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Diarrhea, Demyelinating Neuropathy and Dyspnea: An Occam's Razor Dilemma

Abimbola Aderinto-Adike[1,*], Hung Q Doan[1], Cima Nowbakht[1], Elizabeth Looke-Stewart[1], Soma Jyothula[2]

[1]Houston Methodist Hospital, Department of Medicine, 6565 Fannin Street, Houston TX 77030 USA
[2]Houston Methodist Hospital, Department of Pulmonary and Transplant Medicine, 6565 Fannin Street, Houston TX 77030 USA
*Corresponding author: aoaderinto@tmhs.org

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Abstract POEMS disease is a rare paraneoplastic syndrome resulting from an underlying plasma cell disorder. We present a unique case of POEMS disease with predominant clinical symptoms of diarrhea and paresthesias.

Keywords: *POEMS disease, paraneoplastic disease, diarrhea, paresthesias, shortness of breath*

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1. Introduction

Initially described by Crow in 1956 and then Fukase in 1968, POEMS syndrome was initially called Crow-Fukase syndrome by Nakanishi in a 1984 review of 102 cases in Japan. [1] The present acronym, POEMS, was coined by Bardwick et al in 1980. [2] POEMS is a rare disease entity, with an acronym that encompasses some of its cardinal features including Polyradiculoneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell neoplasm and Skin changes [3] However, there are other key clinical manifestations of this disease not included in its acronym including sclerotic bone lesions, extravascular volume overload, elevated VEGF level and thrombocytosis. [4] Although a known manifestation of this syndrome, diarrhea is an uncommon clinical presentation of POEMS syndrome and its pathophysiology is not understood. [4] Here we present the case of a patient with a distinctive presentation of POEMS syndrome which complicated her diagnosis. The patient's chief complaint was untreatable diarrhea over a period of months. In addition, our patient also reported shortness of breath, tingling sensations in her hands and feet, skin changes, leg swelling and weight loss. She was found to have a lamba-restricted plasmacytoma, an elevated VEGF level, osteoblastic lesions, polyneuropathy, extravascular volume overload, hepatomegaly, hypothyroidism and developed an ischemic stroke one month after her initial diagnosis. Although our patient's clinical manifestations were easily consistent with the major and minor criteria for diagnosis of POEMS syndrome, this case is unique given diarrhea is an uncommon chief presentation of the syndrome. In addition, we highlight a rare syndrome that often presents a diagnostic dilemma to physicians but one that should be considered when patients present with seemingly unrelated clinical manifestations. Its addition to the literature on POEMS disease expands our understanding of the disease's natural history and should enable timely diagnosis and treatment for patients with similar presentations. As we begin to understand the full spectrum of the disease's manifestations, we can also gain a better understanding of its underlying mechanisms and how best to treat it.

2. Case Presentation

A 66 year old woman without significant history presented with diarrhea. Her symptoms had initially begun eight months prior to presentation. She noted persistent, multiple, loose, non-bloody bowel movements per day not associated with meals. She also described painful, tingling and shocking sensations in her hands and feet. She noted redness of her skin, in addition to progressive lower extremity swelling and shortness of breath. Despite the leg swelling, she endorsed a 50 lbs weight loss since the diarrhea began.

On physical examination, she was afebrile, hemodynamically stable, with oxygen saturation of 95% on 2L of oxygen. She was cachectic with temporal muscle wasting and plethora of her face and chest with cyanotic changes in the extremities. She had rales in the lower lung fields bilaterally with dullness to percussion up to the mid lung fields. Her abdomen was protuberant with a liver span of 18 cm.

Initial laboratories included white count 7.07 k/ul, platelets 335 k/ul, serum albumin 3.4 g/dl, alanine aminotransferase 14 U/L, and aspartate aminotransferase 12 U/L. Infectious work up including HIV and viral hepatitis panel were negative. TSH was 12.85 ulU/ml with a free T4 of 0.5 ng/dl. *Clostridium difficile* was negative. Stool osmotic gap was consistent with a secretory diarrhea.

Colonoscopy revealed hyperplastic polyps without amyloid deposition. Serum protein and urine protein

electrophoresis were normal. Serum light chains were elevated (Lamda 9.47 mg/ml {normal 0.6-2.6} and Kappa 7.38 {normal 0.26-1.65}) with a normal ratio. A computed tomographic study of the chest showed bilateral pleural effusions, with a T10 sclerosing lesion. Thoracentesis was consistent with an exudative pleural effusion. Computed tomography of the abdomen showed a liver span of 22 cm, with multiple sclerotic lesions in the ribs, vertebral bodies and pelvis.

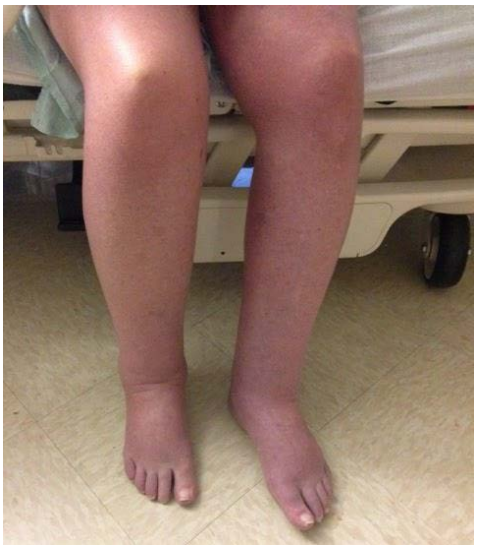

Figure 1. Bilateral peripheral edema and acrocyanosis in our patient

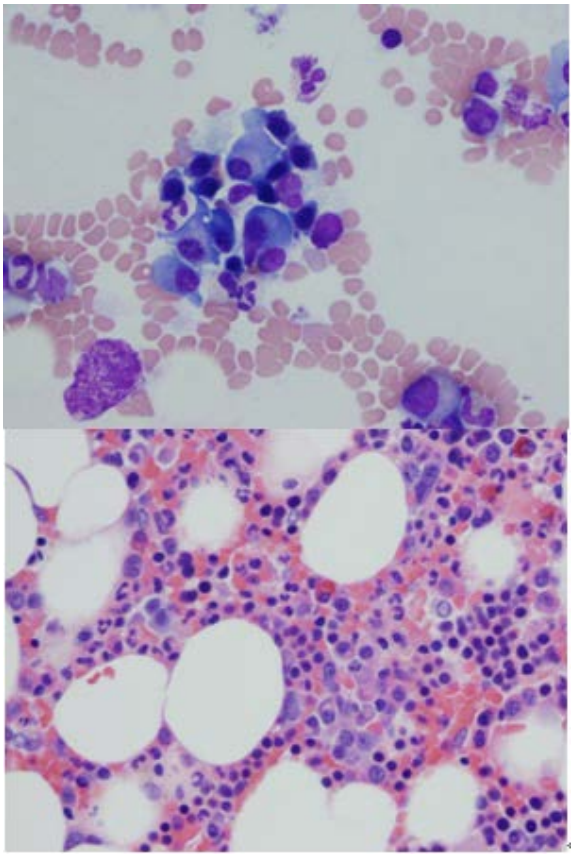

Figure 2. T10 vertebrae biopsy with plasmacytoma and IgA lambda specificity

Ultimately, biopsy of the T10 vertebral lesion was consistent with a lambda restricted plasma cell neoplasm. Electromyography was consistent with severe demyelinating sensorimotor neuropathy. VEGF level was 188 pg/ml (normal 9 – 86 pg/ml). Her constellation of symptoms was consistent with POEMS disease, and chemotherapy with lenalidomide, dexamethasone, and bortezomib was initiated. A month later, the patient suffered from an acute ischemic stroke.

3. Discussion

In a patient presenting with a heterogeneous collection of symptoms where conventional tests do not lead to a unifying diagnosis, approaching Occam's razor may prove useful. POEMS syndrome is a rare disease represented in case reports, case series and small retrospective studies. Its pathophysiology is not well understood and its symptomatic display expands widely past its acronym as represented in our patient.

Our patient had multiple seemingly unrelated initial symptoms including diarrhea, polyneuropathy, severe peripheral edema, and worsening shortness of breath. Polyneuropathy, one of two mandatory diagnostic requirements, is the most common symptom affecting 100% of diagnosed patients. [3] The second mandatory diagnostic requirement is a monoclonal plasma cell dyscrasia seen on biopsy of the osteosclerotic lesions (seen in 95% of cases) with lambda chain predominance. [3] An M-protein spike may sometimes be seen on serum protein electrophoresis (24-54%) but is often not seen, even with immunofixation. [4] Our case highlights the importance of pursuing biopsy of the osteoblastic bone lesions typically seen in this disorder to make a definitive diagnosis of a monoclonal plasma cell neoplasm.

Nevertheless, diarrhea was our patient's chief complaint. Diarrhea in POEMS disease is not well described or understood, but has been previously reported. [4] Extravascular fluid overload is also common, seen in as many as 87% of cases and includes ascites, pleural effusions, and peripheral edema, all of which our patient had contributing to her shortness of breath. [3] Endocrinopathies, are another hallmark of the disease, and may affect any and potentially all axes. Most commonly, hypogonadism, hypothyroidism and adrenal insufficiency are the most common endocrinopathies seen with POEMS disease. [4] Our patient had hypothyroidism and was initiated on thyroid supplementation. The dermatological manifestations in POEMS disease are varied occurring in up to 90% of patients, [4] and range from flushing, plethora and acrocyanosis like our patient to hypertrichosis and hyperpigmentation [4].

An elevated VEGF level is one of the other major criteria for diagnosis of POEMS disease. Vascular Endothelial Growth Factor (VEGF) is the cytokine that best correlates with disease activity and VEGF is used as a marker to monitor response to therapy. However, there have been mixed trials with using anti-VEGF therapy [5].

There are no randomized control trials available for treatment regimens. Treatment options for POEMS disease are based on theories and anecdotes with regimens adapted from other plasma cell dyscrasias such as multiple myeloma [4,6] Our patient had disseminated bone marrow involvement with multiple bone lesions. She was started on systemic chemotherapy with lenalidomide, bortezomib and dexamethasone with modest improvement in her

symptoms, although still early in the course of treatment. Symptomatic management is very important for quality of life. [6] Our patient was also on diuretics for anasarca with therapeutic thoracentesis for recurrent pleural effusions, and gabapentin for peripheral neuropathy. A month into treatment, she suffered from an acute ischemic cerebrovascular event and is currently undergoing physical therapy. Patients with POEMS disease are at increased risk of arterial and venous thrombosis during their course of disease. [4] About one in ten patients with POEMS disease will have a cerebrovascular event. [7] Risk factors for thrombosis include thrombocytosis and plasmacytosis [7].

4. Conclusion

POEMS syndrome is a rare plasma cell disorder with very limited pathophysiologic understanding, and thus poses a diagnostic and therapeutic challenge. POEMS presents with a myriad of symptoms that may appear unrelated, thus requiring physician awareness for a timely diagnosis which plays a key role in improving patient outcomes in this syndrome.

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