SMART Syndrome: A Case Report

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Research Article

Keywords: Brain radiation, Stroke-like migraine attacks after radiation therapy

Posted Date: January 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1224291/v1

Abstract

Introduction: Stroke-like migraine attacks after radiation therapy (SMART) syndrome, is a late complication of brain radiotherapy. (1) Symptoms are commonly subacute in onset and involve migraine type of headache, seizures, focal neurologic deficits.(2) . MRI findings are usually unilateral and posterior predominant cortical-subcortical hyperintensity, swelling and prominent gyriform (cortical and leptomeningeal) gadolinum enhancement in the areas of brain that underwent irradiation with or without diffusion restriction.(1) There is no standard treatment protocol of SMART syndrome. Antiepileptics and corticosteroids are commonly used drugs.

Case Report: A 65 years old woman diagnosed with breast cancer with brain metastases and treated with more than 50 Gy brain radiotherapy. A couple of months later patient presented with acute right sided weakness and numbness, episodic myoclonic jerking of the right arm and leg and gait instability. MRI and magnetic resonance angiography of the brain with gadolinium revealed left parietooccipital cortical diffusion restriction and accompanying dilatation of the left posterior cerebral artery as new findings. Computed tomography perfusion revealed increased perfussion in the affected area. The patient was diagnosed with SMART syndrome.

Management & Outcome: The patient was treated with dexamethasone (16 mg/day) and anticonvulsant therapy. Myoclonic seizures had almost completely remitted. However, her cognitive impairment persisted, then the patient arrested because of aspiration a month later.

Discussion: Besides confirming SMART syndrome, diagnostic investigations is also important to exclude other etiologies. Posterior reversible encephalopathy syndrome, post-ictal changes, meningoencephalitis and cerebrovascular diseases are radiological differential diagnosis which should be considered.(3) Proper and early diagnosis of SMART syndrome is significant to refrain unneccessary aggressive approaches and for appropriate treatment to prevent sequela lesions.

Introduction

Stroke-like migraine attacks after radiation therapy (SMART) syndrome, is a rare syndrome and delayed complication of brain radiotherapy. SMART syndrome was first defined in 1995.(1) Symptoms of SMART syndrome are commonly subacute in onset and involve migraine type of headache, seizures, focal neurologic signs such as aphasia, hemianopsia, hemiparesis, sensory deficits which can be seen in stroke.(2) These findings are generally reversible; however, neurological deficits and imaging sequelae may become permenant in described cases. (4) In a case series including 11 patients, 5 patients (45%) were recovered partially after treatment and laminar cortical necrosis was seen in 3 of them (27%). (4)

Magnetic resonance imaging (MRI) examination is necessary for both detecting SMART-specific findings and ruling out other etiological reasons. MRI pattern of SMART syndrome presents usually unilateral and posterior predominant cortical-subcortical hyperintensity, swelling and prominent gyriform (cortical and

leptomeningeal) gadolinum enhancement in the areas of brain that underwent irradiation with or without diffusion restriction.(1)

SMART syndrome is a clinical and radiological diagnosis and must be based on a coherent medical history. Even though there is no targeted treatment of SMART syndrome, corticosteroids may improve neurological deficits. There are reports of patients with partial or complete recovery of symptoms after pulse therapy with corticosteroids. (1)

In this report, we present a case of SMART syndrome with characteristic clinical and radiological findings who was treated with corticosteroids and anticonvulsant therapy.

Case Report

A 65 years old woman diagnosed with breast carcinoma. The patient was treated with neoadjuvant chemotherapy, surgery and breast irradiation.

Three years later, MRI showed irregular metastatic lesions with microhemorrhages in the left parietooccipital and right cerebellar lobes. Following tumour excision, pathology result was compatible with breast cancer metastasis. Antiepileptic treatment was started after surgery. The patient received focal brain radiation. Left occipital cavity, residual tumor and right cerebellar lesion were irradiated with 30 Gy each in 6 fractions by stereotactic body radiotherapy (SBRT). After radiotherapy MRI showed reduction of multiple brain metastases in comparison to the previous result and there was no newly developing lesion.

A follow up visits, two years later, MRI demostrated increase in metastatic lesions and the disease was progressing. The patient was treated with whole-brain radiotherapy (WBRT) at 30 Gy in 12 fractions. In the MRI, a significant reduction in the diffuse edema in the posterior part of the right cerebellar and left hemisphere, a significant reduction in the left lesion enhancement and stable right cerebellar contrast enhancement were observed.

A couple of months later patient presented with a two-day history of acute right sided weakness and numbness, episodic myoclonic jerking of the right arm and especially right leg and gait instability. She had speech diffuculty. Physical examination was unremarkable. On neurologic examination, she had confusion and she was agitated and not oriented. Her speech was meaningless. Pupils were symmetric and reactive. Direct and indirect pupillary reflexes were positive. Cerebellar testing, motor, sensory and cranial nerve examinations were limited by poor cooperation. Initial laboratory results were all unremarkable except for thrombocytopenia. Platelet count was 63 (x 10^3/μL).

Computed tomograpy (CT) scan of the head did not demonstrate any acute abnormalities, showed chronic stable left occipital postsurgical changes. Lumbal punction was not performed due to lack of evidence of meningeal irritation. MRI and magnetic resonance angiography (MRA) of the brain with gadolinium revealed left parietooccipital cortical diffusion restriction and accompanying dilatation of the

left posterior cerebral artery as new findings. Initial necrotic metastatic lesions in the right cerebellum and left parietooccipital lobes and diffuse T2 hyperintensity were also demonstrasted.

Computed tomography perfusion (CTP) demonstrated increased cerebral blood flow (CBF) and cerebral blood volume (CBV) and reduced mean transit time (MTT) at the posterior cerebral artery (PCA) territory of the left hemisphere.

The patient was diagnosed with SMART syndrome based on radiologic findings, clinical features and history of brain irradiation.

Electroencephalogram (EEG) showed diffuse theta wave and epileptiform discharges in the left parietooccipital lobe. She was treated with dexamethasone (16 mg/day) and loading dose of phenytoin (1000 mg). Levetiracetam could not be performed due to history of rash with levetiracetam. The patient received pregabaline (1x75 mg) and clonazepam (2x5 drops).

During follow up in the oncology department, EEG was performed to rule out non convulsive status epilepticus because of continuing of myoclonic jerkling of the right upper and lower extremities. There was no significant change in EEG.

The patient was not treated with valproate due to thrombocytopenia and with diphenylhydantoin due to the risk of interaction with current chemotherapy. Lacosamide (2x50 mg) was given and control EEG demonstrated no epileptiform discharges. After all treatment, myoclonic seizures had almost completely remitted. However, her cognitive impairment persisted. At follow up, the patient arrested because of aspiration a month later and follow-up imaging could not be done.

Discussion

We report a patient who had typical clinical and radiological picture is compatible with the SMART syndrome. SMART syndrome is a unique, rare neurologic complication of brain radiation and includes temporary, reversible neurological dysfunction which may present with migrainous headache, seizures. (5)

The pathophysiology of the SMART syndrome is not clearly unknown. It is known that radiation may cause vasculopathy that leads to distruption of blood brain barrier. (5, 6) On the other hand, trigeminovascular system is affected by radiation which results in impairment of homeostasis. (5, 6) Development of SMART syndrome is related with radiation dosage exceeding 50 Gy; however, some cases of SMART syndrome have been described with radiation dosage less than 50 Gy. (6, 7) Our patient was treated with more than 50 Gy.

MRI findings may include typical gyriform, unilateral cortical gadolinium enhancement and minimal leptomeningeal enhancement.(4) In our case; slight cortical diffusion restriction was main MRI finding without cortical enhancement. Perfusion CT revealed increased perfussion in the affected area (Figure I).

Previous reports also documented increased perfusion with perfusion CT, MR perfusion(8), single photon emission tomography and positron emission tomography in SMART syndrome. (9)

Besides confirming SMART syndrome, diagnostic investigations is also important to exclude other etiologies. Neuroimaging with gadolinium enhanced brain MRI and MR or CT angiography, lumbar puncture for CSF analysis, EEG, serum lactic acid level could be beneficial to rule out other etiologies which have similar presentations with SMART syndrome. (10)

Posterior reversible encephalopathy syndrome (PRES) has similar clinical presentation which consists headaches, neurological deficits and seizures with SMART syndrome. Gyral enhancement is a radiological finding which may be seen in PRES.(3) Underlying mechanism of PRES is thought to be vascular pathology related with altered integrity of blood brain barrier, neuroradiological changes in PRES tend to be seen in bilateral hemispheres.(11) Post-ictal changes, meningoencephalitis and cerebrovascular diseases are radiological differential diagnosis which should be considered.(3)

There is no standard treatment protocol of SMART syndrome. Antiepileptics and corticosteroids are commonly used drugs. There are cases recovered without corticosteroid treatment at least partially.(12) However steroid therapy should be considered as spare unnecessary invasive procedures.(12) Moreover, corticosteroids has shown encouraging outcome in some cases.(1)

Most cases reported in the literature had complete recovery, but about 15% exhibited permenant sequelae in a large case series. (1) Despite high-dose corticosteroid therapy, the expected benefit from the treatment could not be seen in our patient due to the advanced stage of malignancy.

Conclusion

This report highlights a rare but reversible late complication of brain radiation. Clinical suspicion and neuroimaging findings are significant to diagnose SMART syndrome. SMART syndrome should be considered in all patients with history of radiation therapy who present neurological deficits and parieto-occipital MRI alterations. Proper and early diagnosis of SMART syndrome is significant to refrain unneccessary aggressive approaches, such as brain biopsy and for appropriate treatment to prevent sequela lesions including cortical laminar necrosis hence neurologic deficit.

Declarations

Research Ethics And Patient Consent

Written informed consent for patient information and images to be published was provided by the patient’s legally authorized representative.

Funding: The authors received no financial support for this article.

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

The data is availbility statement:N/A (Case report)

Author Contributions: Concept – SB, HCY; **Design** – SB, HCY; **Supervision** – A SB, HCY; **Resources** – SB, HCY, KKO, BT; **Materials** – SB, HCY, ŞP, KKO; **Data Collection and/or Processing** – SB, HCY; **Interpretation** – SB, HCY, ŞP; **Literature Search** – SB, HCY; **Writing** SB, HCY, BT NK **Manuscript** – SB, HCY, ÖD; **Critical Review** – SB, HCY, DCG.

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Figures

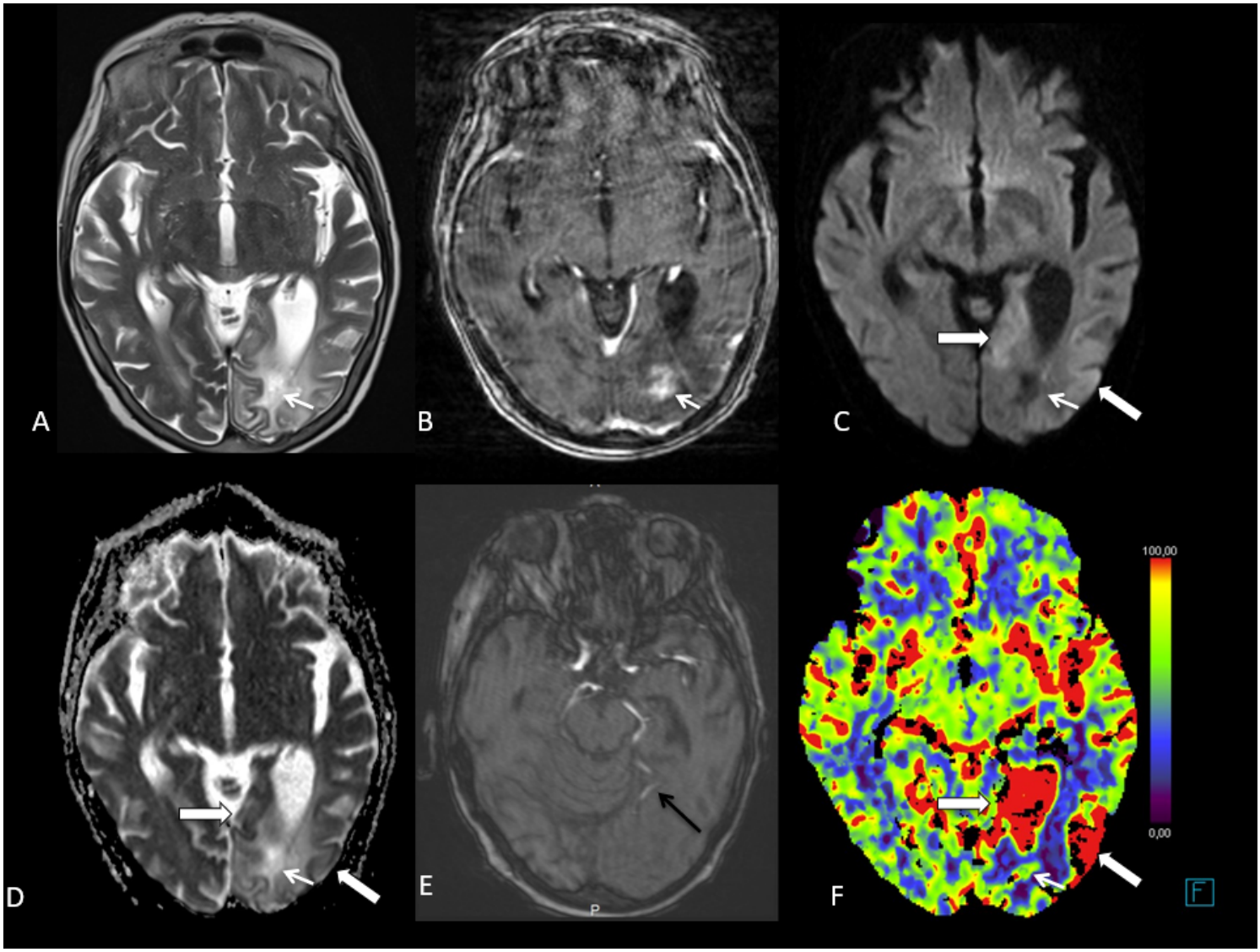

Figure 1

Heterogeneous T2 hyperintense necrotic lesion (thin arrows) (**a**, T2WI) with contrast enhancement (**b**, postcontrast T1WI) did not demonstrate diffusion restriction (**c,d**; DWI and ADC map) or increased perfusion (**f**, CBF map). Left parietooccipital cortical slight diffusion is seen as hyperintensity on DWI and hypointensity on ADC map (thick arrows). Note the PCA dilatation on TOF-MRA (**e**, black arrow). Areas with diffusion restriction showed prominent increased perfusion (**f**, CBF map)