American Journal of Ophthalmology Case Reports 36 (2024) 102142

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Bilateral neovascular glaucoma associated with Radium-223 infusions for prostate cancer

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ARTICLE INFO

Keywords:
Radium-223
Neovascular glaucoma
Uveitis
Hyphema
Neovascularization
Secondary angle closure glaucoma

ABSTRACT

Purpose: To report two cases of neovascular glaucoma associated with Radium-223 infusion.
Observations: Presented are two patients with metastatic prostate cancer who developed uncontrolled intraocular pressure secondary to neovascular glaucoma requiring surgical intervention. Both patients had received six cycles of Radium-223, a calcium mimetic that causes DNA double strand breaks and tumor cell death in bony metastases as part of their treatment regimen for metastatic prostate cancer. One patient had been a prior glaucoma suspect while the other had no significant ocular history.
Conclusions and importance: Radium-223 may increase vascular permeability contributing to uveitis and promote angiostimulatory growth factors that can lead to neovascularization. We postulate this is through possible disruption in VEGF signaling pathways as well as Ra-223's calcium mimetic properties that could affect the trabecular meshwork. Neovascular glaucoma is uncommonly reported with Ra-223. There is one other case report that experienced uveitis and hyphema within weeks of the Ra-223 infusion. This case report has a similar proposed biologic mechanism. A literature review using the key words "radium-223, neovascularization, secondary angle closure glaucoma, neovascular glaucoma" did not yield any prior reports of neovascular glaucoma associated with Ra-223. The goal of this case series is to argue there is biological plausibility and to contribute to current literature of possible ocular complications of Ra-223 infusion.

1. Introduction

Radium 223 (Ra-223) is a targeted radiotherapy used in patients with prostate cancer metastatic to the bone. Ra-223 is a targeted radiotherapy of alpha particles that mimics calcium.[1–3] Radium is used in patients with prostate cancer metastatic to bone as it forms complexes in areas of rapid bone turnover.[3] It induces double stranded DNA breaks of the cells of concern, hence its anti-tumor effect for bone metastases. While this radioisotope prefers bone, it has been found in all tissues of the body.[3] The most common side effects include nausea, vomiting, diarrhea, and peripheral edema.[4]

There are not many reported ocular side effects of Ra-223. There is one other case report that experienced uveitis and hyphema within weeks of the Ra-223 infusion. However, our literature review using the key words "radium-223, neovascularization, secondary angle closure glaucoma, neovascular glaucoma" did not find any prior reports of neovascular glaucoma (NVG) associated with Ra-223. Here we present two cases of NVG in patients with a history of receiving Ra-223 as part of their treatment regimen for prostate cancer.

2. Case 1

Patient 1 is a 65-year-old male with a history of stage IV prostate cancer with metastasis to the bone first diagnosed in June of 2016. His treatment course consisted of a T5-T7 laminectomy the same month of diagnosis with epidural spinal tumor resection followed by 30Gy of palliative radiation therapy to the thoracic and lumbar spine after initiating dexamethasone. July of 2016 treatment with bicalutamide daily and leuprolide acetate injection every three months. Radiation oncology initiated treatment with radium-223 in April of 2017 at which time he was continuing to receive leuprolide acetate. He completed six cycles of radium-223 in September 2017. Twelve months after his final dose of Ra-223 he experienced acute onset of flashing lights, floaters, and visual distortion in the right eye. An outside optometrist diagnosed him with open angle glaucoma and started medical therapy. He was referred to our clinic due to uncontrolled IOP.

Visual acuity (VA) OD was 20/40, IOP 42 mmHg, and gonioscopic exam was unrevealing – open to scleral spur without neovascularization or synechiae. The anterior segment exam was normal. The fundoscopic

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https://doi.org/10.1016/j.ajoc.2024.102142
Received 4 October 2023; Received in revised form 22 July 2024; Accepted 14 August 2024
Available online 22 August 2024

exam did not reveal any signs of ischemia, neovascularization, or vein occlusion but did show a pale optic nerve with a cup-to-disc ratio of 0.8. Maximal medical therapy (MMT) controlled his IOP. However, one month later, the patient had elevated IOP in the 30s OD with shallowing of the anterior chamber associated with inflammation and florid neovascularization of the iris (NVI) and of the angle (NVA). An Ahmed glaucoma drainage device was implanted to control his IOP and intravitreal Avastin administered for his severe neovascularization. He eventually developed anterior uveitis in both eyes which responded well with topical steroids. At this time, IOP was well controlled in both eyes.

In March of 2021 he presented in the left (opposite) eye with blurry vision and IOP of 48 mmHg. Repeat gonioscopy revealed the right eye was completely closed while the left eye was open deep to scleral spur with a few clock hours of peripheral anterior synechiae. He then underwent transscleral cyclophotocoagulation in the right eye (that already had the Ahmed tube) and a trabeculectomy with mitomycin C was performed in the left eye. VA remained HM OD and 20/30 OS with good IOP control OU. However, the Humphrey visual field OS went from full to split-fixation due to the rapid progression of his glaucoma.

3. Case 2

Patient 2 is a 74-year-old male with history of hypertension, coronary artery disease, well controlled type 2 diabetes (A1c 6.0), and stage 4 prostate cancer with metastasis to the bone who was an established clinic patient. He had been followed as a glaucoma suspect due to a history of high intraocular pressures. He was on travaprost nightly in both eyes. He underwent external radiation with radiation seed implant for his prostate cancer in 2003. Later, he began therapy with degarelix, leuprolide acetate, denosumab, enzalutamide, and Ra-223.

He recieved six cycles of Ra-223 treatment from November 2019 through April 2020. About 12 months after finishing his last dose, he presented to our clinic with complaints of blurry vision, floaters, and flashes of light in both eyes. VA 20/25 OD and 20/30 OS with IOP 40 OU. The anterior exam revealed 4+ RBC OU and 0.5 mm hyphema OD, NVI OU, and posterior synechiae OU. Gonioscopy showed open angle for about one quarter of the circumference and closed angle for three quarters of the circumference with multiple peripheral anterior synechiae. There was diffuse NVA and active blood layering of the trabecular meshwork OU. The posterior exam did not show evidence of ischemia, diabetic retinopathy, or vein occlusion to explain the diffuse neovascularization. Cup to disc was 0.7 OD and 0.4 OS. He started maximal medical therapy with improvement of his IOP to 22 OU. However, given his overall presentation, surgery was recommended, and the patient received Baerveldt-350mm^2 glaucoma drainage devices and intravitreal Avastin OU. He had good follow up for over 1 year where his IOP remained around 6 OD and 11 OS on brimonidine BID OU. His eyes remained quiet.

4. Discussion and conclusion

Both patients received six cycles of Ra-223 infusion for metastatic prostate cancer and approximately twelve months after the last dose experienced blurry vision with an inflammatory response with synechiae and neovascularization of the iris and angle with severe secondary angle closure. Both patients had documentation of an open angle on gonioscopy prior to NVA noted on subsequent exams. Both patients needed urgent glaucoma surgery to control the IOP. To date, there is one other case report of a patient developing anterior uveitis OU and hyphema OS two weeks after his Ra-223 infusion therapy for metastatic prostate cancer.[1] Our patients similarly developed inflammation and neovascularization.

Ra-223 is used in patients with bony metastasis from prostate cancer since it mimic calcium and induces cell death in areas with high cell turn over.[2,3] However, while it targets bone, Ra-223 has been found in all tissues in the body. It is known that disruption of these tumor cells can alter several signaling pathways and feedback loops of morphogenetic proteins including VEGF.[1] It is also known that VEGF promotes angiogenesis and has been a popular target of immunotherapies that treat neovascularization in the retina.[1] It is therefore possible that in some patients with genetic predisposition or certain risk factors may be vulnerable to the changes in VEGF signaling pathways induced by Ra-223 leading to inflammation and angiogenesis.

It is also possible given the calcium mimetic properties of Ra-223, that the isotope binds with the calcium channels located on the ciliary body epithelium (fluid production) and/or the calcium channels located on the trabecular meshwork (fluid drainage).[2] The interaction with the ciliary body epithelium can cause dysfunction or cell death.[3] While this is clearly not a common mechanism given the lack of adverse ocular events reported with this medication, it is possible there are some rare genetic variabilities in calcium receptors that have an increased avidity to this particular calcium mimetic making these patients more vulnerable to complications. These factors could contribute to the inflammation, neovascularization of the iris and angle, increased IOP, angle narrowing, bleeding, and scarring as seen in our patients.[5–8] It is not clear whether the development of NVG and Ra-223 infusion was causal or coincidental, but the goal of this case series is to argue there is biological plausibility and to contribute to current literature of possible ocular complications of Ra-223 infusion. While these cases are observational and do not prove that neovascular glaucoma is caused by administration of radium 223, this should alert clinicians to refer patients receiving this medication to an ophthalmologist if they experience visual symptoms.

Patient consent

Both patients were consented with our institution's policy.

Acknowledgement and disclosures

No funding or grant support

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

CRediT authorship contribution statement

Chelsea M. Viscardi: Writing – review & editing. **Jonathan Y. Rho:** Writing – original draft, Conceptualization. **Charles R. Blake:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

1. Bloom JR, Castillejos AG, Jones B, Patel N, Rosenstein BS, Stock RG. Ocular complications with the use of radium-223: a case series. *Radiat Oncol.* 2022;17(1):97.
2. Jo AO, Lakk M, Frye AM, et al. Differential volume regulation and calcium signaling in two ciliary body cell types is subserved by TRPV4 channels. *Proc Natl Acad Sci U S A.* 2016;113(14):3885–3890.
3. Morris MJ, Corey E, Guise TA, et al. Radium-223 mechanism of action: implications for use in treatment combinations. *Nat Rev Urol.* 2019;16(12):745–756.
4. Xofigo [Package Insert] Wayne NJ. *BayerHealthcare Pharmaceuticals.* Inc; 2013.

5. Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: a review. *Open Ophthalmol J*. 2010;4:52–59.
6. Ganekal S, Dorairaj S, Jhanji V, Kudlu K. Effect of topical calcium channel blockers on intraocular pressure in steroid-induced glaucoma. *J Curr Glaucoma Pract*. 2014;8(1):15–19.
7. Sacco R, Guidoboni G, Jerome JW, et al. A theoretical approach for the electrochemical characterization of ciliary epithelium. *Life (Basel)*. 2020;10(2).
8. Abu-Hassan DW, Acott TS, Kelley MJ. The trabecular meshwork: a basic review of form and function. *J Ocul Biol*. 2014;2(1).