Clinical Reasoning:
A 52-year-old man with spells of altered consciousness and severe headaches

SECTION 1
A 52-year-old right-handed man with a history of petit mal seizures as a child was transferred to our hospital after a spell of sudden loss of consciousness. His illness began 1 month earlier with fatigue and bilateral hand tremor. Two weeks later, he experienced a severe headache of sudden onset without associated nausea, vomiting, or focal neurologic symptoms. This lasted for a few hours, abating after several doses of ibuprofen and acetaminophen. One week later, he suddenly became confused while driving. He continued to drive normally, but had a befuddled facial expression and did not respond to questions from his wife. He returned to normal within 10 minutes. Over the next 2 weeks, he had several similar spells. He also developed recurrent, sudden, severe headaches that occurred several times per day. The pain began in the shoulders, spreading to the occipital region and then the entire head over 1–2 minutes. It was severe enough to cause him to fall to his knees and cry out in pain. These episodes occurred more frequently when lying in bed than when he was standing or sitting, and were associated with nausea. He was admitted to another hospital for evaluation of these symptoms and transferred to our facility after a 1-hour spell of "unresponsiveness," which resolved spontaneously, while there.

Further questioning revealed additional symptoms. After the first episode of altered consciousness, his personality changed. His wife described him as "vacant" and "not as active and happy-go-lucky" as usual. He developed a slowly progressive, mild dysarthria; difficulty walking due to frequent “buckling” of the right knee; and numbness in the right medial forearm and little finger. He also described difficulty in using his hands to perform tasks such as putting toothpaste on a toothbrush, which he described as being like “putting two magnets together.” Finally, he had lost about 25 pounds over the preceding 3 months.

In addition to the childhood seizures, his past medical history was notable for a fungal infection of the lung in 1997 for which he had been admitted to an intensive care unit. The details of this illness were not known beyond the fact that he was treated for several months with an antibiotic. He had a remote smoking history.

Questions for consideration:
1. What is the differential diagnosis for this clinical presentation?
2. What features of the history are most useful in narrowing the differential diagnosis?
SECTION 2
In developing a differential diagnosis, one must first distill the crux of the clinical syndrome from the history. In this case, the history has two main components: spells of altered consciousness and episodes of severe headache. These occur independently. The spells of altered consciousness are most consistent with complex partial seizures. The sudden, severe headaches have a broader differential diagnosis, including venous sinus thrombosis, posterior reversible encephalopathy syndrome, CNS vasculitis, reversible cerebral vasoconstriction, and meningoencephalitis.1 A history of multiple recurrences without severe neurologic sequelae argues strongly against subarachnoid hemorrhage and cervical artery dissection. Migraine is unlikely in light of the sudden onset, postural variations, and associated intermittent confusion. Episodic intracranial hypertension from a mass lesion, hydrocephalus, meningitis, or some combination of these diagnoses is an important consideration given the positional nature of the headaches.

Equally crucial to formulating a neurologic differential diagnosis is to begin to localize the disease process within the nervous system from the history. Doing so allows one to narrow the list of possible etiologies. This patient’s clinical syndrome points to a multifocal or diffuse disease process. Complex partial seizures localize to the frontal or temporal lobe. While the long duration of the event and the postictal period suggests a temporal lobe focus, it is impossible to precisely localize the seizure focus in this case solely from the history. The personality change suggests dysfunction of anterior portions of the frontal lobe, caudate nucleus, or the anterior thalamus, while the difficulty with hand coordination suggests a cerebellar or parietal lobe lesion. Numbness in the medial right arm and little finger suggests a lesion of the ulnar nerve or C8 root, while the knee buckling may localize to the femoral nerve, lumbar roots, thoracic spinal cord, or medial left frontal lobe. Without further semiologic characterization, the dysarthria could localize to a number of structures and therefore is of little localizing value.

On examination, the patient was afebrile and had normal vital signs. He was thin and appeared chronically ill. There was no meningismus. The remainder of the general medical examination was unremarkable. On neurologic examination, he was listless, somewhat inattentive, and seemed unconcerned with his illness. The cranial nerves were normal and there was no papilledema. Motor examination revealed a right pronator drift and a low-amplitude, high-frequency action tremor in the arms. Muscle stretch reflexes were normal with the exception of brisk knee reflexes. Plantar responses were equivocal on the right and extensor on the left. Pinprick sensation was reduced on the medial aspect of the right hand, including the little finger. Sensation of light touch and vibration as well as cortical sensory function were normal. There was no appendicular ataxia.

Questions for consideration:
1. Based on the history and examination, what is your clinical formulation?
2. What diagnostic tests would be useful to test this hypothesis?
SECTION 3

We are considering the case of a 52-year-old man with a remote history of a fungal lung infection who presents with the following clinical syndrome:

- Severe episodic headaches associated with nausea and vomiting and provoked by assumption of the supine position, most consistent with episodic intracranial hypertension. This suggests the presence of a mass lesion, disease of the leptomeninges, or both.
- Recurrent spells of altered behavior and consciousness consistent with complex partial seizures, indicating focal cortical dysfunction in the frontal or temporal lobes.
- Personality changes suggestive of frontal lobe dysfunction.
- Right upper extremity sensory changes in the C8/ulnar distribution, suggesting involvement of the peripheral nerves or spinal nerve roots.
- Dysarthria.
- Right lower extremity weakness.

While other localizations are possible, this combination of findings best localizes simultaneously to the frontal lobe cortex and the meninges. When considered along with the history of weight loss and remote history of a fungal lung infection, likely etiologies include subacutely progressive meningoencephalitides such as those caused by fungi and mycobacteria, autoimmune inflammatory conditions, and neoplastic processes such as lymphoma and metastatic carcinoma. To narrow this list down, imaging and CSF analysis are necessary.

Results of complete blood count, electrolytes, renal function, and coagulation studies were normal. C-reactive protein and erythrocyte sedimentation rate were not elevated and testing for antinuclear and antineutrophil cytoplasmic antibodies as well as rheumatoid factor was negative. Blood cultures and serologic testing for numerous fungi, HIV, and syphilis were negative. The purified protein derivative test was nonreactive. CT of the chest, abdomen, and pelvis were unremarkable.

Brain imaging revealed a lesion in the anteroinferior right frontal lobe. The CT examination without contrast showed a hypodense mass with a thin, slightly hyperdense rim. On MRI (figure), the lesion was heterogeneous, with mixed T1 and T2 signal intensity. The center had increased signal on both T1 and T2 sequences, while the rim was hypointense on T1 and T2. There was mild, heterogeneous enhancement along the lesion’s rim and diffuse leptomeningeal enhancement. The gradient echo sequence revealed increased susceptibility artifact primarily along the rim. Diffusion-weighted imaging displayed restricted diffusion in the center of the lesion.

MRI of the spine with contrast can be helpful in distinguishing among inflammatory, infectious, and neoplastic diseases and can provide valuable anatomic information. For example, focal enhancing lesions of the leptomeninges at the right C8 nerve root would be supportive of a multifocal neoplastic process and would confirm the findings of our history and physical examination. However, because the patient’s severe headaches were provoked by supine positioning and his condition was rapidly deteriorating, a spine MRI was not performed.

CSF was obtained by lumbar puncture performed after brain imaging. The opening pressure was 360 mm H2O and the unspun fluid was yellow and viscous. After centrifugation, xanthochromia was present. The protein level was 1,991 mg/dL and the glucose concentration 48 mg/dL. Although a simultaneous serum glucose was not checked, it was never less than 100 mg/dL during the entire admission. The erythrocyte count was 13/μL and there were 34 leukocytes/μL (34% lymphocytes, 42% monocytes, 4% atypical cells). There was no evidence of malignant cells on cytology and flow cytometry. No organisms were apparent on the gram stain or fungal smear, and cultures for bacteria, fungi, and mycobacteria as well as PCR for herpes simplex virus, Epstein-Barr virus, cytomegalovirus, and varicella zoster virus were negative.

Question for consideration:

1. How does the information provided by the imaging and CSF analysis help your diagnostic process?
SECTION 4

Imaging studies demonstrated a well-demarcated mass lesion with an enhancing rim in the right frontal lobe and leptomeningitis (figure). These findings confirm the clinical localization and provide information for the generation of an etiologic differential diagnosis.

The signal characteristics of the lesion on MRI provide important information. The T2 hypointense rim is caused by hemosiderin, while the high T1 and T2 signal intensity in its center is indicative of subacute blood. The subacute blood is also responsible for the restricted diffusion. This combination of findings can be seen in a relatively limited number of conditions, including cavernous malformations, arteriovenous malformations, subacute intracerebral hemorrhages, contusions, abscesses, and tumor (primary or metastatic). The intense enhancement of the leptomeninges on the postcontrast images indicates the presence of leptomeningeal inflammation. The combination of hemorrhage and restricted diffusion with diffuse leptomeningitis further narrows the list of possible etiologies to the following: abscess with associated meningitis (bacterial, fungal, or mycobacterial), focal tumor with diffuse neoplastic meningeal infiltration (metastatic tumors from a variety of tissues, lymphoma, or glioblastoma), infarct or hemorrhage with associated meningitis (primary CNS vasculitis, systemic vasculitis with CNS involvement, or meningovascular syphilis), or a focal inflammatory mass with associated meningitis (sarcoidosis).

The highly elevated protein level, slightly low glucose concentration, mild lymphocytic-monocytic pleocytosis, and elevated opening pressure found on CSF analysis are all indicative of an inflammatory process, providing support to the differential diagnosis formulated on the basis of the clinical and imaging findings. However, due to the absence of a more specific finding, such as identification of a pathogen or malignant cells in the fluid, these results do not help to narrow down the list of possible diagnoses.

**Question for consideration:**
1. Are any other useful diagnostic tests available for this patient?
SECTION 5
Empiric treatment for a bacterial abscess with meningitis was started on hospital day 4, but this did not lead to clinical improvement. Because of the severity of the patient’s illness and the failure of less invasive testing to establish a diagnosis, a right frontal craniotomy and subtotal resection of the lesion were performed 5 days after his admission to our hospital. Intraoperatively, the frontal lobe appeared swollen and bulged through the dura as soon as it was opened. The lesion itself appeared as a cavity filled with brown/greenish material. Along the floor of the anterior cranial fossa, there was meningeal reaction and the mass was adherent to the underlying dura. Microscopic examination of the resected lesion revealed pseudopalisading nuclei with infiltrating lymphocytes and glial fibrillary acid protein–expressing neoplastic astrocytes, consistent with a WHO grade IV astrocytoma (glioblastoma). Thus, our final diagnosis was a partially necrotic and hemorrhagic glioblastoma of the inferior right frontal lobe with definite intracranial and possible spinal leptomeningeal metastases.

Dexamethasone 2 mg every 6 hours was started once the pathologic diagnosis was made. The patient’s postoperative course was unremarkable. He was transferred to a hospital closer to his home on postoperative day 6 and was scheduled to begin treatment with whole brain radiation and temozolomide 4 weeks after the resection. However, his health declined precipitously after transfer, and he died 4 weeks later.

DISCUSSION
Meningeal involvement in association with glioblastomas was first described by Guillemin and Verdun in 1911. Bernat posited three mechanisms by which this association might occur: chemical meningitis due to tumor rupture and release of necrotic, lipid-containing contents; tumor hemorrhage with release of blood breakdown products into the subarachnoid space; and tumor seeding of the meninges with resultant inflammation due to an immunologic response, as was the case in the patient described here. Autopsy studies have shown that as many as 20% of patients with high-grade cerebral gliomas have leptomeningeal metastases. Only approximately 4% of patients with supratentorial malignant gliomas, however, exhibit symptoms referable to this process. Furthermore, meningeal metastases from glioblastomas most often present late in the course of the disease, after the primary tumor has been diagnosed. Few cases have been reported in which meningeal metastases were responsible for the presenting symptoms in patients with glioblastomas. Interestingly, younger patients with glioblastomas may be at relatively higher risk for this secondary leptomeningeal seeding.

Meningeal metastatic disease from glioblastomas responds poorly to radiation or chemotherapy and carries a grave prognosis. The average survival after the onset of symptoms due to meningeal involvement was 2–3 months in one study. These survival data are derived largely from patients in whom meningeal disease was a late manifestation and therefore may not apply to patients in whom meningeal disease manifests early in the course of the disease.

When clinically apparent, leptomeningeal metastases from glioblastomas most often cause a syndrome similar to subacute meningitis with headache, confusion, and neck and back pain. A wide variety of focal neurologic symptoms can be seen, the most common being cranial nerve palsies, radiculopathies, and myelopathy. These symptoms are probably caused by infiltration, mass effect, and inflammation at the sites of leptomeningeal tumor deposits. In addition, symptomatic hydrocephalus can occur. Finally, a vasculopathic syndrome with multifocal infarctions caused by occlusion of small, leptomeningeal-based blood vessels encased by tumor cells has been described.

The CSF in patients with leptomeningeal metastases from a glioblastoma is typically abnormal, with a lymphocytic pleocytosis, elevated protein, and sometimes hypoglycorrhachia. CSF cytology, however, is negative in more than 50% of patients. Staining cells found in the CSF for glial fibrillary acidic protein may increase the diagnostic yield of cytology when gliomatosis is suspected. Imaging findings associated with glioblastoma leptomeningeal metastases include hydrocephalus, periventricular and leptomeningeal enhancement, and sulcal effacement. Unfortunately, with the exception of cytology, none of these findings clearly differentiates glioblastoma leptomeningeal metastases from other causes of subacute meningitis.

The rarity and nonspecific nature of its clinical, laboratory, and imaging manifestations makes the diagnosis of leptomeningeal metastases from glioblastoma difficult when a primary tumor is not apparent. As illustrated by this case, this difficulty can be overcome by the use of a disciplined diagnostic approach that includes systematic consideration and synthesis of all elements of the case, including the history, physical examination, laboratory, and imaging data. Finally, this case demonstrates the utility of brain biopsy when less invasive diagnostic modalities have failed to confirm a diagnosis.
REFERENCES
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