POEMS syndrome: a challenging diagnosis of a rare disease

Introduction

A 43-year-old man of Nigerian origin presented to both primary and secondary care services on multiple occasions over the course of 9 months with a variety of symptoms, including erectile dysfunction, darkening of facial skin, weight loss and subsequent peripheral neuropathy. Blood tests revealed a thrombocytosis and an elevated serum globulin level, which serum electrophoresis confirmed to be an IgG Kappa monoclonal band. Computed tomography and magnetic resonance imaging demonstrated multiple bony lytic lesions. Immunohistopathological analysis of biopsy samples of bone lesions revealed plasma cells with kappa light chain restriction. Specialist haematology and neurology opinion was sought and a diagnosis of POEMS syndrome was made. The patient was treated with bortezomib, cyclophosphamide and dexamethasone (VCD) combination chemotherapy and planned autograft bone marrow transplant.

This report outlines the presenting features, investigation and management of this very rare condition, in a case which includes many of the classical clinical features of POEMS syndrome.

Discussion

POEMS syndrome is a multisystem disease developing in the context of a plasma cell malignancy. The name is an acronym derived from five clinical features that characterize the condition: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

This case unequivocally fits the diagnostic criteria as established by Dispenzieri (2007) with four major and three minor criteria being met. Despite this 'typical' presentation, there was a 9-month delay in obtaining the diagnosis and a period of significant diagnostic uncertainty. This delay arose from the broad differential diagnosis for each of the individual complaints, and the rare nature of the unifying diagnosis.

The manifestations of POEMS syndrome are not limited to the acronym, with several other clinical and laboratory findings important in the diagnosis of the syndrome. Diagnostic criteria were first proposed in 2003 (Dispenzieri et al, 2003) and revised by the same author in 2007 (Dispenzieri, 2007). According to these criteria a diagnosis of POEMS syndrome is made when a patient with polyneuropathy and a monoclonal plasma cell-proliferative disorder has at least one further major criteria (sclerotic bone lesions, Castleman disease, vascular endothelial growth factor elevation) plus at least one minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilloedema, thrombocytosis/polycythaemia).

The pathogenesis of POEMS syndrome remains unclear. Many factors have been implicated including elevated levels of cytokines such as IL-6 (Fukatsu et al, 1992) and vascular endothelial growth factor (Soubrier et al, 1997). It is not understood how these factors contribute to the varied clinical features of POEMS syndrome; however, increased levels of vascular endothelial growth factor in the vasa nervorum may lead to endothelial disruption and nerve damage (Scarlato et al, 2005) explaining the polyneuropathy characteristic of the condition.

A Cochrane review (Kuwabara et al, 2012) identified that there are no rand-

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Case Report

A 43-year-old Nigerian-born man presented to both primary and secondary care on multiple occasions over the course of a year with a diverse range of symptoms.

The initial presenting complaint was erectile dysfunction. Sildenafil treatment was initially effective but subsequently erectile dysfunction became refractory to this treatment. At that time the patient reported skin changes to his face, with the skin appearing darker.

Three months later he began experiencing symptoms of transient chest and back pain on exertion, increasing lethargy and weight loss. Blood tests demonstrated thrombocythemia (platelet count 800 x 10^9/litre). The patient proceeded to develop numbness and weakness predominantly affecting the lower limbs. He also noted difficulty climbing stairs, impaired balance, and decreased exercise tolerance, with altered sensation to his soles and pins and needles in his lower limbs.

During the 4-month period after the onset of neurological symptoms no diagnosis was made. At this point the patient was admitted to hospital with sudden onset abdominal pain. The pain resolved with conservative management but during the admission, transient episodes of upper limb weakness were recorded in addition to a progression of the existing lower limb weakness.

The patient had no significant past medical history, and had been fit and active before this. He was a non-smoker with occasional alcohol intake, and there was no significant family history. He had travelled to Nigeria a year previously, where he reported contact with tuberculosis. *Table 1* summarizes the results of investigations performed following admission to a teaching hospital.

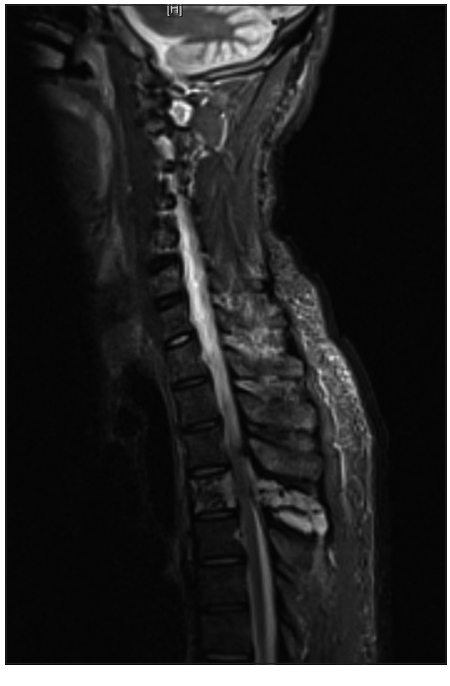
Following confirmation of the diagnosis of POEMS syndrome associated with plasma cell myeloma, treatment was coordinated by the haematology team and the patient was commenced on six cycles of VCD chemotherapy (bortezomib, cyclophosphamide and dexamethasone) with further plans for an autograft bone marrow transplant. Testosterone replacement therapy was initiated.

Table 1. Summary of relevant investigations

Laboratory	Routine bloods on admission	Thrombocytosis with mildly raised serum globulin and elevated lactate dehydrogenase levels. Other routine bloods unremarkable
	Haematology	Blood film showed a thrombocytosis with giant platelets. Serum electrophoresis revealed an IgG Kappa monoclonal light chain band
	Biochemistry	Serum vascular endothelial growth factor levels were elevated at 9684 pg/ml (normal <707 pg/ml)
	Immunology	Immunological assays were negative for all autoantibodies tested (anti-nuclear antibodies, dsDNA, anti-neutrophil cytoplasmic antibody, anti-tissue transglutaminase, anti-GM1, anti GQ1b). Tumour markers (prostate-specific antigen, Ca 19.9, carcinoembryonic antigen, CA 125 and β-human chorionic gonadotrophin) were all negative
	Endocrine	Low serum testosterone and low or normal follicle-stimulating hormone and luteinizing hormone indicating secondary hypogonadism. Thyroid function, parathyroid hormone and calcium homeostasis all within normal range. Normal short synacthen test
	Microbiology	Multiple blood cultures performed with no growth. Negative HIV test. Bone marrow biopsy was performed with auramine staining and culture for mycobacteria; both were negative
Imaging	Computed tomography of the chest, abdomen and pelvis	Multiple bony lesions in the ribs, acetabulum and vertebral bodies
	Magnetic resonance imaging (*Figure 1*)	Multiple mixed sclerotic and lytic foci in the ribs, thoracic vertebral bodies and left scapula. Lymphadenopathy also noted
Histology	Bone marrow aspirate and trephine biopsy from vertebral lesion	High percentage of plasma cells, with bone marrow trephine biopsy confirming large numbers of plasma cells with kappa light chain restriction. Consistent with a diagnosis of plasma cell myeloma

omized controlled trials studying the treatment of POEMS syndrome and therefore gave no strong recommendations on the best treatment of the condition. One group recommends different treatments dependent on age, with patients over 65 years of age receiving melphalan or lidomide plus dexamethasone, and patients 65 years or under being considered for autologous peripheral blood stem cell transplantation (Li and Zhou, 2013). Further clinical trials need to be performed to further our treatment of POEMS syndrome. BJHM

Figure 1. Magnetic resonance imaging of cervical and thoracic spine showing multiple mixed sclerotic and lytic lesions.



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LEARNING POINTS

- POEMS syndrome is a rare, multisystem disease developing in the context of a plasma cell malignancy, named as an acronym of five clinical features which characterize the condition: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Other clinical features beyond these may also occur.
- The combination of thrombocytosis, paraproteinaemia, evidence of endocrinopathy and lytic bone lesions should be sufficient to provoke consideration of POEMS syndrome. Initial investigations should be targeted at confirming the presence of a plasma cell malignancy.
- As a rare condition, optimal management strategies have yet to be determined, but chemotherapy and consideration of autologous peripheral blood stem cell transplantation remains the mainstay of treatment.
- This case highlights the potential for significant diagnostic delay in the confirmation of the diagnosis, which in turn delays specific treatment. Early involvement of specialist opinion in the assessment of unexplained symptomatology could potentially reduce this diagnostic delay.