

Case Report

Acute Inflammatory Reaction After Radiotherapy to Bilateral Orbital Metastasis from Melanoma

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Background

Orbital melanoma is a subtype of periocular melanoma that can present from primary, secondary (arising from local invasion), or metastatic disease [1]. Melanoma metastasis to the orbit is rare with the majority of metastases occurring in subcutaneous tissue, nonregional lymph nodes, lungs, liver, brain, and bone [2]. Despite melanoma being relatively radioresistant, radiation therapy can be considered in an adjuvant or palliative setting [3]. In the palliative setting specifically, radiation therapy is highly effective in alleviating symptoms due to mass effect [3]. However, significant ocular and orbital complications may occur as a direct result of radiation therapy.

Case presentation

A man in his 50s with stage IV primary cutaneous melanoma with bilateral orbital metastases developed tumor progression despite two orbitotomies for oncologic resection, one-year treatment with ipilimumab and nivolumab, and three cycles of temozolomide. A plan was made to treat the right orbital mass with palliative radiation therapy to a dose of 30 gray (Gy) in 10 fractions. Four hours following his first fraction of radiation therapy, he developed severe right eye pain unresponsive to non-steroidal anti-inflammatory drugs. Eye examination was notable for injection, chemosis, proptosis, hyperglobus of the right eye with mucoid discharge, and right ophthalmoplegia with incomplete eyelid closure (Figure 1). Ophthalmological examination demonstrated preservation of color vision, brightness perception, and visual acuity.

MRI of the orbits demonstrated progression of his right orbital mass with increased proptosis, a stretched appearance of the optic nerve, and tethering of the posterior globe (blue arrow). Increased swelling due to acute inflammatory reaction in the right orbital mass (green arrow). The left orbital mass remains stable (red arrow). This acute

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swelling of the right orbital mass was deemed to be likely related to an inflammatory reaction to his first radiation treatment. Intravenous dexamethasone at a dose of four



Figure 1: Redness, chemosis, proptosis, and hyperglobus of the right eye with mucoid discharge four hours after the patient's first radiation therapy.

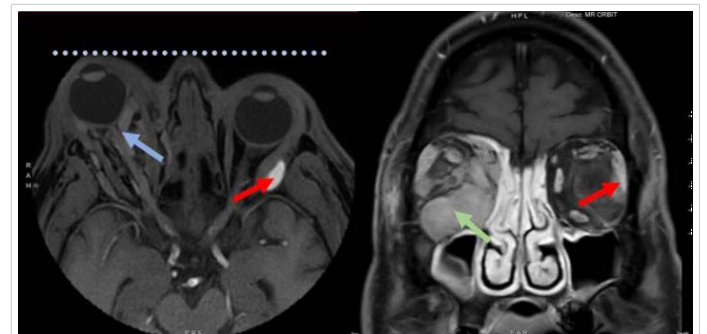


Figure 2: Axial (left) and coronal (right) T1 MRI images with contrast demonstrating greater right eye proptosis (dotted line) with a stretched appearance of the optic nerve and tethering of the posterior globe (blue arrow). Increased swelling due to acute inflammatory reaction in the right orbital mass (green arrow). The left orbital mass remains stable (red arrow).

milligrams was administered with significant improvement in ocular symptoms. He was discharged with a 9-day oral dexamethasone taper along with dorzolamide/timolol eye drops, brimonidine eye drops and Lacri-Lube ointment.

The patient proceeded with radiation therapy as planned and tolerated the remainder of his treatments with gradual improvement in his right eye pain and swelling. One month following radiation therapy, the patient's proptosis, hyperglobus, and chemosis were mildly improved and temozolomide was restarted (Figure 3). MRI of the orbits two months following radiation therapy showed an interval decrease in the size of the bilateral orbital masses and continued improvement in right eye proptosis (Figure 4).

Discussion

Orbital metastases from any malignancy are relatively rare, with metastatic melanoma accounting for approximately 5-20% of all cases [2]. Treatment often involves immunotherapy, chemotherapy, and radiation therapy, however, the prognosis remains poor [4]. Radiation therapy is especially beneficial for patients who are unable to undergo surgery, yet require tumor control for preservation of vision and palliation of pain [5]. Orbital radiotherapy has been shown to reduce tumor load and alleviate orbital symptoms with long-term toxicity including cataracts, optic neuropathy, radiation retinopathy, and corneal scarring [4]. However, radiation can also induce an acute inflammatory response leading to swelling and an increase in tumor size

following treatment [6]. Though this sterile inflammatory response can lead to unwanted symptoms, the increase in inflammatory cells following radiation is important in killing tumor cells. Therefore, the symptoms of inflammation did not rule out further treatment for this patient but were a sign that the therapeutic effects of radiation were occurring; however, the effects of edema need to be controlled to limit the compressive effects of important vessels such as the optic nerve.

Radiation therapy activates pro- and anti-inflammatory signaling pathways, stimulating the immune system and leading to tumor cell death [6]. While one of the goals of radiation therapy is aimed at modulating anti-tumor immune responses, it may also stimulate factors that contribute to excess inflammation, fibrosis, and tumor invasion [6]. Ionizing radiation activates several immunological proteins and transcription factors, such as nuclear factor kappa B (NF- κ B), tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6 and IL-8 [6]. These transcription factors and cytokines play a major role in the regulation of genes that stimulate inflammatory and angiogenic processes [6]. Radiation therapy can also further indirectly induce inflammation through NF- κ B activation of cyclooxygenase-2 (COX-2), which is one of the key enzymes in the inflammatory cascade [6].

Conclusion

In our case, the rapid increase in size and enhancement on an MRI points to an inflammatory reaction due to radiation therapy. The efficacy of corticosteroids further implicates inflammation as the pathological cause, supporting the role of anti-inflammatory agents for future treatments. It is imperative to identify radiation-induced inflammation in tumors to promptly initiate treatment to prevent optic nerve damage and provide adequate relief of symptoms.

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Figure 3: Improvement in redness, proptosis, hyperglobus, and chemosis of the patient's right eye two months following radiation therapy.

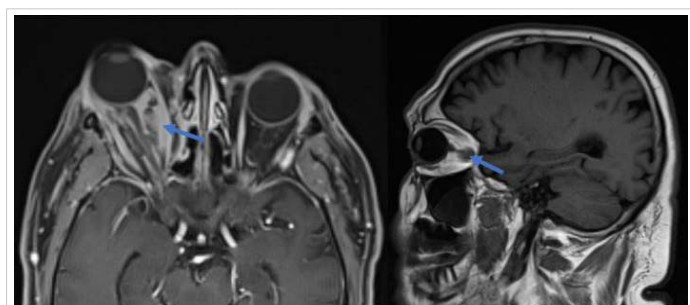


Figure 4: Axial (left) and sagittal (right) T1 MRI images with contrast demonstrating a mild decrease in the size of the large right-sided intra-orbital mass (blue arrow) with improvement of proptosis two months following radiation therapy.