CASE REPORTS

POEMS Syndrome: A case report and review

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ABSTRACT

POEMS syndrome is a rare multi-system condition that arises from an underlying plasma cell disorder. We report a case of a 69-year-old lady who presented with symptoms of exertional breathlessness and leg swelling, and a recent history of peripheral neuropathy, borderline diabetes mellitus and monoclonal gammopathy of undetermined significance (MGUS). The development of worsening right heart failure, which remained refractory despite diuretic therapy, pulmonary hypertension, organomegaly, hypothyroidism, chronic kidney disease, right pleural effusion and ascites, did not lead to a definitive diagnosis until cutaneous abnormalities were recognised. A presumptive diagnosis of POEMS was subsequently confirmed with the finding of raised serum levels of VEGF and bone marrow histopathology. Our case highlights the complex nature of this multi-system syndrome, the potential for delayed diagnosis and the importance of an integrated sub-specialty approach to management.

Key Words: POEMS syndrome, Monoclonal gammopathy of undetermined significance, Sensory polyneuropathy, Pulmonary hypertension, Pleural effusion, Vascular endothelial growth factor

1. INTRODUCTION

POEMS syndrome is a rare paraneoplastic disorder that was first described in 1938 in a patient with peripheral neuropathy, solitary plasmacytoma, hyperpigmentation and elevated cerebral spinal fluid protein.[1] The acronym POEMS was suggested in 1980 to include the key clinical features that are seen in this syndrome, namely, Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder and Skin manifestations.[2] Other important features that were not included in the POEMS acronym have since been recognized. These include papilloedema, extravascular volume overload, leading to pleural effusions, ascites and edema, pulmonary hypertension, sclerotic bone lesions, Castleman disease (angiofollicular lymph node hyperplasia), thrombocytosis and elevated serum vascular endothelial growth factor (VEGF). The multi-system nature of the condition requires a broad-minded approach to diagnosis and an integrated strategy of sub-specialty working. Our case shows how the seemingly disconnected constellation of varied features may not be recognised as syndromic until late in the disease and emphasizes how awareness of the condition is of prime importance in making the diagnosis.

2. CASE PRESENTATION

A 69-year-old female with previously good health was referred by her primary care physician to a neurology outpatient clinic to investigate symptoms of tingling and numbness in her feet of 6 months duration. Clinical examination and nerve conduction studies were consistent with a sensory polyneuropathy of the lower limbs. Serum B12 was minimally reduced at 179 ng/L (191-663 ng/L) and a formal glucose tolerance test was consistent with borderline diabetes. Serum electrophoresis showed an elevated IgA lambda paraprotein and IgG kappa protein at 6.0 g/L and

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6.4 g/L respectively, with elevated serum free Kappa light chains of 39.01 mg/L (3.30-19.40 mg/L) and free Lambda light chains at 60.18 mg/L (5.70-26.30 mg/L). These findings were concluded to represent monoclonal gammopathy of undetermined significance (MGUS) and a peripheral neuropathy secondary to Vitamin B12 deficiency. She was treated with gabapentin 100 mg three times daily and hydroxocobalamin 1 mg intramuscular injections three times a week for 2 weeks. Her symptoms persisted despite Vitamin B12 replacement.

Fourteen months after her initial presentation she developed exertional breathlessness and ankle swelling prompting referral to cardiology outpatients. On attendance, she was found to have a loud pulmonary second heart sound, elevated serum N-terminal of the pro-hormone brain natriuretic peptide (NT pro-BNP) at 90 pmol/L (< 42 pmol/L) and a systolic pulmonary artery pressure (sPAP) of 70 mmHg estimated on transthoracic echocardiography (TTE).

Subsequent right heart catheterization (RHC), coronary angiography and left ventriculography showed normal coronary arteries, good left ventricular (LV) function and moderate pulmonary hypertension (PH) (mean pulmonary artery pressure [m PAP] was 30 mmHg and pulmonary capillary wedge pressure [PCWP] was 15 mmHg). A diagnosis of pre-capillary pulmonary hypertension was made and further investigations were performed to identify the cause.

She underwent computed tomography pulmonary angiography (CTPA), auto-antibody screening and lung function testing (LFTs). CTPA showed a moderate right-sided pleural effusion with enlarged main pulmonary artery (MPA) (see Figure 1) and LFTs showed a restrictive pattern (FEV1, 1.55 L, 66% predicted; FVC, 1.98 L, 71% predicted and FEV1/FVC, 78.16%) with reduced diffusion capacity of carbon monoxide (DLCO, 3.18 mmol min^{-1} kPa^{-1}, 41% predicted). Diagnostic pleurocentesis showed lactate dehydrogenase (LDH) of 178 U/L and pleural protein concentration of 38 g/L. Serum LDH was not measured but the serum protein was 57 g/L which confirmed an exudative pleural effusion according to Light's criteria and cytology was unremarkable. Autoimmune screening included anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, complements (C3c and C4), crithidia dsDNA antibodies, myeloperoxidase and proteinase 3 antibodies and cyclic citrullinated peptide antibodies (CCP), all of which were negative.

Therapy with oral furosemide 60 mg once a day and sildenafil 20 mg three times daily was commenced. Cardiac magnetic resonance imaging (MRI) showed septal flattening due to right ventricular (RV) pressure overload but did not identify any features of amyloidosis and excluded an intra-cardiac shunt (see Figure 2). Over the course of next 2 months she developed hypothyroidism (thyroid stimulating hormone [TSH] -9.82 mU/L), impaired renal function (eGFR 54 ml/min/1.73 m^2) and a large multi-loculated right pleural effusion that required admission for thoracocentesis on two occasions. Her condition deteriorated despite medical therapy and she was referred for further investigations at the nearest pulmonary hypertension center.

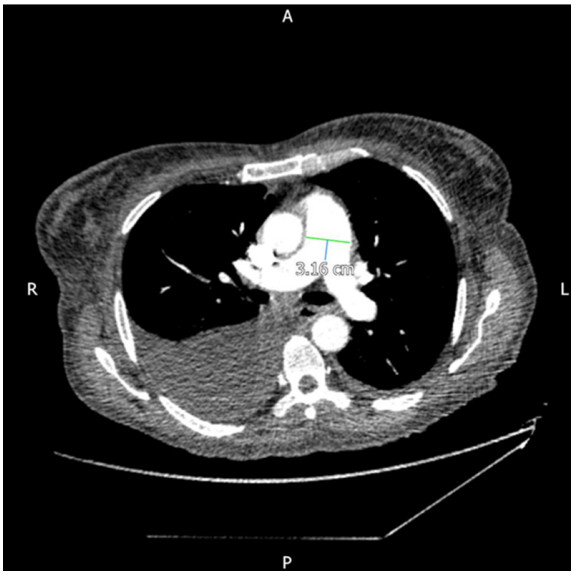

Figure 1. CTPA showing enlarged main pulmonary artery and right pleural effusion

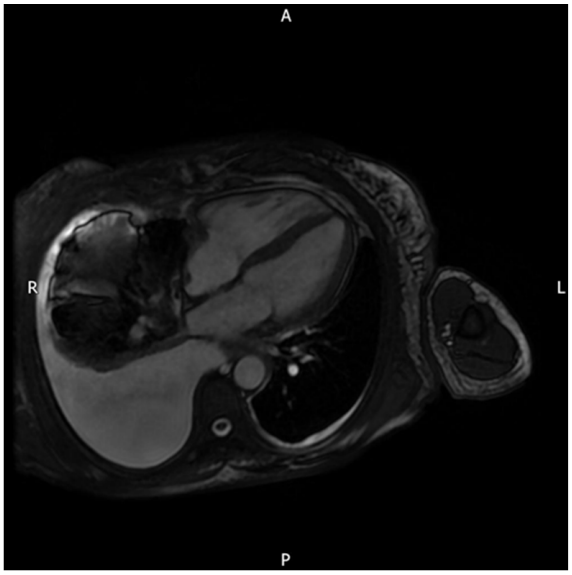

Figure 2. Cardiac MRI showing septal flattening due to right ventricular pressure overload and bilateral pleural effusions with a normal left ventricle

At the pulmonary hypertension center, additional imaging

was arranged to investigate the development of weight loss, worsening right heart failure and ascites. CTPA confirmed enlargement of the MPA measuring 31 mm, an enlarged RV with straightening of the interventricular septum and a multi-loculated right pleural effusion (see Figure 3a). Small volume bilateral axillary, supraclavicular and sub-pectoral lymphadenopathy and a lytic lesion within the manubrium were newly identified. Further imaging with ultrasound (US) and CT confirmed the presence of ascites with hepatosplenomegaly (see Figure 3b).

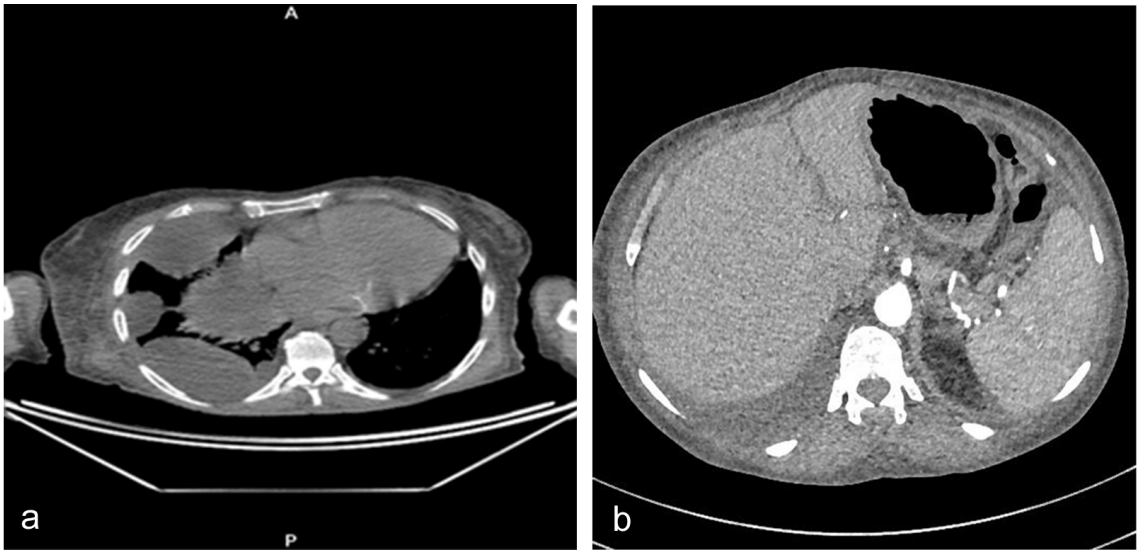

Figure 3. a. CTPA showing a multi-loculated right pleural effusion; b. Abdominal CT showing hepatosplenomegaly and ascites

RHC was repeated and showed mPAP of 31 mmHg with a cardiac output (CO) of 5.5l/min and pulmonary vascular resistance (PVR) of 349 dynes/sec/cm^{-5} (see Table 1). There was no evidence of left ventricular dysfunction and, in conclusion, pulmonary hypertension was considered to be a component of an undiagnosed systemic disorder rather than the primary cause of her deterioration. Bone marrow biopsy was also performed at the tertiary center to exclude amyloidosis and she was returned to our center pending results of the biopsy.

Table 1. Right heart catheterization findings

	Measurements	Normal Range
Mean right atrial pressure	2 mmHg	2-6 mmHg
Systolic right ventricular pressure	58 mmHg	15-25 mmHg
Diastolic right ventricular pressure	16 mmHg	0-8 mmHg
Mean pulmonary artery pressure	31 mmHg	10-20 mmHg
Pulmonary artery wedge pressure	7 mmHg	6-12 mmHg
Pulmonary capillary wedge pressure	15 mmHg	4-12 mmHg
Cardiac output	5.5 L/minute	4.0-8.0 L/minute
Cardiac index	3.3 L/min/m²	2.5-4.0 L/min/m²
Pulmonary vascular resistance	349 dynes/sec/cm^{-5}	< 250 dynes/sec/cm^{-5}

A further deterioration in symptoms of breathlessness led to subsequent emergency admission to our hospital during which she was assessed by the respiratory team. Examination identified white nails with clubbing, facial lipoatrophy and widely distributed small haemangiomata (see Figure 4), none of which had been identified previously. The constellation of skin manifestations, combined with the other clinical findings of polyneuropathy, hepatosplenomegaly, MGUS, pulmonary hypertension, pleural effusion, diabetes and hypothyroidism led to a working diagnosis of POEMS syndrome. Subsequent ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan did not show any osteosclerotic lesions, and

histopathological examination of a resected axillary lymph node was unremarkable. Serum VEGF levels were raised at 4,758 pg/ml (normal value < 771 pg/ml), which was interpreted as confirming the diagnosis of POEMS.

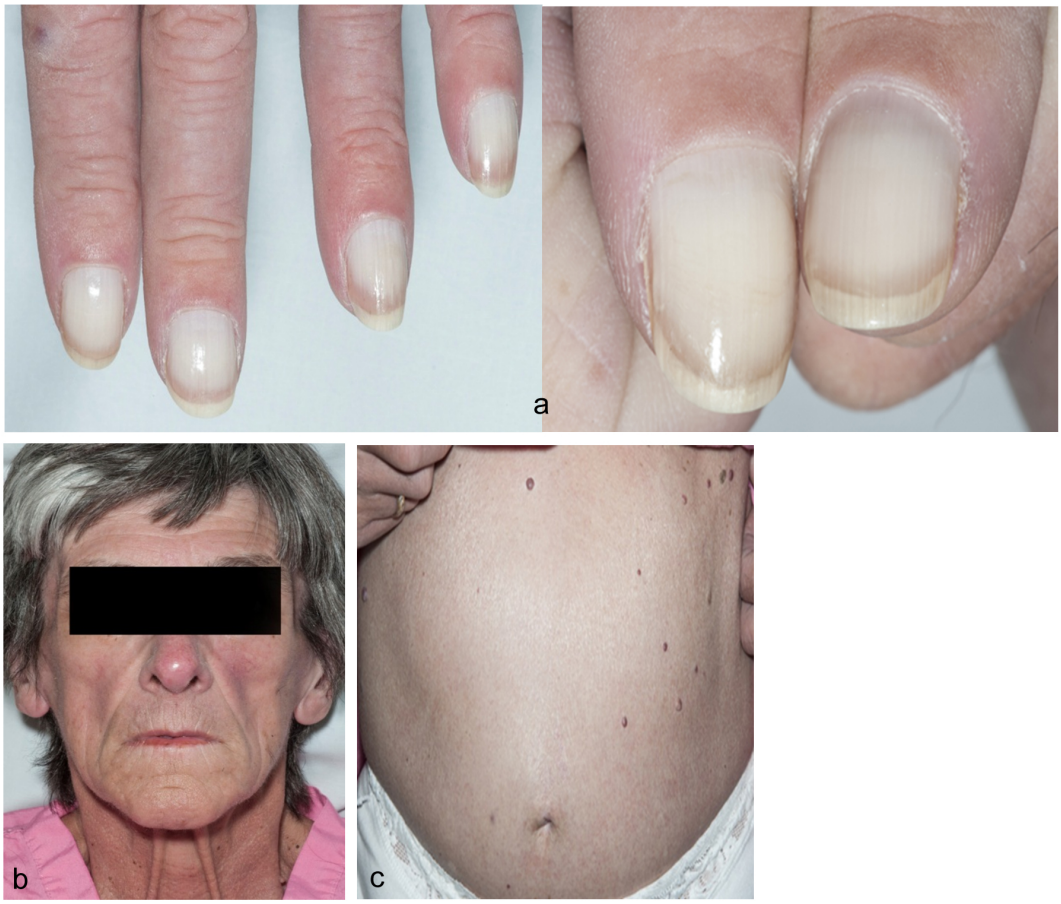

Figure 4. a: Appearance of the fingers, showing white nails with finger clubbing; b: Facial lipoatrophy; c: Abdominal wall haemangiomata

Bone marrow biopsy performed at the pulmonary hypertension center demonstrated infiltration of 20% plasma cells with no evidence of amyloidosis. Treatment was commenced with cyclophosphamide 500 milligram (mg) once weekly, thalidomide 50 mg once daily on every day of the cycle and dexamethasone 20 mg once daily on day 1-4 and day 15-18 of the first cycle.

Unfortunately, during the first cycle of chemotherapy, she developed complications of severe sepsis and respiratory failure that were unresponsive to intensive care support, and she passed away 6 weeks after the diagnosis had been made and almost 2 years after her initial presentation.

3. Discussion

POEMS syndrome is a rare multisystem disorder that arises due to an underlying plasma cell dyscrasia. Polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes are the most common presenting features of this syndrome but extravascular edema, sclerotic bone lesions, clubbing, and pulmonary hypertension are also often seen. The initial diagnostic criteria proposed in 2003[3] were revised in 2007[4,5] in view of the positive predictive value of VEGF levels (see Table 2). The initial presenting feature in the majority of patients is a polyneuropathy (one of the mandatory diagnostic criteria) that most commonly is a "stocking" sensory change, followed by motor defects but with cranial nerve sparing. Cerebral infarction[6] is the presenting complaint in 5%-10% of patients. Cerebrospinal fluid (CSF) protein tends to be raised and all patients have an underlying abnormal monoclonal plasma cell proliferative disorder. M protein (the remaining mandatory criterion) may not be evident on serum electrophoresis and further evaluation with serum and urinary immunofixation is required. The predominant light chain subtype is lambda. The heterogeneous constellation

of features in POEMS, and the difficulty in differentiating from other plasma cell disorders such as multiple myeloma and light chain amyloidosis, can lead to a significant delay in diagnosis.

Table 2. A combination of polyneuropathy and monoclonal plasma cell proliferative disorder plus 1 of 3 major criteria and 1 of 6 minor criteria

Diagnostic Criteria for POEMS syndrome*	
Mandatory (Major) Criteria (both required)	Polyneuropathy
	Monoclonal plasma cell proliferative disorder
Major Criteria (only one required)	Sclerotic bone lesions
	Castleman disease
	Elevated VEGF levels
Minor Criteria (only one required)	Organomegaly (hepatomegaly, splenomegaly, lymphadenopathy)
	Extravascular fluid overload (ascites, pleural effusions and edema)
	Endocrinopathy (adrenal, pituitary, gonadal and parathyroid)
	Skin changes (hyperpigmentation, hypertrichosis, plethora, white nails and acrocyanosis)
	Papilloedema
Other Features	Pulmonary hypertension, restrictive lung disease, weight loss, clubbing, fever and hyperhidrosis

*Diagnostic criteria, adapted from Dispenzieri et al. [4, 5]

Pulmonary conditions that have been associated with POEMS syndrome include pleural effusions, pulmonary hypertension, respiratory muscle weakness and restrictive lung disease with a reduced gas transfer. The most common symptoms are breathlessness, chest pain, cough and orthopnea. Several retrospective series show that pleural effusions are present in 3%-43% of patients.[5, 7–10] In a case series of 96 patients, 42% had pleural effusions at the time of diagnosis: 29% of these patients underwent diagnostic thoracocentesis and all were defined as exudates according to Light's criteria.[11] 37.5% patients had ascites and 26% had a pericardial effusion.

A large series from the Mayo clinic[9] looked at pulmonary involvement in 137 patients diagnosed with POEMS syndrome between 1987 and 2003. The presence of cough and impaired neuromuscular respiratory function were associated with reduced survival. Lung function testing was performed in 32 of 137 patients, of whom 75% had abnormalities which included a restrictive defect and an isolated DLCO reduction.

In a case series of 154 patients, 27% had pulmonary hypertension (defined as a sPAP > 50 mmHg) and patients were more likely to have signs of extravascular volume overload, as seen in the current case. Patients presenting in this manner experienced a delay in diagnosis compared to those presenting without pulmonary hypertension.[6]

Allam et al.[10] reported only 8.5% of their 137 patient had pulmonary hypertension within 2 years of diagnosis although only 25 patients from this case series underwent echocardiographic screening for pulmonary hypertension. The mean right ventricular systolic pressure (RVSP) was 47 mmHg and median survival for those patients with PH was 63.3 months. The influence of PH on survival was not evident in this series, but the sample size may have been too small to show any difference. In this case series, the presence of PH was thought to be a late manifestation that leads to delayed diagnosis and treatment, with a likely impact on survival.

Cutaneous manifestations are observed in up to 44% of patients with POEMS syndrome.[12] The commonest lesions are haemangiomata, which are firm papular lesions on the trunk and proximal limbs and vary on histopathology between cherry haemangiomata and glomerular haemangiomata. Glomerular haemangiomata are rarely seen except in patients with POEMS syndrome and, consequently, their presence is highly suggestive of the diagnosis. Other features include hyperpigmentation, hypertrichosis, plethora, flushing, white nails, clubbing and facial lipoatrophy.

Endocrinopathy constitutes one of the minor criteria and most commonly includes hypogonadism, hypothyroidism, diabetes and adrenal insufficiency. It is one of the least understood features of POEMS syndrome and, because of the high prevalence of diabetes and thyroid disease in the wider population, the current diagnostic criteria require the presence of additional endocrine abnormalities.[4] Asymptomatic osteosclerotic bone lesions are another important diagnostic feature and, in large case series, are described in 30% to 95% of patients.[13] CT imaging is a more sensitive method of detection than plain radiography but monitoring may be best performed using ^{18}F-FDG PET imaging.[13]

The pathogenesis of POEMS syndrome remains unclear but it is understood that the proangiogenic cytokine VEGF is of

central importance.[14] This cytokine, which is produced by plasma cells, induces microangiopathy, neovascularisation and increases microvascular permeability with consequent extravascular volume overload, papilloedema and edema-induced polyneuropathy. Plasma VEGF levels > 200 pg/ml are of predictive value for POEMS with a sensitivity and specificity of 68% and 95%, respectively.[15] The monitoring of therapeutic response using VEGF levels has been proposed and, since these correlate with the severity and the treatment response of pulmonary hypertension, VEGF may also play a role in the development of pulmonary hypertension.[16] Other cytokines that may have a role include IL-1β, IL-6 and IL-12.[5]

The lack of evidenced-based practice from randomized clinical trials has meant that treatment is guided by case series. Plasma cell-targeted therapy would appear to be associated with the most successful outcome. In patients with an isolated osteosclerotic bone lesion (plasmacytoma) and no diffuse bone marrow involvement with plasma cells, the treatment of choice is radiotherapy. In a case series of 35 patients, radiotherapy alone led to a 4-year survival of 97%.[17] In contrast, disseminated bone marrow involvement with plasma cell-infiltrates requires systemic treatment with corticosteroids, alkylator-based therapy or peripheral blood stem cell transplantation (PBSCT). The first case report of treatment with PBSCT was in 2001[18] but a case series of patients that were treated with high dose melephalan and then PBSCT[19] reported no drug-related deaths and relapse-free survival at 3 years. In addition, neurological and other symptoms improved significantly. More recently D'Souza et al.[20] reported long term outcome in 59 patients treated with autologous PBSCT; 92% of patients showed a clinical response and 5 year survival was reported to be 94%. Nevertheless, PBSCT has been associated with significant morbidity and 40% of the patients develop complications. Therefore, patient selection criteria are of critical importance and, in patients older than 65 years and /or with severe organ dysfunction, treatment should be with melphalan/dexamethasone or lenalidomide/dexamethasone.[4]

The first prospective trial of melphalan and dexamethasone21 employed 12 cycles of therapy in 31 patients and achieved a response rate of 100% in VEGF levels, 81% in haematological response, and all patients experienced some improvement in neurological symptoms. A systemic review of the use of lenalidomide in more than 60 patients has confirmed a treatment response in the majority.[5] There have been very few case reports on bortezomib and thalidomide, and the use has been limited due to risk of drug-induced peripheral neuropathy. Anti-VEGF therapy with drugs such as bevacizumab is of unclear benefit.[6]

Supportive treatment that includes the use of diuretics to reduce extravascular fluid overload and hormonal replacement with thyroxine or corticosteroids is required in nearly all patients. Analgesia with gabapentin has been used to relieve neuropathic pain and patients with severe neuropathy require ankle-foot orthotics. Severe respiratory muscle weakness may be managed using continuous positive airway pressure (CPAP) and/or bi-level positive airway pressure (BIPAP) which can improve oxygenation, reduce the risk of infection and the development of pulmonary hypertension.

Despite improved understanding of the diagnosis and management of POEMS there is a need for international collaboration to deliver further therapeutic trials. Autologous PBSCT is currently considered to be first line treatment for younger patients with normal organ function and diffuse plasma cell infiltration. Those who are ineligible should be offered melphalan and dexamethasone. Novel agents such as lenalidomide, thalidomide, and bortezomib also have shown encouraging results but need further evaluation.

4. Conclusion

Early diagnosis is often a challenge in POEMS syndrome due to its rarity, multi-organ involvement, likely presentation to multiple specialties and a consequent potential lack of diagnostic overview. The current case was managed synchronously by a number of medical specialties and a definitive diagnosis was delayed until 18 months after initial presentation. Adherence to the basic principles of clinical methods is of paramount importance to identify the multiple and varied features that constitute POEMS. However, timely diagnosis is ultimately dependent on an awareness and recognition of the constellation of features that are pathognomonic of the syndrome.

Conflicts of Interest Disclosure

The authors have no competing interests to declare.

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