Quintessential Case of POEMS Syndrome Associated With Multicentric Castleman Disease

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Abstract
Castleman disease (CD) is a rare lymphoproliferative disorder, closely related to Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, and Skin changes (POEMS) syndrome. We report a typical patient of multicentric CD with POEMS syndrome with all the classical features.

Keywords
POEMS, Castleman disease

Introduction
Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, and Skin changes (POEMS) syndrome is an uncommon paraneoplastic disorder associated with an underlying plasma cell dyscrasia. Castleman disease (CD) is another rare disorder. CD is one of the major criteria in the diagnosis of POEMS syndrome. There are only few reports of CD with POEMS syndrome with all the features and we are reporting one such case. A total of 11% to 25% of patients with POEMS can have associated CD and some series have reported 50% association.

Case Report
Fifty-nine years old male, presented with complaints of bilateral swelling of legs of 3 years duration, bilateral axillary swelling, back pain, hip pain, and numbness of feet of 1 year duration. He was diagnosed with primary hypogonadism and primary hypothyroidism when he was evaluated for bilateral gynecomastia since 1 year. Examination revealed generalized lymphadenopathy, bilateral pedal oedema, and bilateral gynecomastia. Neurological examination showed bilateral symmetrical sensory neuropathy of both upper and lower limbs.

The positive finding on blood work was the presence of a monoclonal band (M band) in the protein electrophoresis which on immunofixation confirmed IgG lambda which is classical of POEMS. Bone marrow study was normal with no plasmacytosis. Magnetic resonance imaging (MRI) of the hip showed osteolytic lesion in the right acetabulum (Figure 1A). Computed tomography (CT) images of the spine showed sclerotic lesions in D6 and D11 (Figure 1B). Image-guided biopsy from the acetabular lesion confirmed plasma cell neoplasm (Figure 2A) with lambda restriction. Right axillary lymph node biopsy confirmed hyaline vascular type of CD (Figures 2B and C). The endocrine profile was consistent with primary hypogonadism. Nerve conduction velocity showed demyelinating polyradicular sensory motor neuropathy. We had initiated treatment with thalidomide, cyclophosphamide, and prednisolone.

Figure 1 (A). MRI Showing Right Acetabular Fracture as Pointed.

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Discussion and Review of Literature

It is estimated that approximately 4,300 to 5,200 new cases of CD are diagnosed each year in the United States. POEMS syndrome and CD are closely linked and both are rare conditions. Diagnostic confirmation of CD is by histopathology. Histologically, there are 3 types namely hyaline vascular, plasmacytic, and mixed type. The histopathological subtype in POEMS-associated CD is mostly hyaline vascular. Interleukin 6 and vascular endothelial growth factor (VEGF) are associated with pathogenesis. VEGF is associated best with disease activity in POEMS syndrome and used to monitor disease activity in POEMS syndrome. Mostly, the plasma cells in POEMS syndrome are lambda light chain restricted as in our patient.

The following are the diagnostic criteria for POEMS syndrome.2

**Mandatory Major Criteria (Both Are Required)**
Polyradiculopathy, monoclonal plasma cell disorder.

**Other Major Criteria (One of Them Required)**
CD, sclerotic bone lesion, elevated VEGF

**Minor Criteria (Any One Is Required)**
Organomegaly (liver, spleen, or lymphadenopathy).
Extravascular volume overload, endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic).
Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, and flushing, white nails.)
Papilledema.
Thrombocytosis and polycythemia.

**Other Symptom and Signs of POEMS**
Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12.

All the characteristics included in the POEMS acronym need not be present for the diagnosis. There is also a plasma cell variant of CD without evidence of clonal plasma cell disorder. It is thought that the pathologic plasma cells in POEMS syndrome are also involved in concurrent CD. Our patient has fulfilled most of the criteria of POEMS except for the skin changes and he had a proven CD by histopathology. He had a classical demyelinating peripheral neuropathy, lymphadenopathy, endocrinopathy, fluid retention, and monoclonal plasma cell disorder. Peripheral neuropathy can occur in 10% CD patients without POEMS which is of lesser severity. It is more severe with concurrent CD and worst in

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**Figure 1 (B).** PET CT Showing Sclerotic Lesion in D6 and D11 Vertebrae as Pointed.

**Figure 2.** (A) Biopsy From the Right Acetabular Lesion Showing Sheets of Plasma Cells, ×400. Lymph Node Biopsy Showing Hyalinized Follicle as Pointed With Sclerosed Blood Vessel Traversing into the Germinal Centre (Lollipop lesion) Characteristic of Castleman Disease: (B) ×200 and (C) ×400.
POEMS without CD. CD is basically categorized into unicentric and multicentric CD (MCD). MCD is further classified into idiopathic MCD (iMCD), POEMS-associated MCD, and human herpesvirus (HHV8)-associated MCD. iMCD is further subdivided into iMCD not otherwise specified (NOS) and TAFRO MCD. TAFRO is the acronym for thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, and organomegaly. HHV-associated MCD is often associated with human immunodeficiency virus (HIV) infection.

Pathologically, CD has 3 subtypes namely hyaline vascular type, plasma cell type, and mixed type. POEMS-associated CD is typically hyaline vascular as in our patient. Treatment of CD depends on whether it is unicentric CD (UCD) or MCD. The treatment of UCD is local excision. MCD treatment depends on the subtype. HHV-8-associated MCD is treated with rituximab. iMCD is managed with IL6 blockade treatment depends on the subtype. HHV-8-associated MCD is treated with rituximab. iMCD is managed with IL6 blockade and siltuximab which is the drug of choice. Tocilizumab is another option. In refractory cases, variety of other agents like rituximab, sirolimus, and cyclosporine are tried. POEMS-associated CD is managed by myeloma-directed therapies including high-dose therapy with autologous stem cell transplantation. Agents used for myeloma therapy like proteosome inhibitors, immunomodulators, daratumumab, and steroids can be used. The outcome of therapy depends on the subtype of CD. UCD has the best outcome. Among the MCD according to 1 publication from France, the overall survival for iMCD was 100%, HIV negative HHV MCD 89%, and HIV positive HHV MCD was 65%. A Chinese Phase II trial had used a combination of thalidomide, cyclophosphamide, and prednisolone (TCP regimen) for patients with iMCD with a response rate of around 48%. Our patient has been started on the TCP protocol as this combination will cover both CD and POEMS. Interestingly, patients with POEM-MCD without an osteosclerotic bone lesion fare much worse than patients with a bone lesion. On follow-up, patient showed considerable improvement in general well-being with resolution of pedal oedema. On serum electrophoresis, the M component is reducing. There is a good clinical and biochemical response.

Conclusion

Our case exemplifies the association between CD and POEMS syndrome and one has to look diligently for POEMS in a case of MCD and vice versa.

Authors’ Contributions

The manuscript has been read and approved by all authors. Krishnarathnam Kannan and Induja Muthiah Vaikundaraja prepared the manuscript. Kanchan Murhekar and Swathy Pitti Umasankar provided the pathology support.

Declaration of Conflicting Interests

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