



A Case Report on Idiopathic-Multi-centric Castleman's Disease Associated POEMS- Syndrome

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Abstract: Castleman's Disease is a rare lymphoproliferative disorder of idiopathic etio-pathogenesis and was first described by Dr Benjamin Castleman in 1954. It is a rather rare disease entity in clinical practice. However, the incidence cannot be ignored. It may affect a single lymph node (Unicentric CD) or multiple lymph nodes throughout the body (Multicentric CD). Management depends upon the type and severity of the disease and early recognition of the condition. Our case report is that of a 60-year-old female patient with underlying comorbidities including type 2 diabetes mellitus, hypothyroidism who presented with complaints of generalized weakness, weight loss, hair loss, non-resolving muco-purulent rhinorrhea, bilateral pedal edema and multiple, non-tender, firm and mobile left sided Level I and II 'AJCC' cervical lymphadenopathy of >2cm which was later biopsied and diagnosed to be Castleman's disease associated POEMS syndrome. The aim of this report is to consider CD as a differential diagnosis in patients presenting with similar clinical picture and early identification and treatment may provide a better prognosis. We would also like to highlight 3 take home points: 1) The significance of histology in differentiating it from other lymph proliferative conditions. 2) LN excision of the bothersome LN can be diagnostic and may be considered therapeutic to some extent even in MCD. 3) Steroid therapy has beneficial effects to control progression of the disease.

Keywords: Castleman's Disease, POEMS Syndrome, Lymph Node Hyperplasia, HIV, Paraproteinemia

1. Introduction

Castleman's Disease is a rare lymphoproliferative disorder of idiopathic etio-pathogenesis was first described by Dr Benjamin Castleman in 1954. It is a rather rare disease entity which is a lymphoproliferative disorder having many presentations. The symptoms can range from simple B-symptoms to various autoimmune phenomenon to a frank POEMS syndrome. However, the incidence cannot be ignored. It may affect a single lymph node (Unicentric CD) or multiple lymph nodes throughout the body (Multicentric CD). Management depends upon the type and severity of the disease and early recognition of the condition. We present the

case of a 60-year-old female patient with Castleman's disease associated POEMS syndrome. The aim of this report is to consider CD as a differential diagnosis in patients presenting with similar clinical picture and further confirmation to be done with excisional biopsy of an involved lymph node.

2. Case

A 60 year old female, known case of type 2 diabetes mellitus, hypothyroidism presented with complaints of generalized weakness, weight loss, hair loss, non-resolving muco-purulent rhinorrhea of two weeks and bilateral pedal edema of one week duration. On examination; vitals were stable, there was pallor, widespread purpura, multiple, non-

tender, firm and mobile left sided Level I and II 'AJCC' cervical lymphadenopathy of >2cm and bilateral pitting pedal edema. There was no clubbing, cyanosis or unguinal changes of significance. Abdomen was distended with mild hepatosplenomegaly (HSM), bilateral upper and lower extremities showed distal to proximal glove and stocking paresthesia with mild-moderate impairment of two point discrimination, other systems were unremarkable. Excisional biopsy of the left cervical lymph node (LCLN) was suggestive of Castleman's disease (CD) of hyaline vascular type. Patient was started on broad spectrum Intravenous antibiotics, topical steroid, for sinusitis, and dermatological manifestations respectively. She was discharged with oral antibiotics along with other supportive treatment. After 2 weeks of follow-up, oral prednisolone was initiated and tapered over 4 months. Symptomatic improvement was reported by the patient on 10 months follow up. Major therapeutic interventions done were diagnostic excision of largest lymph node (LN) and initiation of prednisolone. Currently the patient remains asymptomatic.

3. Discussion

CD, is a rare lymphoproliferative disease of unknown etiology [1] describing a group of three immunologic disorders that occur in individuals of all ages and share a similar microscopic lymph node appearance, with signs and symptoms related to the release of cytokines, particularly interleukin 6. [2, 3] Its subtypes include [4]:

1. Unicentric: Single site of Lymphoproliferation.
2. Multicentric: Multiple sites of lymphoproliferation. It has 2 subgroups.
 - a) Human herpes virus 8 (HHV 8) associated Multicentric CD (MCD). Among HHV-8-associated MCD, patients who are immunocompromised, such

as those with human immunodeficiency virus (HIV) infection [3] are at increased risk of developing Kaposi sarcoma, non-Hodgkin lymphoma, and Hodgkin lymphoma.

- b) HHV 8 negative MCD /Idiopathic MCD (IMCD) [4] which has 3 further sub-groups.

IMCD-POEMS syndrome (Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes).

IMCD-TAFRO syndrome (Thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly).

IMCD-NOS (Not otherwise specified).

POEMS is a paraneoplastic syndrome that can co-occur with HHV-8-negative MCD. HHV-8 negative MCD patients, who do not have POEMS or TAFRO are considered IMCD-NOS.

Histopathological variants include [5].

a) Hyaline vascular b) Mixed and c) Plasmacytic variants [4]. Etiology of CD is unknown though studies have shown viral stimulation, angiogenesis, Interleukin-6 [5], and clonal cell proliferation in the pathophysiology of the disease. General treatment modalities include LN excision in case of UCD which may even be curative in most cases [6]. Due to the variable prognosis and multi factorial etiology of MCD no treatment consensus has been documented. Although; most of the time, treatment is focused on immunosuppression and immunomodulation with steroids and chemotherapeutic agents respectively [7, 8]. Monoclonal antibodies (Siltuximab and Rituximab) have shown some efficacy [9].

Clinically our patient may be categorized as having CD variant of POEMS. The diagnosis of Classic POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present [10] (Table 1).

Table 1. Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

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|-------------------------------------|--|
| Mandatory major criteria | 1. Polyneuropathy (typically demyelinating) 2. Monoclonal plasma cell-proliferative disorder (almost always λ) |
| Other major criteria (one required) | 1. Castleman disease 2. Sclerotic bone lesions 3. Vascular endothelial growth factor elevation |
| Minor criteria | 1. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 2. Extravascular volume overload (edema, pleural effusion, or ascites) 3. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) 4. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, white nails) 5. Papilledema 6. Thrombocytosis/polycythemia |

Classic POEMS syndrome patients have monoclonal plasma cell dyscrasia whereas patients with CD variant of POEMS tend to have polyclonal hypergammaglobulinemia [11]. Our patient meets all the criteria which includes: polyneuropathy, confirmation of Castleman's Disease on excisional biopsy of cervical lymph nodes, organomegaly including both hepatomegaly, splenomegaly and cervical lymphadenopathy, bilateral lower limb edema denoting extravascular volume overload. Her endocrinopathies included hypothyroidism and type 2 Diabetes Mellitus.

Complete blood count revealed thrombocytosis. Hence our patient meets all the criteria except for monoclonal plasma cell dyscrasia, thus classifying it as Castleman disease variant of POEMS.

4. Investigation and Clinical Features

At admission we noted: anemia (Hb: 8.4 gm%, HCT: 24.3%), leukocytosis (TC: 23,700 cells/mm³) with normal differential count percentage, thrombocytosis (6.01 lakh/mm³),

high ESR (140mm/hr) and hypothyroidism (T3: 0.95, T4: 4.83, TSH: 5.750). Liver function test showed mild hyperproteinemia (Total protein: 8.3 gm %) with A/G reversal (2.5/5.8), other parameters were within normal limits. Renal function test showed hypocalcemia (7.3 mg/dL), hyponatremia (129mmol/L), elevated Urine protein/creatinine ratio of 0.42, serum urea, creatinine, uric acid, lactate dehydrogenase and urine routine were within normal limits. Markers for human immunodeficiency virus (HIV), hepatitis B, C and syphilis were negative. Serum protein electrophoresis and Peripheral smear showed polyclonal hypergammaglobulinemia and moderate hypochromic microcytic anemia with mild leukocytosis and eosinophilia respectively. Urine Bence Jones protein was negative.

Ultrasonogram of Abdomen showed HSM with para aortic lymphadenopathy (10 mm). A Contrast Enhanced - Computerised Tomography (CECT) of thorax and CT of para nasal sinuses revealed multiple enhancing LN in both axillae and mediastinum with mild cardiomegaly and pan-sinusitis with deviated nasal septum and inferior turbinate hypertrophy on right side. No mass or destructive lesions were reported.

Fine needle aspiration cytology from LCLN showed chronic granulomatous lymphadenitis suggestive of tuberculosis. Sputum staining for acid fast bacilli was negative. Excisional biopsy of the LCLN (3.5x2x1cm) showed follicles throughout the cut sections, germinal centers with expanded mantle zone arranged in concentric 'Onion skin' appearance suggestive of Castleman's disease (CD) of hyaline vascular type. Leukocyte associated nuclear antigen marker of the LN specimen for HHV-8 was negative.

5. Conclusion

The aim of this discussion is to point out the importance of considering CD as a differential diagnosis in patients with similar presenting syndromes despite the rarity of these diseases in clinical practice.

We would like to highlight 3 take home points:

- 1) The significance of histology in differentiating it from other lymph proliferative conditions.
- 2) LN excision of the bothersome LN can be diagnostic and may be considered therapeutic to some extent even in MCD.

- 3) Steroid therapy has beneficial effects to control progression of the disease.

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