The natural history of POEMS syndrome: clinical characteristics, risk factors and outcomes

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Abstract

Objective: POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin lesions) is a paraneoplastic disorder resulting in severe neurological disability. Understanding the natural history of POEMS will assist in more accurate and timely diagnosis, risk stratification and effective management.

Methods: Retrospective longitudinal cohort study from 1998 to March 2019, with 7184 person-months of follow up time. Hospital databases were utilised to collate presenting features, investigations, therapies and response.

Results: One hundred patients included, with median follow up time of 59 months (1-252). Mean symptom onset to diagnosis was 15 months (1-77), with 54% patients initially misdiagnosed as having Chronic Inflammatory Demyelinating Polyneuropathy. Median number of multi-system features at diagnosis was 7. Ninety-six (96%) presented with neuropathy which was length dependent in 93 (93%) and painful in 75 (75%). At diagnosis, 35% of patients were wheelchair or bedbound, with median ONLS of 6, improving to 3 following treatment ($p<0.05$). Five-year survival was 90% and 82% at 10 years, with five and 10-year progression free survival of 65% and 53%. Non-treatment with autologous stem cell transplantation, non-haematological response and non-VEGF response are significant risk factors in multivariate analysis to predict progression or death. Risk factors are incorporated to develop a risk score enabling stratification of high and low risk cases.

Conclusions: POEMS syndrome is a rare multi-system condition with delayed diagnosis and poor neurological function at presentation. Therapy has favourable outcomes. Patients at high risk of death or progression can be identified which may allow for more active monitoring and influence management.

Introduction

POEMS syndrome is a rare multi-system, autoinflammatory paraneoplastic condition, defined by the presence of an inflammatory peripheral neuropathy and a monoclonal plasma cell disorder. Pathogenesis of POEMS syndrome is not completely understood. The monoclonal plasma cell dyscrasia is thought to influence an overproduction of proinflammatory cytokines with downstream effects. Vascular endothelial growth factor (VEGF), a potent multifunctional cytokine responsible for angiogenesis and vascular hyperpermeability, is markedly elevated in untreated POEMS compared to other haematological malignancies and inflammatory neuropathies and therefore felt to play some role [1–3].

Despite the existence of internationally recognised diagnostic criteria for POEMS [4] the disease remains difficult to diagnose. The neuropathy with demyelinating neurophysiology can be misattributed to a diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP); the subtle monoclonal plasma cell disorder is often overlooked, and systemic features are often attributed to unrelated co-morbidities. Unfortunately, because of resistance to CIDP treatments and diagnostic delays, patients are typically severely disabled with multiple medical comorbidities and poor performance status by the time of diagnosis [5]. POEMS syndrome necessitates multidiscinplinary collaboration to diagnose and manage the diverse disease aspects effectively.

This study provides an in depth and detailed description of the largest single centre cohort of POEMS patients studied in Europe, which includes 100 patients over 20 years. We pay particular focus on the peripheral and central neurological features of disease, neurological

function and recovery. We establish risk factors for progression or death in POEMS syndrome and define an easily applicable risk score to stratify high and low risk cases. Such data and those already published can be utilised to ascertain appropriate investigative and management strategies to improve diagnosis and treatment.

Materials and methods

A retrospective review of all patients with a diagnosis of POEMS syndrome attending the national POEMS service at University College London Hospital (UCLH), UK from 1998 to March 2019 was performed with our institutional database. Patients who fitted internationally recognised diagnostic criteria for POEMS were selected [4]. Clinical features, laboratory, radiological, neurophysiological and histopathological findings were collected, as were treatments and outcome. Patients' local physicians or general practitioners were contacted for patients for whom incomplete follow-up data were available in the year preceding data collection. Definitions of response to treatment and progression were based on five main domains, and based on previously reported measures [6,7]:

- **Clinical –** Four clinical response categories have been used: Clinical improvement (Ci), clinical progression (Cp), mixed clinical response (Cm) and Clinical stability (Cs). This was based on patient and physician qualitative reports of constitutional symptoms and systemic feature.
- **Neuropathy-** defined by clinical examination, neurophysiology, modified Rankin Score [8] and Overall Neuropathy Limitation Score (ONLS) [9]. Progression defined as worsening of functional ability by an increase of ONLS by ≥1.

- **Haematological –** evaluated according to modified International Myeloma Working Group criteria [10].
    - Complete response (H-CR): negative bone marrow (BM), negative immunofixation (IF) of serum and urine.
    - Very good partial response (H-VGPR): 90% reduction in Monoclonal (M)-protein or IF positive as long as M-protein at least 0.5g/dL at baseline.
    - Partial response (H-PR): 50% reduction in M-protein or IF positive as long as baseline M-protein was at least 1.0g/dL.
    - No response (H-NR): not fulfilling the above.

  Progression defined by re-emergence of serum/urine M-protein if undetectable or increase by 25% from lowest post treatment value.

- **Serum Vascular Endothelial Growth Factor (sVEGF) Biochemical -** The upper limit of the normal range (ULN) was determined at 771 pg/mL. Responses were defined as below.
    - Complete response (VEGF-CR): normalisation of levels.
    - Partial response (VEGF-PR): >50% reduction of sVEGF if baseline over 2000 pg/ml.
    - No response (VEGF-NR): doesn't fulfil the above.
    - Not evaluable (VEGF-NE): initial sVEGF not raised/not taken.

  Progression defined by persistent (≥2 recordings) sVEGF elevation ≥771pg/ml from a previously normal result. If lowest post treatment value was ≥771pg/ml (i.e. not normalised), a persistent rise in sVEGF of >50% from lowest post treatment value was defined as progression.

- **FDG-PET (radiological) response**
    - Complete response (R-CR): disappearance of Standardised Uptake Units (SuV) avidity.
    - Partial response (R-PR): >50% reduction of SuV avidity of lesions.
    - No response (R-NR): doesn't fulfil the above
    - Not evaluable (R-NE): initial PET scan does not show avidity.

  Progression defined by increase in size or avidity of lesion, or new plasmacytomas.

Statistical methods

Baseline characteristics were presented by number and percentage or median and interquartile range (IQR) for continuous data. Wilcoxon signed rank test was performed to compare pre and post treatment sVEGF levels and ONLS scores. Kaplan-Meier methods were used to plot progression free and overall survival by time. Survival was calculated from time of diagnosis. Progression free survival was defined from the time of treatment to progression.

Risk factor identification was performed by comparing log-rank univariate analysis of all potential risk factors to the outcome of death or progression. Continuous variables were transformed into categorical variables based on routine cut off variables i.e. pulmonary hypertension defines by pulmonary artery systolic pressure >50mmHg. Variables with strong significance ($p<0.01$) were included in a multivariate model.

Factors which remained significant in the multivariate model were utilised to build a risk score for poor outcome (death or progression). The variable with the lowest hazards ratio

(HR) was assigned a value of 1, and other variables assigned a score relative to their HR. Risk scores were plotted on Kaplan Meier curves and similar trends combined to identify the optimum number of subgroups. Once ascertained, pairwise log-rank comparison was applied to determine the difference in risk between low and high-risk groups.

Standard Protocol Approvals, Registrations and Patient Consents

The study was approved by the Health Research Authority and London Queen Square Research Ethics Committee. All patients provided informed written consent.

Data Availability

Anonymised data will be shared by request from any qualified investigator.

Results

A total of 100 patients were included, of which follow-up data were available for 97 patients (97%). Median follow up was 59 months (range 1 to 252 months). The average interval from symptom onset to diagnosis was 15 months (range 1-77 months). Demographic data and diagnoses made prior to POEMS syndrome are detailed in table 1, and clinical and investigational features are summarised in table 2.

Polyneuropathy

Ninety-six (96%) patients had evidence of polyneuropathy on examination and neurophysiological testing. Two patients without evidence of polyneuropathy had the Castleman variant POEMS syndrome, in which the neuropathy is typically mild [11]. The

majority (90%) of patients presented with a sensorimotor neuropathy, with a small proportion presenting with pure sensory (5%) or motor symptoms (1%). Three of the five patients with pure sensory neuropathy had Castleman variant POEMS. A definite length dependent, symmetrical progression in sensory symptoms was observed in 93 (93%) of those with neuropathy. No patients presented with polyradiculoneuropathy with early proximal involvement. On presentation, sensory symptoms were varied with numbness most commonly to the foot in 14 (14%), 'short sock' distribution in 13 (13%) and the knees in 25 (25%). In the upper limbs, numbness was most commonly to the fingers (12%) and wrists in 26 (26%). Sensory examination was varied, but most commonly vibration was reduced to the elbows and the anterior superior iliac spine, pin prick to the mid forearm and the knees, and joint position sensation normal in the upper limbs and absent at the hallux. Pain was a commonly reported symptom, with 75 (75%) patients complaining of neuropathic pain, initially developing as a bilateral cramping, tight sensation in the calf, but not specifically cramp.

By the time POEMS was diagnosed, 9 (9%) patients were bedbound requiring hoists to transfer and 27 (27%) were wheelchair bound. Of those still ambulant, 14 (14%) were already using a frame, 26 (26%) using one or two sticks and 23 (23%) unaided or using orthotics (see figure 1). The median modified Rankin Scale (mRS) was 3 and the median ONLS was 6 at presentation. In contrast the median ONLS for the Castleman variant POEMS patients (n=14, 14%) was 2.

Neurophysiological data were collected for 96 (96%) patients. Findings were broadly homogenous, with reports of a sensory (83%) and motor (87%) neuropathy with conduction

velocity slowing (85%)) and secondary axonal loss (72%). Four studies were reported as normal, two of which were in Castleman variant patients without clinical evidence of neuropathy. Only two studies reported conduction block and none temporal dispersion.

When a lumbar puncture was performed (65%), cerebrospinal fluid (CSF) protein was abnormally raised in 100% of samples, the median value being 1.25g/L, and the highest being 9g/L (range 0.6-9g/dL, normal <0.4g/L). A sensory nerve biopsy was performed in 17 (17%) cases. All cases were reported as having loss of large and small myelinated fibres (ranging from mild to severe fibre loss). Review of 12 biopsies showed frequent active axonal degeneration in seven, occasional in three and absent in two. Widespread epineural neovascularisation with haemosiderin deposits in the vicinity was seen in one biopsy, with focal neovascularisation evident in further three biopsies. Epineural perivascular lymphocytes were mildly increased in numbers in four, scarce in six and absent in two biopsies. Endoneural T lymphocytes were frequent (up to 10 per transverse section) in three biopsies and rare to absent in the other nine biopsies. Teased fibres were available for four biopsies and showed frequent segmental demyelination in a single case with no evidence of segmental demyelination in the other three cases. Electron microscopy was available for review for 10 cases and showed un-compacted myelin in five. Onion bulb formations, a feature of chronic demyelinating / re-myelinating process, was not seen in any of the 10 biopsies, but several denuded axons were seen in 1/10 biopsies and abnormally thin large myelinated fibres were observed in four biopsies.

Central nervous system features

Central nervous system involvement is also seen in POEMS syndrome. Nine patients experienced a stroke, seven of which were ischaemic and two subarachnoid haemorrhages. Ischaemic stroke was the presenting feature in three patients before other systemic features were discovered and the diagnosis of POEMS made. Of the ischaemic strokes, there were three middle cerebral artery infarcts, one lacunar, and three in the posterior circulation. Four patients had concomitant thrombocytosis, one had erythrocytosis. Three of these four experienced venous thromboembolism.

A retrospective review of 41 brain MRIs of patients with POEMS syndrome were compared to a control group of 19 brain MRIs from patients with CIDP. Images were interpreted by two consultant neuroradiologists blinded to the diagnosis. MRI scans from POEMS patients demonstrated smooth diffuse meningeal thickening of the cerebral convexities and falx in 29/41 (71%), meningeal collections in 4/41 (10%) and white matter lesions in 17/41 (41%). Of the 29 cases of pachymeningitis, only nine had documentation of such on the patients' initial hospital radiology report; an additional 20 were identified following retrospective but blinded review. Despite the hypothesised role of angiogenic factors contributing to meningeal thickening in POEMS syndrome [12], no correlations were found between VEGF and maximal meningeal thickness or any vascular abnormalities or between disease duration and meningeal thickness. Twenty-nine/45 patients had spinal MRI, with brachial and lumbrosacral plexus thickening in 17 patients (59%). When compared to an age and sex matched cohort of CIDP cases (19 brain and 26 spine MRIs), none of the brain MRIs that were performed had meningeal thickening ($p<0.0001$), 42% had white matter abnormalities and 35% thickened nerve roots. Details of these MRI findings have been published separately [13].

Monoclonal plasma cell dyscrasia

Of the 100 patients, 55 (55%) were found to have a paraprotein on serum protein electrophoresis (SPE). The median paraprotein level was 4g/dL (range undetectable-17 dL). Serum immunofixation (IF) detected an abnormality in 78% of which 34 (44%) were IgG, 42 (53%) were IgA, and two were biclonal (3%). Seventy-seven of 78 (98%) were lambda light chain restricted, and only one patient had a kappa paraprotein. Had immunofixation not been performed, a monoclonal protein would have been missed in 23 patients. Twenty-one (21%) had both negative serum protein electrophoresis and immunofixation. A monoclonal plasma cell disorder was confirmed in 11 of these cases through bone marrow biopsy and ten targeted plasmacytoma biopsy. Urinary Bence Jones Protein was detectable in five patients with negative SPE and IF and therefore would otherwise have been missed during routine non-invasive investigation.

Serum free light chains (SFLC) were abnormal in 65 of 82 cases (79%) performed at presentation. SFLC demonstrated both raised kappa and lambda in 41 cases (50%), raised kappa and normal lambda in 16 (20%), and normal kappa and raised lambda in eight (10%). When the kappa light chain was raised with normal lambda, the kappa light chains were only minimally raised above the upper limit of normal, with a median value of 28.5mg/L (upper limit 19.4mg/L). In such cases, lambda light chains were often concurrently raised but under the upper limit of normal, with a median level of 17.3mg/L (upper limit 26.3mg/L), resulting in a median ratio of 1.8. The kappa:lambda SFLC ratio was normal on 65 occasions (78%), high in only 14 and low in four illustrating the low detection ability for this test. The most likely abnormal result is both raised kappa and lambda SFLCs, resulting in a normal kappa:lambda ratio. Urinary Bence Jones protein was detectable in 15 cases.

Bone marrow aspirate and trephine was performed in 86 of 100 cases. Thirty one of 86 (36%) were reported as normal, and 55/86 (64%) displaying features of a plasma cell neoplasm with abnormal CD138 plasma cells and lambda light chain restriction in 30. A clonal population of between 1-5% was most commonly reported on bone marrow histology (42%). The most frequent histological description was of megakaryocyte hyperplasia. Patients who did not undergo bone marrow biopsy had histopathological confirmation of plasmacytoma through targeted bone lesion biopsy.

Targeted bone lesion biopsy was performed in 42% cases. Sites for biopsy included the pelvis (27), spine (15), humerus (2), ribs, sternum and skull (1). Thirty-eight of 42 were abnormal (90%), with median plasma cell proportion of 10%.

Castleman Disease

Castleman disease (CD) typical histology was found in 14 patients on targeted lymph node biopsy. Note that of the 42 patients with lymphadenopathy, only 18 underwent a targeted lymph node biopsy as the diagnosis was considered secure from other evidence. The additional discovery of CD histology in patients with a secure POEMS diagnosis was not deemed clinically relevant in most cases hence the lack of biopsy.

Endocrinopathy

Endocrinopathy was found in 68% of the patient cohort at diagnosis. Thirty-two (32%) had more than one endocrine abnormality. The most common deficiencies at the end of follow-up were hypogonadotrophic hypogonadism (72%), hypothyroidism (45%), abnormal glucose

metabolism (16%) and adrenal insufficiency (15%). Endocrine abnormalities are discussed in a separate publication elsewhere in more depth [14].

Organomegaly and lymphadenopathy

Organomegaly was seen in 63% of cases. Forty-two percent were found to have lymphadenopathy, 31% had splenomegaly and 23% hepatomegaly. Fifty percent of patients with organomegaly had more than one organ involved.

Skin

Skin changes were detected in 69% of patients. The commonest abnormality was acrocyanosis (46%) followed by hypertrichosis (25%) and glomerular haemangiomata in (23%) patients. Scleroderma-like skin thickening was seen in 14%. See figure 2 for clinical images. Nail changes were noted in 25% patients, the most common description being a leukonychia, and clubbing in 10%.

Extravascular volume overload

At presentation, 70 (70%) had some form of extravascular volume overload. Peripheral oedema, pleural effusion and ascites was seen in 66 (66%), 16 (16%) and six (6%) patients respectively. Three patients required recurrent ascitic drainage procedures.

Papilloedema

Papilloedema was recorded in 30 patients (30%). Not every patient had formal ophthalmology review with retinal photographs, and therefore this value may be underreported, but is similar to other reported series [4].

Bone lesions

A total of 81% were found to have at least one bone lesion detected on radiographic imaging (skeletal survey, CT, MRI, bone scan, PET-CT). A solitary lesion was detected in 31 cases, two to three lesions in 20 and over three in 30. The majority of lesions were reported as being sclerotic (45), with 12 lytic and 24 were mixed lytic and sclerotic.

Vascular Endothelial Growth Factor (sVEGF)

sVEGF has been routinely available at UCLH since 2009, although some patients prior to this date had sVEGF tested on an ad hoc research basis. Pre-treatment sVEGF was available on 89 (89%) patients and was above normal in 84 (94%). Eleven pre-treatment sVEGFs were not available. Median pre-treatment VEGF was 3594pg/ml, ranging from 200 to 30,101pg/ml. sVEGF levels taken in the 6 months following systemic therapy demonstrate a significant reduction with a median sVEGF of 685pg/ml ($z=6.578$, $p<0.0005$). Each treatment modality demonstrated significant reduction of sVEGF post treatment (radiotherapy, autologous stem cell transplantation (ASCT), lenalidomide and cyclophosphamide to $p<0.005$) (see figure 3 for details).

Serum VEGF results both before and after treatment were available in 89 cases, demonstrating a biochemical VEGF-CR in 50 (56%), VEGF-PR in 21 (23%) and VEGF-NR in 18 (20%).

Other symptoms and signs

Forty-one complained of significant weight loss of over 5kg during presentation. Disabling excessive fatigue was described in 22%. Hyperhidrosis was a symptom described by 12% of patients. This may however be a consequence of coexistent endocrine abnormalities, which were present in eight of the 12 cases.

Thirty-four patients had thrombocytosis and eighteen polycythaemia. All polycythemic patients were negative for a mutation in the JAK2 or TET2 genes. Thirty-four patients experienced venous arterial or venous thromboembolism, with deep vein thrombosis (n=24) or pulmonary embolus (n=4) prior to the diagnosis of POEMS being established. Fourteen patients with thromboembolism had concomitant thrombocytosis. Twelve patients experienced myocardial infarction.

Lung function testing was performed in 33 patients. Sixteen of 33 (48%) demonstrated patterns consistent with restrictive lung disease and 4/33 (12%) an obstructive pattern. Transfer factor for carbon monoxide (TLCO) was reduced in 24 patients, five mild (60-80% predicted), 13 moderate (40-60% predicted) and six severe (less than 40% predicted). Echocardiography or cardiac MRI was performed in 53 (53%) of patients, in which 7/53 (13%) demonstrated impaired left ventricular ejection fraction. Fifteen (28%) of the studies demonstrated echocardiographic evidence of pulmonary hypertension with pulmonary artery systolic pressure of over 40mmHg. All of these patients had peripheral oedema.

Treatment

Single or multiple courses of intravenous immunoglobulin (IVIG) were provided to 40% of patients and glucocorticoids to 21% before the diagnosis of POEMS was established. Ten received immunomodulatory therapies (azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate and/or rituximab). Indications for treatment were for non-POEMS diagnoses (CIDP and Guillain-Barré Syndrome). To date, 98 patients have received at least one modality of POEMS directed therapy. Sixty-seven required only one treatment modality, compared to 21 who required a second line, and 10 three or more treatments. In all cases, where systemic treatment was given, this was in conjunction with steroids, usually dexamethasone 80mg to 160mg per cycle. See table 3 for frequencies of treatment modalities used.

Outcomes and survival

With a median follow up of 59 months (range 1-230 months) and 7279 person months total analysis time, the median overall survival (OS) was not reached (figure 4a). Five and ten-year OS was 90% (95% CI 83-96%) and 82% (95% CI 71%-92%) respectively. Twelve patients from the 100 studied have died; causes of death have been due to POEMS syndrome in seven, cardiopulmonary failure in three, myelodysplastic syndrome in one and multi-organ failure due to sepsis in one. Five-year Progression Free Survival (PFS) was 65% (95% CI 53%-76%) and ten-year PFS was 53% (95% CI 37%-68%), with progression of any sort occurring in a total of 32 patients (see figure 4a). Pairwise log rank comparisons demonstrate a statistically significant prolongation of PFS for patients treated with ASCT vs chemotherapy, X^2 (1) = 9.58, p= .002, and ASCT vs radiotherapy, X^2 (1)= 5.27, p=0.022.

Thirty-five percent of patients were either wheelchair or bedbound prior to receiving treatment, compared to 11% post treatment. Overall median pre-treatment ONLS score was six, which improved to four by three years and three at the most recent follow up, demonstrating significant ongoing improvement following treatment ($p<0.05$ - see figure 1). Patients in whom the diagnosis of POEMS was made in less than six months from symptom onset had significantly lower ONLS scores at four, compared to those diagnosed after six months at six ($p<0.05$) suggesting that delay to diagnosis influences neuropathy severity.

Death and Progression risk factors

Variables selected for the multivariate analysis were haematological non-response, VEGF non-response, non-ASCT therapy and low albumin. Variates remaining significant were haematological non-response (HR 4.8, 95% confidence interval (CI) 2.0-11.7, P=0.000), VEGF non-response (HR 2.7, 95% CI 1.0-7.1, P=0.033) and non-ASCT therapy (at any stage of the patients' treatment) (HR 4.5, 95% CI 1.6-12.4, P=0.003). Low albumin lost significance in the model (HR 1.6, 95% CI 0.7-3.8) and was therefore not included in further analysis. Risk scores were ascertained relative to respective HRs as follows; VEGF-non-response, score 1; Haematological non-response, score 2; non-ASCT, score 2, with a total risk score of five.

Survival curves were compared for patients with all calculated risk scores and two distinct sub-groups created; low risk, score 0-2; high risk, score 3-5. Pairwise log rank comparisons demonstrated a statistically significant difference in progression or death outcomes between high and low risk groups, $X^2 = 63.8$, $p=0.000$ (Figure 4c).

Discussion

POEMS is a rare and likely underreported cause of neuropathy. The majority of patients are misdiagnosed as initially having CIDP, with a median time to POEMS diagnosis of almost a year, by which time 35% patients are bed or wheelchair bound. The neuropathy in POEMS syndrome is typically of a subacute onset over months with numbness, dysesthesias and often calf pain followed by symmetrical, ascending length dependent weakness. Anecdotally, several patients in the cohort described the calf pain as a progressive muscular ache as if they had run too far. This was often misdiagnosed as claudicant peripheral vascular disease before the discovery of neuropathy. The clinical distribution of the weakness is typically distal at onset, with the frequent absence of proximal weakness, with other systemic features (such as unexpected volume overload in the young for instance) differentiating the condition from CIDP. CSF albuminocytologic dissociation and electrophysiology displaying a sensorimotor, symmetrical distal neuropathy with primary demyelination and secondary axonal loss, often with absent lower limb responses are typical for POEMS neuropathy [15]. Because of the progressive and disabling nature of neuropathy, it is crucial to identify POEMS syndrome early in the disease course and initiate therapy to prevent worsening disability. The combination of an inflammatory neuropathy and a lambda light chain monoclonal protein should serve as a 'red flag' for POEMS syndrome. "Once identified, other features of POEMS syndrome should be sought, including the clinical features of oedema, skin changes and papilloedema, laboratory testing for VEGF and endocrinopathy, and imaging to identify bone lesions, organomegaly and nodal enlargement of Castleman Disease"

Identification of a monoclonal plasma cell disorder in POEMS is crucial to the diagnosis. This study demonstrates the relatively poor sensitivity of serum protein electrophoresis and necessity of immunofixation of the serum and urine, coupled with bone marrow biopsy or

imaging for identification of plasmacytoma in suspected cases. Serum free light chain analysis is often unrevealing with both light chains raised and a resultant normal ratio. Wang et al have demonstrated the largest proportion of bone marrow cells in POEMS syndrome are polyclonal despite the coexistence of clonal disease[16] , which would result in this light chain pattern. Fifteen cases demonstrated raised kappa light chains with normal lambda, however in such cases, the kappa light chain level was often minimally elevated over the upper limit of normal, and kappa to lambda ratio remained small at 1.8 suggesting again polyclonal increase of both light chains rather than a significant predominant kappa chain.

There are similar demographic and clinical characteristics to this UK cohort compared with the three previously described large POEMS cohorts from the USA, China and Japan. A lower frequency of organomegaly and higher rates of bone lesions are similar to the USA cohort compared to China and Japan (see table 2). Extravascular volume overload was present at a frequency much higher than the USA (70% compared to 29%) and more comparable to China. The difference in frequency between the USA and Chinese cohorts was initially assumed to be ethnicity related but is evidently not the case and may be related to ascertainment bias or other reasons unknown.

Papilloedema, headaches and stroke are not uncommon central nervous system manifestations in POEMS syndrome. Systematic analysis of 41 MRI brain scans revealed cranial pachymeningitis as a very common association in POEMS syndrome at 71%. This association has been previously documented in nine Italian patients [12], but not identified in other cohorts or at this frequency. The finding of cranial pachymeningeal thickening is not associated with CIDP, and therefore becomes a useful diagnostic clue when discovered. Due to its clinical utility and the high frequency seen in POEMS syndrome, the authors suggest that (non-infective, non-malignant) cranial pachymeningeal thickening and enhancement should be included as a minor supportive POEMS diagnostic criterion. Other criteria for

POEMS have been described iteratively from major cohorts and this finding is commoner in these patients than several other features.

Cardiopulmonary manifestations are common in POEMS syndrome. In our cohort, 24/33 of patients (72%) had evidence of poor gas transfer and 15/53 (28%) had echocardiographic evidence of pulmonary hypertension. The frequency may be higher as not all patients received cardiac and pulmonary investigations, and often those that did were for planning towards ASCT, in which patients are typically deemed medically fit for ASCT with minimal comorbidities. The physiological mechanism of cardiopulmonary manifestations are unclear but postulated to be secondary to cytokine-derived endothelial cell proliferation and vessel stenosis [17]. Cardiopulmonary disease was not a significant predictor of PFS or OS in this cohort but the number of affected patients were small. Myocardial infarction has been reported in POEMS syndrome [17]. The direct relationship and pathogenesis is not clear, but appears to be of higher incidence compared the general population.

Five and ten-year survival in treated POEMS syndrome patients is favourable. ASCT demonstrates improved PFS and OS when compared with other treatment modalities, but this may be in part due to selection bias of more systemically well patients. Several studies have recently demonstrated significant haematological and VEGF response following treatment with lenalidomide [18,19], including in patients originally deemed unfit for ASCT who then underwent ASCT at later date [20], and in relapsed disease [21]. Twenty six were deemed unfit for ASCT first line so received lenalidomide treatment in this cohort, of which eight went on to receive ASCT successfully. More analysis is required to define lenalidomide's effectiveness in different treatment regimens.

Non-treatment with ASCT, non-haematolgical and non-sVEGF response following therapy are all significant factors predicting the risk of progression or death in POEMS syndrome.

Failure to achieve haematological or VEGF response suggests persistence of pathological drivers in POEMS syndrome and therefore treatment failure, both of which demonstrated high hazards ratios towards progression or death. As mentioned previously, the true benefit of ASCT in preventing progression or death is difficult to quantify as younger patients with fewer comorbidities are selected for ASCT and thus may skew results towards favourable outcomes. Utilising the multivariate model allows for easily applicable risk score quantification, which may be considered useful in the management of POEMS patients through identification of high risk cases which may allow for closer follow up and more aggressive treatment strategies responding to changes early, compared to low risk patients in which a ‘watch and wait’ approach may be more appropriate.

Appendix 1: Authors

Name	Location	Contribution
Stephen Keddie	**Queen Square, London, UK**	Data collection, analysis and writing of the paper
David Foldes	**UCLH, London, UK**	Data collection revising manuscript for intellectual content
Francisca Caimari	**UCLH, London, UK**	Collecting data on and analysis of endocrine data
Stephanie Baldeweg	**UCLH, London, UK**	Collecting data on and analysis of endocrine data
Joshua Bomsztyk	**UCLH, London, UK**	Data collection, study design and revisions for intellectual content
Oliver Ziff	**UCLH, London, UK**	Data collection, study design and revisions for intellectual content

Janev Fehmi	**John Radcliff, Oxford, UK**	Data collection, study design and revisions for intellectual content
Aviva Cerner	**UCLH, London, UK**	Data collection, study design and revisions for intellectual content
Zane Jaunmuktane	**UCLH, London, UK**	Nerve biopsy interpretation, manuscript revision for intellectual content
Sebastian Brandner	**UCLH, London, UK**	Nerve biopsy interpretation, manuscript revision for intellectual content
Kwee Yong	**UCLH, London, UK**	Study conception, data collection, design, analysis and revisions for intellectual content
Hadi Manji	**Queen Square, London, UK**	Study conception, data collection,

		design, analysis and revisions for intellectual content
Simon Rinaldi	**John Radcliff, Oxford, UK**	Study conception, analysis and revisions for intellectual content
Mary Reilly	**Queen Square, London, UK**	Study design, analysis and revisions for intellectual content
Shirley D'Sa	**UCLH, London, UK**	Study conception, data collection, design, analysis and revisions for intellectual content
Michael Lunn	**Queen Square, London, UK**	Study conception, data collection, design, analysis and revisions for intellectual content

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Figures

Figure 1: Level of mobility and Overall Neuropathy Limitation Score pre and post treatment

A=Mobility level pre-treatment and on most recent follow up (as percentage).

B= ONLS taken pre-treatment, at three years post treatment (if applicable) and on most recent follow up (as percentage) demonstrating sustained and improving neurological function several years following therapy.

Figure 2: Typical skin lesions of POEMS syndrome

A= Multiple glomerular haemangiomata throughout the trunk and upper limbs. B= A close up view of a typical glomerular haemangiomata. C= Peripheral oedema and skin thickening. D= Hypertrichosis of the upper limbs. E= Acrocyanosis of the feet.

Figure 3: Serum Vascular Endothelial Growth Factor values pre and post treatment with radiotherapy, lenalidomide or Autologous Stem Cell Transplantation

Serum VEGF levels within six months pre-treatment and six months post treatment to determine response. This demonstrated significant reduction in all forms of treatment at $p<0.005$.

Figure 4: Kaplan Meier overall survival, treatment outcomes and risk prognostication

Kaplan Meier survival estimate curves demonstrating (A) = overall survival (OS) and progression free survival (PFS). (B) = progression free survival by treatment types of

radiotherapy (RTx) vs chemotherapy vs autologous stem cell transplantation (ASCT). (C) = overall survival and progression free survival outcome stratified by risk score. Pairwise log rank comparison is statistically significant, p=0.00

Table 1: POEMS syndrome demographics and number of clinical features at presentation

Characteristic	**N=100**	**%**
Median age, y (range)	56 (31-84)	
Male sex	68	68
Ethnicity		
White British	62	62
White other	16	16
Black African	11	11
Black Caribbean	3	3
Asian Pakistani	2	2
Asian Indian	4	4
Chinese	1	1
Not specified	1	1
Diagnosis prior to POEMS syndrome		
CIDP	54	54
GBS	5	5
MGUS	1	1
B12 deficient neuropathy	1	1
Scleroderma	2	2
Number of POEMS features at diagnosis		
3 features	1	1
4 features	3	3
5 features	9	9
6 features	25	25

7 features	22	22
8 features	22	22
9 features	10	10
>10 features	8	8

Table 2: Comparison of clinical features of patients in the present cohort and three previous series.

POEMS features	**Number**	**%**	**Nakanashi % (n=102)**	**Dispenzieri % (n=99)**	**Li % (n=99)**
Polyneuropathy					
Peripheral neuropathy	96	96	100	100	99
Raised CSF protein	65/65	100‡	97	100	96
Monoclonal plasma cell disorder	100	100	NA	100	100
Serum protein electrophoresis	55	55			
Serum immunofixation	78	78	75	85	92
IgM- λ	0	0‡	0	1	0
IgG- λ	34	44‡	54	48	22
IgA- λ	42	53‡	41	52	71
Biclonal	2	3‡			
IgG -κ	1	2‡	1	0	2
IgA- κ	0	0	4	0	1
Serum free light chain abnormal	65/83	78‡			
Kappa: lambda ratio					
Normal κ:λ	65	78‡			
>κ:λ	14	17‡			
<κ:λ	4	5‡			
Urine Bence Jones Protein	15	15			
Bone marrow abnormality	55/86	64‡			
0-4% PC	25	29‡			

	5-9% PC	15	17‡			
	10-14% PC	16	18‡			
	Lambda restriction					
Plasmacytoma biopsy abnormal		38/42	90‡			
Castleman disease		14	14	63	73	58
Bone lesions		81	81	55	97	27
	Solitary lesion	31	38†			
	2-3 lesions	20	25†			
	>3 lesions	30	37†			
	Sclerotic	45	55†	55	46	19
	Lytic	12	15†	14	2	8
	Mixed	24	30†	30	49	0
Vascular endothelial growth factor elevation		84/89	94‡			
Endocrine abnormality		68	68			
Organomegaly		63	63	82	50	86
	Splenomegaly	31	31	39	22	71
	Hepatomegaly	23	23	82	24	47
	Lymphadenopathy	42	42	65	26	75
Skin abnormalities		69	69	NA	68	90
	Hyperpigmented	25	25			
	Acrocyanosis	46	46			
	GH	23	23			
	Hypertrichosis	20	20			
	Skin thickening	14	14			
	Nail changes	12	22			

Extravascular volume overload		70	70	NA	29	88
	Peripheral Oedema	66	66	91	24	85
	Pleural effusion	16	16	40	3	43
	Ascites	6	6	62	7	55
Papilloedema		30	30	62	29	64
Thrombocytosis		34	34	NA	54	55
Polycythemia		18	18	19	18	9
Other						
	Weight loss	41	41			
	Fatigue	22	22			
	Clubbing	10	10			
	Hyperhydrosis	12	12			
	VTE	34	34			
	Myocardial infarction	12	12			
	Stroke	9	9			
	Pachymeningitis	29/41	71†			

Note if value recorded as _/_, this denotes number of positive results/total taken.

‡ Percentage represents percent positive of those taken or abnormal.

† Percentage of those patients with bone lesions.

CSF= cerebrospinal fluid, PC= plasma cells, PTH= parathyroid hormone, GH= growth hormone, VTE= venous thromboembolism

Table 3: Treatment modalities used

Treatment	First line	Second line	Third line	Total Number
Radiotherapy	27	1	1	29
Cyclophosphamide	7	5	1	13
Melphalan	2	2	2	6
Bortezomib	3	1	0	4
Lenalidomide	26	9	1	36
Autologous SCT	33	12	5	50

SCT – stem cell transplant