

The Syndrome of Stroke-like Migraine Attacks After Radiation Therapy Associated With Prolonged Unresponsiveness in an Adult Patient

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Introduction: The syndrome of stroke-like migraine attacks after radiation therapy (SMART) is an extremely rare complication of cerebral irradiation. It is characterized by reversible episodic neurological dysfunction, commonly associated with headaches and occasionally with seizures, occurring years after cranial radiotherapy. Approximately a dozen cases have been reported in adult patients to date.

Case Report: In 1997, a 48-year-old man underwent resection of a right cerebellar metastasis from renal cell carcinoma, followed by whole-brain irradiation. Two years later he began experiencing recurrent episodes of headache associated with reversible left hemiparesis, dysphasia, visual field defects, and confusion. Over subsequent years these episodes increased in frequency, and in 2009 and 2010 the patient experienced 2 episodes associated with seizures and characterized by severe depression in level of consciousness (GCS 5); the latter of these was particularly prolonged, with neurological recovery requiring almost 6 months. Cortical and leptomeningeal gadolinium enhancement was demonstrated on magnetic resonance imaging during the second episode. Repeated electroencephalography studies did not demonstrate any epileptiform activity, and extensive workup including brain biopsy failed to identify any neoplastic, vascular, or infective pathology. The diagnosis of SMART syndrome was therefore made.

Conclusions: Reduced level of consciousness of such severity and duration as observed here has not previously been described in SMART syndrome. This report, however, suggests that an excellent prognosis can be expected even in cases of prolonged unresponsiveness. The pathogenic mechanisms of SMART syndrome remain unclear, but may involve pathways common to both migraine and epilepsy.

Key Words: SMART syndrome, cranial irradiation, reversible neurological deficits, migraine, epilepsy

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As a result of improved survival of patients with brain malignancies, delayed effects of cerebral radiation are increasingly being encountered. Most commonly such complications involve focal necrosis and progressive leukoencephalopathy, typically presenting as a progressive decline in

cognitive and neurological function. In 1995, Shuper and Packer¹ first described an unusual episodic pattern of reversible neurological deficits in children with a past history of cerebral irradiation—now known as the syndrome of stroke-like migraine attacks after radiation therapy (SMART). We report an unusual case of this extremely rare condition occurring in an adult patient.

CASE HISTORY

A 62-year-old man presented in July 2010 to our department with severe headache and symptoms of unilateral hemisphere dysfunction. His past medical history was significant for renal cell carcinoma with a solitary right cerebellar metastasis diagnosed in 1996. This was treated with right radical nephrectomy and resection of the cerebellar metastasis, followed by whole-brain irradiation (5040 cGy) completed in 1997. His personal and family histories were negative for seizure disorder or migraine.

In 1999 he began experiencing brief episodes of right-sided headache, which were often associated with neurological dysfunction characterized by left facial droop, left arm weakness and numbness, left visual field defect, dysphasia, and confusion. The episodes typically lasted between 2 hours and 2 days, followed by complete resolution of the symptoms. Initially he would experience these spells about once a year, but they gradually increased in severity and frequency, occurring once or twice a month in 2008. Magnetic resonance imaging (MRI) in 2003 demonstrated widespread white matter changes consistent with radiation-induced damage, but no gadolinium enhancement or other abnormalities were detected.

In March 2009 he was admitted with acute onset headache and left hemiparesis, left-sided neglect, dysphasia, and confusion. Over the course of several hours he became unresponsive and remained so for several days. During this admission 2 brief seizures were observed; an electroencephalogram (EEG) revealed generalized slowing with no epileptiform discharges, although the study was performed interictally and epileptic spells therefore could not be excluded. MRI demonstrated progression of the previously reported white matter changes, as well as a neuroepithelial cyst in the left temporal area and a cluster of cystic areas along the right occipital horn; all of these findings were again consistent with radiation-induced damage. Gadolinium study was not performed at this time because of the presence of renal failure. His blood results were unremarkable and cerebrospinal fluid (CSF) studies showed a normal cell count and chemistry, and negative Gram stain, viral panel, and cultures. Paraneoplastic screen, including tests for anti-amphiphysin, PNMA2 (Ma2/Ta), CV 2.1, Ri, Recoverin, SOX1, Titin, Yo, and Hu antibodies, was negative. Diagnosis of a likely prolonged postictal state was made and the patient was started on phenytoin. His neurological function recovered completely within 5 weeks.

In July 2010 the patient was admitted again after awakening with a severe headache and neurological deficits similar to those during the previous presentation. Over the subsequent 48 hours he became unresponsive (GCS 5), with dense left hemiparesis. A number of focal seizures were observed, with interictal EEG again showing right hemispheric slowing with no epileptiform activity. Blood tests and CSF studies were also unremarkable. Because of the severely impaired

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level of consciousness the patient was at risk for aspiration and required intubation and intensive care unit admission.

MRI performed during weeks 1, 4, and 7 of his hospitalization demonstrated a localized area of contrast enhancement in the right parieto-occipital region, thought to be consistent with a combined cortical and leptomeningeal pattern (Fig. 1). The radiation-induced findings remained unchanged from previous scans.

Given the presence of contrast enhancement, we considered the possibility of tumor recurrence and proceeded to biopsy of the enhancing lesion. This, however, revealed no evidence of neoplasia, but demonstrated the presence of small areas of necrosis with abundant macrophages, and mild to moderate gliotic changes in the surrounding tissues. Prominent perivascular reactive cell infiltrates, consisting chiefly of lymphocytes, were also seen. The biopsy findings were consistent with a recent reactive process, etiology of which could not be determined.

Given the history of seizures, the patient's condition was again initially ascribed to a prolonged postictal state and treatment with levetiracetam and clobazam was started. He remained unresponsive for 4 weeks, after which his neurological function began to recover at an extremely slow pace, returning to near-baseline over the following several months. On discharge 6 months after admission he was alert and orientated, showing only mild (MRC 5-/5) weakness of distal left arm and proximal left leg, and a mild left facial droop.

After discharge the patient continued to suffer from frequent brief episodes, occurring almost every other day, characterized by headache, confusion, dysphasia, and left hemiparesis. Notably, initiation of treatment with verapamil led to a marked reduction in their frequency, with the patient experiencing a spell once every 2 months. He remained on levetiracetam and clobazam and no further seizure-like episodes were seen until a recent readmission in August 2012 with aspiration pneumonia, during which several seizures were observed, in association with a generalized exacerbation of his episodic neurological dysfunction. He has remained stable since discharge the following month.

DISCUSSION

The case presented is characterized by recurrent episodes of headache with reversible neurological dysfunction of variable duration and severity, associated on some occasions with seizures, and occurring several years after whole-brain radiation therapy. Given the episodic nature of the deficits and the history of witnessed seizures, the differential diagnosis was suspicious for an underlying prolonged postictal state. Indeed, the unrevealing interictal EEG could not exclude an underlying seizure disorder. However, the seizures invariably occurred

well after the onset of the neurological deficits, and thus appeared to represent a component of a symptom complex rather than a primary abnormality. The possibility of an underlying migraine diagnosis was also thought unlikely because of the prolonged duration of some of the episodes, as well as the lack of any personal or family history of migraine.

MRI revealed findings consistent with prior surgery and cranial irradiation. However, these stable abnormalities could not account for the episodic nature of the patient's symptoms. The clinical presentation, in the setting of cortical and leptomeningeal gadolinium enhancement on MRI during the most severe episode, was suspicious for a neoplastic process; tumor recurrence was, however, excluded by brain biopsy. Other possible causes of the abnormal enhancement, such as ischemia, vascular malformations, or infective process were also ruled out by extensive workup including CSF studies, diffusion and perfusion-weighted MRI, and histologic analysis.

The findings were therefore consistent with the diagnosis of SMART syndrome. This condition has been defined clinically as transient and reversible neurological dysfunction (including hemispheric deficits, migrainous headache, and seizures) occurring years after whole-brain radiation therapy.^{2,3} Around 25 cases have been reported to date, with less than a half occurring in adult patients. Duration of the episodes has been reported to range from several hours to 6 weeks.⁴⁻⁶ Whereas most of the episodes experienced by our patient resolved within 48 hours, one of the events was of a duration far exceeding any of the previously documented cases. Another unique feature of the clinical presentation was the severity of mental status impairment in 2 of the episodes; although confusion has previously been described as a feature of SMART syndrome,^{2,7} depression in the level of consciousness of such degree as to require prolonged intubation has not previously been reported.

MRI findings of focal gyral thickening and transient cortical gadolinium enhancement represent commonly observed features of SMART syndrome, and have been included in various proposed diagnostic criteria.^{1,2,4} It should, however, be noted that no gyriform enhancement or thickening was seen in 2 of the previously published cases.⁵ The imaging abnormalities seen during the major episode in our case were also less striking than those seen in many of the previous



FIGURE 1. Transverse (A), sagittal (B), and coronal (C) sections of magnetic resonance imaging T1 sequence with gadolinium, taken 1 week after onset of the episode. Areas of localized cortical and leptomeningeal enhancement are seen, most prominent in the right superior parietal region. Also note postoperative changes in the posterior fossa from previous resection of right cerebellar metastasis. Multiple cystic lesions, most likely neuroepithelial cysts, are seen in relation to the ventricles.

reports, consisting essentially of a localized, mixed-pattern contrast enhancement. These observations suggest that florid radiologic abnormalities may not always be present, and should therefore not be seen as a necessary diagnostic criterion of SMART syndrome.

The pathophysiology of SMART syndrome remains poorly understood. Delayed adverse effects of cerebral radiotherapy include focal necrosis as well as diffuse-pattern white matter changes,⁸ with the proposed underlying mechanism including endothelial injury and demyelination.^{9,10} These effects are gradual in onset, with a stable or slowly progressive course, and are thus distinct from the mechanisms involved in SMART syndrome. It has been suggested that the cortical thickening noted on MRI may occur as a result of disruption to the blood-brain barrier (BBB), causing cortical edema in a process of vasculopathy similar to that seen in posterior reversible encephalopathy syndrome.⁶ However, given the existence of SMART syndrome cases without gyral thickening, it is possible that the cortical edema may be comparable to that observed in postictal states in patients with a past history of systemic chemotherapy;¹¹ rather than being part of the pathogenic mechanism itself, the cortical swelling may form as a result of seizure activity in an area of damage to the BBB through prior chemotherapy or radiotherapy. Similarly, the contrast enhancement seen in our case may represent a prolonged postictal hyperemia. The fact that the imaging changes described in SMART syndrome have in virtually all cases occurred in the posterior areas suggests that the BBB in these regions may be particularly susceptible.

The case of SMART syndrome presented here is the first to include histologic findings; gliosis and perivascular cell infiltrates were observed, indicative of a recent reactive process. Interestingly, the presence of gliosis and perivascular inflammatory infiltrates was also reported in acute reversible MRI lesions associated with focal seizures.¹² It was suggested that these changes may have occurred as a result of previous venous congestion. Although the cause of the histologic findings in this case could not be ascertained, the possibility of an occlusive vascular disorder cannot be excluded. This raises the question of whether such vasculopathic changes were seizure-induced, or whether they represent a primary pathophysiological mechanism.

Notably, however, a recent study on cerebrovascular reactivity found little evidence to support vascular pathology as the primary cause in SMART syndrome.¹³ Instead, a neuronal mechanism has been proposed^{6,13}; this may occur through the effects of radiation on the trigeminovascular system causing a reduced threshold to cortical spreading depression in a manner comparable to that described in migraine with stroke-like episodes.¹⁴ It may in fact be the case that the neuronal activation generated by cortical spreading depression leads to focally reduced threshold for epileptogenic activity, thus increasing the risk for seizures.¹⁵ Given that subacute venous congestion has previously been associated with seizures and focal reversible MRI changes,¹² it is possible that seizures in SMART syndrome may lead to postictal perfusion changes resulting in cortical edema in areas of previously damaged BBB. Intriguingly, the pathogenesis of SMART syndrome may thus involve mechanisms common to both migraine and epilepsy—conditions that are increasingly seen as overlapping in both clinical and pathophysiological aspects.¹⁶

In addition, the peculiar similarity of the clinical presentation seen in SMART syndrome to that commonly observed in MELAS syndrome raises the possibility of mitochondrial dysfunction as a pathogenic mechanism in this rare complication of cerebral

irradiation. Although investigation for mitochondrial abnormalities using MR spectroscopy was unrevealing in a previously reported case of SMART syndrome,¹³ interaction with mitochondrial DNA (mtDNA), both directly and through generation of reactive oxygen species, is in fact thought to play an important role in radiation-induced cellular damage.¹⁷ Given the relatively inefficient mtDNA repair mechanisms and the lack of adequate replication cycle check points in mitochondria, the mtDNA aberrations tend to progressively accumulate, and brains of gamma-irradiated mice have been found to exhibit increased mtDNA polyploidization.¹⁸ With ageing-related mtDNA damage compounding the radiation-induced alterations,^{19,20} it may be that an impairment of energy and calcium homeostasis with resultant neuronal dysfunction only occurs once a certain threshold of aberrant mtDNA accumulates; as such, the interval between neuronal dysfunction and the initial radiation insult would be in keeping with one of the hallmarks of SMART syndrome—its delayed onset, typically years after radiotherapy treatment.

Given the small number of cases reported to date, there is no clear consensus regarding effective treatment approaches to SMART syndrome. Anticonvulsant medications such as valproate, carbamazepine, and levetiracetam have been commonly used, with favorable outcomes particularly in cases in which the episodic neurological dysfunction is associated with seizures.^{2-5,7} Verapamil has been used in a minority of cases,^{1,2,4,7} with a reported reduction in headache severity and/or in frequency of episodes, consistent with our observation. One report described a patient with confusional episodes responding to treatment with short courses of corticosteroids.⁷ The role of other medications, including warfarin and aspirin, is of unclear benefit.^{1,4}

In conclusion, we present a case of SMART syndrome characterized by 2 particularly severe episodes with prolonged unresponsiveness. Virtually complete recovery of neurological function was observed, suggesting that an excellent prognosis can be expected even in patients with episodes exceeding several weeks in duration. Although SMART syndrome remains an extremely rare complication of cerebral irradiation, improvements in cancer survival rates will likely lead to a rise in its frequency. A high index of suspicion is important to make a rapid diagnosis of this syndrome and thus avoid unnecessary and potentially harmful invasive testing, as was the case here and in a number of previous reports.^{2,6,7}

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