

Stroke-Like Migraine Attacks After Radiation Therapy [Smart] Syndrome. Suspicion means prompt piagnosis

Flor-Goikoetxea- Gamo A^{1,2}, Alcalá-Vicente C³, Piquer-Belloch J^{1,2}, Cremades-Mira A⁴, Rodríguez-Mena R^{1,2}, Riesgo-Suarez P^{1,2}, Llacer-Ortega JL^{1,2}, Rovira-Lillo V^{1,2} and Roca-Barber A^{1,2}

¹Department of Neurosurgery, Hospital de la Ribera, Alzira, Spain

²Chair of Neuroscience and Social Change - NED Foundation – International University of Valencia [VIU]. Valencia, Spain

³Department of Neurology, Hospital de la Ribera, Spain

⁴Department of Pathological Anatomy, Hospital de la Ribera, Alzira, Spain

*Corresponding author:

Flor-Goikoetxea- Gamo A,
Department of Neurosurgery, Hospital de la Ribera,
Alzira, Chair of Neuroscience and Social Change
- NED Foundation – International University of
Valencia [VIU]. Valencia, Spain,
E-mail: aflorgoikoetxea@yahoo.es

Received: 20 Apr 2023

Accepted: 01 May 2023

Published: 10 May 2023

J Short Name: ACMCR

Copyright:

©2023 Flor-Goikoetxea- Gamo A. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially

Citation:

Flor-Goikoetxea- Gamo A, Stroke-Like Migraine Attacks After Radiation Therapy [Smart] Syndrome. Suspicion means prompt diagnosis. Ann Clin Med Case Rep. 2023; V10(18): 1-6

1. Abstract

1.1. Background: Stroke-like migraine attacks after radiation therapy [SMART] syndrome is a rare and delayed complication of radiation therapy to the brain. Less than 100 cases have been described in literature since it was first reported in 1995. On average, presentation is about more than 20 years after radiotherapy and patient normally present with stroke-like deficits, epileptic seizures and migraine. MRI is characteristic for unilateral and mainly parieto-occipital cortical hyperintensities and gyriform enhancement. The importance of characterizing this syndrome for prompt recognition and diagnosis is essential to avoid unnecessary biopsies and provide reassurance to the patient.

1.2. Case Description: We describe a 49-years-old female treated with craniospinal radiation for a IV ventricle tumor. 29 years later she was admitted in our hospital presenting migraine-like attacks, behavioral changes, bilateral loss of vision, seizures, confusion and gait instability.

1.3. Conclusions: As the global cancer survival rates improved considerably during last decades, long-term side effects of complementary treatment as radiotherapy are likely to be more often observed. SMART syndrome represents a characterizable and a distinguishable entity which can be differentiated from tumor re-

currence. The knowledge and awareness of this syndrome would substantially avoid unnecessary aggressive investigations and would significantly improve patient expectation and management.

2. Introduction

Stroke-like migraine attacks after radiation therapy [SMART] syndrome represents a delayed complication of brain radiation therapy [1-2]. Onset of symptoms can variably appear after radiation therapy and consist of commonly self-limiting stroke-like symptoms. Its pathophysiology remains poorly understood and MRI is the imaging modality of choice for investigation.

In this work we present a case of a patient with SMART syndrome who was managed in our neurosurgery department and make a review of the existing literature. We also try to contribute to find the main clinical and radiographic features and treatment strategies of this kind of patients. Our aim is to enforce the awareness and high degree of suspicion which could aid the medical community to make an earlier diagnosis and therefore avoid invasive investigations and treatments.

3. Case Description

In 1991, a 13 year-old female patient was brought to the emergency room with low level of consciousness due to an obstructive hydrocephalus caused by a fourth ventricle tumour. Following the

insertion of a VP shunt and resection of desmoplastic medulloblastoma the patient was treated with 50 Gy two-dimensional cranial radiation therapy [30 Gy/18 fractions in the whole brain and 20 Gy/10 fractions in the posterior cranial fossa]. The spinal cord was also irradiated with 20 Gy in 20 fractions. The patient kept clinical and radiological stability during her follow-up.

In 2020, she was admitted in our department with migraine-like attacks, partial seizures and behavioral changes that evolved in a few weeks to bilateral loss of vision, gait instability and confusion. Brain postcontrast T1 weighted MRI images revealed right occipital gyral and leptomeningeal contrast enhancement and thickening associated with hyperperfusion in perfusion weighted imaging. T2 and FLAIR weighted MRI showed diffuse cortical swelling and signal increase in the region while diffusion-weighted imaging didn't demonstrate any restriction. Spinal MRI discarded the presence of leptomeningeal metastases. Cerebrospinal fluid analysis displayed only a little increase in proteins [65 mg/dL] and ruled out the presence of malignant cells. Electroencephalogram confirmed electrographic discharges in right temporo-parieto-occipital region, consistent with radiological findings. The presence of epileptic activity like acute shapes and paroxysmal spikes was observed in right front-temporal region associated with signs of a more diffuse encephalopathy (Figures 1-3).

During hospitalization she developed secondary-generalized seizures with persistent post-ictal weakness in left leg and confusion, lasting for several days. He was treated with 1000 mg levetiracetam and high doses of dexamethasone. Due to the lack of specific diagnosis the neuro-oncology committee decided to perform a neuronavigation-guided brain biopsy which didn't contribute with any histopathological finding. During the hospital stay she had a gradual clinical improvement and was discharged fully recovered.

One month later the patient presented to the emergency department after suffering from a new episode of tonic-clonic seizure. The encephalogram displayed several and abundant epileptic activity and signs of focal injury in right temporo-occipital region. The treatment was adjusted to 1500 mg of levetiracetam and high doses of dexamethasone again. New MRI showed a mild improvement of the gyrus thickening and leptomeningeal contrast enhancement. The neuro-oncology committee decided to proceed with an open biopsy performed with a little craniotomy which result was encephalitis.

The patient was discharged with a total clinical recovery. During follow-up apart from the clinical stability control MRI still shows complete resolution of the abnormalities in the right occipital cortex.

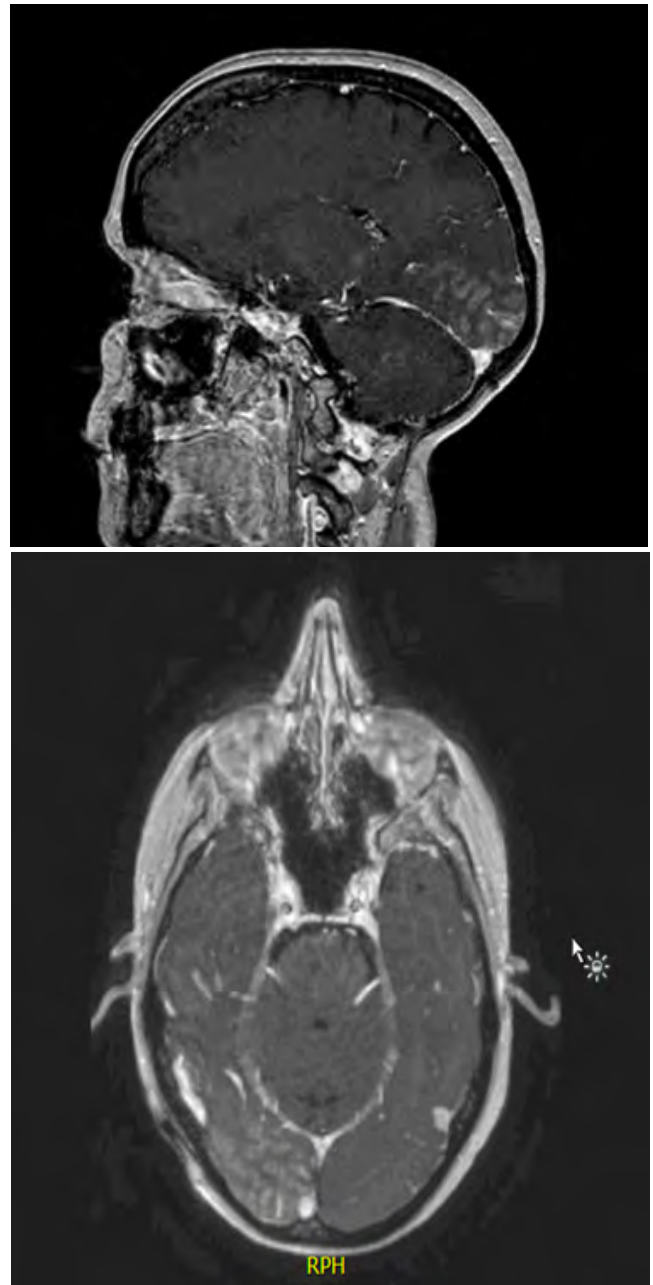


Figure 1: A and B, Cortical edematous changes with gyri-like enhancement is seen in the right occipital lobe.



Figure 2: C and D, After 3 months, she completely recovered.

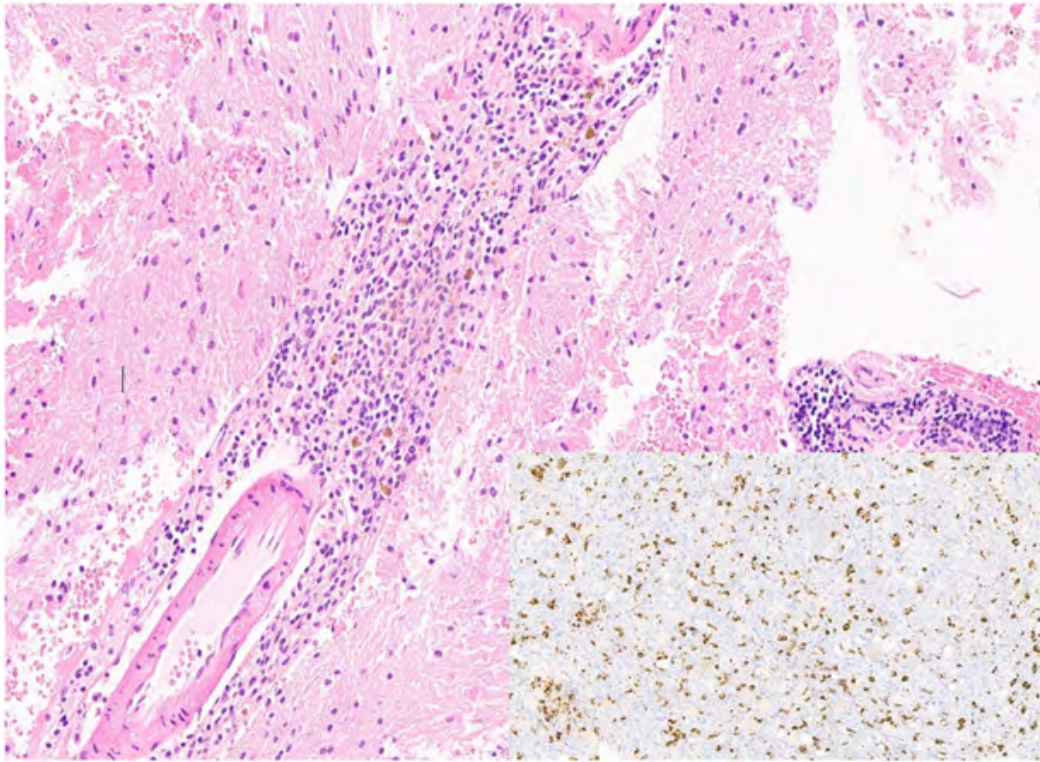


Figure 3: Characteristic findings of perivascular cuffs of lymphocytes. Microglial and macrophage response (inset). x200.

4. Discussion

SMART syndrome represents a late complication of brain radiation characterized by recurrent neurologic symptoms. As the global cancer survival rates improved considerably during last decades, long-term side effects of complementary treatment as radiotherapy have also been much frequently described. Less than 100 cases have been described in literature since it was first reported in 1995 by Shuper et al [3]. Although it has been described mainly in patients treated with radiation for central nervous system tumors, there is no specific tumor type association [3,4].

Differential diagnosis is extremely important. The presentation of a new neurological deficit and new enhancement regions in MRI in a patient with history of radiation therapy for brain tumor normally leads physician to disclose the most common diagnosis of local tumor recurrence, leptomeningeal disease, ischemic disease, infection, paraneoplastic disorders and autoimmune syndromes [4,5,6]. Once this is ruled out and as an exclusion diagnosis; SMART syndrome should be strongly considered as one of the possible diagnoses. Recognition of this syndrome is considered imperative as it can avoid the need for invasive diagnostic testing and can provide reassurance to the patient.

The SMART syndrome acronym and its actual diagnostic criteria were firstly proposed by Black et al. in 2006. Those diagnostic criteria included remote history of cranial radiation, prolonged and reversible unilateral cortical dysfunctions, transient unilateral gadolinium gyral enhancement and exclusion of other attributable disorders [7,8].

The symptoms range can include subacute migraine type of headache, seizures, focal cortical symptoms like aphasia, sensory defects, hemiparesis or homonymous hemianopsia, and encephalopathy signs with altered mental state. Headache and seizures are present in most of the cases. Symptoms typically appear over days and resolve in a period which fluctuates from weeks to months [7]. Onset of symptoms can variably appear 1-37 years after radiation therapy. Most of the reported cases were related with higher doses than 50 Gy, though this syndrome can also occur with lower doses [4,5,6]. Even if SMART syndrome is generally considered a self-limiting condition, several authors have reported permanent neurological and longterm imaging sequela [5,9]. Ota et al. observed that factors such as older age, presence of linear subcortical SWI/T2*WI hypointensity, restricted diffusion and the use of steroids could be associated with a poorer clinical outcome [5].

Even if the pathophysiology is not actually clear, delayed radiation seems to induce neuronal dysfunction which may cause neuronal cortical hyperexcitability, endothelial damage, altered autoregulation and subsequent blood-brain barrier disruption, resulting in a late edema, hyperperfusion, necrosis and leukoencephalopathy. The alternative explanation hypothesizes that radiation can damage the trigeminovascular system which would reduce the threshold to cortical spreading depression, leading to migrainous aura and seizures [10,11,12]. Due to the high prevalence of seizures in SMART syndrome it is also speculated about their cause and effect in the pathogenesis and presentation of this syndrome; something which remains unanswered for the moment [12].

Characteristic MRI findings show a preferential manifestation in the parieto-occipital cortex as in our case; indicating that this area could be more vulnerable and susceptible to damage from radiation therapy than others [10,11]. Common imaging findings in SMART syndrome include reversible unilateral gyral T2 and FLAIR hyperintensity with cortical gadolinium enhancement in a distribution not related to vascular territories. Imaging could also have bilateral effects, including diffusion restriction, linear subcortical SWI/T2 WI hypointensity, increased MRI perfusion imaging, late complications of brain radiation such as cavernoma, siderosis and microhemorrhages and subcortical edematous changes [8,11]. Other reported imaging findings include hypermetabolism of the lesion on FDG-PET/CT and decreased NAA with increased Cr and Cho peaks on MRS [5]. Patients with remaining cortical laminar necrosis and infarction/gliosis during follow-up MRI have been associated with incomplete recovery [8].

Different symptomatic treatment algorithms have been reported in small case series but, there is currently no clear guidelines on effective treatment approaches in this syndrome. Treatment is usually targeted towards controlling the symptoms and preventing important outcomes, such as stroke and epilepsy [5,7,9]. For this respect, treatment management is complex and may involve anti-seizure medication, analgesic, anti-hypertensives, anti-platelet and steroid therapy.

In literature, SMART syndrome is treated either with or without steroid therapy; in other words, they are not considered as a standard of care [9,10,11]. Among the published case reports, several patients without this treatment approach have completely recovered [10,11]. The anti-edema and anti-inflammatory effect of steroids arises from their influence on endothelial cells and pericytes which constitute the blood-brain barrier and the cytokine regulation. Even good prognosis in the absence of steroids treatment has been reported, acute steroid pulse therapy can be effective in improving and even resolving clinical and MRI abnormalities secondary to SMART syndrome. In this line, short term treatment with steroids may be helpful in reaching an early diagnosis and, consequently, in obviating the need for invasive diagnostic testing, preventing from unnecessary brain biopsies [12,14]. According to this, brain biopsy seems to be more frequently performed in the non-steroid group [12].

Long-term steroid treatment is controversial and is not generally recommended. Apart from its side effects, it is theorized that they can influence in the endogenous repair processes of the damaged myelin sheath by oligodendrocyte progenitor cells, which are responsible of remyelination. This mechanism could probably be underneath the described neuropsychiatric and cognitive impairments related to long-term therapy [5]. Efficacy of calcium channel blockers, such as Verapamil, remains debated in SMART syndrome but, considering the dysfunction in vasoreactivity involved in its pathophysiology, they have been proposed as part of

the complementary acute-phase treatment [9]. Endothelial injury and “string of beads” pattern in angiography similar to reversible posterior leukoencephalopathy syndrome has also been reported in SMART syndrome, so calcium channel antagonists can also be beneficial like in this condition. Calcium channel blockers are proposed for other different reason, they may be helpful in controlling headache, as they are used in standard migraine or cluster headache. As well, they may be used as an anti-hypertensive medication, controlling the hypertension as a hypostatized triggering condition of this syndrome [15,16].

Seizures are often a component of SMART syndrome, so the use of anti-seizure treatment seems reasonable [13], as well as analgesic ones, especially efficacious antimigraine drugs. In this line, treatments like valproate or topiramate may be a beneficial therapy for both conditions. Finally, SMART syndrome symptoms include stroke-like episodes, so most patients are treated with empiric early anti-platelet treatments. In this line, hyperacute reversible cerebral ischemia and various degrees of arterial stenosis in the vascular distribution has also been reported. According to the vascular disfunction happening in this syndrome, which would predispose to cerebrovascular events and therefore to permanent neural injury, the secondary stroke prevention with anti-platelet drugs has been strongly recommended [13,17].

5. Conclusion

SMART syndrome represents a rare entity which should be suspected whenever gyriform enhancement is observed in the parieto-occipital region in any patient with migraine-type headaches, seizures, and stroke-like symptoms with a remote history of brain radiation. Because of advances in cancer treatment and subsequent improvement in life expectancy, SMART syndrome may be increasingly observed in patients with history of cranial radiation therapy. Appropriate suspicion and prompt diagnosis of SMART syndrome is essential to undergone with early symptomatic treatment and to avoid unnecessary invasive brain biopsy and other expensive tests.

References

1. Ramanathan SR, Sreedher G, Malhotra K. Ann Indian Acad Neurol. 2016; 19(3): 399–401.
2. Pruitt A, Dalmau J, Detre J. Episodic neurologic dysfunction with migraine and reversible imaging findings after radiation. Neurology. 2006; 67: 676-78.
3. Shuper A, Packer RJ, Vezina LG, Nicholson HS, Lafond D. Complicated migraine-like episodes' in children following cranial irradiation and chemotherapy. Neurology. 1995; 45(10): 1837-40.
4. Kerklaan JP, Nijeholt GJ, Wiggeraad RGJ. SMART syndrome: a late reversible complication after radiation therapy for brain tumours J Neurol. 2011; 258(6): 1098-1104.
5. Ota Y, Leung D, Lin E, Liao E, Kurokawa R, Kurokawa M, et al. Prognostic Factors of Stroke-Like Migraine Attacks after Radiation

- Therapy (SMART) SyndromeAJNR Am J Neuroradiol. 2022; 43(3): 396-401.
6. Singh AK, Tantiwongkosi B, Moise AM, Altmeyer WB. Stroke-like migraine attacks after radiation therapy syndrome: Case report and review of the literatureNeuroradiol J. 2017; 30(6): 568-573.
 7. Day LB, Rajendram P, Kalia LV. An Intelligent Diagnosis: SMART Syndrome American journal of Medicine. 2021; 134(7): P863-865.
 8. Biju RD, Dower A, Benjamin G. Moon and Peter GanAD, Am J Case Rep. 2020; 21: e921795-1–e921795-7.
 9. Oliveira AD, Anzolin E, Medeiro MS, Machado R. SMART Syndrome Identification and Successful Treatment. Case Rep Neurol 2021; 13: 40-45.
 10. Jia W, Saito R, Kanamori M, Iwabuchi N, Iwasaki M, Tominaga T, et al. SMART (stroke-like migraine attacks after radiation therapy) syndrome responded to steroid pulse therapy: Report of a case and review of the literature. NeurologicalSci. 2018;12: 1-4.
 11. Taguchi M, Bonner K, Memon AB. Cureus. 2022; 14(2): e21930.
 12. Panigrahy N, Aedma S, Lee M. Cureus. 2022; 14(6): e25691.
 13. Singh AK, Tantiwongkosi B, Moise AM, Altmeyer WB. Stroke-like migraine attacks after radiation therapy syndrome: Case report and review of the literature. Neuroradiol J. 2017; 30(6): 568-573.
 14. Jia W, Saito R, Kanamori M, Iwabuchi N, Iwasaki M, Tominaga T, et al. Stroke-Like Migraine Attacks after Radiation Therapy Syndrome: Clinical and Imaging Characteristics. NeurologicalSci. 2018; 12: 1-4.
 15. Singh TD, Hajeb M, Rabinstein AA. SMART syndrome: restrospective review of a rare delayed complication of radiation. European journal of neurology. 2020.
 16. Dominguez M, Malani R. Stroke-Like Migrain attacks after radiation therapy (SMART) Syndrome: A comprehensive Review. Current Pain and Headache Report. 2021; 25(5): 33.
 17. Patel UK, Patel K. Stroke-Like migrain attacks after radiation therapy (SMART) Syndrome- a case series and review. Neurological Sciences. 2020; 41(11): 3123-3134.