

# Castleman Disease: Aging is not an Obstacle Despite of Being a Rare Disease



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## Abstract

Castleman's Disease (CD) is a clinicopathological entity associated with lymphoproliferation. It could be presented as localized form of CD is referred to as unicentric (UCD), or the systemic. Form as multicentric (MCD) which is characterized by episodic systemic inflammatory symptoms and reactive lymphadenopathy. Here, we report a case 88 years old female patient who was initially clinically presented with a picture suspected to have lymphoma, but was later histologically confirmed to have CD. This case report underlines the importance of definitive histological diagnosis in patients presented with lymphadenopathies and multi organ involvement associated with systemic symptoms. The distinctiveness of MCD from malignant lymphoma is still under debate especially in HIV negative old patients.

**In conclusion:** As CD is rare, similar to other rare and orphan diseases, the diagnosis of needs to be made histologically. Treatment modalities include surgery, which is curative for unicentric disease, and systemic therapy, which is needed for multicentric disease. This case highlights the diagnostic value of lymph node excision biopsy in HIV-infected patients.

**Keywords:** Castleman's disease; Unicentric; Multicentric; Lymphadenopathy; Lymph node; Human immunodeficiency virus; Human herpes virus-8; Rituximab; Interleukin 6

**Abbreviations:** CD: Castleman's Disease; UCD: Unicentric; MCD: Multicentric; IL-6: Interleukin 6; HHV-8: Human Herpes Virus-8; HIV: Human Immunodeficiency Virus; iMCD: idiopathic MCD

## Introduction

Castleman's Disease (CD) is a heterogeneous group of lymphoproliferative disorders of uncertain etiology [1] presenting with lymphadenopathy. It is histologically and prognostically distinct from malignant lymph-node hyperplasia. It was first diagnosed in a group of patients with benign localized hyperplastic lymph-nodes in 1956 by Castleman et al. [2]. It presents as a localized or a systemic disease, most commonly in neck, axilla, mediastinum and pelvis [3]. CD presented with variable three histologic subtypes: hyaline vascular, plasma cell and mixed, while clinically there are two clinical types: multifocal (multicentric) or localized (unicentric) [3].

## Synonyms of castleman's disease

Angiofollicular Lymph-Node Hyperplasia, Giant Benign Lymphoma, Giant Lymph-Node Hyperplasia, Lymphoid Hamartoma

## Case Presentation

An 88 years old female patient referred to KING KHALED UNIVERSITY HOSPITAL, RIYADH with a history of weight

loss, lethargy, decreased appetite, associated with fever and productive cough with a picture suggestive of community acquired pneumonia of two weeks duration, with irrelevant past medical history. Upon examination, the patient did not appear chronically ill. His vitals included a blood pressure of 163/73mmHg, a respiratory rate of 25 breaths per minute and a temperature of 37.5 °C. Generalized lymphadenopathy was also detected, especially bilateral cervical and right axillary areas. The lymph nodes were hard, non-tender, mobile and measured 1-2cm in diameter. Examination of the heart and abdomen revealed no abnormalities. Lung examination revealed bilateral diminished air entry with bilateral sonorous rhonchi. Routine investigations such as full Blood count and biochemical profile (including hepatic function tests) were found to be within normal range except for mild leukocytosis. Serology for HIV was negative. Tumor markers were normal.

Computerized tomography revealed bilateral lung consolidation patches with bilateral parapneumonic effusion together with widespread generalized lymphadenopathy involving the neck, chest/mediastinum, abdomen, axillae, and

pelvis with no organomegaly (Figure 1). She was assessed because of her age to be high risk of having any hidden malignancy. Excision biopsy of the accessible axillary node was performed and this was reported as a lymphoproliferative picture (increased number of follicles containing amorphous hyaline material and some small blood vessels) between simple reactive changes and frank lymphoma, suggesting Castleman's Disease (CD). The immunohistochemical studies showed predominant plasma cell infiltrate of the lymph node (CD138 +ve), which are kappa and lambda phenotype, HHV-8 immunostain show focal

nuclear positivity in the lymphoid cells. So, histological findings confirmed features that were in keeping with early human herpes virus type 8 (HHV- 8)-associated multicentric (CD) (Figure 2-4). She was referred to a hematologist as a case of MCD. Because of her age and multiple comorbidities we have tried to weigh the risk of starting treatment versus the possibility of recurrent lethal infection and septicemia if left untreated. She was commenced on low dose of steroid therapy (prednisone 0.5mg/kg) and monthly rituximab 375mg/m<sup>2</sup> every 28 days which successfully induced disease remission and symptomatic relief.

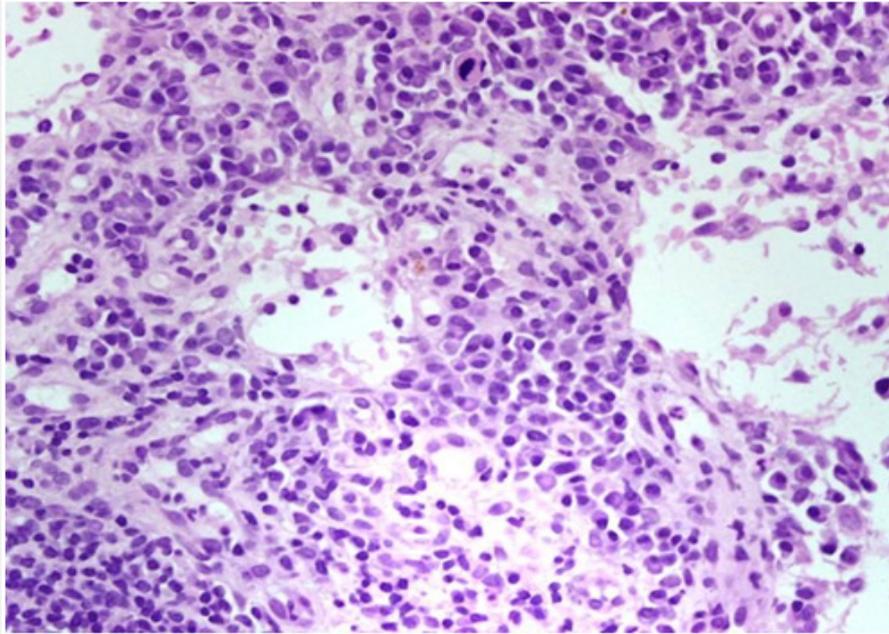


Figure 1: A high power view of the lymph node showing heavy plasma cell infiltrate (H&E stain, original magnification X400).

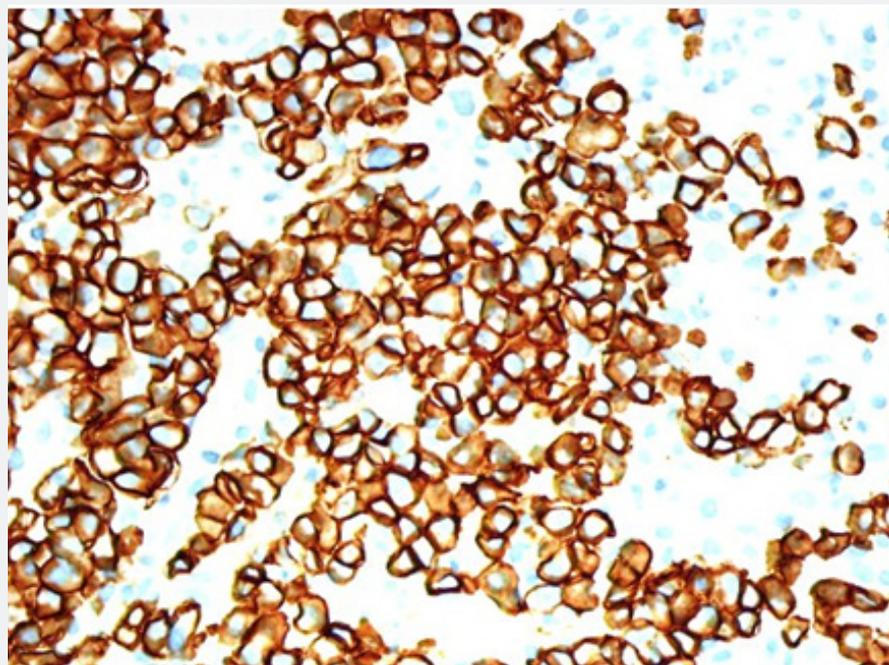
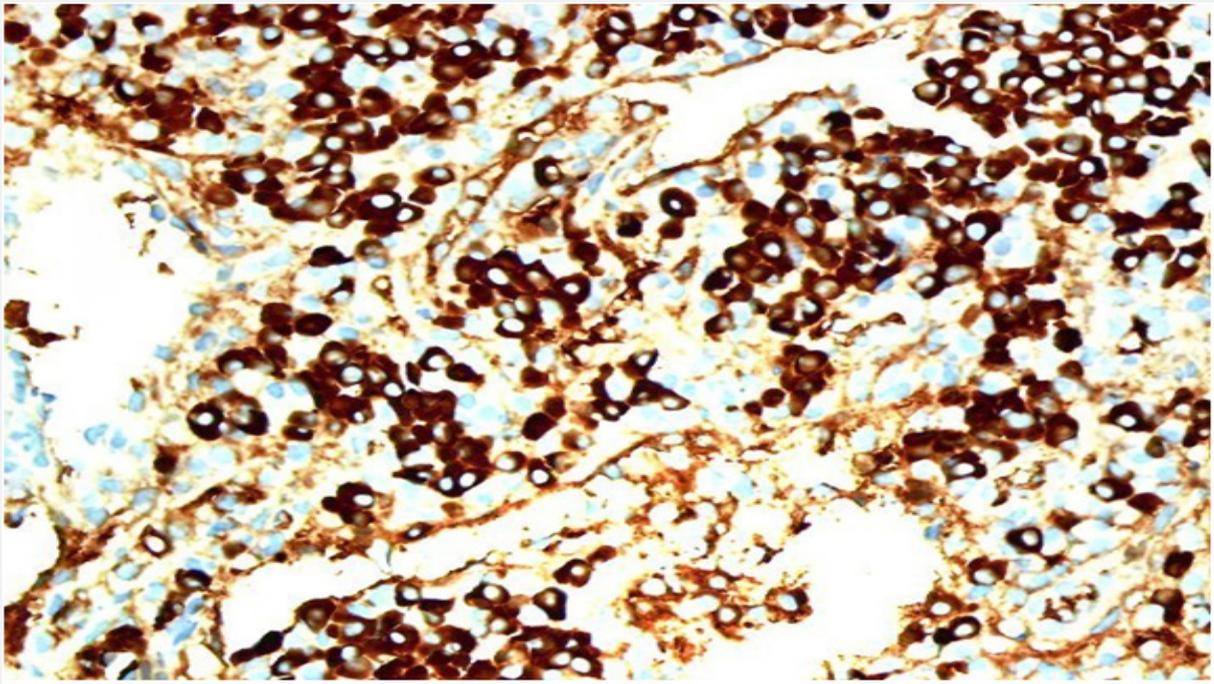
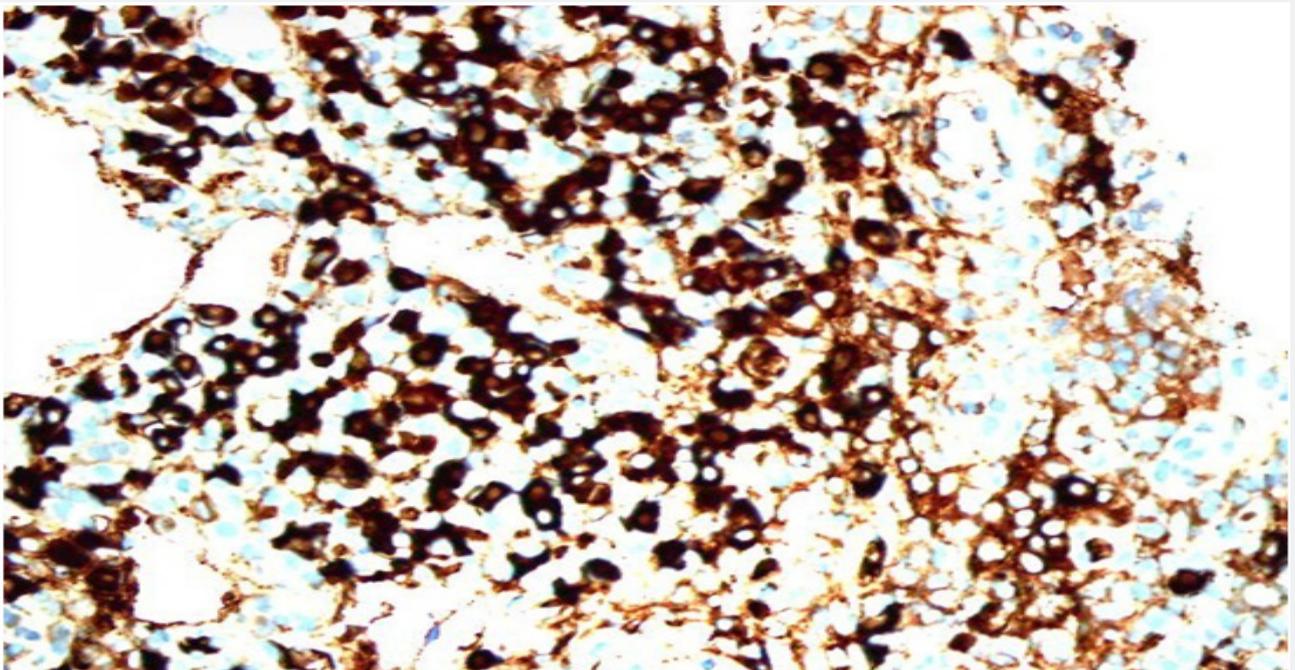


Figure 2: CD138 The immunohistochemical studies shows predominant plasma cell infiltrate of the lymph node.



**Figure 3:** The immunohistochemical studies shows predominant plasma cell infiltrate of the lymph node which are kappa.

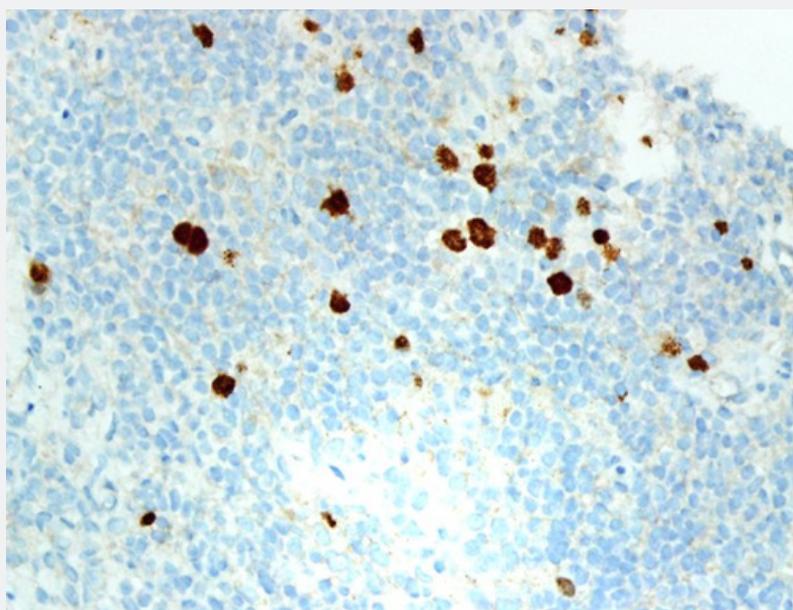


**Figure 4:** The immunohistochemical studies shows predominant plasma cell infiltrate of the lymph node and lamda phenotype.

### Discussion

Castleman's Disease (CD) is a lymph proliferative disorder, which is histologically characterized by angiofollicular Lymph-node hypertrophy [4]. It may be borne in mind especially in the differential diagnoses of localized/diffuse lymphadenopathy,

with or without systemic manifestations (Figure 5). Our case report, attempts to provide a new insight into this rather rare and relatively benign disorder, which, though mimicking lymphoma clinically, still it varies from the latter histologically, prognostically and in its management [4].



**Figure 5:** HHV-8 immunostain show focal nuclear positivity in the lymphoid cells. (Immunohistochemistry stain, original magnification X 400).

CD is a spectrum of disorders, could be presented as the localized form, which is referred to as unicentric (UCD), and the systemic form as multicentric (MCD). UCD is, by definition, localized to one site. It is characterized by lymphoid hyperplasia associated with excessive angiogenesis [1]. It is asymptomatic in over 50% of patients [5] and is often discovered incidentally.

MCD is characterized by episodic systemic inflammatory symptoms and reactive lymphadenopathy. MCD can be chaotic in behaviour and life threatening, with multiorgan failure resulting from excessive secretion of interleukin 6 (IL6) and other proinflammatory cytokines [6].

Infection with human herpes virus-8 (HHV-8) is well established as an etiology of human immunodeficiency virus (HIV)-associated MCD and a significant proportion of HIV negative MCD cases [7].

Multicentric CD is characterized by a predominantly lymphadenopathic presentation consistently involving peripheral lymph-nodes and manifestations of multisystem involvement. It is considered as a systemic B cell lymphoproliferation, probably arising in immunoregulatory deficit, and resulting in the outgrowth of clonal B-cell populations [1]. It is always symptomatic. Symptoms, primarily a consequence of elevated Interleukin-6 (IL-6) production, are asthenia, weight loss and fever [4]. Polyadenopathy is common with a mean of four sites involved and is often associated with hepatosplenomegaly [4]. Histological diagnosis is made upon biopsy of an excised peripheral lymph-node.

Histologically, there are three major variants of CD: The hyaline vascular variant, commonly seen in UCD, in which follicles are surrounded by a broad mantle zone composed of concentric rings of small lymphocytes (a so-called onion skin appearance). The plasma cell variant, which is more common in MCD, accounting for more than 75% of cases and a mixed variant [8].

HHV-8-positive MCD is characterized by proliferation of plasma cells and HHV-8-positive plasmablastic cells. The plasmablasts may coalesce to form microlymphomas, which are nonclonal [9].

The classification of MCD has been previously based on HIV status, recently, it is now based on HHV-8 status, as it was recently recognized that immunodeficiency associated with HIV infection or other immune compromised states that renders the patients vulnerable to infection with HHV-8. Efforts are ongoing to identify other potential etiologies in HHV-8 negative MCD, now referred to as idiopathic MCD (iMCD); possible etiologies are viral, inflammatory or neoplastic disorders. A syndrome of thrombocytopenia, generalized anasarca, bone marrow fibrosis, renal dysfunction and organomegaly (TAFRO syndrome) was described in a subset of patients with iMCD [10]. HHV-8-associated MCD may be considered as a single clinicopathological entity regardless of HIV status. MCD in the context of Human Immunodeficiency Virus (HIV) infection is well known and linked to human HHV-8. There are limited published data surrounding HHV-8-related CD among HIV-negative patients [11].

Here, we report a case of an 88 years old lady who was initially clinically suspected to have lymphoma (owing to clinical features at presentation), but was later histologically confirmed to have HHV 8 positive and HIV negative MCD. This case report underlines the importance of definitive histological diagnosis in patients with lymphadenopathic presentation associated with systemic symptoms and the distinctiveness of MCD from malignant lymphoma. The diagnostic criteria for CD require a lymph node biopsy. A not infrequent problem that faces physicians in clinical practice is identifying accessible nodes for biopsy in patients who are suspected to have CD.

Management of Localised CD is much easier as it is treated by surgical excision which allows full recovery without relapse in almost all cases. However, no therapeutic consensus exists for MCD as in our case and diverse treatments (surgery/corticotherapy/chemotherapy) are used, often in combination [4]. Anti-interleukin-6 antibody has also been successfully tried in the alleviation of systemic manifestations [12]. Single-agent chemotherapy may yield short-term responses. For example, treatment with oral etoposide or rituximab (anti CD20) monotherapy to patients without evidence of organ failure resulted in clinical remission lasting 6 and 12 months in 2 patients [13]. Multi-agent chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) has yielded long-term remissions [13].

The five-year survival rate in MCD is 82% and this prognosis appears to be far better than that encountered with malignant lymphomas [4].

In our case, because of her comorbidities we have chosen the monotherapy regimen with Rituximab 375mg/m<sup>2</sup> i.v. on days 1, 8, 15, 22 In 250-500ml NS (concentration 1-4mg/ml) over 3-8h and her general condition has been improved with no more signs of recurrent sepsis.

## Conclusion

This case report brings to light the importance of obtaining definitive histological diagnosis in patients presenting with lymphadenopathy and systemic symptoms. Multicentric Castleman's disease is a relatively uncommon cause for such a presentation. Though clinically synonymous with lymphoma, it is an entity that is distinct from malignant lymphoproliferative

disorders histologically and prognostically. It may be borne in mind as a differential diagnosis in lymphadenopathic presentations with symptoms of systemic involvement.

## References

1. Frizzera G (1988) Castleman's disease and related disorders. *Semin Diagn Pathol* 5(4): 346-364.
2. Castleman B, Iverson L, Menendez VP (1956) Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer*, 9(4): 822-830.
3. Abdessayed N, Bdioui A, Ammar H, Gupta R, Mhamdi N, et al. (2017) Retroperitoneal unicentric Castleman's disease: A case report. *Int J Surg Case Rep* 31: 54-57.
4. Sarrot-Reynauld F (2001) Castleman's Disease; Orphanet encyclopaedia p. 1-4.
5. Herrada J, Cabanillas F, Rice L, Manning J, Pugh W (1998) The clinical behaviour of localized and multicentric Castleman disease. *Ann Intern Med* 128(8): 657-662.
6. Fajgenbaum DC, Ruth JR, Kelleher D, Rubenstein AH (2016) The collaborative network approach: a new framework to accelerate Castleman's disease and other rare disease research. *Lancet Haematol* 3(4): e150-e152.
7. Suda T, Katano H, Delsol G, Kakiuchi C, Nakamura T, et al. (2001) HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. *Pathology international* 51(9): 671-679.
8. Talat N, Belgaumkar AP, Schulte KM (2012) Surgery in Castleman's disease: a systematic review of 404 published cases. *Ann Surg* 255(4): 677-684.
9. Oksenhendler E, Boulanger E, Galicier L, Du MQ, Dupin N, et al. (2002) High incidence of Kaposi sarcoma-associated herpes virus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 99(7): 2331-2336.
10. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, et al. (2017) International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. *Blood* 129(12): 1646-1657.
11. Codish S, Abu-Shakra M, Ariad S, Zirkin HJ, Yermiyahu T, et al. (2000) Manifestations of three HHV8-related diseases in an HIV-negative patient: immunoblastic variant multicentric Castleman's disease, primary effusion lymphoma, and Kaposi's sarcoma. *Am J Hematol* 65(4): 310-314.
12. Beck JT, Hsu SM, Wijdenes J, Bataille R, Klein B, et al. (1994) Brief report: alleviation of systemic manifestations of Castleman's disease by monoclonal antiinterleukin-6 antibody. *N Engl J Med* 330(9): 602-605.
13. Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, et al. (2008) Multicentric Castleman's disease in HIV infection: a systematic review of the literature. *AIDS Rev* 10(1): 25-35.



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