Clinical Pathologic Conference

A 20-Year-Old Man With Back Pain and Lower Extremity Weakness

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A 20-year-old man presented with 1 week of low back pain and progressive lower extremity weakness. Results of cerebrospinal fluid analysis demonstrated elevated total protein and a mildly elevated white blood cell count with lymphocytic predominance. Findings from imaging studies revealed a multifocal, heterogeneously enhancing, intramedullary lesion involving the cervicothoracic spinal cord and nodular enhancement of the cauda equina. The patient eventually underwent spinal surgery for tissue diagnosis. The differential diagnosis, pathologic findings, and diagnosis are discussed.

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Report of a Case

A 20-year-old Middle Eastern man with no significant medical history presented with 1 week of back pain and bilateral lower extremity weakness. Findings from an initial evaluation, including testing for vitamin B₁₂, thyrotropin, human immunodeficiency virus (HIV), and Lyme disease were unremarkable. The patient presented 1 week later with progression of his weakness to involve the upper extremities. Neurological examination findings demonstrated subtle decreased strength throughout the right upper and lower extremities (4+/5 on the Medical Research Council scale), bilaterally brisk reflexes in the upper and lower extremities, sustained clonus at the right patella and ankle, and a Babinski sign on the right side. His mental status and findings from the cranial nerve examinations were normal. Skin examination revealed a hyperpigmented papular rash overlying his right posterior scapula, causing concern for possible varicella-zoster rash. Empirical treatment of varicella-zoster was therefore initiated, while further diagnostic evaluation was pursued. His symptoms continued to worsen during the following weeks. Six weeks after his initial presentation, he developed progressive distal upper extremity weakness and new sensory deficits, with decreased sensation in his right leg. Written consent was obtained from the patient. Institutional review board approval was waived by Massachusetts General Hospital.

Laboratory and Imaging Studies

Results of serum analysis included a normal complete blood cell count, electrolyte levels, liver function tests, coagulation studies, and angiotensin-converting enzyme levels. Results of testing for anti-Ro, anti-La, antirentenopinal antibodies, tuberculosis (purified protein derivative and T-SPOT [Oxford Immunotec]), HIV, mycoplasma (IgG and IgM), and Lyme disease antibodies were negative. Results of cerebrospinal fluid (CSF) analysis demonstrated markedly elevated total protein of 4.3 g/dL, a normal glucose level of 34 mg/dL, a white blood cell count of 18/μL (60% lymphocytes), a red blood cell count of 255/μL, a lactate dehydrogenase level of 248 U/L, negative oligoclonal bands, negative bacterial and mycobacterial cultures, negative mycoplasma IgM and positive IgG titers, and negative polynucleotide chain reaction for VZV, Epstein-Barr virus, and herpes simplex virus. Results of testing for CSF VZV IgG antibodies were positive; however, results of IgM titers were negative. Results of CSF cytology demonstrated no malignant or atypical cells, but a mixed population of histiocytes and lymphocytes were interpreted as reactive.

Initial magnetic resonance imaging (MRI) of the cervical and thoracic spine revealed a heterogeneously enhancing intramedullary spinal cord lesion that spanned from C6 to T3 with surrounding edema (Figure 1). Findings from the MRI of the brain were normal. Given his clinical worsening, MRI of the spine was repeated 1 week after initiating acyclovir sodium treatment and revealed a finding of interval development of numerous nodular enhancing lesions in the cauda equina. Given the patient’s origin from the Middle East, he was empirically given praziquantel for possible schistosomiasis until his urine schistosomiasis antigen, stool ova and parasite, and CSF and serum schistosomiasis IgG results returned negative.

Clinical Discussion (Dr Etherton)

The differential diagnosis for an expansile enhancing intramedullary spine lesion extending over multiple levels in an otherwise healthy young man includes transverse myelitis (which could be caused by neuromyelitis optica, Sjögren syndrome, systemic lupus erythematosus, Behçet syndrome, or sarcoidosis), infectious myelitis (eg, secondary to VZV, human T-lymphotropic virus 1, Lyme disease, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, or schistosomiasis), intramedullary spinal cord tumors, and vascular pathology (eg, spinal cord infarction or dural arteriovenous fistula).
The CSF albuminocytological dissociation and a cystic-necrotic expansile intramedullary spinal cord lesion could suggest an inflammatory longitudinally extensive transverse myelitis (LETM). Although the patient had no history of demyelinating disease and normal findings on the brain MRI, the first presentation of neuro-myelitis optica can be a fulminant necrotic LETM, as in this patient. A similar presentation can be seen with Sjögren syndrome–associated myelitis and may precede development of sicca symptoms. However, the lack of optic neuritis and negative results of Ro and La antibody testing argue against these diagnoses, as does the patient’s continued worsening despite corticosteroid treatment. Longitudinally extensive transverse myelitis rarely occurs in multiple sclerosis (2%-3% of cases); however, the opticospinal variant of multiple sclerosis has been shown to present with LETM in 59% of cases. The absence of oligoclonal bands and a presentation that would have been atypical for multiple sclerosis made this diagnosis unlikely.

Given the patient’s Middle Eastern origin, Behçet syndrome was considered. Although neurological involvement in Behçet most commonly affects the brainstem and basal ganglia, spinal cord involvement has been observed in 14% of patients. The lack of aphthous or genital ulcers in this patient made this diagnosis less likely.

Infectious myelitis can be caused by bacterial, viral, fungal, and parasitic etiologies. Infections considered in this case included HIV, human T-lymphotropic virus 1, VZV, and acute schistosomiasis. Human immunodeficiency virus–associated vacuolar myelopathy usually presents more insidiously than in this patient, and findings on neuroimaging are either normal or reveal spinal cord atrophy. Human T-lymphotropic virus 1–associated myelopathy presents similarly clinically and radiographically to HIV-associated myelopathy, and CSF oligoclonal bands may be present. The negative HIV serological results, lack of travel to human T-lymphotropic virus 1–endemic areas, and imaging findings in this case made either of these diagnoses less likely. Primary VZV or reactivation of latent VZV can produce LETM or myeloradiculitis, although this is more commonly seen in elderly persons or immunocompromised individuals. In this case, there was no evidence of an immunocompromised state or acute VZV infection (negative VZV PCR and IgM titers). The finding of a positive IgG titer was believed to be more consistent with prior exposure rather than reactivation of VZV. Acute schistosomiasis can

Figure 1. Magnetic Resonance Imaging of the Spine

A and B, Sagittal T2 and T1 postcontrast sequences of the cervical spine showing an expansile lesion extending from C3 to T2 with effacement of cerebrospinal fluid spaces and heterogeneous enhancement. C and D, Sagittal and axial T1 postcontrast sequences of the lumbar spine showing leptomeningeal enhancement of the conus medullaris and multiple enhancing nodules along the cauda equina nerve roots and thecal sac.
cause myelopathy, typically involving the lower spinal cord and cauda equina, with T2-hyperintense intramedullary expansile lesions seen on MRI and diffuse contrast enhancement of the spinal cord or nerve roots.6 However, results of the patient’s schistosoma urine antigen, stool ova and parasite, and schistosoma IgG testing were negative.

Tumors of the spinal cord are rare, with a reported incidence of 0.74 per 100,000 person-years.8 Extramedullary tumors (such as meningiomas, 29%; nerve sheath tumors, 24%; and ependymomas, 23%) account for most primary spinal tumors.8 Intramedullary spinal tumors comprise 5% of all spinal cord tumors and typically represent low-grade astrocytomas and ependymomas. Malignant gliomas, such as glioblastoma, account for only 1% to 3% of all spinal cord tumors and generally present in the second and third decades of life.8,9 The expansile necrotic intramedullary nature of the patient’s lesion and the appearance of new spinal cord lesions on follow-up imaging suggested a malignant process, such as a spinal cord anaplastic astrocytoma or glioblastoma.

Decompressive laminectomy (C6-T2) and debulking of the mass were performed (Figure 2A).

Neuropathological Discussion
(Drs Oakley and Frosch)

Findings on neuropathological assessment revealed highly pleomorphic cells, frequent mitoses, microvascular proliferation, and necrosis (Figure 2B and C). There were multiple regions with gemistocytic features consisting of cells with abundant eosinophilic cytoplasm (Figure 2B). Owing to the patient’s young age, the lesion’s location in the spinal cord, the presence of cells with dense eosinophilic cytoplasm, and apparent drop metastases along the cauda equina, a diagnosis of atypical teratoid rhabdoid tumor was initially considered. However, the tumor cells subsequently stained strongly positive for nuclear switch/sucrose nonfermentable-related matrix-associated actin-dependent regulator of chromatin subfamily b, member 1/Integrase interactor 1 protein as well as for cytoplasmic glial fibrillary acidic protein, an intermediate filament protein expressed in astrocytes. These findings excluded the diagnosis of atypical teratoid rhabdoid tumor and established the diagnosis of glioblastoma.

Further molecular profiling revealed the presence of a p53 mutation (R237C). No mutations in isocitrate dehydrogenase 1 and 2 (wildtype IDH1 [OMIM 147700] or IDH2 [OMIM 147650]) were identified. Furthermore, fluorescent in situ hybridization analysis identified focal MET (OMIM 164860) amplification in approximately 10% of cells. Epidermal growth factor receptor was not amplified. The MGMT (OMIM 156569) promoter was not methylated.

Taken together, the molecular genetic profile of this patient’s tumor was consistent with a glioblastoma with poor prognostic features.10

Clinical Outcome

The patient began receiving craniospinal irradiation 3 weeks after surgery, with a plan to add chemotherapy with temozolomide treatment after completion of radiation therapy. However, given the rapid progression with worsening cord edema, adjuvant therapy with bevacizumab, 10 mg/kg, was initiated 28 days following surgery. Unfortunately, the patient’s course was complicated by spinal wound

Figure 2. Intraoperative and Histological Features of the Resected Tumor

A. Intraoperative photograph of the cervicothoracic spinal cord following the C6-C7 and T1-T2 laminectomies and dural exposure. The involved spinal cord is notably exophytic compared with the visualized more cranial levels. B. The tumor displays areas of pleomorphic cells, frequent mitoses, microvascular proliferation, and necrosis (hematoxylin-eosin, original magnification ×20). C. Area of prominent gemistocytic features and frequent mitoses (hematoxylin-eosin, original magnification ×40).
dehiscence noted approximately 2 weeks after radiation therapy was initiated. After extensive discussion between the patient and his care team, the decision was made to pursue palliative measures. The patient died 6 months after symptom onset.

Conclusions

Primary spinal cord tumors are rare, and intramedullary spinal cord tumors are the rarest among these, accounting for approximately 3% to 5% of all spinal cord tumors. In the pediatric and adult population, primary malignant spinal cord tumors comprise only 0.01% to 0.03% of all central nervous system tumors. In contrast, glioblastoma is the most common primary neoplasm of the brain, accounting for 40% to 50% of all astrocytomas. The disparity between the occurrence of brain and spinal cord glioblastoma has been attributed to the relative paucity of neuralgic cells in the spinal cord. In fact, given the relatively higher incidence of intracranial glioblastoma, drop metastases of glioblastoma from the brain to the spine are more common than primary spinal glioblastoma.

Spinal glioblastoma appears to be more common in individuals younger than 45 years. It most commonly affects the cervicothoracic region. Involvement of the conus medullaris, as in this case, is rare, with fewer than 20 published cases.

The evaluation for spinal glioblastoma includes gadolinium-enhanced MRI of the entire neuroaxis to assess for metastases and surgical planning. Obtaining tissue samples for pathological analysis, either by biopsy or resection, is essential for guiding further therapy.

Most authors suggest a combination of radiotherapy, as either focal spine or craniospinal irradiation, and adjuvant chemotherapy with temozolomide. Others have also included therapy with intrathecal administration of interferon beta as an approach to enhance chemosensitivity to temozolomide. Gross total resection for cytoreduction should be considered when feasible. In 89 patients with high-grade (World Health Organization grade III or IV) astrocytomas, gross total resection was associated with increased survival compared with subtotal resection, biopsy, or nonsurgical interventions (23 months vs 9 months, respectively). However, surgical morbidity is common, given the challenge of distinguishing between normal and malignant tissue during operative intervention owing to the invasive nature of the tumor.

In a series of 18 patients who underwent surgical resection of grade III or IV astrocytomas of the spine, 11 (61%) demonstrated worse functional status following surgery. Unfortunately, despite surgical and medical interventions, the average survival time for spinal glioblastoma ranges from 6 to 18 months.

This case highlights the diagnostic challenges of an enhancing and expansile intraspinal lesion in an otherwise healthy individual and illustrates the therapeutic difficulties and poor prognosis of primary malignant glial neoplasms of the spinal cord.