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Melanoma Masquerade: A Case of Melanoma Masquerading as Orbital Lymphangioma

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Abstract

Secondary orbital melanoma is more common than primary orbital melanoma, and early detection is essential given the significant mortality associated with late-stage disease. This is especially challenging in patients with a retained phthisical eye, where limited direct visualization of the globe can result in delayed diagnosis and treatment. There are currently no formal guidelines for prophylactic enucleation of a blind eye; most enucleations in this setting are for patient comfort and cosmesis rather than malignancy prevention. A 68-year-old male with a 12-year history of a retained, non-painful phthisical eye presented to the emergency department with a progressively enlarging orbital mass for one year. The etiology of his earlier vision loss in the phthisical eye was unclear. Contrast-enhanced CT and MRI studies showed a large, heterogeneous enhancing left orbital mass with fluid levels, osseous remodeling, and absence of an intact left globe, which favored a lymphangioma diagnosis. He underwent superior orbitotomy for biopsy, and the mass grossly resembled a lymphangioma with cystic cavities containing coagulated blood. Pathology was consistent with melanoma. Orbital exenteration was recommended; a PET scan revealed stage IV disease with hepatic and osseous metastases. The patient elected against exenteration given his poor prognosis, and he is currently undergoing palliative chemotherapy.

Categories: Emergency Medicine, Ophthalmology
Keywords: diagnostic mimicry, lymphangioma, orbital melanoma, phthisical eye, phthisis bulbi, secondary orbital melanoma

Introduction

Melanoma is a frequently diagnosed malignancy; however, ocular and orbital involvement accounts for only 3%-5% of all melanoma cases [1,2]. Though rare, this pathology is critical to recognize, as mortality without treatment is high. Clinicians should maintain a high index of suspicion for ophthalmic or orbital malignancy in any patient with a retained phthisical eye that presents with proptosis, orbital pain, ophthalmoplegia, or eyelid edema. A phthisical eye, also known as an end-stage eye, is a shrunken, non-functional eye. The diagnosis of ocular melanoma is generally made based on dilated fundus examination, B-scan ultrasound, optical coherence tomography, and fluorescein angiography [3]. However, in cases where the phthisical eye cannot be adequately visualized or examined, the disease may progress undetected, increasing the risk of orbital extension and metastatic disease.

Uveal melanoma is the most common primary intraocular cancer in adults, representing ~85% of all ocular melanomas. The remaining 15% of cases originate from the conjunctiva or orbit [4-6]. In the United States, the incidence of ocular melanoma is roughly five to ten cases per one million people annually. This equates to an approximate incidence of 1 in 200,000 people according to the National Comprehensive Cancer Network (NCCN). The disease primarily affects Caucasians, particularly those with fair skin and light-colored eyes, and is more common in men than women [1,3,4,6-8].

Genetically, choroidal melanoma typically begins with a mutation in the GNAQ or GNA11 genes distinguishing it from cutaneous melanoma which more frequently involves BRAF or NRAS mutations. Therefore, if molecular testing for an orbital melanocytic tumor reveals GNAQ or GNA11, it is more likely to be of uveal/choroidal origin. Of note, due to the GNAQ/GNA11 mutation occurring upstream of RAS, response of these tumors to BRAF inhibitors (venurafenib, dabrafenib) is not seen. Additional risk factors for choroidal melanoma include congenital ocular melanocytosis, ocular melanocytoma, and BAP1 tumor predisposition syndrome [4,6].

Prognosis of choroidal melanoma remains poor, largely due to its high metastatic potential. Despite successful treatment of the primary tumor, around 50% of patients develop metastatic disease, most commonly hepatic. The condition is typically fatal within a year following hepatic involvement. While the overall five-year relative survival rate for uveal melanoma is approximately 78%, this rate declines sharply in metastasis. Staging of the disease is based on the American Joint Committee on Cancer (AJCC) classification system. The estimated 5-year metastasis and death rates are 5% and 3% for stage I, 17% and

9% for stage II, 44% and 27% for stage III, and nearly 100% for stage IV by just one year [1,3-4,6,9].

There remains a gap in the literature standardizing a workup for arising melanomas in a retained phthisical eye. Similarly, there is no standardized approach to surveillance or recommendations on when such eyes should be removed. This case presentation highlights the work-up necessities of evaluating a phthisical eye.

Treatment strategies for choroidal melanoma aim to control the primary tumor before metastasis occurs. Of note, these interventions have not significantly improved long-term survival [2,5]. The prognosis remains poor due to the absence of effective systemic therapies for metastatic disease. Unlike cutaneous melanoma, choroidal melanoma responds poorly to chemotherapy and immune checkpoint inhibitors [4].

A notable advancement is the development of Tebentafusp (Kimmtrak), the first systemic therapy approved for metastatic choroidal melanoma. Tebentafusp is a first-in-class immune-mobilizing monoclonal T-cell receptor against cancer (ImmTAC) that enhances the antitumor immune response. Despite its promise, its use is limited to patients who express HLA-A*0201 (human leukocyte antigen), limiting eligibility to a small proportion of the population [2,10].

This case illustrates how melanoma can remain occult in a phthisical eye and masquerade as a benign orbital lesion, and it supports a low threshold for tissue sampling and diagnosis in a progressive orbital lesion with an unexaminable globe.

Case Presentation

A 68-year-old male with a 12-year history of a painless, retained left phthisical eye presented to the Emergency Department (ED) with a right-sided facial droop and a large left ocular mass (Figures *1*, *2*). The patient reported complete vision loss in the left eye several years ago, though the etiology of the vision loss was unclear. Over time, the eye became phthisical (shrunken, calcified), but it was not removed as it was not causing him any pain. He had worn a scleral shell prosthetic over the phthisical eye for cosmesis for several years.

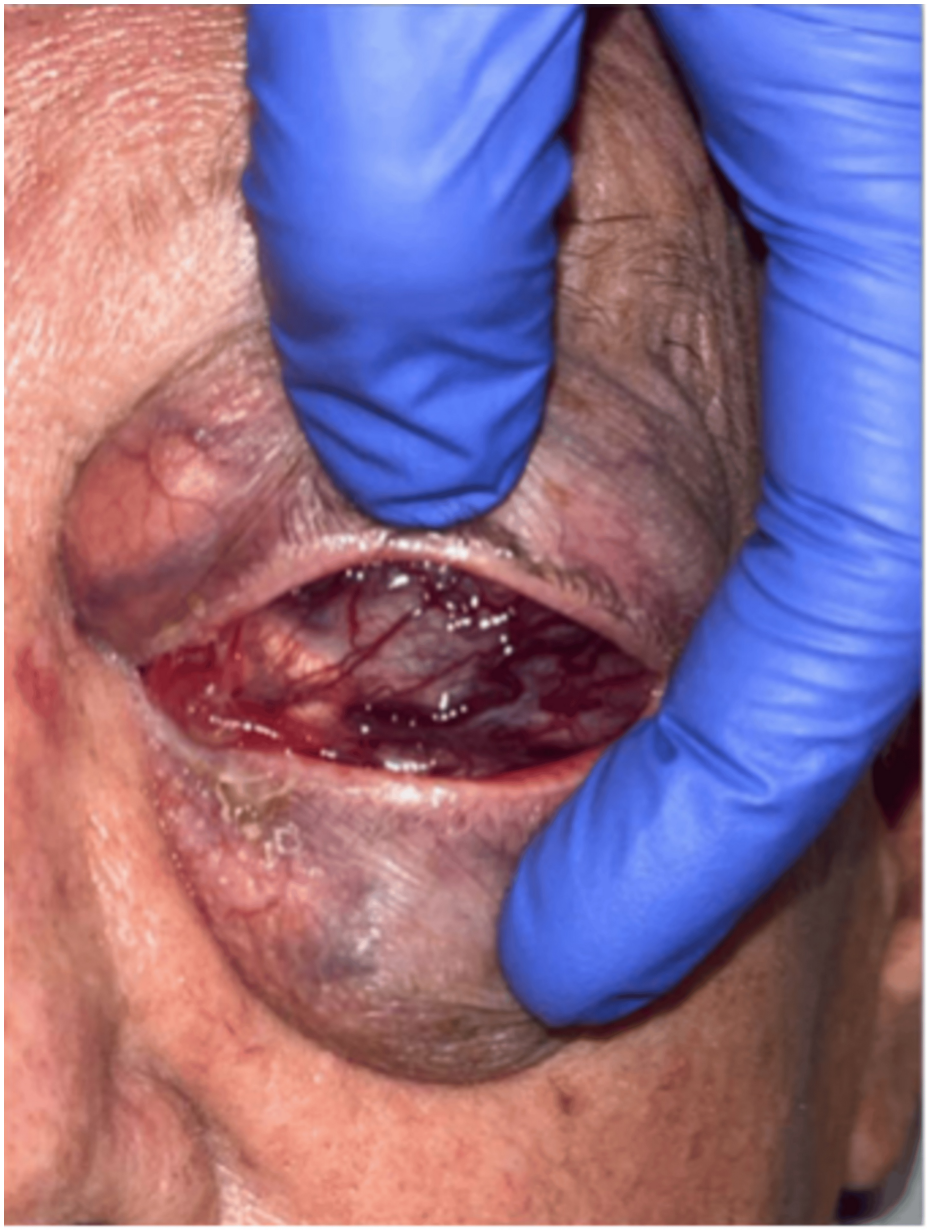


FIGURE 1: Frontal clinical photograph at presentation showing a large, indurated left orbital mass with prominent overlying superficial vessels that precludes eyelid closure.

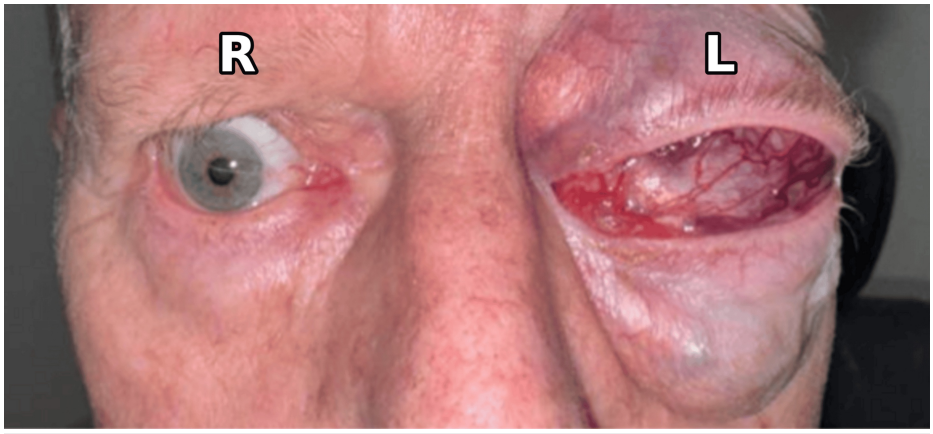


FIGURE 2: Frontal photograph comparing the left orbital mass with the unaffected right eye, showing marked left periocular proptosis/soft-tissue expansion/asymmetry.

Approximately one year prior to ED presentation, he noted intermittent swelling of the left orbit, particularly when exerting himself. The swelling then became chronic, which made it difficult for his prosthetic to properly fit. He later developed severe left orbital pain when lying supine, which resolved in the upright position. He did not seek medical attention until he developed a right facial nerve palsy, which prompted presentation to the ED.

On presentation, he was noted to have a right facial droop involving the upper and lower face and a large indurated left orbital mass that precluded eyelid closure. Prominent superficial vessels were noted, and the phthisical globe was neither visible nor palpable. Examination of the right eye was unremarkable. He was hemodynamically stable. No cervical vascular abnormalities or lymphadenopathy were appreciated.

Laboratory studies were unremarkable. Contrast-enhanced computed tomography (CT) of the orbits showed the following: (i) A large heterogeneously enhancing and expansile left orbital mass with anterior extension into the preseptal soft tissues and posterior extension to the level of the orbital apex, (ii) associated thinning and destruction of the orbital walls, with localized extension into the anterior cranial fossa and left frontal and maxillary sinuses, and (iii) absence of an intact left globe. Magnetic resonance imaging (MRI) brain and orbits with and without contrast showed a large heterogeneous enhancing expansile mass within the left orbit with osseous remodeling of the orbit but without destruction or intracranial extension (Figure *3*). Contrast-enhanced CT is the better modality for cortical bone. MRI shows cortical erosion poorly, and cortical erosion exists on a continuum, likely contributing to the discrepancy between the two images. Given the less aggressive features of the mass and the presence of fluid levels, primary considerations included lymphatic or venolymphatic malformation. Pleomorphic adenoma of the lacrimal gland or orbital meningioma were considered less likely based on radiologic appearance. Melanoma, metastatic disease to the orbit, or lymphoma was also considered unlikely given the prolonged time course. MRI also showed asymmetric enhancement involving the right facial nerve suggestive of Bell's palsy.

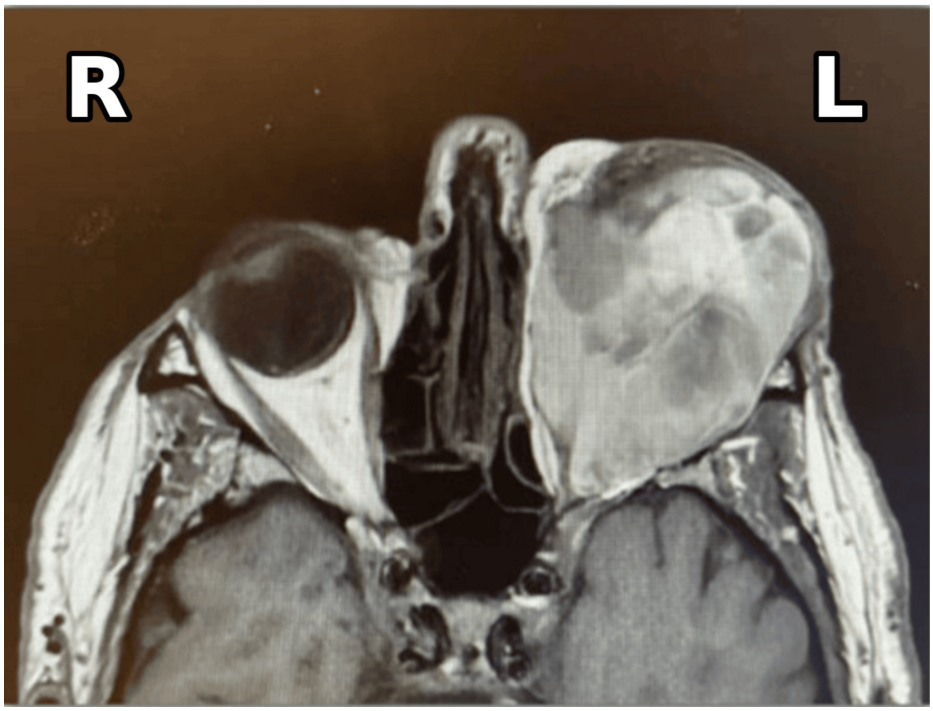


FIGURE 3: Axial T1 FLAIR MRI of left, large, heterogeneous orbital mass.

FLAIR: Fluid-attenuated inversion recovery

Following ED evaluation, he was scheduled for prompt follow-up in the oculoplastic clinic, and the decision was made to proceed with a biopsy of the mass to determine appropriate management. He underwent a lateral superior orbitotomy within a few days, which revealed a cystic, chocolate-colored mass containing dark hemorrhagic fluid. Gross appearance of the mass was suspicious for lymphangioma.

Specimens were sent to pathology in formalin (Figures *4*, *5*). Pathology was consistent with melanoma. No NRAS or BRAF gene variants were detected (Figure *6*). Comprehensive genomic profiling revealed HLA-A*010101G and HLA-A*020101G positivity and positive Signatera (141.88 MTM/mL). Both of these HLA alleles encode major histocompatibility complex class 1 molecules that present melanoma-associated antigens to cytotoxic T-cells. Identification of certain alleles can guide the selection of immunotherapy. The positive Signatera result indicates that tumor DNA is circulating in the blood, which suggests metastatic disease.



FIGURE 4: Intraoperative photograph during left superolateral orbitotomy.



FIGURE 5: Intraoperative photograph during left superolateral orbitotomy and biopsy.

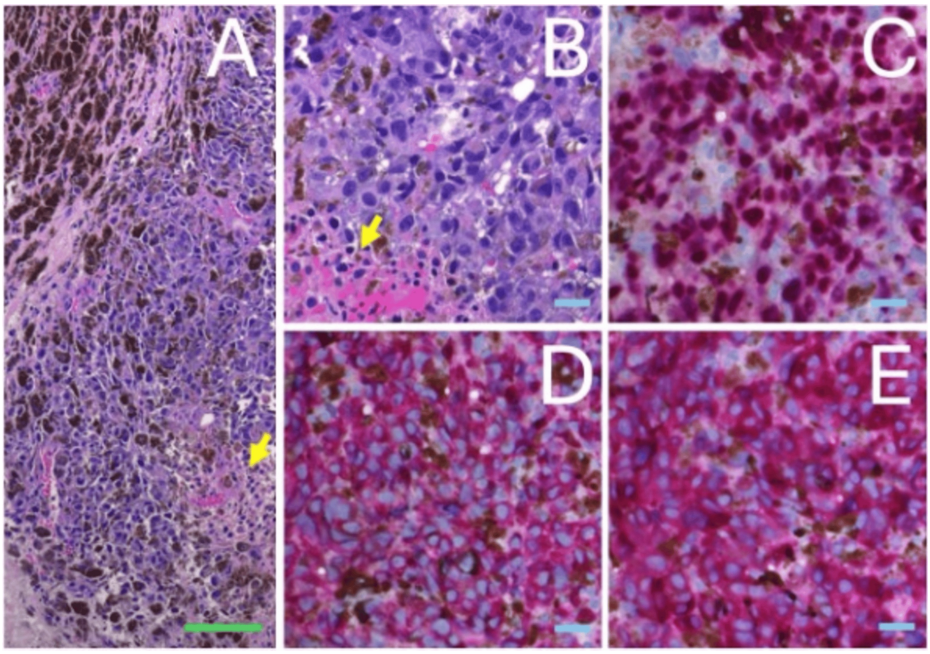


FIGURE 6: Microscopic examination on H&E stain reveals a malignant melanocytic neoplasm.

(A and B) Microscopic examination on H&E stain reveals a malignant melanocytic neoplasm composed of spindle and epithelioid cells arranged in fascicles, nests, and sheets. The tumor cells exhibit variable amounts of eosinophilic cytoplasm and enlarged nuclei with irregular contours, vesicular chromatin, and frequent prominent nucleoli. Mitotic figures are identified. The tumor demonstrates variable pigmentation, with foci of tumor necrosis (arrow). Immunohistochemistry for SOX10 (C), HMB-45 (D) and MART1 (E) Demonstrate diffuse immunoreactivity in the tumor cells. Green and blue scale bars represent 200 and 50 µm, respectively.

Given the confirmed diagnosis of melanoma, a PET scan was advised to determine the extent of spread, and exenteration of all orbital contents was recommended. The PET scan revealed hepatic and bony metastases consistent with stage IV malignancy (T4b, NX, cM1c(1), AJCC Cancer Staging Manual). The patient elected not to proceed with orbital exenteration given poor prognosis and was started on chemotherapy. He was initially treated with 480 mg nivolumab plus 160 mg relatlimab-rmbw given IV over a 30-minute infusion every four weeks from April of 2025 to August of 2025 without improvement. He was then switched to carboplatin and paclitaxel via IV infusions given every 21 days based on genetic tumor marker positivity, which suggested increased susceptibility to this treatment.

Discussion

This case is unusual for several reasons: melanoma appeared in a long-standing blind phthisical eye where the posterior segment could not be visualized, indolent behavior with orbital symptoms that progressed slowly, and radiologic and gross appearance mimicked a benign lymphangioma. Each of these features has been reported before but rarely together. Comparing this case report with prior reports helps explain why the diagnosis was delayed and suggests how similar cases could be recognized sooner.

Uveal melanoma hidden in eyes with opaque media is a recognized diagnostic pitfall. Before modern imaging, about 10% of blind painful eyes were found to contain unsuspected malignant tumors on histopathology [11]. In a 2026 UK series of 664 eye-removal specimens, unsuspected malignancy was found in 0.75%, and preoperative B-scan ultrasonography had failed to detect it in every case [12]. Single case reports parallel this case more closely. A case report describing a 62-year-old man whose melanoma developed in an eye that had been blind from trauma for 35 years stressed how hard it is to detect occult uveal melanoma in phthisical globes [13]. A case series described seven uveal melanomas found only after evisceration of blind painful eyes where tumor-related inflammation and necrosis led to misdiagnoses of endophthalmitis, orbital cellulitis, or idiopathic orbital inflammation [14].

This case shares the main features of these reports of a blind eye with a posterior segment that could not be examined, and an initial attribution of symptoms to benign or inflammatory disease. However, it differs in how it presented. In most prior reports, the melanoma was found inside the globe, either incidentally or on histopathology or by ultrasound. In this case, the orbital component dominated the presentation, and the intraocular source was inferred only afterward. Shields et al. described a comparable pattern, where small inconspicuous choroidal melanomas produced large symptomatic orbital masses that were first mistaken for

primary optic nerve tumors [15]. In this case, no ocular, scleral, or optic nerve tissue was available for examination. The phthisical globe was neither visible nor palpable at presentation; CT showed no intact globe, and only an incisional orbital biopsy was obtained because the patient declined exenteration. The choroidal origin is therefore inferred from the clinical setting rather than demonstrated histopathologically.

Physicians evaluating an orbital mass next to a long-standing phthisical eye will reasonably consider common benign processes first, such as chronic orbital inflammation, organizing hematoma, or post-surgical scarring. Benign orbital lesions that present as slowly progressive masses include cavernous venous malformation, lymphatic malformation, schwannoma, lacrimal gland adenoma, and idiopathic orbital inflammation. Cavernous malformations are the most common benign adult orbital tumor, and lymphoma is the most common orbital neoplasm in adults aged 60 years or older [16]. Malignant possibilities include uveal melanoma, orbital lymphoma, and metastatic disease. Breast, prostate, melanoma, and lung cancer are the most frequent sources of orbital metastasis [16].

Secondary orbital melanoma, usually from extra-scleral extension of a uveal primary, is much more common than primary orbital melanoma [17]. Even so, extra-scleral extension is uncommon. 5.8% of 2,135 patients with posterior uveal melanoma have been found to have extra-scleral extension, and massive orbital extension in only 0.5% of patients [18]. In a large enucleation series, extraocular spread occurred through aqueous channels, ciliary arteries, vortex veins, ciliary nerves, and rarely the optic nerve [19]. Taken together, the rarity of massive orbital extension, the lack of visible intraocular tumor, and the slow clinical course made a benign diagnosis seem more likely at presentation.

Primary orbital melanoma makes up less than 1% of orbital neoplasms [20]. In a 13-patient series, the typical presentation was a short history of rapidly increasing proptosis [21]. However, a primary orbital melanoma enlarged painlessly over several years, showing that slow growth does not rule out malignancy [22]. In this case, ocular and oculodermal melanocytosis, blue nevi, and cutaneous conjunctival primaries were not formally excluded, and no periocular or scleral tissue was available to look for a melanocytic precursor. The available molecular data give only indirect support for uveal origin. No BRAF or NRAS variants were detected, which does not exclude cutaneous or conjunctival primary, but hepatic metastases are consistent with uveal melanoma.

The resemblance to a lymphatic malformation is the most instructive feature of this case. Pigmented uveal melanomas classically appear hyperintense on T1-weighted and hypointense on T2-weighted MRI because melanin shortens T1 and T2. This pattern was seen in 93% of melanomas in an early series [23]. Lymphatic malformations by contrast typically show low T1 and high T2 signal in cystic spaces, with thin septal enhancement and fluid-fluid levels when hemorrhage has occurred [24]. In this case, contrast-enhanced CT showed a large, heterogeneously enhancing, expansile left orbital mass extending from the preseptal soft tissues to the orbital apex, with thinning and destruction of the orbital walls and localized extension. MRI showed a large, heterogeneous, enhancing, expansile mass with fluid levels and osseous remodeling without definite bone destruction or intracranial extension. The fluid levels and less aggressive appearance on MRI made lymphatic or venolymphatic malformation the leading radiologic diagnosis. At orbitotomy, the mass was cystic and chocolate colored with dark hemorrhagic fluid, which reinforced the radiologic impression of lymphangioma. A likely explanation for the overlap is that melanomas can develop hemorrhagic cystic necrosis and can look cystic and loculated, like a lymphatic or venolymphatic malformation. Imaging alone cannot reliably tell benign vascular or lymphatic lesions from melanoma, and tissue diagnosis is essential when an orbital lesion has atypical features of progression.

The slow course in this patient contrasts with the usual behavior of melanoma with orbital involvement. Extraocular extension is linked to shorter survival and metastasis-free survival in enucleated uveal melanoma [25]. The five-year metastasis-free estimate was 54% for tumors with extraocular extension alone, compared with 90% for tumors without ciliary body involvement or extraocular extension [26]. Median survival after presentation was 24 months [21].

Painful blind eyes remain the leading indication for enucleation. Conservative management of painless, stable phthisical eye is reasonable. Eye removal has costs and risks, with early decline in quality of life, persistent appearance-related distress, and reduced vision-related quality of life reported [27]. One study showed 11.8% of patients had clinical anxiety and 13.8% had clinical depression after enucleation [28]. Operative risks include bleeding, infections, and pain. For these reasons, a patient may choose to keep a phthisical eye. A patient with extensive metastatic disease may also decline enucleation or exenteration given the poor prognosis.

On the other hand, there is evidence of a small but real risk of hidden malignancy in end-stage eyes, and preoperative ultrasonography can miss it [12]. When eye removal is planned, and an intraocular tumor cannot be reliably excluded, enucleation is preferred over evisceration. Evisceration is absolutely contraindicated when intraocular malignancy is suspected [11], and all specimens should undergo histopathologic examination [12]. MRI is particularly valuable for imaging uveal melanoma, but no standardized surveillance protocol exists for phthisical eyes. Based on this case and the literature reviewed, we propose a hypothesis for a lower threshold for orbital MRI and tissue diagnosis in blind eyes when any of

the following is present: new pain, progressive orbital signs, change in globe size or position, or an orbital mass. While prophylactic enucleation of every phthisical eye is not supported, developing explicit criteria for imaging and for enucleation in this group could allow earlier diagnosis. The main limitation of a single case report is that it cannot establish how often melanoma arises in phthisical eyes or whether surveillance would change outcomes.

Conclusions

This case illustrates the potential for malignancy to develop in a long-standing phthisical eye that cannot be adequately monitored, and it highlights the limitations of imaging in evaluating an orbital mass. The tumor was initially thought to be a lymphatic malformation based on its radiologic and gross appearance. Histopathology showed melanoma, which we hypothesize extended into the orbit from a choroidal primary. Similar masquerades have been reported for vascular anomalies and optic nerve sheath meningioma, but mimicry of a lymphatic malformation in a phthisical eye has rarely been described. The patient's indolent course is unusual for uveal melanoma with orbital extension. Clinicians should consider melanoma when a new or progressive orbital mass appears next to a blind eye with opaque media, especially when a supposedly congenital lesion such as a lymphatic malformation first appears in adulthood. In that setting, MRI and early tissue diagnosis should be pursued rather than prolonged observation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Acquisition, analysis, or interpretation of data: Nash B. Grantham, Andrew P. Pirotte, Nima Sarani, Sarah Hommez, Jason Sokol, Sara Walden, Michael Edwards, Logan Hunt

Drafting of the manuscript: Nash B. Grantham, Andrew P. Pirotte, Nima Sarani, Sarah Hommez, Jason Sokol, Sara Walden, Michael Edwards, Logan Hunt

Critical review of the manuscript for important intellectual content: Nash B. Grantham, Andrew P. Pirotte, Nima Sarani, Sarah Hommez, Jason Sokol, Sara Walden, Michael Edwards, Logan Hunt

Supervision: Andrew P. Pirotte, Nima Sarani, Jason Sokol

Disclosures

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