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# Castleman's Disease. A Review

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## Abstract

***Castleman's disease is characterized by a non-clonal lymph node hyperplasia. Pathologically it is classified as hyaline vascular, plasmacytic, or mixed cellularity types, and clinically it may adopt a unicentric (localized) or multicentric presentation. An association of the disease with HIV infection has been found. Many uncertainties remain concerning the etiopathogenesis and the optimal treatment of this rare condition.*** **(AIDS Rev. 2009;11:3-7)**

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## Key words

***Castleman's disease. HIV infection. Human herpes virus type 8. Kaposi's sarcoma. Human interleukin-6.***

## Introduction

Castleman's disease (CD) is a non-clonal lymph node hyperplasia that was first described in 1954[1]. The condition is also known by a number of descriptive synonyms, including follicular lymphoreticuloma, angiofollicular lymph node hyperplasia, giant cell lymph node hyperplasia, benign giant lymphoma, and lymphoid hamartoma.

Castleman's disease is a heterogeneous disorder. Clinically it may adopt a unicentric (localized) or multicentric presentation, and pathologically it is classified as hyaline vascular, plasmacytic, or mixed cellularity types. The hyaline vascular variant is found in most unicentric cases, and the plasmacytic variant is found in most multicentric cases (Table 1)[2].

The infrequency of CD has precluded comprehensive studies on the condition, and for that reason the disease is imperfectly understood. In recent years, interest in the disease has increased due to its association with HIV infection[3]. In this article, after a thorough evaluation of the literature, we review the present knowledge on CD, including recent advances in the pathogenesis and treatment of the disorder.

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## Etiopathogenesis

The etiology and pathogenesis of CD is probably diverse, as is the disease itself. Human herpes virus type 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus, is present in almost all cases of CD occurring in HIV-infected patients, and also in some cases of CD occurring in HIV-negative patients. Moreover, some studies have found a correlation between the quantity of HHV-8 DNA in CD-affected tissues and the intensity of symptoms provoked by the disease. For these reasons, the agent is speculated to play a role in the etiology of at least some cases of CD, but definitive conclusions have not been reached as HHV-8 could be a simple bystander[2]. Alternatively, HIV might itself predispose to the development of the condition.

Inflammatory mediators are important in the pathogenesis of CD. Among them, human interleukin-6 (IL-6) has been found to be especially relevant as it may act

**Table 1. Differential features between unicentric and multicentric Castleman's disease**

| | Unicentric | Multicentric |
|---|---|---|
| Predominant pathology | Hyaline vascular | Plasmacytic |
| Systemic symptoms | Rare | Common |
| Treatment | Surgery, irradiation | Chemotherapy, rituximab, other systemic |
| Prognosis | Favorable | Poor |

as a potent stimulus for the proliferation of B-cells, and is abundantly expressed in CD-affected tissues. Moreover, experimental studies have shown that increased production of IL-6 can provoke many of the manifestations of CD.

The HHV-8 IL-6 may also contribute to the development of CD, as it has been shown to induce the production of human vascular endothelial growth factor and angiogenesis, and can also stimulate the proliferation of B-cells. Other possible mediators in CD development are epidermal growth factor and interferon alpha[4].

## Pathology

Castleman's disease, independent of the histologic type, is characterized by architectural changes in lymph nodes that generally affect all compartments.

In the hyaline vascular type, lymph node follicles tend to show atrophic or regressing germinal centers, with penetrating small hyalinized vessels and follicular dendritic cells, which may be disrupted or have many tight connections. These centers are surrounded by broadened mantle zones composed of concentric rings of small lymphocytes in an onion skin-like configuration. In the interfollicular region, plasmacytoid dendritic cells, fibroblastic reticulum cells, and small T lymphocytes are present and a prominent vascular proliferation can also be seen. Sinuses are rarely observed.

In the plasmacytic type, lymph node follicles tend to show hyperplastic, instead of regressing, germinal centers. The interfollicular region characteristically contains sheets of plasma cells which are polyclonal. A prominent vascular proliferation is not seen, and patent sinuses are commonly present. These histopathologic features are not specific for CD, and can be seen in other conditions that cause reactive lymph node hyperplasia such as infectious and rheumatic diseases[5]. This histologic type is the predominant one in HIV-infected people, although in these patients the lymph node infiltrate is predominantly composed of large immature plasma cells, i.e. plasmablasts. These cells may express λ light-chain restricted immunoglobulins, but are almost always truly polyclonal. Nevertheless, occasionally the plasmablast cell infiltrate may transform into real plasmablastic monoclonal lymphoma that in most cases is clinically very aggressive[6].

Cases of CD with mixed cellularity, both unicentric and multicentric, are also sometimes seen. In patients with HHV-8 infection, the herpesvirus can be detected in affected tissues, especially in the mantle zone of lymph nodes.

## Epidemiology

Castleman's disease is a rare condition, with the real incidence unknown. It occurs equally in women and men, and no race predominance has been observed. The unicentric hyaline vascular type is the most common one and accounts for about two-thirds of all cases; this type of CD occurs in all age groups, but seems to be more common in the third decade of life. The plasmacytic type predominantly presents in the sixth decade of life.

In HIV-infected subjects, CD most commonly presents in the fourth decade of life, and is more prevalent in men than in women. The occurrence of the disease seems to bear no relationship to CD4 cell count or HIV viral load. In these patients, CD frequently coexists with Kaposi's sarcoma, an AIDS-defining condition[7,8].

Multicentric CD is occasionally associated with the polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, also known as Crow-Fukase syndrome, a condition where HHV-8 infection may also be present[9].

## Clinical manifestations

The clinical features of CD vary substantially from case to case. The unicentric hyaline vascular type usually presents as one or several enlarged lymph nodes. They may produce local symptoms, such as pain, due to tissue expansion. But they may also be completely asymptomatic and incidentally detected when explorations or tests for unrelated reasons are carried out. The most common sites of presentation are the mediastinum, the abdomen, and the axillary and cervical regions, but the disease may appear in virtually any area of the organism. Systemic symptoms and laboratory test abnormalities are rare. On the other hand, in the unicentric plasmacytic type, in addition to enlarged lymph nodes, constitutional symptoms and laboratory abnormalities, similar to those of multicentric CD (see below), are common. This means that clinical presentation correlates more with the histologic type than with the anatomical presentation[10].

In the multicentric plasmacytic type, systemic symptoms are common and many times severe. They are the presenting complaint in most cases. The majority of patients have fever, which may be quite high. Night sweats, weakness, anorexia, and weight loss are also prevalent. Almost all patients have multifocal lymphadenopathy. The enlarged lymph nodes are frequently painful. Hepatosplenomegaly is also common. Seizures and other central and peripheral nervous system symptoms can also be seen[11]. Pulmonary symptoms, such as cough, dyspnea, and hemoptysis, and a variety of skin rashes can also appear. In advanced or severe cases, ascites, pleural effusions, and peripheral edema are frequent. Analyses may show a wide range of abnormalities. Anemia, especially of chronic disease, is present in most patients. Thrombocytopenia is also prevalent. Other common alterations are accelerated erythrocyte sedimentation rate, raised C-reactive protein, increased liver enzymes, elevated creatinine, hypoalbuminemia, and polyclonal hypergammaglobulinemia[12]. Also characteristic is the increased serum levels of IL-6. Bone marrow plasmacytosis is frequently observed.

Image studies in CD frequently display lung infiltrates and a variety of tissue abnormalities throughout the body in addition to lymph node enlargement. Contrast enhancement is typical of CD lesions, and calcification is occasionally seen[13,14].

The clinical course of CD is extraordinarily variable. There are cases that remain essentially asymptomatic for months or years, especially those of the unicentric hyaline vascular type. However, there are cases, especially of the multicentric plasmacytic type, that rapidly progress and may even cause death within weeks. Recurrent exacerbations and remissions are not rare.

In HIV-infected patients, CD is generally multicentric, of the plasmacytic or mixed cellularity types. Symptoms tend to be more severe than in the general population, and an accelerated clinical course is common. Infections frequently complicate the course of the disease. Interestingly enough, rapid progression of CD may occur within a few weeks of initiation of antiretroviral therapy, presumably as a consequence of the immune reconstitution inflammatory syndrome (IRIS)[3,7,15]. That kind of reaction is common with several opportunistic infections after starting treatment against HIV disease[16]. About 20% of cases of CD in HIV-infected patients progress into non-Hodgkin's lymphoma, generally of aggressive nature. Progression into Hodgkin's lymphoma and other modalities of cancer has also been reported. The occurrence of these malignant transformations seems to be independent of the degree of immunodeficiency[17].

## Diagnosis

A biopsy is necessary to establish the diagnosis of CD. The lymph node is the preferred site most of the times. The normal appearance of a small sample of cells, isolated from the entire lymph node, may lead to failure to diagnose CD with the use of fine needle aspiration. For that reason, a generous specimen, generally an excisional biopsy, is required.

As the histopathologic findings of the plasmacytic type of CD are nonspecific, other conditions, especially rheumatic and viral infectious diseases, must be excluded before diagnosis is made[18].

## Treatment

The heterogeneity and the rarity of CD have precluded properly designed studies to determine the

optimal therapy for the condition. Therefore, treatment recommendations are based on small series of patients, results obtained in other similar conditions, or expert opinion.

Unicentric CD, either hyaline vascular or plasmacytic type, is generally treated with excisional surgery. When surgery is not feasible, irradiation may be considered. Both may be curative. But in some cases, simple observation may also be an adequate option.

Multicentric CD is rarely completely asymptomatic, and therefore simple observation is almost never a good option. Surgical excision of affected tissues, such as splenectomy, is seldom curative, and generally achieves only a transient relief of symptoms, related to a "debulking" effect. Therefore, patients with this modality of the disease almost always require systemic therapy. We will briefly comment on the different options available.

Glucocorticosteroids improve symptoms, reduce lymph node size, and correct most blood analyses abnormalities. But the benefit is transient and recurrence of symptoms is usual upon discontinuation of treatment. Moreover, the prolonged use of these drugs is associated with a variety of significant side effects such as bone decalcification, increased risk of infection, etc. For these reasons, glucocorticosteroids are generally reserved for temporary or adjuvant use only. These drugs can be useful in the treatment of the IRIS-related exacerbations of CD that may occur after starting antiretroviral therapy in HIV-infected patients.

Thalidomide, a drug with multiple biological effects, including an antiangiogenic effect, has traditionally been used in CD with moderate success[19]. The efficacy of the drug can improve when combined with other medications[20]. The teratogenicity of the drug is a serious inconvenience for its use.

Chemotherapy is probably the best option for most cases of symptomatic CD. For the less severe cases, single agents, such as cyclophosphamide, vinblastine, or etoposide, may be used. For the more severe cases, multidrug combinations, like those used in the treatment of lymphomas, are required; for example, cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). These modalities of therapy must be used with care because of their frequent side effects and the increased risk of infection associated with their use. In HIV-infected patients, the potential interactions with antiretrovirals and other needed medications is an additional problem[21]. Cases of CD resistant to chemotherapy have also been reported.

Rituximab is a monoclonal antibody to the antigen CD20, which is present in HHV-8-infected lymphoid cells. Although experience with this parenterally administered drug is still limited, it has shown promising results in small series of patients with CD, with prolonged remission of the disease. Reactivation of Kaposi's sarcoma seems the main adverse effect[22,23]. Whether rituximab can enhance the activity of chemotherapy or other modalities of treatment is still unknown.

Tocilizumab is a monoclonal antibody to the human IL-6 receptor. The drug has demonstrated significant success in a few studies, with amelioration of symptoms, reduction in the size of affected lymph nodes, and improvement of blood analyses abnormalities, although side effects such as dyslipidemia or infection may occur[24].

Antiviral agents with activity against HHV-8, such as ganciclovir, valganciclovir, cidofovir, or foscarnet, could theoretically have a role in the treatment of CD[3,25]. Other potentially useful drugs include interferon alpha, retinoic acid, and bortezomib[26]. But at this time, insufficient data exist to recommend any of these agents in clinical practice.

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