CASE REPORT

JIACM 2026; 27 (3): 215-19

Idiopathic Multicentric Castleman Disease Presenting as TAFRO Syndrome

Rajnish Singh, Shreyasee Patra**, Brijesh Sharma***, Madhubala Negi***, Archana Mohan****, Tanvi Suri****, Shivanshu Gangwar******

Abstract

Idiopathic multicentric Castleman disease (iMCD), particularly the TAFRO variant, is a rare and potentially life-threatening lymphoproliferative disorder that often presents a profound diagnostic dilemma due to its nonspecific systemic manifestations. We report a 42-year-old previously healthy woman who presented with prolonged high-grade fever followed by progressive anasarca with ascites, pleural effusion, lymphadenopathy and hepatosplenomegaly. The constellation of symptoms of fever, polyserositis, organomegaly and laboratory results showing bicytopenia, renal dysfunction, hypoalbuminaemia, elevated inflammatory markers, and marked hyperferritinaemia raised suspicion for autoimmune diseases, chronic infections such as tuberculosis, haematologic malignancy, and other lymphoproliferative disorders which were ruled out after extensive work-up. PET-CT demonstrated generalised FDG-avid lymphadenopathy. Excisional lymph node biopsy showed plasma cell–type Castleman disease; HHV-8 was negative and POEMS criteria were not met. Elevated interleukin-6 levels, together with thrombocytopenia, anasarca, renal dysfunction, and organomegaly, supported a diagnosis of idiopathic multicentric Castleman disease, TAFRO variant. Treatment with high-dose corticosteroids followed by tocilizumab led to rapid clinical and laboratory improvement. This case underscores the importance of maintaining a high index of suspicion for idiopathic-MCD in patients with unexplained systemic inflammation and multiorgan involvement, and highlights the central role of histopathology in resolving a complex diagnostic challenge.

Introduction

Castleman's disease (CD), first described in 1954 by Dr Benjamin Castleman[1], is a rare, nonclonal lymphoproliferative disorder characterised by lymph node enlargement often mimicking malignant and benign conditions. Although exact mechanism is unclear, CD is believed to arise from immune dysregulation leading to proliferation of B lymphocytes and plasma cells[2]. Clinically, it is classified into unicentric (UCD), involving a single nodal region, and multicentric (MCD), which features multiple lymph node regions. UCD typically presents as localised, asymptomatic lymphadenopathy, whereas MCD manifests with systemic involvement such as constitutional symptoms, organomegaly, anaemia, and elevated inflammatory markers[3]. Idiopathic MCD (iMCD) is particularly rare (incidence approximately 5 per million patient-years)[4] and poses significant diagnostic and therapeutic challenges due to its heterogenicity.

We report an unusual case of a 42-year-old woman presenting with fever and anasarca, subsequently diagnosed with MCD.

Case Presentation

A 42-year-old previously healthy woman presented with a 6-week history of daily high-grade fever with chills (up to 102° F), followed two weeks later by progressive generalised oedema beginning in the lower limbs, advancing to facial puffiness and abdominal distension. She also reported dry cough with pleuritic chest pain.

There was no history of weight loss, night sweats, loss of appetite, jaundice, any rash, joint pains, oral ulcers, excessive hair fall, frothy urine, burning micturition, loose stools, palpitation or dizziness. She was initially admitted in a different hospital where she had received antibiotics for presumed sepsis but without any improvement.

On physical examination she had pallor, bilateral pitting pedal oedema, axillary and inguinal lymphadenopathy, hepatosplenomegaly with moderate ascites and bilateral pleural effusion.

Baseline laboratory investigations showed bicytopenia (Hb-6.5 g/dL, Platelet count - 35,000/mL). Renal function was deranged; urea - 115 mg/dL and serum creatinine - 3.4 mg/dL. Serum total protein was 5.17 gm/dL with a serum albumin of 2.10 gm/dL; rest LFTs were within normal limits. Chest X-ray showed bilateral pleural effusion. Inflammatory markers ESR and q-CRP were high, serum ferritin levels were above 2000 ng/mL, iron studies suggested anaemia of chronic disease.

**Professor and Head, **Senior Resident, ***Professor, ****Resident, Department of General Medicine, *****Senior Resident, Department of Pathology, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.*
Corresponding Author: Dr Shreyasee Patra, Senior Resident, Department of General Medicine, ABVIMS and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 8130367556, E-mail: shreyaseep@gmail.com

Ascitic fluid examination was suggestive of low SAAG high protein ascites with predominantly lymphocytic cells. Pleural fluid studies also showed exudative pattern. ADA was within normal limits in both fluid studies. Mantoux test was negative. 24 hr urinary protein came out to be 1714 mg/day. Serological tests for hepatitis B, hepatitis C and HIV were non-reactive. Urine and blood cultures were sterile.

Direct Coombs test was positive, with mildly elevated serum LDH. ANA (by IFA), ANCAs and ENA were negative. SPEP showed polyclonal gammopathy suggestive of chronic inflammation; no M spike was seen.

USG whole abdomen and pelvis showed hepatosplenomegaly with moderate ascites and a suspicious right ovarian lesion (ORADS 3-4). Tumour markers and ascitic fluid were negative for malignancy. Ovarian carcinoma was ruled out after imaging by CECT (Chest and abdomen) and MRI-Pelvis. Bone marrow aspiration and biopsy showed reactive cellular marrow with trilineage hematopoiesis, no blasts or plasma light chain restriction were seen.

A PET-CT was done which showed generalised lymphadenopathy on both sides of diaphragm (bilateral axillary, cervical, mediastinal, abdominal and inguinal) with avid uptake. Right inguinal excision biopsy was sent. IgG4 was increased but ratio of IGg4/IgG was normal. Lymph node biopsy report showed sheets of small mature plasma cells in interfollicular area and in medulla with few hyperplastic follicles, occasional mantle zone thickening with "onion skin" appearance suggestive of Castleman's disease-plasma cell type. IHC for CD 20 was positive. To find out etiological association, IHC for HHV8 was done which came out to be negative. IL-6 levels were found to be high = 30.87 pg/mL (normal <5.9 pg/mL).

Based on the presence of fever, thrombocytopenia, polyserositis, proteinuria and hepatosplenomegaly along with lymph node biopsy findings and in absence of any evidence of lymphoproliferative disorders or autoimmune conditions like Sjogren's disease, diagnosis of iMCD – TAFRO variant was made.

Management

The ECOG performance status of our patient being 2 - 3, she was initiated on in intravenous methyl prednisolone 500 mg/day for 3 days followed by in intravenous Tocilizumab (8 mg/kg) infusion. She improved clinically and laboratory parameters also showed improvement (Table I). She was discharged on oral prednisolone with advice to come for further dose of Tocilizumab biweekly.

Table I: Laboratory investigations during hospital stay.

Parameters	At Admission	3rd week of hospital stay	Before discharge
Hb (g/dL)	6.4	5.8	9.2
PLT (/cmm)	35,000	50,000	60,000
ESR (mm/hr)	85	20	5
qCRP (mg/dL)	109	25.4	18
Serum Albumin (g/dL)	2.10	2.06	4.2
Ferritin (ng/mL)	>2,000		1,000
LDH (U/L)	283	319	187
ALP U/L	167	200	156
Urea (mg/dL)	115	122	20
Creatinine (mg/dL)	3.4	1.4	0.6
Proteinuria (mg/24 hrs)	1,748	1,194	1,420

Discussion

Castleman's Disease is an exceedingly rare lymphoproliferative disorder that closely mimics more common autoimmune diseases, chronic infections, chronic lymphoproliferative disorders and malignancies.

The Castleman Disease Collaborative Network (CDCN) classifies multicentric Castleman disease (MCD) into three aetiologic subtypes: HHV-8-associated MCD, POEMS-associated MCD, and idiopathic multicentric Castleman disease (iMCD)[5]. HHV-8-associated MCD, driven by viral infection, occurs predominantly in immunocompromised individuals, most commonly with HIV co-infection while POEMS-associated MCD is distinctively linked to plasma cell dyscrasia.

The CDCN emphasizes on a diagnosis of exclusion for idiopathic multicentric Castleman disease (iMCD) which is further subdivided into iMCD not otherwise specified (iMCD-NOS) and the more aggressive iMCD with TAFRO – thrombocytopenia, anasarca, myelofibrosis, renal dysfunction and organomegaly. These criteria require the absence of HHV-8 infection and POEMS syndrome and a careful evaluation to rule-out alternative conditions that can produce Castleman-like histopathology, including autoimmune diseases, infections, haematological disorders, and inflammatory conditions such as IgG4-related disease (IgG4-RD).

Fig. 4 below describes the key steps in the diagnosis and classification of Castleman disease (CD) as proposed by the CDCN[5].

Establishing the aetiology and clinical variant holds

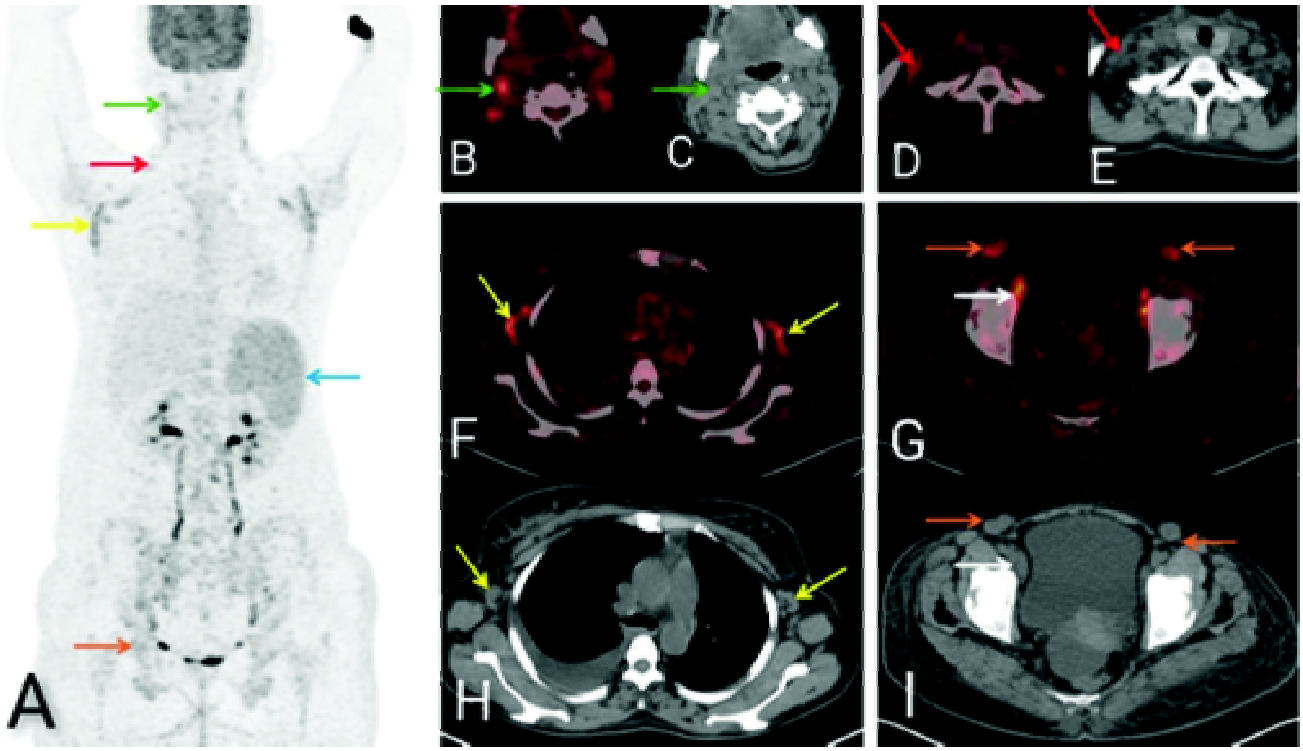


Fig. 1: *18 FDG PET/CT images (maximum intensity projection image – A); fused axial cuts showing diffusely increased FDG uptake in the spleen (blue arrow; A) and multiple FDG avid bilateral cervical (green arrow; B and C), supraclavicular (red arrow; D and E), axillary (yellow arrow; F and H), abdominal, external iliac (white arrow; G) and inguinal (orange arrow; G and I) lymph nodes; mild pleural effusion and ascites also seen.*

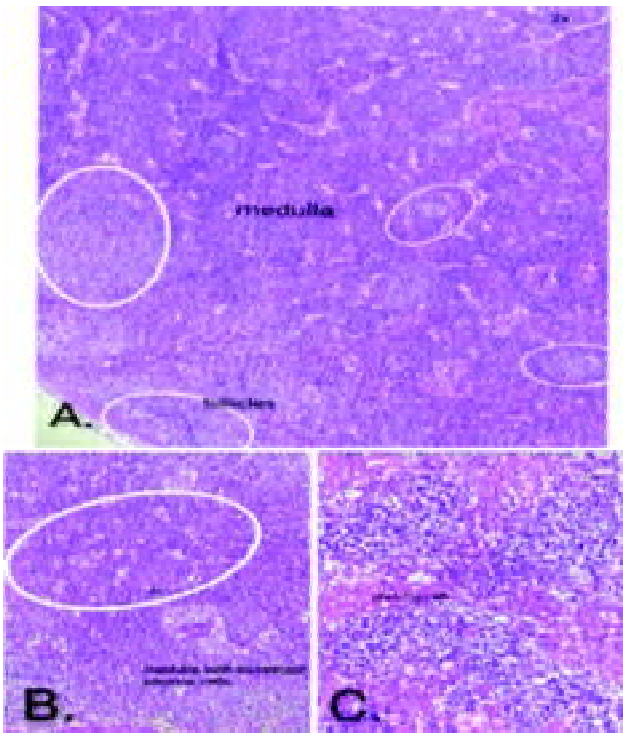


Fig. 2: *HPE of lymph node*
A – Medulla with atrophic germinal follicles; B – Medulla with increased plasma cells (x 400 H and E); C – Plasma cell (x 1000 H and E)

paramount significance as it influences the treatment modalities and prognosis. While UCD typically responds well to surgical excision with near-normal life expectancy, MCD carries a less favourable course. Before anti-IL-6 era, 5-year survival in HIV-negative MCD was approximately 65% as reported in a 2012 case series[6]. The TAFRO variant may progress rapidly with life-threatening organ dysfunction and severe clinical course[7].

Multicentric Castleman disease (MCD) requires systemic therapy guided by aetiology and the symptom severity as described in Fig. 5 below. HHV-8-associated multicentric Castleman disease is treated with rituximab alone in mildly symptomatic patients, while rituximab plus etoposide is used for severe disease or organ dysfunction; anthracycline-based chemotherapy may be considered when Kaposi sarcoma co-exists[5]. Other treatment modalities include antiviral therapy comprising of ganciclovir, foscarnet, and cidofovir effective against HHV-8 replication pathways. POEMS-associated disease requires therapy targeting plasma cell dyscrasia.

In idiopathic MCD, asymptomatic patients may be observed. Severely symptomatic or critically ill patients, including suspected TAFRO syndrome, should receive corticosteroids with anti–IL-6 therapy for rapid inflammatory control. Rituximab-based chemotherapy (e.g., R-CHOP/CVP) is

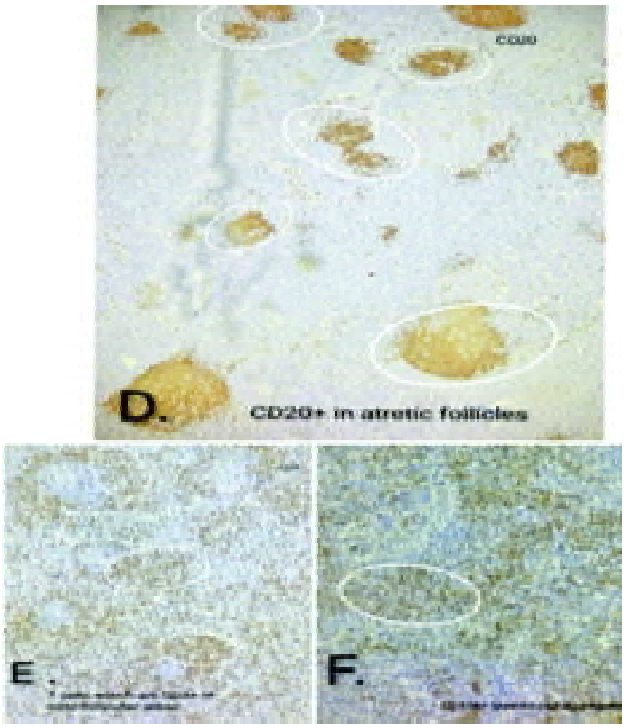


Fig. 3: *Immunohistochemistry of lymph node*
D – Showing CD 20 positivity within atretic germinal follicles; E – T-cells CD3+ in the interfollicular areas showing mantle zone thickening (onion-skin appearance), F – Sheets of plasma cell aggregates (CD 138+) in the interfollicular area; indicating plasma cell variant of Castleman's Disease.

reserved for cases refractory to or lacking access to anti-IL-6 therapy, with possible siltuximab maintenance after remission. Non-severe cases may be managed with siltuximab ± short-course steroids or rituximab with thalidomide, especially in immune cytopenias[5].

Tocilizumab, a monoclonal antibody that antagonises the IL-6 receptor (IL-6R) has been reported to exhibit significant reductions in lymphadenopathy and resolution of constitutional symptoms and signs in patients of i-MCD TAFRO[8].

Fig. 5 below describes the therapeutic algorithm for idiopathic multicentric Castleman as suggested by the CDCN.

Given the patient's prolonged fever, hepatosplenomegaly, anasarca, polyserositis, bicytopenia, and renal dysfunction, differentials included autoimmune disorders (SLE, sarcoidosis), chronic lymphoproliferative diseases, infections (tuberculosis, brucellosis), and malignancy. Extensive workup excluded these causes. PET-CT revealed generalised lymphadenopathy not detected on initial CT. Although IgG4-related disease was suspected, the IgG4/IgG ratio was normal. Excisional lymph node biopsy showed plasma cell variant Castleman disease with CD20 positivity. Histology, elevated IL-6, HHV-8 negativity, and absence of POEMS features confirmed iMCD-TAFRO.

Early initiation of corticosteroids and tocilizumab resulted in marked improvement , clinical and in laboratory parameters(Table I). Our patient was discharged on oral steroids with planned biweekly tocilizumab maintenance.

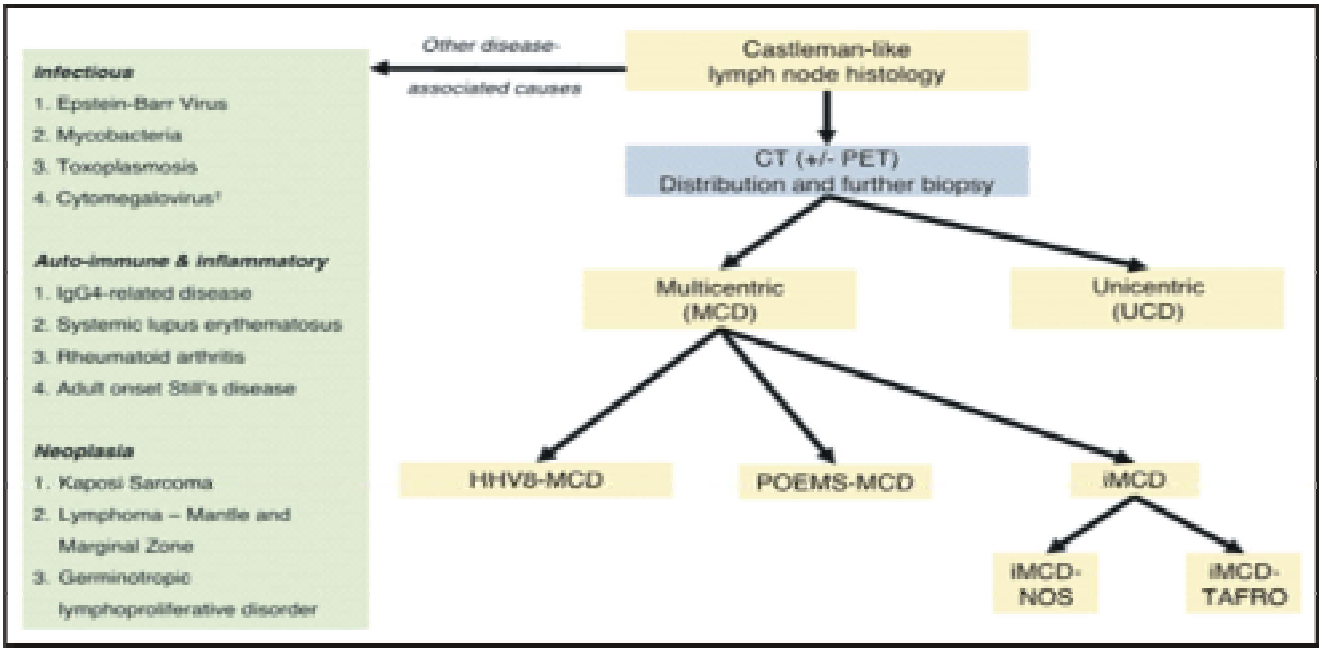


Fig. 4: *Approach to the diagnosis and classification of CD as proposed by the CDCN[5].*

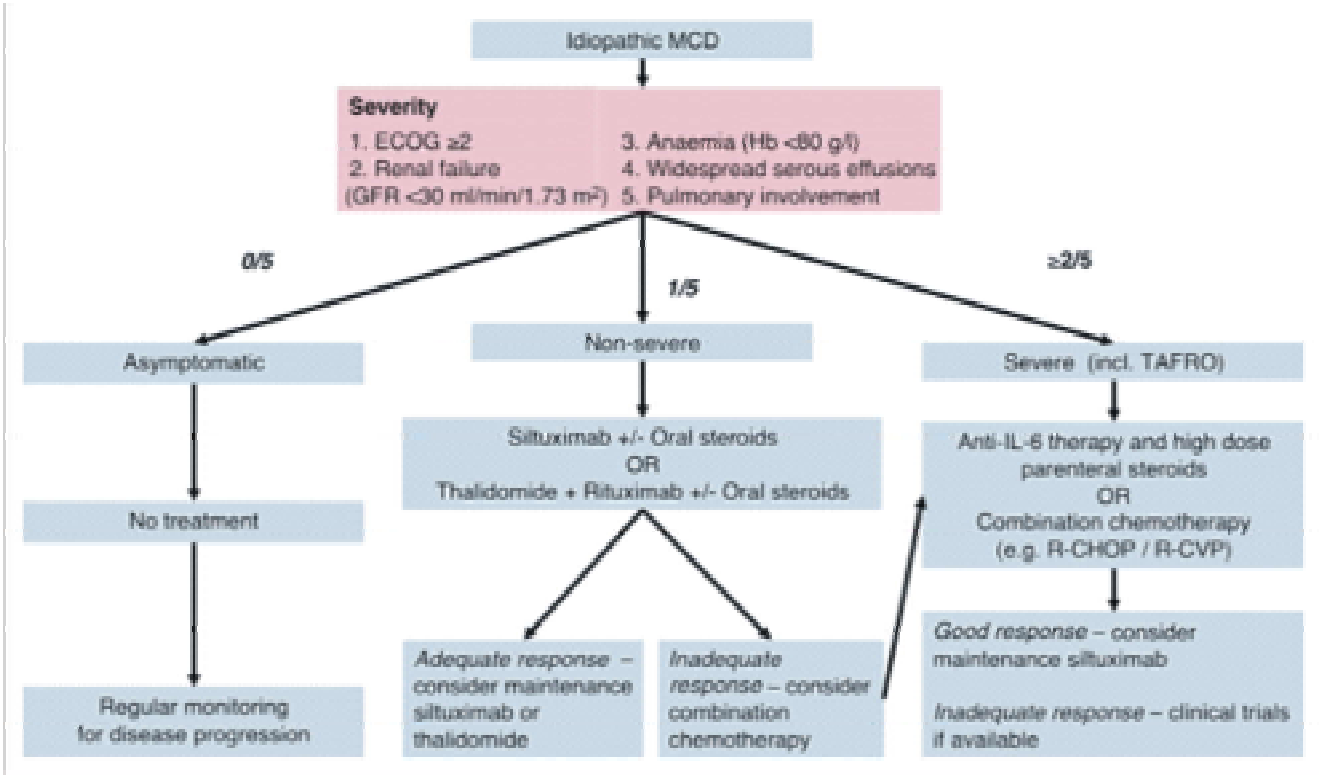


Fig. 5: *Suggested therapeutic algorithm in idiopathic multicentric Castleman disease based on severity scoring from the Castleman Disease Clinical Network. Anti-IL-6 therapy, anti-interleukin-6 therapy; ECOG, Eastern Cooperative Oncology Group Perfor mance Status score; GFR, glomerular filtration rate; Hb, Haemoglobin; MCD, multicentric Castleman disease; R-CHOP, rituximab-cyclophos phamide, doxorubicin, vincristine (Oncovin) and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, and prednisone; TAFRO, Thrombocytopenia, Anasarca, myelofibrosis, Renal dysfunction and Organomegaly*[5].

Conclusion

Castleman's disease presents a significant diagnostic challenges due to its nonspecific clinical, laboratory, and radiological findings and requires a multidisciplinary coordination amongst clinician, pathologist and radiologist as seen in this case. A high index of suspicion, careful exclusion of mimickers, and confirmatory histopathology are critical for diagnosis. Early recognition and targeted therapy, particularly anti-IL-6 agents in iMCD, can significantly improve patient-related outcomes and prevent complications.

Acknowledgement

The authors sincerely acknowledge the Department of Pathology, Dr. Ram Manohar Lohia Hospital, and the Department of Radiology, AIIMS, New Delhi, for their valuable assistance in establishing the diagnosis.

References

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. *N Engl J Med* 1954; 251: 396-400.
2. Han X, Zhou DB. Advances in aetiology and management of Castleman's disease. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2009; 31 (5): 639-43.
3. Dispenzieri A, Gertz MA. Treatment of Castleman's disease. *Curr Treat Options Oncol* 2005; 6 (3): 255-66.
4. Simpson D. Epidemiology of Castleman disease. *Haematol Oncol Clin North Am* 2018; 32 (1): 1-10.
5. Lomas OC, Streetly M, Pratt G *et al*. The management of Castleman disease. *Br J Haematol* 2021; 195 (3): 328-37.
6. Dispenzieri A, Armitage JO, Loe MJ *et al*. The clinical spectrum of Castleman's disease. *Am J Haematol* 2012; 87 (11): 997-1002.
7. Masaki Y, Arita K, Sakai T. Castleman disease and TAFRO syndrome. *Ann Haematol* 2022; 101 (3): 485-90.
8. Kapriniotis K, Lampridis S, Mitsos S, Panagiotopoulos N. Biologic agents in the treatment of multicentric Castleman disease. *Turk Thorac J* 2018; 19 (4): 220-5.