

CASTLEMAN'S DISEASE: A RARE PRESENTATION OF CERVICAL LYMPHADENOPATHY

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Abstract

Castleman's disease is a rare lymphoproliferative disorder. Castleman's disease is a disease which involves massive non-malignant proliferation of lymphoid tissues that usually presents as mediastinal masses as well as other groups of lymph nodes. That is why, sometimes, confusion may arise whether the lymphadenopathy is benign or malignant. However, some authors describes, histologically and prognostically Castleman's disease is distinct from malignant lymph-node hyperplasia.

Key words: Castleman's disease, lymphoproliferative disorder.

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Introduction

Castleman's disease is a rare lymphoproliferative disorder. Sometimes, physicians get confused of Castleman's disease with other lymphoproliferative disorders. Castleman's disease was first described in a group of patients with benign localised hyperplastic lymph nodes by Castleman et al. In 1965^{1,2}. The excision biopsy itself will help both in the diagnosis and in planning the treatment³.

Case History

A 14 year old male, Muslim, student hailing from Bagerhat district was admitted into Department of Medicine, Dhaka Medical College Hospital, Dhaka, on 20th May 2013 with the complaints of multiple nodular painless and discrete swellings in the right side of the neck for one year. According to the statement of the patient he was reasonably well one year back. Then he developed multiple swellings on the right side of the neck which were painless & slowly increasing in size without any discharge. He also complained that he developed on and off low-grade intermittent fever for last one year. He noticed that one of his swellings is gradually increasing in size. Other systemic enquiry revealed no abnormality. For his recent illness he

consulted with different local physician and treated with different types of antibiotics. He was undergone FNAC. However, the result was nonspecific. No significant past history was found. He comes from lower middle class family. All his family members are in good health.

On physical examination, his vital signs were normal including an oral temperature of 99⁰ F. Enlarged lymph nodes were found on the right side of the neck which were 3 in number, variable in size (larger one 3 cm in diameter) firm in consistency, discrete, non tender, free from overlying skin and underlying structure. There was no discharging sinus. On examination of abdomen there was no organomegaly. Other systemic examination including respiratory system revealed no abnormality.

Laboratory investigation revealed Normal CBC with ESR. PBF showed non-specific findings; urine R/E was normal; serum creatinine: 0.70 mg/dl. Chest x-ray & ECG were normal. HIV screening was Negative. Mantoux test was insignificant. Sputum for AFB was negative. Histopathology study of lymphnode biopsy is consistent with hyaline vascular variant of CD. The patient was treated symptomatically and large 2 lymphnodes were surgically removed. He was completely symptom free for next 6 months in repeated follow-up.

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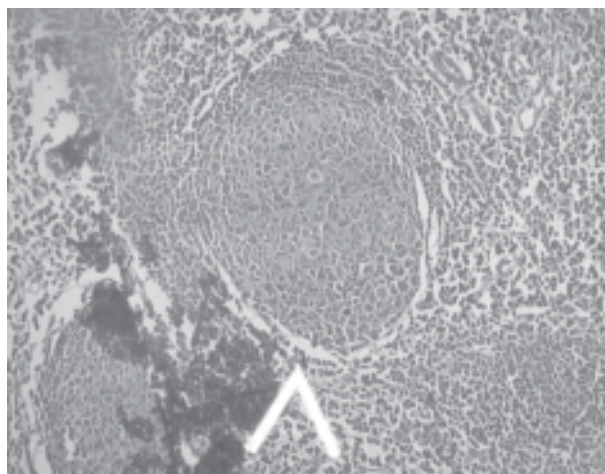


Fig 1: Histopathological photomicrograph of lymph node biopsy showing hyaline vascular type of Castleman's Disease.

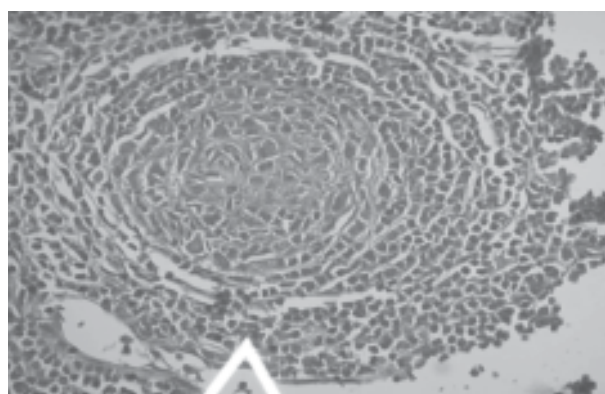


Fig 2: Hyaline vascular type of Castleman's Disease (more magnified).

Discussion

Castleman's disease is a disease which involves massive non-malignant proliferation of lymphoid tissues that usually presents as mediastinal masses as well as other groups of lymph nodes⁴. However, some authors described, histologically and prognostically Castleman's disease is distinct from malignant lymph-node hyperplasia. It is also known as angiofollicular lymph-node hyperplasia/giant benign lymphoma / giant lymph-node hyperplasia / lymphoid hamartoma². Castleman disease clinically classified into two main types: 1) localized or unicentric and 2) multicentric⁵. The two main forms are again subdivided based on how the lymph node tissue appears under a microscope. These are called microscopic subtypes.

- A. Hyaline vascular type: It is most common & found in Unicentric disease. But in rare cases it is found in multicentric Castleman's disease.
- B. Plasma cell variant: It is slightly more likely to be multicentric, but it is sometimes unicentric.
- C. Mixed subtype: It shows areas of both types. It occurs less often.

The main characteristic of Castleman's disease is overgrowth of B lymphocytes. Definite cause is not known; nonetheless, there are some factors associated with it.

- Human herpes virus type 8 viral stimulation: Human herpes virus type 8 (HHV-8) is found in the lymph node B cells of many people who are HIV-positive and have multicentric variety.
- HIV-association
- Role of IL-6: - High levels of IL-6 are often seen in the multicentric form of CD. But it's not clear what causes the high levels of IL-6. . HHV-8 has also been shown to cause infected cells to make a form of IL-6.
- Role of angiogenesis and vascular endothelial growth factor (VEGF)

Ninety per cent of cases are symptomless or have only the pressure symptoms, 10% have systemic signs⁶. In a study of 113 patient of CD in Mayo Clinic and University of Nebraska, Dispenzieri et al. found that median age of the cohort was 43 years (range 4.2–78). Forty-seven percent were male. Overall, 60 (53%) patients had multicentric CD. The breakdown by histology was: plasma cell variant, 54; hyaline vascular, 54; and mixed histology, 5. Patients with hyaline vascular disease were more likely to have unicentric disease; whereas, patients with plasma cell variant more commonly had multicentric disease. Three patients were under the age of 10, all of whom had unicentric hyaline vascular disease. Testing for a monoclonal protein was done in only 54 patients. Of these 29 had a monoclonal protein documented - 3 in the unicentric group and 26 in the multicentric group⁷.

The clinical findings and course differ greatly among the various types of Castleman's

disease. Unicentric disease usually presents as hyaline vascular subtype; is the most common type, accounting for approximately 80% of patients, and presents equally in men or women. A single node or chain of lymph nodes is involved, usually in the mediastinum, but may also occur in the cervical, axillary or abdominal regions. The enlarged nodes may be identified either incidentally or through symptoms related to local mass effects. Systemic symptoms are unusual. In The Plasma cell variant of unicentric disease, however, constitutional symptoms and laboratory abnormalities, much like in multicentric disease, may be prominent in addition to enlarged lymph nodes. This subtype represents about 10-20% of cases^{8,9}.

Although multicentric disease is less common, it is far more varied in clinical manifestation than unicentric disease. Systemic symptoms, sometimes severe and life-threatening, are the presenting feature in most cases. The great majority of patients experience fevers, which may be quite high, night sweats, weakness, fatigue, anorexia and significant weight loss.

They may become edematous and develop ascites, pleural or pericardial effusions and skin rashes. Occasionally, frank central nervous system symptoms, such as seizures, may occur. Virtually patients having multifocal lymphadenopathy and hepatosplenomegaly is found in more than half of the cases. The evaluation of a patient with an established diagnosis of multicentric disease will likely show a wide range of laboratory abnormalities. Anaemia, especially anaemia of chronic disease or haemolysis, is present in a majority of patients along with frequent thrombocytopenia, elevated erythrocyte sedimentation rate, hypoalbuminemia, abnormal liver function test results and a polyclonal increase in immunoglobulins. The patient may exhibit renal failure, including nephritis. Excessive IL-6 production can replicate many of these manifestations of Castleman’s disease. The clinical course is variable and may be progressive over months or episodic with recurrent exacerbations over years¹⁰. Occasionally, patients may be essentially asymptomatic or have spontaneous abatement of symptoms⁸.

Contrast and comparison between unicentric and multicentric Castleman’s disease:

	Unicentric	Multicentric
Usual Age of onset	Fourth decade	Sixth decade
Symptoms	Incidental or occasional systemic symptoms	Frequent constitutional symptoms, autoimmune manifestations, peripheral neuropathy, POEMS syndrome
Organomegaly	Rare	Frequent
Distribution of lymphadenopathy	Central (mediastinal, abdominal are most common)	Peripheral plus central
Laboratory abnormalities	Occasional Anemia, high ESR and CRP Hypergammaglobulinemia	Common Anemia, thrombocytopenia, High ESR and CRP, abnormal LFT results, low albumin and renal dysfunction
Pathology	HVV, occasionally PCV or mixed	PCV, mixed, occasionally HVV
HIV association	No	Sometimes
HHV-8 association	No	Yes
Therapy	Surgery, occasionally radiation if inoperable	Assorted systemic therapy with variable success
Progression to lymphoma	Rare	Common
Clinical course	Benign	Usually aggressive

Abbreviations: POEMS: peripheral neuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LFT: liver function tests; HVV: hyaline vascular variant; PCV: plasma cell variant; HHV-8: human herpesvirus 8.

To treat the patients the following options are adopted:

- 1) Surgical excision: This is highly recommended for localised and asymptomatic patients.
- 2) Chemotherapy: Currently, chemotherapy will be the first option chosen in most symptomatic patients. Lots of chemotherapeutic drugs have been tried in different centres. Chemotherapy, ranging from the use of single agents to multidrug combinations, has been tried in different centres; some were successful, some failed. Oral chlorambucil and cyclophosphamide have been effective in some patients, and are generally well tolerated. Single-agent vinblastine¹¹, oral etoposide. may also have activity. Single alkylating agent therapy may be most appropriate for the patient who is fragile or in whom a prompt response is not required. Combination chemotherapy regimens that have established roles in NHL, such as cyclophosphamide, vincristine and prednisone (CVP) or cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), have significant activity. When combination chemotherapy is used, patients need to be carefully selected and closely monitored because of the elevated risk of infection. Patients with HIV-associated Castleman's disease may be at especially high risk for complications with standard combination chemotherapy. Although it is likely that the tolerance of HIV-infected patients would be improved through the use of HAART, potential drug interactions need to be considered. In addition, it has been suggested that the use of HAART may precipitate or exacerbate multicentric Castleman's Disease⁸.
- 3) Radiation therapy: Radiotherapy does have therapeutic activity and is a treatment option for patients not deemed good surgical candidates or in patients with incomplete surgical excision. The review of the literature documents that radiotherapy has the ability to achieve complete radiographic and clinical resolution of disease in

patients with unicentric Castleman's disease.

- 4) Others:
 - A. Interferon- α
 - B. Thalidomide
 - C. Monoclonal antibodies (anti-IL-6 & anti-IL 6R antibodies):
 - D. Rituximab
 - E. HAART for HIV associated Castleman's disease.

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