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Case Report

Stroke-Like Migraine Attacks After Radiation Therapy (SMART) Syndrome: A Case Report With Vertigo, Dysmetria, And Impaired Tandem Gait

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ABSTRACT

SMART syndrome is a rare, delayed complication of brain radiation. The acronym SMART stands for stroke-like migraine attacks following radiation therapy. This case is one of the first to describe episodic vertigo, dysmetria, and impaired tandem gait following proton beam radiotherapy for a craniopharyngioma.

An 18-year-old male presented with migraine headaches, upper and lower limb weakness, episodic vertigo, and dysmetria with impaired tandem gait. This occurred following proton-beam radiotherapy, which was completed at around 11 years of age for recurrent craniopharyngioma. Magnetic resonance imaging (MRI) of the brain demonstrated a T1 hyperintense signal in the cortex of the right parietal and temporal lobes consistent with SMART syndrome. In addition, a subcortical hyperintense signal was seen in the right parietal, temporal, and frontal lobes.

Atypical presentations of SMART syndrome are out there, and it is essential to recognize them in patients presenting with neurological symptoms following radiation therapy so that diagnosis and treatment can be done.

1. Introduction

Stroke-like migraine attacks following radiation therapy (SMART) syndrome is an uncommon neurological condition that can occur following head and neck radiotherapy [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. It has a subacute onset, and initial manifestations usually include migraine-like headaches, which are commonly described as unilateral and throbbing with associated photophobia and phonophobia [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. There could also be an aura preceding these migraines. Cortical symptoms are seen, such as aphasia, hemiparesis, neglect, and visual field abnormalities [8]. Seizures were also reported in some patients and could be of any type. These symptoms form the basis of the syndrome's name. It was initially described in 1995 by Shuper et al. [9], who followed a group of children who developed migrainous headaches and stroke-like symptoms following brain radiotherapy for tumors of the posterior fossa. SMART syndrome is an exceptionally rare condition that has only been reported in a limited number of documented cases since it was first identified [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. It affects both the pediatric [9] and adult age groups who have undergone cranial radiation for intracranial malignancies (e.g., Medulloblastoma, Astrocytoma) or for head and neck cancers (e.g., Laryngeal, Hypopharyngeal). Furthermore, patients who have had metastatic cancer to the brain with subsequent radiation treatment are also affected [6]. The latency period between radiation therapy and the development of symptoms is typically 14 years [11]. The initial description of the syndrome was in pediatric patients [9]. Our case represents one of the four currently reported occurrences of SMART syndrome following proton beam radiotherapy [5, 7, 10]. Interestingly, our patient experienced vertigo, a symptom infrequently observed in SMART syndrome, which was similarly described by Huang et al. [5].

2. Case presentation

An 18-year-old male from United Arab emirates, and family history of migraine and thalassemia trait with no reported allergies, presents to the outpatient clinic with a several-year history of episodic throbbing headaches associated with nausea, photophobia, and phonophobia occurring 1-2 times a month, lasting for around a day, that usually improve with rest, hydration, and over-the-counter analgesics. He also describes weakness in the left upper limb and right lower limb, as well as tremors in his hands. He also recently described episodes of vertigo with a feeling of instability, which are severe enough to halt all activities of daily living. These episodes occur 1-2 times a month, during sleep, and sometimes affect his ability to move his mouth and talk. These attacks are not related to his headaches. Additionally, he experiences intermittent episodes of shaking, sweating, and dizziness, which generally resolve within a few minutes of sitting. There are no attacks of decreased awareness. He had normal range vitals for the first clinic encounter with Tympanic Temperature of 36.3 degrees, Peripheral Pulse Rate of 80

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bpm, Respiratory Rate of 20 breaths/min, Systolic Blood Pressure of 126, Diastolic Blood Pressure of 84, and Oxygen Saturation of 99%.On physical examination, there was a visual field deficit more prominent on the right side, bilateral finger-to-nose dysmetria, a difficult tandem gait, and mild left upper limb and right lower limb weakness.

His past medical history includes craniopharyngioma, which was diagnosed at the age of 7 **(Figure 1)** and treated with surgical resection 3 times for recurrence, followed by proton-beam radiotherapy after the third time. He had a placement of a ventriculoperitoneal shunt at the age of 8 years. He developed panhypopituitarism following surgery, secondary adrenal insufficiency, central hypothyroidism, central diabetes insipidus, delayed puberty, growth hormone deficiency with very low Insulin-like growth factor 1 (IGF1) and insulin like growth factor binding protein 3 (IGFBP3) levels, and microcytic anemia and has been on hormone replacement since then with hydrocortisone, thyroxine, desmopressin, and testosterone intramuscular injections. He also takes anti-calcitonin gene-related peptide (anti-CGRP) rescue therapy for the migraines and betahistine for the vertigo, which were prescribed after he reported that beta-blocker therapy had not helped with the tremors or the episodes of shaking, sweating, and dizziness, as he was on propranolol 10 mg/kg twice daily.

The latest MRI of the brain illustrated T1 hyper-intense signals in the cortex of the right parietal and temporal lobes, suggestive of cortical laminar necrosis **(Figure 3)**, as well as subcortical hyper-intense signals in the right parietal and frontal lobes. Optic pathway thinning was seen, which was considered a normal post-operative finding, and mild enlargement of the third ventricle. The rest of the ventricular system showed normal caliber and configuration with hydrocephalus **(Figure 3)**. A diagnosis of SMART syndrome was made, and the patient was started on Verapamil with continued clinical monitoring. The decision to initiate our patient on Verapamil is based on its already established benefit in preventing migraines and vasospastic pathophysiology. SMART syndrome is currently thought to involve impaired cerebrovascular autoregulation, radiation-induced vascular dysfunction, and cortical spreading depression, all of which contribute to the presentation with stroke-like and migrainous symptoms [4, 5, 6, 8]. Verapamil has been widely utilized and approved for the prophylactic treatment of migraines by preventing cortical spreading depression and stabilizing vascular tone. Since current literature predicts that these pathophysiological mechanisms also contribute to the development of SMART syndrome, Verapamil was initiated.

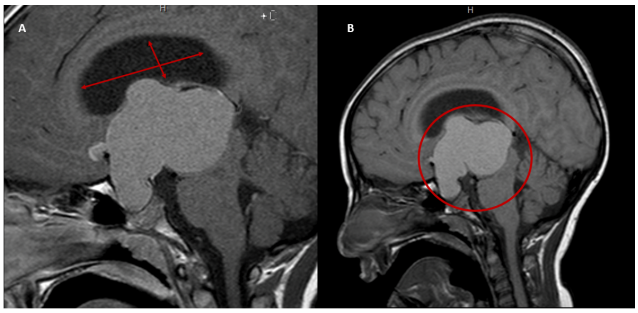

Figure 1: Presurgical sagittal views of MRI brain with contrast demonstrating a lobulated homogeneous mass in the suprasellar region. Mass appears moderately hyperintense on T1, measuring 47 x 64 mm (right panel). Post contrast view (left panel) demonstrates a thin enhancing rim but not significant enhancement of the mass, suggestive of a cystic structure filled with high protein content fluid. Obstructive hydrocephalus is noted.

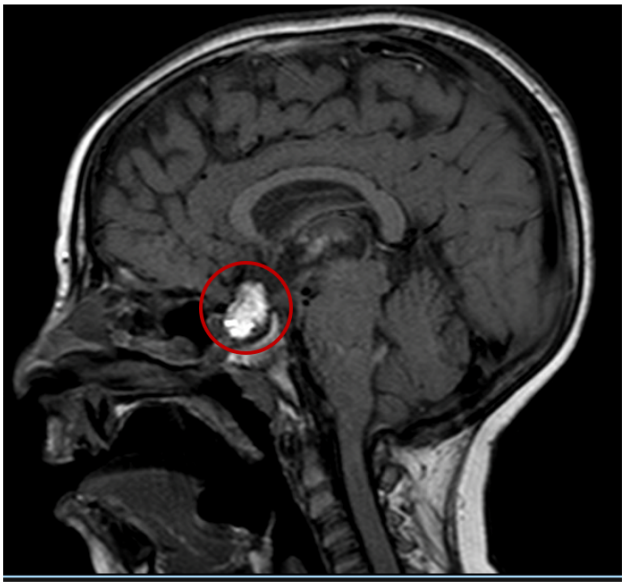

Figure 2: Post-transsphenoidal removal of Craniopharyngioma, sagittal views of MRI brain with contrast demonstrating a 13 x 21 mm organized blood clot at the place of completely resected tumor. Appearing to have high signal intensity on both pre- and post-contrast T1 sequences (right and left panels, respectively).

3. Discussion

SMART syndrome is an extremely rare, delayed neurological condition seen following brain radiotherapy. It has a subacute onset with manifestations including migraines with or without aura, stroke-like cortical symptoms such as hemiparesis, neglect, and aphasia, and seizures [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The acronym SMART stands for stroke-like migraine attacks following radiation therapy and was first termed by Black et al. [2], although the first ever described cases were by Shuper et al. [9], who described a series of pediatric patients with severe migraines and stroke-like symptoms following radiation.

Pathophysiology is not completely understood, but theories have been postulated. These theories include radiation-induced trigeminovascular endothelial dysfunction [6], impaired cerebrovascular autoregulation [5], cortical spreading depression [4], and disruption of the blood-brain barrier [8]. Radiation-induced mitochondrial dysfunction has also been theorized [1]. Imaging findings seen in SMART syndrome include transient or permanent unilateral gyriform enhancement with or without T2/FLAIR hyperintensity involving the cortex and adjacent white matter in the area that was previously treated with radiation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Diagnostic criteria were initially proposed by Black et al. [2] and included 1) a remote history of external beam cranial irradiation; 2) prolonged, reversible signs and symptoms referable to a unilateral cortical region beginning years after cranial irradiation, including seizure, migraine with or without an aura, and stroke-like symptoms; 3) transient, diffuse, unilateral gyriform enhancement sparing the white matter within a previous radiation field; and 4) not attributed to another disorder [2], but are not the gold standard

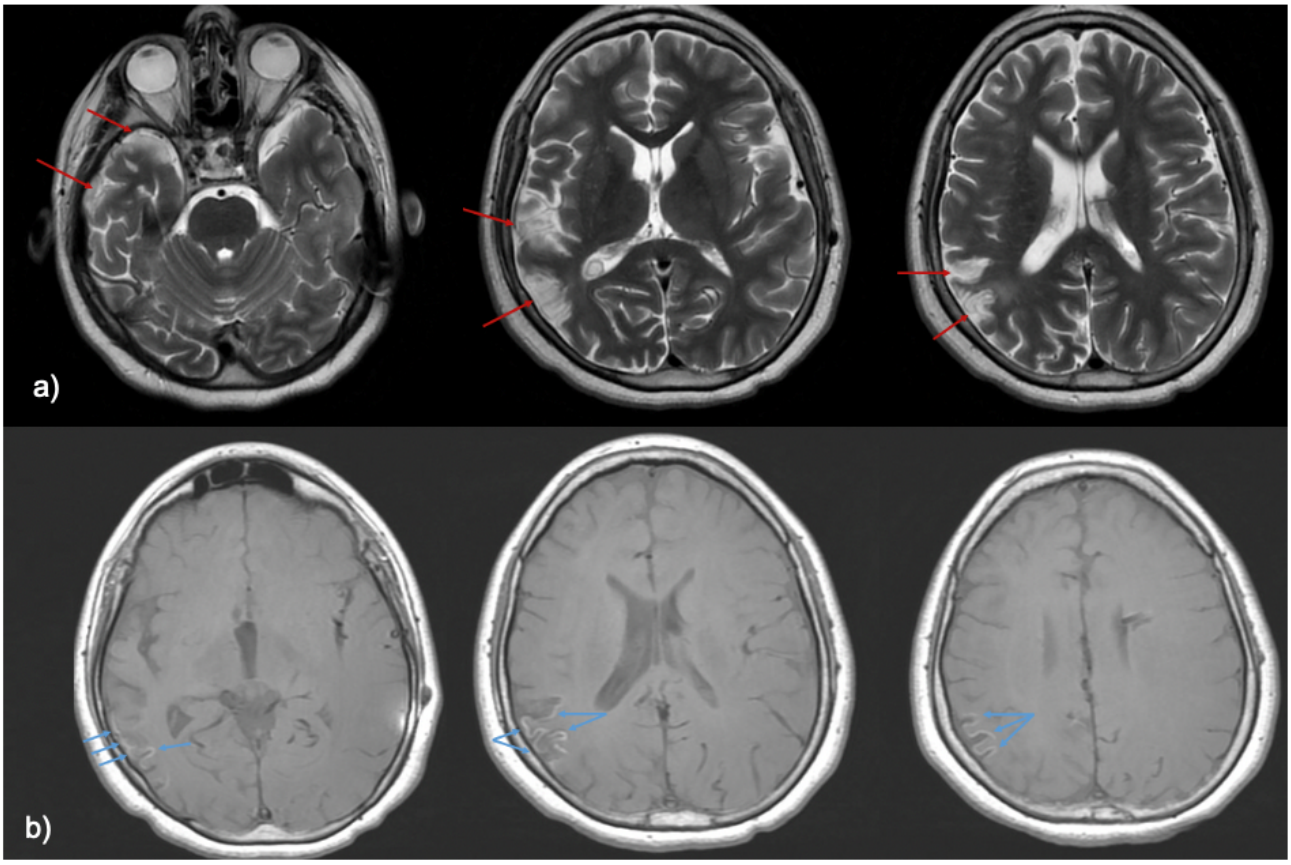

Figure 3: Overall stable findings with chronic changes in the surgical bed, there is a right posterior lateral temporal parietal region localized cortical T2 hyperintense signal with encephalomalacia (panels labelled "a", red arrows) and diffuse gyral T1 hyperintense signal compatible with laminar necrosis (panels labelled "b", blue arrows), suggestive of SMART syndrome.

as further cases of SMART syndrome have been reported that do not strictly adhere to these criteria [12].

Our case represents one of the four reported instances of SMART syndrome following proton beam radiotherapy [5, 7, 10]. Notably, our patient experienced vertigo, a symptom infrequently observed in SMART syndrome, which was similarly described by Huang et al. [5]. In addition, cerebellar signs, including dysmetria and impaired tandem gait, were documented by Maramattom et al. [7] and were also observed in our patient, although their case involved radiotherapy delivered directly to the brainstem. Huang et al. [5] proposed that proton beam radiotherapy may accelerate the onset of SMART syndrome, as evidenced by their patient's symptom development within 2 years. In contrast, in the case series by Winter et al. [10], symptoms emerged within 4 years in one patient and 14 months in another. Although this case does not strictly meet the imaging criteria proposed by Black et al. [2] due to the absence of transient gyriform enhancement and the presence instead of cortical laminar necrosis [12], it fits within an increasingly recognized spectrum of atypical SMART syndrome presentations [5, 7, 10]. Given the patient's history of proton beam radiotherapy, characteristic clinical symptoms, and exclusion of other etiologies, this case aligns with a broader, evolving definition of SMART syndrome that acknowledges irreversible imaging findings such as laminar necrosis as potential manifestations, especially in severe or delayed onset presentations [12]. This reinforces the need for flexible diagnostic criteria and clinical awareness of SMART syndrome variants in post-radiotherapy patients.

Also, Maramattom et al. [7] reported focal brainstem and leptomeningeal enhancement, a finding previously not seen, and suggested that brainstem SMART syndrome be termed as "Be-SMART syndrome". It is important to note in our patient that, while he did have cerebellar signs on examination (dysmetria and impaired tandem gait), his MRI findings show no involvement of the brainstem or cerebellum. In our patient, cortical laminar necrosis was observed, which is a recognized complication of proton beam radiotherapy linked to vascular dysfunction [13]. This finding suggests a potential shared pathophysiological pathway between SMART syndrome and radiation necrosis [5, 13]. Moreover, Huang et al. [5] have proposed that the presence of radiation necrosis may lower the threshold for developing SMART syndrome, serving as a precipitating factor in its onset. Currently, cortical laminar necrosis in SMART syndrome cases is thought to correlate with permanence of symptoms and lack of meaningful recovery [12], as is the case with our patient, with persistence of symptoms for several years. Previously, SMART syndrome was thought to be reversible but has been described as being permanent in a case series by Black et al. [12].

This case presents a complex and atypical variant of SMART syndrome that doesn't fit neatly into previously described categories. At the same time, the reported cases involved a 38-year-old man with classic hemispheric SMART symptoms like migraines, transient aphasia, and MRI showing gyriform enhancement after proton beam therapy [5]. The second described a teenage girl with brainstem-only symptoms now referred to as Be-SMART [7], our 18-year-old patient falls somewhere in between. He experiences not only migraines but also crossed limb weakness, tremors, dysmetria, vertigo, and transient speech difficulties during sleep, suggesting more widespread cerebral involvement. His MRI findings are also distinct, showing cortical laminar necrosis and subcortical signal changes, rather than the typical gyriform enhancement. What further sets this case apart is the latency. His symptoms appeared nearly a decade after proton RT, in contrast to the accelerated onset seen in the Winter et al. [10] case series, where the only other SMART cases following proton therapy occurred at 14 months and 4 years post-treatment. Treatment with verapamil was initiated, consistent with current practice, but the addition of CGRP-targeted therapy and betahistine reflects a more tailored approach to his diverse symptoms. Altogether, this case might represent a diffuse or overlapping SMART subtype somewhere between classic and Be-SMART and highlights the need to broaden the clinical and radiologic spectrum by which we understand SMART syndrome.

4. Conclusion

Our case highlights an atypical presentation of SMART syndrome following proton beam radiotherapy for a craniopharyngioma, marked by episodic vertigo, dysmetria, and impaired tandem gait—symptoms not typically associated with this syndrome. The MRI findings of cortical laminar necrosis and subcortical hyperintensity suggest a potential shared vascular pathophysiology between SMART syndrome and radiation necrosis. Recognizing such atypical features is crucial for clinicians evaluating patients with a history of brain irradiation, as early and accurate diagnosis can lead to targeted treatment and help avoid unnecessary invasive procedures.

Conflicts of Interest

The authors declare that they have no competing interests.

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Institutional Review Board (IRB)

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient's parents have given their informed consent to publish this case (including publication of the images).

Large Language Model

None

Authors Contribution

MA and AY provided conceptualization; MA and MH curated and collected information; MA, MH, and AY provided writing and original draft preparation; MA was in charge of supervision; MH has reviewed and proofread the final manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability

Patient data related to this study are not publicly available but can be obtained upon request from the corresponding author.

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