Unusual case of recurrent SMART (stroke-like migraine attacks after radiation therapy) syndrome

Ramnath Santosh Ramanathan, Gayathri Sreedher[1], Konark Malhotra[2], Zain Guduru[2], Deeksha Agarwal[2], Mary Flaherty[2], Timothy Leichliter[3], Sandeep Rana[4]

Department of Neurology, Neurology Chief Resident, [2]Neurology, [4]Associate Professor of Neurology, [3]Allegheny General Hospital, Allegheny Health Network, Pittsburgh, Pennsylvania, [1]Pediatric Neuro-Radiology, Akron Childrens Hospital, Akron, Ohio, United States

Abstract

Stroke-like migraine attacks after radiation therapy (SMART) syndrome is a rare delayed complication of cerebral radiation therapy. A 53-year-old female initially presented with headache, confusion and left homonymous hemianopia. Her medical history was notable for cerebellar hemangioblastoma, which was treated with radiation in 1987. Her initial brain MRI (magnetic resonance imaging) revealed cortical enhancement in the right temporo-parieto-occipital region. She improved spontaneously in 2 weeks and follow-up scan at 4 weeks revealed no residual enhancement or encephalomalacia. She presented 6 weeks later with aphasia. Her MRI brain revealed similar contrast-enhancing cortical lesion but on the left side. Repeat CSF studies was again negative other than elevated protein. She was treated conservatively and recovered completely within a week. Before diagnosing SMART syndrome, it is important to rule out tumor recurrence, encephalitis, posterior reversible encephalopathy syndrome (PRES) and stroke. Typically the condition is self-limiting, and gradually resolves.

Key Words

Migraines, radiation therapy, SMART syndrome

For correspondence:
Dr. Ramnath Santosh Ramanathan, 420 East North Ave, Suite 206, Allegheny General Hospital, Allegheny Health Network, Pittsburgh, Pennsylvania-15212, United States.
E-mail: dr.santosh7@gmail.com

Ann Indian Acad Neurol 2016;19:399-401

Introduction

Shuper *et al*., first described complicated migraine like attacks after radiation therapy in four children in 1995.[1] Friedenberg and Dodick in 2000 described reversible neuroimaging changes in the context of migraine with seizures.[2]

However, Bartleson *et al*., were the first to postulate a relationship between remote cranial radiation therapy and recurrent migraine like attacks in 2003 in two patients and also proposed diagnostic criteria.[3] Black *et al*., first used the terminology SMART syndrome and also proposed revised diagnostic criteria in 2006.[4] The diagnosis of SMART syndrome relies on the reversibility of the condition, but Black *et al*., later in 2013 reported that it might not be the case in a significant proportion of cases.[5]

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.168634

We report a patient who fulfills the diagnostic criteria for SMART syndrome with recurrent clinical symptoms and neuroimaging findings following radiation therapy for cerebellar hemangioblastoma 27 years ago. Neuroimaging in recurrent episodes of SMART syndrome with involvement of contralateral side has not been reported to our knowledge and we present such a case. To our knowledge, this is the first case of recurrent SMART syndrome.

Case Report

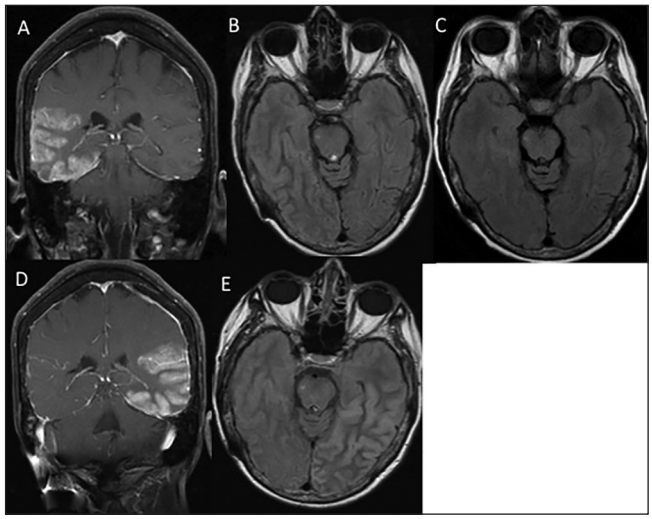
A 53-year-old female with a past medical history of cerebellar hemangioblastoma was treated with posterior fossa radiation therapy (dose unknown) in 1987. Later, she developed hydrocephalus and underwent right parieto-occipital shunt placement. She initially presented with headache, left homonymous hemianopsia and confusion in 2014. She denied any previous history of migraine-like headache. She complained of right temporal pressure like headache initially with photosensitivity and blurred vision bilaterally lasting few hours but denied nausea/vomiting. She complained of

right-sided headache a day or two before she developed left homonymous hemianopsia and confusion.

Magnetic resonance imaging (MRI) of brain [Figure 1a and b] done during this initial admission showed unilateral gyriform cortical enhancement of the right temporo-parieto-occipital gray matter. Cerebrospinal fluid (CSF) studies were negative except for mild elevation in protein. CSF HSV, EBV, CMV PCR and JC virus was negative. CSF cytology and flow cytometry was negative for malignant cells. Paraneoplastic profile was also negative. Patient was treated with acyclovir initially pending CSF results for possible herpes infection. Patient's symptoms remained stable. Decision was made to obtain follow up neuroimaging studies with close observation and monitoring as outpatient since patient denied biopsy.

Follow-up MRI brain [Figure 1c] in four weeks demonstrated complete resolution of previous lesions without residual encephalomalacia. Patient was asymptomatic then.

She presented to the hospital again in 6 weeks time with complaints of aphasia and headache, which she described as left temporal throbbing pain with associated photosensitivity, phonophobia lasting for 6-8 hours but there was no associated osmophobia, visual disturbances, nausea or vomiting. Again she had been complaining of headache about 1-2 days prior to the complaints of aphasia. MRI brain [Figure 1d and e] demonstrated unilateral gyriform cortical enhancement but this time it was in the left temporo-parieto-occipital gray matter. Again CSF studies and paraneoplastic profiles were negative except for mildly increased CSF protein. Patient was again started on acyclovir, which was discontinued after HSV PCR came back negative. Electroencephalogram (EEG) showed left focal slowing with no epileptiform discharges. During both admissions, patient had a normal blood pressure. She was not treated with steroids during either episode. Patient did not have positron emission tomography (PET) scan during or after either of the episode. The final follow up MRI brain [Figure 2] done four weeks after the second attack demonstrated complete resolution of the previous left sided lesion.



Figures 1: (a) Initial MRI T1 post contrast coronal image showing confluent gyriform enhancement of right temporo-occipital region, (b) Initial MRI Axial FLAIR showing hyperintense lesion in the right temporo-occipital region, (c) Interval Follow up MRI Axial FLAIR shows resolution of the previous lesion, (d) Readmission MRI T1 post contrast coronal image shows confluent gyriform enhancement of left temporo-occipital region and (e) Readmission MRI Axial FLAIR image shows hyperintense lesion in the left temporo-occipital region

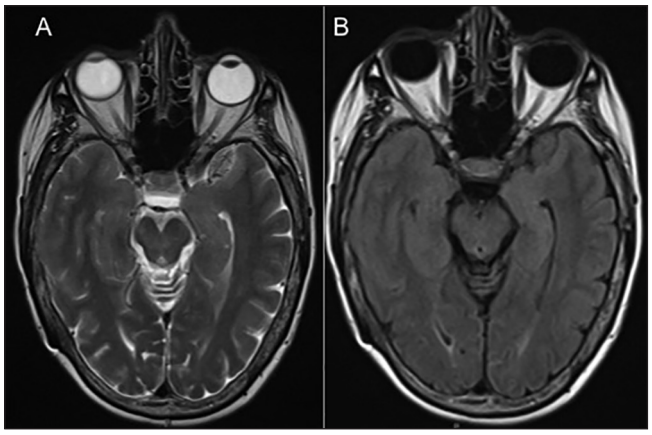
Discussion

SMART syndrome is a rare delayed complication of radiation therapy characterized by transient reversible neurological symptoms such as recurrent migrainous headaches, with or without aura, hemispheric dysfunction and seizures with characteristic MRI brain changes in the form of cortical gyriform enhancement. The symptoms and neuroimaging findings generally at least partially or completely resolve in a few weeks. SMART syndrome is not linked to any particular brain tumor and has been reported after focal as well as whole brain radiation for primary brain tumor or metastasis.

The delayed reversible neurological complications of brain irradiation have been recently classified as SMART and peri-ictal pseudoprogression (PIPG). Di Stefano *et al*., recently reported acute late-onset encephalopathy after radiation therapy in five patients, which was highly responsive to steroids, and they proposed to call it acute late-onset encephalopathy after radiotherapy (ALERT syndrome) and also hypothesized that SMART, PIPG and ALERT syndrome are the spectrum of acute late-onset complications of brain irradiation.[6]

Rheims *et al*., suggested that the appearance of new contrast-enhancing lesions on MRI in cancer patients treated with radiation should not be always considered as tumor recurrence and that transient seizure-related MRI changes could mimic PIPG.[7] PIPG probably is the same spectrum of phenomena as SMART but is characterized by absence of headache, less significant neurological impairment and more rapid recovery, and the reported cases tend to show more meningeal enhancement and/or cortical enhancement than seen in SMART syndrome.

SMART syndrome predominantly involves unilateral temporo parieto occipital cortex with cortical enhancement on post-



Figures 2: Follow up MRI brain Axial T2W (a) and FLAIR (b) images 4 weeks after readmission shows complete resolution of the left sided temporo-occipital hyperintense lesions

gadolinium T1-weighted sequences. Black *et al*., report a 55% chance for clinical recurrence with SMART syndrome. Up to 45% have been reported to have incomplete recovery. There is no clear consensus about the dose of radiation required to produce SMART syndrome though some reports suggest high dose radiation (>5000 centiGray) may be required.[8] Maloney *et al*., reported occurrence of SMART syndrome in a patient (who had received radiation therapy remotely) who underwent craniotomy and temporal lobectomy for recurrent metastatic tumor resection.[9]

Diagnostic criteria was initially proposed by Bartleson *et al*., in 2003 but later revised by Black *et al*., in 2006. The diagnostic criteria includes:

a. Remote history of cranial radiation,
b. Prolonged, reversible unilateral cortical signs and symptoms beginning years after radiation with manifestations including visuo-spatial deficit, confusion, hemiparesis, aphasia, seizures, headaches with attacks, antecedent migraine with or without aura starting after radiation,
c. Transient, diffuse, unilateral cortical gray matter enhancement sparing white matter, and
d. Not attributed to any other disorder.

The typical neuroimaging findings in SMART syndrome are transient, diffuse, unilateral cortical gray matter thickening with enhancement sparing the white matter, typically having predilection for the posterior fossa involving temporo-parieto-occipital regions. The frontal lobes are usually spared. These transient MRI changes cannot be attributed to post ictal state especially in patients presenting with seizures as concurrent EEG mostly does not show any ictal or epileptiform discharges and generally shows ipsilateral slowing though Bradshaw *et al*., have suggested epileptiform activity during seizures can be seen in cases of SMART syndrome and it should not be regarded as inconsistent with a diagnosis of SMART syndrome, provided seizures do not explain the onset of clinical and radiological features.[10] Post-ictal MRI changes are not limited to parieto-occipital changes in patients presenting with seizures. It has been postulated that there may be a narrow time interval for evaluation of enhancement on brain MRI as cases of SMART syndrome have been reported without typical MRI changes. In our case cortical enhancement in a symmetric manner in the contralateral hemisphere may reflect orientation of the radiation port. Minimal residual laminar necrosis and volume loss in the affected cortex is commensurate with prior reports. Cortical laminar necrosis was reported in 27% cases of SMART syndrome in one series.[5]

The pathophysiology of SMART syndrome is unknown. Vascular instability, endothelial dysfunction and metabolic etiologies are postulated. Familial hemiplegic migraine presents with similar symptoms and hence similar genetic abnormalities in SMART syndrome have been postulated. It has been also been proposed that SMART syndrome might be a reversible radiation vasculopathy similar to PRES (posterior reversible encephalopathy syndrome) as PRES may also present with similar symptoms and demonstrate disruption of the blood brain barrier with endothelial dysfunction. Genetic etiology and precipitating factors are so far not elucidated.

Before the diagnosis of SMART syndrome can be established, it is important to rule out tumor recurrence, encephalitis, cerebritis, vasculitis, mitochondrial encephalopathy, lactic acidosis and stroke like syndrome (MELAS), PRES and stroke. The possibility of tumor recurrence should also be considered as Kerklaan *et al*., reported tumor recurrence in three of their four reported cases of SMART syndrome.[11] The history of radiation therapy is a necessary component for diagnoses. Recognizing the syndrome is important to avoid invasive testing.

Conclusion

The knowledge of SMART syndrome in the differential diagnosis of reversible neurological dysfunction manifesting remotely after radiation therapy helps to avoid unnecessary invasive investigations, in patient reassurance and also alleviates anxiety related to uncertainty.

Authors have no disclosures; there are no competing interests, no acknowledgment or financial disclosures to be done.

References

1. Shuper A, Packer RJ, Vezina LG, Nicholson HS, Lafond D. 'Complicated migraine-like episodes' in children following cranial irradiation and chemotherapy. Neurology 1995;45:1837-40.
2. Friedenberg S, Dodick DW. Migraine-associated seizure: A case of reversible MRI abnormalities and persistent nondominant hemisphere syndrome. Headache 2000;40:487-90.
3. Bartleson JD, Krecke KN, O'Neill BP, Brown PD. Reversible, strokelike migraine attacks in patients with previous radiation therapy. Neuro Oncol 2003;5:121-7.
4. Black DF, Bartleson JD, Bell ML, Lachance DH. SMART: Stroke-like migraine attacks after radiation therapy. Cephalalgia 2006;26:1137-42.
5. Black DF, Morris JM, Lindell EP, Krecke KN, Worrell GA, Bartleson JD, *et al*. Stroke-like migraine attacks after radiation therapy (SMART) syndrome is not always completely reversible: A case series. AJNR Am J Neuroradiol 2013;34:2298-303.
6. Di Stefano AL, Berzero G, Vitali P, Galimberti CA, Ducray F, Ceroni M, *et al*. Acute late-onset encephalopathy after radiotherapy: An unusual life-threatening complication. Neurology 2013;81:1014-7.
7. Rheims S, Ricard D, van den Bent M, Taillandier L, Bourg V, Désestret V, *et al*. Peri-ictal pseudoprogression in patients with brain tumor. Neuro Oncol 2011;13:775-82.
8. Armstrong AE, Gillan E, DiMario FJ Jr. SMART syndrome (stroke-like migraine attacks after radiation therapy) in adult and pediatric patients. J Child Neurol 2014;29:336-41.
9. Maloney PR, Rabinstein AA, Daniels DJ, Link MJ. Surgically induced SMART syndrome: Case report and review of the literature. World Neurosurg 2014;82:240.
10. Bradshaw J, Chen L, Saling M, Fitt G, Hughes A, Dowd A. Neurocognitive recovery in SMART syndrome: A case report. Cephalalgia 2011;31:372-6.
11. Kerklaan JP, Lycklama á Nijeholt GJ, Wiggenraad RG, Berghuis B, Postma TJ, Taphoorn MJ. SMART syndrome: A late reversible complication after radiation therapy for brain tumours. J Neurol 2011;258:1098-104.

How to cite this article: Ramanathan RS, Sreedher G, Malhotra K, Guduru Z, Agarwal D, Flaherty M, *et al*. Unusual case of recurrent SMART (stroke-like migraine attacks after radiation therapy) syndrome. Ann Indian Acad Neurol 2016;19:399-401.
Received: 16-04-15, **Revised:** 18-05-15, **Accepted:**04-06-15

Source of Support: Nil, **Conflicts of Interest:** None declared.