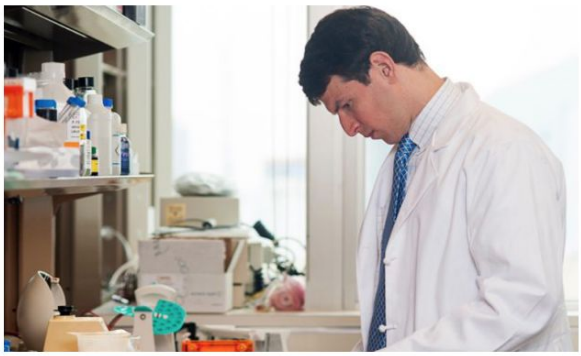



Castleman Disease

A toolkit for the newly diagnosed patient and their loved ones

CDCN
CASTLEMAN DISEASE COLLABORATIVE NETWORK

Contents

A Letter From Dr. David Fajgenbaum, MD, MBA, MSc

Dear Castleman disease patient or loved one,

I wish that you did not need to join this community. I wish that there was not a need to have an international community of patients, loved ones, physicians and researchers through the Castleman Disease Collaborative Network. I wish that this disease wasn't such a mystery to the medical community with so much to learn. But I don't know what I would do if I didn't have this community, because I also have Castleman disease, and the CDCN gives me hope for my future, hope that we can cure this disease, and a family to turn to in my most difficult times. Welcome to the Castleman disease family. We are here for you.

"Welcome to the Castleman disease family. We are here for you."

I was diagnosed with the idiopathic multicentric subtype (iMCD) during my third year of medical school. I spent five months hospitalized in critical condition, had my last rites administered to me when my doctors thought I would not survive, and chemotherapy saved my life though I have relapsed multiple times since then. When I first became sick, there was no international effort to advance research and treatment. There wasn't a community of patients and loved ones. My family and I felt completely alone and we began to lose hope. We're fighting to change that through the CDCN.

Right now, with your new diagnosis, we're here to be a resource to help you in any way that we can with finding a physician, understanding more about Castleman disease, connecting with others who "get it," and learning out how you can contribute to turning our hope for a cure into a reality through research (e.g., contributing samples, raising funds to enable research, joining the international registry, sharing your ideas for important areas of research). This Toolkit will provide information to you about each of these resources and more. I have the incredible honor of working with countless other patients, loved ones, physicians, and researchers who generously devote their time and energy to supporting patients like you and I. Please reach out if there is anything that we can do to help at info@castlemannetwork.org or (610) 304-0696.

Co-Founder & Executive Director, Castleman Disease Collaborative Network

To-Do List

- ☐ Join the CDCN as a patient or loved one (cdcn.org/join)
- ☐ Sign up for email updates on our homepage (cdcn.org) so you can find out about our progress!
- ☐ Make an appointment with a Castleman disease expert. The CDCN's physician referral list will be sent to you after you join the CDCN.
- ☐ Track your abnormal labs (see page 10) so you can monitor your blood for signs of a new flare.
- ☐ Read the articles listed on pages 22-24 and share this list of resources with your physician.
- ☐ Get involved in high-impact research so that we can figure out Castleman disease!
    - o Sign up to donate blood samples to the Castleman disease Biobank, Castlebank
    - o Join the Castleman Warriors as they fight to raise awareness and funds for Castleman disease research! (cdcn.org/get-involved/castleman-warriors)
- ☐ Get connected with other patients and loved ones!
    - o Attend the CDCN's annual Patient and Loved One Summit (https://cdcn.org/annual-events/patient-and-loved-one-summit/)
    - o Join the Castleman Warriors as they fight to raise awareness and funds for Castleman disease research! (https://cdcn.org/patients-loved-ones/become-a-warrior/)
    - o Email Mileva Rapasky (mileva@castlemannetwork.org) to be connected with a Patient and Loved One Ambassador.
    - o Connect with other patients and loved ones on facebook:
        - CDCN Facebook page: https://www.facebook.com/cdcn2/
        - Castleman disease Support Group Facebook page: https://www.facebook.com/groups/403839776489587/
        - International Castleman Disease Organization: https://www.facebook.com/groups/48343887930/
- ☐ Attend, sponsor or donate to the CDCN's annual Quest for a Cure Gala fundraiser! (cdcn.org/quest)
- ☐ Raise funding for CDCN research to help to unlock the mysteries of Castleman disease!
    - o You can donate directly yourself (cdcn.org/donate)
    - o Become a Castelman Warrior, so you have your own fundraising page and a network of patients supporting you (https://cdcn.org/patients-loved-ones/become-a-warrior/).
- ☐ Follow the CDCN
    - o Instagram (@curecastleman)
    - o Twitter (@curecastleman)
    - o YouTube http://www.youtube.com/c/CastlemanDiseaseCollaborativeNetwork

Questions? You can contact us by email (info@castlemannetwork.org) or call 610-304-0696

What is Castleman Disease?

Castleman disease (CD) describes a group of at least four immunologic disorders: unicentric CD, HHV-8-positive multicentric CD, idiopathic multicentric CD, and POEMS-associated multicentric CD. These disorders have a variety of causes, symptoms, and treatments, but are all characterized by a similar set of findings when lymph nodes are examined under the microscope. The immune system's normal response to fighting off an infection is inflammation. In some CD patients, inflammatory cells become hyper-activated and produce excess molecules (called chemokines and cytokines) that can lead to flu-like symptoms, lymph node enlargement, and dysfunction of vital organs including the liver, kidneys, and bone marrow.

CD is a very rare disease, with only an estimated 4,300-5,200 new cases diagnosed in the U.S. per year[1]. If we compare this number to the estimated number of new cases of lung cancer diagnosed in 2018 (approximately 234,030)[2] or to the number of U.S. patients living with diabetes in 2020 (26.9 million)[3] it's easier to understand why most physicians may not have much, or any, experience in treating this disease. CD also does not discriminate – it can occur in patients of any age, gender, or ethnic background.

CD is first subdivided into two broad categories – unicentric CD (UCD) and multicentric CD (MCD) – based on the number of lymph nodes or regions of lymph nodes that show characteristics of CD under a microscope. A patient with a single enlarged lymph node (or single region of enlarged nodes) displaying CD features is diagnosed with unicentric Castleman disease (UCD). A patient with enlarged nodes in multiple regions of the body with the same CD features, along with the symptoms and laboratory test results common to MCD, is diagnosed with multicentric Castleman disease (MCD). The characteristic features (see page 9) of a CD lymph node must be identified by a pathologist.

Further, there are three subtypes of MCD: HHV-8 associated MCD, idiopathic MCD, and POEMS-associated MCD. If an MCD patient's lymph node or blood sample is found to be infected with human herpesvirus-8 (HHV-8), he/she is diagnosed with HHV-8-associated MCD. While many of these patients are HIV-positive, HIV-negative individuals may be diagnosed with HHV-8-associated MCD as well.

If an MCD patient is HIV-negative and his/her lymph nodes and blood sample are HHV-8-negative, he/she may have HHV-8-negative or idiopathic MCD (iMCD). See pages 10 -11 for information on the clinical features, laboratory abnormalities, and diseases that must be excluded in order to diagnose iMCD. Some patients with iMCD experience a specific set of clinical symptoms that are described as the TAFRO subtype of iMCD. TAFRO stands for Thrombocytopenia (low platelet count), Anasarca (ascites, swelling), Fever (elevated body temperature), Reticulin fibrosis (evaluated in bone marrow biopsy), and Organomegaly (lymphadenopathy and/or hepatomegaly/splenomegaly). The largest published study of TAFRO can be found here: http://onlinelibrary.wiley.com/doi/10.1002/ajh.24242/full. Patients with iMCD who do not have TAFRO features are said to have iMCD-not otherwise specified (iMCD-NOS).

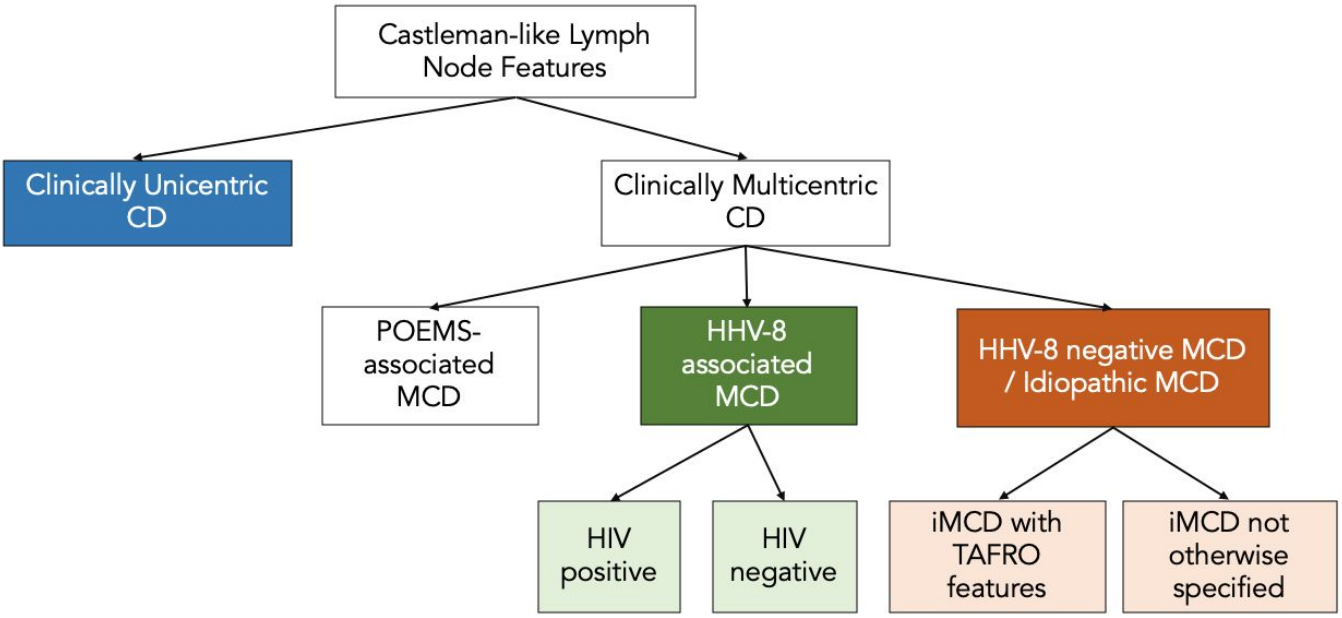
POEMS-MCD is a type of MCD that has only recently been recognized as a separate entity. POEMS-MCD is diagnosed in patients with HHV-8 negative MCD who are simultaneously diagnosed with POEMS syndrome. POEMS is a paraneoplastic syndrome, most commonly associated with osteosclerotic myeloma, that is caused by disordered plasma cells. Its characteristic symptoms include Peripheral neuropathy (damage to peripheral nerves), Organomegaly (hepatosplenomegaly), Endocrinopathy (diseases of the endocrine glands), Monoclonal gammopathy (blood samples contain abnormal monoclonal protein, called

[1] Munshi, N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of claims database to characterize and estimate the incidence rate for Castleman disease. *Leuk Lymphoma.* Published online September 29, 2014; doi: 10.3109/10428194.2014.953145
[2] LA Website: http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/lung-cancer/resource-library/lung-cancer-fact-sheet.html
[3] CDC website: https://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm

M protein), and Skin changes. Researchers believe that the disordered plasma cells that cause POEMS also cause MCD.

Symptom severity differs greatly among CD patients and can range from relatively asymptomatic to life-threatening multi-organ failure (e.g., kidney, liver, bone marrow, heart, lung failure). It is very important to understand the subtype of CD that you have, because each subtype requires different treatment approaches.

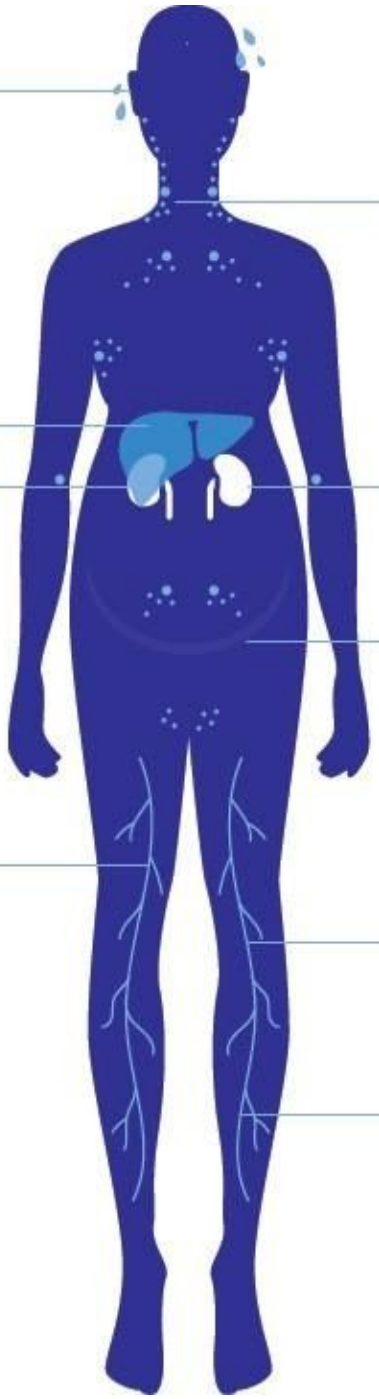
Subtypes of Castleman Disease



Comparison of the Subtypes of Castleman Disease

	Unicentric CD (UCD)	HHV-8-Associated Multicentric CD (HHV-8+ MCD)	Idiopathic Multicentric CD (iMCD)
% of Cases	50%	25%	25%
Regions Affected	Enlarged lymph node in one region	Multiple regions of enlarged lymph nodes	Multiple regions of enlarged nodes
Common Age of Diagnosis	Mostly children and young adults, but can occur at any age	Mostly adults 40-60 years old, but can occur at any age	Mostly adults 40-60 years old, but can occur at any age
Gender	Slightly more common in females	More common in males	Slightly more common in males
Symptoms	Usually has no symptoms, but there can be discomfort associated with an enlarged lymph node and occasionally "Multicentric CD-like symptoms"	Wide range from mild flu-like symptoms to severe episodes of sepsis-like, life-threatening organ failure and death	Wide range, from mild flu-like symptoms to severe episodes of sepsis-like life-threatening organ failure and death
Causes	The cause of the disease is unknown	HHV-8 triggers the disease, and patients are often already immunocompromised (e.g., from HIV or immunosuppressant medications)	Typically involves anti-IL-6 therapy (e.g., siltuximab approved in US, EU, and Canada; tocilizumab approved in Japan), with or without chemotherapy (e.g., cyclophosphamide, etoposide, rituximab)
Treatment	Surgery. UCD patients with paraneoplastic pemphigus need additional treatments	Can be controlled with B cell depletion therapy (rituximab), but cytotoxic chemotherapy is sometimes also needed	Common, but varies depending on treatment used
Chance of Relapse	Rare	With close monitoring, less common than iMCD	Common, but varies depending on treatment used
Cure	With surgical removal of the affected lymph node, most symptoms go away and there have been no reported cases of UCD transforming into MCD	None yet. We need your help to find it!	None yet. We need your help to find it!
5-Year Survival Rate	95% - 1 in 20 patients die. Most UCD deaths are in patients who are also diagnosed with paraneoplastic pemphigus or a blood cancer.	65% - 1 in 3 patients with MCD die within 5 years (study did not separate into HHV-8- positive or negative), but new data shows a 90% 5-year survival rate for HHV-8 positive MCD patients treated with rituximab.	65% - 1 in 3 patients with MCD die within 5 years (study did not separate into HHV-8- positive or negative)

iMCD Signs and Symptoms



FLU-LIKE SYMPTOMS
Experience fevers, night sweats, fatigue, and weight loss

LYMPH NODE
- Enlargement of lymph nodes in multiple regions is seen in MCD
- Enlargement of lymph nodes in only one region is seen in UCD

ELEVATED C-REACTIVE PROTEIN LEVELS
The best marker of this disease

LIVER DYSFUNCTION
Can present with an enlarged liver, low albumin, fluid accumulation

KIDNEY DYSFUNCTION
Can contribute to low albumin, is reflected by elevated creatinine

FLUID ACCUMULATION
Low albumin levels cause edema, pleural effusions, and ascites (fluid in belly)

VERY LOW PLATELETS OR HIGH PLATELETS
Tiny blood cells that help your body form clots to stop bleeding

ANEMIA
Low red blood cells or low hemoglobin

HYPERGAMMAGLOBULINEMIA
Elevated antibodies in the blood

Diagnosis of Castleman Disease

Because Castleman disease is very uncommon and can vary in the way it manifests, it can take anywhere from a few days to many years to diagnose CD. Additionally, CD symptoms can be similar to those of other conditions so multiple tests must be conducted in order to rule out other possibilities.

Regardless of the subtype, all patients require an excisional lymph node biopsy as the first step in diagnosis. This involves surgically removing the enlarged lymph node(s). A pathologist examines the structure of the lymph node tissue under a microscope and determines whether it possesses histological features that are consistent with CD, called "Castleman-like features."

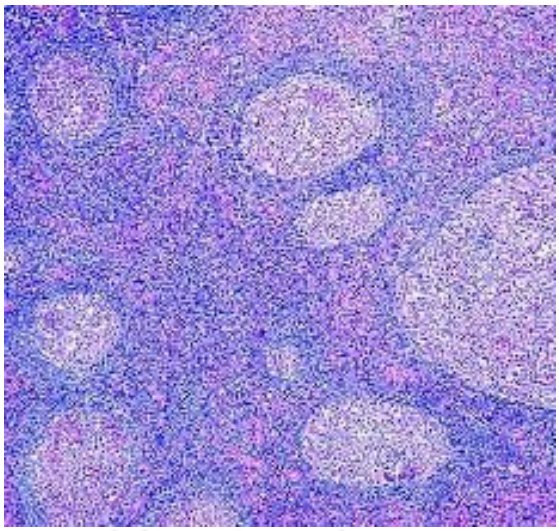


*Figure SEQ Figure * ARABIC 1: Microscopic structure of a lymph node*

The histological features of CD include "atrophic germinal centers," "widened mantle zones," "increased vascularity," "follicular dendritic cell prominence," and "increased plasma cells." Each of these features can be seen in normal lymph nodes and in lymph nodes belonging to individuals with other diseases; it is the constellation of multiple features combined with suggestive lab work that leads to a CD diagnosis.

After the lymph node is surgically removed and examined under a microscope, you will be assessed for how many regions of enlarged lymph nodes you have (1 region: unicentric or >1 region: multicentric). If multicentric, the next step is to be tested for HHV-8. If HHV-8-negative, the next step is to be evaluated for the TAFRO clinical subtype (see page 6). Publication of the first-ever international diagnostic criteria for HHV-8-negative/idiopathic MCD in January 2017 (see page 10-11) has helped to shorten the time until diagnosis for iMCD patients. Formal criteria for diagnosing UCD and HHV-8-associated MCD have not yet been established.

Following diagnosis, there are different types of doctors who may be involved in your care, including primary care physicians (PCP), surgeons, hematologist-oncologists, rheumatologists, immunologists, and infectious disease doctors, among others.

Disclaimer: *These are the technical criteria that need to be met to be given the diagnosis of HHV-8-negative/idiopathic MCD (iMCD). While the terminology may be confusing, we are providing it here so that you may review it with your or your loved one's physician. You can also find the complete article at:* http://www.bloodjournal.org/content/129/12/1646.long

Diagnostic Criteria for HHV-8-negative/ idiopathic MCD

Major Diagnostic Criteria (need both present to diagnose)

1. Histopathological lymph node features consistent with the idiopathic MCD spectrum include (need Grade 2-3 for either regressive germinal centers or plasmacytosis at minimum):
    1. Regressive/atrophic/atretic germinal centers, often with expanded mantle zones composed of concentric rings of lymphocytes in an 'onion skinning' appearance
    2. Follicular dendritic cell prominence
    3. Vascularity, often with prominent endothelium in the interfollicular space and vessels penetrating into the germinal centers with a 'lollipop appearance'
    4. Sheet-like, polytypic plasmacytosis in the interfollicular space
    5. Hyperplastic germinal centers
2. Enlarged lymph nodes (>1cm in short-axis diameter) in two or more lymph node stations

Minor Criteria (need at least 2 out of 11 criteria with at least 1 laboratory criterion)

Laboratory

1. Elevated CRP (greater than 10mg/L) or ESR (greater than 15mm/hr)
2. Anemia (hemoglobin less than 12.5g/dL for males, hemoglobin less than 11.5g/dL for females)
3. Thrombocytopenia (platelet count less than 150k/μL) or thrombocytosis (platelet count greater than 400k/μL)
4. Hypoalbuminemia (albumin less than 3.5g/dL)
5. Renal dysfunction (eGFR <60 mL/min/1.73m2) or proteinuria (total protein >150mg/100ml)
6. Polyclonal hypergammaglobulinemia (total gamma globulin or immunoglobulin G >1700mg/dL

Clinical

1. Constitutional symptoms: night sweats, fever (>38°C), weight loss, or fatigue (>2 CTCAE lymphoma score for B-symptoms)
2. Large spleen and/or liver
3. Fluid accumulation: edema, anasarca, ascites, or pleural effusion
4. Eruptive cherry hemangiomatosis or violaceous papules
5. Lymphocytic interstitial pneumonitis

Exclusion Criteria: In addition to the above criteria, the diagnosis requires that the following be excluded to rule out other conditions that mimic idiopathic MCD:

Infection Related Disorders:

1. HHV-8 (infection can be documented by blood PCR, diagnosis of HHV-8-associated MCD requires positive LANA-1 staining by IHC, which excludes idiopathic MCD)
2. Clinical EBV-lymphoproliferative disorders such as infectious mononucleosis or chronic active EBV (Detectable EBV viral load not necessarily exclusionary)
3. Inflammation and adenopathy due to other uncontrolled infections, e.g. acute or uncontrolled CMV, toxoplasmosis, HIV, active tuberculosis

Autoimmune/autoinflammatory diseases (requires full clinical criteria; detection of autoimmune antibodies alone is not exclusionary):

1. Systemic lupus erythematosus

2. Rheumatoid arthritis
3. Adult-onset Still disease
4. Juvenile idiopathic arthritis
5. Autoimmune lymphoproliferative syndrome (ALPS)

Malignant/lymphoproliferative disorders (these disorders must be diagnosed before or at the same time as idiopathic MCD to be exclusionary):

1. Lymphoma (Hodgkin and non-Hodgkin)
2. Multiple myeloma
3. Primary lymph node plasmacytoma
4. Follicular dendritic cell sarcoma
5. POEMS syndrome

Questions to Ask Your Doctor About Your Diagnosis

‣ Which type of Castleman disease (CD) do I have?
First, you will need to determine your initial diagnosis - UCD or MCD. If you are diagnosed with MCD, ask whether you have HHV-8-associated or HHV-8-negative/idiopathic MCD (iMCD). If you have HHV-8-negative/idiopathic MCD (iMCD), ask whether you have features of TAFRO syndrome (see page 5). Answers to these questions will help you and your physician determine the best treatment approach for your subtype.

‣ What testing do I need to confirm my diagnosis or determine the subtype?
You will need an excisional lymph node biopsy and comprehensive blood work to confirm a diagnosis of CD. You may also need imaging of your body (CT scans, PET scans, MRI). If you have MCD, you should additionally be tested for HIV and human herpesvirus-8 (HHV-8), which can be done through blood work or staining of your lymph node. Physicians will also need to conduct tests to exclude diseases that cause symptoms similar to CD. You can refer to the Diagnosis of CD and Diagnostic Criteria (page 10-11) sections to see a list of the tests that should be done, and review these sections with your doctor.

‣ Have you treated patients with CD before?
Patients often see their primary care physician (PCPs) for first evaluation of their symptoms or present to a hospital for evaluation. PCPs sometimes refer patients to other physicians for diagnostic evaluation. A surgeon will biopsy, or surgically remove, your enlarged lymph node. It will then be sent to a pathologist for testing. You will likely never meet the pathologist, but they are also a vital part of your diagnostic process. Many providers will not have treated CD patients before, so after a diagnosis of CD is suspected or confirmed, you may need to be referred to a specialist. These specialists include hematologists/oncologists, rheumatologists, or infectious disease doctors.

If you need help finding a physician with experience treating CD, the CDCN can provide you with a list of experts from around the world. If your physician is interested in obtaining more information, please suggest they join the CDCN as a physician by visiting: https://cdcn.org/physicians-researchers

‣ What can I expect as follow-up for my disease?
Frequency of follow-up visits and types of disease monitoring will vary according to diagnosis, disease subtype, and symptom severity.

‣ What are my abnormal lab tests?
Because CD is rare, the CDCN encourages all of our patients to track their lab values – specifically the abnormal ones – when they were/are sick. These can vary greatly between patients. A good place to start is to look at the Diagnostic Criteria for HHV-8-negative MCD (see page 10) to determine which lab tests on that list were/are abnormal for you. Tracking these values for trends may help you to identify when you are experiencing a flare and whether or not your treatment is working.

‣ What do you typically recommend for treatment of my specific subtype of CD?
Treatment varies greatly between UCD, HHV-8-associated MCD, iMCD, and POEMS-associated MCD. See page 15 for a list of treatment approaches that are generally considered by treating physicians.

FAQs

‣ What causes CD?

Data suggest that UCD is caused by proliferation of an abnormal group of follicular dendritic cells. These cells have genetic mutations that confer survival and proliferation advantages. This causes the affected lymph node to become enlarged, leading to the compressive symptoms often associated with UCD.

HHV-8-associated MCD is caused by an infection with HHV-8 (human herpesvirus-8). Many patients with HHV-8-associated MCD have immune systems that have been significantly suppressed by HIV or another cause (i.e. a genetic disorder, an immunosuppressive medication). The virus initiates and drives the production of molecules that lead to symptoms of MCD.

Far less is known about the causes of HHV-8-negative/iMCD and POEMS-MCD. Interleukin-6 (IL-6; an inflammatory cytokine) is a disease driver in many cases of iMCD, which explains why IL-6-inhibiting medications are so effective in treating these patients. The cause of increased IL-6 and other inflammatory cytokines are unknown. In patients whose iMCD does not respond well to IL-6 inhibitors, alternative inflammatory molecules are likely involved.

Data suggests that abnormal plasma cells are drivers of POEMS-MCD, and inflammatory molecules like vascular endothelial growth factor (VEGF) and interleukin-12 play a role in this disease.

‣ What are some of the possible causes of HHV-8-negative or idiopathic MCD (iMCD)?

Four hypotheses have been proposed as potential causes of iMCD and are currently under intense investigation:

1. Autoimmune hypothesis: There may be antibodies directed against healthy tissue in the patient that stimulate the immune system to be overactive thus causing the release of inflammatory molecules or "cytokines" that lead to iMCD symptoms.
2. Autoinflammatory hypothesis: There may be a genetic defect in the ability to turn off the immune system, which leads to hyper-activity.
3. Paraneoplastic syndrome hypothesis: There may be acquired oncogenic ("cancer-causing") mutations that cause cytokines to be secreted by either cells within CD lymph nodes or from cells associated with a simultaneously-present cancer.
4. Pathogen hypothesis: There may be an undiscovered pathogen (i.e. a virus other than HHV-8) that is causing uncontrolled immune activation and cytokine release similar to the way that HHV-8 does in HHV-8-associated MCD.

‣ What are the risk factors for developing CD?

Very little is known about the risk factors for this disease. To date, no risk factors for UCD or HHV-8-negative MCD (iMCD) have been identified, though the possibility of a genetic predisposition is being investigated. Risk factors for HHV-8-associated MCD include anything that significantly suppresses the immune system therefore predisposing individuals to uncontrolled HHV-8 infection (HIV, genetic disorders, immunosuppressive medications, and organ transplantation).

‣ How prevalent is CD?

Estimates suggest the incidence of UCD, HHV-8-associated MCD, and iMCD combined to be approximately 4,300 to 5,200 new cases diagnosed in the U.S. per year. MCD is estimated to account for one in three CD cases, with about one-third of those being HHV-8- associated MCD and two-thirds being HHV-8-negative MCD (iMCD).

‣ What is the risk of recurrence?

- UCD: The risk of recurrence of UCD is rare after a lymph node has been successfully removed by surgery. However, there have been rare cases of patients with UCD who develop a recurrence in the same or a different region. Sometimes it can be confusing to distinguish whether a patient is having a UCD recurrence or if they were misdiagnosed with UCD and actually have MCD. See FAQs below for more details on UCD recurrences.
- HHV-8-associated MCD and iMCD: Recurrence with both forms of MCD is common and unpredictable.

What are the demographics of CD?

CD can occur in males and females of any age, including young children. UCD is more common in 20-30 year-olds, and HHV-8-associated MCD and iMCD are more common in 40-60 year-olds. UCD is slightly more common in females, while HHV-8-associated MCD and iMCD are slightly more common in males.

Is CD a form of cancer (neoplastic process)?

Data suggest that UCD is likely a neoplastic process caused by abnormal proliferation of follicular dendritic cells. These cells have been found to possess mutations that confer proliferation and survival advantages. Patients with HHV-8-associated MCD and iMCD sometimes have signs and symptoms that are difficult to distinguish from an aggressive lymphoma. There are also a number of case reports of CD patients being subsequently diagnosed with a hematologic malignancy. Further research is needed to better understand the relationship between iMCD and these malignancies.

What is the relationship between HHV-8-negative/idiopathic MCD and cancer risk?

Hematologic malignancies are diagnosed at an increased frequency within two years of idiopathic MCD diagnosis. The exact reason for this increased risk is not known. We suggest that a search for an underlying malignancy be conducted in all newly diagnosed HHV-8-negative MCD (iMCD) patients. Further research is needed to better understand the relationship between HHV-8-negative MCD (iMCD) and malignancies.

What are the symptoms of CD?

Symptoms depend on the subtype of CD.

- UCD: Patients often have no symptoms except for discomfort associated with the enlarged lymph node pushing on nearby structures. Some patients can demonstrate iMCD-like symptoms. Other UCD patients can go on to develop paraneoplastic pemphigus, which is a very serious disorder requiring prompt treatment.
- iMCD and HHV-8-associated MCD: Patients with iMCD or HHV-8-associated MCD can present with a wide range of symptoms from mild flu-like episodes to severe, life-threatening multi-organ failure.

Some of the systemic symptoms of MCD include:

- Fever and night sweats
- Fatigue
- Loss of appetite
- Cachexia (weakness and wasting of the body, muscle atrophy, unintended weight loss)
- Nausea and vomiting
- Numbness in the hands and feet
- Enlarged liver and/or spleen
- Eruption of cherry hemangiomas (cherry red papules that form from an abnormal growth of blood vessels on the skin)
- Edema (swelling), ascites (fluid accumulation in the abdomen), and/or other symptoms of fluid overload (extensive fluid accumulation, if present, may results in a net weight gain despite cachexia)
- Decreased urine output and systemic toxicity due to kidney failure
- Bruising, easy bleeding, and risk of infection due to bone marrow failure

‣ What abnormal laboratory values are typically seen in CD?

- UCD: Most UCD patients do not have abnormal blood test results, but some may see similar changes to those seen in iMCD (below).
- iMCD and HHV-8-associated MCD: Individuals will often demonstrate several abnormal blood test results listed in the Diagnostic Criteria for iMCD (see page 6). Patients with the TAFRO subtype of iMCD may have a low platelet count (Thrombocytopenia), swelling in their abdomen and extremities due to fluid accumulation (Anasarca), excessive reticulin staining on bone marrow biopsy (Fibrosis), kidney (Renal) failure, and/or an enlarged liver and/or spleen (Organomegaly) in addition to other symptoms of HHV-8-negative (iMCD). Other iMCD patients often have elevated platelet counts, less severe fluid accumulation, and elevated gamma globulin levels.

‣ What lymph node changes are seen in CD?

CD lymph nodes demonstrate several characteristics upon review of the biopsy specimen under the microscope, which can be divided into one of three variants:

1. Hyaline-Vascular or Hypervascular (HV): characterized by widened mantle zones composed of concentric rings of small lymphocytes in an "onion skin" pattern around small atrophic germinal centers, capsular fibrosis with broad fibrous bands throughout the lymph node, an increased number of lymphoid follicles, penetrating hyalinized vessels and dysplastic follicular dendritic cells (FDCs). Most commonly seen in UCD.
2. Plasma Cell (PC): the germinal centers are hyperplastic rather than atrophic, the interfollicular region contains sheets of plasma cells and vascular proliferations, the FDC network is normal, and there is preserved lymph node architecture.
3. Mixed: Displays features of both the HV and PC variants.

The reliability and significance of these histopathological variants is unclear, as there are reports of transitions between HV and PC variants on subsequent biopsies as well as the simultaneous presence of both types in separate lymph nodes within the same patient. Also, these same features can be seen in other diseases that behave similarly to CD.

‣ What are the treatment options for CD?

- UCD: Surgical removal of the enlarged lymph node is the first line of therapy against UCD. If removal is not possible or curative, the below iMCD treatments may also be used to treat UCD.
- HHV-8-associated MCD: Treatment of HHV-8-associated MCD with rituximab to deplete B cells is highly effective. If patients relapse, additional administration of rituximab is often effective to induce a subsequent remission. Occasionally, additional treatments, such as cytotoxic chemotherapies are needed. If the patient is HIV positive, then antiretroviral therapy to control the HIV infection is very important.
- POEMS-MCD: The first-line treatment of POEMS-MCD depends on the presence of bone lesions (regions of bone tissue damage). If bone lesions are present, patients may be treated with standard myeloma therapy (high dose chemotherapy and autologous stem cell transplant (ASCT)). If there are no bone lesions present, the treatment regimen for iMCD (siltuximab, rituximab) may be considered, but data is limited.
- iMCD: Treatment should begin with siltuximab, the only FDA-approved therapy for iMCD. This drug targets interleukin-6, a big contributor to the inflammatory response in some Castleman patients. This drug is well tolerated and highly effective in approximately one-third to one-half of iMCD patients. Administration is life-long based on what is currently known about the drug and the disease.

  For patients that do not improve with siltuximab, the following classes of therapies may be considered:

  - Conventional anti-inflammatory (i.e. corticosteroids) and immunosuppressive therapy (i.e. sirolimus, cyclosporine, rituximab): Corticosteroids can improve symptoms during acute exacerbations of iMCD, but most patients relapse when they are tapered. Sirolimus, which suppresses immune cell proliferation and activation, has been used successfully in iMCD

patients not responding to siltuximab. Cyclosporine, which decreases the growth and activity of T cells, is being used more frequently as some physicians are treating MCD more like a systemic inflammatory disease. Rituximab, which eliminates B-cells, is effective in most cases of HHV-8-associated MCD and some cases of iMCD but typically does not provide long- term disease control in iMCD.

- Chemotherapy: Chemotherapy regimens that have traditionally been used to treat lymphomas (i.e. cyclophosphamide, doxorubicin, vincristine, and prednisone a.k.a. CHOP, or cyclophosphamide, etoposide, rituximab) have also shown to be effective in the most severely ill iMCD patients by eliminating a large portion of their inflammatory cells. However, relapses are common and the side effects are significant.
- Alternative anti-IL-6 therapy (tocilizumab): Tocilizumab targets interleukin-6 receptor, so it is occasionally used in place of or following siltuximab therapy. It has been approved to treat iMCD in Japan. Like siltuximab, tocilizumab generally requires life-long administration and is not effective in all patients.
- Therapies targeting other cytokines and inflammatory cell pathways: Recently, therapeutic approaches targeting new inflammatory cell pathways related to iMCD have been reported. These potential treatment options need to be further explored, particularly for patients who do not respond to anti-IL-6 therapy. Bortezomib, thalidomide, and anakinra are other drugs that have been used.

To learn more about specific treatments, please visit
https://cdcn.org/physicians-researchers/imcd-treatment-targets/

‣ How will this affect my life expectancy?

It is impossible to know how this diagnosis with affect your life expectancy, but based on large studies of hundreds of patients the following generalizations can be made:

- UCD: UCD does not usually affect one's life expectancy (>95% will survive for at least 5 years after diagnosis). However, there are UCD patients that develop paraneoplastic pemphigus, lymphomas, or sarcomas, which can be fatal.
- HHV-8-associated MCD: Approximately 90% of individuals diagnosed with HHV-8-associated MCD will survive for at least 5 years after diagnosis if appropriately treated with B cell depleting therapy (rituximab).
- iMCD: Approximately 55-75% of individuals diagnosed with iMCD will survive for at least 5 years after diagnosis. With the advent of therapies, such as siltuximab, which became the first FDA-approved therapy for iMCD in 2014, we expect to see survival rates improve.

‣ Is it safe for me to get pregnant?

To date, no studies have been done on this important question, so we can't provide a definitive answer. This is one of several areas that we're actively researching through our ACCELERATE Registry www.cdcn.org/accelerate

‣ What is the CDCN doing to combat CD?

A major reason that CD patients may die from their disease is that it is so poorly understood by the medical community. We're here to change that. The CDCN was developed in August 2012 by a group of physicians and researchers who are dedicated to finding a cure for Castleman disease and supporting patients along the way.

So far we have:

- Connected the global community of 500+ physicians and researchers through the three largest-ever Castleman disease research meetings and an online discussion board

- Assembled a Scientific Advisory Board of 32 experts from eight countries
- Engaged with patients on the Scientific Advisory Board, Leadership Team, and all research meetings, as well as through an annual patient summit, online discussion board, physician referrals, and educational materials
- Established the current state of medical knowledge for Castleman disease through an article published in the top hematology journal, *Blood*
- Worked with the research community to determine high-priority research projects for the International Research Agenda (IRA). Seventeen of these studies are currently underway and others are waiting for enough funds to be raised to enable them.
- Established the first-ever Diagnostic Criteria for idiopathic MCD

▸ How can I help accelerate finding a cure for CD?

- Join the *Patient and Loved Ones* database here:https://cdcn.org/patients-loved-ones/patient-login/
- Join the *ACCELERATE registry* here: https://cdcn.pulseinfoframe.com/portal/register
- Donate samples to research! Express your interest here: https://cdcn.org/samples-2/
- Donate funding to research: https://cdcn.org/join-the-fight/donate/

▸ What happens if I have the opportunity to contribute my samples for research?

We will speak with you by phone and then send you a kit by mail with two sets of tubes and instructions for how to fill them.

One set of the tubes is meant for your next scheduled draw.
The other set is to be filled in the event you have a flare up of your disease—if you get sick again after a period of remission.

Castleman Disease in Pediatric Patients

Castleman disease is rare in the pediatric population. The disease appears to be the same as that found in adult patients, but more research is needed. Please refer to the Castleman Disease section (page 5) for more specific information regarding the disease pathophysiology.

Pediatric patients with Unicentric Castleman Disease (UCD):

- UCD is more frequently found in children and adolescents than adults and may affect females slightly more than males[4]
- UCD symptoms in children are generally similar to those experienced by adults with UCD.
- Treatment is also the same for pediatric patients with UCD. In UCD patients, surgical removal of the enlarged lymph node is usually curative. If surgery is not possible, this is considered unresectable UCD. These patients may require treatments used for HHV-8-negative MCD (iMCD).
- Complications of UCD can include paraneoplastic pemphigus or POEMS syndrome and associated malignancies have been reported.

Pediatric patients with idiopathic Multicentric Castleman Disease (iMCD) and HHV-8-associated MCD:

- iMCD is less common in children, but approximately 20% of published cases affect individuals 18 years or age or younger. If a pediatric patient is diagnosed with iMCD, it is important that they are tested for HHV-8 infection. If they are positive for HHV-8, they have HHV-8-associated MCD. If they are negative for HHV-8 infection, they have HHV-8-negative (idiopathic) MCD (iMCD).
- Please see description of signs, symptoms and treatments for iMCD and HHV-8-associated MCD above as these are the same for pediatric and adult MCD patients.

Support for the newly diagnosed pediatric patient and their caregivers:
It is very scary when your child is diagnosed with a rare disease. We recommend connecting with other caregivers of pediatric CD patients. To do so, please email Mileva Repasky (mileva@castlemannetwork.org), she is the mother of one of our youngest CD patients, and can also connect you with our CastleKid families.

The CDCN can also help to connect you with pediatric specialists that are experts in treating Castleman disease to ensure that your child receives the best care possible.

[4] Farruggia, P. et al. "Castleman's disease in childhood: report of three cases and review of the literature" Italian Journal of Pediatrics. 2011.

How Can I Get Involved in the Fight Against CD?

Get involved in high-impact research that will help us to figure out CD!

1. Join the ACCELERATE Registry! https://cdcn.org/patients-loved-ones/join-the-registry/

The ACCELERATE Registry collects medical and patient reported information about CD in order to better study the disease. If you are a patient or a family member of a deceased patient with CD, you may be eligible to participate. Participation will require a pathology report that suggests Castleman disease.

What is the registry process?

First, go to the ACCELERATE website at https://cdcn.org/patients-loved-ones/join-the-registry/ It will take you about 15-20 minutes to register. You will be directed to an online portal to answer a few questions about your eligibility to participate. If you are eligible, you will be asked to read and complete an informed consent form that will further explain the study. You will then be directed to additional online questionnaires that will ask you questions about your contact information, demographic information, diagnosis, family history, hospitalizations, and physicians that you have seen for CD. You will also be asked to upload a pathology report suggesting "Castleman disease," but it is not required. Uploading the report will greatly increase the speed with which we can confirm your enrollment in the study. If you were able to upload a copy of your pathology report, we will quickly confirm your enrollment in the study. Otherwise, we will need to seek a copy from your physician. After you have completed all of the forms, your information will be directed to us and we will begin requesting your medical records.

Once your enrollment is confirmed, you will be sent an email every three months asking you to complete a few brief questionnaires (2-4 minutes) about how you've been doing, your recent medications, and your recent hospital and clinic visits. Because it is important that we obtain accurate information, we may also ask you to review and confirm certain information about your medical history. We will continue to seek your medical records in order to better understand your experience with Castleman disease. If at any point during the study you have questions about your participation, we encourage you to reach out to Sheila at 215-349-5713.

2. Donate samples to CD research!

Sample donation is important for the future of research on rare and poorly understood diseases like Castleman disease. Because CD is a rare disease, it is difficult for researchers to come across CD samples to test for research. By donating a blood sample or a previously removed lymph node sample, you can be a part of this fight to unlock the mysteries surrounding Castleman disease. Each sample is precious and is used in the best way possible. With information learned through research of samples, a cure for a currently incurable disease is possible. Please fill out the Sample Donation Interest Survey (cdcn.org/samples) to express interest in donating samples to CD research. We will contact you when we are prepared to coordinate the collection of your sample.

3. Donate funding to CD research!

CDCN research is not possible without donations from patients and their loved ones to cover the costs of this important work. You can donate directly yourself (cdcn.org/donate) or become a Castleman Warrior (see page 20), so you have your own fundraising page and a network of patients supporting you (https://cdcn.org/patients-loved-ones/become-a-warrior/).

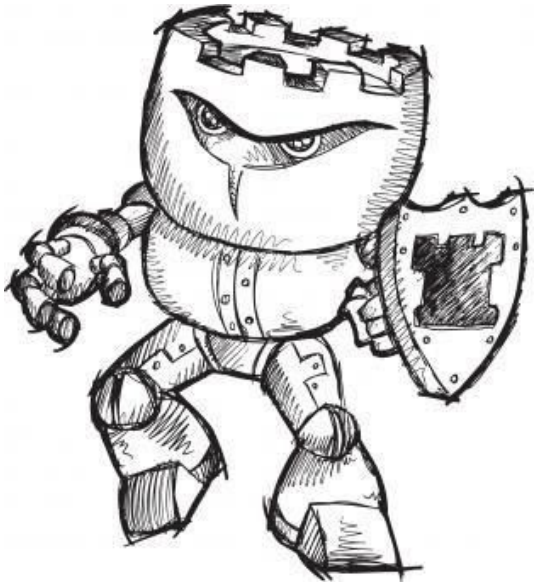
Castleman Warrior Program

This program was designed as a way to unite patients and loved ones together in their ability to raise awareness and funds for the CDCN.

As a warrior you have the ability to work together with other members of the team to host fundraising events, raise awareness in the community, participate in monthly warrior team calls, and have your own personalized warrior page.

The warrior team continues to grow and successfully raised enough money to fund a research study. Becoming a part of this warrior family gives you a voice and helps you fight back against this disease.

Consider joining the fight and become a warrior today:
To join: https://cdcn.org/patients-loved-ones/become-a-warrior/
Check out some of our current Warriors: https://cdcn.org/castleman-warriors/



Additional Resources

Castleman Disease Collaborative Network (CDCN): www.cdcn.org
The CDCN is dedicated to accelerating research and therapy for Castleman Disease through global collaboration, funding high-impact research grants, and patient engagement. Membership consists of physicians, researchers, patients, and patient advocates from around the world. Affiliated websites include:

- CDCN Facebook: https://www.facebook.com/cdcn2/
- CDCN Instagram: @curecastleman
- CDCN Twitter: @CureCastleman

RareConnect Castleman Disease Community: www.rareconnect.org/en/community/castleman-disease
RareConnect Castleman Disease Community is a joint project between the Castleman Disease Collaborative Network (CDCN), Castleman's Awareness and Research Effort (CARE), and the International Castleman's Disease Organization (ICDO), which offers information about living with Castleman Disease, and a live forum. Members of the community can also contribute personal stories and submit questions. RareConnect is a patient-led initiative where patient organizations partner with EURORDIS (European Organization for Rare Diseases), an international patient organization, to create communities and provide moderators from within their network. The goal is to help patients with rare diseases interact with and learn from their peers and medical experts.

International Castleman's Disease Organization
A facebook group that partners with CDCN in order to connect CD patients around the world. Please join the ICDO facebook page to connect with other patients and loved ones: https://www.facebook.com/groups/48343887930/

Castleman Disease Support Group
A facebook group that partners with the CDCN in order to help connect CD patients for support. Please join this page to connect with other patients and loved ones and grow our Castleman community: https://www.facebook.com/groups/403839776489587/

Key Points from Important Publications
to Share with Your Healthcare Provider

Pediatric Publications:

Jun Z, et al. "Clinical and Experimental Study of Castleman Disease in Children." Pediatric Blood & Cancer. 2014. DOI 10.1002/pbc

- A retrospective study that describes the clinical manifestations, diagnosis, and treatment of Castleman disease in children.

Burlakov V, Kozlova A, Shcherbina A, et al. "Clinical Characterization of Castleman's Disease in A Group of Pediatric Patients." Annals of the Rheumatic Diseases. 2016;75:404-405. http://ard.bmj.com/content/75/Suppl_2/404.3

- A retroactive analysis of the clinical manifestations, pathomorphology, and treatment efficiency in histologically confirmed pediatric Castleman disease cases.

Sarra Benmiloud, Sana Chaouki, Samir Atmani, and Moustapha Hida, "Multicentric Castleman's Disease in a Child Revealed by Chronic Diarrhea." Case Reports in Pediatrics, vol. 2015, Article ID 689206, 4 pages, 2015. Doi:10.1155/2015/689206

- Case report of a pediatric Castleman disease patient whose initial presenting symptom was chronic diarrhea; Castleman disease diagnosis was determined upon the appearance and biopsy of an abdominal mass.
- A rare case that underlines challenges in diagnosis and long interval between onset of symptoms and diagnosis.

Unicentric Castleman's Disease:

Bowne W, et al. "The Management of Unicentric and Multicentric Castleman's Disease: A Report of 16 Cases and a Review of the Literature." Cancer. 1999; 85(3): 706-717.

- An analysis of UCD and MCD patient response to various treatment regimens by comparing clinical, radiologic, and laboratory data.

Talat N, Belgaumkar AP, Schulte KM. "Surgery in Castleman's disease: a systematic review of 404 published cases." Ann Surg. 2012; 255:677. https://www.ncbi.nlm.nih.gov/pubmed/22367441

- Systematic review of published Castleman disease patients to determine the role of surgery beyond initial tissue-based diagnosis.

Multicentric Castleman Disease:

Fajgenbaum D, et al. "International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease." Blood. 2017.

- Outlines laboratory, clinical and pathological features of idiopathic MCD. Also outlines exclusionary diagnoses required to make a diagnosis of CD.
- HHV-8-associated MCD and UCD patients have the same lymph node pathology described for idiopathic MCD, but may lack the systemic symptoms of idiopathic MCD.

Li Y, et al. "Clinical and pathological characteristics of HIV- and HHV8- negative Castleman disease." Blood. 2017.

- Outlines the clinical and pathological characteristics of idiopathic MCD.

Liu A et al "Idiopathic multicentric Castleman's disease: a systematic literature review." Lancet Haematology. 2016.

- A systematic literature review aimed to characterize the clinical features, treatments, and outcomes of idiopathic multicentric Castleman disease.

Fajgenbaum D, van Rhee F, Nabel C. "HHV-8-negative or idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and treatment." Blood. 2014; 123(19): 2924-2933.

- Idiopathic MCD was initially thought to be caused by tumors in the lymph node. This paper discusses a new disease model in which swollen lymph nodes are not the cause of CD symptoms, but are instead the result of immune system overactivation.

Fajgenbaum D, Ruth J, Kelleher D, Rubenstein A. "The collaborative network approach: a new framework for accelerating Castleman's disease and other rare disease research." Lancet Haematology. 2016.

- This paper described the organizational framework of the CDCN and how it is working to accelerate research of CD.

Newman S at al. "Taking Control of Castleman disease: Leveraging Precision Medicine Technologies to Accelerate Rare Disease Research." Yale Journal of Biology & Medicine. 2015.

- A review of the CDCN's novel structure that leverages the approaches of precision medicine as a model for scientific discovery, as well as to help in the advancement of patient care.

Noriko Iwaki, David C. Fajgenbaum, Christopher S. Nabel, et al. "Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease." American Journal of Hematology. 2016. 2016; 91:220–226.

- Outlines a subtype of idiopathic MCD that experience severe symptoms including thrombocytopenia, ascites, reticulin fibrosis, renal failure and organomegaly.

Treatment:
Please check out our new Therapeutic Target Database here: cdcn.org/about-castleman- disease/treatments

Behnia F, Elojeimy S, Matesan M, Fajgenbaum D. "Potential value of FDG PET-CT in diagnosis and follow-up of TAFRO syndrome." Ann Hematol. 2016.

- Discusses the role of imaging modality in the recommended work-up of suspected and diagnosed TAFRO syndrome iMCD patients.

Van Rhee F, et a. "Siltuximab for multicentric Castleman's disease: a randomized, double-blind, placebo-controlled trial." The Lancet Oncology. 2014; 15(9): 966-974.

- Outlines the effectiveness of siltuximab in idiopathic MCD patients. Siltuximab is the only FDA-approved drug specifically for HHV-8-negative MCD.

Markham A, Patel T. "Siltuximab: first global approval." Drugs. 2014; 74(10): 1147-1152.

- Siltuximab approved for idiopathic MCD.

Fajgenbaum D, Kurzrock R. "Siltuximab: a targeted therapy for idiopathic multicentric Castleman disease." Immunotherapy. 2016; 8(1), 17–26.

- Treatment of idiopathic MCD with siltuximab.

Kurzock R et al. "A phase I, open-label study of siltuximab, an anti-IL-6 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma, multiple myeloma, or Castleman disease." Clin. Cancer Res. 2013; 19(13): 3659-3670.

- Phase I study of siltuximab in CD patients.

Turcotte LM et al. "Sustained remission of severe Multicentric Castleman disease following multiagent chemotherapy and tocilizumab maintenance." Pediatric Blood Cancer. 2014; 61(4): 737-739.

- Case report of a severe pediatric MCD patient indicating sustained remission following treatment with multi-agent chemotherapy and targeted maintenance therapy with tocilizumab.

Glossary of Terms

Autoimmune disease: a disease in which the immune system attacks normal healthy tissue, mistaking it for a foreign organism.

Auto-inflammatory disease: a disease in which the immune system causes hyperinflammation due to genetic mutations that prevent it from being able to turn off inflammation.

Benign: a term used to refer to tumor cells that are non-malignant. Lymph nodes of CD patients have been considered to be "benign" for many years, but this is a misnomer because the lymph nodes of CD patients are not tumors. The cells within the lymph node are proliferating due to high levels of inflammatory proteins (chemokines and cytokines), not because they are benign tumors or because there are malignant cells.

Chemokines and Cytokines: chemical substances that immune cells use to communicate with other immune cells. In CD, these proteins in the blood are thought to contribute to CD symptoms.

Doctors/Specialists: A primary care physician (PCP) may treat CD or may prefer to make a referral to a specialist, which may include a surgeon, a medical oncologist, a hematologist-oncologist, a virologist, or a radiation-oncologist.

Diagnostic Criteria: In January 2017, the CDCN published the first-ever diagnostic criteria for idiopathic MCD that that defines what physicians should look out for and what they need to rule out to diagnose CD. An international group of 34 expert physicians from eight countries on five continents created these diagnostic criteria, then published in top hematology journal, *Blood*.

Human herpesvirus-8 (HHV-8): also known as Kaposi's sarcoma-associated herpesvirus, HHV-8 is one of seven currently known cancer-causing viruses (oncoviruses). Because most healthy immune systems are able to prevent the spread of this virus, HHV-8 usually only causes problems in individuals with immunosuppressed or weakened immune systems (e.g., HIV infected).

HHV-8-associated MCD (Human Herpesvirus-8-positive MCD): this is a subtype of MCD in which patients have lymph nodes that test positive for HHV-8. No medications are approved specifically for treatment of HHV-8-associated MCD, though patients tend to respond well to rituximab.

HHV-8-negative MCD (Human Herpesvirus-8-negative MCD): this is a subtype of MCD in which patients have lymph nodes that test negative for HHV-8. Siltuximab (Sylvant) is the only treatment approved by the FDA specifically for this patient population, which means the drug has been studied in this patient population and proven to be effective in some patients.

Hyperinflammatory disorder: a disorder involving the excessive activation of immune cells and subsequent release of inflammatory chemical messengers (chemokines and cytokines). There are a variety of triggers for the immune cell activation such as foreign organisms, autoimmune mechanisms, and organ transplant rejection.

Idiopathic: The term often given to diseases for which the cause is unknown.

Idiopathic MCD (iMCD): The origin of this subtype of CD is unknown. Also known as HHV-8-negative MCD.

Immune system: a complex network of cells and proteins that fight infections throughout the body. Lymph nodes are the home base for immune cells.

Interleukin-6 (IL-6): one type of cytokine, which is found and used by every healthy immune system. It is often found to be abnormally elevated in Castleman disease as a source of hyperinflammation and is thus a therapeutic target. This is what siltuximab and tocilizumab block.

Lymph node: one of many small organs that are distributed throughout the body with the function of filtering the blood for foreign particles and serving as the location where activated immune cells go to work together. Many lymphocytes, including B cells, T cells, and plasma cells, are concentrated in lymph nodes. Lymph nodes become enlarged during states of inflammation.

Lymphocyte: a type of white blood cell (immune cell) used to fight infections. Occasionally, lymphocytes drive diseases by attacking normal tissue directly or releasing cytokines. Includes B-cells, T-cells, and plasma cells. The lymph node is the home base for these cell types.

Lymphoproliferative disorder: a disorder involving the abnormally rapid production (proliferation) of lymphocytes. This typically refers to diseases where the proliferation is due to a malignant mutation, such a lymphoma or multiple myeloma. Castleman disease is often considered to be a lymphoproliferative disorder because lymphocytes proliferate due to cytokine signaling, but researchers are beginning to think it should be more appropriately considered a hyperinflammatory disorder.

Multicentric Castleman Disease (MCD): comprises approximately 30% of CD patients. It involves more than one region of enlarged lymph nodes. MCD symptoms can range from no symptoms to severe symptoms requiring hospitalization, including fatigue, night sweats, fevers, weight loss and organ dysfunction. Most patients are diagnosed in their mid-50s, but this disease can affect patients of any age. There is no known cure for MCD, but symptoms may be managed with medications.

MCD can also be categorized based on the appearance of lymph nodes under the microscope (histological subtype): hyaline vascular, plasma cell, or mixed cell.

Neoplastic: a term used to refer to tumor cells that are malignant or cancerous.

Paraneoplastic syndrome: a disease in which cancerous cells release substances or cause the release of substances that generate a separate set of symptoms in the patient not directly associated with the malignancy.

Pathologist: A doctor that interprets changes caused by diseases in tissues and body fluids. A hematopathologist is a pathologist that specializes in diseases of the blood and lymphoid tissues, such as CD.

Plasma cell: a type of lymphocyte that produces large quantities of antibodies, which are proteins used by the immune system to destroy bacteria and viruses; B-cells become plasma cells during their final stage of maturation.

TAFRO Syndrome: an acronym that stands for thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly and is a variant of HHV-8-negative MCD recently described in Japan.

Tests: There is no single test that can diagnose CD. Some examples of tests that are required to make a diagnosis of CD include: physical examination, blood tests, imaging tests such as X-rays, MRI, CT or PET scans, and lymph node biopsies.

Unicentric Castleman Disease (UCD): comprises approximately 70% of cases of CD. It involves a single lymph node or one region of enlarged lymph nodes. UCD patients tend to have limited symptoms but may have symptoms related to expansion of the affected lymph node compressing surrounding structures. Most patients are diagnosed in their mid-30s, but it can affect people of any age. Typically, UCD is treated with surgical removal of enlarged lymph nodes. Many people are cured with surgery if complete removal of swollen lymph nodes is achieved. Sometimes swollen lymph nodes cannot be removed and these patients may continue to have symptoms.

After UCD patients successfully have their affected lymph nodes removed, they may have a UCD recurrence. UCD recurrence is considered enlargement of lymph node(s) in a single region of the body after complete removal of initial swollen lymph nodes. These recurrences may occur in the same location as the first lymph node enlargement or it may occur in a different region of the body.