Castleman's Disease: Report of Four Cases and Review of the Literature

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Abstract- Castleman's disease (CD) is a rare benign lymphoproliferative disorder with unknown etiology and pathogenesis. It presents in two identified clinical forms of unicentric or multicentric. The disease is usually found incidentally in the mediastinal or hilar region in asymptomatic patients. In unicentric CD, constitutional symptoms are uncommon, and they can be misdiagnosed as lung infections or malignancy. Although imaging studies are helpful, but definitive diagnosis can be made with pathologic examination. Complete surgical resection is the method of choice for treatment of localized CD, and the prognosis is excellent. In this study, we elucidate clinical features and therapeutic consequences of four cases of unicentric CD referred to our department and review the literature on the diagnosis and management of this relatively rare disorder. Because of the rarity of the disease and nonspecific signs and symptoms of CD it must be considered in differential diagnosis of pulmonary and mediastinal masses.

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Introduction

Castleman's disease (CD), which is also known as angiomatous lymphoid hyperplasia, giant lymph node hyperplasia or angiofollicular mediastinal lymph node hyperplasia is a rare lymphoproliferative disorder that typically involves lymph node tissue throughout the body. Castleman and colleagues in 1954 described the disease as a localized lymph node hyperplasia in the mediastinum and characterized the pathology (1).

The most common sites are the mediastinum, abdomen and the neck, but axillary fossa, bowel mesentery, retroperitoneum, pelvis, and pancreas may also be involved (3-9).

The disease symptoms may present at any age but mostly seen before the age 30. There is no predominance in sex or race (1,10).

Many clinical conditions such as polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, lymphoma, and pemphigus vulgarize, myasthenia gravis, cutaneous Kaposi's sarcoma, recurrent pleural effusion, Hashimoto thyroiditis, and amyloidosis may be accompanied by the disease (11-16).

There is no known etiology, but the abnormal autoimmune response and viral infections like human herpes virus 8 (HHV-8) and human immunodeficiency virus (HIV) infection are described as probable etiology (1,10,17).

Many pieces of evidence support the role of over production of cytokines like interleukin 6 by hyperplastic B lymphocytes and plasma cells of lymphoid organs in the etiology of CD.

Castleman's disease can present in the form of "localized, unicentric'' as a single mass with no symptom or in the form of "generalized, multicentric'' as generalized lymphadenopathy with severe systemic symptoms (18-20).

Histologically, it has three variants, hyaline vascular (HV) type (80%-90% of cases), the plasma cell (PC) type (10% of cases) and the intermediate mixed type (1-2%) (20-23).

Surgical resection is the treatment of choice for the localized hyaline vascular types having a good prognosis, but because of the probability of recurrence or lymphoma transformation of multicentric and plasma cell variants they need multi-modality management of surgery and adjuvant chemoradiotherapy (1,24).

Here we elucidate four cases of unicentric Castleman's disease referred to our institution and

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reviewed the literature on the diagnosis and management of this relatively rare disorder.

Case Report

Case 1

A 38-year-old healthy female was referred to our department with a history of occasional non-productive cough and chest pain. She had no other symptoms like fever, fatigue or weight loss and her past medical history was normal. On physical examination, there were no pathologic findings, no lymphadenopathy or organomegaly. Peripheral blood counts, C-reactive protein level, and erythrocyte sedimentation rate, were within normal limits.

X-ray imaging revealed a mass-like lesion in the right lung and a high-resolution multislice computed tomography (CT) scan showed a 4×4 cm well-demonstrated mass with regular contours in the right middle zone (Figure 1,2).

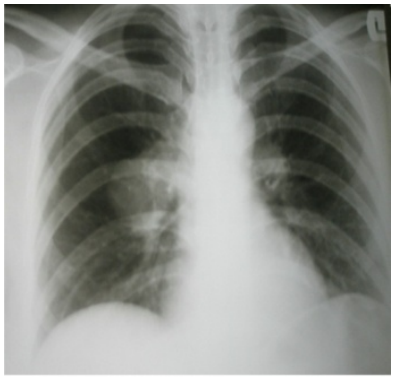

Figure 1. Chest X ray: Mass lesion located in the right hilum region (Case 1)

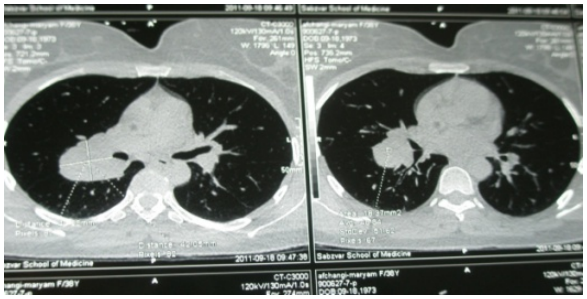

Figure 2. Thoracic computed tomography scan showed a 4×4 cm mass lesion with regular contours located in the right middle zone.

Fiberoptic bronchoscopy showed normal findings. The patient underwent a right thoracotomy, and a 5 cm fragile mass with smooth margins was detected in the major fissure between the upper and lower lobe. The mass was completely enucleated without any bleeding because there was no parenchymal invasion and vascular adhesion to the lung parenchyma. The histopathological finding was suggestive of Castleman's disease of hyaline vascular type.

The postoperative period was uneventful, and there has been no evidence of recurrence.

Case 2

A 34-year-old man admitted to our hospital with atypical chest pain. He had no history of fever, night sweating, weight loss or fatigue. There was no history of smoking or alcohol abuse.

On physical examination and electrocardiography, no pathologic findings were identified. Complete blood cell count, biochemistry panel, renal and liver function and erythrocyte sedimentation rate were all normal.

To evaluate atypical chest pain, a contrast-enhanced CT scan of the chest was performed which detected a well-defined lobulated mass of soft-tissue appearance in the middle mediastinum, measured 5×3×2 cm with evidence of pressure effect on the adjacent vasculature and bronchial structures.

A right posterolateral thoracotomy was performed, and a highly vascularized 5.5×3.5 cm tumor was found in the middle mediastinum with extension to the posterior mediastinum which was tightly adhered to the aorta and azygos vein. The tumor was completely separated from the contiguous tissue using sharp and blunt dissection or electrocautery.

Histopathological examination of the specimen showed Castleman's, HV type.

Chylothorax as a result of thoracic duct disruption during thoracic dissection occurred on the fifth postoperative day.

The patient was successfully treated by reoperation and thoracic duct ligation. He was discharged in good general condition, and there was no evidence of tumor recurrence on follow up thoracic imaging.

Case 3

A 24-year-old man with a diagnosis of tonsillar hypertrophy was candidate for surgery. On his paraclinical examinations, a solitary posterior mediastinal mass was accidentally detected and therefore referred for thoracic surgery. He had no other complaints.

During surgery, a 3×5 cm mass was found in the posterior mediastinum. The mass was then inoculated meticulously from surrounded structures. Histopathological evaluations showed a hyaline vascular type of unicentric Castleman's disease. The patient was

discharged without complications.

Case 4

A 27-year-old woman with symptoms of nonproductive cough and dyspnea presented

To thoracic department. Hematological and biochemical parameters were within normal limits. Chest X-ray revealed a lesion with regular margins in the right hilum.

CT of the chest detected a 6×4 cm well-defined mass in the hilum of the right lung (Figure 3).

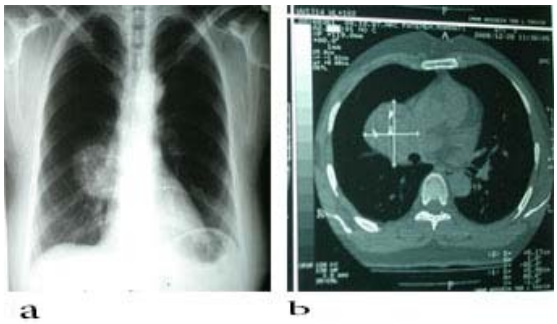

Figure 3. (a) Chest X-ray: A large lesion with regular margins located in the right hilar region. (b) Computed tomography scan of the chest showed a well-defined soft tissue mass in the right hilum.

A right posterolateral thoracotomy was performed. The lesion was a highly vascular, round and well-circumscribed mass, measured 4×6×3.5 cm which arouses from the right hilum without invasion to the surrounding parenchyma. The mass was dissected from the hilum and completely excised.

Definitive pathology was consistent with a diagnosis of hyaline-vascular type Castleman's disease. The patient was discharged without complications, and the follow-up CT scan showed complete resolution of the disease.

Discussion

Castleman's disease is a rare disorder with three histologic variants (hyaline vascular, plasma cell, and mixed) and two clinical types (unicentric and multicentric) (1).

Keller *et al.,* in 1972 described the characteristics of two pathologic types of CD. Unicentric type is characterized by small follicles surrounded by vessel proliferation and hyalinization. It is presented by the slow growing of solitary lymph nodes mostly in the central part of the body (mediastinal, abdominal) without prominent systemic symptoms (24,25).

In contrast, multicentric variants are characterized by large follicles with polyclonal plasma cells surrounding them, and less hyalinization and vascularization are observed (24). It is defined by generalized lymphadenopathy, hepatosplenomegaly, constitutional symptoms (fever, fatigue and weight loss), hemolytic anemia, peripheral neuropathy and POEMS syndrome (1,25).

Anemia, thrombocytopenia, high sedimentation rate, hypergammaglobulinemia, abnormal liver function tests, hypoalbuminemia and renal dysfunction, are common in multicentric CD (26).

Unicentric forms have benign course and commonly affect younger patients usually before the fourth decade, but multicentric forms are more aggressive, more prone to lymphoma formation and occur in older patients (18,27).

Common pathological types of unicentric CD include hyalovascular subtype and less commonly plasma cell subtype. Hyaline vascular CD is the most common subtype accounts for 80%-90% of cases and usually involves a solitary mediastinal lymph node or can present in the neck, axillary and abdomen. It is commonly asymptomatic or has limited symptoms of local mass effect. Plasma cell variants of unicentric CD accounts for 10-20% and have more systemic symptoms and abnormal laboratory tests (1,25).

The histologic features of multicentric CD are almost plasma cell or mixed subtypes, but occasionally hyaline vascular forms can be seen. Multicentric variants involve multiple lymph nodes in different sites. The association with HIV and HHV-8 infections has been shown (1). The patients experience severe systemic signs and symptoms like high fever, night sweating, malaise, fatigue, anorexia, weight loss, hepatosplenomegaly, ascites and pleural or pericardial effusions. Because of overproduction of IL-6 by hyperplastic lymph nodes they have anemia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein and erythrocyte sedimentation rate and abnormal liver and renal function (26).

Chest X-ray and CT scan are the most useful diagnostic modalities for diagnosis of unicentric thoracic Castleman's disease. They appear as an accidental single hyper vascular round mass or lymphadenopathy in the mediastinum, pulmonary hilar, pleural space, pericardium, intercostal space or within the lung parenchyma, and depending on the location mimic thymoma, lymphoma, neurogenic tumors, bronchial adenomas, pericardial cyst or solitary lung mass (3,10,19).

Abdominopelvic masses, if large enough or calcified, may be seen on radiographs. Multicentric CD presents

as bilateral mediastinal or hilar enlargement, diffuse reticulonodular pulmonary infiltrations, hepatosplenomegaly, generalized lymphadenopathy and ascites (10,19).

The treatment and prognosis mainly depend on the histological type. Preoperative histological diagnosis can be made by ultrasound or CT guided biopsy (3).

Complete surgical excision is the treatment of choice for unicentric CD either the hyalovascular or plasma cell variants. Pneumonectomy may be necessary in cases of hyaline vascular CD because of the risk of the massive bleeding due to hypervascularity (3, 25,28).

In these situations, preoperative angiography and embolization of the tumor feeding arteries can be considered to reduce intraoperative bleeding (29,30).

The prognosis is excellent, and 5-year survival is 100%. Adjuvant radiotherapy is considered as an alternative to incomplete resection or when surgery is not possible (5,10).

On the other hand, because of systemic involvement of multicentric CD, surgery is not a beneficial method, and patients need multiple systemic chemotherapy, corticosteroids, monoclonal antibodies, or radiation therapy. All patients require close follow up for the detection of recurrence or malignant transformation (3,6,25,31).

Castleman's disease is a rare lymphoproliferative disorder of unknown etiology. The most common sites of the unicentric types are in the thorax, especially in the mediastinum. It has polymorphic clinical and radiological features. Intrapulmonary CD is extremely rare, so it is important to remember Castleman's disease as a differential diagnosis in lung parenchymal lesions especially in asymptomatic patients. Unicentric localized CD response to complete surgical resection and the prognosis is excellent.

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