Commentary

Intrathoracic Castleman's disease: "An important clinical mimicker"

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Castleman's disease (CD) also known as angiofollicular lymph node hyperplasia, giant lymph node hyperplasia, follicular lymphoreticuloma, or benign giant lymphoma,[1] is a poorly understood uncommon and heterogeneous lymphoproliferative disorder. It is characterized by nonneoplastic (but potential for malignant transformation is present)[2] lymph node hypertrophy that typically presents either as more frequent unicentric type (unicentric CD [UCD]) or multicentric CD (MCD) according to the extent of the disease and can mimic many diseases.[3] The former usually presents in early adulthood with localized with only one group of lymph nodes enlarged and are mostly asymptomatic or mildly symptomatic. While MCD patients present in the fifth or sixth decade of life with heterogeneous signs and symptoms, including multiple disseminated enlarged lymph nodes, fever, night sweats, fatigue, and anemia.[1] The mediastinum is the most common sites for unicentric disease while MCD or multifocal disease is usually a systemic disease with multisite lymphadenopathy and/or hepatospleenomegaly.[3,4] Since its first description in 1954, as atypical lymph node hyperplasia, many nodal and extranodal sites have been described; however, parenchymal lung involvement of the disease is exceedingly rare. When involved, radiological manifestation along with nonspecific systemic symptoms may erroneously be diagnosed as community-acquired pneumonia, lung malignancies, or tuberculosis, especially in areas with high tuberculosis incidence and proper identification of these cases is very important.[1,5,6] Even the index case of CD, first described by Castleman *et al*. in 1954, received antitubercular drugs before complete surgical resection, which on histopathology examination revealed a new syndrome characterized by hyperplasia of mediastinal lymph nodes with regressed germinal centers. Other differentials depending on the radiological presentation of intrathoracic CD, may include lymphoma, thymomas, reactive lymphadenitis, sarcoidosis, bronchial adenoma, pleural tumors, pericardial cyst toxoplasmosis, cytomegalovirus, mononucleosis, human immunodeficiency virus (HIV), cat scratch disease, rheumatologic diseases, sarcoma, hemangiopericytoma, neural crest-derived neoplasms, such as paraganglioma, neurofibroma, or schwannoma and chest wall tumors.[1,5,6]

The etiopathogenesis of the disease is not fully understood, however, recently a pivotal role of interleukin-6 (IL-6) in both UCD and MCD along with association of HIV and human herpesvirus 8 (HHV-8) with MCD have been described. In cases where clear etiological agent is not identifiable, other proposed predisposing factors may include chronic inflammation or infection, undiagnosed immunocompromised states, and autoimmune processes.[7]

Lymphoproliferation by production and differentiation of plasma cells in CD is thought to be driven by dysregulated and overproduced cytokine IL-6 by various cells in response to various inflammatory disease processes which stimulates B-cell proliferation and induces the expression of vascular endothelial growth factor, cause of increased angiogenesis in these patients.[6,8,9]

Systemic inflammatory and hematological manifestations of patients with MCD are thought to be primarily a consequence of elevated IL-6 production.[10] Although histopathological examination of excisional biopsy of affected lymph node tissue still remains the gold standard for diagnosis of CD,[11] contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and angiography are valuable diagnostic tools.[6] Mediastinal lesions on chest radiograph may mimic thymoma, lymphoma, or other solid tumors while hilar lesions may imitate lung malignancies.[12] On higher imaging, CD may present as a homogenous or heterogenous soft tissue mass on CT scan or MRI.[5] Thoracic CD typically presents as a well-defined, oval/rounded, mediastinal, or hilar mass of soft tissue density with homogenous contrast enhancement in UCD variants after medium contrast injection, due to its hypervascular nature while heterogenous or atypical enhancement such as poor contrast, target, or concentric enhancement patterns is found in MCD variant.[12] Further, a lesser degree of the enhancement is found in the plasma cell variant.[13] CT-guided fine-needle aspiration (FNA) of the mass is usually nondiagnostic in both UCD and MCD and are frequently "negative for malignant cells."[2,9-11] According to Deschênes *et al*.,[14] FNA can be useful in diagnosing some cases of CD, but in author's opinion, excision biopsy should be preferred whenever possible.

Three histopathological variants of CD have been recognized: (1) hyaline vascular characterized by lymphoid follicular proliferation at different levels of maturity, small lymphocytes of the mantle zones are arranged in concentric rings around the germinal center ("onion-skinning") and small, hyalinized radially arranged blood vessels ("lollipop" follicle) within and between follicles, (2) plasmacytic variant has preserved nodal architecture with hyperplastic follicles of varying sizes with sheets of mature-appearing plasma cells in the interfollicular region with low vascularity, and (3) mixed type. Most of the UCD patients (90%) have hyaline vascular type, whereas most of the MCD patients have plasma type.[1,3,7,8] Thus, review of histopathology slides by an experienced pathologist is recommended in cases of suspected CD else diagnosis can be delayed. Varied histological features of CD give rise to a broad differential diagnosis including both benign and neoplastic entities, further excluded on the basis of careful histological examination, immunohistochemical, flow cytometry, molecular genetics, and correlation with clinico-radiological and laboratory findings.

A battery of laboratory tests can be advised in CD patients, including a complete blood count, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), complete metabolic panel, HIV testing, plasma HHV-8 DNA levels, and if possible levels of cytokines, most notably IL-6 and IL-10.[9] Other necessary investigations can be performed on the basis of clinical presentation to rule out autoimmune disorders, rheumatoid arthritis, and other connective tissue diseases before attributing the morphological changes to CD, especially in cases of MCD.[7]

Considering the critical role of IL-6 in disease perpetuation and driving of symptomatology, the use of an antihuman IL-6 receptor monoclonal antibody rituximab siltuximab, tocilizumab is exciting new additions to the treatment armamentarium.[3,7,9] The management of UCD includes complete surgical resection of the affected lymph nodes, which is curative in most cases with good prognosis, the landscape for the management of MCD continues to evolve.[15] In cases of UCD where surgery is impossible, neo-adjuvant therapy (rituximab/steroids with or without cytoxan), IL-6(R) mAb therapy, novel agents (e.g., bortezomib, lenalidomide) or embolization and local radiotherapy can be advised. In cases of multicentric CD, various treatment options have been used with varied success including high-dose corticosteroids alone or in conjunction with rituximab or alkylating agents, such as cyclophosphamide and chlorambucil.[7] Rituximab monotherapy has been recommended for initial systemic therapy due to high likelihood of initial response with associated long-term, progression-free survival rates.[16] Selected patients with resistant or rapidly progressive or fulminant disease, a combination chemotherapy regimens such as rituximab plus CHOP or rituximab plus cyclophosphamide, vincristine, and prednisone are other options. In cases of disease progression even after second-line therapy, alternative single-agent or combination chemotherapies with or without rituximab, bortezomib, antiherpesvirus therapies, or other IL-6 - directed therapy, for example, siltuximab or tocilizumab may be considered.[6] The potential concomitant infections, malignancies, and associated syndromes of CD also require careful attention during management. MCD should be followed at regular intervals given the relapsing, remitting nature of the disease, and high risk for the development of non-Hodgkin's lymphoma and Kaposi sarcoma.[6]

In conclusion, intrathoracic CD continues to pose diagnostic challenge and may mimic many pathological conditions. In spite of its rarity, CD should be considered in the differential diagnosis of asymptomatic or oligosymptomatic pulmonary nodules/mass lesion associated with systemic symptoms. Appropriate diagnostic workup based on clinical presentation, imaging and histopathological evaluation by an experienced pathologist should be performed to arrive at an accurate diagnosis and advise appropriate therapy due to its progressive clinical course, increased risk for the development of lymphoma, and guarded prognosis. Awareness of CD is important in physicians because of vexingly complex nature of the disease at times which can be life threatening if suboptimally managed.

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