As a result of the improved survival of patients with brain malignancies, late-onset effects of cerebral radiation are increasingly being encountered. The most common complications of brain radiation include focal necrosis, progressive leukoencephalopathy, and progressive decline in cognitive and neurological function. Stroke-like migraine attacks after radiation therapy (SMART) is a syndrome that is considered to be a delayed complication of whole-brain irradiation. Patients suffer from recurrent episodes of complicated migraine symptoms, consisting of transient neurologic deficits such as hemiparesis, aphasia, and sensory disturbances. Since it was first described in 1995, 42 cases of SMART have been reported in the literature.[1-17] Although SMART syndrome is an extremely rare condition, improvements in cancer survival rates have likely resulted in a rise in its frequency. Here, we summarize the epidemiology, clinical presentation, pathogenesis, neuroimaging, treatment, and outcomes of SMART, and to propose diagnostic criteria for this disorder.

**Epidemiology**

SMART affects both genders but is more frequently seen in men with male to female ratio of 2.2:1. Differences in endogenous sex hormones may provide an explanation for the higher prevalence of SMART in males although the prevalence of brain tumors, in general, is slightly higher in males than females.

The age at onset of SMART varies widely from 3.5 to 88 years. The interval in years between radiotherapy and the diagnosis of SMART ranges from 1 to 35 years, but most of the patients were diagnosed between 1 and 5 years. For the
27 patients with data on the radiation dose, the mean was 47.70 Gy (range: 15–64 Gy). Most patients were given a radiation dose between 50 and 64 Gy. The overall incidence of SMART is currently unknown with the limited number of cases in the literature.

**Clinical Characteristics**

SMART manifests itself in a chronic manner. All patients had received brain irradiation for various indications many years before onset of the SMART. Tumor was located in the posterior aspects of the brain (posterior fossa, pineal, cerebellum, and parietal-occipital-temporal lobes) in the majority of cases. Most of the tumors originated in central nervous system. These include ependymoma, medulloblastoma, astrocytoma, pinealoblastoma, oligoastrocytoma, primitive neuroectodermal tumor, etc. However, a small proportion of these tumors were metastatic. There does not appear to be an association between SMART and a particular tumor type.

Patients with SMART typically present usually with a varying symptomatology related to cortical dysfunction and neurological deficits, shown in Table 1. The clinical presentation is dominated marked by the chronical onset of headache. In our literature review of SMART patients, 38 patients reported headache. Headache due to SMART can be associated with nausea, emesis, photosensitivity, and focal neurological deficits. The focal neurological deficits frequently include seizure, aphasia, transient or permanent visual disturbances, hemiparesis, hemiparesthesia, hearing loss, and altered consciousness. In our literature review, neurologic deficits have been observed in 33–74% and seizures in 70–82% of patients.

**Pathogenesis**

The pathogenesis of SMART is poorly understood and currently unknown. Until now, cases of SMART have been mainly reported in western countries. Although SMART syndrome may have a relationship with race, climate, diet and living environment, publication bias cannot be excluded. With its diverse clinical and radiographic features, the underlying mechanisms of SMART may be multi-factorial.

**Table 1: Clinical features of SMART**

| Symptoms/signs referable to cortical dysfunction | Seizure |
|-----------------------------------------------|---------|
| Migraine (with or without nausea, emesis, and photosensitivity) |         |
| Symptoms/signs referable to neurological deficits |         |
| Aphasia (dysarthria, word finding difficulties) |         |
| Visual disturbances (complete visual loss, hemianopia) |         |
| Hemiparesis |         |
| Hemiparesthesia |         |
| Hearing loss |         |
| Possible additional features |         |
| Cognitive dysfunction |         |
| Intention tremor |         |
| Abnormal fatigue |         |

SMART: Stroke-like migraine attacks after radiation therapy.

Owing to the fact that the majority of patients received radiation doses of exceeding 50 Gy, it has been proposed that there may be a minimum threshold radiation dose required for the disease’s onset. However, one reported patient developed SMART after a radiation dose of only 15 Gy, suggesting that radiation dose may not play an important role.

Gliosis and perivascular cell infiltrates are typical findings on histology, while acute reversible magnetic resonance imaging (MRI) lesions are often associated with a focal seizure. It was suggested that these changes may have occurred as a result of previous venous congestion. It is uncertain if such vasculopathic changes are seizure induced, or whether they represent a primary process. Given that the clinical presentation of the posterior reversible encephalopathy syndrome (PRES) has similarities to SMART and radiation may damage endothelial cells, SMART may be a reversible radiation vasculopathy comparable with PRES.\(^{[18]}\)

However, a study on cerebrovascular reactivity provided little evidence to support vascular pathology as the primary cause in SMART. Consequently, a hypothesis of postradiation neuronal dysfunction has been proposed.\(^{[19]}\) The irradiation affects the trigeminovascular system, ion channels, mitochondria, or some combination of these resulting in migraine-like episodes. In addition, the disruption of trigeminovascular system and blood brain barrier (BBB) may lead to a lowered threshold for cortical spreading depression, thus increasing the risk for seizures. Given that subacute venous congestion has previously been associated with seizures, the pathogenesis of SMART syndrome may be closer to migraine or epilepsy than cerebrovascular diseases.

Previous studies have shown that genes play a role in familial hemiplegic migraine. Thus, it is possible that SMART syndrome could involve genes associated with hemiplegic migraines. Although the specific association is not clear, genetic analysis of this disorder may prove valuable in the future.

**Auxiliary Examination**

**Neuroradiological findings**

All of the patients underwent MRI study. Imaging plays a crucial role in the diagnostic process. MRI findings in SMART show a high degree of similarity among affected individuals. The hallmark features on MRI are reversible, transient, unilateral cortical gadolinium enhancement as well as the correlative abnormal T2 and fluid attenuated inversion recovery (FLAIR) signal. The lesions involve gray and white matter, predominantly in the posterior aspects of the brain. Given the majority of reported patients received local radiation to the posterior fossa, it is presumed that the posterior lobes are particularly vulnerable to radiation damage. Local radiation may also enhance the susceptibility of these brain regions to vascular disruptions. The mechanism of the reversible, transient T2 signal changes on MRI are
unclear, Friedenber and Dodick[16] proposed that the MRI changes result from meningeal/parenchymal hyperperfusion, edema, or inflammatory plasma protein extravasation after disruption of the BBB. However, a few patients did not demonstrate MRI changes. We believe that there is a time window in which to capture these changes.

The clinical courses of four patients were complicated by severe headache, cortical blindness, and delirium lasting up to 48 h.[11] However, they had normal cerebral angiography. Single photon emission computed tomography scan was performed in three patients and demonstrated hyperperfusion in the region of previous cranial irradiation.[6] Fluorodeoxyglucose positron emission tomography was performed in one patient and demonstrated hypermetabolism in the involved areas.[6]

Brain magnetic resonance spectroscopy was described in one patient and showed a decrease of N-acetyl-aspartate (NAA), and increases of creatine (Cr) and choline (Cho), suggesting neuronal destruction or transient neuronal impairment with mild nonspecific gliosis.[17] The decrease in NAA may be due to the neuronal cell loss and elevated Cho may correlate with cellular proliferation and density. Moreover, increases in total Cr can be associated with increased glial metabolism inflammatory response after damaged BBB.

**Electroencephalogram**

SMART may show a nonspecific diffuse slowing pattern. Some patients may even be normal, without epileptiform discharge. However, ictal electroencephalogram (EEG) during a witnessed seizures showed diffuse or focal epileptic discharges in a few patients.[10,11,15] Given that the seizures do not explain the clinical and radiological features and most cases failed to show epileptiform discharge, epileptiform activity during clinical seizures should not be regarded as inconsistent with a diagnosis of SMART.[11]

**Laboratory analyses**

Routine laboratory determinations including complete blood count, serum electrolytes, liver and renal function tests, and immunologic studies are usually normal. Cerebral spinal fluid (CSF) opening pressure is always normal. CSF testing such as glucose and protein levels may reveal normal or nonspecific abnormalities that are inconsistent with any inflammatory, infective, or neoplastic etiology.[6,10,15] If performed, other CSF studies including bacterial, viral, and immunologic studies produce normal results.

**Histologic findings**

Five patients proceeded to biopsy of the enhancing lesion for suspicion of tumor recurrence.[15,16] One patient’s histologic findings revealed gliosis and perivascular cell infiltrates, while the others failed to demonstrate any pathologic etiology.

**Diagnosis**

Diagnosis of SMART is based on medical history, clinical characteristics, and radiological investigations. Extensive investigations are mandatory to exclude alternative diagnoses that may mimic SMART. To date, validated diagnostic criteria for SMART syndrome are not available, Bartleson et al.[5] and Bradshaw et al.[11] highlighted core features of SMART syndrome, which were history of cranial irradiation, completely reversible clinical manifestations and reversible signal changes on MRI. Due to the varied clinical presentation and the potential for diagnostic confusion, we propose the following diagnostic criteria: (1) Remote history of therapeutic external beam cranial irradiation for malignancy; (2) prolonged, reversible clinical manifestations mostly years after irradiation, which may include migraine, seizures, hemiparesis, hemisensory deficits, visuospatial defect, aphasia, confusion, etc.; (3) reversible, transient, unilateral cortical gadolinium enhancement with correlative abnormal T2 and FLAIR signal of the affected cerebral region; (4) eventual complete or partial recovery with the length of recovery duration ranging from hours to days to weeks; (5) no evidence of residual or recurrent tumor; (6) not attributable to another disease.

**Differential diagnosis**

Several disorders likely to present with similar findings should be carefully excluded [Table 2]. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL),[19] familial hemiplegic migraine,[20] PRES, and tumor recurrence are the five alternative diagnoses most strongly favored in the initial evaluation.

MELAS presents with focal or generalized seizures, recurrent acute stroke-like episodes, and MRI changes like SMART. However, the stroke-like episodes in MELAS are

| Table 2: Differential diagnosis of SMART syndrome |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| SMART: Stroke-like migraine attacks after radiation therapy; MELAS: Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes; PRES: Posterior reversible encephalopathy syndrome; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; FHM: Familial hemiplegic migraine; SHM: Sporadic hemiplegic migraine; PMP: Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. |
SMART syndrome can be a self-limiting disease since the majority of patients recovered completely back to their antecedent clinical baseline, with recovery taking 1.5–2.5 months. However, a few patients had an incomplete clinical recovery with residual neurological sequelae. These include dysphasia, hemiparesis, or neuropsychological and cognitive dysfunction. Although some patients had shown complete resolution or decreased frequency of episodes over time, some patients continued to have regular events. Hence, the clinical course seems to be relapsing–remitting in nature.

CONCLUDING REMARKS
SMART is an extremely rare delayed complication of brain irradiation. Since 1995, this condition has attracted the attention of many clinicians and neuroradiologists, leading to an increasing number of case reports and small case series. To date, there are more than 40 cases reported in the literature. The pathogenesis of SMART syndrome may be closer to migraine or epilepsy than cerebrovascular diseases. However, the mechanism of pathogenesis remains unclear, which stresses the need for further studies of this condition. Until now, no specific treatment has been identified for this syndrome. Valproate and levetiracetam have benefit in terminating seizures; antiplatelet agents along with anticonvulsants appear to be candidates for reducing the risk of stroke and prevent migraine attacks. However, steroid treatment is a controversial method, which stresses the need for further studies to confirm this issue. Although a majority of the patients recovered completely, some patients can have a relapsing–remitting clinical course associated with residual neurological sequelae.

SMART is an extremely rare delayed complication of brain irradiation. However, improvements in cancer survival rates have likely resulted in a rise in its frequency. Hence, awareness and recognition of this disorder are important to make a rapid diagnosis and avoid aggressive interventions such as brain biopsy or cerebral angiography. Further studies are needed to determine the exact etiology of this disorder, its mechanism of pathogenesis, potential biomarkers as well as the optimal form and duration of treatment.

ACKNOWLEDGMENT
We thank to Harrison Xiao Bai for grammatical help after we completed this review.

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Received: 04-04-2015 Edited by: Yuan-Yuan Ji
How to cite this article: Zheng Q, Yang L, Tan LM, Qin LX, Wang CY, Zhang HN. Stroke-like Migraine Attacks after Radiation Therapy Syndrome. Chin Med J 2015;128:2097-101.

Source of Support: Nil. Conflict of Interest: None declared.