About Castleman’s Disease
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# About Castleman’s Disease

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ICDO Mission Statement

The International Castleman's Disease Organization is a non-profit institution committed to promoting the health of patients through advocacy, education, leadership, research, and service. This advocacy commitment is conducted through patient referrals to quality 'centers of excellence' where healthcare professionals and scientists research this rare disease for a comprehensive healthcare / treatment program.
What Is Castleman's Disease

Castleman’s disease is a benign disorder first described by Dr. Benjamin Castleman in 1956. Castleman’s disease is also referred to as angiofollicular hyperplasia, and is a non-clonal disease of the lymph nodes. As the name angiofollicular hyperplasia implies there is a follicular hyperplasia of lymph nodes with abnormally increased interfollicular vascularity. Castleman’s disease can be classified as a) unicentric versus multicentric, based on clinical and radiological findings, b) hyaline vascular versus plasmacytic versus mixed cellularity variety based on histopathology and c) as HIV negative versus HIV positive based on the HIV status of the patient. All three factors need to be taken into account in the assessment of patients.

Unicentric Castleman’s Disease

Unicentric Castleman’s Disease is usually a slow growing solitary mass typically located in the mediastinum or mesenteries. Typically, there are no constitutional symptoms and no elevation of acute phase reactants (Interleukin 6, ESR and CRP). Symptoms, if present, are due to a mass effect of bulky lymphadenopathy. In a few cases abnormal clonal, cytogenetic findings have been described arising from a dysplastic follicular dendritic cell network, but it remains unclear how these findings are related to Unicentric Castleman’s Disease. In 90-95% cases surgical resection is curative and usually there is no progression to lymphoma or association with other tumors. The prognosis is excellent with a 5 yr survival of close to 100%.

Multicentric Castleman’s Disease

In multicentric Castleman’s Disease there is usually widespread lymphadenopathy with, in some instances, hepatosplenomegaly. “B” symptoms including severe fatigue, night sweats, fever, weight-loss, and anorexia are typically present. These symptoms
are typically driven by overproduction of interleukin 6. Overproduction of interleukin 6 also results in an acute phase reactions with elevated ESR, CRP, fibrinogen, thrombocytosis, and hypergammaglobulinemia, while hemoglobin and albumin levels are decreased.

 Patients typically have peripheral edema that is poorly responsive to loop-diuretics and suffer from anemia and hypoalbuminemia. Approximately 20% of patients have peripheral neuropathy. The disease is non-clonal with no IgH or TCR gene rearrangements. Other conditions associated with multicentric Castleman’s Disease include autoimmune hemolytic anemia, multiple myeloma, amyloidosis, Pemphigus, and overlap syndromes with POEMS1. Multicentric Castleman’s Disease runs a more aggressive course and can progress to non-Hodgkin’s lymphoma. Multicentric Castleman’s Disease often requires systemic therapy.

### Histopathologic Classification of Castleman’s Disease

The histopathology of hyaline vascular Castleman’s disease shows that the lymphnode germinal centers are poorly formed with dysplastic / atrophic CD21+ follicular dendritic cell networks surrounded by an expanded mantle zone consisting of rims of small CD20+ lymphocytes arranged in an onion skin manner. There is increased interfollicular vascularity with capillary proliferation and endothelial hyperplasia. Plasmacytic variety of Castleman’s Disease is characterized by both more numerous and larger hyperplastic follicles, which have more expanded mantle zones compared to hyaline vascular Castleman’s disease. Sheets of plasma cells of plasma cells are present in the interfollicular areas. The mixed cellularity form of Castleman’s Disease has features of both hyaline vascular and plasmacytic types Castleman’s Disease.

1A condition characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.”
**Relationship Between Histological Type and Unicentric Versus Multicentric Disease**

Classically it is thought that Unicentric Castleman’s disease is usually of the hyaline vascular variety and multicentric disease (MCD) of the plasmacytic type or mixed cellularity variety. These relationships are based on the analysis of the small numbers of patients since Castleman’s disease is rare. Review of 37 patients with Castleman’s disease treated at University of Arkansas for Medical Sciences, which is the largest single institution experience in the world with Castleman’s Disease, found that patients with Unicentric Castleman’s disease indeed have as pathology the hyaline vascular variety. However, the histopathology of multicentric disease can be evenly divided between hyaline vascular variety on one hand and plasmacytic type and mixed cellularity variety on the other hand. Mixed cellularity clinically behaves more like plasmacytic type rather than hyaline vascular disease.

HIV status is important as HIV+ patients with multicentric Castleman’s Disease have much more frequent plasmacytic disease and the clinical course is less favorable than in HIV-negative patients. Furthermore, a good case can be made for HHV-8 being the causative agent in HIV+ Castleman’s Disease patient. HIV+ patients have more often Kaposi’s sarcoma and more frequently progress to non-Hodgkin’s lymphoma.

**Pathogenesis of Castleman’s Disease**

**Causes**

The exact cause of Castleman’s Disease is not known. Some researchers speculate that increased production of interleukin-6 (IL-6) may be involved in the development of Castleman’s Disease. IL-6 is a substance produced by structures within the lymph nodes.

Human Herpes Virus 8 is a g-Herpes virus, which is homologous to Epstein-Barr virus and Herpes Virus Siamuri, and is tropic
(homes in) for B-lymphocytes. HHV8 has been associated with Kaposi’s sarcoma, Primary Effusion Lymphoma (PEL) and multicentric Castleman’s Disease. HHV-8 seropositivity in normal population varies from 5-35%, whereas in HIV+ patients it varies from 12-50%. Also quantitative PCR (QPCR) detection of HHV8 DNA in HIV+ patients antedates development of MCD (5-25%). There is presence of HHV8 DNA in Lymph nodes and peripheral blood mononuclear cells in HIV+ patients with multicentric Castleman’s disease. Viral IL6 and other cellular homologue genes are exposed in lymph nodes from HIV+ patients. Also QPCR for HHV8 DNA can be used for monitoring disease activity and response in HIV+ patients.

HHV8 DNA positivity by nested PCR and vIL6 protein has been detected in lymph nodes of HIV negative patients (paraffin blocks), as well as vIL6, vBCL-2, vCyclin-D, and viral G-protein coupled receptor. However, no conclusive evidence so far has been found that HHV8 has been involved in HIV- patients.

**Epidemiology**

Castleman’s Disease is a rare disorder of the lymphatic system that affects males and females in equal numbers. All types of Castleman’s Disease may affect individuals of any age; however, the plasma cell type has greater prevalence among young males and females. Children are rarely affected by this disorder.

**Castleman’s Disease Symptoms**

IL6 has been implicated in the pathophysiology of CD. It causes B-cell proliferation resulting in hyperplastic follicles and hence the enlarged lymph nodes (LNS). IL6 also increases secretion of vascular endothelial growth factor (VEGF), causing angiogenesis (new blood vessel formation) and capillary polarization of T lymphocytes to a Type 2 cytokine profile leading to autoimmune phenomena including AIHA, ANA positivity and elevation of IgE. with endothelial hyperplasia.
IL6 induces an acute phase reaction comprising increases in ESR, CRP, IgGs, serum fibrinogen, and serum Amyloid A Protein (SAA). Increased SAA levels may result in AA Amyloidosis, whilst hyperfibrinogenemia may play a role in venous thrombosis and pulmonary emboli. Finally, B-type symptomatology is virtually always associated with increased IL6 levels.

**Diagnosis**

The diagnosis of CD is based upon a thorough clinical evaluation that includes a detailed patient history, laboratory studies, including IL6 and ESR, CRP, histopathology of affected lymph node(s) and a variety of imaging techniques (preferentially PET-scanning). PET-scanning complements CT-scanning by giving information regarding the metabolic status of the involved lymph nodes. Usually the standard uptake values (SUV) of FDG-avid lymph nodes are less than those observed with active lymphoma. However, after therapy with for instance IL6-receptor antibody disappearance of all increased metabolic activity can be observed in responding patients. PET scanning therefore is not only useful in diagnosis, but also in assessment of response to therapy.

**Castleman’s Disease Clinical Manifestations**

In most cases, Castleman’s Disease is characterized by a single, solid growth within lymphatic tissue in the chest, stomach, or neck. Growth may also occur in other lymphatic tissue throughout the body. Usually the growths represent abnormal enlargement of the lymph nodes normally found in these areas. There are three types of Castleman’s Disease: hyaline-vascular type; plasma cell type; and a third type that affects more than one area of the body (generalized or multicentric Castleman’s) has been also been identified.

In most cases of the hyaline-vascular type of Castleman’s Disease, individuals exhibit no symptoms of this type of the
disorder (asymptomatic) or may develop a non-cancerous (benign) growth in the lymph tissue; most frequently in the chest. Symptoms with this type are usually secondary to the size and location of the growth. For example, a growth may form in a vein, resulting in a bulge and possible obstruction in the involved blood vessel.

In the plasma cell type of Castleman’s Disease, individuals may exhibit a variety of symptoms including fever, fatigue, excessive sweating, weight loss, skin rash, early destruction of red blood cells, leading to unusually low levels of circulating red blood cells (hemolytic anemia), and/or abnormally elevated amounts of certain immune factors in the blood (hypergammaglobulinemia).

Multicentric or generalized Castleman’s Disease affects many areas of the body. Individuals with this type of Castleman’s Disease often exhibit symptoms similar to those associated with the plasma cell type. In addition, some individuals may have an enlarged liver and spleen (hepatosplenomegaly). Some cases of multicentric Castleman’s Disease have been associated with POEMS Syndrome. (For more information on this disorder, choose “POEMS” as your search term in the Rare Disease Database.) Researchers have speculated that individuals with this type of Castleman’s Disease may have a greater risk of developing malignant complications such as Kaposi’s Sarcoma or malignant lymphoma.

**Treatment**

Surgical excision is the preferred treatment in most cases of unicentric Castleman’s Disease and adjuvant therapy e.g. steroids and/or rituxan before surgery may be useful to shrink bulky or inoperable disease. In some cases, radiotherapy has proven effective, although this is currently usually avoided.

A number of therapies have been used for multicentric disease: intravenous immunoglobulin, anti-viral drugs e.g. acyclovir, (Val)
ganciclovir in HIV+ and HHV8+ disease, combination chemotherapy (e.g. CHOP and in intractable cases even autologous stem cell transplantation. Other therapies include the anti-angiogenesis factor thalidomide and anti-IL6 therapy. Surgery may also be useful in debulking disease).

Anti-IL6 therapies include suramin, anti-IL6- or anti-IL6 receptor antibody. Suramin is polysulfonated urea compound originally used for trypanosomiasis. Suramin inhibits viral reverse transcriptase and it has a number of biological effects, which include inhibition growth factor and cytokine binding to their respective receptors e.g. IL6, L2, PDGF, and FGF. Suramin also modulates cytokine secretion. Anti-IL6 antibody is particularly effective in controlling IL6 related symptoms, but can also induce disease regression with durable remissions. Recent clinical trials with antibodies directed at the IL6 receptor or IL6 itself, conducted in Japan and the USA respectively, have demonstrated that targeting of the IL6 signaling cascade is a highly effective therapeutic strategy with rapid resolution of symptoms and slow involution of lymph nodes.

**Castleman’s Disease Variants**

**Hyaline Vascular Variant**

The hyaline vascular sub-type accounts for 90% of cases of Castleman’s disease and patients are generally asymptomatic (58% to 97%). Most patients come to clinical attention when a solitary middle or posterior mediastinal mass (adenopathy) is detected incidentally on chest radiographs. In order of frequency, the intrathoracic sites involved include the anterior mediastinum, particularly right paratracheal, hilar nodes, and the posterior mediastinum. About 70% of affected patients are less than 30 years old, and males are affected more than females (4:1 in the AFIP series), while other authors state that there is no sex preference. Symptomatic patients may complain of dry cough, dyspnea, or recurrent infection due to airway compression.
Lesions may demonstrate slow growth. Histologically, there is extensive capillary proliferation within the affected lymph nodes, and a lymphocyte predominant infiltrate surrounding small germinal centers. The treatment is surgical with a low recurrence rate if the resection is complete. Rare cases have been complicated by the development of vascular neoplasms that resemble Kaposi’s sarcoma, or Hodgkin’s lymphoma.

**Plasma Cell Variant**

In this form there is typically multicentric (thoracic, mesenteric, and retroperitoneal) lymph node involvement (although localized nodal involvement can be found in 10% of cases).

Histologically there are sheets of mature plasma cells within interfollicular tissues that surround normal to large germinal centers and the intense capillary proliferation seen in the hyaline vascular sub-type is absent. Dysregulation of interleukin-6 has been implicated in the pathogenesis of the plasma cell variant of Castleman disease. Affected patients typically have systemic symptoms such as fever, weight loss, moderate anemia, elevated ESR, polyclonal hypergammaglobulinemia, and hypoalbuminemia. Non-Hodgkins lymphoma and Kaposi’s sarcoma occur with increased frequency in patients with the multicentric variant. Patients with multicentric disease tend to be older individuals in their 5th or 6th decade. Treatment combines steroids and chemotherapeutic agents, although no single regimen has been effective in achieving a durable remission. Prognosis is poor with an overall mortality of 50% and a median survival of 26 months. Patients with multicentric disease and an associated neuropathy have an extremely poor prognosis despite treatment with steroids and chemotherapy. The clinical and histopathologic abnormalities associated with multicentric plasma cell variant Castleman’s disease are similar to those found in osteosclerotic myeloma or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein abnormality, and skin abnormalities). These patients often need autologous transplantation as do patients with POEMS.
**Related Disorders**

Symptoms of the following disorders can be similar to those of Castleman's Disease. Comparisons may be useful for a differential diagnosis:

Hodgkin’s Disease is a form of cancer of the lymphatic system. Tumors occur in the lymph nodes and/or the areas around the nodes. Symptoms associated with this disorder may include fever, night sweats, weight loss, and/or enlarged or swollen lymph nodes. The tumors occur most often in the chest, stomach, or spleen. Hodgkin’s Disease is usually progressive and may spread to involve lymph nodes located in other areas of the body. The exact cause of Hodgkin’s Disease is not known. (For more information on this disorder, choose “Hodgkin” as your search term in the Rare Disease Database.)

The following disorders may be associated with Castleman’s Disease as secondary characteristics. They are not necessary for a differential diagnosis:

Malignant Lymphoma is a general term for a group of lymphatic tumors. Malignant lymphomas generally occur in the chest, stomach, or abdomen. Symptoms common to many forms of malignant lymphomas include fevers, excessive sweating at night, weight loss, and/or an abnormally enlarged liver and/or spleen (hepatosplenomegaly).

Kaposi’s Sarcoma is a malignant tumor of the of blood vessels that often occurs in the skin and that may spread to other parts of the body. Affected individuals may have skin lesions (e.g., papules, plaques, etc.) that may grow and come together (coalesce). In some cases, the lesions may reduce in size and number (regress). In addition, on rare occasions these lesions may be painful.
References: Castleman's Disease:


Castleman's Disease Symptoms/Variants:
Frits vanRhee, MD - Castleman’s Disease. ; Classification of Castleman’s Disease.

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