

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Long-Term Outcomes After Autologous Stem Cell Transplantation in Patients With POEMS Syndrome



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### **H&O** What are the components of POEMS syndrome?

**AD** POEMS stands for **p**olyradiculoneuropathy, **o**rgano-megaly, **e**ndocrinopathy, **m**onoclonal plasma cell disorder, and **s**kin changes. The other features that are important but that are not included in the acronym are **p**apilledema, **e**xtravascular volume overload, **s**clerotic bone lesions, and **t**hrombocytosis (PEST). The disease relates to, but is not necessarily caused by, increased levels in vascular endothelial growth factor (VEGF).

Peripheral neuropathy is typically the most dominant feature of the syndrome. Other symptoms that are notable for patients include anasarca (extravascular volume overload) and endocrine changes, which can range from erectile dysfunction to adrenal insufficiency to hypoparathyroidism. The diagnostic criteria are listed in Table 1.

### **H&O** How common is POEMS syndrome, and are there any risk factors?

**AD** The syndrome is very rare. In one series, the prevalence was 3 per 1 million people. Although POEMS syndrome was thought to be more common in people of Japanese descent, that racial predilection is now less clear. The median age of a POEMS patient is approximately 50 years. The youngest patients are in their 20s.

### **H&O** What is the associated morbidity and mortality for patients with POEMS syndrome?

**AD** The morbidity is significant. Patients can have profound peripheral neuropathy characterized by paresis or paralysis,

loss of sensation, and/or pain starting in the feet (and later appearing in the hands), which moves proximally, leaving patients in wheelchairs. Some patients have such severe fluid retention that they need paracentesis to keep the fluid down. Patients can have severe fatigue related to endocrine abnormalities, medications used to treat their neuropathy, or pulmonary hypertension or impaired pulmonary function.

Left unchecked, the disease is progressive and fatal. With treatment, the prognosis is excellent, with median survival historically being about 4 times better than that seen in multiple myeloma.

### **H&O** Has chemotherapy been successful in patients with POEMS syndrome?

**AD** The chemotherapeutic drugs that appear to work the best so far are the same drugs that help patients with multiple myeloma: alkylators, immunomodulatory drugs (IMiDs; such as lenalidomide [Revlimid, Celgene] and thalidomide [Thalomid, Celgene]), and bortezomib (Velcade, Millennium Pharmaceuticals). Given how rare the disease is, however, there are limited data on the use of these drugs. Use of the anti-VEGF antibody bevacizumab (Avastin, Genentech) has been disappointing.

### **H&O** How has autologous stem cell transplantation (ASCT) been used in these patients?

**AD** ASCT is merely the application of a high-dose alkylator. It is one of my favorite treatments for these patients since they receive high-intensity therapy at one time, stopping the process of deterioration. The other advantage of ASCT is that patients with POEMS can be hard to follow,

**Table 1.** Criteria for the Diagnosis of POEMS Syndrome\*

		Affected (%) <sup>†</sup>
<b>Mandatory Major Criteria</b> (both required)	1. Polyradiculoneuropathy (typically demyelinating)	100
	2. Monoclonal plasma cell disorder (almost always I)	100 <sup>‡</sup>
<b>Other Major Criteria</b> (1 required)	3. Castleman disease <sup>§</sup>	11–25
	4. Sclerotic bone lesions	27–97
	5. Vascular endothelial growth factor elevation	
<b>Minor Criteria</b> (1 required)	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)	45–85
	7. Extravascular volume overload (edema, pleural effusion, or ascites)	29–87
	8. Endocrinopathy (adrenal, thyroid, <sup>¶</sup> pituitary, gonadal, parathyroid, or pancreatic <sup>‡</sup> )	67–84
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, or white nails)	68–89
	10. Papilledema	29–64
	11. Thrombocytosis/polycythemia <sup>#</sup>	54–88
<b>Other Symptoms and Signs</b>	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, or low vitamin B <sub>12</sub> values	

\*The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, 1 of the 3 other major criteria, and 1 of the 6 minor criteria are present.

<sup>†</sup>Summary of frequencies of POEMS syndrome features based on the largest retrospective series.

<sup>‡</sup>Takatsuki and Nakanishi series are included even though only 75% of patients had a documented plasma cell disorder. Since these are among the earliest series describing the syndrome, they are included.

<sup>§</sup>There is a Castleman disease variant of POEMS syndrome that occurs *without* evidence of a clonal plasma cell disorder that is not accounted for in this table. This entity should be considered separately.

||A plasma VEGF level of 200 pg/mL has 95% specificity and 68% sensitivity for a diagnosis of POEMS syndrome.

<sup>¶</sup>Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

<sup>#</sup>Approximately 50% of patients will have bone marrow changes that distinguish it from a typical monoclonal gammopathy of unknown significance or myeloma bone marrow.

POEMS=polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes; VEGF=vascular endothelial growth factor.

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that is, they have tiny monoclonal proteins, there can be fluctuation in VEGF levels that are not 100% correlated with disease, and the neuropathy is very slow to improve. Doctors who treat these patients may not realize that there is a lag between administration of successful treatment and improvement in the peripheral neuropathy—as long as 6–36 months. Mistakenly, physicians may rapidly switch from chemotherapy regimen to chemotherapy regimen at times when an adjustment is not needed. That method may be appropriate in multiple myeloma—if the M protein does not change, one switches regimens. This principle does not hold as true in patients with POEMS syndrome. The nice thing about transplant is that every patient we have treated has had a response. Moreover, the timing of even considering the move to “the next therapy” would not occur until 100 days after transplant since this is the typical time point for post-transplant evaluation for most diseases.

### H&O What were the findings in your recent study of ASCT in POEMS?

**AD** We reported on the long-term outcomes of patients with POEMS who receive ASCT, with an

emphasis on progressive disease, timing of progression, types of progression, risk factors for progression, and therapies that may or may not have worked at progression. With a median follow-up of 45 months, the progression-free survival was 98%, 94%, and 75% at 1, 2, and 5 years, respectively. The 5-year survival was 94%. Factors associated with progression included an immunoglobulin G-lambda monoclonal component (hazard ratio [HR], 7.5; 95% confidence interval [CI], 2.3–28.3;  $P=.0008$ ), fluorodeoxyglucose (FDG)-avid lesions on baseline positron emission tomography (HR, 6.4; 95% CI, 1.2–120;  $P=.03$ ), lack of complete hematologic response (HR, 5.4; 95% CI, 1.8–16.7;  $P=.003$ ), and age of 50 years or younger at transplant (HR, 4.4; 95% CI, 1.3–20;  $P=.01$ ). The most common progression events were radiologic, followed by rising levels of VEGF. Progression of symptoms was rare. It was possible to salvage most patients with IMiDs or radiation. We also described a system of monitoring response and progression among patients with POEMS after ASCT that focuses on plasma VEGF, serum monoclonal protein, FDG avidity on positron emission tomography scan, and clinical responses.

### H&O Did the study confirm expectations?

**AD** Since I have personally cared for the majority of these patients, the 5-year PFS of 75% felt about right, but it was nice to have an actual number placed on the outcome. The fact that “symptomatic” progression was rare speaks to the importance of following these patients carefully to prevent clinical deterioration. The finding that those patients with FDG-avid lesions were most likely to progress makes the concept of adjuvant radiation at a year more appealing.

### H&O Does the study raise any additional questions?

**AD** It raises several questions, including whether patients with POEMS should receive maintenance therapy. I think these data would suggest not since the majority have been doing so well for so long. Other questions include whether patients with FDG-avid lesions 1-year post-ASCT should receive radiation, and whether patients who have not achieved a complete response should receive additional therapy.

### H&O Are there any other areas of ongoing research in POEMS?

**AD** The mechanism of POEMS syndrome is by far the most interesting question. What is driving this disease?

Why do virtually all of these patients have a lambda clone, and, more specifically, a lambda clone that uses the *IGLV 1-40* or *IGLV 1-44* genes? What is the significance of the sclerotic bone lesions? POEMS syndrome is a fascinating disease, which is fortunately treatable. The key is early diagnosis because the more advanced the neuropathy at presentation, the more residual neuropathy for the patient, which reduces quality of life.

### Suggested Readings

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