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Radiation-induced central demyelination, report of a rare subacute complication and review of the literature

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Abstract

A 26-year-old woman with a right frontal diffuse astrocytoma, isocitrate dehydrogenase-mutant, WHO Grade II was treated with resection and radiotherapy (54 Gy in 30 fractions by volumetric modulated arc therapy). Ten weeks after radiation, she developed left leg weakness, and a brain magnetic resonance image demonstrated multifocal acute demyelinating brain lesions within regions that received 10-30 Gy. She improved with high dose steroids and subsequently resumed temozolomide. She had no prior history of a demyelinating disorder. The mechanisms of neurotoxicity from radiation include vascular injury, demyelination, and oxidative damage to neural stem cells and oligodendrocytes; though the pathophysiology is not fully understood. Subacute demyelination in the absence of known demyelinating disease is rare with only four cases previously described. This rare complication can be successfully managed with steroids when symptomatic. It is important to consider demyelination if new distant enhancing lesions arise following radiation of a primary brain tumor when findings are atypical for recurrence.

Keywords: Demyelination, radiation, astrocytoma, glioma

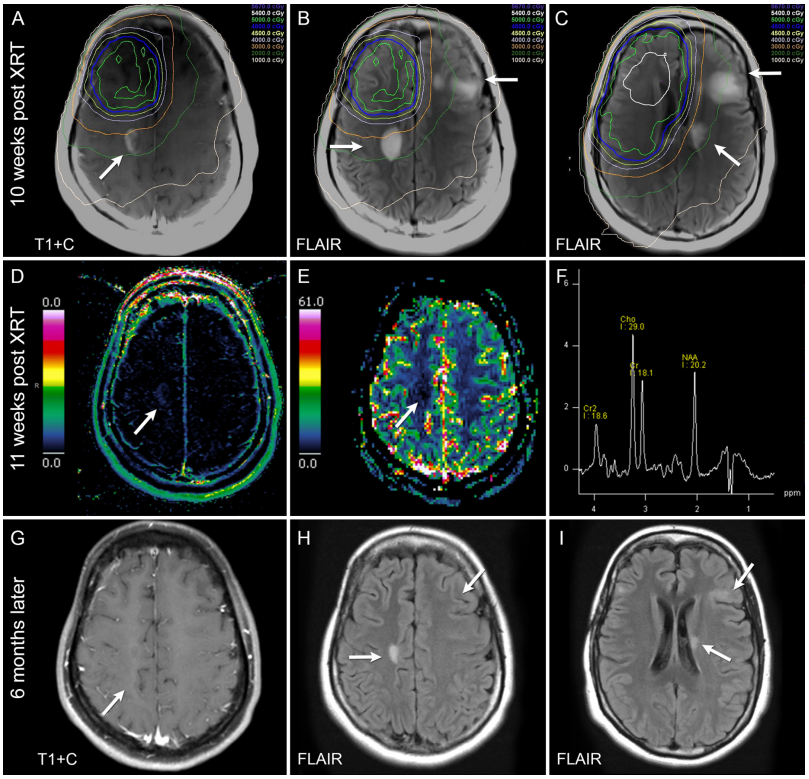

Figure 1. Top Row (A-C): Axial T1 post-contrast and FLAIR images with overlaid radiation treatment plan demonstrates an incomplete ring enhancing, FLAIR hyperintense lesion in the right posterior frontal lobe (A; arrow). There are also left frontal lobe juxtacortical non-enhancing white matter FLAIR hyperintense lesions (B, C; arrows) in the 1000-3000 cGy isodose zones. The imaging findings are consistent with acute demyelination. Middle Row (D-F): DCE perfusion MRI shows no significant increase in capillary permeability in the right posterior frontal lobe partially ring enhancing lesion (D; arrow). Dynamic susceptibility contrast perfusion MRI reveals no elevation of the rCBV in the lesion (E; arrow). MR spectroscopy demonstrates a choline to creatinine ratio < 2:1 and no significant depression of the NAA peak in the right posterior frontal lesion (F). The advanced imaging features also support demyelination. Bottom Row (G-I): Six months later, there is no longer enhancement associated with the right posterior parasagittal frontal lobe lesion (G, arrow) and there is interval decrease in size of the white matter FLAIR hyperintense lesions bilaterally (H, I; arrows)

Fifteen months after completing radiation, she developed right-sided acute vision loss associated with painful eye movements without optic nerve edema on funduscopic exam, consistent with optic neuritis. Humphrey's visual field 30-2 demonstrated marked constriction of the visual field with generalized depression in the right eye and inferior visual field deficits in the left eye. Optical coherence tomography retinal nerve fiber layer was unremarkable in both eyes. A subsequent lumbar puncture demonstrated normal protein (28 mg/dL), 0 RBCs per HPF, and 0 WBCs per HPF. IgG index was normal and oligoclonal bands were negative. She was treated with 1 g of methylprednisolone IV daily for 3 days followed by prednisone 80 mg by mouth for 11 days per the optic neuritis treatment trial[6]. She had significant improvement in her HVF testing with resolution of her pain. Her right optic nerve had received 41.6 Gy during radiation. She continues to be monitored for tumor recurrence and demyelinating episodes clinically and radiologically on surveillance imaging for tumor recurrence and demyelination without antitumoral or immunosuppressive treatment.

DISCUSSION

Central demyelination is a very rare subacute complication of radiation therapy and is important to distinguish from tumor progression due to implications on management. In our case, white matter lesions occurred subacutely in lower isodose zones ranging from 10-30 Gy, 10 weeks after completing radiation, similar to previously reported cases[7-10]. At the time of her multifocal acute demyelination, she had no prior history of a demyelinating disorder and did not fulfill criteria for multiple sclerosis by the 2017 revised

Table 1. Case details of reported radiation induced demyelination without prior history of demyelinating disease

Source	Age/ Gender	Initial diagnosis and location	Radiation dose	Demyelination symptoms and timing	Imaging or pathology finding of lesion	Clinical course
Lampert *et al.*[7] 1959	32/F	Basal cell carcinoma at left external auditory meatus	57 Gy in 20 fx	Blurred vision, diplopia, nausea, vomiting, and ataxia 2.5 months post radiation	Pathology: Demyelination of left temporal lobe, thalamus, left cerebellum, inferior pons, and entire medulla	Progressed to akinetic mutism followed by decorticate posturing and died 1 month later
Lampert and Davis[8] 1964	64/M	Tonsil carcinoma	57.02 Gy in 24 fx	13 weeks post radiation	Pathology: Demyelination of lower pons and upper medulla	Died 1 week after symptom onset, no treatment
Monro and Mair[9] 1968	56/M	Pituitary adenoma	38.62 Gy	Lethargy, memory loss, right arm and leg weakness with dysarthria 2 months post radiation	Pathology: Left temporal loss of myelin and axons in white matter with amygdala necrosis	Developed progressive somnolence, treated with IV heparin, continued to deteriorate and died from left perirenal hematoma.
Milic and Rees[10] 2017	39/F	Left temporal oligodendroglioma (WHO Grade II)	56 Gy in 30 fx	12 weeks post radiation developed headache, gait ataxia, complex ophthalmoplegia, right ptosis, left facial weakness, and appendicular ataxia	Imaging: New FLAIR hyperintense lesions with 1 contrast enhancing (bifrontal). Additional periventricular and juxtacortical FLAIR hyperintense lesions.	CSF demonstrated oligoclonal bands IV methylprednisolone x 3 days then prednisone taper. 2.5 years later alive with persistent fatigue, limb ataxia, and weight loss
Trevino *et al.*, 2020 (summarize of this review article)	26/F	Right frontal diffuse astrocytoma, IDH1-mutant, WHO Grade II (ATRX loss, unknown MGMT promoter methylation status)	54 Gy in 30 fx	10 weeks post-radiation developed left leg weakness and hemiplegic gait. 15 months post-radiation developed right optic neuritis (optic nerve received 41.6 Gy)	Imaging: Bifrontal and left periventricular FLAIR hyperintense lesions in the 10-30 Gy isodose curve; some lesions demonstrated incomplete ring-enhancement.	CSF demonstrated elevated protein and elevated myelin basic protein. Oligoclonal bands and IgG index were negative at the time of optic neuritis. Multifocal demyelination treated with IV methylprednisolone x 3 days followed by prednisone taper. Symptoms improved and the MRI lesions resolved on follow up imaging. Optic neuritis treated with IV methylprednisolone x 3 days followed by 11 days prednisone 80 mg per ONTT

Most women were young with ages 26-39 while the men presented at older ages ranging from 56-64 years old. Most patients were treated with greater than 50 Gy and developed significant neurologic symptoms in the subacute period ranging from 10-13 weeks after completing radiation. All patients were significantly symptomatic with variable response to steroids. There were more frequent deaths or severe permanent neurologic symptoms in the earlier reported cases described from 1959-1968, and these patients were not treated with steroids. M: Male; F: Female; Gy: Gray; fx: fraction; EBRT: external beam radiotherapy; ADL: activities of daily living; GK: gamma knife; FLAIR: fluid attenuation inversion recovery; LP: lumbar puncture; MS: multiple sclerosis; MRI: magnetic resonance imaging; WHO: World Health Organization; IV: intravenous; IDH1: isocitrate dehydrogenase-1; ATRX: alpha thalassemia/mental retardation syndrome X-linked; MGMT: O6-methylguanine DNA methyltransferase; CSF: cerebral spinal fluid; IgG: Immunoglobulin G; mg: milligrams; ONTT: Optic Neuritis Treatment Trial

with multiple sclerosis, but not with other autoimmune disorders[21,22]. Taken together, this data argues against the common thought that radiation induced damage occurs only in the high isodose radiation zones.

In the early 1960s prior to both CT scan use and modern treatments for multiple sclerosis and demyelination, several patients ultimately progressed to death without treatment[7,8]. However, since the advent of MR brain

8. Lampert PW, Davis RL. Delayed effects of radiation on the human central nervous system; Early and late delayed reactions. Neurology 1964;912-7.
9. Monro P, Mair W. Radiation effects on the human central nervous system 14 weeks after x-radiation. Acta Neuropathol 1968;11:267-74.
10. Milic M, Rees JH. Acute demyelination following radiotherapy for glioma: a cautionary tale. Pract Neurol 2017;17:35-8.
11. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
12. Flowers A. Control of both oligodendroglioma and multiple sclerosis with chemotherapy with temozolomide: case report. Neurology 2013;80:105.
13. Miller RC, Lachance DH, Lucchinetti CF, Keegan BM, Gavrilova RH, et al. Multiple sclerosis, brain radiotherapy, and risk of neurotoxicity: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys 2006;66:1178-86.
14. Marks JE, Wong J. The risk of cerebral radionecrosis in relation to dose, time and fractionation. A follow-up study. Prog Exp Tumor Res 1985;29:210-18.
15. Dörr W, Hendry JH. Consequential late effects in normal tissues. Radiother Oncol 2001;61:223-31.
16. Brandes AA, Franceschi E, Tosoni A, Blatt V, Pession A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol 2008;26:2192-7.
17. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, et al. CNS complications of radiotherapy and chemotherapy. Lancet 2009;374:1639-51.
18. Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. Int J Radiat Oncol Biol Phys 2011;79:1487-95.
19. Thiessen B, DeAngelis LM. Hydrocephalus in radiation leukoencephalopathy: results of ventriculoperitoneal shunting. Arch Neurol 1998;55:705-10.
20. Kumar AJ, Leeds NE, Fuller GN, Van Tassel P, Maor MH, et al. Malignant gliomas: MR imaging spectrum of radiation therapy-and chemotherapy-induced necrosis of the brain after treatment. Radiology 2000;217:377-84.
21. Gregory AP, Dendrou CA, Attfield KE, Haghikia A, Xifara DK, et al. TNF receptor 1 genetic risk mirrors outcome of anti-TNF therapy in multiple sclerosis. Nature 2012;488:508-11.
22. Bureau JF, Drescher KM, Pease LR, Vikoren T, Delcroix M, et al. Chromosome 14 contains determinants that regulate susceptibility to Theiler's virus-induced demyelination in the mouse. Genetics 1998;148:1941-9.