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Case Report

A Novel Presentation of POEMS Syndrome: A Call for A Unified Diagnostic Criteria

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Abstract

POEMS syndrome is a rare multisystemic disorder in the setting of a paraneoplastic process. It is a constellation of findings including polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell proliferation, and skin changes. Currently, there is no specific case definition that exists for the condition. Herein, we report the case of a 47-year-old female who presented with a case of POEMS syndrome. Her unique presentation qualifies for POEMS syndrome. Moreover, she also presents other common symptoms of the syndrome that are excluded by the current criteria. The report will therefore serve as a much-needed call for a review and unifying of POEMS syndrome criteria.

Keywords: POEMS Syndrome; Multiple myeloma; Diagnostic criteria; Internal medicine; Oncology

Introduction

POEMS syndrome is a constellation of systemic manifestations in a paraneoplastic process, specifically related to plasma cell dyscrasias. The acronyms "POEMS" consists of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, and Skin changes such as hyperpigmentation, hypertrichosis, plethora, bruise, acrocyanosis, or flushing. In the realm of medical complexities, paraneoplastic processes involve the manifestation of symptoms in organs and tissues that are not directly affected by the primary tumor. Within this spectrum, POEMS syndrome stands out due to its association with plasma cell dyscrasias, and its acronym succinctly captures the diverse range of clinical features observed. The causes and physiopathology of the disorder are still under investigation. Current literature has proposed the proliferation of cytokines as a contributing factor. Elevation of many growth factors and pro-inflammatory cytokines, particularly Vascular Endothelial Growth Factor (VEGF), can explain the pathophysiology of the syndrome [1,2]. POEMS syndrome is a rare disease with limited literature and a wide variety of presentations. Currently, there is no specific case definition that exists for this condition. Herein, we report the case of a 47-year-old female who presented with a unique case of POEMS syndrome. This article delves into the intricate landscape of POEMS syndrome, spotlighting the complexities through the lens of a unique case presentation. Our aim is to shed light on the urgent need for a unified and comprehensive diagnostic criteria, considering the diverse presentations observed in patients. By exploring this atypical case, we embark on a call for a critical review and refinement of existing criteria to improve diagnostic accuracy and patient outcomes.

Case Presentation

A 47-year-old woman with unknown past medical history presented to the emergency room with generalized weakness and left flank pain for the past two weeks. She reported an associated flank bruise and a dull aching abdominal discomfort, both of which have worsened in the past three days. Her symptoms were exacerbated with standing and exertion. She also endorsed heavier than usual menses and occasional tingling sensation in her legs. Family members reported recent yellowish discoloration of her skin and intermittent tremors. In addition, she reported intermittent deep, diffused, sharp pain on her legs bilaterally at night when she was in bed, which was unimproved with use of Tylenol. She did not have a primary care physician and is not on any medication.

Review of systems revealed tremors in the upper extremities, weakness in her lower extremities, nausea, vomiting, tendency to easily bruise and bleed, and bilateral leg swelling. Physical examination demonstrated icteric sclera, a 2/6 low pitched ejection murmur, bibasilar rales, bilateral grade II pretibial edema, jaundice, hematoma on left flank, and a mild ataxic gait.

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IgA 65 - 421 mg/dL	>7,100 ^	
Albumin 3.75 - 5.01 gm/dL	2.45 v	
Alpha 1 Globulin 0.19 - 0.46 gm/dL	0.23	
Alpha 2 Globulin 0.48 - 1.05 gm/dL	0.38 v	
Beta Globulin 0.48 - 1.10 gm/dL	3.54 ^	
Gamma 0.62 - 1.51 gm/dL	6.10 ^	
Total Protein-Electrophoresis 6.3 - 8.2 gm/dL	12.7 ^	
BILL_Electropho gm/dL	9.13	

Figure 1: Electrophoresis shows elevated β-globulin, γ-globulin, and high Immunoglobulin A.

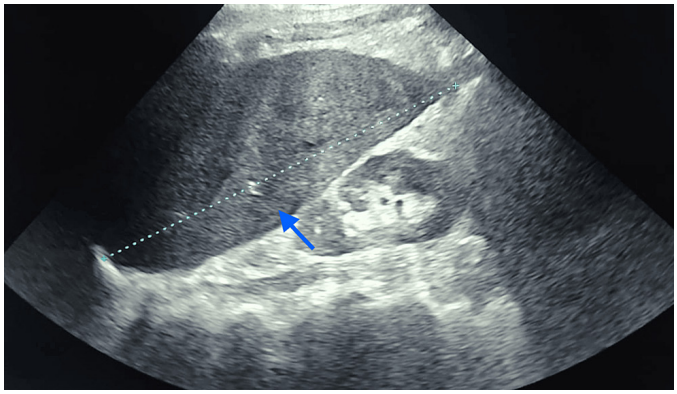

Figure 2: Right Upper Quadrant Ultrasound shows hepatomegaly measuring 20.5 cm craniocaudal without discernibly focal lesion (blue arrow).

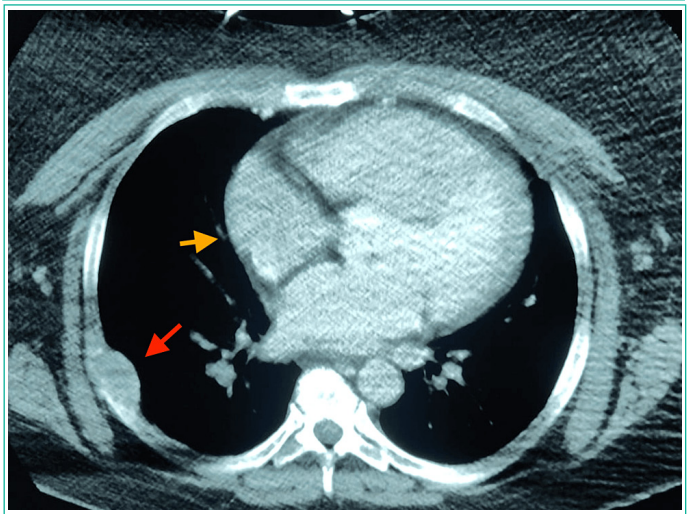

Figure 3: CT Abdomen Pelvis W Contrast reveals cardiomegaly (orange arrow), lytic and expansile lesion involving the right posterolateral sixth rib (red arrow).

Vital signs on admission revealed a temperature of 97.8 °F, blood pressure of 141/65 mmhg, heart rate of 99 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 98% on room air. A complete blood count revealed severed pancytopenia across all blood lines including red blood cells, white blood cells, and platelets. A comprehensive metabolic panel demonstrated high total protein level content of 10.8 gm/dL (normal: 6.1-7.9 gm/dL) with low albumin of 1.7 gm/dL (normal: 3.5-4.8 gm/dL). Urinalysis showed presence of blood and bilirubin. Protein electrophoresis revealed markedly low Immunoglobulin M and G, elevated levels in β-globulin and γ-globulin, along with a remarkable high Immunoglobulin A of more than 7100 mg/dL (normal: 65-421 mg/dL) (Figure 1). Transthoracic echocardiogram revealed severe pulmonary hypertension with pulmonary arterial systolic pressure of 74 mmHg. Abdominal ultrasound was positive for hepatomegaly (Figure 2). CT abdomen and pelvis was significant for expansile lytic lesions involving the right posterolateral sixth ribs measuring 3.2 x 1.7 x 2.3 cm (normal thickness: 0.9-2.6 mm) concerning for metastatic disease (Figure 3). She was later diagnosed with multiple myeloma. This further supports the significance of POEMS syndromes in her case, which was caused by an underlying malignant process.

The patient remained clinically stable throughout her hospitalization. Bone marrow biopsy revealed greater than 10% clonal bone marrow plasma cells. Oncology was consulted for treatment management. However, due to the patient's lack of insurance, she was challenged for follow-up and monitoring. VEGF measurement was planned as part of the patient's management. Unfortunately, the patient's inability to follow up for additional studies has made this information unobtainable.

In summary, pertinent clinical features include generalized weakness exacerbated with standing and exertion, left flank bruising, bilateral lower extremities tingling and neurogenic pain, bibasilar rales, hematoma, and ataxic gait. Pertinent labs and imaging findings consist of severed pancytopenia, elevated total protein, low albumin, notable high Immunoglobulin A, pulmonary hypertension, cardiomegaly, hepatomegaly, and lytic lesions in ribs.

Discussion

This case presents an atypical presentation of POEMS syndrome. There is little literature and research about the disease. According to the widely used criteria, by Dispenzieri, diagnosis of POEMS syndrome requires two mandatory criteria with fulfilling at least one major and one minor criterion [3] (Table 1).

A notable concomitant disease worth mentioning is POEMS-associated Castleman disease. Castleman disease is a rare lymphoproliferative disorder that manifests as multiple lymphomegaly in the body that is strongly associated with POEMS syndrome. There is approximately 11% to 30% patients with POEMS syndromes whose lymph node biopsy were positive for concomitant Castleman disease [4]. If follow-up was possible for this patient, a histological finding of this patient's lymph nodes biopsy could potentially suggest the diagnosis of Castleman disease.

This patient met the major criteria of monoclonal plasma proliferation of IgA and sensory neuropathy consisted of paresthesia and neurogenic pain in the lower extremities. Although lytic lesions were present in our patient, she didn't fit the other major criteria of "sclerotic" lesions. Meanwhile, she satisfied multiple minor criteria including organomegaly, extravascular volume overload, pulmonary hypertension, and skin change. Despite fully meeting the diagnosing criteria, the diversity of her clinical symptoms, which are missing in Dispenzieri criteria, should prompt for reconsideration of the diagnosing criteria.

There are several key clinical symptoms missing from the current diagnostic criteria. A study of pulmonary hypertension as a relevant feature for POEMS syndrome reviewed the echocardiograms in 154 patients. The study demonstrated 27% of coexisting pulmonary hypertension [5]. Other common symptoms

Table 1: Dispenzieri's POEMS syndrome criteria.

Mandatory major criteria	• Polyneuropathy (typically demyelinating) • Monoclonal plasma cell-proliferative disorder
Other major criteria (one required)	• Castleman disease, sclerotic bone lesions • Vascular endothelial growth factor elevation
Minor criteria	• Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Extravascular volume overload (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails), • Papilledema • Thrombocytosis/polycythemia

include pericardial effusion, pleural effusion, and peripheral edema, which are also unlisted in the current criteria. In addition, Dispenzieri also lists polyneuropathy as a "mandatory major criterion". However, there is insufficient data for polyneuropathy being classified as a mandatory major criterion. Yishay conducted a retrospective study in 629 patients with MGUS and plasma-cell dyscrasias and found according to the newly suggested criteria that only four patients with polyneuropathy were eligible for POEMS syndrome. In those four patients, one of the patients later developed other medical conditions that would qualify for polyneuropathy [6]. In addition, the criteria regarding sclerotic bone lesions are another questionable major symptom. A literature-based study of POEMS syndrome revealed that 372 out of 846 patients were positive for bone lesions, in which only 239 sclerotic bone lesions were identified [7]. Moreover, multiple previous cases have recognized that lytic bone lesions have been found in atypical presentations of POEMS syndrome [8]. The patient in this case exhibited lytic, instead of sclerotic, bone lesion, further supporting that sclerotic bone lesion criteria is unreliable. For a more ideal criteria, sclerotic bone lesions as a major criteria should be excluded since this presentation is less commonly found in POEMS syndrome. Rather, a more suited criteria should include common clinical symptoms such as pulmonary hypertension or pleural effusion. This would help clinicians by increasing the sensitivity for diagnosis despite atypical presentations.

Due to the insufficiency of Dispenzieri's criteria, other clinicians have attempted to propose different criteria to incorporate broader and unique presentations of POEMS syndrome. Suichi recommended 3/5 major criteria that resulted in better sensitivities and specificities of 100% and 100%, respectively [9]. Other authors have proposed to look for other defining features such as refractory ascites, peripheral edema, gynecomastia or organomegaly of unknown origin [10]. As suggested by Morizane, Charli, and their colleagues [11,12], we also believe there needs to be reconsideration in defining the diagnostic criteria of POEMS syndrome. Evidently, literature has shown that Dispenzieri's criteria provides a framework for diagnosing POEMS syndrome, but is insufficient for several reasons, such as accounting for other atypical presentations as mentioned previously. Additionally, the defining symptoms may be confounded and derived from other disease processes or take longer to manifest. Due to the flaws discussed previously regarding Dispenzieri's criteria and the discrepancy regarding the most relevant clinical findings in POEMS syndrome [9-12], a review of the new criteria is needed for a more accurate diagnosis.

Conclusions

As of today, there is no standardized definition for POEMS syndrome. Patients with the syndrome have been shown to display a broad variety of symptoms, many of which may exclude the pertinent mandatory or major criteria upon presentation according to Dispenzieri's criteria. The patient in this case is an example of an atypical presentation of POEMS syndrome. Even though she did fully meet Dispenzieri's criteria, she has many other symptoms which were not included in the current criteria. These "unincluded" symptoms, however, have been well documented in existing literature for POEMS syndrome. A more accurate and unified criteria would benefit many patients who present with atypical clinical presentations. Because POEMS syndrome has many differentials that present similarly, proper diagnosis is imperative in guiding clinicians to focus their management on treating the condition and improving patient outcomes.

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