Acquired hypogammaglobulinaemia and sarcoidosis

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Summary

A syndrome has been described in which hypogammaglobulinaemia is associated with splenomegaly and haemolytic anaemia and also non-caseating granulomata in lymph nodes, liver, spleen and skin. This report describes a patient with this syndrome who in addition had a positive Kveim and elevated serum angiotensin converting enzyme (SACE), suggesting the diagnosis of sarcoidosis.

KEY WORDS: hypogammaglobulinaemia, sarcoidosis, haemolytic anaemia, uveitis.

Introduction

Many patients with hypogammaglobulinaemia have been reported since Bruton's first case (1952), but Prasad and Koza (1954) first described the association of this disorder with hypersplenism and haemolytic anaemia. A patient with haemolytic anaemia, hypogammaglobulinaemia and non-caseating granulomata in a lymph node and spleen was reported by Prasad, Reiner and Watson (1957) and a second patient with hypogammaglobulinaemia was reported to have sarcoidosis (Zinneman, Hall and Heller, 1954) but neither patient was assessed by Kveim test or estimation of serum angiotensin converting enzyme (SACE). Serum immunoglobulins are generally raised in patients with sarcoidosis (Scadding, 1967), although two patients with sarcoidosis and selective deficiency of IgA have been reported (Sieglar, 1978).

The patient described in the present report had hypogammaglobulinaemia, with clinical and laboratory evidence which supported the diagnosis of sarcoidosis.

Case report

The patient was 72 years old when she presented in 1976 with a 3-week history of increasing tiredness.

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The only abnormality on examination was a low grade pyrexia and a just palpable spleen. Her haemoglobin was 6.6 g/dl, white cell count (WBC) $2.4 \times 10^9/l$, platelet count $144 \times 10^9/l$ and a reticulocyte count 4.4%. The direct antiglobulin test was negative. The bone marrow showed erythroid hyperplasia with storage iron. The total bilirubin was raised at 28 $\mu g/l$. A provisional diagnosis of haemolytic anaemia was made. The alkaline phosphatase and alanine transaminase were normal, but the total globulin concentration was low at 20 g/l. Further investigation showed all immunoglobulins to be low: IgA 0.3 g/l, IgG 1.5 g/l, IgM 0.2 g/l. A liver biopsy was normal.

During the 3 weeks following admission without any treatment the reticulocyte count and bilirubin became normal and the haemoglobin rose to 10.0 g/dl. The patient had two minor infective lesions, a boil in the left axilla and a sty on the left eyelid, both of which resolved spontaneously.

Later in this admission, a retinal abnormality was thought to be choroidal tubercles. Although a tuberculin test had not been performed treatment was commenced with Mynah 300 (300 mg ethambutol; 100 mg isoniazid) three times daily. The diagnosis of tuberculosis was not sustained following an ophthalmological opinion when the fundal lesions were attributed to the anaemia. The Mynah 300 was stopped when the patient developed an extensive skin rash which was diagnosed as drug sensitivity. Six months later she was discharged from the medical clinic, on no treatment, with a haemoglobin of 12.0 g/dl.

Five years later, in 1981, the patient again presented with anaemia. The haemoglobin was 8.7 g/dl, WBC $2.8 \times 10^9/l$, platelets $156 \times 10^9/l$, and reticulocyte count 1.0%. The direct antiglobulin test was still negative. On examination the spleen had enlarged to the umbilicus. Investigations showed a normoblastic marrow and no haemosiderin in the urine. Ham's test was negative. The chest X-ray was normal with no hilar enlargement. The immunoglobulins were even lower: IgA 0.19 g/l, IgG 1.3 g/l, IgM 0.18 g/l.

Radioisotope studies demonstrated a shortened red cell life ($T_{1/2}^{51\text{Cr}} = 20.5$ days) with excess counts over the spleen, but no evidence of extramedullary erythropoiesis.

In October 1981 the patient developed a macular skin rash which on biopsy showed a non-caseating granulomata. A Kveim test was performed after the rash had cleared spontaneously. Dr D. Mitchell, Brompton Hospital, London provided the Kveim antigen and histology of the injection site showed typical granulomata. The serum angiotensin converting enzyme was elevated on two occasions: 94 and 84 nmol/ml/min (normal range 16–52 nmol/ml/min).

In December 1981 the patient developed septicaemia and pneumonia due to *Streptococcus pneumoniae*, which responded to treatment with amoxycillin. Following recovery from this infection the patient's immune function was assessed. The absolute number of B cells measured by mouse rosettes, and T cells measured by sheep rosettes was normal. The measurement of suppressor cells and helper cells by the monoclonal antibodies OKT8 and OKT4 respectively were also normal. Treatment with immunoglobulin by intramuscular injection (25 mg/kg weekly) was commenced.

In April 1982, the patient's general condition had deteriorated and oral prednisolone 10 mg was started. She responded rapidly to this treatment with an increase in haemoglobin to 14.2 g/dl and a reduction in spleen size to 4 cm below the costal margin.

However, in May 1982, the patient was found to have uveitis in the right eye. This was treated initially with local steroids, but she subsequently also developed anterior and posterior uveitis in the left eye. The vision in the right eye deteriorated rapidly and was unaffected by large doses of systemic steroids (60 mg prednisolone daily). Treatment with azathioprine failed to stop the unrelenting deterioration of her vision.

The patient died in January 1983, following an episode of septicaemia. A post-mortem examination was performed 3 days following the death. It was concluded that the cause of death was pneumonia and the clinical diagnosis of septicaemia was supported by the finding of many small brain abscesses. No granulomata were seen microscopically in the lymph nodes, liver or spleen. The enlarged spleen showed evidence of many hyalinized infarcts and the pathologist considered these were probably the result of high dose steroid treatment on granulomata. There was no evidence of lymphoma.

Discussion

This patient had the clinical features of primary hypogammaglobulinaemia (Prasad and Koza, 1954; Rosen and Janeway, 1966), with recurrent pyogenic

infections, splenomegaly, a haemolytic anaemia and non-caseating granulomata in the skin.

The patient's haemolytic anaemia was direct Coombs' test negative. However, patients with acquired hypogammaglobulinaemia have been described with a Coombs' positive haemolytic anaemia (Asherson and Webster, 1980). Webster *et al.* (1981) have commented on the high incidence of autoimmune disease in these patients in spite of the inability to produce protective levels of antibody following infection.

The aetiology of acquired hypogammaglobulinaemia has not been established. There is some evidence from studies both in humans (Waldman *et al.*, 1979; Dosch, Jason and Gelfand, 1982) and animals (Blaese *et al.*, 1974) that a rise in the T suppressor cell population might result in hypogammaglobulinaemia. In this patient, the absolute numbers of B cells, T cells, T suppressor cells and T helper cells were all normal.

This patient had a positive Kveim test, non-caseating granulomata in transient skin lesions, splenomegaly, bilateral uveitis and a high serum angiotensin converting enzyme on two occasions. The haemolytic anaemia and splenomegaly responded dramatically to low dose steroid treatment. This is compelling evidence for a diagnosis of sarcoidosis. However, serum immunoglobulin levels are generally raised in patients with sarcoidosis, particularly those with recent or active disease (Scadding, 1975) and sarcoidosis usually presents in younger patients. There was no evidence of any chronic infection in this patient which might have caused the granulomata.

It has not been possible to make a positive diagnosis of sarcoidosis in previously reported patients with associated hypogammaglobulinaemia and granulomata because neither the Kveim test nor SACE were available. The clinical course in this patient illustrates that active sarcoidosis can co-exist with humoral immunodeficiency.

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