International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 10 Issue 3 ǁ 2022 ǁ PP. 63-66

A Review on Castleman Disease

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Date of Submission: 05-03-2022 Date of acceptance: 21-03-2022

I. INTRODUCTION:

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 was first described in the 1950s by Benjamin Castleman as localized mediastinal lymph node enlargement characterized by increased numbers of lymphoid follicles with germinal center involution and marked capillary proliferation, including follicular and interfollicular endothelial hyperplasia. In 1969, Flendrig described the plasma cell (PC), the hyalinized, and the "intermediate" (or mixed) histopathological variants. Further descriptions over the years provided insight into clinicopathologic associations.

Definition

Castleman disease or giant lymph node hyperplasia or angiofollicular lymph node hyperplasia is a disorder of unknown cause that often involves mediastinal lymph nodes. Castleman disease can also be described as hyaline-vascular, plasmacytic, or mixed based on the microscopic appearance.

Castleman disease describes a group of disorders with a wide range of symptoms that each has enlarged lymph nodes that share similar appearances when reviewed under the microscope. Castleman disease is first classified based on the number of regions of enlarged lymph nodes that demonstrate these abnormal features.

Unicentric Castleman disease (UCD) is the most common form of the disorder which involves a single enlarged lymph node or single region of enlarged lymph nodes, usually in the chest or abdomen whereas multicentric Castleman disease (MCD) involves multiple regions of enlarged lymph nodes.

There are two sub-types of MCD. A subset of MCD caused by human herpesvirus-8 (HHV-8; also known as Kaposi sarcoma-associated herpesvirus). These cases are called HIV-8-associated MCD. There are also MCD patients who are negative for the HHV-8 virus, and the cause is unknown. These cases are called HHV-8 negative or "idiopathic" MCD (IMCD).

Etiology:

The exact cause of UCD and iMCD is not known. Viruses, genetic mutations acquired over the course of life, and inflammation have all been proposed as possible causes of UCD. Recent research suggests that acquired genetic mutations are the likely cause of UCD.

HHV-8 is the well-established cause of HHV-8-associated MCD, which accounts for approximately 50% of all cases of MCD, HHV-8-associated MCD often occurs in individuals infected with human immunodeficiency virus (HIV). The HIV weakens the immune system's ability to control the HHV-8 infection. The HHV-8 virus causes MCD by making its own IL-6 and causing cells to proliferate.

Approximately 50% of MCD cases are negative for HHV-8 and the cause is unknown or idiopathic." Recently, four possible causes have been hypothesized: a virus, genetic mutation acquired over the course of life, an inherited genetic mutation, or autoimmunity. Some researchers speculate that increased production of interleukin-6 (IL-6) for one of the above causes may be involved in the development of iMCD. IL-6 is a substance normally produced by cells within the lymph nodes (plasma cells) and in healthy individuals serves to coordinate the immune response to infection. However, IL-6 is not elevated in all cases, and neutralizing IL-6 is not effective for the treatment of all cases.

Risk factors

Castleman disease can affect people of any age. But the average age of people diagnosed with unicentric Castleman disease is 35. Most people with the multicentric form are in their 50s and 60s. The multicentric form is also slightly more common in men than in women.

The risk of developing multicentric Castleman disease is higher in people who are infected with a virus called human herpesvirus & (HHV-8).

Pathophysiology:

Data suggest that UCD is more likely a clonal neoplastic process, and the most likely cell of origin is stromal, specifically the follicular dendritic cell. Uncontrolled HHV8 infection is the etiological driver in HHV8-MCD. In immunocompromised individuals, HHV8 can replicate in lymph node plasmablasts and transcribe the viral homolog of interleukin-6 (IL-6; vIL-6) that drives symptoms, signs, and lymph node pathology along with a cascade of other cytokines including human IL-6. It has been postulated that HHV8 may be able to cause immunoglobulin M–positive (IgM^+) naive B cells to differentiate into plasmablasts without undergoing the germinal center reaction. Human IL-6 expression can be localized to germinal center follicular dendritic cells.

The cause of the increased IL-6 and other cytokines in iMCD is unknown. Speculation regarding whether iMCD is an autoimmune, infectious, or clonal disease abounds, but data are limited. The hypothesis that iMCD is driven by infection with a virus other than HHV8 is becoming less credible.

Clinical presentation:

UCD is characterized by a single enlarged lymph node or multiple enlarged lymph nodes in a single region of the body, such as the chest, abdomen, or neck. In most cases of UCD, individuals exhibit no symptoms (asymptomatic). Occasionally, patients experience symptoms due to the size and location of the growth. For example, a growth may form next to a vein, resulting in a bulge and possible obstruction in the involved blood vessel. Occasionally, individuals with UCD 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). These symptoms are typically seen in MCD. These symptoms usually disappear after surgical excision of the UCD lymph node.

Both HHV-8-associated MCD and IMCD are characterized by multiple regions of enlarged lymph nodes and episodic inflammatory symptoms, such as fever, weight loss, skin rash, destruction of red blood cells, leading to unusually low levels of circulating

red blood cells, and/or abnormally increased amounts of certain immune factors in the blood (hypergammaglobulinemia). Many individuals with MCD may exhibit an abnormally large liver and spleen (hepatosplenomegaly).

HHV-8-associated MCD is most commonly diagnosed in HIV-infected or otherwise immunocompromised individuals. Thus, HHV-8-associated MCD patients may experience additional symptoms related to their HIV infection or other conditions.

Diagnosis

- Blood and urine tests, to help rule out other infections or diseases. These tests can also reveal anemia and abnormalities in blood proteins that are sometimes characteristic of Castleman disease.
- Imaging tests, to detect enlarged lymph nodes, liver or spleen. A CT scan or MRI of neck, chest, abdomen and pelvis may be used. Positron emission tomography (PET) scans also may be used to diagnose Castleman disease and to assess whether atreatment is effective.
- Lymph node biopsy, to differentiate Castleman disease from other types of lymphatictissue disorders, such as lymphoma. A tissue sample from an enlarged lymph node is removed and examined in the laboratory.

Complications

People with unicentric Castleman disease usually do well once the affected lymph node is removed. Multicentric Castleman disease may lead to life-threatening infections or organ failure. People who also have HIV/AIDS generally have the worst outcomes.

Having either variety of Castleman disease may increase risk of lymphoma

Related Disorders

Symptoms of the following disorder can be similar to those of Castleman disease. Comparisons may be useful for a differential diagnosis:

Hodgkin lymphoma 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 disease as secondary characteristics. They are not necessary for a differential diagnosis:
Some cases of iMCD have been diagnosed in patients with Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (**POEMS syndrome**)syndrome.
There is an increase rate of cancer diagnosed in patients with iMCD and HHV-8-associated MCD.
Patients with HHV-8-associated MCD are at increased risk of developing Kaposi's sarcoma, which is a malignant skin tumor 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.

Treatment. Treatment depends on the type of Castleman disease

Unicentric Castleman disease

Unicentric Castleman disease can be cured by surgically removing the diseased lymph node. If the lymph node is in the chest or abdomen-which is often the case-major surgery may be required.

If surgical removal isn't possible, radiation therapy may be an effective way to destroy the affected tissue. It need follow-up exams, including imaging, to check for relapse.

Multicentric Castleman disease

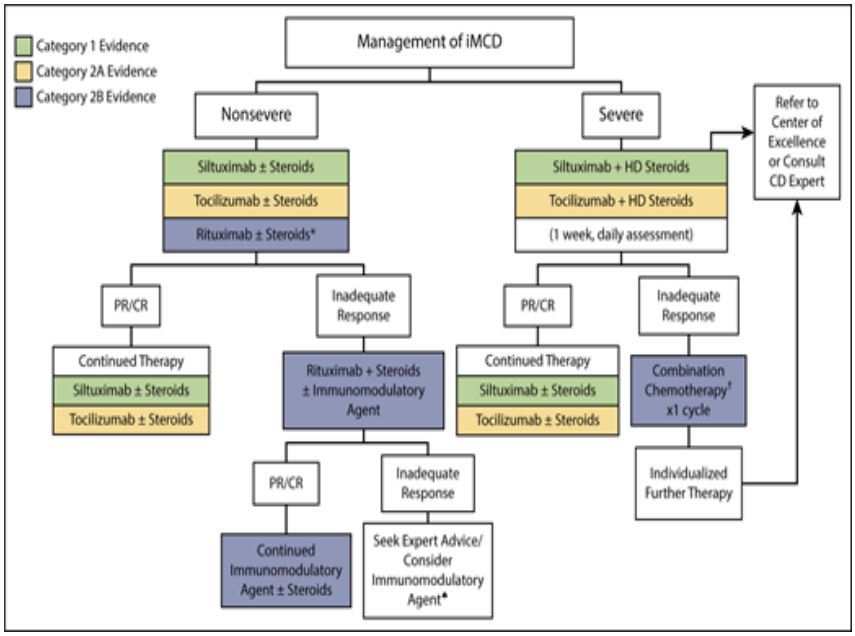
Treatment for multicentric Castleman disease generally involves medications and other therapies to control cell overgrowth. Specific treatment depends on the extent of the disease and on whether having HIV or HHV-8 infection or both.

Treatment options for multicentric Castleman disease may include:

- Immunotherapy. The use of drugs such as siltuximab (Sylvant) or rituximab (Rituxan) can block the action of a protein that is produced in excess in people who have multicentric Castleman disease.
- Chemotherapy. This type of medication can slow the overgrowth of lymphatic cells.

The doctor may recommend adding chemotherapy if the disease doesn't respond to immunotherapy or if having organ failure. These include drugs which target and neutralize IL-6 (siltuximab or Sylvant) or the receptor for IL-6 (tocilizumab or Actemra). In 2014, Sylvant (siltuximab) was approved to treat patients with iMCD. This is the first and only FDA-approved drug to treat patients with iMCD. Approximately half of iMCD patients do not improve with IL-6 neutralization. These patients are often treated with chemotherapy or newer treatment options such as rituximab, sirolimus, or anakinra.
Corticosteroids. Drugs such as prednisone can help control inflammation. Antiviral drugs. These drugs can block the activity of HHV-8 or HIV if you have one or both of those viruses.

For idiopathic MCD,



II. CONCLUSION:

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.

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