Necrotic Uveal Melanoma Mimics Orbital Cellulitis: A Review

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Keywords

Necrotic uveal melanoma · Orbital cellulitis · Orbital inflammation · Spontaneous necrosis

Abstract

Background: Uveal melanoma is the most common primary intraocular malignancy in adults, often resulting in painless vision loss. We report a case of necrotic uveal melanoma presenting with orbital inflammation mimicking orbital cellulitis and present a comprehensive review of the literature and tabulation of reported cases. **Summary:** Our review found 44 published reports of spontaneously necrotic uveal melanoma involving 55 patients. Of these reports, 26 patients (47%) presented with orbital cellulitis. Presenting symptoms of necrotic uveal melanoma with orbital cellulitis included proptosis (82.8%), pain (80.7%), vision loss (61.5%), and restricted extraocular movements (46.2%). **Key Messages:** Uveal melanoma can rarely mimic orbital cellulitis. Autoinfarction and tumor necrosis causes secondary orbital inflammation. Intraocular malignancy must remain in the differential for patients with orbital inflammation and vision loss.

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Introduction

Uveal melanoma is the most common primary intraocular malignancy, accounting for 85% of intraocular malignancies and affecting 2–8 people per million population [1, 2]. Uveal melanoma develops from uveal melanocytes of neural crest origin, most commonly from the choroid or ciliary body (98%) [1–3]. Patients have varying presentations with blurry vision being the most commonly reported symptom (37.8%), followed by an asymptomatic presentation in 30.2%, photopsia in 8.6%, floaters in 7%, visual field loss in 6.1%, and pain in 2.4% [4].

Orbital inflammation can be a rare manifestation of uveal melanoma. We report a patient with necrotic uveal melanoma presenting with acute painful vision loss, proptosis, and orbital inflammation. In addition, we detail a review of published cases of necrotic uveal melanoma presenting with orbital cellulitis.

Case Presentation

A 64-year-old Caucasian male presented to the Emergency Department with a 3-day history of acute vision loss of the right eye with associated periorbital edema, pain radiating to the forehead, and subjective fever and chills. He had no past medical history. On

Fig. 1. a, b External photographs of the right eye demonstrating eyelid edema and erythema, conjunctival injection and chemosis, and hyphema at initial presentation. **c** External photograph two months after initial presentation demonstrating conjunctival injection, shallow anterior chamber, and fibrinoid debris in the anterior chamber without a clear view of the pupil.

Fig. 2. Axial T1 MRI with contrast image demonstrating right eye proptosis, orbital inflammation, intraocular debris and hemorrhage, and an enhancing intraocular mass.

examination, he was afebrile. Visual acuity was no light perception in the right eye and 20/20 in the left eye. A right relative afferent pupillary defect was present. There was mild right-sided proptosis. The intraocular pressure of the right eye was elevated to 88 mm Hg. The right upper and lower eyelids were tender to palpation, edematous, and erythematous (shown in Fig. 1a). Anterior segment examination demonstrated diffuse severe conjunctival chemosis and a total hyphema obscuring visualization of the posterior segment (shown in Fig. 1b, c). B-scan ultrasonography demonstrated vitreous hemorrhage but no retinal detachment or visible mass. The left eye was unremarkable. MRI of the orbits demonstrated proptosis and diffuse orbital inflammation; however, there was no evidence of sinusitis, foreign body, or abscess. There was enhancement of an intraocular lesion in the right eye (shown in Fig. 2). Though the imaging was suspicious for malignancy, an intraocular tumor could not be definitively distinguished from intravitreal hemorrhage. There was no improvement in symptoms despite intravenous vancomycin and ceftriaxone. Laboratory testing, including a complete blood count,

coagulation panel, hypercoagulability panel, and sickle cell screen, was all within normal limits. Magnetic resonance venogram was negative for thrombosis or fistula. Though definitive diagnosis could not be made by imaging, the patient was clinically diagnosed with an intraocular tumor. Enucleation of the blind and painful eye was performed. Histopathology demonstrated a pigmented mass of necrotic spindled and epithelioid cells in the posterior segment (shown in Fig. 3a–c). There was corneal stromal neovascularization and loss of endothelial cells. The iris, ciliary body, and neurosensory retina were necrotic. Due to the extent of the necrosis, the presence of iris neovascularization and angle closure could not be excluded. The choroid was still viable and showed a reactive inflammatory process to the necrotic mass. There was no viable tumor or extrascleral extension. The sclera was edematous. Immunohistochemistry staining with Sox10 was unsuccessful as the necrotic cells did not stain. However, Fontana-Masson staining confirmed that the pigment present within the necrotic cells and within the macrophages was melanin. Systemic surveillance with MRI of the abdomen and pelvis demonstrated a 0.9-cm enhancing right hepatic lobe mass. Follow-up imaging demonstrated additional hepatic metastases. Core needle biopsy of the hepatic mass stained positive for Melan-A and SOX10, consistent with metastatic uveal melanoma. The patient was treated with immune checkpoint inhibitors, nivolumab 1 mg/kg and ipilimumab 3 mg/kg, which was followed by microwave ablation of the hepatic lesions. Subsequent surveillance imaging of the chest, abdomen, and pelvis demonstrated progression of metastatic lesions in all segments of the liver and multiple lung nodules of indeterminate significance. Surveillance imaging of the brain remained negative. The patient is alive at 17 months from the initial presentation, 13 months after enucleation.

Literature Review

A comprehensive review of the relevant literature with a tabulation of previously reported cases of necrotic uveal melanoma presenting as orbital cellulitis was conducted (Table 1). Scopus and PubMed were searched for cases of spontaneous necrotic uveal melanoma that presented with

Fig. 3. **a** $\times 2$ magnification micrograph of the posterior chamber of the globe. From left to right: necrotic tumor, melanin-laden macrophages (melanophages), edematous choroid, and sclera (hematoxylin and eosin stain). **b** $\times 60$ magnification micrograph of tumor showing “ghosts” of both spindled and epithelioid cells. Pigment is present in the majority of these cells (hematoxylin and eosin stain). **c** $\times 60$ magnification micrograph of Fontana-Masson stain confirming that the pigment in the cells is melanin.

orbital inflammation. Cases were included if they presented with orbital inflammation and symptoms of orbital cellulitis including proptosis and restriction of extraocular movements, or if they were described as presenting with “orbital cellulitis” or “pseudocellulitis,” and if they were later diagnosed as necrotic uveal melanoma by histopathology. Cases were excluded if symptoms presented after treatment or if there was no histopathologic confirmation of diagnosis.

Our review found 44 published reports and series of spontaneously necrotic uveal melanoma involving 55 patients. Of the 55 patients with necrotic uveal melanoma, 26 patients (47%) presented with orbital inflammation. Cases 1–26 are shown in Table 1. The mean age of presentation was 64 years (range 24–89 years), and 69.2% of patients were male. Presenting symptoms included proptosis (82.8%), pain (80.7%), vision loss (61.5%), and restricted extraocular movements (46.2%). Of those presenting with vision loss, 50% presented with chronic (>1 month) gradual visual loss. The fundoscopic view to the choroid was obscured in 58% of cases due to hyphema, corneal edema, intravitreal hemorrhage, or a dense cataract. Nineteen patients (73.1%) received a B-scan ultrasound, 16 patients (61.5%) received a CT scan, and 4 (15.3%) received an MRI. Eighteen (94.7%) of the B-scan ultrasounds, all of the CT scans, and 3 (75%) of the MRIs demonstrated evidence of a mass. The uveal melanoma involved the choroid in 80.8%, ciliary body in 7.7%, and was unspecified in 11.5% of cases. Histologically, 42.3% had a mixed epithelioid and spindle cell morphology, 23.1% had a spindle cell morphology, 11.5% had an epithelioid morphology, and 23% had an unknown or unreported morphology.

Enucleation was performed in 19 patients (73.1%), exenteration in 5 patients (19.2%), and evisceration in 2 pa-

tients (7.7%). All 5 patients who were managed by exenteration had extraocular extension of the uveal melanoma. While there were 2 reported cases, evisceration is usually avoided in patients with a vague clinical history and without adequate visualization of the fundus in an effort to decrease tumor seeding. Of the 2 cases reported by Eagle et al. [5] who underwent evisceration, 1 patient had subsequent surgery to remove the scleral shell; however, there was no evidence of residual tumor (case 1). The second patient (case 19) was found to have extrascleral extension; however, there was no follow-up data regarding further management or outcome. Extraocular extension was present in 10 patients (38.4%). Of these patients, treatment included exenteration in 5 patients (cases #3, 9, 13, 15, and 17), enucleation with lateral orbitotomy in 2 patients (cases 11 and 14), enucleation with posterior tenonectomy in 1 patient (case #24), standard enucleation in 1 patient (case# 25), and evisceration in 1 patient (case #19). Two patients with extraocular extension received adjuvant external beam radiation therapy (cases # 11 and 13). Only 2 patients were reported to have metastatic disease and both received adjuvant treatment consisting of cytarabine (case #3) and immune checkpoint inhibitors, nivolumab and ipilimumab (case #26). Three other patients were deceased within 1 year, indicating possible metastatic disease. Only 16 reports (61%) included follow-up information.

Discussion

The first published case of necrotic uveal melanoma presenting with orbital inflammation was by Kline et al. [6] in 1977. Since then, there have been an additional 22

Table 1. Review of necrotic uveal melanoma presenting as orbital cellulitis

Publication	Case No.	Age, years	Sex	IOP, mm Hg	Vision	Histology	Tumor location	Extraocular extension	View to fundus	Imaging modality	Imaging results	Symptoms of cellulitis	Treatment	Patient outcome
Kline et al. [6]	1	63	M	Unknown	LP	Mixed epithelioid and spindle B	Choroid	No	Yes	B-scan ultrasound	Round, large choroidal mass, retinal detachment	Eyelid edema, conjunctival chemosis, proptosis, pain, vision loss	Enucleation	Unknown
Fraser and Font [7]	2	66	M	80	NLP	Unknown	Choroid	No	Yes	None	None	Proptosis, "red eye," vision loss	Enucleation	Unknown
Sassani et al. [8]	3	74	F	56	NLP	Epithelioid	Choroid	Yes	No, due to dense cataract	B-scan ultrasound CT scan	Large, solid, vascularized mass within the globe Left orbital mass extending posteriorly from the globe to the orbital apex	Chemosis, proptosis, loss of EOM, pain	Pre/postoperative radiation, exenteration, chemotherapy (cytarabine)	Melanoma cells in CSF, deceased at 11 months
Margo et al. [9]	4	81	F	Unknown	NLP	Mixed cells	Choroid	No	No, due to corneal edema	B-scan ultrasound CT scan	Mass in posterior pole Mass in posterior pole	Eyelid edema/erythema, chemosis, restricted EOM, pain	Enucleation	Unknown
Lea et al. [10]	5	82	F	50	NLP	Unknown	Choroid	No	No, due to dense cataract	CT scan CT scan (19 months later)	Well-defined, enhancing mass No mass; proptosis, scleral thickening, and attenuation of the retrobulbar fat	Eyelid edema/erythema, proptosis, restricted EOM, pain, vision loss	Enucleation	Alive at 6 months
Rose et al. [11]	6	63	M	45	NLP	Spindle cells	Choroid	No	Unknown	B-scan ultrasound CT scan	Bilobular mass in posterior segment Proptosis, soft tissue swelling, intraocular mass	Eyelid edema, conjunctival chemosis, proptosis, restricted EOM, pain	Enucleation	Unknown
7	7	41	M	43	HM	Unknown	Choroid	No	Yes	B-scan ultrasound CT scan	Intraocular mass posterolaterally Intraocular mass, proptosis, increased soft tissue orbit and eyelids	Eyelid conjunctival chemosis, proptosis, restricted EOM, systemic malaise, vomiting, pain	Enucleation	Unknown
										B-scan ultrasound CT scan	Choroidal mass, total retinal detachment Intraocular mass, orbital soft tissue swelling, scleral thickening	Periorbital edema/erythema, proptosis, orbital pain, vision loss	Enucleation	Unknown
Tabassian et al. [12]	8	51	M	48	NLP	Unknown	Choroid	No	No, due to intravitreal hemorrhage	B-scan ultrasound CT scan	Choroidal mass, total retinal detachment Intraocular mass, orbital soft tissue swelling, scleral thickening	Periorbital edema/erythema, proptosis, orbital pain, vision loss	Enucleation	Unknown
Mauriello et al. [13]	9	75	M	Unknown	NLP	Mixed polygonal epithelioid and spindle cells	Ciliary body	Yes	Yes	CT scan	Soft tissue density extended through large scleral defect	Conjunctival injection, proptosis, supraorbital pain, vision loss	Exenteration, palliative radiotherapy	Deceased at 1 year
Brannan et al. [14]	10	64	M	Unknown	NLP	Spindle cells	Choroid	No	No, due to hyphema and corneal edema	B-scan ultrasound	Mass in posterior segment	Eyelid edema, conjunctival chemosis, pain	Enucleation	Unknown
Fezza et al. [15]	11	71	M	30	20/400	Mixed spindle B and epithelioid	Choroid	Yes	Yes	CT scan MRI	Intraconal mass lateral to optic nerve abutting globe Nonenhancing orbital mass	Eyelid edema/erythema, chemosis, restricted EOM, vision loss	Lateral orbitotomy, enucleation, adjuvant radiation	Unknown

Table 1 (continued)

Publication	Case No.	Age, years	Sex	IOP, mm Hg	Vision	Histology	Tumor location	Extraocular extension	View to fundus	Imaging modality	Imaging results	Symptoms of cellulitis	Treatment	Patient outcome
Biswas et al. [16]	12	40	F	Unknown	NLP	Epithelioid	Choroid	No	Yes	B-scan ultrasound	Lobulated mass lesion arising from the choroid	Eyelid edema, conjunctival chemosis, pain, vision loss	Enucleation	Alive, no metastases at 2 years
										CT scan	Temporal mass close to the orbital wall			
Goh et al. [17]	13	24	M	69	LP	Mixed spindle B and epithelioid	Choroid	Yes	No, due to hyphema	B-scan ultrasound	Mass lesion arising from the choroid, extending into the vitreous cavity	Eyelid edema, conjunctival chemosis, proptosis, vision loss	Exenteration	Alive, no metastases at 2 years
										CT scan	Homogeneous, posterolateral mass; periorbital infiltration			
Goh et al. [17]	14	85	F	50	NLP	Mixed epithelioid and spindle	Choroid	Yes	No, due to corneal edema and dense cataract	B-scan ultrasound	Solid retrobulbar mass of homogeneous echogenicity	Eyelid edema, chemosis proptosis, restricted EOM, pain on retropulsion of globe, serous discharge, fever	Lateral orbitotomy, enucleation	Unknown
										CT scan	Retrobulbar mass, periorbital soft tissue swelling, proptosis			
Safianik et al. [18]	15	84	M	Unknown	LP	Mixed spindle, epithelioid, and pleiomorphic atypical cells	Unknown	Yes	Unknown	CT scan	Retrobulbar, intraconal lesion displacing the globe	Eyelid edema/erythema, proptosis, restricted EOM, ocular discharge, pain, vision loss	Subtotal exenteration	Deceased at 3.5 months
Blasi et al. [19]	16	56	F	32	LP	Spindle shaped	Ciliary body	No	Unknown	B-scan ultrasound	Solid lesion from ciliary body into anterior chamber	Eyelid edema/erythema, proptosis, pain, vision loss	Enucleation	No metastases, alive at 1 year
Marback et al. [20]	17	25	F	30	NLP	Mixed spindle A, spindle B, and epithelioid	Choroid	Yes	Unknown	B-scan ultrasound	Solid lesion	Edema, chemosis proptosis, pain, vision loss	Subtotal exenteration	Unknown
										CT scan	Choroid thickening representing a mass or detachment			
Eagle et al. [5]	18	89	F	70	NLP	Mixed cell type	Unknown	No	No, due to intraocular hemorrhage	CT scan	Intraconal orbital mass abutting the posterior surface of the globe	Eyelid edema/erythema, conjunctival chemosis, pain, vision loss	Evisceration, subsequent removal of scleral shell	Deceased at 6 days postoperatively
										CT scan	Periorbital edema, ocular injection, proptosis, pain			
Nair et al. [21]	20	24	M	36	NLP	Spindle A cells	Choroid	No	No, due to hyphema	B-scan ultrasound	Acoustically dense dome-shaped mass filling posterior segment, choroid excavation, total retinal detachment	Eyelid edema, chemosis, proptosis, restricted EOM, pain, vision loss	Enucleation	No metastases at 3 months
										CT scan	Mass filling vitreous cavity			
Nalcaci et al. [22]	21	68	M	38	NLP	Spindle cells	Choroid	No	No, due to mass	B-scan ultrasound	Intraocular mass	Eyelid edemas/erythema, chemosis proptosis, restricted EOM, pain, vision loss	Enucleation	No systemic metastases at 6 months
										MRI	Mass filling vitreous cavity			
Oh et al. [23]	22	63	M	Unknown	LP	Unknown	Choroid	Yes	No, due to vitritis	B-scan ultrasound	Mushroom-shaped lesion emanating from choroid with low internal reflectivity, subtotal retinal detachment	Periorbital edema/erythema, chemosis, restricted EOM	Enucleation	Unknown
										CT scan	Orbital cellulitis and high-density material within globe			

Table 1 (continued)

Publication	Case No.	Age, years	Sex	IOP, mm Hg	Vision	Histology	Tumor location	Extraocular extension	View to fundus	Imaging modality	Imaging results	Symptoms of cellulitis	Treatment	Patient outcome
Singh et al. [24]	23	56	M	56	NLP	Unknown	Choroid	No	No, due to hyphema	B-scan ultrasound	Homogeneous mound-like mass in vitreous cavity, vitreous hemorrhage	Eyelid edema, proptosis, low-grade fever, chills, nausea, pain, vision loss	Enucleation	No metastatic disease at 6 months
										MRI	Intraocular polypoidal mass, T2-hyperintense signals suggestive of vitreous hemorrhage			
										PET CT	18-Fluorodeoxyglucose (¹⁸ FDG)-avid, homogeneously enhancing asymmetric soft tissue thickening encasing eye circumferentially, no metastases			
Li et al. [25]	24	61	M	37	Unknown	Spindle shaped	Choroid	Yes	No, due to hyphema and corneal opacification	B-scan ultrasound CT scan	Choroidal mass with collar button-shaped configuration Hyperdensity in the vitreous cavity	Eyelid edema/erythema, proptosis, pain	Enucleation, posterior tenotomy	Unknown
Vasanthapuram et al. [26]	25	60	M	62	NLP	Epithelioid	Choroid	No	Unknown	B-scan ultrasound	Mushroom-shaped intraocular mass with choroidal excavation	Shallow anterior chamber, mid-dilated and fixed pupil	Enucleation	Unknown
Current manuscript	26	64	M	88	NLP	Mixed spindle and epithelioid cells	Choroid	No	No, due to intravitreal hemorrhage	B-scan ultrasound MRI	Dense vitreous hemorrhage, no evident masses Vitreous hemorrhage, proptosis, panophthalmitis, small preseptal rim-enhancing collection may represent subconjunctival fluid collection/abscess	Eyelid edema/erythema/tenderness, proptosis, pain, vision loss	Enucleation, chemotherapy (nivolumab, ipilimumab)	Metastatic disease, alive at 6 months
										NLP, no light perception; LP, light perception; HM, hand motion; CF, count fingers; EOM, extraocular movements; M, male; F, female.				

case reports or series, encompassing an additional 25 patients, reporting necrotic uveal melanoma presenting with symptoms mimicking orbital cellulitis [5–26]. The cause for the necrosis is not fully understood; however, it is likely that the orbital inflammation in these patients is caused by an inflammatory process triggered by the tumor necrosis. Through the release of inflammatory mediators and cytokines, such as tumor necrosis factor and IL-6, necrotic tissue is capable of inciting uveitis, episcleritis, and panophthalmitis [24]. Inflammation has been attributed to the cytotoxic effects of released cellular debris after a spontaneous infarction [27].

Several potential mechanisms of tumor autoinfarction have been proposed. Reese et al. [27] proposed that lymphocytic activation of endothelial cells leads to thromboses and vessel occlusion, leading to spontaneous infarction and subsequent necrosis. Others have proposed that the rapidly expanding tumor infarcts as it outgrows its blood supply [13, 21, 23].

A proinflammatory phenotype of uveal melanoma has been described in association with increased HLA class 1 and class 2 expression and increased infiltration by macrophages and lymphocytes [28]. Though increased immune infiltration is a positive prognostic factor in other cancers, it is associated with a negative prognosis in uveal melanoma [28]. Several studies have demonstrated the presence of a lymphocytic infiltrate in a high percentage of necrotic uveal melanomas [27, 29, 30]. Of the reviewed cases, 53.8% contained epithelioid cells, which are also associated with increased cellular infiltrate and higher HLA class 1 and 2 expression [31, 32]. Based on the previously reported association between necrotic uveal melanoma and increased inflammatory infiltrate, it is possible that patients with necrotic uveal melanoma have a predilection towards the inflammatory phenotype, with subsequent vascular damage and autoinfarction [27–32]. Alternatively, posterior segment tumors can induce neovascularization of the iris, possibly also through an inflammatory mechanism [33, 34]. This can result in necrosis secondary to acute angle closure.

In our case, histopathologic examination revealed extensive necrosis of the iris, ciliary body, and neurosensory retina. There was a reactive inflammatory process to the necrotic mass, with numerous melanin-laden macrophages infiltrating the darkly pigmented mass of necrotic spindle and epithelioid cells. The tumor size could not be determined because the exact transition between the necrotic tumor and the necrotic response to the tumor was unclear. Our case is only the second case where no viable tumor cells were identified on histopathology [10].

Conclusion

Orbital inflammation is a rare manifestation of uveal melanoma. Autoinfarction and tumor necrosis leads to a proinflammatory state which may lead to orbital inflammation, even in the absence of extrascleral extension of the tumor. Necrotic tumors may not be visible, thus an occult tumor must always be considered and ruled out in patients with severe ocular inflammation where the view to the fundus is obscured.

Statement of Ethics

This study did not require review by our Institutional Review Board. We report a case of necrotic uveal melanoma presenting with orbital inflammation mimicking orbital cellulitis and present a comprehensive review of the literature and tabulation of reported cases. Written consent was obtained from the patient to publish medical history and clinical photographs.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Ahmad Abdel-Aty prepared the manuscript and conducted the literature review. Wendy L. Linderman contributed to the preparation of the manuscript and in the development of inclusion/exclusion criteria for reviewed articles. Ninani Kombo evaluated clinical data and contributed to the preparation of the manuscript. John Sinard provided interpretation of the histopathology and contributed to the preparation of the manuscript. Renelle Pointdujour-Lim evaluated clinical data and contributed to the preparation of the manuscript.

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