

## An Unusual Presentation of Idiopathic Multicentric Castleman Disease: The Great Masquerader

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### ABSTRACT

Castleman disease is an uncommon, non-clonal, lymphoproliferative disorder characterized by lymphadenopathy and symptoms related to hypercytokinemia. Clinically it is classified as unicentric and multicentric disease. Multicentric disease is further subclassified as HHV-8 associated disease and idiopathic disease, which is the rarest subtype. The incidence of idiopathic disease is estimated to be 5 per million person years. The diagnosis of Idiopathic Multicentric Castleman disease is complicated by an array of clinical mimics and non-specific symptoms. We report a rare case of Idiopathic Multicentric Castleman disease in a young female where a detailed pathological work up helped to secure the diagnosis and exclude its mimics.

**Keywords:** Multicentric, Idiopathic, Castleman Disease, Plasma Cells

### Introduction

Castleman disease (CD), first described by Benjamin Castleman, is a poorly understood, uncommon, heterogeneous group of non-neoplastic chronic lymphoproliferative disorder.<sup>[1]</sup> The clinical presentation and imaging, classifies the disease as localized/ unicentric disease involving only a single site and multicentric, involving multiple sites.<sup>[2,3]</sup> The mediastinum is the most common site for unicentric disease while Multicentric Castleman Disease (MCD) is usually a systemic disease with multisite lymphadenopathy and symptoms like fever, frequent infections, arthralgia, rash, anasarca, pleural effusion, weight loss and hepatosplenomegaly.<sup>[4,5]</sup> A subset of MCD is caused by human herpesvirus-8 (HHV-8), whereas HHV-8-negative MCD cases are idiopathic (iMCD).<sup>[6]</sup> Owing to its rarity and varied clinical presentation, MCD continues to pose a diagnostic challenge and may mimic many pathologic conditions. We report one such case with an unusual clinical presentation in a young female, which illustrates the polymorphic clinical and diagnostic features of Castleman's disease and lays emphasis on the importance of Histopathology and Immunohistochemistry (IHC) to clinch the diagnosis.

### Case Report

A 22-year-old female presented with low grade fever with weight loss, mild hepatosplenomegaly and massive bilateral submandibular, anterior cervical, axillary lymphadenopathy also involving parotid, mesenteric and

abdominal lymph nodes. She also had small, evanescent, non-pruritic erythematous rash on bilateral shin.

She had a surgical history of cholecystectomy done six months back for cholelithiasis and a past history of tonsillectomy for tonsillar hypertrophy at age 8. She also had past medical records of waxing and waning generalized lymphadenopathy over the last 15 years along with repeated episodes of fever with lower respiratory tract infection. During this period, on one such episode of fever, pulmonary infiltrates with mediastinal lymphadenopathy was detected on CT which was suggestive of Pulmonary Tuberculosis. However, with empirical Anti-Tubercular therapy there was only mild regression in size and the lymph nodes continued to persist. Also, FNAC and lymph node biopsy along with IHC and clonality study was done twice in the past which revealed florid lymphoid hyperplasia.

Her current signs and symptoms along with her past medical history led to the clinical work up for a differential diagnosis of Autoimmune disease, IgG4 associated lymphadenopathy and Lymphoma.

The initial laboratory workup showed microcytic hypochromic anaemia with Hb of 10g/dl, normal WBC and platelet counts and an elevated Erythrocyte Sedimentation Rate of 119 mm/hr. Biochemical parameters that were abnormal, were an elevated Serum protein (9.58g/dl) with decreased A:G ratio (0.6) due to increase in Serum globulin (5.99g/dl) and elevated IgG levels (4910mg/dl) with normal

IgG4, IgM, IgA, IgE and C3 levels. SGOT, SGPT and LDH levels were elevated. Renal and thyroid function tests were normal. Comprehensive Autoimmune and Collagen Vascular Disease work up was negative. Serology for HIV, HbsAg and HCV were negative. HIV fourth generation assay (P24Ag+HIVab) was also non-reactive. EBV (VCA)-IgM and IgG were both positive. Direct Coombs test was negative and fibrinogen levels were normal. CT showed enlarged parotid, bilateral cervical, axillary, mesenteric, iliac nodes, mild hepatosplenomegaly with small focal subsegmental area of air space consolidation with break down in left lower lobe of lung. Flow cytometry for double negative T cells (TCR  $\alpha\beta$ +DNT) for Autoimmune Lymphoproliferative syndrome (ALPS) was negative.

Cervical Lymph node excision biopsy submitted for histopathological examination revealed architectural distortion in terms of expanded mantle zone and interfollicular zone expansion with sheets of plasma cells intermingled with plasmablasts in the interfollicular area. The marginal and intranodal sinuses were dilated [Figure 1a-d]. No granulomas, no Reed-Sternberg cells and no evidence of primary or metastatic malignancy. These features suggested a morphological diagnosis of Castleman Lymphadenopathy- Plasma cell variant. Reflex comprehensive IHC panel comprising of LCA, CD20, CD3, BCL-2, BCL-6, CD15, CD30, CD138, MUM1, Kappa and Lambda cocktail and Ki-67 ruled out both Hodgkin and non-Hodgkin lymphoma. CD138 and MUM1 positivity highlighted the plasma cells [Figure 1e,f]. Kappa and Lambda cocktail confirmed that the dense plasma infiltrate is polyclonal in nature. EBV associated lymphadenopathy was ruled out by negative CISH for EBER. IgG4 related disease was ruled out by a negative IgG4 IHC. Tissue culture for mycobacterium species was negative. Serological correlation with IL6 and HHV8 was suggested. HHV8 serology turned out to be negative and serum IL6 level (16.15pg/ml-reference range 0-7pg/ml) was raised.

Corroborating the morphology with IHC, raised serum IL6 and negative HHV8 serology, the final diagnosis was made as Idiopathic Multicentric Castleman Disease. She was started on Rituximab monotherapy and is showing improvement in symptoms with significant regression in size of cervical lymph nodes. Follow up CT chest and abdomen showed no evidence of mediastinal or abdominal lymphadenopathy.

## Discussion

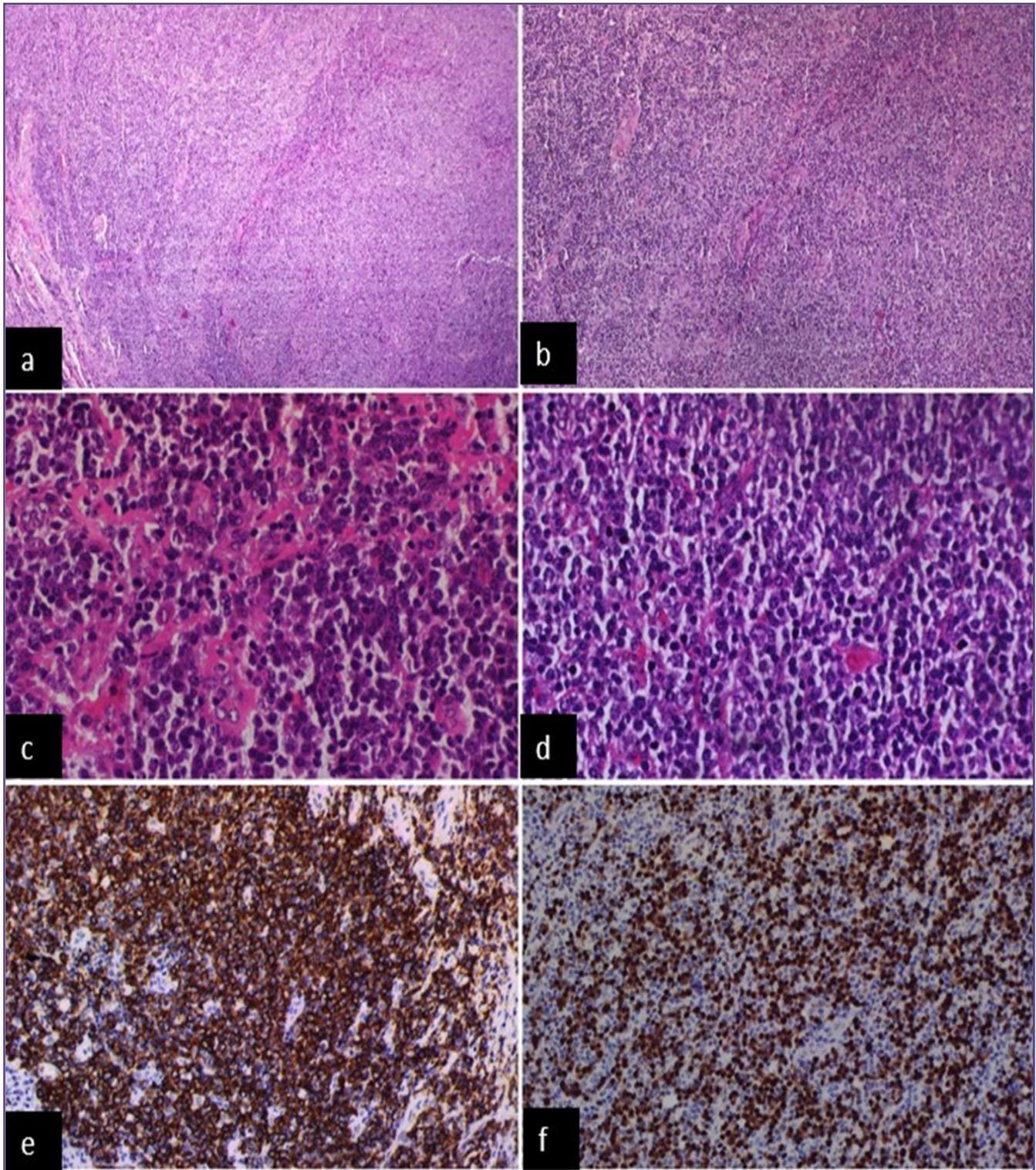
Castleman disease is a rare and heterogeneous group of diseases, characterized by non-clonal lymphoproliferation.<sup>[7]</sup> Unicentric disease (UCD) usually presents in young

adults with localized masses. In contrast, Multicentric Castleman's Disease (MCD) commonly presents in the age group of fifth to sixth decade with diffuse lymphadenopathy and is frequently associated with multi-organ involvement and systemic inflammatory symptoms. MCD is more aggressive than the localized variant and can present with exacerbations and remissions.<sup>[8]</sup>

MCD has been etiologically linked to Human Herpesvirus-8 (HHV-8), also known as Kaposi sarcoma-associated Herpes virus, especially in HIV-infected individuals.<sup>[3]</sup> HHV8 negative MCD also known as idiopathic MCD (iMCD) is extremely rare, can present in any age group and accounts for one third to one half of all cases of MCD.<sup>[9]</sup> The etiology of this group is obscure. Our case, after comprehensive work up and being negative for HHV 8 was diagnosed with this rare category of iMCD as per The International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease.<sup>[9]</sup> The incidence of iMCD has been estimated to be five per million person years.<sup>[10]</sup> The largest case series from India by Singh et al had a significantly higher proportion of UCD cases than MCD cases.<sup>[11]</sup> To the best of our knowledge there has been only sporadic cases of iMCD reported in India.<sup>[12,13]</sup> The diagnosis is complex as is evident from the elaborate work-up that was required for our case.

CD is classified into 3 recognizable histopathological variants. The Hyaline vascular variant shows characteristic features like hyalinized vessels penetrating the atrophic germinal centres with concentric rings of small lymphocytes widening the mantle zone also known as the onion skin appearance. The Plasma cell variant shows hyperplastic germinal centres with interfollicular sheet-like polyclonal plasmacytosis. The Mixed variant shows overlapping features of both. MCD is most commonly associated with the plasma cell variant.<sup>[9]</sup> Our case was histologically consistent with the plasma cell variant and IHC markers like MUM1 and CD138 with kappa and lambda antibodies helped in confirming the presence of polytypic plasma cells.

Although the genesis of iMCD is not completely understood, the role of IL6, a cytokine involved in acute phase reaction has been emphasized in the mechanism of lymphoproliferation, plasma cell proliferation and systemic symptoms.<sup>[9]</sup> The causative association with IL-6 has been based on several observations such as the removal of the lymph node masses causing drop in IL-6 levels and treatment with IL-6 antibody causing resolution of symptoms.<sup>[14]</sup> In addition, serum IL-6 levels have been proved to be high in Castleman's disease as was seen in our case. However, owing to its rarity, the etiology that drives



**Fig. 1** a,b- Lymph node architecture effaced by presence of plasma cells in the interfollicular area and within germinal centres (H and E,50x), c,d- Sheets of plasma cells with increased vascularity (H and E,200x), e-Immunohistochemistry for CD138 membranous positivity highlighting the plasma cells(200x), f-Immunohistochemistry for MUM1 showing strong nuclear positivity in the plasma cells(200x).

this IL-6 hyperproduction in idiopathic MCD has not been completely described in literature and poses an interesting area for further research.

The diagnosis of MCD is riddled by the clinical heterogeneity and overlap with other disorders such as Lymphoma, Autoimmune diseases and Infections. A close mimic is IgG4 related disease as it can also involve multiple organs, show diverse and non-specific clinical symptoms and on biopsy shows sheets of plasma cells.<sup>[15]</sup> Normal serum IgG4 levels and negative IHC staining for IgG4 in the plasma cells of the lymph node biopsy helped us exclude IgG4 related disease in our patient. When there is pulmonary involvement with lymphadenopathy and non-specific symptoms as in our case, MCD may also be erroneously diagnosed as Tuberculosis, especially in high incident countries like India. Even the index case of CD described by Castleman, received anti-tubercular drugs before surgical resection.<sup>[1]</sup> Therefore, awareness of this rare disease and a detailed work up is imperative for the correct diagnosis and treatment.

## Conclusion

Idiopathic Multicentric Castleman disease is the rarest of the CD spectrum and continues to be an enigmatic disease and a diagnostic challenge. Diagnosis requires integration of clinical findings with histopathology, serology, immunohistochemistry and exclusion of mimics like autoimmune diseases, infections and lymphoma. Our case report attempts to add to the understanding of this rare disease.

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