Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Dosimetry 46 (2021) 374–376

Medical Dosimetry

journal homepage: www.meddos.org

Clinical Case Study

Early-onset symptomatic radiation necrosis after stereotactic radiosurgery in the setting of COVID-19 infection

Eduardo Weltman, MD[*,†], Rupesh Kotecha, MD[‡,§,**]

[*] Department of Radiation Oncology, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[†] Discipline of Radiation Oncology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil
[‡] Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA
[§] Herbert Wertheim College of Medicine, Florida International University, Miami, FL, USA

ARTICLE INFO

Article history:
Received 4 March 2021
Revised 27 March 2021
Accepted 6 April 2021

Keywords:
Radiation necrosis
Stereotactic radiosurgery
COVID-19
Coronavirus
Adverse radiation effect

ABSTRACT

In this brief report, we describe the case of a previously healthy 51-year gentleman who was treated with stereotactic radiosurgery to a dose of 12 Gy to a small right-sided vestibular schwannoma. MRI of the brain performed after treatment revealed stable treated disease but subsequently, the patient developed symptomatic COVID-19 based on PCR along with multiple cranial neurologic deficits, including right facial paralysis, hemifacial anesthesia, and anesthesia of the ipsilateral hard palate and tongue. MRI of the brain was repeated and demonstrated radiation necrosis in the adjacent brainstem for which he was treated with Pentoxifylline and Vitamin E, dexamethasone, and Bevacizumab with only partial improvement. The dose-volume metrics of the brainstem from his radiotherapy plan as well as the trajectory of his imaging findings do not match this clinical picture from radiotherapy alone. We review the basic pathogenesis of the inflammatory response to infection from the SARS-CoV-2 virus as well as the pathogenesis of radiation necrosis. Heightened awareness about potential risks with high-dose radiotherapy in patients with symptomatic COVID-19 should be considered.

Radiation necrosis (RN) is the primary dose-limiting treatment-related toxicity following stereotactic radiosurgery (SRS) and occurs in approximately 5% to 10% of patients with brain metastasis,[1] but is rarely described in patients with benign tumors given the lower doses prescribed for treatment. Several factors have been associated with risk of RN including multiple dose-volume metrics, prior radiotherapy, time from treatment, concurrent systemic therapies, certain regions of the brain parenchyma, histology of the tumor, etc.[2] Since December 2019, the novel coronavirus (COVID-19) has become the centerpiece of healthcare prioritization and multiple reports have documented numerous sequela resulting from prior infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Yet, reports on increased risk of radiation toxicity from infection with SARS-CoV-2 have yet to be empirically demonstrated.

A previously healthy 51-year-old gentleman with no significant past medical history presented with unilateral sensorineural hearing loss and MRI of the brain revealed a $14 \times 8 \times 5$ mm enhancing mass in the right cerebellopontine angle consistent with a vestibular schwannoma. He was treated with LINAC SRS to a dose of 12 Gy prescribed to the 89% isodose line (Fig. 1) with corresponding dose metrics to the brainstem of 10 Gy to 1 cc, 12 Gy to 0.5 cc, and 13 Gy to 0.03 cc (Fig. 2). MRI of the brain performed approximately 1 month after treatment demonstrated stable disease without any radiographic change in tumor dimensions, cystic evolution of the tumor, or RN (Fig. 3). Approximately 3 months after SRS, the patient developed symptomatic COVID-19 based on PCR and recovered with a negative test performed 2 weeks later. Subsequently, the patient developed multiple central nervous system (CNS)-related symptoms including right facial paralysis, right hemifacial anesthesia, and anesthesia of the right-side of the hard palate and ipsilateral tongue. An MRI of the brain was therefore repeated, approximately 4.5 months from SRS, with significant radiographic changes on comparison to his past imaging studies: necrosis in the center of the tumor, thin peripheral enhancement, and enhancing stranding in the adjacent brainstem with new surrounding vasogenic edema consistent with RN (Fig. 3). Given the radiographic features and clinical symptomatology, the patient was subsequently treated with several regimens, including pentoxifylline (1200 mg/day) and vitamin E (400 mg/day), dexamethasone (16 mg/day) and bevacizumab (5 mg/kg every 4 weeks).

** Reprint requests to Rupesh Kotecha, MD, Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Office 1R203, Miami, FL 33176, USA.

E-mail address: rupeshk@baptisthealth.net (R. Kotecha).

https://doi.org/10.1016/j.meddos.2021.04.002
0958-3947/

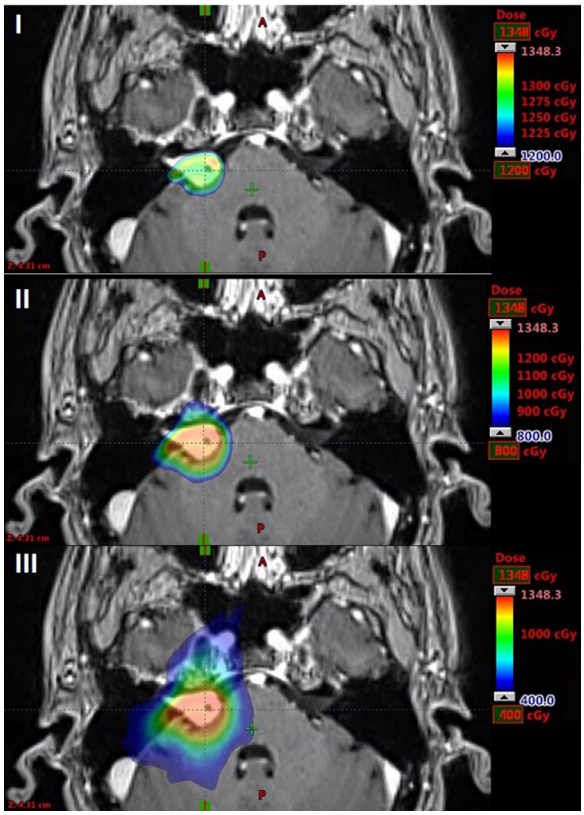

Fig. 1. Axial treatment planning CT scan demonstrating the isodose distribution by minimum dose limits of 12 Gy (I), 8 Gy (II), and 4 Gy (III) with corresponding color maps.

Follow-up MRI of the brain demonstrated continued necrosis in the tumor but improvement in the enhancement pattern in the adjacent brainstem. Currently, the patient is 6 months out from treatment and has residual neurologic deficits with very limited facial paralysis regression, but significant improvement in his facial sensation.

This case example demonstrates development of RN in a patient treated for a benign tumor without any identifiable patient or treatment-related risk factors but after a diagnosis of SARS-CoV-2. In fact, the 3 most common factors associated with RN (total dose, volume of brain irradiated, and time since treatment) do not match this clinical scenario given the 12 Gy prescription, <1 cc receiving 10 Gy brainstem dose, and interval from treatment of only 5 months; however, shortly following viral infection. Multiple series have evaluated single fraction dose limits to the brain including parameters such as V10Gy and V12Gy.[3,4] In this particular circumstance, the low prescription dose and low V10 dose (<1 cc) would be extremely unusually associated with development of symptomatic RN. Therefore, potential other etiologies must be considered, such as the patient's SARS-CoV-2 infection. The pathogenesis of the virus and its effect on the innate and adaptive immune systems can be divided into 4 key stages: inhibition of the expression of interferon type 1, disruption of downstream signaling pathways, immune exhaustion due to the rapid influx of activated neutrophils and inflammatory monocytes/macrophages, and ultimately, cytokine storm.[5] Similarly, 2 predominant theories exist regarding the pathophysiology of RN after SRS: the vascular injury theory, which is predicated on endothelial cell apoptosis leading to increased oxygen-free radicals and a subsequent inflammatory milieu; and the glial cell theory, in which damage to oligodendrocytes results in hypoxia-inducible factor release and inflammatory cascade.[2] Therefore, given the immune reaction in the setting of COVID-19 patients, clinicians should be mindful about potential heighted risks with high-dose radiotherapy. At present, management of patients in this setting should include treatment of the viral infection as well as management of the RN with oral pentoxifylline and vitamin E, oral corticosteroids, bevacizumab, hyperbaric oxygen therapy, laser interstitial thermal therapy, and surgery, as necessary.

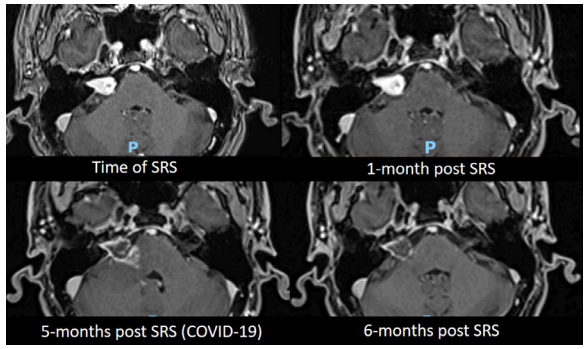

Fig. 3. Axial T1-post contrast MRIs of the brain before and after treatment with SRS and after infection with SARS-CoV-2.

Authors' Contributions

Conception and design: E.W., R.K.
Critical review of manuscript: E.W., R.K.

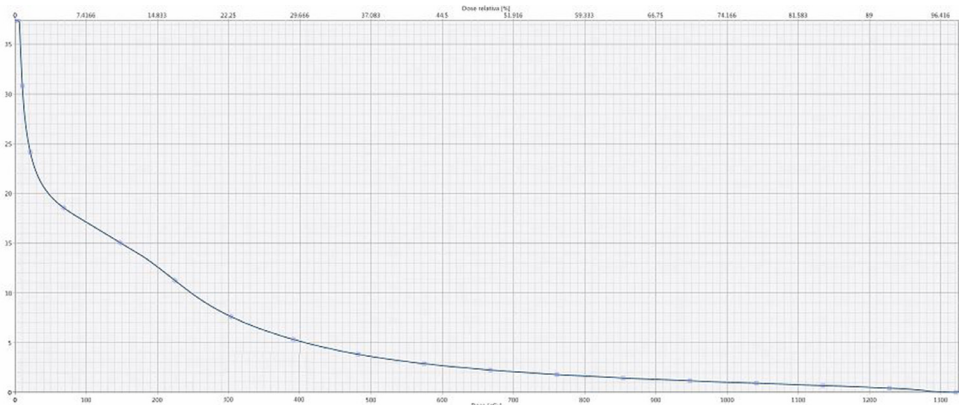

Fig. 2. Dose-volume histogram of the brainstem for the patient with a vestibular schwannoma treated to 12 Gy in 1 fraction. Absolute volume of the brainstem is plotted on the y-axis and dose (cGy) is plotted on the x-axis.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

E. Weltman declares no conflicts of interest. R. Kotecha received honoraria from Elsevier, Elekta AB, Accuray Inc, Novocure Inc, and Viewray Inc.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors appreciate the patient's approval in publishing this case report.

References

1. Miller, J.A.; Bennett, E.E.; Xiao, R.; *et al.* Association between radiation necrosis and tumor biology after stereotactic radiosurgery for brain metastasis. *Int. J. Radiat. Oncol. Biol. Phys.* **96**:1060–9; 2016. doi:10.1016/j.ijrobp.2016.08.039.
2. Vellayappan, B.; Tan, C.L.; Yong, C.; *et al.* Diagnosis and management of radiation necrosis in patients with brain metastases. *Front. Oncol.* **8**:395; 2018. doi:10.3389/fonc.2018.00395.
3. Minniti, G.; Clarke, E.; Lanzetta, G.; *et al.* Stereotactic radiosurgery for brain metastases: Analysis of outcome and risk of brain radionecrosis. *Radiat. Oncol.* **6**:48; 2011. doi:10.1186/1748-717X-6-48.
4. Korytko, T.; Radivoyevitch, T.; Colussi, V.; *et al.* 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. *Int. J. Radiat. Oncol. Biol. Phys.* **64**:419–24; 2006. doi:10.1016/j.ijrobp.2005.07.980.
5. Taghizadeh-Hesary, F.; Akbari, H. The powerful immune system against powerful COVID-19: A hypothesis. *Med. Hypotheses* **140**:109762; 2020. doi:10.1016/j.mehy.2020.109762.