Multicentric Castleman Disease: Report of Rare Disease in Kuwait.
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Abstract
We report a rare case of multicentric Castleman disease diagnosed in Kuwait.

A 56-year-old man presented with fever of unknown origin and generalized lymphadenopathy. Laboratory investigations revealed mild anemia and polyclonal gammopathy. Bone marrow biopsy demonstrated 15% increase in plasma cells. Viral screenings including HIV were negative. Lymph node biopsy showed follicular hyperplasia with inter-follicular plasma cells infiltrate with a typical morphology of plasma cell variant of Castleman disease. The patient was treated with methyl-prednisone pulse therapy and showed good response.

Conclusion
Multicentric Castleman is a rare disease and clinicians and pathologists should be aware of it and should be considered in the differential diagnosis of fever of unknown origin and generalized lymphadenopathy.

Key words
Castleman disease, lymphadenopathy, plasma cell disorders.

Introduction
Castleman disease (CD) is a rare lymphoproliferative disorder which was first described in 1956 by Benjamin Castelman without well-known understood pathogenesis (1). Heterogenous factors are believed to be involved in the pathogenesis including human herpes virus 8 (HHV-8) and interleukin 6 (IL-6). The clinical presentation of CD is classified into unicentric and multicentric. Unicentric CD which is estimated to be 70% of the cases usually presents with solitary mass commonly involving the mediastinum and the neck with a benign course. The multicentric variant as the name indicates involves multiple organ system and the patient often presents with generalized lymphadenopathy and constitutional symptoms (fever, weight loss, generalized fatigue). In addition, this variant can be associated with ascites, pleural effusion, renal impairment, organomegaly and can be complicated by lymphoma (2).

The pathology of CD is classified into hyaline vascular type, plasma cell variant and mixed type. The former is usually associated with unicentric clinical presentation. On the other hand, the plasma cell variant is associated with a multicentric disease. In this report, we describe a new case of multicentric CD diagnosed in Farwaniya Hospital, Kuwait and elaborate on the clinical presentation and the current treatment modalities.

Case Report
A 56-year old man presented with fever, shortness of breath, bilateral lower limb swelling and generalized weakness. The physical examination revealed a febrile, pale patient with generalized lymphadenopathy and pedal edema. Other systemic examination showed scattered crackles in the lungs and mild hepatomegaly. There were no signs of peripheral polyneuropathy. After the first presentation, the patient was admitted several times to the hospital over 10 months period with recurrent chest infection.

During that period, the patient underwent extensive laboratory and radiological testing to identify the underlying cause. The laboratory investigations revealed a normochromic normcytic anemia with high ESR (> 100). The liver and kidney profile showed hypoalbuminemia...
and renal impairment at one stage of the disease which was corrected. Angiotensin converting enzyme (ACE), serum calcium, and thyroid function were within normal limits. Serum protein electrophoresis showed polyclonal gammopathy and negative Bence Jones protein. The patient had negative test for HIV, hepatitis screening and acid fast bacilli culture. He also underwent CT scan to the chest and abdomen that identified generalized lymphadenopathy. A bone marrow biopsies was performed and demonstrated a normocellular marrow with depleted iron store and 15% plasma cells. Several lymph node biopsies were performed which revealed follicular hyperplasia. However in the last biopsy, the lymph node showed follicular hyperplasia with germinal center and thickened blood vessels (figure 1). The interfollicular spaces were markedly infiltrated with sheets of plasma cells (figure 2). Immunohistochemical stains for kappa (1:5000, Dako) and lambda (1:5000, Dako) light chains were performed at indicated dilutions. The stains confirmed the polyclonal proliferation of the plasma cells. The features are diagnostic of Castleman disease, plasma cell variant.

During the different hospital admissions the patient was treated with broad spectrum antibiotics. After the diagnosis of CD was achieved the patient started on methyl prednisolone pulse therapy 60mg, with good response.

Discussion

Castleman disease is a rare systemic disease with variable clinical course. The pathogenesis of CD is not well established however there are some associations. Human herpes virus-8 (HHV-8) a lymphotropic virus known to be associated with Kaposi sarcoma which can be associated with CD. Hence, the investigators thought of possible association of CD with HHV-8. Subsequently, HHV-8 was identified in patients with CD (3). Interleukin-6 is inflammatory mediator has been noted to be associated with CD. Animal model studies demonstrated that the over expression of IL-6 is associated with production of symptoms resembling multicentric CD (4). In addition, infection with HHV-8 is associated with over-expression of viral IL-6.

Multicentric CD has a wide spectrum of clinical presentation. Similar to our case, the patients usually present with generalized lymphadenopathy, fever and constitutional symptoms. In addition to that, the patient may have associated organomegaly, ascites, pleural effusion and associated autoimmune disorders. Several conditions associated with CD include: Kaposi’s sarcoma, human immunodeficiency virus infection and POEMS an acronym for (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes). Laboratory investigations of Multicentric CD show a range of abnormalities. The patients has anemia of chronic disease and elevated ESR. In severe cases, the liver and renal function will be impaired. Polyclonal gammopathy are typical finding as seen in our patient (2). In a small series of multicentric CD bone marrow examination revealed plasmacytosis with lymphoid follicle

Fig. 1 : Follicular hyperplasia with germinal center and thickened blood vessels.

Fig. 2 : Interfollicular spaces markedly infiltrated with sheets of plasma cells
and positive expression of HHV-8. The plasmacytosis is likely to increase in IL-6 (5). There is no consensus regarding the management of multicentric CD. Steroids have been frequently used as systemic therapy with good response reaching 60-70%. Steroids are used predominantly to relieve the acute symptoms. However, it is not a curative treatment. This treatment is associated with steroids side effects in general and bacterial infections (6). Chemotherapeutic agents have been used as treatment of CD either as a single agent or in combination. Different agents are used include doxorubicin, vincristine, cyclophosamide, melphalan and chlorambucil. However, again there is no effective regimen. Like steroid, the patients treated with chemotherapeutic reagents are prone to serious infections (7). Rituximab is a monoclonal antibody directed against CD20 a cell surface marker known to be expressed on the cells in CD. The experience with anti-CD20 is still limited but some response have been noted in HIV-positive and HIV-negative patients (8). As stated earlier about the role of IL-6 in the pathogenesis, the neutralizing antibodies against IL-6 have demonstrated clinical efficacy resulting in resolution of symptoms. However, benefits were transient and symptoms recurred soon after discontinuation of the therapy (9). Alternative approach has been the use of monoclonal antibody against IL-6 receptor. In an early study, CD treated with this antibody showed amelioration of symptoms. However, the symptoms recurred after stopping the medication (10).

**Conclusion**

Castleman disease is a rare multi-system disease in which the patients commonly present with generalized lymphadenopathy and constitutional symptoms. Therefore, this should be considered in the differential diagnosis of lymphoma, connective tissue disease and chronic infections and clinicians and surgical pathologists should be aware of it.

**References**