POEMS Syndrome

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Abstract
POEMS syndrome is defined by the presence of a peripheral neuropathy (P), a monoclonal plasma cell disorder (M), and other paraneoplastic features, the most common of which include organomegaly (O), endocrinopathy (E), skin changes (S), papilledema, edema, effusions, ascites, and thrombocytosis. Virtually all patients will have either at least one sclerotic bone lesion or co-existent Castleman's disease. Not all features of the disease are required to make the diagnosis, and early recognition is important to reduce morbidity. The peak incidence of the POEMS syndrome is in the 5th and 6th decades of life; the prevalence of POEMS syndrome is unknown. The cause of POEMS syndrome is unknown; it is frequently confused with chronic inflammatory demyelinating polyneuropathy. This misdiagnosis is problematic since therapies that are effective in patients with chronic inflammatory demyelinating polyneuropathy (intravenous gammaglobulin, plasmapheresis, and azathioprine) are not effective in patients with POEMS. The mainstays of therapy for patients with POEMS include irradiation, corticosteroids, and alkylator-based therapy, including high dose chemotherapy with peripheral blood stem cell transplant.

Keywords
POEMS syndrome, Castleman's Disease, chronic inflammatory demyelinating polyneuropathy, paraneoplastic syndrome, vascular endothelial growth factor, osteosclerotic myeloma, Crow-Fukase Syndrome, PEP syndrome, or Takatsuki syndrome

Disease name and synonyms

POEMS syndrome (*i.e.* Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes)
Other names for the syndrome include osteosclerotic myeloma, Crow-Fukase Syndrome, PEP (Polyneuropathy, Endocrinopathy, Plasma-cell dyscrasia) syndrome, or Takatsuki syndrome (Nakanishi T*, et al*, 1984).

Definition/diagnostic criteria

POEMS syndrome is a paraneoplastic disorder related to an underlying plasma cell dyscrasia. The dominant clinical feature in POEMS syndrome is a chronic progressive polyneuropathy with a predominant motor

disability (Bardwick PA, *et al*, 1980; Dispenzieri A, *et al*, 2003). The acronym POEMS captures several dominant features of the syndrome. Well-recognized associated features not included in the acronym include sclerotic bone lesions, Castleman Disease, papilledema, peripheral edema, effusions, ascites, thrombocytosis, polycythemia, fatigue and clubbing. Not all features are required to make the diagnosis; at a minimum, however, a patient must have: the peripheral neuropathy; monoclonal plasma cell disorder; a sclerotic bone lesion or Castleman disease; and at least one of the other features without other attributable cause (Dispenzieri A, *et al*, 2003). (Table 1). Though the vast majority of patients have osteosclerotic myeloma, these same patients usually have only 5% bone marrow plasma cells or less and rarely have hypercalcemia or renal insufficiency. These characteristics and the superior median survival differentiate POEMS syndrome from multiple myeloma.

History

Associations between plasma cell dyscrasia and peripheral neuropathy (PN) were well recognized as early as the 1950's (Crow R, 1956). While only 1-8% of patients with classic multiple myeloma have neuropathy (Evison G, *et al*, 1983; Reitan JB, *et al*, 1980), a third to a half of patients with osteosclerotic myeloma have neuropathy (Driedger H, *et al*, 1980; Iwashita H, *et al*, 1977; Mangalik A, *et al*, 1971). Moreover, it was found that patients with osteosclerotic myeloma were more likely to have "striking features," which include clubbing, skin pigmentation, dusky discoloration of skin, white finger nails, mild lymphadenopathy, and ankle edema (Crow R, 1956; Iwashita H, *et al*, 1977). Other authors reported patients with osteosclerotic myeloma and peripheral neuropathy with organomegaly, skin changes, endocrinopathy, edema, hypertrichosis, gynecomastia, and ascites (Driedger H, *et al*, 1980; Fukase M, *et al*, 1969; Imawari M, *et al*, 1974; Iwashita H, *et al*, 1977; Waldenstrom JG, *et al*, 1978). A syndrome distinct from myeloma associated neuropathy became to be recognized. In 1980 Bardwick coined the acronym POEMS, to represent polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-proteins (M), and skin changes (S) (Bardwick PA, *et al*, 1980). This definition omits several important features. It has led some authors and physicians to incorrectly believe that all 5 features are required for the diagnosis of the syndrome, an assumption that is patently incorrect.

Epidemiology

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. The prevalence of POEMS syndrome is unknown. Initially, it was believed to be more common in people of Japanese decent, but with increasing awareness of the entity, is has also been observed in people of European, African, Hispanic and Asian decent (Dispenzieri A, *et al*, 2003; Singh D, *et al*, 2003; Soubrier M, *et al*, 1994).

Etiology

The cause of POEMS syndrome is unknown. It is tempting to incriminate the presence of lambda light chains in the pathogenesis because of their unexpected frequency (greater than 95% of cases), but histopathologic review of affected organs and nerves does not support that it is a form of deposition disorder (Bergouignan FX, *et al*, 1987; Nakanishi T, *et al*, 1984). Soubrier *et al* have recently demonstrated restricted usage of Vλ2 genes in 2 patients with POEMS syndrome (Soubrier M, *et al*, 2004). Antibodies to Human Herpes Virus HHV-8 were reported in 78% of patients with POEMS syndrome and Castleman's disease and in 22% of those with POEMS syndrome without Castleman's disease (Belec L, *et al*, 1999a).

The most appealing hypotheses regarding POEMS pathogenesis, however, are those implicating cytokines, more specifically vascular endothelial growth factor (VEGF) (Emile C, *et al*, 1993; Feinberg L, *et al*, 1999; Gherardi RK, *et al*, 1996; Hashiguchi T, *et al*, 2000; Hitoshi S, *et al*, 1994; Nakazawa K, *et al*, 1992; Orefice G, *et al*, 1994; Rose C, *et al*, 1997; Saida K, *et al*, 1996; Soubrier M, *et al*, 1997). Though patients frequently have higher levels of IL-1β, tumor necrosis factor α, and IL-6 than patients with multiple myeloma (Gherardi et al. 1996), increased levels of vascular endothelial growth factor (VEGF) are frequently found and often decrease with successful therapy (Soubrier M, *et al*, 1997; Watanabe O, *et al*, 1998). VEGF targets the endothelial cell, 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 and in bone tissue, and it could be an important regulator of

osteoblastic differentiation. Both IL-1β and IL-6 have been shown to stimulate VEGF production (Soubrier M*, et al*, 1997). Plasma and serum levels of VEGF have been shown to be markedly elevated in patients with POEMS (Hashiguchi T*, et al*, 2000; Soubrier M*, et al*, 1997; Watanabe O*, et al*, 1996) and correlate with the activity of the disease (Soubrier M*, et al*, 1997). It is postulated that the VEGF is secreted from the plasma cells (Watanabe O*, et al*, 1998) and platelets (Hashiguchi T*, et al*, 2000) promoting vascular permeability, angiogenesis, monocyte/macrophage migration, potentially resulting in arterial obliteration. Hashiguchi has demonstrated VEGF release from aggregated platelets in patients with POEMS (Hashiguchi T*, et al*, 2000). VEGF could account for the organomegaly, edema, and skin lesions. The role it would play in the polyneuropathy is less clear, but descriptions of narrowed or closed lumina of endoneurial blood vessels, raise the possibility of microthrombosis (Watanabe O*, et al*, 1998).

Clinical manifestations

Peripheral neuropathy

All patients have peripheral neuropathy, which generally dominates the clinical picture. 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, though rapid progression is also possible. Some patients have significant pain. 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.

Through the neuropathy resembles chronic inflammatory demyelinating polyneuropathy, POEMS neuropathy has a motor dominance, with marked slowing of conduction velocities with prolonged distal latencies, and progressive dispersion of the compound muscle action potential with stimulation of motor nerves more proximally. On needle electromyelography distal fibrillation potentials and enlarged, polyphasic voluntary motor unit action potentials with decreased recruitment are found (Kelly JJ, Jr.*, et al*, 1983; Sung JY*, et al*, 2002). The cerebrospinal fluid protein levels are elevated. In general, nerve biopsies demonstrate a combination of axonal degeneration and demyelination. Nerve biopsies demonstrate minimal mononuclear cell infiltration around the epineurium (usually in a perivascular location) and a decrease in number of myelinated axons of all sizes with segmental demyelination and remyelination (Kelly JJ, Jr.*, et al*, 1983; Saida K*, et al*, 1997; Umehara F*, et al*, 1990). Severe endoneurial edema may also be seen, and uncompacted myelin lamellae are observed without immunoglobulin or amyloid deposition (Vital C*, et al*, 2003).

Organomegaly

The liver is palpable in about one-half of patients (Table 2). Splenomegaly and lymphadenopathy are present almost as frequently. Between 11-30% of POEMS patients have documented Castleman disease (giant lymph node hyperplasia, angiofollicular lymph node hyperplasia). This is likely a conservative estimate, as many patients do not undergo lymph node biopsies. The association between Castleman disease and POEMS syndrome is not fully understood though their association is well recognized (Belec L*, et al*, 1999b; Bitter M*, et al*, 1985; Dispenzieri A*, et al*, 2003; Gherardi RK*, et al*, 1991; Mandler RN*, et al*, 1992; Nakanishi T*, et al*, 1984; Pareyson D*, et al*, 1994; Soubrier M*, et al*, 1994; Vital C*, et al*, 1994).

Endocrinopathy

Endocrine abnormalities are defining features of the syndrome. Diabetes mellitus and gonadal dysfunction are the most common endocrinopathies (Table 2). Testicular atrophy and gynecomastia may be present. Chemical aspects of primary and secondary hypothyroidism hypogonadism, adrenocortical insufficiency, and diabetes mellitus have all been described. On necroscopy, endocrine glands studied have appeared architecturally normal and without defining characteristics (Bardwick PA*, et al*, 1980; Bitter M*, et al*, 1985; Bosco J*, et al*, 1991; Gherardi R*, et al*, 1988; Sasano T*, et al*, 1998; Shichiri M*, et al*, 1998; Soubrier M*, et al*, 1994; Stewart PM*, et al*, 1989).

Monoclonal plasmaproliferative disorder

By definition all patients have a monoclonal plasmaproliferative disorder (Table 2). The monoclonal protein is not large and will be missed on serum protein electrophoresis in nearly one third of patients if immunofixation is not also done (Dispenzieri A*, et al*, 2003). Additional patients will be discovered by using

the serum immunoglobulin free light chain assay (Dispenzieri A*, et al*, 2004) and immunofixation of the urine. Fewer than 10% of patients will have no evidence of a circulating monoclonal protein, but will have biopsy proof of a plasmacytoma, typically monoclonal lambda. In our series of 99 patients, all patients were monoclonal lambda.
Though there will be clonal plasma cells detected on biopsy of sclerotic lesions, there may or may not be a clonal plasma cell infiltrate in the bone marrow biopsy of the iliac crest. In general the number of plasma cells is low (median 5%), and the bone marrow is frequently hypercellular and reported out as either "reactive" or as a "myeloproliferative disorder."

Skin changes
Skin changes occur in 50-90% of patients, with hyperpigmentation among the most common manifestations (Table 2). Coarse, longer than normal, black hair often appears on the extremities. Other skin changes include rapid accumulation of hemangiomata, plethora and/or acrocyanosis, skin thickening, white nails and clubbing (Brazis PW*, et al*, 1990; Crow R, 1956; Dispenzieri A*, et al*, 2003; Nakanishi T*, et al*, 1984; Soubrier M*, et al*, 1994).

Sclerotic bone lesions
Osteosclerotic lesions occur in approximately 95% of patients; one-half have a solitary sclerotic lesion and at least a third have multiple sclerotic lesions (Table 2). It is common to have mixed osteosclerotic and osteolytic lesions and one can easily overlook a small sclerotic rim surrounding a large lytic lesion. The pelvis, spine, ribs, and proximal extremities are most often involved. The lesions may be modest in size and misinterpreted as benign bony sclerosis, benign fibrous dysplasia, nonossifying fibroma, aneurysmal bone cyst, or a vertebral hemangioma.

Papilledema
Papilledema is present in as many as 55 % of patients (Table 2) (Dispenzieri A*, et al*, 2003; Nakanishi T*, et al*, 1984; Soubrier M*, et al*, 1994). Patients are most commonly asymptomatic but may describe headache, transient obscurations of vision, scomata, enlarged blind spots, and progressive constriction of visual field. Physical exam includes optic disc edema (usually bilateral) and blind spots (Brazis PW*, et al*, 1990).

Extravascular volume overload (edema, effusions, ascites)
Pitting edema of the lower extremities is common (Table 2). Ascites and pleural effusion occur in approximately one-third of patients.

Thrombocytosis
Thrombocytosis occurs in at least 50% of patients (Table 2). They may even have a diagnosis of essential thrombocytosis (Dispenzieri A*, et al*, 2003; Kelly JJ, Jr.*, et al*, 1983) which resolves when the POEMS syndrome is effectively treated. In contrast to classic multiple myeloma, anemia is not a feature and mild erythrocytosis is present in about 20% of patients.

Pulmonary dysfunction
Pulmonary hypertension, restrictive lung disease and impaired diffusion capacity of carbon monoxide may occur (Dispenzieri A*, et al*, 2004; Iwasaki H*, et al*, 1993; Lesprit P*, et al*, 1998; Mufti GJ*, et al*, 1983). Improvement of POEMS-associated pulmonary hypertension after therapy has been reported. The levels of TNF-α, IL-1β, IL-6, and VEGF observed in these patients appeared to correlate with disease activity. Whether the digital clubbing seen in up to 13% of POEMS patients is a reflection of underlying pulmonary hypertension and/or parenchymal disease is yet to be determined. In our recent transplant series, more than 90% of patients had abnormal pulmonary function tests. Restriction due to neuromuscular weakness was most common, followed by impaired diffusion capacity of carbon monoxide.

Thrombosis
Both arterial and venous thromboses have been described in the setting of POEMS. In our series of 99 patients, there were 18 patients suffering serious events such as stroke, myocardial infarction, and Budd-Chiari syndrome (Dispenzieri A*, et al*, 2003). Lespirit *et al.* reported that 4 of 20 patients had arterial occlusion (Lesprit P*, et al*, 1996). Affected vessel included iliac, celiac, carotid, subclavian, mesenteric, and femoral. Additional patients have been reported to have gangrene, ischemia, myocardial infarction, splenic infarcts and strokes. Serious thrombotic events including pulmonary embolism, Budd Chiari have also been described. Whether the thrombotic tendency is due to patients' paresis, the use of corticosteroids, chemotherapy and/or elevations of proinflammatory cytokines or VEGF is

unknown. Further study is required to determine whether there is an association.

Renal failure

Renal dysfunction in POEMS syndrome is rare and nearly half of the affected patients have co-existent Castleman disease. A total of 4 patients in our series developed renal failure as preterminal events (Dispenzieri A*, et al*, 2003). Light chain deposition is observed in neither the tubules nor the glomeruli, making the renal pathology distinct from that seen in other plasma cell dyscrasias. Instead, membranoproliferative features and evidence of endothelial injury are characteristic. 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 (Nakamoto Y*, et al*, 1999; Navis GJ*, et al*, 1994; Sano M*, et al*, 1986; Soubrier M*, et al*, 1999; Viard JP*, et al*, 1988).

Prognosis

The course of POEMS syndrome is chronic and patients' median survival is about four times that of patients with classic multiple myeloma. At the Mayo Clinic 99 POEMS patients treated without peripheral blood stem cell transplantation had a median survival of 13.8 years (Dispenzieri A*, et al*, 2003); median survival has not yet been reached in our transplant cohort (Dispenzieri A*, et al*, 2004). Individual reports of patients with the disease for more than 5 years are not unusual and in one French study, at least seven of fifteen patients were alive for more than 5 years, with the longest survivor alive at 25 years. The number of POEMS features does not affect survival (Figure 1) (Dispenzieri A*, et al*, 2003; Soubrier M*, et al*, 1994).

Relapse is possible in patients who have responded to therapy. The most common causes of death are cardiorespiratory failure, progressive inanition, infection, capillary leak like syndrome, and renal failure (Dispenzieri A*, et al*, 2003; Nakanishi T*, et al*, 1984). The neuropathy may be unrelenting and contribute to progressive inanition and eventual cardiorespiratory failure and pneumonia. Stroke and myocardial infarction, which may or may not be related to the POEMS syndrome, are also observed causes of death. Patients do not die of classical myeloma, which is progressive bone marrow failure or hypercalcemia.

Treatment

There are no randomized controlled trials in patients with POEMS. Information about benefits of therapy is most typically derived retrospectively (Table 3). Given these limitations, however, there are therapies which appear to benefit patients with POEMS syndrome, including radiation therapy, alkylator based therapies, and corticosteroids (Dispenzieri A*, et al*, 2003). Single or multiple osteosclerotic lesions in a limited area should be treated with radiation (Davis L*, et al*, 1972; Iwashita H*, et al*, 1977; Morley JB*, et al*, 1967). If the patient has widespread osteosclerotic lesions, systemic therapy is necessary. In contrast to chronic inflammatory demyelinating polyneuropathy, plasmapheresis and intravenous immunoglobulin do not produce clinical benefit. If the patient has widespread osteosclerotic lesions, systemic therapy—possibly high dose chemotherapy with peripheral blood stem cell transplant--is necessary. In appropriate candidates, peripheral blood stem cells should be collected before the patient has prolonged exposure to alkylating agents (Dispenzieri A*, et al*, 2004). If the selected therapy proves to be effective, response of systemic symptoms and skin changes tend to precede those of the neuropathy, with the former beginning to respond within a month, and the latter within 3-6 months. We have seen patients who have continued to improve for two to three years after effective therapy.

Supportive Care

The physical limitations of the patient should not be overlooked while evaluating and/or treating the underlying plasma cell disorder. As always a multidisciplinary, thoughtful treatment program will improve a complex patient's treatment outcome. A physical therapy and occupational therapy program is essential to maintain flexibility and assist in lifestyle management despite the neuropathy. In those patients with respiratory muscle weakness and/or pulmonary hypertension, overnight oxygen or continuous positive airway pressure (CPAP) may be useful

Chemotherapy

Corticosteroids

No prospective studies support the use of corticosteroids in the treatment of POEMS syndrome, but case reports and personal observation would suggest that corticosteroids

have activity (Dispenzieri A*, et al*, 2003; Nakanishi T*, et al*, 1984; Orefice G*, et al*, 1994; Sano M*, et al*, 1986). In our experience at least 15% of patients treated with single agent corticosteroids derive clinical improvement and another 7% have stabilization of their disease. This therapy should not be considered definitive therapy, but rather temporizing therapy.

Alkylator based therapy
Cyclophosphamide as a single agent or in combination with prednisone can result in substantial clinical improvement in as many as 40% of patients (Dispenzieri A*, et al*, 2003; Nakanishi T*, et al*, 1984). We typically use intravenous cyclophosphamide (with or without prednisone) in patients who are too sick to go immediately to transplant or those who are rapidly deteriorating while awaiting approval for peripheral blood stem cell transplant.
Melphalan is among the most effective agents against plasmaproliferative disorders. Based on retrospective data approximately 40% of patients with POEMS syndrome will response to melphalan and prednisone. As in the case of radiation therapy in POEMS patients, the neurologic improvement begins as long as 3 to 14 months later, and improvement can continue for months to years thereafter (Dispenzieri A*, et al*, 2003; Kuwabara S*, et al*, 1997). Limiting the melphalan exposure is important because secondary myelodysplastic syndrome or acute leukemia can occur. If the patient is considered to be a candidate for peripheral blood stem cell transplantation, melphalan-containing regimens should be avoided until after stem cell harvest.

High dose chemotherapy with hematopoietic stem cell transplant
High dose chemotherapy with peripheral blood stem cell transplant is an emerging therapy for patients with POEMS (Table 4; Figure 2). The first report was that of a 25 year old female who was treated with high-dose chemotherapy followed by bone marrow transplantation; she died of multi-organ failure 63 days after her stem cell transplant (Wong VA*, et al*, 1998). Subsequently, there have been an additional 26 transplanted patients published (Dispenzieri A*, et al*, 2003; Jaccard A*, et al*, 2002; Peggs KS*, et al*, 2002; Rovira M*, et al*, 2001; Soubrier M*, et al*, 2002) (Figure 2). All patients have had improvement of their neuropathy over time; as in the case with radiation therapy and other chemotherapy, improvement of the peripheral neuropathy takes months to years. Other clinical features improve after stem cell transplant, including levels of VEGF in several of the patients studied (Jaccard A*, et al*, 2002; Soubrier M*, et al*, 2002).
It has been our observation that the transplant related morbidity and mortality is higher in patients with POEMS than patients than in patients with classic multiple myeloma. Thirty-seven percent of our patients spent time in the intensive care unit and thirty-seven percent required mechanical ventilation. Though only one of our patients died (6.2% mortality rate), if the published experience of transplanted POEMS patients is pooled, the mortality figure is 2/27 or 7.4%. These numbers appear higher than the 2% transplanted related mortality observed in patients with multiple myeloma (Attal M*, et al*, 1996) but lower than the 14% transplant related mortality observed in patients with primary systemic amyloidosis (Gertz MA*, et al*, 2002).

Thalidomide
There have been anecdotal reports of beneficial application of thalidomide to patients with POEMS (Sinisalo M*, et al*, 2004). There is a theoretical rationale (anti-vascular endothelial growth factor and anti-tumor necrosis factor effects) for using the drug in these patients. Enthusiasm for its use in POEMS syndrome, however, should be tempered by the following: 1) thalidomide causes peripheral neuropathy in 20% of myeloma patients receiving the drug (Singhal S*, et al*, 1999); 2) thalidomide has been shown to worsen fluid retention in patients with primary systemic amyloidosis (Dispenzieri A*, et al*, 2003); and 3) as a single agent, thalidomide is no more effective than oral alkylators in patients with plasma cell disorders. More research is required before this drug can be recommended in this syndrome.

Radiation Therapy

External Beam Radiation
In those patients with a single, dominant osteosclerotic lesion, localized external beam radiation is generally considered to be first line therapy (Davis L*, et al*, 1972; Dispenzieri A*, et al*, 2003; Iwashita H*, et al*, 1977; Morley JB*, et al*, 1967; Reitan JB*, et al*, 1980). Solitary lesions, i.e. an osteosclerotic plasmacytoma with the associated paraneoplastic syndrome of POEMS, should be treated like any other plasmacytoma because there is the potential for cure (Figure 3). Most experts recommend

treating solitary plasmacytomas with doses of 40 to 50 Gy encompassing all disease with a margin of normal tissue. Non-neurologic manifestations, like hyperpigmentation, edema, hypertrichosis, gynecomastia, hepatosplenomegaly, tend to improve more quickly than the neurologic features (Dispenzieri A*, et al*, 2003; Takatsuki K*, et al*, 1983). In our experience, more than half of patients treated with radiation will respond, and patients have excellent survival (Figure 3). Durable responses are possible. No neurologic improvement may be observed until after at least 3 to 6 months; continued improvement can occur over the next several years. This peculiar characteristic of delayed neurologic response further confounds interpretation of case reports utilizing other systemic therapy. Several authors have attributed clinical improvement from other therapies (Authier FJ*, et al*, 1996; Benito-Leon J*, et al*, 1998; Coto V*, et al*, 1991) in patients who have received prior radiation therapy, not recognizing that the benefit may have been due to the prior radiation therapy.

Skeletal targeted therapy

Our group was the first to report the use of skeletal targeted radiation as part of the treatment strategy for patients with POEMS (Hogan WJ*, et al*, 2001). 153-Samarium-EDTMP was included as part of the conditioning regimen prior to peripheral blood stem cell transplantation in a patient with POEMS. Sternberg et al reported a case of a patient with POEMS who was treated with Strontium-89 after having failed one cycle of combination chemotherapy (Sternberg AJ*, et al*, 2002). This patient received 5 doses of Strontium-89 and prednisone. Though both patients did demonstrate clinical improvement, one cannot make any firm recommendations about the utility of skeletal targeted radiation therapy based on these two isolated reports.

Surgery

An open or closed biopsy of a sclerotic lesion is a common approach to document the diagnosis. Though surgical excision of sclerotic lesions have been reported (Broussolle E*, et al*, 1991; Furuzono H*, et al*, 1993; Rotta FT*, et al*, 1997), this approach is not considered standard given the associated morbidity. If an excisional biopsy is performed, the tumor bed is generally irradiated.

Other Therapies

Since the original diagnosis of patients with POEMS is often chronic inflammatory demyelinating polyneuropathy, patients commonly receive immunomodulatory therapies like intravenous gamma-globulin, plasmapheresis, and drugs like azathioprine. In our experience, these drugs are not useful, but since they are commonly used with corticosteroids or radiation, it often difficult to elucidate their role. There are two anecdotal reports of tamoxifen providing benefit (Barrier JH*, et al*, 1989; Enevoldson TP*, et al*, 1992). The one “positive” case report of interferon stabilizing the syndrome (Coto V*, et al*, 1991) is uninterpretable because the patient was previously treated with irradiation; the benefit ascribed to the interferon could have easily been from the prior radiation therapy. Another author reports no benefit from interferon use (Arima F*, et al*, 1992). All-trans-retinoic acid was used in a patient to suppress production of proinflammatory cytokines (Authier FJ*, et al*, 1996); though there was clinical improvement, the observation is confounded by concurrent radiation therapy.

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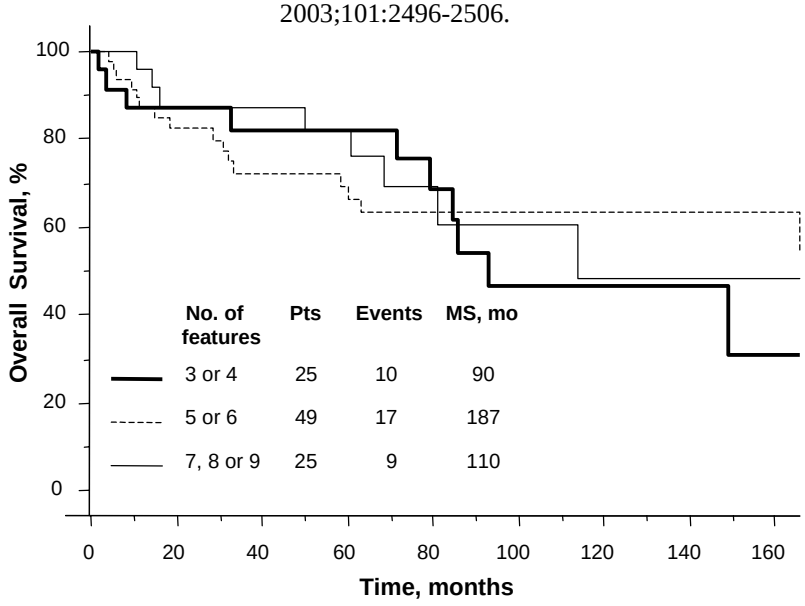

Figure 1. Survival on the basis of number of features at presentation in 99 patients.

P = not significant. MS, median survival; Pts, patients. This research was originally published in Blood. Dispenzieri et al. POEMS Syndrome: Definitions and Long-term Outcome. ***Blood***. 2003;101:2496-2506. © by the American Society of Hematology.

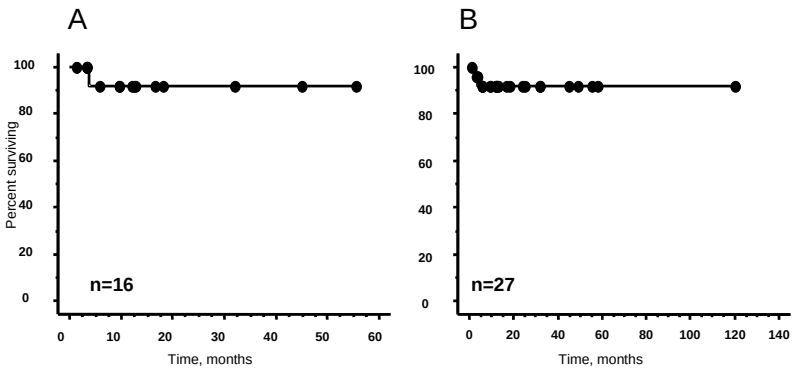

Figure 2. Overall survival after peripheral blood stem cell transplant

A. Sixteen Mayo Clinic patients
B. Reported world experience including 16 Mayo patients and 11 previously reported patients (Jaccard A*, et al*, 2002; Peggs KS*, et al*, 2002; Rovira M*, et al*, 2001; Soubrier M*, et al*, 2002). This research was originally published in Blood. Dispenzieri et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. ***Blood***. 2004;104:3400-3407. © by the American Society of Hematology.

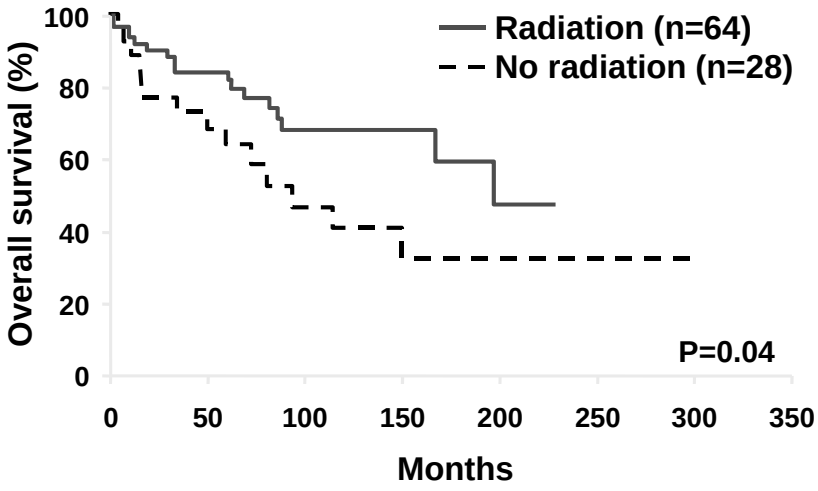

Figure 3. Survival on the basis of treatment with radiation in 99 patients.

P < 0.04 for comparison of the 2 groups. This research was originally published in Blood. Dispenzieri et al. POEMS Syndrome: Definitions and Long-term Outcome. ***Blood***. 2003;101:2496-2506. © by the American Society of Hematology.

Table 1. Criteria for the Diagnosis of POEMS Syndrome*

(This research was originally published in *Blood*. Dispenzieri et al. POEMS syndrome: definitions and long-term outcome. Blood. 2003;101:2496-2506. © the American Society of Hematology)

Major criteria	Polyneuropathy
	Monoclonal plasma cell-proliferative disorder
Minor criteria	Sclerotic bone lesions†
	Castleman disease†
	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)
	Edema (edema, pleural effusion, or ascites)
	Endocrinopathy (adrenal, thyroid,‡ pituitary, gonadal, parathyroid, pancreatic‡)
	Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)
	Papilledema
Known associations	Clubbing
	Weight loss
	Thrombocytosis
	Polycythemia
	Hyperhidrosis
Possible associations	Pulmonary hypertension
	Restrictive lung disease
	Thrombotic diatheses
	Arthralgias
	Cardiomyopathy (systolic dysfunction)
	Fever
	Low vitamin B_{12} values
	Diarrhea

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

*Two major criteria and at least 1 minor criterion required for diagnosis.

†Osteosclerotic lesion or Castleman disease is almost always present.

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

Table 2. Clinical Features POEMS Patients—Three Series

This table was modified from table originally published in Blood. Dispenzieri et al. POEMS Syndrome: Definitions and Long-term Outcome. ***Blood***. 2003;101:2496-2506. © by the American Society of Hematology.

	(Dispenzieri A, et al, 2003)	(Soubrier M, et al, 1994)	(Nakanishi T, et al, 1984)
	% n=99	% n=25	% n=102
Peripheral neuropathy	100	100	100
Organomegaly	46	NS	NS
Hepatomegaly	25	68	78
Splenomegaly	22	52	35
Lymphadenopathy	26	52	61
Endocrinopathy	71*	NS	NS
Diabetes	3	36	25
Hypothyroidism	17	36	
Monoclonal plasma cell dyscrasia	100	100	75
Skin Changes	68	NS	NS
Hyperpigmentation	46	48	93
Acrocyanosis and plethora	19	NS	NS
Hemangioma/telangectasia	9	32	NS
Hypertrichosis	26	24	74
Thickening	5	28	61
Sclerotic bone lesions	97	68	54
Osteosclerotic only**	47	41	56
Mixed sclerotic and lytic**	51	59	31
Lytic only**	2	0	13
> 1 lesion**	54	59	45
Papilledema	29	40	55
Extravascular volume overload	39	NS	NS
Peripheral edema	29	80	89
Ascites	15	32	52
Pleural Effusion	9	24	35
Castleman disease	11	24	19
Other Features			
Thrombocytosis	54	88	NS
Polycythemia Hb >15 g/dl females and >17g/dl males	18	12	19
Clubbing	5	32	49

Comment: the percentages for all series uses the total number of patients in the series as the denominator
*Includes gonadal and adrenal abnormalities
**Of patients with bone lesions

Table 3.—Response to Therapy in Patients With POEMS Syndrome

This research was originally published in Blood. Dispenzieri et al. POEMS Syndrome: Definitions and Long-term Outcome. ***Blood***. 2003;101:2496-2506. © by the American Society of Hematology.

Treatment	No. of patients	Response to treatment, %			
		Improved	Stable	Progression	Unknown
Radiation	70†	54	4	16	26
Melphalan and prednisone	48	44	12	12	31
Combination chemotherapy*	15	27	7	33	33
Cyclosporine or azathioprine	4	0	0	100	0
Cyclosporine or azathioprine, plus prednisone	6	50	0	17	33
Prednisone or dexamethasone	41	15	7	20	59
Plasmapheresis	16	0	12	87	0
Plasmapheresis plus prednisone	14	21	0	14	64
Intravenous immunoglobulin	9	0	0	89	11

*Includes vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; vincristine, Adriamycin, and dexamethasone; cyclophosphamide, Adriamycin, vincristine, and prednisone; and cyclophosphamide-based chemotherapy.

†Sixty-four patients were treated with 70 courses of radiation.

Table 4. Response after PBSCT (median follow-up 10.8 months)*

This research was originally published in Blood. Dispenzieri et al. POEMS Syndrome: Definitions and Long-term Outcome. ***Blood***. 2003;101:2496-2506. © by the American Society of Hematology.

	N	Response, %	Stable, %	Not evaluated, %
Neurologic	16	87	…	13
Subjective	16	87	…	13
Nerve conduction studies (at 1 yr)	11	36	9	55
Neuropathy impairment score	16†	25	12	56
Hematologic	16	56	6	37
Non-secretory	3	NA	NA	100
Immunofixation only	7	43	14	43
SPEP evaluable	6	100‡	…	…
Organ	11	82	…	18
Hepatomegaly	5	60	…	40
Splenomegaly	10	50	20	30
Lymphadenopathy	7	71	29	0
Extravascular volume overload	14	79	…	21
Ascites	6	83	…	17
Effusion	4	100	…	…
Edema	14	79	…	21
Skin Changes	13	54	15	31
Papilledema	4	50	…	50
Endocrine	13	23	8	69
Pulmonary	15	20	…	80

*1 died before evaluation and 1 too soon to evaluate
† One patient showed borderline worsening at 15 months, but at 24 months, patient reported substantial improvement; no repeat neuropathy impairment score was performed.
‡2 complete responses, 3 VGPR, and 1 minimal response