

POEMS syndrome complicated with multiple ischemic vascular events: case report and review of literature

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Abstract: POEMS syndrome (acronym consisting of: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) is an uncommon disorder associated with an underlying plasma cell dyscrasia. There is no single specific test for POEMS, and due to its rarity and heterogeneity, patients are often mis- or underdiagnosed. Castleman disease (CD) is a rare lymphoproliferative disorder, closely related to POEMS syndrome; ~11%–30% of POEMS patients are associated with concomitant CD. In contrast to frequently published reports on vascular events in POEMS syndrome affecting coronary arteries or lower limbs, cases of cerebrovascular events are rarely mentioned in literature. We hereby report a patient with POEMS syndrome accompanied by CD who presented recurrent strokes and splenic infarction.

Keywords: POEMS, chronic inflammatory demyelinating polyradiculopathy, M protein, thrombotic risk, stroke, recurrent ischemic events

Introduction

POEMS syndrome is an uncommon disorder associated with an underlying plasma cell dyscrasia. The acronym derives from its main features: polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. Additional findings include: papilledema, extravascular volume overload (ascites, edema, and pleural effusion), abnormal pulmonary function, elevated vascular endothelial growth factor (VEGF) levels, fever, sclerotic bone lesions, erythrocytosis, thrombocytosis, and predisposition toward thrombosis.^{1,2}

The disorder was first named osteosclerotic myeloma, Crow–Fukase syndrome, or Takatsuki syndrome.^{3,4} Later, Scheinker reported a case with solitary plasmacytoma, sensorimotor polyneuropathy, and skin lesions.⁵ POEMS acronym was used by Bardwick et al, when 2 cases having features mentioned before were reported.⁶ The median age of diagnosis is in the fifth and sixth decade of life.¹

Castleman disease (CD) is a rare lymphoproliferative disorder with giant angiofollicular lymph node hyperplasia. The most frequent symptoms and clinical features are fatigue, weight loss, night sweats, fever, lymphadenopathy, and hepatosplenomegaly.⁷ CD and POEMS syndrome are closely related. Approximately 11%–30% of POEMS patients are associated with CD.⁸ This subtype was first described by Dispenzeri et al a few years ago.⁹

Arterial and venous thromboses, mainly involving the coronary and lower limbs arteries, have been reported in POEMS patients.^{10,11} There are only few reports on POEMS syndrome associated with CD complicated with cerebrovascular events.^{12–18}

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In this paper, we present a patient diagnosed with this subtype with thrombotic complications, recurrent strokes, and splenic infarction.

Case presentation

A 45-year-old female presented with significant weight loss (about 28% of body weight during the past year), night sweats, and severe pain in the lower extremities. She had no history of smoking, hypertension, hyperlipidemia, or alcohol consumption. The patient had been diagnosed 1 year before presentation with chronic inflammatory demyelinating polyradiculoneuropathy. She had been treated with acetylsalicylic acid, carbamazepine, and small doses of corticosteroids with no clinical improvement. On referral to our hospital, there was progressive weakness of left limbs and numbness. Physical examination showed a female with cachexia (BMI = 16.8 kg/m²), facial lipoatrophy, skin hyperpigmentation, hypertrichosis, hyperhidrosis, sclerodermiform cutaneous thickening, white nails, Raynaud phenomenon, muscle atrophy, non-tender axillary lymph nodes measuring 2.0×1.5 cm, and hepatosplenomegaly. No signs of extravascular volume overload were noted. A neurological examination revealed left-side hemiparesis and sensory loss in the left limbs. Sensorimotor demyelinating and axonal polyneuropathy in upper (median and ulnar nerves) and lower limbs (peroneal, tibial, and sural nerves), prolonged distal motor latency, and slowed velocity of both motor and sensory nerve conduction were the main findings on nerve conduction studies. Ophthalmic fundus examination presented bilateral papilledema. CT scan identified a newly emerged area of infarction in the right frontal parietal occipital area.

Laboratory studies are presented in Table 1. Hypoparathyroidism and secondary amenorrhea (most likely a functional hypothalamic amenorrhea) were identified as endocrine abnormalities. The clinical and laboratory abnormalities constellation suggested POEMS syndrome. No tests for VEGF, interleukin-1 β (IL-1 β), IL-6, tumor necrosis factor- α (TNF- α), known to be involved in the pathogenesis, were available at our center.

On skeletal survey, lytic lesions with a sclerotic rim were present on proximal extremities. On thorax and abdomen CT scan, multiple enlarged axillary, mediastinal and mesenteric lymph nodes along the iliac vessels (maximum diameter of ~2 cm), minimum pleural effusion, hepatomegaly, and splenomegaly with chronic infarction were observed. Transthoracic echocardiography revealed normal left ventricle volume and ejection fraction, no pericardial effusion, no signs of pulmonary hypertension, but interventricular

Table 1 Summary laboratory tests at diagnosis

Laboratory tests	Normal/negative	Abnormal findings
Complete blood cell count:	130–400×10 ⁹ /L	800×10 ⁹ /L
Thrombocytosis		
Erythrocyte sedimentation rate (mm/h)		13
C-reactive protein (mg/L)	0–5	11.6
Coagulation tests	Normal	
Fibrinogen (mg/dL)	276–471	542
Blood chemistry	Normal	
Liver function tests	Normal	
Lipid profile	Normal	
Fasting and postprandial blood sugar	Normal	
Serum calcium (mg/dL)	8.2–10.7	6.2
Serum total protein	Normal	7
Albumin (g/dL)	3.5–5.0	3.1
Serum immunofixation		IgA- λ monoclonal protein
IgA (mg/dL)	70–400	527
λ free light chains (serum) (mg/L)	5.7–26.3	130
Cryoglobulin	Negative	
Thyroid stimulating hormone	Normal	
Anti-thyroid antibodies	Normal	
ANA, rheumatoid factor, C3, C4 complement	Negative	
HIV, hepatitis B, C	Negative	
Bone marrow aspirate		4% morphologically atypical plasma cells

Abbreviations: ANA, antinuclear antibodies; IgA, immunoglobulin A.

septal thickening with granular appearance suggestive of an infiltrative cardiomyopathy. A fat-pad abdominal biopsy specimen was negative for amyloid deposits. Due to patient's poor clinical status, no pulmonary function tests were performed at baseline.

Axillary lymph node biopsy (Figure 1) revealed thickening of the mantle and marginal zone with small lymphocytes surrounding the germinal center, which were hyalinized and hypoplastic with “onion peel” appearance, and surrounded by blood vessels. Immunohistochemical analysis was positive for: CD3 in frequent parafollicular reactive T cell lymphocytes; CD 20 in reactive B cells; <5% Ki67 plasma cells with κ/λ ratio ~3/1. These histological findings were consistent with mixed type (the hyaline vascular type and plasma cell form of CD). Antibodies for human herpes virus 8 were negative. A diagnosis of POEMS associated with CD was established.

She was treated for plasma cell dyscrasia with CyBorD protocol (cyclophosphamide, bortezomib, and dexamethasone) ×4 cycles as induction therapy, along with supportive care (acetylsalicylic acid 75 mg daily, prophylactic

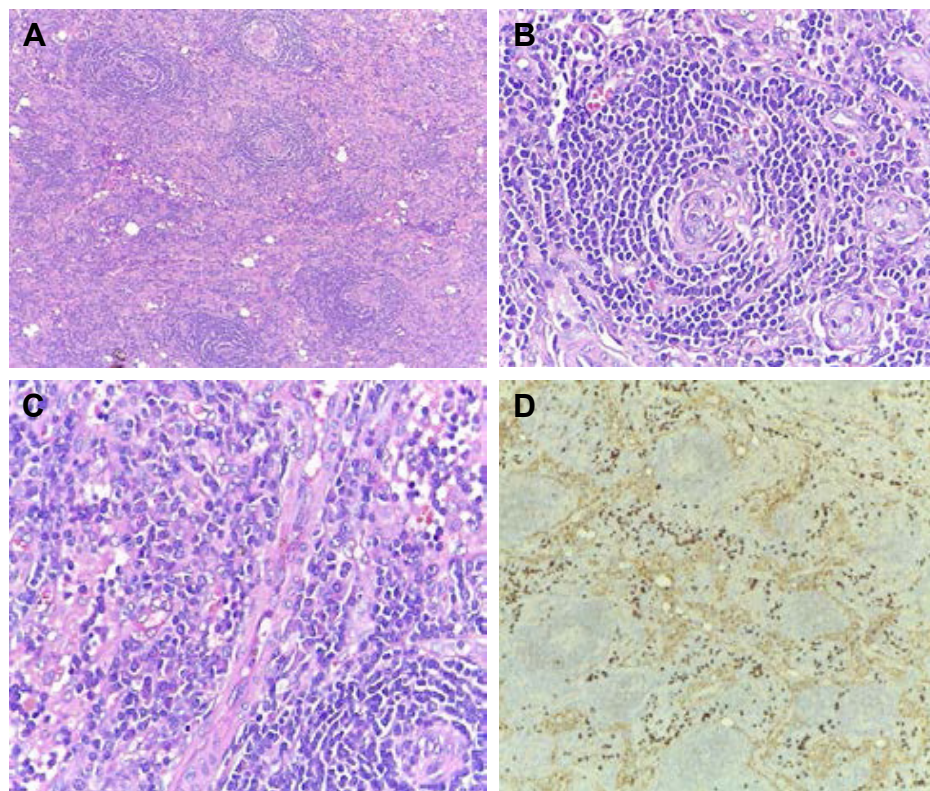


Figure 1 Lymph node biopsy (A, B) revealed follicular hypoplasia, thickening of the mantle and marginal zone with small lymphocytes surrounding the germinal center, which were hyalinized and hypoplastic, and gave rise to the “onion peel” appearance (A: H&E $\times 40$, B: H&E $\times 10$); (C) Immunohistochemical analysis: plasma cells infiltrating among interfollicular areas with λ light chain restriction (IHC $\times 10$); (D) plasma cells infiltrating among interfollicular areas (H&E $\times 40$).

low-molecular-weight heparin, calcium, vitamin D to correct hypoparathyroidism-induced hypocalcemia, and analgesics). Because of the preexisting POEMS neuropathy, bortezomib was administered subcutaneously. A partial improvement on neurological function (improved neuropathic pain, but the patient was still not able to walk without support) and clinical status (weight gain, muscle strength, and diminished night sweats) were noticed. The organomegaly and the endocrine abnormalities did not resolve.

After 4 cycles of CyBorD, a CT scan for evaluation was performed; it revealed enlarged lymph nodes >2 cm diameter (larger than the previous examination), bilateral pleural effusion, and hepatosplenomegaly with chronic spleen infarction. Laboratory screening presented thrombocytosis $600 \times 10^9/L$, higher inflammatory syndrome (fibrinogen 680 mg/dL, C reactive protein 26.53 mg/L), LDH 249 U/L (NR 81–234 U/L) and increasing level of free λ chains. Furthermore, she had neurological deterioration: aggravated neuropathic pain and sudden onset of speech difficulties. Cerebral CT scan showed a newly emerged area of infarction, involving the middle cerebral artery. All these findings (especially recurrent cerebrovascular ischemic attack) were suggestive of progressive disease and her treatment was

changed to melphalan/prednisone protocol. Her clinical condition deteriorated soon after initiating treatment. She presented respiratory distress probably caused by impaired neuromuscular respiratory function and progressive neurological deterioration. Unfortunately, she died soon after the deterioration occurred, due to pulmonary sepsis.

We mention that written informed consent was provided by the patient and the patient’s next of kin to have the case details published.

Discussion

Diagnosis of early POEMS syndrome represents a challenge in clinical practice. It includes presence of polyradiculoneuropathy (typically demyelinating) and monoclonal protein plasma cell disorder (almost always λ), at least 1 of the 3 major criteria (CD, sclerotic bone lesions, and elevated VEGF) and at least 1 minor criterion: organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, or thrombocytosis/polycythemia.⁹ Our patient presented demyelinating polyradiculoneuropathy, IgA λ monoclonal protein, 2 major criteria (CD and sclerotic bone lesions), and several minor criteria: organomegaly, extravascular volume overload (pleural effusion in

evolution), hypoparathyroidism, skin changes, papilledema, and thrombocytosis.

CD, also a rare systemic disorder, includes 2 types: localized and multicentric. Three histological forms are described: hyaline vascular, plasma cell, and mixed type. Multicentric CD (MCD) is generally plasma cell type, but the hyaline vascular type has also been described in some patients. Localized CD usually presents in young adults (20–30 years old), compared with MCD (40–50 years old). Patients present systemic symptoms, multiple enlarged lymph nodes, and organomegaly.¹⁹ Lymph node biopsy is mandatory for diagnosis. The histological findings in our case were consistent with CD mixed type. POEMS associated with CD was the diagnosis of our patient. The association between CD and POEMS is not fully understood, though it is well recognized. An association with MCD was reported in approximately half of POEMS patients.^{1,20,21}

Pathogenesis of POEMS is not entirely known. Elevated levels of proangiogenic and proinflammatory cytokines like VEGF, IL-6, TNF- α are believed to be the hallmark of pathogenesis. VEGF is considered the driving cytokine in the regulation of endothelial cell proliferation, migration, and permeability and it is responsible for features as extra-vascular volume overload and papilledema. It was also suggested that increased VEGF levels induce higher endoneuronal pressure because of edema and increased microvascular permeability, possibly explaining the nerve damage.²² However, other mechanisms may be involved, as results of studies using anti-VEGF monoclonal antibody (bevacizumab) treatment are variable.^{23,24} The impact of these cytokines on the vascular system in POEMS is proven by the frequently associated thrombotic accidents. Most of the previous reports refer to lower limb and coronary artery thrombosis, and only a few described POEMS being associated with CD and cerebrovascular involvement.^{18,25,26} The pathophysiological mechanism of vascular events remains unclear. Kang et al suggested a causal relationship between vascular events and raised IL-6 that induces hyperfibrinogenemia.¹⁸ Other authors discussed that IL-1 β , TNF- α , and histological abnormalities of intracranial vessels (scleroderma-like skin changes and non-inflammatory vasculopathy) could be triggers for thrombosis.^{10,11} Results of a retrospective study from Mayo Clinic stated thrombocytosis and evidence of plasma cell proliferation on bone marrow as independent thrombotic risk factors. The 5-year risk of ischemic stroke was 13.4%.²⁷ Abnormalities of the coagulation system have also been reported. One study showed that patients present elevated levels of circulating coagulation factors (fibrinopeptide

A and thrombin–antithrombin complex) during the active phase of illness, but normal values of factors related to fibrinolysis (plasminogen, α 2plasmin inhibitor plasmin complex, and fibrin degradation product).²⁸

Considering that this patient was a young female without any known cardiovascular risk factors, we suspected that the recurrent cerebrovascular ischemic events, associated with another extra-cerebrovascular event (chronic splenic infarction), were most likely the result of POEMS syndrome associated with CD. Our patient also presented hyperfibrinogenemia on both ischemic events, higher the second time; thrombocytosis; and evidence of plasma cell proliferation on bone marrow aspirate.

The median survival of POEMS syndrome is ~14 years.^{1,29} Until now, no standard risk stratification has been published. There are only few reports on clinical features associated with poor outcome: fingernail clubbing, extravascular volume overload, respiratory symptoms, and pulmonary hypertension.^{1,29} Our patient also presented respiratory manifestations related to impaired neuromuscular respiratory function within 2 years of the onset of her symptoms. In fact, the major cause of morbidity was the respiratory distress, which led to pulmonary sepsis and demise. Recent reports suggest that POEMS patients with coexisting CD have an inferior overall survival compared with those without, and this is related to infection, cardiopulmonary failure, and renal failure.³⁰

Respiratory dysfunction and subsequent failure were also enhanced by the recurring cerebrovascular events. It is interesting to highlight the presence of thrombocytosis and bone marrow plasmacytosis in our case, both reported as increased risk factors for cerebrovascular thrombosis.²⁷

Since there are no clinical trials with POEMS patients, therapeutic decisions are based on reported cases, and usually include treatment protocols used in classic plasma cell disorders. The treatment decision is based on the extent of the plasma cell infiltration. For patients with bone marrow involvement, systemic therapy is preferred. Corticosteroids provide symptomatic improvement, but with limited response duration.^{31–33} Promising results were reported with alkylator agents.³⁴ High-dose chemotherapy with melphalan and peripheral blood stem cell transplant can also be effective, according to case series reported in literature with neurologic improvement for all patients, some of them with durable responses.^{35–38} Other promising treatments include lenalidomide and thalidomide, drugs with anti-VEGF and anti-TNF activity.^{39,40} Activity of proteasome inhibitors in POEMS was demonstrated in a few reports.^{41,42} In our patient, bortezomib was administered subcutaneously with cyclophosphamide

and dexamethasone for 4 cycles at first with clinical improvement, but response duration was limited. She later presented rapidly progressing disease; therefore, another therapeutic strategy was used. No response assessment was possible because the patient died shortly after the second stroke due to neurological deterioration and pulmonary infection.

Supportive care plays an important role in the treatment of POEMS patients (control of extravascular volume overload and hormone replacement therapy when necessary). The question of using cytoreductive therapy in POEMS patients with coexisting CD remains a problem that is open for debate. More and more data are favoring the use of hydroxyurea in addition to anticoagulation and/or antiplatelet therapy to reduce the risk of vascular events recurrence, especially when risk factors like thrombocytosis/bone marrow plasmacytosis are identified.²⁷ An argument in favor of this theory might be the case presented before – the second stroke occurred at the time of progressive disease with thrombocytosis, after systemic treatment for the underlying disorder associated with supportive care, which included antiplatelet therapy and prophylactic anticoagulation. Whether cytoreductive treatment should be included in POEMS patients with coexisting CD remains to be seen, but a careful follow-up and interdisciplinary approach (hematologist/neurologist) are crucial for a better outcome of these patients.

Conclusion

Patients diagnosed with POEMS present heterogeneous clinical and laboratory features. For this reason, often the diagnosis, treatment, and follow-up represent a major challenge. A careful examination of medical history and a thorough physical examination can contribute to a rapid diagnosis. A prompt multidisciplinary approach reduces the risk of irreversible complications, which are also related to shorter survival. Thus, we hope that this review and report of a patient with POEMS syndrome accompanied by CD will emphasize the recognition of thrombotic risk associated with this disorder.

Disclosure

The authors report no conflicts of interest in this work.

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