SMART syndrome

SMART syndrome, an acronym for stroke-like migraine attacks after radiation therapy, is an uncommon delayed complication of brain radiotherapy. It is probably a more severe manifestation of peri-ictal pseudoprogression (PIPG).

Epidemiology

Since the first case of stroke-like migraine attacks after radiation therapy (SMART) syndrome was described by Shuper et al. [1] in 1995, nearly one hundred cases have been reported worldwide [2] Although SMART syndrome is extremely rare, improvements in cancer survival rates are very likely to result in an increase in the frequency of this entity.

Pathophysiology

The pathophysiology of SMART syndrome is poorly understood. In all the cases reported, patients had previously received brain radiation therapy. Although the syndrome was initially associated with high doses (>50Gy), cases have also been reported in patients receiving lower doses [3] [4] all cases occurred after doses ranging from 15 to 64Gy [5].

Neurotoxicity disrupts the blood-brain barrier, damages endothelial cells, and causes vascular smooth muscle cell proliferation and vascular fibrinoid necrosis, ultimately leading to vascular occlusion. This explains why the pathogenesis of SMART syndrome was attributed to these factors. However, in the series published by Black et al., [6] brain biopsy studies did not identify vascular alterations, but rather nonspecific gliosis. Proposed causes of SMART syndrome include disruption of the trigeminovascular system and radiation-induced neuronal dysfunction, which suggests that the syndrome may bear a greater resemblance to migraine or epilepsy than to cerebrovascular disease [7].

Clinical features

Patients usually present with seizures and subacute stroke-like episodes with symptoms such as hemiplegia, aphasia, and hemianopia [8] These episodes have been associated with headaches and are often preceded by a migraine-like aura [9] [10].

Involves complex migraines with focal neurologic findings in patients following cranial irradiation for central nervous system malignancies.

In most instances, patients have a history of seizures

SMART syndrome is characterised by subacute onset of neurological symptoms (aphasia, hemianopsia or complete vision loss, hemiparesis, hemiparaesthesia, hearing loss), seizures, migraine-like headache, and encephalopathy of varying severity, ranging from mild psychomotor retardation to severely impaired consciousness [11].1 In the largest series published to date, [12] the most frequent symptoms were neurological deficits and headache. SMART syndrome completely resolved in most cases, but some patients were left with sequelae or even experienced relapses. The course of the syndrome seems to be relapsing-remitting.

Pathology

The precise mechanism that underlies SMART syndrome is uncertain and biopsies obtained from some patients do not reveal specific abnormalities above and beyond those expected in previously irradiated brain [13]

It is hypothesized that SMART syndrome represents an exacerbation of normal post-ictal phenomena due to prior radiotherapy [14]

Diagnosis

They can be generally summarized as follows:

patient: history of cranial irradiation (typically years ago) with no residual/recurrent tumor

clinical: prolonged (usually reversible) symptoms referrable to a unilateral cortical area that has been irradiated

imaging: prominent gyral enhancement (usually transient) within an area of previously irradiated brain

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Mean time from brain radiation therapy to diagnosis of SMART syndrome was 10 years (range, 1-35) [15]

Diagnostic criteria for stroke-like migraine attacks after radiation therapy syndrome.

(1) History of brain radiation therapy for malignancy

(2) Prolonged, reversible clinical manifestations (mostly years after radiation therapy), which may include migraine, seizures, hemiparesis, hemisensory deficits, visuospatial defect, aphasia, etc.

(3) Reversible, transient, unilateral cortical gadolinium enhancement, associated with abnormal T2-weighted and FLAIR signal of the affected cerebral region

(4) Eventual complete or partial recovery, with the duration of recovery ranging from hours to weeks

(5) No evidence of residual or recurrent tumour

(6) Not attributable to another disease [16].

Radiographic features

CT

On initial imaging, a region of relatively minor low density with mass effect can be seen. Features of laminar necrosis in the involved territory, such as cortical calcifications, can be seen following the initial episode.

MRI

MRI is the modality of choice to investigate SMART syndrome. Importantly, imaging abnormalities do not precede or coincide with symptom onset; rather, it takes 2-7 days for imaging abnormalities to develop [17] As such, if imaging is performed early, a repeat scan is advisable a week later to have a better chance of identifying abnormalities.

MRI typically shows unilateral cortical hyperintensities on T2-weighted and FLAIR sequences, with gyriform enhancement, predominantly in the temporal, parietal, and occipital lobes. Diagnosis of SMART syndrome is clinical and radiological and must be based on a compatible medical history. In 2015, Zheng et al. [18] reviewed the criteria established by Black et al. [19] and proposed a new set of diagnostic criteria. Alternative diagnoses include brain radiation necrosis. Although brain radiation necrosis may occur at any time, it has been reported to present at 10 to 16 months post-treatment in several series [20] [21] [22] [23] Although no pathognomonic radiological signs of brain radiation necrosis have been described, MRI typically reveals necrotic lesions, usually with surrounding oedema and mass effect. These findings are described as having a “Swiss cheese” or “soap bubble” appearance [24] [25] [26].

Treatment

Little is known about the mechanisms behind the disorder, making successful treatment challenging.

No targeted treatment is available; management of these patients focuses on symptom control. While corticosteroids may improve neurological deficits, their use continues to be controversial [27] [28] [29] [30] [31] [32].

SMART syndrome was initially thought to be self-limiting with gradual and complete resolution over the course of several weeks; typically occurring within 2-5 weeks but can take up to 3 months 4,6.

However, incomplete clinical recovery is not uncommon (up to ~45% of subjects in one series 6). In a smaller proportion of patients (~27%) permanent imaging sequelae are also encountered consistent with cortical laminar necrosis, visible within a few weeks of presentation

Case reports

Armstrong et al. reported 2 new cases of SMART syndrome in pediatric patients as well as review all documented cases of the syndrome. Each of our 2 pediatric patients suffered multiple episodes. Attacks were characterized by severe headache, visual disturbance, aphasia, and weakness. Recovery occurred over several days to weeks. The data from all documented reports of SMART syndrome indicate a greater prevalence for male gender. An age-dependent pattern of onset was also observed, with a greater variability of syndrome onset in patients who received cranial irradiation at a younger age. SMART appears to be a reversible, recurrent long-term complication of radiation therapy with possible age- and gender-related influences [33].

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