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POEMS: How mandatory are the diagnostic criteria? a case report

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Case Report

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Abstract

Background

POEMS syndrome is a rare multisystem paraneoplastic disorder associated with plasma cell dyscrasias. The diagnosis is based on a constellation of clinical features, including the mandatory presence of polyneuropathy and a monoclonal plasma cell proliferative disorder, together with additional major and minor criteria. However, the clinical spectrum of POEMS syndrome is broad, and atypical presentations that do not fulfill established diagnostic criteria may be overlooked. Reports of such cases are important to improve recognition of this rare condition. We describe a patient with features suggestive of POEMS syndrome who presented without the typically mandatory feature of polyneuropathy.

Case presentation

A 60-year-old Sri Lankan woman with diabetes mellitus and hypothyroidism presented with a six-month history of asthenia, anorexia, significant weight loss of 18 kg, skin hyperpigmentation, and progressive abdominal distension due to refractory ascites. Clinical examination revealed hepatosplenomegaly and cervical lymphadenopathy but no clinical evidence of peripheral neuropathy. Laboratory investigations demonstrated normocytic anemia, renal dysfunction, and normal inflammatory markers. Ascitic fluid analysis revealed a lymphocytic, non–portal hypertensive ascites. Imaging confirmed hepatosplenomegaly and lymphadenopathy, and cervical lymph node biopsy demonstrated Castleman disease. Serum protein electrophoresis revealed an IgG lambda monoclonal band, while nerve conduction studies were normal. Based on the constellation of findings—including organomegaly, extravascular volume overload, skin changes, monoclonal gammopathy, and Castleman disease—the patient was treated for atypical POEMS syndrome with lenalidomide and dexamethasone. This resulted in a rapid and dramatic resolution of ascites, supporting the diagnosis.

Conclusions

This case highlights that POEMS syndrome may occur without polyneuropathy while still presenting with a convincing clinical phenotype. In atypical presentations where standard diagnostic criteria are not fully met, clinicians should rely on comprehensive clinical evaluation, pattern recognition, and multidisciplinary discussion. Early recognition and timely treatment can lead to significant clinical improvement, particularly in resource-limited settings.

Background

POEMS syndrome, an acronym for Polyneuropathy, Organomegaly, Endocrinopathy, presence of an M Protein and Skin changes is a rare paraneoplastic syndrome, associated with plasma cell disorders. The acronym does not encompass the multitude of other clinical features associated with the syndrome,

such as papilloedema, extravascular volume overload, sclerotic bone lesions, and thrombocytosis or erythrocytosis. Due to its complexity and multi-systemic involvement, the exact prevalence is not known. Diagnosis of this syndrome is difficult even when all diagnostic criteria are fulfilled due to its collection of seemingly unrelated features. In the absence of typical diagnostic criteria in atypical presentations, the diagnosis remains even more evasive.

We report the case of a 60-year-old female from Sri Lanka who presented with differential ascites who was ultimately diagnosed with POEMS syndrome, despite the absence of the mandatory criterion of neuropathy. We aim to highlight the importance of being vigilant of atypical presentations and through this, challenge the restrictive diagnostic criteria.

Case Presentation

This patient is a 60-year-old female, with diabetes mellitus and hypothyroidism. In early 2024, she developed gradual onset asthenia, severe anorexia and loss of 18 kilograms of body weight over 6 months. She also noted progressive hyperpigmentation of the skin overlying her arms. (Fig. 1) There was no fever during this period, and her systems review was normal. Three months following the onset of her constitutional symptoms, she developed mild lower limb oedema with disproportionate abdominal distension. There was no associated abdominal pain, jaundice, altered bowel habits or postmenopausal bleeding. She denied a contact history of tuberculosis. She presented to us, six months after the onset of her constitutional symptoms, due to the progression of her abdominal distention.

On admission, she was noted to be pale and had bilateral non-tender cervical lymphadenopathy. The lymph nodes were discrete, rubbery and the largest measured 3–4 centimetres in diameter. She was noted to have hyperpigmentation over the extensor surfaces of her arms and forearms, with sparing of the buccal mucosa, and palmar creases. Mild pretibial pitting oedema was noted. Cardiovascular examination was normal with no postural drop in blood pressure, and lungs were clear. Abdominal examination revealed moderate painless hepatosplenomegaly and gross ascites. Neurological examination was normal with no clinical evidence of peripheral neuropathy. Cranial nerves were intact and there was no papilloedema on fundoscopy.

During investigation, she was found to have anaemia with a haemoglobin level of 10.7 g/dl. Her blood picture showed normochromic, normocytic cells with mild rouleaux formation. White blood cell counts and platelet counts were normal. A summary of her blood investigations is given in Table 1.

Table 1
Summary of investigations

Investigation	Result
FBC	White blood cells- 6.7 x 10^3/µl Haemoglobin 10.7g/dl Mean Corpuscular Volume – 89.1fL MeanCorpuscularHaemoglobin-28.1pg Platelets 175 x 10^3/µl
ESR	8mm/hr
CRP	13mg/dl
Creatinine	2.3mg/dl
AST	9U/L
ALT	10U/L
Albumin	3.8mg/dl
Globulin	2.3mg/dl
T4	0.9ng/dl (0.7- 2)
Thyroid stimulating hormone	9.327mU/L (0.35–4.94)
Follicular stimulating hormone	50IU/L (25–130)
Luteinizing hormone	32IU/L (15–50)
Random Cortisol	12mcg/dl (5–25)
Hepatitis B, C	Negative
HIV 1 and 2	Negative

Mantoux testing yielded a negative result. Ascitic fluid aspirate revealed the presence of a non-portal hypertensive lymphocytic ascites, with a serum to ascitic fluid albumin gradient of 0.7g/dl. Cell counts were 210 lymphocytes with 10 polymorphonucleocytes. Culture and tuberculous testing carried out on the ascitic fluid were negative. A 2D echocardiogram showed a hypertensive heart with an ejection fraction of 55% and a small pericardial effusion. No evidence of constrictive pericarditis was seen.

A colonoscopy to rule out the presence of bowel malignancy was normal. Ultrasound scan of the abdomen showed hepatosplenomegaly with normal liver echotexture, and Doppler ultrasonography of the hepatic and portal veins did not reveal any thrombi. A contrast enhanced computed tomography (CECT) scan of the chest, abdomen and pelvis confirmed hepatosplenomegaly and ascites, but in

addition showed prominent aortocaval and paraaortic lymph nodes, with the largest being 7.5mm in diameter.

At this point, a cervical lymph node biopsy was performed, which revealed evidence of lymphoid follicular hyperplasia with atretic germinal centers, focal vascularization and onion skin appearance, conclusive of early Castleman disease.

Focused investigation in the line of a paraproteinemia was then carried out. Her serum protein electrophoresis showed a monoclonal band in the gamma region, with a paraprotein level of 1g/L. Immunofixation confirmed a monoclonal band composed of IgG and Lambda chains. On bone marrow biopsy, there was hypercellularity with 6–8% of plasma cells. Skeletal survey did not identify the presence of lytic lesions. Nerve conduction study was normal with normal motor conduction velocities and normal sensory nerve action potentials. Vascular endothelial growth factor (VEGF) levels were not done due to limited resources.

During her hospital stay, there was notable worsening of her ascites. Therapeutic aspiration of the peritoneal fluid was required with increasing frequency, necessitating paracentesis every other day.

A multidisciplinary discussion was held with the involvement of internal medical and haematology teams. Based on supportive evidence of other cases of POEMS that did not fulfill the mandatory criteria, and reports of refractory ascites being an indication for treatment, it was decided to treat her as for an atypical presentation of POEMS syndrome. Accordingly, she was started on a combination of lenalidomide 20mg daily and dexamethasone 20mg daily. Following the initiation of treatment, ascites resolved promptly and noticeably. She also did not require further paracentesis. However, due to concerns over her dropping eGFR, the frequency of chemotherapy was reduced (to every other day) and this resulted in an immediate worsening of her ascites, thus confirming her treatment response.

Discussion

POEMS syndrome poses various diagnostic challenges. It has a diverse set of symptoms, overlaps with numerous mimics and progresses slowly till evolution into a clinically distinguishable entity. Diagnostic criteria have been laid down by expert panels to make the process of diagnosing this enigmatic entity easier. However, the spectrum of POEMS remains vast, and classical diagnostic criteria may sometimes fail to capture rare presentations. We report one such case of atypical POEMS where the diagnosis was established despite lack of conformance with standard diagnostic criteria, with good therapeutic success.

This patient presented with differential ascites, hepatosplenomegaly and generalized lymphadenopathy in association with significant constitutional symptoms. The differential diagnoses considered in her case were peritoneal tuberculosis, bowel or gynaecological malignancy with peritoneal deposits and lymphoproliferative disorder. The symptom profile and the lymphocytic nature of ascites fit in with all the aforementioned differentials. Tuberculosis was deemed unlikely due to the negative Mantoux testing and

the negative tuberculous studies performed on ascitic fluid and sputum. A solid organ tumour with peritoneal metastasis also seemed unlikely due to the normal findings on CECT imaging, colonoscopy, tumour marker screen and ascitic fluid cytology. The cervical lymph node biopsy with its characteristic histopathological features of Castleman disease helped to clinch the diagnosis and guide further investigation down a more focused path.

For POEMS, the mandatory criteria are polyneuropathy and the presence of a monoclonal plasma cell proliferative disorder. The major criteria are the presence of sclerotic bone lesions, elevated VEGF levels and Castleman disease. Minor criteria comprise organomegaly, extravascular volume overload (ascites, pleural effusion, oedema), endocrinopathy (adrenal, thyroid, pituitary, parathyroid), skin changes, papilloedema, thrombocytosis or polycythaemia. Confirmation of the diagnosis requires both the mandatory criteria, one major and one minor criterion. (1)

Castleman disease is a rare nonclonal lymphoproliferative disorder, prevalent in 11–30% of patients diagnosed with POEMS syndrome. (2) VEGF elevation noted in POEMS, increases vascular permeability, causes extravasation of fluid and selective third space accumulation, leading to oedema, pleural effusions and ascites. However, a localized manifestation of fluid overload as seen with differential ascites in our patient, remains an uncommon presentation of POEMS. (3)

In our patient, there was initial hesitancy for establishing a diagnosis of POEMS even in the presence of Castleman syndrome due to the absence of neuropathy. Neurological involvement in POEMS is almost omnipresent, causing it to be recognized as a mandatory criterion for diagnosis. The peripheral neuropathy in POEMS is usually of demyelinating type.

A study of 99 confirmed cases of POEMS syndrome reported that 85% were initially misdiagnosed, with the average time period from symptom onset to diagnosis being 18 months. (4) Reasons for delayed diagnosis include the overlap between clinical presentation of POEMS with that of many other conditions, and the insidious evolution of indiscernible symptoms until a collectively recognizable clinical profile develops. (2)

In light of this, it is important to note that not all cases of POEMS meet diagnostic criteria, with such entities being known as incomplete or atypical cases of POEMS. (5) Our patient, despite the lack of neuropathy, had other evidence of POEMS including Castleman disease, monoclonal plasma cell disorder with IgG Lambda, organomegaly, extravascular fluid overload and skin involvement in the form of hyperpigmentation. When Castleman disease is diagnosed in a patient whose clinical picture is compatible with POEMS, in the absence of peripheral neuropathy or a monoclonal protein, it is termed the Castleman variant of POEMS syndrome. Furthermore, the constellation of symptoms seen in our patient, when taken together would not fit in to any other unifying diagnosis.

There are other reported cases of atypical POEMS in the literature that have been diagnosed in the absence of neuropathy as mandatory criteria. Morizane and colleagues reported a case of a 43-year-old female presenting with organomegaly, endocrinopathy, a monoclonal protein, and sclerotic bone lesions

with normal nerve conduction studies. (6) She was diagnosed to have an atypical form of POEMS syndrome. Hassun and colleagues also published a report of a middle-aged male presenting with scleredema and a monoclonal gammopathy with elevated VEGF levels who was treated as for evolving POEMS syndrome, in the absence of peripheral neuropathy. (6)

The first therapeutic challenge that results with atypical POEMS is the decision on when to initiate treatment. Usually, these patients are followed up over time, to watch for the development of other diagnostic features, instead of proceeding with treatment.

Atypical cases with debilitating symptomatology, such as in our case can be considered for treatment. Suyani and colleagues describe the complete remission of disease in response to lenalidomide, cyclophosphamide and dexamethasone in a patient with incomplete POEMS syndrome. The patient had presented with bilateral claw hands and foot drop, with evidence of neuropathy on nerve conduction studies. She also had papilloedema and hepatosplenomegaly, but had no monoclonal plasmacytosis. (7) Li, Qiang MM and colleagues also describe a case of POEMS syndrome, presenting with skin manifestations, lymphadenopathies, pedal oedema, immunoglobin A-λ restricted paraproteinemia, and elevated vascular endothelial growth factor in the absence of neuropathy, treated with vincristine, adriamycin, dexamethasone, with some improvement in limb strength and pain. (8)

Strictly adhering to the diagnostic criteria will delay both diagnosis and treatment in these cases that are clinically suggestive but atypical in presentation. As for our patient, the initiation of treatment lead to rapid resolution of ascites, which was the most debilitating symptom for her. Despite our inability to test VEGF levels in this patient, its elevation is known to lead to capillary leak and volume overload and the prompt resolution of the ascites after treatment confirms that the pathophysiology of the disease if VEGF mediated.

The second therapeutic problem in POEMS syndrome is the therapeutic regime. Radiotherapy, chemotherapy and bone marrow transplant are among the treatment options available. Systemic therapy remains the most reasonable treatment option, and lenalidomide or bortezomib with dexamethasone is the recommended regime unless the patient is eligible for an autologous stem cell transplant. (9)

We use our case to highlight the importance of recognizing the wide spectrum of POEMS syndrome, outside of the conventional box of diagnostic criteria. In rare diseases such as POEMS, reports of atypical presentations are important to increase clinician vigilance and prevent missing of a diagnosis due to restrictions posed by standard diagnostic criteria. Our case report adds to the existing knowledge on atypical presentations of POEMS and also discusses important therapeutic decisions.

Conclusions

This case report describes a patient who was diagnosed with atypical POEMS syndrome in the absence of standard mandatory criteria and was treated with systemic chemotherapy for debilitating symptoms. We aim to illustrate how diagnostic anchoring to polyneuropathy may contribute to under-recognition of

atypical POEMS. We also aim to expand the current knowledge on the spectrum of POEMS that is not captured in standard diagnostic criteria, and make a case for expanding indications for treatment. We also would like to emphasize the importance of clinical acumen in diagnosis in a resource limited setting and the use of symptom reversal as a diagnostic aid. It is useful to have multidisciplinary contributions when diagnosing and treating such complex cases, for which existing clinical evidence and experience are inadequate.

Abbreviations

POEMS – Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes

VEGF – Vascular endothelial growth factor

FBC – Full blood count

ESR – Erythrocyte sedimentation rate

CRP – C-reactive protein

CECT – Contrast-enhanced computed tomography

HIV – Human immunodeficiency virus

IgG – Immunoglobulin G

TSH – Thyroid-stimulating hormone

eGFR – Estimated glomerular filtration rate

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this case report in accordance with the policies of the National Hospital of Sri Lanka, as it describes a single patient with no identifiable information. Written informed consent was obtained from the patient for publication of this case report.

Consent for publication

Written informed consent for publication of clinical details and images was obtained from the patient. The patient understood that her identity would remain anonymous. A copy of written consent given by the patient is available for review by the Editor in Chief of JMCR

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RL (Dr. Raahya Lafir) was the primary physician involved in the patient's care, conceptualised the report, and wrote the manuscript.
MNV (Dr. M. N. Vidanapathirana), PK (Professor Panduka Karunanayake), and AS (Dr. Ahalyaa Shivashangar) contributed to patient management, critical revision of the manuscript, and supervision of the work.
All authors read and approved the final manuscript.

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Figures



Figure 1

Hyperpigmentation of left arm and forearm