Case Report:

Multicentric castleman disease with hyaline vascular pattern: a very rare case report

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Abstract:
Castleman disease is a clinicopathological entity associated with angiofollicular lymph node hyperplasia of obscure pathogenesis. Unicentric presentation of this disease affecting single lymph nodes in the mediastinum seems to be the most common presentation. We report a case of a 39 year old female who was initially clinically suspected to have either tuberculosis or lymphoma (owing to clinical features at presentation), but was later diagnosed with multicentric Castleman disease with hyaline vascular pattern on microscopic examination. This case report underlines the importance of definitive histological diagnosis in patients with lymphadenopathic presentation associated with systemic symptoms and the distinct entity of multicentric Castleman disease from malignant lymphoma and tuberculosis. Diagnosis and treatment of this rare disorder is discussed. Castleman’s disease should be considered as differential diagnosis in a patient with lymphadenopathic presentation associated with systemic symptoms.

Key words: Castleman disease, angiofollicular hyperplasia

Introduction:
Castleman disease, also known as giant lymph node hyperplasia is a rare lympoproliferative process of obscure pathogenesis described for the first time in 1956 by Benjamin Castleman as a thymoma-like lesion which was localized mediastinally. It was previously called Castleman’s disease. It is histologically and prognostically distinct from malignant lymph-node hyperplasia. It is a clinicopathological diagnosis. Castleman disease is of two types, unicentric or the localized form and the multicentric or aggressive form. Mixed patterns have been reported in the literature. Our objective was to present a patient with lymphadenopathy associated with systemic symptoms and the distinct entity of multicentric Castleman disease from malignant lymphoma and tuberculosis.

Case presentation:
A 39-year-old female presented to us with a 3-years history of asthenia, and lack of well being and on and off vague abdominal pain. Also, during this period she developed multiple painless swelling in the neck. The patient was a chronic smoker. Past history of abdominal hysterectomy was present for fibroid uterus. On physical examination she was of normal built, weight loss was not present and multiple non tender lymph nodes were palpable in the neck examination, particularly submandibular, upper, middle and lower deep cervical group, and also posterior triangle and supraclavicular group of lymph nodes were significantly enlarged on left side. Most of them were matted, although some of them were discrete. The axillary nodes were also enlarged on left side. Liver was palpable just below the subcostal margin.
Laboratory blood tests results showed a hemoglobin level of 11.5 gm/dl, TLC of 5,500, DLC- P45, L48, M02, E08. Platelet counts were normal. Liver and renal functions, serum sodium and potassium were normal. HCV and HBV serologic results were negative. Imaging studies were made. Abdominal ultrasound was normal, however, ultrasound neck revealed large hypoechoic bulky lymph nodes with preserved hilar fat in few, seen in bilateral posterior triangle, along juglar vein, and submandibular and also supraclavicular region, with largest measuring 4.1 x 1.4cms on left side( level three). Abdominopelvic CT scan showed multiple moderately enhancing preaortic, paraaortic, common and internal ileac, obturator, inguinal, aorto caval, retroaortic, mesenteric group of lymph nodes, largest in right internal iliac region measuring about 3.7 x 3.8 x 3.3cms in size. Hepatosplenomegally was present. CECT scan of chest revealed bilateral supraclavicular, prevascular, left aortic, retroesophageal, pretracheal, paratracheal, subca rinal, axillary, cervical(level four, seven) lymph nodes, largest measuring 1.6 cms x 3.5 cms in left supraclavicular region. There was moderate post contrast enhancement. Multiple reticulonodular opacities were present both upper and lingular lobe. There was patchy consolidation with soft tissue nodule in right upper lobe. Mosaic perfusion was noted in both lungs.

The patient was subjected to biopsy of left cervical lymph nodes. Excisional biopsy of left submandibular lymph node was performed under general anaesthesia. The size of the excised lymph node was 3 x 2.5cms and was sent for histopathological examination. The histop athological report showed hyaline vascular type of Castleman disease (Figure 1), hence a diagnosis of multicentric Castleman disease was made. Immunohistochemistry studies could not be performed because of the non compliance on part of the patient. Postoperatively, patient was started on corticosteroids and she made an excellent recovery. She is under follow up.

Discussion:

Castleman disease constitutes a clinicopathological entity, represented by lymph node hypertrophy and histologically characterized by angiofollicular lymphoid hypertrophy [3]. It is a rare disorder and can be found wherever lymphoid tissue is present [3]. Castleman disease is also known as giant or angiofollicular lymph node hyperplasia, angiofollicular lymphoid hyperplasia, lymphoid hamartoma, angiofollicular lymph node hyperplasia, benign lymphoma or follicular lymphoreticulum [3]. It is a very rare condition characterized by non-malignant tumors that may develop in the lymph node tissue at a single site or throughout the body [4]. It must be distinguished from reactive lymph node hyperplasia and malignancies and tuberculosis [2].

The etiology of Castleman disease is unclear, proposed predisposing factors include immunocompromised states, chronic inflammation or infection, and autoimmune processes [5]. An abnormal production of IL-6, which is a B cell growth factor causing lympho-proliferation and plasma cell differentiation may be the key factor in pathogenesis of Castleman’s disease [6]. Males and females are affected equally and the age is ranged from 8 to 66 years [1-3]. The most prominent sites are mediastinum (60-75%), neck (20%) or less commonly abdomen (10%) and axilla(4%) [1-3]. As Castleman disease may present in many different sites, so presentation is varied. The disease has been subdivided on clinical grounds in two patterns unicentric (single lymph node) and multicentric (systemic) and based on histological appearance (microscopic subtypes) into hyaline vascular pattern, plasma cell
predominance, or mixed lesions \cite{1-3, 5}. Hyaline vascular type is the most common, it tends to be localized, but in rare cases it is multicentric. The plasma cell type is slightly more likely to be multicentric, but it is sometimes localized. The mixed subtype shows areas of both types and occurs less often.

The unicentric (localized) pattern is, by definition, localized to one site. It occurs much more frequently than the multicentric and its main site is thorax (71%), specifically in the mediastinum or pulmonary hilum. It usually presents with an indolent course with few or no symptoms other than those directly associated with the enlargement of the lymph node mass or with compression effect in respective area like diarrhoea, cough, dyspnea, chest pain, back pain, respiratory infection and sometimes as pyrexia of unknown origin, weight loss or anaemia \cite{5}.

Unicentric form is usually benign, and in over 90% cases, removal of the enlarged node is curative, with no further complications \cite{1, 5}. Prognosis is excellent \cite{7, 8}.

The multicentric form is a systemic illness, involving lymph nodes separately or in aggregations. Involvement of retroperitoneum, neck, parotids, muscles, splenomegaly or disseminated lymphadenopathy with systemic symptoms including autoimmune phenomena is seen. Overproduction of interleukin-6 results in many symptoms, which can include severe fatigue, night sweats, fever, and weight loss. Often, patients have peripheral oedema, anaemia, and hypoalbuminemia, and approximately 20% of patients have peripheral neuropathy. It is clinically more aggressive and malignant course \cite{3}. It acts similar to and eventually become lymphoma in many cases. It is important to distinguish AIDS-related multicentric Castleman’s disease from other forms of multicentric Castleman’s disease \cite{9}. A POEMS (Peripheral polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammapathy [M-Protein] and Skin signs) syndrome is observed in few patients \cite{10}.

The differential diagnosis include infectious and inflammatory lesions such as tuberculosis, Hodgkin's lymphomas, thymomas, lymphadenitis, sarcoidosis, toxoplasmosis, cytomegalovirus, mononucleosis, HIV, cat scratch disease and rheumatologic diseases \cite{3, 11}. Laboratory findings may reveal raised levels of macrophage colony stimulating factor, TNF beta, gamma interferon, erythrocyte sedimentation rate, C-reactive protein, leucocyte and platelet counts \cite{12}. Low levels of blood counts may be seen. Imaging of Castleman’s disease is nonspecific. The lesions may present as a homogenous or heterogenous soft tissue mass on CT scan. Magnetic Resonans Imaging (MRI) findings are nonspecific.

Tissue diagnosis is mandatory to avoid mismanagement. The classical histopathological picture consists of presence of thickened hyalinized capillaries within the follicle centres. Also there is perifollicular vascular proliferation with concentric layering of cells within germinal centres. There may be more than one germinal center within a single follicle \cite{1, 2}.

Treatment for the former can be focused upon the same protocols used for treating the underlying AIDS \cite{9}. There is no standard therapy for multicentric Castleman’s disease. Treatment modalities include antiviral drugs such as ganciclovir for human herpesvirus type 8 (HHV-8), chemotherapy, radiotherapy, corticosteroids, immunomodulators, immunoglobulins, monoclonal antibodies against IL-6, interferon, plasmapheresis and thalidomide. Patient’s clinical status and medical history with respect to infections may impact the final outcome. Left untreated, it usually
has a downhill course and becomes unresponsive to current treatment regimens [3, 4, 9, 11].

**Conclusion:**
Castleman’s disease may mimic a neoplasm and should be considered in a patient with lymphadenopathic presentation associated with systemic symptoms.

[ Microphotograph of slide showing lymphoid follicles (white arrow), marked vascular proliferation and hyalinisation of blood vessels (curved black arrow). Interfollicular stroma shows numerous hyperplastic vessels and admixture of plasma cells. The periphery of the follicle shows layering of lymphocytes (black arrow). ]

**References:**
