

[CASE REPORT]

Stroke-like Migraine Attacks after Radiation Therapy (SMART) Syndrome Followed by Cerebral Infarction

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Abstract:

A 36-year-old man with a history of irradiation for acute lymphoblastic leukemia developed headache with cortical dysfunction lasting for 4 weeks. The clinical features were consistent with stroke-like migraine attacks after radiation therapy (SMART) syndrome. Six months later, he developed cerebral infarction due to occlusions of the left anterior and middle cerebral arteries. This is the first case report describing SMART syndrome followed by severe cerebral infarction. Although an association between the two episodes was not assumed, this case indicates that protective therapies against infarction might need to be considered for patients with SMART syndrome.

Key words: stroke-like migraine attacks after radiation therapy syndrome, irradiation, late-onset complication, acute lymphoblastic leukemia, cerebral infarction

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Introduction

While anticancer therapies have been steadily improving, the long-term outcomes are not yet fully understood. Among the therapies used to treat cancer, irradiation carries a particular risk of various early- and late-onset complications. Stroke-like migraine attacks after radiation therapy (SMART) syndrome has recently gained attention as a late-onset complication of cranial irradiation; it is characterized by migraine-like episodes that are prolonged, but usually reversible (1).

We herein describe the case of a long-term survivor of acute lymphoblastic leukemia (ALL) who was treated with chemotherapy and irradiation. He developed severe headache with cortical dysfunction lasting for 4 weeks, and subsequent severe cerebral infarction due to arterial occlusions.

Case Report

In 1995, a 15-year-old, right-handed Japanese boy devel-

oped ALL. He was treated with systemic chemotherapy consisting of intravenous methotrexate (MTX), cyclophosphamide, vincristine, and adriamycin and intrathecal injection of MTX and cytarabine. These treatments led to complete remission. However, 3 years later, he experienced a relapse of ALL with central nervous system (CNS) invasion. He was treated with intense chemotherapy including intrathecal injections again, along with total body irradiation (12 Gy in 4 fractions) and auto-peripheral blood stem cell transplantation. As a result of these therapies, he again made a full recovery, and no recurrence was observed. Neither he nor his family had any history of migraine or epilepsy.

At 36 years of age and 7 days prior to his admission, he suddenly developed visual disturbance and severe occipital headache. Non-steroidal anti-inflammatory drugs and acetaminophen proved ineffective for achieving relief from headache, which was gradually exacerbated. Three days before his admission, he became unable to use a spoon normally and could not put his right fingers in the holes of scissors; he could still use scissors as usual with his left fingers. One day before his admission, he became largely silent and

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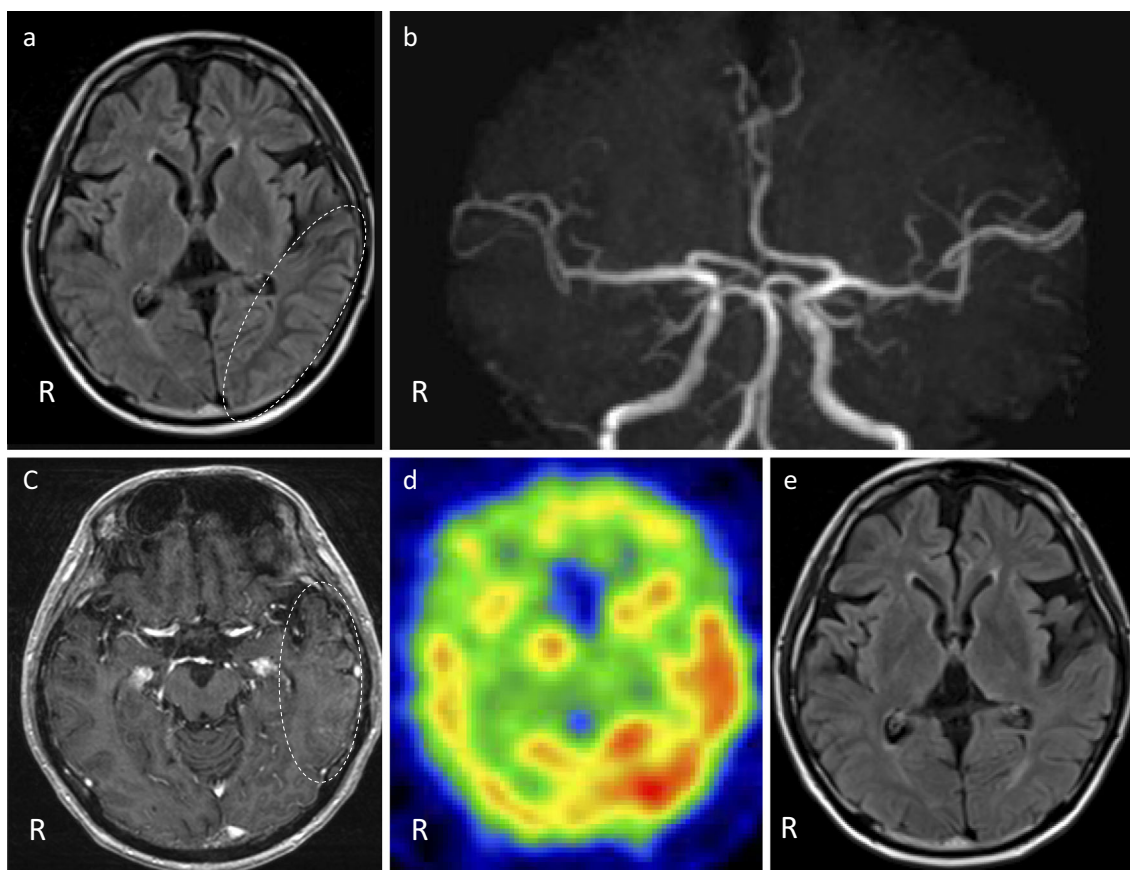


Figure 1. Images obtained during the migraine-like episode. a) Cortical swelling in the left parieto-occipital lobe (surrounded by a dotted line) on fluid-attenuated inversion recovery imaging. b) Magnetic resonance angiography showed no stenosis or occlusions. c) Mild gadolinium-enhancement (surrounded by a dotted line) in the cortex of the left temporal lobe. d) Single photon emission computed tomography showed hyperperfusion of the lesions. e) Follow-up MRI performed 4 months after admission showed improvement of the edematous changes to the left parieto-occipital cortex. In each figure, “R” indicates the right side.

could only speak a few words. Although he could obey simple orders, he could not name most objects. At this point, he was admitted to our hospital.

A neurological examination revealed severe mixed aphasia, right hemianopia, and ipsilateral pyramidal signs. Evaluation for apraxia was impossible due to aphasia. A transient generalized seizure was observed once. The results of blood and cerebrospinal fluid (CSF) analyses were mostly normal, aside from a slightly increased concentration of protein in the CSF (56 mg/dL); no leukemic cells were observed. The serum lactic and pyruvic acid concentrations were normal. A serum polymerase chain reaction to detect JC virus yielded a negative result. Repeated electroencephalography (EEG) showed diffuse slowing, but no epileptic activity. Magnetic resonance imaging (MRI) of the head on hospital day 1 showed diffuse cortical swelling of the left parieto-occipital lobes on fluid-attenuated inversion recovery (FLAIR) imaging, but no abnormalities were evident on diffusion-weighted imaging (Fig. 1a). Other findings on MRI included mild atrophy of the bilateral hemispheres, multiple white matter lesions, and microbleeds. These lesions showed no changes during the clinical course, and were therefore considered to

be older lesions that had originated from the past ALL and related treatments. No findings suggestive of recurrent leukemia or venous sinus thrombosis were seen. The results from magnetic resonance angiography (MRA) were unremarkable, and no stenosis of the major intracranial arteries was detected (Fig. 1b). Contrast-enhanced MRI on hospital day 3 showed mild gadolinium enhancement in the left temporal lobe cortex (Fig. 1c). Single photon emission computed tomography (SPECT) on hospital day 5 showed hyperperfusion of the left hemisphere (Fig. 1d).

Despite treatment with several antiepileptic agents, including fosphenytoin and levetiracetam, and venous anesthesia, the patient’s cortical deficits remained for 3 weeks. However, he then started showing gradual improvement and recovered without sequelae. He was discharged 6 weeks after admission. Follow-up MRI and SPECT performed 4 months after admission showed the complete resolution of the abnormalities in the left hemisphere, and no vascular abnormalities were apparent on MRA (Fig. 1e). He was prescribed levetiracetam (1,000 mg/day).

Six months after admission, he suddenly developed right hemiparesis and aphasia without headache, and was readmit-

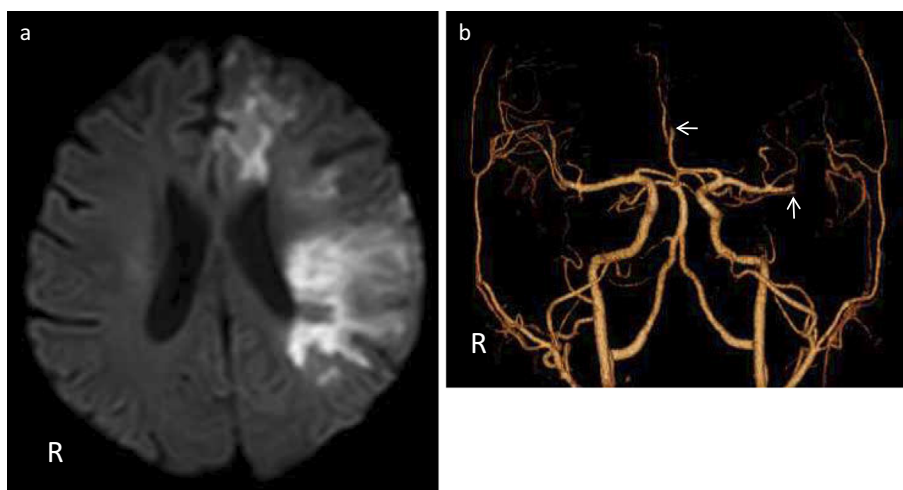


Figure 2. Images of the cerebral infarction. a) Large infarctions were apparent in the territories of the left middle cerebral artery and anterior cerebral artery on diffusion-weighted imaging. b) Computed tomography angiography showed occlusions in the left middle and anterior cerebral arteries (arrows). In each figure, “R” indicates the right side.

ted to our hospital. Neurological examinations showed severe mixed aphasia, right hemispatial neglect, and ipsilateral hemiplegia. MRI of the head showed a broad infarction in the territories of the left anterior cerebral artery (ACA) and middle cerebral artery (MCA), and computed tomography angiography (CTA) showed occlusions of the major branches of these vessels (Fig. 2). Cortical gadolinium enhancement was not detected on MRI. SPECT showed severe hypoperfusion of the left hemisphere. The results of coagulation tests were unremarkable, and the patient was negative for D-dimer, lupus anticoagulant, and anti-cardiolipin antibodies. Continuous electrocardiography showed sinus rhythm. Transthoracic echocardiography did not reveal any abnormalities, including septum defects and abnormal right-to-left shunt flow. Aortic and cervical CTA did not show any plaques or abnormalities. The patient was treated with argatroban, verapamil, and rosuvastatin. Follow-up MRA performed on hospital day 8 showed partial recanalization of the left ACA, with persistent occlusion of the left MCA. Severe aphasia and right hemiplegia remained as sequelae.

Discussion

The present case showed two distinct episodes. The first episode involved severe headache with various cortical dysfunctions, with radiological abnormalities in the left hemisphere seeming to match the neurological symptoms. As differential diagnoses, relapsed ALL, migraine, epilepsy, encephalitis, reversible cerebral vasoconstriction syndrome (RCVS), posterior reversible encephalopathy syndrome, venous sinus thrombosis, hemiplegic migraine, mitochondrial diseases and progressive multifocal leukoencephalopathy were considered. However, all of these were excluded or considered very unlikely. From the hyperperfusion on SPECT, we eventually considered the possibility of non-convulsive status epilepticus (NCSE), and administered anti-

epileptic therapies. The patient subsequently recovered without any sequelae within 4 weeks, but as repeated EEG had shown no apparent epileptic activity, the effect of the treatments was unclear.

The second episode involved a large cerebral infarction due to left ACA and MCA occlusion. Cerebral embolism was initially considered, but investigation for embolic sources detected no abnormalities. On the other hand, follow-up MRA showed partial recanalization of the ACA. Vasoconstriction was suspected as the etiology, and RCVS was considered. In this episode, however, the patient did not describe symptoms consistent with the thunderclap headache characteristic of RCVS (2). Similarly, no causative agents that could have triggered RCVS were detected.

The pathophysiology of the two episodes is largely unknown. However, we suspected that these sequential CNS events may have been related to the past history of ALL. MRI of the head showed multiple white matter lesions, microbleeds, and diffuse brain atrophy for his age, suggesting considerable cerebral damage due to ALL and the intense therapies that he had undergone.

SMART syndrome has recently been recognized as a late-onset complication of cranial irradiation (1). This rare syndrome generally develops several months or years after treatment, with the patient developing severe headache alongside various cortical dysfunctions lasting days or weeks (3). The neurological symptoms are usually reversible; however, recurrent or progressive cases have recently been reported (4). The radiological hallmark for the diagnosis of SMART syndrome is the characteristic finding of, is cortical gadolinium enhancement in a single hemisphere (1); cerebral hyperperfusion has also been reported in several cases (5). Although the pathophysiology remains largely unknown, radiation-induced endothelial dysfunction or abnormal neural excitability are suggested to potentially play a role in its development (3).

The first headache episode in the present case corresponded to SMART syndrome in many ways. The following tentative diagnostic criteria for this syndrome were proposed in a recent review article: remote history of cranial irradiation; prolonged, reversible headache or cortical deficits; unilateral cortical gadolinium enhancement with abnormal signals in the affected hemisphere on T2-weighted imaging; eventual complete or partial recovery; no evidence of residual or recurrent tumor; and not attributable to any other disease (3). The findings in the present case seemed to be consistent with these criteria. Conversely, the patient in the present case had only received 12 Gy of irradiation, which is lower than the radiation doses reported in all previously reported cases of radiation-associated SMART syndrome. Basically, most reported cases involved doses of over 50 Gy (6). However, Farid et al. reported the case of a 20-year-old woman who developed SMART syndrome after receiving a dose of only 15 Gy, indicating that the radiation dose might not be crucial for the development of SMART syndrome (7). As other risk factors for this syndrome, time since irradiation, male sex, and genetic susceptibility have been discussed (8). As for the present case, we hypothesized that intense chemotherapies, including intravenous and intrathecal MTX, might have caused additional harm to the cerebral tissue (9). Taken together, we suspected that the first headache episode belonged to the spectrum of SMART syndrome.

While the headache episode and cerebral infarction showed subsequent and ipsilateral development, an association between the two episodes was not assumed. In this regard, Black et al. reported on SMART syndrome complicated by cerebral infarction in three patients (10). Those infarctions, however, developed during the migraine-like episodes and were relatively small in comparison to the infarction seen in our case. To the best of our knowledge, no previous reports have described a patient with SMART syndrome followed by distinct cerebral infarction due to large-vessel occlusions as was observed in the present case. Considering the poor outcome of the present case, patients with SMART syndrome might be at risk of cerebral infarction, and clinicians should pay attention to this risk. Although a consensus on the treatment for SMART syndrome has yet to be established, preventive treatments for infarction, including anti-thrombotic, anti-vasoconstriction, and endothelial protective therapies might need to be considered.

We reported a case in which an unusual migraine-like episode and cerebral infarction occurred in a long-term survivor of ALL. The limitations of the present case report must be taken into account. We could not completely exclude several rare conditions or diseases, including refractory NCSE, sporadic hemiplegic migraine and atypical RCVS. The present case, however, might suggest that severe, late-onset CNS can occur as a complication of irradiation. Further cases need to be accumulated to clarify the long-term complications that are potentially related to radiation.

The authors state that they have no Conflict of Interest (COI).

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