POEMS SYNDROME: A REVIEW

Amol D. Gholap*1, Santosh S. Borude 1, Anand M. Mahajan1

1- Department of Pharmaceutics, Sharadchandra Pawar College of Pharmacy, Otur, MS, India-412409

*Address for correspondence
Mr. Amol Dilip Gholap
Department of Pharmaceutics, Sharadchandra Pawar College of Pharmacy, Otur,
Tal-Junner, Dist- Pune, MS, India-413706.
Mob. No: +91-9766867053
E-mail- amolgholap16@gmail.com

Summary

POEMS syndrome is a rare paraneoplastic syndrome secondary to a plasma cell dyscrasia. Recognition of the complex of a combination of peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes, papilledema, extravascular volume overload (peripheral edema, pleural effusions, and ascites), sclerotic bone lesions, thrombocytosis, and Castleman disease is the first step in effectively managing the disease. A rise in the blood levels of vascular endothelial growth factor is usually confirmatory. More than 95% of patients will have monoclonal lambda sclerotic plasmacytoma(s) or bone marrow infiltration. In patients with a dominant sclerotic plasmacytoma, first line therapy should include radiation to the lesion. Retrospective analysis and personal experience would dictate that systemic therapy be considered for patients with diffuse sclerotic lesions or absence of any bone lesion and for those who have not demonstrated stabilization of their disease 3 to 6 months after completing radiation therapy. For those patients with diffuse disease, systemic therapy is indicated. Useful approaches include therapy with corticosteroids, low dose alkylator therapy, and high dose chemotherapy with peripheral blood stem cell transplant.

Keywords: POEMS syndrome; Multiple myeloma; Castleman’s Disease; Monoclonal gammopathy of undetermined significance; Paraneoplastic syndrome.

Introduction

POEMS syndrome is a paraneoplastic disorder associated with an underlying plasma cell dyscrasia. The major clinical feature of the syndrome is a chronic progressive polyneuropathy
with a predominant motor disability.\textsuperscript{1, 2} The acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) captures several dominant features of the syndrome. Important traits not included in the acronym include elevated levels of vascular endothelial growth factor, sclerotic bone lesions, Castleman Disease, papilledema, peripheral edema, ascites, effusions, thrombocytosis, polycythemia, fatigue and clubbing. Other names for the syndrome include osteosclerotic myeloma, Crow-Fukase Syndrome, and Takatsuki syndrome.\textsuperscript{3, 4} Though the majority of patients have osteosclerotic myeloma, these same patients usually have only 5% bone marrow plasma cells or less (almost always monoclonal lambda), and rarely have anemia, hypercalcemia or renal insufficiency. These characteristics and the superior median survival differentiate POEMS syndrome from multiple myeloma.

**History**

Scheinker’s autopsy case in 1938 was the first report of what we now call POEMS syndrome.\textsuperscript{1, 4–6} His patient was a 39 year-old man with a solitary plasmacytoma, sensorimotor polyneuropathy, and localized patches of thickened and deeply pigmented skin on the chest.\textsuperscript{5, 7} The complexity of the interaction of plasma cell dyscrasia and peripheral neuropathy became increasingly evident in 1956 with Crow’s description of two patients with osteosclerotic plasmacytomas with neuropathy, and other “striking features,” which included clubbing, skin pigmentation, dusky discoloration of skin, white finger nails, mild lymphadenopathy, and ankle edema.\textsuperscript{5} As many as 50% of patients with osteosclerotic myeloma were noted to have peripheral neuropathy\textsuperscript{7, 9, 10} in contrast to 1–8% of multiple myeloma patients.\textsuperscript{11, 12}

Other authors reported patients with osteosclerotic myeloma and peripheral neuropathy with organomegaly, skin changes, endocrinopathy, edema, hypertrichosis, gynecomastia, and ascites.\textsuperscript{7, 13–18} A syndrome distinct from multiple myeloma associated neuropathy became to be recognized. In Iwashita’s 1977 review of the literature, the 30 patients with osteosclerotic myeloma and PN, as compared to the 29 patients without PN, more commonly had hyperpigmentation, edema, skin thickening, hepatomegaly, hypertrichosis, and clubbing.\textsuperscript{5} In 1980 Bardswick described 2 patients and coined the acronym POEMS.\textsuperscript{1} In 1981, Kelly et al. reported on 16 cases seen at Mayo,\textsuperscript{19} and in 1983 and 1984 two large series of cases collected from Japan were reported solidifying the existence of a distinct pathological entity. Another series from France further bolstered these concepts in the early 1990s with a report of 25 patients.\textsuperscript{20} Diagnostic criteria revisited. Establishing diagnostic criteria for any syndrome is fraught with difficulty, POEMS notwithstanding.

They must be broad enough to diagnose patients early to avoid cumulative morbidity, but narrow enough that patients without the syndrome are not mislabeled as having the syndrome. Soubrier et al demonstrated that prognosis was not dependent on the number of features present in these patients. We confirmed that in our series of patients and proposed criteria, which were later criticized for being too broad. With increasing information about the role of cytokines in this disorder, Arimura et al. have suggested including elevated levels of vascular endothelial growth factor (VEGF) as one of the diagnostic criteria.\textsuperscript{22} The pathogenesis of this multisystem disease is complex, but there has been some progress in our understanding. Elevations of proangiogenic,\textsuperscript{23, 25–33} and pro-inflammatory\textsuperscript{25–27, 32} cytokines are the hallmark of this disorder. As will be discussed, little is known about the plasma cells except that more than 95% of the time they are lambda light chain restricted. Prior hypotheses have included implication of hyperestrogenemia\textsuperscript{20} and HHV.\textsuperscript{8, 34–36} The coagulation pathway and its relationship to VEGF has also been proposed,\textsuperscript{22} but more data will be required to solidify this hypothesis.

Though the cytokine network is highly complex and interrelated, VEGF appears to be the dominant driving cytokine in this disorder. VEGF normally targets endothelial cells and induces a rapid and reversible increase in vascular permeability. It is important in angiogenesis, and osteogenesis is strongly dependent on angiogenesis. VEGF is expressed by osteoblasts, in
bone tissue, macrophages, tumor cells (including plasma cells), and megakaryocytes/platelets. Both IL-1β and IL-6 have been shown to stimulate VEGF production. Though POEMS patients have higher levels of IL-1β, TNF-α, and IL-6 than classic multiple myeloma patients and controls this relationship appears to be less consistent. Moreover, levels of IL-1 receptor antagonist and sTNF-receptor are also increased in POEMS.

Plasma and serum levels of VEGF are markedly elevated in patients with POEMS and correlate with the activity of the disease. The principal isoform of VEGF expressed is VEGF165. VEGF levels are independent of M-protein size. Increased VEGF has been found in ascitic fluid and the cerebrospinal fluid. Increased VEGF could account for the organomegaly, edema, skin hemangiomata, and the occasional mesangioproliferative changes found on renal biopsy. It could be an important regulator of osteoblastic differentiation. Arimura et al. studied the direct effects of VEGF on blood nerve barrier function using an animal model and found that VEGF increased the microvascular permeability inducing endoneurial edema. The authors postulate that this increased permeability could allow serum components toxic to nerves, like complement and thrombin, to induce further damage.

In one study of human nerve biopsies of POEMS patients, more than 50% of endoneurial blood vessels had narrowed or closed lumina with thick basement membranes, strong polyclonal immunoglobulin staining in the endoneurium (consistent with blood-nerve barrier opening), and thrombin-antithrombin complexes immunohistochemically. In yet another study of nerve biopsies, VEGF was highly expressed in blood vessels and some non-myelin-forming Schwann cells, but the expression of VEGF receptor was down-regulated as compared to normals. Elevated levels of matrix metalloproteinases and tissue inhibitor of metalloproteinases (TIMP) have been observed in patients with POEMS. Serum levels of VEGF and TIMP-1 were strongly correlated with each other.

The significance of these findings is not yet fully understood. Little is known about the plasma cell clone in this disease, but aneuploidy and deletion of chromosome 1350 have been described. The light chain variable gene usage of two patients’ clones has been described; both belonged to the Vk1 family and had 92–93% identity with the λe gene. Though at least 95% of all patients with POEMS have monoclonal lambda plasma cells, there is no convincing data to support that POEMS is a deposition disease like primary systemic amyloidosis. Nerve biopsies do not have deposition of monoclonal proteins are auto-antibodies against peripheral nerve antigens (SGPG and SGLPG glycolipids, GM1, GD1a, GD1b, GT1b gangliosides) found. Finally, aberrations in the coagulation cascade have been implicated.

Circulating coagulation factors like fibrinopeptide A, thrombin-antithrombin complex are increased during the active phase of illness, but other factors relating to fibrinolysis, plasminogen, a2 plasmin inhibitor plasmin complex, and FDP did not increase. Clinical features (Fig. 1)
Figure 1. It shows the Percent of Patients with Feature at Diagnosis. The bars represent the percent of patients with feature in the Mayo Series; the numbers over the bars represent the percent of patients with feature in three other large series.\textsuperscript{3, 4, 20}

The peak incidence of the POEMS syndrome is in the 5th and 6th decades of life, unlike multiple myeloma, which has a peak incidence in the 7th and 8th decades. Symptoms of peripheral neuropathy usually dominate the clinical picture.\textsuperscript{19} Symptoms begin in the feet and consist of tingling, paresthesias, and coldness. Motor involvement follows the sensory symptoms. Both are distal, symmetric, and progressive with a gradual proximal spread. Severe weakness occurs in more than one-half of patients and results in inability to climb stairs, arise from a chair, or grip objects firmly with their hands.

The course is usually progressive and patients may be confined to a wheelchair. Impotence occurs but autonomic symptoms are not a feature. Bone pain and fractures rarely occur. Patients gradually lose weight to muscular atrophy. They report fatigue, which may be cytokine mediated or due to associated respiratory disease. Because patients become so restricted in their movement due to their neuropathy, it is rare for them to report dyspnea despite markedly abnormal pulmonary testing. As time progresses, muscle weakness is more marked than sensory loss. Touch, pressure, vibratory, and joint position senses are usually involved. Loss of temperature discrimination and nociception is less frequent.

The cranial nerves are not involved except for papilledema. Hyperpigmentation is common. Coarse black hair may appear on the extremities. Other skin changes include skin thickening, rapid accumulation of glomeruloid angiomata, flushing, dependent rubor or acrocyanosis, white nails and clubbing. Testicular atrophy and gynecomastia may be present. Pitting edema of the lower extremities is common. Ascites and pleural effusion occur in approximately one-third of patients. The liver is palpable in almost one-half of patients but splenomegaly and lymphadenopathy is found in fewer patients. On lymph node biopsy, the histology is frequently angiofollicular lymph node hyperplasia (Castleman’s Disease) or Castleman Disease-like.\textsuperscript{2, 4} Patients may develop arterial and/or venous thromboses during their course. Lespirit et al. observed 4/20 patients to have arterial occlusion. In the Mayo series, there were 18 patients suffering serious events such as stroke, myocardial infarction, and Budd-Chiari syndrome.\textsuperscript{2} Affected vessels include carotid, iliac, celiac, subclavian, mesenteric, and femoral. The POEMS associated strokes tend to be end artery border-zone infarctions. Gangrene has of lower extremities can occur.

Whether the thromboses are due to the use of corticosteroids, chemotherapy and/or elevations of proinflammatory cytokines or VEGF is unknown. It seems likely that VEGF and platelets play a role in arterial occlusion. VEGF protein is present in platelets and megakaryocytes. When vascular injury occurs at endothelial cells, platelets aggregate to repair damaged vascular intima and to release VEGF.\textsuperscript{40} Laboratory investigationsThrombocytosis is common, and polycythemia may be seen.\textsuperscript{2, 19} Anemia and thrombocytopenia are not characteristic unless there is co-existing Castleman’s Disease. Hypercalcemia and renal insufficiency are rarely present. The size of the M-protein on electrophoresis is small (median 1.1 g/dL) and is rarely more than 3.0 g/dL.

The M-protein is usually IgG or IgA and almost always of the lambda type.\textsuperscript{2, 3} Levels of serum erythropoietin are low and are inversely correlated with VEGF levels. Bence Jones proteinuria is uncommon. Protein levels in the cerebrospinal fluid are elevated in virtually all patients. Plasma cells are not present in the CSF, but increased levels of IL-6 receptor and VEGF45 have been described.

Bone marrow usually contains <5% plasma cells, and when clonal cells are found they are almost always monoclonal lambda. Osteosclerotic lesions occur in approximately 95% of patients, and can be confused with benign bone islands, aneurysmal bone cysts, non-ossifying fibromas, and fibrous dysplasia. Some lesions are densely sclerotic, while others are
lytic with a sclerotic rim, while still others have a mixed soap-bubble appearance (Fig. 2). Bone windows of CT body images are often very informative. FDG-avidity is variable. As mentioned, levels of VEGF are almost always elevated in patients with active POEMS. IL-1b, TNFa and IL-6 levels are often also increased. Serum VEGF levels are 10–50 times higher plasma levels of VEGF, making it ambiguous which test is better.

![Figure 2](image)

Figure 2. It shows the Bone lesions in POEMS syndrome. Diffuse sclerotic lesions seen on bone windows of CT scan. Mixed lytic and sclerotic lesion, “soap bubble lesion”. Lytic lesion with sclerotic rim right ischium FDG avidity of lesion seen in Fig. 2C.

The higher level observed in serum is attributable to the release of VEGF from platelets in vitro during serum processing. Because plasma is a product of an anticoagulated sample, there is less platelet activation and therefore less platelet VEGF contributing to the plasma measurement than the serum sample. Tokashiki et al argue that serum VEGF is the better test because it reflects the VEGF contribution from both the serous and platelet compartments. However, the counter-argument is that the amount VEGF release by platelets may vary due to collection and processing technique, making serum measurements of VEGF less reliable. Endocrinopathy is a central but poorly understood feature of POEMS. In a recent large series from the Mayo Clinic, approximately 84% of patients have a recognized endocrinopathy, with hypogonadism as the most common endocrine abnormality, followed by thyroid abnormalities, glucose metabolism abnormalities, and lastly by adrenal insufficiency. The majority of patients had evidence of multiple endocrinopathies in the four major endocrine axes (gonadal, thyroid, glucose and adrenal). Nerve conduction studies an electromyelography demonstrate a polyneuropathy with prominent demyelination as well as features of axonal degeneration, which are similar to the findings of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Biopsy of the sural nerve usually shows both axonal degeneration and demyelination. VEGF is highly expressed in blood vessels and some non-myelin-forming Schwann cells, but the expression of VEGF receptor 2 is downregulated as compared to normals. In most cases of POEMS syndrome, the nerve biopsy shows typical features of uncompacted myelin lamellae.

At ultrastructural examination there are no features of macrophage-associated demyelination, which are seen in some cases of chronic inflammatory demyelinating polyneuropathy. Renal dysfunction is usually not a dominant feature of this syndrome. A slight excess in urinary protein is not unusual. In our experience approximate 9% of patients have
proteinuria exceeding 0.5 g/24 hours and only 6% have a serum creatinine greater than or equal to 1.5 mg/dL. A total of 4 patients in our series developed renal failure as preterminal events. Renal disease is more likely to occur in patients who have co-existing Castleman Disease. The renal histology is diverse with membranoproliferative features and evidence of endothelial injury being most common. On both light and electron microscopy, mesangial expansion, narrowing of capillary lumina, basement membrane thickening, sub-endothelial deposits, widening of the sub-endothelial space, swelling and vacuolization of endothelial cells, and mesangiolysis predominate. Standard immunofluorescence is negative, and this differentiates from primary membranoproliferative glomerulitis. Rarely infiltration by plasma cells nests or Castleman-like lymph proliferation can be seen.

The pulmonary manifestations are protean, including pulmonary hypertension, restrictive lung disease, impaired neuromuscular respiratory function, and impaired diffuse capacity of carbon monoxide, but improve with effective therapy (Fig. 3). In a series of 20 patients with POEMS, followed over a 10-year period, 25% manifested pulmonary hypertension. Findings on autopsy or biopsy are those of classic pulmonary hypertension, including eccentric intimal fibrosis, medial hypertrophy, and marked dilatation of arteries and arterioles. Whether the digital clubbing seen in POEMS is a reflection of underlying pulmonary hypertension and/or parenchymal disease is yet to be determined.

Parallels between hypertrophic osteoarthropathy and POEMS including digital clubbing, periostosis of tubular bones, pachydermia, hyperhydrosis, and acro-osteolysis, have been drawn.

Figure 3. It shows the Pulmonary Findings Pre and Post Therapy. Pre-treatment pulmonary function tests and CXR Post-treatment pulmonary function tests and CXR.

Conclusion

POEMS Syndrome is a complex, but fascinating syndrome, which share elements with other diseases most notably other plasma cell dyscrasias and Castleman’s Disease. Unraveling the elements of this paraneoplastic syndrome has the potential to provide insight into a number of other disorders. For now, the revolution in myeloma treatment provides many excellent treatment options for these patients. One of the greatest practical challenges on is making the diagnosis in a timely fashion to prevent severe irreversible neurological disability.

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