Case Report

An unusual cause of type 2 respiratory failure

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Abstract

We present a female patient who was referred for management of respiratory failure. She was being evaluated and managed as worsening chronic inflammatory demyelinating polyneuropathy with type 2 respiratory failure. Initial examination showed hypertrichosis, clubbing and papilledema along with severe distal and proximal motor-predominant weakness with impending respiratory failure. She was managed with noninvasive ventilation (NIV) and plasmapheresis awaiting diagnostic investigations. Immunofixation showed an "M band" and free lambda chain levels were elevated. Radiographs showed the classic osteosclerotic lesions of POEMS (polyradiculoneuropathy, organomegaly, endocrinopathy, M-protein and Skin abnormalities) syndrome. Six weeks after commencing radiotherapy to the osteosclerotic lesions, the patient responded favorably and remains off nocturnal NIV support.

Keywords: Chronic inflammatory demyelinating polyneuropathy, multiple myeloma, plasmapheresis, polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, type 2 respiratory failure

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Introduction

Clinical clues apparent on examination can expand or narrow the differential diagnosis substantially, even when the patient is seen first for management of a life-threatening condition in the Intensive Care Unit (ICU). We present a female patient with presumed chronic inflammatory demyelinating polyneuropathy (CIDP) in whom recognition of hypertrichosis, clubbing and papilledema suggested POEMS (polyradiculoneuropathy, organomegaly, endocrinopathy, M-protein and Skin abnormalities) syndrome.

Case Report

A 35-year-old female patient was seen by the ICU consult services for management of impending respiratory failure. She had presented with cough, sputum, worsening limb weakness and orthopnea for one-week. Weakness was symmetrical in all four limbs and she was unable to move any of her limbs across the bed. She was unable to roll to one side or lift her head off the pillow. Orthopnea was associated with breathlessness at rest. She had presented with insidious progressive weakness of all limbs 7 months prior to the current symptoms to another hospital. Nerve conduction studies had shown evidence of distal, motor-predominant demyelinating polyneuropathy. Magnetic resonance imaging of the spine with contrast was normal. Cerebrospinal examination was acellular and showed raised proteins (1.3 g/dL), without any oligoclonal bands. Human immunodeficiency virus enzyme linked immunosorbent assay (ELISA), venereal disease research laboratory antibodies and antinuclear antibodies by ELISA were negative. CIDP was diagnosed, and she was started on 0.75 mg/kg prednisolone. Weakness continued to worsen despite 3 months of treatment. She was initiated on 2 g/kg intravenous immunoglobulins monthly, along with 0.5 mg/kg steroids, 1.5 mg/kg azathioprine and Osteoporosis prevention therapy. Weakness remained static till one-week prior to the time of her current presentation. She remained bed bound with support needed for all activities of daily living. She had no previous history of smoking, alcohol or other drug abuse or animal exposure. There was also no relevant family history.

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On examination, she was afebrile, normotensive, with a respiratory rate of 40 cycles/min and pulse rate of 106 beats/min. There was evidence of accessory muscle use, with flaring of alae nasi and paradoxical movement of the diaphragm on inspection. General examination also showed bilateral pitting pedal edema to the level of the knee, grade 2 pandigital clubbing, diffuse skin hyperpigmentation with mucosal sparing and hypertrichosis [Figure 1]. Neurological examination confirmed normal mental status and muscle weakness: power in both lower limbs was graded 1/5 and in the upper limbs was 2/5, according to the medical research council (MRC) scale. All deep tendon reflexes were absent. Impaired touch and vibration sensation in the lower limbs below the knee were noted. Plantar reflexes could not be elicited. Cranial nerve examination showed reduced gag with normal sensation. Fundus examination showed papilledema. Chest and cardiovascular were normal. Abdominal examination did not show organomegaly. Arterial blood gas showed respiratory academia due to acute respiratory acidosis (pH 7.3, PaO_2 80 mm Hg on 4 L/min oxygen, $PaCO_2$ 50 mm Hg, HCO_3 28 mEq/L). Computed tomography of the head was normal. Echocardiography revealed normal ejection fraction, normal valves with no evidence of pulmonary hypertension. Bilateral lower limb venous Doppler did not show any evidence of venous thrombosis and quantitative D-dimers (Immunoturbidometry, Lister Metropolis) were negative. She was unable to complete a forced vital capacity maneuver or perform breath hold required for respiratory muscle testing. Sniff measurements and ultrasonography of diaphragmatic muscles were not performed given the obvious paradoxical movements clinically. Her body mass index at admission was 23.4 kg/m^2. Serum potassium, magnesium, and phosphorus were normal. Her remaining investigations are summarized in Table 1.

She was initiated on parenteral piperacillin-tazobactam, azithromycin, enoxaparin, oxygen at 4 L/min (approximate FiO_2 0.4) with bilevel noninvasive ventilation (NIV) (BiPAP 14/4 cmH_2O, ResMedS9 VPAP™ Auto). Plasmapheresis with 2 L exchanges using 5% albumin replacement was started on alternate days for possible worsening of CIDP and was continued for six sessions.

The simultaneous features of clubbing, hypertrichosis and papilledema along with progression of weakness despite treatment prompted further evaluation. Radiographs of the skull, pelvis, and spine [Figure 2] showed osteosclerotic lesions over the right femur and spine. Bone scan was normal. Ultrasound examination showed splenomegaly; there was no evidence of hepatomegaly, enlarged nodes or ascites. Serum immunofixation showed an "M band" in the gamma region (1.5 g/L) with serum albumin levels of 2.43 g/dL (normal 4–6 g/dL). Free lambda chain levels were elevated at 29.60 mg/L (normal, 5.71–26.3 mg/dL) with normal free kappa chain value of 11 mg/L (normal 3.3–19.4 mg/L). Serum β2-microglobulin was 3550 ng/mL (normal 670–2143 ng/mL). Bone marrow biopsy from the right iliac crest showed normocellular marrow, absence of lymphoid aggregates or plasma cell rimming and megakaryocyte hyperplasia.

Discussion

A diagnosis of POEMS syndrome was made. POEMS syndrome is a rare paraneoplastic syndrome because of an underlying Plasma cell disorder (PCD).[1]

The pathogenesis of POEMS syndrome involves λ-chain producing monoclonal plasma cell clone from the sclerotic bony lesions. Vascular endothelial growth factor (VEGF) levels are high but may not be the sole pathogenic mechanism, as anti-VEGF therapy has shown inconsistent results.[2]

The diagnosis of POEMS syndrome is made by the Dispenzieri criteria [Table 2].[3,4] The differential

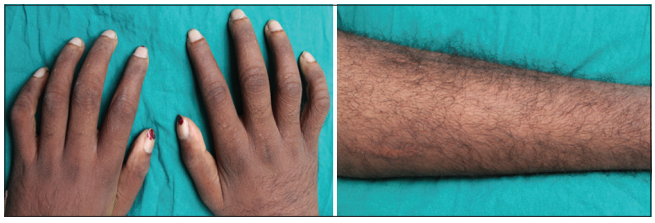

Figure 1: Composite clinical photographs showing grade 3 clubbing (left), with severe distal weakness and a correctible claw-hand deformity and hypertrichosis (right)

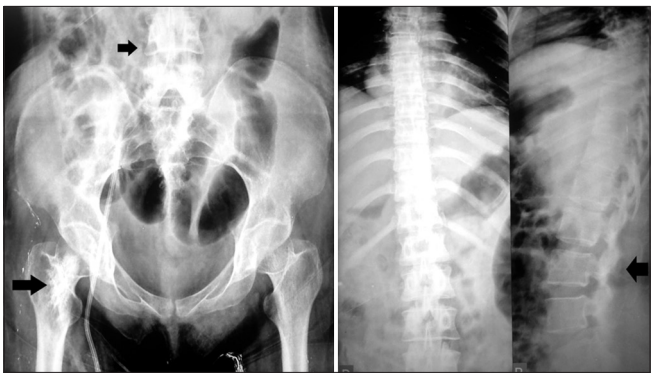

Figure 2: Composite radiographs of the pelvis and hips (left) showing a sclerotic lesion over the right femur and thoraco-lumbar spine (right), showing another lesion over the lumbar spinous processes (black arrows)

Table 1: Summary of clinical Investigations in the index patient

Test	Result
Hematological	
Hemoglobin, Hematocrit	11 g/d, 34%
Total leukocyte count	13400/μL
Total Platelet count	660000/μL
Erythrocyte sedimentation rate	40 mm/h (normal 0-20)
Mean corpuscular volume (MCV)	82.8 fL (normal 90±9)
Mean corpuscular hemoglobin (MCH)	33.5 pg (normal 30±3)
Peripheral smear	Normocytic, normochromic with thrombocytosis
Biochemistry	
Sodium	138 (normal 135-145 mEq/L)
Potassium	4.4 (normal 3.5-5.5 mEq/L)
Serum Creatinine	0.8 (<1 mg/dL)
Serum total proteins	4.91 (normal 6.4-8.2 g/dL)
Serum albumin	2.43 (normal 3.57-5.42 g/dL)
Total Calcium	8.1 (normal, 9-10.5 mg/dL); corrected 9.4
Phosphate	3.1 (normal 2.4-4.1 mg/dL)
Albumin: Globulin ratio	0.98 (normal 1.1-2.2)
Immunoglobulin G	905 (normal 700-1600 mg/dL)
Immunoglobulin A	149 (normal 70-400 mg/dL)
Immunoglobulin M	88 (normal 40-230 mg/dL)
Urine microscopy, albumin	Negative
Microbiology	
Blood cultures x 2	Sterile
Sputum bacterial cultures	Sterile
Urine aerobic cultures	Sterile
Acid-fast smear x 2 by Zeihl-Neelson's	Negative
Serology	
Human immunodeficiency virus serology (ELISA)	Negative
Rheumatoid factor, anti-nuclear antibody, anti-nuclear cytoplasmic antibody	All negative
Lactate dehydrogenase (LDH)	468 U/L (normal 240-480)
C-reactive protein (semi-quantitative)	Elevated
Thyroid stimulating hormone	12.0 (normal, 0.35-5.5 mIU/mL)
Free T3	3.4 (normal, 2.3-4.2 pg/mL)
Free T4	0.48 (normal, 0.89-1.76 μg/dL)
8 A.M Cortisol	12.6 (normal 4.3-22.4 μg/dL)
Fasting blood glucose	72 mg/dL

diagnosis includes vasculitis, connective tissue disease, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma (MM), MM or solitary plasmacytoma. The composite clinical and laboratory findings [Table 1] differentiates POEMS syndrome from these other disorders.[5] Plasma VEGF level of greater than 200 pg/mL has a specificity of 95% and sensitivity of 68% in support of diagnosis of POEMS syndrome. This entity can be distinguished from other PCDs by the prominent neuropathy, minimal to absent renal disease, thrombocytosis and organomegaly.[5]

Treatment is directed at abolishing the underlying plasma cell clone. In patients without diffuse marrow involvement and/or > 3 skeletal lesions, radiation to the isolated sclerotic lesions improves the symptoms over the next 3–36 months and may be curative. Half of nonresponders or progression occurs within 12 months of radiation. In those with disseminated bone marrow involvement, chemotherapy with melphalan-dexamethasone, lenalidomide, and autologous stem cell transplantation are potential therapeutic options. Thalidomide and bortezomib have activity in POEMS syndrome but have potential to worsen the neuropathy.[3] The course is usually chronic with a median survival of 14 years.[4]

The index patient presented with findings of advanced peripheral and phrenic nerve neuropathy as a result of the delay of 18 months prior to diagnosis. Evaluation confirmed POEMS syndrome without generalized bone marrow plasmacytosis. She was managed with local radiotherapy to proximal right femur and lumbosacral area (40 Gy, 2 Gy/cycle, total 20 cycles), thromboembolism prophylaxis, limb and respiratory rehabilitation, percutaneous gastrostomy

Table 2: Diagnostic criteria for the POEMS* syndrome

Criteria	Characteristic	Comment
Mandatory major criteria	Demyelinating polyneuropathy	100%; peripheral ascending symmetric motor-sensory. 10-15% severe pain
	Monoclonal plasma cell-proliferative disorder (almost always λ)	100%
Other major criteria (one required)	Castleman disease ^	11-25%
	Sclerotic bone lesions	27-97%
	Vascular endothelial growth factor elevation	
Minor criteria	Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy)	45-85%
	Extravascular volume overload (edema, pleural effusion or ascites)	24-89%
	Endocrinopathy# (adrenal, thyroid, pituitary, gonadal, parathyroid and pancreatic)	67-84%; often multiple axis abnormalities
	Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing and white nails)	26-74%54-88%
	Papilledema	30-52%
	Thrombocytosis/polycythemia	
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12 values	4% have clubbing, 1/3 have weight loss, fatigue

Diagnosis is made by the presence of both the mandatory criteria, at least one major criteria and at least one minor criterion, *Polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal Plasma cell disorder (PCD) and Skin findings, ^The Castleman variant of POEMS syndrome typically presents with little to no neuropathy, higher VEGF, anemia or thrombocytopenia and several of the minor criteria, #Diabetes and thyroid abnormalities alone do not meet the minor criteria given the high prevalence of these abnormalities in the general population, POEMS: Polyradiculoneuropathy, organomegaly, endocrinopathy, M-protein and skin abnormalities syndrome

feeds and nocturnal bilevel NIV. She improved objectively 6 weeks after completion of radiotherapy with upper limb power improving to 3/5 and lower limb power to 2/5 and absent paradoxical respiratory movements. Nocturnal bilevel NIV has been stopped at 3 months. She remains on follow-up at 6 months with clinical assessment monitoring the weakness, sensory loss and pulmonary function testing by spirometry.

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