CASE REPORT

Huge splenomegaly, a rare presentation of multicentric Castleman's disease in an HIV-infected patient: a case report and literature review

Malihe Hasannezad[1#], Abdolkarim Haji Ghadery[2#], Sara Ghaderkhani[3], Armin Vazirian[3], Fereshteh Ameli[4], Farid Azmoudeh-Ardalan[4], Mohammad Reza Rafiian Naini[3], Ladan Abbasian[1]

[1]Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High Risk Behaviors, Department of Infectious Diseases, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Radiology, Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Infectious Diseases, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

[#]These authors contributed equally to this work.

Abstract

Introduction: Castleman's disease (CD) is characterized by non-neoplastic lymph node hyperplasia, and may be localized in a single lymph node (unicentric) or occurs systemically (multicentric). Nowadays, multicentric CD is most commonly observed in individuals infected with human immunodeficiency virus (HIV) type 1, in association with Kaposi's sarcoma. Histopathologic and immunohistochemical evaluation of excised lymph node as well as imaging modalities, such as computed tomography (CT) and magnetic resonance imaging, are required for the diagnosis of CD.

Case description: We present a case of 46-year-old HIV-infected woman with fever, weakness, weight loss, and splenomegaly in the past 18 months. On physical examination, pale conjunctiva, jaundice, multiple cervical, inguinal, and axillary lymphadenopathies as well as hepatosplenomegaly were detected. Chest CT scan showed alveolar opacity in the lower lobe of the right lung and multiple lymph nodes in the mediastinum and bilateral perivascular, cervical, and axillary areas. Abdominopelvic CT scan showed huge splenomegaly, hepatomegaly, and multiple bilateral para-aortic, celiac, and inguinal lymphadenopathies, which were further confirmed as CD in pathological examination.

Conclusions: Huge splenomegaly is a rare manifestation in CD. Among the more prevalent differential diagnoses, CD in patients with HIV and huge splenomegaly was emphasized as important differential diagnosis.

HIV AIDS Rev 2024; 23, 3: 268-272
DOI: https://doi.org/10.5114/hivar/151536

Key words: splenomegaly, multicentric Castleman's disease, patients with HIV, case report.

Address for correspondence: Ladan Abbasian, Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran, e-mail: la-abbasian@sina.tums.ac.ir

Article history:
Received: 23.04.2022
Revised: 16.06.2022
Accepted: 22.06.2022
Available online: 20.09.2024

International Journal of HIV-Related Problems
HIV & AIDS Review

Introduction

Castleman's disease (CD), also known as angiofollicular and giant lymph node hyperplasia, is a rare lymphoproliferative disorder. CD is categorized into two major forms: unicentric CD (UCD) and multicentric CD (MCD). UCD is often asymptomatic and usually cured with surgical excision, whereas MCD is always symptomatic and characterized by constitutional symptoms, lymphadenopathy, splenomegaly, raised inflammatory markers, and cytopenia [1]. In human immunodeficiency virus (HIV)-infected patients, MCD is associated with human herpesvirus 8 (HHV-8) infection [2]. The diagnosis of CD requires histopathologic and immunohistochemical analysis made upon biopsy of excised lymph node. Two major histological variants of the disease are hyaline vascular and plasmocytic. UCD is most commonly the hyaline vascular type, and MCD is typically the plasma cell type [3]. In this paper, we described a case of 46-year-old HIV-infected female patient with MCD who presented with massive splenomegaly, which is a rare manifestation.

Case description

A 46-year-old HIV-infected woman presented with intermittent fever, weakness, and fatigue, which persisted for 18 months. She gradually developed abdominal pain, nausea, and vomiting, and was diagnosed with pancreatitis (spleen size of 151 mm at that time). After several months, she sensed a heaviness in the abdomen and developed huge splenomegaly. She also mentioned a 5 kg weight loss in the last months. Finally, she developed jaundice before admission to our hospital.

This patient was diagnosed with HIV five years ago, and the source of HIV infection was her husband (sexual transmission). Tenofovir, emtricitabine, and efavirenz were prescribed, and the patient was adherent to the treatment. The patient's initial CD4+ count was 126 cells/mm^3, most recent CD4+ cell count was 180 cells/mm^3, and viral load has been undetectable for the last three years. The patient's CD4+ count and viral load trends are presented in Table 1. Despite ART treatment, low CD4+ count might have occurred due to CD disease, which caused pancytopenia. Firstly admitted 18 months ago, her laboratory findings showed pancytopenia, elevated liver enzymes, and alkaline phosphatase, with no abnormal findings in bone marrow aspiration. She was hospitalized several times and underwent a bone marrow biopsy based on the identified findings, including lymphadenopathy, pancytopenia, and hepatosplenomegaly. She underwent several blood transfusions due to severe anemia, and eventually came to our hospital with worsening of symptoms and abdominal pain in addition to productive cough and jaundice.

The patient was fully conscious on the first visit, and her temperature was 38 centigrade. Pale conjunctiva, jaundice, multiple cervical, inguinal, and axillary lymphadenopathies, abdominal distention, and hepatosplenomegaly were detectable on physical examination.

On abdominopelvic CT scan, huge splenomegaly (270 mm) with a compressive effect on the left kidney and hypodense areas without enhancement was seen in the spleen. Hepatomegaly with a dilated portal vein (16 mm), a prominent intra-hepatic bile duct, and a common bile duct of 11 mm in diameter were detected. Also, multiple bilateral para-aortic, and celiac and inguinal lymphadenopathies (maximum diameter of 14 mm) were identified as well as calcified foci in the pancreas, suggestive of chronic pancreatitis (Figure 1). On pulmonary CT scan, alveolar opacity in the lower lobe of the right lung, and multiple lymph nodes in the mediastinum and bilateral perivascular, cervical, and axillary areas were observed (Figure 2). Cardiac ejection fraction was 50% on echocardiography. Patient's initial laboratory tests were as follows: pancytopenia (WBC: 2900/ml, Hgb: 8.5 gr/dl, platelet count: 76000/ml), elevated erythrocyte sedimentation rate (ESR) (120 mm/h; normal reference range (NRR): 0-30 mm/h), interleukin 6 (IL-6) (657 pg/ml; NRR: < 17 pg/ml), high C-reactive protein (CRP) (36 mg/l; NRR < 10 mg/l), alanine transaminase (ALT) (84 IU; NRR: 3-33 IU), aspartate aminotransferase (AST) (142 IU; NRR: 7-55 IU), alkaline phosphatase (1056 IU/l; NRR: 44-147 IU/l), lactic acid dehydrogenase (LDH) (627 U/l; NRR: 140-280 U/l), total bilirubin (3 mg/dl), NT-PRO-BNP (1252 pg/ml), and D-dimer (679 ng/ml; NRR < 250 ng/ml). Leishmania Ab, IgG, and IgM test was negative. Other laboratory findings, including serum electrolytes and proteins, blood and urine culture, urinalysis, iron profile (ferritin and TIBC), and coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio) were within normal ranges. Sputum smear and PCR for mycobacterium were negative.

During her stay in the hospital, the patient complained of pain and heaviness in the abdomen as well as fever and cough. Due to severe anemia, various packed cells were prescribed to the patient. Levofloxacin was administered due to diagnosis of bacterial pneumonia.

Table 1. Patient's CD4+ count and viral load trend annually

Year	2017	2018	2019	2020	2021
CD4+ count (cells/mm^3)	126	Not available	145	153	180
Viral load (copies/ml)	2591	Not available	293	Undetectable	Undetectable

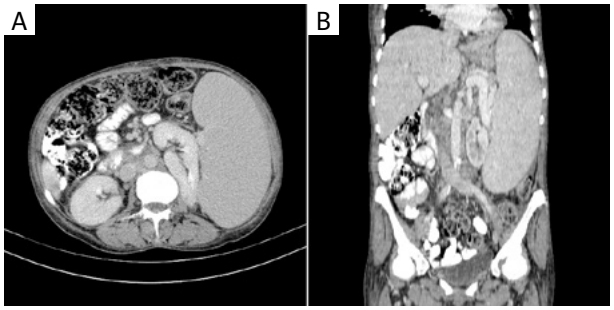

Figure 1. Abdominal CT scan of the patient. Axial (**A**) and coronal (**B**) views of the abdomen with huge splenomegaly (270 mm), and hepatomegaly and inguinal lymphadenopathies

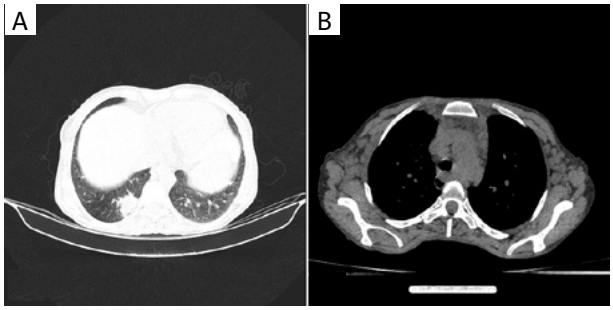

Figure 2. Chest CT scan of the patient. Parenchymal (**A**) view of chest CT scan with alveolar opacity in the lower lobe of the right lung. Mediastinal (**B**) view with multiple lymph nodes in the mediastinum

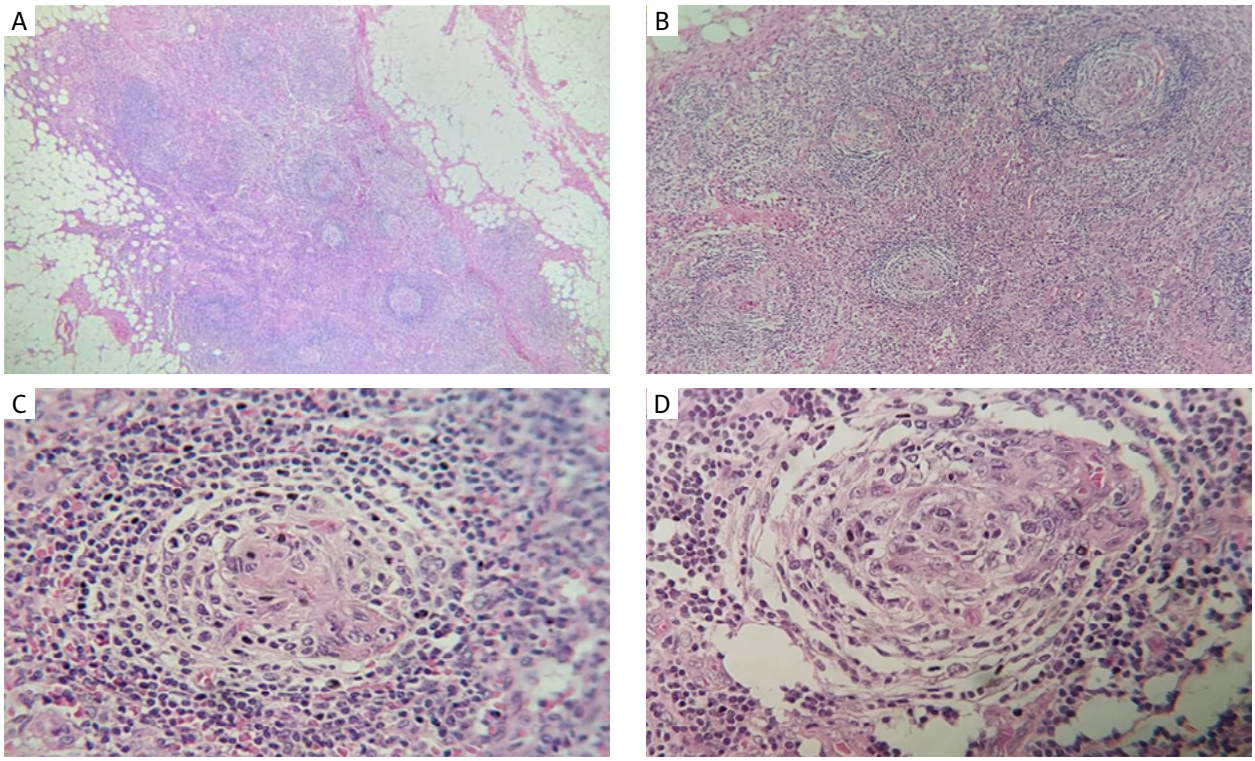

Figure 3. Histopathology of the lymph node characteristic of hyaline-vascular Castleman disease (HV-CD) (hematoxylin-eosin (H&E) staining). (**A**) (40× H&E): Photomicrograph showing lymph node with follicular hyperplasia, composed of lymphoid follicles of variable size and shape. Outside the follicles, inter-follicular region is greatly expanded by proliferation of high endothelial venules and a mixed cell population of inflammatory cells. (**B**) (100× H&E): The distinctive follicles show atrophic hyalinized germinal centers and a broad mantle zone. At right angles, a "lollipop" appearance in the follicle. Hyalinized mantle zones are expanded and consist of several concentric layers of mature lymphocytes around the follicles, creating an onion skin appearance. (**C**) and (**D**) (400×, H&E): Blood vessels penetrate the germinal center; cores of the germinal centers are composed mostly of follicular dendritic cells (FDCs), endothelial cells of proliferating vessels, and scant residual follicle center B-cells

Subsequently, she underwent bone marrow, lymph node, and liver biopsy.

In the liver biopsy, the only pathological finding was hemosiderin in phagocytes. PCR and smear for mycobacterium were negative, and Leishman's body was not detected. Bone marrow biopsy revealed an increase in plasma cells, and no Leishman's body. PCR and smear for mycobacterium were negative. Microscopic examination of the lymph node showed an abundance of CD20 cells, follicular hyperplasia in lymph nodes with hyalinized

germinal centers, and a broad mantle zone, which was mostly composed of follicular dendritic cells (FDCs), endothelial cells of proliferating vessels, and scant residual follicle center B cells (Figure 3). After the bone marrow pathology report, the patient was referred to an oncologist with MCD diagnosis for chemotherapy.

Discussion

Castleman's disease is a rare lymphoproliferative disorder that affects the body's lymph nodes and immune cells. CD was first described by Benjamin Castleman in 1956 [4]. Despite the rarity of the disease, CD has recently attracted much research interest due to its association with HHV-8 and HIV. HIV-infected individuals are at increased risk of MCD, and the incidence of HIV-associated MCD has increased since the introduction of antiretroviral therapy (ART) for HIV treatment [5]. While reasons for an increased number of MCD related to ART are uncertain, Casper *et al.* [6] showed on multivariate analysis that non-Caucasian ethnicity, increased age, and nadir CD4+ count > 200/μl are risk factors for developing MCD in HIV-infected patients.

HIV-associated MCD presents with non-specific symptoms suggestive of an inflammatory illness accompanied with fever, fatigue, night sweats, weight loss, łymphadenopathy, splenomegaly, and hepatomegaly. Subsets of patients may demonstrate edema, body cavity effusions, and cutaneous and neurological findings [7]. Typical laboratory results in MCD include universal anemia, thrombocytosis, hypoalbuminemia, polyclonal hypergammaglobulinemia, and increased levels of CRP, ESR, and IL-6 [1, 8]. Diagnosis is confirmed upon an examination of excisional biopsy of a lymph node. The classical features observed in MCD lymph node biopsy include follicular hyperplasia, regressively transformed germinal centers, and radially penetrating hyalinized capillaries; mantle zones are expanded with concentric layers of small lymphocytes imparting an "onion skin" appearance and an inter-follicular expansion of plasma cells [9,10]. The exact pathogenesis of CD is still unknown, but a review of literature suggests that excessive release of IL-6 and unregulated B cell proliferation are associated with CD [11, 12]. Moreover, IL-6 is considered responsible for the growth and differentiation of lymphocytes and plasmacytes, leading to lymph node enlargement and hepatosplenomegaly accompanied with B symptoms (i.e., fever, night sweats, weight loss) [13].

On a CT scan, CD classically presents with slightly hypodense to isodense lesions, while the degree of enhancement varies on contrast-enhanced CT images [14], and can often show calcification or high vascularization in lesions [15]. Lesions larger than 5 cm can show low central attenuation due to central fibrosis, and intralesional calcification can occur in 30% of lesions [16]. According to a systematic review that included 72 patients with HIV-associated MCD, splenomegaly was present in 86% of patients at the time of diagnosis [17]. However, huge splenomegaly has rarely been reported in CD patients. Ricciardi *et al.* [18] showed CD in a common variable immunodeficiency patient with huge splenomegaly (greater than 30 cm in ultrasound examination). Jain *et al.* [19] also reported massive splenomegaly in a 28-year-old CD patient with myelofibrosis and TAFRO syndrome. Another case report by Suneja *et al.* [20] demonstrated a 48-year-old patient with CD and kidney involvement who developed massive splenomegaly in follow-up visits after one year. Another case of CD with non-cirrhotic portal hypertension and ascites was reported with splenomegaly (20 cm in ultrasound examination) [21].

In the current paper, we presented a patient with a rare presentation and an indolent process. As opportunistic infections, such as kala-azar and mycobacterium, especially in endemic regions, are the priority of differential diagnosis, MCD should be considered along with other findings in HIV- infected patients.

Conclusions

Here, MCD in HIV-infected patient with huge splenomegaly is presented. As massive splenomegaly is relatively rare in HIV patients, we aimed to draw clinicians' attention to show a possible differential diagnosis.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

References

1. Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. AIDS 1996; 10: 61-67.
2. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995; 86: 1276-1280.
3. Cronin DM, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. Adv Anat Pathol 2009; 16: 236-246.
4. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling thymoma. Cancer 1956; 9: 822-830.
5. Powles T, Stebbing J, Bazeos A, Hatzimichael E, Mandalia S, Nelson M, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol 2009; 20: 775-779.
6. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol 2005; 129: 3-17.
7. Oksenhendler E. HIV-associated multicentric Castleman disease. Curr Opin HIV AIDS 2009; 4: 16-21.

8. Bower M, Powles T, Williams S, Davis TN, Atkins M, Montoto S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Intern Med 2007; 147: 836-839.
9. Du M, Bacon C, Isaacson P. Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 and lymphoproliferative disorders. J Clin Pathol 2007; 60: 1350-1357.
10. Dupin N, Diss TL, Kellam P, Tulliez M, Du MQ, Sicard D, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood 2000; 95: 1406-1412.
11. Yabuhara A, Yanagisawa M, Murata T, Kawai H, Komiyama A, Akabane T, et al. Giant lymph node hyperplasia (castleman's disease) with spontaneous production of high levels of b-cell differentiation factor activity. Cancer 1989; 63: 260-265.
12. Leger-Ravet M, Peuchmaur M, Devergne O, Audouin J, Raphael M, Van Damme J, et al. Interleukin-6 gene expression in Castleman's disease. Blood 1991; 78: 2923-2930.
13. Murakami M, Kamimura D, Hirano T. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. Immunity 2019; 50: 812-831.
14. Zhao S, Wan Y, Huang Z, Song B, Yu J. Imaging and clinical features of Castleman disease. Cancer Imaging 2019; 19: 1-8.
15. Hill A, Tirumani S, Rosenthal M, Shinagare A, Carrasco R, Munshi N, et al. Multimodality imaging and clinical features in Castleman disease: single institute experience in 30 patients. Br J Radiol 2015; 88: 20140670. DOI: 10.1259/bjr.20140670.
16. Meador TL, McLarney JK. CT features of Castleman disease of the abdomen and pelvis. Am J Roentgenol 2000; 175: 115-118.
17. Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. AIDS Rev 2008; 10: 25-35.
18. Ricciardi L, Furci F, Ieni A, Macrì A. Castleman disease in a patient with common variable immunodeficiency. Case Rep Immunol 2019; 2019: 5476383. DOI: 10.1155/2019/5476383.
19. Jain P, Verstovsek S, Loghavi S, Jorgensen JL, Patel KP, Estrov Z, et al. Durable remission with rituximab in a patient with an unusual variant of Castleman's disease with myelofibrosis – TAFRO syndrome. Am J Hematol 2015; 90: 1091-1092.
20. Suneja S, Chidambaram M, Herzenberg AM, Bargman JM. Kidney involvement in multicentric castleman disease. Am J Kidney Dis 2009; 53: 550-554.
21. Pinto AL, Gomes M, Cipriano MA, Ribeiro ML. Non-cirrhotic portal hypertension associated with multicentric Castleman's disease: a case report. Acta Oncol 2018; 57: 703-705.