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# CASTLEMAN'S DISEASE*

## A Case Report

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**Angiofollicular lymph node hyperplasia or Castleman's Disease (CD) is a rare lymphoproliferative disorder that manifests itself as a local or generalized tumor-like condition affecting both lymph nodes and non-nodal tissues, usually in the chest and abdomen. Hyaline vascular and plasma cell types have been identified histologically. A new clinical form of CD with multisystemic involvement has been defined as multicentric Castleman's disease. It is very rare in childhoed. In this paper we present an eight-year-old boy with multicentric Castleman's disease.** *Key words: angiofollicular lymph node hyperplasia, immunglobulin light chain, immunohistochemistry.*

Angiofollicular lymph node hyperplasia or Castleman's Disease (CD) was first described by Castleman and colleagues[1] in 1956. Keller et al.[2] classified the lesions into two types based on clinical and pathological criteria. The more common one, the hyaline vascular type, is characterized by small, hyalinized follicle centers with radially penetrating vessels and prominent interfollicular vascular proliferation. Patients with this type are usually asymptomatic, but occasionally it can give rise to symptoms due to the mass effect. The plasma cell type is characterized by large hyperplastic follicles with intervening sheets of plasma cells. More recently a lymphoproliferative disorder with similar histologic features but more generalized or extensive lymph node involvement has been reported as multicentric CD. Identification of systemic or multicentric CD is based on not only histology but also a combination of clinicopathologic criteria[3]. Although CD can be encountered at any age, most patients are between the ages of 30 and 40 years at presentation, and the disease is very rare in the pediatric age-group, especially the multicentric variant[4,5]. In this paper we present an eight-year-old boy who was diagnosed with multicentric CD.

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## Case Report

An eight-year-old boy was admitted to Erciyes University hospital for mediastinal enlargement and hepatosplenomegaly. He had been diagnosed with hepatitis two months earlier, with elevated serum transaminase and bilirubin levels, but the serologic markers for hepatitis A, B, C and D had been negative. He had been fainting for a month and EEG findings were consistent with epilepsy, carbamazepine therapy was initiated.

On examination he had pertibial edema, uveitis and hepatosplenomegaly. Laboratory data revealed a urinalysis of (++++) proteinuria, a urinary protein loss of 108 mg/m$^2$/h, a hemoglobin of 11.6 g/dl, a white cell count of 12,200/mm$^3$, and an erythrocyte sedimentation rate (ESR) of 105 mm/h. The tuberculin skin test was negative, C-RP 31 mg/dl (N: < 10), rheumatoid factor 55 IU/ml (N: < 25), ANA (-). Bone marrow aspiration was normal.

Serum BUN, creatinine, sodium, potassium, calcium, phosphorus, alkaline phosphatase, AST and ALT were within normal limits. Serum total protein was 5.2 g/dl, albumin 2.1 g/dl, triglyceride 149 mg/dl, and cholesterol 259 mg/dl. Serum IgG was 1670 mg/dl (N: 700-1630), IgA 187 mg/dl (N: 73-186) and IgM 132 mg/dl (N: 65-206). Chest x-ray showed mediastinal enlargement (Fig. 1). Abdominal

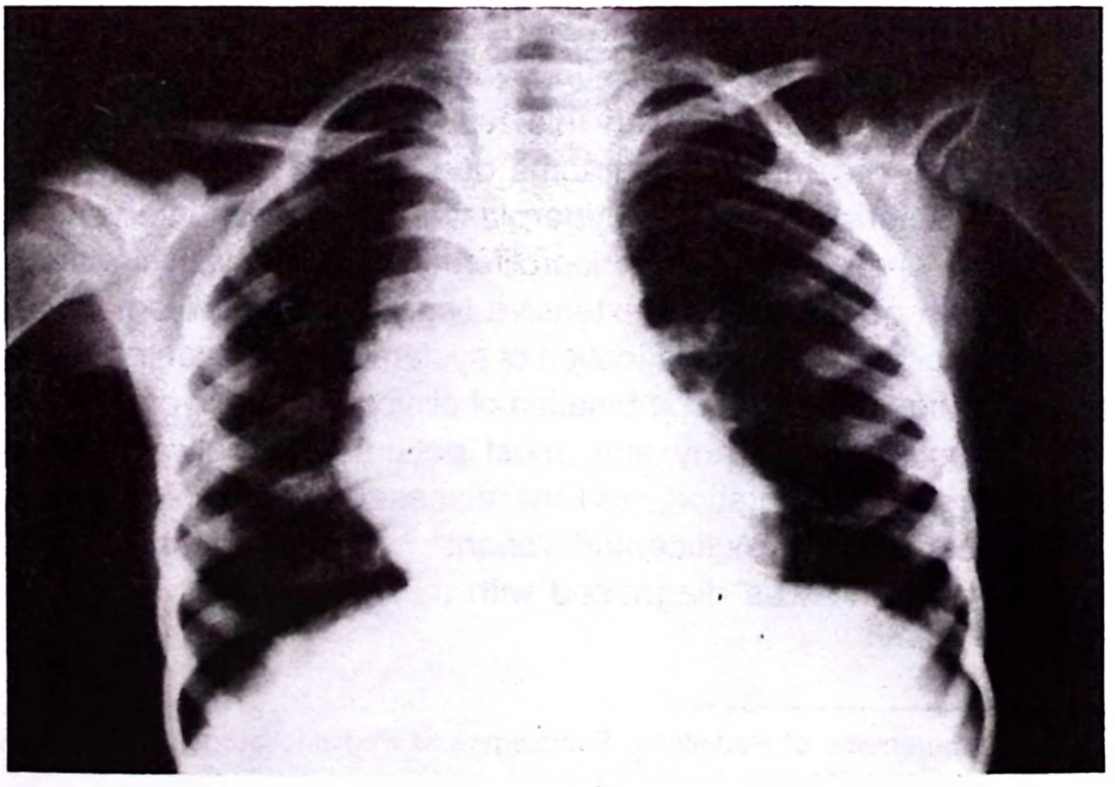

Fig. 1: Postero-anterior chest x-ray showing mediastinal enlargement.

ultrasonography (USG) revealed hepatosplenomegaly and hepatic and splenic hilar lymphadenopathy. Thoracal computed tomography (CT) showed right paratracheal and right inferior mediobasal lymphadenopathy. The findings of the mediastinal

lymph node biopsy were as follows: macroscopically the involved lymph node was firm, encapsulated and 4 x 2 x 1 cm in dimensions, while the cross-section was solid and gray-yellow in color; microscopic examination revealed that the nodal architecture was altered by an increased number of large, lymphoid follicles. In the germinal centers of the follicles were proliferating capillaries and deposits of hyaline material. Surrounding the germinal centers were multiple concentric layers of small and mature lymphocytes (onion-skin appearance). There were scattered histiocytes and some large Reed-Sternberg-like cells between the lymphocytes. The diagnosis was made as angiofollicular lymph-node hyperplasia, hyaline vascular type (Fig .2). Immune histochemical staining resulted as positive staining with λ and κ light chains (Fig. 3).

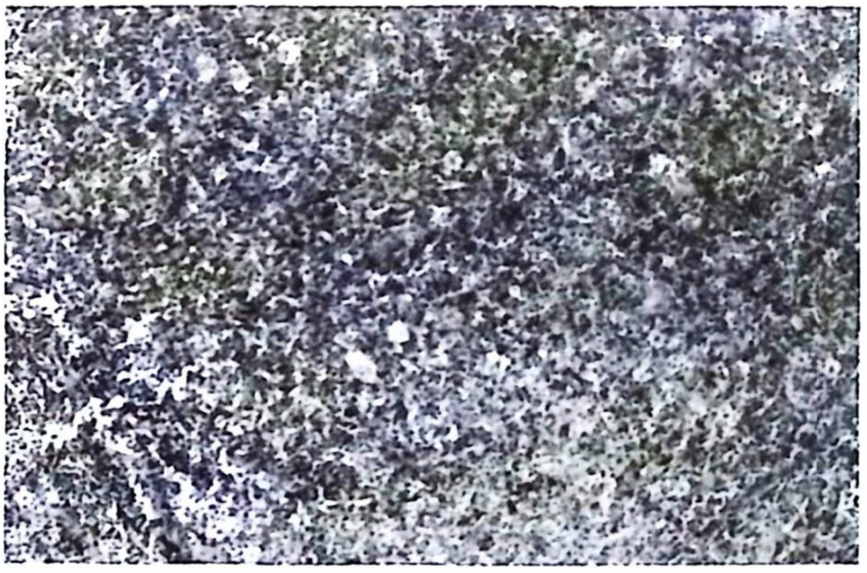

Fig. 2: Histologic appearance of lymph node. Note hyalinized follicle centers (H.E. x 100).

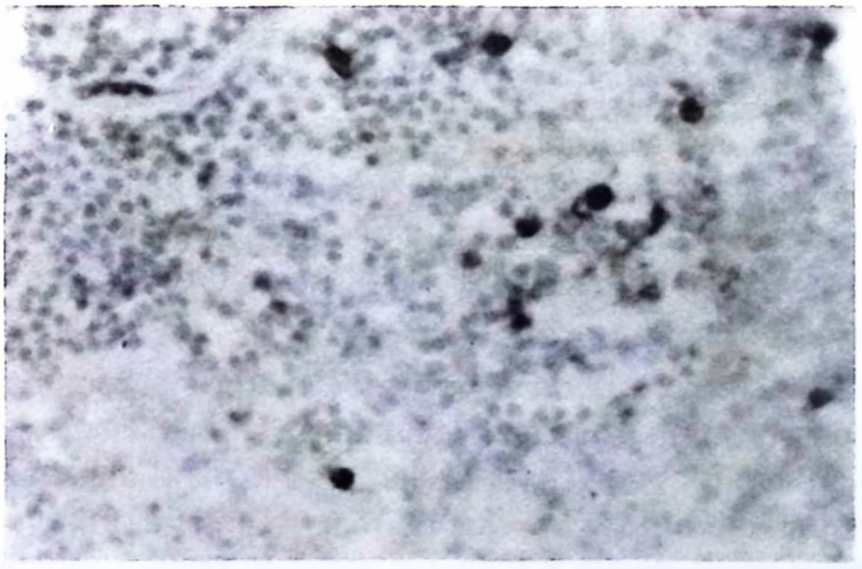

Fig. 3: Positive immunohistochemical staining with λ light chain (x 400).

After a follow-up period of five months the patient was asymptomatic, but in the sixth month the disease relapsed with mediastinal lymphadenopathy, fever and elevated acute-phase reactants.

## Discussion

Castleman's disease, especially the multicentric variant, is rarely seen in children. To date approximately 80 cases have been reported in children and adolescents (up to and including 18 years of age). The majority of cases have been 14 years or older at presentation. Only 13 cases of children less than 14 years in age at presentation have been published[4]. None of them had multisystemic involvement as in our case.

The etiology of CD is unclear. The hyaline vascular type seems to be a chronic reactive lymphoid hyperplasia, although the causal agent(s) remains undiscovered. An abnormal immune reaction or immune dysregulation, or an endothelial proliferation or proliferation of autoantibody producing B cells has been suggested in the etiology. Even though the etiologic agent remains unclear, it has recently been proposed that the stimulus for the B-cell proliferation is intervening production of interleukin 6 (IL-6), a B cell growth factor, being secreted by germinal centers. The symptoms, signs and abnormal laboratory findings of CD resolve with monoclonal anti IL-6 antibody treatment[6,7].

The clinical presentation may suggest infection, malignancy or autoimmune or collagen vascular disease[4,5]. Initially our patient was diagnosed with lymphoma.

Lymphadenopathy is universal. In general, the lymph nodes are modestly increased in size, occasionally larger and surgically unresectable. The most common sites are the abdomen, the mediastinum, the hila of the lungs and the neck[3-5]. The majority of pediatric cases have the localized form, but our case had the multisystemic or multicentric form, given the multisystemic involvement and laboratory findings.

As in our case, hepatic and splenic enlargement is present in the majority of cases[3]. Skin rashes are common, ranging from maculopapular to nodular or lichenoid eruptions, and histopathologic changes similar to CD may be found in skin lesions[8]. Our patient had a maculopapular eruption over the torso during hospital follow-up.

Neurologic manifestations, such as sensory motor neuropathy, seizures and pseudotumor cerebri as well as central nervous system masses or leptomeningeal infiltration have been reported[9]. Our patient had fainting attacks with some EEG changes, although the cranial CT was normal. It remained unproven whether or not the patient's neurological symptoms were secondary to the neurological involvement of CD.

A wide variety of rheumatologic symptoms and signs including arthralgia effusion, myalgia, keratoconjunctivitis sicca, xerostomia and Reyn phenomenon have accompanied multicentric CD[5]. We did not observe a these findings in our patient. Renal dysfunction may be manifested by protei hematuria and renal insufficiency. Proteinuria as in the presented case ca significant and could be a major cause of the development of hypoalbumir and thus nephrotic syndrome. Different forms of renal involvement have reported[10]. Our patient did not have a renal biopsy but had proteir hypoalbuminemia, hypertriglyceridemia and hypercholesterolemia. Nepl syndrome resolved spontaneously within a week.

Most patients have mild to moderate anemia at the time of diagnosis. The cell count is generally normal, but both thrombocytopenia and thrombocy have been reported. Bone marrow examination may show a modest plasmocy without distinguishing features. The ESR is usually elevated, the median b approximately 80 mm/h. Almost all patients have a polyclonal increas gammaglobulin levels, frequently in IgG and IgA. Antinuclear antibody, rheum factor, positive VDRL, cryoglobulins and inhibitors of factor VII and VIII been reported in some cases[3, 5]. The patient had moderate anemia, elev ESR, IgG and IgA, and the rheumatoid factor was positive.

Most cases of CD, including multicentric CD, are polyclonal as determine immunohistochemical staining for immunoglobulin light chains, but some c are not[4]. Our case was also positive for $\lambda$ and $\kappa$ light chain.

To our knowledge no case of CD with uveitis has been reported so far. Our had bilateral active uveitis and all other possibilities ruled out; the uveitis resc with medical treatment and did not recur during follow-up. This may be the case of CD with uveitis reported in the literature. In adults the course of multice CD is unpredictable, but a high mortality rate has been reported in the litera Higher survival rates have been reported in childhood[3, 4]. Intervening infect are a common cause of death in the systemic form[5].

Patients with multicentric CD are at increased risk of developing malignanc especially malignant lymphoma and Kaposi's sarcoma. On the other hand, r patients with CD are at an age group at which cancers are not uncommo

In the differential diagnosis, especially in multicentric types, Hodgkin's lymphc mixed cellularity type, must be ruled out. This entity includes eosinophils, Re Sternberg cells and fibrosis but lacks hyalinized germinal centres. Follicular lymph may be confused with CD. In follicular lymphoma evenly distributed nodules of sir sizes and shapes can be seen; the nuclei are also atypical. In addition, immunobl lymphadenopathy, toxoplasmosis lymphadenitis, thymoma and plasmocytoma n be ruled out in the differential diagnosis of angiofollicular lymph node hyperpla

Localized variants of CD respond well to surgical excision. Different therapeutic regimens including radiotherapy, steroids and some antineoplastic drugs have been used in adults. Massey et al.[11] used steroid therapy in an unresectable CD patient, but the patient did not respond to therapy. The same patient was treated successfully with radiotherapy. We did not use any therapeutic regimen except for the uveitis, and the patient had a good outcome during follow-up. However, in the sixth month of follow-up, the disease relapsed with mediastinal enlargement, fever, hepatosplenomegaly and elevated acute phase reactants.

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