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Case Report

CASE REPORT

Rare and rarer: co-occurrence of stroke-like migraine attacks after radiation therapy and Charles Bonnet syndromes

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Abstract

A 30-year-old man presented with new onset severe headache and homonymous hemianopia, with a subsequent seizure, on a background of a right parietal astrocytoma resected at age 5 with adjuvant chemotherapy and radiotherapy. Magnetic resonance imaging of the brain revealed post-surgical and radiotherapy changes only and a clinical diagnosis of Stroke-like Migraine Attacks after Radiation Therapy (SMART) syndrome was made. Vision subsequently recovered gradually over a 6-week period, however, during the recovery phase he reported well formed hallucinations in the affected hemi-field consisting of small mammals, particularly possums, which gradually became less distinct as vision recovered; a phenomenon which was felt likely to represent the Charles Bonnet syndrome.

BACKGROUND

SMART syndrome is a delayed complication of brain irradiation consisting of migraine headaches, transient focal neurologic deficits and seizures. Although this condition is rare, it is likely of increasing importance for several reasons. Firstly, there are a greater number of long-term survivors of brain radiation therapy as we are becoming more successful at managing intracerebral primary malignancies. Secondly, given an upward trend in the number of cases and case series published in the literature since it was first described in 1995 [1], it likely represents an under-recognized and emerging iatrogenic condition. Awareness of this syndrome is critical as its early recognition may prevent a patient from receiving unnecessary and highly invasive investigations such as brain biopsy.

Although a set of diagnostic criteria for the syndrome have been proposed [2], it is recognized that there is wide clinical spectrum of the disease. Notably there is variability in time of onset after radiation, recurrence and reversibility of the neurologic deficits, presence of seizures as well as with the neuroradiological findings.

In this case we highlight the main clinical features of the syndrome developing in the absence of the classic magnetic resonance imaging (MRI) changes, as well as a novel clinical development in the recovery phase.

CASE PRESENTATION

A 30-year-old man presented to the emergency department with a right-sided retro-orbital headache of rapid onset 2 days

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previously. He also reported bumping into objects such as doorways and tables on his left side over a similar period.

At age 5 he had a right parieto-occipital anaplastic astrocytoma resected, with adjuvant chemotherapy and radiation therapy. He had 3D conformal external beam radiotherapy at a dose of 6000 cGy over 30 fractions applied directly to the right parieto-occipital field. His last follow-up MRI was at age 15 and reported to show post-surgical change and some giant Virchow–Robin spaces, presumed secondary to radiotherapy. Prior to this presentation there was no history of headache or seizures and no recorded neurological deficit. He ran his own gardening business.

On examination he was normotensive and afebrile. He was alert and orientated with no signs of meningism. Examination revealed only a dense left homonymous hemianopia. A computed tomography scan of the head at this time showed multiple cystic lesions in keeping with historic imaging.

The following day an MRI brain revealed multiple periventricular and posterior sub-cortical cystic lesions in keeping with post-radiation changes with surrounding non-specific T2 high signal (Fig. 1A), post-contrast scans revealed no enhancement (Fig. 1B). A screen for vasculitis was weakly positive for antinuclear antibody at 1:160 but negative for extractable nuclear antigen, dsDNA, p-ANCA and c-ANCA.

At this time, a provisional diagnosis of stroke-like migraine attacks after radiation therapy (SMART) syndrome was made, despite not having the classic radiological evidence to support it. The differential diagnosis considered in our case included: local tumour recurrence or leptomeningeal disease, a stroke, the posterior reversible encephalopathy syndrome (PRES) and the genetic condition mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS).

On Day 4 of admission his headache worsened despite symptomatic treatment. A lumbar puncture (LP) was performed which had a normal opening pressure of 13 mm of water. The CSF sample was acellular with a normal protein and glucose. The headache did not improve following the LP and that evening he became distressed and complained of a 'spinning white light' in his vision. Shortly after this he had a 3 min tonic–clonic seizure, requiring midazolam, with a prolonged period of post-ictal agitation. He was transferred to the intensive care unit (ICU) for further observation. An electroencephalogram (EEG) showed right cortical dysfunction with a slow delta frequency with admixed alpha frequencies. He was initiated on sodium valproate 500 mg bd.

He was discharged from ICU after 24 h but remained in hospital to treat complications of the seizure, including shoulder dislocation and aspiration pneumonitis. During this time the headache improved spontaneously and he remained seizure-free.

On Day 10, formal visual field testing confirmed a persisting left homonymous hemianopia. He was headache free and discharged home to be reviewed following a further MRI.

On review 8 weeks after the initial presentation he was well and headache free. He was back at work. There had been no further seizures and he remained on sodium valproate. MRI appearances were unchanged.

His visual loss had improved gradually over the 6 weeks after discharge and at the time of review fields were full to confrontation, however, during the recovery phase he had reported both to family members and his general practitioner (GP) seeing small animals, particularly groups of possums, in his blind hemi-field. He was not distressed by this, recognizing the images to be hallucinatory, however, his GP felt the symptoms may represent seizure activity and increased his sodium valproate dose. Shortly after this, as his vision improved, the hallucinations became less distinct and subsequently disappeared.

At this stage we believed possible alternative diagnoses such as stroke, tumour recurrence, leptomeningeal disease, PRES and MELAS could be excluded. This was based on the observation that he had remained normotensive during the entirety of his admission, he had normal serial MRI scans unchanged from age 15 with no evidence of diffusion restriction or tumour recurrence, a normal LP and normal inflammatory markers. The test of time showed that, clinically, this man with a history of cranial irradiation at a young age had a transient migraine headache lasting days, a single seizure and a visual field deficit which had resolved over weeks—a triad that is classical for SMART syndrome.

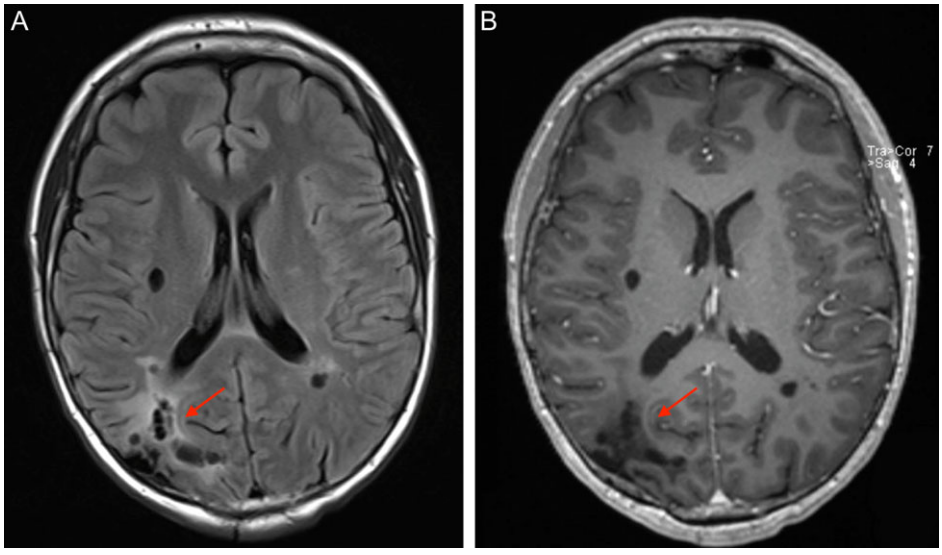

Figure 1: MRI scan performed on Day 3 post-onset of headache. (**A**) Axial, T2 FLAIR, showing giant Virchow–Robin spaces in the previous radiotherapy field (red arrow) and surgical bed with surrounding non-specific T2 high signal. (**B**) T1-weighted post-contrast sequence with no evidence of local enhancement.

DISCUSSION

What is now known as SMART syndrome was first reported in 1995 in children with prior cranial irradiation who presented with transient episodes of unilateral headache and focal neurological signs. Reports of adult patients with similar clinical features with imaging abnormalities were first published in 2003 [3]. The spectrum of clinical findings has subsequently expanded with other patient cases to include seizures [4–6], recurrent episodes [7] and permanent deficit [8]. The pathophysiology of the condition remains unknown.

Classically, transient diffuse unilateral cortical gadolinium enhancement is seen on MRI and has been proposed by several groups as a diagnostic criterion for SMART syndrome [2, 9]. However, it is appreciated that MRI changes are not evident in all attacks [10–12] and that there may be a variable time window to capture such changes [8, 12, 13]. Postulated mechanisms for these reversible imaging abnormalities, which are not specific for SMART syndrome, include local meningeal/parenchymal hyperperfusion or inflammatory extravasation following blood-brain-barrier disruption [14].

Onset of SMART is usually between the first 1–5 years after radiotherapy [2] but reported up to 37 years after treatment [10]. Ages of affected patients have ranged from 3 to 88 years [2]. The majority (55%) of patients recover fully after SMART, however, a significant portion of patients have persistent neurological deficits including hemiparesis, aphasia or cognitive impairment [8]. Seizures are commonly recognized and can include focal seizures, generalized seizures and status epilepticus [6]. Electrocephalogram can be normal during an active period of SMART, however, non-specific slowing is most commonly seen. Focal or diffuse epileptic discharges have been observed on ictal EEG during clinical events [2].

Treatment for SMART is supportive without evidence-based guidelines. Sodium valproate and levetiracetam have been used most commonly for seizures [2]. Corticosteroids have been administered in many patients, however, their impact remains unclear [10]. Use of aspirin and verapamil has been described for prophylaxis of recurrent events, however, the effectiveness of this approach has not been substantiated.

Charles Bonnet (1720–93) was a Swiss naturalist and philosopher who first described the visual hallucinations of an otherwise well man with blindness due to cataracts. Visual release hallucinations are an under-recognized symptom in people with varying degrees of visual impairment, and are more common in elderly patients with a reported prevalence of 10–15% [15]. Hallucinations are generally well formed and may include people, landscapes or animals and can change in character, complexity or duration over time [16]. We believe this is the first reported case of Charles Bonnet syndrome occurring in the context of SMART syndrome. As expected, upon resolution of the visual field deficit, the patient's hallucinations ceased.

CONCLUSIONS

SMART syndrome is a rare transient neurological syndrome observed in a growing population of patients who have previously received radiation therapy to the brain. Although unilateral post-gadolinium cortical enhancement on MRI is highly suggestive of the condition, its absence should not preclude a diagnosis of SMART syndrome. SMART syndrome remains a diagnosis of exclusion and alternative diagnoses should be considered and appropriately ruled out. Early diagnosis is important to avoid inappropriate interventions and to be able to counsel patients on the generally positive prognosis. In patients with visual field deficits, awareness of the possibility of Charles Bonnet syndrome may help alleviate distress from the transient visual hallucinations.

DECLARATIONS

Ethics approval and consent to participate

The patient has consented for the use of personal health information including reports, test results, clinical images and radiology to be accessed and used for the purposes of publication as a medical case report.

Availability of data and material

The data that support the findings of this study are available from Queensland health but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Queensland health.

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AUTHORS' CONTRIBUTIONS

All authors were involved in the clinical inpatient care of the patient and contributed to writing the article. M.B. continues to follow-up the patient in an outpatient setting. P.B. reviewed the literature for previous cases of SMART syndrome and wrote the background and case presentation. M.D. wrote the discussion. All authors read and approved the final article.

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Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

GUARANTOR

All three authors are guarantors for this article.

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