A SELF-TEST OF CLINICAL RECOGNITION

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A 47-year-old man with leiomyosarcoma and altered mental status

A 47-YEAR-OLD previously healthy man presented with increasing lower extremity edema, weight loss, abdominal swelling, and early satiety. Workup revealed a large retroperitoneal mass, which a computed tomography (CT)-guided biopsy showed to be a high-grade leiomyosarcoma. The tumor was considered unsuitable for resection. He began chemotherapy with polyethylene glycol-coated liposomal doxorubicin but had no response to it. Treatment with ifosfamide and mesna was begun instead. TABLE 1 shows his blood chemistry values before ifosfamide treatment. His complete blood count was normal at that time.

Ifosfamide 3.75 g was given over 1 hour on 2 consecutive days. Mesna (a uroprotective agent) was given before each ifosfamide infusion, and at 3 and 6 hours after.

TABLE 1

The patient's blood chemistry values before and during ifosfamide treatment

SUBSTANCE	BEFORE TREATMENT	DURING TREATMENT	NORMAL RANGE
Sodium, mEq/L	128	135	135–145
Potassium, mEq/L	5.2	4.3	3.5–5.0
Chloride, mEq/L	89	95	98–110
Bicarbonate, mEq/L	—	21	24–28
Blood urea nitrogen, mg/dL	41	48	10–25
Creatinine, mg/dL	1.1	1.4	0.7–1.4
Albumin, g/dL	2.4	—	3.5–5.0

THE PATIENT DEVELOPS MENTAL STATUS CHANGES

Near the end of the second day of treatment, the patient's wife noticed that his mental status was somewhat vague. He developed diarrhea with four or five semisolid stools, and became increasingly confused and restless. No seizures were noted. He is brought to the hospital for further evaluation.

Physical examination. The patient is drowsy and cachectic and gives minimal verbal responses. He can sit up spontaneously but cannot follow commands. His temperature is 35.9°C, pulse 100, and blood pressure 90/70 mm Hg. There is no neck rigidity or meningismus. His pupils are equal and reactive to light. There is no cranial nerve deficit. Muscle strength is at least 4 (on a scale of 5) in all muscle groups, and tone is normal. Deep tendon reflexes are brisk but symmetric. The Babinski sign is present bilaterally, and sustained clonus can be elicited bilaterally by dorsiflexing the feet. The chest and cardiovascular systems appear normal. The abdomen is protuberant with ascites. His laboratory values at this point are also shown in TABLE 1.

A CT scan of the brain is normal except for loss of grey-white demarcation.

WHAT IS THE DIAGNOSIS?

1 What is the most likely cause of this patient's altered mental status?

- ❑ Central pontine myelinolysis
- ❑ Metastases to the central nervous system
- ❑ Paraneoplastic encephalomyelitis
- ❑ Ifosfamide-induced encephalopathy
- ❑ Hyponatremic encephalopathy

Myelinolysis is a neurologic syndrome that follows rapid correction of hyponatremia.[1] It classically affects the central pons but can also involve extrapontine areas. Symptoms usually start 3 days after hyponatremia has been corrected,[2] and consist of spastic quadriparesis and pseudobulbar palsy. Consciousness is impaired, and although this may be mild, it may progress to coma and death. Initial CT scans or magnetic resonance imaging (MRI) scans are usually normal, while later scans show the characteristic lesions. MRI is the more sensitive of the two imaging studies in defining the late lesions. One can usually avoid this complication by increasing the serum sodium level slowly in cases of chronic hyponatremia, by no more than 10 mEq/L in 24 hours and no more than 21 mEq/L in 48 hours. In our patient, the temporal course and neurologic picture do not suggest central pontine myelinolysis.

Metastases usually cause focal neurologic deficits and not a rapid encephalopathy. In addition, leiomyosarcomas do not usually metastasize to the brain.

Hyponatremic encephalopathy can present in a fashion similar to that seen in our patient; however, the patient was not hyponatremic.

18% of patients receiving ifosfamide develop encephalopathy

Limbic encephalitis is a paraneoplastic syndrome characterized by a triad of profound memory impairment, dementia, and psychiatric disturbances including depression, anxiety, psychosis, and seizures.[3] The symptoms evolve over a period of weeks to months. Anti-Hu antibodies are found in the serum. Pathological examination shows neuronal loss, perivascular lymphocytic cuffing, microglial nodules, and glioses throughout the neuraxis with particular involvement of the limbic area.[3] Seventy-eight percent of cases are associated with small-cell carcinoma of the lung.[4] Treatment with steroids, plasmapheresis, immunosuppressants, or combinations of these drugs has not been shown to be beneficial, and treating the primary tumor has rarely led to reversal of the encephalitis.[5] In our patient, the temporal course and the clinical picture did not fit that of limbic encephalitis.

Ifosfamide-induced encephalopathy, the cause of this patient's altered mental status, has been reported in 18% of patients receiving this drug,[6] an alkylating agent similar to cyclophosphamide. The condition is characterized by metabolic encephalopathy of varying severity, blurred vision, mutism, seizures, and even irreversible coma. Low pretreatment serum albumin levels, high pretreatment creatinine levels, and tumors located below the renal pedicles increase the risk of developing ifosfamide-induced encephalopathy. The exact etiology of the neurotoxicity is not known.

THERAPY

2 What would be the most appropriate therapy for this patient?

- ❑ Diazepam
- ❑ Mesna
- ❑ Flumazenil
- ❑ Methylene blue

Diazepam was previously used in treating ifosfamide-induced encephalopathy, but has fallen from favor. The rationale for using diazepam was that the evolution and severity of clinical neurotoxicity correlated with sequential electroencephalographic changes, progressing from background slowing to continuous delta activity and the appearance of sharp and triphasic waves. A few cases of nonconvulsive status epilepticus were also reported. Use of intravenous diazepam led to clinical and electroencephalographic recovery in a few patients—but only a few.[7,8]

Mesna combines with metabolites of ifosfamide (4-hydroxyifosfamide and acrolein) in the urinary tract to prevent urotoxicity. It does not prevent ifosfamide neurotoxicity and may itself have some neurotoxic effects.

Flumazenil is a benzodiazepine antagonist and has no role in treating ifosfamide-induced encephalopathy.

Methylene blue was first reported as useful in treating ifosfamide encephalopathy in 1994,[9] and is now the treatment of choice.[10] The rationale for using methylene blue is that patients with ifosfamide encephalopathy have an excess of glutaric acid and sarcosine in the urine. This condition is believed to be similar to glutaric aciduria type II, which is a defect in

mitochondrial fatty oxidation that results from defective electron transfer to flavoproteins and which has been treated with methylene blue as an electron acceptor.

The patient received two 50-g doses of methylene blue intravenously, and recovered considerably. More doses were given prophylactically before and after each ifosfamide infusion in his second course of chemotherapy. The patient experienced another episode of mental status changes, but this was mild and resolved completely with a single infusion of methylene blue.

Unfortunately, the patient's leiomyosarcoma did not respond to chemotherapy, and he eventually died of it.

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CME ANSWERS

CME 2 CREDIT HOURS

Answers to the CREDIT TEST on page 63 of this issue

1 C 2 A 3 D 4 D 5 B 6 C 7 D 8 C 9 B 10 B