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Clinicopathologic analysis of a case of small cell lung carcinoma metastatic to the retina

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ABSTRACT

Purpose: Tumor metastases to the retina are a relatively rare occurrence. We report a unique case of retinal metastasis of a systemic malignancy with clinical and histopathologic correlations.

Observations: A 62-year-old female with a history of stage IV small cell carcinoma of the lung (SCC, status post chemotherapy and maintenance immunotherapy) presented with hand motions vision and vitreous hemorrhage, status post prior vitrectomy and biopsy that was non-diagnostic. She was found to have unilateral retinal metastatic tumor and underwent a repeat vitrector-assisted biopsy which confirmed the diagnosis. The eye became blind and painful due to recurrent non-clearing vitreous hemorrhage and ghost cell glaucoma and was enucleated. Detailed histopathologic analysis of the globe confirmed small cell carcinoma metastatic to the retina and vitreous cavity and sparing the choroid.

Conclusions and importance: This case demonstrates the importance of maintaining a high index of suspicion for metastasis in patients with a known history of malignancy who present with new vitreoretinal lesions.

1. Introduction

Tumor metastases to the retina are relatively uncommon—reportedly accounting for less than 1% of all ocular metastases.[1,2] Prior case reports and case series have reported retinal metastases from multiple extraocular primary malignancies including adenocarcinoma of the lung, breast, skin, and stomach.[2–8] While choroidal metastases are far more common, retinal metastases can present with retinal hemorrhage, exudation, ischemia, detachment, vitreous hemorrhage, or secondary glaucoma.[2,9] In a single-center series of eight cases, retinal metastases were most frequently misdiagnosed as infectious or inflammatory retinitis.[2] Patients typically present with multiple synchronous metastases to other extraocular organs at the time of presentation with retinal metastasis, which portends a poor survival prognosis.[2,4–6,9] This report describes a case of retinal metastasis presenting as subretinal and later vitreous hemorrhage and details the clinicopathological correlations.

2. Case report

A 62-year-old female with a history of stage IV small cell carcinoma (SCC) of the lung was referred for second opinion on a right eye mass and associated recurrent vitreous hemorrhage. She had previously been diagnosed with SCC metastatic to the mediastinum and the left pelvis fifteen months prior and had undergone four cycles of systemic chemotherapy with carboplatin, etoposide, and atezolizumab followed by atezolizumab maintenance therapy, which was stopped seven months prior to presentation and restarted two months prior to presentation. Magnetic resonance imaging (MRI) of the brain and orbits with contrast two months prior to presentation showed a 6× 2 mm retinal mass lesion in the right eye. Positron emission tomography (PET) scan showed no evidence of extraocular disease. The patient's past medical history was significant for chronic obstructive pulmonary disease (with a 45-pack-year smoking history), hypertension, hyperlipidemia, and atrial fibrillation (on rivaroxaban).

The patient's past ocular history was notable for presumed exudative age-related macular degeneration (AMD) of the right eye (diagnosed five

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months prior to presentation with macular subretinal hemorrhage thought to be choroidal neovascular membrane, treated with one intravitreal bevacizumab injection) and dry AMD of the left eye. She presented a month later with vitreous hemorrhage, subretinal masses with associated necrosis, and exudative retinal detachment on examination (Fig. 1A), and underwent pars plana vitrectomy with biopsy of the retinal lesions, injection of intravitreal vancomycin and cefepime, and endolaser. Cytopathologic analysis of the biopsy showed no definitive evidence of malignancy. The patient subsequently developed vitreous hemorrhage and neovascularization of the angle for which she was treated with intravitreal bevacizumab. She then underwent a second pars plana vitrectomy with anterior segment washout, *trans*-retinal biopsy, and pan-retinal photocoagulation one month prior to presentation to our center; pathologic analysis again showed no evidence of malignancy.

The patient then presented to our clinic with intermittent headaches, recurrent vitreous hemorrhage, and cataract of the right eye limiting the view to the posterior segment. The best corrected visual acuity (VA) was light perception in the right eye and 20/20 in the left eye. Intraocular pressure (IOP) was within normal limits in both eyes. Right eye examination revealed 3+ nuclear sclerosis and 4+ posterior subscapular cataract with hemorrhage staining the posterior lens capsule, with a poor view to the posterior segment (Fig. 1B) The left retinal exam was normal (Fig. 1C). Ultrasound of the right eye (Fig. 1D and E) showed dense vitreous hemorrhage, diffuse retinal thickening and hyperreflective retinal lesions.

The patient then underwent phaco-vitrectomy; after cataract extraction and lens implantation, plana vitrectomy was performed to clear out the extensive vitreous hemorrhage with the cutter connected to a specimen collection tube. The retina was diffusely infiltrated in all four quadrants with associated subretinal hemorrhage. A highly elevated portion of the tumor nasally—extending anterior to the ora serrata—was biopsied using the 25-gauge vitrector and specimen sent for cytology which confirmed small cell carcinoma (Fig. 2). Endolaser was applied to the biopsy site.

One week postoperatively, the patient presented to clinic with headache, light perception vision, and intraocular pressure (IOP) of 43. Examination revealed red blood cells in the anterior chamber and recurrent vitreous hemorrhage. The patient elected for comfort care with intraocular pressure-lowering therapy only, declining repeat vitrectomy and anterior segment washout or ocular radiotherapy. Despite treatment with maximal topical therapy (timolol twice daily, dorzolamide twice daily, brimonidine three times daily, and bimatoprost once at bedtime) and methazolamide 50 mg orally three times daily, the patient presented two weeks later with no-light perception vision and IOP of 50 and reported significant eye pain and headache. Her examination was otherwise stable. In addition to recurrent posterior segment hemorrhage, ghost-cell glaucoma was also thought to be contributing to pressure issues. Given the very guarded prognosis for recovery of vision with further surgery or radiotherapy, and given the patient's blind, painful right eye, she elected for enucleation. Surgery was uncomplicated; a silicone sphere implant was placed. Notably, tumor re-staging with a repeat PET scan was completed prior to enucleation and had revealed only right eye activity/FDG avid lesion, with no evidence of extraocular recurrent and/or other metastatic disease.

Pathology from the enucleated globe showed small cell carcinoma invading retina. Gross inspection of the specimen revealed diffuse, irregular retinal thickening and extensive neovascularization extending from the retinal surface. Cytopathologic analysis revealed tumor cells scattered along the anterior vitreous face and extending throughout the retina and the vitreous cavity; this is also seen on the histology slides (Fig. 3). Extensive subretinal and intraretinal hemorrhage was seen. No choroidal involvement or optic nerve invasion was noted (Fig. 3). The patient underwent systemic immunotherapy treatment following the enucleation of the right eye and is currently doing well without evidence of recurrence or metastasis, 36 months later.

3. Discussion

Metastatic invasion of the retina is rare with a handful of cases published in reports and case series and, even less commonly, with clinicopathologic studies.[2,3,5–14] Less than 1% of ocular metastases are

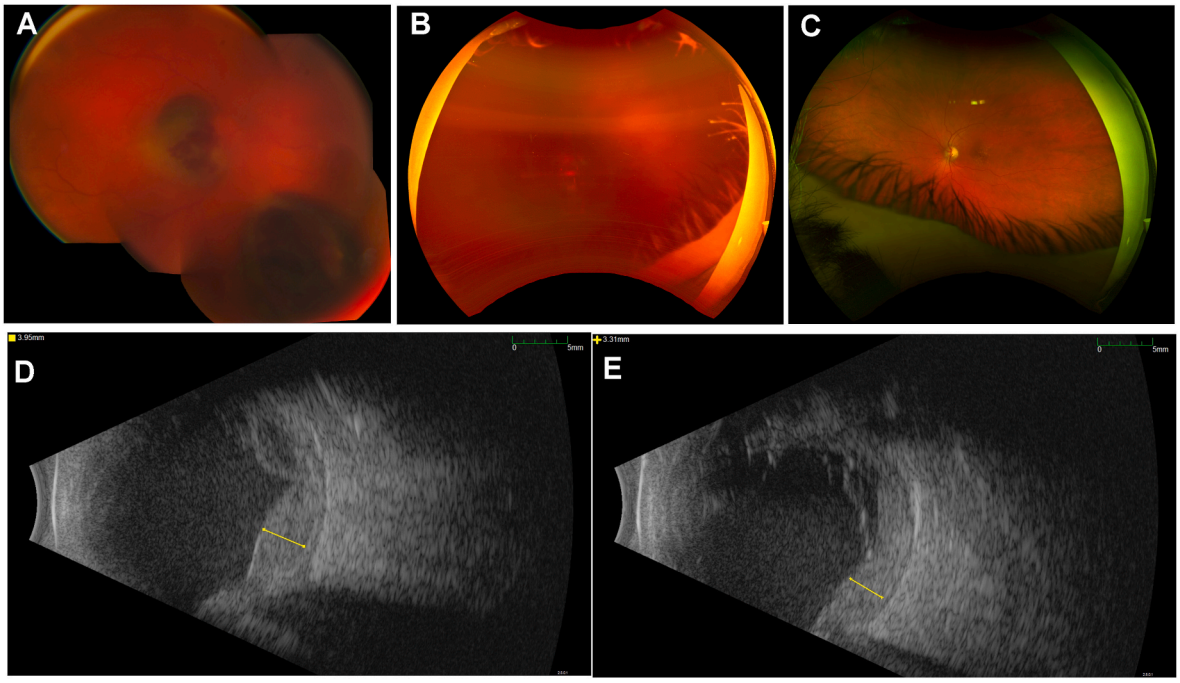

Fig. 1. Color fundus photographs of the (A) the right eye prior to the first vitrectomy with outside provider showing subretinal lesions and hemorrhage and vitreous hemorrhage, fundus photos of the right and left eyes (B, C) and B-scan ultrasounds of the right and left eyes (D, E) at presentation at our institution. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

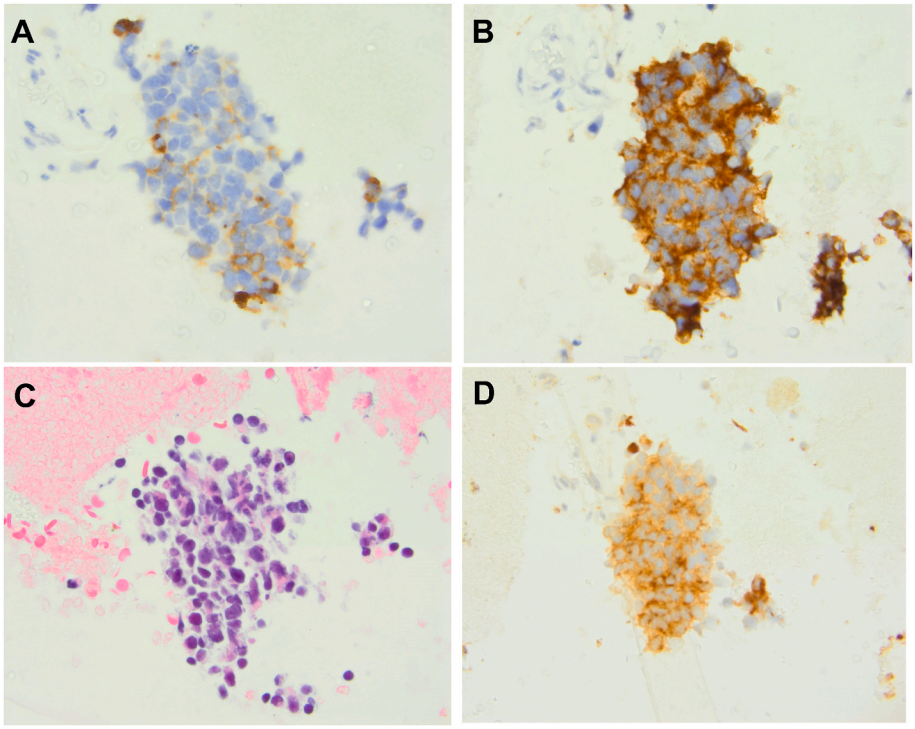

Fig. 2. Cytology after vitrectomy showing small cell carcinoma (A) chromogranin x600, (B) keratin x 600, (C) hematoxylin and eosin x600, (D) synaptophysin x600.

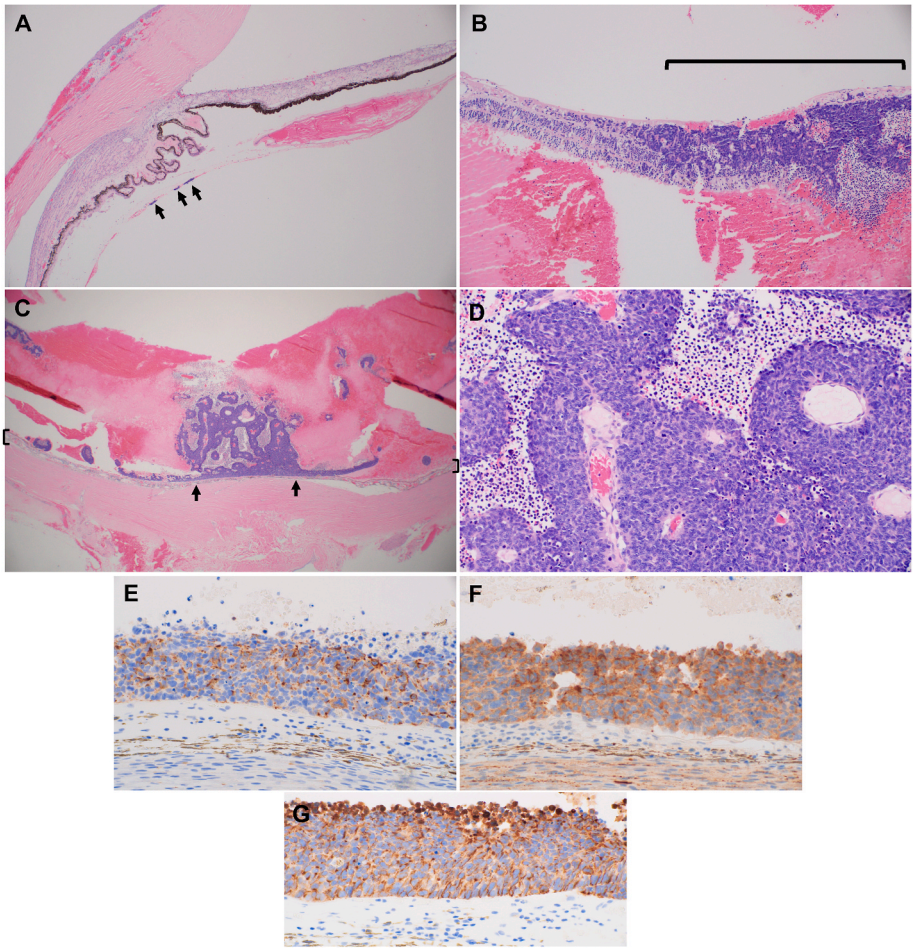

Fig. 3. Histological sections of the enucleated right eye. (A) Low magnification view of right eye angle with Soemmering's ring cataract and red blood cells and small blue cells layered on the anterior hyaloid face (arrows). (B) Retina cross-section showing, on the left side of the image, normal retinal layers and, on the right side of the image, obliterated retinal layers with significant infiltration by small round blue cells with near total retinal replacement and necrosis). There is vitreous hemorrhage, intraretinal hemorrhage and significant underlying subretinal hemorrhage. (C) Cross-section through retinal mass showing that the choroid is preserved and uninvolved. (D) High magnification view of mass. The constituent cells are small, round, and blue. They are pleomorphic with numerous mitotic figures and apoptotic cells present. (E–G). Cells stained brown with neuroendocrine markers chromogranin (E) and synaptophysin (F) and with carcinoma marker pancytokeratin (G). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reported to occur in the retina.[2] Other groups have previously reviewed the range of case reports and case series in detail.[2,9,11] The mechanism of intraocular metastasis involves the hematogenous spread of tumor cells. The anatomy of the arterial blood supply to the eye dictates the predilection of tumor cell deposits within the eye. Specifically, while the posterior choroid—with its rich vascular supply—is the most favored site of intraocular metastases, the retina and optic nerve head, which are supplied by the single central retinal artery, are more rarely involved.[11] When the retina is involved, the inner retina is preferentially invaded by tumor cells, which are likely disseminated through the central retinal artery supplying the inner retina.[2,11]

Retinal metastases arise from a variety of extraocular primary malignancies including lung and breast adenocarcinoma, gastrointestinal tract malignancies and cutaneous melanoma.[2–8,11] In a recent single-center retrospective case series, 8 retinal metastases were reported including 4 cases of cutaneous melanoma and 4 cases of carcinoma seen over the course of 40 years.[2] Similar to our patient, the majority of cases (7 out of 8) presented with unilateral disease. In contrast to cutaneous melanoma metastases which are typically reported as brown or golden yellow, carcinoma metastases typically appear yellow-white and can be associated with vitreous cells localized to the area overlying the site of retinal involvement.[2,11] Carcinoma metastases to the retina can resemble retinitis due to this vitreous seeding of tumor cells.[11,14] Indeed, Shields et al. reported retinal metastases cases were most commonly initially misdiagnosed as infectious or inflammatory retinitis.[2]

Interestingly, our patient was previously diagnosed and treated for presumed neovascular AMD in the affected eye, which was an uncommon presenting diagnosis in the Shields series (1 out of 8 cases).[2] Retinal metastases can present with a range of examination findings including intraretinal hemorrhage, subretinal hemorrhage, vitreous hemorrhage, subretinal fluid, exudates, exudative retinal detachment and/or secondary glaucoma.[2,9,11] Presentation of retinal metastasis with vitreous hemorrhage (as seen at the time this patient presented to our clinic) or with subretinal hemorrhage is rarely reported in the literature.[7,15] This uncommon presentation and multiple negative retinal biopsies delayed definitive diagnosis in this patient. Notably, retinal biopsy may not yield the diagnosis as seen in our case. Shields et al. reported that fine needle biopsy yielded the diagnoses in only 4 of the 8 cases in their series. Given the patient's history of systemic malignancy, a high index of suspicion for an underlying metastatic process was maintained by all providers. Detailed pathological analysis, which revealed subretinal, intraretinal, and vitreous hemorrhage, significant infiltration of the retina with near total retinal replacement by small round blue cells and necrosis, and complete lack of involvement of the choroid, established the diagnosis of retinal metastasis.

Retinal metastases are typically associated with poor survival prognosis with metastasis-related deaths reported to occur between 2 months and 5 years after initial presentation.[2,9] This case is unique as the patient presented while in apparent remission on immunotherapy and was otherwise systemically well as was confirmed on restaging PET scan. Given the absence of extraocular involvement in this patient, the hope is that the enucleation will improve her prognosis compared to the more commonly cited survival times.

4. Conclusions

To our knowledge, this is the first case of retinal metastasis of a primary small cell carcinoma presenting with subretinal and later vitreous hemorrhage and with corresponding clinicopathologic analysis to establish the definitive diagnosis presented in the literature. Diagnosis of retinal metastasis can be made more difficult by non-diagnostic retinal biopsies. This case highlights the importance of maintaining a high index of suspicion for metastasis in patients with a known history of malignancy who present with new or recurrent retinal or vitreous hemorrhage.

Patient consent

Signed consent obtained.

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Authorship

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

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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