CASE REPORTS

Auto-immune neutropenia in an infant

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Summary

A case of neutropenia in an infant is described, associated with repeated minor infections which responded to treatment with antibiotics. A granulocyte agglutinin was detected in the serum. Following treatment with prednisolone the neutropenia remitted, the antibody disappeared and the infections ceased. Treatment was discontinued after three months and the child remained well five months later. Reports of similar cases are reviewed and the significance of the antibody discussed.

Introduction

Auto-immunity is an acknowledged cause of haemolytic anaemia and thrombocytopenia. Recent reports have drawn attention to cases of neutropenia probably due to a similar mechanism (Leading Article, 1976; Boxer *et al.*, 1975). Only a few cases have been substantiated and they have varied widely in age, clinical course and response to treatment. However, three patients have been reported (Lalezari *et al.*, 1975; Nepo *et al.*, 1975; Kay *et al.*, 1976) to which is now added a fourth, which belong to a distinct group showing the features of chronic benign neutropenia of childhood.

Case report

The patient was the first child of unrelated Turkish parents. She was born at term by normal delivery and weighed 3.33 kg. She was well until 7 months of age when she presented with cough, fever and malaise for one week and was treated with oral penicillin. The haemoglobin was 10.1 g/dl, and the

white cell count $4.2 \times 10^9/l$ ($4200/\mu l$), neutrophils $0.7 \times 10^9/l$ ($700/\mu l$). After one week the white cell count was $6.9 \times 10^9/l$ (neutrophils 0.69). The Paul Bunnell test was negative. Two weeks later she flew to Turkey where she had several ear infections which were treated with oral ampicillin.

She was seen again two months after her initial presentation, with a two-week history of pyrexia and diarrhoea, which consisted of ten or more loose green stools/day. Examination at that time showed a pink right ear drum, no lymphadenopathy and no other abnormal findings.

Investigations showed: haemoglobin 10.5 g/dl; WBC $9.3 \times 10^9/l$ (neutrophils 0.09, lymphocytes 8.1, monocytes 0.9, eosinophils 0.2); platelets $520 \times 10^9/l$; ESR 80 mm in 1 hr; albumin 42 g/l, globulin 31 g/l with a slight increase in α_2 -globulin on electrophoresis; IgA 1.12, IgM 1.8, IgG 11.3 g/l. A rectal swab grew *Salmonella schwarzengrund*, but blood cultures, nasal swab and urine showed no growth. LE latex and anti-nuclear antibody tests were negative. Bone marrow was moderately hypercellular and showed marked granulocytic hyperplasia with normal morphology and maturation up to the metamyelocyte stage, but a virtual absence of mature neutrophils. There was no increase in blast cells and erythropoiesis and megakaryocytes were normal. Leucocyte antibody tests were performed as described below and showed a granulocyte agglutinin to a titre of 1 : 8 and a leucocytotoxic antibody. The direct Coombs test and tests for platelet antibodies were negative.

Two days after admission she developed a fever of $40^\circ C$ and was treated with penicillin and gentamicin, with rapid resolution of her fever. At that time her white cell count was $7 \times 10^9/l$ with neutrophils less

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than 1%, all unsegmented. She was started on prednisolone 40 mg daily and 72 hr later her white cell count was $9 \times 10^9/l$ (neutrophils $4 \times 10^9/l$). No white cell antibodies were then detectable. The prednisolone was tailed off after 3 months, and there has been no relapse after a further 5 months. Tests for white cell antibodies have remained negative.

Leucocyte antibody methods

Fresh normal leucocytes from the same donor were used for both the techniques described below.

Leucocyte agglutination

The leucocyte agglutination method was based on that of Goudsmit and van Loghem (1953). A granulocyte suspension was prepared from fresh blood by dextran sedimentation of the red cells. The patient's serum was titrated by doubling dilutions in normal saline and equal volumes of each dilution and the granulocyte suspension incubated at 37°C for 90 min. A volume of 1% acetic acid stained with methyl violet was added immediately before examining the deposits microscopically for agglutination.

Cytotoxic antibody detection

Cytotoxic antibodies were detected by a modification of the method of Engelfriet and Britten (1966). Normal target lymphocytes were separated from defibrinated blood on Ficoll-Triosil heavy density reagent, washed and resuspended in buffered saline. Four volumes of the cell suspension were incubated with six volumes of the patient's serum for 2 hr at 37°C. The supernatant was then removed and replaced by four volumes of human complement for a further 30 min incubation, followed by addition of one volume of 2% trypan blue and reincubation for a further 30 min. At the end of this time the cells were examined microscopically, death of more than 70% indicating the presence of a cytotoxic antibody in the test serum. Known positive and negative controls were included.

Discussion

Iso-immune selective neutropenia, although rare, is a well recognized occurrence, especially in the neonatal period (Lalezari and Radel, 1974). An auto-immune aetiology in some cases of neutropenia can be expected by analogy with haemolytic anaemia and thrombocytopenia. Four children (including the present patient) have been described who developed neutropenia in infancy with demonstrable neutrophil antibodies.

The occurrence of an anti-neutrophil antibody in a neutropenic patient does not prove a causal relationship. The most convincing report is that of Lalezari *et al.* (1975) who demonstrated a specific anti-NA2 antibody in a patient with NA2 positive

neutrophils. In the present case, the evidence, as in those of Nepo *et al.* (1975) and Kay *et al.* (1976), although strong, is circumstantial. Other patients have been described differing only in the failure to detect an antibody (e.g. Kaufman, 1975). However, it is probable that an antibody is implicated in many of these and failure to demonstrate it is due to lack of suitable technology. In the present case, tests for leucocyte agglutinins and cytotoxic antibodies were positive. The former detects granulocyte agglutinins and the latter primarily anti-lymphocyte antibodies.

It is likely that many granulocyte antibodies are not detectable by direct agglutination. Many more may be revealed by indirect tests, conceptually equivalent to the indirect Coombs test, in which antibody uptake by test neutrophils may be detected by various methods. The physical presence of the antibody has been demonstrated by immunofluorescence (Boxer, Yokoyama and Lalezari, 1972), and by antiglobulin consumption (van Loghem *et al.*, 1958). The presence of an antibody appears to interfere in a variety of ways with neutrophil function and this has been turned to account by using panels of function tests as indicators of the antibody reaction (Boxer and Stossel, 1974; Kay *et al.*, 1976). These methods will only detect free antibody in the serum. There is no satisfactory equivalent to the direct Coombs test, largely owing to the very low neutrophil counts encountered, although Dixon, Rosse and Ebbert (1975) have succeeded with quantitation of platelet-bound antibody in immune thrombocytopenia.

Children with auto-immune neutropenia may display a benign clinical course in spite of severe neutropenia. In those cases treated with steroids there has been a prompt neutrophil response which may be maintained after stopping treatment, as in the present case and that of Nepo *et al.* (1975), although relapse may also occur (Lalezari *et al.*, 1975). This suggests a course similar to that of auto-immune haemolytic anaemia where a remission may be hoped for after a period of steroid cover in those clinically severe enough to warrant it. Probably many cases of 'chronic benign neutropenia of childhood' are, in fact, examples of auto-immune neutropenia and as improved techniques of antibody detection become available the number of proved cases will increase.

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Pituitary coma with continuing menstruation

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Summary

A case of pituitary coma with continuing menstruation is presented. This association is extremely rare, but a history of recent menstrual periods does not exclude advanced hypopituitarism from the differential diagnosis of severe hyponatraemia.

Introduction

The pattern of hormone deficiency in pituitary failure is variable and the occurrence of deficiencies of single hormones is well recognized (Hall, 1974). Although menstrual cycles and even pregnancy are known to occur in patients with partial hypopituitarism (Simpson, 1959), gonadotrophin loss is usually an early if not the first feature of most patients with hypopituitarism (Sheehan, 1939). This is a report of a patient, presenting with coma due to advanced pituitary failure, who was still menstruating.

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Case report

A 50-year-old housewife was admitted to hospital in July 1976 48 hr after an episode of unconsciousness lasting several hours from which she had made a spontaneous recovery. A previous attack had occurred in September 1975. Following both attacks, which were unrelated to fasting, she had noticed a dull frontal headache and sweating. After the first attack, she had been seen in out-patients and found to have a fasting blood sugar of 2.7 mmol/l (43 mg/dl) with normal plasma electrolytes. She had felt generally unwell since the death of her husband 4 years previously, and for 2 years had noticed increasing lethargy.

She had had normal pregnancies and had lactated normally over 24 and 16 years previously. She had been under regular review in gynaecological out-patients for vaginal prolapse since 1973 and there is a well documented account of her menstrual history. During the 12 months before admission she had had