Case study

MULTICENTRIC CASTLEMAN DISEASE; A RARE CASE OF GENERALISED LYMPHADENOPATHY IN INDIA

ABSTRACT:

Castleman disease is a type of hematological disorder, classified based on the number of the regions of enlarged lymph node, histopathological features, and association with human herpes virus 8. It may be unicentric with single region of the lymph node enlarged, or multicentric with multipleregionsof lymphadenopathy. Somecases of MCD are caused by human herpes virus8(75%) while in others it isHHV8 negative. The epidemiology of idiopathic MCD is poorly understood due to lack of diagnosis since it is a difficult clinical diagnosis and also require analysis from a pathologist that is not available worldwide. Diagnosisand treatmentareincredibly challenging as it can presents with wide array of manifestation from asymptomatic to systemic manifestation.There is no exact treatment guideline, Anti IL6 monoclonal antibody with or without systemic steroid is the mainstay of treatment.Here, we report a case that was initially suspected to have a lymphoma but later histologically was confirmed to have Multicentric Castleman's Disease

Keywords: Castleman disease (CD), HHV8, Unicentric, Multicentric CD, Tocilizumab

Introduction:

Castleman's disease is an uncommon B-cell disorder characterized by non-neoplastic lymph node hypertrophy (1)Dr Benjamin Castleman has described the first case of Castleman Disease involving single lymph node region which is now called as Unicentric CD(2) later it has been observed that it can affect multiple lymph node regions which is now known as Multicentric CD. Three characteristic histopathologicalsubtypes of CD are hyalin vascular, plasmablastic and mixed variants (3). Human herpes virus 8 associated MCD occur most commonly among HIV infected individual or otherwise immunocompromisedindividuals. The etiology and pathogenesis of HHV8 associated MCD has been well understood where idiopathic or HHV8 negative MCD has been poorly understood. Limited data exist regarding the epidemiology and treatment pattern of iMCD, in the United States, particularly

among patients receiving care in nonacademic settings (4). In the U.S, the annual incidence and prevalence of iMCD is estimated at 3.4 cases per million and 6.9 cases per million respectively(4). The presentation of idiopathic MCD isquitevaried from mild constitutional symptoms to life threatening cytokine storm, organ failure, death. There are four clinicalsubgroupsof idiopathic MCD- (a) POEMS associated MCD- polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes. It is a paraneoplastic syndrome that co-occurs with MCD. (b) Idiopathic MCD-TAFRO syndrome- thrombocytopenia, anasarca, myelofibrosis, renal dysfunction and organomegaly occur in some patients with MCD. (c) Idiopathic MCD-IPL-some patient with MCD may have thrombocytosis, hypergammaglobulinemia and mixed or plasmacytic histopathological features. (d) Idiopathic MCD-not otherwise specified (iMCD-NOS), these patients may have thrombocytosis, hypergammaglobulinemia, and mixed or plasmacytic histopathological picture (5). iMCD has been treated with wide variety of agents like corticosteroid, rituximab, and combined chemotherapy.Recently monoclonal antibody against IL6 has been approved for treatment of iMCD (6).

CASE REPORT:

Forty-year-old man without any comorbidity presentedto our medicine department with 4 months history of intermittent fever& constitutional symptoms, abdominal distension &swelling of both lower limbs for last two months and exertional dyspnea, easy fatiguability, palpitation for last one month. He had no history of chronic cough, hemoptysis, joint pain, oral ulcer, skin rash or alopecia. He had no complaint of jaundice or gastrointestinal bleeding. Patient is cultivator by occupation and had no history of high-risk sexual behavior. Physical examination revealed severe pallor, puffiness of the lower eyelid, bilateral swelling of both lower limbs and generalized lymphadenopathy (cervical, axillary,inguinal, epitrochlear, popliteal)**(Figure 1A)**. Those lymph nodes werenontender, enlarged,and firm in consistency. There was dull note on mediastinum percussion.

He had mild hepatosplenomegaly with ascites **(Figure 1B)**.

In the blood work, he had severe anemia with thrombocytopenia (hemoglobin 4 gm/dl, TLC 5000, platelet count 80,000/). All inflammatory markers were high (CRP-37.48, ESR-128mm/hour, Ferritin-1183, Procalcitonin-5.64, LDH-778).

Renal function test was normal. He had hypoalbuminemia with all other liver functions were normal. 24-hour urinary protein collection was 876mg/day. Serological tests for hepatitis B, hepatitis C, HIV were negative. ANA was 2+ coarse speckled pattern in 1:160 dilution but ANA specific antibodies were negative. DCT was positive (IgG type).

CECT thorax and whole abdomen revealed multiple enlarged mediastinal and hilar nodes largest measuring 2.3 × 2.5 cm, multiple enlarged retroperitoneal lymph nodes largest measuring 3.7× 2.7 cm with mild hepatosplenomegaly**(Figure 2A&B)**. Ascitic fluid study corresponds to non-portal hypertension secondary to proteinuria.

Whole body PET- CT scan was done which revealed metabolically active lymph node on both sides of diaphragm likely lymphoproliferative disorder**(Figure 3).**

In bone marrow study, reticular fibrosis and increased number of megakaryocytes were found. Histopathology of lymph node showed there are a few follicles with germinal centers, focal sclerosis of vessels within the germinal centers, in the interfollicular area there is presence of sheets of plasma cells, no Reed-Sternberg cells are identified, compatible with Castleman Disease**(Figure 4 A &B)**.

To find out etiological association of MCD,we did qPCR of HHV-8 but it was negative. IL-6 was done which was remarkably high and strongly favored to MCD.

Due to presence of thrombocytopenia, anasarca, proteinuria, organomegaly patient has been classified as iMCD-TAFRO variant. Patient was classified as severe disease ECOG performance status 4, features of volume overload, proteinuria, severe anemia, and thrombocytopenia.

Patient was treated with high dose steroid (injection Methylprednisolone 500mg/day for 5 days followed by tablet Prednisolone 2 mg/kg/day) and injection Tocilizumab 8mg/kg 2 weeks apart. After 1 dose of Tocilizumab and 5 days of methylprednisolone patient has improved drastically as evidenced by defervescence, improvement of platelet count, hemoglobin and decreased all inflammatory markers.

At present, patient has been taken treatment under our care, weare planning to give Tocilizumab 400mg 2 weeks apart and continuation of high dose oral Prednisolone with strict monitoring of improving parameters.

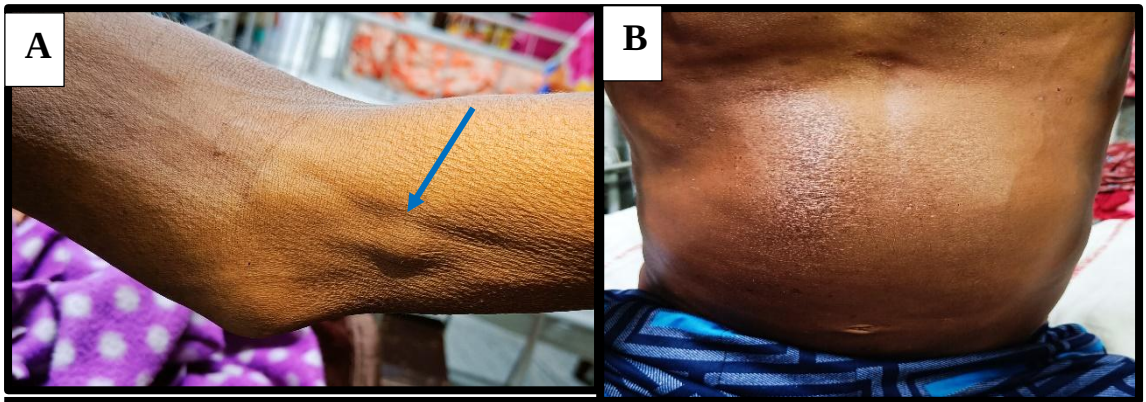

Figure1: **A) Shows enlarged epitrochlear lymph node (blue arrow). B) Shows ascites with venous prominence of anterior abdominal wall**

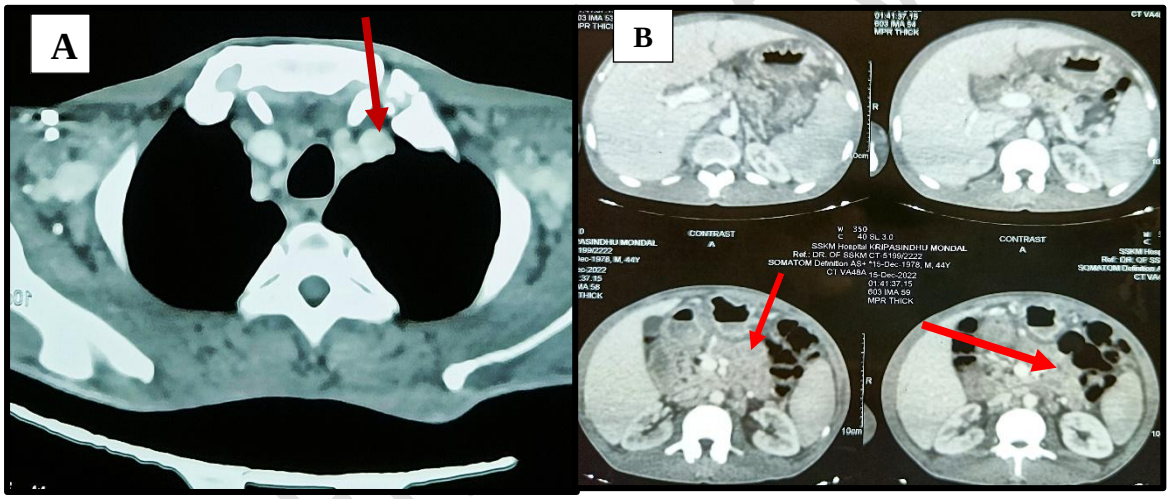

Figure 2 (CECT Thorax and Abdomen): A) Shows multiple enlarged lymph node (red arrow) B) Shows multiple mesenteric and retroperitoneal lymph nodes (redarrow).

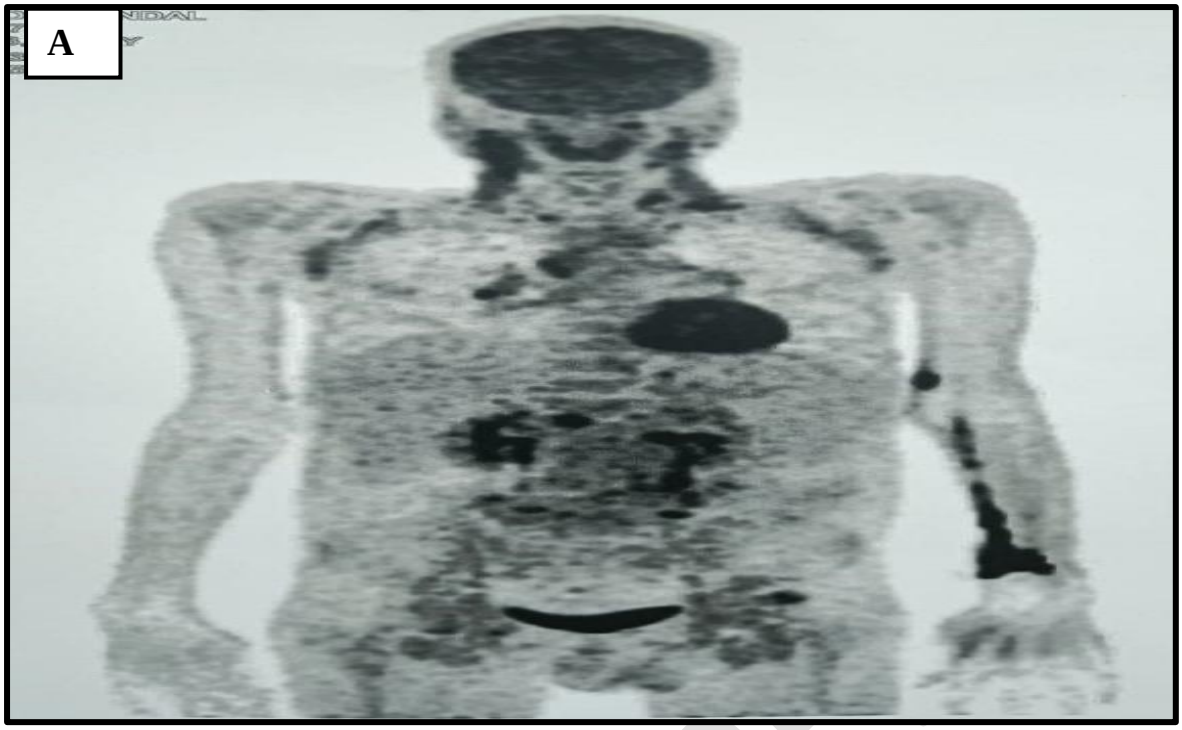

Figure 3 (^{18}FDG PET Scan): Shows metabolically active lymph nodes on both sides of diaphragm.

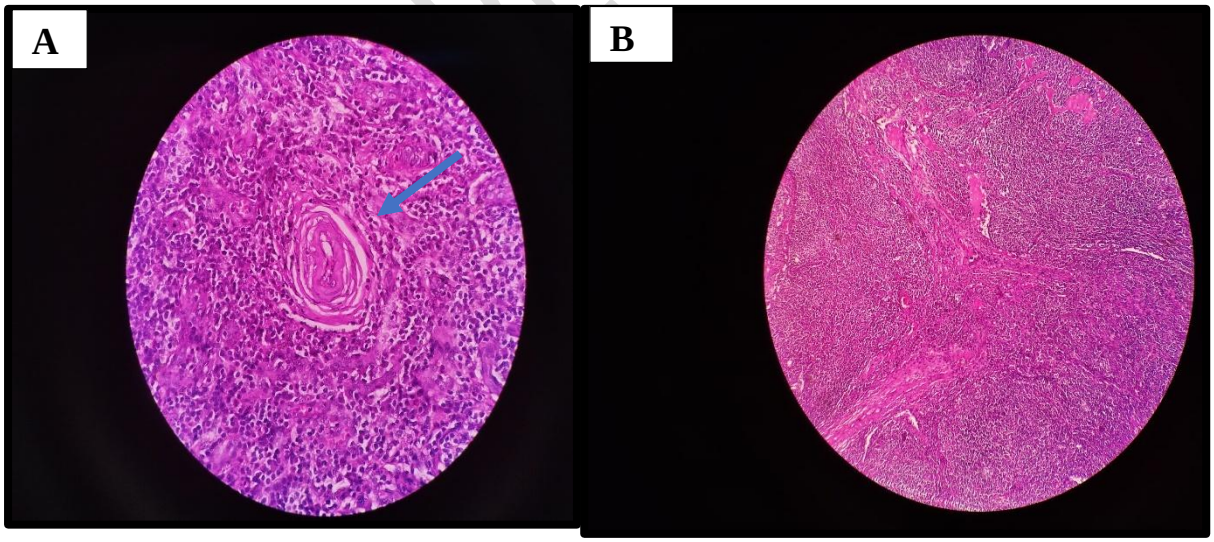

Figure 4 (HPE Lymph node):A) Shows sclerosis of vessel within germinal center (blue arrow) B) Sheets of plasma cells in the interfollicular area, featurescompatible with Multicentric Castleman Disease (x400 H&E).

DISCUSSION:

In the view of chronic fever with generalized lymphadenopathy, hepatosplenomegaly, ascites, severe anemia, thrombocytopenia, high LDH, with proteinuria and hypoalbuminemia we thought the possibilities of chronic lymphoproliferative disorders, systemic chronic infections like tuberculosis, chronic malaria, chronic kala-azar, autoimmune diseases like SLE, RA, sarcoidosis, and systemic mycosis. Relevant investigations were done to rule out those differential diagnosis.

Castleman disease is an exceedingly rare lymphoproliferative disorder that closely mimics common diseases like chronic infectious diseases, autoimmune disorders, and chronic lymphoproliferative disorders. That is why it creates diagnostic dilemma among physicians. As most of the time it presents as asymptomatic, unifocal, soft tissue mass without any systemic sign and symptoms, the diagnosis is often missed.

The etiology of iMCD is unknown, although it is hypothesized to involve one or more of the following mechanisms; autoimmunity/autoinflammatory, paraneoplastic or infections with a virus other than HHV8. 6500 to 7700 new cases are diagnosed per year in the United States, with 1650 cases of MCD. Idiopathic MCD accounts for 33% to 58% of published MCD cases.

Fine needle aspiration cytology is non diagnostic as aspiration of lymphoid tissue leads to false interpretation of lymphoma. However, both unicentric and multicentric CD have been associated with lymphoma. As a result, definitive diagnosis is made by excisional biopsy and histopathological examination. The histopathological picture of hyalin vascular type CD is onion skin pattern of concentric expansion of mantle zone around burned-out germinal center (5). In plasma cell type of CD, there is extensive proliferation of plasma cell around the intact follicle (5).

CD is the polyclonal proliferation of the lymphoid tissue, when monoclonal proliferation occur it turns into malignant lymphoma (7).

There are some peculiarities among the laboratory finding of CD,it has been shown that 9 to 71% cases of CD may have positive direct Coombs test and 12 to 37% cases may have positive anti-nuclear antibody (8). In our case the patient is positive for both ANA and DCT.

Most of the patient with UCD can be treated with surgical resection. Where patients with MCD need systemic therapy. Those with systemic manifestation is difficult to treat. These patients are treated with high dose systemic glucocorticoid, combination chemotherapy and anti IL6 monoclonal antibody (6).

CONCLUSION:

Though the Castleman disease is exceedingly rare disorder it should always be kept in mind as it the close mimickers of common systemic illness. As the early diagnosis and prompt treatment may give rise to satisfactory response& prevent progression to malignant diseases.

ETHICAL APPROVAL:

None required.

CONSENT:

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

REFERENCE

1. Iyer S, Bhatti MI, Halliday M. Castleman's disease-A case report. Int J Surg Case Rep. 2010;1(3):25-6. doi: 10.1016/j.ijscr.2010.06.005. Epub 2010 Oct 15. PMID: 22096669; PMCID: PMC3199674.
2. El-Osta HE, Kurzrock R. Castleman's disease: from basic mechanisms to molecular therapeutics. Oncologist. 2011;16(4):497-511. doi: 10.1634/theoncologist.2010-0212. Epub 2011 Mar 25. PMID: 21441298; PMCID: PMC3228122.
3. Wojtyś M, Piekarska A, Kunc M, Ptaszyński K, Biernat W, Zaucha JM, Waloszczyk P, Lisowski P, Kubisa B, Grodzki T. Clinicopathological comparison and therapeutic approach to Castleman disease-a case-based review. J Thorac Dis. 2019 Nov;11(11):4859-4874. doi: 10.21037/jtd.2019.10.73. PMID: 31903277; PMCID: PMC6940266.
4. Simpson D. Epidemiology of Castleman Disease. Hematol Oncol Clin North Am. 2018 Feb;32(1):1-10. doi: 10.1016/j.hoc.2017.09.001. PMID: 29157611.
5. Kojima, Masaru et al. “Idiopathic multicentric Castleman's disease. A clinicopathologic and immunohistochemical study of five

cases.” *Pathology, research, and practice* vol. 201,4 (2005): 325-32. doi: 10.1016/j.prp.2005.01.006

6. Tomohiro Koga, Remi Sumiyoshi, Atsushi Kawakami, Kazuyuki Yoshizaki, A benefit and the prospects of IL-6 inhibitors in idiopathic multicentric Castleman's disease, *Modern Rheumatology*, Volume 29, Issue 2, 4 March 2019, Pages 302–305, https://doi.org/10.1080/14397595.2018.1532383

7. Venkateswaran J, Balakrishna J. Castleman disease PathologyOutlines.com website https://www.pathologyoutlines.com/topic/lymphnodescastleman.html. Accessed March 30th, 2023.

8. Anwar, Ghulam Rabbani et al. “A Case of Castleman Disease: A Diagnostic Dilemma.” *Cureus* vol. 13,4 e14372. 8 Apr. 2021, doi:10.7759/cureus.14372