

Clinical Reasoning: A 54-year-old woman with transient episodes of headache and neurologic dysfunction

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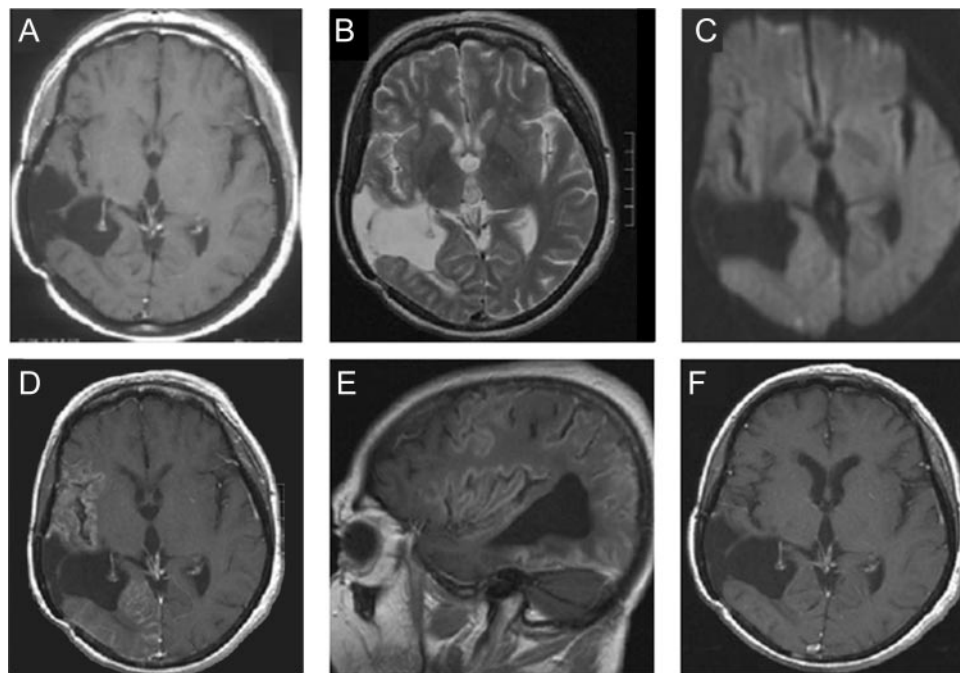
SECTION 1

A 54-year-old woman with a 13-year history of resected oligodendroglioma (treated with resection and whole brain radiation therapy with focus on brain tumor [40 Gy]) was admitted with acute left hemiparesis (Medical Research Council [MRC] 2/5), left hemineglect, confusion, and multiple episodes of throbbing right parietal headache lasting for hours. Blood pressure levels were normal (<140/90 mm Hg) on repeat measurements. The patient was afebrile and neurologic examination disclosed no signs of meningeal irritation.

The patient reported having a similar episode (mild left hemiparesis [MRC 4/5] following a right parietal

throbbing headache) 11 years ago. The episode lasted less than 24 hours and the patient recovered completely from her symptoms. Her treating physician considered this episode as a focal seizure, ordered no further diagnostic workup, and changed her antiepileptic medication from phenytoin (100 mg TID) to phenobarbital (50 mg BID). The patient had no history of headaches before the diagnosis of her brain tumor. She had no family history of migraine. One year after the radiation therapy, she started developing episodes of migraine of moderate to severe intensity with a frequency of 2–6 attacks per year. The headache attacks were typically unilateral (right-sided) and lasted for several hours (5–53 hours). The pain was of pulsating nature and was

Figure Brain MRI



Axial T1 sequence (A) showing no gyral enhancement 7 years before presentation and 6 years after oligodendroglioma resection. Axial T2 (B) and diffusion-weighted imaging (C) sequences show no evidence of acute cerebral ischemia during the stroke-like episode. Axial (D) and sagittal (E) T1 sequences show thick gyral enhancement of the right parieto-occipital region during the episode. Axial T1 sequence (F) showing complete resolution of the enhancement 3 months after the stroke-like episode.

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aggravated by physical activity. The patient occasionally reported that the headache was accompanied by nausea or vomiting. She had no sensitivity to light or sound. Usually, the migraine attacks were not preceded by any symptoms of aura and were relieved by nonsteroid inflammatory drugs followed by resting and sleep. On 2 occasions the patient reported that the headache attacks were preceded by an aura of scintillating scotomas lasting for 10–20 minutes. Due to the recurrent episodes of headache, a brain MRI was performed 6 years after the resection of oligodendroglioma that showed no evidence of gyral enhancement in the affected cortex and no recurrent or residual tumor (figure, A).

The patient underwent emergent brain MRI during her present hospitalization. Axial T2, fluid-attenuated inversion recovery, and diffusion-weighted imaging sequences were negative for acute cerebral ischemia (figure, B and C). Axial and sagittal T1 sequences with gadolinium showed diffuse right parieto-occipital gyral enhancement not conforming to vascular territories (figure, D and E).

Questions for consideration:

1. What is your differential diagnosis at this time point?
2. What additional diagnostic tests would you consider at this time point?

GO TO SECTION 2

SECTION 2

Repeat electroencephalography showed slowing over the right hemisphere with no epileptiform activity. No vascular imaging tests (carotid duplex, brain magnetic resonance angiography) were ordered given the absence of ischemia on brain MRI. The patient was not placed on any antiplatelet or antithrombotic medication. Her neurologic condition was attributed to seizure activity. Consequently, carbamazepine (400 mg BID) and levetiracetam (1,500 mg BID) were added to phenobarbital (50 mg BID). Confusion and left hemineglect improved within 48 hours of ictus, but left hemiparesis persisted. At this time point, tumor recurrence was contemplated as the most likely diagnosis. Rehabilitation therapy was started on the third day of hospitalization. Three weeks later, the hemiparesis improved substantially (MRC grade 4/5), and she was fully alert and oriented and her left hemineglect had completely resolved. Repeat brain MRI at 3 months after the index event showed complete resolution of gadolinium enhancement without any evidence of tumor recurrence (figure, F).

Question for consideration:

1. What is your differential diagnosis at this time point?

DISCUSSION The patient fulfilled the clinical and neuroimaging criteria of stroke-like migraine attacks after radiation therapy (SMART syndrome),¹ which should always be considered in the differential diagnosis of headache and transient episodes of neurologic dysfunction in patients with a history of radiation therapy.¹⁻⁵ More specifically, our patient had a remote history of external beam cranial irradiation (criterion A),¹ and had prolonged reversible neurologic manifestations (hemiparesis, hemineglect, confusion) referable to a unilateral cortical region that were accompanied by headache (criterion B).¹ Brain MRI showed transient diffuse unilateral cortical gadolinium enhance-

ment of the cerebral gyri sparing the white matter within a previous radiation field (criterion C).¹ Finally, our diagnostic evaluation in combination with the patient's history excluded other causes of transient neurologic dysfunction accompanied by reversible brain imaging abnormalities including posterior reversible encephalopathy, status epilepticus, meningoencephalitis, CNS vasculitis, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (criterion D).¹

The present case highlights the importance of diagnosing SMART syndrome promptly in patients with a remote history of brain radiation therapy presenting with reversible episodes of neurologic dysfunction associated with migraine attacks and transient gyral enhancement on brain MRI. A high level of clinical suspicion is required by the treating physician to make a swift diagnosis of this syndrome and avoid extensive diagnostic evaluations as well as multiple interventions.^{1,2} Moreover, rapid recognition of SMART syndrome can reassure the patients that their symptoms will eventually resolve and are not related to tumor recurrence.

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MYSTERY CASE RESPONSES

The *Neurology*[®] Resident & Fellow Section invited residency programs, medical student preceptors, and individuals to utilize this Mystery Case as an educational tool to develop trainees' clinical reasoning skills. The responses were solicited through group e-mail and, for the first time, through social media including Facebook[®] and Twitter[®]. Groups or individuals read the case presentation, developed their own differential diagnoses, and determined what diagnostic testing should be performed.

We had 23 responses to this Mystery Case, 3 of which were submitted via social media. All submis-

sions were from individuals. All were well-reasoned and thoughtful and many were detailed, including extensive discussions of the differential and possible testing and treatment options.

All respondents considered the patient's previous radiation exposure and headache history. The most common diagnosis proposed was sporadic hemiplegic migraine. Seven respondents included the correct diagnosis of SMART syndrome. Additional considerations, in descending order of the number of times cited, included TIA; stroke; seizure; headache with neurologic deficits and CSF lymphocytosis syndrome; subacute sclerosing panencephalitis; acute disseminated encephal-

lomyelitis; lymphoma; vasculitis; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; recurrent tumor; and radiation-induced necrosis.

The most frequently recommended diagnostic tests were EEG and lumbar puncture. The other recommendations in descending order of the number of times they were cited included magnetic resonance angiogram, traditional angiogram, brain biopsy, FDG-PET, magnetic resonance spectroscopy, and lactate level.

This is the second Mystery Case published in the Resident & Fellow section of *Neurology*[®]. This is the

first to use social media outlets to solicit responses; the majority of responses were submitted by electronic mail but it is unclear how many respondents were made aware of the case due to Facebook[®] or Twitter[®]. This interesting case demonstrates the importance of a thorough knowledge of the complications of radiation therapy in order to avoid unnecessary and potentially harmful testing or treatments.

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