Rare disease

Polyneuropathy: a poetic diagnosis

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A 60-year-old woman presented with subacute progressive lower extremity weakness. This was associated with a 40lb weight loss and fevers. She was previously healthy, aside from renal transplantation 9 years earlier for end stage renal disease resulting from IgA nephropathy. On examination, she had clubbing, a single lymph node in the right cervical chain, and objective findings of lower extremity weakness with lower motor neuron findings. Investigations revealed a thrombocytosis and elevated CSF protein. Electromyographic evidence of diffuse polyradiculopathy with demyelination was documented. On imaging, she had a large lytic/sclerotic lesion in the right scapula measuring 8 cm, a pericardial effusion, and borderline splenomegaly. Pathological assessment of the excised lymph node revealed Castleman-like changes; biopsy of the right scapular lesion revealed λ -restricted plasma cells, in the absence of a monoclonal protein in the bone marrow or periphery. A diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) with plasmacytoma was established; a post-transplant lymphoproliferative disorder was suspected.

BACKGROUND

Polyneuropathy is a common clinical dilemma encountered by physicians and its differential diagnosis is both broad and daunting. On this basis, we believe our case report will be both interesting and relevant to the

readership of BMJ. We hope to meet three learning objectives through sharing this case. Our first aim is to provide the reader with an overview of the various causes of polyneuropathy (metabolic, drug/toxin associated, inflammatory, infectious, paraneoplastic and hereditary derangements), while emphasising that plasma cell dyscrasias are an underappreciated aetiology of this clinical presentation. This case illuminates the rare but fascinating POEMS syndrome, a diagnostic label based on several but not all of its features: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. This diagnosis can be easily missed if it is not considered because of its various, seemingly disparate, clinical and laboratory features. As such, we hope this case presentation will ensure that healthcare providers will entertain this diagnosis in the right clinical context.

Figure 1 CT thorax demonstrating a right scapular lytic lesion with cortical breakthrough.

Figure 2 Microscopic section of the core biopsy from the right scapular bone lesion (H&E, 1000x oil) showing a proliferation of mature plasma cells. Immunohistochemical studies (not shown) revealed the plasma cells to be cytoplasmic λ light chain restricted.

Finally, another unique feature of this case is that the POEMS syndrome occurs in this patient several years following organ transplantation, suggesting a post-transplant lymphoproliferative disorder (PTLD). In fact, we believe ours to be the first reported case of PTLD-associated POEMS syndrome. While PTLD-associated POEMS syndrome is a rare entity, PTLD itself is a clinical occurrence that will confront physicians, and this aspect of the case adds an interesting dimension for consideration by the BMJ's readers.

CASE PRESENTATION

A 60-year-old woman presented with a 3-month history of progressive lower extremity weakness. Her medical history was significant for IgA nephropathy leading to renal transplant 9 years before; she was on cellcept, prednisone and tacrolimus. She had recent transient ischaemic attacks manifesting as amaurosis fugax and blurry vision; during investigations, bilateral papilloedema was discovered without an apparent cause. She had treated hypothyroidism and new onset type two diabetes. She did not use alcohol or recreational drugs. During her neurological decline, she reported no headaches, nausea, vomiting, bowel or bladder dysfunction or sudden onset focal deficits. She reported a 40lb weight loss and fevers occurring over this time period.

On examination, the patient appeared cachectic with mild peripheral oedema and clubbing. A single lymph node was palpable in the right cervical chain. Neurological examination revealed bilateral lower extremity muscle atrophy, fasciculations and an inability to raise legs against gravity (power 2/5). She had decreased lower extremity vibration sense and reflexes; toes were downgoing.

INVESTIGATIONS

- ▶ Complete blood count showed moderate thrombocytosis ($700 \times 10^9/l$)
- ▶ Normal renal and liver function tests, and electrolytes
- ▶ Thyroid stimulating hormone (4.13 mU/l), B12 (144 pmol/l) and HbA1c (6.2%)
- ▶ Lumbar puncture: normal opening pressure, normal white blood cell ($2 \times 10^6/l$), elevated protein (1.53 g/l); negative cultures, viral PCR and cytology
- ▶ Negative Epstein-Barr virus, human herpes virus-8, HIV and Venereal Disease Research Laboratory tests
- ▶ Non-diagnostic bone marrow; serum protein electrophoresis and serum free light chains were negative for a monoclonal protein
- ▶ Negative autoimmune, vasculitic and cryoglobulinaemic testing
- ▶ Central nervous system imaging was non-contributory
- ▶ Electromyographic studies: diffuse polyradiculopathy of the lower extremities with primary demyelination
- ▶ CT thorax/abdomen/pelvis: lytic/sclerotic scapular lesion, pericardial effusion and splenomegaly (figure 1)
- ▶ Lymph node excision – pathology consistent with Castleman-like changes. Following excision, constitutional symptoms remitted
- ▶ Metastatic survey: mixed lytic/sclerotic lesion measuring 8×3 cm in the right scapula
- ▶ Biopsy of the lesion revealed λ -restricted plasma cells.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of polyneuropathy is broad and includes the following aetiologies¹:

- ▶ Metabolic: diabetes mellitus; kidney or liver failure; thyroid dysfunction; nutritional deficiency, especially B vitamin deficiency; malabsorption including IBD and celiac disease
- ▶ Drugs/Toxins: antibiotics, antiarrhythmics, antihypertensives, chemotherapies; heavy metals, organophosphates
- ▶ Inflammatory: connective tissue disease, vasculitis, cryoglobulinaemia, sarcoidosis, amyloidosis, acute inflammatory demyelinating polyneuropathy (including GBS), chronic inflammatory demyelinating polyneuropathy.
- ▶ Infectious: *Campylobacter Jejuni*, leprosy, lyme disease, HIV, hepatitis B or C, cytomegalovirus, West Nile virus
- ▶ Paraneoplastic: carcinoma, lymphoma, plasma cell dyscrasias/monoclonal gammopathies
- ▶ Hereditary: Charcot-Marie-Tooth, hereditary storage diseases.

TREATMENT

The patient received radiotherapy, total dose 35 Gy, to her scapular lesion.

OUTCOME AND FOLLOW-UP

There was marked improvement in the patient's neurological status; following treatment she had 4/5 lower extremity power and was able to walk with assistance.

DISCUSSION

POEMS syndrome is a rare paraneoplastic disorder, so named for its cardinal features of polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes. Other associated features include papilloedema, effusions, clubbing, thrombocytosis and Castleman disease. A case series of 99 patients diagnosed between 1960 and 1998 and followed at the Mayo Clinic revealed peripheral neuropathy to be the dominant clinical finding among patients with POEMS.² A monoclonal plasma cell dyscrasia was uniformly observed as well. These findings are consistent with the results of two other large case series from Japan and France that included 102 and 25 patients, respectively.^{3 4}

The pathophysiology is not well understood. Pro-inflammatory cytokines like IL-1 β , IL-6, tumour necrosis factor- α , and growth factors like vascular endothelial growth factor are elevated in POEMS and may play a pathogenic role.⁵ As with other paraneoplastic syndromes of the nervous system, neurological dysfunction often brings the patient to medical attention before discovery of the plasma cell dyscrasia itself.⁶

A unique feature of this case is that the plasmacytoma occurred following solid organ transplantation, suggesting a PTLD. The majority of PTLD cases are of B cell origin and up to 70% of PTLD are associated with EBV.⁷ Therapeutic options depend on the clinical context and may include reduction of immunosuppression, chemotherapy, radiation, rituximab and surgery.⁸ In the treatment of an isolated plasmacytoma, radiation therapy is preferred over systemic treatment (figure 2). To our knowledge, this is the first reported case of PTLD-associated POEMS syndrome.

Learning points

- ▶ Polyneuropathy has a broad differential diagnosis (metabolic, drug/toxin related, inflammatory, infectious, paraneoplastic and hereditary derangements); plasma cell dyscrasias are an underappreciated cause.
- ▶ The POEMS syndrome is a rare but fascinating multi-organ diagnosis. It can be easily missed if it is not considered because of its various, seemingly disparate, clinical and laboratory features. The diagnosis should be entertained when polyneuropathy occurs in tandem with other symptoms affecting several organ systems.
- ▶ There is a well-described link between immunosuppressive therapy and plasma cell dyscrasias. When a single, dominant plasmacytoma is discovered, preferred management is radiotherapy. Other therapeutic options may include reduction of immunosuppression, chemotherapy, radiation, rituximab and surgery.

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Competing interests None.

Patient consent Obtained.

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