Immunoglobulin for neonatal agranulocytosis

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SUMMARY An infant with an alloimmune agranulocytosis whose granulocyte count temporarily returned to normal during intravenous, high dosage immunoglobulin treatment is described.

Agranulocytosis and profound neutropenia in the neonatal period is a serious condition associated with high mortality. Most patients develop fever associated with skin infections, pneumonia or septicaemia, or both, within the first days of life. The infections are predominantly caused by *Staphylococcus aureus*, and less often by *Escherichia coli* or β haemolytic streptococci. Prophylaxis with antibiotics has been recommended for these infants.¹

A boy with neonatal agranulocytosis was investigated. It was considered that the cause was probably an alloantibody on the boy's neutrophils directed to parental antigen. Treatment with high dose intravenous immunoglobulin temporarily restored his neutrophil count.

Case report

This boy was born at 39 weeks' gestation and weighed 3.6 kg. He is the second child of healthy, unrelated parents. At age 3 days, a pemphigoid exanthema developed, and *Staphylococcus aureus* was cultured. Cloxacillin was given intravenously, and during the following days the lesions healed. Fever (39°C) was observed on day 10 and the boy

Figure Neutrophil count and white blood count (WBC) during the first 50 days of life.

Intravenous immunoglobulin (IVG) was given for three consecutive days. Lowest border of normal range for neutrophils are: Cord blood $5.5 \times 10^9/l$; at 12 to 24 hours of age $10 \times 10^9/l$; at 72 hours of age $2.5 \times 10^9/l$, and from 1 month of age $1.5 \times 10^9/l$.
○=neutrophils; ●=WBC.

was again started on intravenous antibiotics (ampicillin and netilmicin). His white blood count on days 7 and 10 showed a progressive neutropenia (Figure) and repeat determinations over the following days showed agranulocytosis. Antibiotics were stopped and the child was referred to this hospital. Prophylactic co-trimoxazole was given. A bone marrow aspirate showed normal cellularity and normal myelopoiesis. In vitro tests for cellular immunity gave normal values for T cells and B cells, and the lymphocytes responded normally to mitogens. IgG was 5.6 g/l, IgA 0 g/l, and IgM 2.4 g/l at 3 weeks of age. Leucocyttagglutinin tests were repeatedly positive. Further testing using serum from the child and the mother and white blood cells from the father showed that the mother had a cytotoxic antibody to HLA-A24 bearing cells, an HLA antigen common for the father and the elder sister, but not the patient. The serum of the mother and the infant also contained an antibody that reacted with the father's granulocytes. The antibody was not further defined regarding its specificity for the granulocyte antigens NA1 and NA2. Serum from the child did not agglutinate the mother's granulocytes. Subcutaneous adrenalin increased the white blood count from $7.1 \times 10^9/l$ to $22.3 \times 10^9/l$, but failed to liberate any neutrophils.

Intravenous immunoglobulin

Because of the possibility of further serious infections, and after informed consent from the parents, it was decided to treat the child with high dose intravenous immunoglobulins. Gammonativ (Kabi-Vitrum, Sweden), a native human immunoglobulin prepared according to the Cohn method and stabilised with an equal amount of human albumin, was given according to the regimen proposed by Imbach for immune thrombocytopenia (400 mg/kg for five consecutive days).² For convenience, however, the total dosage was given within three consecutive days instead of five. In the next 11 days the granulocytes rose to $1.6 \times 10^9/l$ (Figure), later declining to values varying between 0.3 and $0.7 \times 10^9/l$ for the next eight weeks, without any further infectious episodes. Thereafter the neutropenia gradually returned to normal and remained well above $1 \times 10^9/l$ from the patient's 16th week of life.

Discussion

Neonatal neutropenia is most commonly caused by acquired bacterial or viral infections. Acquired neutropenia is usually of short duration, however, and is seldom profound. Agranulocytosis points to

other underlying diseases either of the haematopoietic stem cell or the granulocyte progenitor, or to diseases associated with an abnormal peripheral neutrophil destruction. Progenitor disease was ruled out by normal habitus, normal bone marrow smear, and normal specific immunology. Alloimmunity to paternally inherited granulocyte antigens was found to be the likely cause. It is a very rare but well defined cause of neonatal neutropenia,¹ which should resolve in two to 17 weeks. Plasma exchange followed by infusion of maternal granulocytes has been suggested as treatment in cases of life threatening infections.

In immune thrombocytopenia Imbach and co-workers² showed that it was possible to treat and obtain a cure with high dose intravenous immunoglobulin treatment. Many recent reports confirm their finding, and this mode of treatment has also been applied successfully to alloimmune neonatal thrombocytopenia.³

The response to intravenous immunoglobulin in immune thrombocytopenia is most favourable in the acute form of the disorder. In chronic disease the results parallel those in our case—a prompt rise but one which only lasts for two to three weeks.

In this boy, immunoglobulin infusion resulted in a temporary return to normal of the granulocyte count over a time period corresponding to the expected half life for IgG of three weeks. This agrees with a recent report on immunoglobulin treatment for an immune neutropenia in older children.⁴ High dose immunoglobulin treatment seems to be a safe and easy method of curing, at least temporarily, immune neutropenia, and covering a critical period of high risk for serious infectious complications. It should bear substantially fewer complications than plasma exchange. Intravenous immunoglobulin treatment is not, however, indicated in other forms of neutropenia, and should not be given to a newborn or any other child who just happens to be neutropenic.

References

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