POEMS neuropathy: optimising diagnosis and management

S Keddie[1], S D'Sa[2], D Foldes[2], AS Carr[1], MM Reilly[1], MP Lunn [1]

1. MRC Centre for Neuromuscular Disease, National Hospital of Neurology and Neurosurgery and Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK.
2. Cancer Division, University College London Hospitals NHS Foundation Trust, London, UK

Tables: 3

Figures: 5

Word count: 4800

References: 40

Funding: Dr Keddie is funded by a ABN/Guarantors of Brain Clinical Training Research Fellowship.

Conflicts of interest: Nil

Ethics: All patients signed consent forms to allow for their case histories and clinical images to be published.

Abstract

POEMS syndrome is a rare and disabling autoinflammatory condition, typified by a typical peripheral neuropathy and the presence of a monoclonal plasma cell disorder. The acronym 'POEMS' represents the complex and multi-system features of the disease, including polyneuropathy, organomegaly, endocrinopathy, a monoclonal plasma cell disorder, and skin disease. The diagnosis of POEMS is a significant challenge because of the heterogeneity of clinical presentations and variation of POEMS features. Patients are often misdiagnosed with another cause of inflammatory neuropathy and receive one or more ineffective immunomodulatory medications resulting in delayed diagnosis and further clinical deterioration before a diagnosis is made.

University College London Hospital sees one of the largest reported POEMS cohorts in Europe, and runs a multi-specialist clinic to assist with diagnosis, treatment and ongoing support. This review draws upon our experience to present the typical features of POEMS syndrome, and highlight diagnostic conundrums commonly experienced supplemented with clinical cases. We will provide an investigative guide for clinicians when considering POEMS as the diagnosis, and propose a treatment algorithm which centres on the site and degree of monoclonal cell proliferation.

Introduction

POEMS syndrome, first coined by Bardwick in 1980, is an acronym to describe the clinical phenotype of a rare and disabling multisystem, autoinflammatory condition featuring polyneuropathy, organomegaly, endocrinopathy, the presence of a monoclonal plasma cell disorder and skin disease [1]. Larger cohort studies have revealed several other characteristic findings, including papilloedema, extravascular volume overload, sclerotic bone lesions and

thrombocytosis (abbreviated to 'PEST' as a supplementary aide memoire [2]). The pathogenesis of POEMS syndrome is not understood, but is thought to be related to the monoclonal plasma cell proliferative disorder and the impact this has on inducing a cytokine driven inflammatory response [3–7]. Vascular endothelial growth factor (VEGF), a potent angiogenic cytokine, was found to be markedly raised in the serum of POEMS patients [8]. Reported treatment trials blocking VEGF with bevacizumab resulted in worsening of neuropathy and some deaths[9,10]. This suggests although VEGF is a useful biomarker for disease detection and monitoring [3,4,8,11], its role in pathogenesis is poorly understood.

Dispenzieri et al proposed the widely accepted diagnostic criteria in 2003 in an attempt to standardise the number of features and investigation findings necessary to make a diagnosis of POEMS syndrome [2] (see table 1). Polyneuropathy and a monoclonal plasma cell disorder are hallmarks of the clinical disease, and therefore mandatory criteria for diagnosis. As is typical in medicine, textbook definitions very rarely reflect what is seen in clinical practice. Although there are clear diagnostic criteria, POEMS syndrome remains notoriously difficult to diagnose. Despite the presence of a monoclonal lambda light chain plasma cell dyscrasia in 95% of cases [13] coupled with the highly sensitive biomarker VEGF [4], misdiagnosis remains likely. The heterogeneity of clinical presentations, with patients commonly presenting with only a limited number of the features described contributes to the diagnostic difficulties. The subtlety or lack of bone marrow abnormality provides false reassurance of the absence of a monoclonal plasma cell disorder. The typically inflammatory neuropathy mimics that of the much more familiar chronic inflammatory demyelinating polyneuropathy (CIDP); over 60% of patients are initially diagnosed as CIDP [14], resulting in treatment with ineffective immunomodulatory therapy and subsequent clinical deterioration due to delayed diagnosis by a median of 12 months [14]. Features such as endocrinopathy, papilloedema and skin conditions are non-specific, and may not typically be attributed to a neurological syndrome. Furthermore, investigations may be misinterpreted or down-played, resulting in reports which may not synthesise the whole picture. With all the diagnostic uncertainty and misleading information in such a complex disease, it is little wonder clinicians fail to consider the diagnosis.

Once the diagnosis is made, uncertainties still remain regarding treatment. Treatment is directed at the underlying clonal plasma cell disorder and depends on the distribution of the disease and extent of bone marrow involvement. Novel chemotherapeutic agents and autologous stem cell transplantation allow for significant improvement of disease free survival. However, treatment selection, assessing response, accurately monitoring disease and identifying relapses is complex and requires multiple investigational modalities. Indeed, the multisystem nature of POEMS and its compounding disabilities requires multi-disciplinary support and assistance.

This review aims to guide clinicians through the diagnostic process towards making a diagnosis of POEMS syndrome. We describe the 'typically atypical' POEMS patient, and illustrate some of the diagnostic conundrums of POEMS using case examples. We provide recommendations for the thorough

investigative workup required to diagnose POEMS syndrome, and the commonly misreported findings to look out for. A treatment guideline is proposed, and recommendations for monitoring patients and identifying relapses is provided.

The typically atypical presentation of POEMS syndrome

Neuropathy

The diagnostic criteria for POEMS syndrome are displayed in table 1. The presence of polyneuropathy and a monoclonal plasma cell disorder are fundamental to the diagnosis. The polyneuropathy in POEMS syndrome shares many similar characteristics to CIDP, with development of a subacute, progressive motor predominant polyradiculoneuropathy. Both conditions display albuminocytological dissociation on cerebrospinal fluid analysis and electrophysiological evidence of demyelination with f-wave prolongation, slowed conduction velocity and temporal dispersion. However, the neuropathies are very different and clues in the history, examination and neurophysiological findings to distinguish POEMS neuropathy from CIDP are detailed in see table 2. In practice, neurophysiology results may be misinterpreted and reported as fitting diagnostic criteria for CIDP [15], and for this reason we recommend all patients presenting with an inflammatory neuropathy to have appropriate investigations for the presence of a monoclonal plasma cell proliferative disorder (serum and urine protein electrophoresis, immunofixation and serum free light chain assay), and consideration of VEGF included at the outset, and certainly if there is a lambda light chain paraprotein. The finding of a lambda light chain and/or a raised VEGF should prompt further thorough investigation, detailed below. The neurohistopathology of POEMS nerves is of axonal and demyelinating lesions with uncompacted myelin lamellae [16,17]. Uncompacted myelin is non-specific, and with much more sensitive biomarkers such as a monoclonal proliferative disorder with lambda light chains and raised VEGF [3,4], we do not recommend nerve biopsy to distinguish POEMS from CIDP. It may however be indicated to rule out suspected vasculitis, amyloid or an infiltrative disorder, all of which may cause a painful or non-steroid or IVIG responsive neuropathy like POEMS.

Monoclonal plasma cell disorder

Once POEMS syndrome is considered, the presence of a monoclonal plasma cell disorder must be proven to make the diagnosis. This requires detection of monoclonal proteins (paraproteins) formed by a single heavy chain (M, G or A) and a light chain (kappa or lambda) which is usually, but not always secreted. Around 10% of patients with polyneuropathy of otherwise unknown cause have a monoclonal gammopathy [18]. A low level stable paraprotein is not infrequently discovered in older persons, and often attributed to an insignificant monoclonal gammopathy of unknown significance (MGUS). Interestingly the majority of monoclonal gammopathies found in association with neuropathy are IgM (78%) and kappa (88%) [19]. For reasons unknown, gammopathies in POEMS syndrome are characteristically IgA and IgG (52 and 47% respectively) and almost never IgM [2]. Lambda light chain predominates and is seen in 95% of POEMS cases [2]. Although IgA or IgG lambda monoclonal proliferation can exist in cases of MGUS,

this peculiar pattern of heavy and light chain combination should serve as a 'red flag', strongly alerting clinicians to consider the diagnosis of POEMS or light chain amyloidosis.

Demonstration of a monoclonal plasma cell disorder can be through serological testing, urine, bone marrow or biopsy specimen histopathology. Serum protein electrophoresis (SPE), immunofixation and serum free light chain (SFLC) analysis must all be performed to detect a subtle plasma cell disorder with appropriate sensitivity. Many haematology laboratories do not provide immunofixation and serum free light chain analysis if preliminary investigations are unrevealing, and therefore neurologists must work with their laboratories to enable such testing as routine for all POEMS suspected cases. An example of this in clinical practice is below.

Case example 1: *The importance of thorough haematological investigations*
A 56 year old male with a background history of treated Castleman's disease presented in 2004 with lower limb neuropathic sounding pain. This progressed over 3 years to involve oedema and weakness with bilateral foot drop, and neurophysiology revealed a severe sensorimotor neuropathy with axonal loss on electromyography (EMG). Six SPE examinations were performed across a 3-year period, all of which were negative. In 2007, the first immunofixation was performed, and demonstrated a low level IgA lambda paraprotein not visible on SPE. This demonstrates the utility of immunofixation. If immunofixation and serum free light chain analysis are not performed, a monoclonal paraprotein will be missed in about 30% of POEMS cases [2].

Urine protein electrophoresis (UPEP), immunofixation and light chain analysis are performed through urine collection, and are often not sent for practical reasons. However, a random (as opposed to 24 hour collection) urine sample is all that is required to detect monoclonal proteins. The natural homeostatic ultrafiltration of urine is a serum free light chain concentrator, and can result in patients who are serum negative having positive urine results.

Case example 2- *The importance of testing the urine*
A 38 year old female presented with a demyelinating neuropathy diagnosed as probable CIDP, who had at least three SPE, immunofixation and SFLC assessments over two years, all of which were normal. The urinary Bence Jones Protein was positive, with free lambda light chains detected by immunofixation. By the time of detection, the patient had received prednisolone, 2 courses of intravenous immunoglobulin (IVIG), methotrexate and plasma exchange without any improvement. We use this example to stress the importance of sending all tests, including urine as part of the full investigative workup, where Bence Jones Protein or urinary light chains may be the only evidence of a monoclonal plasma cell disorder.

Bone marrow aspiration and trephine should be performed for immunophenotypic evaluation once a monoclonal plasma cell disorder is detected serologically or in the urine. Examination of the bone marrow provides an invaluable tool in the diagnosis and classification of plasma cell dyscrasias and to ascertain extent of disease [20]. Two thirds of bone marrow biopsies demonstrate a plasma cell malignant clone in POEMS [21] typically at a low level of around 5-10%, often with a very high proportion of abnormal cells restricted to expressing lambda light chains (≈90%). The presence of bone marrow lymphoid aggregates rimmed by monotypic or polytypic plasma cells should lead haematopathologists to raise the possibility of POEMS syndrome [21] (see figure 2). Megakaryocyte hyperplasia and clustering is also seen in POEMS syndrome bone marrow histology, and can therefore lead to the misinterpretation of a myeloproliferative disorder. However, one third of bone marrow biopsies will not demonstrate evidence of a plasma cell clone. This is because the monoclonal plasma cell disorder is limited to multifocal or solitary plasmacytomas (a discrete solitary mass of neoplastic monoclonal plasma cells in soft tissue or bone) [2,21,22]. For this reason, a non-diagnostic bone marrow result should necessitate further investigation for plasmacytomas through whole body imaging such as PET-CT. The CT modality enables sclerotic and lytic lesions to be identified and FDG-PET provides pointers to glucose-avid plasmacytomata. The most FDG-avid, accessible bone lesion should be biopsied to obtain histological confirmation of the diagnosis. The extent and location of monoclonal plasma cell disorder influences treatment decisions and is discussed further.

Multi system features

The wide-ranging multi system features of POEMS are displayed in table 1. Endocrine disturbance is seen in 65% of our UK POEMS cohort, with a high incidence of hypogonadism and hypopituitarism. Hypogonadism and hypopituitarism are most frequently manifested as erectile dysfunction and gynaecomastia in men, and early menopausal symptoms in women. The baseline prevalence of diabetes and thyroid disease is too high to include as diagnostic criteria for POEMS syndrome, unless there is a distinct temporal relationship with the onset of symptoms. Organomegaly of the spleen, liver or lymph nodes is detected in around 50% of our cohort. Red flags that should alert neurologists to the diagnosis of POEMS syndrome include 'glomeruloid haemangiomata'; dome shaped red-brown papular (sometimes pedunculated) nodules on the trunk or proximal extremities which are thought to develop secondary to overexpression of VEGF (see figure 1). Papilloedema is rare in inflammatory neuropathy [23] so when discovered should trigger investigation for POEMS syndrome where it is seen in around 40% [2]. If it is severe enough to be haemorrhagic, the haemorrhage is subretinal and very striking (see figure 1). Neuropathy in a young patient with unexplained peripheral oedema and skin changes suggesting capillary leak does not occur in CIDP and again are clinical clues to POEMS syndrome. Capillary leakage also occurs in the lungs, abdomen and heart resulting in poor gas transfer, ascites and pericardial effusions in severely affected patients.

Patients rarely present with the perfect cluster of symptoms described in the POEMS acronym. We have seen a variety of patients with POEMS variants and will present two examples below.

Case example 3- *POEMS without the 'P'*
A 45 year old male presented with a two year history of pain in the right lower limb on walking. Investigations revealed compression of the right femoral artery with lymphadenopathy, which on biopsy was reported as 'reactive changes'. He was suspected of having Castleman disease, but a repeat biopsy of another node to look for evidence for this was reported as reactive, with no evidence of Castleman's. An IgA lambda paraprotein was found on SPE/immunofixation, in association with an endocrinopathy with low testosterone. Serum VEGF was more than 5000pg/ml (ref range 5-771pg/ml). PET imaging revealed osteosclerotic lesions throughout the spine. A bone marrow trephine contained more than 15% plasma cells. Clinical examination revealed several glomerular haemangiomata on the trunk. Apart from pain in the lower right leg which was likely vascular in origin, there were no neuropathic symptoms in the limbs. Clinical examination and neurophysiology demonstrated no evidence of a neuromuscular disorder. The patient was diagnosed with POEMS syndrome based on the multitude of findings, but strictly does not fit the diagnostic criteria due to absence of polyneuropathy. The patient is awaiting an autologous stem cell transplant as first line therapy.

Case example 4- *'*O*MS'*
This patient presented following a seizure and was found to have had a left occipital stroke. During the investigation, both thrombocytosis and a raised haematocrit were noted, with negative myeloproliferative genetic tests (Jak2 and Cal-R mutations). An IgG lambda paraprotein was detected on SPE. A bone marrow biopsy revealed a 15% lambda-restricted plasma cell clone. Imaging revealed multiple lymph nodes and an L4 sclerotic lesion. Acrocyanosis of the peripheries was noted on clinical examination. There was no evidence of endocrinopathy. The sVEGF was markedly elevated at 11,000pg/ml (ref range 5-771pg/ml). The patient had no clinical or electrophysiological evidence of neuropathy. Lymph node biopsy revealed angiofollicular lymph node hyperplasia, consistent with Castleman's disease. Treatment with 5 cycles of lenalidomide, cyclophosphamide and dexamethasone was completed, to be followed by autologous stem cell transplantation. A recent PET scan has shown resolution of lymph nodal disease and sVEGF of 1074pg/ml after 4 cycles of lenalidomide and dexamethasone.

Castleman's disease is a lymphoproliferative disorder, which can be limited to a single group of lymph nodes (unicentric) or multiple lymph nodes and organs such as the spleen and thymus (multicentric). Castleman's can be present in up to 30% POEMS cases [24] on lymph node biopsy. POEMS patients with Castleman's are said to have less severe neuropathy, which may explain why there can be such heterogeneity. Other cases of atypical POEMS have been reported in the literature with an argument to redefine the diagnostic criteria and include the entity of Castleman's Disease Variant of POEMS [25]. An atypical presentation of POEMS with a positive VEGF is probably more likely to be POEMS than another

disease, and therefore VEGF is a useful test when faced with an atypical presentation. Guidance on interpreting results such as this is available through specialist clinics.

Investigating POEMS syndrome

Extensive investigations are required to confirm the presence or absence of a multitude of systemic features at diagnosis, during monitoring and following treatment. We propose an investigative guideline in table 3. Skeletal surveys and CT chest, abdomen and pelvis can be useful to identify mixed sclerotic and lytic bone lesions, but involve significant irradiation. Whole body MRI is often employed as a screening tool and PET CT is the most useful imaging modality to identify FDG-avid plasmacytomas or lymph nodes for biopsy.

The role of VEGF

VEGF has been proven to be a highly accurate surrogate biomarker of disease detection and activity in POEMS. Plasma and serum levels are markedly elevated compared to patients with other plasma cell dyscrasias ($P<0.001$), peripheral neuropathy ($P<0.001$) and connective tissue disease/vasculitis ($P<0.009$) [26,27]. Hypoxia, anaemia and low iron can lead to false positive results, but rarely as high as POEMS positive samples, which are 2 to 3 times the upper limit of normal [27]. False negative results can occur from patients treated within the last month with steroids and should be interpreted with caution [6,10]. Serum VEGF levels are 10-50 times higher than that of plasma in both health and disease, as serum contains VEGF released by ex vivo platelet activation during the clotting process, as well as the serum [6]. Both tests are similarly useful in the diagnosis and monitoring of POEMS, but for clarity, we advise using either the serum or the plasma for each patient and not both. Levels displayed in this paper are all serum VEGF.

Case example 5: *Anaemia and low iron induces VEGF production*

This 20 year old mechanic presented with acute global weakness following a sore throat, diagnosed as Guillain-Barré Syndrome. IVIG was initiated and the patient improved and was able to return to work. For the following year he experienced relapses on a two monthly basis. Each episode was responsive to steroids, IVIG or PLEX. Neurophysiology demonstrated a demyelinating polyradiculoneuropathy. There was albuminocytologic dissociation on CSF analysis. MRI revealed thickened nerve roots. No monoclonal paraprotein was detected by SPE, immunofixation or SFLC analysis. PET was normal. There were no bone lesions on imaging. Clinically there was no evidence of POEMS features other than neuropathy. A diagnosis of CIDP was made. A sVEGF was taken, and was found to be significantly raised at 1627pg/ml. A repeat sample result, 5 months after the first, was 2615 pg/ml. Bone marrow biopsy was then performed which was normal. Persistent iron deficiency anaemia was noted despite oral supplementation. Iron deficiency was thought to be driving the high sVEGF, and therefore was treated more aggressively with intravenous iron following normal endoscopy and colonoscopy. Subsequently, the sVEGF level dropped to 800pg/ml after 4 months, and is due further testing in due course.

Case example 6: *Hypoxia induces VEGF production*
A 55 year old female presented with a 10 month history of progressive weakness, numbness and pain in the distal lower limbs was diagnosed with POEMS following bone marrow biopsy and a sVEGF of 5657 pg/ml. Lenalidomide and dexamethasone was selected as initial treatment with co-trimoxazole prophylactic cover. Within one month of treatment, sVEGF reduced from 5657 to 599 pg/ml. The patient developed a rash, and co-trimoxazole stopped and dapsone initiated. Subsequently the patient developed methaemoglobinaemia secondary to dapsone, inducing hypoxia. sVEGF increased at this time to 1303pg/ml. Dapsone was stopped and the sVEGF rapidly normalised. See figure 3 for details.

Both cases illustrate that despite VEGF being highly sensitive and specific for POEMS syndrome, iron deficiency and hypoxia induce VEGF production so should be considered as a possible contributing factor when one is faced with abnormal values close to the upper limit of normal (ref range 5-771pg/ml). There have been other reported cases of patients with high false positive VEGF results such as in connective tissue disease and vasculitis [6]. For this reason, the VEGF level should be interpreted in the context of a typical POEMS neuropathy and a lambda light chain plasma cell dyscrasia to diagnose POEMS.

Treating POEMS syndrome

Despite VEGF being a sensitive biomarker of POEMS syndrome, trials of the anti-VEGF monoclonal, bevacizumab, yielded ineffective, if not detrimental results [9,10]. The mainstay of treating POEMS syndrome is therefore through suppression of the monoclonal plasma cell proliferation. This can be done in a number of ways, and depends on the extent of disease, co-morbidities and patient fitness.

As mentioned before, the monoclonal plasma cell disorder can consist of diffuse bone marrow infiltration, and/or solitary/ multifocal plasmacytomata. Patients with bone marrow involvement on bone marrow biopsy, or three or more plasmacytomas are considered to have systemic disease; two or fewer plasmacytomas is considered focal disease. Figure 4 provides a treatment algorithm dependent on the extent of disease.

Focal disease (One or two plasmacytomata)
Radiotherapy to two or fewer plasmacytoma lesions is first line treatment in focal disease. The objective is to obtain complete remission with minimal side effects whilst avoiding protracted treatment when compared to systemic therapies. From 67 patients with POEMS at the UCLH service, 22 patients have been treated with radiotherapy as first line. Eleven patients went onto have second line systemic therapy due to clinical or biochemical relapse, after an

average of 22 months (median 13 months). Eleven patients have remained clinically stable, with our longest surviving patient at 19 years post radiotherapy.

Case example 7- *How to treat focal lesions*
A 73 year old male with a background of ischemic heart disease presented in 2011 with generalised lower limb weakness, and bilateral foot drop. By six months the patient was wheelchair bound with little hand movement. Clinical examination revealed fluid overload, no evidence of skin lesions, organomegaly or papilloedema. Investigations revealed a severe length dependent sensorimotor demyelinating neuropathy and he was totally dependent on his family for his daily needs. Blood tests revealed evidence of subclinical hypothyroidism, and an IgG lambda paraprotein of 3g/L. Cerebrospinal protein level was significantly elevated at 2.8 g/L, with no cells. For this reason, a sVEGF was performed (11,000pg/ml, normal range 5-771pg/ml). A skeletal survey and follow up PET-CT demonstrated a solitary 'soap-bubble' lesion of the proximal left femur (see figure 5). A soap-bubble appearance is an expansile, often eccentric, vaguely trabeculated space with a thin sclerotic sharply defined margin, and usually signifies osteoclastomas/ giant cell tumours of the bone [28]. Bone marrow aspirate and trephine histology was normal. The femoral lesion was biopsied, which demonstrated a CD138 plasma cell infiltrate. The patient was given IV methylprednisolone for 3 days to stabilise his condition, resulting in an acute coronary syndrome for which he received coronary stents. Due to the poor stability of the femoral lesion, an intramedullary nail was inserted, and 25 fractions (total 50 Gray) radiotherapy was directed at the lesion. The sVEGF three months following fell to 506 pg/ml and the patient started to notice improved power in the lower limbs. He continues to improve; 5 years post radiotherapy the sVEGF has remained in normal limits, repeat imaging of the femoral lesion is stable, and the patient can now walk 200 yards with orthotics and is independent in activities of daily living.

Generalised disease (three or more plasmacytomas or positive bone marrow histology)
Systemic treatment should be used for patients with generalised disease. Melphalan conditioned Autologous Stem Cell Transplantation (ASCT) is the gold standard, with chemotherapy used for patients deemed unfit for transplantation.

Due to small patient numbers, treatment algorithms for POEMS syndrome have been adopted from multiple myeloma or light chain amyloidosis. High dose chemotherapy plus ASCT is the current gold standard treatment for POEMS syndrome, with good haematological control with progression free survival of 98%, 94% and 75% at 1, 2 and 5 years [29–31] and good organ-specific response levels, with 100% patients achieving 'a degree of neurological recovery' [32,33]. The ASCT for POEMS syndrome at University College London was performed in 1999 [34] for a 56 year old male, who remains in remission, fully ambulant with a most recent sVEGF of 276 pg/ml. Thirty-six have been performed subsequently, and only three patients have required further treatment with systemic chemotherapy. Age, comorbidities and physiological fitness should be considered prior to ASCT. We quote a 5-10% risk of the need for intensive care

treatment, and 3-5% risk of mortality, depending on performance status [31,35]. Engraftment syndrome has been quoted to occur in around 20%-50% of patients [31], however we have not seen this in our cohort of 36 treated patients. Patients can relapse, and in such cases, low dose long-term chemotherapy is an option, or a second ASCT but evidence is lacking.

Patients not deemed fit for ASCT can be treated with chemotherapeutic agents as pre-transplant induction therapy, enabling transplantation at a later date, or long term if stem cell transplantation is not an option. Broadly speaking, chemotherapy used to be based on an alkylating agent (such as melphalan or cyclophosphamide) and dexamethasone [30,36]. Thalidomide and lenalidomide, potent inhibitors of tumour secreting cytokines such as interleukin 6, tumour necrosis factor and VEGF are emerging as treatments for POEMS syndrome. We are now often using lenalidomide as first line therapy. A systematic review of lenalidomide in POEMS reported neuropathy improvement in 90% of cases, and a progression free survival estimate at 12 months of 93% [37]. We have seen remarkable rapid improvement in clinical status, particularly in fluid overload, VEGF and haematological response using lenalidomide and dexamethasone. Peripheral neuropathy with thalidomide, and risk of thrombosis with both agents require careful monitoring and the need for prophylactic low molecular weight heparin. Bortezomib as a single agent, or combined with cyclophosphamide has demonstrated promising results in 25 patients, but can also cause or worsen peripheral neuropathy [38].

Case example 8- *Choosing the correct therapy*
A 69 year old male was suspected of having POEMS syndrome on the basis of demyelinating polyneuropathy, fluid overload, skin changes (acrocyanosis and hypertricosis) and papilloedema. Investigations revealed an IgG lambda paraprotein of 9g/l, sVEGF of 2843pg/dl and a solitary plasmacytoma of the left ilium which demonstrated plasma cell infiltration. Bone marrow biopsy of the right ilium was normal. Nineteen fractions of local radiotherapy were provided. Three months following radiotherapy, the patient was noted to have weight loss and worsening neuropathy, and sVEGF had doubled to 4865pg/ml. Disease reassessment included a repeat PET-CT scan which demonstrated evidence of multifocal skeletal lesions with persistent avidity in the index lesion. Retrospective analysis of the original PET scan revealed evidence of bone lesions which previously had not been reported. Due to the presence of systemic disease, Lenalidomide and Dexamethasone were initiated with prior stem cell harvesting with a view to autologous stem cell therapy. Systemic induction immunomodulatory therapy was used prior to transplant in an attempt to limit the collective volume of multifocal skeletal plasmacytomas.

Disability management

Multi-disciplinary input is essential when caring for patients with POEMS syndrome. Disability management through the use of orthotics, walking aids and home adaptations should be provided through physiotherapy and occupational therapy services, preferably in a multidisciplinary environment. Neuropathy in

POEMS classically takes around 2-3 years post-treatment before significant improvement begins. A retrospective review of 60 POEMS patient post ASCT showed a median improvement in the neuropathy impairment score of 18 points (66 to 48 points) in 12 months and 30 points at a median follow up of 60 months.[32] We typically refer patients for neuro-rehabilitation both early in disease and once neuropathy starts to improve. Educational and emotional support can be provided through specialist nurses and psychologists, and we refer patients to the POEMS Facebook group (search 'POEMS syndrome' on Facebook for the page).

Monitoring

Assessing response to treatment and monitoring is complex and requires thorough investigation and clinical assessment to determine response. Broadly, the following categories are used to assess response:

1) **Haematological response:** This is defined by the clearance of monoclonal proteins and plasma cells from the blood and bone marrow respectively. This can be misleading, as the monoclonal component in POEMS tends to be very subtle, and patients can improve significantly despite the absence of a monoclonal protein response [30].
2) **VEGF:** VEGF tends to correlate with disease activity, and should normalise (serum level<771pg/ml) over 6 months, but again can show discordance with response.
3) **PET-CT imaging**: This can be useful to demonstrate reduction in standardised uptake values (SUV_{max}) of previously avid lesions. Reductions in SUV take many months (often more than 12).
4) **Organ response:** Organ response can be difficult to quantify, but the following markers would indicate improvement
    - Reduction in weight secondary to resolution of fluid overload
    - Shrinkage of enlarged organs or lymph nodes
    - Shrinkage or disappearance of glomeruloid haemangiomata
    - Improvement in pulmonary and cardiac function
    - Improvement in neuropathy severity scores such as RODS-CIDP or MRC sum scores.

Collating all the above provides an overall picture of the patient's disease status. Any worsening of clinical, radiological or haematological indicators should instigate further investigation with the tests highlighted in table 3, ultimately with consideration of a bone marrow biopsy where appropriate.

Case example 9- *Assessing and monitoring response to treatment*
A 72 year old farmer was diagnosed in 2012 with POEMS on the basis of a demyelinating peripheral neuropathy, organomegaly, IgG lambda paraprotein of 6g/dl and a solitary FDG-avid pubic bone lesion on PET-CT imaging. Bone marrow biopsy also demonstrated 10% plasma cell infiltration. sVEGF level was 3917 pg/ml. At the time of diagnosis, the patient was unable to stand. Systemic

therapy with melphalan and dexamethasone was initiated, and focal radiotherapy to the pubic bone lesion was delivered as 30Gy in 10 fractions, completed in February 2013. At four months following treatment, repeat PET–CT imaging demonstrated no change to the pubic bone lesion, but more reassuringly, sVEGF had reduced to 550pg/ml, and paraprotein level had halved to 3g/dl. At this stage, repeat bone marrow biopsy was indicated to ascertain the degree of residual disease burden. This demonstrated 1% plasma cell infiltration, and at six months the patient started to show signs of neuropathy improvement in reduction of pain and increased mobility. It was therefore decided to continue monitoring at this stage. If the bone marrow was persistently abnormal this would indicate ongoing disease, in conjunction with the unchanged appearance of the pubic bone lesion, and therefore consideration of systemic/immunomodulatory therapy. Repeat PET imaging one year following treatment in February 2014 demonstrated reduced avidity of the lesion from SUV_{max} of 14.1 to 4.9. sVEGF remained low at 350pg/ml, and the paraprotein undetectable. This case demonstrates that PET avid lesions can persist despite there being a response to treatment and the importance of considering multiple factors when assessing response to therapy. The patient remains well, and demonstrated this by jogging into the clinic room on his last visit.

POEMS syndrome is a devastating condition for many patients, unless prompt diagnosis and provision of effective treatment prevents significant disability and the multitude of associated features. Identification of a demyelinating peripheral neuropathy, a lambda light chain monoclonal plasma cell disorder and raised VEGF are key to making the diagnosis. Investigations identify focal from systemic disease, which guides subsequently highly effective treatment in the form of radiotherapy, chemotherapy or autologous peripheral stem cell transplantation.

Learning points

1) Not all patients with POEMS present with the classic features described in the acronym.
2) We recommend all patients presenting with an inflammatory neuropathy to have appropriate investigations for the presence of a monoclonal plasma cell proliferative disorder, and if abnormal,consideration of VEGF.
3) Patients are deemed to have focal or systemic disease based on the extent of monoclonal plasma cell dyscrasia, and this should guide subsequent treatment options.

VEGF testing is performed currently at the Department of Neuroimmunology, at the National Hospital for Neurology and Neurosurgery, London and has a turnaround time of around 2 weeks.

Table 1: Diagnostic criteria for POEMS syndrome

Criteria	
Mandatory major criteria	1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder
Other Major criteria (one required)	3. Castleman disease 4. Sclerotic bone lesions 5. Raised Vascular endothelial growth factor
Minor criteria	6. Organomegaly (spleen/liver/ lymph nodes) 7. Extravascular volume overload 8. Endocrinopathy (adrenal, thyroid*, pituitary, gonadal, parathyroid, pancreatic*) 9. Skin changes 10. Papilloedema 11. Thrombocytosis/polycythemia
Other useful features	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/ restrictive lung disease, thrombotic diathesis, diarrhoea, low vitamin B_{12}.

*Due to high prevalence of thyroid disease and diabetes, this diagnosis alone is not sufficient to meet criteria for endocrinopathy.

Table 2: History, examination and neurophysiological findings to distinguish POEMS neuropathy from CIDP

Assessment	POEMS syndrome	CIDP
History	Length dependent sensory and motor neuropathy	Patchy predominantly motor neuropathy with both proximal and distal features at onset
	Presence of pain typical (65%) [17]	Pain atypical
	Other multi-systemic symptoms present: Gynaecomastia Erectile dysfunction	Multi systemic features less likely and unrelated

		Weight loss Skin changes Oedema History of DVT	
Examination	**General**	Finding of lymph nodes, skin lesions, organomegaly, papilloedema, peripheral oedema	Neuropathy likely in isolation
	Neuropathy	Dramatic distal weakness, predominantly UL flexors> ext. LL DF>>PF. Early distal wasting.	Evidence of proximal and distal weakness.
Investigation	**Blood/urine for monoclonal protein** [30,39]	Monoclonal IgA or IgG typical. IgM rare. Almost always lambda light chain	MGUS in 10-20%. Distribution of classes and light chains balanced. Consider MAG and GM1.
	Thrombocytosis [30]	Seen in 54% patients	Seen in 1.5%
	VEGF	Likely >2x ULN (ref range sVEGF 5-771pg/ml)	Almost never raised unless anaemia, renal failure. Unlikely ever >2xULN
	Neurophysiology [14,17,40]	Axonal and demyelinating. Preferential lower limbs, intermediate > distal nerve CV slowing. Conduction block (6%) and temporal dispersion unlikely.	Less axonal loss. Patchy proximal and distal demyelination. Conduction block (23%) and temporal dispersion more common.
	Nerve biopsy[16,17]	More axonal degeneration, diffuse myelinated fibre loss, increased epineurial blood vessles. Uncompacted myelin lamellae.	Endoneurial inflammation, multifocal myelinated nerve fibre loss.
	Imaging	Sclerotic and lytic bone lesions on xray/CT/PET	Not routinely required.
		Solitary lesion can represent	

		plasmacytoma-needs biopsy to confirm	
Treatment	**Steroids**	Mild response	Responsive*
	Immune therapy	Not responsive to IVIG/PLEX	Responsive to IVIG/PLEX*

*Note approximately 20% of CIDP patients will be poorly or unresponsive to steroids, IVIG and PLEX.

Table 3: Investigative work-up for suspected POEMS cases

Feature	**Investigation**	**Typical abnormality**
Polyneuropathy	NCS/EMG	Axonal and demyelinating. Preferential lower limbs, intermediate > distal nerve CV slowing. Conduction block (6%) and temporal dispersion unlikely.
	Nerve biopsy**	Not necessary if diagnosis is clear with elevated VEGF levels. Axonal degeneration, diffuse myelinated fibre loss, increased epineurial blood vessles. Uncompacted myelin lamellae.
	Cerebrospinal fluid**	Albuminocytological dissociation. Normal cell count. Mild increase opening pressure. Not specific so not always necessary.
Organomegaly	CT chest/abdomen/pelvis and	Lymph node, spleen, liver

	PET CT		
Endocrinopathy*	Adrenal	Cortisol	Typically low- Addisonian
	Thyroid	TSH, T4	Hypo or hyperthyroid
	Pituitary	LH, FSH, IGF-1, ACTH, Prolactin	Typically hypofunctioning
	Gonadal	Testosterone, oestradiol	Typically low
	Parathyroid	PTH	
	Pancreatic	HbA1c, glucose	Typically raised
Monoclonal plasma cell disorder	Serum protein electrophoresis		IgG or IgA lambda monoclonal, low kappa:lambda ratio.
	Immunofixation		
	Serum free light chain analysis		
	Urine protein electrophoresis/immunofixation		Bence Jones Protein
	Bone marrow biopsy +/- targeted bone lesion biopsy		Presence of plasma cells on immunofixation, typically lambda light chain restricted
Skin	Clinical diagnosis; history and examination		Acrocyanosis, hypertrichosis, nail changes, glomerular haemangiomata
Papilloedema	Ophthalmological assessment		
Extravascular volume overload/ cardiac involvement	Echocardiogram**		Reduction of left or right ventricular ejection fraction, elevation of pulmonary artery pressure. Evidence of previous ischemia.
Sclerotic bone lesions	CT bone windows, PET CT imaging		Sclerotic lesions / mixed lytic with sclerotic
Thrombocytosis	Full blood count		Increased platelets
Pulmonary function	Pulmonary function tests**		Pulmonary hypertension, restrictive disease, respiratory muscle weakness, reduced diffusion capacity.

*Endocrinopathy bloods should be taken fasted in the morning before breakfast
** Test not essential for diagnosis, but useful

References

1. Bardwick, P. . *et al.* Plasma Cell Dyscrasia with Polyneuropathy, Organomegaly, Endocrinopathy, M Protein, and Skin Changes: The POEMS Syndrome: REPORT ON TWO CASES AND A REVIEW OF THE LITERATURE. *Medicine (Baltimore).* **59,** 311–22 (1980).
2. Dispenzieri, A. *et al.* POEMS syndrome: Definitions and long-term outcome. *Blood* **101,** 2496–2506 (2003).
3. Gherardi, R. K. *et al.* Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood* **87,** 1458–65 (1996).
4. Souza, A. D. *et al.* Brief report The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. **118,** 4663–4666 (2015).
5. Kanai, K. *et al.* Markedly upregulated serum interleukin-12 as a novel

biomarker in POEMS syndrome. *Neurol.* **79,** 575–582 (2012).
6. Briani, C. *et al.* Pentraxin-3 and VEGF in POEMS syndrome: A 2-year longitudinal study. *J. Neuroimmunol.* **277,** 189–192 (2014).
7. Michizono, K. *et al.* Circulating levels of MMP-1, -2, -3, -9, and TIMP-1 are increased in POEMS syndrome. *Neurology* **56,** 807–810 (2001).
8. Watanabe, O., Arimura, K., Kitajima, I., Osame, M. & Maruyama, I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. *Lancet* **347,** 702 (1996).
9. Kanai, K., Kuwabara, S., Misawa, S. & Hattori, T. Failure of treatment with anti-VEGF monoclonal antibody for long-standing POEMS syndrome. *Intern Med* **46,** 311–313 (2007).
10. Sekiguchi, Y. *et al.* Ambiguous effects of anti-VEGF monoclonal antibody (bevacizumab) for POEMS syndrome. *J. Neurol. Neurosurg. Psychiatry* **84,** 1346–8 (2013).
11. Watanabe, O. *et al.* Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. *Muscle and Nerve* **21,** 1390–1397 (1998).
12. Soubrier, M. *et al.* Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. *Arthritis Rheum* **40,** 786–787 (1997).
13. Dispenzieri, A. POEMS syndrome. *Blood Rev* **21,** 285–299 (2007).
14. Nasu, S. *et al.* Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. *J. Neurol. Neurosurg. Psychiatry* **83,** 476–9 (2012).
15. Köller, H., Kieseier, B. C., Jander, S. & Hartung, H.-P. Chronic Inflammatory Demyelinating Polyneuropathy. *N. Engl. J. Med.* **352,** 1343–1356 (2005).
16. Vital, C. *et al.* Crow-Fukase (POEMS) syndrome: a study of peripheral nerve biopsy in five new cases. *J. Peripher. Nerv. Syst.* **8,** 136–44 (2003).
17. Koike, H. *et al.* Neuropathic pain correlates with myelinated fibre loss and cytokine profile in POEMS syndrome. *J. Neurol. Neurosurg. Psychiatry* **79,** 1171–1179 (2008).
18. Rison, R. A. & Beydoun, S. R. Paraproteinemic neuropathy: a practical review. *BMC Neurol.* **16,** 13 (2016).
19. Vallat, J. M. *et al.* Link between peripheral neuropathy and monoclonal dysglobulinemia: A study of 66 cases. *J. Neurol. Sci.* **137,** 124–130 (1996).
20. Kumar, S., Kimlinger, T. & Morice, W. Immunophenotyping in multiple myeloma and related plasma cell disorders. *Best Pract. Res. Clin. Haematol.* **23,** 433–451 (2010).
21. Dao, L. N. *et al.* Bone marrow histopathology in POEMS syndrome: A distinctive combination of plasma cell, lymphoid, and myeloid findings in 87 patients. *Blood* **117,** 6438–6444 (2011).
22. Soubrier, M. J., Dubost, J. J. & Sauvezie, B. J. POEMS syndrome: a study of 25 cases and a review of the literature. French Study Group on POEMS Syndrome. *Am. J. Med.* **97,** 543–53 (1994).
23. Farrell, K., Hill, A. & Chuang, S. Papilledema in Guillain-Barré Syndrome. *Arch. Neurol.* **38,** 55 (1981).
24. Li, J. & Zhou, D. New advances in the diagnosis and treatment of POEMS syndrome. 303–315 (2013). doi:10.1111/bjh.12236
25. Misawa, S. & Kuwabara, S. Polyneuropathy, organomegaly,

endocrinopathy, monoclonal gammopathy and skin changes (Crow-Fukase) syndrome: Diagnostic criteria and treatment perspectives. *Clin. Exp. Neuroimmunol.* **4,** 318–325 (2013).
26. Souza, A. D. *et al.* Brief report The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. **118,** 4663–4666 (2017).
27. Pihan, M. *et al.* Raised Vegf: Usefulness in the Diagnosis of Poems Syndrome. *J. Neurol. Neurosurg. Psychiatry* **85,** e4.92-e4 (2014).
28. Yochum, T. & Rowe, L. *Essentials of skeletal radiology*. (Lippincott Williams & Wilkins, 1996).
29. D'Souza, A. *et al.* Long-term outcomes after autologous stem cell transplantation for patients with POEMS syndrome (osteosclerotic myeloma): a single-center experience. **120,** 56–62 (2012).
30. Dispenzieri, A. POEMS syndrome: 2017 Update on diagnosis, risk stratification, and management. *Am. J. Hematol.* **92,** 814–829 (2017).
31. Cook, G. *et al.* High-dose therapy and autologous stem cell transplantation in patients with poems syndrome: A retrospective study of the plasma cell disorder sub-committee of the chronic malignancy working party of the European society for blood & marrow transplantation. *Haematologica* **102,** 160–167 (2017).
32. Karam, C. *et al.* Polyneuropathy improvement following autologous stem cell transplantation for POEMS syndrome. *Neurology* **84,** 1981–1987 (2015).
33. Kuwabara S.; Kanai, K.; Suzuki, Y.; Kikkawa, Y.; Sawai, S.; Hattori, T.; Nishimura, M.; Nakaseko, C., S. . M. Neurologic improvement after peripheral blood stem cell transplantation in POEMS syndrome. *Neurology* **71,** 1691–1695 (2008).
34. Peggs, K. S. *et al.* Peripheral blood stem cell transplantation for POEMS syndrome. *Bone Marrow Transplant.* **30,** 401–404 (2002).
35. Dispenzieri, A. *et al.* Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome. *Eur. J. Haematol.* **80,** 397–406 (2008).
36. Kuwabara S, N. C. *et al.* Cochrane Database of Systematic Reviews Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome (Review) i Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syn. (2012). doi:10.1002/14651858.CD006828.pub3
37. Zagouri, F. *et al.* Lenalidomide in patients with POEMS syndrome: a systematic review and pooled analysis. *Leuk. Lymphoma* **55,** 2018–2023 (2014).
38. He, H., Fu, W., Du, J., Jiang, H. & Hou, J. Successful treatment of newly diagnosed POEMS syndrome with reduced-dose bortezomib based regimen. *Br. J. Haematol.* (2017). doi:10.1111/bjh.14497
39. Dimachkie, M. M. & Barohn, R. J. Chronic inflammatory demyelinating polyneuropathy. *Curr. Treat. Options Neurol.* **15,** 350–366 (2013).
40. Mauermann, M. L. *et al.* Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. *J. Neurol. Neurosurg. Psychiatry* **83,** 480–6 (2012).