A 54-year-old man presented with progressive asymmetric leg pain and weakness. He had a history of invasive squamous cell carcinoma that was fully treated 2 years earlier. His leg symptoms progressed relentlessly during several months. Imaging studies demonstrated enhancement of the cauda equina and leptomeninges of the lower spinal cord. Initial cerebrospinal fluid examination showed an elevated protein concentration and lymphocytic pleocytosis with no malignant cells on cytological analysis. There was short-term improvement in symptoms and cerebrospinal fluid abnormalities with intravenous steroids. Two additional cerebrospinal fluid studies showed normal cytological findings, elevated IgG synthesis, and elevated antibody titers to varicella-zoster virus. Over time, the patient worsened, developed cranial neuropathies, and ultimately died. The pathological diagnosis and the approach to the clinical data are discussed.


A 54-year-old man came to the emergency department with a 3-month history of progressive leg cramps, low back pain, left thigh numbness, and bilateral lower extremity weakness. The symptoms started with cramps in the left leg and numbness over the anterior left thigh. Gradually, loss of sensation and pain spread to involve the entire left leg and then the right leg. The pain was described as diffuse and throbbing and did not improve with rest or analgesics. He denied bladder and bowel impairment.

His history was significant for squamous cell carcinoma (SCC) of the left temple treated with Mohs surgery 2 years earlier. Posis and left forehead weakness were present after the surgery because of local facial nerve injury. Owing to deep extension of the tumor, he also received external beam radiation. A full-body positron emission tomographic scan after treatment showed no evidence of residual tumor. He was a former smoker and used alcohol occasionally. There was no history of neurological disorders in his family.

On physical examination, a surgical defect was present with atrophy of the left temporalis. Neurological examination revealed sensory loss in the left V2 and V3 distribution, left forehead flattening, and mild left ptosis. He also had reduced hearing on the left. Strength in both upper and lower extremities was normal. There was weakness in both lower extremities. The Medical Research Council Scale grade was 4 to 4 on the right and 3 to 4 on the left. Weakness was diffuse except for prominent impairment in left ankle and toe dorsiflexion. There was diffuse muscle atrophy in his left lower extremity. Tendon reflexes were absent in the upper and lower extremities. Plantar responses were flexor on the right and equinovarus on the left. There was decreased sensation to light touch and pain in the left L4-L5 dermatome and right S1-S2 dermatome. He was able to walk with assistance but was limited by weakness and pain.
Peripheral blood cell counts and chemistry findings were within normal limits.

Magnetic resonance imaging (MRI) of the entire neuraxis was obtained on initial presentation. Head MRI revealed atrophy of soft tissue and muscle in the left temporal region and enhancement involving the V3 segment of the trigeminal nerve. There was diffuse enhancement and thickening of nerve roots in the cauda equina as well as increased T2 signal and enhancement along the surface of the spinal cord extending from T3 to conus (Figure 1).

Results of cerebrospinal fluid (CSF) examinations and additional serum studies are presented in Table 1 and Table 2. The initial CSF examination revealed an elevated protein concentration and pleocytosis. Cytological analysis showed only mature and reactive lymphocytes. Gram staining and culture of the CSF were negative. Nerve conduction studies and electromyography revealed active denervation and evidence of an axonal motor-predominant neuropathy affecting the lower extremities with localization to multiple lumbosacral roots. Because of these findings and the patient's intractable pain, intravenous methylprednisolone (1 g/d for 5 days) was administered. He reported an improvement in strength and reduction in pain in the lower limbs, although objective assessment of strength was unchanged. A second CSF examination revealed a reduction in the protein concentration and cell count. The CSF cytological analysis and culture results were again unremarkable. Findings on computed tomographic imaging of the chest, abdomen, and pelvis were unremarkable. A gallium scan showed no lesions suggestive of sarcoidosis.

He was transferred to the rehabilitation service, where he was making progress in physical therapy for gait and strength. About a week later, he developed sudden onset of new right facial droop. Examination revealed evidence of complete right facial neuropathy, and cranial imaging showed no changes compared with the previous study. For the diagnosis of acute facial neuropathy, oral acyclovir was initiated and a third CSF examination was conducted. The CSF protein concentration continued to be elevated but pleocytosis had resolved. Additional CSF studies (Table 2) revealed an elevated CSF IgG synthesis rate and elevated titer of IgM and IgG for varicella-zoster virus (VZV). Because of the latter finding, intravenous acyclovir was administered. Examination of the CSF using polymerase chain reaction, however, showed no evidence of VZV DNA.

Despite treatment, the patient’s clinical condition continued to worsen. He developed worsening dysarthria and dysphagia and increasing weakness of the lower extremities as well as episodic confusion. Additional MRI showed no significant changes to the previously described findings. He refused a proposal to perform an open neurosurgical biopsy of a lumbar root and elected to have comfort care. A percutaneous endoscopic gastrostomy tube was placed and supportive care was provided. The patient died at home 5 months after initial presentation to the hospital. An autopsy was performed.

**LABORATORY AND IMAGING STUDIES**

Figure 1. Neuroimaging findings. A, T1-weighted sagittal postgadolinium magnetic resonance image of the spine shows enhancement of the lumbosacral roots and the superficial aspect of the lower spinal cord. B, T1-weighted axial postgadolinium magnetic resonance image of the lumbosacral spine shows enlargement and enhancement of the cauda equina roots.

**Clinical Discussion (Dr Navalkele)**

This patient presented with sensory deficits and pain in the legs, progressive bilateral asymmetric lower extremity weakness, and absence of reflexes, which were consistent with lumbosacral polyradiculopathy (cauda equina syndrome). Additionally, he had sensory loss in the left V2 and V3 trigeminal nerve distribution suggestive of cranial nerve involvement. The MRI confirmed abnormalities of the cauda equina and trigeminal nerve. Electrophysiological studies also supported this neurological localization.

Differential diagnosis for polyradiculopathy includes multilevel spondylotic disease; autoimmune diseases such as inflammatory demyelinating polyradiculoneuropathy, neurosarcoidosis, paraproteinemia, and Sjögren disease; viral infections such as VZV, cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, and herpes simplex virus types 1 and 2; bacterial infections such as *Borrelia*, *Treponema pallidum*, *Corynebacterium diphtheriae*, and *Mycobacterium*; protozoal infections such as *Toxoplasma*; and neoplastic diseases including leptomeningeal lymphoma and metastatic carcinoma. Serial CSF analysis in our patient revealed lymphocytic pleocytosis and an elevated protein concentration, suggesting an inflammatory, infectious, or neoplastic process.

Keeping in mind the clinical history and the neuroimaging and CSF findings, the differential diagnoses could be narrowed to neurosarcoidosis, lymphomatous or carcinomatous meningitis, or infectious myeloradiculopathy (including Lyme disease, cytomegalovirus, and VZV).

Approximately 5% of patients with systemic sarcoidosis have nervous system involvement.1 Neurosarcoidosis can affect any part of the nervous system including cranial nerves, nerve roots, and the spinal cord. In our patient, lymphocytic pleocytosis and an elevated CSF protein concentration as well as responsiveness to steroids would be consistent with neurosarcoidosis. In a review of 172 patients with spinal neurosarcoidosis, a minority (12.8%) presented with disease limited to the meninges and cauda equina.2 In this series, a high CSF protein concentration was the most common abnormality. Elevated
cord involvement. In the setting of cauda equina and cranial involvement, and fewer than 1% had isolated spinal involvement, 9% had cerebellar involvement, 14% had corpus callosal involvement, 12% had thalamic–basal ganglia involvement, 16% had thalamic–basal ganglia involvement, 51% had thalamic–basal ganglia involvement, 51% had thalamic–basal ganglia involvement, and 51% had thalamic–basal ganglia involvement.

By imaging, 38% had cerebral hemisphere involvement, more than 50% presented with systemic disease, or lymphoma can be present in the absence of systemic disease. While neurosarcoidosis needs to be considered, the aggressive clinical course and the localization of the disease process in this case would be somewhat unusual.

The central nervous system (CNS) is involved in 10% of patients with systemic lymphoma, or lymphoma can be limited to the CNS. Primary CNS lymphoma most commonly presents in patients who are immunocompromised but also rarely presents in immunocompetent patients. In a review of 248 immunocompetent patients with systemic lymphoma, or lymphoma can be present in the absence of systemic disease. While neurosarcoidosis needs to be considered, the aggressive clinical course and the localization of the disease process in this case would be somewhat unusual.

Levels of angiotensin-converting enzyme in the serum or CSF were found in fewer than half of the patients. A gallium scan did not show lesions consistent with systemic sarcoidosis in our patient, although neurosarcoidosis may be present in the absence of systemic disease. While neurosarcoidosis needs to be considered, the aggressive clinical course and the localization of the disease process in this case would be somewhat unusual.

The central nervous system (CNS) is involved in 10% of patients with systemic lymphoma, or lymphoma can be limited to the CNS. Primary CNS lymphoma most commonly presents in patients who are immunocompromised but also rarely presents in immunocompetent patients. In a review of 248 immunocompetent patients with systemic lymphoma, more than 50% presented with a focal mass lesion. By imaging, 38% had cerebral hemispheric involvement, 16% had thalamic–basal ganglia involvement, 14% had corpus callosal involvement, 12% had periventricular region involvement, 9% had cerebellar involvement, and fewer than 1% had isolated spinal cord involvement.¹ In the setting of cauda equina and cranial nerve involvement, leptomeningeal spread of systemic lymphoma is more likely than primary CNS lymphoma. Although findings on cytological analysis and flow cytometry of CSF were unremarkable on 3 occasions, the diagnosis still remains in the differential.

Leptomeningeal carcinomatosis from cutaneous SCC was described in 1995 in a patient with recurrent cutaneous SCC with perineural invasion and later cauda equina spread.² Leptomeningeal spread was also described in a 72-year-old man who presented with cauda equina syndrome 6 years after the initial presentation with SCC and in a 59-year-old man who presented with confusion and cranial nerve palsy 2 years after presentation with SCC.³ Large tumor size, poorly defined borders, recurrent disease, immunosuppression, rapid growth, prior radiation, and high pathological grade characterize SCC tumors at risk for neurological metastasis. Our patient had a history of cutaneous SCC with deep extension requiring treatment with radiation in addition to Mohs surgery. Loss of sensation over the left V2 and V3 distribution with enhancement of the left V3 nerve on brain MRI could represent SCC invasion along the trigeminal nerve from the region of the initial tumor. Although rare, leptomeningeal spread from cutaneous SCC is a strong possibility in this case.

Another diagnostic possibility was VZV myeloradiculopathy, which must be considered in light of the positive CSF serological findings for IgG and IgM antibodies against VZV. The usual neurological presentation of VZV in adults is a monoradiculopathy with characteristic rash, but cases of disseminated nervous system VZV have been reported. In our case, polymerase chain reaction testing results for VZV in the CSF were negative. However, Gilden et al⁶ have suggested that VZV encephalitis and myelitis cases can have a protracted course, and in those cases, DNA detection is not always sensitive. Patients in their report improved with antiviral treatment, but our patient continued to deteriorate despite treatment with high-dose intravenous acyclovir. Other infections that are much more likely to produce a pattern of meningealitis are cytomegalovirus (in the setting of AIDS) or Lyme disease. However, laboratory testing results for both of these entities were negative.

NEUROPATHOLOGICAL DISCUSSION
(DR GEORGESCU)

A complete autopsy performed on this patient revealed purulent left lower lobe bronchopneumonia with Staphylococcus aureus as the immediate cause of death. Signifi-
cant gross abnormalities were present in the spinal cord in the form of abnormal pallor and firmness of the posterior columns bilaterally and an incidental small schwannoma at the level of the cauda equina. Microscopically, sections from cranial nerve V showed increased fibrosis surrounding the nerve bundles on the left side, most likely due to radiotherapy, but no residual neoplastic cells. In contrast, the spinal nerve roots, especially dorsal ones, dorsal root ganglia, spinal nerves, and soft tissue surrounding the nerves were massively infiltrated by neoplastic cells at all cord levels (Figure 2). The neoplastic cells also surrounded vessels in the spinal cord. The infiltrate consisted of atypical cells with a moderate amount of eosinophilic cytoplasm and large, moderately pleomorphic nuclei with irregularly condensed chromatin (Figure 2B). Mitoses were occasionally observed (not shown). Immunohistochemical staining with cytokeratin 5/6 that labels cells of squamous origin showed strong positivity in the malignant cells (Figure 2A and C). Another marker of squamous cell origin, p63, was faintly positive in some malignant cells but had less well-preserved reactivity in the autopsy tissues as demonstrated by lack of positivity in the patient’s prostate and only faint positivity in the skin (not shown). The neoplastic cells infiltrated the leptomeninges in a loose pattern singly, in small aggregates, or in intersecting files (Figure 2D). More distinctively, they were organized in cuffs along the epineurium and perineurium and penetrated the endoneurial interstitial space in rows (Figure 2B and C). These cells in single-file pattern further longitudinally lined the axons, leading to massive spread and myelin destruction as confirmed by Luxol fast blue myelin staining (Figure 2E) as well as by neurofilament staining (not shown). In addition, sections of the spinal cord throughout showed foamy cells and markedly decreased myelin in the posterior columns (Figure 2F), indicative of ascending wallerian degeneration of dorsal root ganglion axons. A consequence of motor axon damage was noted in the anterior horns of the spinal cord, where a subset of motor neurons showed chromatolysis (Figure 2G). This phenomenon reflects a reparative effort of the cell body in response to axon damage but often precedes apoptosis.

**CONCLUSIONS**

The final diagnosis in this case was leptomeningeal carcinomatosis from invasion of cutaneous SCC into the CNS. We hypothesized that the initial event was perineural invasion along the trigeminal nerve followed by leptomeningeal spread. The incidence of perineural invasion of cutaneous SCC is 3.7% to 14%, with the highest metastatic rates from lesions of the temple, lips, and dorsal hands.\(^7^8\) A review of 520 patients treated at MD Anderson Cancer Center revealed that the facial nerve and the maxillary and mandibular branches of the trigeminal nerve were the most common nerves involved in perineural invasion.\(^8\)

Although a leptomeningeal malignant neoplasm was a strong antemortem consideration, the diagnostic dilemma in this case arose after findings on cytological evaluations of CSF were negative on 3 occasions. Glantz et al\(^9\) concluded that at least 10.5 mL of CSF should be drawn to increase the yield of the cytological examination. Earlier CSF processing, obtaining CSF from the leptomeningeal disease site, and repeating the procedure more than once would also help in minimizing false-negative results. General practice is to repeat the cytological analysis of a large volume of CSF on 3 occasions. Chamberlain\(^10\) has reported that approximately 25% of patients with leptomeningeal metastasis will continue to have negative cytological findings despite following these recommendations.

Certain SCCs avidly adhere to neuronal structures. This characteristic may allow them to invade the CNS along cranial nerves and may also keep the malignant cells from circulating freely in the CSF. Hence, leptomeningeal dis-
ease with neurotropic SCC may be especially likely to show negative CSF cytological findings despite a large burden of tumor.

In this case, the history and imaging findings of progressive multilevel neurological symptoms in a patient with a history of cutaneous invasive SCC should lead to the diagnosis of leptomeningeal carcinomatosis. There are only a few case reports of SCC with leptomeningeal and cauda equina involvement, and the prognosis has been uniformly dismal regardless of therapy. In our case, the presumptive antemortem diagnosis was correct and the patient made the decision to defer additional diagnostic or therapeutic intervention.

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REFERENCES