Case report

Multicentric Castleman's disease associated with rheumatoid arthritis: a possible role of hepatitis B antigen

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SUMMARY A patient with seropositive rheumatoid arthritis and a carrier of hepatitis B surface antigen developed angiofollicular hyperplasia (multicentric Castleman's disease). The hepatitis B virus and the rheumatoid factor may have had a role in the aetiology of this lymphatic disorder. The development of Castleman's disease in association with these factors may provide another clue supporting the reactive nature of this disease.

Castleman's disease (angiofollicular lymph node hyperplasia), first described as a localised hyperplastic lymphoid process of the mediastinum, is a lymphoproliferative disorder of unknown cause.¹ Later, multicentric giant lymph node hyperplasia involving extramediastinal lymphoid tissues was described.² Whether it is an autoimmune disorder, a reaction to an unidentified infectious agent, an immunodeficiency disease, or an autonomous lymphoproliferative disorder has not been determined.³

Lymphadenopathy, usually adjacent to areas of active synovitis, is found in 29–82% of patients with rheumatoid arthritis.⁴ Characteristic, although not pathognomonic, histological features of lymph nodes from patients with rheumatoid arthritis show reactive follicular hyperplasia throughout both cortex and medulla, with prominent plasmacytosis in the interfollicular region.⁵

We report a patient with seropositive rheumatoid arthritis and a carrier of hepatitis B surface antigen (HBsAg) who developed huge axillary and cervical lymphadenopathy. Serial lymph node biopsies disclosed the classical morphological features of multi-

centric Castleman's disease of the hyaline vascular and plasmacytic type.

Case report

CLINICAL SUMMARY

A 45 year old man was seen in our rheumatology clinic with right axillary lymphadenopathy. Two years previously rheumatoid arthritis had been diagnosed based on symmetrical pain and swelling of the proximal interphalangeal joints, morning stiffness of one hour's duration, rheumatoid nodules on the left forearm, and positive rheumatoid factor. For nine months he was treated with ibuprofen and hydroxychloroquine. Thereafter, aurothioglucose and tetracosactrin in weekly intramuscular injections were added. Four months later he developed nausea, anorexia, abdominal pain, and jaundice. A liver biopsy specimen was characteristic of infectious hepatitis with positive immunoperoxidase staining for HBsAg. Despite the causal relation between the hepatitis and HBsAg the aurothioglucose and tetracosactrin injections were discontinued, and treatment was maintained with ibuprofen and hydroxychloroquine.

Physical examination showed synovial thickening, tenderness of the proximal interphalangeal joints, a cyst in the right popliteal fossa, and rheumatoid nodules along the extensor aspect of the left

Accepted for publication 30 August 1988.

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forearm. Non-tender, huge lymph nodes, 8 cm diameter, were palpated in his right axilla. The liver and spleen were palpable.

Relevant laboratory studies showed an erythrocyte sedimentation rate of 40 mm/1st h (Westergren), haemoglobin 140 g/l, white blood cells $7.5 \times 10^9/l$ with a normal differentiation count, and positive latex fixation and sheep red cell agglutination tests (1/640 and 1/128 respectively). Hepatitis B surface antigen, anti-HBc, and anti-HBe were found in the serum. Antibodies to nuclear antigens, Epstein-Barr virus, and cytomegalovirus were not detected. A Venereal Disease Research Laboratory test was

negative and an electrocardiogram and chest radiogram were normal. An axillary lymph node was biopsied. Six months later, during which time his rheumatic disease was completely asymptomatic, he developed enlarged lymph nodes in both axillae, and another biopsy specimen was taken from the left axilla. Four months later, following persistent fever, weakness, night sweats, and cervical lymphadenopathy, a chest radiogram showed mediastinal lymphadenopathy (Fig. 1), and abdominal computed tomography disclosed enlarged para-aortic and retroperitoneal lymph nodes. Bone marrow aspiration showed normal red cell line and plasmacytosis of 5%. A third biopsy specimen was obtained from a cervical node.

PATHOLOGICAL STUDIES

All three lymph nodes examined from this patient showed the characteristic features of angiofollicular lymph node hyperplasia. The first biopsy specimen showed many large hyperplastic follicles and relatively few hyaline vascular centres (Fig. 2). The interfollicular areas showed extensive vascularity with many sheets of plasma cell infiltrating the whole node. Immature large and intermediate sized lymphoid cells were also seen between the plasma cells. This histopathological pattern corresponds to multicentric Castleman's disease, proliferative or hyperplastic type.⁶ The histological features of the two lymph nodes excised later during the patient's

Fig. 1 Patient showing axillary lymphadenopathy. Note also the enlarged cervical lymph nodes.

Fig. 2 Biopsy specimen from the first lymph node showing hyperplastic follicle. Note the concentric arrangement of the small lymphocytic cells around the centre. (Haematoxylin and eosin.)

Fig. 3 Biopsy specimen from the second lymph node showing a hyaline vascular centre. Note the blood vessel at the left entering perpendicularly into the small centre. (Haematoxylin and eosin.)

Fig. 4 Biopsy specimen from the cervical lymph node showing interfollicular areas infiltrated heavily by sheets of plasma cells. (Haematoxylin and eosin.)

treatment were of the hyaline vascular type (Fig. 3). Specifically, these follicles showed vessels entering perpendicularly to their centre and their arrangement was more concentric, bound by small lymphocytes. The interfollicular areas contained many blood vessels together with sheets of mature plasma cells (Fig. 4). Immunoperoxidase staining with antibodies

against light and heavy chains showed that the lymphoid cells exhibited a polyclonal pattern. Immunoperoxidase staining with anti-HBs antibody was negative.

IMMUNOLOGICAL STUDIES

Pertinent immunological studies included a total

serum protein of 91 g/l, of which 65 g/l were globulin fractions. A protein electrophoresis showed no paraprotein, albumin 30%, α_1 globulins 4%, α_2 globulins 8.0%, β globulins 7.1%, and γ globulins 51%. On quantitative immunoelectrophoresis the IgG was 30 g/l (normal 8–17), IgM 4.5 g/l (0.65–2.8), and IgA 4.7 g/l (0.9–4.5). Total white blood cell count was 7.5×10^9 /l with 40% lymphocytes. The T lymphocytes comprised 55% and B cells 15%. When OKT antibodies were used the ratio OKT4/OKT8 was 2.1 (2–3). Serum antibodies to HIV were not detected (Elavia, Diagnostic Pasteur, France).

Isolation of HBs-anti-HBs complexes was performed using the methods described by Gazitt *et al.*⁷ Briefly, the patient's serum was passed through a C1q affinity column containing agarose polyacrolein microspheres of 100–200 μ m diameter. The effluent was then passed through an anti-HBs affinity column (2 mg monoclonal anti-HBs coupled to 1 ml microsphere beads). The titres of HBsAg were determined in the effluents before and after passage through the anti-HBs affinity column by solid phase radioimmunoassay (Ausria, Abbott, Chicago, IL). Material absorbed to the two affinity columns was eluted by 10 ml of 1 M glycine-HCl buffer pH 2.5, dialysed against phosphate buffered saline, and concentrated by diquat dibromide. The protein content was determined according to Lowry^{7a} and samples were analysed by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (not shown). The patient's serum contained 33 μ g/ml HBsAg in immune complexes and 3 μ g/ml in its free state.

Discussion

Castleman's disease was first described as a localised hyperplastic lymphoid process of the mediastinum characterised histologically by peculiar Hassall-body-like germinal centres and marked vascular proliferation.¹ Gaba *et al* described the multicentric giant lymph node hyperplasia, which involved axillary, retroperitoneal, and other lymph nodes as well as the spleen.² Subsequently, Castleman added the plasma cell type to his original hyaline vascular type.⁸ Frizzera *et al* described 15 patients with multicentric Castleman's disease of plasmacytic type, two of whom had arthralgias and two others xerostomia and xerophthalmia. None of them fitted completely the syndrome of rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus.^{3–9} Recently, Weisenburger *et al* added a clinicopathological description of 16 more cases with angiofollicular lymph node hyperplasia, and none of them had rheumatoid arthritis.¹⁰

At some time during their illness 50–70% of patients with rheumatoid arthritis may develop lymphadenopathy.⁵ Histologically, lymph nodes of patients with rheumatoid arthritis are difficult to distinguish from those in Castleman's disease of the plasma cell type. Despite these similarities Keller *et al* found no case of rheumatoid arthritis among 81 patients with plasma cell type Castleman's disease.⁸ On the other hand, recurrent biopsies of enlarged lymph nodes from patients with rheumatoid arthritis over a 14 year period failed to detect the hyaline vascular type of Castleman's disease.⁵

The development of multicentric Castleman's disease in our patient with rheumatoid arthritis deserves comment. Firstly, such an association may be coincidental. Alternatively, lymphadenopathy may be associated with ingestion of drugs, such as phenytoin,¹¹ ibuprofen, hydroxychloroquine, aurothioglucose, and tetracosactrin, however, have not been implicated in the development of lymphadenopathy resembling Castleman's disease. Features suggesting that Castleman's disease may be an immunological disorder included lymphoid depletion in the T area of the spleen, an association with Kaposi's sarcoma, and the presence of auto-antibodies in the sera of some patients.^{6–12} A defined immunological stimulus accounting for these features has not been identified, however. Conceivably, the hepatitis B virus may have played an important part in the development of Castleman's disease in our patient. Besides being a chronic carrier of hepatitis B virus, the patient had received weekly injections of aurothioglucose and synthetic corticotrophin for four months before the development of hepatitis. Synthetic corticotrophin may have enhanced replication of hepatitis B virus which, modified by the gold salt treatment, caused infectious hepatitis and the increase of HBsAg in the serum.¹³ The production of anti-HBs antibodies may have in turn resulted in a large amount of immune complexes containing these two components. Thus the presence of at least three independent stimulating factors—that is, immune complexes, hepatitis B virus antigen, and rheumatoid factor, caused continuous stimulation of the lymphatic system and the development of angiofollicular hyperplasia (Castleman's disease). No data are available regarding the presence of HBsAg in the blood of patients with Castleman's disease.^{9–10} Patients with chronic liver dysfunction and bile duct damage, however, have been reported to develop nodal lesions identical to Castleman's disease of plasma cell type.⁹ The HBsAg carrier state of these patients is unknown. The possible role of HBsAg in Castleman's disease needs to be confirmed by epidemiological studies in larger groups of patients.

This study was supported by the Adolfo and Evelyn Blum research fund for arthritis.

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