

SMART syndrome[☆]

Síndrome de SMART



Dear Editor:

Survival rates among patients with cancer have increased in recent years. However, the prognosis of lung cancer continues to be poor, especially at advanced stages of the disease¹; brain metastases require radiation therapy in most cases.² This has led to an increase in the incidence of late adverse effects of brain radiation, such as leukoencephalopathy and radiation necrosis.³ Since the first case of stroke-like migraine attacks after radiation therapy (SMART) syndrome was described by Shuper et al.⁴ in 1995, nearly one hundred cases have been reported worldwide.⁵ 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. We describe the case of a patient who presented SMART syndrome.

Our patient was a 62-year-old woman, a smoker of 40 packs/year, with history of stage IIA papillary adenocarcinoma of the lung (pT2bN0M0) diagnosed in 2013. She underwent pulmonary lobectomy and received chemotherapy (4 sessions of cisplatin and docetaxel). She presented tumour progression in 2015, and 3 brain metastases were detected. She underwent surgical removal of the right occipital lesion and received whole-brain radiation therapy (30 Gy over 10 sessions). Three years later, she consulted due to visual alterations and weekly episodes of 4-12 hours' duration of holocranial pulsating headache of 7-8/10 intensity on the verbal analogue scale, associated with photophobia (but not phonophobia or osmophobia), clinophilia, and increased sensitivity to mechanical stimulation. The patient reported painless vision loss and progressive, sustained weakness of the left arm and leg. The physical examination revealed no fever, normal blood pressure, left homonymous hemianopsia, visual agnosia, and hemiparesis affecting the left arm and leg. A complete blood count, biochemical analysis, and autoimmunity study all yielded normal results. An electroencephalography revealed no abnormalities. A brain MRI scan revealed postsurgical changes in the right occipital pole and above this location, involving the right parietal and occipital lobes. The affected region displayed cortical thickening and hyperintensity on T2-weighted sequences, associated with subcortical oedema and marked gyral enhancement (Fig. 1). Treatment with intravenous dexamethasone (4 mg/6 h) improved visual and motor symptoms.

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 (>50 Gy), cases have also been reported in patients receiving lower doses^{6,7}; all cases occurred after doses ranging from 15 to 64 Gy.⁸ Neurotox-

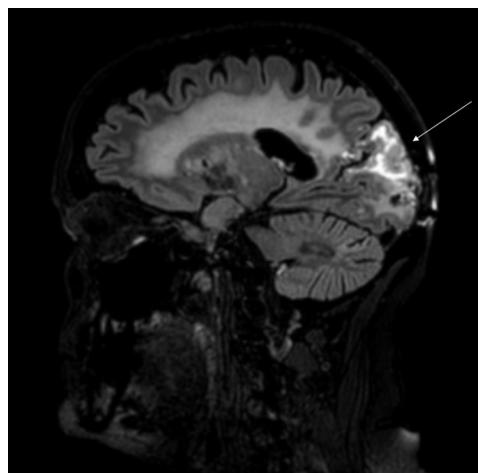


Figure 1 T2-weighted brain MRI (sagittal plane). Cortical thickening and hyperintense signal associated with subcortical oedema and gyral enhancement.

icity 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.,⁹ 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

Mean time from brain radiation therapy to diagnosis of SMART syndrome was 10 years (range, 1-35).⁵

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.¹⁰ In the largest series published to date,⁵ 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.

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.¹⁰ reviewed the criteria established by Black et al.¹¹ and proposed a new set of diagnostic criteria (Table 1). 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.¹¹⁻¹⁵ 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.^{13,16,17} No targeted treatment is avail-

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Table 1 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

Source: Zheng et al.¹⁰

able; management of these patients focuses on symptom control. While corticosteroids may improve neurological deficits, their use continues to be controversial.^{7,11,18–21}

SMART syndrome should be considered in all patients with history of radiation therapy who present neurological deficits and parieto-occipital MRI alterations.

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Vitamin E deficiency ataxia in a family with possible cardiac involvement[☆]



Ataxia por déficit de vitamina E en una familia con posible afectación cardíaca

Ataxia with vitamin E deficiency (AVED) is an autosomal recessive disorder caused by mutations in the gene that encodes α -tocopherol transfer protein (*TTPA*), located on chromosome 8q12.3.¹ These mutations cause low vitamin E levels due to impaired hepatic transport of the vitamin despite adequate intestinal absorption.² The condition is characterised by a cerebellar syndrome with ataxia, extensor plantar reflex, areflexia, and sensory deficits, resembling Friedreich ataxia.^{3,4} However, it may present with other neurological (dystonia, tremor, myoclonus) and non-neurological symptoms (retinitis pigmentosa, xanthelasma, tendon xanthomas, or cardiac alterations).⁵

We present the case of a 27-year-old woman who had presented difficulty speaking and walking since the age of 8 years. At a later age she developed cerebellar ataxia with falls. Her paternal grandmother presented gait alterations, and her parents were consanguineous (Fig. 1). Her father presented hypertrophic obstructive cardiomyopathy.

General examination of the patient revealed kyphoscoliosis and pes cavus. The neurological examination revealed scanning speech and transient gaze-evoked nystagmus at bilateral extreme gaze positions, associated with a mild increase in saccadic latency. The patient also presented generalised hypotonia, bilateral dysmetria, dysidiadochokinesia, truncal ataxia with positive Romberg sign, gait instability, wide-based gait with irregular walking cadence, difficulty in tandem walking, generalised areflexia, bilateral Babinski sign, and reduced vibration sensitivity in both legs. A brain MRI scan revealed platybasia. Electromyography detected marked alterations in the dorsal column and pyramidal tracts for both the upper and the lower limbs. A transthoracic echocardiogram revealed no alterations.

Our first diagnostic hypothesis was Friedreich ataxia, given the symptoms of progressive ataxia with areflexia and presence of bilateral Babinski sign, although a study of the frataxin gene detected no abnormalities. A biochemical analysis confirmed vitamin E deficiency,

with an α -tocopherol concentration of 4.72 $\mu\text{mol/L}$ (normal range, 18.6–46.2 $\mu\text{mol/L}$). The remaining laboratory parameters yielded normal values. Diagnosis of AVED was confirmed by *TTPA* gene sequencing: the patient was found to be a homozygous carrier of the pathogenic variant c.513_514insTT. α -Tocopherol levels were normal in the patient's mother and low in her father (11.61 $\mu\text{mol/L}$). Both parents were heterozygous carriers of the c.513_514insTT mutation.^{6–8} Genetic testing for cardiomyopathy revealed that the father was a heterozygous carrier of *MYH6* mutation c.4288T>G. This gene encodes the α heavy chain subunit of cardiac myosin, which is mainly expressed during the development. Mutations in *MYH6* have been linked to a wide range of heart diseases, including different types of dilated/hypertrophic cardiomyopathy,⁹ such as familial hypertrophic cardiomyopathy 14 (OMIM #613251). The c.4288T>G mutation results in the replacement of leucine with valine at position 1430. According to a bioinformatic study, this is a variant of uncertain significance.

Our patient started treatment with parenteral vitamin E dosed at 800 mg/day; however, plasma vitamin E levels

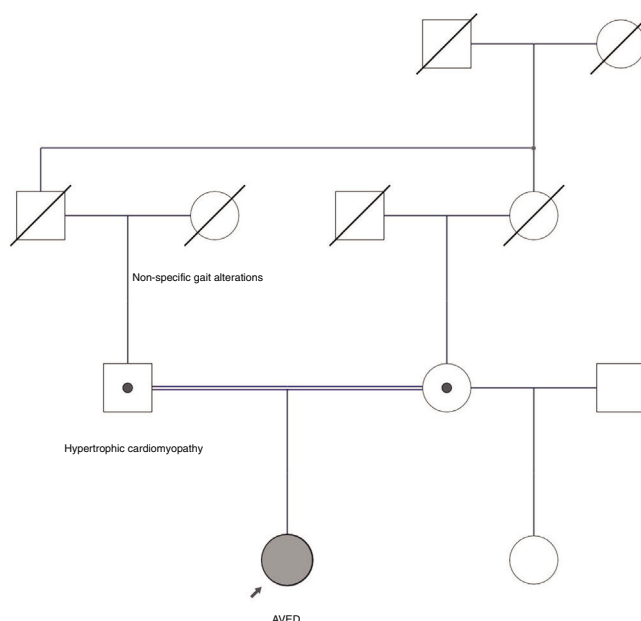


Figure 1 Pedigree chart of our patient's family. Her parents are consanguineous (first cousins) and both carry a heterozygous pathogenic mutation. The father had hypertrophic cardiomyopathy. The paternal grandmother presented non-specific gait alterations. No genetic data are available from deceased relatives.

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