Clinical Reasoning:

A 51-year-old man with cervical pain and progressively deteriorating gait

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SECTION 1

A 51-year-old Caucasian man presented with cervical pain, right hand weakness, and progressively deteriorating gait. Onset of symptoms occurred 1 month before admission with cervical pain that worsened during neck flexion. A few days later he noticed reduced dexterity and numbness of his right hand. During the following 3 weeks, his gait became increasingly unstable. Additionally, he reported erectile dysfunction and urinary hesitancy. No previous trauma was recalled. His medical and family history was unremarkable except for hypertension that was treated with angiotensin-converting enzyme inhibitors.

On admission, the patient was able to walk unaided. Neurologic examination revealed mild right hemiparesis that mainly involved the triceps, the intrinsic hand

muscles, and the iliopsoas, as well as an ipsilateral reduction of proprioceptive and vibratory sensation. Pain and temperature sense were decreased below T1-T2 level prominently on the left. Tendon reflexes were hyperactive bilaterally particularly on the right. In addition, a positive Babinski sign was noted on the right side. On cranial nerve examination, right lid ptosis was observed; the right pupil was small and dilated poorly in the dark, indicating Horner syndrome.

Questions for consideration:

1. What is the differential diagnosis? How does the subacute progression of symptoms narrow the differential?
2. What is the next step in management for this patient? What additional testing would you order?

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

The neurologic examination findings resemble those of a Brown-Séquard syndrome involving the right hemicord in the superior cervical region. Considering the lack of supraspinal semiology, Horner syndrome most likely is attributed to impairment of the descending sympathetic tract in the lateral column of the cervical cord. The presence of bilateral hyperreflexia as well as the pain and temperature sensation deficit that is recognized on both sides at a lower level implies that other medullary regions may be affected. The differential diagnosis includes spondylotic myelopathy, demyelinating processes such as multiple sclerosis (MS), acute disseminated encephalomyelitis, neuromyelitis optica (NMO) spectrum disorders, and idiopathic transverse myelitis, primary or metastatic spinal cord tumors, connective tissue diseases (e.g., systemic lupus erythematosus, Sjögren syndrome), neurosarcoidosis, infections (e.g., herpes simplex virus 2, varicella-zoster virus, cytomegalovirus, syphilis, HIV), spinal vascular malformations, fibrocartilaginous embolism, and paraneoplastic syndromes (table e-1 on the *Neurology*® Web site at www.neurology.org). The prolonged evolution

of symptoms lessens the probability of conditions that are associated with acute myelopathy such as vascular events, MS, neuromyelitis optica, or fibrocartilaginous embolism.

Cervical MRI showed 3 intramedullary lesions at levels C1-C2, C3-C4, and C5-C6. These lesions were slightly hypointense on T2-weighted images (figure, A) and enhanced homogeneously after contrast administration with minimal leptomeningeal involvement (figure, D). All lesions were surrounded by perifocal edema. Brain MRI was normal. CSF displayed mononuclear pleocytosis (65 cells/mm³), increased protein (137 mg/dL), and normal CSF glucose. CSF cultures for common bacterial pathogens, *Mycobacterium tuberculosis*, and fungi were negative. Immunoglobulin G (IgG) index was within normal limits and oligoclonal bands were absent. CSF cytology was negative for the presence of malignant cells. Immunophenotyping of CSF by using flow cytometry showed a mixed population of B and T cells. PCR analysis of CSF for immunoglobulin heavy chain and TcR- γ chain gene rearrangements did not reveal the presence of B or T cell monoclonality.

Figure Cervical cord MRI

Evolution of imaging findings on T2-weighted images (A-C) and T1-weighted images after gadolinium administration (D-F) on admission, after 10 days at the end of corticosteroid treatment, and 6 months into the course of the illness. Initially MRI showed 3 intramedullary lesions that displayed a slightly hypointense core on T2-weighted images and enhanced homogeneously with contrast material (A and D). After corticosteroid treatment (B and E), the lesions were smaller and the perifocal edema had subsided. Six months after presentation, the lesion located at C3-C4 was enlarged, with considerable mass effect (C and F).

Serum anti-NMO IgG testing was negative. CT of the chest and the abdomen did not reveal signs of extra-neural malignancy. A panel of onconeural antibodies that included anti-Hu and anti-CV2 antibodies was also negative. Slit-lamp examination was unremarkable.

Routine laboratory investigation that included complete blood count, erythrocyte sedimentation rate, hepatic and renal biochemical markers, serum protein electrophoresis, and thyroid function tests was normal. Testing was also negative for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antibodies against double-stranded DNA, anti-Sm antibody, Ro antigen, La antigen, and rheumatoid factor. Serologic

examination for HIV, Epstein-Barr virus, and hepatitis A, B, and C viruses was negative. Serum angiotensin-converting enzyme was within normal limits. Whole-body gallium scan was normal. Spinal cord biopsy was suggested, which the patient refused due to fear of potential postoperative complications.

Questions for consideration:

1. What is the differential diagnosis at this time point?
2. Would you consider the initiation of any treatment or would you proceed with further diagnostic workup?

GO TO SECTION 3

SECTION 3

The laboratory results at this point remain inconclusive. Lesions with low signal intensity on MRI T2-weighted images are uncommon. They are usually encountered in neurosarcoidosis and less frequently in other conditions such as CNS lymphomas, tuberculomas, and a subset of meningiomas.

On the sixth day of his hospitalization, the patient was treated with IV methylprednisolone (1 g/day for 5 days). During the first day of treatment, the patient reported dramatic improvement of his symptoms. His neck pain had subsided and he felt that coordination of his right hand was almost restored. At completion of therapy, he displayed normal muscle strength, and sensory examination was also normal except for a mild disturbance of proprioception that was limited to his right leg. MRI showed a reduction in the size of the lesions and the surrounding edema (figure, B and E).

The patient was discharged and scheduled for re-evaluation after 1 month. At follow-up, he reported recurrence of the neck pain and walking difficulties. Examination revealed right hemiparesis and bilateral reduction of proprioception and vibratory sense. Repeat cervical MRI showed enlargement of the lesion that was located at C3-C4 with perifocal edema that extended into the thoracic region. Brain MRI was normal. CSF cell count was normal (2 cells/mm³) but protein remained increased (144 mg/dL). Considering the patient's reluctance to undergo a biopsy and the previous potent albeit short-lived response to steroids, a new course of IV methylprednisolone was initiated. After completion of therapy, oral prednisone was prescribed (1 mg/kg/day). Once again, the patient exhibited remarkable clinical improvement during the first days of treatment that lasted through the next month. Thereafter, his symptoms took a deteriorating course. The addition of monthly cyclophosphamide cycles (20 mg/kg/session) was ineffective and eventually he became quadriparetic. MRI performed 6 months after onset confirmed further enlargement of the intramedullary mass at C3-C4, spinal cord expansion, and extensive edema (figure, C and F).

A decompressive laminectomy was performed at levels C3 and C4 and a grayish intramedullary tumor was revealed. The histologic differential diagnosis included many tumors, i.e., primitive neuroectodermal tumor, metastatic undifferentiated carcinoma, metastatic amelanotic melanoma, and anaplastic oligodendroglioma. Immunohistochemistry showed that tumor cells were immunopositive for CD45, CD20, and Pax-5, markers specific for B-cell lineage. The diagnosis was high-grade B-cell lymphoma (figure e-1). CT rescans of the chest and the abdomen, as well as bone marrow biopsy, were normal, excluding systemic involvement. Treatment consisted of combination therapy with high-dose methotrexate, intrathecal methotrexate, high-dose cytarabine,

and intrathecal rituximab, without improvement. Salvage therapy with spinal radiation (30 Gy) was targeted to the site of the lesion and the adjacent regions. Radiotherapy effectively reduced tumor size; however, neurologic status was unchanged. Currently, 18 months after initial presentation, the patient is clinically stable, but remains quadriparetic and is hospitalized in a specialized rehabilitation center.

DISCUSSION Primary CNS lymphoma (PCNSL) is a malignant extranodal non-Hodgkin lymphoma. PCNSL occurs more frequently in patients with congenital or acquired immune deficiency. Apart from HIV infection, pharmacologic immune suppression and autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis are major risk factors.¹ PCNSL represents 1%–3% of CNS tumors in adult immunocompetent patients. PCNSL commonly presents as a parenchymal mass. However, it occasionally arises in other locations, such as the leptomeninges and the eyes. Primary intramedullary spinal cord lymphoma (PISCL) is rare, and according to our search only 42 cases are reported in the literature.^{2,3,4,5}

PISCL usually manifests as a progressive medullary syndrome with loss of muscle strength, sensory disturbances, or sphincter dysfunction, depending on tumor location and size. PISCL is a diagnostic challenge because heterogeneous inflammatory processes such as idiopathic transverse myelitis, MS, NMO, and neurosarcoidosis often present with similar clinical features.

Multifocal intramedullary involvement was observed in nearly half of the patients (table e-2). The cervical region was mostly affected (69%). Concomitant intracranial involvement was documented in approximately half of the cases. In general, PCNSL as well as PISCL remain restricted to the nervous system, although exceptions to this rule have been reported.^{3,4} The predilection of PCNSL for neural tissue has been associated with the affinity of lymphoma cells to the endothelium of tumor vessels that express interleukin-4 (IL-4), as well as mediators of IL-4 signaling that promote B-cell growth and survival.⁶

MRI results in our case were not consistent with previous reports that described PISCL as invariably hyperintense on T2-weighted images. The lesions were characterized by a hypointense core with surrounding hyperintense edema on T2-weighted images. Homogenous gadolinium enhancement is a constant finding. PISCL displays persistent gadolinium enhancement, in comparison to MS lesions, which rarely enhance for more than 2 months.⁵

CSF examination usually reveals a nonspecific lymphocytic pleocytosis and raised protein. CSF cytology is rarely useful, although repeated lumbar punctures improve the diagnostic yield. Immunophenotyping

of CSF by using flow cytometry and PCR testing for the detection of clonal lymphocytic populations increases diagnostic sensitivity. In most cases, biopsy of the spinal lesion is necessary in order to obtain a definite diagnosis, although several cases have been diagnosed based on tissue samples from extramedullary sites. Histologically, the vast majority of PCNSL and PISCL are high-grade lymphomas of B-cell origin.

Our patient initially demonstrated a remarkable response to corticosteroid treatment. Sensitivity to corticosteroids is a well-recognized feature of PCNSL and a potent therapeutic response may be an important prognostic factor.⁷ Management of PCNSL evolved during the past 2 decades from radiotherapy-based therapies to combined modalities that include various chemotherapy agents. High-dose methotrexate alone or in combination with other agents has been shown to prolong survival in patients with PCNSL, with median overall survival approaching 48 months.⁸ Radiotherapy as salvage therapy induces complete remission in about one-third of patients after failure of chemotherapy.⁹

In cases with a high index of suspicion, clinicians should aim for an early diagnosis with histologic confirmation, given the fact that delayed recognition of this rare entity may have a negative impact on treatment effectiveness and overall prognosis.

AUTHOR CONTRIBUTIONS

Dr. Rallis: attending physician, manuscript design, review of the literature. Dr. Tsirigotis and Dr. Papageorgiou: design and supervision of lymphoma therapy, patient follow-up. Prof. Sgouros: planning and execution of spinal cord biopsy. Dr. Foukas and Prof. Panayiotides: histologic confirmation of diagnosis. Dr. Oikonomopoulos: interpretation of imaging results. Dr. Kouloulas: supervision of radiotherapy. Dr. Andronas and Dr. Arvaniti: implementation of diagnostic investigation, clinical follow-up.

Prof. Voumvourakis and Prof. Stamboulis: supervision of clinical care, diagnostic workup and treatment, review of the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2013;80:e230-e234

DOI 10.1212/WNL.0b013e318294b2bf

This information is current as of May 27, 2013

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