Neuro-Oncology Practice
6(2), 156–158, 2019 | doi:10.1093/nop/npy055 | Advance Access date 2 January 2019

Limbic encephalitis following intracranial radiation for suprasellar meningioma

Adrian Budhram, David M. Pelz, Lee Cyn Ang, Barbara J. Fisher, and Maria MacDonald

Department of Clinical Neurological Sciences, Western University, London, Ontario, Canada (A.B., M.M.); Department of Medical Imaging, Western University, London, Ontario, Canada (D.M.P.); Department of Pathology and Laboratory Medicine, Western University, London, Ontario, Canada (L.C.A.); Department of Radiation Oncology, Western University, London, Ontario, Canada (B.J.F.)

Corresponding Author: Adrian Budhram, MD, University Hospital, Department of Clinical Neurological Sciences, Western University, 339 Windermere Rd, London, ON, Canada, N6A 5A5 (adrian.budhram@medportal.ca).

Keywords
autoimmune | encephalitis | limbic | meningioma | radiation

Case Presentation

A 56-year-old woman with a history of a subtotally resected left suprasellar WHO Grade 1 meningioma reported increasing left-sided retroorbital headaches. Head MRI showed progression of residual left cavernous sinus tumor. Radiation treatment was delivered, and she received 50.4 Gy over 28 fractions to a highly conformal volume using volumetric modulated arc therapy with multiple noncoplanar arcs (Fig. 1A). Two days after her 28th radiation treatment she presented with bizarre behavior, followed by seizures leading to intubation. Head MRI revealed diffusion restriction in the mesiotemporal lobes. There was no appreciable reduction in the size of the meningioma postradiation. Cerebrospinal fluid examination showed mildly elevated protein, a normal white blood cell count, and no oligoclonal bands. Infectious testing was negative for HIV, syphilis, Lyme, Whipple disease, flaviviruses, herpes simplex virus (HSV), varicella zoster virus, and enterovirus. Antibody testing was negative for antinuclear antibodies, antiglutamic acid decarboxylase antibodies, antithyroid antibodies, anti–N-methyl-D-aspartate receptor (NMDAR) antibodies, anti–voltage-gated potassium channel (VGKC) complex antibodies, and antibodies to Hu, Yo, Ri, CV2, amphiphysin, and Ma2. Whole-body PET/CT was unremarkable.

The patient received phenytoin and levetiracetam for seizure control, and completed a 3-week course of acyclovir without improvement. Methylprednisolone and intravenous immunoglobulin was administered for possible limbic encephalitis (LE). She was extubated but remained stuporous and was hypothermic. Repeat head MRI showed persistent T2-signal abnormality in the mesiotemporal lobes extending into the hypothalamus, and new gyriform enhancement involving the right more than left mesiotemporal lobes (Fig. 1, B and C). A right temporal lobe biopsy was performed, revealing a T-cell–predominant encephalitis with no microorganisms seen (Fig. 1, E-H).

The patient had transient clinical improvement the month following immunotherapy, but 1 month after that she deteriorated and became comatose. Repeat head MRI showed worsening T2-signal abnormality and enhancement of the limbic structures. She received methylprednisolone, plasma exchange, and rituximab 4 months after the onset of her encephalopathy, and dramatically improved. She became awake and conversational, although her short-term memory was poor. Follow-up assessment 1.5 years after disease onset confirmed sustained clinical neurologic improvement, and repeat head MRI at that time showed no progression of T2-signal abnormalities, predominantly right-sided temporal lobe encephalomalacia, and resolution of enhancement (Fig. 1D).

Discussion

We describe a patient with acute encephalopathy occurring 2 days after radiation for residual left suprasellar meningioma. Although acute radiation injury was considered, the clinicoradiographic presentation was incompatible with this diagnosis. Radiation-induced brain injury may be observed after fractionated brain radiation, and is typically described in terms of acute,

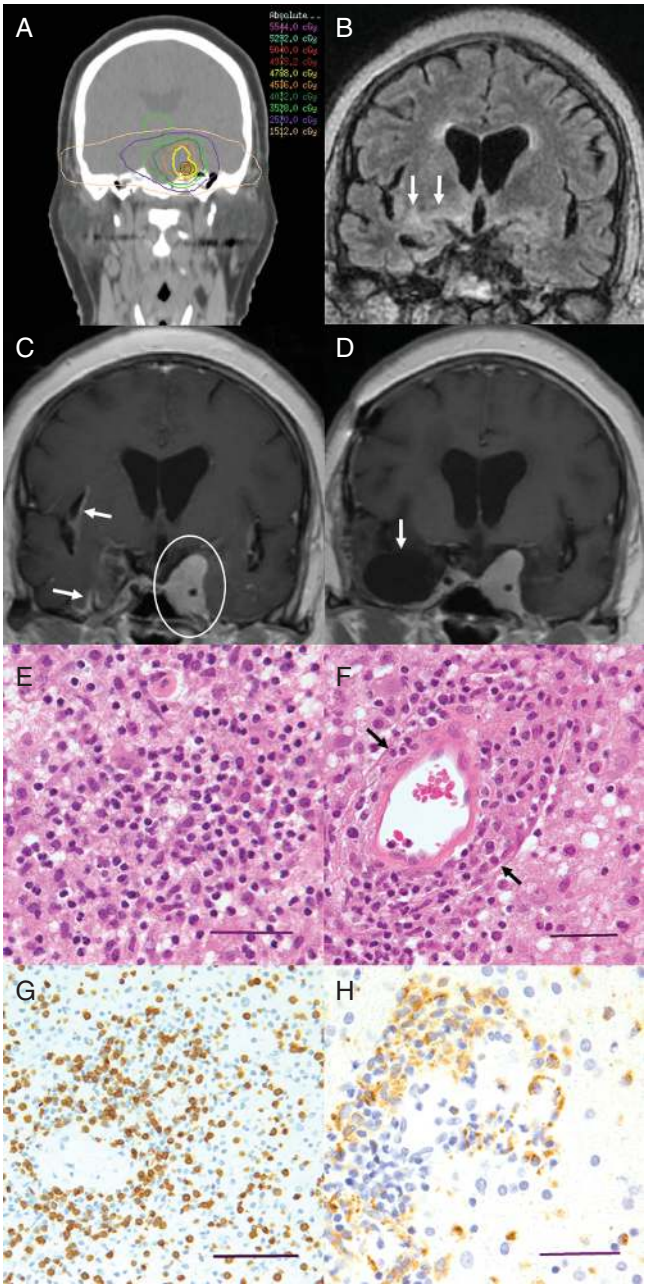

Fig. 1 Neuroimaging and pathology of patient with limbic encephalitis after intracranial radiation. A, On coronal head computed tomography isodose contours for radiation treatments are seen, and show a low radiation dose to the right temporal lobe. B (arrows), Six weeks after onset of encephalopathy postradiation, on coronal head magnetic resonance T2-weighted fluid-attenuated inversion recovery imaging there is prominent T2-hyperintensity of the right more than left mesiotemporal lobes extending to the hypothalamus. C (arrows), On T1-weighted postgadolinium imaging new gyriform enhancement predominantly involving the right insula and mesiotemporal lobe is seen, as well as the right orbitofrontal and interhemispheric cortices. C (circle), The avidly enhancing suprasellar meningioma extending into the left cavernous sinus is also seen. D (arrow), On follow-up magnetic resonance T1-weighted postgadolinium imaging 1.5 years after presentation, predominantly right-sided temporal lobe encephalomalacia with complete resolution of enhancement is seen. E (bar = 50 μm), On right temporal lobe biopsied tissue, hematoxylin and eosin stain shows chronic inflammation in the brain parenchyma indicative of encephalitis. F (arrows, bar = 50 μm), A vessel showing transmural inflammation in keeping with concomitant vasculitis is seen. Immunolabeling for G (bar = 100 μm), CD3+-positive cells and H (bar = 50 μm), CD68+-positive cells reveals that the inflammatory infiltrate consists mainly of T-cells and macrophages, respectively.

early delayed, and late delayed injury.[1] Acute brain injury classically presents days to weeks after irradiation with headache, nausea/vomiting, and altered mental status. The MRI is usually unchanged, and with conventional fractionation dosing the symptoms of acute brain injury typically resolve spontaneously or with steroid administration.[1] In contrast our patient had neuroimaging suggestive of LE,[2] and although she received targeted radiation to the left parasellar region her radiographic abnormalities were more marked in the contralateral right mesiotemporal lobe (Fig. 1, A-D). The gyriform gadolinium enhancement seen was concerning for an inflammatory etiology, and a T-cell–predominant inflammatory process was identified pathologically on biopsied brain tissue. Overall, her presentation was in keeping with LE rather than acute radiation toxicity. Nevertheless, we found the strong temporal association between her radiation treatment and the development of LE to be of great interest. A radiation-induced immune-mediated reduction in tumor burden distant to the radiation site is known as the abscopal effect, and is likely due to an immune response to neoantigens liberated by tumoral cellular stress and injury.[3] Radiation can also cause cellular neuronal damage, microvascular disturbance, and endothelial dysfunction,[4] which could similarly lead to neuronal antigenic exposure to the immune system and breakdown of immune tolerance. This may be analogous to post-HSV autoimmune encephalitis, wherein neuronal injury secondary to viral infection is posited to trigger autoimmunity toward cell surface antigens.[5,6] We sent for NMDAR and VGKC complex antibodies in our patient, but more extensive testing for antibodies to other cell surface antigens that may cause LE was not available to us at the time[7]; this could be helpful in future cases. Although the underlying disease mechanisms are unclear, this case highlights the importance of considering LE in the differential diagnosis of acute encephalopathy after intracranial radiation.

Funding

None to disclose.

Conflict of interest statement. None declared.

References

1. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: a review. *Front Oncol.* 2012;2:73.
2. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* 2016;15(4):391–404.
3. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S,Formenti SC. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer.* 2018;18(5):313–322.
4. Lumniczky K, Szatmári T, Sáfrány G. Ionizing radiation-induced immune and inflammatory reactions in the brain. *Front Immunol.* 2017;8:517.
5. Leypoldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology.* 2013;81(18):1637–1639.
6. Armangue T, Moris G, Cantarín-Extremera V, et al; Spanish Prospective Multicentric Study of Autoimmunity in Herpes Simplex Encephalitis. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology.* 2015;85(20):1736–1743.
7. Dalmau J, Graus F. Antibody-mediated encephalitis. *N Engl J Med.* 2018;378(9):840–851.