



## Brief Communications

### SMART – Not Always Only “Stroke-Like”

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Stroke-like migraine attacks after radiation therapy (SMART) is a syndrome observed in a delayed fashion in patients following brain radiation therapy. It is a rare but important differential diagnosis of migraine in these patients, often presenting with migraine-like headache. In addition, there may be focal neurological deficits or seizures. In general, it is regarded as a reversible condition, therefore termed stroke-like. Our case illustrates that there may also be ischemic stroke associated with SMART leading to an unfavorable course, even after prior remission.

**Key words:** SMART, stroke, migraine, seizure, MRI, radiation

**Abbreviations:** DWI diffusion-weighted imaging; MRI magnetic resonance imaging; SMART stroke-like migraine attacks after radiation therapy

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#### INTRODUCTION

Stroke-like migraine attacks after radiation therapy (SMART) is a syndrome observed following a long latency period in patients with a history of prior brain radiation therapy.<sup>1-6</sup> It is a rare but important differential diagnosis of migraine in these patients, often presenting with headache, focal deficits, or seizures. In general, it is regarded as a reversible condition.<sup>1,2</sup> However, there may be recurrence of symptoms<sup>3,7</sup> and, as our case illustrates, there may also be ischemic stroke related to SMART and the clinical course is not necessarily benign.

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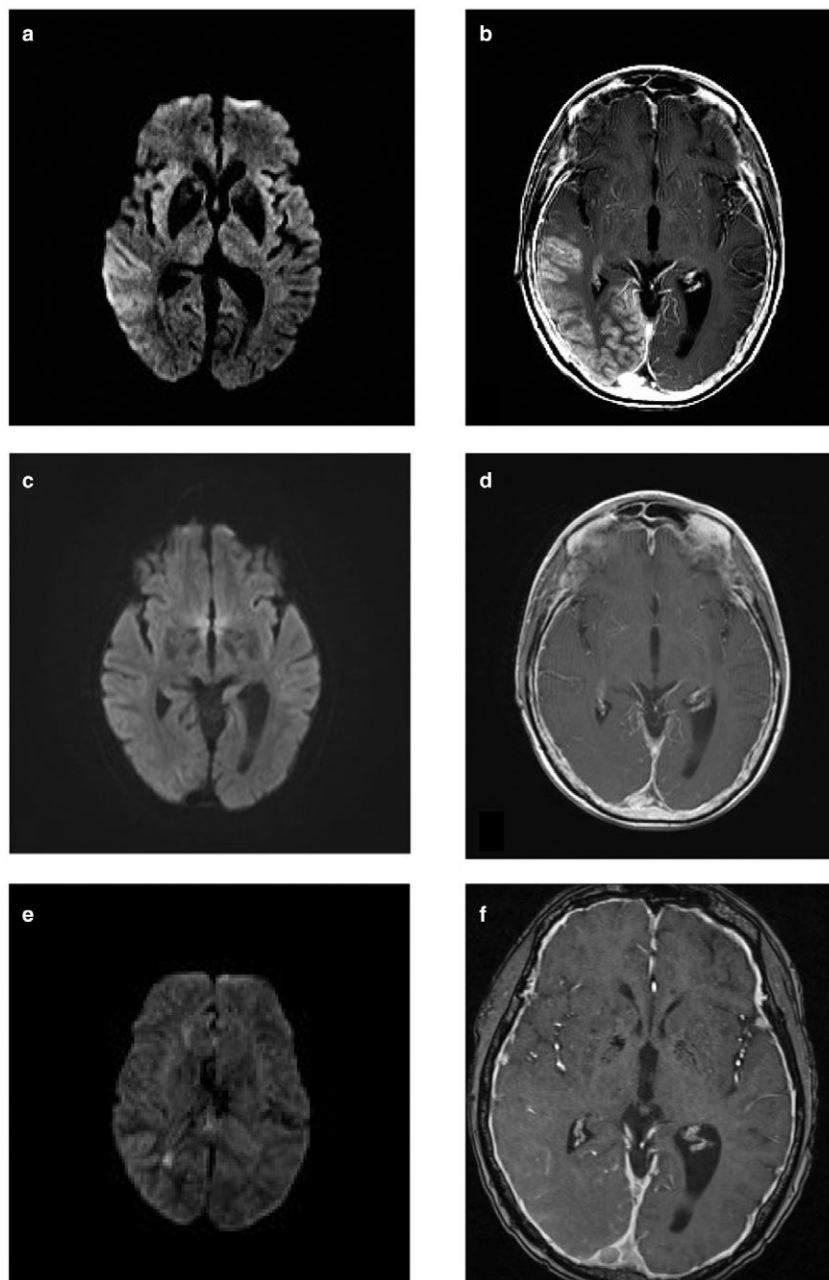
#### CASE PRESENTATION

A 45-year-old female patient treated with radiation of the whole neuro-axis for medulloblastoma 30 years ago presented with new onset migraine-like headache and behavioral changes as well as deterioration of a preexisting residual gait ataxia as a consequence of the cerebellar tumor. Within the prior 6 months to 1 year, similar episodes with less severe headache had occurred; all resolved spontaneously and had led to a diagnosis of migraine with aura at a different institution.

At the time of current presentation in our hospital, cranial magnetic resonance imaging (MRI) showed right temporo-parietal hyperintense cortical swelling with concomitant diffusion restriction on diffusion-weighted imaging (DWI, Fig. 1a) and extensive gyriform cortical contrast enhancement (Fig. 1b). These alterations had not been observed in previous MR imaging performed for routine tumor follow-up.

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*Conflict of Interest:* None.



**Fig. 1.**—Serial MRIs (DWI/T1-contrast-enhanced) in SMART: at initial presentation, there is diffusion restriction on DWI (a) as well as extensive gyriform cortical contrast enhancement on contrast-enhanced T1 images (b), characteristic of SMART. At follow-up after 5 weeks, these changes had completely resolved, with no residual diffusion restriction or gyriform contrast enhancement (c,d). Six months later, the patient presented with new focal seizures, now a circumscribed area of diffusion restriction on DWI indicating a small subacute ischemic infarction (e) within the region previously affected by the SMART-related changes; this time, only subtle cortical contrast enhancement was observed (f).

Time-of-flight (TOF)-MR angiography was unremarkable, without any focal narrowing of the intracranial vessels. In particular, there were no signs of radiation-induced vasculopathy or post-radiation Moya-Moya phenomenon. Additionally, contrast-enhanced MRI did not indicate structural vascular pathology. Given the characteristic imaging findings and the

patient's history, a diagnosis of SMART syndrome was made.<sup>1-3</sup>

An extensive diagnostic work-up including EEG without detection of epileptic discharges, blood and CSF analyses, as well as chest and abdominal CT-imaging ruled out other differential diagnoses, especially tumor recurrence.

The clinical course over the following weeks was favorable with complete recovery to the patient's baseline status. Follow-up MRI obtained 5 weeks later showed complete resolution of the signal alterations, with no residual diffusion restriction or gyri-form contrast enhancement (Fig. 1c,d).

Approximately 6 months later, the patient again presented with migraine-like headache as well as with fluctuating alteration of consciousness and responsiveness, suggestive of epileptic seizures. Overall, these symptoms were present for approximately 2 weeks prior to admission, with aggravation over time. An EEG now showed epileptic discharges and repetitive seizure patterns. Therefore, antiepileptic treatment with levetiracetam, lacosamide, and initially midazolam was started.

In contrast to the first MRI, new brain MRI imaging showed only subtle right temporo-parietal contrast enhancement (Fig. 1f). However, on DWI, there was a circumscribed area of diffusion restriction, indicating a small subacute ischemic infarction of the parieto-occipital periventricular white matter on the right side, localized within the region previously affected by the SMART-related alterations (Fig. 1e). Besides SMART, the ischemia was considered as the potential trigger for the new onset seizures. In addition to antiepileptic treatment, secondary prevention with aspirin was started. Extensive diagnostic stroke work-up, including TOF-MRA of the intracranial vessels, extracranial arterial ultrasound as well as cardiac work-up, was otherwise unremarkable. After seizure control and concomitant clinical improvement, the patient was transferred to rehabilitation.

## DISCUSSION

SMART is a rare but important differential diagnosis of migraine, occurring up to decades after brain radiation.<sup>1-3</sup> Often, it presents with migraine-like episodes and is most frequently reversible, yet with possible recurrent clinical episodes, as in our case. In addition, there have been cases reported without complete clinical recovery.<sup>3</sup> Importantly, as our case illustrates, it may be associated with epileptic seizures as well as ischemic lesions, even after an initial clinical improvement. Overall, reports on ischemic stroke associated with SMART are scarce.<sup>3,8</sup>

In our case, the recurrent headache is most likely an expression of SMART itself. Epileptic seizures may be related to SMART and may be underdiagnosed in this condition.<sup>9</sup> On the one hand, in our case, the presence of ischemia could represent another source of seizure trigger, given the far less severe SMART-related imaging changes compared to the initial presentation, when no seizures had occurred. On the other hand, fluctuating levels of consciousness had been reported to have occurred during a period of 2 weeks prior to the second admission, thus most likely before the ischemia. During this second symptomatic episode, MR findings characteristic of SMART were not as striking as during the initial presentation. Therefore, it remains debatable whether this episode was related to SMART. However, again there was subtle cortical gyri-form cortical contrast enhancement (Fig. 1f), not observed in the last follow-up MRI (Fig. 1d). In addition, the ischemic lesion (Fig. 1e) was localized within the region of SMART-related changes. Finally, the clinical presentation again involved migraine-like headache during the second episode. Therefore, it is suggestive that the ischemia was related to vascular mechanisms underlying SMART.

To date, the pathophysiology of SMART as a consequence of remote brain radiation is incompletely understood and may include mechanisms such as cerebral hyperexcitability, impaired cerebral autoregulation, disturbance of endothelial function, and blood-brain barrier. Reversible hemispheric hypoperfusion has been reported in SMART.<sup>10</sup> Furthermore, given the frequent temporo-parieto-occipital localization of SMART and the possible radiation-induced endothelial damage, there may be underlying pathophysiological mechanisms of reversible functional vascular impairment comparable to those in the posterior reversible encephalopathy syndrome (PRES).<sup>11</sup> Vascular damage with impaired vasoreactivity may be a potential underlying mechanism of migrainous headache and stroke in these subjects. Therefore, besides antiepileptic therapy and standard secondary stroke prevention, treatment addressing cerebral vasoreactivity such as calcium antagonists may be considered.

Overall, an awareness of migraine-like headache due to SMART and its characteristic imaging findings, as illustrated in our case, is of importance, as it may avoid redundant diagnostic work-up in patients

with a history of brain radiation, especially invasive procedures such as brain biopsy to rule out tumor recurrence. In addition, our case of SMART-related stroke illustrates that the manifestation is not necessarily only “stroke-like,” even after an initial remission of symptoms and imaging findings.

## STATEMENT OF AUTHORSHIP

### Category 1

#### (a) Conception and Design

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#### (b) Acquisition of Data

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### Category 2

#### (a) Drafting the Manuscript

Vanessa Haller, Nils Peters

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### Category 3

#### (a) Final Approval of the Completed Manuscript

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