Multicentric Castleman's disease: "A rare entity that mimics malignancy"

Dear Sir,

Castleman's disease is a rare disorder characterized by two histopathological varied subtypes but differs in their clinical symptoms, progression, and response to therapy. Most often this disease has predilection for the lymph nodes in sites of the neck, mediastinum, and abdomen where the nodes conglomerate in the disease process. Parenchymal lung involvement of the disease is exceedingly rare.[1]

Angiofollicular or giant lymph node hyperplasia was first described in 1954 by Benjamin Castleman as a cause of mediastinal lymphadenopathy.[2] The disease has been classified on clinical profile as localized or multicentric Castleman's disease (MCD) and on pathological findings as a hyaline vascular pattern (HV) 90% of cases, plasma cell predominance (PC) 8–9%, and a mixed variant 1–2% of cases.[3] The etiology is largely unknown, but it is proposed to be due to antigenic hyperstimulation of unknown origin. Definitive diagnosis is achieved mainly by histopathological analysis as clinical and radiological features overlap and are nonspecific.[4]

A 51-year-old heterosexual male of Caucasian origin, a chronic smoker since 15 years presented to our hospital with a history of chronic cough, episodic chest pain, and dyspnea of 3 months duration. The patient had no other comorbid illness. The patient had a history of being treated for pneumonia 6 months back with a course of parenteral antibiotics. He was diagnosed with smear negative pulmonary tuberculosis and was on antitubercular treatment for a month without clinical and radiological response.

On examination, vital parameters were stable, and there was no peripheral lymphadenopathy. Respiratory examination revealed an impaired percussion note in right suprascapular area with crackles. Other systemic examinations were normal.

Laboratory analysis revealed white blood cell count 8400/cumm (neutrophils - 71, lymphocytes - 25, eosinophils – 01, and monocytes - 03), hemoglobin - 13.0 g%, and an elevated ESR of 23 mm/h. Other routine biochemical parameters including bleeding and clotting parameters were within normal limits. Serological markers for human immunodeficiency virus and hepatitis virus (B and C) titers were negative. Collagen vascular disease workup was negative. His sputum for acid fast bacilli (AFB) by Ziehl–Neelsen stain was negative. Ultrasonogram of the abdomen revealed a normal scan. Chest X-ray showed right-sided upper zone opacity [Figure 1a]. The computerized tomography (CT) of the chest revealed well-defined, smoothly marginated, and solid mass lesion [Figure 1b] in the right upper lobe which showed peripheral contrast enhancement with small nonenhancing areas [Figure 1c]. There were incidental emphysematous changes in the rest of the lungs [Figure 1d lung window]. There were associated right tiny paratracheal and hilar lymphadenopathies. Bronchoscopy showed mucosal irregularity in right upper lobe bronchus. Bronchial lavage and brush cytology were

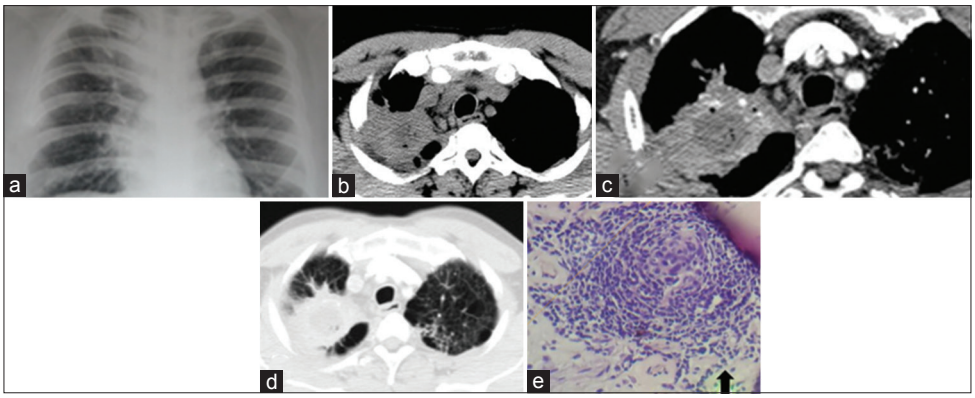

Figure 1: (a) Chest radiograph showing a right upper zone opacity. (b) Computerized tomography axial chest showing a soft tissue density lesion in the right upper lobe with central hypodensity and surrounding irregular borders; (c) lesion shows predominant peripheral contrast enhancement; (d) lung window showing the opacity and surrounding emphysematous changes; (e) Microscopy of the lesion (×40, high power). Arrow shows the lymphoid follicle with hyperplasia and concentric arrangement of lymphocytes. Interfollicular area shows plasma cell infiltration

negative for malignant cytology, AFB stain, and also for tuberculosis by Gene Xpert analysis. Bronchoscopic biopsy from irregular mucosa was inconclusive. Percutaneous CT-guided biopsy was performed. Two CT biopsy specimens were reported as negative for tuberculosis and malignancy, but no other opinion was possible from the tissue specimen. A third CT-guided biopsy was done, and the histopathological study revealed linear fragments of tissue with areas showing lymphoid follicular hyperplasia. The lymphocytes were arranged in a concentric pattern in the mantle zone. The interfollicular region showed infiltration by PCs and occasional Russell bodies [Figure 1e], suggestive of PC type of Castleman's disease. The patient declined any further treatment and was lost for follow-up.

HV type is generally the more common subtype than the PC type and often involves the mediastinum or the pulmonary hilum. The PC variant can involve lymph nodes discretely or more often as nodal aggregation leading to its multicentric nature. It is usually associated with autoimmune state and has an aggressive course.[4]

Etiology of Castleman's disease is unknown. The frequent concomitant presence of the HV and PC types albeit at separate sites, the transience of their morphological nature from one subtype to the other, and progression from a localized to multicentric nature during the course of the disease have suggested that CD is a single disease caused due to immune dysregulation. Moreover, both forms have been attributed with B- and T-cell impaired functions, with the development of autoantibodies. A critical event in the evolution of CD has been suggested to be an overproduction of a B-cell growth factor like cytokine interleukin-6 (IL-6), causing lymphoid proliferation and PC differentiation and thus triggering the oncogenesis of plasmacytoma. Kaposi's sarcoma associated virus, human herpes virus-8 (HHV-8), which has been found in numerous cases of CD, more so in the multicentric type, may play a critical role in producing IL-6 and also angiogenic factors release. A possible differentiation block may lead to the development of a malignant lymphoma. Kaposi's sarcoma or other malignant neoplasias can be consequences of the immunodeficiency typical of CD. An association of CD with thymic carcinoma and lung carcinoma are reported.

It is universally accepted that, although the etiology of MCD is often heterogeneous, the presence of cytokine IL-6 has bearings on the clinical manifestations of MCD. Another proposed cause of MCD is paracrine or autocrine IL-6 generation. Once an inflammation sets in due to viral infection trigger, IL-6 is released from inflammatory cells and this in turn stimulates PC proliferation. Then, IL-6 and its downstream cytokines activate the IL-6-producing cells, leading to IL-6 overproduction. This hypothesis is generally accepted as some patients treated with tocilizumab had a good resolution of the clinical symptoms followed by a gradual drop in serum IL-6 levels. This autoimmune reactivation of IL-6-producing cells is one another presumed etiology for MCD.[3,4]

Clinical presentation in these set of patients is varied. The mean age for diagnosis is 35 years, with an equal male: female ratio. The mean size of the lesion is 5–9 cm; 70% of lesions are located in the mediastinum or hilum of lung, with the abdomen being the next most frequent site.[5] Localized disease is generally benign in nature and often is known to present as an asymptomatic incidental mass or with some compression effect in the respective area, pyrexia of unknown origin and weight loss or anemia.[6] In contrast, patients with multicentric disease have symptoms of systemic illness involving the retroperitoneum, neck, parotids, and muscles. It can also present as a disseminated lymphadenopathy. Patients with MCD may also manifest with vague and varied systemic symptoms such as fever, night sweats, anorexia, malaise, weight loss, hepatosplenomegaly, and chronic anemia. It is aggressive and usually the fatal course is associated with infectious complications and risks for malignant tumors such as lymphoma or Kaposi sarcoma.

Patients with MCD may reveal raised serum C-reactive protein level, polyclonal hyperglobulinemia, anemia of microcytic hypochromic nature, low albumin level, and high cholesterol levels of unknown significance.

HHV-8 is frequently isolated, especially in human immunodeficiency virus (HIV)-positive individuals more so in the Western countries.

MCD is often seen to overlap with the rare entity of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin pigmentation syndrome. Other associations of MCD is concomitant presence of IgG4-related disease, Kaposi sarcoma, and other collagen vascular diseases.[7,8] MCD is thereby increasingly recognized as a morphologic disease syndrome uniting a group of diseases with varied etiologies.

For a physician diagnosing MCD is often a challenging and arduous task. It has been observed from various studies the median duration lapse between disease onset and the time of diagnosis is 27.5 months, indicating the diagnostic difficulties.

Malignant lymphomas and myeloid malignancies like myeloproliferative neoplasms and myelodysplastic syndromes lead to systemic inflammation and lymphadenopathy simulating MCD. The clinical, histological features of IgG4-related disease is often so similar to MCD that in some cases it could be quite similar and indistinguishable. The diagnosis of intrapulmonary unicentric Castleman's disease with tissue specimen is also risky with these hypervascular masses due to the risk of massive hemorrhage during biopsy by transbronchial needle aspiration or during excision by thoracotomy. Non-tissue diagnosis is very difficult mainly because of the lack of reliable specific findings on most imaging studies.

To our knowledge, isolated parenchymal pulmonary involvement is very rare in CD; a handful of cases have previously been reported.[4,5]

Surgical excision is a reasonable curative option for a localized disease. Multicentric disease is often associated with systemic symptoms with a guarded prognosis. Its management includes a multimodality approach comprising of respective surgery, concurrent chemotherapy, steroids, and radiation. Recent therapeutic advances suggest anti-IL-6 receptor antibody therapy as a promising option.[9] Adjunctive radiotherapy could be an option in patients who are at high risk of recurrence or unsuitable for surgery.

MCD should be considered in the differential diagnoses of patients presenting with peripheral, thoracic lymphadenopathy, even parenchymal lesions, and nonspecific systemic symptoms. Clinicians and pathologists need to work in tandem to unearth this unusual entity, especially in cases where multiple representative biopsy specimens are negative for tuberculosis and malignancy. Early diagnosis is imperative given its progressive clinical course and increased risk for development of lymphoma. Empiric treatment options include steroids, chemotherapy, and newer biologically-targeted therapies like monoclonal antibodies.

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Conflicts of interest
There are no conflicts of interest.

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