

Stroke-like migraine attack after cranial radiation therapy: the SMART syndrome

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ABSTRACT

We describe a patient who experienced a prolonged episode of headache, drowsiness, seizure, unilateral weakness, delusion and hallucination due to a stroke-like migraine attack after cranial radiation therapy. Stroke-like migraine attack after radiation therapy (SMART) syndrome is a rare complication of therapeutic brain irradiation.

CASE REPORT

A 46-year-old man presented with severe throbbing headache centred on the right orbit and forehead three days after an injection of Ozurdex (a dexamethasone intravitreal implant used to treat radiation-induced macular oedema). He also experienced drowsiness, difficulty speaking and left arm tingling and weakness.

Eleven years previously, he was treated for Philadelphia chromosome-positive acute lymphoblastic leukaemia. His management included splenectomy, chemotherapy and allogenic stem cell transplantation. He had received cranial irradiation (24 Gy) and whole-body irradiation (12 Gy). He was now in complete remission. Complications had included chronic graft-versus-host disease, cardiomyopathy and radiation-induced retinopathy requiring left eye enucleation. He also had attacks, dating back 9 years, which consisted of evolving paraesthesia in either arm, spreading over minutes on to the face, sometimes becoming bilateral. He sometimes also had blurred vision or expressive dysphasia. Severe episodes were accompanied by drowsiness and could last up to 48 h. Rizatriptan helped to settle the attacks. To explain these episodes, our possible diagnoses included migraine, posterior reversible encephalopathy syndrome, cerebral vasculitis, arterial thromboembolic events, cerebral venous

sinus thrombosis, infective processes, seizures and relapse of acute lymphoblastic leukaemia; we excluded all except migraine. He underwent extensive investigations that were normal including MR cerebral angiography, echocardiogram, thrombophilia screen, EEG and repeated extended cerebrospinal fluid (CSF) analyses. Mutation screening for mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) was negative. MR scan of brain 9 years before acute presentation had showed mild radiotherapy-related cortical atrophy evolving over years to white matter leukoariosis (figure 1A). His other regular medications included amitriptyline, aspirin, atorvastatin, prednisolone and mycophenolate mofetil.

On examination at presentation, he was drowsy but scored 15 on the Glasgow coma scale when roused. He had a left hemiparesis and neglect. His right pupil was light-responsive and the fundus was normal. He was afebrile and general examination was normal.

Extensive re-evaluation for infection, vasculitis, autoimmune and leukaemic processes was negative. The CSF opening pressure was 26.5 cm and contents were normal, including extended virological examination. Contrast-enhanced MR scan of brain on day 2 of admission showed the known extensive white matter leukoencephalopathy, but with new cortical swelling and enhancement in the right cerebral hemisphere (figures 1B and 2), which did not respect any vascular border.

MR scan of brain with spectroscopy on day 10 showed increased right-sided cortical swelling (figure 1C). Susceptibility-weighted imaging also showed multiple small cavernomas (presumed to be radiation-induced). There was no lactate rise on spectroscopy.



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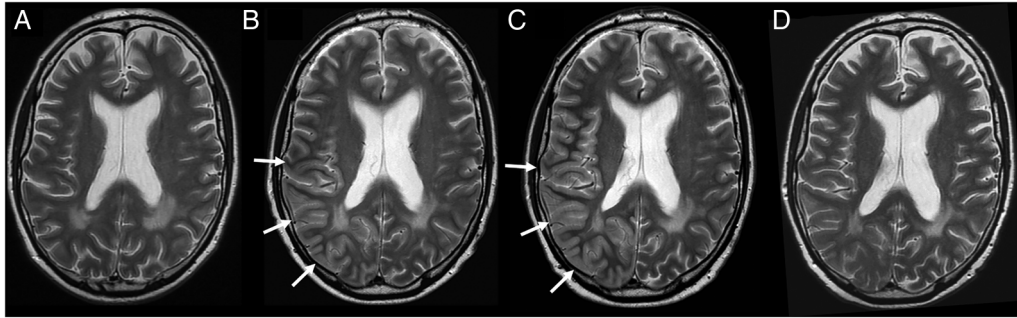


Figure 1 MR scan of brain (axial T2-weighted): (A) 7 months before the acute presentation with stroke-like migraine attack after cranial radiation therapy. (B) Two days into the acute presentation, showing right posterior frontal, parietal and occipital cortical T2 hyperintensity and swelling (arrows). (C) Ten days into the presentation showing more marked cortical oedema (arrows). (D) Two months after the acute presentation, with resolution of the cortical oedema. Note the static bilateral parietal leukoaraiosis.

We diagnosed stroke-like migraine attack after cranial radiation therapy (SMART) syndrome, based on the clinico-radiological findings. During his first week of hospitalisation, he developed episodes of complex partial seizures, which settled with levetiracetam and sodium valproate. He continued to have headache, confusion and drowsiness punctuated by periods of delusional speech, visual hallucinations and disturbed behaviour requiring benzodiazepine sedation. An EEG showed no epileptic activity during these periods.

After 3 weeks, he became more alert. On day 39, he was transferred to a neurorehabilitation facility for 2.5 months. The left hemiparesis and neglect resolved, but his abnormal mental state persisted for some weeks. This was treated with quetiapine. We stopped the sodium valproate due to hyper-ammonaemia. A non-contrast MR scan of brain 2 months after onset (figure 1D) showed his right-sided cortical oedema had improved.

Over the next six months, he had four episodes lasting less than an hour in which he had confusion and it was uncertain whether these were due to migraine or epileptic seizures. He has now largely recovered.

DISCUSSION

As mentioned earlier, SMART syndrome is an acronym for ‘stroke-like migraine attacks after

radiation therapy’.¹ Patients with a remote history of brain radiotherapy develop a distinctive set of clinico-radiological features comprising recurrent attacks of prolonged hemispheric neurological symptoms and signs, usually headache, and sometimes seizures, in association with transient cortical gadolinium enhancement and swelling (see box 1 for the 2006 diagnostic criteria). Patients may have a personal history of migraine or seizures pre-dating the onset of their SMART episodes.² We do not know the minimum dose of brain irradiation that predisposes to the syndrome, but unlike our patient, most reported cases have had a much greater radiation exposure (>50 Gy).^{1 3} We do not know whether our patient’s Ozurdex injection contributed or was merely coincidental.

SMART syndrome is probably quite rare. The first report in 1995⁴ described four children with ‘complicated migraine-like episodes after cranial irradiation’. There have since been further case series.^{2 3} Most cases show a latent period between irradiation and onset of between 14 months and 30 years. Neurological impairment may not be fully reversible.²

MR brain scan findings in SMART syndrome include cortical T2 and fluid-attenuated inversion recovery hyperintensity affecting one hemisphere, with gyral enhancement (see box 2 for radiological

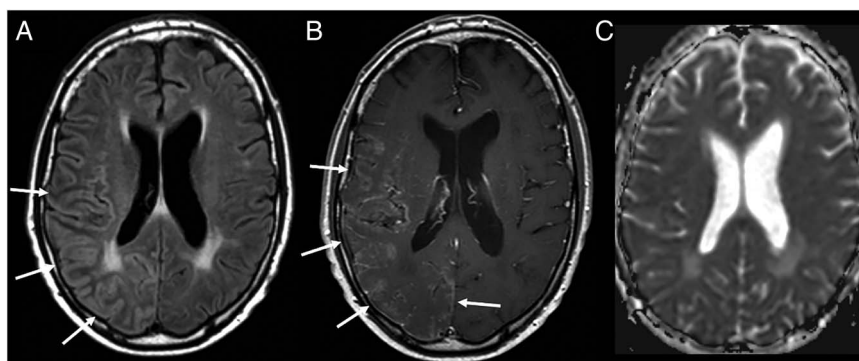


Figure 2 MR scan of brain (axial) on day 2 of the acute presentation showing (A) right posterior frontal, parietal and occipital cortical hyperintensity and swelling (arrows) on fluid-attenuated inversion recovery, with corresponding cortical enhancement on the postcontrast T1-weighted image (B). Note the absence of diffusion restriction on the corresponding diffusion-weighted imaging apparent diffusion coefficient map (C).

Box 1 Black *et al*'s¹ revised diagnostic criteria for stroke-like migraine attack after cranial radiation therapy syndrome

- A. Remote history of external beam cranial irradiation without evidence of residual or recurrent neoplasm
 - B. Prolonged, reversible signs and symptoms referable to a unilateral cortical region beginning years after irradiation
- Manifestations may include
- ▶ confusion
 - ▶ seizures
 - ▶ headache with the attacks
 - ▶ visuospatial deficits
 - ▶ hemisensory deficits
 - ▶ hemiparesis
 - ▶ aphasia
 - ▶ antecedent migraine with or without aura starting after irradiation.
- C. Transient, diffuse, unilateral cortical gadolinium enhancement of the cerebral gyri sparing the white matter within a previous radiation field
 - D. Not attributable to another disorder

differential diagnosis of gyral signal change) and are most prominent in the temporal, parietal and occipital regions. Diffusion-weighted abnormalities are either minimal or absent.² MRI changes may occur without clinical or EEG evidence of epileptic seizures^{1–3}. The MRI abnormalities may not be evident in every attack, and changes may also be delayed 2–7 days after onset and tend to resolve within 2–5 weeks.² SMART syndrome may be complicated by cerebral infarction and some scans show permanent sequelae due to cortical laminar necrosis.²

Four cases with pathological examination have shown only non-specific gliosis.² Postulated mechanisms include an impaired trigemino-vascular system, cerebral hyperexcitability, postradiation neuronal dysfunction, mitochondrial damage and vascular endothelial injury.^{1–3} The unilaterality of MRI abnormalities in SMART syndrome is reminiscent of familial hemiplegic migraine, which can sometimes be

Box 2 Radiological differential diagnosis of diffuse gyral signal abnormalities

- Acute infarction (arterial or venous)
- Posterior reversible encephalopathy syndrome
- Viral encephalitis
- Mitochondrial disorders, for example, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and other metabolic conditions, for example, urea cycle disorders
- Postseizure cortical swelling
- Hemiplegic migraine

associated with cortical oedema and enhancement contralateral to the hemiplegic side.²

There is no evidence base to guide treatment. Corticosteroids, antiplatelet agents, propranolol and verapamil have all been used with uncertain benefit. Early symptomatic treatment of seizures is important.

SMART syndrome is a diagnosis of exclusion, and continued surveillance for other causes remains important. An awareness of SMART syndrome may prevent unnecessary investigations.

Key points

- ▶ Stroke-like migraine attack after cranial radiation therapy (SMART) syndrome is a rare late complication of therapeutic cranial irradiation.
- ▶ This syndrome has a unique clinical and radiological picture, with neurological deficits attributable to a unilateral cortical region, usually with headache and seizures, together with swelling and gadolinium enhancement of the affected cortex.
- ▶ Neurological recovery may be complete or incomplete.
- ▶ There is no evidence base to guide treatment.
- ▶ SMART syndrome remains a diagnosis of exclusion; awareness of the syndrome may prevent an unnecessary brain biopsy.

Correction notice This article has been corrected since it was published Online First. In Box 1, point A, the phrase “without evidence of residual or recurrent symptoms” has been removed from the sentence “Remote history of external beam cranial irradiation without evidence of residual or recurrent neoplasm without evidence of residual or recurrent symptoms”.

Contributors SYL was involved in the drafting and revision of the manuscript, as well as the literature search and review. JB contributed to the writing of the manuscript. RD was the first to raise the diagnosis of SMART syndrome in this patient. He also provided the neuroimaging figures for the manuscript and contributed to the discussion section of the text. MO was responsible for extensive review and editing of the manuscript.

Competing interests None declared.

Patient consent Obtained.

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