82 POEMS Syndrome and Disease Produced by Other Monoclonal Immunoglobulins

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82.1 POEMS Syndrome

82.1.1 Introduction

POEMS syndrome (acronym of *p*olyradiculoneuropathy, *o*rganomegaly, *e*ndocrinopathies, *m*onoclonal protein, and dermopathy, *s*kin) is a rare multisystemic disease due to an underlying plasma cell neoplasm. The pathogenesis of the syndrome is not well understood. Other names of the POEMS syndrome that are less frequently used are osteosclerotic myeloma, Takatsuki syndrome, or Crow-Fukase syndrome.

82.1.2 Clinical and Laboratory Manifestations

POEMS predominate in male being the age of maximum incidence (50–60 years).

Characteristic manifestations are:

*P*olyneuropathy: Typically demyelinating. Peripheral, ascending, symmetrical and affecting both sensation and motor function. It is the dominant characteristic.
*O*rganomegaly: Hepatomegaly (50%), splenomegaly, or lymphadenopathy.
*E*ndocrinopathy: Present in 84% of patients: gonadal, thyroid, pituitary, parathyroid, pancreatic, adrenal (in order of frequency, and many times multiple).
*M*onoclonal protein: Almost always λ light chain. Usually Ig A or IgG and ≤3 g/dL. Bone marrow smear <5 to 10% plasma cells.
*S*kin changes: Hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, white nails, plethora, acrocyanosis, flushing.
Other important manifestations are: — *P*apilledema (in one third of patients) — *E*xtravascular volume overload — *S*clerotic bone lesions[a] (95%) — *T*hrombocytosis (in 54%) — VEGF elevation[b] — Castleman disease (in 11–30%)

[a]Radiology and CT/PET can be useful

[b]VEGF = Vascular endothelial growth factor is the cytokine that correlates best with disease activity. The helpful cutoff for plasma and serum VEGF levels for diagnosis are >200 pg/mL (specificity 95%, sensitivity 68%) and >1920 pg/mL (specificity 98%, sensibility 73%), respectively

82.1.3 Diagnosis

Not all the features within the acronym are required to make the diagnosis. There are other relevant features not included in the POEMS acronym also important: PEST

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Table 82.1 Criteria for the diagnosis of POEMS syndrome

The diagnosis of POEMS syndrome is confirmed when: — Both mandatory major criteria + — Another of the other three major criteria + — At least one of the minor criteria	
Mandatory major criteria	**Other major criteria**
Polyneuropathy Monoclonal immunoglobulin	Castleman disease Sclerotic bone lesions VEGF elevated
Minor criteria	**Other symptoms and signs**
Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (edema, pleural effusion, or ascites) Endocrinopathy[a] Skin changes Papilledema Thrombocytosis/erythrocytosis[b]	Digital clubbing Weight loss Hyperhidrosis Low vitamin B12 values Diarrhea Pulmonary hypertension/restrictive lung disease Thrombosis

Adapted from Dispenzieri (2017)

[a]Hypogonadism is the most frequent, and because of the high prevalence of diabetes mellitus and thyroid abnormalities, these two last abnormalities alone are not sufficient to meet this minor criterion

[b]Anemia and/or thrombocytopenia are rare, unless associated with Castleman disease

(*p*apilledema, *e*xtravascular volume overload, *s*clerotic bone lesions, *t*hrombocytosis/erythrocytosis), elevated VEGF levels, abnormal pulmonary function tests, and a predisposition to thrombosis.

There is a Castleman variant of POEMS syndrome that may be associated with a clonal plasma cell disorder. When Castleman disease variant of POEMS syndrome occurs without evidence of plasma cell disorder, then this entity should be considered separately.

Clinical criteria for POEMS diagnostic are shown in Table 82.1.

82.1.4 Prognosis

Chronic course, median survival of nearly 14 years, rarely progression to multiple myeloma.

The number of POEMS features does not affect survival.

Risk factors associated to better survival are: albumin >3.2 g/dL, achievement of a complete hematological response and younger age. Lower VEGF levels, better response to treatment.

Risk factors associated to shorter survival are: clubbing, extravascular volume overload, respiratory symptoms, papilledema, and coexisting Castleman disease.

Thrombocytosis and high bone marrow infiltration are associated with risk of cerebrovascular accidents.

Patients candidates for radiation therapy have a better overall survival.

82.1.5 Standard Treatment

82.1.5.1 In Case of an Isolated Bone Lesion (or Multiple, But Localized)

Radiotherapy to affected site(s) improves the symptoms of POEMS syndrome and can be curative.

82.1.5.2 Rest of Patients (Disseminated Disease)

– MEL/DEX
– LENA/DEX, THAL/DEX, BOR (these last two agents are of limited use due to the intrinsic risk of peripheral neuropathy), CY/DEX.

– Plasmapheresis, IVIg, IFN-α, tamoxifen, ATRA, bevacizumab (anti-VEGF agent), argatroban, and strontium-89 (mostly single-case reports).
– Attention to supportive care is mandatory (physical therapy, orthotics, etc.).
– Auto-HSCT.

82.1.5.3 Response Criteria

Monitoring the response to treatment in POEMS syndrome is a challenge. Patients must be followed carefully comparing the deficits to baseline. VEGF is an imperfect marker due to discordances between disease activity and response. The size of monoclonal protein is typically small making standard MM response criteria inapplicable. Patients can present clinical benefit without M-protein response therefore a clinical scoring system which can focus on organ-specific response would be useful clinically. So, response criteria for POEMS syndrome could be done as follows: hematological response using a modified amyloid response criteria, VEGF response, CT/PET response, and a simplified organ response (polyneuropathy assessment, pulmonary function tests, and extravascular overload).

82.1.6 Autologous HSCT (Table 82.2)

Table 82.2 Main characteristic of auto-HSCT for POEMS disease treatment

Background	— In MM, another gammopathy, auto-HSCT, has a high rate of responses — In amyloidosis, a disease with similarities to POEMS syndrome with "low tumor" burden, auto-HSCT offers encouraging results
Indication	POEMS syndrome with disseminated disease and: — Good general condition — Without response to standard treatment (MEL + DEX 2–3 months) — With high-risk factors (?)
Conditioning	MEL 140–200 mg/m^2[a]
Stem cell source	PBSC, mobilization with G-CSF ± CY (3 g/m^2)[b,c]
Morbidity	— High rate of engraftment syndrome (up to 50%) (see Chap. 42), important to recognize and treat promptly with PRD. In these cases, higher than expected transfusion need and delayed engraftment — No organ toxicities as observed in amyloidosis
Mortality	As in other auto-HSCT, recently reported 3.3% at 1-year NRM[d]
Response[d,e]	Usually delayed, from 6 months post-auto-HSCT to 24–72 months

[a]With lower dose, inferior responses
[b]Mobilization failure is described, for this reason if there is no response after three courses of MEL + DEX, proceed to mobilization
[c]The incidence of engraftment syndrome can be reduced if mobilization is done with CY + G-CSF
[d]Cook et al. (2017)
[e]In the largest series, 3-year PFS 84% and OS 94%, and 5-year PFS 74% and OS 89%

82.2 Monoclonal Ig Deposition Disease

82.2.1 Introduction

Monoclonal Ig deposition is a clonal plasma cell dyscrasia in which light-chain and/or heavy-chain subunits of Igs form non-fibrillar deposits in various tissues, causing organ dysfunction. Light-chain deposition disease is the most common of these entities.

82.2.2 Clinical Manifestation/ Laboratory

Kidney
— Always affected: nephrotic syndrome, hypertension, and rapidly progressing renal insufficiency
— Immunofluorescence shows deposition of light chains along glomerular and tubular basement membranes → nodular glomerulosclerosis
— Deposits are non-fibrillar, almost always composed of κ chain, and do not stain with Congo red dye

Heart and liver
— Less frequently affected: restrictive cardiopathy, myocardial infarction, cholestatic jaundice, hepatic failure

Monoclonal gammopathy
— Electrophoresis, immunofixation of serum and/or urine, serum-free light chain measurement

Table 82.3 Main characteristic of auto-HSCT for monoclonal Ig deposition disease treatment

Background	— As in POEMS syndrome (see Table 82.2)
Indication	— Patients in good general condition and with basic requirements for auto-HSCT — Patients not responding to previous MM-like treatment
Conditioning	Melphalan 140–200 mg/m^2
Stem cell source	PB, mobilization with G-CSF ± CY (3 g/m^2)
Morbidity	Some patients require hemodialysis (HD) before and during the procedure. In that case, MEL should be administered after HD
Mortality	As in other auto-HSCT
Response	In the few cases reported: — Hematological responses are described secondary to the control of the monoclonal gammopathy — It can improve renal function. In selected cases, kidney transplantation could be an option if the patient achieves a CR and remain in HD

82.2.3 Diagnosis

Based on the biopsy of the affected organ (almost always kidney)

82.2.4 Treatment

Controversial, not standard due to the low incidence. Conventional chemotherapy commonly used for MM is unsatisfactory. Possible alternatives are:

– MEL + prednisone
– VAD (vincristine, doxorubicin, DEX)
– THAL/DEX, BOR/DEX
– Auto-HSCT (see Table 82.3)

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