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Case Report

Idiopathic multicentric Castleman disease: a mysterious case of generalized lymphadenopathy

Nikhil Sebastian[1]*, Shoaib Nawaz P. N.[1], Ramya Ananthkrishnan[1], Kumanan J.[1], Archana Lakshmanan[2], Thirumalairaj Raja[1]

[1]Department of Medical Oncology, [2]Department of Pathology, Apollo Cancer Centre, Chennai, Tamil Nadu, India

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***Correspondence:**
Dr. Nikhil Sebastian,
E-mail: drnikseban@gmail.com

ABSTRACT

Castleman disease is a syndrome with significant clinico-pathological overlap between malignancy, autoimmune causes and infectious etiologies. It is a spectrum and can vary in extent from unicentric to multicentric disease with generalized lymphadenopathy, organ involvement, constitutional symptoms and cytopenias, and in severity from non-severe to severe disease with TAFRO symptoms. Idiopathic multicentric Castleman disease (iMCD) is a diagnosis of exclusion after multiple causes as per diagnostic criteria are excluded. Treatment varies between the disease severity types with anti-IL 6 antibodies for non-severe disease to cytotoxic chemotherapy agents for severe disease with TAFRO symptoms. We hereby report a case of a non-severe type of iMCD with a prolonged course and delayed arrival at the diagnosis, owing to the rarity of this condition, which stresses the need for a reduced threshold to consider MCD, early in the differential diagnosis. Interestingly there were positive auto-antibodies and elevated IgG4 levels in this patient, but applying strict criteria helps to distinguish the diagnosis.

Keywords: Idiopathic multicentric, Castleman disease, IgG4 disease, IL-6, Tocilizumab

INTRODUCTION

Castleman disease (CD) encompasses several clinicopathological disorders with overlap between malignancy, autoimmune conditions, and infectious disorders.[1] CD may be classified into unicentric or multicentric disease. A subset of patients with MCD is known to be etiologically related to human herpesvirus-8 (Kaposi sarcoma-associated herpesvirus), and this group is termed HHV-associated MCD.[2] A smaller subset where the etiology is unknown is termed idiopathic MCD (iMCD).

Idiopathic multicentric Castleman disease is a rare disorder with an estimated annual incidence and prevalence of 3.4 and 6.9 cases per million, respectively.[3] The clinical presentation includes generalized lymphadenopathy and systemic inflammatory symptoms, with investigations revealing a polyclonal lymphoproliferation, cytopenias, and multiple organ system dysfunction. iMCD can be life threatening in its severe form with cytokine storms often including interleukin-6. The etiology of iMCD is unknown. It is hypothesized to be due to one or more of the following: autoimmunity/autoinflammation (i.e., pathologic auto-antibodies or germline genomic alterations in inflammatory pathways); paraneoplastic (i.e., somatic mutations in clonal cells); or infection with a virus other than HHV-8.[4]

iMCD can be diagnosed with different histomorphologic pictures- “hyaline vascular”, “plasmacytic,” or a mixture of both of these are co-existing with typical clinical features.[5] A great amount of clinical and histological overlap is present in iMCD with malignancy, autoimmune and infectious disorders, and hence is a diagnosis of

exclusion. The first diagnostic criteria for diagnosis of iMCD was developed by Fajgenbaum et al.[6]

CASE REPORT

We report the case of a 39-year-old lady from Mauritius, who had complaints of right-sided neck swelling which was first noticed in 2010. The swelling in the right side of the neck had a waxing and waning nature and was associated with constitutional symptoms like fever, chills, rigors, and fatigue. She also had associated difficulty in swallowing food.

She underwent a biopsy of the right cervical node in 2010 which was reported elsewhere as a reactive pattern with thickened capsule and storiform fibrosis, with few germinal centers recognized in the lymphatic tissue. She was treated with symptomatic medications. She underwent further excision biopsy of a lymph node, once more in the same year. The findings have been similar with the possibility of viral lymphadenitis including infectious mononucleosis, and less likely Hodgkin lymphoma. The block was sent for review elsewhere in The UK and was reported as lymphoid hyperplasia. Sections showed a lymph node with thickened capsule and generally preserved architecture. Secondary follicles with enlarged mantle zone and reactive germinal centers (BCL2 negative and high Ki67). Monocytoid B cells that are CD4 and CD8 positive are seen in interfollicular areas. CD21 staining was also positive in the meshwork.

In 2012 for the same complaints the right cervical node was biopsied and the histopathology showed similar findings. A viral screen showed IgG, but not IgM positivity for CMV, rubella and toxoplasmosis.

In 2014, she was found to be positive for dsDNA. Rest of the autoimmune panel was negative. Hypothyroidism was detected with elevated anti-TBG (356 U/l) and was started on thyroxine supplementation. She also was provisionally diagnosed elsewhere to have ANA-negative SLE and was started on prednisolone and hydroxychloroquine sulfate. During this period from 2015 to 2018, she had good symptom control with prednisolone. But due to adverse effects, prednisolone had to be discontinued.

She had intermittent self-subsiding relapses in late 2020 with neck swelling causing breathing difficulty and dysphagia. She underwent a computed tomography (CT) scan which showed generalized lymphadenopathy in the neck, thorax and abdomen-pelvis. Biopsy was repeated from the right cervical node on 06.10.2020 which was reported as “more in favor of reactive than neoplastic changes".

She reported to our center in August 2022 with a progression in size of the neck nodes with a similar large swelling on the left side of the neck. A PET CT whole body showed hypermetabolic cervical, supraclavicular, mediastinal, internal mammary and right axillary lymphadenopathy. The images of diagnostic PET CT are shown in Figure 1.

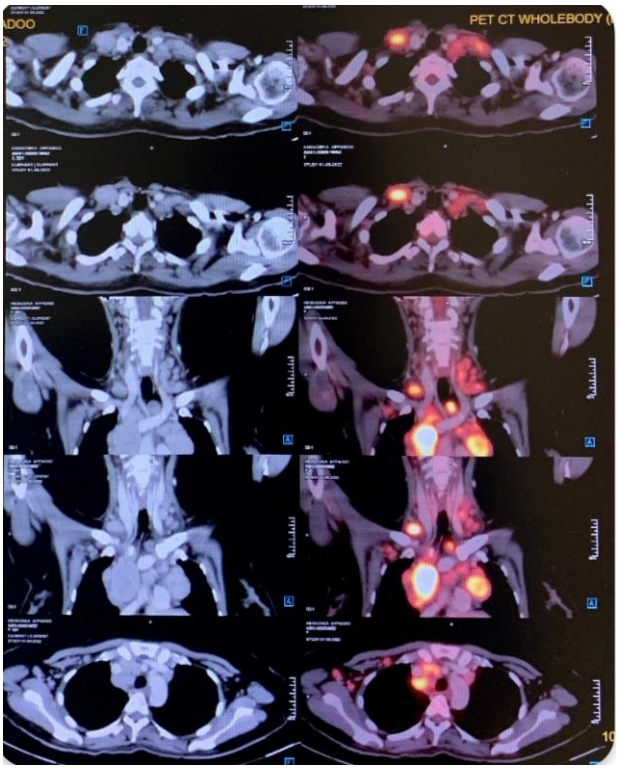

Figure 1: Diagnostic PET CT showing contiguous generalised lymphadenopathy above diaphragm.

The tissue block of the biopsy done in 2020 was reviewed and was reported to have lymph nodes with paracortical expansion, Castleman-like features, areas of storiform fibrosis and paracortical plasma cell infiltrate. Immunohistochemistry showed a reactive pattern with elevated IgG4 plasma cell infiltrate (40-50/high powered field). Ratio of IgG4 positive plasma cells to IgG positive cells was 25% (This requires to be more than 40% as per the criteria for IgG4 disease).[7] HHV8 LANA1 was negative. Based on these immunomorphologic findings, the differentials considered were Castleman disease, Immune-mediated lymphadenopathy and IgG4-related lymphadenopathy. A repeat lymph node biopsy was done and confirmed the above findings. The representative images of histopathology and immunohistochemistry are as shown in Figures 2 and 3 respectively.

Blood investigations revealed anemia and thrombocytosis with elevated C-reactive protein (CRP). Serum protein electrophoresis and immunofixation was done which showed polyclonal hypergammaglobulinemia with no M band. Quantitatively serum IgG was elevated, and hence with a differential diagnosis of IgG4 disease, serum IgG4 was checked and was found to be increased at 527 mg/dl. Interleukin-6 was highly elevated at 1001.9 pg/ml. She underwent autoimmune work up which was negative for anti-ds DNA, but showed low positivity (1:40 dilution) for ANA with an AC-1 homogeneous nuclear pattern which is

typically associated with anti-dsDNA antibodies.[8] She did not satisfy other criteria required for the diagnosis of SLE.[9]

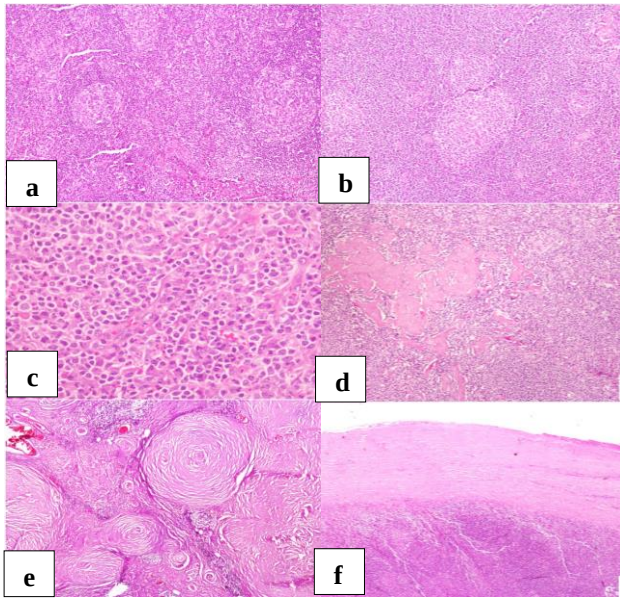

Figure 2: (a): H&E-40X- follicles with mantle zone expansion, (b) H&E-40X- twinning of follicles, (c) H&E-400X)- increased plasma cells, (d) H&E-100X- nodular hyalinisation, (e) H&E-40X)- storiform fibrosis, and (f) H&E-40X)- thickened capsule.

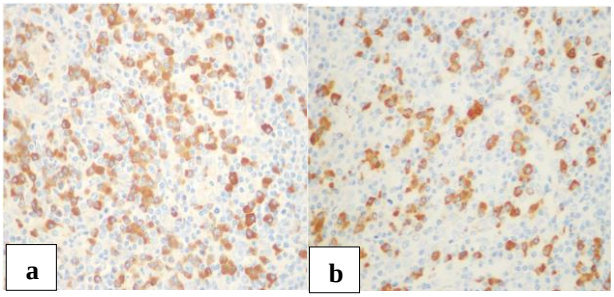

Figure 3: (a) IgG count of 140-150/hpf, and (b) IgG4 count of 40 to 50/hpf.

According to the International consensus diagnostic criteria for iMCD, she was diagnosed with iMCD, which was non-severe according to the CDCN severity criteria and with no TAFRO symptoms.[6]

Since it was non-severe, cytotoxic chemotherapy is not indicated, and the first line recommended treatment is the administration of anti-IL 6 antibodies as per the International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease.[10] Due to the unavailability of siltuximab, she was started on tocilizumab. Tocilizumab was administered at a dose of 8 mg/kg (480 mg) intravenous infusion every 2 weeks.

A reassessment was done after 6 cycles in December 2022. The images of PET CT compared with the images at diagnosis are depicted in Figure 4. IL-6 reduced from 1001.9 pg/ml to 64.6 pg/ml. Hb improved from 8.3 gm/dl to 11.4 g/dl. CRP decreased from 91.1 and normalized to 3.22 mg/l (ULN <5 mg/l). ESR was 4 mm/1st hour. Albumin was 4.0 g/dl prior to and after the treatment. PET CT done in December 2022 showed a complete metabolic response.

She continued 6 more cycles over the next 3 months and a repeat assessment with PET CT whole body was done in April 2023 which maintained the complete metabolic response.

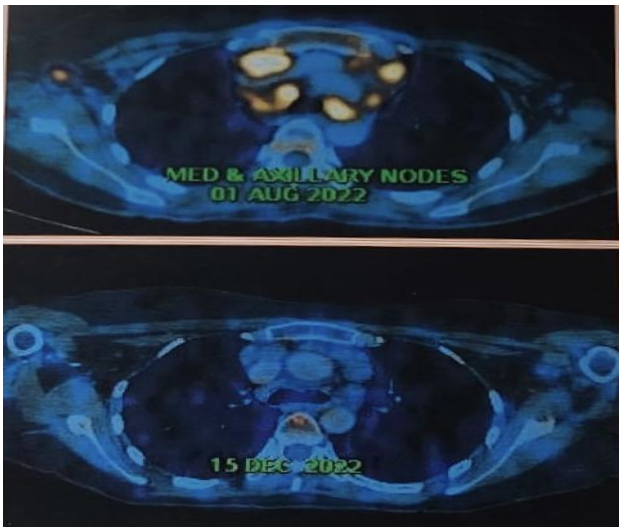

Figure 4: Comparison of images from diagnosis to those after 3 months showing complete metabolic response.

DISCUSSION

Castleman disease was first described by Benjamin Castleman in 1950 as a disease with primary mediastinal lymphadenopathy.[11] Later, it was classified as unicentric and multicentric Castleman disease. The histopathology varies depending on the subtype and is not uniform and specific to the disease. Castleman-like features have been described in a variety of other conditions such as rheumatoid arthritis, IgG4-related disease, systemic lupus erythematosus, adult-onset still disease and systemic juvenile idiopathic arthritis.

Idiopathic multicentric Castleman disease is a rare systemic inflammatory disease with lymphadenopathy, cytopenias and organ dysfunction. They often have cytokine storms including elevated IL-6. They constitute nearly a third of multicentric Castleman disease. They can affect people of any age or sex. They often show significant overlap with other malignancies, autoimmune conditions and infections.

Fajgenbaum et al laid down criteria for diagnosing iMCD which include both major and minor criteria.[6] iMCD is clinically stratified according to the severity as severe and non-severe by the Castleman disease Collaborative

network (CDCN). Severe iMCD includes those with ECOG ≥2, stage IV renal dysfunction (eGFR <30; creatinine >3.0) or anasarca and/or ascites and/or pleural/pericardial effusion (effects of hypercytokinemia/low albumin), pulmonary involvement /interstitial pneumonitis with dyspnea, haemoglobin ≤8.0 g/dl. Those without any of these criteria are termed as non-severe. A new group termed thrombocytopenia, anasarca, reticulin fibrosis in marrow, renal dysfunction organomegaly (TAFRO) has been identified, which is often a severe disease which may be life-threatening.[12] Those without the TAFRO symptoms are termed as iMCD-NOS.

Nearly 30% of patients with iMCDs have a random elevation of autoantibodies.[13] The presence of autoantibodies alone without pertinent clinical findings should not prompt us in diagnosing any autoimmune disease or to consider overlap syndromes. There are case reports of overlapping symptomatic presentations which were initially misdiagnosed as SLE, and later in view of poor response to treatment with immunosuppressive agents, nodal biopsy revealed a picture of MCD.[14]

iMCDs often show increased tissue IGg4 positive plasma cells and elevated serum IgG4 levels creating a diagnostic dilemma with IgG4 disease. The serum IgG4 levels more than 135 mg/dl is one of the laboratory criteria for IgG4 disease. Ratio of IgG4-positive plasma cells/IgG-positive cells has to be greater than 40% and the number of IgG4-positive plasma cells has to be greater than 10 per high-powered field to fulfil the pathological criteria of IgG4 disease. In our patients' case, the ratio is 25%, and hence not in favour of IgG4 disease.[7]

Treatment for iMCD includes anti-IL 6 antibody and steroids. Anti-IL 6 antibody recommended by the FDA is siltuximab, and in situations of unavailability recommends Tocilizumab, based on the studies by Nishimoto et al.[10,15] In non-severe disease there is some evidence for treatment with rituximab and steroids in those who do not have markedly elevated IL-6 levels. In cases of poor response with the initial therapy in non-severe disease, can consider adding an immunomodulatory agent which includes thalidomide, cyclosporine A, sirolimus, anakinra, or bortezomib. In severe MCD if there is poor response to the initial anti-IL 6 therapy, one cycle of chemotherapy like R-CHOP or R-VDT-PACE is done following which the therapy is individualised based on the response to chemotherapy. Treatment of TAFRO cases needs to be aggressive, and the Japanese TAFRO research group recommends high-dose steroids, tocilizumab, and cyclosporine A for patients with TAFRO syndrome.[16]

CDCN has recommended criteria for response assessment. IL-6 will be spuriously elevated after anti-IL 6 therapy and should not be checked for assessing response. CDCN criteria includes symptomatology, laboratory and radiological features. To define an improvement, each of the symptoms- fatigue, anorexia, fever and weight loss has to come down by at least one point on the CTC scale. Lab criteria includes hemoglobin, ESR, albumin and GFR. Radiological criteria include assessment of reduction in the size of the lymph nodes.

CONCLUSION

Idiopathic multicentric Castleman disease is an extremely rare disease which often gets misdiagnosed due to marked clinical heterogeneity and lack of specific criteria thereof. Hence, a good collaboration between the lab and clinical team and following strict criteria will prevent misdiagnosis thereby preventing mistreatment.

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