



Review Articles

POEMS SYNDROME: an Update

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Competing interests: The authors have declared that no competing interests exist.

Abstract. POEMS syndrome is a rare, chronic and disabling condition. The causes of this condition remain unknown; however, chronic overproduction of proinflammatory cytokines appears to be a major contributor. Early diagnosis is essential to start treatment before the clinical state of the patient becomes compromised.

A complete evaluation of the disease at its onset is critical to the treatment decision. In localized disease, curative doses of radiation (50 Gy) is the recommended therapy. On the other hand, patients with disseminated disease should be given systemic therapy. Treatment-related morbidity can be minimized by an efficient induction therapy that modifies the cytokine status, improving clinical condition and control disease severity before mobilization and transplantation. Patients not suitable for hematopoietic stem cell transplantation (HSCT) are usually treated with alkylator-based therapy. Novel agents may also offer benefits to patients with a poor performance status or renal dysfunction, and induce transplantation eligibility. Given the biological characteristics of POEMS, immunomodulatory effects and the absence of neurotoxicity, lenalidomide appears to be an effective therapy for the treatment of POEMS, both as short induction therapy before PBSCT and in non-transplant eligible patients, as it showed high response rate and durable responses.

At present, however, guidelines for the diagnosis and treatment of POEMS are not available and appear advocated.

Keywords: POEMS, Plasma Cell Dyscrasia, Osteosclerosis, Neuropathy.

Citation: Nozza A. POEMS SYNDROME: an Update. *Mediterr J Hematol Infect Dis* 2017, 9(1): e2017051, DOI: <http://dx.doi.org/10.4084/MJHID.2017.051>

Published: September 1, 2017

Received: May 26, 2017

Accepted: August 5, 2017

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Introduction. POEMS syndrome is a multisystemic disease secondary to a plasma cell dyscrasia. POEMS is an acronym for a range of distinct features [peripheral neuropathy (P), organomegaly (O), endocrinopathy (E) monoclonal plasma-cells proliferative disorder (M) and skin changes (S)], even if the diagnosis does not require that all these symptoms are present. Furthermore, many others clinical signs are not included in the definition of POEMS, such as sclerotic bone lesions, papilledema, edema

ascites and effusions, pulmonary hypertension, Castleman' disease (CD), thrombocytosis and erythrocytosis, and increased of serum vascular endothelial growth factor (VEGF).^{1,2} POEMS SYNDROME has also been called osteosclerotic myeloma, Crow-Fukase syndrome, PEP syndrome (plasma cell dyscrasia, endocrinopathy, polyneuropathy), or Takatsuki syndrome. POEMS syndrome is a rare disease, but it is often under-recognized.

The primary clinical features of this syndrome is a progressive polyneuropathy with a predominant motor disability. The disease is potentially fatal, and patient's quality of life deteriorates due to a progressive neuropathy, massive peripheral edema, pleural effusion, and ascites. Serious complications such as multiorgan failure due to capillary leak syndrome, restrictive lung disease, and pulmonary hypertension result in an adverse prognosis.

Despite its seriousness, at present no guidelines or standardized criteria for the diagnosis and treatment of POEMS syndrome are available. This narrative review provides an update of the current evidence on this condition. Literature research was last updated in May 2017.

Pathogenesis. Although significant progress has achieved in the diagnosis, management, and treatment of POEMS syndrome, its pathophysiology remains unknown. Up-regulation of various pro-inflammatory cytokines and growth factors (tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL1), interleukin-6 (IL6) and above all vascular endothelial growth factor (VEGF) play a crucial role in the pathogenesis of the POEMS syndrome, contributing to vascular leak and polyneuropathy.³⁻⁵ In particular, VEGF is markedly elevated in POEMS patients and correlates with the activity of the disease. Unfortunately, VEGF inhibition with specific inhibitors (e.g., bevacizumab) did not result in an effective treatment thus suggesting that VEGF may be only one component of a much more complex cytokine network.^{6,7} It has also been proposed that clonal B/plasma cells with genetic

mutations of the V-region of the Ig lambda gene could produce excess cytokines (primarily, VEGF) through an yet undiscovered mechanism, leading to the clinical manifestations of POEMS.⁸

Diagnostic Criteria. POEMS syndrome is a rare disease, with diverse clinical manifestations, which lead the patient on a diagnostic "Odyssey" across multiple specialists, without a correct and definitive diagnosis. Moreover, the clinical features of POEMS widely differ from patient to patient, and all symptoms are not always present. Therefore, patients may experience a delay in the initiation of appropriate treatment.

Early diagnosis is critical to reduce the morbidity rate and increase survival. However, the median time from onset of diagnosis is 13-18 months.⁹

Diagnostic criteria for POEMS were first proposed in 2003¹⁰ and were revised in 2007 after the diagnostic relevance of VEGF level was confirmed.¹¹ In more details, clinical features have been divided into mandatory criteria, major criteria, and minor criteria, in line with the indications of The International Myeloma Working Group (**Table 1**).¹² The presence of both "mandatory criteria," at least one major criteria and at least one minor criteria are needed for the diagnosis of POEMS syndrome.

Mandatory Criteria.

Polyneuropathy. Patients in the early stage of POEMS are frequently misdiagnosed with CIDP (chronic inflammatory demyelinating polyneuropathy), as both conditions involve the peripheral nerves and may present with albumin-

Table 1. Diagnosis criteria for POEMS syndrome.

Mandatory criteria	Polineuropathy
	Monoclonal plasmacells disorder
Major criteria	Osteosclerotic or mixed sclerotic/lytic lesions
	Castleman's Disease
	Elevated serum or plasma vascular endothelial growth factor (VEGF)
Minor criteria	Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy)
	Vascular volume overload (peripheral edema, ascites, pleural effusion)
	Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic disorders excluding diabetes mellitus and hypothyroidism)
	Skin changes (Hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, phlebotomias, acrocyanosis, flushing, white nails)
	Papilledema
	Thrombocytosis, Polycitemia
Others signs or symptoms	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diathesis, diarrhea, low B12 value

cytologic dissociation in the cerebrospinal fluid.¹³ Moreover, nerve conduction studies and electrophysiological examination can be used to distinguish POEMS from other polyneuropathies with more prominent sign of axonal degeneration and more neurogenic injury in lower limbs muscles.^{14,15}

Symptoms of peripheral neuropathy are usually particularly evident, and consist in tingling, paresthesia, and coldness; motor involvement follows sensory symptoms. Cranial nerves are not involved except for papilledema. Severe weakness is frequently reported, and patients experience an inability to climb stairs, rise from a chair or to hold a firm grip. Over time, muscle weakness becomes more marked than the sensory loss.

Peripheral neuropathy is due to endothelial injury, caused directly or indirectly by abnormal activation of endothelial cells by VEGF expressed in the nerves.⁵

Monoclonal plasma cells proliferative disorder. All patients have a monoclonal protein (M-protein, lambda-type chain), which can be detected either in serum and/or urine with immunofixation tests.⁸ The concentration of this protein is modest (median 1,0 mg/dl). Bence Jones proteinuria is uncommon.¹⁶ Serum protein electrophoresis is normal in 25% of patients, while in the remaining patients it presents a polyclonal gammopathy patterns: in these cases, M-proteins could be overlooked if immunofixation is not performed. In addition, although the immunoglobulin free light chains are elevated in 90% of POEMS patients, the ratio is abnormal in only 18% of cases,¹⁷ thus making this test of limited value.

Information on plasma cells in POEMS is scant. In more than 95% of cases, they are lambda-light restricted.¹⁸ The V-region of the Ig lambda gene interested was limited to the V lambda 1 subfamily (IGLV1).^{8,19} Kang et al. reported in 20 newly diagnosed POEMS cytogenetic aberrations similar to other plasma cell dyscrasias, but with a different incidence.²⁰ In particular, 14q32 (IGH) translocation was observed in 45% of the cases and included the t(4;14) and t(11;14) translocation (15% and 25% of the cases, respectively). In addition, 25% of the patients presented deletions of 13q14 and 20% had an amplification of 1q21. No significant correlation between clinical features and cytogenetic abnormalities was observed, although patients with IGH

translocations were more likely to exhibit papilledema.

Major Criteria.

Bone lesions. Osteosclerotic lesions are reported approximately in 95% of patients¹¹ even if several reports from China showed a lower rate of bone lesions (27-41%) which may suggest ethnic differences.^{9,21}

Bone lesions could be sclerotic, lytic with sclerotic rims or mixed sclerotic/lytic lesions with soap-bubble appearance. Lytic lesions without sclerotic rims are uncommon. In about half of patients, a single bone lesion is found, while in the others lesions are multiple. The pelvis, spine, ribs and proximal extremity are the most common sites of bone lesions. Hypercalcemia is not usually reported at diagnosis; bone pain and fractures are sporadic.

Imaging approaches used for evaluation of bone involvement in POEMS are simple skeletal radiograph and computed tomography of bone. (**Figure 1**) Bone uptake in bone scintigraphy has been described, although false negatives are possible.^{22,23} Lesions have variable FDG uptake, but positron emission tomography (PET) scan usually does not identify all lesions.²⁴ PET scan can, however, be useful in monitoring response to therapy in patients with high baseline FDG uptake.^{25,26}

Castleman's disease. CD is a rare lymphoproliferative disorder with many different presentations, ranging from asymptomatic single lymph node to multifocal disease with a plethora of symptoms. CD and POEMS are frequently associated, and approximately 15-24% of patients with POEMS syndrome also have CD, the majority of them had hyaline vascular type.^{10,16,27} However, this proportion may be an underestimation since many patients do not undergo lymph node biopsy. Multicentric CD with and without peripheral neuropathy tend to be different; those patients with peripheral neuropathy are more likely to have edema and impaired peripheral circulation, and they are also more prone to have a monoclonal lambda protein in their serum and/or urine. In these patients, neuropathy is more often sensory and subtle; these patients show high levels of VEGF and IL6, and a higher frequency of thrombocytosis.²⁸

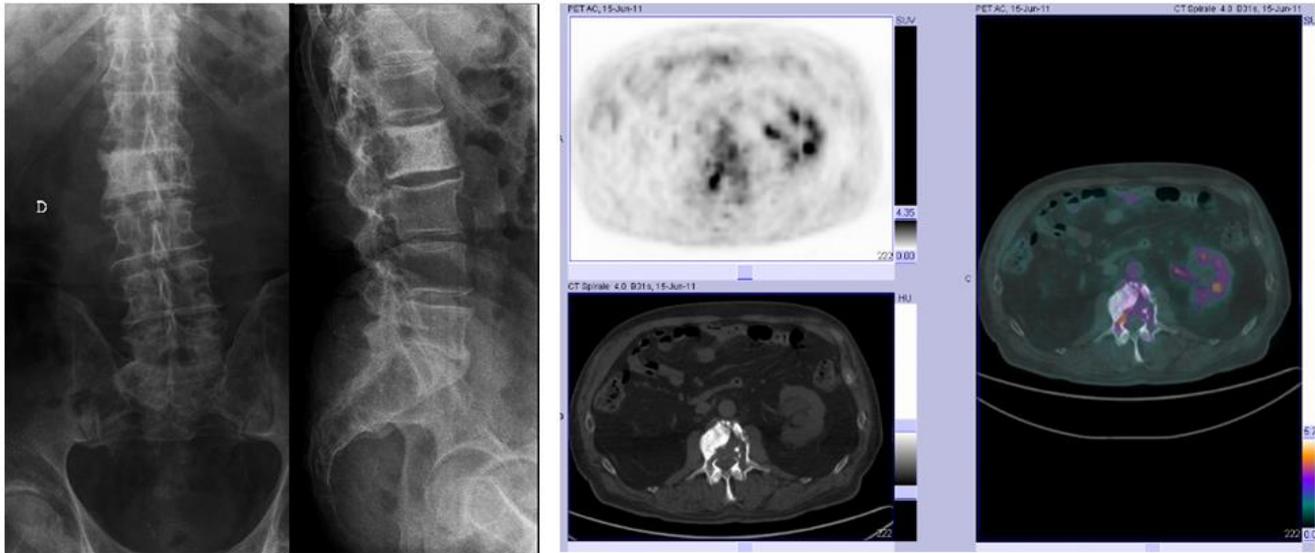


Figure 1. Bone lesion evaluation in a newly POEMS Syndrome with standard x-ray and TC-PET.

VEGF serum levels. VEGF is expressed by osteoblasts, bone tissue, macrophages, tumor cells, plasma cells, and megakaryocytes; both IL1 and IL6 have been shown to stimulate VEGF production.

VEGF normally targets endothelial cells and induces a rapid and reversible increase in vascular permeability. Increased VEGF could account for some clinical characteristics of POEMS, such as organomegaly, edema, skin changes and neuropathy, increasing microvascular permeability of the blood vessels with endoneurial edema.^{29,30} Serum VEGF levels tend to be 5-10 fold higher in POEMS syndrome compared with healthy controls or patients with other neuropathic disorders.³¹

Many studies confirm that VEGF levels could be used as a biomarker to monitor disease activity and differentiate POEMS syndrome from amyloidosis, monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM) and CIDP.^{29,31,32} It is still unclear the best approach for VEGF evaluation, whether in serum or plasma. Serum VEGF levels are affected by the release of platelet-derived VEGF because of ex vivo platelet activation during the clotting process or because of the presence of thrombocytosis in some patients.³³ Furthermore, the normal and pathologic reference ranges for VEGF (in serum or plasma) are not well defined to date, even if a VEGF value more than 1000 pg/ml is considered pathological.

Minor Criteria.

Organomegaly. Hepatomegaly, splenomegaly, and lymphadenopathy at the onset of POEMS

syndrome have been reported in 50-78% of patients.^{10,34} When present, organomegaly is mild, and bulky disease is unusual. Lymphadenopathy could be related to concomitant CD, although lymph node biopsy is performed in a minority of patients.¹⁶

Extravascular volume overload. Extravascular volume overload (peripheral edema, ascites, pleural effusion, pericardial effusion) is reported in 80% of POEMS patients.³⁵ Peripheral edema and ascites are more common than pleural or pericardial effusion. Cytological and biochemical analysis of ascites document the characteristics of exudate. Vascular injury change of the peritoneal surface and/or permeability of the capillaries in visceral peritoneum are considered a mechanism of extravascular volume overload.³⁶ Extravascular volume overload can cause important morbidity in POEMS, and it is associated with shorter survival.¹¹

Endocrinopathy. Endocrinopathy is a crucial but poorly understood feature of POEMS syndrome. The majority of patients have evidence of multiple endocrinopathies in the four principal axes (gonadal, thyroid, glucose and adrenal), such as hypogonadism, diabetes mellitus, hypothyroidism, hyperprolactinemia, adrenal insufficiency, gynecomastia and hypoparathyroidism.¹ The etiology of endocrinopathy is unknown, even if VEGF could be a major contributor.

Most information regarding these abnormalities and POEMS comes from case reports or small series. In a retrospective evaluations on 170

POEMS cases, 84% of patients documented at least one endocrine abnormality at presentation or during the disease.³⁷

Hypogonadism is the most common endocrine abnormality: this condition, with lower levels of testosterone and erectile dysfunction, is reported in over 70% of males.³⁸ Moreover, gynecomastia in men and irregular menses in woman have been described.³⁴ Given the high prevalence of diabetes mellitus and hypothyroidism in the general population, these endocrine abnormalities are not considered among the criteria for the diagnosis of POEMS syndrome.

Skin changes. Skin changes were described in more than 75% of POEMS patients at diagnosis.^{10,34} Major dermatological findings consist in hyperpigmentation and hemangiomas, present as multiple red-purple lesions especially on the trunk and proximal limbs. Others skin changes are hypertrichosis (especially of extremities or face, present in one-fourth of cases), acrocyanosis, white nails, hyperemia, erythema, flushing, rubor and clubbing (**Figure 2**).³⁸ A high prevalence of acquired facial lipoatrophy preceding POEMS diagnosis was also described.³⁹ Of note, a rapid improvement in hemangiomas, hyperpigmentation, hypertrichosis, and vascular skin changes is often associated with treatments for POEMS.



Figure 2. Skin changes in POEMS syndrome: acrocyanosis, white nails and clubbing.

Papilledema. Papilledema, usually bilateral, is an early sign of POEMS syndrome. This finding is reported in 29-64% of patients and correlates with poor prognosis.⁴⁰ An association between papilledema and plasma VEGF levels was also described.⁴¹ In a recent study, serum VEGF concentrations were significantly different in patients with papilledema, and those without; the serum levels of this cytokine decreased, and papilledema alleviated after treatment.⁴² Cerebrospinal fluid protein levels in POEMS are increased in all patients, with level >100 mg/dL in more than half of patients showing average total cell count.⁴³

Hematological alterations. In POEMS patients, thrombocytosis is common (50%), and polyglobulia may be observed (15%).¹¹ Patients with thrombocytosis and erythrocytosis are often diagnosed as a chronic myeloproliferative disease before considering the diagnosis of POEMS syndrome. In these patients, JAK2 evaluation is always negative. Anemia is rare unless the patient present concomitant CD.

Others Signs and Symptoms.

Pulmonary manifestation. These findings include pulmonary hypertension, restrictive lung disease, reduced muscular function, impaired diffusion lung CO (DLCO). Pulmonary hypertension is reported in 27-48% of patients.^{44,45} Pulmonary hypertension is reversible after successful treatment of POEMS syndrome; survival of these patients is worse than in those without pulmonary hypertension.⁴⁴

Patients with pulmonary hypertension are more likely to present extravascular volume overload. Whether the digital clubbing seen in POEMS is a reflection of underlying pulmonary hypertension and/or parenchymal disease is not clear yet.

Bone marrow Histopathology. A recently published study identified several and distinctive histopathologic features in bone marrow of POEMS Syndrome patients.²⁰ Monoclonal plasma cells (majority λ light chain restricted), are usually less than 10%. Lymphoid aggregates were found in more than 40% of patients, rimmed by polyclonal plasma cells. Megakaryocyte hyperplasia is present in one-half of bone marrow of POEMS, with megakaryocytic clustering and cytologic atypia, thus mimicking a

myeloproliferative neoplasm. However, JAK2 mutation is always negative. This histopathological evidence is highly suggestive of POEMS.

Differential Diagnosis. The median time from onset of symptoms to diagnosis of POEMS ranges from 13 to 18 months; indeed, many patients are initially misdiagnosed as having other disorders, such as CIDP. Also, some conditions are associated with a plasma cell disorder and polyneuropathy, with or without bone lesions. Many studies confirm that VEGF levels could be useful for differentiating POEMS syndrome from amyloidosis, MGUS, MM and CIDP: In these diseases, VEGF levels are usually low.^{29,31,32} Features contributing to the differential diagnosis are reported below.

MGUS. MGUS is characterized by an M-protein in serum, without other systemic findings. It should be noted that polyneuropathy may be seen in patients with MGUS.⁴⁶

Multiple myeloma. A polyneuropathy is a rare event in MM patients, and it is related to concomitant amyloidosis. Bone lesions in MM are not sclerotic, but normally osteolytic; moreover, the presence of anemia, hypercalcemia, renal insufficiency, and a high proportion of bone marrow plasma cells, which are frequently present in MM, are not characteristics of POEMS.

Solitary plasmacytoma of bone. Patients with solitary plasmacytoma of bone usually show only a single osteolytic bone lesion, whereas in POEMS syndrome the bone lesions are osteosclerotic. Systemic signs and symptoms, such as anemia, hypercalcemia, and renal insufficiency are absent in solitary plasmacytoma.

Amyloidosis. Amyloidosis is often associated with monoclonal gammopathy, skin lesions, and polyneuropathy. Biopsy of involved tissues (fat aspirate, bone marrow, kidney, heart, sural nerve) allows making a differential diagnosis with POEMS, showing typical amyloid fibrils.

Chronic inflammatory demyelinating polyneuropathy (CIDP). Both CIDP and POEMS are characterized by a subacute motor-dominant demyelinating polyradiculoneuropathy. Nerve

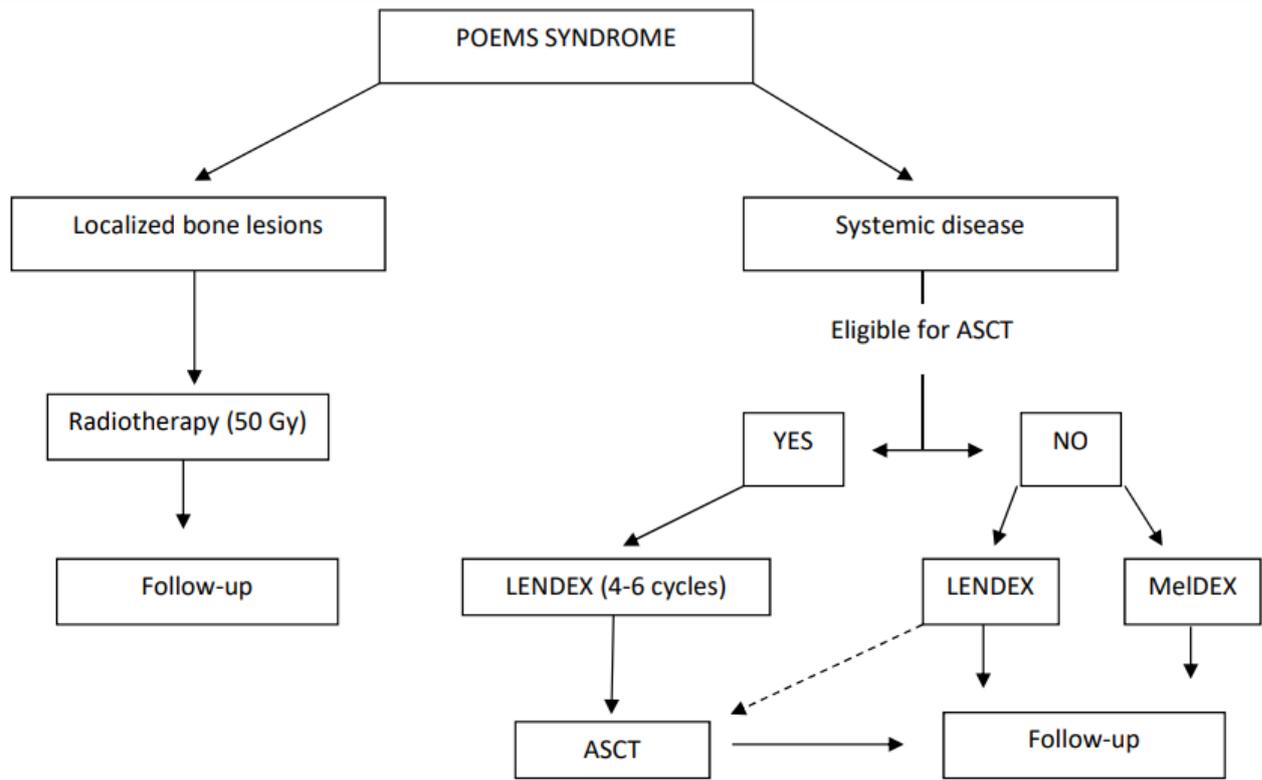
conduction study and electromyography can adequately distinguish POEMS syndrome from CIDP.^{15,47} Compared with CIDP, POEMS patients demonstrate greater axonal loss (reduction of motor amplitudes and increased fibrillation potentials), more considerable slowing of the intermediate nerve segments, less frequently temporal dispersion and conduction block, and absent sural sparing.

Treatment. The clinical course of POEMS syndrome is usually chronic and disabling, with a progressive worsening of the clinical condition and quality of life. The median survival of these patients is about 14 years, during which patients received some different therapies.^{10,48} However, due to its rarity and the difficulties encountered in its diagnosis, only one randomized controlled study has been completed in POEMS.⁴⁹ To date, evidence on POEMS treatment has been collected only in retrospective studies, often with small sample size.

Treatment for newly-diagnosed POEMS syndrome depends on the extension of the disease (**Figure 3**) In patients with isolated bone lesion without bone marrow clonal plasma cells involvement, curative doses of radiation (40-50 Gy) is the recommended therapy. In patients with a disseminated disease (more bone lesions and/or bone marrow plasmacytosis), systemic therapy is recommended.⁵⁰

Radiotherapy. Approximately 26% of newly-diagnosed POEMS patients present localized bone lesions. In this setting, radiotherapy (RT) improves symptoms and can also be curative.⁵¹ The rate of clinical and hematological response ranges from 47 to 75%, and from 45 to 50%, respectively.^{51,52} In a series of 35 POEMS patients, RT resulted in a 4-year overall survival (OS) rate of 97% and a 4-year failure-free survival rate of 52%.⁵² More than 50% of patients treated with RT show a substantial improvement of neuropathy, although this effect it is not evident for at least six months in some subjects.¹⁰ The maximal response could be not attained until 2–3 years since the first evidence of effect. Other features like anasarca, papilledema, pulmonary hypertension and skin changes may show an earlier improvement, usually seen few months after the end of radiotherapy.^{53,54}

If the bone lesion is large, RT could be considered as primary therapy despite bone



Patients Non eligible for ASCT:

- Age (>65 yrs)
- Concomitant disease (non related to POEMNS Syndrome)
- clinical conditions related to Active POEMS disease : if clinical status improves after short LENDEX therapy, these patients can be transformed to receive ASCT

Figure 3. POEMS SYNDROME: Treatment strategy.

marrow infiltration. Systemic treatments may be added according to clinical response.

Systemic treatments. In patients with a disseminated disease, systemic therapy is recommended.⁵⁰ Treatments used in immune-mediated neuropathies (plasmapheresis, IV Ig) are almost invariably ineffective in POEMS. Corticosteroids, either given orally or intravenously, are also rarely effective and usually only attenuate symptoms for a short time, without affecting progression.⁵⁵ Therapies for POEMS are borrowed from other plasma cell dyscrasias and include autologous stem cells transplantation (ASCT), alkylating agents such as melphalan or cyclophosphamide, or “new drugs” (thalidomide, lenalidomide, Bortezomib).

Autologous stem cell transplantation. ASCT is considered the preferred initial therapy for young patients. It is associated with a durable response, even if some patients may experience relapse.²⁶ A recent multicenter retrospective analysis suggested the effectiveness of ASCT when incorporated into the clinical management of POEMS.⁵⁶ Complete response was reported in 48.5%, partial response in 20.8%, less than a partial response in 30.7% of patients. With a median follow up of 48 months, 90% of patients were alive, and 16.5% of patients had progressed. The 1-year non-relapse mortality was 3.3%. The likelihood of PFS and OS were 84% and 94% at three years, 74% and 89% at five years, respectively. Tandem transplant has been applied in a case report, but no further information is available.⁵⁷

However, clinical conditions related to the disease (effusion, pulmonary hypertension, renal

impairment) and severe end-organ dysfunction make some young patients ineligible for upfront ASCT. Kanai et al. reported an overproduction of IL12 and VEGF in untreated POEMS patients.⁵⁸ In these patients induction therapy (cyclophosphamide or lenalidomide, thalidomide or bortezomib in combination with high-dose dexamethasone) modifies the hypercytokinemia status, improving clinical condition and control disease severity making more patients eligible for ASCT. The use of induction therapy before ASCT also reduces the incidence of peritransplant complications.^{59,60}

The optimal regimen for peripheral blood stem cell (PBSC) collection is still controversial; PBSCs could be collected using rather high-dose cyclophosphamide plus G-CSF or G-CSF alone.^{61,62} Factors associated with inadequate mobilization are hepatomegaly, splenomegaly, ascites and renal failure:^{60,62} all these symptoms are related to disease severity, indicating that relieving the disease activity before mobilization is crucial for mobilization. Induction therapy before mobilization reduces the level of various cytokines and could also limit the risk of an inadequate mobilization and adverse events.

The efficacy of plerixafor with G-CSF has been reported in two poor mobilizers.⁶³ Indeed, although ASCT has a high activity in POEMS, it is a potentially lethal procedure associated with significant morbidities, such as engraftment syndrome. This complication is reported in 23-47% of transplants and is characterized by fever, rash, diarrhea, weight gain, as well as respiratory symptoms and signs that occur 7-15 days since stem cell infusion.⁶⁴ Normalization of cytokine milieu with pre-transplant induction therapy reduces the incidence of this complication.⁶⁰

Alkylator-based therapy. In patient nonsuitable for ASCT, alkylator-based therapy with melphalan or cyclophosphamide plus corticosteroids could be the treatment of choice. These treatments are associated with clinical and neurological response in approximately 40-50% of patients and a 2-year OS rate of 78%.¹⁰ However, limiting exposure to alkylating agents is important because secondary hematological neoplasia (leukemia, myelodysplasia) could occur.

In the first prospective clinical trial performed in POEMS syndrome, 31 newly-diagnosed patients were treated with 12 cycles of melphalan

and dexamethasone.⁶⁵ After a median follow-up of 21 months, 81% of the patients showed an hematologic response, 100% had a reduction of serum VEGF levels, and 100% experienced improvements in neurological symptoms. However, only scant data on the long term effect of this therapy is available.⁶⁵

Thalidomide. Given its antiangiogenic, anti-inflammatory, and immunomodulating properties, thalidomide has been tested in POEMS syndrome. It showed evidence of clinical efficacy, but its neurotoxicity makes thalidomide unsuitable for patients with this condition, due to preexisting severe neuropathy.⁶⁶⁻⁶⁸ The results of a multicenter, randomized, double-blind study comparing thalidomide plus dexamethasone versus dexamethasone alone showed a reduction of VEGF serum level with thalidomide, but also an increase of side effects without hematological response.⁶⁹

Lenalidomide. In POEMS patients, several cytokines other than VEGF are elevated. Lenalidomide, a thalidomide-derived immunomodulatory analog, blocks the increased secretion of IL6, TNF-alpha, and VEGF. These molecules stimulate T cell proliferation and the production of IL2, IL10, and IFN-gamma, while they inhibit IL1beta and IL6 and modulate IL12 production. Therefore, lenalidomide appears the most promising drug for the treatment of POEMS syndrome.

Lenalidomide efficacy in the pre-treated setting has been reported in several case reports or small series of patients, with long-lasting responses and good tolerability.⁷⁰⁻⁷⁴ In a retrospective pooled analysis of 51 subjects, the 12 newly diagnosed patients treated with lenalidomide showed a 12-month PFS rate of 93% and a 24-month rate of 47%.⁷⁵

More recently, the efficacy of lenalidomide as frontline therapy has been further confirmed.^{76,77} Overall, the efficacy of lenalidomide was promptly evident, with stabilization or improvement of symptoms already after first cycles, rapid resolution of vascular volume overload, skin changes and pulmonary hypertension. Importantly, a sufficient number of CD34+ cells was harvested after lenalidomide treatment.

In an unpublished series from our Center, we treated with lenalidomide 18 subjects, 13 pretreated and 5 with new diagnosed not eligible for HSCT (Nozza et al., manuscript submitted). With a median follow-up of 39 months, progression-free survival (PFS) at three years was 59%, and overall survival (OS) was 100%. After six months of therapy, 83% of the patients had improved clinical and neurological conditions, particularly regarding regression of edema and ascites, amelioration of skin lesions and regression of adenopathies. A rapid neurological improvement was documented in all but one patient, and correlated with a statistically significant improvement in neurophysiologic parameters. In addition, we reported a reduction of VEGF already after one cycle of lenalidomide.

On these bases, lenalidomide, as an induction therapy before the transplant, can improve the patient clinical status and decrease transplant-related morbidity. Furthermore, it can be used as a salvage therapy after relapse.

Bortezomib. Bortezomib, alone or in combination, has been used in newly-diagnosed and in relapsed patients, with highly satisfactory responses on neuropathy, serum VEGF level, and extravascular overload.⁷⁸⁻⁸¹ However, the potential risk of progression of existing neuropathy associated with the use of bortezomib may limit its usage in patients with POEMS syndrome.

Bevacizumab. Since most patients with POEMS syndrome present increased serum VEGF levels, therapy with anti-VEGF factors is considered an appealing strategy. Badros et al. first reported the efficacy of anti-VEGF therapy in patients with POEMS.⁶ In a study of 17 patients treated with bevacizumab (only one in monotherapy), bevacizumab based-therapy resulted in a rapid decrease in the serum VEGF levels, which, however, was not necessarily associated with clinical improvement.⁸² Moreover, some patients showed improved neuropathy and systemic symptoms, but this effects could also be related to the association of bevacizumab with other cytotoxic drugs. Six out of 17 treated patients died without showing any response. The reduced effectiveness of bevacizumab may be linked to the fact that several cytokines (IL-6, IL-12, TNF- α) other than VEGF are elevated in POEMS syndrome. Therefore, inhibition of VEGF alone is

not sufficient to suppress disease activity. It has also been suggested that sudden VEGF removal with bevacizumab therapy may cause a collapse of newly-formed fragile vessels, since VEGF is a major angiogenic factor, and may lead to an increase capillary leakage.⁸³

Response Evaluation. At present, there are neither guidelines nor standard criteria for the assessment of the response in POEMS patients. The reduction of M-Protein, the modification of the VEGF value and the improvement of clinical or neurological parameters/symptoms present at the onset are often used in clinical practice to assess the response to treatment. In POEMS syndrome, M-protein size is typically small, thus making standard MM response criteria inapplicable in most cases. Moreover, patients can obtain clinical benefit even without hematologic response.⁶⁵ Free light chains ratio is in the range in the majority of patients, therefore making this test not especially useful for response evaluation in POEMS.¹⁷ There are also challenges using vascular endothelial growth factor (VEGF) as a response criterion, also because VEGF assays are not standardized. There is even disagreement about which measurement – either serum or plasma - should be preferred.

From a clinical standpoint, there are no criteria able to define the responses or improvements for most of the clinical parameters in POEMS: often measurements are relegated to the vague “improvement” or undefined “response” category. For evaluating the most important symptom of POEMS syndrome (peripheral neuropathy), the Overall Neuropathy Limitations Scale (ONLS), a simple tool, has been used; however, it does not distinguish between sensory, motor, or painful variants of neuropathy.

The issue of response evaluation in POEMS has recently been raised by Angela Dispenzieri,⁸⁴ who stressed the need to use common and plain language.

In our Institute, we decided to assess patients at diagnosis, during treatment periods and follow-up by the following tools: (i) three neurological scales (ONLS: to assess limitations and disability caused by peripheral neuropathy, Medical Research Council (MRC) scale to evaluate muscle strength, Inflammatory Neuropathy Cause and Treatment (INCAT) disability score to evaluate sensations in the arms and legs, and nerve conduction studies

(EMG). (ii) a specifically-developed clinical scale (Clinical Response Evaluation Scale, CRES), which takes account the modification of ten clinical features [monoclonal protein, blood alteration, organomegaly (liver and spleen), lymphadenopathy, endocrinopathy, skin alteration, peripheral edema, effusions (pleural, ascites), impaired lung function (by spirometry), bone lesions]; (iii) serum VEGF levels, in order to evaluate improvement of motor conduction velocity, distal latency and distal CMAP amplitude. The variation of the score of these scales during treatment could estimate the magnitude of clinical response.

Prognosis and Relapse. The course of POEMS syndrome is chronic and progressive, but ASCT and novel agents may prolong survival. At present, there is no standard risk stratification for POEMS syndrome, but some features such as extravascular volume overload, pulmonary hypertension, fingernail clubbing, renal dysfunction, have been associated with shorter OS.^{9,62} However, the level of serum VEGF and the number of clinical features at onset do not appear to affect OS.¹¹

Recently, Whang et al. retrospectively analyzed 362 newly diagnosed POEMS patients, identifying four baseline clinical variables associated with poorer OS (age >50 years, pulmonary hypertension, pleural effusion and estimated glomerular filtration rate <30 ml/min).⁸⁵ These clinical variables were included in a nomogram, which could predict the 5- and 10-year OS. This nomogram is not ready for routine practice, but these four variables should be taken into consideration for counseling patients.

The incidence of relapse or progression have been reported in some studies, but they included only a limited number of patients with a short follow-up.^{26,52,73} A retrospective analysis of 262 relapsed patients with POEMS syndrome has been recently published.⁸⁶ The Authors reported that 4% of patients with POEMS had a primary refractory disease, 20% showed a progression of disease within five years and an additional 10% after five years. Low albumin at onset and failure to achieve a complete hematological response with

induction therapy were independent risk factors for PFS in relapsed patients.

Systemic treatment should be initiated in the case of clinical/symptomatic relapse, and observation is reasonable in patients with isolated hematological relapsed or with VEGF elevation. The majority of relapsed patients could be salvaged with second-line therapy, showing prolonged PFS in more than 90% of cases.⁷³ RT be also considered in relapsed patients with 1 or 2 bone lesions on PET, with a long-lasting disease control. However, at present, it is not possible to define the best salvage therapy in POEMS, due to the lack of randomized trials and the small sample size and methodological limitations of available studies. Overall, lenalidomide, alone or in combinations with high-dose dexamethasone, seems the most promising molecule in this setting of patients, with remarkable results even with prolonged treatments and a good tolerability profile.^{73,75}

Conclusions. POEMS syndrome is a rare disease, often unrecognized. Its etiology is uncertain, although VEGF appears a major contributor to the onset of many symptoms. Differential diagnosis and the rapid recognition of POEMS remain key issues since treatment should be started as early as possible to prevent the worsening of the clinical condition of patients.

In localized disease, RT is the treatment of choice. Lenalidomide may also be considered as initial short-term therapy (4-6 months) in young patients with POEMS syndrome eligible for high-dose therapy and HSCT, as well as in those patients whose clinical conditions could be exclusion criteria, in order to induce a rapid improvement and transform transplantation eligibility. In addition, lenalidomide might represent a suitable long-term therapy in patients who are not candidate for transplant, or who relapsed after high-dose systemic therapy.

Acknowledgments. Editorial assistance for the preparation of this manuscript was provided by Luca Giacomelli, Ph.D.; this assistance was supported by internal funds.

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