Stroke-like migraine attacks after radiation therapy syndrome: a case report and literature review

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\textbf{Abstract}

Stroke-like migraine attacks after radiation therapy syndrome is a late complication of cranial radiation. It typically presents as reversible, unilateral cortical signs and symptoms such as confusion, hemiparesis, seizures, and headaches. Magnetic resonance imaging is also required for diagnosis, demonstrating cortical linear gadolinium enhancement. Typically, these magnetic resonance imaging findings resolve as patients experience partial or complete improvement in their symptoms and signs after a few weeks. Although a very rare condition, it is becoming increasingly observed as survival rates from brain tumors improve. In this report, we describe a typical case of stroke-like migraine attacks after radiation therapy syndrome and present a review of the literature.

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\section*{Introduction}

As the survival from brain tumors improves, complications of brain radiotherapy are being increasingly observed [1]. One of these consequences is stroke-like migraine attacks after radiation therapy (SMART) syndrome. SMART syndrome occurs as a late complication of cranial radiation [2]. It occurs with both focal and whole brain radiotherapy, and although the exact radiation dose is not known, most cases are reported to have received at least 50 Gy [2,3]. The pathophysiology of SMART syndrome is not known entirely, but multiple factors thought to contribute include radiation vasculopathy with endothelial dysfunction, neuronal injury as well as genetic and metabolic factors [2].

SMART syndrome typically manifests as reversible, unilateral cortical signs, and symptoms beginning years after cranial irradiation. Typically, these symptoms then partially or completely resolve in a few weeks [2]. According to the diagnostic criteria proposed by Bartleson et al, later revised by Black et al, symptoms can include visuospatial defect, confusion, hemiparesis, aphasia, seizures, and headaches. A previous history of cranial radiation is also necessary for diagnosis. SMART syndrome is a diagnosis of exclusion, and thus other causes such as tumor recurrence must be ruled out.
Magnetic resonance imaging (MRI) demonstrating cortical linear gadolinium enhancement is required for diagnosis. SMART syndrome is a very rare condition, with 42 documented cases reported by a 2015 review [6].

Case report

A 63-year-old retired truck driver presented with a 1-week history of dysphasia, headache, and right-sided sensory symptoms. This was on a background of a low grade temporoparietal astrocytoma, diagnosed 11 years prior, and having received radiotherapy 9 years beforehand (with a total radiation dose of 52.2 Gy over the course of 6 weeks). Recent follow-up MRI had demonstrated a left greater than right radiation leukoencephalopathy and some residual low-grade tumor. He had been diagnosed with complex partial seizures some years prior and commenced on lamotrigine. Compliance had been erratic in the week before admission.

Examination demonstrated a predominantly receptive dysphasia and a right inferior quadrantanopia. Computed tomography and computed tomography angiogram demonstrated no new abnormalities. He was diagnosed initially with migraine with aura. He deteriorated over several days developing a complete hemianopia, dense hemiplegia, and worsening dysphasia headache and drowsiness. A clinical diagnosis of SMART syndrome was made.

An MRI was obtained and T1-weighted imaging postgadolinium administration showed new cortical enhancement peripheral to the known temporoparietal tumor, with subtle cortical enhancement extending into the left occipital lobe (Fig. 1). Subtle linear cortical restricted diffusion was also seen in areas of contrast enhancement (Fig. 2). He subsequently developed treatment refractory complex partial status epilepticus, requiring additional clobazam, intravenous levetiracetam, valproate, and eventually midazolam infusion. An electroencephalogram demonstrated left-sided periodic lateralizing epileptiform discharges.

Follow-up MRI 3 weeks later demonstrated resolution of the restricted diffusion and cortical enhancement, confirming diagnosis of SMART syndrome. Tumor size was stable throughout this period, suggesting that tumor progression was not responsible for the patient’s presentation (Fig. 3). To date there has been clinical improvement but incomplete resolution, and the patient was discharged after 7 weeks for ongoing rehabilitation.

Discussion

This report demonstrates a case of a rare, but increasingly described condition. This patient presented with the hallmark features of SMART syndrome. He had received a relatively high dose of cranial radiation years earlier and presented with slowly evolving hemispheric migraine-like symptoms. MRI findings of unilateral cortical enhancement in the parietooccipital region were consistent previous reports, and resolution of MRI findings mirrored improvement in the patient’s clinical condition. MRI findings and the clinical syndrome evolved before the development of status epilepticus.

SMART syndrome is a diagnosis of exclusion. The clinical and radiological features most closely mimic mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes and status epilepticus with “Todd’s paresis.” Other
important clinical and radiological differential diagnoses include tumor recurrence, familial or sporadic hemiplegic migraine, posterior reversible encephalopathy syndrome, cerebral vasculitis, cerebral amyloid-associated inflammation, infective or immune-mediated meningoencephalitis, and headache neurological deficits and lymphocytosis syndrome [2,6]. Routine blood tests such as complete blood count, electrolytes, urea and creatinine, and immunological testing are usually normal. Cerebrospinal fluid (CSF) testing is usually normal or may demonstrate a mild CSF pleocytosis with elevated CSF protein [6]. Electroencephalogram may demonstrate slowing or epileptiform features. A migraine-like headache is common, but not universal.

The typical MRI findings of SMART syndrome are a transient, diffuse, unilateral cortical grey matter thickening with white-matter sparing enhancement on T1-weighted sequences postgadolinium. Usually, it affects the temporoparietooccipital regions, suggesting these areas may be more vulnerable to radiation than others [2]. Some authors have also suggested restricted diffusion to be present in SMART syndrome, whereas others have reported minimal or absent diffusion-weighted changes [5,7]. MRI findings usually resolve as the patient’s clinical condition improves [8].

There is no clear agreement as to the treatment of SMART syndrome. Anticonvulsants have been used in most cases, whether or not seizures have occurred clinically. In particular,
antiepileptics with known “migraine aura” prevention action may be useful, as cortical spreading depolarizations are a postulated mechanism [1,5,9]. For long-term prophylaxis of episodes of SMART syndrome, aspirin and verapamil have been used to good effect [3,4,10–12]. The efficacy of steroids has shown mixed results [5,13,14].

Although initially described as a temporary or reversible condition, a recent case series [5] demonstrated that reversibility is not universal, with nearly half of cases showed incomplete resolution. Recurrence was also common, with 55% of patients experiencing recurrent symptoms [5]. In our case, the patient required rehabilitation because of ongoing neurological deficits. Furthermore, there have been reports of irreversible neurological deficits in a number of patients [1,5]. In these patients, MRI findings may include cortical laminar necrosis or ischemia. In one case, marked atrophy in the temporoparietal lobe was observed in a patient with residual neurological deficits [8].

This report demonstrates a typical case of SMART syndrome. SMART syndrome should be considered as a cause for cortical symptoms with corresponding enhancement on MRI when other differential diagnoses have been excluded. Clinicians should be able to recognize the features of SMART syndrome as a timely diagnosis can avoid unnecessary testing and alleviate patient anxiety. Although a rare condition, it is becoming an increasingly recognized clinical entity because of increased survival from brain tumors.

Acknowledgement

The authors would like to thank Dr Michael Wilks for his assistance with the MRI interpretation of the case.

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