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POEMS syndrome

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Abstract

POEMS syndrome is a paraneoplastic disorder secondary to plasma cell dyscrasia. It is characterized by the presence of polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin changes (S). There are also several other associated features not included in the acronym, such as sclerotic bone lesions, Castleman's disease, papilledema and thrombocytosis/polycythemia. The pathophysiological mechanism of the disorder is not well understood, although a very important role is attributed to vascular endothelial growth factor (VEGF) and other cytokines that arise in the blood during this syndrome. The treatment for POEMS syndrome has not been standardized. Many strategies have been used, such as irradiation, corticosteroids, alkylating agents and high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation. Recently, new agents, including thalidomide, lenalidomide and bevacizumab, have emerged as therapeutic options in these patients.

Introduction

POEMS syndrome is a rare paraneoplastic syndrome; the acronym, coined in 1980 by Bardwick *et al.*, refers to the presence of *P*eripheral neuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal gammopathy and *S*kin changes, but there are other features not included in the acronym that are seen frequently and are important for diagnosis. The first report of POEMS syndrome was in 1938 with the case of Scheinker's autopsy of a 39-year-old man with a solitary plasmacytoma, sensorimotor polyneuropathy and localized patches of thickened and deeply pigmented skin on the chest (1). Subsequently, there have been many other single reports of patients affected by osteosclerotic myeloma and peripheral neuropathy with organomegaly, endocrinopathy, edema, hypertrichosis, gynecomastia and ascites (2-6).

Dispenzieri *et al.* suggested that for the diagnosis of POEMS syndrome we could distinguish major and minor criteria (7). These criteria were recently revised based on increasing information about the role of cytokines in this disorder and according to Arimura *et al.*, who suggested including elevated levels of vascular endothelial growth factor (VEGF) as one of the diagnostic criteria (8) (Table I). In the latest revision by Dispenzieri *et al.* (Table II), the major criteria for diagnosis were polyneuropathy and monoclonal plasma cell proliferative disorder; minor criteria included sclerotic bone lesions, Castleman's disease, VEGF elevation, organomegaly, extravascular volume overload (edema, pleural effusion or ascites), endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic), skin changes, papilledema and thrombocytosis/polycythemia. For diagnosis, patients must show two major criteria and at least one minor criterion. Other symptoms and signs reported in POEMS syndrome are clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea and low vitamin B12 levels. Possibly associated with the syndrome are arthralgias, cardiomyopathy (systolic dysfunction) and fever (9).

The peak incidence of POEMS syndrome is in the fifth and sixth decades of life (7, 10); the median age at presentation is 51 years and 63% are men (7). It has been reported mainly in Japanese individuals, although affected individuals from other ethnic backgrounds have also been described (6, 7, 10, 11).

Pathogenesis

POEMS syndrome is not a deposition disease like primary systemic amyloidosis, as demonstrated by histopathological review of affected organs and nerves (6, 12, 13). Many factors have been implicated in the pathogenesis of the disease. Prior hypotheses have included the implication of hyperestrogenemia (10) and human herpesvirus type 8 (HHV-8) (14-16). Many other reports show that POEMS syndrome appears to be mediated by an imbalance of proinflammatory cytokines.

Table I: Criteria for diagnosis of POEMS according to Arimura.

Major criteria	• Polyneuropathy (chronic and sensorimotor disturbances)
Minor criteria	• M protein • Organomegaly (lymphadenopathy, hepatomegaly, splenomegaly, kidney enlargement) • Anasarca (ascites, pleural effusions) • Skin changes (hyperpigmentation, hypertrichosis, angiomatosis) • Endocrinopathy (impotence, menoxenia, glucose intolerance, thyroid dysfunction) • Papilledema • Increased serum VEGF (> 500 pg/ml)

Table II: Criteria for diagnosis of POEMS according to Dispenzieri.

Major criteria	• Polyneuropathy • Monoclonal plasma cell proliferative disorder (almost always λ) • Sclerotic bone lesions • Castleman's disease • VEGF elevation • Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy) • Extravascular volume overload (edema, pleural effusion, ascites)
Minor criteria	• Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, white nails) • Papilledema • Thrombocytosis/polycythemia
Other signs and symptoms	• Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 levels
Possible associations	• Arthralgias, cardiomyopathy (systolic dysfunction), fever

Interleukin-1β (IL-1β), IL-6 and tumor necrosis factor α (TNF-α) have been reported to be increased in association with the syndrome (17-19). Both IL-1β and IL-6 have been shown to stimulate VEGF production (20), which is also considered an important pathogenic factor in POEMS syndrome (8, 22).

VEGF induces a rapid and reversible increase in vascular permeability, is a growth factor for endothelial cells and is considered important in angiogenesis (18). A report by Mineta *et al.* showed that the mean VEGF level in patients with POEMS syndrome is significantly higher than in healthy controls (8). The correlation between serum VEGF concentrations and the severity of this disorder suggests that VEGF may be a causative agent. In fact, the efficacy of therapies might be related to their ability to interfere with VEGF production and action. Serum VEGF levels have been found to be inversely correlated with the clinical course, response to therapy and severity of endoneurial vessel involvement (13, 23), suggesting that they may be strongly predictive of response to therapy.

One pathogenic theory for the role of VEGF is that this molecule, secreted from plasma cells (24) and platelets (22), promotes vascular permeability, angiogenesis and monocyte/macrophage migration, potentially resulting in arterial obliteration. Based on these findings, VEGF could account for the neuropathy, organomegaly, edema and skin lesions in POEMS (8). In terms of neuropathy, there is currently no evidence to suggest that any of the characteristics of the disease (axonal degeneration, segmental demyelination or subperineurial edema) are the result of immune-mediated damage to the nerve components. An alteration of the blood-nerve barrier and abnormalities of serum coagulation factors, owing to the elevation of VEGF, have been proposed as being involved in the pathogenesis of nerve damage (13, 25). In a report by Scarlato *et al.,* a structural analysis of POEMS nerves revealed endothelial cytoplasmic enlargement, opening of the tight junctions between endothelial cells and the presence of many pinocytic vesicles adjacent to the cell membranes, suggesting an alteration in the permeability of endoneurial vessels; no deposition of immunoglobulin (Ig) or amyloid was detected (13).

Organomegaly is characterized by marked vascular proliferation associated with VEGF elevation. Skin changes, especially hemangioma, may be caused by angiogenesis due to VEGF and edema may be caused by VEGF-induced hyperpermeability.

Clinical characteristics

Peripheral nerves are one of the principal targets in POEMS syndrome (26). The presence of a chronic, progressive, distal sensorimotor polyneuropathy is essential in establishing diagnosis, along with monoclonal plasma cell proliferative disorder (7), but patients are frequently diagnosed initially with chronic inflammatory demyelinating polyneuropathy (CIDP). A report by Sung *et al.* compared nerve conduction studies of patients with CIDP with nerve conduction studies of patients with POEMS syndrome. In POEMS patients there was slowing of nerve conduction that was more predominant in the intermediate than the distal nerve segments, rare con-

duction block and more severe attenuation of compound muscle action potentials in the lower than the upper limbs. However, findings in the CIDP patients were characterized by multifocal conduction slowing that was occasionally dominant distally, frequent conduction block and less discrepancy between upper and lower limb nerves (27).

Clinically, 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 half of the patients and results in an 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. As time progresses, muscle weakness is more marked than sensory loss. Touch, pressure, vibratory and joint position senses are usually involved. Subclinical to very symptomatic respiratory compromise from neuromuscular weakness also occurs.

Organomegaly (hepatomegaly, splenomegaly and/or adenomegaly) is present in 50-78% of affected individuals in different series (6, 7, 10). Liver and spleen enlargement is usually associated with normal histological findings. About 50% of the patients have hepatomegaly, splenomegaly and adenopathy are found in fewer patients, and on lymph node biopsy the histology is frequently angiofollicular lymph node hyperplasia (Castleman's disease) (6, 7).

In terms of endocrinopathy, hypogonadism is the most common endocrine abnormality, followed by thyroid abnormalities, glucose metabolism abnormalities and adrenal insufficiency (28). The majority of patients have evidence of multiple endocrinopathies in the four major endocrine axes (gonadal, thyroid, glucose and adrenal). The endocrine glands studied appeared architecturally normal and without defining characteristics (1, 10, 29-31).

The size of the monoclonal immunoglobulin (M protein) on electrophoresis is small (median 1.1 g/dl; rarely more than 3.0 g/dl) (9), usually IgG or IgA and almost always the λ type (5, 7). There is a small clonal plasma cell infiltrate in the bone marrow; in general the median percentage of plasma cells is 5%, and the bone marrow is frequently hypercellular and reported as either "reactive" or as a "myeloproliferative disorder" (32).

The most common skin change that occurs in POEMS patients is hyperpigmentation (7), which can be diffuse or localized and is unrelated to adrenal insufficiency (10). Other skin abnormalities associated with the disease are acrocyanosis, hypertrichosis, thickening and skin angioma (33).

Sclerotic bone lesions are one of the most common findings in POEMS syndrome; almost 95% of patients present with osteosclerotic lesions, half of them have a solitary sclerotic lesion and at least a third have multiple sclerotic lesions. It is common for patients to have osteosclerotic and osteolytic lesions (32). Some lesions are densely sclerotic, while others have a mixed soap bubble appearance (9).

Between 11% and 30% of POEMS patients have documented Castleman's disease or Castleman's-like disease (6, 10). The association between Castleman's disease and POEMS syndrome is not fully understood, although it is well recognized (6, 10, 14, 15, 34-63). Several published cases of "interesting features" associated with Castleman's disease are likely cases of POEMS syndrome (64-67).

Clubbing may occur in up to 13% of patients (32). The pathogenesis of this feature is unknown, although it could be a function of undiagnosed pulmonary hypertension (68).

Pulmonary manifestations of POEMS syndrome are common and both symptomatic and asymptomatic respiratory involvement is frequent on presentation in patients with POEMS syndrome. Pulmonary manifestations of POEMS syndrome include pulmonary hypertension, which has been reported in up to 25% of patients with this syndrome (19, 69-77), restrictive lung disease, respiratory muscle weakness and an isolated diminished diffusing capacity (78). The exact pathophysiological mechanism of pulmonary hypertension in patients with POEMS syndrome is unclear, although it is likely to be cytokine-mediated (73-76, 79). Pulmonary hypertension appears to improve with treatment of POEMS syndrome (70, 72, 76, 80, 81).

Patients may also develop arterial and/or venous thrombosis during the disease course (9). Ischemic disease of the coronary and lower limb arteries has often been reported in patients with POEMS syndrome (17, 82), and affected vessels include the carotid, iliac, celiac, subclavian, mesenteric and femoral vessels (18, 83-85).

Prognosis

The prognosis for patients with POEMS syndrome has previously been reported to be poor, with median survival estimated to be 12-33 months (6). However, in a recent study in 99 patients with POEMS Dispenzieri *et al.* reported a median survival of 165 months (7). In fact, the course of POEMS syndrome is chronic and patients typically survive for more than a decade, in contrast to patients with multiple myeloma (9). Soubrier *et al.* concluded that prognosis was not dependent on the number of features present in these patients (10), but additional features typically arise over time if treatment is unsuccessful or if the diagnosis is delayed (7). Response to therapy is predictive of survival (7). The most common causes of death are cardiorespiratory failure, progressive inanition, infection, capillary leak-like syndrome and renal failure. More recently, researchers have identified respiratory symptoms to be predictive of adverse outcome (86).

Treatment

The treatment of POEMS syndrome has not been standardized. Many strategies have been used, including plasmapheresis and intravenous immunoglobulin, which do not produce a clinical effect. If the selected therapy proves to be effective, the response of systemic symp-

toms and skin changes tends to precede that of neuropathy, with the former beginning to respond within a month and the latter within 3-6 months (32). Many patients have continued to improve for 2-3 years after effective therapy. A response is defined as stabilization or improvement of signs and symptoms as reported by the patient and the treating physician. Radiation is the preferred treatment for an isolated plasmacytoma (2, 87-89) and, as reported by Dispenzieri *et al.*, more than half of the patients treated with radiation will respond with excellent survival and a durable response (32).

The first-line treatment in patients with diffuse disease, or with relapse or incomplete remission, is chemotherapy. Alkylating agents appear to be the treatment of choice in this disease. In fact, melphalan is the most effective agent against plasma cell proliferative disorder. Based on retrospective data, approximately 40% of patients with POEMS syndrome will respond to melphalan and prednisone (2, 90). Cyclophosphamide is another alkylating agent that can control the disease in up to 40% of patients when used as a single agent or in combination with prednisone (6, 7).

Cyclophosphamide and melphalan are able to reduce neoplastic burden and mobilize $CD34^+$ cells and alkylating agents may be useful as a conditioning regimen for autologous peripheral blood stem cell transplantation (aPBSCT). Many reports have demonstrated that aPBSCT is an effective therapeutic option for patients with POEMS syndrome, with universal improvement in neuropathy and other features (91-94). However, significant morbidity has also been reported to be associated with the procedure, poor pulmonary reserve being an important source of procedure-related morbidity. Delays in diagnosis are associated with increased morbidity for patients (95) with additional features, such as abnormal pulmonary function. In our experience (96), aPBSCT should be performed early after diagnosis, when patients are fit for transplantation without progressive neurological symptoms. Therapy prior to aPBSCT should achieve stabilization of symptoms and mobilization of stem cells; for these reasons, an intermediate dose of cyclophosphamide is recommended. Recently, Dispenzieri *et al.* reported data from 30 patients with POEMS treated with a high dose of chemotherapy and aPBSCT. The data confirm that after aPBSCT there is improvement of the syndrome, but also show that patients with POEMS are at high risk for a corticosteroid-responsive engraftment-type syndrome (fever, cutaneous rash, pulmonary infiltrates, diarrhea within 24 h of first appearance of neutrophils), and splenomegaly and lymphadenopathy appear to increase the risk for post-transplant complications (97).

There are little data on the long-term outcome of patients treated with aPBSCT. We reported on 4 patients who had progressive and stable improvement of clinical condition 40.5 months (median) after transplantation (96). A report by Wiesmann *et al.* described a successful aPBSCT in a patient with POEMS syndrome after a follow-up of 6 years (98), but recently, Giglia *et al.* reported a relapse after successful aPBSCT in a patient with a very good partial response for persistence of IgA λ band. After relapse, the patient was successfully treated with radiotherapy, and the authors suggested the use of an antibody directed against VEGF (bevacizumab) for patients who do not achieve complete remission after transplantation (99).

Few studies have presented data on the efficacy of targeting VEGF with the selective antibody bevacizumab as a therapeutic approach. The first report on the use of this agent described 2 patients who were treated successfully with bevacizumab (100). On the other hand, several other reports described worsening of the clinical condition in 3 patients treated with the antibody (101-103). An initial clinical improvement was described, with the subsequent course complicated by severe adverse events leading to multiorgan failure and death. The authors hypothesized that rapid reduction of high VEGF levels might lead to increased apoptosis of motor neurons and endothelial cells, with subsequent worsening of the clinical course. They also suggested caution in using bevacizumab, since the role of VEGF in this disease remains unclear. Kanai *et al.* suggested that bevacizumab is effective when administered in the early stage of the disorder before structurally abnormal vessels develop systemically. In fact, the duration of the disorder was shorter in cases with a good response to bevacizumab than in those failing therapy (102). Finally, another report suggested the use of bevacizumab to improve the clinical condition in patients who do not undergo aPBSCT because of poor condition at diagnosis (104). Based on this finding, we suggest that bevacizumab could be used before applying more standard treatments.

Immunomodulators such as thalidomide and lenalidomide are powerful drugs against malignant plasma cells because they reduce the production of proinflammatory and proangiogenic cytokines (105, 106). Thalidomide has antiangiogenic, antiinflammatory and immunomodulating properties and has been successfully used in the treatment of immunological disorders and multisystem diseases such as multiple myeloma. There are two reports on the use of thalidomide in POEMS syndrome. The first report was by Sinisalo *et al.* in a woman who failed previous treatment with melphalan and prednisolone. The patient was treated with thalidomide 200 mg, and after 8 months of treatment she experienced an episode of transient ischemic attack (TIA; she had a previous history of TIA). During the ensuing months an overall beneficial response was noted, and after 24 months of treatment with thalidomide her general condition had improved dramatically without any neurological side effects (107). In the other case, Kim *et al.* reported the successful use of thalidomide and dexamethasone in a woman who was refractory to chemotherapy and could not be submitted to aPBSCT. After 2 months of treatment, the patient's clinical condition improved, and after 20 months of follow-up she was in good condition (108). Both authors presume that the effectiveness of thalidomide is related to modulation of cytokines. In particular, Kim *et al.* showed that IL-6 levels are correlated with treatment response and

disease activity. The use of thalidomide in POEMS syndrome, a condition in which the dominant complaint is sensorimotor peripheral neuropathy, is limited by the high incidence of drug-induced peripheral neuropathy with long-term use.

In contrast, the next-generation immunomodulatory drug lenalidomide has a much lower risk for peripheral neuropathy. There is only one report of the use of this drug in a patient with POEMS who could not undergo aPBSCT due to poor performance status. The patient experienced marked improvement of his condition and his treatment plan is to consolidate his response with aPBSCT (109).

Conclusions

The diagnosis of POEMS syndrome is never easy because of the complexity of the disorder. It is very important to reach a diagnosis in a short time from the first symptoms to avoid the progression typical of POEMS syndrome and ineffective therapy. A multidisciplinary approach will provide the best results for patients, especially cooperation between neurological experts and hematologists. Radiation therapy, alkylating agents and aPBSCT are effective treatments for this syndrome, but prospective studies are needed to examine other therapeutic options for this rare disease, especially before and after autologous transplantation. These studies might evaluate the best therapy to improve the clinical condition of patients unfit for transplantation and maintenance therapy in patients with residual disease after transplantatation. It is also important to establish the role of new drugs in the treatment of this disorder. Because of the rarity of the syndrome, multicenter, prospective trials are required to standardize the treatment.

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