



# Atypical imaging findings of presumed stroke-like migraine attacks after radiation therapy syndrome in the brainstem

Yoshiaki Ota<sup>1</sup> · Denise Leung<sup>2</sup> · Toshio Moritani<sup>1</sup> · Aristides A. Capizzano<sup>1</sup>

Received: 25 January 2021 / Accepted: 1 March 2021

© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

## Abstract

The authors present an atypical case of presumed stroke-like migraine attacks after radiation therapy (SMART) syndrome in the brainstem. A 29-year-old male, who had been treated with resection and subsequent craniospinal radiation for posterior fossa medulloblastoma 21 years before, presented with subacute progressive left hemiparesis evolving over 4 days. Hematological findings, cerebrospinal fluid (CSF), and electroencephalogram (EEG) were unremarkable. Magnetic resonance imaging (MRI) showed a round area of hyperintense FLAIR signal centered within the pons associated with central restricted diffusion, peripheral enhancement, and small paramagnetic low susceptibility signal foci consistent with petechial hemorrhage. Positron emission tomography (PET), perfusion MRI, and MR spectroscopy revealed no evidence of tumor recurrence. The diagnosis of SMART syndrome is presumed from the conventional and advanced imaging findings, clinical history, and clinical course.

**Keywords** SMART syndrome · Brainstem · SWI · PET-CT · MRS · DSC MR perfusion

## Introduction

Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a rare delayed complication of whole brain irradiation, craniospinal irradiation, or selective radiosurgery. It has been reported that SMART syndrome occurs 10 years after initial radiation therapy or later and is accompanied with seizures or focal neurologic deficits in conjunction or not with migraine attacks [1–4]. Focal neurologic deficits are typically subacute in onset and may involve hemianopsia, hemiplegia, aphasia, facial drop, or visual loss. Symptoms resolve after weeks in many cases but can sometimes persist, with incomplete resolution [1, 2].

The characteristic MR imaging findings include reversible unilateral gyriform abnormal T2 and FLAIR signal with mass effect, and cortical enhancement reminiscent of subacute infarction, but not consistent with vascular distribution [2].

Other reported MRI features are cortical SWI blooming and leptomeningeal enhancement. In this article, we present a case with a novel imaging feature of SMART syndrome with pontine involvement.

## Case presentation

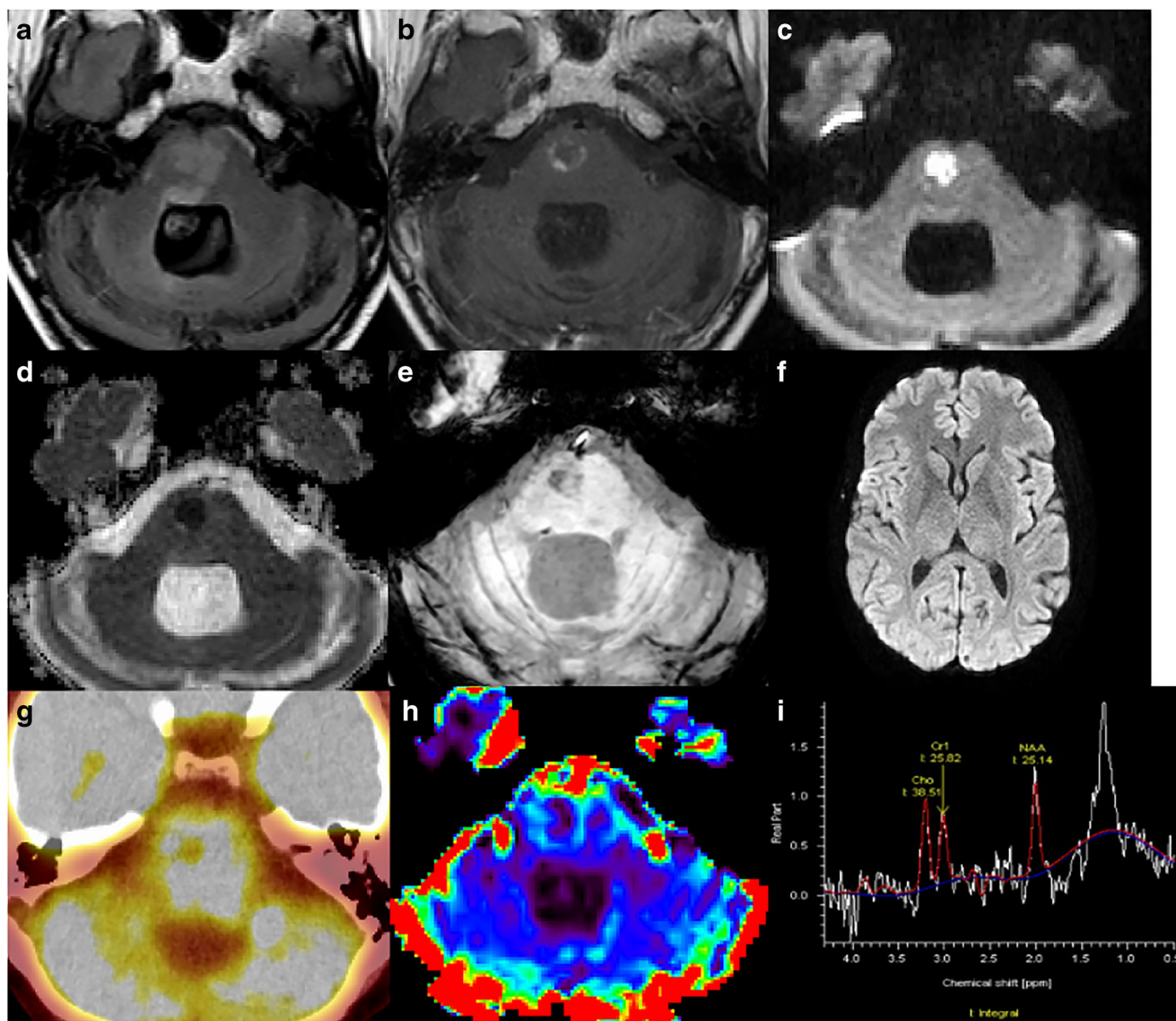
A 29-year-old male presented with subacute progressive left hemiparesis evolving over 4 days. He had a history of posterior fossa medulloblastoma that was resected and treated with craniospinal radiation with posterior fossa boost to 55.4 Gy and adjuvant chemotherapy with lomustine, cisplatin, and vincristine 21 years before. The patient did not have any episode of migraine. Hematological findings, cerebrospinal fluid (CSF) analysis, and electroencephalogram (EEG) were unremarkable. Myelin basic protein (MBP) was not assessed.

Brain MRI demonstrated a round area of hyperintense FLAIR signal centered within the pons associated with central restricted diffusion, peripheral enhancement, and small paramagnetic low susceptibility signal foci consistent with petechial hemorrhage (Fig. 1a–e). There was no abnormal DWI signal intensity at the level of the basal ganglia or hemispheric white matter (Fig. 1f). The lesion displayed a combination of central restricted diffusion consistent with cytotoxic edema outlined by rim contrast enhancement and surrounding

✉ Yoshiaki Ota  
yoshiako@med.umich.edu

<sup>1</sup> Division of Neuroradiology, Department of Radiology, University of Michigan, 1500 E Medical Center Dr, UH B2, Ann Arbor, MI 48109, USA

<sup>2</sup> Division of Neuro-oncology, Department of Neurology, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA



**Fig. 1** (a, b) MRI shows FLAIR hyperintense lesion associated with peripheral enhancement in the pons. (c, d) DWI and ADC map show restricted diffusion in the lesion. (e) Susceptibility-weighted image shows peripheral hypo-intensity. (f) DWI at the level of the basal ganglia shows no abnormal signal. (g) PET-CT shows low metabolic

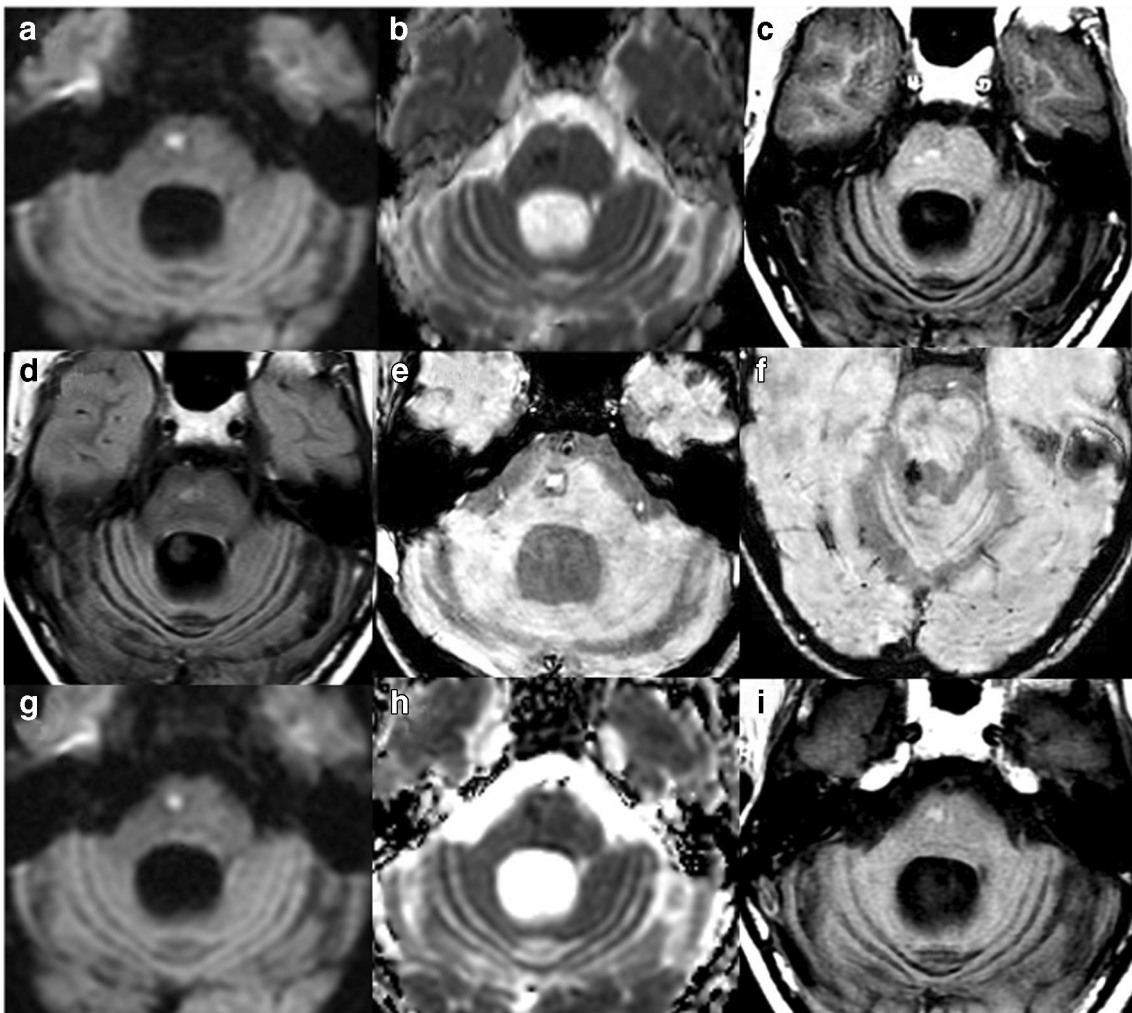
activity in the lesion. (h) rCBV shows slight increase in the peripheral area with low central value. (i) PRESS MR spectroscopy voxel of  $15 \times 15 \times 15 \text{ mm}^3$  is placed in the lesion, and spectral curve at TE 135 ms shows reduced NAA signal with no increased choline and large lipid peak

vasogenic edema. FDG-PET-CT showed reduced metabolic activity in the lesion, and no FDG avid lesions in the whole body (Fig. 1g). Dynamic susceptibility contrast (DSC) MR perfusion imaging showed slight increase of relative cerebral blood volume (rCBV) in the periphery of the lesion with centrally reduced value (Fig. 1h). MR spectroscopy revealed reduced N-acetyl-aspartate (NAA) signal, lack of choline signal increase, and lipid and lactate resonances consistent with anaerobic metabolism and necrosis (Fig. 1i).

After 5 days of 10 mg of dexamethasone, the left-sided weakness improved, and he was discharged. He was later treated with 4 doses of bevacizumab. At 13-month imaging follow-up, MRI demonstrated resolution of vasogenic edema,

almost complete resolution of enhancement with a residual small focus of T1 shortening with restricted DWI, associated with peripheral hypo-intensity on SWI which on phase image represented diamagnetic effect, likely from bevacizumab-related coagulation necrosis (Fig. 2a–e). There was another low signal focus on SWI at the right pontomesencephalic junction consistent with cavernoma, stable across multiple scans (Fig. 2f).

Clinical follow-up revealed substantial improvement in hemiparesis with physical therapy, although he was not fully back to baseline. At 20-month imaging follow-up, MRI showed a further smaller focus of T1 shortening and restricted diffusion (Fig. 2g–i).



**Fig. 2** Thirteen-month imaging follow-up of (a) DWI, (b) ADC map, (c) T1WI, and (d) FLAIR shows small residual restricted diffusion and resolved vasogenic edema. (e) SWI shows peripheral hypo-intensity, likely due to coagulation necrosis. (f) There was another low signal

focus on SWI at the right pontomesencephalic junction consistent with cavernoma. Twenty-month imaging follow-up of (g) DWI, (h) ADC, and (i) T1WI shows a smaller focus of T1 shortening and restricted diffusion in the central pons

## Discussion

SMART syndrome is a known rare, but benign radiation-induced complication. Diagnostic criteria include the following: (1) remote history of cranial radiation; (2) prolonged, reversible unilateral cortical signs and symptoms beginning years after radiation with manifestations including visuo-spatial deficit, confusion, hemiparesis, aphasia, seizures, and headaches with migraine attacks with or without aura; (3) transient, diffuse, unilateral cortical gray matter enhancement sparing white matter; and (4) not attributed to any other disorder [3].

Brain MRI displays hyperintense cortical T2 and FLAIR signal with gyriform enhancement, reminiscent of a subacute infarction [1, 2]. SMART syndrome is not related to a particular tumor and has been reported after focal or whole brain radiation. The onset of symptoms varies from 1 to 37 years after completion of radiation

therapy with doses of 50 Gy or more [2, 4]. There is no specific treatment for SMART syndrome, but steroids and anti-epileptic drugs have been clinically used [5]. One study showed that 45% of cases had an incomplete recovery with permanent imaging sequelae [2]. The pathophysiology of SMART syndrome is postulated to be vasculopathy, endothelial dysfunction, or energy failure, but histopathology has showed no specific findings [2, 5, 6]. Blood tests are usually unremarkable. CSF testing is usually normal or may demonstrate a mild CSF pleocytosis with elevated CSF protein. EEG may demonstrate slowing or epileptiform features [2]. A migraine-like headache is common, but not universal. Apart from gyriform enhancement, cortical DWI restriction in the acute lesion and SWI hypo-intensity within the periventricular white matter, which is related to radiation-induced cavernous hemangiomas, were reported [4, 7]. The later was also observed in this case, which presented a stable cavernoma in the right

aspect of the tectum. Other findings include hypermetabolism on F-18-FDG PET-CT, increased cerebral blood flow and cerebral blood volume at the acute lesion in CT and MR perfusion, and decreased NAA/creatinine ratio and slightly increased choline peak in the lesion in proton MR spectroscopy [8–11]. However, almost all imaging findings are based on case reports or small case series because of the rarity of the condition.

The main differential diagnoses of SMART syndrome include tumor recurrence, acute perforator infarct, subacute lacunar infarct from pontine perforator branches, radiation necrosis, or postictal changes. It may be possible to differentiate SMART syndrome from these other entities based on clinical history, clinical course, and imaging findings. It is particularly important to exclude tumor recurrence, which was considered the main concern in the present case given patient's history of posterior fossa medulloblastoma. FDG-PET-CT, MR spectroscopy, DSC-MRI, and lumbar puncture can help to differentiate SMART syndrome from tumor recurrence. Acute perforator infarct can be ruled out based on the lesion shape, enhancement pattern, association with vasogenic edema, and ADC time course with no evidence of ADC normalization on 13- and 20-month follow-up MRIs. Moreover, clinical course in combination with the imaging findings can help to rule out subacute lacunar infarct from pontine perforator branches given the non-ictal clinical onset.

Radiation necrosis usually occurs within the first 2 years but can be seen later as well, and patients with the condition have a more protracted course, with often incomplete recovery. Radiation necrosis in this case is unlikely, given the very delayed presentation of 21 years after radiation and subsequent quick improvement.

Our case displayed a combination of central cytotoxic edema, outlined by a contrast enhancing rim, and surrounding vasogenic edema. On 13-month follow up, along with substantial clinical improvement, there was resolution of the vasogenic edema and contrast enhancement with a small residual focus of restricted diffusion, which could represent coagulative necrosis associated with treatment of bevacizumab. From the imaging point of view, other differential diagnoses include acute leukoencephalopathy [12], rhombencephalitis, and demyelinating disease. These can involve the brainstem but were less likely in this present case given no recent history of chemotherapy or toxic agent exposure and no evidence of infection, autoimmune disease, or new malignancy.

We postulate that the pontine finding is a delayed complication of radiation therapy to the posterior fossa within the spectrum of SMART syndrome, secondary to energy metabolic derangement leading to cytotoxic edema.

Clinicians and radiologists should be aware that SMART syndrome has various clinical manifestations and imaging findings and can be associated with a pontine lesion in patients who received radiation to the posterior fossa.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethic approval** All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Our institutional review board approved this retrospective single-center study and waived the requirement for informed consent. Data was acquired in compliance with all applicable Health Insurance Portability and Accountability Act regulations.

## References

1. Black DF, Bartleson JD, Bell ML, Lachance DH (2006) SMART: stroke-like migraine attacks after radiation therapy. *Cephalalgia* 26(9):1137–1142. <https://doi.org/10.1111/j.1468-2982.2006.01184.x>
2. Black DF, Morris JM, Lindell EP, Krecke KN, Worrell GA, Bartleson JD, Lachance DH (2013) Stroke-like migraine attacks after radiation therapy (SMART) syndrome is not always completely reversible: a case series. *AJNR Am J Neuroradiol* 34(12):2298–2303. <https://doi.org/10.3174/ajnr.A3602>
3. Bartleson JD, Krecke KN, O'Neill BP, Brown PD (2003) Reversible, stroke-like migraine attacks in patients with previous radiation therapy. *Neuro-Oncology* 2:121–127. <https://doi.org/10.1093/neuonc/5.2.121>
4. April D, Lall N, Steven A (2020) Stroke-like migraine attacks after radiation therapy syndrome. *Ochsner J* 20(1):6–9. <https://doi.org/10.31486/toj.19.0090>
5. Singh AK, Tantiwongkosi B, Moise AM, Altmeyer WB (2017) Stroke-like migraine attacks after radiation therapy syndrome: case report and review of the literature. *Neuroradiol J* 30(6):568–573. <https://doi.org/10.1177/1971400917690009>
6. Armstrong AE, Gillan E, DiMario FJ Jr (2014) SMART syndrome (stroke-like migraine attacks after radiation therapy) in adult and pediatric patients. *J Child Neurol* 29(3):336–341. <https://doi.org/10.1177/0883073812474843>
7. Khanipour Roshan S, Salmela MB, McKinney AM (2015) Susceptibility-weighted imaging in stroke-like migraine attacks after radiation therapy syndrome. *Neuroradiology* 57(11):1103–1109. <https://doi.org/10.1007/s00234-015-1567-8>
8. Pruitt A, Dalmau J, Detre J, Alavi A, Rosenfeld MR (2006) Episodic neurologic dysfunction with migraine and reversible imaging findings after radiation. *Neurology* 67(4):676–678. <https://doi.org/10.1212/01.wnl.0000228862.76269.62>
9. Nar Senol P, Gocmen R, Karli Oguz K, Topcuoglu MA, Arsava EM (2015) Perfusion imaging insights into SMART syndrome: a case report. *Acta Neurol Belg* 115(4):807–810. <https://doi.org/10.1007/s13760-015-0483-3>

10. Biju RD, Dower A, Moon BG, Gan P (2020) SMART (stroke-like migraine attacks after radiation therapy) syndrome: a case study with imaging supporting the theory of vascular dysfunction. *Am J Case Rep* 21:e921795. <https://doi.org/10.12659/AJCR.921795>
11. Gómez-Cibeira E, Calleja-Castaño P, Gonzalez de la Aleja J, Sierra-Hidalgo F, Ruiz Morales J, Salvador-Alvarez E, Ramos-Gonzalez A (2015) Brain magnetic resonance spectroscopy findings in the stroke-like migraine attacks after radiation therapy (SMART) syndrome. *J Neuroimaging* 25(6):1056–1058. <https://doi.org/10.1111/jon.12227>
12. McKinney AM, Kieffer SA, Paylor RT, SantaCruz KS, Kendi A, Lucato L (2009) Acute toxic leukoencephalopathy: potential for reversibility clinically and on MRI with diffusion-weighted and FLAIR imaging. *AJR Am J Roentgenol* 193(1):192–206. <https://doi.org/10.2214/AJR.08.1176>

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.