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Update on the POEMS syndrome

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Abstract

POEMS syndrome is an acronym for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. It is a rare paraneoplastic disorder related to plasma cell neoplasm. However, its pathophysiology has not yet been clearly elucidated. The production of pro-inflammatory cytokines is thought to play an important role in the pathogenesis of POEMS syndrome. Vascular endothelial growth factor level reflects disease activity, which is helpful for the diagnosis and evaluation of treatment response. Conventional agents such as corticosteroids and melphalan are effective and safe combination regimens. Autologous hematopoietic stem cell transplantation is another option for high-risk transplant-eligible patients. Radiotherapy is effective in patients with localized lesions. The anti-myeloma agents lenalidomide, thalidomide, and bortezomib have shown good treatment outcomes for POEMS syndrome; however, large-scale studies with long-term follow-up are required. Early identification and active treatment can improve the outcomes of POEMS syndrome patients.

Key Words POEMS syndrome, Polyneuropathy, Transplantation, Vascular endothelial growth factor

INTRODUCTION

POEMS syndrome is an acronym for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin change syndrome. As the name "syndrome" suggests, it is a disease that is not confirmed by a single biopsy or blood test but is diagnosed by identifying a collection of symptoms. Although ambiguous, it is not difficult to understand the disease once a physician encounters a patient with typical presentation. It is a rare disease with an incidence of approximately 3 in 100,000, with male predominance [1]. Early diagnosis and active treatment can produce good results; however, the symptoms worsen, and the prognosis is poor without a quick and accurate diagnosis. Moreover, it is important for not only hematologists, but also neurologists, endocrinologists, and dermatologists, who may encounter these symptoms for the first time, to understand this disease. Herein, I review the diagnosis and treatment of POEMS syndrome in the context of the Korean medical system.

DIAGNOSIS

There is no single diagnostic test for POEMS syndrome; a diagnosis is made if a collection of symptoms meets certain diagnostic criteria (Table 1). The diagnosis must meet two mandatory major criteria, one of three other major criteria, and one of six minor criteria [2, 3]. The major mandatory criteria are demyelinating polyneuropathy and monoclonal plasma cell proliferative disorders. Demyelinating polyneuropathy may be unfamiliar outside neurology; patients typically complain of difficulty walking as they lose strength in their lower extremities and quickly become unable to walk because of weakness or pain [4]. Therefore, POEMS syndrome should be suspected in patients with chronic inflammatory demyelinating polyneuropathy who do not respond to the treatment. A study showed that vascular endothelial growth factor (VEGF) testing for all patients with acquired demyelinating neuropathy prevented delays in diagnosis and improved patient prognosis compared with testing only those patients who have failed treatment [5]. The monoclonal protein test as a screening tool is an easily accessible test in the clinic, although some patients do not show M protein despite repeated examinations.

Another major criteria is monoclonal plasma cell disorder. All tests to differentiate multiple myeloma should be performed because myeloma-directed therapy is required in active myeloma cases. In 91% of cases, the monoclonal protein is lambda, but there are cases reported as kappa type [6].

Table 1. Diagnostic criteria.

Mandatory major criteria	Polyneuropathy Monoclonal plasma cell proliferative disorder (almost always λ)
Any one of the following three other major criteria:	Sclerotic bone lesions Castleman's disease Elevated levels of VEGF
Any one of the following six minor criteria:	Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, or ascites) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, white nails) Papilledema Thrombocytosis/polycythemia

Bone marrow findings of POEMS syndrome show few monoclonal plasma cells, but, they are rimmed by plasma cells in most cases. Megakaryocyte hyperplasia and clusters were frequently observed [6].

VEGF is a cytokine produced by plasma cells that increases vascular permeability and causes capillary leak syndrome, leading to pleural effusion, ascites, and peripheral edema [7]. In addition, increased vascular permeability causes optic disc swelling and papilledema [8]. VEGF testing is useful for diagnosing and evaluating treatment response [5]. Although still debatable, a cut-off limit of 200 pg/mL VEGF has a sensitivity of 68% and specificity of 95%, whereas a cut-off of 1,920 pg/mL gives a sensitivity of 73.3% and a specificity of 97.6% [9, 10].

Osteosclerotic bone lesions are present in 95% of patients and can be detected using standard-or low-dose computed tomography (CT). Whole-body CT is helpful to evaluate the extent of organomegaly or fluid overload [11]. ^{18}Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET-CT) is another useful tool for the diagnosis, evaluation, and follow-up of patients with POEMS syndrome because it can provide information on bone lesions, organ involvement, effusion, and the metabolic status of the lesions [12].

To define endocrinopathy, diabetes and thyroid disease alone are insufficient because they are quite common; hence, other endocrine abnormalities should be evaluated. Tests for hypogonadism, abnormal adrenal function, and calcium metabolism are also required.

More than 90% of patients have cutaneous manifestations. Skin changes include hyperpigmentation, hemangioma, skin thickening, and hypertrichosis [13]. Abnormal cutaneous manifestations are associated with pulmonary function tests [13]. To diagnose these skin findings, a whole-body skin examination should be performed.

Thrombocytosis and polycythemia were included in the minor criteria; however, anemia and thrombocytopenia could be associated with Castleman disease.

In addition, pulmonary symptoms, central nervous system involvement, and renal dysfunction were also observed.

Because the criteria are so complex, a Japanese group suggested new criteria with polyneuropathy, monoclonal gammopathy, and VEGF elevation as major criteria and extravascular volume overload, skin changes, organomegaly, and sclerotic bone lesions as minor criteria [14].

PATHOGENESIS

The pathophysiology of the POEMS syndrome is not yet fully understood. Pro-inflammatory cytokines, such as VEGF, interleukin (IL)-1β, and IL-6, produced by plasma cells could play a critical role in the pathogenesis of the disease [7]. Recently, genetic analysis was performed to elucidate the mechanism of POEMS syndrome. The study found 308 somatic mutations in 285 genes using whole-exome sequencing, while target sequencing identified 20 mutations in seven recurrently mutated genes: *KLHL6, LTB, EHD1, EML4, HELPHL1, HIPK1,* and *PCDH10.* None of the driver gene mutations found in myeloma driver genes were detected. RNA sequencing showed a transcription profile specific to POEMS syndrome, different from the monoclonal gammopathy of undetermined significance and multiple myeloma [15]. In contrast, Chen *et al.* [16] revealed 11 genes related to light chain amyloidosis and multiple myeloma (*BIRC3, LRP1B, KDM6A,* and *ATM*) using target sequencing. This study suggests possible similarities in mutational profiles between POEMS syndrome and myeloma or amyloidosis, although there is high heterogeneity of the mutational spectrum in POEMS [16]. Currently, no genetic markers can predict survival.

RESPONSE CRITERIA

The response is complicated because it is evaluated for each affected organ. Therefore, the definitions were slightly different for each study, but the most frequently used responses in the studies were as follows (Table 2):

1) Hematologic response: Hematologic response is assessed by electrophoresis and immunofixation, as in multiple myeloma. Complete response (CR) was defined as <5% plasma cells in bone marrow aspirates and negative serum and urine immunofixation. A very good partial response (VGPR) is over 90% reduction in M-protein, plus urine M-protein

Table 2. Response criteria.

Hematologic response	CR: negative bone marrow and negative immunofixation of serum and urine VGPR: over 90% reduction in M-protein, plus urine M-protein level of <100 mg per 24-h PR: 50% reduction in M-protein or positive immunofixation as long as the baseline M protein is at least 1.0 g/dL
PET responses	CR: the disappearance of all FDG uptake lesions PR: ≥50% improvement in the sum of the maximum standardized uptake value of FDG-avid lesions No response: the failure to meet CR or PR criteria
VEGF response (evaluable: ×2 UNL)	CR: normalization of VEGF PR: a decrease of over 50% VEGF No response: the failure to meet CR or PR criteria Progression: 50% increase from the lowest level
Clinical response (clinical improvement, clinical progression, mixed clinical response, and clinical stability)	Peripheral neuropathy, organomegaly, papilledema, erythrocytosis/thrombocytosis, endocrinopathy, extravascular fluid overload (ascites, effusions, edema) Pulmonary function tests

Abbreviations: CR, complete response; PR, partial response; UNL, upper normal limit; VGPR,very good partial response.

level of <100 mg per 24-h. PR is defined as a 50% reduction in M-protein or positive immunofixation as long as the baseline M protein is at least 1.0 g/dL [17].

2) PET response: CR was defined as the disappearance of all FDG uptake lesions. A PR was defined as ≥50% improvement in the sum of the maximum standardized uptake value of FDG-avid lesions. No response was defined as failure to meet the CR or PR criteria.

3) VEGF response: VEGF normalization was defined as CR. PR was defined as a decrease of >50% VEGF. No response was defined as failure to meet the CR or PR criteria.

4) Clinical response: The clinical response is divided into four categories: clinical improvement, clinical progression, mixed clinical response, and clinical stability. The parameters included peripheral neuropathy, organomegaly, papilledema, erythrocytosis, thrombocytosis, endocrinopathy, extravascular fluid overload (ascites, effusions, and edema), and abnormal pulmonary function tests.

Organomegaly [lymphadenopathy, splenomegaly, hepatomegaly, and extravascular fluid overload (edema, ascites, pericardial effusion, and pleural effusion)] was assessed by CT or sonography.

RISK STRATIFICATION

Wang *et al.* [18] evaluated the risk of POEMS syndrome in patients aged >50 years, and pulmonary hypertension, pleural effusion, and an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 were associated with inferior overall survival (OS). The Mayo Clinic analyzed the treatment outcomes of 262 patients who progressed after the primary treatment. The 5-year progression-free survival (PFS) and OS were 58% and 78%, respectively; low albumin level at diagnosis and failure to achieve complete hematologic response after frontline treatment were the independent risk factors [19]. Extravascular volume overload [1], respiratory symptoms, pulmonary hypertension [20], and Castleman disease [21] are reported as inferior prognostic markers.

TREATMENT

In the 1980s, the median survival of patients with POEMS syndrome was 33 months when treated with corticosteroids, and survival has since been improved after introducing myeloma agents to suppress monoclonal plasma cell proliferation [22].

A melphalan plus dexamethasone regimen has improved neurological symptoms and organ response [23]. Melphalan 10 mg/m^2 plus dexamethasone 40 mg per day on days 1 to 4 every 28 days for 12 cycles showed 80.6% hematologic response (CR, 38.7%; PR, 41.9%) and 100% neurological response rate. The melphalan and dexamethasone combination is an effective regimen; however, it is difficult to use as a primary treatment in young patients because of stem cell toxicity and lack of long-term results.

Anti-myeloma agents such as lenalidomide, thalidomide, and bortezomib have demonstrated good outcomes in POEMS syndrome. A Japanese study reported that thalidomide effectively reduced VEGF but did not show a hematological response. However, the risk-benefit should be considered as there is a risk of aggravation of the neuropathy due to the thalidomide itself, with 54% of patients experiencing bradycardia [24]. A combination of lenalidomide 25 mg daily for 21 days per 28-day cycle plus dexamethasone 40 mg or 20 mg per week improved the VEGF response and clinical symptoms such as neuropathy and peripheral edema and were reported to have mild and manageable hematologic toxicity [25]. In another phase 2 study, lenalidomide 10 mg plus dexamethasone for 12 cycles reduced VEGF levels, and 85% overall response was observed, with 46% of patients achieving complete hematologic response and 95% achieving neurologic response, and with an estimated 3-year OS and PFS of 90% and 75%, respectively [26]. POEMS syndrome is related to thrombosis; hence, the thrombosis risk must

be considered when using immunomodulatory agents. A bortezomib based regimen (bortezomib 1 mg/m^2 IV on days 1, 4, 8, and 11; cyclophosphamide 200 mg IV on days 1 to 4; dexamethasone 20 mg IV on days 1 to 4 and 8 to 11) showed 88.2% VEGF response, 41.2% complete hematologic response, and 76.5% overall hematologic response. Neurologic symptoms improved in 95% of patients, and there were no adverse events above grade 3 [27]. A bortezomib study of 69 patients (bortezomib 1.3 mg/m^2 per week subcutaneous, dexamethasone 40 mg orally on the same day, 4 doses per cycle, 35 d cycle, for 9 cycles) showed 88.1% neurological response, 46.4% complete hematologic response, 71.2% VEGF response, and a 2-year OS of 95.7%. Grade 1 bortezomib-induced peripheral neuropathy occurred in only two patients who improved following discontinuation of the drug, making a bortezomib-based regimen a therapeutic option for POEMS syndrome [28]. In addition, there are case reports of treatments used for myeloma, such as daratumumab, but larger studies are required [29, 30].

Autologous hematopoietic stem cell transplantation (ASCT) achieves a better hematologic response and long-term survival [31]. Since engraftment syndrome frequently occurs during transplantation, early identification and active steroid use should be considered [32], and melphalan conditioning and mobilization of peripheral blood stem cells using granulocyte colony-stimulating factor (G-CSF) monotherapy is recommended. In the Japanese group, comparison of cyclophosphamide versus G-CSF alone was retrospectively analyzed, and a sufficient number of 2.0×10^6 CD34 cells/kg was collected in both groups, but severe capillary leak symptoms occurred in two patients in the chemotherapy group [33]. Long-term follow-up of 36 patients with ASCT showed a 5-year OS of 90.1%, PFS of 63.2%, and clinical relapse rate of 34% [31]. The European Society for Blood and Marrow Transplantation published retrospective data from 127 patients treated with ASCT, wherein 48.5% showed hematologic CR, 20.8% PR, and a 1-year non-relapse mortality of 3.3%, 5-year PFS was 74%, and 5-year OS was 94%. At the time of transplantation, performance status has been identified as a risk factor for disease progression [34]. A Korean study in which ASCT was performed for the POEMS patients with advanced disease and poor performance status showed a 3-year overall survival rate of 77.8% [35]. ASCT, melphalan plus dexamethasone, lenalidomide, and dexamethasone were compared, and there was no survival difference. However, ASCT showed higher hematologic and VEGF CR rates than melphalan plus dexamethasone in medium-to high-risk patients, and PFS was better than lenalidomide and dexamethasone [36].

In patients with clustered or limited multiple lesions covered by a single radiation field, radiotherapy improved hematologic response, VEGF response, and reliable clinical response [17, 37]. Radiation is recommended for patients with isolated bone lesions without clonal plasma cells [2].

RELAPSED OR REFRACTORY DISEASE

Although the treatment outcomes of patients with POEMS syndrome have improved, there is little data regarding relapse or refractory disease. In relapsed or refractory POEMS syndrome, low dose lenalidomide 10 mg daily and dexamethasone 40 mg once weekly showed 77% overall hematologic response and 44% CR. The 2-year OS and PFS were 92%, and there was no treatment-related mortality or toxicity above grade 3 [38]. In the second ASCT, 4 cases were reported, and thalidomide, lenalidomide, and bortezomib were used as salvage regimens. VEGF and hematologic responses were achieved in all patients, of which three patients had long-term survival, and one showed progression. Other agents related to the pathogenesis of POEMS, including bevacizumab targeting VEGF, IL-1 inhibitors, and IL-6 inhibitors, have not been investigated in a cohort study. It seems that bevacizumab did not provide benefits for POEMS in the case series [39]. Therefore, a second ASCT could be considered an option for relapsed or refractory POEMS syndrome [40].

CONCLUSION

Early identification and active treatment can improve the treatment outcomes of patients with POEMS syndrome. Despite the good results of new agents, upfront ASCT for transplant-eligible patients and melphalan plus dexamethasone for transplant-ineligible patients are considered the best treatment options within the Korean medical system.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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