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Castleman disease, a dilemma in HIV patients: A clinical presentation and diagnostic approach

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Abstract
The first case of CD was described in 1950. Castleman disease (CD) is a rare group of heterogeneous lymphoproliferative disorders that share histopathological features related to the increased release of cytokines, particularly interleukin 6 (IL-6). CD has many etiologies, presentations, treatments, and outcomes. CD can be classified as unicentric Castleman disease (UCD) or Multicentric Castleman disease (MCD). UCD affects a single group of lymph nodes, whereas MCD affects multiple groups of lymph nodes. There are no known risk factors for UCD. MCD can either be idiopathic or associated with an immunocompromised state which may lead to the proliferation of B-lymphocytes as well as plasma cells in lymphoid organs in different body regions. Moreover, MCD has a preference for male over female patients. The average age for diagnosing MCD is the sixth decade. Contrarily, UCD has no gender preference and it is typically diagnosed in the fourth decade. UCD can present as asymptomatic lymphadenopathy or as a progressive enlargement of the lymph nodes. UCD is incidentally diagnosed on imaging of the chest or abdomen. MCD may present with lymphadenopathy, cytopenia or constitutional symptoms. The treatment options for UCD and MCD may include monoclonal antibodies, cytotoxic therapy, chemotherapy, radiotherapy or surgery.

Keywords: Castleman disease, UCD, MCD, HIV, IL-6, PGL, immunodeficiency, HHV8, surgery

Introduction
The estimated ten-year prevalence of CD in the US was 2.4 per million persons [1]. The incidence rate for UCD is estimated at (15-19) cases per million patient-years. The incidence rate for MCD is estimated at (5- 6) cases per million patient years [2]. CD was first described in the 1950s by Benjamin Castleman. CD was defined as an enlargement localized to the mediastinal lymph node with an increase in lymphoid follicles with germinal center involution and marked capillary proliferation; including follicular and inter follicular endothelial hyperplasia [3]. In the 1980s, CD was categorized for the first time as a unicentric CD, involving a single group of lymph nodes, or as a multicentric CD, involving multiple lymph node groups. The association between HIV and MCD was later discovered in the 1980s. In the 1990s, (HHV8) was identified as the etiological driver of all HIV+ and some HIV− MCD. Takai *et al*. recognized a severe form of idiopathic MCD (iMCD) in 2010. The Castleman Disease Collaborative Network (CDCN) proposed a classification system retaining the UCD vs. MCD nomenclature, and dividing MCD by etiological driver into (HHV8-associated MCD), idiopathic MCD (iMCD), and POEMS-associated MCD. (HHV8-associated MCD) can be subclassified into HHV8-associated MCD in HIV seropositive patients or HHV8-associated MCD in HIV seronegative patients. Idiopathic MCD can be subclassified into (iMCD-TAFRO) or (iMCD-NOS). (iMCD-TAFRO) exhibits a cluster of clinical and laboratory features such as thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, and organomegaly. Patients who are described by (iMCD-NOS) do not meet the criteria for (iMCD-TAFRO), as (iMCD-NOS) presents with less severe symptoms. (POEMS-associated MCD) displays a spectrum of clinical and laboratory features such as polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes [4].

Case presentation
A 57-year-old male was diagnosed with HIV in 2002. He reports six months of progressive asymptomatic cervical and axillary lymphadenopathy.

Additionally, he reported fatigue and occasional night sweat. He denied fever, weight change, or pet exposure. The rest of the system's review was unremarkable. He was compliant with his HIV medication (Emtricitab-Rilpivir-Tenofovir 200-25-25 mg), taking one tablet twice daily. His recent HIV viral load was undetected, his CD4 T-cell count (524/uL), (normal range = 359 - 1,519/uL) and CD4 T-Helper cell percent (27.6%), (normal range = 30.8 - 58.5%). He reported a remote history of intravenous drug use (IVDU). He denied tobacco smoking or other illicit substance use. He denied recent sickness or travel. He lives alone and is employed. He is COVID vaccinated and boosted (Pfizer vaccine). On the physical exam, his vitals were as noted in (Table 1).

Blood Pressure	128/80 mmHg
Pulse Rate	80 PPM
Respiratory Rate	14 BPM
Oxygen Saturation	97%
Temperature	99F° (37.2)° C
Body Weight	220 Lb
Basic Metabolic Index	30 Kg/M2

On examination of the neck, there was a left smooth non-tender mobile cervical lymph node enlargement measuring around 3x2cm. A smooth non-tender mobile swelling was noted in the right axillary lymph node which measured approximately 4 x 4 cm. The overlying skin was normal with no erythema or ulceration. Both swellings were not adherent to the overlying skin. Splenomegaly was appreciated on the abdominal exam. The rest of the physical exam was unremarkable. Laboratory investigation showed the following: mild anemia with a hemoglobin level of (10.5 g/dL), (normal range= 11.6 - 16.8 g/dL). Thrombocytopenia with platelets count of (100x10*3/µL), (normal range=150 - 372 10*3/uL). Leukopenia (Wbc 3500/µL), (normal range= 4-11 * 10^3/µL). Hypoalbuminemia (albumin 1.6 g/dL), (normal range=3.5-5.2 g/dL). Renal dysfunction (serum creatinine 1.7 mg/dL), (0.70 - 1.33 mg/dL). Proteinuria (150 mg/g), (normal range= <30mg/g). Elevated ESR (70 mm/h), (normal range = 0-15 mm/ hour). Elevated C-reactive protein level (14 mg/dL), (normal range< 0.5 mg/dL). Elevated Ferritin level (170 ng/mL), (normal range 13.0-150.0 ng/mL). Elevated fibrinogen level (623 mg/dL), (normal range=238 - 445 mg/dL). Hypergammaglobulinemia on serum protein electrophoresis with elevated IgG, predominantly IgG 1 subclass. Elevated kappa to lambda ratio K/L (4.10), (normal range=0.26 - 1.65). Elevated Kappa level (14.90 mg/dL), (normal range=0.33 - 1.94mg/dL) and elevated lambda level (3.63 mg/dL), (normal range=0.57 - 2.63 mg/dL). Elevated Interleukin-6 (IL-6) level (32.4 pg/mL), (normal range= <=7.0 pg/mL). Elevated vascular endothelial growth factor (VEGF) level (100pg/mL), (normal range= 31 - 86 pg/mL). Elevated Interleukin 2 (IL-2) level (2.9pg/mL), (normal range= <1.9 pg/mL). Undetectable ANA.

The viral serology panel showed detectable EBV IgG antibodies. EBV virus (IgM) antibody was undetectable. Hepatitis C virus antibody was undetectable. HBsAg and Anti-HBs were undetectable. The antibodies for CMV (IgM/IgG) both were undetectable. A peripheral blood PCR for (EBV DNA), (CMV DNA), and (HHV8 DNA) was undetectable. An ultrasound examination revealed well-circumscribed enlarged lymph nodes, measuring 3.4 cm and 3 cm in the axillary and left cervical region. Increased blood flow was noted on the doppler. A CT scan with contrast of the chest, abdomen, and pelvis revealed scattered small borderline lymph nodes throughout the anterior and posterior cervical triangles bilaterally. Multiple small and borderline enlarged bilateral nodes were seen in the Mediastinum, Hilum, and Axilla. An enlarged Porta hepatis lymph node. An enlarged portacaval lymph node. PET scans revealed mild metabolic activity corresponding to scattered small lymph nodes throughout the mediastinum, hila, and bilateral axilla but higher metabolic activity within the abdomen, pelvis, and inguinal regions. The patient was admitted to the hospital and underwent an excisional biopsy of the left deep cervical nodes and left axillary lymph nodes. A gross exam of the specimen showed enlarged lymph nodes. A microscopic (histologic) description showed Benign lymph nodes with plasmacytic, hyperplastic, and regressive lead transformed germinal centers. Numerous mature plasma cells were seen throughout. Increased follicles with follicular hyperplasia and regressed transformed follicles were also noted. There was vascular proliferation penetrating directly into germinal centers consistent with the lollipop sign. There was no apparent B-cell population and Reed-Sternberg type cells were not identified. A CD138 stain showed numerous positive plasma cells. HHV8 and EBV in situ hybridization stains were negative. Immunohistochemical stains revealed that the germinal center's cells were positive for CD20, CD79a, CD10, BCl-6, and Ki-67. Immunohistochemical staining was negative for CD3, CD5, and BCL-2. A bone marrow biopsy depicted hypercellular bone marrow without evidence of malignant neoplastic proliferation. Hematology/Oncology service was consulted and Rituximab was started.

Discussion

HIV is a global pandemic, and it is a lymphotropic virus [5] with a high predilection for T-cell infection. The revised CDC HIV classification system is based on CD4 T-lymphocyte counts and clinical conditions associated with HIV infection. This system displays three ranges of CD4 + T-lymphocyte and three clinical categories. Persistent generalized lymphadenopathy (PGL) is one of the clinical categories. PGL is defined as lymph node enlargement of over 1 cm in two or more extra inguinal sites for more than three months.

HIV lymphadenopathy can occur with any HIV T-lymphocyte category such as HIV category (1) CD4 + T-lymphocyte > 500 uL, HIV category (2) (CD4 + T-lymphocyte 200-500 uL) or HIV category 3 CD4 + T-lymphocyte <200 uL [6]. One study found that HIV lymphadenopathy affects axillary lymph nodes in 84% of cases, followed by cervical lymph nodes in 60% of cases [7]. HIV lymphadenopathy is categorized as reactive and non-reactive. Reactive HIV lymphadenopathy may account for 50% of cases and is attributed to HIV infection, EBV reactivation, or both. Infectious and neoplastic pathologies are responsible for Non-reactive lymphadenopathy cases. Non-reactive infectious lymphadenopathy is responsible for a small percentage in non-TB endemic countries. Neoplastic lymphadenopathy (Non Hodgkin Lymphoma, Kaposi sarcoma, and CD) represents a large percentage of the non-reactive lymphadenopathy cases.

Clinical manifestations such as (fever, unintentional weight loss, and a larger lymph node) will help determine if the probability for HIV lymphadenopathy is likely to be non-reactive lymphadenopathy (8). Pathologic classification for CD includes hyaline vascular type (HV-CD), plasma cell type, mixed type, and human herpesvirus (HHV)-8 associated CD. The hyaline vascular CD is characterized by lymphoid follicles with germinal centers surrounded by small concentric lymphocytes forming an onion skin-like structure. In hyaline vascular CD (HV-CD), the center of the lymphoid follicles is penetrated by hyalinized capillaries known as the lollipop sign. Moreover in HV-CD, small lymphocytes and immature plasma cells are present in the interfollicular zones with vascular proliferation as well as hyalinization. Plasma cell type CD is characterized by the presence of sheets of mature plasma cells in the interfollicular zone and shows less vascularity. The mixed type CD has characteristics of both HV-CD and plasma cell type [9]. UCD presents as asymptomatic, slowly growing isolated lymphadenopathy (commonly in the mediastinum or abdomen) but may compress surrounding organs resulting in compressive symptoms. MCD displays various systemic constitutional symptoms such as fever, night sweat, fatigue, and malaise. The hyperbolic effect of elevated IL-6 leads to multiple regional lymphadenopathies with hepatosplenomegaly and polyclonal hypergammaglobulinemia. High fibrinogen levels result in deep venous thrombosis (DVT) and other thromboembolic diseases. The elevated levels of VEGF in CD are associated with thrombotic microangiopathy. Hypoalbuminemia in CD leads to edema, ascites, pleural and pericardial effusion, or anasarca partly from reduced intravascular oncotic pressure. The increased levels of hepcidin can lead to anemia. Death may result from renal insufficiency with multiorgan failure in severe cases of iMCD. Diagnosing CD is arduous and requires two major criteria and at least two minor criteria. The major criteria for diagnosing CD includes clinical presentation and histopathologic evidence of CD. The clinical presentation involves a single enlarged lymph node in (UCD) or multiple enlarged lymph nodes in (MCD). The histopathologic evidence will help in reaching the diagnosis of CD after excluding other possible differential diagnoses like infectious etiologies, malignant neoplasia, and autoimmune disorders. The minor criteria can be divided into two categories, either clinical or laboratory criteria.

The clinical criteria includes the following

1. B symptoms: Fatigue, fever, weight loss, and night sweats
2. Splenomegaly or Hepatomegaly
3. Volume overload states like edema, anasarca, and pleural effusion.

The Laboratory criteria includes

1. Anemia
2. Thrombocytopenia or thrombocytosis
3. Hypoalbuminemia
4. Renal dysfunction or proteinuria
5. Elevated CRP or ESR
6. Polyclonal hypergammaglobulinemia

IL-6 plays a vital role in the pathogenesis of CD. Elevated levels of IL-6 and soluble IL-2 receptor (sIL2R), VEGF, IgA, IgE, lactate dehydrogenase, β-2-microglobulin are essential for supporting the diagnosis of CD but do not specifically determine the presence of the disease. When there is a clinical scenario where CD is suspected, a thorough workup is required, which involves:

1. Serology tests for HHV8 and HIV to find any association with CD.
2. PCR testing for HHV8 DNA in peripheral blood.
3. Serum protein electrophoresis.
4. CT scan of the chest, abdomen, and pelvis.
5. Skeletal survey.
6. PET scan.
7. Bone marrow examination.

The workup will determine the extent of the disease and help rule out other diagnoses.

The treatment for CD is challenging due to many options in treatment, including Monoclonal antibodies, Cytotoxic drugs, radiation, surgery, and autologous stem cell transplant. MCD in patients with seronegative HIV and HHV8 can be treated with Tocilizumab (anti- IL-6R antibody) or Siltuximab, an anti–IL-6 antibody. Both are considered first-line therapy. MCD with seropositivity for HHV8, antiviral therapeutics targeting HHV8 replication pathways such as (Cidofovir, Foscarnet, and Ganciclovir) are beneficial. Novel immunomodulatory agents like rituximab, thalidomide, bortezomib, IL-1 antagonist anakinra, and interferon-alpha are also effective. Immunomodulatory agents and chemotherapy should be reserved for relapsed cases, and patients must be educated that not all cases of MCD can be treated. UCD can be treated effectively with surgical intervention [10], and the prognosis is generally good. However, UCD has a predilection for the mediastinum and may adhere to the surrounding major vessels, making surgical resection challenging. In such scenarios, chemotherapy with radiation can be used to shrink the tumor size; making surgical resection feasible [11].

Conclusion

CD is a lymphoproliferative disorder that displays a spectrum of clinical presentations related to excess pro-inflammatory cytokines release. It can be classified as UCD if a single group of lymph nodes is involved or as MCD, if multiple groups of lymph nodes are affected. CD can either be idiopathic or associated with immunodeficiency causing abundant proliferation of plasma cells and B lymphocytes. Furthermore, there is evidence of the association of CD with HIV. The diagnosis of CD is challenging and requires a high degree of clinical suspicion with the presence of clinical and histopathologic evidence. The clinical presentation varies from asymptomatic persistent PGL to PGL with multiorgan dysfunction. From a Pathological perspective, CD is classified into hyaline vascular type (HV-CD), plasma cell type, mixed type or human herpesvirus (HHV)-8 associated CD. The differential diagnosis of CD could be infectious or neoplastic. Infectious pathologies that mimic CD include HIV, EBV, and TB. Neoplastic pathologies that may present like CD include NHL and Kaposi sarcoma. The diagnosis of CD is challenging and requires a combination of laboratory, radiological and pathological expertise. Treatment of CD may include chemotherapy, radiotherapy, or surgical treatment. In some patients, a combination of therapeutic options is needed. A discussion with the patient regarding

the possibility that not all CD cases respond to therapy is essential before starting a treatment plan.

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