Cancer Association of South Africa (CANSA)

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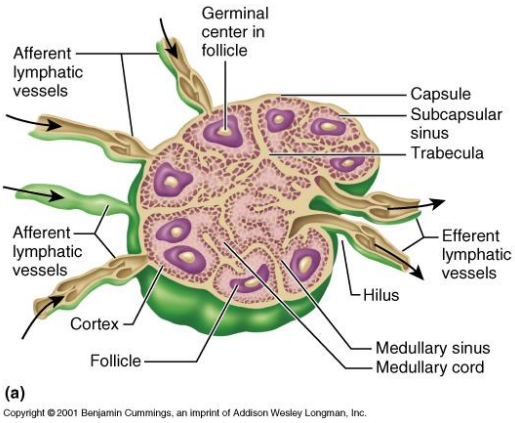
Fact Sheet on Castleman Disease

Introduction

Lymph nodes are a characteristic part of the lymphatic system and these lymph nodes are often located in clusters around the neck, armpit and groin, as well as the inside of the centre of the chest and the abdomen. The lymph nodes function in the synthesis of cells which form part of the immune system that fight against pathogenic infection. The lymph nodes also act as a 'filter', removing cells recognised as foreign due to their different genetic makeup from the lymph fluid.



[Picture Credit: Lymph Node]

According to the presence of bacteria and other pathogenic organisms in the lymph fluid, the number of lymphocytes produced is regulated. This allows for the lymphatic system's response to the infection to depend on the magnitude of the infection. The magnitude of the production of lymphocytes also determines the swelling of the lymph nodes (a higher production would lead to greater swelling). The lymphatic system includes the tonsils, adenoids, spleen and the thymus.

Castleman Disease

Castleman Disease is characterised by a proliferation of cells in the lymphatic system. Castleman's Disease is subdivided into two forms: unicentric Castlemam Disease (CD) and multicentric Castleman Disease (MCD).

Castleman Disease (CD), also known as giant lymph node hyperplasia, lymphoid hamartoma, or angiofollicular lymph node hyperplasia, is a group of uncommon lymphoproliferative disorders that share common lymph node histological features that may be localised to a single lymph node (unicentric) or occur systemically (multicentric). Even though CD is not officially a cancer, one form of this disease (known as *multicentric Castleman Disease*) acts very much like lymphoma. In fact, many people with this disease eventually develop lymphomas. And like lymphoma, CD is often treated with chemotherapy or radiation therapy.

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Benjamin Castleman (born 17 May 1906, died 29 June 1982) was an American physician and pathologist best known for describing Castleman Disease (angiofollicular lymphoid hyperplasia) in the 1950s.

[Picture Credit: Dr Benjamin Castleman]

Dispenzieri, A. & Faigenbaum, D.C. 2020.
"Castleman disease (CD) describes a group of at least 4 disorders that share a spectrum of characteristic histopathological features but have a wide range of etiologies, presentations, treatments, and outcomes. CD includes unicentric CD (UCD) and multicentric CD (MCD), the latter of which is divided into idiopathic MCD (iMCD), human herpes virus-8 (HHV8)-associated MCD (HHV8-MCD), and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD (POEMS-MCD). iMCD can be further subclassified into iMCD-thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly (iMCD-TAFRO) or iMCD-not otherwise specified (iMCD-NOS). Advances in diagnosis, classification, pathogenesis, and therapy are substantial since the original description of UCD by Benjamin Castleman in 1954. The advent of effective retroviral therapy and use of rituximab in HHV8-MCD have improved outcomes in HHV8-MCD. Anti-interleukin-6-directed therapies are highly effective in many iMCD patients, but additional therapies are required for refractory cases. Much of the recent progress has been coordinated by the Castleman Disease Collaborative Network (CDCN), and further progress will be made by continued engagement of physicians, scientists, and patients. Progress can also be facilitated by encouraging patients to self-enroll in the CDCN's ACCELERATE natural history registry (#NCT02817997; www.CDCN.org/ACCELERATE)."

Kim, H.J., Han, J.H., Bang, C.H., Park, K.S., Cho, S.G., Yoo, D.S., Kim, K.M., Park, H.J., Park, Y.M., Lee, J.Y. & Lee, J.H. 2019.
Castleman's disease is a rare disease of the lymph nodes and related tissues, presenting as angiofollicular or giant lymph node hyperplasia. Although various skin manifestations have been reported to occur in Castleman's disease, a comprehensive study of cutaneous disorders in Castleman's disease is lacking. Therefore, the aim of this study was to investigate Castleman's disease-associated cutaneous disorders. The medical records of 57 patients with Castleman's disease who visited our hospitals from January 2007 to May 2018 were analysed retrospectively. Patients were classified according to the presence of skin involvement. Plasma variant-type Castleman's disease and multicentric Castleman's disease were more commonly found in patients with Castleman's disease with a cutaneous disorder than in those without a cutaneous disorder. In addition, the skin disorders were classified according to pathomechanisms: immune complex-related (paraneoplastic pemphigus, xanthogranulomas), cytokine-related (vasculitis-like lesion, cherry angioma, hyperpigmentation), and non-specific (pruritus). This study builds on previous case reports of cutaneous disorders in Castleman's disease and proposes a new classification system.

Sopfe, J., Endres, A., Campbell, K., Hayes, K., Trout, A.T., Liang, X., Lorsbach, R., O'Brien, M.M. & Cost, C.R. 2019.
BACKGROUND: Castleman disease (CD) is an uncommon lymphoproliferative disorder that is rare in pediatric populations; the literature describing this population is sparse. We sought to describe

pediatric CD, including unicentric CD (UCD) and human herpes virus-8 (HHV8)-negative multicentric CD (MCD), in a multi-institutional cohort.
METHODS: We retrospectively reviewed 24 patients, aged 0 to 26 years at diagnosis, who were diagnosed with CD between January 1, 2005, and May 16, 2017, at two tertiary children's hospitals. Demographic and clinical data were collected.
RESULTS: Most patients (75%, 18/24) presented with UCD. All patients with MCD were HHV8-negative. The most common histopathologic variant was hyaline vascular (75%, 18/24). Plasma cell variant occurred in 33% (2/6 [95% confidence intervals (CI), 4-78%]) of patients with HHV8-negative MCD and 17% (3/18 [95% CI, 4-41%]) of patients with UCD. Systemic symptoms were present in 4 of 6 of patients with HHV8-negative MCD and 8 of 18 of patients with UCD. Anemia and laboratory inflammation occurred in both UCD and MCD patients, with nonsignificantly higher rates of anemia and elevated C-reactive protein in MCD patients. All but two UCD patients underwent gross total resection as definitive therapy. Among HHV8-negative MCD patients, a combination of resection, chemotherapy, and immunotherapy was used. No UCD patients and three of six HHV8-negative MCD patients experienced disease progression/relapse prior to lasting remission. There were no deaths.
CONCLUSION: Pediatric patients with CD most commonly have unicentric, hyaline vascular variant disease. Pediatric patients with both UCD and MCD commonly have systemic inflammation and, despite risk of progression/relapse in MCD patients, ultimately have excellent survival.

Synonyms of Castleman Disease (CD)
Synonyms include:

- angiofollicular lymph node hyperplasia
- angiomatous lymphoid
- Castleman tumour
- giant benign lymphoma
- giant lymph node hyperplasia
- hamartoma of the lymphatics

Incidence of Castleman Disease in South Africa
Because Castleman Disease (CD) is not officially a cancerous condition, the National Cancer Registry (2016) does not provide information about its incidence in South Africa.

Possible Complications of Castleman Disease (CD)
People with unicentric Castleman Disease usually do well once the affected lymph node is removed. However, having Castleman Disease may increase one’s risk of lymphoma.

Complications of multicentric Castleman Disease can be life-threatening and may include:

- Infection leading to the failure of multiple organs
- Cancer, such as Lymphoma or Kaposi's sarcoma

The outlook for people with multicentric Castleman Disease (MCD) varies, depending on the nature of their disease. The presence of HIV/AIDS tends to worsen the outcome.

Research also indicates that people who have MCD with POEMS syndrome that does not involve bone lesions may have worse outcomes, while people who have multicentric Castleman disease with the bone lesion variant of POEMS syndrome tend to do better.

POEMS syndrome (also known as Crow–Fukase syndrome, Takatsuki disease, or PEP syndrome) is a rare medical syndrome. It is defined as the combination of a plasma-cell proliferative disorder (typically myeloma), polyneuropathy, with effects on many other organ systems.

Causes of Castleman Disease (CD)

The main feature of Castleman Disease (CD) is an overgrowth of lymphocytes (immune cells) called B cells. The cause of this overgrowth is not certain, but it seems to be related to problems with the way a person's immune system is working. Many people with CD have abnormally high blood levels of certain substances made by immune system cells. For example, in the multicentric form of CD (MCD), the body often makes too much of a protein called interleukin-6 (IL-6). IL-6 normally helps regulate immune function. Too much IL-6 can cause lymphocytes to grow and divide too quickly. But it is not clear what causes the high levels of IL-6.

One cause seems to be infection with human herpesvirus-8 (HHV-8), also known as Kaposi sarcoma herpesvirus (KSHV) (because it can cause Kaposi sarcoma). HHV-8 is often found in the lymph node cells in people who have MCD, especially those who are HIV positive. HHV-8 can cause infected cells to make a form of IL-6, which could explain how it leads to CD.

Many people are infected with HHV-8, but in people with normal immune systems the virus does not seem to cause problems. People infected with HIV, however, often have weakened immune systems, which might allow HHV-8 to grow and cause problems. This could explain why people infected with HIV are more likely to get MCD. Still, some people with HIV who develop MCD do not have weakened immune systems, so it is not clear if this is the only reason.

HHV-8 has not been found in all cases of MCD. And it is not clear what causes the localised (unicentric) form of CD. Researchers are still looking for the causes of CD in these other cases.

Castleman Disease is a rare disorder that affects males and females in equal numbers. All types of CD 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. Persons with HIV are at increased risk of developing multicentric Castleman Disease.

Types of Castleman Disease (CD)

Castleman Disease (CD) is grouped as follows:

Localised (unicentric) Castleman Disease - this is the more common type of Castleman Disease (CD), affecting only a single group of lymph nodes, usually in the chest or abdomen.

Multicentric Castleman Disease - Multicentric Castleman Disease (MCD) affects more than one group of lymph nodes. It can also affect organs that contain lymphoid tissue. This form is often associated with HIV and HHV-8 and results in systemic symptoms, serious infections, fevers, weight loss, fatigue, night sweats, and nerve damage that can cause weakness and numbness. Anaemia and hypergammaglobulinaemia are common. In addition, MCD may transform to Lymphoma.

Multicentric Castleman Disease can be further classified as:

- Multicentric Castleman Disease without POEMS syndrome
- Multicentric Castleman Disease with POEMS syndrome that involves areas of abnormal bone (osteosclerotic lesions)
- Multicentric Castleman Disease with POEMS syndrome without osteosclerotic lesions

Pierson, S.K., Stonestrom, A.J., Shilling, D., Ruth, J., Nabel, C.S., Singh, A., Ren, Y., Stone, K., Li, H., van Rhee, F. & Faigenbaum, D.C. 2018.
"Human Herpesvirus-8 (HHV-8)-negative/idiopathic multicentric Castleman disease (iMCD) is a poorly understood disease involving polyclonal lymphoproliferation with dysmorphic germinal centers, constitutional symptoms, and multi-organ failure. Patients can experience thrombocytopenia, anasarca, reticulin fibrosis, renal dysfunction, organomegaly, and normal immunoglobulin levels, - iMCD-TAFRO. Others experience thrombocytosis, milder effusions, and hypergammaglobulinemia, - iMCD-Not Otherwise Specified (iMCD-NOS). Though the etiology is unknown in both subtypes, iMCD symptoms and disease progression are believed to be driven by a cytokine storm, often including interleukin-6 (IL-6). However, approximately two-thirds of patients do not respond to anti-IL-6 therapy; alternative drivers and signaling pathways are not known for anti-IL-6 nonresponders. To identify potential mediators of iMCD pathogenesis, we quantified 1129 proteins in 13 plasma samples from six iMCD patients during flare and remission. The acute phase reactant NPS-PLA2 was the only significantly increased protein (P = .017); chemokines and complement were significantly enriched pathways. Chemokines represented the greatest proportion of upregulated cytokines, suggesting that iMCD involves a chemokine storm. The chemokine CXCL13, which is essential in homing B cells to germinal centers, was the most upregulated cytokine across all patients (log2 fold-change = 3.22). Expression of CXCL13 was also significantly increased in iMCD lymph node germinal centers compared to controls in a stromal meshwork pattern. We observed distinct proteomic profiles between the two iMCD-TAFRO patients, who both failed anti-IL-6-therapy, and the four iMCD-NOS patients, in whom all three treated with anti-IL-6-therapy responded, suggesting that differing mechanisms may exist. This study reveals proteomic differences between flare and remission and the potential to molecularly define iMCD subgroups."

Signs and Symptoms of Castleman Disease (CD)
Unicentric Castleman Disease - many people with unicentric Castleman Disease (CD) do not notice any signs or symptoms. The diseased lymph node is usually located in the chest, neck or abdomen. When signs and symptoms are present, they may include:

- A feeling of fullness or pressure in the chest or abdomen that can cause difficulty breathing or eating
- An enlarged lump under the skin in the neck, groin or armpit
- Unintended weight loss

- Less commonly, fever, night sweats and weakness

Multicentric Castleman Disease - most people with multicentric Castleman Disease (MCD) experience:
- Fever
- Night sweats
- Fatigue and weakness
- Loss of appetite
- Unintended weight loss
- Enlarged lymph nodes, usually around the neck, collarbone, underarm and groin areas
- Enlarged liver or spleen

Other, less common symptoms include:
- Nerve damage in the hands and feet that leads to numbness (peripheral neuropathy)
- Skin rash

Diagnosis of Castleman Disease (CD)
The diagnosis of Castleman Disease is made by tissue sampling (biopsy) of an affected lymph node. The tissue sample is examined by a pathologist (a physician specialised in the diagnosis of diseases from tissue samples) under a microscope, and additional special tests may be done on the tissue sample. A number of blood tests that evaluate immune function may also be performed, but the diagnosis itself depends upon identifying the abnormal lymph node tissue.

Abrahamson, J.S. 2019.
Castleman disease is a heterogeneous nonmalignant lymphoproliferative disorder. Major distinctions include unicentric versus multicentric presentation; hyaline vascular, plasmacytic, or mixed pathology; and HHV8-associated (typically HIV-positive) versus idiopathic disease. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Dr. Jeremy S. Abramson stated that rituximab is preferred as initial therapy for HHV8-positive disease, and chemotherapy can be added for patients with fulminant disease (antiretrovirals should always be used as well for those who are HIV-positive). Siltuximab is the preferred frontline therapy for idiopathic disease.

Treatment of Castleman Disease (CD)
Treatment for Castleman Disease can involve a combination of different approaches, including:
- Surgery to remove involved lymph nodes
- Medications to reduce the abnormal immune response
- Radiation therapy to destroy areas of affected lymph nodes that cannot be removed surgically

Boutboul, D., Fadlallah, J., Chawki, S., Fieschi, C., Malphettes, M., Dossier, A., Gérard, L., Mordant, P., Meignin, V., Oksenhendler, E. & Galicier. L. 2019. "We retrospectively analysed 71 cases of Unicentric Castleman disease, a rare, usually asymptomatic, benign lymphoproliferative disorder presenting as a unique nodal mass. Although surgery is considered as the gold standard therapy, only 38 patients (54%) underwent initial surgical resection and 95% were cured. An additional 9 patients had surgery after an attempt at medical reduction. Reduction therapy was used in 21 patients with a 55% response rate, but without evidence for an optimal regimen. Radiotherapy was limited to 8

patients because of associated toxicity. Watch and wait was considered in 13 asymptomatic patients and 11 of these remained stable for up to 17 years."

Several different classes of medications have been used to treat Castleman Disease:

- Corticosteroid drugs suppress the immune response. They can be useful in people with immune system disorders and some cancers. These drugs may be given alone, or sometimes in combination with the type of chemotherapy drugs used to treat cancers.
- The following chemotherapy drugs are most often used in Castleman Disease
    - carmustine (BiCNU),
    - cladribine (Leustatin),
    - chlorambucil (Leukeran),
    - cyclosphamide (Cytoxan),
    - doxorubicin (Adriamycin, Rubex),
    - etopside (Vepesid),
    - melphalan (Alkeran),
    - vinblastine, and
    - vincristine (Oncovin).
- Chemotherapy and corticosteroids may also be combined with radiation therapy to destroy the abnormal tissue.
- Immunotherapy involves administering drugs that boost or strengthen the body's natural immune response. Immunotherapy drugs include
    - siltuximab (Sylvant), a monoclonal antibody drug that binds to IL-6.
    - Rituxmab (Rituxan) is a monoclonal antibody often used to treat lymphoma that is also sometimes used to treat Castleman disease.
    - Tocilzumab (Actemra) is an IL-6 receptor antagonist antibody that also has been used.
- Immunomodulating drugs such as thalidomide (Thalomid) and lenalidomide (Revlimid) are used to treat multiple myeloma and some lymphomas, and also can be helpful for some people with Castleman Disease.
- Interferon-alfa (a man-made version of an immune-boosting substance produced by the body) is occasionally used to treat Castleman Disease.
- Anti-viral medications such as ganciclovir, valganciclovir, and foscarnet have been successfully used to treat multicentric Castleman Disease associated with infection with the virus HHV-8.

Kounatidis D, Rontogianni D, Sampaziotis D, Vardaka M, Giatra C, Dolapsakis C, Margellou E, Vallianou NG. 2019.
"Multicentric Castleman Disease (MCD) presents with enlarged lymph nodes in multiple regions and systemic inflammatory symptoms, due to the dysregulation of cytokines, most commonly interleukin-6 (IL-6). Human herpes virus-8 (HHV-8) is strongly related to MCD (HHV-8-associated MCD) and is being implicated in cytokine dysregulation in patients, the majority of whom are HIV positive or immunosuppressed. Preferred treatment of HHV-8-associated MCD depends on the presence or not of concurrent Kaposi sarcoma and on whether the patient has life-threatening organ failure or poor performance status thought to be related to HHV-8-associated MCD. Herein, we describe a female patient with HHV-8 positive, HIV negative MCD, who responded well to the administration of rituximab once weekly for four weeks alone for three cycles."

Zhang, L., Zhao, A.L., Duan, M.H., Li, Z.Y., Cao, X.X., Feng, J., Zhou, D.B., Zhong, D.R., Fajgenbaum, D.C. & Li, J. 2019.
"Idiopathic multicentric Castleman disease (iMCD) is a rare lymphoproliferative disorder. The anti-interleukin 6 (IL-6) therapy siltuximab is not available everywhere, and is not effective for over one-half of patients. Alternative treatment approaches are urgently needed. In the first iMCD clinical trial directed against a target other than IL-6 signaling, we investigated a thalidomide-cyclophosphamide-prednisone (TCP) regimen in newly diagnosed iMCD patients. This single-center, single-arm, phase 2 study enrolled 25 newly diagnosed iMCD patients between June 2015 and June 2018. The TCP regimen (thalidomide 100 mg daily for 2 years; oral cyclophosphamide 300 mg/m^2 weekly for 1 year; prednisone 1 mg/kg twice a week for 1 year) was administered for 2 years or until treatment failure. The primary end point was durable tumor and symptomatic response for at least 24 weeks. Twelve patients (48%) achieved the primary end point with no relapse, 3 patients (12%) demonstrated stable disease, and 10 patients (40%) were evaluated as treatment failure. Even when considering all patients, there were significant ($P < .05$) improvements in median symptom score, IL-6 level, hemoglobin, erythrocyte sedimentation rate, albumin, and immunoglobulin G. Among responders, the median levels of all evaluated parameters significantly improved, to the normal range, after treatment. The regimen was well tolerated. One patient died of pulmonary infection and 1 patient had a grade 3 adverse event (rash); 2 patients died following disease progression. Estimated 1-year progression-free survival and overall survival were 60% and 88%, respectively. The TCP regimen is an effective and safe treatment of newly diagnosed iMCD patients, particularly when siltuximab is unavailable. This trial was registered at www.clinicaltrials.gov as #NCT03043105."

Kapriniotis, K., Lampridis, S., Mitsos, S., Patrini, D., Lawrence, D.R. & Panagiotopoulos, N. 2018.
"Multicentric Castleman disease (MCD) causes an extensive range of systematic symptoms and can be life-threatening if not treated promptly and appropriately. The pathophysiology of the disease remains unclear; however, interleukin 6 (IL-6) pathway and human herpesvirus 8 infection appear to play an important role. As a result, the treatment of MCD remains complex and often insufficient, although a plethora of therapeutic approaches have been used. Between these, biological agents in the form of monoclonal antibodies against specific pathogenic processes of the disease have improved survival rates significantly. In the present study, we review the clinical results of rituximab, which targets B lymphocytes, siltuximab and tocilizumab, which target the IL-6 pathway, bortezomib, which is a selective proteasome inhibitor, and anakinra, which is an interleukin 1 receptor antagonist. The introduction of these biological agents in the treatment of MCD appears to be promising in the first studies performed. However, more clinical trials are required to assess the efficacy and safety of each agent and to form therapeutic strategies that will be widely accepted."

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