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Metastatic papillary renal cell carcinoma to the retina and vitreous

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ABSTRACT

Purpose: To describe the presentation, evaluation, and management of vitreoretinal metastasis from papillary renal cell carcinoma.

Observations: A 53-year-old woman presented with a six-week history of dark floaters in the right eye. Vitreous veils and white pre-retinal plaques were identified in the posterior pole and extended to a temporal peripheral lesion suggestive of retinal infiltration. Optical coherence tomography revealed clumps of pre-retinal hyper-reflective material in the macula and a large hyper-reflective plaque-like lesion involving the internal limiting membrane in the temporal periphery. Fluorescein angiography demonstrated patchy hyperfluorescence with mild leakage at the temporal lesion and there was no evidence of choroidal involvement on indocyanine green angiography. Vitreoretinal biopsy confirmed the diagnosis of metastatic papillary renal cell carcinoma which spurred further systemic metastatic evaluation. Choroidal metastasis developed 15 months later in the fellow eye highlighting different types of intraocular metastatic spread in the same patient.

Conclusions and Importance: This case report illustrates a rare presentation of papillary renal cell carcinoma with metastasis to the retina and vitreous. Ophthalmologists should be aware of the appearance and imaging characteristics of retinal and vitreous metastases, which can be the first presentation of a new or newly metastatic malignancy. These lesions can resemble infectious or inflammatory mimickers and may require biopsy to secure the diagnosis and to guide vision- and life-preserving treatment.

1. Introduction

Cancer is a leading cause of death in the United States, second only to heart disease. Earlier detection, innovative treatments, and careful surveillance all contribute to improved survival for patients living with a cancer diagnosis. As life expectancy increases for these individuals, it is important for primary care and subspecialized physicians to recognize the ophthalmic complications that stem from cancer or its treatment. While uveal metastases account for the majority of intraocular tumors in adults, vitreoretinal metastatic disease occurs infrequently and can be difficult to diagnose. These lesions can mimic an infectious or inflammatory process and often require biopsy to confirm the diagnosis and guide treatment. Renal cell carcinoma has been previously shown to exhibit choroidal metastasis, however, intraocular spread to the retina and vitreous is exceedingly rare.

2. Case report

A 53-year-old Caucasian female with a past medical history of migraine, hypothyroidism, cervical dysplasia, and papillary renal cell carcinoma diagnosed 1.5 years prior on radical nephrectomy presented to the ophthalmology clinic with a six-week history of dark floaters and “spider webs” in the vision of her right eye. She denied flashing lights, photophobia, or pain, but described blurring of her entire visual field without a focal scotoma. She denied any changes in the fellow eye. 6 months prior to presentation, she underwent endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal lymph nodes which demonstrated metastatic papillary renal cell carcinoma for which she was actively treated with pazopanib.

Visual acuity was 20/60 in the right eye and 20/20 in the left eye. Intraocular pressures, confrontation visual field testing, ocular motility, and the pupillary exam were normal. Anterior segment examination revealed mild nuclear sclerosis of the lenses bilaterally and no evidence of inflammation. Dilated fundus examination of the right eye revealed

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numerous spherical white vitreous opacities and vitreous veils. Diffuse, white, pre-retinal and perivascular plaques were noted throughout the posterior pole and extended to a larger lesion in the temporal periphery that was concerning for retinal infiltration (Fig. 1). The optic disc had sharp margins and there were no retinal hemorrhages, vascular tortuosity, or vessel sheathing. Fundus examination of the left eye was unremarkable.

Optical coherence tomography of the macula revealed clumps of pre-retinal hyper-reflective material as well as a large hyper-reflective plaque-like lesion adherent to the internal limiting membrane with internal hyporeflective spaces in the temporal periphery (Fig. 2). Fluorescein angiography identified stippled hypofluoresence from vitreous opacities and patchy hyperfluorescence with mild leakage at the temporal lesion. Similar findings were illustrated on indocyanine green angiography, however there was no evidence of choroidal involvement. Further investigations including complete blood count, erythrocyte sedimentation rate, and c-reactive protein, as well as tests for tuberculosis, syphilis, toxoplasmosis, brucellosis, histoplasmosis, sporotrichosis, blastomycosis, bartonellosis, cryptococcosis, *Tropheryma whipplei*, and bacterial and fungal blood cultures were all unremarkable. Subsequent MRI of the brain with gadolinium contrast demonstrated multiple ring-enhancing lesions and leptomeningeal disease concerning for new central nervous system metastasis.

A diagnostic pars plana vitrectomy was performed and histopathology of the vitreous and retinal biopsy demonstrated intra- and pre-retinal clusters of carcinoma cells positive for keratin AE1/AE3 and PAX8 immunostains, consistent with the diagnosis of metastatic papillary renal cell carcinoma (pRCC) (Fig. 3). The patient was treated with whole brain radiation and a change in systemic therapy from pazopanib to nivolumab. Unfortunately, there was limited visual recovery of the right eye secondary to proliferative vitreoretinopathy and vitreous hemorrhage despite additional surgical intervention and intravitreal methotrexate injections. 15 months later, multiple choroidal lesions developed in the left eye also thought to represent metastatic papillary renal cell carcinoma, creating the scenario of sequential, vitreoretinal metastasis in one eye and choroidal metastasis in the fellow eye (Fig. 4). Unfortunately, the patient expired due to complications of her disease approximately 18 months from her initial presentation to our department.

3. Discussion

Renal cell carcinoma (RCC) arises from the epithelial cells of the renal tubular system and represents 85–90% of primary renal malignancies, with clear cell (ccRCC) (75%) and papillary (pRCC) (15%) being the most common histologic subtypes.[1] RCC is among the 10 most common cancers worldwide, accounting for 2% of all systemic malignancies, with more than 63,000 new cases diagnosed in the United States each year.[1] Genetic loss of function mutations on chromosome 3 affecting the tumor suppressor genes Von Hippel-Lindau (VHL), protein polybromo-1 (PBRM-1), and BRCA1-associated protein-1 (BAP-1) have been well described to underlie the disease.[1] Historically, pRCC has been associated with favorable outcomes compared to ccRCC. However, more recently, pRCC (type 2) has been shown to frequently present with locally advanced or metastatic disease when compared to ccRCC and patients with metastatic non-ccRCC (including pRCC) are often younger, have a shorter median overall survival of approximately 13 months (versus 22.3 months for ccRCC), and a shorter time to treatment failure.[2,3] Treatment of metastatic RCC often involves the use of immunotherapies targeting the vascular endothelial growth factor (VEGF) signaling pathway (sorafenib, sunitinub, pazopanib, etc.), mammalian target of rapamycin (MTOR) inhibitors (everolimus, temsirolimus), and targeted antibodies against the programmed cell death protein 1 (PD-1) (pembrolizumab, nivolumab, etc.), among others.[1,2] Despite these treatments, the 5-year survival rate of patients with distant metastatic renal cell carcinoma remains poor at approximately 15%.

Metastatic disease is the most common malignancy in the eye and often involves the uveal tract due to the high rate of blood flow through the choroid. One study examined 1310 eyes in 1111 patients with uveal metastasis and found the choroid (90%) to be the most common location, followed by iris (8%), and ciliary body (2%).[4] The most common primary tumors were the breast (37%) and lung (27%), followed distantly by the kidney (4%) and others. In the cases of metastatic renal cancer to the uvea, 96% presented with a known history of primary renal malignancy, and the prognosis was poor with a survival rate of 26% at two years and no survivors at five years.[4] Another study of 62 patients with metastatic RCC found an even 50% split of intra-vs. extraocular spread to the orbit and all intraocular metastases were found within the uveal tract, with none reported to involve the retina or vitreous.[5]

While uveal metastatic disease has been well described, metastatic disease to the retina and vitreous is rare with only a few case reports and series published in the literature. Among these malignancies, cutaneous melanoma appears to be the most common, however retinal-vitreous metastases from lung carcinoma, breast carcinoma, gastrointestinal malignancies, urothelial carcinoma, and hepatocholangiocarcinoma have also been reported.[6–8] These patients typically present with new blurred vision and floaters as the predominant symptoms but may lack other signs of ocular inflammation including conjunctival injection, chemosis, or anterior chamber cell. A review of 20 cases of retinal metastasis described retinal patches and perivascular infiltrates from cutaneous melanomas as having brown or black pigmentation, whereas metastatic carcinomas were white in appearance.[9] Because these lesions are not contained within the choroid, there was a prominence of vitreous seeding for retinal metastases compared to their uveal tract counterparts. Recently, a case of choroidal metastasis in one eye and retinal metastasis in the fellow eye from a pulmonary mucinous carcinoma was

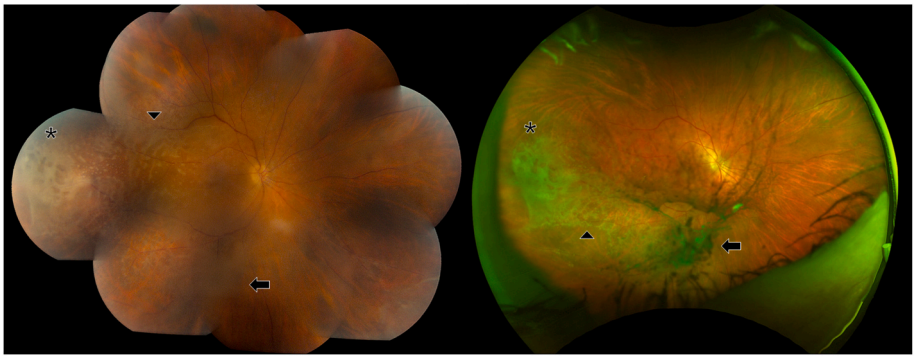

Fig. 1. – Fundus photos, right eye. Color montage (left) and ultra-widefield (right) fundus imaging demonstrate spherical vitreous opacities (arrow) and white pre-retinal plaques (arrowhead), extending from the macula towards a large white retinal infiltrate in the temporal periphery (asterisk). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

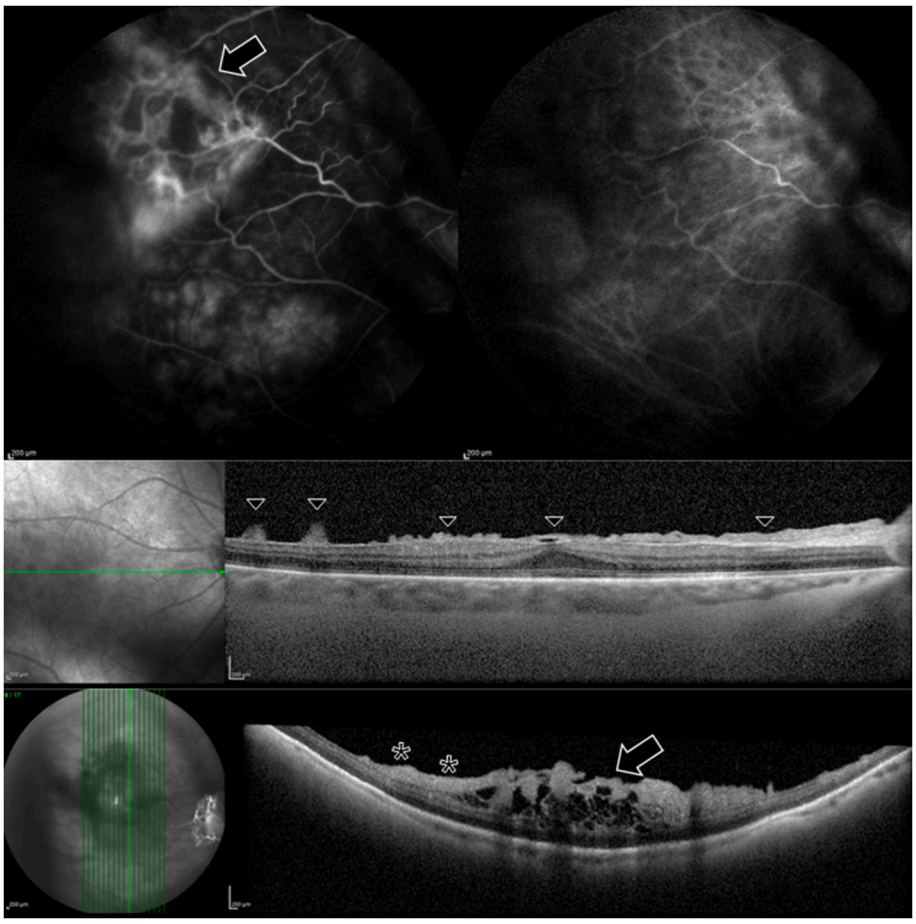

Fig. 2. – Ocular imaging, right eye. Top: Fluorescein angiography (IVFA) & Indocyanine green angiography (ICG). IVFA (left) demonstrates a patchy temporal retinal hyperfluorescence pattern with mild leakage (arrow). ICG-A (right) shows no evidence of choroidal infiltration. Middle: Optical coherence tomography (OCT) of the right macula demonstrates pre-retinal hyper-reflective material along the internal limiting membrane (arrowheads). Bottom: OCT image of the temporal plaque-like lesion adherent to the internal limiting membrane (asterisks) and causing hyporeflective spaces and disorganization of the inner retinal architecture (arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

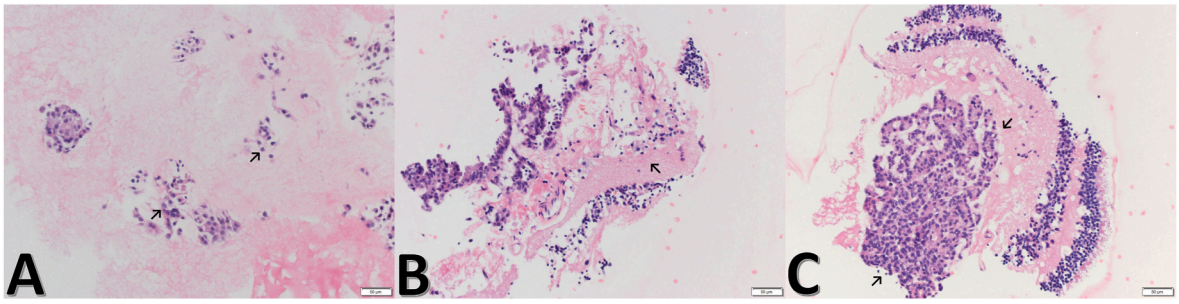

Fig. 3. – Histopathology of the vitreoretinal biopsy. The vitreoretinal biopsy demonstrates aggregates of carcinoma cells with irregular nuclei and prominent nucleoli growing in sheets and small papillary clusters (arrows) in the vitreous (A) and infiltrating the retina (arrows) (B and C) (Hematoxylin-eosin; ×200 original magnification).

described, suggesting a likely mechanism of hematogenous spread for both retinal and choroidal metastases.[10]

Cases of retinal metastasis can often behave as a masquerade syndrome mimicking retinitis or vasculitis, vascular or vaso-occlusive disorders with exudation, endophthalmitis, or other infectious, inflammatory, or neoplastic etiologies. In a series of eight patients with retinal metastasis, five had an initial misdiagnosis of retinitis and five had died within one month of the ophthalmic evaluation, highlighting the challenges in diagnosis and poor prognosis these patients endure.[8] Diagnostic vitrectomy can provide a tissue diagnosis and help distinguish metastatic disease from ocular diseases of infectious or inflammatory etiology.

Ocular treatment considerations of metastatic disease depend on the clinical scenario, but may include systemic chemotherapy, immunotherapy, plaque brachytherapy, external beam radiation, and photodynamic therapy. In all cases, consultation with medical and radiation oncologists is paramount for effective management of widespread disease.

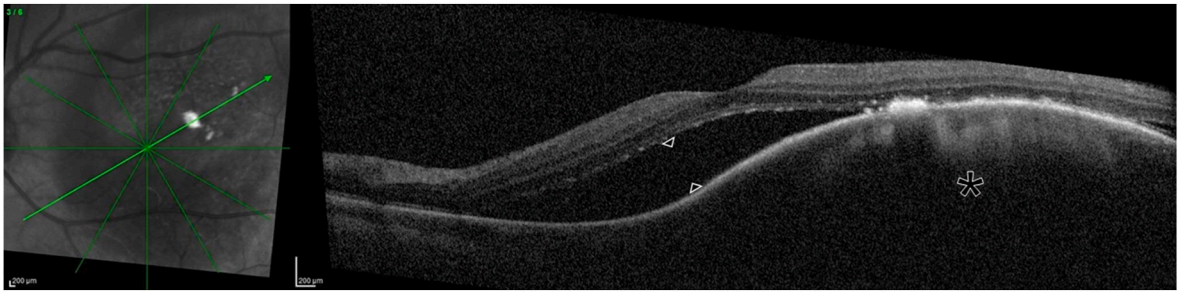

Fig. 4. – Choroidal metastasis in the fellow eye. Optical coherence tomography (OCT) of the left macula demonstrates the temporal macula draped over a dome shaped hyper-reflective choroidal lesion (asterisk) with subretinal fluid (arrowheads) beneath the fovea.

4. Conclusion

This case highlights the importance of including metastatic disease in the differential diagnosis of new visual floaters, blurred vision, and other common ocular symptoms in patients with an oncologic history. Ophthalmologists should be familiar with the appearance and imaging characteristics of vitreoretinal metastasis as a prompt examination may provide valuable reassurance or uncover a new or newly metastatic malignancy requiring life sustaining care. Despite the unfavorable mortality statistics these patients face, an accurate diagnosis provides the best chance to initiate systemic treatment and preserve vision and quality of life.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

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

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Aaron M. Fairbanks: Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization. **Diva R. Salomao:** Writing – review & editing, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Andrew J. Barkmeier:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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.

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