SAGE Open Medical Case Reports
Volume 11: 1–5

DOI: 10.1177/2050313X231175720
journals.sagepub.com/home/sco
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Castleman's disease: A report of two cases at a tertiary hospital in Northern Tanzania

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Abstract

Castleman's disease is a rare lympho-proliferative disease entity characterized by variable clinical presentations, distinctive histological manifestations, and prognosis. Its incidence and etiology are unclear. An interplay of HIV and human herpesvirus-8 has been implicated. Although its localized variety is benign, other types can be multifocal with adverse systemic manifestations. Human herpesvirus-8 Castleman's disease affects mainly HIV-positive individuals; however, individuals who are immunocompromised from other causes can also be affected, thus necessitating investigations for HIV. Herein, we report two patients presenting with long-standing lymphadenopathy. Histopathology, immunohistochemical testing and clinico-pathological correlation confirmed the diagnosis of Castleman's disease. The patients were successfully treated with surgery and/or rituximab. They were symptoms free in the subsequent follow-up visits. A brief review of the literature is also provided.

Keywords

Castleman's disease, case report, Tanzania

Date received: 17 February 2023; accepted: 27 April 2023

Introduction

Castleman's disease (CD) was initially described by Benjamin Castleman in the 1950s. It is a rare group of lympho-proliferative disorders characterized by enlarged hyperplastic lymph node(s).[1] There are two distinct clinical manifestations that can be identified: (1) unicentric Castleman's disease (UCD) whereby patients present with localized signs and symptoms, including isolated lymphadenopathy, and (2) multicentric Castleman's disease (MCD) characterized by a systemic progressive disease with lymphadenopathy of multiple sites.[2,3]

CD displays a variety of histological patterns, including mixed, hyaline-vascular (HV), and plasma cellular types. Hyaline-vascular forms of CD are the most commonly described instances. The majority of UCDs are HV in nature and occur without any symptoms or with a limited mass impact. Often times, the clinical course of UCD is indolent. However, compared to UCD, MCD mostly affects plasma cells and has an aggressive biological behavior with poorer clinical outcome.[4] Herein, we are presenting two CDs that went misdiagnosed for years.

Furthermore, we have discussed its clinical features, types, relevant investigations emphasizing the importance of histopathology to seal the diagnosis from other lympho-proliferative conditions; and current treatment modalities are discussed.

Case presentation

Case 1

A 75-year-old man presented with multiple neck swellings for 4 years and breathing difficulties associated with a productive cough and yellowish sputum for 2 weeks. He reported a history of receiving pulmonary tuberculosis (TB) treatment more than three times in his life. He also reported that his brother suffered similar problem and

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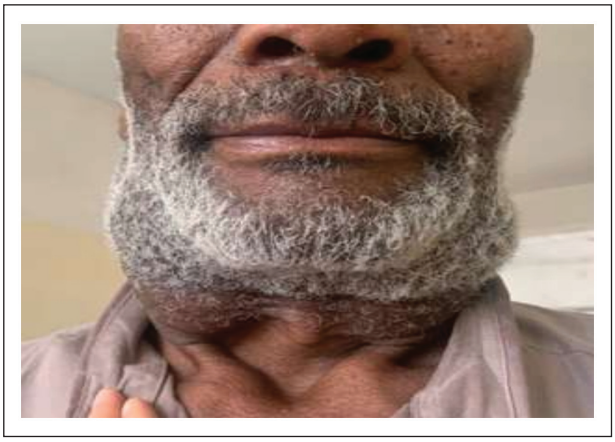

Figure 1. Photographs of a patient with cervical and submental lymphadenopathy.

possibly died of respiratory complications from numerous neck swellings.

On physical examination, the patient was alert, had finger clubbing, and had several mobile, firm, unmated lymph nodes in the submandibular (Figure 1), cervical, supraclavicular, axillary, and inguinal regions. Hepatomegaly, bilateral basal crepitation, respiratory rate of 24 breaths per minute, and saturation of 93% on 4 L of oxygen were also noted. Examination of other systems was essential unremarkable.

A computed tomography (CT) scan of the chest and abdomen revealed bilateral axillary, mediastinal, hilar, and cervical lymphadenopathy. Left lower lobe consolidation, right apical and basal consolidation, a moderate pleural effusion on the left paraaortic, mesenteric, iliac, and inguinal lymph node enlargement with calcification in the center were evident (Figure 2). Gene Xpert for TB and HIV testing results came back negative, routine blood parameters were within normal limits. Diagnosis of malignant lymphoma was entertained. Histopathology of excisional biopsy from one of the neck mass revealed mantle zones thickening with lymphocytes arranged in layers giving the appearance of skin onion skin (Figure 3(a)-(b)). In addition, the cell did not express human herpesvirus-8 (HHV-8) immunoreactivity. However, the concentric rings of follicular cells were positive for CD21 while the germinal centers cells demonstrated CD10 immunopositivity. The diagnosis of idiopathic MCD with supplemental bacterial pneumonia was suggested and the patient was kept on chemotherapy (Rituximab) as well as antibiotics (Ceftriaxone and Azithromycin) and steroids (Hydrocortisone). He improved remarkably and has been symptoms free for 1 year of follow-up.

Case 2

A 57-year-old male, HIV-infected with a suppressed viral load and low CD4 count was referred to our facility from a peripheral health center for treatment of a senile cataract and right neck swelling that had been visible for 20 years. The patient had no prior history of fever or weight loss, but did report having received anti-TB treatment twice without any improvement.

On examination, he was awake, had an enlarged lymph node in his right neck that was firm and movable and had normal skin surrounding it. His physical examination was normal. Histopathology of incisional biopsy from the neck mass demonstrated a reactive lymph node highlighting prominent vascular proliferation and hyalinization of the vessel walls (Figure 3(c)), and follicle surrounded by mantle zone composed of concentric rings of small lymphocytes with onion skin like skin appearance (Figure 3(d)). Test for HHV-8 was positive; the findings were in favor of CD. He was scheduled for surgical resection whose histopathology confirmed the diagnosis of CD. The patient was advised to maintain follow-up as outpatient after surgical resection and has been well for almost 1 year after the surgery.

Discussion

The causes of CD are mostly unknown. One established etiologic agent is HHV-8, also known as Kaposi's sarcoma herpes virus. HHV-8 can be shown in approximately 50% of cases of plasma cell variant CD, including most MCD cases, and in most cases arising in patients with HIV infection.[4] In HHV-8+ cases of CD, the virus primarily infects mantle zone B-cells, most of which are large and described as immunoblasts or plasmablasts. The HHV-8 viral load in peripheral blood mononuclear cells correlates with aggressiveness of disease. HHV-8 encodes for a homolog of human interleukin 6 (IL-6) that is an early lytic antigen. Viral IL-6 can stimulate human IL-6-induced cellular pathways and, by this mechanism, is believed to be involved in pathogenesis.[5]

As it was the case in our patient, UCD may be asymptomatic or may present as an enlarging lymph node or mass; secondary symptoms related to the mass (compression or pain). Virtually, all subtypes of MCD show systemic inflammatory manifestations, including fever, weight loss, and hepatomegaly. In addition, lymphadenopathy is almost constant in patients with MCD which is either peripheral, intrabdominal or mediastinal lymph nodes. Unlike it was in case 1, patients with MCD can be associated with HIV infection. Moreover, patients with MCD have a higher risk of coexistent chronic infections and can be associated with Kaposi's sarcoma, with the latter much more common in HIV-positive patients.[6–8] Patients with MCD subsequently may develop lymphomas.[9] Furthermore, anemia, hypoalbuminemia, cytopenias, and elevated inflammatory markers are common.

The incidence of UCD is unknown and can occur at any age, however, it is mainly reported in adults in the literature with a slight feminine predominance (60%).[10] As it was in case 2, UCD is mostly asymptomatic with a single-site lymph node enlargement. Although localized CD most often

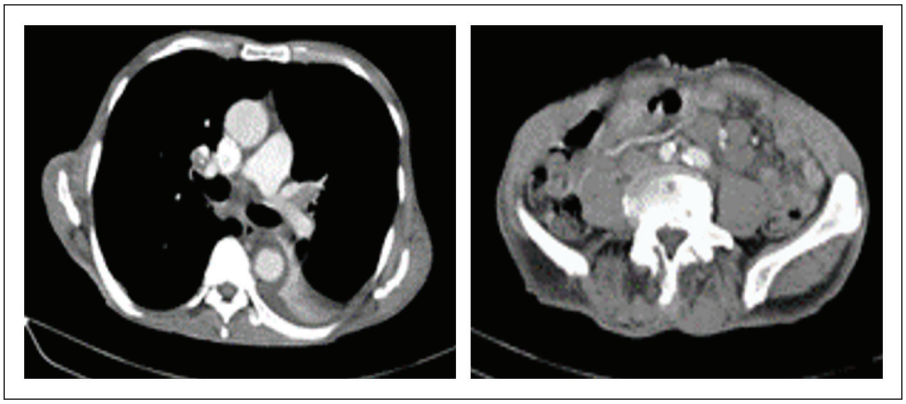

Figure 2. Thoraco-abdominal CT scan—mediastinal, hilar, and cervical lymphadenopathy (left); apical and basal consolidation, left lower lobe consolidation and left moderate pleural effusion, lymph node biopsy—necrotizing inflammation (right).

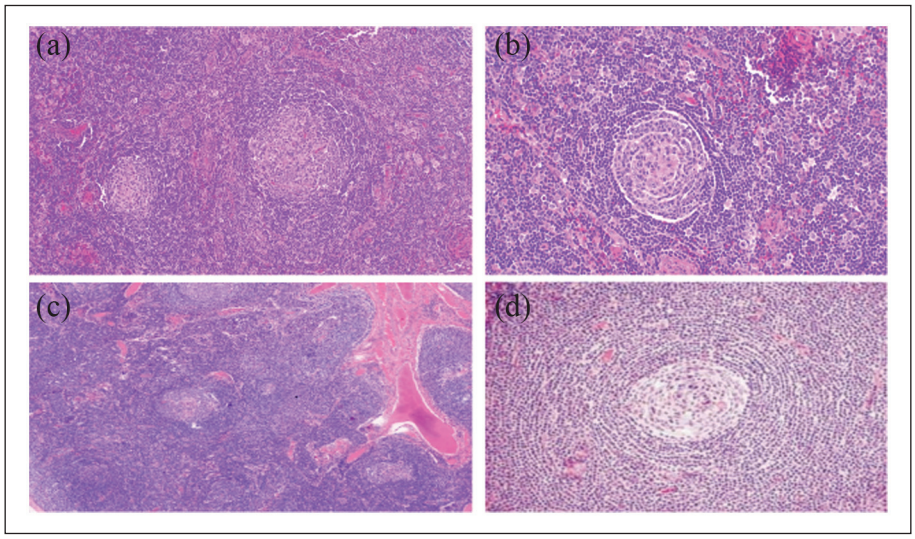

Figure 3. Histopathology of Castleman's disease displaying thickened mantle zones with lymphocytes arranged in layers—"onion skin appearance" H&E staining; low power (20×) original magnification (a); intermediate power (100×) original magnification (b and c); lymph node follicle surrounded by mantle zone composed of concentric rings of small lymphocytes, H&E staining, 40× original magnification (d).

occurs in the mediastinum, it may occur in any other areas of the body where lymph nodes are found, such as the lung, neck, axilla, mesentery, pelvis, or retroperitoneum.[6] It is often discovered incidentally during routine examination, chest X-rays, or due to discomfort secondary to local compression. Diagnosis is confirmed by histopathological assessment of the lymph node biopsy sent postoperative. Surgery is the gold standard treatment of UCD and has been advocated as the cornerstone of treatment most widely accepted therapy in the literature therefore; thus, the upfront excision decision was taken in our case for diagnostic and treatment.[10–12] The majority of CD patients do not seek treatment until they have comorbid conditions that affect or interfere with their quality of life. The majority of MCD cases that are documented involve male patients who are older than 50 years and either have advanced HIV or have additional conditions like Kaposi's sarcoma.[6] With the introduction of antiretroviral therapy (ART), the incidence of HHV-8-MCD has increased and there is a complex interplay between HIV and HHV-8 and immune dysregulation of patients with HIV that is controlled by ART. Prognostically, HHV-8-MCD caries poorer prognosis, especially HIV-positive patients.[5–7] MCD affects mainly HIV-positive individuals; but individuals who are immunocompromised from other causes can also be affected. HHV-8-MCD in individuals who are HIV negative accounts for 2%–50% of cases and this variation depends on the prevalence of HHV-8 in the region.[6]

Histopathological analysis, which distinguishes between three forms of CD—HV, plasma cell, and mixed variant—is used it to confirm diagnosis. The most prevalent clinical form is hyaline-vascular types;[7] 90% of

instances show follicular hyperplasia, regressed germinal centers, and vascular proliferation, whereas plasma cell types show large lymphoreticular nodules, Russell bodies, and hyaline blood arteries, and mixed types show characteristics of both HV types and plasma variants.[7,8]

As it was in case 1, HV-CD usually presents as a large mass involving a lymph node (or group of lymph nodes). The hyaline variant represents 80%–90% of all cases of localized of CD. This variant occurs over a broad age range and, in most studies, males and females are equally affected. If patients with HIV infection are excluded, HV-CD occurs in younger patients than does plasma cell variant CD.[9] The management for this uncommon and poorly known disease is largely controversial. However, the recommended treatment approaches are based on the severity of the condition; although not supported by strong evidence.[5–7] Symptomatic UCD can be surgically treated when symptoms are persistent. Patients with diseases that are not amenable to surgical resection, may benefit from tumor volume reduction therapy using vascular ablation, radiation, steroids, embolization or cryoablation of feeding vessels, rituximab, and follow-up evaluation.[10–13] Rituximab (375 mg/m^2 weekly for 4 weeks) is advised as the first line of treatment for HHV-8-MCD with mild symptoms. If there are severe organ dysfunction or systemic symptoms, etoposide (100 mg/m^2 weekly for 4 weeks) should be considered. If there are severe symptoms and concurrent Kaposi's sarcoma, anthracycline therapy has been recommended.[14,15]

Potential caveat in our case is the limited access to comprehensive diagnostic tests. For instance, we were not able to perform flow cytometry, kappa/lambda, CD138 immunohistochemistry (IHC) as well as viral IL-6 due to financial constraints. Thus, we were unable to confidently exclude potential differential diagnoses of conditions, such as reactive lymphoid hyperplasia with "Castleman-like" features. Expression of IL-6 has been demonstrated in Kaposi's sarcoma, primary effusion lymphoma, MCD, and in an MCD-like systemic inflammatory syndrome observed in HIV-positive patients.

CD is a rare, poorly understood lympho-proliferative disorder that share common lymph node morphological features.[1,2] Patients with CD can have markedly different presentations and clinical courses, with some lesions requiring innovative approaches to therapy. The major unifying feature for CD is the histologic appearance. Nevertheless, the histologic findings of CD are not specific. Thus, CD as presently defined, is heterogeneous and most likely represents multiple distinct diseases that share common histologic reaction patterns.[3]

Conclusion

CD is an unusual heterogeneous group of lympho-proliferative disorders with some common morphological features involving lymph nodes or extranodal sites. This report describes two cases of CD we encountered in our facility. Persistent lymphadenopathy due to CD may easily be confused clinically with other common causes of lymphadenopathy like lymphoma, TB, and nodal metastases. Thus, histopathology is the mainstay diagnostic approach. It is also important to remember that all patients diagnosed with CD should receive a systemic survey to exclude the possibility of ignored lesions. Surgical removal and or neo-adjuvant chemotherapy may be useful in symptomatic cases.

Acknowledgements

The authors would like to thank Ms Ruth Moshi, Ummil-Khairat Jaabir Koosa, and Daniel Mbwambo for supporting this study as well as the patient for allowing us to use his medical information for academic purpose in this publication.

Author contributions

E.N. and A.M. conceived the study. E.N., L.S., E.M., and K.K. participated in data acquisition and were involved in the patient management. A.M. reviewed histopathology specimen and made histopathology images. E.N. made initial manuscript draft. A.M. critically reviewed and made the final manuscript version. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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