Surgically Induced SMART Syndrome: Case Report and Review of the Literature

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Key words
- Radiation
- SMART syndrome
- Trigeminovascular system

Abbreviations and Acronyms
GKRS: Gamma knife radiosurgery
MRI: Magnetic resonance imaging
RT: Radiation therapy
SMART: Strokelike migraine attacks after radiation therapy
WBRT: Whole-brain radiation therapy


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BACKGROUND: **Strokelike migraine attack after radiation therapy is a recently described clinical entity characterized by transient hemispheric dysfunction manifesting as, but not limited to, visuospatial deficits, confusion, hemisensory deficits, hemiparesis, aphasia, seizures, and, most prominently, headache in patients with a history of remote external beam radiation therapy to the brain. The radiographic hallmark on magnetic resonance imaging is the presence of transient, diffuse, unilateral gadolinium enhancement of the cortex with white matter sparing, usually corresponding to the previous radiation field.**

CASE DESCRIPTION: **We present a case of strokelike migraine attacks after radiation therapy syndrome diagnosed immediately following a craniotomy and temporal lobectomy for recurrent metastatic tumor resection after prior gamma knife radiosurgery and whole-brain radiation therapy.**

CONCLUSION: **SMART syndrome should be considered in the differential diagnosis of postsurgical patients with remote history of cranial irradiation and significant, new transient neurologic deficits not explainable by any other mechanism. It is possible that manipulation of the trigeminal ganglion, or the dura of the Meckel cave, contributed to triggering the manifestations of this syndrome in our patient during the immediate postoperative period.**

CLINICAL PRESENTATION

A 56-year-old right-handed woman presented in April 2005 with a history of stage 4 infiltrating adenocarcinoma of the right breast. At the time of diagnosis she was also discovered to have lung metastases. Following lumpectomy, she was treated with paclitaxel (Taxol), followed by six cycles of docetaxel (Taxotere) and trastuzumab (Herceptin). She was then maintained on trastuzumab and letrozole (Femara). She responded well and her malignancy was considered to be in remission by February 2006.

In March 2006 she consulted for new disabling headaches. The pain was holocephalic and accompanied by "white spots" in her vision, nausea, vomiting, photophobia, and phonophobia. A brain magnetic resonance imaging (MRI) showed two small enhancing intracranial lesions worrisome for metastases. A lumbar puncture revealed normal opening pressure and cerebrospinal fluid content, including absence of malignant cells on cytologic examination. The headaches were not felt to be directly due to the small intraparenchymal tumors, which were considered incidental. She was started on nortriptyline with some improvement in her headaches. A follow-up MRI 1 month later showed enlargement of the previously seen lesions and several new small enhancing masses consistent with multiple cerebral metastases. She underwent Gamma Knife™ (Elekta instruments, Norcross, Georgia, USA) radiosurgery (GKRS) to treat the five metastatic tumors, with each tumor receiving a marginal dose of 20 Gy and a maximum dose of 40 Gy to volumes ranging from 0.6 to 2.2 mL. A follow-up MRI 4 months later showed resolution of the intracranial tumors and she was once again felt to be in remission.

Serial MRI scanning over the next year showed enlargement of an enhancing mass at the location of a previously treated left parieto-occipital tumor. She continued to experience headaches that seemed worse following administration of trastuzumab but not so severe as to warrant discontinuation of the medication (23). The enlarging left parieto-occipital enhancing mass was resected in July 2007 without complication. The pathology was consistent with metastatic high-grade carcinoma.

In April 2009, she noticed a change in pattern of her headaches that continued to be temporally related to trastuzumab administration. These new features included flashes of light in a starburst pattern lasting approximately 20–30 minutes followed by increasingly severe headache. MRI scan at that time showed recurrence of right temporal and right occipital tumors, previously treated with Gamma Knife. She then received whole-brain radiation therapy (WBRT) receiving 3750 cGy in 15 fractions completing in July 2009. She remained clinically stable with intermittent headache and no new neurologic symptoms.

A follow-up MRI in June 2010 showed an area of increasing enhancement on the floor of the right middle fossa concerning for tumor progression despite prior GKRS and WBRT (Figure 1). An MRI obtained in September 2010 demonstrated mild increase in size of the right middle fossa lesion to 12 mm. In December of 2010 she

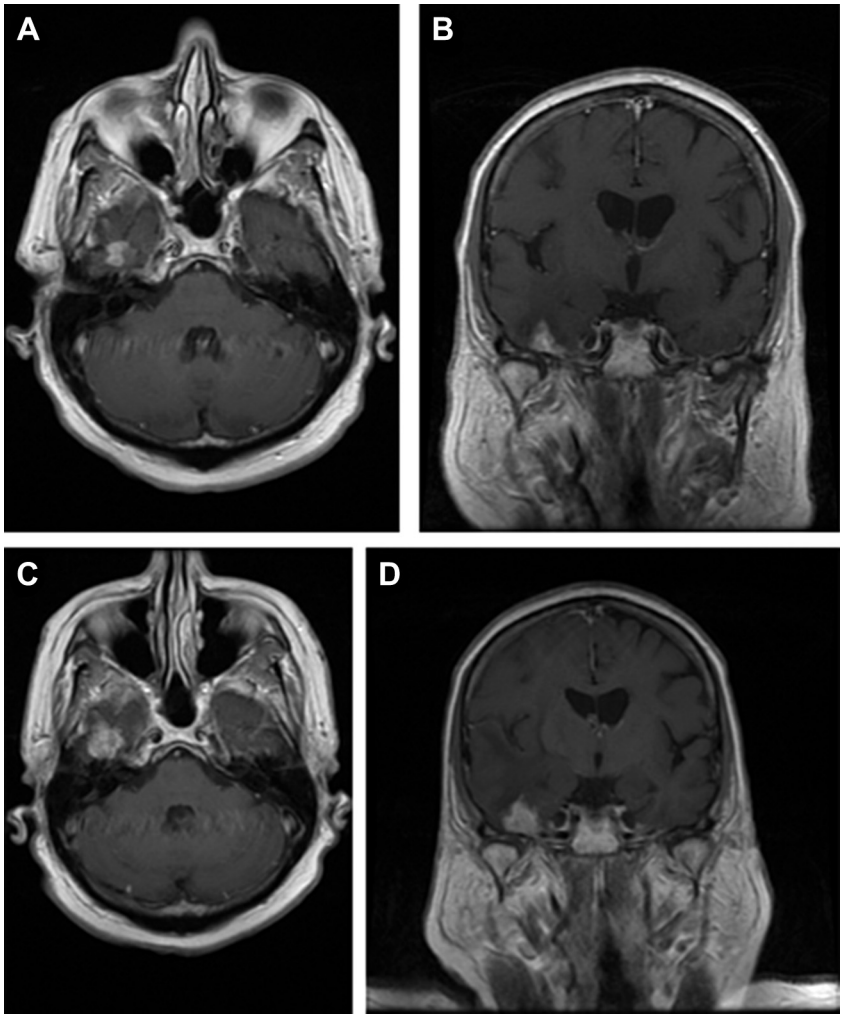

Figure 1. From June 2010 **(A, B)** to April 2011 **(C, D)**, T1 sequences with gadolinium show enlargement of the circumscribed contrast enhancing lesion on the floor of the right middle fossa. It measured 10 mm in its greatest dimension in June 2010, and 21 mm by April 2011.

was tried on lapatinib (Tykerb) but did not tolerate it, and continued on with trastuzumab and letrozole.

In May, 2011 she underwent a right frontotemporal craniotomy and anterior temporal lobectomy for removal of the enlarging right middle fossa tumor. The tumor had a dural attachment, which also was excised. There was no evidence of hemorrhage or necrosis within the temporal lobe mass. Pathology confirmed moderately differentiated adenocarcinoma, with infiltration of the subtemporal dura. Although the surgery was uncomplicated, the patient was slow to awaken from anesthesia. Once awake, she began complaining of severe head pain and was noted to have left spasticity and hemi-neglect. An urgent head computed tomography (Figure 2) only showed expected postoperative changes and right hemispheric edema, which was unchanged when compared with preoperative imaging.

She was treated with lorazepam (Ativan) and levetiracetam (Keppra) for suspected seizures without any improvement. The following morning she was alert and oriented, but still complained of severe right-sided headache. She had left-homonymous hemianopsia, right gaze preference, severe left spastic hemiparesis, left facial droop, and left hypoesthesia. Another head computed tomography confirmed the absence of any acute changes. An electroencephalogram did not show epileptiform activity; she only had the expected focal slowing over the right frontotemporal head region.

Having excluded ischemia or seizures as the etiology for new prominent neurologic symptoms following an uncomplicated anterior temporal lobectomy, the diagnosis of SMART syndrome was considered. High-dose dexamethasone (20 mg intravenous) was given in addition to her postoperative regimen (4 mg intravenously every 6 hours), with only partial relief of her headache and no change in her focal deficits. However, on postoperative day 2, her headache significantly improved along with partial resolution of her right hemispheric deficits. Brain MRI confirmed gross total resection of the right temporal lobe lesion and showed no acute ischemia. Asymmetric contrast enhancement in the area of the resection cavity and right hemisphere was observed (Figure 3), but this subtle cortical enhancement was of unknown significance. Electroencephalogram captured complex partial seizures in the early morning of postoperative day 3 that were effectively treated. Her headache and neurologic deficits were essentially resolved by postoperative day 4. She was discharged on postoperative day 7 without focal neurologic deficits.

In June 2011, she was restarted on trastuzumab and letrozole. In her scheduled follow-up visit in March 2012, she reported persistent spells of headache, sometimes associated with mild and transient left-sided weakness and speech difficulty, but without recurrent symptoms of right hemispheric dysfunction.

DISCUSSION

The SMART syndrome was first described by Bartleson et al. in two patients with prior history of radiation therapy (RT) (2). They later proposed the diagnostic criteria listed in Table 1 (3). To date, there have been 25 suspected cases described in the literature (articles restricted to English); 8 women and 17 men (Tables 2 and 3) (2-5, 11, 16, 18, 19, 21). None of them have been temporarily related or attributed to recent intracranial surgery, although many cases have history of prior craniotomies and