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DELAYED DIAGNOSIS OF POEMS SYNDROME, HOW AI TOOLS CAN ENHANCE DIAGNOSTIC ACCURACY

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ABSTRACT

Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome is a rare multisystem disorder often misdiagnosed due to its wide-ranging manifestations and clinical overlap with common medical conditions. We present a case of a 76-year-old male who initially presented with bilateral lower extremity oedema and fatigue. Despite multiple specialist evaluations and worsening symptoms with characteristic clinical features, including peripheral neuropathy, thrombocytosis, and sclerotic bone lesions, POEMS syndrome was not investigated until the haematology service saw the patient during his hospitalization. Earlier evaluations prior to hospitalization revealed an IgG lambda monoclonal protein, splenomegaly, papilledema, and an elevated vascular endothelial growth factor (VEGF) level of 10,999 pg/ml, confirming the diagnosis of POEMS syndrome.

This case underscores the importance of early identification of markers related to POEMS syndrome. The patient's presentation also fulfilled the PEST acronym (which stands for papilledema, extravascular volume overload, sclerotic bone lesions, and thrombocytosis), a helpful clinical reminder for internists. Due to his poor functional status and age, he was ineligible for an autologous stem cell transplant and was treated with a combination of daratumumab, lenalidomide, and dexamethasone. After 4 months of treatment, he showed significant clinical improvement and a greater than 50% reduction in VEGF levels. This case illustrates the diagnostic challenges of POEMS syndrome and the important role internists can play in early recognition. Prompt VEGF testing, investigation with artificial intelligence tools, and inclusion of POEMS syndrome in the differential can reduce unnecessary consultations and healthcare costs, while enabling timely therapy.

KEYWORDS

POEMS syndrome, PEST, VEGF level, daratumumab

LEARNING POINTS

- When a patient has a constellation of symptoms including peripheral neuropathy and monoclonal gammopathy, POEMS syndrome needs to be added to the working diagnoses.
- Common cognitive biases may delay diagnosis of a rare disease such as POEMS syndrome, leading to adverse clinical outcomes and increased healthcare costs.
- Earlier screening of the patient's symptoms via artificial intelligence tools could have prompted an appropriate diagnosis and combat common cognitive biases.

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INTRODUCTION/BACKGROUND

Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-cell proliferative disorder, and skin changes (POEMS) syndrome commonly presents as a motor polyradiculoneuropathy, and its associated systemic features are often overlooked or attributed to other medical conditions. This, combined with the rarity of the condition (prevalence of 1 in 300,000), makes POEMS syndrome a diagnostic challenge. At a large quaternary UK hospital system, the average time from symptom onset to diagnosis was 9 months[1]. We present a case of 76-year-old male who had these symptoms as well as papilledema, extravascular volume overload, sclerotic bone lesions, and thrombocytosis (PEST), before becoming wheel-chair dependent and hospitalized. This case illustrates the value of a thorough review of the patient's physical examination as well as existing laboratory findings and the importance of considering rare diagnostic possibilities in clinical reasoning. Our case also highlights the utility of daratumumab-based combinations in treatment of rare plasma cell disorders.

CASE DESCRIPTION

A 76-year-old male with a history of hypertension presented to the emergency department initially for epigastric pain and increased bilateral lower extremity swelling associated with generalized fatigue. His pro-B-type natriuretic peptide (proBNP) was elevated at 1,366 pg/ml and his transthoracic echocardiogram revealed an ejection fraction of 65-69% with indeterminate diastolic function. The patient had thrombocytosis with a platelet count of 614 $\times 10^3$/µl. Computed tomography (CT) scan of the chest, abdomen, and pelvis showed a sclerotic lesion in the T12 vertebra body unchanged from 2 years prior, and multiple new sclerotic foci through the pelvis *(Fig. 1)* and thoracolumbar spine. His peripheral oedema was attributed to the new diagnosis of diastolic heart failure. He was subsequently discharged from the emergency department with diuretics and the elevated platelet count was not further evaluated.

The patient saw a neurologist 2 months later as he developed tingling in both feet and difficulty with ambulation due to decreased leg strength. Serum protein electrophoresis (SPEP) revealed monoclonal protein of 0.2 g/dl; IgG was elevated at 2,100 mg/dl (upper limit of normal 1,685 mg/dl). Serum immunofixation identified an IgG lambda monoclonal protein with increased free kappa light chains at 13.9 mg/dl (ULN 2.89 mg/dl) and free lambda light chains at 16.3 mg/dl (ULN 3.26 mg/dl) along with normal free kappa/free lambda ratio of 0.85. Nerve conduction studies with electromyography done 1 month later showed evidence of a distal sensory and motor peripheral neuropathy with mixed axonal and demyelinating features. At this point, he would have met the diagnostic criteria for POEMS syndrome: polyneuropathy, monoclonal plasma cell-proliferative disorder, sclerotic bone lesions and extravascular volume overload[2]. The patient continued to see a nephrologist for his peripheral oedema and a rheumatologist for evaluation of



Figure 1. Computed tomography scan of the chest, abdomen, and pelvis without contrast. Axial view showing a sclerotic focus involving the pelvic bone.



Figure 2. Computed tomography scan of the chest, abdomen, pelvis without contrast. Axial view demonstrating splenomegaly with a craniocaudal length of 16.4 cm.

fatigue. The patient presented to the emergency department a week later as he became wheelchair bound. Neurosurgery and orthopaedic services were also consulted at that time for acute onset back pain. However, POEMS syndrome was still not entertained as a diagnostic possibility until a consultation to haematology. He had additional features such as splenomegaly *(Fig. 2)*, thrombocytosis (platelet count - 561 $\times 10^3$/µl), blurred vision with papilledema on eye examination, skin changes such as hypertrichosis and multiple endocrine abnormalities including hypothyroidism and hypogonadism *(Table 1)*. The patient also had clinical features consistent with the PEST acronym as he had papilledema, extravascular volume overload, sclerotic bone lesions, and thrombocytosis. His serum vascular endothelial growth factor (VEGF) level was elevated at 10,999 pg/ml (ULN 115 pg/ml). A bone marrow biopsy showed hypercellularity with plasmacytosis and a 20% lambda light chain-restricted plasma cell population, confirming the diagnosis of POEMS syndrome.

Considering his age and Eastern Cooperative Oncology Group (ECOG) performance status of 2, he was deemed

	Before treatment	After 4 months of treatment	Reference range
WBC (×10³/µl)	11.28	4.97	4.4-11.3
Hemoglobin (g/dl)	14.0	12.1	14-17.4
Platelet count (×10³/µl)	561	381	145-445
TSH (µIU/ml)	12.3	1.41	0.4-4
Plasma VEGF (pg/ml)	10,999	143	0-115
Serum protein electrophoresis			
M-Spike (g/dl)	0.2	0.1	0
IgG (mg/dl)	2,100	881	723-1,685
IgA (mg/dl)	293	153	69-382
IgM (mg/dl)	122	55	63-277
Kappa free light chain (mg/dl)	13.9	3.94	0.82-2.89
Lambda free light chain (mg/dl)	16.3	6.49	0.91-3.26
Kappa/lambda free light chain ratio	0.85	0.61	0.52-1.51

Abbreviations: WBC, white blood cells; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.

Table 1. Pertinent laboratory values prior to and after treatment.

ineligible for autologous peripheral blood stem cell transplantation (PBSCT). Based on a retrospective study, 5 out of 6 patients with refractory POEMS syndrome had complete responses with decreases of VEGF to normal levels with daratumumab (anti-CD38 monoclonal antibody targeting the plasma cell clone) containing combination chemotherapy therapy[3]. Our patient was started on treatment with subcutaneous daratumumab (1800 mg of per week during cycles 1 and 2; 1800 mg every 2 weeks during cycles 3 through 6), along with oral lenalidomide (10 mg on days 1 through 21 of each cycle) and 10 mg of intravenous dexamethasone (10 mg on days 1, 8, 15, and 22) during a 28-day cycle. The dose of lenalidomide was adjusted based on creatinine clearance. The patient had significant clinical improvement with ability to ambulate independently, as well as resolution of peripheral oedema and thrombocytosis within 7 weeks. He had partial haematological response (greater than 50% decrease in VEGF) at 4 months after initiation of therapy with almost completion normalization of VEGF level at 143 pg/ml *(Table 1)*.

DISCUSSION

The pathogenesis of POEMS syndrome is not well understood. Elevated VEGF messenger ribonucleic acid (mRNA) expression in bone marrow plasma cells is believed to increase vascular permeability, which causes some of the physical manifestations of the disease. This case illustrates the multisystem manifestations and the potential for delayed diagnosis in a patient with POEMS syndrome given the rarity of the condition.

Availability and confirmation biases, which are commonly encountered psychological biases in clinical reasoning, likely played a role in the delayed diagnosis. Availability bias, where physicians recollect common diagnoses, they see often and thus neglect rare diagnoses, played a definitive role in the delay in diagnosing POEMS syndrome in this case. While each individual clinical manifestation has multiple common explanations, it is important to consider the full clinical picture to generate differential diagnoses to direct testing. Confirmation bias was also in effect when clinicians were fixated on some differentials and tended to fit the clinical features to suit those differentials. Consequently, they did not pay attention to findings such as thrombocytosis and sclerotic bone lesions in this case that do not fit with the diagnosis or suggest alternative diagnoses.

We are now in a new era of artificial intelligence (AI) tools, where physicians can put the constellation of symptoms into OpenEvidence (Cambridge, USA) and receive the most probable diagnosis within seconds. Specifically for this case, POEMS syndrome is the most likely diagnosis when the amalgamation of symptoms (diastolic heart failure, neuropathy, splenomegaly, hypothyroidism, hypogonadism, elevated IgG lambda monoclonal protein, acute back pain, wheelchair bound, peripheral oedema, sclerotic lesions) is entered into OpenEvidence[4]. In a complex case like this, a thorough review of the patient's history is a must during admission so that principal medical conditions are identified, and treatment is not delayed because of rare diagnoses. In fact, there are ongoing studies utilizing OpenEvidence to address the knowledge gaps often encountered in primary

care as compared to specialty practices[5]. By using AI tools, physicians can combat availability and confirmation bias.

Additional healthcare costs were generated in unnecessary specialist consultations such as rheumatology and nephrology and repeated hospitalizations in the case of this patient. In the National Health Service in the UK, the average cost-per-POEMS-patient misdiagnosis was £14,701 to £20,214[1]. Early recognition of POEMS syndrome, facilitated by AI tools is critical for the timely initiation of appropriate antineoplastic therapy and alleviation of the patient's symptoms.

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