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Sarcoidosis associated with combined immunodeficiency

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Summary

The association of multiple non-caseating granulomata and a positive Kveim test is normally considered to be indicative of a diagnosis of sarcoidosis. However, although depressed cell-mediated immunity is commonly described, it is extremely rare to find a humoral immune paresis.

A patient is reported who had multiple granulomata, depressed cellular and humoral immunity and a positive Kveim test.

Introduction

Sarcoidosis is usually accompanied by normal or raised serum immunoglobulin levels. We report a case of sarcoidosis associated with combined immunodeficiency.

Case report

A 23-year-old housewife was referred to the Haematology department of King's College Hospital from the ENT department in April 1977, following discovery of pancytopenia. There was a history of recurrent sinusitis since childhood treated by bilateral nasal washouts, and a submucous resection for a deviated nasal septum had been performed 3 months before. There was no other past medical history or family history of note.

Clinical examination revealed bilateral cervical lymphadenopathy, enlarged tonsils and moderate splenomegaly. Results of investigations were as follows:

Hb, 9·7 g/dl; WBC, $2{\cdot}2 \times 10^9$/l (neutrophils 6%, lymphocytes 85%, eosinophils 2%, monocytes 7%); platelets, 74×10^9/l; ESR, 37 min in 1st hr (Westergren); Paul Bunnell test, negative; blood group, O Rhesus positive; total protein, 60 g/l; albumin, 35 g/l; IgG, 21·7 g/l; IgM, 1·65 g/l; IgA, none detected; autoantibody screen, negative; bilirubin, 110 μmol/l; AST, 40 i.u./l; alkaline phosphatase, 200 i.u./l; prothrombin time, 13 sec (control 13 sec); calcium, 2·2 mmol/l; chest X-ray, normal; lymphangiogram showed abnormal lymph nodes in left para-aortic region; a bone marrow biopsy showed hypercellularity only. An exploratory laparotomy and splenectomy were performed in May 1977. The spleen and para-aortic lymph nodes were enlarged. Histological examination of the spleen (wt 450 g), liver and lymph nodes showed numerous histocytic non-caseating granulomata with preservation of normal follicular structure. Postoperatively a Mantoux (1 : 100) test, a Kveim test and tests for brucellosis, toxoplasmosis and tuberculosis were all negative. Haematological indices returned to normal.

Between May 1977 and March 1978 the patient experienced 3 episodes of pneumonia and developed a left pleural effusion which required drainage by thoracotomy. Lung biopsy performed at operation showed interstitial lymphoid infiltrates and pleural changes consistent with pneumonia, but no granulomata.

Further investigations at this time show: IgG 0·94 g/l, IgA, $<0{\cdot}25$ g/l; IgM, 0·17 g/l; urinary 24-hr calcium excretion, 1·54 mmol/l. Delayed hypersensitivity skin tests were negative to *Candida*, PPD and varidase. Total peripheral blood lymphocyte count was $2{\cdot}07 \times 10^9$/l, 20% of which formed rosettes with sheep erythrocytes and 32% carried surface immunoglobulin. Lymphocyte transformation with phytohaemagglutinin was markedly reduced. Barium meal and follow-through and jejunal biopsy were both normal. Repeat Mantoux (1 : 100) test was negative. A Kveim test (Kveim antigen K19) was positive (Fig. 1).

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A diagnosis of sarcoidosis was made and treatment with prednisone, 40 mg daily, was started on 16 March 1978. Regular weekly injections of 1·5 g of human γ-globulin were also given but were stopped

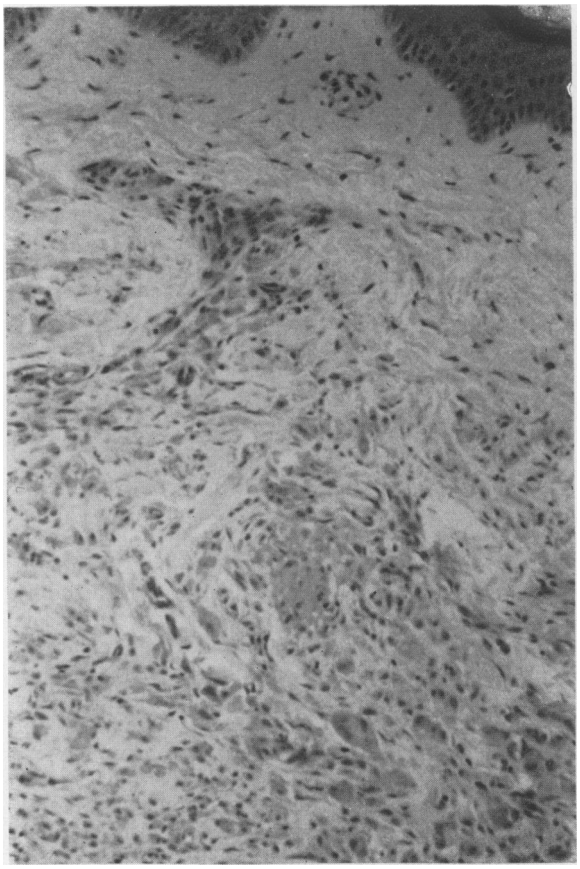

FIG. 1. Kveim biopsy from forearm, showing granulomata.

in August 1978 following 2 anaphylactoid reactions. Prednisone was tailed off in September. The patient has remained reasonably well since then. The most recent investigations have shown:

Normal Hb, WBC and platelets; IgG, $<1{\cdot}5$ g/l; IgA, 0·56 g/l; IgE, $<0{\cdot}05$ g/l; IgD, $<0{\cdot}018$ g/l; C_1-inhibitor normal; immune complexes, using a ^{125}I-C1q binding test (Zubler, Langer and Lambert, 1976), normal; granulocyte function was normal. Anti-A titre, none detected; anti-B titre, 1 : 2. Serum typhoid and para-typhoid antibodies 2 weeks after TAB vaccine, <1 : 20. The ability of peripheral blood mononuclear cells to respond to specific mitogenic stimuli was reduced, using 'T' mitogens, phytohaemagglutinin and concanavalin A, and strongly reduced using the preferential B cell mitogen, pokeweed. Suppressor cell activity was measured in 2 different ways: first, the suppressor activity related to production of prostaglandin E_1 and E_2 was measured using indomethacin inhibition (Goodwin, Bankhurst and Messner, 1977) and second, the short-lived suppressor cell activity was measured using an overnight incubation (Bresnihan and Jasin, 1977). With the first technique, a normal suppressor cell activity was found (50% increase, normal range 57%±20%), while the short-lived suppressor cell activity was reduced (0·54, normal range $>1{\cdot}2$). Repeat Kveim test (Kveim antigen K12) was negative.

Discussion

This patient presented with hypersplenism and initially had a selective IgA deficiency. The past history of repeated respiratory tract infection may have been due to IgA deficiency a deviated nasal septum or neutropenia. Postoperatively, a combined deficiency of IgG, IgA and IgM developed. A cellular immune deficiency was also demonstrated. The possible aetiological role of splenectomy in the development of hypogammaglobulinaemia remains conjectural. A small percentage of selective IgA-deficient subjects has been shown to possess an IgA-specific subset of suppressor cells, while in common variable hypogammaglobulinaemia excess suppressor cell activity appears either as a primary or secondary phenomenon in most patients (Waldman *et al.*, 1978). Suppressor cell activity in the present patient was, however, reduced in the short-lived suppressor cell assay and normal in the prostaglandin mediated suppressor cell activity.

Multiple granulomata have been described from patients with primary acquired agammaglobulinaemia. These patients may also have hypersplenism (Rosen, 1971). However, the association of multiple granulomata and combined immunodeficiency with a positive Kveim test has, as far as the authors are aware, only been reported on one previous occasion (Bronsky and Dunn, 1965). A positive Kveim test has previously been noted in patients with aggamaglobulinaemia. These were considered to be false-positive reactions, although one of the 2 patients had splenomegaly (Messerschmitt, Faille and Gonthier, 1975). The occurrence of multiple granulomata in immunodeficiency syndromes may result from macrophage-indigestible antigen interactions (Editorial, 1975). However, in this patient pre-splenectomy levels of IgG were raised with normal levels of IgM, and granulomata were already present. The postoperative development of the IgM and IgG deficiencies could have been related to removal of the spleen in a patient with an already compromised immune system.

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