Clinical Exacerbation of Multiple Sclerosis Following Radiotherapy

Colleen B. Murphy, MD, BSc; Stanley A. Hashimoto, MD, FRCPC; Douglas Graeb, MD, FRCPC; Brian A. Thiessen, MD, FRCPC

Background: Radiation of the central nervous system in patients with demyelinating disease may have deleterious effects.

Objective: To describe a 30-year-old woman with multiple sclerosis who developed an attack of demyelination 2 months following radiotherapy for a parotid malignancy.

Results: Magnetic resonance imaging demonstrated new hyperintense lesions that corresponded to both the localization of the patient’s symptoms and to the area defined by the 50% isodose radiation field.

Conclusion: Radiation treatment likely triggered an exacerbation of multiple sclerosis.

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The neurotoxic effects of cranial radiotherapy are well known, ranging in severity from transient cerebral edema to radionecrosis. Disseminated plaques of demyelination that developed after radiation have been previously described. Whether patients with underlying central nervous system disease are more susceptible to these toxic effects is uncertain. We describe a patient with multiple sclerosis (MS) who developed a clinical attack of demyelination shortly after therapeutic radiation for a parotid tumor.

REPORT OF A CASE

A 30-year-old right-handed woman was diagnosed as having MS in May 1996 following the onset of limb paresthesias. An examination revealed only mild impairment of fine motor control in both hands. Her cerebrospinal fluid contained oligoclonal bands with an elevated IgG synthesis rate. Magnetic resonance imaging (MRI) revealed multiple periventricular and corpus callosal lesions (Figure 1). Evoked potentials were normal.

In November 1996, she developed a right parotid mass. Following resection, microscopic examination of the specimen revealed adenoid cystic carcinoma. Radiation therapy began in April 1997 with 5000 rad (50 Gy) delivered over 5 weeks in 25 fractions. As shown in Figure 2, the right cerebellum and brainstem were included within the 50% isodose line.

One month after completion of radiotherapy, she developed significant fatigue. A short course of intravenous corticosteroids at a local hospital coincided with new neurologic symptoms, including incoordination, slurred speech, imbalance, dysphagia, and diplopia. A subsequent course of oral corticosteroids was associated with some improvement. She was transferred to a tertiary care hospital 4 weeks after symptom onset, 10 weeks after completion of radiotherapy.

On admission, an examination revealed her to be afebrile and normotensive. She was missing her right ear and parotid gland as a result of prior surgery. Neurologically she was alert and fully oriented, with preserved memory and intact speech and comprehension. Pupillary and fundoscopic examination results were unremarkable. There was horizontal gaze–evoked nystagmus, also present on upgaze and more prominent on right gaze. Square wave jerks occurred with attempted fixation. There was a right paresis of cranial nerve VI. Complete right facial palsy had resulted from the prior surgery. The lower cranial nerves were intact. Tone and motor power were normal. Sensation to light touch, pinprick, and temperature was normal; stereognosis and graphesthesia were intact. The deep-tendon reflexes were 2+ and equal; the plantar responses were flexor. There was right-sided dysmetria in both upper and lower extremities as well as truncal ataxia. Her gait was wide-based and unsteady.

The results of hematologic tests, a urinalysis, and an electrocardiogram were normal. An MRI scan was obtained (Figure 3) and compared with the MRI from 16 months earlier (Figure 1). The interval appearance of multiple hyperintense lesions on proton density and T2-weighted images were noted, mainly within the 50% isodose line of the prior radiation field. Minimal gadolinium en-
Enhancement was observed in the periphery of the right pontine lesions and left cerebellar peduncle lesion (new). A tiny lesion in the left pons remained unchanged during the interval assessment.

Following completion of a 2-week course of oral corticosteroids, her symptoms resolved. There has been no recurrence of MS symptoms over 3 years of follow-up.

The presence of new neurologic symptoms and appropriate clinical and radiologic findings are all compatible with a diagnosis of an acute MS exacerbation. The prior diagnosis of MS and the gradual resolution of symptoms with corticosteroids support this diagnosis. It is notable that the area defined by the 50% isodose radiation field (Figure 3) corresponds to the region containing the newly identified hyperintense lesions on MRI (Figure 2), as well as to the patient’s symptoms.

This patient’s MS had been clinically quiescent prior to radiotherapy. Her neurologic symptoms appeared 6 weeks following completion of radiotherapy. An “early delayed” syndrome of radiation damage has been associated with focal neurologic signs believed to be secondary to transient demyelination. These lesions are usually seen with large doses of cranial irradiation, near brain tolerance. Prior cases of demyelination as part of the early delayed syndrome received substantially more radiation to the brainstem than this case. Although tumoricidal doses of radiation occasionally have deleterious effects on normal brains, the effects on patients with underlying demyelinating disease are less well understood.

As depicted here and previously reported, the brains of patients with MS appear to respond differently to radiation than patients without demyelinating disease. Peterson et al7 described a series of patients who received postoperative radiation for presumed neoplastic lesions, which were later demonstrated to be demyelinating. Four patients had either a previous diagnosis or current signs and symptoms compatible with MS. Patients were treated with standard tumoricidal doses of radiation, between 4000 and 6000 rad (40-60 Gy); however, the subsequent morbidity and mortality was more severe than that expected with demyelinating pseudotumors. Four of the 5 patients developed progressive neurologic disease. Two became bed-bound, and both of the patients with MS died within months as a result of progressive demyelination.

The severe clinical outcome demonstrated by Peterson et al7 is in contrast with the natural history of large demyelinating pseudotumors as described by Kepes.8 Thirty-one patients were included in this study, and al-
though all patients underwent surgical procedures to obtain a tissue diagnosis, none received subsequent radiation treatment. Patients were observed to have an excellent response to steroids, with disappearance of these large lesions on follow-up scans. Most patients did not develop progressive or recurrent disease.

In our patient, demyelinating lesions developed at sites of the brain that were previously unaffected, within the radiation portals. Although we cannot histologically compare our case with other cases of radiation-related demyelination, the radiologic appearance is in keeping with typical MS plaques, and the clinical course is consistent with an MS exacerbation. McMeekin et al\(^7\) described a clinicopathologic study of a woman with a glomus jugulare tumor treated with radiation therapy, followed by activation of quiescent MS with plaques confined to the radiation fields. These lesions may have developed in part due to an underlying predisposition to demyelination seen among patients with MS. The location of the lesions in our patient indicates that the radiation treatments may have triggered the MS exacerbation.

Radiation-induced demyelination has been previously demonstrated in animal models. The neurologic signs and perivascular cellular infiltrates characteristic of experimental allergic encephalomyelitis have been demonstrated in radiated rats.\(^8\) The extent of both paralysis and lesion burden correlate with the dose of radiation delivered. An autoimmune cause has been postulated, with radiation altering the myelin sheath, resulting in the release of an antigenic substance. Radiation-induced damage to the blood-brain barrier is likely contributory together with direct vascular and oligodendrocyte damage.

We have reported a case of clinical exacerbation of MS with radiologic evidence of demyelinating lesions following incidental brainstem irradiation during treatment of a parotid malignancy. We believe that radiation may have damaged the blood-brain barrier, allowing the immune system and central nervous system antigens to interact with white matter and produce demyelinating plaques.

Our finding that preexisting MS appears to have been activated by radiation is similar to that of McMeekin et al.\(^7\) This case also lends further support to the view of Peterson et al\(^7\) that conventional doses of radiation may result in enhanced toxicity when administered to patients with underlying demyelinating disease.

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Corresponding author and reprints: Brian A Thiessen, MD, FRCPC, Division of Neurology, British Columbia Cancer Agency, Department of Medical Oncology, 600 W 10th Ave, Vancouver, British Columbia V5Z 4E6, Canada (e-mail: bthiessen@bccancer.bc.ca).

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