A Young Woman With Blurred Vision and Distal Paresthesias

Nathan H. Kung, MD; Nancy L. Bartlett, MD; Nabeel R. Yaseen, MD; Gregory P. Van Stavern, MD; Robert C. Bucelli, MD, PhD

A 29-year-old woman presented with blurred vision and distal paresthesias. Her initial evaluation revealed severe bilateral optic disc edema with distal lower-extremity sensory and motor deficits and electrodiagnostic evidence of a length-dependent mixed demyelinating and axonal polyneuropathy. The results of routine diagnostic testing, including laboratory tests, magnetic resonance imaging, and lumbar puncture, were nondiagnostic. A targeted biopsy was ultimately required for diagnosis. In this article, we discuss the differential diagnosis and outline the clinical evaluation indicated for a patient presenting with demyelinating polyneuropathy and concurrent papilledema.

Report of a Case

A woman in her late 20s presented to the neuro-ophthalmology department for optic disc edema discovered during a routine examination. She reported mild visual blurring but denied headache, pulsatile tinnitus, visual obscurations, or visual impairment. Her medical history included elevated platelet counts on recent blood tests (591 × 10^3/μL [to convert to ×10^9/L, multiply by 1]) and amenorrhea attributed to use of a hormonal intrauterine device. She took no medications. She smoked 10 cigarettes daily and denied alcohol or drug use. Review of systems included a 27-kg weight loss on a diet and several months of progressive burning and tingling over the plantar surfaces of both feet. She also reported occasionally tripping over her toes. Outside electrodiagnostic testing suggested a demyelinating polyneuropathy, and intravenous immunoglobulin followed by oral corticosteroids were given at an outside institution for presumptive chronic inflammatory demyelinating polyneuropathy (CIDP), without benefit.

On neurologic examination, visual acuity was 20/20 in both eyes without abnormalities in motility, alignment, or pupillary function. She correctly identified 4 of 11 Ishihara color plates, a finding attributed to congenital color vision loss in the setting of a positive family history of color vision impairment. The external and diluted anterior chamber eye examination findings were normal. Dilated fundus examination revealed severe bilateral optic disc edema with choroidal folds that extended through both maculae, the latter indicating sufficient optic nerve distension to impinge on the globe. Humphrey SITA Standard visual fields revealed enlarged physiologic blind spots bilaterally with a prominent nasal defect in the left eye (Figure 1). She also had sensory loss in the distal lower extremities to all modalities (including loss of distal proprioception), weakness in the bilateral distal upper and lower extremities (including 4/5 ankle dorsiflexion), and generalized areflexia. She was 168 cm tall and weighed 76 kg (body mass index [calculated as the weight in kilograms divided by height in meters squared], 27).

Laboratory and Radiologic Data

Magnetic resonance imaging of the brain and orbits with intravenous contrast revealed no structural lesions (Figure 1). Magnetic resonance venography without intravenous contrast revealed stenosis without thrombosis of the transverse venous sinuses. Cerebrospinal fluid (CSF) analysis revealed the following: opening pressure, 26 cm H₂O (reference range, <25 cm H₂O); red blood cells, 0.000001 × 10^9/μL (to convert to ×10^9/L, multiply by 1); white blood cells, 1/μL (to convert to ×10^9/L, multiply by 0.001); protein, 0.075 g/dL (reference range, 0.015–0.045 g/dL [to convert to grams per liter, multiply by 0.0555]); and cytologic test results, negative. Acetazolamide was titrated to 1000 mg twice daily, given the elevated opening pressure with severe papilledema.

Laboratory testing revealed an elevated platelet count and hypothyroidism. Serum and urine immunofixation revealed no monoclonal protein, and the serum free light chain ratio was normal despite a mild elevation in κ and λ chains. The results of antinuclear antibody (ANA) testing were positive at 1:320, but test results for other autoimmune and peripheral neuropathy autoantibodies were negative (Table 1).

Electromyography (EMG) and nerve conduction studies (NCSS) performed at our institution revealed diffusely absent sensory nerve action potentials, absent or reduced compound muscle action potentials without conduction block or temporal dispersion, and relatively uniform slowing of conduction velocities in the peroneal, median, and ulnar nerves (18-25 m/s). Bilateral median and left ulnar F-wave studies revealed severely prolonged minimal latencies, normal persistence, and normal chronodispersion. In addition, EMG revealed evidence of concurrent axon loss with acute and chronic neurogenic changes in a length-dependent pattern (eAppendix 1 in the Supplement).

**Table 1**

<table>
<thead>
<tr>
<th>Test</th>
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<tr>
<td>Platelet count</td>
<td>591 × 10^3/μL</td>
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</tr>
<tr>
<td>White blood cells</td>
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<td>&lt;5/μL</td>
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<tr>
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<tr>
<td>Cytologic test results</td>
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**Figure 1**

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**Clinical Pathologic Conference**

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This patient presented with severe papilledema without obvious structural origin and a mixed demyelinating and axonal polyneuropathy, a unique combination of symptoms with a relatively limited differential diagnosis. Because most neuropathies are primarily axonal, the presence of a demyelinating component in this patient is particularly unique.

The initial evaluation of a polyneuropathy of this severity in a young individual begins with EMG and NCSs to characterize the neuropathy as axonal or demyelinating. Clinical features suggestive of a primary demyelinating polyneuropathy can include motor predominance, preserved muscle bulk out of proportion to the degree of weakness, global areflexia, and hypertrophic nerves. Hereditary demyelinating polyneuropathies have more uniform slowing of conduction velocities, and findings such as temporal dispersion, conduction block, or asymmetry are uncommon. Therefore, electrodiagnostic findings in this patient might initially suggest a hereditary demyelinating polyneuropathy with secondary axon loss and concurrent pseudotumor cerebri. However, the relatively rapid progression of this patient’s neuropathy and abnormal CSF profile warrant a thorough investigation for alternative causes.

Human immunodeficiency virus (HIV) has many peripheral nervous system manifestations, including demyelinating polyneuropathy. Therefore, HIV testing is indicated as part of the initial evaluation of all patients presenting with polyneuropathy. Vitamin B₁₂ and folate deficiency should also be considered, but neither of these would account for a primary demyelinating polyneuropathy. Furthermore, the vision loss in nutritional-deficiency optic neuropathy is slowly progressive and only rarely associated with disc edema. Patients with subacute combined degeneration as a result of vitamin B₁₂ or copper deficiency also have upper motor neuron signs, which were absent in this patient.

Diabetes mellitus can cause optic disc edema and neuropathy. Diabetic papillopathy is an incompletely understood disorder that presents with optic disc edema, commonly in the setting of recently improved glycemic control. The largest case series suggests that the disc edema may be bilateral in approximately half of cases. However, the diagnosis remains one of exclusion because of its rare and uncertain nature. In this patient, the elevated opening pressure and protein exclude the diagnosis. Furthermore, the typical neuropathy associated with diabetes is a length-dependent, sensory predominant, primary axonal polyneuropathy. Entrapment mononeuropathies are common. Patients with diabetes can rarely have a mixed axonal-demyelinating polyneuropathy with evidence of primary demyelination, although this is generally limited to patients with longstanding disease and poor blood glucose control.

In this patient, HIV, vitamin B₁₂, and hemoglobin A₁c test results were normal. Patients with a cardiac history should also be queried about the use of amiodarone, a known toxic cause of bilateral disc edema and demyelinating polyneuropathy. Lupus is associated with papilledema and multiple forms of peripheral neuropathy. In most cases, the papilledema and intracranial hypertension are due to infiltrating perivascular immune complexes with or without fibrinoid necrosis.

Figure 1. Clinical Images

A Partially empty sella  B Stenosis without thrombosis of the transverse venous sinuses  C Flattening of the posterior globes  D No structural lesions  E Humphrey SITA standard 24-2 visual field of the left eye  F Humphrey SITA standard 24-2 visual field of the right eye  G Fundus photograph of the right eye  H Fundus photograph of the left eye

Top, Magnetic resonance images of the brain showing a partially empty sella, stenosis without thrombosis of the transverse venous sinuses, flattening of the posterior globes, and no structural lesions. Bottom, Humphrey SITA Standard 24-2 visual fields of the left eye and right eye. Fundus photographs showing moderate to severe papilledema in the right eye and left eye. Peripapillary hemorrhages can be seen in inferotemporal portions of both optic discs.
nial hypertension parallel an increase in disease activity, then improve after immunosuppressive treatment of the lupus. However, a causative pathophysiologic link has not been established. Lupus also causes papilledema in the setting of cerebral venous thrombosis with antiphospholipid antibodies. As with diabetes, lupus is most commonly associated with a distal sensory-predominant axonal polyneuropathy, but weakness may occur acutely or subacutely in the setting of vasculitis or mononeuritis multiplex. In addition, CIDP has been reported in lupus, but whether this is coincidence or a true association remains unclear. In this patient, ANA test results were positive, but the EMG and NCS findings were not consistent with either of the above mentioned neuropathies seen in patients with lupus.

Benign and malignant monoclonal gammapathies have also been associated with optic disc disease and mixed axonal-demyelinating polyneuropathies. Serum and urine immunofixation should be performed to evaluate for a monoclonal protein. Although most patients with a paraproteinemic neuropathy will have a monoclonal IgM protein, any heavy chain type can be associated with amyloidosis or an underlying plasma cell neoplasm. Additional testing can distinguish malignant conditions from a monoclonal gammapathy of undetermined significance. This patient did not have a detectable monoclonal gammapathy on serum and urine testing.

The syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) should also be considered, especially when a monoclonal protein is found. This paraneoplastic syndrome arises in the setting of a clonal plasma cell proliferation and causes a unique demyelinating polyneuropathy with concurrent axon loss and widespread disease in multiple organ systems, including papilledema, thrombocythemia, and endocrine dysfunction, all of which were noted in this patient.

Acute inflammatory demyelinating polyneuropathy (a demyelinating form of Guillain-Barré syndrome) and CIDP can cause acute to subacute weakness with electrodiagnostic evidence of demyelination and secondary axon loss. Papiledema has been associated with both conditions. Although the mechanism of papilledema is uncertain, the most tangible hypotheses relate to obstruction of the arachnoid granulations from increased CSF protein.

In this patient, acute inflammatory demyelinating polyneuropathy is ruled out by the clinical history, given the progression beyond 4 weeks from onset. Although it was reasonable for the refer-

<table>
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<th>Table 1. Notable Laboratory Results*</th>
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<tr>
<td>Component</td>
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<td>Complete blood cell count</td>
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<td>Antinuclear antibody</td>
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<td>Hemoglobin A1c, %</td>
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* The results of the following tests were normal: basic metabolic panel, hepatic function panel, vitamin B12, homocysteine, methylmalonic acid, serum protein electrophoresis, serum or urine immunofixation, serum free light chains, IgA, IgM, IgG, double-stranded DNA, antineutrophil cytoplasmic antibody, extractable nuclear antigen, rheumatoid factor, C3/C4, cryoglobulins, human immunodeficiency virus, hepatitis B, hepatitis C, and anti-MAG, anti-SGPG, anti-GM1, anti-GaINAc-GD1a, anti-GD1a, anti-GD1b, anti-asiato-GM1, anti-sulfatide, anti-TS-HDS, anti-GALOP, and anti-Hu antibodies.

Figure 2. Pathologic Specimens

A, Coronal computed tomographic (CT) image of the spine revealing sclerotic lesions at T5 and T9. B, Axial CT image highlighting the sclerotic lesion at T5. C, Bone marrow specimen from T5 vertebral body revealing an abnormally increased number of plasma cells (arrowheads) (original magnification $\times 600$). D-E, In situ hybridization of $\kappa$ and $\lambda$ light chains revealing an abnormal $1:2$ ratio of positivity (original magnification $\times 100$). F, Axillary lymph node specimen with Castleman disease-like changes with an involuted germinal center (lower left of image), increased interfollicular distance, and increased vascular proliferation (original magnification $\times 200$).
ring physicians to consider CIDP, a previous study identified EMG and NCS features that aid in distinguishing CIDP from POEMS, with POEMS having more uniform demyelination (ie, without temporal dispersion or conduction block) and lacking the sural sparing seen in CIDP, similar to hereditary neuropathies and consistent with the findings in this patient. Although exceptions exist, this patient’s lack of response to intravenous immunoglobulin therapy also warranted reconsideration of the CIDP diagnosis. On the basis of this patient’s unique EMG and NCS findings and multiorgan involvement, we would recommend an aggressive evaluation for POEMS.

Clinical Course

Weeks after her initial diagnostic evaluation, the patient was noted to have bilateral lower extremity edema and endorsed a few months of progressive skin hyperpigmentation on her face and distal extremities. Splenomegaly was identified on physical examination, measuring 18.5 cm on computed tomography of the chest, abdomen, and pelvis. Computed tomography also revealed anasarca and diffuse lymphadenopathy, but no nodes were hypermetabolic on follow-up positron emission tomography.

Additional specialists considered essential thrombocytopenia and lymphoma as causes of her generalized lymphadenopathy. When bone marrow biopsy specimens revealed only megakaryocyte hyperplasia and positron emission tomography revealed no hypermetabolic activity, an atypical presentation of lupus was also considered.

Despite the lack of a serum or urine paraprotein and given the patient’s unique EMG and NCS findings and multiorgan involvement, a serum vascular endothelial growth factor (VEGF) level was checked and revealed an elevated level at 6240 pg/mL (reference range, 62-707 pg/mL). This finding led to a review of her computed tomographic scans, which identified sclerotic lesions in the T5 and T9 bodies. A biopsy of the T5 vertebral body and an axillary lymph node confirmed the diagnosis.

Pathologic Findings

The sclerotic T5 lesion (Figure 2) had increased plasma cells that comprised approximately 10% of the marrow cellularity, including occasional large neucleolated forms. In situ hybridization revealed an inverted 1:2 ratio of κ to λ light chains, indicating a λ restricted plasma cell proliferation. The axillary lymph node (Figure 2) had Castleman disease–like changes with involuted germinal centers, increased vascular proliferation, and increased plasma cells in the interfollicular regions. Having fulfilled all diagnostic criteria, she was diagnosed as having POEMS (Box).

Conclusions

POEMS is a multisystem paraneoplastic disorder associated with a monoclonal plasma cell proliferation. The pathophysiologic mechanisms of POEMS are incompletely understood but correlate with high levels of cytokines and other inflammatory mediators secreted by the plasma cell neoplasm. Interleukin 1b, interleukin 6, tumor necrosis factor α, and VEGF have all been implicated. Although VEGF correlates best with disease activity, a lack of definite benefit with targeted therapies (eg, bevacizumab) suggests a complicated pathophysiologic mechanism.

POEMS is frequently misdiagnosed, particularly when specialists fail to consider the chief complaint in the context of additional systemic manifestations that may fall outside their subspecialty. The absence of a detectable monoclonal gammopathy on serum and urine testing provided an additional diagnostic challenge in this case. However, if POEMS is suspected, this finding is frequent enough (12% of some cohorts) that more invasive testing (eg, bone marrow biopsy) should be pursued, as in this case.

The papilledema in POEMS may be due to intracranial hypertensión from increased CSF protein, leading to disruption of arachnoid granulations. However, some patients have a normal opening pressure and CSF protein level, suggesting alternative mechanisms, including VEGF-induced microvascular hyperpermeability.

The neuropathy in POEMS is associated with uncompacted myelin lamellae, but the pathophysiologic mechanism is unknown. Immunoglobulin deposition, seen in other paraproteinemic neuropathies, is not a consistent finding. In addition to the electrodagnostic features that aid in distinguishing POEMS from CIDP (ie, more uniform demyelination without temporal dispersion, conduction block, or sural sparing), POEMS classically causes more prominent lower-extremity weakness (relative to the concurrent upper and lower-extremity weakness typically present in CIDP).

The neurologic prognosis of POEMS in patients receiving radiation therapy and autologous stem cell transplant is favorable. Patients with disabling neuropathy improve, generally with a delay of 6 to 12 months.

This patient underwent a left optic nerve sheath fenestration due to deteriorating vision and persistently elevated opening pressure (26 cm H₂O on repeat examination) just before starting her radiation and chemotherapeutic regimen. Because of the timing of her concurrent radiation treatments, chemotherapy, and autologous

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**Box. Diagnostic Criteria of POEMS Syndrome**

**Mandatory Major Criteria**

1. Polyneuropathy (classically demyelinating)
2. Monoclonal plasma cell proliferative disorder (classically lambda)

**Other Major Criteria (1 required)**

1. Castleman disease
2. Sclerotic bone lesions
3. Vascular endothelial growth factor elevation

**Minor Criteria**

1. Organomegaly
2. Extravascular volume overload
3. Endocrinopathy
4. Skin changes
5. Papilledema
6. Thrombocytopenia or polycythemia

Abbreviation: POEMS, polynueropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes.
stem cell transplant, we were not able to definitively assess the contribution of her fenestration to her visual improvement. However, after transplant, her papilledema resolved, and her visual fields, strength, and gait improved (eAppendix 2 in the Supplement). She was able to walk unassisted. She is back to work and continues to improve.

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Author Contributions: Dr Bucelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kung, Van Stavern, Bucelli.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kung, Van Stavern, Bucelli.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Bucelli.
Study supervision: Van Stavern, Bucelli.

Conflict of Interest Disclosures: None reported.

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Additional Contributions: We are indebted to our patient for all the learning opportunities that arose from the opportunity to care for her. Written consent was obtained for publication of the case report and associated images. We acknowledge the assistance of Manu Goyal, MD (Department of Radiology, Washington University in St Louis, St Louis, Missouri), and George Harocopos, MD (Department of Ophthalmology, Division of Ocular Pathology, Washington University in St Louis, St Louis, Missouri), in preparing the magnetic resonance images and optic nerve sheath pathology reports contained within this article and within the eAppendix. We also gratefully acknowledge the assistance of Glenn Lopate, MD (Department of Neurology, Division of Neuromuscular Medicine, Washington University in St Louis, St Louis, Missouri), in participating in a Grand Rounds discussion of this case at our institution.

REFERENCES