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# MULTICENTRIC HYALINE VASCULAR-TYPE CASTLEMAN'S DISEASE: A CASE REPORT.

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**ABSTRACT** Castleman's disease is a rare lymphoproliferative disorder presenting with localized or disseminated lymphadenopathy and systemic symptoms. It can be categorized clinically as unicentric or multicentric, histopathologically as hyaline vascular, plasma cell, or mixed variant, and etiologically, considering the subtypes based on causative viral agents or associated with other syndromes. The multicentric type can mimic other haematological malignancies, ranging from asymptomatic to multiple organ involvement. Although its pathophysiology is not well known, the current approved treatments are directed towards interleukin-6, CD-20, and viral agents. The authors present a 79-year-old woman presented with a history of a rapid worsening of constitutional symptoms. Examination revealed pallor, hepatosplenomegaly, and palpable axillary and left inguinal lymphadenopathy. Investigation showed anaemia, thrombocytopenia, high levels of beta2-microglobulin, and high acute phase reactants, especially of IL-6. The Total-Body 18FDG-PET scan revealed multiple laterocervical, mediastinal, inguinal and paraortic lymphadenopathies. She underwent an excisional biopsy of the left-superior para-aortic lymph node with a retroperitoneal surgical access. The lymph node biopsy was consistent with hyaline vascular-type Castleman's Disease without human herpersvirus-8 markers. She started targeted therapy with Siltuximab with immediate improvement. Castleman disease has a broad spectrum of clinical manifestations, associations, and complications that bring a diagnostic challenge, requiring a multidisciplinary approach. Clinicians should be familiar with its features because proper diagnosis and aggressive targeted treatment are the pillars of proper management of these patients.

**KEYWORDS :** Castleman's disease, hyaline vascular, lymphadenopathy, multicentric.

## INTRODUCTION

Castleman disease, also known as angiofollicular or giant lymph node hyperplasia, is a rare lymphoproliferative disorder that was first described by Castleman et al in 1954 [1]. Based on the histologic criteria, Castleman disease is classified into three types: hyaline vascular, plasma cell, and mixed hyaline vascular plasma cell type [2]. CD also has two clinicopathological presentations, namely: unicentric Castleman disease (UCD) and multicentric Castleman disease (MCD) forms, wherein the unicentric forms are more common [1,2,5,6,8]. The UCD form presents as a solitary (unifocal) lymph node lesion especially in the mediastinum and less commonly in extrathoracic sites and may not be accompanied by systemic symptoms such as fever, night sweats, fatigue, weight loss, splenomegaly, anemia, and hypergammaglobulinaemia [1,2,5,6,8]. The MCD form, on the other hand, presents as a multifocal lymph node lesion with generalized lymphadenopathy, especially in the neck region, associated with more aggressive systemic symptoms such as fever, night sweats, fatigue, cachexia, splenomegaly, cytopenia, and hypoglobulinemia/hyperglobulinemia, hence resembling a malignant (Hodgkin's) lymphoma [1,2,5,6,8]. Furthermore, this MCD form can be subcategorized into three subtypes, namely: human herpes virus-8 associated MCD (HHV8-MCD), polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes-associated MCD (POEMS MCD), and idiopathic MCD (iMCD) [2,6,8,9]. Additionally, iMCD is further subdivided into two types, namely: iMCD associated with thrombocytopenia, anasarca, fever, reticulin myelofibrosis and renal dysfunction and organomegaly (iMCD-TAFRO) and iMCD not associated with TAFRO hence not otherwise specified (iMCD-NOS) [2,8]. It is also noted that non-idiopathic MCDs occur in the background of human immunodeficiency virus (HIV) infection especially in association with Kaposi sarcoma herpesvirus (KSHV) or HHV8 as well as in association with secondary amyloidosis [1,2,6,8,10]. Histomorphologically CD is distinct from malignant lymphoma; however, these two lesions can coexist or even, indeed, mimic each other [1,6,11-18]. In such scenarios, immunohistochemical (IHC) evaluation of the lymph node specimen in addition to routine H&E histopathological evaluation becomes the gold standard in arriving at a definitive diagnosis [1,5,11,13-15,19]. This case is reported because of its rarity and thus should be considered in the differential diagnosis of generalized lymphadenopathy, and also to show how important IHC is in resolving diagnostic dilemmas in lymph node pathology.

## CASE PRESENTATION

A 79-year-old woman was admitted to our hospital because of diffuse lymphadenopathy. During the last haematological examination in 2018, the patient had no signs of suspected lymphadenomegaly related to haemopathy (non-pathological ultrasound character <15mm in diameter) and was subjected to serological blood chemistry tests to exclude CMV, EBV, Bartonella and Toxoplasma infections. The patient's past medical history includes outcomes of removal of squamous cell carcinomas of the lower limbs, cholecystectomy due to lithiasis and removal of uterine fibroid, diverticulosis of the colon, COPD in heavy smoker, steatotic hepatomegaly, horseshoe kidneys with cortical cysts and CRF, arterial hypertension, dyslipidemia. Multiple intolerances reported, absence of B-symptoms and of superficial palpable axillary or inguinal adenomegaly. After performing a total body $^{18}$F-FDG PET/CT scan in February

2021, the patient comes to our attention with the diagnosis of multiple uptaking lymph nodes of possible lymphomatous nature, located in the supra and subdiaphragmatic areas, in particular at the right laterocervical 1st level (SUVmax 7.1), in the epiaortic area (SUVmax 6.9), in the retrocrural region (multiple findings, the most uptaking with SUVmax 7.6) and in the paraaortic area (SUVmax 7.2) **[Figure 1, 2]**. An ultrasound diagnostic examination is then performed which highlights an increase in the size of an enlarged lymph node in the left inguinal area (already known from 2018), for which an excisional biopsy is proposed, detecting sclerolipomatosis. Hematological re-evaluation is also required, which recommends repeating the biopsy sampling on the most uptaking and probably most significant lymph node.

A contrast enhanced and nonenhanced CT scan was performed, which confirms the presence of three enlarged lymph node packets already known at the site: laterocervical 1st level right (14x9mm), epiaortic (14x14mm) and paraaortic at the thoraco-abdominal passage (28x23mm). Thus we planned an abdominal lymphadenopathy biopsy of the left-superior periaortic lymph node, with retroperitoneal surgical access, in collaboration with the Vascular Surgery colleagues. The histological diagnosis revealed an overall preserved architecture with congestion of the sinuses and lymphatic follicles, which presented concentric hyperplasia of the mantle zone and sclerotized, involved germination centers; the interfollicular areas were characterized by prominent vascular proliferation and hyalinization of vessel walls. The in-situ hybridization detected also the presence of plasma-cells (CD138 +, IgG +, IgG4 scarce) and a regular relationship between kappa / lambda light chains of the immunoglobulins.

It is also observed a regular distribution of CD3 and CD20 immunoreactivity, respectively positive in the paracortical and in the cortical areas; low activity of ki67 in the involuted germinal centers, which resulted as CD10 + / BCL6 + / BCL2-; hyperplasia of the CD23 + dendritic follicular cell networks. The lymph node biopsy was consistent with hyaline vascular-type Multicentric Castleman's Disease without human herpersvirus-8 markers. At the next haematological check, after 10 days, the patient presented symptomatic with expired general conditions, persistent pain in the left flank, expanded and meteoric abdomen, ascitic effusion (confirmed by the abdominal CT scan performed the same day), mucocutaneous pallor and declining edema in chronic venous insufficiency with skin discoloration and venous angiectasias.

At physical examination we detected besides submental lymphogranulia, laterocervical, axillary and inguinal palpables lymphadenomegalies (20mm). The high dosage of IL-6 was adequate for setting up a targeted therapy with Siltuximab, that she started with immediate improvement.

**Figure 1. 1st level laterocervical right enlargedand uptaking lymph node.**

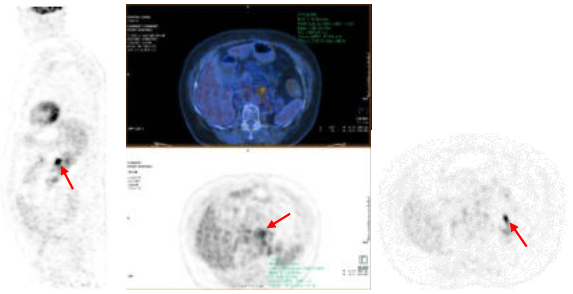

**Figure 2. Left-superior paraaortic enlargedand uptaking lymph node.**

## DISCUSSION

CD is a rare clinicopathological disease entity with various subtypes [1,2,5]. The etiology of CD remains largely unknown; however, it is of note that some association with immunosuppressive conditions mediated by HIV, Epstein Barr virus, KSHV (Kaposi's sarcoma-associated herpes virus) or HHV-8 (human herpes virus-8) as well as secondary amyloidosis have been found in some cases [2,6,8-10,20]. The incidence of CD also remains largely unknown; however, it is of note that the prevalence of CD is approximately < 1 per 100,000 worldwide. The majority of CD cases are adults, particularly females, within the third to fourth decade for UCD and fourth to fifth decade for MCD, with UCD accounting for approximately 87% of CD cases [1,18].

The hyaline vascular (HV) subtype of CD is characterized histomorphologically by prominent vascular proliferation and hyalinization of vessel walls admixed with variable follicular patterns such as lollipop follicles, onion skin mantle zone, and mantle zones fusion with twinning of germinal centers [1,22,23]. This subtype accounts for approximately 90% of cases and commonly seen in the unicentric form (UCD) of the disease, among young adults [1,4,5,23]. It is asymptomatic in over 50% of cases, indeed most cases are often discovered incidentally on imaging studies, detected as a soft-tissue mass located in the neck or mediastinum and more rarely in the retroperitoneum [4]. The plasma cell subtype of CD is characterized histomorphologically by sheets of mature plasma cells within the interfollicular zones of the lymph node interspersed by surrounding hyperplastic germinal center with deteriorated vascularity [1,11]. The MCD form of CD is associated with the plasma cell variant [1]. It usually affects older patients and clinically it is characterized by generalized lymphadenopathy, constitutional symptoms, multisystem organ involvement, and deranged laboratory findings [6,9,18,24]. These constitutional symptoms are considered a consequence of a very serious hypercytokinemia-driven inflammatory syndrome mostly caused by interleukin-6interleukin-2 (IL2), and vascular endothelial growth factor (VEGF) [1,6,8,9,18,20,25]. These constitutional symptoms include: pallor, chronic diarrhea, asthenia, fever, weight loss, generalized lymphadenopathy, edema (sometimes ascites and/or anasarca), and hepatosplenomegaly [1,6,8,9,18]. The deranged laboratory findings include: anemia, thrombocytosis or thrombocytopenia, hypoalbuminemia, hypocholesterolemia, hypergammaglobulinemia, proteinuria, increased acute phase reactants (such as serum C-reactive protein), and increased chemical mediators of inflammation levels (such as IL6, IL2, and VEGF) [6-9]. MCD is further subclassified according to the presence/absence of HIV/HHV-8. Almost half of MCD cases are caused by HHV-8 infection in HIV-positive individuals, while approximately half of the patients with MCD are HIV/HHV-8 negative, and these cases were referred to as idiopatic MCD [1,6,10]. The idiopatic variant shows histological features of both hyaline vascular and plasma cell variant of CD. The clinical progression of MCD is often fatal due to high risk of opportunistic infections and likelihood of malignant neoplastic transformation often to Kaposi sarcoma and lymphoma [2,6,18]. Our patient in this case report was diagnosed with the hyaline vascular-type

multicentric HH8-negative CD. She presented with mucocutaneous pallor, expanded and meteoric abdomen, ascitic effusion, declining edema and generalized lymphadenopathy consistent with MCD in addition to other histological characteristics associated with this subtype of CD in agreement with CD literature reviewed above. Interestingly, it is of note that though MCD is associated with HIV and HHV-8 infection, with some studies even demonstrating the presence of the HHV-8 sequence in approximately 60 to 100% of patients infected with HIV and 20 to 41% in those who were not, our index patient was HIV negative and her IHC evaluation was also negative for HHV-8 expression antibodies [1,14,15,25]. Yuanyuan et al have concluded that $^{18}$F-FDG PET/CT is effective in evaluating the involved lymph nodes throughout the body in patients with MCD [26]. The gold standard for our diagnosis in this case was a combination of $^{18}$F-FDG PET/CT scan, routine histopathological and IHC evaluations of her abdominal lymph node biopsy. Indeed IHC evaluation in combination with routine histopathological evaluations has been recommended as a standard method for lymph node examination especially where routine histopathological evaluation is nonspecific [1,5,11-15,19]. Surgical resection of the affected lymph node is the treatment of choice for UCD, usually with no risk of recurrence; however, the MCD variant requires multimodal therapies with cytotoxic chemotherapy or CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, or prednisolone)/CHOP (cyclophosphamide, vincristine, doxorubicin, dexamethasone, or prednisolone), corticosteroids (dexamethasone/prednisolone), immunomodulators (lenalidomide or thalidomide, bortezomib, interferon □), intravenous immunoglobulins, plasmapheresis, radiotherapy, monoclonal antibodies (tocilizumab, siltuximab, and rituximab) and autologous hematopoietic stem cell transplantation. The latter guidelines for idiopathic MCD presume the evaluation of the severity of the disease to decide the best treatment approach, being anti-IL6 monoclonal antibody the first line of treatment, with siltuximab or, as an alternative, tocilizumab [2,6,9,18,20]. In accordance with these literature our patient was successfully treated with Siltuximab. It is of note that a combinations of these treatment options give a better prognosis in MCD [9,18,20]. The IL-6 monoclonal antibodies (tocilizumab and siltuximab) are particularly useful in the alleviation of systemic manifestation [6,18,20]. Fortunately, a 5-year survival rate of 82% have been reported in MCD, a much better prognosis when compared with lymphoma [27].

CD is extremely rare, so it is necessary to improve the awareness of its diagnosis. It is helpful to refer to imaging results for the diagnosis of CD and make treatment plans based on pathological results. Multicentric hyaline vascular subtype of CD can present as a diagnostic dilemma because of its overlapping clinicopathological presenting features similar to malignant (Hodgkin's) lymphoma. Hence, this case report brings to the fore the importance of carrying out IHC evaluation of lymph node biopsy specimens for definitive diagnosis in view of expert management.

## CONFLICT OF INTEREST

The author declares no conflict of interests regarding the publication of this paper.

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