9 \) per L and serum IgG levels \(<1800\) mg per dl. During IV-IgG therapy (between the fourth and twelfth days of life), serum IgG levels \(>1800\) mg per dl maintained mean platelet count of \(14 \times 10^9\) per L in the presence of same antibody titer. When serum IgG levels dropped to 1800 or below, the platelet counts also dropped to less than \(10 \times 10^9\) per L, suggesting serum IgG greater than \(1800\) mg per dl as a critical value.

In this patient, the passively transferred antibody activity seems to be very high because two double volume exchange transfusions did not make any significant difference in the platelet counts. Thus, without adjuvant treatment of high dose immunoglobulin therapy, this patient would have had a prolonged hospital stay with a need for innumerable platelet transfusions, along with the accompanying risk of infections and development of sensitization towards donor platelet antigens.

In conclusion, the current authors have shown that in a neonate with passive immune thrombocytopenia, serial estimations of platelet antibody titers and serum IgG levels may be used as predictors for the dose and duration of IV-IgG therapy.

References