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Clinical Reasoning: A 40-year-old man with CIDP-like illness resistant to treatment

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SECTION 1

A 40-year-old man developed tingling and numbness in the feet 2 years ago. Three months later, he noticed difficulty standing on his toes. Outside evaluation showed a small immunoglobulin G (IgG) lambda paraprotein, elevated CSF protein of 335 mg/dL (<40 mg/dL), and nerve root thickening with mild gadolinium enhancement in the cauda equina region on lumbar spine MRI. He

was presumed to have Guillain-Barré syndrome (GBS) and was treated with IV immunoglobulin (IVIg).

Questions for consideration:

1. What is the differential diagnosis of this patient's neuropathy?
2. How do the CSF, serum, and MRI findings help you with this differential?

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SECTION 2

The differential diagnosis for the patient's initial presentation, i.e., acute to subacute onset lower limb predominant, sensorimotor neuropathy, is wide. Inflammatory neuropathies such as GBS, chronic inflammatory demyelinating polyneuropathy (CIDP), or sarcoidosis can present in this manner. Infectious etiologies such as HIV, Lyme disease, and West Nile virus need to be ruled out but are less likely due to the absence of systemic features and absence of inflammatory cells in the CSF. Toxins and metabolic causes are important considerations but the history and initial laboratory studies are not suggestive. The presence of monoclonal gammopathy is concerning and warrants further workup as it may be associated with an underlying hematologic disorder such as amyloidosis, lymphoma, or myeloma. A tumor causing a paraneoplastic syndrome needs to be excluded. The MRI findings and elevated CSF protein would support an inflammatory etiology. The progression of symptoms over 3 months is longer than expected for GBS, and would favor a chronic inflammatory process such as CIDP or sarcoidosis.

The patient's symptoms progressed despite initial IVIg treatment. Within 3 months, he developed paresthesias in his hands and severe ankle weakness. Nerve conduction studies (NCS) showed a demyelinating sensorimotor neuropathy without conduction block. The

patient was diagnosed with CIDP and treated with oral prednisone 60 mg daily, mycophenolate mofetil 1g bid, and monthly 1 g/kg IVIg infusion. His condition stabilized during the next 12 months. Thereafter, over a period of 3 months he had a rapid neurologic decline and became wheelchair-bound. During that time, the patient noticed a left clavicular mass. X-ray of the lesion suggested chronic osteomyelitis, and ultrasonography was nondiagnostic. An excisional biopsy showed large collections of inflammatory cells. The patient was diagnosed with osteomyelitis and treated with antibiotics. Because of his worsening weakness, the IVIg was increased to once every 10 days and 1 g of weekly IV methylprednisolone was added.

Over the next 2 months, the patient's strength improved dramatically, and he was able to climb stairs again. Subsequently, he was seen at our institution. Neurologic examination showed mild proximal and severe distal weakness in all limbs, absent ankle jerks, and length-dependent sensory loss. He had plethoric facies, early clubbing, and bilateral papilledema. Visual acuity was normal. Additionally, he reported erectile dysfunction of 1 year's duration.

Question for consideration:

1. What further testing is warranted in a patient with apparent CIDP who is requiring increasing amounts of immunotherapy?

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SECTION 3

Laboratory evaluation demonstrated mild thrombocytopenia of $140 \times 10^9/\text{L}$ (normal $150\text{--}450 \times 10^9/\text{L}$) and elevated prolactin of 24 ng/mL (3–13 ng/mL). The rest of the blood workup, including kidney and liver function tests, B₁₂, folate, HbA1c, inflammatory markers, vascular endothelial growth factor (VEGF), and copper levels, was normal. HIV, Lyme, syphilis, cytomegalovirus, Epstein-Barr virus, and viral hepatitis serologies were negative. Immunofixation was normal, although he previously had an IgG lambda monoclonal protein. Repeat CSF analysis showed elevated protein of 166 mg/dL without other abnormalities. Skeletal bone survey showed the known left clavicular lesion. Chest x-ray was unremarkable.

NCS showed absent peroneal and tibial compound motor action potentials (CMAPs) and reduced

ulnar and median CMAPs of 0.6 mV and 0.7 mV, respectively. Motor conduction velocities were slow, ranging from 16 to 24 m/s. F-waves were markedly prolonged bilaterally. No conduction block or temporal dispersion was present. Sensory nerve action potentials were absent in the right arm and leg. Needle EMG showed widespread fibrillation potentials and large motor unit potentials. Autonomic tests were normal. Quantitative sensory testing showed length-dependent dysfunction of large myelinated sensory nerve fibers (abnormal vibration).

Questions for consideration:

1. What is your interpretation of the clinical findings and test results?
2. How do these findings affect your differential diagnosis?

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SECTION 4

The test results reveal a mixed demyelinating and axonal sensorimotor polyradiculoneuropathy, predominantly involving large myelinated fibers. Blood workup is unremarkable except for mild thrombocytopenia that is probably due to immunosuppressive therapy, and raised prolactin level, which may account for the erectile dysfunction.

A chronic sensorimotor polyneuropathy with proximal and distal involvement (polyradicular pattern) and demyelination (slowed conduction velocities and long F-wave latencies) is suggestive of CIDP. Temporal dispersion and conduction block are often but not always present, and axonal loss may occur with severity and chronicity. However, both the poor response to immunosuppressive therapy and initial IgG lambda paraprotein are concerning for an alternative etiology. The repeat immunofixation was negative, but a small amount of monoclonal protein may be either suppressed by high-dose methylprednisolone or obscured by hypergammaglobulinemia caused by IVIg therapy. The clinicopathologic features of paraproteinemic neu-

ropathies depend on a combination of factors including type of paraprotein (immunoglobulin M, IgG, immunoglobulin A, light chains), underlying disorder (plasmacytoma, myeloma), and associated amyloid deposition.¹ The clavicular lesion and monoclonal paraprotein could be clues to an underlying hematologic disorder such as multiple myeloma, lymphoma, or polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell neoplasm and skin changes syndrome (POEMS). A paucity of blood test abnormalities may argue against it, but much of the POEMS-specific testing was done after high doses of corticosteroids, which are known to temporize the syndrome. The dramatic neurologic improvement after resection of the bone lesion is noteworthy. Neurosarcoidosis can cause chronic, asymmetric, sensory-greater-than-motor polyradiculoneuropathy. Thickening and enhancement of nerve roots and plexus may be seen on MRI. Demyelinating features are rare and would make it less likely.

Question for consideration:

1. What further evaluation would be helpful?

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SECTION 5

A nerve biopsy is indicated when the peripheral neuropathy is atypical, severe, and progressive, such as in this case, to rule out vasculitis, amyloidosis, malignancy, sarcoidosis, or other inflammatory cause. The sural nerve biopsy in this patient showed segmental demyelination (6%) and axonal degeneration (15%) on teased fiber analysis, and moderately reduced myelinated nerve fiber density. Endoneurial edema, epineurial perivascular inflammation, and mild neovascularization were present (figure). Reevaluation of the clavicular biopsy slides with additional immunostaining revealed extensive infiltration of monotypic lambda light chain restricted plasma cells, scattered foamy macrophages, and fibrosis.

The nerve biopsy results suggest an inflammatory neuropathy with some demyelinating features. Severe and long-standing CIDP often results in a hypertrophic neuropathy and onion bulbs are often seen on nerve biopsy. Axonal degeneration can be seen in severe, long-standing CIDP. Absence of granulomas makes sarcoid less likely, but there could be proximal granulomas missed on the biopsy. The immunostaining pattern on the clavicular biopsy confirms a lambda-restricted plasmacytoma. The increased number of small blood vessels in the nerve biopsy may relate to increased levels of VEGF seen in POEMS

syndrome.² In this patient, a polyradiculoneuropathy in the setting of a monoclonal plasma cell disorder is consistent with POEMS syndrome, both of which are mandatory criteria for the diagnosis.

The diagnosis of CIDP should be questioned when patients do not respond to standard immune-modulating treatments, although some patients eventually respond to other potent agents like rituximab.³ The most likely explanation for the clinical improvement and disappearance of the IgG lambda is the removal of the plasmacytoma (not the increased immunotherapy), which was initially thought to be osteomyelitis.

Not all the features within the POEMS acronym are necessary for diagnosis, and other important features outside the acronym include papilledema, extravascular fluid overload, sclerotic bone lesions, elevated VEGF, thrombocytosis, and abnormal pulmonary function. Full diagnostic criteria have been described by one of the authors.⁴

Hypogonadism is the most common endocrine abnormality. Monoclonal protein in the serum is found in about 75% of cases, and associated light chain is almost always lambda. Serum or plasma VEGF levels tend to be 5- to 10-fold elevated, but may be affected by corticosteroid treatment. Interleukin-1 β , tumor necrosis factor- α , interleukin-6, and interleukin-12 are often elevated.^{5,6}

Figure Sural nerve biopsy

(A) Axonal degeneration (arrows) and demyelination (between arrowheads) on teased nerve fiber preparations; (B) reduced myelinated fiber density, with selective decrease of large fibers, occasional degenerating profiles, and subperineurial edema on methylene blue-stained epoxy sections; (C) mildly increased number of blood vessels on smooth muscle actin staining; and (D) small epineurial perivascular inflammatory collections with CD45 immunostaining.

Neuropathy is the dominant clinical feature in POEMS syndrome, and the most common presentation is of a slowly progressive, symmetrical, sensorimotor polyradiculoneuropathy.¹ Sensory symptoms often precede motor involvement; tingling and prickling are common; and neuropathic pain is reported in 10% to 15% of cases. The autonomic system is usually unaffected. Nerve conduction studies may suggest POEMS syndrome rather than CIDP. Greater reduction in motor amplitudes, greater slowing of conduction velocities, less prolonged distal motor latencies, less frequent temporal dispersion and conduction block, no sural sparing, greater number of fibrillation potentials in a length-dependent pattern, and higher terminal latency indices are present in POEMS cases compared to CIDP.⁷

Prognosis is dependent on the extent of plasma cell involvement, and is independent of the number of clinical criteria present. Major long-term disability is due to neuropathy but long-term outcomes have not been studied. Solitary plasmacytoma can be treated with radiotherapy; more extensive disease requires systemic chemotherapy or hematopoietic stem cell transplant.⁸ This case demonstrates 2 important points: 1) the value of thoroughly investigating a monoclonal protein in the context of neuropathy and 2) the value of questioning the diagnosis of CIDP when the neuropathy does not clearly respond to immunotherapy.

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R.L.: study concept and design, drafting and revising the manuscript. C.K., A.D., and P.J.D.: drafting and critical review of the manuscript.

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