CASTLEMAN’S DISEASE- A RARE ENTITY
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Abstract : Castleman’s disease is a lymphoma-like disorder which can present as a localised or generalised lymphadenopathy, along with systemic symptoms. It is postulated to be associated with HHV 8 virus. We present to you a case of Castleman’s disease, who presented to us with abdominal distension and lymphadenopathy involving supraclavicular and axillary nodes. On examination, patient had pallor and multiple supraclavicular, axillary and inguinal nodes enlarged. Investigations revealed anemia, relative lymphocytosis with normal renal and liver function tests. Imaging studies revealed a right side pleural effusion and ascites. Histopathology of lymph node specimen showed angiolymphoid follicular hyperplasia, suggestive of Castleman’s disease supported by immunohistochemistry.

Keyword : Castleman’s disease, angiolymphoid follicular hyperplasia

Case report:
A 38 year old female presented to us with history of abdominal distension, fever, easy fatiguability and dyspnea of 3 months duration. She also gave history of weight loss of 2 months duration. She had no further history suggestive of cardiac and respiratory symptoms. Her bowel and bladder habits were normal. Her past history and personal history were insignificant. She was married and had 3 children with no history of abortions. On examination, she was emaciated, pale, not icteric. She had bilateral pitting pedal edema and enlarged lymph nodes involving cervical, axillary and inguinal group with largest node measuring 5*3 cm (axillary). Lymph nodes were discrete, firm, not tender and mobile. Cardiovascular examination was normal. Respiratory system examination showed absent breath sounds in the right infra axillary region and infrascapular region with stony dullness on percussion. Abdomen was distended with free fluid.

Investigations: Complete blood count and peripheral smear showed raised ESR, microcytic hypochromic anaemia with lymphocytosis and few atypical lymphoid cells. Renal and liver parameters were normal. Chest X-ray confirmed a right sided pleural effusion. Echocardiography was normal. In view of ascites, ultrasonogram of abdomen was done which showed free fluid in the abdomen with mild hepatosplenomegaly but no evidence of intraabdominal lymphadenopathy. Viral markers were negative. Portal Doppler study was normal. Ascitic fluid was tapped and sent for analysis. Ascitic tap was hemorrhagic in nature with cytology showing lymphocytes and mesothelial cells in a hemorrhagic background suggestive of a reactive effusion. Ascitic fluid ADA was negative. Mantoux was negative (0mm). ANA was negative. Coagulation profile was normal. Serum electrophoresis showed hypergammaglobulinemia. Bone marrow aspiration and biopsy was done. Bone marrow aspirate showed adequate hematopoietic elements with scattered infiltrates of lymphocytes and plasma cells but with no evidence of lymphoproliferative disorder or granuloma. Axillary lymph node was excised and sent for biopsy. Lymph node biopsy showed mildly thickened capsule and follicles showing expanded mantle zone extending into subcapsular region with regressively transforming germinal centres. Greater magnification demonstrates single follicle with expanded mantle zone (onion skin appearance) and pale staining centre showing prominent FDC (follicular dendritic cells). Immunohistochemistry was done which showed the following pattern: LCA positive, CD 3 positive (inter follicular), CD 15 negative, CD 30 negative, LMP negative, CD 20 positive (follicles) CD 5 negative, CD 23 positive (follicular dendritic cells in germinal centre and mantle zone) BCL 2 negative (follicles) thus, follicular lymphoma and mantle cell lymphoma were ruled out.

Fig 1. Bone marrow aspirate showing normal hematopoietic elements with lymphocytes and plasma cells
A diagnosis of Multicentric Castleman's disease was made. Patient showed the possibility of granulomatous disorder and lymphomas, a final diagnosis was confirmed through bone marrow studies and lymph node biopsy. In a background of generalized lymphadenopathy and constitutional symptoms, with bone marrow studies and lymph node biopsy ruling out the possibility of granulomatous disorder and lymphomas, a final diagnosis of Multicentric Castleman's disease was made. Patient was started on oral steroids and patient improved symptomatically.

Discussion:
Castleman's disease is a benign disorder first described by Dr. Benjamin Castleman in 1956. Castleman's disease is also referred to as angiofollicular hyperplasia, and is a non-clonal disease of the lymph nodes. It is a rare disease with exact incidence rates not known. It has no age, sex or ethnic predilection. Castleman's disease can be classified as unicentric and multicentric disease. Unicentric Castleman's disease is usually a slow growing solitary mass typically located in the mediastinum or mesenteries. There are no constitutional symptoms and no elevation of acute phase reactants (Interleukin 6, ESR and CRP). Symptoms if present are due to a mass effect of bulky lymphadenopathy. In 90-95% cases surgical resection is curative and usually there is no progression to lymphoma or association with other tumors. The prognosis is excellent with a 5 year survival of close to 100%. In multicentric Castleman’s disease there is usually widespread lymphadenopathy with in some instances hepatosplenomegaly. “B” symptoms including severe fatigue, night sweats, fever, weight-loss, anorexia are typically present. These symptoms are typically driven by overproduction of interleukin 6. Overproduction of interleukin 6 also results in an acute phase reactions with elevated ESR, CRP, fibrinogen, thrombocytosis, and hypergammaglobulinemia. Patients typically have peripheral edema poorly responsive to loop-diuretics and suffer from anemia and hypoalbuminemia. Approximately 20% of patients have peripheral neuropathy. Other conditions associated with multicentric Castleman’s disease include autoimmune hemolytic anemia, multiple myeloma, amyloidosis, pemphigus, and overlap syndromes with POEMS. Multicentric Castleman’s disease runs a more aggressive course and can progress to non-Hodgkin’s lymphoma. Histopathologically, there are three types of Castleman’s disease: hyaline-vascular type, plasma cell type, and a mixed type. Patients with Castleman’s disease classically have preserved follicles with widened mantle zone on lymph node biopsy. Mantle zone cells express abnormal immunophenotype and are associated with regressed follicles in transformed germinal centres. Prominent FDC(follicular dendritic cells) with or without dysplasia is present. There is no consensus on the underlying etiology of Castleman's disease, but two main theories have been proposed. One theory submits that the disorder represents a reactive lymphoid hyperplasia initiated by chronic antigenic stimulation associated with a viral trigger, most likely mediated through the respiratory or gastrointestinal tract. The other proposes that the masses are due to a developmental growth disturbance of the lymphoid tissue (a vascular lymphoid hamartoma). Beck et al confirmed that the generation of IL-6 in the germinal centers of hyperplastic lymph nodes and subsequent complex interactions with IL-1 and TNF-alpha may be the key elements responsible for the systemic manifestations of Castleman's disease. HIV status is important as HIV positive patients with Multicentric Castleman’s disease have much frequent plasma cell type disease and the clinical course is less favorable than in HIV negative patients. Further, a good case can be made for HHV6 being the causative agent in HIV positive Castleman's disease patient. There is presence of HHV8 DNA in Lymph nodes and peripheral blood mononuclear cells in HIV positive patients with multicentric Castleman’s disease. Surgical removal (excision) of the growth is the preferred treatment in most cases of localized Castleman's disease. In some cases, ionizing radiation (radiotherapy) has proven effective. Corticosteroids have been used to treat specific symptoms that may be associated with the plasma cell and multicentric types of this disorder. Intravenous immunoglobulins, chemotherapy (CHOP regimen), Rituximab (anti CD 20), Thalidomide (anti angiogenesis), anti IL-6 therapies like Suramin and Tocilizumab are also treatment options for Multicentric disease.

References:
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