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Case Report

Multicentric Castleman's disease: a rare case presentation

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ABSTRACT

Castleman's disease (CD), also known as Angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disorder first reported by dr. Benjamin Castleman in 1956. The estimated incidence rate is 5 to 25 per million person-years. Histologically, the CD can be classified as hyaline-vascular type, plasma cell type and mixed type. HHV-8-associated MCD (Multicentric CD) is most commonly diagnosed in HIV-infected or otherwise immunocompromised individuals. Co-occurrence of polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes is known as POEMS syndrome. Treatment of iMCD (idiopathic CD) is challenging, and outcomes are poor because of no uniform treatment guidelines. The anti-interleukin-6 monoclonal antibody Siltuximab with or without corticosteroids is the preferred first-line therapy for iMCD.

Keywords: CD, Angiofollicular lymph node hyperplasia, Giant lymph node hyperplasia, Multicentric CD

INTRODUCTION

Castleman disease (CD) describes a rare group of lymphoproliferative disorders with characteristic histopathological appearances.[1] Unicentric CD (UCD) presents with isolated lymphadenopathy, usually accompanied by mild or localized symptoms. In contrast, the multicentric CD presents with generalized lymphadenopathy accompanied by mild to life-threatening constitutional symptoms**.** UCD in most cases is treated with surgery.

MCD is a systemic disorder with flares of non-specific symptoms like fever, night sweats, weight loss, malaise and fatigue suggestive of a chronic inflammatory syndrome associated with the involvement of multiple nodes. Around 10% of all CD cases are present as MCD and are plasma cell variants.[2-3] MCD is frequently associated with HHV-8 and HIV-positive individuals and carries a poor prognosis.[4] There is also a subgroup of HIV-negative and HHV-8-negative patients with unknown aetiology and pathophysiology, referred to as idiopathic MCD (iMCD).[5] iMCD is slightly more frequent in male children.

MCD is more likely accompanied by acute phase reactions and several autoimmune features. The pleiotropic cytokine IL-6 and other pro-inflammatory cytokines have been found to play a pivotal role in MCD pathogenesis.[6]

CASE REPORT

Unicentric CD

Lymphadenopathy is found mostly in the chest and neck, less commonly in the abdomen or retroperitoneum.[7-9] The clinical presentation of UCD often relates to the localized mass effect on organ function. Systemic symptoms are uncommon with fever in <10% of cases and inflammatory markers including CRP, ESR and tests of organ function usually being normal.[8]

Multicentric CD

MCD usually present with systemic manifestations, e.g., fatigue, night sweats, weight loss, dyspnoea, oedema, pulmonary fibrosis, hepatosplenomegaly and skin lesions (such as cherry-coloured eruptions).[8,10] Such systemic symptoms may present rapidly with signs of organ dysfunction.

Diagnosis

Based on clinical and radiographic evaluation along with histopathological examination.

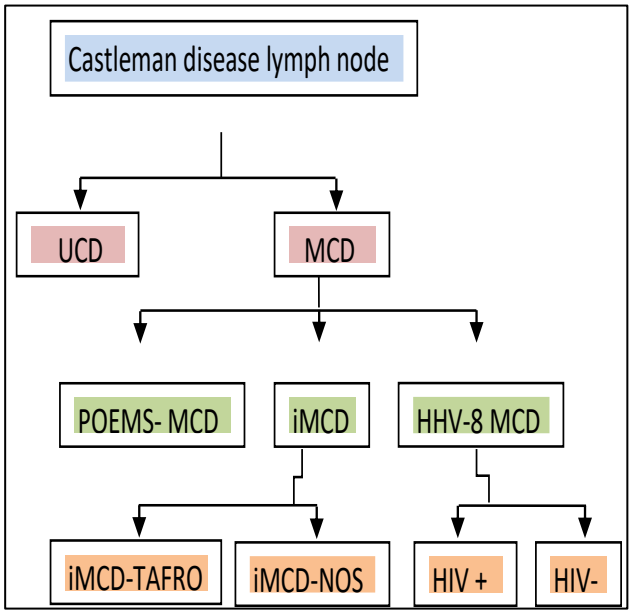

Figure 1: An algorithmic approach for assessment of CD.[11]

Diagnostic criteria

Major criteria (need both): Histopathologic lymph node, enlarged lymph nodes in ≥2 lymph node stations.

Minor criteria (need at least 2 of 11 criteria with at least 1 laboratory criterion): Laboratory-eslevated ESR or CRP, anaemia, thrombocytopenia/tosis, renal dysfunction or proteinuria, polyclonal hypergammaglobulinemia and hypoalbuminemia.

Clinical-Constitutional symptoms, large spleen and/or liver, fluid accumulation, eruptive cherry angiomata or violaceous papules and lymphocytic interstitial pneumonia.

Therapy

Treatment of iMCD is challenging, and outcomes can be poor with no uniform treatment guidelines. Proposed treatment options as per CDCN.[11]

iMCD-NOS and iMCD-TAFRO

First line therapy was of siltuximab/ tocilizumab/ corticosteroids and second line and beyond options were rituximab/ cyclosporine/sirolimus/IVIG

POEMS- associated MCD

If no bone lesions, iMCD-like therapy. If bony lesions, myeloma-type therapy including ASCT.

HHV8-MCD

If HIV-positive, combination with antiretroviral therapy/ rituximab.

Table 1: Consensus diagnostic criteria for iMCD.[11]

Site	Level	Size (cm)	Tender/ NT	Surface	Consistency	Mobility	Matted/ non-matted	Skin over LN
Rt. Submandibular	I b	2×2	Non-tender	Smooth	Rubbery	Non-mobile	Matted	Normal
Lt. Submandibular	I b	2×1	Non tender	Smooth	Rubbery	Non mobile	Matted	Normal
Rt. Supraclavicular	IV	2×3	Non tender	Smooth	Rubbery	Non mobile	Matted	Scar mark +

Prognosis

UCD can be treated with surgical resection and has a good prognosis. However, concomitant HIV, HHV-8 infections and other systemic disorders present with MCD and specific chemotherapy regimens have not been assigned. Moreover, nonspecific clinical features that often go unnoticed also lead to delayed confirmation of its diagnosis. Its prognosis is, therefore abysmal.[12] Both UCD and MCD can sometimes progress to non-Hodgkin lymphoma and have poor outcomes. Written informed consent for the publication of the clinical details and clinical images was obtained from the parents.

A 16-year-old girl, was admitted with chief complaints of fever and cough for 3 months and swelling over the bilateral neck over 2 months. The cough is insidious in onset,non-productive present throughout the day, relieved on steam inhalation and not associated with any postural and diurnal variation. Fever insidious onset documented

up to 101 f, 2 to 6 spikes per day, intermittent type, associated with chills and evening rise of temperature. swelling over the bilateral neck initially on the right-side progress from peanut to lemon size, followed by swelling over the left side. History of significant weight loss present along with generalised weakness. there is no history of, headache altered sensorium, blurring of vision, abnormal body movement, breathlessness, chest pain, petechial rash, or any bleeding from any site. No history of any bony tenderness or night sweat. for the above-mentioned complaint, she was admitted to some other hospital, evaluated for tuberculosis, and started on ATT. Since there was no relief in symptoms, presented to our hospital with a similar complaint. Antenatal and postnatal history was uneventful. There was no H/O TB contact, consanguinity or similar family history.

On physical examination, was hemodynamically stable, and had a fever of 101°F. periorbital oedema, severe pallor and bilateral cervical lymph nodes were palpable, and Prominent neck and chest veins were visible. Sternal tenderness was present. On per abdominal examination, the liver was palpable 2 cm below the right costal margin of a span of 13 cm, soft in consistency, smooth surface and regular margins.

Lab. investigations: Hb 6 g/dL, WBC 17.7 k/uL poly 91% and platelet count 3.2 lacks, and ESR 17 mm, CRP 28.9, retic count 5.2% peripheral smear showed normocytic and normochromic anaemia. CXR s/o mediastinal widening with prominent bronchovascular markings. further TB work up where comes negative.

CECT chest was done s/o large ill-defined enhancing lesion involving the mediastinum with extension, along with pericardial and bilateral pleural effusion

2D ECHO was done s/o moderate pericardial effusion

Pericardial fluid cytology 103 cells including $P_{30\%}$ and $M_{70\%}$ sugar 130, protein 6.0 mg/dl, along with no evidence of any atypical cell.

Shortly after, a bone marrow aspiration was performed, which showed normocellular marrow with normal maturation. during this time an excisional biopsy of the right cervical lymph node. Pathology was consistent with the CD plasma cell variant.

PCR testing reveals No HHV in peripheral blood and the child had negative HIV serology.

Severe iMCD must have at least ≥ 2 of the 5 criteria listed below.[11]

Severe iMCD

Eastern cooperative oncology group performance status ≥2, stage IV renal dysfunction (eGFR ≤ 30; creatinine ≥ 3.0), anasarca and/or ascites and/or pleural and pericardial effusion, haemoglobin ≤8.0 g/dl, pulmonary involvement.

The child had severe CD as it fulfils ≥2/5 criteria which include pericardial effusion and Hb ≤8 gm/dl. As the child did not match the symptoms as per diagnostic criteria for TAFRO [thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, organomegaly], and POEMS. The child was diagnosed with idiopathic severe CD as per diagnostic criteria matching 2 majors, and 5 minor including laboratory criteria.

Treatment

Siltuximab [anti-IL-6 mab] is the first-line therapy for iMCD.[5] Due to the non-availability of the drug siltuximab, the child was started on combination therapy [corticosteroid and cytotoxic chemotherapy]. Prednisolone was started at a dose of 60 mg/msq/day, along with vinblastine [5 mg/msq] fortnightly till maximum response was achieved. Corticosteroid tapering started after systemic symptoms resolved.

DISCUSSION

iMCD is a rare lymph node disorder that can be underdiagnosed. A major barrier to patients obtaining access to effective therapy is the time taken to receive the correct diagnosis. iMCD can be confused with other diseases that can cause similar histopathology and symptoms, for example, Tuberculosis, lymphoma, sarcoidosis, etc. An international working group of 42 experts from 10 different countries forms a CD collaboration network (CDCN) and formulated diagnostic criteria which include major and minor criteria including laboratory criteria.[11] The multicentric CD is characterized by a predominantly lymphadenopathy presentation consistently involving peripheral lymph nodes and manifestations of multisystem involvement. It is considered a systemic B cell lymphoproliferation, probably arising in immunoregulatory deficit, and resulting in the outgrowth of clonal B-cell populations. Symptoms, primarily a consequence of elevated Interleukin-6 production, are asthenia (65%), weight loss (67%) and fever (69%) and Polyadenopathy (84%).[6]

CONCLUSION

This case report brings the importance of a definitive histological diagnosis in patients presenting with lymphadenopathy and systemic symptoms. Multicentric CD is a relatively uncommon cause, though clinically synonymous with lymphoma but different from malignant lymphoproliferative disorders histologically and prognostically.

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