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Large extraocular extension of a choroidal melanoma with orbital inflammation

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ABSTRACT

Purpose: To describe an atypical case of a choroidal melanoma presenting with eyelid edema, chemosis, pain and diplopia and demonstrating significant extraocular extension on ultrasonography and neuroimaging.

Observations: A 69-year-old woman presented with a headache, eyelid edema, chemosis and pain in the right eye. Upon subsequent onset of diplopia, MRI of the orbits was performed and demonstrated a predominantly extraocular, intraconal mass with a small intraocular component. She was started on corticosteroids and referred to the ocular oncology service for evaluation. On fundus examination, she was noted to have a pigmented choroidal lesion consistent with melanoma, and ultrasound showed a large area of extraocular extension. Enucleation, enucleation with subsequent radiation and exenteration were discussed, and the patient requested an opinion from radiation oncology. A repeat MRI obtained by radiation oncology demonstrated a decrease in the extraocular component after corticosteroid treatment. The improvement was interpreted as suggestive of lymphoma by the radiation oncologist who recommended external beam radiation (EBRT). Fine needle aspiration biopsy was insufficient for cytopathologic diagnosis, and the patient elected to proceed with EBRT in the absence of a definitive diagnosis. Next generation sequencing revealed GNA11 and SF3B1 mutations, which supported the diagnosis of uveal melanoma and led to enucleation.

Conclusion and Importance: Choroidal melanoma may present with pain and orbital inflammation secondary to tumor necrosis, which may delay diagnosis and decrease the diagnostic yield of fine-needle aspiration biopsy. Next generation sequencing may aid the diagnosis of choroidal melanoma when there is clinical uncertainty and cytopathology is unavailable.

1. Introduction

Choroidal melanoma is the most common primary intraocular malignancy in adults, and patients are usually asymptomatic or present with painless vision loss.[1,2] Pain rarely occurs, and when it does, it is often secondary to tumor necrosis,[3,4] leading to inflammatory sequalae resulting in atypical presentations and mimicking a broad range of inflammatory and infectious etiologies, with possible diagnostic delay.[5] Steroid treatment often reduces the inflammatory component, but can lead to further diagnostic confusion.

Extraocular extension (EOE) presents in 2–3% of uveal melanoma at the time of diagnosis, is more common in medium and large size tumors, and is typically of limited size.[6–10] However, with larger areas of EOE, the best approach for treatment remains controversial. We report the case of a patient with a choroidal melanoma and a large area of extraocular extension, who initially presented with pain and orbital inflammation responsive to corticosteroids, causing diagnostic uncertainty.

2. Case report

A 69-year-old woman with a history of glaucoma presented to her ophthalmologist with a headache and a painful and inflamed right eye

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(OD). Her visual acuity was 20/40 OD and 20/20 in the left eye (OS). She was noted to have eyelid edema and chemosis and was started on topical tobramycin/dexamethasone 4 times daily OD. She returned the following day without improvement and 500 mg cephalexin was added. Three days later, the patient developed new onset binocular diplopia. While her chemosis had improved, she had limited motility in all gazes OD. Magnetic resonance imaging (MRI) of the orbits was performed for presumed orbital inflammation, and she was started on 40 mg oral prednisone. MRI demonstrated an inferotemporal, predominantly extraocular mass with a small intraocular component that was hyperintense on T1-weighted images and heterogeneously hypointense on T2-weighted images (Fig. 1A). The entire mass measured 12 mm × 10 mm in basal dimensions and 14 mm in thickness. Repeat examination 19 days following initial examination revealed full motility, resolved diplopia, and improved eyelid edema and chemosis, making fundus examination possible, which revealed a pigmented, inferotemporal choroidal mass.

The patient was subsequently referred to the ocular oncology service for an intraocular neoplasm with orbital extension. On presentation her visual acuity was 20/50 OD and 20/25 OS. The intraocular pressures and anterior segment examination were within normal limits OU. Dilated fundus examination OD revealed a dark brown lesion in the inferotemporal mid-periphery measuring 11 mm × 8 mm in basal dimensions (Fig. 1B). B-scan ultrasonography demonstrated a dome-shaped lesion with low internal reflectivity and significant extraocular extension (Fig. 1C). The basal dimensions noted on clinical exam were confirmed on ultrasound and the intraocular component measured 2.6 mm, while the extraocular portion measured 6.9 mm in thickness. The patient was diagnosed with a choroidal melanoma, systemic imaging was ordered and was negative for metastatic disease. She was referred to the oculoplastics service to discuss management options, including enucleation with or without orbital radiation versus exenteration given the extent of the extraocular component.

After discussing treatment options with the oculoplastic specialist, the patient sought an opinion from radiation oncology about the risks and benefits of orbital radiation after enucleation. The radiation oncologist ordered a repeat MRI of the orbits which demonstrated a reduction of the thickness of the mass from 14 mm on the previous scan to 8 mm, consistent with what was seen on ultrasonography. The tumor reduction after steroid administration was interpreted to be suggestive of lymphoma by the radiation oncologist, who recommended external beam radiotherapy (EBRT) in lieu of surgical intervention. We performed a fine needle aspiration biopsy for cytopathology, gene expression profile (GEP) testing, and next generation sequencing (NGS) to obtain a definitive diagnosis. Cytopathology revealed red blood cells with sparse neutrophils and mononuclear leukocytes, indicating an insufficient specimen. Given the negative cytopathology, the radiation oncologist's impression that the lesion was consistent with a lymphoma, and the patient's desire to avoid enucleation or exenteration in the absence of a definitive diagnosis, EBRT was initiated with a total prescribed dose of 30 Gy. She had undergone 18 Gy of radiation when the results of her NGS revealed GNA11 and SF3B1 mutations, supporting the diagnosis of uveal melanoma, and GEP showed the lesion was class 1A and preferentially expressed antigen in melanoma (PRAME) was negative.

Repeat fundus examination and B-scan ultrasonography showed no evidence of additional regression following EBRT, again favoring melanoma. EBRT was discontinued as the dose planned for lymphoma would have been insufficient for uveal melanoma, and the patient underwent enucleation with additional orbital biopsies by the oculoplastics service. Pathology confirmed the diagnosis of a spindle-cell choroidal melanoma with a 2 mm thick intraocular component and an 8 mm extraocular component that had central necrosis (Fig. 2). Histopathology also showed superficial direct invasion of the sclera without a clear communication between the intraocular and extraocular components. The additional orbital biopsies did not reveal evidence of malignancy, suggesting complete surgical excision. At follow-up 6 months after enucleation, the patient demonstrated a well-healed socket without evidence of tumor recurrence and annual systemic surveillance was recommended.

3. Discussion

Necrotic choroidal tumors have been previously reported to result in scleritis, neovascular glaucoma, choroidal detachment, and orbital inflammation among other inflammatory sequalae.[11,12] In previously published reports, this most typically occurs in larger choroidal tumors.[4] Necrotic tumors and the resulting inflammatory sequalae can result in atypical presentations.[5] Tumor necrosis likely occurs from auto-infarction or following growth of the choroidal tumor with insufficient blood supply resulting in ischemia and cellular death.[11] In our case, necrosis of the extraocular component of the lesion likely led to orbital inflammation, explaining the atypical presentation with eyelid edema, chemosis, pain and diplopia. The present case was further complicated by the initial decrease in tumor size following systemic corticosteroid administration. While partial response to corticosteroids has been reported for uveal and orbital lymphoma in some cases, uveal melanoma would not be expected to respond to corticosteroids.[13] In this case, the apparent response to corticosteroids was not related to decreased tumor size but to a reduction in orbital inflammation resulting from tumor necrosis misinterpreted as tumor size reduction.

Ultrasonography may aid in differentiating melanoma from other lesions, but it is not particularly helpful in differentiating between choroidal melanoma and lymphoma as both conditions tend to demonstrate low internal reflectivity. Lymphoma often presents with EOE and ultrasound is more sensitive than neuroimaging at identifying these areas, but uveal melanoma may also demonstrate EOE, as shown in this case.[14] EOE presents in a minority of uveal melanoma cases at the time of diagnosis, and tends to occur in medium and large tumors and in tumors located in the ciliary body, in the peripapillary area, or at the site

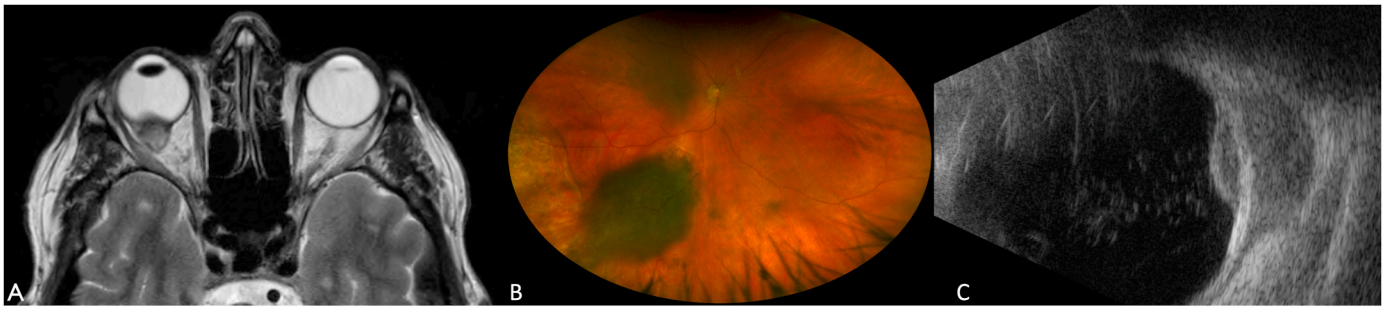

Fig. 1. Axial T2-weighted MRI demonstrating an intraconal mass. The entire mass measured 12 mm × 10 mm in basal dimensions and 14 mm in thickness (A). Fundus photography demonstrating a pigmented inferotemporal choroidal lesion (B). B-scan ultrasonography showing a dome-shaped choroidal lesion with low echogenicity and a large area of extraocular extension posterior to the choroidal lesion (C).

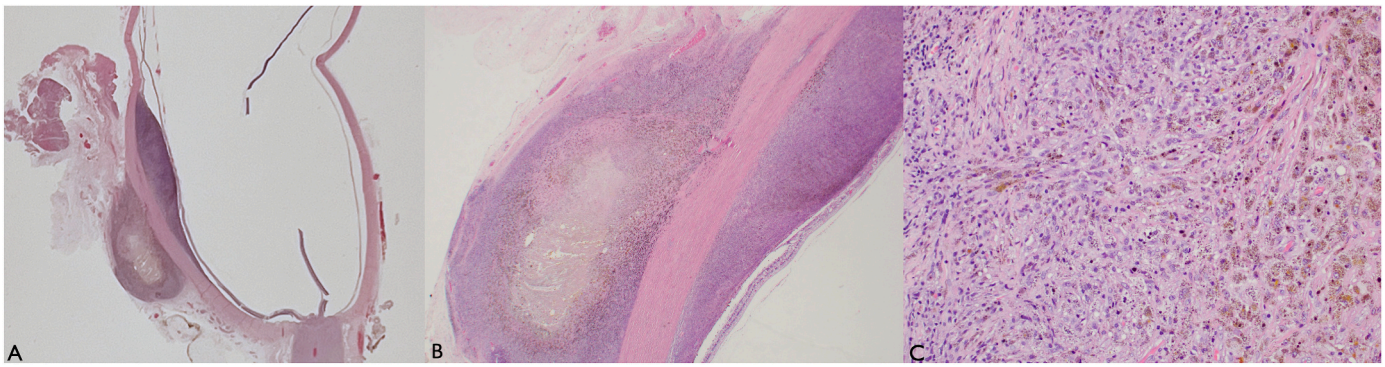

Fig. 2. Histopathology showing a uveal melanoma with extraocular extension at low (A), 20x (B), and 200x (C) magnification. The central portion of the extraocular component demonstrates necrosis with the presence of prominent melanin-laden macrophages.

of the vortex veins.[10] Interestingly, in our case the extraocular component was significantly larger than the intraocular component, which may indicate that the tumor originated from melanocytes in the natural channels of the sclera along ciliary arteries, vortex veins, and ciliary nerves,[10,15] while erosion through the sclera is exceedingly rare and more likely to occur after surgery.[8]

The presence of a distinct, pigmented choroidal lesion on fundus examination was the most helpful identifying feature as this is not consistent with uveal lymphoma. In the setting where other services are involved in clinical decision making, clinical examination alone may not be sufficient, especially when the recommended treatment is invasive. This patient elected to proceed with EBRT hoping to avoid enucleation or exenteration given the lack of cytopathlogical diagnostic confirmation of uveal melanoma. Ultimately, NGS provided sufficient evidence for diagnosis by demonstrating a GNA11 driver mutation and SF3B1 secondary mutation. Mutations in G protein alpha subunits, GNAQ and GNA11, and more rarely CYSLTR2 and PCLB4, are most commonly associated with uveal nevus and melanoma and more rarely with cutaneous or conjunctival melanoma[16,17] but they have also been associated with choroidal hemangioma, particularly in patients with Sturge-Weber syndrome.[18] They are thought to be mutually exclusive initiator mutations found in the majority of uveal melanomas but are not known to play a major role in uveal lymphoma. Secondary driver mutations including EIF1AX, SF3B1, SRSF2, and BAP1 correlate with patient outcome, and in the setting of an initiator GNAQ or GNA11 mutation, are likely indicative of a uveal melanoma.[19] While gene expression profile testing is not validated in non-melanoma uveal lesions, NGS detection of GNA11 and SF3B1 mutations in the current patient were viewed as relatively specific for uveal melanoma, supporting the recommendation for surgical treatment. This may be a useful adjunct in the future for potential choroidal melanomas causing diagnostic uncertainty, especially for thin lesions where samples may be insufficient for cytologic diagnosis,[20,21] or for lesions with significant necrosis where cytopathology may be inconclusive. However, the absence of DNA mutations by NGS should not be considered proof that the lesion is not a melanoma, the same way a negative cytologic diagnosis should not be considered unequivocal proof that a malignancy does not exist.

Management of choroidal melanoma with extraocular extension varies depending on size of EOE and institutional preference and includes globe-preserving therapy, enucleation, modified enucleation, and orbital exenteration with or without adjunctive therapy.[7,9] Adjuvant therapy is often used for cases of large EOE or EOE with incomplete resection, but a survival benefit has not been clearly demonstrated.[9] Given the extent of EOE in our case, globe-preserving therapy was not appropriate, and the patient preferred enucleation to exenteration because of the extent of disfigurement. Considering the risk of local morbidity of adjuvant radiation in the absence of a documented survival benefit and pathology suggestive of complete excision, the patient was observed after enucleation. While no recurrence was present at last follow-up six months following enucleation, long-term follow-up is required to assess for orbital recurrence.

This case highlights an atypical presentation of orbital inflammation from a necrotic choroidal melanoma with significant extraocular extension that responded to steroids causing diagnostic uncertainty. In the setting of differing opinions on diagnosis resulting in different recommendations for treatment and negative cytology, NGS supported the diagnosis of choroidal melanoma, and the patient underwent successful enucleation.

Statement of ethics

The study complied with the guidelines for human studies and animal welfare regulations. The subject gave informed consent, and the study protocol was approved by the institute's committee on human research. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Informed written consent was obtained from participants for publication of the details of their medical case and accompanying images.

Summary statement

Choroidal melanoma typically presents as a painless choroidal lesion. We report an atypical case of a patient presenting with significant extrascleral extension, pain, and orbital inflammation initially responsive to corticosteroid therapy causing diagnostic uncertainty. Next generation sequencing confirmed the diagnosis of uveal melanoma, and the patient underwent enucleation.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Written consent to publish potentially identifying information, such

as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BKW is a consultant for Allergan, EyePoint Pharmaceuticals, Castle Biosciences, Genentech and Regeneron. MDN is a consultant for EyePoint Pharmaceuticals.

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