



## Doppelgänger dilemma: Leiomyoma versus uveal melanoma

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### ABSTRACT

**Background:** Ciliary body tumors can remain undetected and achieve large dimensions. Pigmented ciliary body tumors include: melanoma, leiomyoma and melanocytoma, however correct diagnosis may require tissue diagnosis with immunohistochemical stains.

**Case presentation:** Two men presented with identical ciliochoroidal tumors. Both had darkly pigmented dome-shaped anterior uveal masses, exudative retinal detachments and transillumination shadowing. Ocular PET-CT imaging revealed that both were metabolically active consistent with a diagnosis of cancer. However, immunohistochemical examination revealed one a leiomyoma and the other melanoma.

**Conclusion:** Uveal leiomyoma can be an indistinguishable doppelgänger to ciliochoroidal melanoma, where the diagnosis can only be established by immunohistopathology.

### Introduction

Uveal leiomyoma is a rare benign tumor of neural crest cell origin which can be clinically indistinguishable from a uveal melanoma.<sup>1</sup> A recent study reviewed 80 published cases of ocular leiomyoma from 1899 to 2019 and found that pigmented cilio-choroidal tumors clinically diagnosed as large uveal melanoma were most commonly treated by enucleation.<sup>2–5</sup> However, despite confounding clinical similarities, these 2 tumors have very different prognoses. Though both can cause secondary retinal detachment, macular edema and even extraocular extension, leiomyomas are benign tumors which do not metastasize.<sup>2</sup> Herein, we present 2 anterior uveal tumors which are clinically identical. These doppelgänger ciliary body lesions highlight that pre-enucleation differentiation may not be possible clinically, the need for a high index of suspicion, and use of histopathology with immunohistochemical analysis to achieve the correct diagnosis.

#### Case presentation

Two patients presented to us with ciliochoroidal tumors with nearly identical clinical presentation. The first patient was a 30-year-old male referred for evaluation of a ciliary body tumor in his right eye. The second patient was a 45-year-old male with a 3-month history of blurred vision in the left eye and a similar ciliary body tumor with nearly equivalent epidemiologic and clinical features (Table 1).

These 2 tumors had a shared common presentation of a large dome-shaped ciliary body tumor, which was low-moderately reflective on ultrasound-imaging, blocked light transillumination and had associated exudative retinal detachment (Figs. 1 and 2). Based on these clinical findings, both diagnoses were American Joint Committee on Cancer (AJCC) T4 choroidal melanoma extending into the ciliary body.<sup>6</sup> Positron emission tomography computed tomography (PET-CT) staging revealed both tumors to be hypermetabolic (specific uptake value [SUV] range 3.5–4.2 in patient 1 and SUV range 3.7–4.5 in patient 2). Both were greater than SUV 2.5 and thus consistent with malignancy. There was no radiologic evidence of metastatic disease in either patient. Informed consent included, but was not limited to, observation, biopsy for tissue diagnosis, plaque brachytherapy, proton beam, and primary enucleation.

Patient 1 elected for enucleation, and gross examination of the globe revealed a large dark transillumination defect. Globe sectioning revealed a white ovoid solid cilio-choroidal mass measuring 28 mm in largest basal diameter (transverse) and 18 mm in cross-sectional, antero-posterior extension. The underlying sclera was intact, though the ciliary body was deformed by the tumor. Histopathology revealed proliferating spindle mesenchymal cells with cigar-shaped nuclei disposing vesicular chromatin. Mitotic activity was absent. There was <1% nuclear labelling with Ki-67. The tumor cells were immunoreactive to smooth muscle actin. In contrast, these cells were non-reactive to glial fibrillary acidic protein, S-100, Melan-A, HMB-45 and neurofilament protein. This

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**Table 1**

Comparative clinical and imaging features for 2 patients with large cilio-choroidal tumors.

Feature	Patient 1	Patient 2
Age	30 years	45 years
Gender	Male	Male
Race	Middle-Eastern	Hispanic
Chief Complaint	OD metamorphopsia	OS blurred vision
Best Corrected Visual Acuity	20/20 OU	20/20 OU
Anterior Segment examination	<ul style="list-style-type: none"> <li>• Episcleral sentinel vessels</li> <li>• Trace anterior chamber cell, Posterior subcapsular cataract</li> <li>• No iris neovascularization</li> </ul>	<ul style="list-style-type: none"> <li>• Episcleral sentinel vessels</li> <li>• Quiet anterior chamber</li> <li>• Posterior subcapsular cataract</li> <li>• No iris neovascularization</li> </ul>
Intraocular pressure	16 mm Hg	14 mm Hg
Gonioscopy	<ul style="list-style-type: none"> <li>• No tumor or neovascularization in angle</li> <li>• Focal narrowing of angle</li> </ul>	<ul style="list-style-type: none"> <li>• No tumor or neovascularization in angle</li> <li>• Focal narrowing of angle</li> </ul>
Dilated fundus examination	<ul style="list-style-type: none"> <li>• Large, dome-shaped nasal brown mass with overlying vessels arising from the ciliary body</li> <li>• Inferior serous detachment</li> </ul>	<ul style="list-style-type: none"> <li>• Large, dome-shaped temporal brown mass with overlying vessels arising from the ciliary body</li> <li>• Inferior serous detachment</li> </ul>
Transscleral ophthalmic transillumination	Blocked light transmission	Blocked light transmission
High frequency ultrasound imaging (35 MHz)	<ul style="list-style-type: none"> <li>• Low-medium internal reflectivity</li> <li>• Extending to the iris root, but not into the anterior segment</li> <li>• More than 3 clock hours of ciliary body were involved</li> <li>• No ring-shaped tumor</li> </ul>	<ul style="list-style-type: none"> <li>• Low-medium internal reflectivity</li> <li>• No anterior segment extension</li> <li>• More than 3 clock hours of ciliary body were involved</li> <li>• No ring-shaped tumor</li> </ul>
Low frequency B-scan ultrasound (12 MHz)	<ul style="list-style-type: none"> <li>• Dome-shaped, moderately low reflective choroidal tumor</li> <li>• Largest basal dimension: 18.6 mm</li> <li>• Tumor height: 11.1 mm</li> <li>• No extrascleral extension</li> <li>• Retinal detachment</li> </ul>	<ul style="list-style-type: none"> <li>• Dome-shaped, moderately low reflective choroidal tumor</li> <li>• Largest basal dimension: 18.2 mm</li> <li>• Tumor height: 13.3 mm</li> <li>• No extrascleral extension</li> <li>• Retinal detachment</li> </ul>

immunohistochemical profile was consistent with uveal leiomyoma (Table 2 and Fig. 3). No local recurrence or related systemic disease was noted over 4 years follow-up.

Patient 2 requested tumor biopsy. Aspiration cutter-assisted biopsy was used to obtain tissue for both cytopathology and histopathology.<sup>7</sup> Histopathology showed malignant melanocytes with marked nuclear enlargement, vesicular chromatin, prominent eosinophilic nucleoli and immunohistochemical stains were positive for HMB-45 and Melan-A (Table 2 and Fig. 3). The final histopathologic diagnosis was uveal melanoma. We treated the patient with Proton Beam Therapy and he has been under follow-up for 6 months for local recurrence, ocular side-effects and metastatic disease.

## Discussion

A Doppelgänger is defined as non-biologically related look-alike. Herein, we present 2 ciliochoroidal tumors that were clinically indistinguishable in terms of presentation, tumor color, ultrasound

characters, transillumination and hypermetabolic tumors SUV on PET-CT (Figs. 1 and 2). Both showed no evidence of metastasis. Histopathology with immunohistochemical tissue-staining was reliable diagnostic method to differentiate anterior uveal leiomyoma from melanoma.

Uveal leiomyoma literature consists of case reports, small case series and one major review.<sup>2,8-12</sup> The latter has revealed a number of misconceptions regarding its clinical behavior.<sup>2</sup> For example, uveal leiomyoma was thought to be amelanotic, thus did not cause a transillumination shadow and only seen in young females during their reproductive age.<sup>13</sup> However, nearly 40% of cilio-choroidal leiomyoma can be darkly pigmented, occur in males, have associated supra-ciliary effusion, and nearly two-thirds block light during transillumination transmission partly or completely.<sup>2,14</sup> Furthermore, in these 2 cases, PET-CT uptake did not help in differentiating leiomyoma from melanoma, but does suggest inflammation and hyper-metabolism in both.

This study suggests that the best way to differentiate between these doppelgänger tumors is with a biopsy for immunohistochemical analysis. Biopsy methods include fine needle aspiration biopsy, Finger Iridectomy Technique, transscleral biopsy and enucleation.<sup>7,14,15</sup> Aspiration-cutter biopsy through the iris root can provide a minimally invasive, safe method for obtaining sufficient ciliary body tissue for cytology, histopathology, and immunohistochemical analysis.<sup>15</sup> Uveal leiomyoma will stain positive for  $\alpha$ -smooth muscle actin, muscle-specific actin, desmin, h-caldesmon, and vimentin.<sup>16,17</sup> For both tumors, the treatment choice can be determined by tumor size, location, and secondary ocular complications.<sup>2,18</sup> Smaller tumors can be cautiously observed or resected en bloc following histopathologic confirmation.<sup>2</sup> There are reports of successful treatment of leiomyoma with radiation.<sup>10,11</sup> When biopsy proven leiomyomas are too large to treat with globe sparing local resection or radiation therapy, most have been removed by enucleation.<sup>2</sup> Unlike systemic leiomyoma, ocular leiomyoma have inconsistent expression of sex-steroid receptors and the use of hormonal therapy remains unproven.<sup>2</sup>

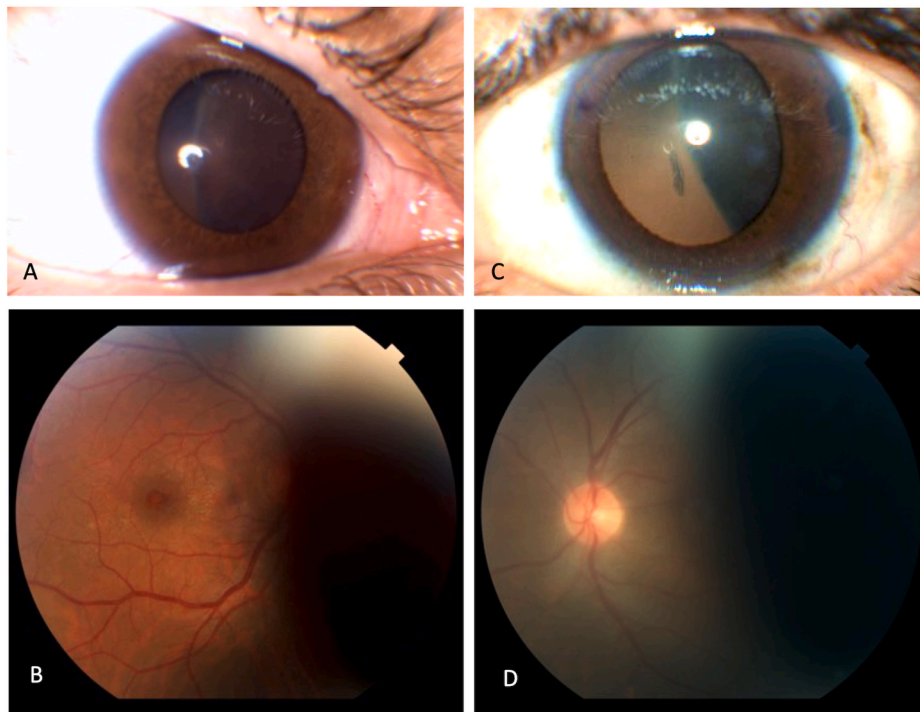
Herein, we have described 2 clinically indistinguishable ciliochoroidal tumors in men. They had similar pigmented surface appearance through the pupil, secondary retinal detachments, ultrasonographic dome-shape and moderate internal reflectivity. Only an intuitive suspicion or routine tissue biopsy or some new imaging modality will likely improve clinical diagnosis and influence treatment options.

## Patient consent

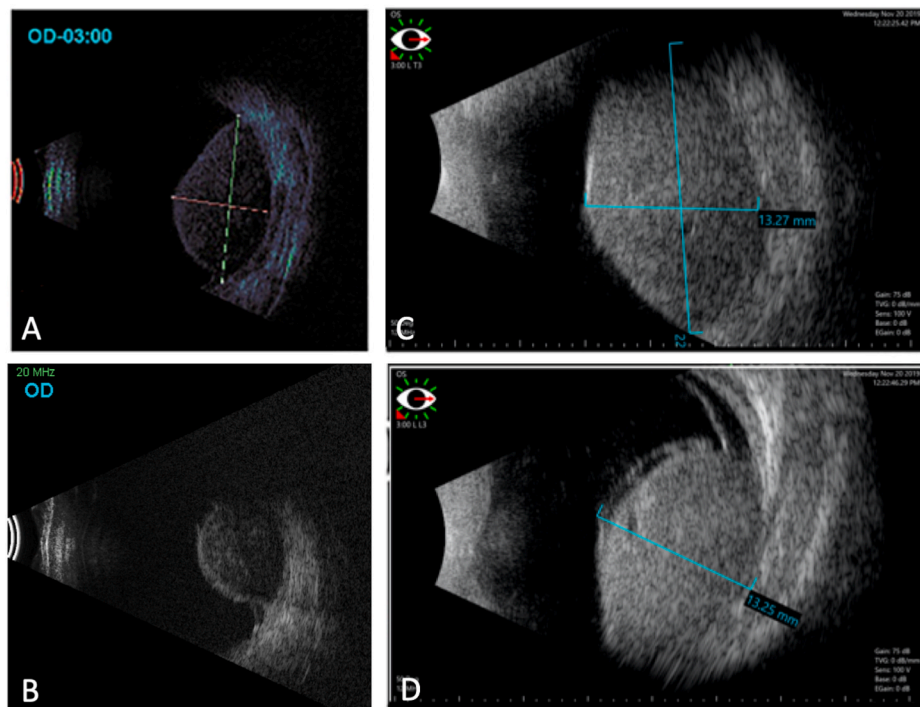
The patients consented to publication of the case in writing. This report does not contain any personal information that could lead to the identification of the patient. Therefore, these cases conform to the Tenet's of Helsinki, the Health Insurance Privacy and Portability Act and have been approved for publication by The New York Eye Cancer Center's IRB and Ethics Committee's.

## 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 doing so we confirm that we followed the regulations of our institutions concerning intellectual property.



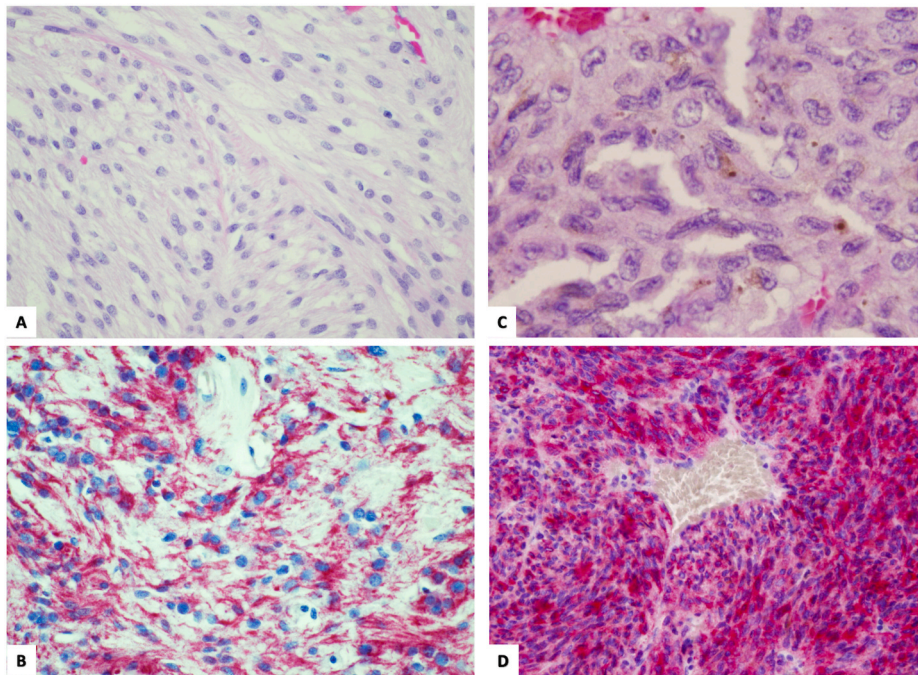
**Fig. 1.** (A–D): A: A 30-year-old man with nasal ciliary body tumor, B: Note the dysmorphic fovea. C: A 45-year-old man with temporal ciliary body tumor, D: Note the dysmorphic fovea.



**Fig. 2.** (A–D): A, B: A 30-year-old man with nasal ciliary body tumor. B-scan ultrasound shows a dome-shaped, moderately low reflective choroidal tumor. Note the small secondary retinal detachment adjacent to the tumor. C, D: A 45-year-old man with temporal ciliary body tumor. B-scan shows a dome-shaped, moderately reflective choroidal tumor. Note the secondary retinal detachment adjacent to the tumor.

**Table 2**  
Comparative pathological and immunohistochemistry features for 2 patients with large cilio-choroidal tumors.

Feature	Patient 1	Patient 2
Gross Pathology	<ul style="list-style-type: none"> <li>• White ovoid solid cilio-choroidal mass</li> <li>• Large dark transillumination defect</li> </ul>	Tissue obtained through aspiration cutter-assisted biopsy
Histopathology	<ul style="list-style-type: none"> <li>• Spindle mesenchymal cells</li> <li>• Cigar-shaped nuclei</li> <li>• Vesicular chromatin</li> </ul>	<ul style="list-style-type: none"> <li>• Malignant melanocytes</li> <li>• Marked nuclear enlargement</li> <li>• Vesicular chromatin</li> <li>• Prominent eosinophilic nucleoli</li> </ul>
Immunohistochemical stains	<ul style="list-style-type: none"> <li>• Smooth Muscle Actin (+)</li> <li>• Glial fibrillary acidic protein (-)</li> <li>• S-100 (-)</li> <li>• Melan-A (-)</li> <li>• HMB-45 (-)</li> <li>• Neurofilament protein (-)</li> </ul>	<ul style="list-style-type: none"> <li>• Melan-A (+)</li> <li>• HMB-45 (+)</li> </ul>



**Fig. 3.** (A–D): A, B: Leiomyoma pathology analysis reveals: 3A (Hematoxylin-Eosin stain, original magnification  $\times 100$ ) shows spindle mesenchymal cells, with cigar-shaped nuclei and vesicular chromatin. 3B Immunohistochemistry of this tumor shows positive immunoreactivity for smooth muscle actin (SMA) (original magnification  $\times 100$ ). C, D: Uveal melanoma pathology reveals: 3C (Hematoxylin-Eosin stain, original magnification  $\times 100$ ) shows histopathologically similar spindle-shaped cells with marked nuclear enlargement and prominent nucleoli. 3D In contrast, immunohistochemistry shows positive immunoreactivity for HMB-45 (original magnification  $\times 100$ ).

### Research ethics

We further confirm that any aspects 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.

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### Declaration of conflict of interest

No conflicting relationship exists for any author.

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