POEMS Syndrome

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SUMMARY

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome is a rare disorder due to an underlying plasma cell clone (PC). The syndrome can affect several organs. The diagnosis is based on the presence of mandatory criteria (polyneuropathy, monoclonal plasma cell disorder) and at least one major and one minor criteria. The therapeutic regimen is determined according to the extent of the patient's sclerotic lesions and the presence of bone marrow involvement.

(BELG J HEMATOL 2020;11(8):381-6)

INTRODUCTION

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin changes) syndrome is a paraneoplastic syndrome defined by Bardwick in 1980. In the literature it also referred to as osteosclerotic myeloma, Takatsuki syndrome or Crow-Fukase syndrome.[1] It is a rare disorder with a reported prevalence of about 0.3 per 100.000.[2] The median age of onset is between 46 and 56 years with a male-to-female ratio of 2.5:1.[2,3] The syndrome is characterized by a peripheral neuropathy and a monoclonal plasma cell disorder (PCD) (both mandatory for diagnosis), associated with at least one of the following major criteria: Castleman disease, sclerotic bone lesion and elevated vascular endothelial growth factor (VEGF), and at least one minor criterion such as papilledema, extravascular fluid overload, organomegaly, endocrinopathy, skin changes, thrombocytosis and/or erythrocytosis. Besides these major and minor criteria, a constellation of other signs is described, including pulmonary problems, clubbing, and thrombotic diathesis (*Table 1*). Of note, all symptoms of the acronym are neither necessarily present nor required for the diagnosis of POEMS syndrome.

PATHOGENESIS

The pathogenesis of POEMS syndrome is still not fully understood. However, overproduction of pro-inflammatory cytokines, particularly VEGF, a potent inducer of vascular permeability, is a major feature and can explain some of the symptoms such as oedema, effusions and polyneuropathy. VEGF is expressed by osteoblasts, macrophages, tumour cells including plasma cells and megakaryocytes/platelets. In POEMS syndrome, polyclonal and monoclonal plasma cells have equally elevated VEGF levels, but monoclonal plasma cells express higher levels of IL6.[4] Nevertheless, given the disappointing results of anti-angiogenic therapy in this setting, VEGF is most likely not the driver of the disease, but more of a surrogate marker. The latter is supported by the fact that levels of IL1 and IL6 (both known to stimulate VEGF), and of TNF-alpha are higher in POEMS syndrome than in multiple myeloma.

MONOCLONAL PLASMA CELL DISORDER

The underlying PCD in patients with POEMS syndrome is most often a plasma cell clone or rarely, another B-lymphoproliferative clone. In most cases, plasma cell proliferation is low with less than 5% of medullary plasma cells, and monoclonal PC are not detected in up to a third of the patients.[5] Monoclonal plasma cells almost always express lambda light chains. Bone marrow biopsies show megakaryocyte hyperplasia in about 50% of the patients.[3] The monoclonal protein (MP) is usually low (4-10 g/L) and generally consists of an IgAλ or an IgGλ. Of note, it has

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest. The authors contributed equally to the redaction.

Keywords: monoclonal protein, osteosclerotic bone lesion, POEMS, polyneuropathy.

TABLE 1. Criteria for the diagnosis of POEMS syndrome. The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.[6,11]

Mandatory major criteria	• Polyneuropathy (typically demyelinating) • Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	• Castleman disease • Sclerotic bone lesions • Vascular endothelial growth factor elevation
Minor criteria (one required)	• Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy) • Extravascular volume overload (oedema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) • Papilledema • Thrombocytosis/polycythaemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values, fever, cardiomyopathy (systolic dysfunction), arthralgia's, fatigue, VTE, myocardial infarction, stroke

Abbreviation: POEMS: polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes, VET: venous thrombo-embolism.

been reported that the MP is detected by electrophoresis in only 54 % of the patients, highlighting the importance of urine and serum immunofixation. A majority of patients have elevated serum free λ light chains, but only a minority of them (20%) display an abnormal Free Light Chain (FCL) ratio.[5]

CLINICAL PRESENTATION

Polyneuropathy is a major characteristic of the syndrome and an essential criterion for its diagnosis. The rare patients without clinical evidence of neuropathy typically have a Castleman variant that is associated with mild neuropathy.[6] Though this neuropathy is usually sensorimotor, a small proportion of the subjects have a purely sensory presentation. The neuropathy usually begins with sensory symptoms (numbness, paraesthesia) distally in the extremities, most commonly the feet, and progresses proximally. Motor symptoms usually follow sensory symptoms and are also symmetric with a proximal extension. Visual change is also a common symptom with papilledema being reported in about 50% of the patients.[7] Skin abnormalities are reported in about two thirds of patients and most commonly consist of haemangiomas (86%), hyperpigmentation (76%), skin thickening (57%), acrocyanosis (57%), hypertrichosis (52%), acquired facial lipoatrophy (52%) or white nails (38%).[8] Organomegaly is seen in half of the subjects (hepatomegaly, splenomegaly and lymphadenopathy). Endocrinopathy is a major, though not well-understood feature of POEMS, found in 84% of the patients in the Mayo Clinic experience. In the report of the Mayo clinic the most frequently observed endocrine abnormalities were hypogonadism (79%) followed by hypothyroidism (58%) and abnormalities in glucose metabolism (48%). In total, 54% of their patients presented multiple endocrinopathies.[9] A majority of patients with POEMS present sexual dysfunction at diagnosis (61-90%). Extravascular volume overload occurs in 29 to 88% of the subjects presenting mostly as peripheral oedema but also as pleural effusion and ascite.[8] About 95% of the patients have at least one bone lesion (47% osteosclerotic only, 51% mixed sclerotic and lytic, and 2% lytic only).[10] Finally, thrombocytosis is found in about half of the patients while 20% of them present with polycythemia.[10]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of POEMS syndrome is challenging, often delayed or even missed. This may have devastating consequences, particularly regarding sequelae of neuropathy. A retrospective study reported an interval of 15 months

TABLE 2. Recommended minimal testing for the diagnosis of POEMS syndrome (Adapted from *Dispenzieri et al,* 2019).[11]

Test	Baseline	Every 3-6 months	Every 1-2 years
History and review of systems			
• detailed neurologic history (numbness, pain, weakness, balance, orthostasis)	X	X	
• history regarding menstrual and sexual function			
• skin pigment, thickening and texture, body hair quantity and texture, colour of distal extremities and development of cherry angiomata	X X	X X	
Physical exam			
• neurological exam	X	X	
• fundoscopy	X		X
• organomegaly, lymphadenopathy, extravascular volume overload	X	X	
• skin (see above)	X	X	
Blood			
• complete blood count (haemoglobin, platelet)	X	X	
• serum protein electrophoresis, quantitative immunoglobulin and immunofixation	X	X	
• vascular endothelial growth factor			
• testosterone, estradiol, fasting glucose, glycosylated haemoglobin, thyroid stimulating hormone, prolactine	X X	X X [a]	X
• follicle stimulating hormone, luteinizing hormone, adrenocorticotropic hormone, cortrosyn stimulation test, serum cortisol, parathyroid hormone	X [a]	X [a]	
Other studies			
• 24-hour urine total protein, electrophoresis and immunofixation	X		X
• bone marrow aspirate and biopsy (test for kappa/lambda by IHC)	X		X [a]
• electrophysiologic study (nerve conduction studies)	X		X [a]
• sural nerve biopsy	X [a]		
• echocardiography to assess right ventricular systolic and pulmonary artery pressures	X		X [b]
• pulmonary function tests including DLCO	X		
• skeletal CT and/or PET/CT for bone lesions, organomegaly, effusions	X	X [a]	X [b]

Abbreviations: DLCO: diffusion capacity of carbon monoxide, IHC: immunohistochemistry.
[a]as clinically indicated; [b]only if affected.

(range 1-77 months) between symptom onset and diagnosis.[6] The minimum testing recommended by *Dispenzieri et al.* is summarised in *Table 2*.[11] The author highlights the importance of carefully checking the patient's history and reviewing all the systems.

POEMS is associated with many different clinical symptoms and may mimic several other diseases. The diagnosis should be considered in all patients with MP and neuropathy. In those cases, the two most commonly missed diagnoses are POEMS and AL amyloidosis. The differential diagnoses consist of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), POEMS, AL amyloidosis, cryoglobulinemia, chronic ataxic neuropathy with ophtalmoplegia, M-protein agglutination and disialosyl antibodies syndrome (CANOMAD), MGUS or MM associated neuropathy. A search for bone lesions and VEGF measurement should be performed if no specific cause for the neuropathy is found. If a so-called chronic inflammatory demyelinating disease is not responding to classical CIDP therapy, one should look for POEMS syndrome, and the

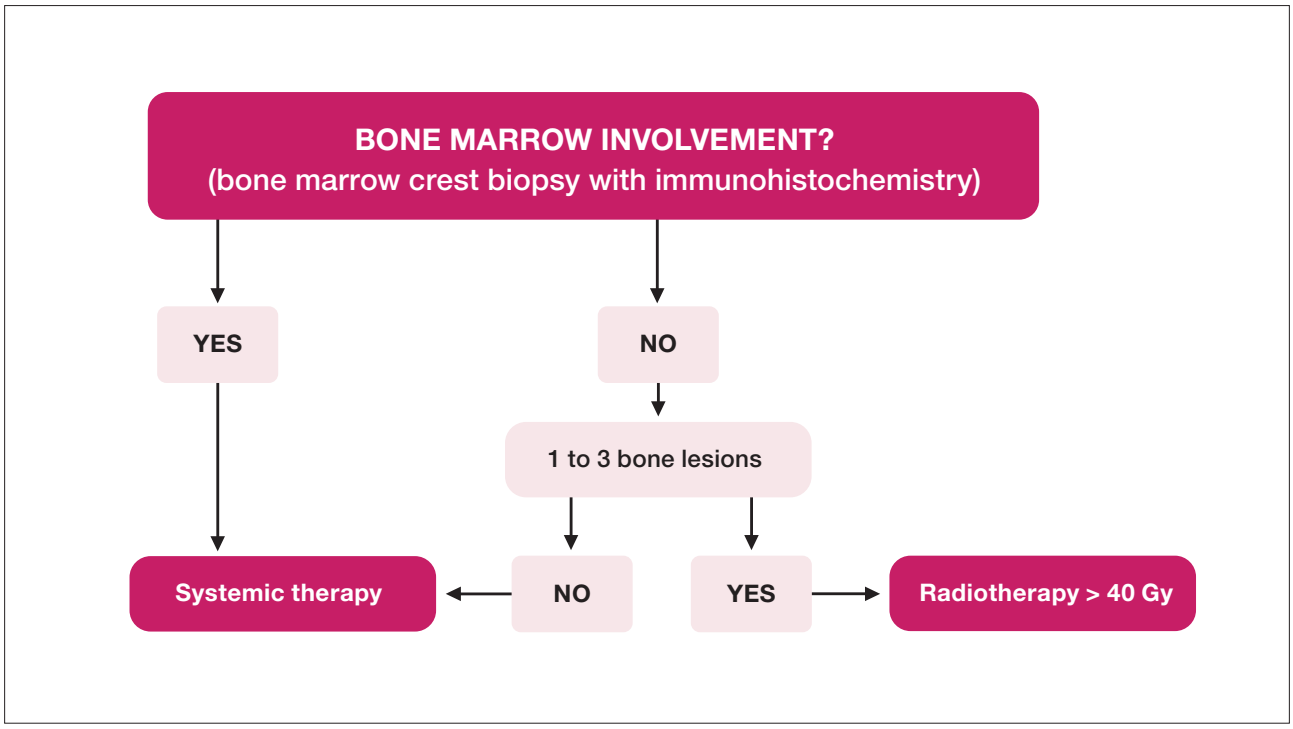

FIGURE 1. Proposed treatment algorithm for POEMS syndrome (adapted from Dispenzieri *et al.*, 2017).[10]

presence of MP should be tracked by urine and serum immunofixation. Also a myeloproliferative syndrome could be misdiagnosed based on the presence of thrombosis or erythrocytosis and be further supported by the presence of megakaryocyte hyperplasia in the medullary evaluation. Careful physical examination and anamnesis could be helpful, and in the absence of JAK 2 or other specific mutations, further tests should be performed to exclude POEMS.

Polyneuropathy (typically demyelinating) and monoclonal PCD (predominately lambda light chain) are mandatory criteria for the diagnosis of POEMS syndrome and are present in 100% of the cases. In addition to this, one of the following major criteria is required: Castleman disease (11-25% of the cases), sclerotic bone lesions (27-97%), or elevated VEGF (two third of the cases, independent of clone size). The diagnosis also requires one minor criterion, listed in *Table 1*. Finally, other symptoms can also occur in patients with POEMS, such as clubbing, pulmonary hypertension, restrictive lung disease, thrombotic diathesis, diarrhea and low vitamin B12 level.

PROGNOSIS AND RISK STRATIFICATION

POEMS syndrome is a chronic disease with a long evolution. Prior to the use of alkylating agents and autologous stem cell transplantation (ASCT), the median overall survival (OS) of patients was approximately 14 years. Luckily, this survival increased in recent years with the introduction of modern therapies. In fact, a retrospective study of the Mayo clinic reported a prognostic improvement over time with a 10-years OS of 55% before 2003 increasing to 79% after 2003.10 In this long-term follow-up study, three factors were associated with a superior OS: younger age, albumin greater than 3.2 g/dL and achievement of a complete hematologic response. Another retrospective study of 362 patients reported that age superior to 50 years, pulmonary hypertension, pleural effusion and glomerular filtration rate below 30 mL/min/1.73 m^2 were adverse prognostic factors associated with a poorer OS.[12]

THERAPY

Due to the rarity of POEMS syndrome, there have been no large randomized controlled trials in this setting. As such, therapy is mostly based on the advice of experts. In general, a treatment targeting the PCD proved to be more successful than therapies targeting VEGF. The therapeutic algorithm proposed by the Mayo clinic is based on the bone marrow involvement by clonal plasma cells (*Table 1*).[11]

TREATMENT OF LOCALIZED DISEASE: NO DISSEMINATED BONE MARROW INVOLVEMENT AND < 4 BONE LESIONS

Patients without bone marrow infiltration and limited bone disease (1-3 lesions) are treated with radiotherapy (40-50 grays). In these patients, treatment can be curative.

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Diagnosis of POEMS syndrome is challenging: do not miss it in patients with rapidly progressive unexplained neuropathy associated with a lambda light chain plasma cell disorder.**
2. **Complete testing should include a careful history, complete clinical examination, complete biology including hormones levels, VEGF level, bone marrow examination (with biopsy), bone imaging (WBLD CT and/or Pet-CT) and electromyography.**
3. **Treatment targets the plasma cell clone with a risk-adapted therapy: radiotherapy if localized disease (no more than 3 bone lesions) and systemic therapy in case of disseminated disease.**
4. **High dose Melphalan and ASCT are very effective for eligible patients. However, engraftment syndrome is frequent.**
5. **For patients who are ineligible for high dose therapy, oral Melphalan-Prednisone is a standard treatment. More recently promising results have been reported with Lenalidomide. Thalidomide and Bortezomib are also effective drugs but should be used with caution due to the risk of exacerbating the peripheral neuropathy. Thromboprophylaxis is required with Thalidomide and Lenalidomide are being used.**
6. **Response monitoring should consider symptoms, serum M-protein and VEGF levels.**
7. **Organ response can be delayed for months and years. Patients could be wheelchair or bedridden due to neuropathy. Multidisciplinary supportive care is mandatory.**

An updated series of 91 patients treated at the Mayo Clinic reported a 10-year OS rate of 70%, with 62% of patients being progression free at 6 years. Of note, after the radiation therapy, it takes approximately 3 months for the neuropathy to stabilize and 6 months to improve.[13]

TREATMENT OF ADVANCED DISEASE: DISSEMINATED BONE MARROW INVOLVEMENT AND MULTIPLE BONE LESIONS

In case of advanced disease, systemic therapy is required. For patients who are ineligible for high-dose chemotherapy and autologous stem cell transplantation (ASCT), low dose melphalan combined with dexamethasone (12 cycles) is an effective alternative. With this regimen, 81% of patients achieving a hematologic response, 100% obtaining a VEGF response and 100% showing at least some improvement in neurologic status. Other promising treatments include lenalidomide, thalidomide, and bortezomib. These drugs have anti-VEGF and anti-TNF properties. Thalidomide and bortezomib are neurotoxic and their use can be challenging, making lenalidomide more convenient. In combination with dexamethasone, lenalidomide induced a complete hematologic response in 46% of POEMS patients, while the neurologic and the VEGF response rates were reported at 95% and 83%, respectively. Of note, lenalidomide increases the risk of thrombosis and its use is not allowed in patients with a previous arterial event. Antithrombotic prophylaxis by low dose aspirin or low molecular weight heparin is mandatory, particularly in patients with polycythaemia and/or thrombocytosis.[11-14]

For eligible patients, high dose melphalan (140-200 mg/m^2) with autologous stem cell transplantation (ASCT) is highly effective, with nearly 100% of patients reaching a hematologic response and neurologic improvement. With this regimen, 75% of patients is still in response at 5 years post-treatment. The principal complication of this procedure is engraftment syndrome (ES), typically occurring between day 7 and 15 after stem cell infusion. ES combines fever, skin rash, diarrhea, weight gain and respiratory symptoms, and requires corticosteroid therapy, usually prednisone 1-2 mg/kg, with a rapid decrease after 48 hours for a maximum of 10 to 14 days. The use of dexamethasone 40 mg daily for 4 days before the stem-cell collection and between collection and ASCT, as well as a short induction with two cycles of lenalidomide-dexamethasone before ASCT may prevent ES.[11-14] Although elevated in the majority of cases, VEGF seems to be a bad target for therapy in POEMS. Nevertheless, follow-up of plasma VEGF levels is

probably the best way, besides hematological and organ responses, to assess therapeutic effectiveness or early subclinical progression. Neurologic scales, such as the Overall Neuropathy Limitations Scale (ONLS), could be used to monitor the neuropathy.

Polyneuropathy can be very debilitating, and patients may be bedridden and require multidisciplinary supportive care. Symptomatic treatment and rehabilitation are imperative in patients with neurological impairment. Orthopaedic shoes and orthotics can improve quality of life and facilitate the patient's recovery by increasing mobility and reducing falls. Neuropathic pain should be treated with drugs such as gabapentin or tricyclic antidepressants[15].

CONCLUSION

POEMS is a rare and probably underdiagnosed syndrome. Diagnosis should be considered in patients with neuropathy and MP, especially if associated with a minor criterion. Treatment will be driven by the extension of the bone disease and the bone marrow involvement. Patients with limited disease can be cured with radiotherapy whereas advanced disease require systemic therapy targeting the PC clone. Overall, the long-term prognosis of patients is good, but polyneuropathy can be very debilitating, highlighting the importance of early diagnosis.

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