RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Clinical Reasoning: A 68-year-old man with a history of lung cancer presenting with right-sided weakness and aphasia

Anoopum Gupta, MD, PhD
Mark R. Etherton, MD, PhD
Kathleen McKee, MD
Jessica M. Baker, MD
Saef Izzy, MD
Steven K. Feske, MD

Correspondence to Dr. Etherton: metherton@partners.org

SECTION 1

A 68-year-old man with paroxysmal atrial fibrillation on warfarin, left subclavian thrombosis treated with carotid-subclavian bypass, and lung adenocarcinoma treated with pneumonectomy, chemotherapy, and prophylactic cranial irradiation and in remission since 1987 was admitted to our neurocritical care unit with acute onset of right-sided weakness, expressive aphasia, and lethargy. On admission his temperature was 101.7°F, and initial blood pressure was 140/60 mm Hg. There was no nuchal rigidity. He was alert and mute with impaired comprehension. He had left gaze preference. Vision was impaired in the right field. There was weakness of the right lower face. Strength was full on the left side, the right arm was weak with only antigravity movement, and he withdrew the right leg to painful stimuli. Babinski sign was present on the right.

He had been in his usual state of health. His family members denied recent infection, trauma, headaches, neck stiffness, or seizure. There was no history of significant travel.

Questions for consideration:

1. What is the expected localization of the lesion?
2. What is the differential diagnosis at this time?
3. What diagnostic tests or additional history would be the most helpful?

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From the Department of Neurology (A.G., M.R.E., K.M., J.M.B., S.I.), Massachusetts General Hospital and Harvard Medical School; and Department of Neurology (A.G., M.R.E., K.M., J.M.B., S.I., S.K.F.), Brigham and Women's Hospital, Boston, MA.

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SECTION 2

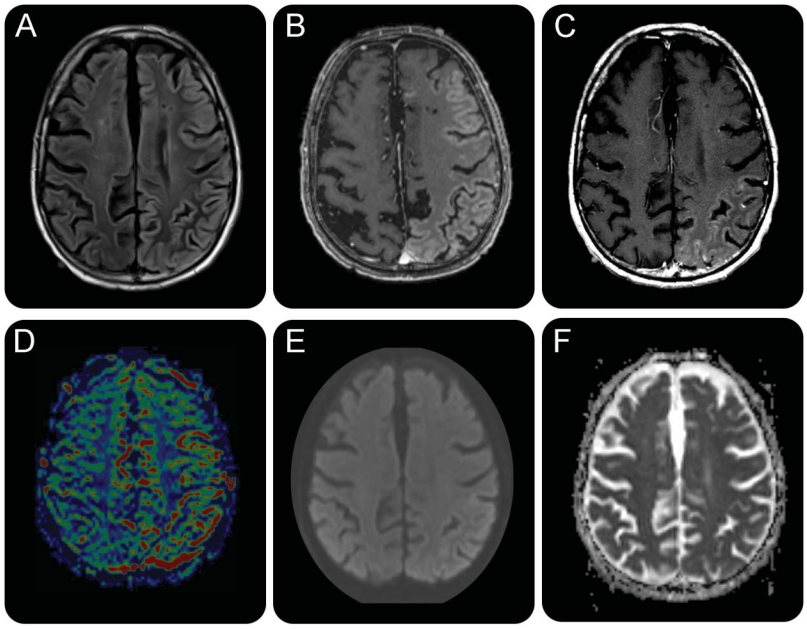
The neurologic examination showed right spastic hemiparesis affecting the face and arm more than the leg with a Babinski sign, paresis of rightward gaze, right homonymous hemianopsia, and global aphasia. These findings suggest a lesion affecting a large portion of the cortex of the left middle cerebral artery (MCA) territory, including the motor cortex in the precentral gyrus, the frontal eye fields in the prefrontal cortex, the anterior and posterior language areas, and the visual cortex or radiations. The differential diagnosis included left MCA territory ischemic stroke; seizures with postictal paralysis; a focal mass lesion such as a hemorrhage, tumor, or brain abscess; demyelinating disease (e.g., acute disseminated encephalomyelitis); inflammatory process (e.g., paraneoplastic encephalitis); complex migraine; and posterior reversible encephalopathy syndrome (PRES). The rapidity of symptom onset makes entities such as ischemic or hemorrhagic stroke, seizures, or PRES much more likely than an expanding mass lesion or demyelinating process. To investigate these possibilities, a head CT should be obtained urgently to rule out hemorrhagic infarct followed by a brain MRI with contrast to further evaluate the brain parenchyma.

Admission laboratory studies were remarkable for an international normalized ratio of 1.6 and normal serum white blood cell count. Initial MRI and magnetic resonance angiography of the head and neck on the day of admission showed no evidence of stroke or ischemia and no abnormal enhancement on postcontrast sequences. The left subclavian bypass was patent. A second brain MRI with perfusion sequence was performed on hospital day 2 and revealed an extensive new region of gyral cortical enhancement within the left temporal, parietal, and occipital lobes with increased cerebral blood flow on perfusion maps (figure). Given the absence of an acute stroke, we pursued EEG, lumbar puncture, and further imaging to investigate the other possibilities raised in our differential diagnosis.

Continuous video EEG for more than 72 hours showed left-sided slowing and brief right-sided lateralized periodic discharges but no seizure activity. CSF studies showed an elevated total protein (82.5 mg/dL), normal glucose, and no white blood cells. CSF cultures were negative, and cytologic examination showed no malignant cells. PET showed no evidence of cancer recurrence systemically or intracranially. Chest x-ray revealed pneumonia, for which he was started on antibiotics.

Further history revealed that approximately 15 years prior to the current presentation the patient had experienced similar transient symptoms of right-sided weakness and mutism during which a brain MRI showed gyral edema and enhancement in the left MCA and posterior cerebral artery territories. Extended EEG monitoring showed only left-greater-than-right–sided slowing in the theta and delta ranges. A repeat brain MRI performed several months later showed resolution of the gyral enhancement, at which point his symptoms had also resolved.

Figure **Abnormal left hemisphere gyral edema and increased perfusion**



MRI sequences showing regions of new gyral edema and enhancement within the left temporal, parietal, and occipital lobes on fluid-attenuated inversion recovery (A), magnetization-prepared rapid gradient-echo (B), and T1 postcontrast (C). There is also asymmetric increased cerebral blood volume along the left cerebral convexity compared with the right on the perfusion maps (D). There is no restricted diffusion on diffusion-weighted imaging and apparent diffusion coefficient maps (E, F).

Question for consideration:

1. What is the final diagnosis?

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SECTION 3

The patient's illness was attributed to SMART (stroke-like migraine attacks after radiation therapy) syndrome, a rare delayed complication of cerebral irradiation that has been reported in small case reports over the last 20 years.[1] Proposed diagnostic criteria include (1) remote history of cranial irradiation without evidence of recurrent neoplasm, (2) prolonged reversible focal neurologic deficits (e.g., hemiparesis, aphasia, seizures), and (3) transient unilateral cortical gyral enhancement sparing the white matter in the field of previous radiation.[2] Our patient presented with sudden onset of recurrent focal neurologic deficits of unilateral weakness and aphasia without the typical headache or seizure that is often, but not always, present at the onset of SMART syndrome, thus raising concern for acute stroke. However, the characteristic unilateral gyriform enhancement and lack of restricted diffusion on MRI after 2 days clearly differentiate these 2 entities. EEG monitoring eliminated ongoing seizures as a possible cause of his presentation. CSF showed no evidence of CNS infection, and an alternative source of fever (pneumonia) was identified. Although imaging findings in PRES are variable, PRES typically affects white matter more than gray matter and rarely shows more than scant enhancement; strictly unilateral findings would be uncommon. Postcontrast brain MRI and PET showed no evidence of recurrent malignancy.

Question for consideration:

1. How would you treat this patient?

Treatment of SMART syndrome is supportive with seizure and blood pressure control. Corticosteroids have been used for acute treatment, but there is no clear evidence of benefit.[3] Aspirin and verapamil have also been suggested for possible reduction in the frequency and severity of recurrent episodes, but strong evidence is lacking.[4] Our patient was managed with aggressive blood pressure control and antiepileptic therapy. Four days into his hospital course, he developed left-sided seizures characterized by evolving fast activity (15 Hz) associated with right-sided motor seizures (twitching of the face, arm, and leg), and antiepileptic agents were augmented. Seizures eventually resolved, and his mental status, aphasia, and right-sided weakness gradually improved to near baseline over his 12-day intensive care unit stay, consistent with the described course of SMART syndrome.

DISCUSSION There is remarkable heterogeneity in the patients affected by SMART syndrome (pediatric and adult patients) and the time interval between radiation therapy and presentation (1–35 years, 20 years on average).[3,4] The initial presentation varies but may include seizure, headache, and focal neurologic deficits such as hemiparesis and aphasia.[3] Imaging is characteristic, usually demonstrating unilateral gyriform enhancement on MRI after 2–7 days. The imaging findings tend to resolve with neurologic recovery,[5,6] which typically occurs gradually over a period of 2–5 weeks.[3] However, most patients will have recurrent events,[4] and 45% of patients have incomplete neurologic recovery.[3]

The pathophysiology of SMART syndrome is unknown. It has been proposed that the syndrome results from radiation-induced vasculopathy with endothelial injury and edema comparable to PRES; however, the predilection for the cortex is very different from PRES.[1,6] One study reported fluorodeoxyglucose PET imaging in 3 patients showing intense hypermetabolism in symptomatic regions that resolved on follow-up imaging.[5] Other hypotheses suggest that postradiation neuronal dysfunction, damage to the trigeminovascular system, migraine-like spreading depression, and ictal hyperperfusion may be contributors to the mechanism underlying SMART syndrome.[7] Alternatively, some have postulated that metabolic or mitochondrial dysfunction may contribute to the pathogenesis of SMART syndrome, given the similarity in the symptomatology of stroke-like episodes and transient cortically based MRI changes seen in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes).[4]

The current case highlights some of the previously described characteristics of SMART syndrome while demonstrating some of the challenges in diagnosis and treatment. Our patient presented with focal neurologic deficits of unilateral weakness and aphasia without the typical headache or seizure that is usually present at onset. His initial presentation was quite concerning for acute stroke, and the surprising absence of diffusion restriction on MRI led us to broaden our differential diagnosis. Unilateral gyriform enhancement became apparent on the second hospital day. Because of our patient's prior carotid-subclavian bypass and concern for blood pressure–dependent perfusion, magnetic resonance perfusion sequences were obtained and revealed increased perfusion in the same distribution as the gyriform enhancement (figure, D). This is consistent with magnetic resonance perfusion studies showing hyperperfusion in the area of MRI abnormalities during the acute phase of SMART syndrome, with subsequent hypoperfusion once symptoms have resolved.[7,8] Consistent with these findings, transcranial Doppler ultrasound of the bilateral MCAs showed that measures of dynamic cerebral autoregulation, phase, and coherence were significantly impaired in the left MCA. Dynamic cerebral autoregulation was assessed using transfer function analysis of the relationship between spontaneous oscillations in mean arterial pressure and flow velocity in the MCA. The phase shift measures the time lag between the 2 oscillating signals;

decreased phase shift suggests temporal synchrony of the oscillations due to impaired autoregulation.[9] Coherence indicates how linearly the fluctuations in pressure are transmitted to cerebral circulation; higher coherence suggests less effective autoregulation. These dynamic findings lend support to vascular autoregulatory dysfunction underlying SMART syndrome.

SMART syndrome represents a rare but serious delayed complication of cerebral irradiation. As this case illustrates, it should be considered in the differential diagnosis of any patient with a history of prior brain irradiation and abrupt onset of cortical symptoms suggestive of stroke or seizure in whom initial imaging is uninformative.

AUTHOR CONTRIBUTIONS

A.G., M.R.E., K.M., J.M.B., S.I., and S.K.F. were involved in project conceptualization, manuscript drafting and revision, and figure design and layout.

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DISCLOSURE

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