Multicentric vs. Unresectable Unicentric Castleman Disease with Active Presentation: An Orphan Rare Disease in a Young Egyptian Female Patient. A Case Report

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Abstract

Background: Castleman disease (CD) is a rare disorder that affects lymph nodes and has a wide range of associated symptoms. The affected lymph nodes show characteristic histological picture. Most of the unicentric Castleman disease (UCD) cases can be cured by complete surgical removal or radiotherapy, while multicentric CD (MCD) is much more complicated and have several subtypes and requires more effort to reach a precise diagnosis and management.

Case presentation: A 17-years old female presented with sever fatigue and abdominal pain. Massive mediastinal lymphadenopathy was detected on radiological studies. Pathology confirmed a plasma cell variant of MCD. Autoimmune disorders, overlapping IgG4-related disease, TAFRO (Thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) syndrome and other malignancies were excluded after a series of investigations. She was HIV-negative, and the human herpes virus-8 status was unknown. The final diagnosis of idiopathic MCD-not otherwise specified (iMCD-NOS) was reached. She showed a very good response to corticosteroids and monoclonal antibody course of treatment. Radiological investigations showed marked regression of the lymph node mass, and there was complete resolution of her symptoms and normalization of the hematological and biochemical parameters.

Conclusion: The diagnosis and management of MCD remain very challenging, and the exclusion of infectious, autoimmune, and neoplastic disorders is necessary.

Keywords: Castleman disease, Idiopathic, Mediastinal lymphadenopathy, Multicentric, Rituximab

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Introduction

Castleman disease (CD) was first described by Benjamin Castleman, more than half a century ago, in a patient with mediastinal mass of lymph nodes (LNs) showing hyperplasia and follicles with hyalinized foci, which is now known as unicentric CD (UCD) 1. Multicentric CD (MCD) is CD affecting multiple LN regions 2.
The plasmablastic variant of MCD usually occurs in HIV-infected or immunocompromised individuals especially with concomitant human herpes virus 8 (HHV-8) which is considered the main etiology of this disease. Castleman disease is an uncommon, complex nonmalignant lymphoproliferative disorder (LPD). In the HHV-8-MCD subtype, viral interleukin-6 (IL-6) initiates a proinflammatory state leading to the evolution of a wide range of symptoms and laboratory abnormalities. The HHV-8-negative MCD is known as “idiopathic MCD” (iMCD). Within iMCD, a severe distinct clinical subtype presents with thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO). Other iMCD cases, often demonstrate less intense inflammatory syndrome, plasmacytic histopathology and hypergammaglobulinemia, are referred to as iMCD not otherwise specified (iMCD-NOS). Multicentric CD can be associated with polyarticular neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell neoplasms and skin changes (POEMS) syndrome.

idiopathic MCD is a rare complex orphan disease. The median age at presentation is around 50-65 years and >50% are males. In UCD the median age at diagnosis is 30–34 years. However, no age is immune and even young children can be diagnosed with any of its forms. Recent studies in iMCD-NOS reported 5-year overall survival rates of 55-77% and studies from tertiary centers reported a 1-year overall survival of >90% Castlemans disease histopathologic classification is split into the hyaline vascular (HV) and plasma cell (PC) types with an intermediate ‘mixed’ type. The mantle zones in HV subtypes encircling atrophic germinal centers (GCs) are extended with concentric rings of lymphocytes, thereby showing the characteristic “onion skin” morphology. The blood vessels could penetrate the GCs, thus showing “lollipop” appearance of follicles. The PC variant is characterized by polymorphous inflammatory infiltrate with sheets of polyclonal PC.

Fajgenbaum et al published the International Consensus Diagnostic Criteria for virology negative iMCD in 2017 and they stated that both major criteria should be present which include: enlarged LNs in 2 or more stations and histopathological features of iMCD. While for fulfilling the minor criteria; at least 2 out of 11 points are required and they should have one laboratory finding at minimum and these include: anemia, thrombocytopenia, hypoalbuminemia, elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), renal impairment and polyclonal hypergammaglobulinemia (total γ globulin or immunoglobulin (Ig) G >1700 mg/dL), clinical minor criteria include constitutional symptoms, organomegaly, fluid retention, pneumonitis or skin manifestations. Exclusion of infection-related, malignant or lymphoproliferative disorders is also required to set the final diagnosis.

We herein report the case of a patient diagnosed with and treated for iMCD-NOS, a rare complex orphan disorder.

Case Presentation

A 17-year-old female with no relevant medical or family history presented at the Hematology Unit - Mansoura Oncology Center in August 2018 with abdominal pain, fever, fatigue, and weakness. On physical examination, there were hepatosplenomegaly and small right axillary lymphadenopathy. Laboratory results revealed microcytic anemia (hemoglobin 7.8 g/dL and mean corpuscular volume 68.5 fl), normal platelet count (482 k/μL), leucopenia (2.4 k/μL), elevated CRP (48 mg/L), hypoalbuminemia (2.8 g/dL), and high ESR (>15 mm/h). Serum protein electrophoresis revealed a polyclonal band at the gamma region of 2.7 g/dL (33.79%) with normal immunofixation (Figure 1, Table 1).

Immunoglobulin assay was normal, ANA, Anti-ds-DNA and CCP antibodies were negative. Direct antiglobulin test (DAT) was positive together with reticulocytosis and indirect hyperbiliuribinemia that occurred later with anemia progression suggesting autoimmune cytopenia. Viral serology (HIV, HBV, HCV and CMV) were negative but EBV IgG was positive. HHV8 and further tests for EBV were not applicable.
Initial computerized tomography (Figure 2) scans showed extensive mediastinal lymphadenopathy including anterior mediastinal and pretracheal (largest measured 22x34 mm), posterior mediastinal on both sides forming paravertebral soft tissue masses circumferentially surrounding the related part of the esophagus with subsequent compression and luminal narrowing (largest on the right side measured 3x6x10.7 cm), and right parahilar LNs (largest measured 26 mm). Cervical lymphadenopathy and hepatosplenomegaly were noted as well.

Bone marrow aspiration revealed 7% PC with no clonality. Bone marrow biopsy findings were in the normal range with no infiltrative lesion or fibrosis with some scattered perivascular PCs representing 10% of cellularity positive for CD138 (Figure 3).

Biopsy from mediastinal LNs showed changes consistent with iMCD of PC variant (prepared sections revealed fragments of lymphoid tissue with multiple hyperplastic lymphoid follicles showing prominent GCs). The interfollicular area showed dense PC infiltrates and the unique “lollipop” appearance. CD3, CD20 and BCL2 revealed mixed positive reaction highlighting the reactive lymphoid follicles and CD138 revealed positive reaction in the PC while CD30 and cytokeratin were negative (Figure 4).

**Figure 1. Serum protein electrophoresis “capillary electrophoresis”**

**Table 1. Results of protein electrophoresis**

<table>
<thead>
<tr>
<th>Protein Type</th>
<th>Value</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>8.00 g/dL</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.49 g/dL, 43.71% (N: 55.8-66.1%)</td>
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</tr>
<tr>
<td>Alpha 1</td>
<td>0.39 g/dL, 4.9% (N: 2.9-4.9%)</td>
<td></td>
</tr>
<tr>
<td>Alpha 2</td>
<td>0.88 g/dL, 11.0% (N: 7.1-11.8%)</td>
<td></td>
</tr>
<tr>
<td>Beta</td>
<td>0.50 g/dL, 6.6% (N: 7.9-13.7%)</td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td>2.70 g/dL, 33.79% (N: 11.1-18.8%)</td>
<td></td>
</tr>
</tbody>
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**Figure 2. Computerized tomography scans showing mediastinal lymphadenopathy and hepatosplenomegaly**
The involvement of multiple LN regions favored the diagnosis of iMCD-NOS in addition to the less intense inflammatory syndrome, normal platelet count, PC histopathology, polyclonal hypergammaglobulinemia, and showing active disease criteria. Another possibility was the diagnosis of unresectable UCD, as positron emission tomography-computed tomography (PET-CT) was not available at baseline for the assessment of LNs criteria and the LNs other than the mediastinal were relatively small.

**Figure 3. Histopathologic features of bone marrow biopsies from a patient with idiopathic multicentric Castleman disease: A) **Average cellularity and reactive plasmacytosis (H-E stain x400). **B) **Reactive perivascular plasma cells (CD138 x400).

Prednisolone (1mg/kg/day) was initiated and then she was started on rituximab (375mg/m²) weekly infusions plus dexamethasone (40mg/day for 4 days) instead of prednisolone for 8 courses. Following treatment, the PET-CT scan showed reduction in the size of mediastinal lymphadenopathy and the right paravertebral posterior mediastinal mass lesion had a low grade metabolically active achieving SUV max 1.7 (80x35x16 mm in CCxTRxAP diameters), with no supra- or infra-diaphragmatic active lesions. The patient showed a complete response as regard her symptoms and biochemical profile (normal biochemistry and hemoglobin levels up to 10-11.9 mg/dl). Currently, she is on regular follow up with no clinical, laboratory or radiological progression.

**Discussion**

This young female patient presented with HIV negative/HHV-8 unknown status (believed to be negative) associated with active disease criteria including fever and elevated CRP and MCD-related symptoms as lymphadenopathy, splenomegaly, jaundice, autoimmune hemolytic anemia (AIHA). Pleural effusion developed after mediastinoscopy guided biopsy which necessitated chest tube insertion. Due to the unavailability of baseline assessment of the metabolic activity small LNs in regions other the mediastinum, the diagnosis of unresectable bulky UCD could not be excluded.

She had an atypical iMCD presentation based on her age, as females in their mid-twenties to mid-forties were rare in a CD study. This raised the suspicion of an underlying autoimmune disorder that could have hastened the onset of CD by increasing the LN hyperplasia due to chronic inflammatory triggers and pathogenic mechanism. Inflammatory cytopenias are common features of MCD.

Our patient fulfilled the two major criteria of the International Consensus Diagnostic Criteria for the diagnosis of iMCD, the histopathologic LN features and the enlarged mediastinal, axillary, and cervical LNs. As for the minor criteria, clinically our patient presented with constitutional symptoms, hepatosplenomegaly. There were no skin lesions nor interstitial pneumonitis. The positive laboratory findings included elevated CRP, high ESR, microcytic anemia and increased total gamma globulin. There was no renal function abnormality.

The characteristic clinicohistopathological features of iMCD may be present in several malignancies, infectious diseases, and autoimmune disorders. Enlarged LNs from patients with collagen diseases display MCD-like histopathology. Our patient’s immune profile was negative except for DAT.
Figure 4. Histopathologic features of mediastinal lymph nodes from a patient with idiopathic multicentric Castleman disease: A) The lymphoid follicles are hyperplastic GCS with hypervascular interfollicular regions (H-E stain x40), B) A blood vessel from interfollicular area that penetrates at right angle into GCs “lollipop follicle” (H-E stain x40), C) Focal fibrotic area (H-E stain x 40), D) The interfollicular region shows sheets of cytologically mature plasma cells (H-E stain x40), E) Reactive follicles (CD20 x 40), F) Interfollicular plasma cells (CD138 x 40)

Polyclonal hypergammaglobulinaemia on the serum protein electrophoresis. AIHA was found in about 30% of iMCD patients. Virology screening came back negative for hepatitis B and C and HIV while EBV IgG was positive. PCR for EBV and HHV-8 were not available. The overlap between IgG4-related disease (IgG4-RD) and iMCD was excluded in our patient as IHC staining of the LN revealed positive IgG4 in <20 PC/HPF. TAFRO syndrome is rare and was first described in Japan and case reports in other countries have been also published. TAFRO was excluded because the platelet count was slightly elevated, bone marrow examination did not show reticulin fibrosis and there was no generalized ansarca at presentation.

Anti-IL-6 monoclonal antibody (anti-IL-6 mAb) are now considered as the preferred first-line therapy for iMCD without HHV-8 infection.
International, evidence-based consensus treatment guidelines for iMCD recommend rituximab (375 mg/m²) for four to eight doses as a first-line alternative to anti–IL-6 mAb therapy for patients with non-severe iMCD. In a previous study conducted on iMCD patients, the overall response rate with rituximab or rituximab-based chemotherapy regimens as first-line therapy exceeded 60%. Rituximab treated patients had inferior progression-free survival compared to those who received siltuximab.

Regarding the treatment of current case, we initiated therapy with corticosteroids with only mild relieve of symptoms but with progression AIHA. After the addition of rituximab and switching to dexamethasone, the patient improved clinically with normalization of inflammatory markers. PET-CT scan showed regression of the low metabolic activity of the mediastinal/paravertebral masses and no supra- or infra-diaphragmatic active lesions. In the CastlemaB trial, twenty-four patients with relapsed/refractory MCD, were treated by rituximab, 22 patients became chemotherapy independent. Most patients responded clinically, and the majority were progression free for 2 years. Siltuximab refractory patients should be offered rituximab as a subsequent option either as monotherapy or in combination with other regimens. Resolution of lymphadenopathy was found to be faster with chemotherapy and rituximab than with anti-IL-6 mAb.

Conclusion

Castleman disease is a complex LPD with various clinical and pathologic manifestations that vary depending on whether the disease is localized or systemic. Monotherapy with CD20 monoclonal antibody limited course could give good response in patients with CD, especially when IL-6 mAb is unavailable.

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Not applicable.

Authors’ contribution

YS, SE, AE, MA, MS, AE, SE, SR, ME & BA equally participated in collecting the clinical, pathological, laboratory and treatment data. AE revised the pathological data. AE collected and revised the radiological data. YS, SE, AE, MA, MS, AE, SE, SR, ME & BA equally participated in writing and editing the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Included in the manuscript.

Ethical considerations

All procedures performed in the study were in accordance with the ethics standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments.

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Study registration

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References


