Familial combined cellular and humoral immune defect with multisystem granulomata

W. H. PERKS AND IAN S. PETHERAM

From Brompton Hospital, Fulham Road, London SW3 6HP, UK

Perks, W. H., and Petheram, I. S. (1978). *Thorax*, 33, 101-105. Familial combined cellular and humoral immune defect with multisystem granulomata. A brother and sister presented with recurrent respiratory infections. Investigations showed combined cellular and humoral immune defects and non-caseating granulomata in lungs, liver, lymph nodes, and skin. Despite antimycobacterial chemotherapy and corticosteroids in the brother and the additional treatment of human immunoglobulin injections in the sister both patients deteriorated with pulmonary and hepatic involvement.

Shortly after the description of 'congenital agammaglobulinaemia' (Bruton, 1952) an 'acquired primary' form of the disease was recognised in adults (Grant and Wallace, 1954; Prasad and Koza, 1954; Prasad *et al.*, 1957). Unlike the congenital variety there is no apparent pattern of inheritance but familial cases have been reported (Wollheim, 1961; Wollheim *et al.*, 1964; Buckley and Sidbury, 1968). Multi-organ non-specific granulomata are a recognised feature of some cases (Rosen, 1971) and have been noted in a patient who also had depression of delayed-type hypersensitivity (Sharma and James, 1971). We are not aware of previous reports of this association in sibships.

We report acquired primary hypogammaglobulinaemia with widespread non-specific granulomata in a brother and sister, both of whom also had evidence of a defect in delayed-type hypersensitivity.

Case reports

CASE 1 The son of Maltese parents, domiciled in Great Britain for four years, presented at the age of 16 with iritis. He had also had purple lesions on both shins for six years. There were no other abnormal physical signs but a chest radiograph showed widespread mottled shadowing of both lungs with some ring shadows and bronchial wall thickening (Fig. 1). Routine haematology and blood biochemistry were normal but a 24-hour urinary calcium was raised at 9.2 mmol/24 hours (N 2.5-7.5). Sputum for acid-fast bacilli was negative on three occasions and Wasserman, Lepromin,

Kveim, and Mantoux tests (1/100) were negative (previous BCG vaccination aged 10). Biopsy of the skin lesion showed 'a large tuberculoid granuloma with one swollen and heavily infiltrated nerve. Very scanty acid-fast bacilli present'. Biopsies from nerve, liver, and unaffected skin revealed no histological abnormalities. He was treated with prednisolone and dapsone with improvement in the iritis but not in the pulmonary shadowing.

When aged 18 he was readmitted with severe measles associated with persistence of Koplik's spots, a right lower lobe pneumococcal pneumonia, and jaundice with a bilirubin of 130 $\mu\text{mol/l}$. After resolution of the pneumonia an open lung biopsy was performed. Histology showed many non-caseating granulomata in the lung and pleura (Fig. 2) with acid-fast bacilli present. He was treated with PAS, isoniazid, streptomycin, and prednisolone for three years but his condition continued to deteriorate.

He was readmitted on four separate occasions with moniliasis of the larynx, palmar warts, iritis, lobar pneumonia, pneumococcal meningitis, and fluctuating jaundice. Liver function tests showed a bilirubin rising to 265 $\mu\text{mol/l}$, SGOT to 199 units (N8-35), and alkaline phosphatase to 75 KA units (N4-14). Serum protein electrophoretic strips on two occasions demonstrated a moderate increase in α_1 and α_2 globulins with a decrease in γ globulin. A liver biopsy showed two granulomata without caseation. The liver parenchymal cells were healthy and no acid-fast bacilli were seen. After antituberculosis chemotherapy had been stopped prednisolone, 7.5 mg daily, was continued.

Fig. 1 *Case 1. Chest radiograph showing widespread mottled shadowing of both lungs with some ring shadows and bronchial wall thickening.*

Fig. 2 *Case 1. Lung biopsy showing several non-caseating granulomata. H and E $\times 185$.*

At the age of 23, because of a rising bilirubin and alkaline phosphatase, he underwent laparotomy. The gall bladder and common bile duct were dilated. There was a stricture of the terminal 1 cm of the common bile duct and the pancreas was indurated and oedematous. Sphincterotomy, cholecystoenterostomy, and wedge biopsy of liver were performed. Histology of the liver showed centrilobular bile retention, and in the portal tracts there was bile duct proliferation and chronic inflammatory cell infiltration. Numerous granulomata, negative for acid-fast bacilli, were present.

At the age of 25 he was admitted with a staphylococcal pneumonia. His jaundice deepened and he died eventually from a Gram-negative septicaemia. At no time during the patient's life was *Mycobacterium tuberculosis* cultured.

CASE 2 The sister of case 1 presented at the age of 25 with left pleuritic chest pain, cough, and copious sputum production. From early childhood she had suffered from recurrent sinus infections and persistent non-productive cough. Examination revealed bilateral basal crackles but neither clubbing nor hepatosplenomegaly. A chest radiograph showed 'increased reticular markings in both upper and lower zones and fairly extensive patchy consolidation in the left lower lobe with dilated bronchi'. A bronchogram showed bilateral basal

bronchiectasis. Sputum for acid-fast bacilli and Mantoux (1/100) and Kveim tests were negative. A rectal biopsy was normal. Histology of a scalene node showed 'numerous follicular lesions with giant cells. The appearances are of sarcoidosis or tuberculosis without caseation. No acid-fast bacilli were seen'. Culture of the node was negative for tuberculosis. A diagnosis of sarcoidosis was made and treatment with intermittent antibiotics and postural drainage was begun.

At the age of 35 she was admitted to hospital with gradual worsening of dyspnoea and productive cough. She was cyanosed, clubbed, jaundiced, and emaciated. There were coarse crackles at both lung bases and hepatosplenomegaly. A chest radiograph showed widespread irregular mottled shadowing with numerous ring shadows and small linear shadows consistent with bronchiectasis (Fig. 3). The haemoglobin was 14.4 g/dl, white cell count $18.3 \times 10^9/l$ (88% neutrophils), and ESR 69 mm in 1 hour. There were no bacterial pathogens, acid-fast bacilli, aspergillus, or eosinophils in the sputum. Blood urea, electrolytes, and calcium were normal. The alkaline phosphatase was 372 IU (N 9–35), SGOT 48 IU (N 6–21), SGPT 57 IU (N 6–33), γ GT 234 IU (N 9–29), and bilirubin 46 $\mu\text{mol/l}$. Serum protein estimation was 67 g/l (N 62–82), of which 36 g/l was albumin and 31 g/l globulin. Serum protein electrophoresis showed a

Fig. 3 Case 2. Chest radiograph showing widespread irregular mottled shadowing with numerous ring shadows and small linear shadows consistent with bronchiectasis.

decreased γ globulin. Immunoelectrophoresis revealed IgA less than 20 IU (N 57–172), IgM 39 IU (N 138–196), and IgG 111 IU (N 57–172). Antibodies to common bacterial and viral pathogens were absent, anti-B isohaemagglutinin titre was 1/4, *Escherichia coli* antibody titre was 1/4 (N > 1/64), and a Mantoux (1/100) was negative (no previous BCG vaccination). Lymphocyte T cell population was normal but lymphocyte transformation to phytohaemagglutinin (PHA) and purified protein derivative (PPD) was impaired. Lymphocyte 5-nucleotidase was 1.9 nmol/h/10⁶ cells (N 15–35). Circulating phagocytosing monocytes were 27% (N 10–20%). A Kveim biopsy was equivocal on two occasions. Serum angiotensin converting enzyme (ACE) was 37 units (N 15–30). A liver biopsy showed several small granulomata with giant cells. No acid-fast bacilli were seen. Lung function studies revealed a mixed restrictive and obstructive picture.

She was treated initially with conventional anti-tuberculosis chemotherapy without improvement and then intramuscular human γ globulin injections. One month after starting immunoglobulin replacement she was readmitted with worsening of breathlessness, deepening of jaundice, and right heart failure. This deterioration was improved by antibiotics and prednisolone at an initial dosage of 60 mg per day. At the time of writing she is being treated with immunoglobulin injections and prednisolone, 10 mg daily, with no symptomatic deterioration but worsening of liver function tests. Immunoglobulin estimations were performed on the mother and sister (the available remaining relatives of the patients described) and found to be within normal limits.

Discussion

The clinical and immunological features suggest that these patients suffered from the same condition. Both had gammaglobulin deficiency and immunoelectrophoresis and antibody studies in the sister showed low levels of immunoglobulin. This deficiency of gammaglobulin, with the low lymphocyte 5-nucleotidase in the sister (Johnson *et al.*, 1977), is compatible with the diagnosis of acquired primary hypogammaglobulinaemia (Grant and Wallace, 1954; Prasad and Koza, 1954; Prasad *et al.*, 1957). The hypogammaglobulinaemia is probably a result of a failure of the B-lymphocytes, which are present in normal numbers, to produce immunoglobulin (Gajl-Peczalska *et al.*, 1973). Although there are normal numbers of T-lymphocytes in the peripheral blood in primary acquired hypogammaglobulinaemia (Webster and Asherson,

1974) in over half of the cases their function is impaired (Douglas *et al.*, 1970) and this feature was demonstrated in the sister. A T-lymphocyte defect was probably present in the brother in view of the negative tuberculin reactivity and recurrent viral and fungal infections. This is of interest because patients with primary acquired hypogammaglobulinaemia, as opposed to combined immune deficiency, do not suffer from viral or fungal infections, probably because there are functional T lymphocytes present (Webster and Asherson, 1974).

Our patients were shown to have multi-organ granulomata and this was associated with one episode each of iritis and hypercalciuria in the brother and a raised serum ACE in the sister (Lieberman, 1975). Both could, therefore, be considered to have sarcoidosis. Against this diagnosis are the atypical clinical and immunological features (Mitchell and Scadding, 1974) and the equivocal or negative Kveim biopsies in the presence of active granulomata (Sharma and James, 1971). Neither multi-system granulomata (Lancet, 1975a) nor the raised ACE are specific to sarcoidosis. The latter has been described in Gaucher's disease (Liebermann and Beutler, 1976) and in hypogammaglobulinaemia with multi-system granulomata (Turton, 1977, personal communication). Sharma and James (1971) reported a similar case to those we have described and concluded that their patient did not have sarcoidosis and that the associated granulomatous response might be due to an unknown immunological mechanism. The presence of acid-fast bacilli in two out of eight biopsies in our case 1 does not necessarily imply active mycobacterial infection as a cause of the illness because on no occasion were bacilli grown and he failed to respond to antilepromatous and anti-tuberculosis chemotherapy.

The familial association of a defect in the cellular and humoral immune response with multi-organ granulomata has not, as far as we are aware, been described previously. Kushner *et al.* (1960) described a family with hypoglobulinaemia, splenomegaly, and leucopenia and concluded that the condition was possibly transmitted by an autosomal dominant gene. A genetic basis has been suggested as the cause of primary 'acquired' hypogammaglobulinaemia (Wolheim *et al.*, 1964) but can only be tentative in our patients as other explanations such as an infective agent common to both brother and sister are possible. Another possibility is that the patients had familial immune deficiency and both developed granulomata as a result of an abnormal interaction of macrophages and 'indigestible antigen' present as a result of the immune defect (Lancet, 1975b).

The treatment of both patients has been disappointing. Steroids and antituberculosis therapy did not halt the clinical deterioration and eventual death of case 1 and the addition of immunoglobulin injections in case 2 has produced no clinical benefit. We feel that further understanding of this unusual condition is essential to make treatment rational.

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Requests for reprints to: Dr. W. H. Perks, Brompton Hospital, Fulham Road, London SW3 6HP, UK.