American Journal of Ophthalmology Case Reports 32 (2023) 101945

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Spontaneous regression of choroidal metastasis from renal cell carcinoma

Sean M. Rodriguez [a], H. Culver Boldt [a,b], Hannah R. Sullivan [c], John M. Rieth [c], Yousef Zakharia [c], Elaine M. Binkley [a,b,*]

[a] Department of Ophthalmology and Visual Sciences, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA, 52242, USA
[b] Institute for Vision Research, 451 Newton Road, 200 Medicine Administration Building, Iowa City, IA, 52242, USA
[c] Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA, 52242, USA

ARTICLE INFO

Keywords:
Choroidal metastasis
Uveal metastasis
Renal cell carcinoma

ABSTRACT

Purpose: To report a case of an elderly man who presented with a choroidal metastasis from renal cell carcinoma that spontaneously regressed prior to any local or systemic treatment.
Observations: An 82-year-old man without a history of metastatic cancer was referred to the ocular oncology service for evaluation of a newly noted amelanotic choroidal lesion. Examination and imaging findings were concerning for choroidal metastasis. Systemic workup revealed previously undiagnosed widely metastatic renal cell carcinoma. The lesion spontaneously regressed prior to the initiation of any treatment for his tumor.
Conclusions and importance: This is a unique case of choroidal metastases from renal cell carcinoma that spontaneously regressed prior to medical or surgical treatment of the primary tumor.

1. Introduction

Choroidal metastasis is the most common malignant intra-ocular tumor in adults. Of patients presenting with metastases to the uveal tract, 66 % have a known primary malignancy, while 34 % have no history of a primary malignancy at diagnosis.[1] The most common sites of choroidal metastasis are breast (37 %), lung (26 %), kidney (4 %), gastrointestinal tract (4 %) and unknown (16 %).[2] An awareness of the clinical features that suggest choroidal metastasis is imperative as the ophthalmologist may be the first to make this diagnosis and correctly refer a patient for systemic evaluation.

Features suggesting choroidal metastasis include a yellow, creamy appearance, location in the posterior pole, multifocal lesions, bilateral lesions, medium-to-high reflectivity on ocular ultrasonography, and characteristic "lumpy-bumpy" appearance along with choroidal compression and shadowing on optical coherence tomography (OCT).[2,3] A careful history and review of old images to identify the presence of a new lesion is also important to distinguish from alternative lesions such as amelanotic choroidal nevus, choroidal granuloma, or choroidal hemangioma.

Historically, the primary treatment for choroidal metastasis has been external beam radiation.[4] More recently, newer systemic therapies have shown efficacy in treating these lesions in addition to a role for photodynamic therapy in some cases.[5,6] Spontaneous regression of choroidal metastases is very rare.[7–9] In other reported cases, the choroidal metastases completely regressed only after the primary tumor was surgically resected.[8,9] Here we describe a unique case of an elderly man who presented with a choroidal metastasis from RCC that spontaneously regressed prior to initiating treatment for his tumor.

2. Case report

An 82-year-old man was referred for evaluation of a newly noted amelanotic choroidal lesion in the left eye. The patient had noted a new scotoma in the superotemporal field of view of his left eye for several months. He had a remote history of a non-ischemic central retinal vein occlusion in the left eye diagnosed in the 1970s. He had no prior history of choroidal nevus or other choroidal lesions. His past medical history was remarkable for prostate cancer diagnosed 13 years prior to presentation that was treated with surgical excision as well as a history of squamous cell carcinoma that was excised. He also reported an unintentional weight loss of 20 pounds over the last year.

Best-corrected visual acuity (VA) at presentation was 20/20 in the right eye and 20/20–3 in the left eye. Anterior segment exam was unremarkable except for the presence of age-appropriate nuclear sclerosis. The posterior segment exam of the right eye was unremarkable and without choroidal lesions. In the left eye, there were collateral vessels over the disc consistent with his previous vein occlusion. Centered

* Corresponding author. Department of Ophthalmology and Visual Sciences University of Iowa Hospitals and Clinics 200 Hawkins Drive Iowa City, IA, 52242, USA.
E-mail address: elaine-binkley@uiowa.edu (E.M. Binkley).

https://doi.org/10.1016/j.ajoc.2023.101945
Received 10 April 2023; Received in revised form 6 October 2023; Accepted 19 October 2023
Available online 20 October 2023

inferior to the optic disc in the left eye, there was a single amelanotic choroidal lesion with overlying subretinal fluid measuring 4.5 x 4.5 × 1.4 mm. There was no lipofuscin or drusen over the lesion surface (Fig. 1A).

Optical coherence tomography (OCT) of the left eye over the lesion showed mild subretinal fluid extending into the inferonasal macula (Fig. 1B). Fundus autofluorescence of the left eye showed central hypoautofluorescence surrounded by mild stippled hyper-autofluorescence over the surface of the choroidal lesion (Fig. 1C). Standardized ocular echography of the left eye showed a dome shaped lesion 1.4 mm in thickness with high internal reflectivity (Fig. 1D–E). Fundus indocyanine green angiography (ICG) of the left eye showed mild punctate increased hyper-cyanescence over the apex of the lesion but no marked early filling or delayed washout to suggest choroidal hemangioma (Fig. 1F–G).

Due to the clinical concern for choroidal metastasis, the patient was referred to the medical oncology service for evaluation. Computed tomography (CT) of the chest, abdomen, and pelvis revealed a large right renal mass invading the renal vein up to the inferior vena cava (Fig. 2A). He also was found to have multiple bilateral pulmonary and left subpleural nodules radiographically consistent with metastases (Fig. 2B). He underwent CT-guided biopsy of the right renal mass which confirmed the diagnosis of metastatic RCC of the clear cell type. MRI brain as part of staging demonstrated an enhancing mass in the left frontal lobe that was also consistent with metastatic disease.

He was seen by ophthalmology approximately one month after his initial presentation prior to initiating systemic therapy for his malignancy. On exam at that time, the choroidal lesion had involuted into a flat scar with overlying retinal pigment epithelial changes, and the subretinal fluid had resolved (Fig. 3 A-B).

He subsequently began systemic treatment with ipilimumab and nivolumab in addition to stereotactic radiation to brain metastases. He initially responded to systemic therapy and was transitioned to single agent nivolumab. He did not require nephrectomy until 22 months following presentation when he developed a renal hematoma due to bleeding from the tumor and the decision was made to perform palliative nephrectomy. Serial ophthalmic examinations have showed no recurrence 24 months since presentation.

3. Discussion

This case demonstrates the rare phenomenon of spontaneous regression of a choroidal metastasis secondary to widely metastatic RCC. Spontaneous regression of metastasis from RCC is a rare but described clinical phenomenon occurring in less than 1 % of patients with RCC.[7,10] It has most frequently been described in the setting of metastasis to the lung.[7] RCC spontaneous regression of choroidal metastasis is rare but has been reported.[7–9] Many of the cases of spontaneous regression of metastasis both to the choroid and other sites occurred after surgical resection of the primary tumor as opposed to our case in which the tumor regressed prior to any intervention.[7–9] The mechanism by which this occurs is not known with certainty, although immune mediated mechanisms have been hypothesized to play a role.[7] It is also not known whether metastasis to the choroid is more or less likely to undergo spontaneous regression relative to metastasis to other sites.[7]

There is no single mechanism that completely explains spontaneous regression after primary tumor resection, but several factors have been proposed that have to do with unique pathophysiologic features of RCC. Analysis of serum in patients with RCC show high levels of angiogenic factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).[11] Angiogenic factors are essential for promoting tumor growth and metastases, and decreasing these factors by surgically decreasing tumor burden is hypothesized to play a role in cases where RCC metastases spontaneously regress. This hypothesis is supported by most cases occurring after kidney resection.[7–9] Additionally, surgical resection decreases tumor burden which has been hypothesized to improve the immune system's ability to control the malignancy.[12] Prior work has also supported the importance of the immune response in

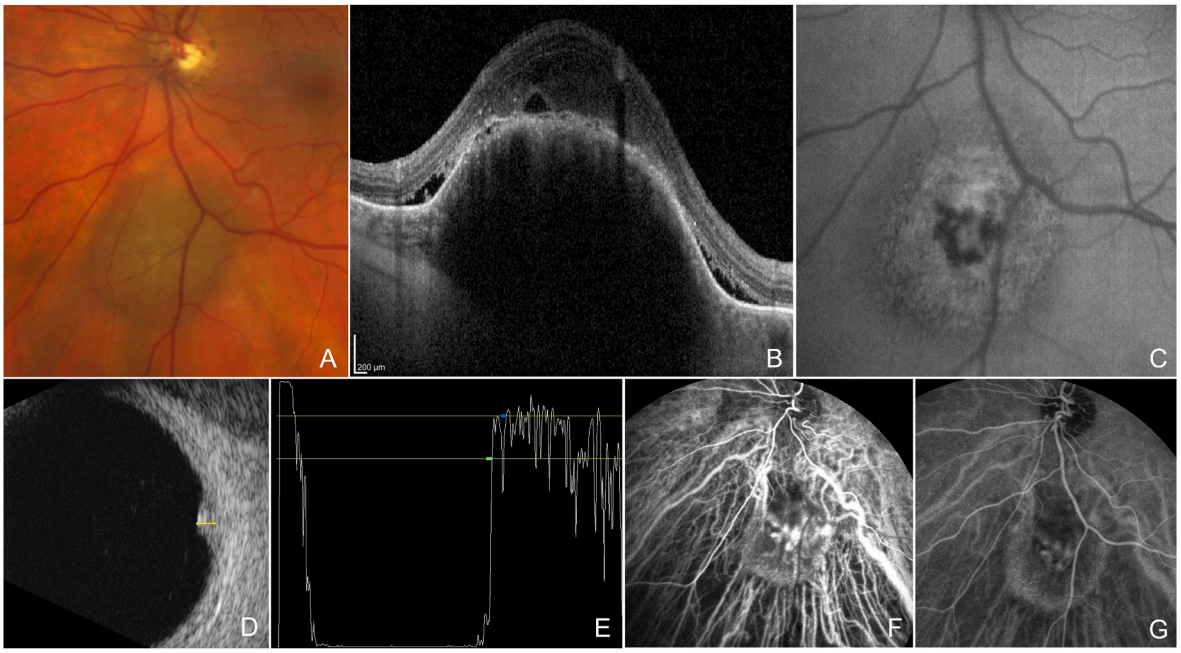

Fig. 1. Clarus color photography (A) demonstrated a choroidal lesion (note that the Clarus camera made this lesion appear more pigmented than was apparent clinically). Optical coherence tomography (OCT) (B) showed an elevated choroidal lesion with overlying retinal thickening and subretinal fluid. Fundus autofluorescence (C) showed stippled hypo- and hyper-autofluorescence with focal central hypo-autofluorescence over the choroidal lesion. B-scan ultrasound (D) showed a dome-shaped lesion measuring 1.4 mm in thickness located at 6:30 in the posterior pole. A-scan ultrasound (E) showed high internal reflectivity. Fundus indocyanine green angiography early frames (F) showed mild punctate increased hyper-cyanescence over the apex of the lesion but no marked early filling. Late frames (G) showed no delayed washout to suggest choroidal hemangioma. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

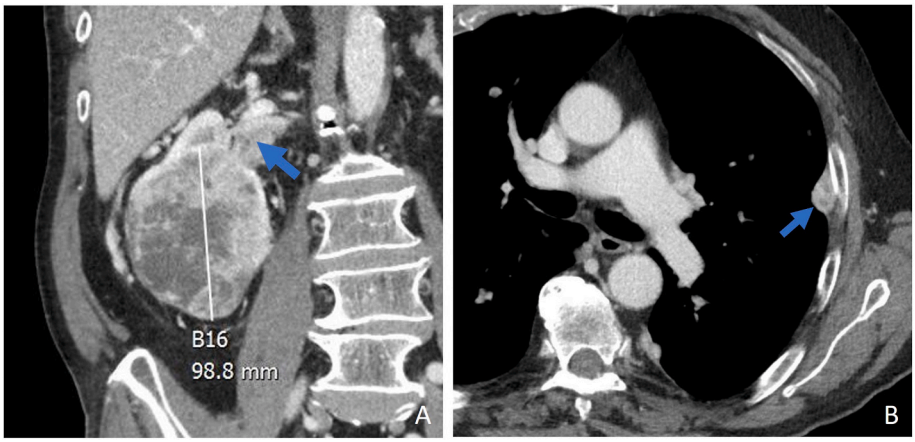

Fig. 2. CT of the abdomen (A) showed a right renal mass with necrosis and extension into the renal vein and into the inferior vena cava (arrow). CT of the chest (B) showed pulmonary metastases (arrow).

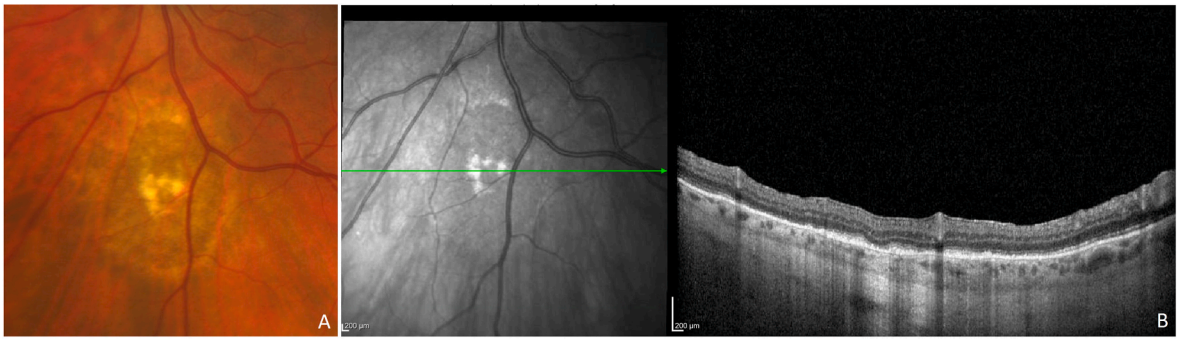

Fig. 3. Color fundus photography (A) demonstrated that the previously seen choroidal lesion had regressed with overlying retinal pigment epithelial changes. OCT (B) showed flattening of the lesion with resolution of the overlying subretinal fluid. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

spontaneous regression; however, the precise mechanisms are not known with certainty.[13] The mechanism in our patient's case is not known given that regression occurred prior to surgical resection, but it is possible that immune mechanisms played a role. Individual tumor genetics may also contribute to this phenomenon and the presence of spontaneous regression in the setting of particular tumor genetic mutations warrants further study.[7] Despite RCC tumors sometimes spontaneously regressing, it still has one of the lowest survival times among cancers that metastasize to the uvea, second only to pancreatic metastases.[2] Our patient's excellent response to anti-CTLA-4 and anti-PD-1 checkpoint inhibitor therapy suggests that there may have been an innate immune response to the tumor which was further optimized with immunotherapy or that his tumor was of a less aggressive variant.

A limitation of this report is that there was no tissue biopsy of the choroidal lesion obtained. Given the potential morbidity with biopsy in the setting of tissue being able to be more easily accessed elsewhere, the patient chose to forgo biopsy of the choroidal lesion. However, the clinical appearance in the absence of a prior history of choroidal lesion and the clinical course in the setting of widely metastatic renal cell carcinoma support the diagnosis of choroidal metastasis. This case highlights the need for the ophthalmologist to include choroidal metastases in the differential diagnosis for new choroidal lesions regardless of the patient's cancer history. Given that ~34 % of patients eventually diagnosed with choroidal metastases had no history of cancer at presentation, this is an opportunity for the ophthalmologist to make a potentially life-saving diagnosis.[1] It is unclear whether spontaneous regression of the choroidal lesions correspond to regression of lesions elsewhere in the body, and the precise mechanisms behind spontaneous tumor regression require further study. Further analysis of the tumor genetics in cases of renal cell metastasis to the choroid may provide insight into this phenomenon. A better understanding of the mechanisms behind spontaneous regression could aid in identifying therapeutic targets in the future.

4. Conclusion

The ophthalmologist can play a key role in identifying and appropriately referring patients with new choroidal lesions concerning for choroidal metastasis. Spontaneous regression of choroidal metastasis is a rare occurrence, but one that treating ophthalmologists should be aware of particularly in the setting of renal cell carcinoma. Immune mechanisms likely play a role in this process and a better understanding of this finding could help to identify potential therapeutic targets in the future.

5. Patient consent

The subject gave written informed consent for publication of this case. The IRB at the University of Iowa determined that this report does not meet the regulatory definition of human subjects' research and did not require formal IRB review since it is a single case report.

Acknowledgements and disclosures

None. The authors have no conflicts of interest to declare.

Funding sources

None.

Authorship

All authors attest that they meet the current ICGME criteria for authorship. Acquisition and analysis (EMB, SMR), drafting and revising for intellectual content (EMB, SMR, HCB, HRS, JMR, YZ), and final approval of the version to be published (EMB, SMR, HCB, HRS, JMR, YZ).

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 and Disclosures

None.

References

1. Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE. Survey of 520 eyes with uveal metastases. *Ophthalmology*. Aug 1997;104(8):1265–1276. https://doi.org/10.1016/s0161-6420(97)30148-1.
2. Shields CL, Welch RJ, Malik K, et al. Uveal metastasis: clinical features and survival outcome of 2214 tumors in 1111 patients based on primary tumor origin. *Middle East Afr J Ophthalmol*. Apr-Jun 2018;25(2):81–90. https://doi.org/10.4103/meajo.MEAJO_6_18.
3. Al-Dahmash SA, Shields CL, Kaliki S, Johnson T, Shields JA. Enhanced depth imaging optical coherence tomography of choroidal metastasis in 14 eyes. *Retina*. Aug 2014;34(8):1588–1593. https://doi.org/10.1097/iae.0000000000000131.
4. Rosset A, Zografos L, Coucke P, Monney M, Mirimanoff RO. Radiotherapy of choroidal metastases. *Radiother Oncol*. Mar 1998;46(3):263–268. https://doi.org/10.1016/s0167-8140(97)00209-0.
5. Bouchez C, Pluvy J, Soussi G, et al. Epidermal growth factor receptor-mutant non-small cell lung Cancer and Choroidal metastases: long-term outcome and response to epidermal growth factor receptor tyrosine kinase inhibitors. *BMC Cancer*. Dec 3 2020;20(1):1186. https://doi.org/10.1186/s12885-020-07630-6.
6. Shields CL, Khoo CTL, Mazloumi M, Mashayekhi A, Shields JA. Photodynamic therapy for choroidal metastasis tumor control and visual outcomes in 58 cases: the 2019 burnier international ocular pathology society lecture. *Ophthalmol Retina*. Mar 2020;4(3):310–319. https://doi.org/10.1016/j.oret.2019.10.009.
7. Janiszewska AD, Poletajew S, Wasiutyński A. Spontaneous regression of renal cell carcinoma. *Contemp Oncol*. 2013;17(2):123–127. https://doi.org/10.5114/wo.2013.34613.
8. Langmann G, Müllner K. Spontaneous regression of a choroidal metastasis from renal carcinoma. *Br J Ophthalmol*. Nov 1994;78(11):883. https://doi.org/10.1136/bjo.78.11.883.
9. Hammad AM, Paris GR, van Heuven WA, Thompson IM, Fitzsimmons TD. Spontaneous regression of choroidal metastasis from renal cell carcinoma. *Am J Ophthalmol*. Jun 2003;135(6):911–913. https://doi.org/10.1016/s0002-9394(02)01973-6.
10. Snow RM, Schellhammer PF. Spontaneous regression of metastatic renal cell carcinoma. *Urology*. Aug 1982;20(2):177–181. https://doi.org/10.1016/0090-4295(82)90356-9.
11. Dosquet C, Coudert MC, Lepage E, Cabane J, Richard F. Are angiogenic factors, cytokines, and soluble adhesion molecules prognostic factors in patients with renal cell carcinoma? *Clin Cancer Res*. Dec 1997;3(12 Pt 1):2451–2458.
12. Lekanidi K, Vlachou PA, Morgan B, Vasanthan S. Spontaneous regression of metastatic renal cell carcinoma: case report. *J Med Case Rep*. Sep 18 2007;1:89. https://doi.org/10.1186/1752-1947-1-89.
13. Okazaki A, Kijima T, Schiller P, et al. Spontaneous regression of multiple pulmonary metastases accompanied by normalization of serum immune markers following cytoreductive nephrectomy in a patient with clear-cell renal cell carcinoma. *IJU Case Rep*. Mar 2021;4(2):95–99. https://doi.org/10.1002/iju5.12252.