49-Year-Old Woman With Back Pain and Loss of Consciousness

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A 49-year-old woman had a 10-month history of low-back pain that had developed insidiously. Two months after the back pain was initially noted, it precipitously worsened, and an evaluation by her local physician included a roentgenogram of the lumbar spine that showed a compression fracture of the L-2 vertebral body. Among the tests done in assessment, a serum IgG level was increased at 3,910 mg/dL. A subsequent bone marrow biopsy specimen showed IgG multiple myeloma. She was treated with melphalan hydrochloride and prednisone for 4 months (total melphalan dose, 172 mg). Her serum IgG decreased to 1,420 mg/dL. Three months later, the serum IgG level increased to 1,600 mg/dL. One month thereafter, she came to the Division of Hematology/Oncology at Mayo Clinic Jacksonville for a second opinion on further treatment.

On physical examination, the patient's weight was 70.9 kg and height was 157 cm. Her vital signs and findings on general physical and neurologic examinations were normal. Laboratory investigations showed abnormal serum IgG and total protein, and review of a slide of the previously obtained bone marrow biopsy specimen confirmed the diagnosis. Three 5-week cycles of chemotherapy were planned, with each cycle consisting of vincristine (0.5 mg/day continuous intravenous infusion) and doxorubicin (10 mg/m² per day intravenously) on days 1 through 4 and dexamethasone (40 mg/day orally) on days 1 through 4, 9 through 12, and 17 through 20 of each 5-week treatment cycle. She returned home to begin treatment.

One month after the aforementioned therapy was begun, while taking dexamethasone only, the patient suddenly felt sharp diffuse pain in her head and neck. The pain began while she was lying down and was associated with an ascending "whiteout" of her visual field bilaterally. The abnormal visual phenomenon lasted seconds and resolved spontaneously. Her headache resolved 2 hours later after she took acetaminophen. She had two similar attacks during the next 3 days, each relieved by acetaminophen or one tablet of Percocet (oxycodone 5 mg and acetaminophen 325 mg). After her third headache, a magnetic resonance image (MRI) of the head showed normal findings. A few days later, she had her fourth headache while in her physician's office. It was similar to her previous attacks and responded to two tablets of Percocet. Electrolytes and a complete blood cell count determined in her physician's office were normal. Later that day, she complained to her husband about brief abdominal discomfort and visual illusions of "colorful starbursts" throughout her visual field. Her husband left the room momentarily but returned because of a sudden noise. He found his wife lying on the floor unresponsive. She had lost continence of bowel and bladder. She regained consciousness less than 5 minutes later but was confused and combative. Vital signs, including blood pressure, were normal. She was transported to a local emergency department.

I. Which one of the following is the most likely cause of this patient's "spell"?

a. Vasovagal syncope
b. Cardiac syncope
c. Generalized seizure
d. Vertebrobasilar transient ischemic attack
e. Aneurysmal subarachnoid hemorrhage

Syncope is a sudden, nontraumatic, temporary loss of consciousness and postural tone. Vasovagal syncope has a biphasic course. A phase of increases in blood pressure, heart rate, total systemic resistance, and cardiac output due to a brief period of apprehension and anxiety is followed by a vasodepressor phase when heart rate slows, blood pressure decreases, cardiac output declines, and cerebral blood flow eventually diminishes. A global reduction of cerebral blood flow by more than two-thirds is necessary to cause syncope. Symptoms of palpitations, salivation, and anxiety characterize the first phase. Progressive sensations of light-headedness, giddiness, abdominal sinking, nausea, urinary urgency, and, ultimately, faintness accompany the vasodepressor component of vasovagal syncope. Postural failure of cerebral perfusion either occurs abruptly or evolves during a period of 15 to 30 seconds. Vasovagal syncope has a benign prognosis. Cardiovascular syncope, how-
ever, has a moderate to severe prognosis. Seizure begins abruptly and may or may not have premonitory symptoms (auras). Olfactory hallucinations and complex psychologic phenomena such as déjà vu and jamais vu are distinctly epileptic auras. Traumatic injury from a fall, urinary incontinence, tongue biting, and involuntary facial and limb movements are also seen with seizures. Confusion, agitation, or headache often occurs after seizure. Our patient’s aura of gastrointestinal discomfort and visual changes, associated with sudden onset of ictus, urinary incontinence, and postictal agitation and confusion, point to seizure as the most likely cause. The vertebrobasilar transient ischemic attack that can be confused with syncope is the drop attack; however, patients with drop attacks retain consciousness. Although higher grades of aneurysmal subarachnoid hemorrhage are associated with loss of consciousness, the change in consciousness does not typically clear in hours.1

Because the patient had a generalized tonic-clonic seizure in the emergency department, she was admitted to the hospital. Later, she was described as being “encephalopathic.” An emergent computed tomographic scan of the head without contrast enhancement showed normal findings. She was given a loading dose of phenytoin. Cerebrospinal fluid analysis showed 3 leukocytes and 2 erythrocytes/μL, 60 mg/dL protein, and 159 mg/dL glucose (serum glucose, 196 mg/dL), and serologic tests for streptococcal, meningococcal, Haemophilus influenzae, cryptococcal, and herpes simplex virus antibodies were negative. She had a mild upper extremity drift on the second hospital day. Brain MRI done the following day showed multiple large subcortical white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) images. None of the lesions enhanced with contrast material. Bilateral occipital lobes were most strikingly involved (Fig. 1). MR angiography and echocardiography showed no abnormalities. On a general chemistry screen, the venous lactate level was increased at 4.9 mmol/L (normal, less than 1.7). A repeated sample a few days later showed a lower but persistently elevated lactate level of 3.1 mmol/L. After 5 days of hospitalization, she was dismissed, and phenytoin was prescribed.

2. Which one of the following neurologic complications is most likely to develop in this patient as a result of her underlying malignant condition?
   a. Radiculopathy
   b. Stroke
   c. Myelopathy
   d. Polyneuropathy
   e. Seizure

Multiple myeloma is characterized by malignant proliferation of a single clone of plasma cells that produce monoclonal immunoglobulin. The plasma cell proliferation usually causes osteolytic lesions, hypercalcemia, anemia, and, occasionally, plasma cell infiltration in various organs and tissues.2 Radiculopathy is the most frequent neurologic complication of multiple myeloma. Often, severe back pain results from compression of the nerve roots by extension of vertebral lesions or by pathologically collapsed vertebral bodies. Stroke due to hyperviscosity syndrome is rare. Compression of the spinal cord causing myelopathy occurs in 5 to 10% of patients,2 and polyneuropathy is clinically detected in only 3 to 5% of patients.2 Seizures are uncommon in multiple myeloma because intracranial involvement by the tumor is rare.

Our patient had no further seizures while taking phenytoin. Her chemotherapy was discontinued because of its possible role in her seizure and headaches. She did not have recurrent headaches after dismissal from the hospital. Because of the MRI abnormalities and the increased lactate levels, she was referred to the Department of Neurology to exclude the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS).
3. Which one of the following symptoms in our patient is most commonly associated with MELAS?
   a. Seizure
   b. Headache
   c. Visual obscuration
   d. Back pain
   e. Syncope

MELAS is associated with mitochondrial transfer RNA mutation at base pair 3243 in approximately 80% of cases. It is a heterogeneous disorder, usually beginning before age 40 years, whose major clinical features are episodic seizures, vomiting, recurrent stroke-like episodes of hemiparesis and hemianopia, and proximal muscle weakness. Headache in association with specific visual phenomena, such as scintillating scotoma, is typical of migraine but not of MELAS. Elevated cerebrospinal fluid and venous lactate levels are seen after generalized convulsive seizures. Studies of natural history have shown consistently increased levels lasting from a few hours to more than 4 days after seizures. Back pain and syncope are unassociated with MELAS.

The patient was asymptomatic at the time of initial assessment at our institution. Findings on neurologic examination also were normal. She had no personal or family history of neurologic diseases including epilepsy, and she had no known risk factors for seizure disorder. Laboratory studies at our institution showed mild anemia (hemoglobin, 10.8 mg/dL). Platelet count, electrolytes, results of liver function tests, glucose, calcium, magnesium, and phosphorus were normal. A repeated lactate determination, 10 days after her last seizure, revealed a further decline to 2.3 mmol/L. MRI of the brain repeated 6 weeks later showed complete resolution of the previously noted abnormalities. Brain MRI spectroscopy also showed normal findings.

4. Which one of the following most likely explains the reversible lesions on magnetic resonance imaging of the brain in our patient?
   a. Hypertensive encephalopathy
   b. Eclampsia
   c. Melphalan neurotoxicity
   d. Doxorubicin neurotoxicity
   e. Generalized tonic-clonic seizure

Hypertensive encephalopathy and eclampsia have been reported to cause reversible MRI abnormalities. Hypertensive encephalopathy is characterized by the subacute onset of headache, seizures, visual disturbance, altered mental status, and focal neurologic signs in the setting of substantially increased blood pressure. The findings of Schwartz and associates support the hypothesis that the MRI abnormalities result from breakthrough of autoregulation with passive overdistention of cerebral arteries. This situation would result in interstitial extravasation of protein and fluid and would cause vasogenic edema in the peripheral vascular distribution of the involved vessel. Our patient had no evidence of profoundly increased blood pressure or eclampsia. Melphalan and doxorubicin have not been reported to induce brain white matter lesions. Generalized tonic-clonic seizures have been reported to cause reversible brain MRI abnormalities such as seen in our patient. Impaired autoregulation resulting from relative hypoxia related to seizure activity in conjunction with increased lactate levels and partial pressure of carbon dioxide has been implicated as the pathophysiologic mechanism.

5. Which one of the following neurologic complications, as a result of our patient's exposure to vincristine, is most likely?
   a. Seizure
   b. Motor neuropathy
   c. Sensory polyneuropathy
   d. Myopathy
   e. Myelopathy

Vincristine therapy associated with encephalopathy, coma, and seizure is rare but has been reported. The underlying mechanism of seizure is unknown, but current theory attributes seizures to vincristine-induced syndrome of inappropriate antidiuretic hormone secretion and hyponatremia. Our patient had no clinical or laboratory evidence of hyponatremia either before or after the seizures. The most common neurologic complication of vincristine therapy is a distal sensorimotor polyneuropathy. The predominant clinical findings are loss of deep tendon reflexes as well as loss of pain and temperature sensation in a stocking-glove distribution. Mild motor findings and vibratory and proprioceptive loss are seen with continued treatment. The mechanism of vincristine neurotoxicity is the disruption and disarray of axonal microtubules, leading to impaired axonal degeneration and minor segmental demyelination. A neuropathy confined to the motor nerve, a myopathy, or a myelopathy would not be expected from vincristine.

**DISCUSSION**

All patients with cancer who have new-onset seizure should undergo a detailed clinical and laboratory evaluation to determine whether evidence exists for a structural lesion, infectious process, or reversible toxic-metabolic derangement. Seizure can result from a primary central nervous system malignant condition or an extraneural primary malignant lesion with metastatic involvement of the parenchyma, dura, or subarachnoid space (carcinomatous or...
lymphomatous meningitis). Imaging of the head should precede a lumbar puncture to exclude a structural lesion. A metabolic derangement such as hypoxia, hypoglycemia, or hyponatremia may be a direct effect of the malignant condition or may be iatrogenic. Hypoxia leading to seizure usually results from cardiopulmonary disease attributable to metastatic lesions or treatment effect. Congestive heart failure resulting from doxorubicin-related cardiac toxicity may cause hypoxia, and cerebral hypoxia may cause seizure. Transthoracic echocardiography done after the seizures in our patient did not show congestive heart failure. The cause of seizure in our patient is unknown. Vincristine may cause hypoxia, and cerebral hypoxia may cause seizures in our patient did not show congestive heart failure. The diagnosis of MELAS needs to be considered in the setting of new-onset seizures associated with increased venous lactate and diffuse MRI abnormalities. The typical MRI findings of MELAS are migrating T2-weighted hyperintensities involving the cortex and immediately subjacent white matter. Relative preservation of deep white matter is characteristic. The MRI findings of selective deep white matter changes and preservation of the cortex would be highly atypical for MELAS. The normal neurologic findings and MRI spectroscopy also argue against MELAS.

Increased venous lactate indicates either tissue hypoxia or failure of metabolism in the presence of normal tissue oxygenation. High lactate levels have been noted in lactic acidosis, glycogen storage diseases, and mitochondrial diseases as well as after convulsive seizures. Other causes of elevated lactate levels include drugs such as phenformin, high-dose fructose or sorbitol infusions, aspirin toxicity, epinephrine, methylprednisolone, and acetaminophen in large quantities. Use of a tourniquet or clenching of the hands during venipuncture, hyperventilation, and muscular exercise can also lead to increased lactate. Albuminocytologic dissociation is seen in diseases such as acute inflammatory demyelinating polyradiculoneuropathy, giant cell arteritis, and some acquired polyneuropathies. It may also occur with certain drugs such as ethanol, phenothiazines, and phenytoin. Phenytoin might have contributed to the cerebrospinal fluid protein noted in our patient. The presumed mechanism is an increase in blood-brain barrier permeability.

The importance of correlating MR findings with neurologic examination cannot be overemphasized. Our patient had multifocal bilateral lesions evident on an MRI, but neurologic examination showed normal findings. This apparent discrepancy was resolved by repeating the MRI. By demonstrating that the MRI lesions were reversible, the differential diagnosis was dramatically reduced, and it became possible to attribute the MR findings and increased lactate levels to her postictal state.

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REFERENCES


Correct answers: 1. c, 2. a, 3. a, 4. e, 5. c