Short reports

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Haemophagocytic reticulosis

A state of chimerism?

Haemophagocytic reticulosis is characterized by pancytopenia and an increased mass of reticulo-endothelial cells in various organs containing engulfed blood cells (see Buist, Jones, and Cavens, 1971; Oehmichen, Narita, and Roloff, 1972; Nézelof and Eliachar, 1973). The pathogenesis is obscure. Autoimmunity, primary histiocytic proliferation, and a graft versus host reaction have been suggested.

A case diagnosed during life is described where cytological and immunological studies as well as experiments with erythrophagocytosis *in vitro* suggest an immune reaction rather than a neoplastic histiocytic proliferation as the pathogenetic mechanism.

Case report

The patient, a boy, was born of a cousin marriage. 3 older sibs and the parents are all healthy. Pregnancy, delivery, and perinatal period were normal. There was no Rh-immunization during pregnancy. BCG vaccination was done at 5 days of age with a normal reaction. After that the child was apparently healthy.

Smallpox vaccination was given at 10 weeks of age. 7 days later the patient was admitted in a bad general condition. The liver and spleen were enlarged. Hb 4.3 g/100 ml, thrombocyte count 28,000, WBC 3500 with 13% granulocytes and 66% lymphocytes. The course was dominated by increasing hepatosplenomegaly and a swinging temperature. There were widespread oral candidiasis and large perianal necrotizing ulcers. A rash of short duration appeared on two occasions. There were no abnormalities of hair or nails and no diarrhoea. The local vaccination reaction developed normally. He was given repeated transfusions, antibiotics, and steroids in high doses but died 4 months after admission.

Laboratory investigations. Before transfusions Hb values had decreased from about 10 to 5 g/100 ml and the granulocytes were 200–500/mm³. Lymphocytes on admission were 2300/mm³ and later between 1200–4000/mm³. Thrombocytes were 25,000–50,000/mm³ before transfusions. Immunoglobulin levels were IgG 0.45 g/100 ml, IgA <0.05 g/100 ml, and IgM 0.04 g/100 ml. Chromosome analysis in lymphocytes from peripheral blood revealed a normal male karyotype in all metaphases studied.

Cytology. The bone-marrow smears were rich in cells with a predominance of early cell types within the erythropoietic and granulopoietic series. A remarkable abundance of macrophages containing cell debris as well as whole cells identified as erythroblasts, erythrocytes, granulocytes, and thrombocytes was noted. Smears from the spleen and liver (fine-needle aspiration biopsy) were extraordinarily rich in large phagocytic cells of various morphology. Endothelial cells, histiocytes, and Kupffer cells were packed with cell debris, red cells, neutrophils, and platelets (Fig. 1a).

Serological investigations and tissue typing. Blood grouping and tissue typing: patient O Rh(+), HL-A 1, 8/W 19, W 16; mother O Rh(–), HL-A W 19, W 15, W 16; father A Rh(+), HL-A 1, 8/W 19, W 16.

The red cells were typed several times within the Rh system. No mixed field appearance was demonstrable. The antiglobulin test was repeatedly negative. No irregular red cell antibodies could be found in the serum. Mixed lymphocyte cultures with the patient's cells and maternal as well as paternal lymphocytes were negative. The patient's lymphocytes were normally transformed when stimulated with phytohaemagglutinin.

Erythrophagocytosis *in vitro*. Leucocytes were obtained from two healthy donors. 10 ml heparinized venous blood was left at room temperature for 1 hour. The buffy coat was pipetted off, centrifuged, and the supernatant plasma removed.

Erythrocytes were suspended in 0.9% NaCl and centrifuged at 1000 *g* for 5 minutes. The packed cells were used in the phagocytosis experiments.

Phagocytosis. The leucocyte concentrate was resuspended in 0.5 ml serum and 0.1 ml of the packed red cells added. The mixture was incubated at 37 °C for 1 hour and centrifuged at 200 *g*. The sediment was spread on slides and stained with May-Grünwald-Giemsa.

The results of the phagocytic experiments are given in the Table. In the presence of the patient's serum monocytes phagocytized red cells obtained from the patient and his mother. In no other combination of serum, leucocytes, and red cells was erythrophagocytosis observed. The most pronounced phagocytosis was noted with the maternal erythrocytes (Fig. 1b).

Discussion

This case fits well into the remarkably uniform picture of haemophagocytic reticulosis, in which the generalized increase of 'reticuloendothelial' cells and the rapidly fatal course may suggest a malignant neoplastic disease (Marrian and Sanerkin, 1963).

(a)

(b)

FIG.—(a) Spleen aspirate with phagocytic endothelial cell (above) and pulp cell (below) containing erythrocytes and pyknotic material. (b) Erythrophagocytosis in vitro by normal monocyte in the presence of the patient's serum and maternal erythrocytes.

TABLE
Results of erythrophagocytosis *in vitro*

Erythrocytes from	Serum from	Leucocytes from	Erythrophagocytosis
Patient	Patient	Healthy donor A	+
Patient	"	" " B	+
Mother	"	" " A	++
Father	"	" " A	—
Patient	Healthy donor A	" " A	—
Healthy donor A	Patient	" " A	—
Healthy donor B	"	" " B	—
Healthy infant	"	" " B	—

However, no focus of convincingly neoplastic cells could be detected. The principal abnormality was instead an exaggerated phagocytic activity in cells of various origin. In addition, phagocytosis of red cells from the patient could be induced *in vitro* using allogenic monocytes if the patient's serum had been added to the system. It is of fundamental interest that red cells from his mother were also phagocytized in this system. Monocytes but no neutrophils phagocytizing red cells were seen. It is known that red cells coated with IgG are readily phagocytized by monocytes and macrophages but not by neutrophils (for review see Huber and Fudenberg, 1970). The *in vitro* and *in vivo* phagocytosis was therefore probably of immune origin.

A resemblance between haemophagocytic reticulosis and graft versus host reaction (GVHR) has recently been pointed out (Oehmichen *et al.*, 1972; Nézelof and Eliachar, 1973). In the present case an unusual degree of histocompatibility might have favoured the survival of a maternal graft and some symptoms were compatible with a GVHR, e.g. anaemia, granulocytopenia, thrombocytopenia, hepatosplenomegaly, and susceptibility to infections. On the other hand diarrhoea and hair loss were not present, the direct Coombs's test was repeatedly negative and lymphocyte counts normal throughout the course. There was thus no convincing clinical evidence for a GVHR.

Instead, the massive phagocytosis of blood cells could be interpreted as a rejection of a maternal haemopoietic graft, i.e. a host versus graft reaction caused by antibodies against maternal blood cells. Observations in the *in vitro* assay may argue for this hypothesis. There was an excessive phagocytosis of red cells obtained from the mother, presumably due to opsonizing factors present in the patient's serum. Phagocytosis of red cells obtained from the child occurred to a lesser extent. This was to be expected if grafted maternal cells alone were the targets of abnormal phagocytosis in the child.

There are no reasons to assume that haemo-

phagocytic reticulosis, as it presented itself in our patient, is a malignant neoplasm. An immune reaction against blood cells seems to be a more likely explanation. Further investigations of haemophagocytic reticulosis should take into account the possibility of a state of chimerism.

Summary

A case of haemophagocytic reticulosis diagnosed during life in a 2½-month-old-boy is described. The clinical course had some traits in common with a graft versus host reaction but several characteristic features of graft versus host reaction were lacking. Haemophagocytic reticulosis may be due to a graft of maternal haemopoietic cells tolerated during the first weeks of extrauterine life but later provoking a host versus graft reaction with formation of antibodies against grafted blood cells. Experiments with erythrophagocytosis *in vitro* supported this hypothesis.

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