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Case Report

Autoimmune Findings Resembling Connective Tissue Disease in a Patient with Castleman's Disease

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Summary **Multicentric angiofollicular lymphnode hyperplasia (multicentric Castleman's disease) may be associated with acute phase reaction and several autoimmune features. Since lymphadenopathy is a common feature in connective tissue disease, a clear distinction between the different disease entities may be difficult. We describe a 26-year-old male patient with predominant cervical lymphadenopathy, hepatosplenomegaly and polyserositis, diagnosed as collagen disease. He showed several autoimmune features including autoimmune haemolytic anaemia, cryoglobulinaemia, positive antinuclear and anti smooth muscle antibodies, serum immune complexes and a sensorimotor polyneuropathy. Under immunosuppressive therapy with prednisolone and azathioprine, only partial remission was achieved. Repeated lymph node biopsy together with the clinical features led to the diagnosis of multicentric Castleman's disease in this patient nine years later. Interleukin-6 (IL-6) seems to play an important role in the pathogenesis of clinical and serum biochemical features in patients with Castleman's disease.**

Key words **Multicentric Castleman's Disease, Autoimmune Features, Collagen Disease, Interleukin-6, POEMS-Syndrome**

INTRODUCTION

Angiofollicular lymph node hyperplasia (Castleman's disease) is a benign immunoproliferative disease, first described by Castleman in 1956 as "mediastinal lymph node hyperplasia resembling thymoma" (1). The multicentric form of the disease usually develops in patients over 50 years old and is associated with generalized lymphadenopathy. It may include autoimmune or hypochromic anaemia, acute phase reaction and POEMS-syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, skin lesions)(2). Since lymphadenopathy is a common feature in connective tissue disease (3), a clear distinction between the different disease entities may be difficult. We describe a 26-year-old patient who was diagnosed with an undifferentiated collagenosis nine years before and was now reevaluated to have multicentric Castleman's disease with several autoimmune features.

CASE REPORT

A formerly healthy 17-year-old white male patient developed fever, asthenia and anorexia with weight loss of 10 kg in March 1985. He showed a generalized lymphadenopathy with hepatosplenomegaly and progressive ascites. Leucocytosis (14,8 /nl), elevated erythrocyte sedimentation rate (ESR) (40 mm n.W.) and hypergammaglobulinaemia (29,54%) were noted. No infectious agent could be demonstrated. Immune complexes and smooth muscle antibodies were positive (titer 1:40), while other autoantibodies were negative (Table I). A lymph node biopsy showed an increased number of lymph follicles with active germinal centers. Because of the development of a nephrotic syndrome and a progressive polyserositis with ascites and pericardial effusion, prednisolone therapy (100 mg/d followed by stepwise reduction to

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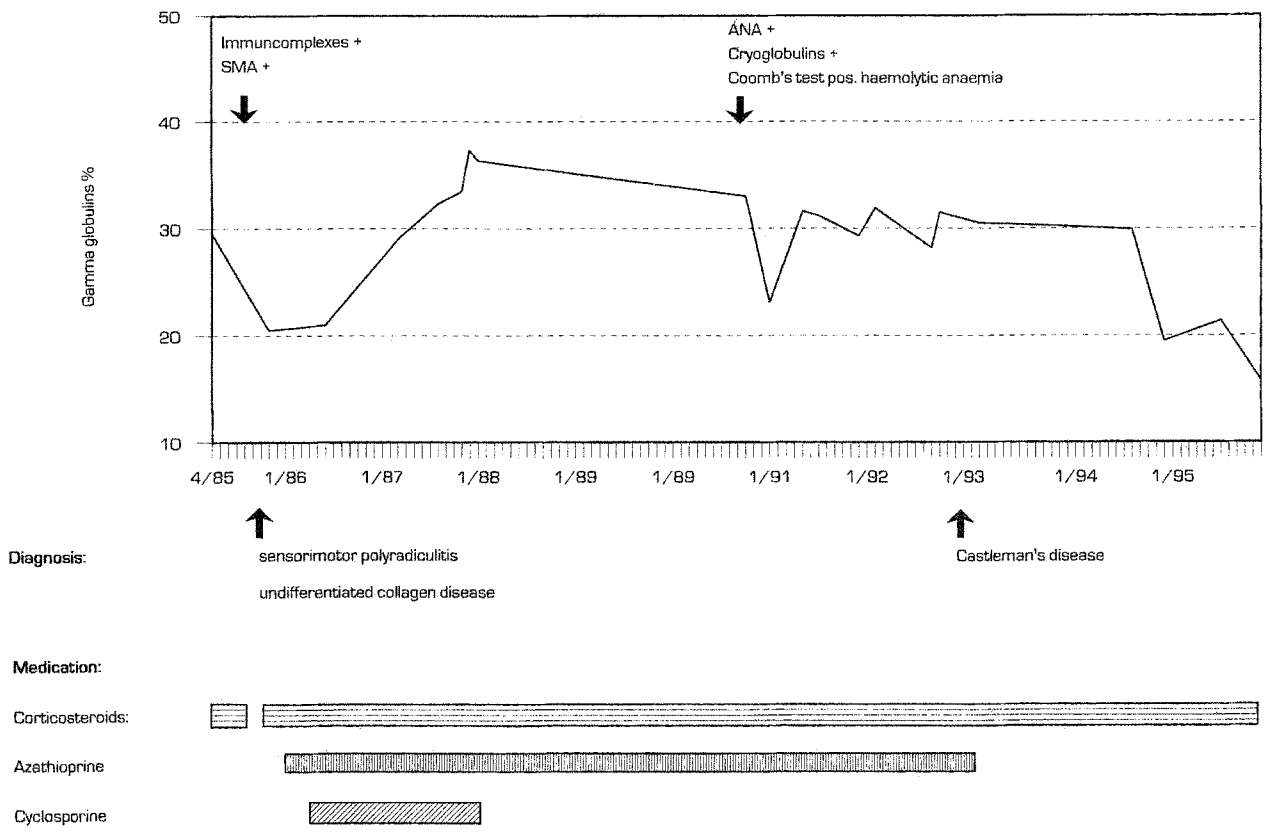

Fig. 1: Time course of hypergammaglobulinaemia, autoimmune findings and diagnosis

10 mg/d) was started in May 1985. The general condition improved promptly. Three months later corticosteroid medication was stopped because of clinical signs for septic infection. No infectious agent could be isolated. In October 1985 the patient developed sensorimotor polyradiculitis Guillain Barré. Cervical lymphadenopathy, hepatosplenomegaly and hypergammaglobulinaemia became prominent again. Plasmapheresis was started and the neurological symptoms ameliorated. A malignant haematological disorder was ruled out by diagnostic splenectomy. At that time the diagnosis of undifferentiated collagen disease was made and an immunosuppressive regimen with prednisolone (100 mg prednisolone/d followed by stepwise reduction) and azathioprine (150 mg/d) was commenced. In the following years the patient suffered from recurrent flare ups of anaemia, weight loss and increasing cervical lymphomas. In March 1986 cyclosporine (140 mg/d) was added but showed no substantial effect and was stopped two years later.

The patient was first referred to our hospital because of recurrent episodes of fever in January 1991. Under immunosuppressive treatment (10 mg prednisolone/d, 75 mg azathioprine/d) clinical examination revealed a patient in a relatively good condition with only slightly en-

Table I: *Laboratory findings at first manifestation of the disease (4/85) and at the the time of diagnosis of Castleman's disease*

	4/85	10/87	1/91	11/93	11/95
ESR (mm 1st hour)	40	> 120	116	92	41
Haemoglobin (g/dl)	10,0	8,0	9,0	13,0	12,4
γ-globulins (%)	29,0	37,3	30	29,8	15,8
IgG (g/l)		37,2	27,2		
		Immune complexes + Smooth muscle Ab 1:40	Cryoglobulins + ANA 1:320 indirect Coomb s test +	ANA -	

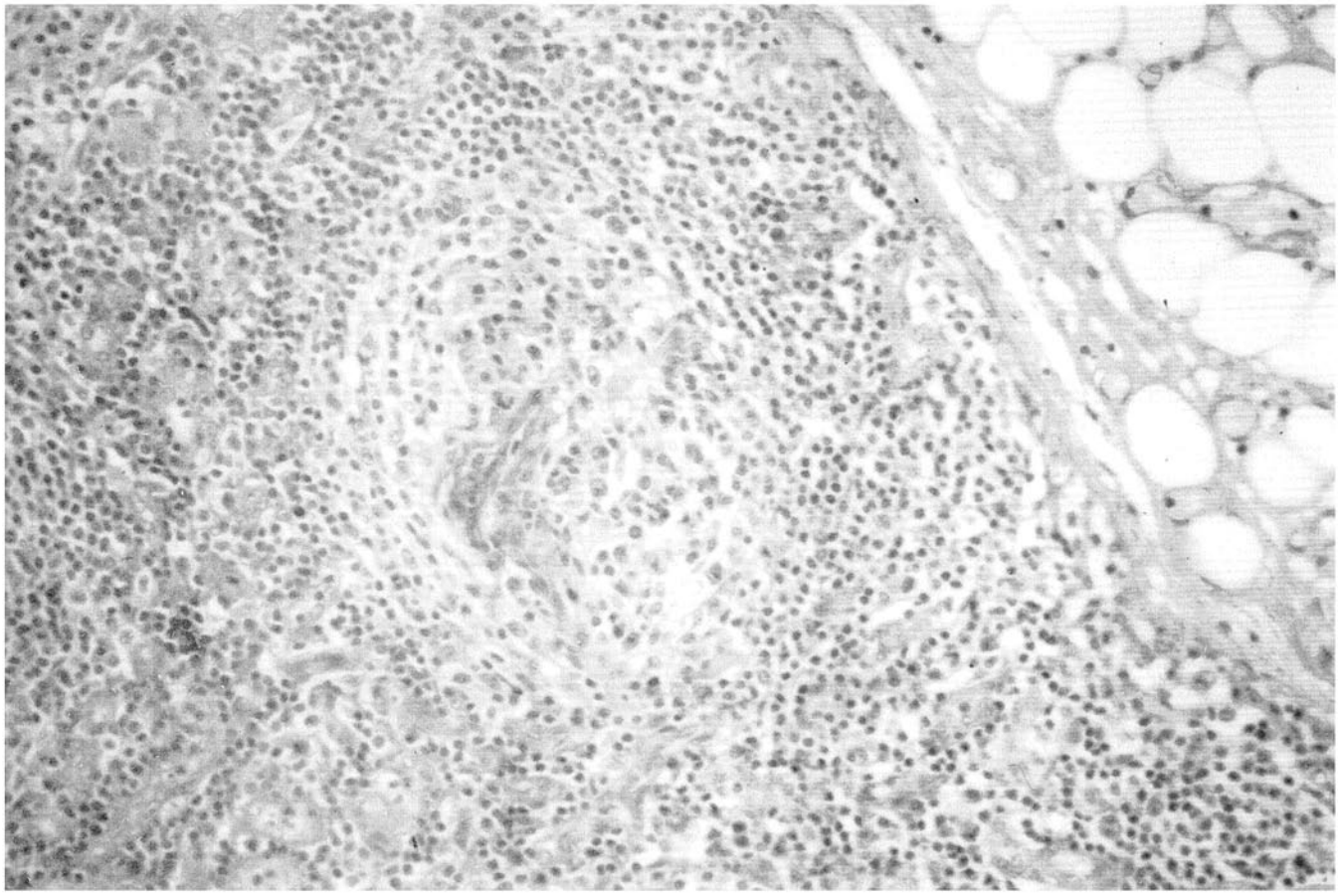

Fig. 2: Lymph node biopsy with altered germinal center due to hypervascularization and marked endothelial proliferation (64x, PAS stain).

larged lymph nodes and persistent leg weakness. Major biochemical abnormalities were detected (Table I): elevated ESR (116 mm/h), normochromic anaemia (Hb 9,0 g/dl) and hypergammaglobulinaemia (30%) due to polyclonal increase of IgG (27,2 g/l). CD4/CD8 ratio was diminished (0,8). ANA were 1:320 positive (homogen pattern), antibodies against extractable nuclear antigen and ds-DNA were negative. The HLA-type was A1, B8, DR3, cryoglobulins could be demonstrated and a Coomb s test positive haemolytic anaemia was diagnosed. A bone marrow aspirate sample showed hyperplastic changes without signs of a myeloproliferative syndrome.

Despite continuous immunosuppression, the patient manifested recurrent fever episodes, lymphadenopathy, hypergammaglobulinaemia and elevated acute phase proteins (Fig. 1). The daily prednisolone intake had to be augmented repeatedly to a maximum of 60 mg/d. Because of clinical and radiological progressive lymphadenopathy a new lymph node biopsy was obtained. Histological examination revealed prominent follicles with an expanded interfollicular region and altered germinal centers. They appeared hypervasculated and there was marked increase in endothelial cell proliferation. In the interfollicular region a striking plasmocytosis was seen. In addition activated high endothelial venules and immunoblasts were increased in number (Figs. 2,3). An elevated serum interleukin-6 level (29 pg/ml, normal range 3-8,5 pg/ml) was measured in a follow-up examination.

The histological appearance together with the clinical and biochemical features led to the diagnosis of multicentric Castleman's disease.

The subsequent follow up of the patient was complicated by a newly diagnosed portal vein thrombosis and the azathioprine therapy had to be stopped because of continuous increase of cholestatic liver enzyme activities. The oral prednisolone medication could not be reduced to less than 20 mg/d, for fear of a recurrent haemolytic crisis in case of a further reduction. During the following years the patient suffered from recurrent septic bacterial pulmonal and gastrointestinal infections, but recovered each time under adequate antibiotic therapy.

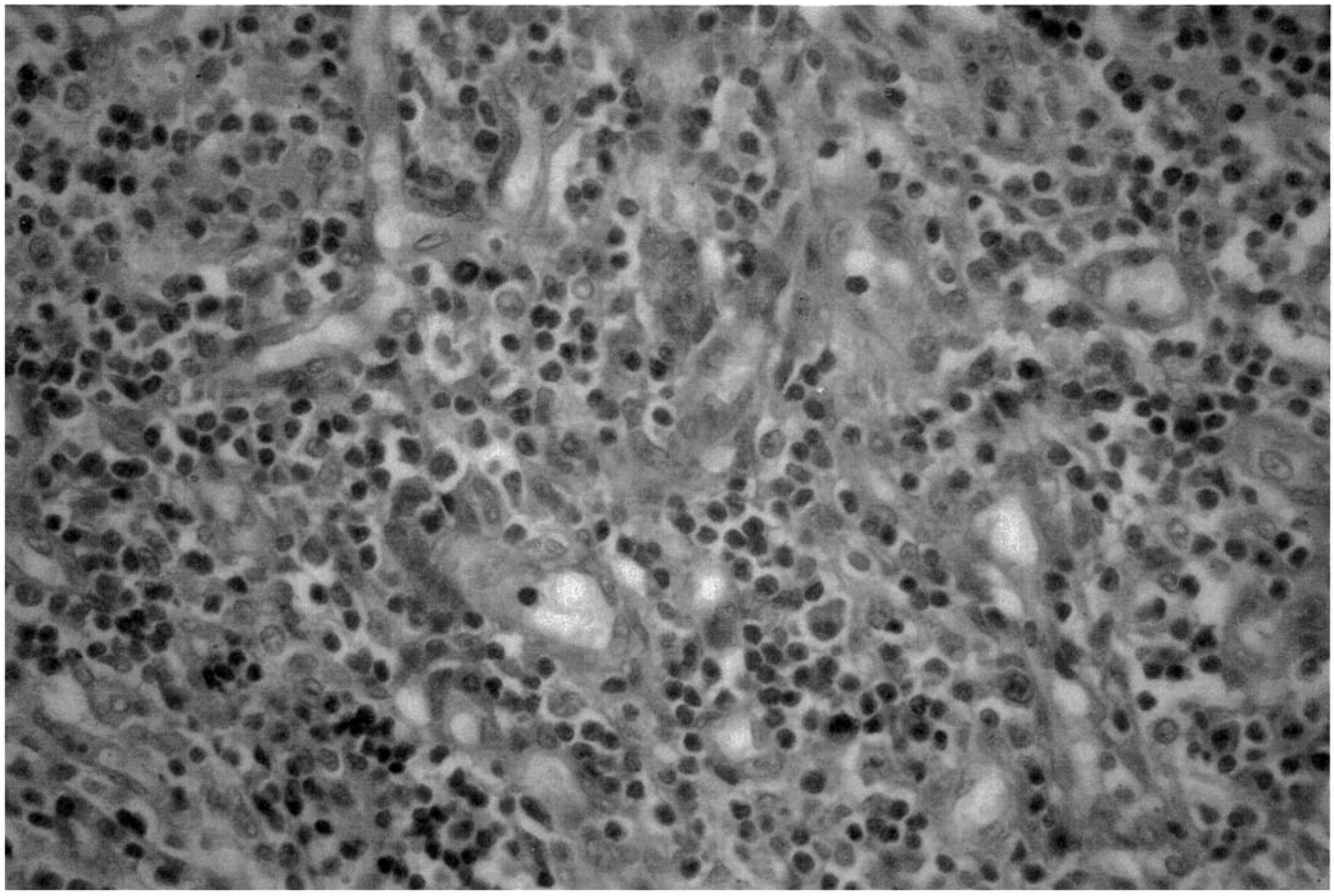

Fig.3: Expanded interfollicular region with plasmocytosis and increased high endothelial venules (102x, PAS stain).

DISCUSSION

Castleman's disease (angiofollicular lymphoid hyperplasia) is a heterogenous group of lymphoproliferative disorders of uncertain cause (4). Two pathomorphological types, a hyaline vascular and a plasma cell variant, have been recognized (5). The hyaline vascular type is more common, and characterized by small hyalin vascular follicles and interfollicular capillary proliferation, while the plasma cell type is dominated by large follicles with intervening sheets of plasma cells. Multicentric disease is a systemic lymphoproliferative disorder characterized by general lymphadenopathy, hepatosplenomegaly and constitutional symptoms which normally occur only in the plasma cell variant (6). Biochemical and clinical features of Castleman's disease are summarised in Table II. Although the Coomb s test is often positive, no other serologic autoimmune markers have been systematically evaluated in larger numbers of patients. There are reports, however, of a few cases in which antinuclear antibodies, rheumatoid factor, positive VDRL, cryoglobulins, and inhibitors of clotting factors VII and VIII have been detected (8, 9).

Table II: *Clinical and laboratory findings in Castleman's disease (7)*

Clinical findings	Laboratory findings
Lymphadenopathy	Increased ESR
General malaise	Increased acute phase proteins
Loss of weight	Polyclonal hypergammaglobulinaemia
Anorexia	Hypoalbuminaemia
Fever	Thrombocytosis
Night-sweat	Anaemia
Splenomegaly	Small amounts of autoantibodies
Skin rash	Proteinuria

Abnormally increased IL-6 production seems to be a critical step in the pathology of the disease. Immunohistochemical and gene expression studies revealed increased IL-6 production in affected lymph nodes in patients with localized Castleman's disease (2, 10). Systemic manifestations could be alleviated by monoclonal anti IL-6 antibodies, and symptoms recover after surgical resection of affected lymph nodes in localised disease (10,

11). Brand et al. reported that mice constitutively producing IL-6 after infection of their bone marrow cells with an IL-6 expressing recombinant retrovirus developed a syndrome closely resembling Castleman's disease (12). Furthermore, increased serum IL-6 levels have been detected in the MLR/lpr mouse. These animals develop spontaneous massive lymphadenopathy accompanied by hypergammaglobulinaemia with presence of antinuclear antibodies (anti DNA, anti SM) and anti-immunoglobulin antibodies (rheumatoid factor). Back crossing experiments suggest a link between the lpr locus and the increased IL-6 production in these mice (13). Unfortunately, IL-6 expression in the lymph-nodes was not examined in our patient, but elevated serum IL-6 levels, although not pathognomic, support the diagnosis of Castleman's disease. The observation that B lymphocytes of the lymphocytic corona of follicles in lymph nodes of Castleman's disease express the CD5 antigen, has been taken to explain the autoimmune manifestations in Castleman's disease as found in our case. The CD5 positive B cells are considered to be an autoantibody producing subset (14).

POEMS-syndrome, also known as Crow-Fukase or Takatsuki-syndrome, is especially reported from Japan (15-17), and its pathogenesis remains unclear. Chronic progressive sensorimotor polyradiculitis is among the most frequently reported neurological manifestations of this syndrome and precedes other abnormalities (18). There are reports of an association of this syndrome either with osteoclastic myeloma or with Castleman's disease (19, 20). Increased IL-6 production was shown to be one of the factors which could link Castleman's disease to the POEMS-syndrome. Our patient demonstrated extensive sensorimotor polyneuropathy which could be interpreted as an overlap with POEMS syndrome. Investigations on other features of this syndrome showed negative results so far.

Two recent publications underscore the difficulties in distinguishing between collagen disease and Castleman's disease as shown in this case. Hosaka et al. reported on three cases of Castleman's disease with typical autoantibody profile mimicking collagenosis (systemic lupus erythematosus [SLE], mixed connective tissue disease [MCTD]). Because of marked lymphadenopathy, lymph node biopsy was performed in all three patients. The histological examination together with the clinical features revealed Castleman's disease (21). Another report described a patient with MCTD which was associated with multicentric Castleman's disease and Crow-Fukase syndrome (22). The specificity of histopathological features in Castleman's disease is controversial. Closely related patterns can be observed in diverse clinical conditions as in autoimmune disorders especially rheumatoid arthritis, Sjögren´s syndrome, primary immunodeficiencies and human immunodeficiency virus infections. Therefore, prior to the diagnosis of Castleman's disease, the above-mentioned conditions must be ruled out first (9).

Localized Castleman's disease has a good prognosis; however, the course of multicentric Castleman's disease is unpredictable. A high mortality rate was observed in a series of 38 cases where only 13% of patients survived after 10 years since time of diagnosis. Infections are a common cause of death in Castleman's disease; 29% of the patients had sepsis or pneumonia as a contributing cause of death. Progression to malignant lymphoma was reported only in a few patients (9).

Limited information is available regarding treatment of Castleman's disease. The use of high doses of corticosteroids has been associated with long and unmaintained remissions in some patients, but often treatment needs to be prolonged at a relatively high dose. For refractory cases, chemotherapeutic regimens designed for Non-Hodgkin´s lymphoma are used either as single agent or in combination therapies (9).

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