Castleman's Disease

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Abstract

Castleman's disease (CD) was first recognized in the 1920s and was further described as a clinicopathologic entity in 1956. It is an unusual condition with idiopathic massive proliferation of lymphoid tissues. The disease remains as a clinicopathologic diagnosis and usually occurs in young adults. Three histological variants (hyaline vascular, plasma-cell and mixed) and two clinical types (localized and multicentric) of Castleman's disease have been described. Hyaline-vascular type (80%) is the most common form of the disease followed by plasma-cell type (20%) and the rarest form is mixed type. Although a variety of cutaneous manifestations in CD have been described, little is known about the specific cutaneous histological findings.

INTRODUCTION

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disorder with benign hyperplastic lymph nodes characterized histologically by follicular hyperplasia and capillary proliferation with endothelial hyperplasia ([1]). The disease was first described by Benjamin Castleman in 1956. In 1970, Flendring and Schillings distinguished two basic pathologic types and one mixed variant ([2]). Based on these features Keller et al in 1972 subclassified the disease as hyaline-vascular (HV), plasma cell (PC) and hyaline-vascular plasma cell types ([3]). Clinically CD can be either unicentric or a multicentric disease (MCD). Unicentric disease is more common. Approximately 90% of cases with the unicentric disease (UCD) are of the hyaline-vascular type. The localized form usually has a benign course and clinical abnormalities frequently resolve after excision of the affected lymph nodes ([3,4,5]). MCD is usually the plasma cell variant and patients present with a systemic illness with generalized peripheral lymphadenopathy, hepatosplenomegaly, frequent fevers, and night sweats ([6]). MCD has a progressive course with potential for malignancy ([6,7,8,9,10]). MCD is associated with non-Hodgkin's lymphoma (NHL) in the absence of human immunodeficiency virus (HIV). In the localized form of plasma-cell type Hodgkin's lymphoma may occur ([11]).

PATHOGENESIS

Several theories have been formulated to account for the spectrum of associated pathologic and clinical features in CD. Although the exact cause of the disease is unknown, results of numerous studies indicate a viral infection as a triggering agent in pathogenetic cascade. The clinical association between MCD and Kaposi's sarcoma has lead to investigation of the possible role of Kaposi's sarcoma-associated herpesvirus, also called human herpesvirus 8 (HHV-8) in CD. HHV-8 is universally found in HIV+ MCD and NHL is seen 15-fold higher in these patients compared to general HIV-positive population ([12,13]). In addition HHV-8 undergoing replicative infection expresses a viral IL-6 gene that activates the human IL-6 receptor ([14,15]). Lymph nodes from various animal models and patients with CD implicate IL-6 as a causative agent for the commonly observed systemic manifestations ([5,16,17,18,19]). IL-6 increases the proliferation and survival of B cells which have the major pathogenetic role in the disease. Treatment of MCD with monoclonal antibodies against IL-6 provides resolution of systemic symptoms ([20]). Although numerous data has accumulated in the role of HHV-8 in HIV+ MCD patients, these data do not explain pathogenesis of HHV-8 negative MCD and UCD which may result from a different source of immune stimulation.

DISCUSSION

Castleman's disease (CD) is characterized by histological changes and proliferation of lymph nodes. Hyaline-vascular type is the most common form (80%) of the disease and has a benign clinical course. Plasma-cell type and mixed form have a diffuse involvement in lymphoid tissue and exhibit a more aggressive course with a risk of transformation to lymphoma ([21], [22]). Frequently most patients are asymptomatic at the time of diagnosis and efforts for diagnosis begin with observation of a mediastinal mass in

chest radiogram. %10-20 of patients present with systemic symptoms (fever, weight loss, hepatosplenomegaly, etc) and diffuse involvement of the disease ([23,24,25,26,27]).

CHARACTERISTICS OF HYALINE-VASCULAR TYPE

Most of the patients are asymptomatic. However few patients may have dyspnea, cough and recurrent infections due to compression of trachea and bronchi by mediastinal mass ([28,29,30,31]). The disease is frequently localized at anterior mediastinum. Rarely, lesions may also be seen in lungs. Recurrent pleural effusions may occur. Few cases have chylothorax ([22,23,24]). Chylothorax occurs with the compression of thoracic ductus by lymph nodes and is diagnosed by a milk-like appearance and a triglyceride level more than 110mg/dl in pleural fluid ([27,29,34]). Ekstrathoracic mass usually presents with pain and may be seen in retro peritoneum, mesentery, central nervous system, orbit, pelvis, cervical region and voluntary muscles ([27]).

Diagnosis is confirmed by radiological techniques and histological examination of lymphoid tissues and lymph nodes. In hyaline-vascular type x-ray finding is usually a big lymphoid mass in mediastinum or proximal hilus. Lymph nodes may have calcification. Computerized tomography (CT) and magnetic resonance imaging (MRI) show involved lymph nodes typically in homogeneous contrast. Thymoma and lymphomas do not have this homogeneous contrast appearance. Vascularity of the involved lymph nodes can be detected by arteriography. In CD, capillary phase angiography is particularly preferred. Before surgical procedures, preoperative embolization can be performed to decrease the risk of bleeding. ([26,27, 29,30,31,32,33]).

Primary treatment of hyaline-vascular type castleman's disease is surgical excision. Complete surgical resection is curative but subtotal resections may be followed by recurrences. In cases with poor prognosis radiotherapy can be another option. Five year survival is 100% in original hyaline-vascular type. Kaposi sarcoma may develop in few cases, particularly with multicentric involvement. Hyaline-vascular variant rarely transforms to malign lymphomas. Wilbur et al. reported the data of 16 cases with following characteristics ([33]).

Figure 1

Table 1: Comparison of unicentric and multicentric CD

Characteristics	Unicentric	Multicentric
Age	21-53	43-54
Finding	Incidental/compression and systemic symptoms	Systemic symptoms
Histology	Hyaline vascular ,mixed	HV, PC
Localization of lymph nodes	Mediastinum, abdomen, pelvis	Peripheral
Organomegaly	None	HV,PC
Clinical course	Benign	Progressive
Differential diagnosis	Lymphoma, thymoma, sarcoma, carcinoma	Lymphoma, AIDS
Treatment	Surgical resection	Surgical, medical(steroid), chemotherapy, radiotherapy

CHARACTERISTICS OF PLASMA CELL VARIANT

This type is characterized with multiple involvements of lymph nodes and lymphoid tissues ([32,33,34]). Frequently involved lymph nodes are in extrathoracic regions like mesentery or retro peritoneum. In computerized tomography, soft tissue mass and calcification in satellite lymphadenopathies can be seen ([30,31,32,33,34,35]). Patients frequently have B symptoms (weight loss, fever). Interestingly, B symptoms resolve after surgical resection of lymph nodes.

Figure 2

Table 2: Clinical conditions that may accompany Castleman's Disease()

Skin	Hematological	Pulmonary
• Pemphigus vulgaris (PC) (37,38)	• Refractory anemia (PC)	o Bronchiolitis obliterans (HV)
• Cutaneous Kaposi sarcoma (HV) (37,38)	• Autoimmune cytopenia (PC)	o Recurrent pleural effusion (HV)
• Glomeruloid hemangioma (PC)	• Thrombotic thrombocytopenic purpura (HV)	o Chylotoraks (mixed)
• Exfoliative dermatitis (mixed type) (34)	• Myelofibrosis (HV)	**Kidney**
• Plane xanthoma (38)	• Lupus anticoagulant (PC)	• Nephrotic syndrome (PC)
• Lichenoid and nodular erupsion (36)	**Onkological**	• Acute renal failure (PC)
• Maculopapular lesions (36)	• Malign lymphoma (PC,HV)	• Glomerulonephritis (PC)
Neurological	• Osteosclerotic myeloma (PC)	**Others**
o Peripheral neuropathy (PC)	• γ light chain disease (HV)	o Amyloidosis (PC)
o Pseudo tumor (PC,HV)	• Extra medullar plasmacytoma (PC)	o Temporal arteritis (HV)
o Myasthenia gravis (HV)	• Nodal kaposi sarcoma (PC)	o Pericardial effusion (HV)

MULTICENTRIC DISEASE

Median age is 56 in patients with multicentric involvement. In addition to local disease, systemic findings are hepatomegaly and generalized lymphadenopathy. Laboratory assessments may reveal anemia, high erythrocyte sedimentation rate, polyclonal hypergammaglobulinemia, granulocytosis and plasmocytosis. It is clinically more aggressive than local disease. The course of the disease is with relapses and remissions and it may transform to malign lymphoma. Besides, patients with peripheral neuropathy are more resistant to therapy ([33]).

In the literature, there are also some reports of Castleman's disease concomitantly with POEMS syndrome. (Polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) ([27,30, 35,36,37]).

In patients with multicentric involvement, the treatment strategy must be based on clinical staging and the regions involved. Serum protein electrophoresis, bone marrow aspiration, pelvis-abdomen-thorax CT and gallium scintigraphy are helpful diagnostic tools in order to distinguish multicentric disease from localized disease ([4,37,38,39,40,41,42,43]).

Multicentric disease has a poor prognosis in spite of systemic therapy. Median survival is 26 months in %50 of patients. ([27]). Combined modalities are preferred in chemotherapy (corticosteroids, cytotoxic agents) ([23]). Also, trials with IL 6 receptor antibodies showed regression of hypergammaglobulinemia and lymphadenopathy after 3 months ([31]). Radiotherapy was performed in some cases but its efficacy could not be defined in these case series ([27]).

In the pathogenesis, IL-6 secreted by activated B cells was held responsible. Patients with high levels of IL-6 have weight loss, fever, anemia, hypergammaglobulinemia and elevated acute phase reactants ([22, 27]). Literature also shows high IL 6, IL 10 and HSV-8 levels in HIV positive patients ([13, 26]).

Although there are some theories about the etiology of Castleman's disease the exact mechanism is still unknown. Chronic low grade inflammation, immune deficiency and autoimmunity are possible responsible mechanisms in the pathogenesis. In addition, there are some speculative theories: Increase of IL-6 levels by abnormal plasma cell proliferation also cause multicentric Castleman's disease in animal models. Moreover, systemic symptoms such as fever, anemia and weight loss are more frequent in patients with high levels of IL-6 when compared with other patients who have lower levels of IL-6 ([13,36]).

Castleman's disease is still not a well-defined clinicopathological entity for clinicians especially during diagnosis and treatment. Because histological and clinical findings of the disease are nonspecific, it may be difficult to distinguish from neoplastic, infectious and autoimmune diseases or may be masked by these diseases. The diagnosis can be made by collaborative study of the clinician and pathologists.

Immunopathogenesis and thus the optimal therapeutic regimen is not known. Nonsteroid anti-inflammatory drugs, combined chemotherapies (vincristine, cyclophosphamide, carmustine), corticosteroids, IL-6 antibody, radiotherapy and surgical resection are the treatment modalities ([37]).

TREATMENT

Complete surgical resection is curative in most of the patients with unicentric Castleman's disease (CD) ([41]). Recurrence in localized disease is rare and has been associated with incomplete surgical removal ([24]). Radiotherapy may be the choice of treatment in partially resected unicentric CD ([39,41]).

In multicentric form it is difficult to define the optimal therapy, because it is a rare disease and clinically heterogeneous. A range of treatment modalities have been studied with different response rates. Corticosteroids have been commonly used in patients with disseminated disease.

Steroids may provide transient remissions, but disease frequently recurs ([4], [42]). The highest rates of sustained remission are gathered with combination therapies that are usually used to treat lymphomas ([4],[42]). However the benefits and side effects must be well balanced especially in patients with poor heath status.

In a multicenter prospective study the safety and efficacy of a humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody (MRA) was evaluated in patients with multicentric CD ([41]). Within 16 weeks, treatment with MRA consistently alleviated lymphadenopathy and all the inflammatory parameters. Nutritional status and fatique scores were significantly improved. Patients who had received oral corticosteroids before study entry were able to do well on a reduced corticosteroid dose. The effect was durable during the extension period and adverse reactions were usually mild and transient. But the study population was HIV negative and HHV-8 positive and the observed efficacy results should better be accepted for this group until new multicentre studies including HIV and HHV-8 positive patients are performed. In an earlier study, symptoms recurred shortly after cessation of the therapy ([40]). Rituximab, a monoclonal anti-CD20 antibody also appears to have promising effects in the treatment of both HIV negative and positive multicentric CD in an increasing number of case reports. There are also some reports showing the efficacy of ganciclovir, interferon alpha and thalidomide.

In conclusion, surgical ablation is the curative treatment in patients with unicentric CD. For multicentric CD patients with good health status, combined chemotherapy is the most efficient therapy. But patients with poor performance status who are not expected to overwhelm the side effects of the combined chemotherapy can be considered for steroids and single agent chemotherapy for palliative treatment. Rituximab seems to be a promising well-tolerated agent. New studies are required for proving the long term efficacy of antiviral agents, IL-6 receptor antagonists and other immunosupressive treatments.

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