



Clinical Reasoning: A 48-year-old man with walking difficulty

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SECTION 1

A 48-year-old football referee presented with a 6-week history of bilateral distal leg weakness, numbness, and worsening mobility, and a 4-week history of tingling in all fingers. Six months earlier he had noted bouts of generalized tiredness lasting minutes at a time although he had continued to complete football games. One month later, he developed bilateral calf tightness and occasional imbalance while walking, and the generalized periods of tiredness were more prolonged, lasting up to 2 hours.

On presentation, the numbness had advanced proximally from the feet to the knees. He had developed a broad-based gait and needed aids to walk. Bladder and bowel function were normal. His appetite was unaffected with no weight loss. On further questioning, he reported erectile dysfunction for more than 1 year. He had a history of hemochromatosis (C282Y homozygote) and received venesections

every 3 months. He was a nonsmoker and drank 12 units of alcohol a week.

Clinical examination revealed normal cranial nerves and upper limbs and bilateral pitting pedal edema up to the midshin. Medical Research Council power was 4/5 hip flexors and extensors, 3/5 at knees, and 1–2/5 at ankles bilaterally. Deep tendon reflexes were absent. Plantar responses were mute. Pinprick sensation was reduced in both feet. Joint position and vibration sense were impaired up to the ankles and knees, respectively. Romberg test was positive with broad-based and high stepping gait. Systemic examination revealed hepatomegaly with no lymphadenopathy.

Questions for consideration:

1. Would you want to clarify any aspect of the patient's history?
2. What is the differential diagnosis for his presentation?

[GO TO SECTION 2](#)

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SECTION 2

Hepatomegaly might be expected in hemochromatosis, but regular venesection points toward the possibility of this being an independent feature. Erectile dysfunction suggests autonomic involvement or hormonal deficiencies. To delineate this, it is worthwhile revisiting the history to enquire about change in shaving frequency, body hair, or gynecomastia, which would suggest sex hormone abnormalities, or palpitations, postural hypotension, diarrhea, or constipation, which would suggest autonomic dysfunction. In our patient, there were no specific features of either.

The findings suggest a length-dependent, sensorimotor, symmetrical polyneuropathy with sensory ataxia. Lack of upper motor neuron signs rules out cord pathology such as transverse myelitis. Diabetes is the most common cause of neuropathy in the Western world, but the speed of onset and sensory ataxia would be unusual. Both of these features could be explained by chronic inflammatory demyelinating polyradiculoneuropathy, although classically this would preferentially affect proximal power. The absence of bowel or bladder dysfunction, a sensory level or saddle anesthesia makes cauda equina pathology unlikely.

Toxic neuropathies secondary to alcohol, lead (predominant motor involvement), thallium (pain, paresthesias, autonomic dysfunction), dimethylaminopropionitrile (sexual dysfunction, distal sensory

impairment), carbon disulfide (sensory ataxia), or ethylene oxide (leg cramps, weakness, numbness, gait ataxia) are possible, but no such exposure was reported. Nutritional deficiency-related neuropathies could cause these features but often present with mixed upper and lower motor neuron signs. Neurosarcoidosis frequently presents with cranial nerve dysfunction. Paraneoplastic etiology should be considered, and progressive bouts of fatigue could point toward systemic involvement, in particular hematologic malignancies. Amyloid neuropathy is a possibility but is often associated with autonomic dysfunction.

The presence of sensory impairment without ocular involvement, upper extremity weakness, respiratory compromise, or a fluctuating course makes a neuromuscular junction disorder highly unlikely. Common muscle disorders would tend to have more proximal involvement, a more chronic course, and no large fiber sensory involvement.

Hemochromatosis has been independently associated with sensorimotor neuropathy with 26% patients having neuropathy in an observational study.¹ No prospective studies exist to ascertain a causal relationship.

Questions for consideration:

1. What investigations are needed for this patient?
2. How would you sequence them?

GO TO SECTION 3

SECTION 3

Nerve conduction studies showed delayed F waves in the upper limbs and motor and sensory conduction abnormalities in lower limbs with no conduction block, suggestive of a distal axonal neuropathy.

Raised CSF protein at 2.76 g/L (normal range 0.1–0.5) with normal glucose and cell counts suggested an inflammatory process at the level of the nerve root.

Our patient had a normal complete blood count except for platelets of $431 \times 10^9/L$ (normal range 150–400). Erythrocyte sedimentation rate, C-reactive protein, creatine kinase, vitamin B₁₂, folate, immunoglobulins (Ig), thyroid function, and electrolytes including calcium were all within normal limits. Serology for HIV, hepatitis, and syphilis were negative, as were cryoglobulins and anti-nuclear, anti-neutrophil cytoplasmic and anti-ganglioside antibodies. Albumin was reduced at 31 g/L. IgG level was raised at 3.8 g/L with raised κ (26.9 mg/L, normal range 3–19) and λ (41.3 mg/L, normal range 5–26), but a preserved κ/λ ratio. An IgG λ paraprotein was present on immunofixation. Raised IgG or IgA can be seen in chronic inflammatory demyelinating polyradiculoneuropathy, raised IgM (with a paraprotein) in distal acquired demyelinating sensory neuropathy, and raised IgG λ in POEMS (polyneuropathy, organomegaly,

endocrinopathy, monoclonal gammopathy, skin changes) syndrome.

Spine MRI revealed abnormal low T1-weighted and T2-weighted signal and high STIR (short T1 inversion recovery) signal of the T7 vertebral body, and CT showed loss of the normal trabecular pattern but no cortical destruction. A whole-body fluoro-deoxyglucose (FDG)-PET scan showed high metabolic activity in the T7 vertebra. Other vertebrae were normal. Bone marrow aspiration was normal. Skeletal survey, renal function, bone profile, and urine Bence Jones protein (myeloma screen) were normal.

Hormonal profile showed a reduced free testosterone of 146 pmol/L (normal >200) and an abnormal cortisol response to a short Synacthen test (200 nmol/L, normal >450) suggesting adrenal insufficiency. Serum vascular endothelial growth factor (VEGF) was markedly raised at 1,698 pg/mL (normal <771). The β_2 microglobulin was normal.

Sensory and motor lower limb responses were absent on nerve conduction studies 3 months later, confirming definite progression.

Questions for consideration:

1. What would your next management steps be?
2. What is the likely diagnosis?
3. What are the therapeutic options?

GO TO SECTION 4

SECTION 4

This patient presented with progressive symmetrical distal lower limb weakness with electrophysiologic evidence of a progressive axonal sensorimotor polyneuropathy. CSF analysis suggested an inflammatory cause. Raised IgG level with an IgG paraprotein and raised κ and λ light chains were observed. Since the κ/λ ratio was normal, our hematologists thought that this was likely to represent monoclonal gammopathy of unknown significance. Bone marrow aspiration was nondiagnostic. IVIg and plasma exchange were not considered because they are ineffective in paraproteinemic neuropathies.

A strong suspicion of a hematologic malignancy driving the neuropathy led us to revisit the imaging. The CT scan of the T7 vertebra showed an expansile lesion with possible sclerotic margins (figure). Musculoskeletal oncologists agreed to biopsy the vertebra.

The biopsy showed a monotonous population of plasma cells with CD38-positive and λ -positive cells on immunocytochemistry. This confirmed a solitary T7 plasmacytoma as the likely etiology for the progressive axonal polyneuropathy, mediated by increased cytokine VEGF production.

POEMS syndrome was diagnosed because the required criteria were fulfilled (table). The patient was initiated on a 3-day IV course of methylprednisolone

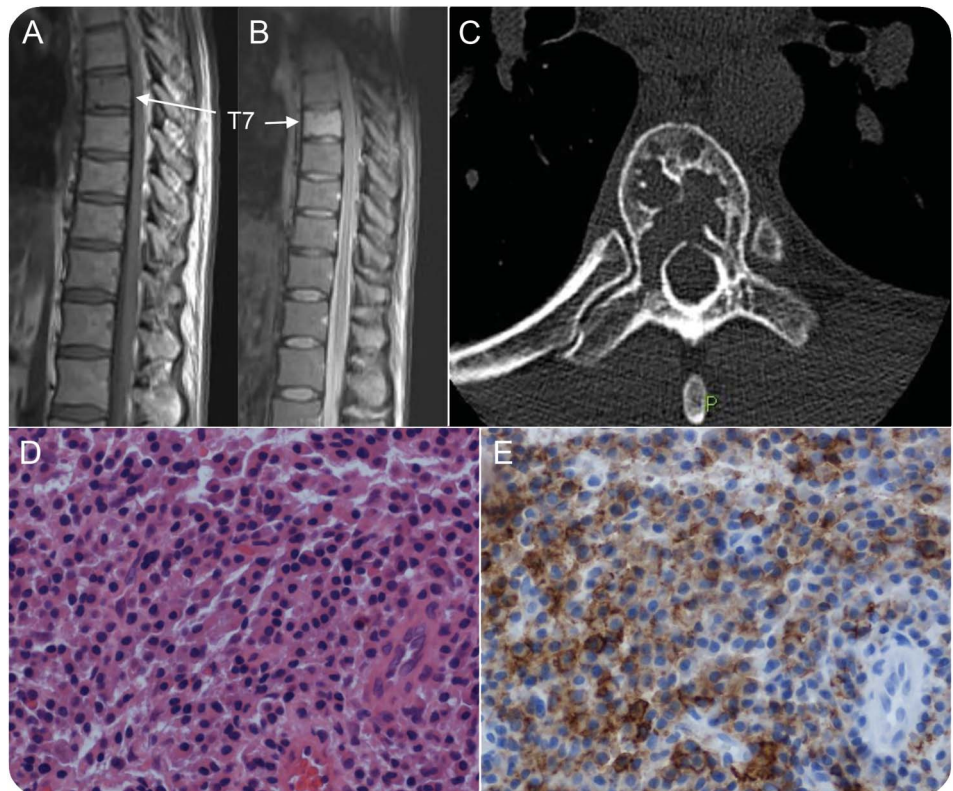
followed by oral prednisolone at 1 mg/kg body weight per day, which was gradually weaned over 6 months. The T7 vertebra was irradiated with a dose of 45 Gy in 25 fractions over a month with no complications.

VEGF levels returned to normal. At 6-month follow-up, there were minor improvements in muscle power, and the patient was managing to mobilize with 2 crutches and bilateral ankle-foot orthoses.

DISCUSSION POEMS syndrome² is a rare multisystem paraneoplastic disorder caused by an underlying plasma cell neoplasia. This is most commonly seen in men (2:1) aged between 20 and 83 years (median 46 years). At least 2 major and 1 minor criteria are needed for diagnosis (table).³ Patients may present to a variety of specialists depending on symptoms, and a progressive neuropathy is most frequently encountered by a neurologist. Endocrine dysfunction commonly involves the gonadal axis followed by the adrenal glands. Hyperpigmentation or hypertrichosis are commonly observed skin changes.

A high degree of suspicion and thorough systemic examination are required for diagnosis. Monoclonal gammopathy identified in peripheral blood gives a definite clue, but identifying the neoplastic lesion can be a

Figure Abnormal T7 vertebra, histology, and immunohistochemistry



(A) T1-weighted sequence showing low signal. (B) Short T1 inversion recovery sequence showing high signal of the T7 vertebral body. (C) Axial CT of T7 sclerotic vertebra. (D) Hematoxylin & eosin stain (200 \times) showing monotonous population of plasma cells (T7 biopsy). (E) Immunocytochemistry showing CD38-positive cells.

Table Diagnostic criteria ⁴ (at least 2 major and 1 minor required)		
Major criteria	Minor criteria	Others
1. Polyneuropathy	1. Organomegaly (spleen, liver or lymph nodes)	Clubbing
2. Monoclonal plasma cell proliferative disorder (λ chain)	2. Endocrinopathy (adrenal, pituitary, gonadal, parathyroid, thyroid, and pancreatic)	Weight loss
3. Castleman disease	3. Extravascular volume overload (peripheral edema, ascites, pleural effusion)	Hyperhidrosis
4. Sclerotic bone lesion	4. Skin changes (hypertrichosis, white nails, hyperpigmentation, hemangiomas, acrocyanosis)	Pulmonary hypertension
5. VEGF elevation	5. Papilledema	Restrictive lung disease
	6. Thrombocytosis/polycythemia	Diarrhea
		Thrombotic diatheses

Abbreviation: VEGF = vascular endothelial growth factor.

challenge. Blood paraprotein can be undetectable. Immunofixation, a more sensitive measure than electrophoresis for identifying low-concentration light-chain Ig, is recommended. Identifying solitary tumors is challenging, and FDG-PET can be very helpful in such situations.

VEGF levels usually normalize 1 month⁴ after treatment, but trends rather than absolute values are considered useful for therapeutic decisions. VEGF is a cytokine secreted by plasma cells and platelets that promotes vascular permeability, angiogenesis, and migration of monocytes and macrophages. Polyneuropathy is believed to be a consequence of neural ischemia caused by thrombosed endoneurial vessels.⁵

There are no randomized controlled trials for best practice management.⁶ Solitary bone lesions as in our patient are managed with localized radiotherapy. In a Mayo Clinic series, complete or partial hematologic, VEGF, FDG-PET, and clinical responses were documented in 31%, 14%, 22%, and 47% of patients treated with radiotherapy, respectively.⁷ Diffuse bone marrow neoplasia is treated with systemic chemotherapy. Case series of dexamethasone combined with several other agents including melphalan, cyclophosphamide, thalidomide, lenalidomide, and bevacizumab have reported a 50% to 80% hematologic response and some neurologic response.

The course of POEMS syndrome is usually chronic with one Japanese series reporting survival greater than 10 years, although estimates range from 33 months ($n = 102$)⁸ to 165 months ($n = 99$)² in different case series. A Cochrane review of both solitary and diffuse disease with therapies including corticosteroids, chemotherapy, radiotherapy, and stem cell transplants reported mild to moderate improvement in limb function and nerve conduction velocities.⁶ Case series of stem cell transplants have reported substantial neurologic improvement or stabilization.⁴

AUTHOR CONTRIBUTIONS

Dheeraj Kalladka: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Ahmed Iqbal: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval. Elaine MacDuff: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. James Overell: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval.

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