JAMA Oncology | Review

# Update on the Diagnosis and Treatment of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes) Syndrome
## A Review

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**IMPORTANCE** POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare plasma cell disorder characterized by demyelinating peripheral neuropathy and clonal plasma cell proliferation. Clinical manifestations are believed to be associated with a surge of inflammatory and angiogenic mediators, including interleukins and vascular endothelial growth factor (VEGF), elicited by clonal and polyclonal plasma cells. The clinical manifestations of POEMS syndrome can be debilitating; therefore, early diagnosis is essential. This review discusses several aspects of POEMS syndrome and includes the most recently published findings, with a special emphasis on diagnosis and treatment strategies.

**OBSERVATIONS** POEMS syndrome may be underdiagnosed because of its rarity, and it can be mistaken for chronic inflammatory demyelinating polyneuropathy; this misdiagnosis may lead to delayed therapy and progressive worsening of symptoms, especially neuropathy. Therefore, in addition to measurement of the VEGF level, patients with a monoclonal protein detected in blood and/or urine and neuropathy should be evaluated for POEMS syndrome with use of imaging to assess whether sclerotic bone lesions, effusions, and organomegaly are present. Clinical trials are scant, and treatment is largely based on small case series in which plasma cell–directed therapies, borrowed from the myeloma armamentarium, were used. High-dose melphalan and autologous hematopoietic cell transplantation may be offered to eligible patients. Lenalidomide and dexamethasone can be prescribed for patients who are ineligible for transplants. The main goals of therapy are to attain complete hematologic and VEGF responses and to reduce symptoms, although it may take up to 3 years for neurologic deficits to be ameliorated.

**CONCLUSIONS AND RELEVANCE** POEMS syndrome should be considered in the differential diagnosis for patients who have peripheral neuropathy and paraproteinemia among other multisystem manifestations. The syndrome can be debilitating if not recognized early in its course; thus, appropriate diagnosis and treatment are important for optimal clinical outcomes.

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POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome—also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takatsuki syndrome—is a rare systemic plasma cell disorder characterized by a constellation of symptoms and signs, chiefly peripheral neuropathy and the presence of a monoclonal protein. The diagnostic criteria are outlined in the **Box**.[1,2] Peripheral neuropathy and the presence of a monoclonal protein are mandatory criteria for diagnosis.[2] Therefore, in a patient with a monoclonal protein and peripheral neuropathy, a thorough investigation for POEMS syndrome should be undertaken. Most diagnoses of POEMS syndrome are made by neurologists and hematologists, and prevalence was reported to be 0.3 per 100 000 population in a Japanese study.[3] Many tests are required to confirm the diagnosis given the systemic nature of the disorder. The aim of therapy is to eradicate the plasma cell clone and provide supportive treatment for the clinical manifestations of the syndrome.

## Pathophysiology

The pathogenesis of POEMS is complex and thought to arise from a cytokine imbalance characterized by an excessive production of multiple proinflammatory and angiogenic cytokines (eg, interleukin 1β, interleukin 6, fibroblast growth factor, hepatocyte growth factor, and interleukin 12) and suppression of anti-inflammatory cyto-

kines, namely transforming growth factor β1, which is activated by a plasma cell clone.[4-7] Vascular endothelial growth factor (VEGF) is present abundantly in plasma cells (both clonal and polyclonal) of patients with POEMS syndrome.[8] It is hypothesized that some of the manifestations of POEMS syndrome are associated with VEGF-induced endothelial dysfunction, vascular wall hypertrophy, and ensuing tissue edema.[4] Vascular endothelial growth factor correlates with disease activity but does not appear to be the main cytokine that mediates the pathophysiology of the disease.[5,9,10] In addition, patients with POEMS syndrome have increased serum levels of matrix metalloproteinases 2 and 9, which are believed to engender the characteristic demyelinating neuropathy, along with elevated levels of tissue inhibitor of metalloproteinases, which correlates with overexpression of VEGF.[11] The interplay of multiple cytokines in addition to VEGF may be the basis for the limited efficacy of VEGF inhibitors.[6,12,13] In contrast to myeloma, the pathophysiology of POEMS syndrome is not marked by tumor burden but rather by a small plasma cell clone.[14] Most patients with POEMS syndrome have a λ-type monoclonal protein with restricted VJ region use by bone marrow plasma cells. This finding was supported by a recent study[15] that implemented sensitive high-throughput immunoglobulin repertoire RNA sequencing and showed that the majority of patients (83%) harbored a lambda light chain clone in their marrow. In addition, 2 specific light chain–variable regions (IgVL1-40 and IgVL1-44) were predominantly expressed by the clonal plasma cells. These findings may have diagnostic implications in uncertain cases. Kourelis et al[16] studied the immune tumor microenvironment in patients with POEMS syndrome using mass cytometry and found expansion of programmed cell death protein 1 (PD-1)–positive $CD4^+$ T cells, whereas naive $CD4^+$ T cells were decreased, indicating a chronic antigenic stimulation of $CD4^+$ T cells and their consequent exhaustion.[16] This finding suggests a potential role for PD-1/PD-L1 inhibitors in the treatment of POEMS syndrome.[17] Bone marrow plasma cell whole-exome and target-region sequencing in a cohort of 42 patients with POEMS syndrome identified recurrently mutated genes, including driver genes present in other plasma cell disorders (myeloma and immunoglobulin light chain amyloidosis).[18] The specific mechanism underlying the pathogenesis of POEMS syndrome remains to be fully elucidated and is under investigation.

**Box. POEMS Syndrome Diagnostic Criteria[a]**

**Mandatory**

Demyelinating polyneuropathy

Monoclonal plasma cell disorder

**Major**

Sclerotic bone lesions

Elevated VEGF[b]

Castleman disease

**Minor**

Extravascular volume overload[c]

Organomegaly[d]

Endocrinopathy[e]

Skin changes

Papilledema

Polycythemia and thrombocytosis

Abbreviations: POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; VEGF, vascular endothelial growth factor.

[a] Both mandatory criteria as well as 1 major criterion and 1 minor criterion are required for diagnosis.

[b] Typically plasma levels >200 pg/mL.[1]

[c] Peripheral edema, pleural effusions, and ascites.

[d] Hepatosplenomegaly, lymphadenopathy.

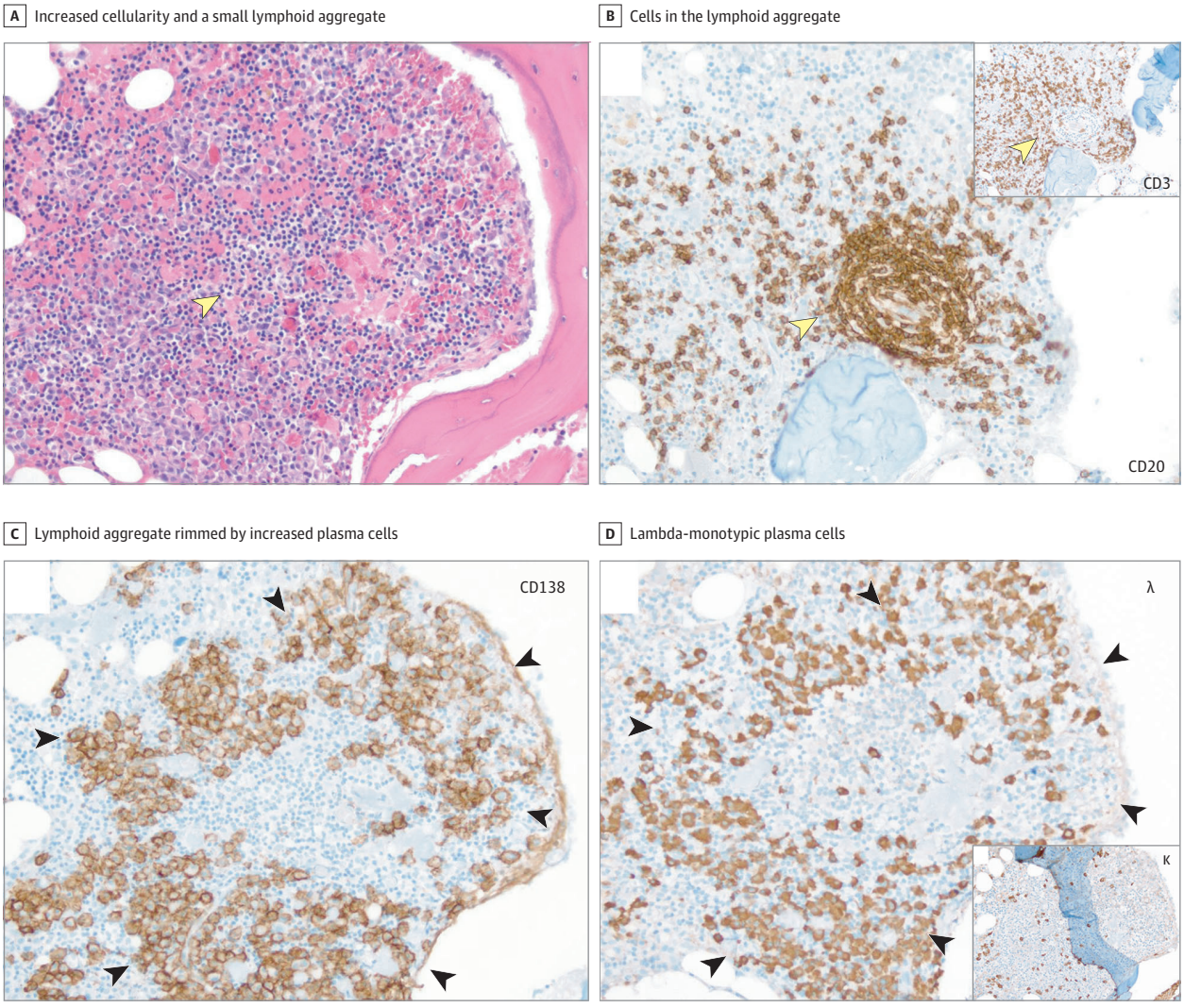
[e] Hypogonadism; adrenal, parathyroid, and pituitary dysfunction. Given the frequent occurrence of thyroid dysfunction and diabetes mellitus, these conditions alone are not diagnostic of POEMS syndrome.

## Clinical Presentation

Patients with POEMS syndrome often present with long-standing neuropathy that progressively worsens throughout the course of the disease. The peripheral neuropathy is length dependent and demyelinating, similar to and commonly misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP).[3,19] Axonal degeneration is more prominent in patients with POEMS syndrome than in those with CIDP and often favors the lower limbs.[3] The neuropathy in POEMS syndrome starts with sensory symptoms (paresthesia, with hyperesthesia being variably present) and evolves over time to produce remarkable motor symptoms, namely severe distal weakness in the hands and feet (foot drop), muscle atrophy, areflexia, and gait dysfunction.[3,20,21] Neuropathic pain and lower limb atrophy are more common in patients with POEMS syndrome than in those with CIDP, and cranial nerve involvement and dysautonomia are exceedingly rare.[3,19] The neuropathy in patients with POEMS syndrome featuring Castleman disease tends to be more sensory.[19] Given the similarity between the neuropathy in patients with CIDP and POEMS syndrome, all patients suspected of having CIDP should be assessed for POEMS syndrome to ensure an accurate diagnosis and proper treatment before further clinical decline occurs. Likewise, in patients with suspected CIDP who do not show improvement with classic CIDP treatment (plasma exchange, intravenous immunoglobulins), POEMS syndrome should be considered.

Early detection of POEMS syndrome is critical to mitigate the debility seen with neurologic progression. Sclerotic bone lesions are present in 95% of patients but do not typically cause bone pain unless they harbor a lytic component.[22,23] Endocrinopathies occurred in 84% of the patients in a large series, with hypogonadism being the most common.[24] Hypogonadism is mostly secondary and characterized by low total testosterone levels, gynecomastia, and irregular menses. Elevated prolactin levels have also been reported. Abnormal glucose metabolism and thyroid derangements are common; adrenal involvement and hypoparathyroidism are less common. Multiple endocrinopathies were found in 54% of patients in 1 study.[24] Endocrine dysfunction is thought to be functional in nature and associated with cytokine imbalances (elevated levels of interleukin 1β and tumor necrosis factor α and low levels of transforming growth factor β1).[7,24] Many dermatologic manifestations have been associated with

Figure 1. Bone Marrow Morphologic Features in POEMS Syndrome




A, Hematoxylin-eosin stain of a bone marrow trephine biopsy sample shows lymphoid aggregates and plasma cells, increased cellularity, and a small lymphoid aggregate (arrowhead) with a regressed, Castleman-like germinal center (original magnification ×100). B, Immunohistochemical stains show CD20+ B cells in the lymphoid aggregate (arrowheads), with fewer CD3+ T cells in the periphery (inset) (original magnification ×100). C, The lymphoid aggregate is rimmed by an increased number of plasma cells (arrowheads), highlighted by CD138 immunohistochemical stain (original magnification ×100). D, Kappa and lambda light chain immunohistochemical stain of plasma cells, which are lambda monotypic, with only a few kappa-positive plasma cells present (arrowheads and inset) (original magnification ×100). POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

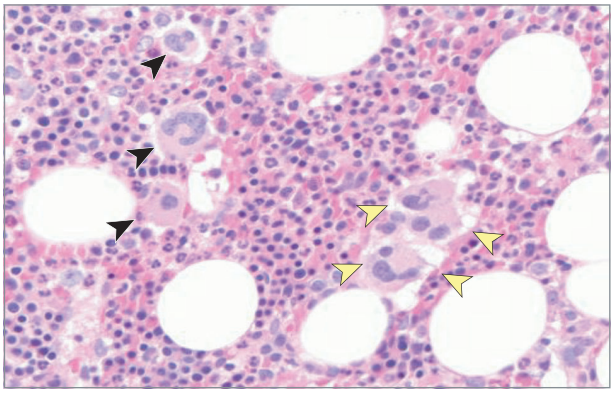
POEMS syndrome. In 1 study,[25] hyperpigmentation and hemangiomata were identified in almost half of the patients, followed by hypertrichosis, vascular skin changes (acrocyanosis and Raynaud phenomenon), and fingernail changes (white nails, clubbing). The study by Miest et al[25] revealed a positive correlation between skin findings and abnormal pulmonary function test results. Extravascular volume overload occurs in at least one-third of patients and manifests peripherally (most commonly) or in serous cavities (ascites, pleural effusions).[2] Papilledema is the most common ocular manifestation and occurs in at least one-third of patients.[26] Because papilledema can be asymptomatic, referral to an ophthalmologist is warranted for initial examination and follow-up.

## Diagnosis

### Diagnostic Criteria

The aforementioned characteristic peripheral neuropathy as well as evidence of a monoclonal plasma cell disorder are the main criteria for diagnosis of POEMS syndrome. A monoclonal protein (M-protein) is present in all patients with POEMS syndrome, but it is typically small, with a median size of 1 g/dL.[9] The lambda subtype is predominant (found in >95% of cases). Serum free light chains are abnormal in at least two-thirds of patients, although the light chain ratio tends to be normal in 80% of cases.[27,28] Distinctive bone mar-

Figure 2. Bone Marrow Megakaryocytic Changes in POEMS Syndrome



Hematoxylin-eosin stain of a bone marrow trephine biopsy specimen showing atypical megakaryocytes (black arrowheads) and megakaryocyte clustering (yellow arrowheads) (original magnification ×400). POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

row findings have been described and are shown in **Figure 1**. A plasma cell clone is detected on bone marrow biopsy for only two-thirds of patients. If a clone is present, the marrow plasma cell burden is often small (<5% in 50% of the patients), and lambda monotypic with concomitant polyclonal plasma cells are usually present. Lymphoid aggregates, often with Castleman-like features such as regressed germinal centers, have been described. These aggregates show rimming by plasma cells in approximately 50% of the biopsy specimens, which seems to be a distinctive feature of POEMS syndrome that is not appreciated in other plasma cell disorders.[29] Megakaryocytic changes in the form of clustering and hyperplasia may be present, which is consistent with the thrombocytosis seen peripherally in POEMS syndrome as shown in **Figure 2**.[29] Sclerotic lesions are almost universal, and lytic lesions mixed with sclerotic rims can also be appreciated. Low-dose whole-body computed tomography (CT) is helpful in detecting these lesions as well as organomegaly (typically affecting the liver, spleen, and/or lymph nodes). Fluorodeoxyglucose avidity is typically found in lesions harboring a lytic component. Lymph node changes consistent with Castleman disease have been reported in up to 30% of patients with POEMS syndrome.[30] However, the Castleman disease variant of POEMS syndrome connotes the absence of a plasma cell clone and is considered a separate entity with different treatment considerations.

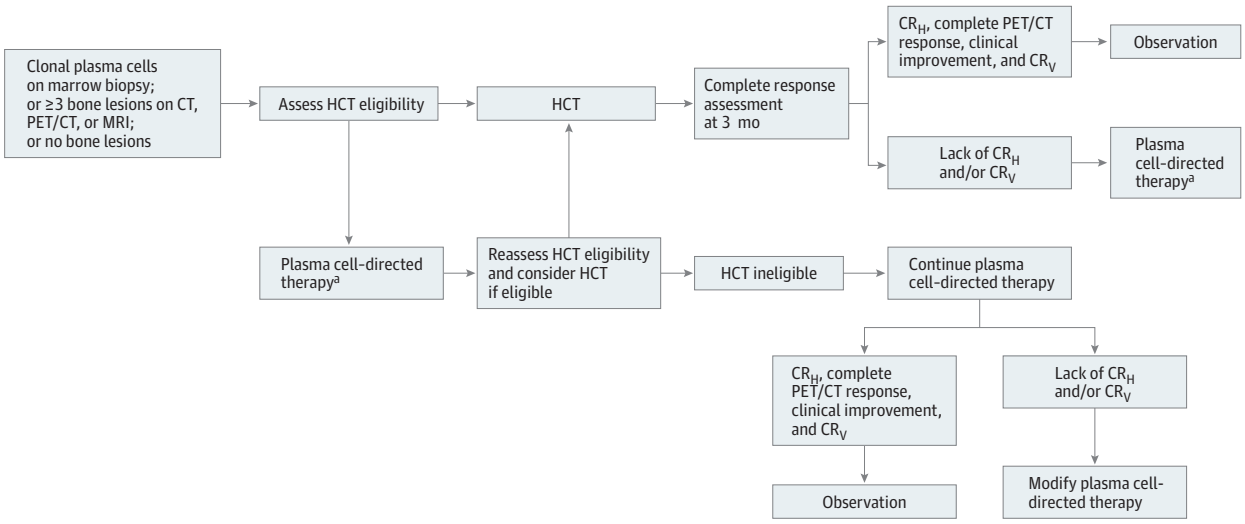
Both serum and plasma VEGF levels may be helpful in supporting the diagnosis of POEMS syndrome and monitoring patients' responses to therapy because VEGF is thought to reflect the activity of the disease. Both serum and plasma levels of VEGF have been used to diagnose and monitor patients; however, serial measurements of VEGF level should be performed consistently in either plasma or serum samples. Serum levels are thought to be higher than plasma levels given the additional amounts of VEGF that leak from platelets during serum manipulation.[31] In 1 study, a plasma VEGF level higher than 200 pg/mL was found to be 68% sensitive and 95% specific for the diagnosis of POEMS syndrome, helping to differentiate it from other plasma cell disorders.[1] Other diseases that have been associated with elevated VEGF levels include those associated with hypoxemic states (eg, chronic obstructive pulmonary disease, sleep apnea), cancers, and vasculitis. These outcomes highlight the importance of interpreting VEGF results in the appropriate clinical context.[32]

POEMS syndrome is a hypercoagulable syndrome, with arterial and venous thromboses reported in up to 30% of patients, and is likely associated with elevated levels of multiple procoagulants such as fibrinogen, fibrinopeptide A, and thrombin-antithrombin complexes.[33] Other factors that contribute to the high thrombotic risk include immobility associated with neuropathy, immunomodulatory drug use, and indwelling catheters used during hematopoietic cell transplant. Myocardial infarction, acute limb ischemia, and cerebrovascular accidents have been reported.[34] A recent registry study[33] reported a preponderance of arterial thromboses, with most thrombotic events occurring when the disease is active (which correlates with an elevated VEGF level), typically before the institution of therapy. The authors suggested the implementation of prophylactic low–molecular-weight heparin and an antiplatelet agent for all patients at the time of diagnosis, which may be curtailed during the course of the disease depending on VEGF levels and remission status.[35] Pulmonary hypertension is thought to occur in at least one-quarter of patients and is the result of chronic vascular wall inflammation and stiffening.[35] A study[36] examining the echocardiographic findings in a small cohort of 27 patients with POEMS syndrome identified subclinical systolic and diastolic dysfunction of the left and right ventricles. The authors attributed the finding to microvascular changes and pulmonary factors, mostly pulmonary hypertension. Polycythemia and thrombocytosis are commonly seen in patients with POEMS syndrome, reflecting the associated myeloproliferation, which is typically seen on microscopic examination of a bone marrow specimen.

## Differential Diagnosis

The differential diagnosis includes other plasma cell and neurologic disorders (mainly CIDP). Cardiac involvement is common in patients with immunoglobulin light chain amyloidosis; however, it is not a prominent feature of POEMS syndrome even though cardiac abnormalities have been described on echocardiography. Hepatomegaly is seen in patients with immunoglobulin light chain amyloidosis and in those with POEMS syndrome, although it is caused by different pathophysiologic mechanisms in these conditions. Although alkaline phosphatase is commonly elevated in patients with hepatic immunoglobulin light chain amyloidosis and transaminitis is often present owing to congestive hepatopathy from advanced heart failure, liver function abnormalities are not typically found in patients with POEMS syndrome early in the disease course. They may occur with worsening pulmonary hypertension and congestive hepatopathy from right heart failure. Kidney involvement with nephrotic range proteinuria is the hallmark of amyloid nephropathy, but patients with POEMS syndrome rarely have kidney dysfunction. One of the distinctive features of the neuropathy associated with immunoglobulin light chain amyloidosis is its sensory nature, which may be accompanied by autonomic features (orthostasis, bowel and bladder dysfunction). Multiple aspects of POEMS syndrome help differentiate it from myeloma because the latter is driven by proliferative plasma cells as opposed to the chronic inflammatory cascade from a small plasma cell clone that is responsible for POEMS syndrome. Myeloma and POEMS syndrome are generally characterized by painful lytic lesions and painless osteosclerotic lesions (except when they harbor a lytic component), respectively.

Figure 3. Approach to Management of POEMS Syndrome




$CR_H$ indicates complete hematologic response; $CR_V$, complete VEGF response; CT, computed tomography; HCT, hematopoietic cell transplant; MRI, magnetic resonance imaging; PET, positron emission tomography; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

[a] Multiple options as in myeloma treatment: lenalidomide-dexamethasone and daratumumab-based therapy. Use of bortezomib and thalidomide is avoided given the risk of neuropathy.

### Diagnostic Workup

An investigation for POEMS syndrome should be undertaken for any patient presenting with demyelinating neuropathy, especially when it is accompanied by fluid overload, thrombocytosis, polycythemia, and ocular symptoms (blurred vision, ocular pain). Because of the multisystem nature of this disorder, a thorough workup is required to make the diagnosis, and it should include neurophysiologic studies, paraprotein testing, radiographic assessment, fundoscopy, and endocrine and cardiopulmonary evaluation. Electromyography and nerve conduction studies are required to characterize the neuropathy. Different bone imaging modalities have not been compared in the workup for POEMS syndrome, although in general, skeletal surveys are often not sensitive enough to detect small osteosclerotic bone lesions. Computed tomography, magnetic resonance imaging, and positron emission tomography (PET)/CT are acceptable methods of imaging the skeleton. Furthermore, whole-body CT allows for detection of organomegaly, ascites, and pleural effusions in addition to detecting more bone lesions than plain radiography.[9] PET/CT can assist in the detection of potentially fluorodeoxyglucose-avid bone lesions, which are typically lytic on CT, as well lymphadenopathy and can be useful for follow-up after radiation therapy.[9,37] Comprehensive paraprotein testing (consisting of serum and urine protein electrophoresis and immunofixation, respectively) and serum free light chain measurements are required. Elevated VEGF levels, whether in serum or plasma samples, are manifestations of POEMS syndrome and are important in tracking disease activity. Papilledema should be assessed by fundoscopic examination.[26] Screening for hypogonadism (testosterone, estradiol), diabetes, and hypothyroidism is advised at the time of diagnosis owing to the potential for subclinical endocrine dysfunction, which would warrant future follow-up and therapy.

## Treatment

The treatment of POEMS syndrome depends on the eradication of the culprit plasma cell clone. Given the scarcity of prospective studies because of the low prevalence of this disease, therapeutic approaches are mostly based on retrospective studies using anti–plasma cell agents typically used in the treatment of myeloma. The treatment approach depends on the presence of marrow plasma cell infiltration and the number of bone lesions seen on imaging studies (**Figure 3**).[2,9,38] In patients with 1 to 3 bone lesions and no clonal plasma cells detected by bone marrow biopsy, radiation therapy is preferred given the excellent clinical responses and long-term disease-free survival. In 1 study, 91 of 291 patients received radiation therapy and achieved a 6-year progression-free survival of 62% and a 10-year overall survival of 70%.[39,40] The median radiation dose is 45 Gy (range, 35-54 Gy).[41,42] Relief of symptoms is slow and occurs over several months, with neuropathy being the symptom requiring the most time for resolution. Patients with POEMS syndrome who have more than 3 bone lesions or marrow involvement by clonal plasma cells should receive systemic therapy. High-dose melphalan (140-200 mg/m$^2$) followed by autologous hematopoietic cell transplant (HCT) has been shown to be 1 of the most effective available therapies for eligible patients (**Table**).[39,43-49] In a large series of 59 patients with POEMS syndrome who underwent HCT, most of whom received melphalan at a dose of 200 mg/m$^2$,more than 90% responded, with overall survival of 94% and 5-year progression-free survival of 25%.[43] After HCT, VEGF levels and fluid overload improved more quickly (within 3 months) than neurologic response, which took up to 3 years to improve.

Radiologic and hematologic responses were seen by the end of the first year of treatment. Disease progression was associated with

Table. HCT Outcomes in the Largest Published POEMS Syndrome Cohorts

| Variable | Mayo Clinic study[43] | Japan study[44] | UCLH (UK) study[45] | European Society for Blood and Marrow Transplantation study[46] |
|---|---|---|---|---|
| Patients, No. | 59 | 95 | 42 | 127 |
| Study years | 1999-2011 | 2000-2011 | 1998-2018 | 1997-2010 |
| Patients who received first-line treatment, % | 42 | 14.3 | 97.6 | 12.6 |
| Time from diagnosis to HCT, median | 4.9 mo | 210 d | 5.5 mo | 7.5 mo (HCT 12 mo after diagnosis in 32%) |
| Most common mobilization regimen(s) | G-CSF alone | C+G and etoposide +G-CSF | C+G and G-CSF alone | Cyclophosphamide based and noncyclophosphamide based |
| Conditioning regimen | HDM (58 patients) | HDM (94 patients) | HDM (all patients) | HDM (123 patients) |
| Time to neutrophil engraftment, median, d | 15 | Not reported | 12 | 13 |
| ES, % | 37 | 15.7 | 7.1 | 23 |
| $CR_H$, % | 57 | 38.8 | 33.3 | 48.5 |
| $CR_V$, % | 48 | 28.6 (4 of 14 patients) | 63.9 | Not reported |
| Clinical response, % | 92 | Most (based on ECOG-PS, Karnofsky PS and ONLS)[a] | 91 | Most had symptom improvement |
| PFS, % | 98 at 1 y; 75 at 5 y | 78.3 at 3 y | 81.6 at 1 y; 76.9 at 5 y | 84 at 3 y; 74 at 5 y |
| TRM, % | 0 | 1 Patient before engraftment | 2.4 | 2.4 |
| OS, % | 94 at 5 y | 88.8 at 5 y | 95.4 at 1 y; 89.5 at 5 y | 94 at 3 y; 89 at 5 y |
| Myelodysplastic syndrome, No. | 2 | 1 | 1 | 2 |

Abbreviations: C+G, cyclophosphamide; $CR_H$, complete hematologic response; $CR_V$, complete VEGF response; ECOG-PS, Eastern Cooperative Oncology Group performance status; ES, engraftment syndrome; G-CSF, granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant; HDM, high-dose melphalan; OS, overall survival; PFS, progression-free survival; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; PS, performance status; TRM, transplant-related mortality; UCLH, University College London Hospitals.

[a] ECOG-PS: 0 to 1 rate increased from 20.0% to 71.6% after HCT. Karnofsky PS: 70% to 100% rate increased from 37.0% to 79.8% after HCT.

lack of complete hematologic response, IgG lambda monoclonal protein, age younger than 50 years, and presence of fluorodeoxyglucose-avid lesions on PET/CT.[43] Similarly, another cohort of patients with POEMS syndrome who underwent transplantation demonstrated the correlation between lack of complete hematologic response and disease progression.[46] The increased use of HCT in the treatment of POEMS syndrome may be associated with the improved survival seen in patients with POEMS syndrome diagnosed after 2003.[39] Many studies of HCT among patients with POEMS syndrome revealed a high rate of transplant-associated complications but a low transplant-associated mortality rate.[39,43,45,46,48] Engraftment syndrome was noted in 37% of the patients and was treated successfully with corticosteroids.[43] Fever was the most common symptom (93% of patients), followed by diarrhea, weight gain, and rash.[48] Neutrophil engraftment may be delayed (median of 16 days), with symptoms of engraftment syndrome occurring beforehand.[48] The presence of splenomegaly and lymphadenopathy was associated with a greater risk of engraftment syndrome and HCT-associated complications. Occurrence of engraftment syndrome may result from a worsening of the deranged cytokine environment caused by marrow reconstitution in these patients.[48] The early institution of corticosteroid therapy was instrumental in improving patient outcomes.[48] Use of immunomodulatory drugs or a short course of dexamethasone before hematopoietic progenitor cell collection has been reported to prevent engraftment syndrome and transplant-associated complications and supports the use of induction therapy before HCT.[9,45,50] Hematopoietic progenitor cell mobilization in patients with POEMS syndrome was studied in an Italian cohort of 25 patients[51] and a Japanese cohort of 37 patients.[52] The authors of these studies found no difference in $CD34^+$ cell yield between granulocyte colony-stimulating factor (G-CSF) and cyclophosphamide plus G-CSF.[51,52] Plerixafor was used successfully in 3 patients who had a peripheral $CD34^+$ cell count of less than 20 cells/μL in the Italian cohort.[52] The aforementioned Mayo Clinic cohort was mostly mobilized with G-CSF alone.[43]

For patients who are not candidates for high-dose therapy, immunomodulatory drugs, alkylating agents, daratumumab, and bortezomib have been used. Immunomodulatory drugs are particularly attractive for treatment of POEMS syndrome given their anti-VEGF effects. Lenalidomide is used more frequently in the treatment of POEMS syndrome than its predecessor thalidomide given the lower risk of associated neuropathy, and it yields rapid neurologic responses. Multiple groups have reported their experience with lenalidomide in prospective and retrospective studies,[53-57] and a meta-analysis was published in 2014. In a phase 2 study,[57] 12 cycles of lenalidomide with dexamethasone were given, with hematologic complete responses observed in almost half of the patients and VEGF and neurologic responses occurring in more than 80% and more than 90%, respectively. Three-year progression-free survival and overall survival were 75% and 90%, respectively. A meta-analysis[56] of 51 patients who received lenalidomide as first-line initial treatment or treatment for a relapse showed VEGF and neurologic responses in almost all patients. An ongoing French phase 2 trial[9] has been examining treatment of patients with newly diagnosed POEMS syndrome and those experiencing relapse with lenalidomide and dexamethasone for 2 cycles in 1 arm, followed by either radiotherapy or HCT as opposed to 9 cycles of lenalidomide and dexamethasone followed by 1 year of lenalidomide alone. Rapid

hematologic and neurologic responses were noted after 2 cycles of treatment.

Bortezomib also has anti-VEGF effects and has been shown to be effective in combination with dexamethasone and cyclophosphamide-dexamethasone, leading to marked improvement in neuropathy as well as high VEGF and hematologic response rates.[58,59] The oral proteasome inhibitor ixazomib is being tested in an ongoing pilot study[60] in combination with lenalidomide and dexamethasone in patients with a new diagnosis or relapse of POEMS syndrome. To date, eleven patients have been analyzed; benefit in terms of VEGF normalization was noted at 3 months (primary end point), and clinical response was noted at a median follow-up of 16 months. Three patients had progressive disease, and 2 of these patients died. Five of 11 patients experienced worsening of their neuropathy. A large retrospective series[61] analyzed the outcomes of 347 patients with POEMS syndrome who received 3 different first-line therapies: HCT, melphalan and dexamethasone, and lenalidomide and dexamethasone. HCT was associated with the highest hematologic and VEGF response rates. Progression-free survival was significantly longer with HCT than with lenalidomide and dexamethasone (87.6% vs 64.9%; $P = .003$), although most patients who underwent HCT had lower-risk disease.

The anti-CD38 monoclonal antibody daratumumab has been used in 3 patients with POEMS syndrome in combination with lenalidomide and dexamethasone.[62,63] One patient received the combination as treatment for a relapse after having undergone HCT, and the other 2 received it as first-line treatment. All patients had remarkable hematologic, VEGF, and neurologic responses. A prospective trial of daratumumab in patients with a new diagnosis or relapse of POEMS syndrome is actively recruiting.[64]

The anti-VEGF monoclonal antibody bevacizumab has not shown a consistent therapeutic effect in patients with POEMS syndrome and may be toxic in this patient population given an observed increase in number of early deaths after its administration.[65,66] We advise against the use of bevacizumab. Plasma exchange has consistently been considered ineffective in the treatment of POEMS syndrome as outlined in the American Society of Apheresis guidelines.[67] Given the associated prothrombotic state, we recommend, at a minimum, prophylactic administration of low-molecular-weight heparin for all patients with active disease.

## Conclusions

POEMS syndrome is a rare systemic plasma cell disorder with myriad clinical manifestations, most prominently peripheral neuropathy. Evaluation for POEMS syndrome is required for any patient with demyelinating neuropathy and presence of an M-protein. Treatment is extrapolated from that used for multiple myeloma and consists of plasma cell–directed therapy or radiation therapy depending on the extent of clonal plasma cell disease. Understanding of the biology of POEMS is advancing and may pave the way for future therapies.

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*Administrative, technical, or material support:* Nakashima.
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