POEMS Syndrome

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Structured Abstract

Purpose of review: To provide an overview of POEMS syndrome, detailing new insights into pathogenesis, prognostic factors, treatments and outcome scores.

Recent findings: With the development of large multi-centre national cohorts of patients, POEMS syndrome is evolving into a well characterised multi-system haematoneurological syndrome. Without early diagnosis significant disability results from the neuropathy. VEGF is a useful and accurate biomarker supporting diagnosis and following disease activity. The past decade has seen a number of therapeutics become available to POEMS patients, repurposed from myeloma treatment. Simple treatment algorithms are based on the extent of monoclonal proliferation and the performance status of patients. Risk factors, prognostic scores and their impact on outcome measures have been developed from deeply phenotyped patient cohorts to predict response rate, progression free and overall survival.

Summary: Understanding links between the monoclonal lambda plasma cell disorder and resulting proinflammatory cytokine milieu is fundamental to determining POEMS syndrome pathophysiology. Similarities to CIDP and some other monoclonal proliferative diseases makes POEMS misdiagnosis common. A range of treatments are available, and more work to identify pathogenic mechanisms and treatment targets as well as prognostic scores will further enable treatment stratification for optimum outcomes.

Keywords

POEMS, polyneuropathy, monoclonal, autologous stem cell transplantation, plasma cell dyscrasia, vascular endothelial growth factor

Introduction

Polyneuropathy Organomegaly Endocrinopathy M-Protein and Skin Changes (POEMS) syndrome is a rare multisystem autoinflammatory disease. Initially described by Crow and Fukase[1] the disease describing acronym was coined by Bardwick in 1980[2]. Although still thought to be rare it is increasingly recognised in a number of presenting forms mainly through neurology and haematology referral sources.

Significant contributions to the diagnosis and management of POEMS have been made over a number of years through the work of the Dispenzieri (USA), Kuwabara (Japan) and Li (China) groups alongside other important smaller groups in France and Italy. These include the definition of core sets of diagnostic criteria [3], the identification of VEGF as a major biomarker for the disease[4–7], contributions to epidemiology and diagnostic findings [3,8–16] as well as a number of studies informing current treatments and outcomes[7,17–33].

As a result of these dedicated studies in a rare disease, the successful diagnosis and treatment of POEMS syndrome is probably more frequent in generalist settings. However, referral to specialist centres with access to autologous stem cell transplantation and specialist immunomodulatory haematology drugs as well as structured rehabilitation and follow up monitoring is recommended.

Text of Review

Epidemiology

POEMS syndrome is a rare disease and the exact incidence and prevalence are unknown. Studies reporting the largest cohorts of POEMS patients are in America (291 patients) [26] and China (476 patients) [7]. Other studies over 5 years old described 102 patients in Japan[8], 25 in France[10] and 29 in India[34]. Such figures are unlikely to accurately reflect the epidemiology but do suggest POEMS is possibly more common in China and Japan than Europe and the USA. POEMS is about 2 ½ times commoner in men than women. The onset of POEMS most frequently occurs in the fifth or sixth decade.

Pathophysiology

The pathophysiology of POEMS syndrome remains poorly understood (see Figure 1). POEMS is intrinsically linked to the presence of the monoclonal plasma cell disorder and a co-existing upregulation of pro-inflammatory cytokines, resulting in a host of downstream multi-system effects. Small volume malignant plasma cell clones are thought to drive the disease. However, little is known about the pathogenic role of these plasma cells. Of notable interest is that they are lambda light chain restricted in over 95% of cases [35]. Furthermore there is restricted usage of immunoglobulin λ light chain variable region (IGLV) genes, strictly derived from IGLV 1-40 and 1-44[36,37], suggestive of some antigenic affinity maturation. A number of common cytogenetic abnormalities found in multiple myeloma are also associated with POEMS causation and prognosis; aneuploidy including monosomy 13 and trisomy 3 and 7[38] and 14q32 translocations and 13q14 deletions have all been described[16] illustrating similarities of the underlying pathogenesis. Drawing together the various malignant and immune driven mechanisms remains an incomplete task.

Vascular Endothelial Growth Factor is a potent angiogenic proinflammatory cytokine found markedly raised in POEMS syndrome[5]. VEGF correlates both with disease activity[5] and predicts treatment response and survival[7] . Wang *et al.* recently demonstrated bone marrow plasma cells as the primary

source of VEGF measured at both mRNA and protein levels, the levels decrease markedly following treatment [39]. Interestingly polyclonal plasma cells secrete the greatest amount of VEGF, whereas the small populations of monoclonal cells are strongly IL6 positive. Monoclonal cell derived IL6 may drive polyclonal plasma cell VEGF release. Since polyclonal plasma cells are more sensitive to chemotherapy this may explain the relative ease of obtaining complete VEGF suppression but less frequent complete haematological response.

VEGF has multiple roles including as a growth factor for endothelial cells, and an important regulator of osteogenesis. Excess VEGF probably plays a pathogenic role in extravascular volume overload, bone lesions, papilloedema, glomerular haemangiomata and arteriopathy in POEMS. VEGF also causes microvascular permeability and endoneurial damage, and leakage of toxic serum components is postulated to cause the neuropathy; more work is needed to prove this pathologically[11]. Wang *et al.* have demonstrated that polyclonal bone marrow cells produce the largest proportion of VEGF as opposed to the abnormal monoclonal cell population. Polyclonal cells are thought to be more sensitive to chemotherapy, which may explain why VEGF suppression often occurs in POEMS syndrome despite persistence of the monoclonal protein[39].

Despite a focus on VEGF, it is unlikely to be the major pathogenic mediator. Supressing VEGF alone with bevacizumab does not lead to clinical recovery of POEMS syndrome and may be harmful[32], suggesting that whilst VEGF is a downstream mediator of some disease features, it is not an initiating factor in POEMS pathogenesis. Alterations in pro-inflammatory cytokines such as fibroblast growth factor, hepatocyte growth factor, tumour necrosis factor, interleukin (IL) 6, IL 12, HIF1α and N-terminal propeptide of type I collagen have been reported in POEMS syndrome[40–42], but more research is required to understand their roles in pathogenic mechanisms.

Diagnosis

Because each major feature of the disease is relevant to disparate medical specialties, the diagnosis is often delayed by a failure to recognise the diagnostic features outside the immediate sphere of knowledge of the specialty. The most recent diagnostic criteria have been published by Dispenzieri *et al.*[43] and details of the major diagnostic criteria are below.

Polyneuropathy

The most disabling feature of POEMS is the demyelinating neuropathy, frequently misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). However early in the disease there is seldom any proximal weakness and throughout the disease course striking distal weakness of the hands and feet predominates[44]. A typical POEMS neuropathy is a symmetrical, sensorimotor length dependent painful neuropathy which progresses proximally over time and is resistant to plasma exchange and IVIG[3,8,10]. Albuminocytological dissociation occurs as in CIDP. Typical electrophysiological features (see below) help support clinical findings. Any patient with an apparently treatment resistant ‘CIDP’ should be evaluated for POEMS syndrome.

OEMS and others

Small numbers of patients, especially those with Castleman Disease can have very mild distal sensory loss or even no demonstrable neuropathy despite fulfilling many or all of the other criteria[45]. These patients may complain of neuropathic symptoms despite entirely normal neurological examinations

by competent neurologists and normal electrophysiology. It is not known if these patients eventually develop the polyneuropathy.

Electrophysiology

Neurophysiology in POEMS syndrome fulfils diagnostic criteria for CIDP in 70% of cases[46] highlighting difficulties with both clinical diagnosis and the criteria. Several studies have tried to distinguish the neurophysiological characteristics of POEMS syndrome from CIDP. Slowed conduction velocity with marked early secondary axonal loss is typical. Motor conduction velocities (MCV) are equally reduced in the upper and lower limbs, and velocities are often slower than CIDP. Uniform demyelination along the nerve with no conduction block (10% compared to 45% in CIDP[47]), normal terminal latency indices (TLi) and F-wave delay proportionate to MCV slowing, as opposed to focal involvement of selected fibres in CIDP is the norm.[47–50] At diagnosis, approximately 50% of nerves with reduced motor conduction velocity MCV have reduced CMAP amplitude[50]. CMAPs in the lower limbs are more severely affected than the upper limbs, with abnormal values in 96% peroneal, 97% tibial, 65% ulnar and 67% median nerves tested in 138 POEMS patients, with 108 and 104 absent responses in the peroneal and tibial nerves respectively[48]. Compared with CIDP, POEMS patients have a far greater reduction in CMAPs, particularly in the lower limbs (peroneal $p<0.0001$, tibial $p<0.001$) reflecting more significant secondary axonal loss. Being a length dependent process, sural sparing is not seen in POEMS syndrome as it sometimes is in CIDP[48].

In the realm of paraprotein associated neuropathies, the neurophysiology of POEMS compared to a neuropathy associated with monoclonal gammopathy of unknown significance (MGUS), both exhibit demyelinating features with reduced conduction velocities, prolonged distal motor latencies and prolonged F-waves. However POEMS demonstrates greater reduced upper and lower limb CMAPs and a greater reduction of median and ulnar MCVs, and the TLI is higher, suggesting slowing is greater in intermediate than distal nerve segments[51].

Monoclonal plasma cell disorder

The POEMS serum paraprotein may be of very low level and is frequently undetectable if sought only by serum protein electrophoresis (SPEP). SPEP is positive in as few as 54% of cases, with higher yield on immunofixation (75-92%). Over 95% of cases are lambda light chain restricted[3,8]. Urine protein electrophoresis and immunofixation may identify an M-protein when serological investigations are negative. A monoclonal plasma cell disorder may possibly only be detectable when a high level of suspicion about the diagnosis results in a bone marrow, lymph node or lesional bone biopsy revealing light chain restricted B-Cells or Castleman Disease. Identification and choice of target lesion is greatly assisted by fluorodeoxyglucose (FDG)-PET scanning, which should be part of the diagnostic workup in every suspected case[14].

Multisystem features

A host of multisystem features occur at different frequencies in POEMS syndrome, with most patients at diagnosis presenting with 5-6 features.[3] Organomegaly is rarely palpable and identified on imaging. Diabetes and thyroid abnormalities are too prevalent in the general population to be considered a diagnostic feature, unless developed at the onset of other characteristic features. Endocrinopathy features are variable, and therefore systematic screening at diagnosis and monitoring is necessary. Skin abnormalities are present in 70% of our cohort (unpublished data), including plethora, acrocyanosis, hypertrichosis, skin thickening, nail changes and glomerular

haemangiomata. The acronym 'PEST', relating to papilloedema, extravascular volume overload, sclerotic bone lesions and thrombocytosis is a useful aide memoire. Cardiopulmonary manifestations of heart failure, pulmonary hypertension, restrictive lung disease and renal disease impact on patients general fitness, ability to tolerate autologous stem cell transplantation[52,53] and overall survival.[20,26] No other organ manifestations predict outcome, but contribute to patients wellbeing.

Imaging features

Organomegaly, bone marrow infiltration and extravascular volume overload are useful diagnostic features of POEMS syndrome identified through radiological investigation. Developments in imaging mean skeletal surveys are now less frequently used, whereas CT, MRI and FDG-PET are increasingly important although it is unclear which modality is most accurate. CT imaging can identify bone lesions and important systemic features such as pleural effusions, ascites, adenopathies and organomegaly. The ability of FDG-PET to identify FDG-avid bone lesions, often representative of active infiltration with plasma cells, is useful in the diagnosis in POEMS as it guides targeted lesional biopsy[14] as well as determining focal or systemic therapy decisions. Furthermore, avidity changes in bones occur sooner than bone changes seen on CT, and may correlate with other favourable post treatment response indicators[14].

POEMS is largely a peripheral nervous system disease. However stroke is not an uncommon presenting feature, although the pathogenesis of POEMS strokes is not understood[54]. Hypercoagulability related to raised VEGF, platelet instability, HIF1a induction, microvascular endothelial swelling, vascular leak (see Figure 1), the presence of a paraprotein and the additional treatment related pro-coagulant effects of lenalidomide may result in vascular occlusion with unusual features on brain imaging. A further recent observation of frequent asymptomatic pachymeningitis is an interesting and previously unreported finding in a significant proportion of patients[55].

Treatment

POEMS is a treatable disease. Untreated the median survival is 33 months, but recent studies of 138 and 362 patients from two large series stratified into good and poor pre-treatment prognosis have demonstrated 5 year survival rates of 79% and 84% and 10 year survival of 62% and 77% [20,26]. Even poor prognosis patients had a 71% survival at 5 years. The keys to successful treatment outcomes are the recognition of the disease, rapid diagnosis and early intervention before irreversible neurological disabilities occur.

Treatment options are relatively straightforward, with simple algorithms to guide decision making[35]. Treatment of POEMS is aimed at the clonal haematologic disease and the cytokine drive as well as supportive care largely for the neurological and endocrine consequences of the disease once the acute management of the unwell presenting patient and the definitive disease directed treatment is over. The medical treatment of POEMS is summarised in a recent paper by Jaccard[56].

Radiotherapy

Where there is no bone marrow involvement and there are 3 or fewer bone lesions, curative radiotherapy doses of 40Gy or more to the solitary myeloma is indicated. Six year progression free survival of 82 patients treated at the Mayo Clinic with radiotherapy, each of whom had between 1

and 3 lesions, was 62 % [57]. There was no difference between those with one, two or three lesions. Radiotherapy is somewhat slow to work and may be given with either dexamethasone (40mg per day for 4 days every 2 weeks), or more recently with lenalidomide and dexamethasone with good results[58].

Autologous stem cell transplantation

Autologous stem cell transplantation (ASCT) is the treatment of choice where radiotherapy is not suitable and where the physical performance status of the patient allows. Priming with dexamethasone[58], thalidomide or lenalidomide or combinations[18,23] may protect against acute engraftment syndrome. Engraftment syndrome occurs 7-15 days after transplant and comprises fluid overload and weight gain, respiratory compromise, skin eruptions and diarrhoea and can be fatal. Most ASCT is performed as Melphalan 140- or 200-Conditioned regimens, and has the highest progression free and overall survival from all the treatment modalities; five year overall survival is reported at 90-95%, and five year PFS at 63-76%[17–19,23,26]. Studies have demonstrated reduced rates of engraftment syndrome with 4 days of 40mg dexamethasone[56], or lenalidomide[17] between stem cell collection and ASCT.

If patients are deemed too unwell to tolerate ASCT (for example age over 70 or significant cardio-respiratory compromise), then systemic chemotherapy can either be used as a long-term treatment, or as a bridging therapy to optimise patients for ASCT at a later date. There are no established guidelines for exactly which chemotherapy to choose or which is most efficacious, but the following is a broad guide.

Melphalan

One prospective trial of Melphalan in POEMS syndrome has been published[59]. Thirty-one patients received 12 cycles of melphalan and dexamethasone treatment. Twenty-five (81%) achieved haematologic response including 38% complete response; 100% had VEGF reduction. There was improvement in ONLS score in all patients within 15 months, and all patients were alive without progression at median follow up of 21 months.

Cyclophosphamide

Retrospective cyclophosphamide treated POEMS cohorts have been described, but no prospective trials exist. 28% of the Mayo Clinic cohort were treated with non-transplant dose alkylator chemotherapy[26] and 23% in the Japanese cohort[8]. Alkylator based therapy data tends to be grouped with all chemotherapeutics and has worst overall survival (10-year OS 46% at the Mayo Clinic) especially compared to ASCT and radiotherapy). This might be attributable to selection bias and poor baseline medical fitness. We tend to use cyclophosphamide only as a mobilisation agent for stem cell harvest.

Thalidomide

The Japanese POEMS Syndrome with Thalidomide (J-POST) trial of 25 POEMS patients demonstrated thalidomide 100-300mg/day plus dexamethasone had greater VEGF reduction and possible improvement in motor function compared to dexamethasone alone [27]. This is further supported by a number of prospective trials, case series and derived best practice guidelines[56]. Thalidomide at a cumulative dose of more than 50g causes neuropathy which may confound improvement in neurological function.

Lenalidomide

Anecdotally, lenalidomide appears to be the most efficacious chemotherapeutic or immunomodulatory agent in POEMS syndrome to date, with reports of rapid resolution of volume overload and VEGF, improvement of neuropathy and haematological response. A systematic review of lenalidomide in 51 POEMS patients demonstrated at least very good partial response in 58% and partial response in 37%. VEGF was reduced in all cases, and neuropathy improved in 92%. An estimate of PFS at 12 months was 94%[60]. A prospective trial of lenalidomide and dexamethasone in 18 patients found clinical and neurological improvement with all patients alive at a median follow up of 39 months and a 3-year PFS of 59%[24]. Li *et al.* studied 138 patients with POEMS and ASCT; of those, 32 patients initially deemed unfit for ASCT were treated with lenalidomide which made subsequent ASCT feasible. Cai *et al.* have also demonstrated effectiveness of lenalidomide in 12 patients with relapsed disease[29]. A low dose lenalidomide regimen of 10mg per day has non-inferior response outcomes and much better safety in a prospective phase II study of 41 patients published in 2018[61] Lenalidomide is prothrombotic and therefore should be used in caution in patients with evidence of venous or arterial thrombosis, thrombocytosis or polycythaemia, all recognised associations with POEMS syndrome.

Bortezomib

He *et al.* have used bortezomib in combination with cyclophosphamide and dexamethasone in 20 patients [21]. Complete haematological response was seen in 41% and partial response in 35%. VEGF response was documented in 88%. Neurological response was measured by a median ONLS improvement from 5 pre-treatment, to 3 after treatment. In myeloma series neuropathy occurs as a result of bortezomib in 1/3 of cases and therefore may confound improvement. Carfilzomib, a second-generation proteasome inhibitor with fewer off target effects and much less neuropathy has not been studied in POEMS syndrome. The Mayo Clinic are currently recruiting patients to trial Ixazomib with lenalidomide and dexamethasone (NCT02921893) which will be of interest.

Prognostic factors, outcomes and response scores

The rich diversity of features in POEMS provides many candidates for biomarkers for prognosis and treatment response. Haemato-oncology studies concentrate on progression free (PFS) and overall survival (OS). High and low risk groups can be identified for PFS and OS from presenting features. Kourelis *et al.* studied the Mayo Clinic's outcome data of 291 POEMS patients, and identified three factors associated with superior OS; younger age, serum albumin < 3.2g/dL and complete haematological response following treatment[26]. Similar risk factors apply to progression after first line treatment[57]. Wang *et al.* have developed a prognostic nomogram for POEMS patients, in which OS and PFS can be estimated through combining patient age, evidence of pulmonary hypertension, pleural effusion and estimated glomerular filtration rate[20]. Kourelis and Dispenzieri validated the nomogram in their Mayo cohort, suggesting it has external validity applicable to a broader patient population.[25]. Misawa *et al.* demonstrated normalisation of VEGF at 6 months post treatment correlated with prolonged relapse free survival, improved grip strength and CMAP amplitudes at 12 months[62]. Zhao *et al.* have also cited the prognostic value of VEGF response alone, and in combination with haematological response as a surrogate endpoint in clinical trials[7].

Summary

POEMS syndrome is a rare condition which appears to be driven by a monoclonal lambda light chain restricted proliferative disorder, resulting in a proinflammatory response, and a range of downstream multisystem responses. VEGF is a key biomarker in diagnosis, response and relapse identification, but is not the only cytokine involved in pathogenesis. Treatment is directed at the monoclonal proliferative disorder, but this could change with the advent of prognostic nomograms to identify patients at risk of refractory disease and relapse. Currently, radiotherapy, chemotherapeutics and ASCT are appropriate therapies for POEMS syndrome, with more patients ultimately being treated with ASCT due to emerging efficacy of pre-optimisation protocols.

Learning points

1) POEMS is a rare disorder in which the pathogenesis is poorly understood, but thought to be intrinsically linked to the presence of the monoclonal plasma cell disorder and secondary to a number of inflammatory cytokines leading to a host of multi-system effects.
2) Neuropathy in POEMS syndrome is typically symmetrical, sensorimotor, length dependent and painful.
3) Typical neurophysiology in POEMS demonstrates conduction velocity slowing with marked secondary axonal loss, often with no responses in the lower limbs. Conduction block and temporal dispersion are uncommon when compared to CIDP.
4) POEMS is treatable with favourable overall and progression free survival. Autologous stem cell transplantation provides the best outcomes but other methods such as radiotherapy and lenalidomide are also highly effective in the correct circumstance.

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Figure 1: A proposed pathogenesis of POEMS syndrome. Central to the pathogenesis is VEGF, although this is not the primary cause. Malignant clonal or autonomous plasma cells drive production of IL6 and proliferation of lymphoid stroma. Released cytokines are responsible for bone resorption and systemic features of disease. A procoagulant state driven by vascular endothelial swelling, platelet aggregation and tissue ischaemia drives HIF1α production which further drives VEGF production. Vascular leak leads to oedema, papilloedema, effusions and reduced lung transfer factors. VEGF drived lasma cell migration , proliferation, survival and release of further cytokines.

VEGF – vascular endothelial growth factor, HIF1α – Hypoxia induced factor alpha-1, BNB- Blood nerve barrier, IL6 – interleukin-6, TNFα – tumour necrosis factor alpha.