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Review Article

# POEMS Syndrome-Clinical Picture and Management

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## Introduction

The term 'POEMS syndrome' was created in 1980 [1]. The acronym derived from words: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes, does not cover the variety of symptoms that can be observed in this disease.

**Keywords:** POEMS, plasma cell dyscrasia, therapy

## Pathophysiology and Epidemiology

One of the most important factors in POEMS mechanism seems to be overproduction of pro inflammatory cytokines eg. Vascular Endothelial Growth Factor (VEGF), tumor necrosis factor-α (TNF--α) and interleukin -6 (IL-6). High levels of these cytokines are responsible for symptoms like edema and effusions in the mechanism of endothelial permeability increase. The disease is actually considered a paraneoplastic phenomenon secondary to plasma cell dyscrasia [2]. Little is known about cytogenetic aspect of the disease. Presence of a small plasmacytic clone makes research problematic [3]. Chen at al analyzed the genetic profile of bone marrow cells in 42 POEMS patients, finding high mutational heterogeneity [4]. In an earlier publication by Nagao et al., based on the molecular analysis of 20 patients, the authors suggested a distinct genetic POEMS plasma cells profile from MGUS and MM cells [5]. The differences in the clinical characteristics of the studied patients and the diagnostic methods do not allow for easy comparison of the two above-mentioned reports.

Although the exact incidence and prevalence is unknown, POEMS is declared to be a rare condition. The first and major challenge in making the diagnosis is coming up with an idea that POEMS might be the explanation of patients problems.

Diagnostic criteria are listed in Table 1.

## Mandatory Criteria

Monoclonal Plasma Cell Disorder (PCD) detection is essential for crucial role of monoclonal plasma cells in the disease pathophysiology. Plasma Cell Myeloma (PCM) or Waldenstrom Macroglobulinemia are revealed occasionally, although the criteria for these diseases are not fulfilled in many cases. Blood and/or urine tests should reveal monoclonal protein presence. Trephine biopsy, more sensitive than bone marrow smear, shows plasma cells in two thirds of patients, at least 95% of which are lambda restricted [6,7]. The average plasma cell percentage does not exceed 5% [2].

Another mandatory criterion is peripheral neuropathy. Ascending symmetric sensory or less often motor symptoms usually occur primarily in distal parts of extremities. They might not be prominent. If POEMS is suspected, whereas neuropathy symptoms are not evident, neurological tests should be conducted. Electromyography reveals an abated nerve conduction, delayed distal latencies and compound muscle action potential [8]. Nerve biopsy, rarely performed, shows demyelination, often with axonal loss, and uncompacted myelin lamellae [9]. The mechanism of POEMS neuropathy is still not well understood though some assumptions about potential mechanisms were published [10].

## Major Criteria

***Castleman disease***. POEMS associated multicentric Castleman disease (POEMS associated MCD -multicentric disease) is distinguished from other MCDs [11]. Histologically often mixed or plasmacytic variant are observed. Castleman variant of POEMS is characterized by a milder neuropathy than in typical form of the disease [12].

***VEGF*** is a sensitive and specific marker in POEMS diagnosis [13]. Although probably not a driving force in POEMS, VEGF is considered the best prognostic marker [14]. The growth of VEGF correlates best with the activity of the disease [15]. This cytokine affects endothelial cells which lead to an increase in its permeability [2]. It is worth mentioning serum levels are 10-50 times higher than plasma levels [16]. When assessing VEGF level one should be aware of the fact, that corticosteroid therapy might profoundly lower the result [2]. Other cytokines, eg Il-12, Il-6, IL-1β, have been shown to play a role in POEMS pathogenesis [2,17]. A correlation between Il-12 level and disease activity was also observed [18].

Novel markers for POEMS have been reported in recent years. Wang et al, in 2014, proposed N-terminal propeptide of type I collagen (P1NP)[19]. In 2020 Isshiki et al described osteopontin, encoded by SPP1 gene, elevation in POEMS patients [20].

***Osteosclerotic lesions*** are revealed in 95% patients in plain radiological tests. However additional presence of osteolysis is often observed. In more than 50% cases the lesions are numerous [8]. Variable fluorodeoxyglucose uptake is seen in PET-CT [21,22], however PET-CT and low dose CT give the benefit of visualizing possible organomegaly and as cites [2].

## Minor Criteria

***Skinchanges.*** A wide range of abnormalities are considered POEMS syndrome connected: hyperpigmentation, hypertrichosis,




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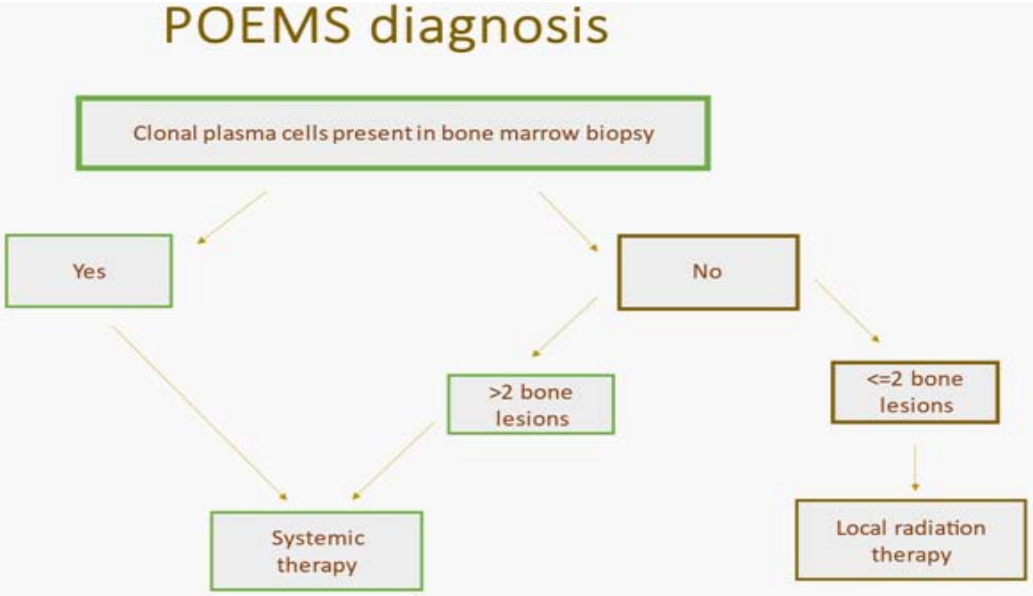


**Figure 1:** Therapeutic algorithm in POEMS.

**Table 1:** POEMS syndrome diagnostic criteria according to Barwick, 1980 [1].

| | |
|---|---|
| MANDATORY<br>*(both required)* | 1. Clonal plasma cell dyscrasia<br>2. Polyneuropathy |
| MAJOR<br>*(1 of 3 required)* | 1. Castleman disease<br>2. VEGF elevation<br>3. Osteosclerotic lesions |
| MINOR<br>*(1 of 6 required)* | 1. Organomegaly: spleno/hepatomegaly, lymphadenopathy<br>2. Endocrinoptahy[A]<br>3. Extravascular volume overload: oedema, pleural effusion, ascites<br>4. Skin changes: hyperpigmentation,hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails<br>5. Papilledema<br>6. Polycythemia/Thrombocytosis |

**A:** Diabetes mellitus or thyroid abnormality alone-does not fulfill minor criterion, **VEGF:** Vascular Endothelial Growth Factor.

glomeruloid hemangiomata, plethora, acrocyanosis, flushing, clubbing, white nails. Even in normal appearing skin biopsy might reveal vascular abnormalities in histopathological examination [23].

***Extravascular overload***. Peripheral oedemas are most characteristic, but fluid might accumulate in peritoneum, pleura and pericardium.

***Endocrine disturbances*** apply to thyroid, parathyroid, adrenal functioning, diabetes mellitus and hypogonadism. Thyroid function abnormalities and diabetes mellitus due to its high prevalence cannot be considered criteria for POEMS [2]. Gonadal axis abnormalities are most commonly observed endocrine symptoms [2,24].

***Papilledema***. Elevated cytokine production leads to increased vascular permeability and optic disc swelling. On the basis of 94 patients analysis Cui et al considered papilledema an independent negative prognostic factor in POEMS [25].

***Organomegaly***. Hepatomegalyas well as splenomegaly might be present. Lymphadenopathy, usually mild, may be a part of Castleman disease [26].

***Polycythemia/Thrombocytosis.*** Increased number of platelets and/or hemoglobin level is describeda common laboratory feature in POEMS syndrome. However 26% POEMS patients were anemicin Li study [27].

Diagnostic and clinical features with differences in frequencies given by distinct authors are listed in Table 2.

In more than 90% patients creatinine level is within normal limits and significant proteinuria is present in less than 10% cases. But cystatin-C is elevated in 71% patients [2]. Pulmonary involvement may vary in severity in POEMS: restrictive lung disease, pulmonary hypertension, reduced diffusion capacity of carbon monoxide. Pulmonary hypertension was diagnosed in 25 [28] to 27% [29] POEMS patients.

## Thrombotic Complications

Based on small studies arterial and venous thrombosis is claimed to appear in 20% of POEMS patients [12]. Therapy regimens used in POEMS, adapted from plasma cell myeloma, such as immunomodulating drugs have prothrombotic effect [2]. However, thrombotic risk in myeloma seems to be lower than in POEMS [30]. Sayar et al analyzed retrospectively data from 83 patients from UK POEMS registry. They revealed that 30% of POEMS cohort experienced arterial and/or venous thrombotic event. According to their observations arterial thrombosis was more common than venous (16 vs 18 cases respectively), and the highest risk period preceded therapy beginning [31]. Based on these results University

**Table 2:** Clinical and laboratory features in POEMS. Differences in frequencies given by distinct authors.

| Feature | Dispenzieri 2019[12] | Zhao 2019[48] | Wang 2017[70] | Jurczyszyn 2022[46] |
|---|---|---|---|---|
| Number of patients | metaanalysis | 347 | 362 | 108 |
| Age | - | >50 y - 40% | >50y -40% | median age 51 |
| Male sex (%) | - | 65,7 | 62 | 72 |
| Polycythemia (%) | 12-19 | | 15 | |
| Thrombocytosis (%) | 54-88 | | 51 | 38 |
| M protein on serum electrophoresis | 24-54 | | | |
| BMPC >10% (%) | - | 3,7 | 3 | |
| Castleman disease (%) | 11-25 | 61,5 | 64 | 23 |
| Splenomegaly (%)<br>Hepatomegaly (%)<br>Lymphadenopathy (%) | 22-70<br>24-78<br>26-74 | 59<br>38<br>64 | 67<br>47<br>65 | 44<br>47<br>46 |
| Any endocrinopathy (%)<br>Gonadal axis abnonrmalities | 67-84<br>55-89 | | >68 | 58<br>31 |
| Bone lesions present (%) | 27-97 | | =>55 | |
| Skin lesions (%) | 68-89 | | >87 | 69 |
| Extravascular volume overload (%) | 29-87 | 84 | >87 | 62 |
| Papilledema | 29-64 | | | 39 |
| Weight loss (%) | 37 | | | 50 |
| Fatigue (%) | 31 | | | 67 |

BMPC: Bone Marrow Plasma Cell Percentage

**Table 3:** Negative and positive prognostic factors in POEMS according to various authors.

| Negative prognostic factor | author | Positive prognostic factor | author |
|---|---|---|---|
| Age >50 | Wang 2017[70] | **Complete hematological response** | Kourelis 2016[34] |
| Pleural effusion | Wang 2017[70] | **Albumin >=3,2 g/dl** | Kourelis 2016[34] |
| eGFR < 30 mL/min/1.73 m2 | Wang 2017[70] | **Low VEGF level** | Scarlato 2005[10] |
| Pulmonary hypertension | Wang 2017[70] | | |
| Ischemic stroke | Feng 2020[33]; Fu 2017[71] | | |
| Thrombosis | Mellors 2022[32] | | |
| Early relapse | Kourelis 2016[34] | | |
| Baseline hypothyroidism | Yang 2020[72] | | |
| Castleman disease presence | Dispenzieri 2019[12]<br>Li 2011[27] | | |
| Papilledema | Cui 2014[25] | | |

eGFR: Glomerular Filtration Rate; VEGF: Vascular Endothelial Cell Growth Factor.

College London Hospitals (UCLH) recommend concurrently prophylactic LMWH and single antiplatelet drug until serum VEGF drops below 1000 pg/mL. If immunomodulating agent is used USLH advises to maintain prophylactic LMWH [31]. Mellors et al analyzed retrospectively the data of 230 POEMS patients. The rate of thrombotic complications was 27% and, as in the report by Sayar et al, the predominance of arterial thrombosis was observed. Among the risk factors for arterial thrombosis, the authors mentioned thrombocytosis, high hematocrit, extravascular volume overload and splenomegaly, and for venous thrombosis hyperprolactinemia only. Recurrent disease was observed in 21% of thrombotic patients [32].

Feng et al analyzed retrospectively 510 POEMS patients. Up to 8% of them suffered from Ischemic Stroke (IS), which occurred mainly within the first three months after the diagnosis. Furthermore recurrent IS were documented in 37% of ischemic patients, but not in those in haematological remission [33]. Mellors at al reported similar IS rates (7%) [32].

## Prognosis and Risk Factors

The number of clinical features present at diagnosis does not determine survival in POEMS [8].

Kourelis et al based on the retrospective analysis of 291 POEMS patients, determined younger age (RR 0.98 [0.96-1.00]), albumin greater than 3.2 g/dL (RR 0.5 [0.32-0.89]) and attainment ofcomplete hematologic response (RR 0.4 [0.2-0.9]) good prognostic factors. These parameters affect RR (relapse rate) and OS (overall survival) [39].

According to Yang observations based on 383 POEMS cases retrospective analysis, baseline hypothyroidism is an independent prognostic factor for OS (82.8 vs. 92.8%) and PFS (68.9 vs. 82.5%) [40].

**Table 4:** Selected response criteria in POEMS. based on Dispenzieri A. POEMS syndrome:

| Feature/Aspect | Complete response | Improvement | Progression |
|---|---|---|---|
| Heamotologic | Negative: immunofixation of blood and urine; bone marrow assesment | ≥ 50% M-spike reduction | ≥ 25% M-spike increase from the lowest level (at least 0,5 g/dl) |
| VEGF | Negative | ≥ 50% reduction | ≥ 50% increase from the lowest level |
| PET-CT | Negative | ≥ 50% reduction in uptake value | ≥ 30% increase in uptake value |

2021 Update on diagnosis, risk-stratification, and management [2].
M-spike - monoclonal protein spike; VEGF - vascular endothelial growth factor; PET-CT-positron emission tomography - computed tomography

Extravascular volume overload [8], pulmonary disorders [41] and ischemic complications [Feng et al] are associated with unfavorable prognosis in POEMS.

Castleman disease presence might negatively influence OS in POEMS patients [2, 31].

Prognostic factors of potential value are listed in Table 3.

## Therapy

The course of treatment is primarily established on the bone disease extent and bone marrow involvement [42]. Therapy scheme is presented in Figure1.

## Limited Stage Disease

Cases with absence of clonal plasma cells in bone marrow biopsy and 1-3 lesions are considered limited stage disease. These patients are treated with radiation therapy at a dose of 35-50 Gy. In Mayo Clinic experience, published in 2013, 4 year OS was 97% and event free survival 52% respectively [43].

## Advanced Disease

Due to the rarity of the disease there are no guidelines for therapy in POEMS, and myeloma therapeutic schedules are regularly implemented.

Neurologic response is usually seen no sooner than after 6 months after treatment implementation, one has to wait for 2-3 years for maximal effect. The lag between therapy and other symptoms relief might be smaller. In case of PET-CT response it takes 6-12 months to illustrate the effect [2].

Although clinical response means quality of life improvement, it is hematological remission that influences patient's outcome. The longest PFS is observed in patients achieving hematological CR with 6 year PFS - 88% [39].

*High dose melphalan and authological stem cell transplantation (HDT/AHCT).*

Autologous stem cell transplantation allows to achieve significant clinical improvement in all surviving POEMS patients [39]. Patients may undergo this procedure either upfront or after preceding induction therapy [40]. According to the International Blood and Marrow Transplant Research (CIBMTR) database, ASCT is performed with no previous therapy in 22% and after induction treatment in 70% [41]. Cook et al analyzed 127 HDT/AHCT patients reported in European Group for Blood and Marrow Transplantation (EBMT) database. Hematologic response was available in 101 cases, with 48% of $HR_{CR}$ (N=49) [42].Tomkins at al analyzed 42 HDT/AHCT cases in the care of UCLH. They identified 33,3 % complete hematological responses $HR_{CR}$, and 16,7% very good partial responses $HR_{VGPR}$. Clinical response was achieved in 86% of patients. 5-year OS was seen in 89,5% [43]. Other data support these observations [39,44,45,46]. Conditioning regimen is adopted from myeloma-melphalan in doses within the range of 140-200mg/m$^2$ [39,47]. HDT/ASCT was more effective than lenalidomide plus dexamethason (Lendex) and considerably more efficient than alkeran plus prednisone (MP) in a large retrospective study of Zhao et al [48]. However it should be mentioned that lowest risk patients were in ASCT cohort in this analysis.

Second ASCT in relapsed patients is a feasible option in selected cases [49,50].

Although the differences in OS between ASCT and non-ASCT patients decrease with the wider use of novel agents, future studies to assess the usefulness of ASCT in this indication are necessary [51].

*Low dose alkylator-based therapy.* Even in the era of novel drugs long term alkylating therapy remains an option. Prospective clinical trial documented at least partial symptom relief in 100% and hematological response in 81% patients [52].

*Immunomodulating agents* are used in induction treatment as well as in relapsed/refractory disease. Due to its neurotoxicity thalidomide is not recommended, but the role of lenalidomide still grows. Lenalidomide is usually introduced in doublets with dexamethasone. In a prospective II phase study Li et al demonstrated 46% complete haematologic responses and 95% neurologic responses with 3-year OS 90% and 3 year PFS 75% in response to lenalidomide/dexamethasone combination [53]. Other publications with prostective trials [54] and retrospective analyses [55] support these results.

*Proteasome inhibitors.* Bortezomib use is considered an effective drug in POEMS. Combinations with dexamethasone and occasionally cyclophosphamide are employed. According to published data bortezomib induces quick symptomatic improvement. Gao et al described a population of 69 patients treated with Veldex (bortezomib, dexamethasone). After a median of 9 cycles 46,4% (N=32) achieved $CR_H$, while 88,1% (N=52)experienced a marked neurological improvement. The authors reported reversible bortezomib induced neuropathy only in 2 patient. After a median follow up of 22,5 months estimated 2-year OS was 95,7% [56]. He and colleges analyzed 20 cases of POEMS treated with VCD (bortezomib, cyclophosphamide, dexamethasone). Bortezomib dose was decreased to 1mg/m$^2$. 41,2% of patients achieved $CR_{H,}$ 95% experienced neurological improvement. No grades => 3 side effects were observed during therapy [57]. Early observations on a small group of 11 patients treated with ixazomib in combination with lenalidomide and dexamethasone are encouraging [58].

There are only single reports on the use of *daratumumab* in POEMS [59,60,61,62].

## Future Therapies

The data on CART based therapy in POEMS is sparse. There are single publications, eg on anti BCMA therapy in a patient with POEMS and myeloma [63].

The data on anti VEGF therapy are conflicting [64]. It has shown benefits in several cases [65,66], but has failed in a few more [67,68].

Before therapy starting it is important to differentiate between PCM and POEMS. Even though therapeutic palette is similar in both cases, potential toxicity of myeloma therapy might be higher in POEMS which influences decision.

## Response Criteria and Monitoring

Given how small the clone in POEMS is, monitoring the response also poses a challenge to the clinician. VEGF is not an ideal disease marker, light chains ratio may remain normal for a long time despite the free light chains increase [69]. The selected response criteria are listed in Table 4. Additionally, various organ response scales are used depending on the initial advancement of the disease.

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