

Posterior choroidal leiomyoma: new findings from a case and literature review

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Abstract

• Posterior choroidal leiomyoma is a sporadic, rare benign tumor that is always confused with anaplastic melanoma. Here we report a case and provide a review. Most of the preoperative findings in our case were suggestive of malignant choroidal melanoma. However, the contrast enhanced ultrasound (CEUS) suggested a benign hemangioma. In summary, the posterior choroidal leiomyomas were yellowish-white in color and most commonly located in the temporal quadrant of the fundus (11/15). They were more frequent in Asians (13/16), the prevalence was almost equal in males and females (9:7), with a mean age of 35y. Microscopically, the tumor typically showed spindle cell bundles and nonmitotic ovoid nuclei arranged in intersecting fascicles. Vitrectomy is now a popular treatment option and definitive diagnosis can be made after immunohistochemistry. Finally, some summarized features of this tumor differ from those previously described. These may help in the diagnosis of posterior choroidal leiomyoma and differentiation from malignant melanoma.

• **KEYWORDS:** choroidal leiomyoma; contrast enhanced ultrasonography; melanoma; vitrectomy

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INTRODUCTION

Leiomyoma is a benign tumor that originates from smooth muscle cells. It was frequently found in the

gastrointestinal tract and uterus. In eyes, they were relatively rare, most commonly found in the anterior uveal segment. It was first reported in the posterior choroid in 1976 and later classified as mesodermal and mesectodermal^[1]. Diagnosis was even more complicated when they occurred in the posterior choroid. The mesectodermal type, which was often misdiagnosed as malignant melanoma due to similar clinical features, was first described in 2002^[2]. In many cases, the correct diagnosis was not made until the eye was removed. Here, we present a case with a controversial preoperative diagnosis and provide a review of posterior choroidal leiomyoma.

ORIGINAL CASE

Ethical Approval The authors have obtained consent from the patient. The consent form included permission to report clinical information in the journal. The patient understands that his/her name and initials will not be published and that due efforts will be made to conceal his/her identity. And this study is consistent with the Declaration of Helsinki.

A 37-year-old woman was referred for evaluation of a choroidal tumor in her right eye. Her primary complaint was gradual blurring of vision over a year, with mild ocular swelling and pain. No abnormalities were found on anterior segment examination. Visual acuity of the right eye was 10 cm counting fingers, and intraocular pressure was 15 mm Hg with no afferent pupillary defect. However, in the temporal fundus, a yellowish-white, dome-shaped mass with scattered pigments was seen. It was surrounded by severe retinal detachment and negligible exudation (Figure 1). We then proceeded to investigate to aid in the diagnosis. Magnetic Resonance Imaging (MRI) showed a dome-shaped mass with enhancement. In fundus fluorescence angiography (FFA) and indocyanine green angiography (ICGA), the tumor showed an immediate filling in the early phase and a slow fading in the final phase. When enhanced, we could clearly see the “dual-circulating sign”. On contrast enhanced ultrasound (CEUS), the lesion appeared as a fast wash-in and slow wash-out mode. As a result, the MRI, FFA, and ICGA were all suggestive of a malignant choroidal melanoma, while the CEUS was suggestive of a benign hemangioma. The relevant examinations are shown in Figures 2, 3, and 4, respectively. As

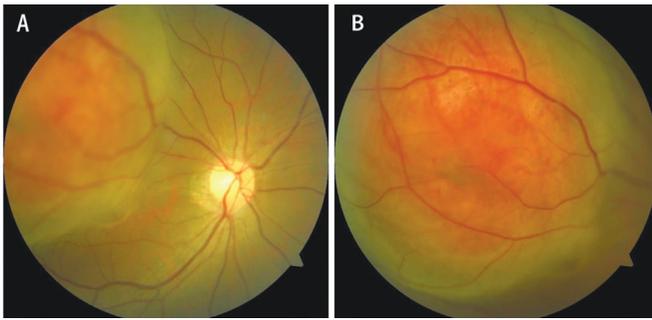


Figure 1 A large amelanotic dome-shaped choroidal tumor with surface pigmentation in the supratemporal quadrant of the right eye. There was a peripheral exudative retinal detachment involving the macula. It is approximately 1.5 disc diameters from optic disc and 7 disc diameters in size.

no metastasis was found after systemic examination and CEUS suggested, the patient finally opted for 23G vitrectomy. The isolated gray-white tissue was approximately 1.7×0.6×0.4 cm³ and was sent for pathology. In hematoxylin and eosin staining (HE), the tumor was composed of spindle-shaped cells with abundant eosinophilic cytoplasm containing round to oval, fine-granular, slightly pleomorphic nuclei with perinuclear cytoplasmic vacuoles. There were scattered melanocytes, but almost without mitosis (Figure 5). Immunohistochemically, the tumor was diagnosed as a choroidal mesectodermal leiomyoma with myogenic and neurogenic features (Figure 6).

SUMMARY OF CLINICAL CASES

Intraocular leiomyomas were found mainly in ciliary body. In previous cases, only four mesectodermal leiomyomas were confined to the posterior choroid. Since it is rare and difficult to distinguish from choroidal melanoma, unnecessary enucleation was often performed. In order to summarize more favorable information, we collected as many of the available reports as possible for leiomyomas that are confined to the posterior choroid. The brief comparisons with choroidal melanoma were made in Table 1^[2-14].

Epidemiologic Analysis

Clinical examinations Totally 16 cases of posterior choroidal leiomyomas all presented as solitary, unilateral, elevated, and amelanotic lesions with predominantly yellowish-white color and scattered pigmentation on the surface. They were easily confused with amelanotic choroidal melanoma. The development of symptoms is highly dependent on the location and growth rate of the tumor. Patients' main complaint was gradual loss of visual acuity due to macular involvement with placoid retinal detachment. Anterior segment examination was usually unremarkable. Due to its location, scleral transillumination is difficult to perform. Semi-transmissive or multi-transmissive transmission patterns have been reported in previous studies. In this case, our mass partially blocked the light when it was illuminated with intraocular light. However,

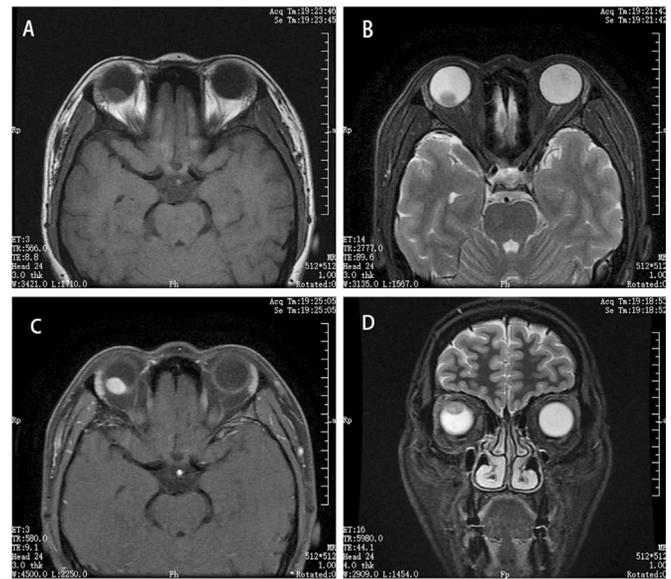


Figure 2 MRI revealed a dome-shaped mass. The mass showed faintly hyperintense to vitreous on T1-WI (A) and markedly hypointense on T2-WI (B), with intense enhancement (C). STIR showed slightly high signal intensity of the mass (D). On T1-WI and T2-WI, it was both isointense to the brain. MRI: Magnetic resonance imaging; T1-WI: T1-weighted image; T2-WI: T2-weighted image; STIR: Short time of inversion recovery.

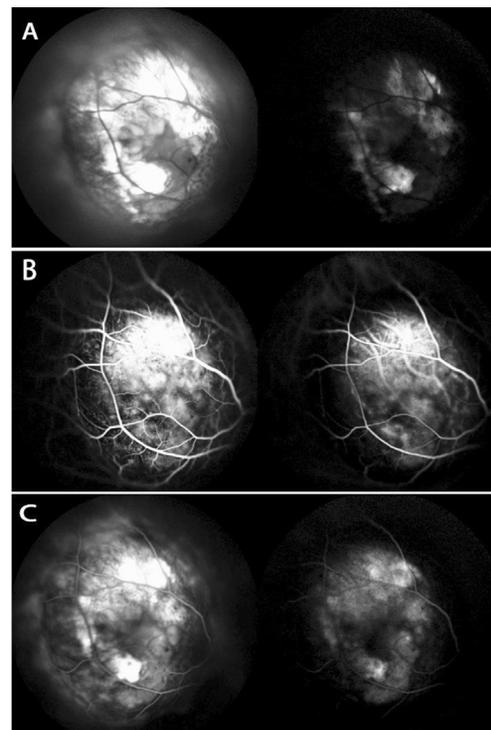


Figure 3 FFA+ICGA. A: A supratemporal lesion on the right side of the optic nerve head with an approximately 18 diopter bulge. B: In the early and middle phases, FFA and ICGA documented complete filling of the large vessels in the tumor. High fluorescence signals and a "dual circulation sign" were observed. The surface of the tumor was weakly fluorescent due to a small number of pigment particles. C: Late phase FFA and ICGA showed intense hyperfluorescence of the mass with almost no significant fluorescence attenuation. It was diagnosed as choroidal malignant melanoma. FFA: Fundus fluorescence angiography; ICGA: Indocyanine green angiography.

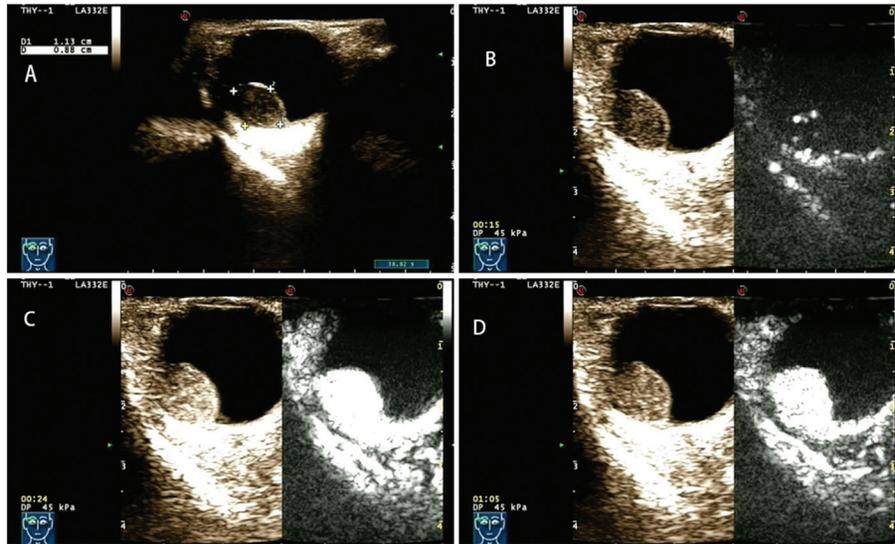


Figure 4 Conventional ultrasonography A dome-shaped, well-circumscribed choroidal mass with low to medium internal reflectivity (A). CEUS was then performed. The contrast agent SonoVue (1.2 mL) was injected through a 20G intravenous needle into the cubital fossa vein. At 15s (B), the agent reached the retina. First the center, then the whole mass was enhanced faster than surrounding tissue. Enhancement peaked at 24s (C). The mass showed homogeneous enhancement. It always had a higher echo intensity than the surrounding tissue. At the end (D), the contrast agent was slowly fading away. The lesion showed fast wash-in and slow wash-out mode. It was considered a choroidal hemangioma. CEUS: Contrast enhanced ultrasound.

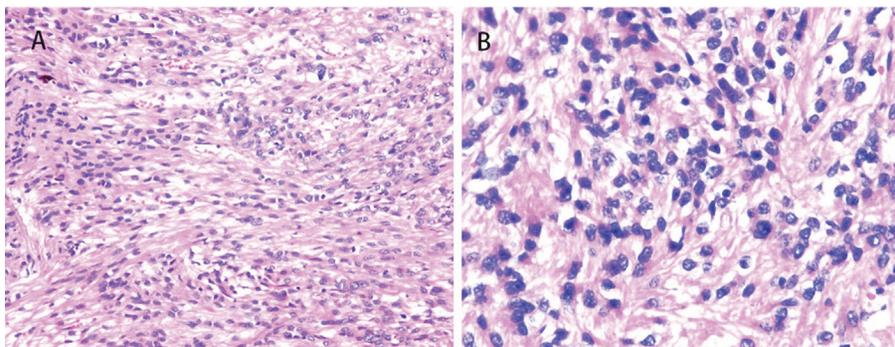


Figure 5 Posterior choroidal mesectodermal leiomyoma A: The tumor was composed of spindle cells with fibrillary eosinophilic cytoplasm (HE×100); B: The nucleus was round to oval and granular, with fibrillary eosinophilic cytoplasm, some of which were indented by cytoplasmic perinuclear vacuoles (HE×200). HE: Hematoxylin and eosin staining.

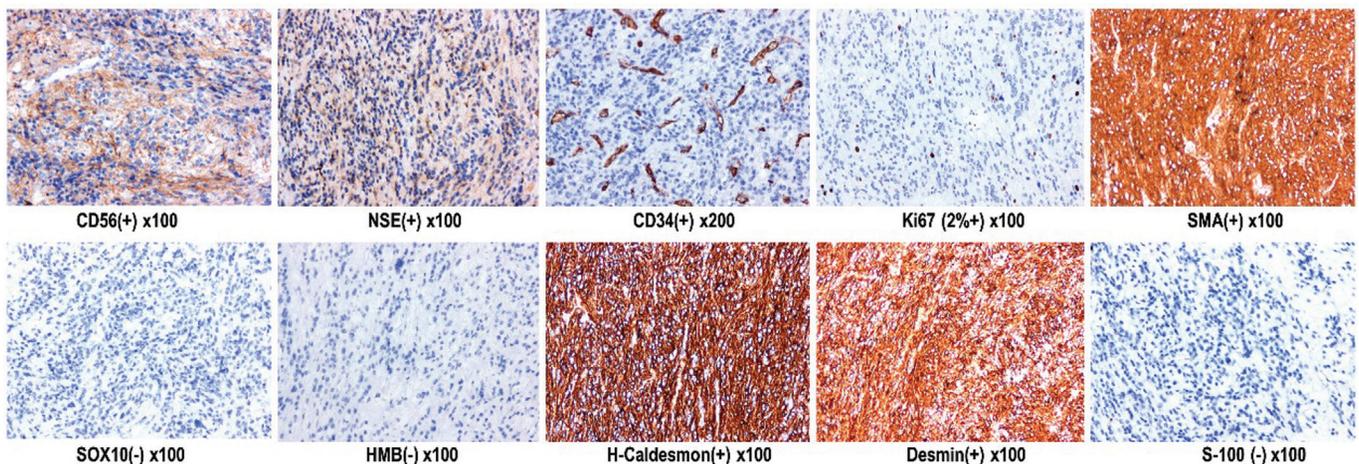


Figure 6 Results of immunohistochemical examinations NSE: Neuron-specific enolase; SMA: Smooth muscle actin; SOX: SRY-related HMG-box; HMB: Human melanoma black.

the size of the tumor would be a confounding factor for the transillumination^[15].

Age, gender, and racial orientation The mean age of the 16 patients with posterior choroidal leiomyoma was 35y

Table 1 Comparison between posterior choroidal leiomyoma and choroidal melanoma

Items	Posterior choroidal leiomyoma	Choroidal melanoma
Appearance	Solitary, dome-shaped, yellowish-white, with placoid retinal detachment	Dome-shaped, orange, with placoid retinal detachment
Transillumination	Semi or multi-transmissive	Cast a shadow
Average age (y)	35	58
Gender	Men and women was 9:7, almost consistent	Men
Racial orientation	Asians (13/16) > Whites (3/16)	Caucasian > Hispanic > Asian > Black
Location	Temporal (11/15), subnasal (3/15)	No quadrant predilection, their margins are generally within 3 mm of the optic disc
CEUS	Rapid wash-in and slow wash-out	Predominantly fast wash-in and wash-out
MRI	Hyperintense on T1WI, hypointense on T2WI, intense enhancement	Hyperintense on T1WI, hypointense on T2WI, intense enhancement
CT	High density with enhancement	High density with enhancement
FFA+ICGA	Early filling, late hyper-fluorescence with prominent leakage 12.5% "Dual-circulation" patterns	Early filling, late hyper-fluorescence with prominent leakage 60% "dual-circulation" patterns
Pathology	Spindle-shaped cell bundles and oval-shaped nuclei in a crossed pattern; no mitosis	Based on diversified types
IHC	SMA (+), MSA (+), Desmin (+); EMA (-), S-100 (-), GFAP (-), HMB-45 (-), Melan-A (-)	HMB-45 (+), SOX10 (+), Melan-A (+), S-100 (+)
Treatment	Enucleation, radiotherapy, vitrectomy	Enucleation, radiotherapy, vitrectomy

MRI: Magnetic resonance imaging; CT: Computed tomography; FFA: Fundus fluorescence angiography; ICGA: Indocyanine green angiography; CEUS: Contrast-enhanced ultrasonography; IHC: Immunohistochemistry; SMA: Smooth muscle actin; MSA: Muscle-specific actin; EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein; HMB: Human melanoma black; SOX: SRY-related HMG-box.

(range: 20 to 57y), which is similar to the previous 35.4y^[16]. Prevalence in men and women was almost the same with a ratio of 9:7. It is interesting to note that men had a higher incidence in the left eye (5/7) and women in the right eye (7/8). Instead, uveal melanoma tended to occur at an older age and was more common in males. The mean age at diagnosis of uveal melanoma was 59-62y in Caucasians, 55y in Japanese, and 45y in Chinese populations, and amelanotic uveal melanoma was 57y^[17-18].

In addition, someone discovered that the incidence of intraocular leiomyomas in women of childbearing age was identical to that of uterine leiomyomas, which may be due to hormonal fluctuations^[11]. However, only 2 of the 80 previously reported cases were associated with uterine leiomyomas^[19]. Our patient also had a uterine leiomyoma. However, the progesterone receptor was negative in her immunohistochemistry (IHC) results. Thus, we agree with the argument that sex steroid receptors in the eye and other parts of the body show inconsistent expression without sex-related association^[19].

Previously, uveal leiomyomas were more reported in Caucasians. However, posterior choroidal leiomyoma was more common in Asians (13/16) than Caucasians (3/16) in our review. Choroidal melanoma, on the other hand, tended to be Caucasian>Hispanic>Asian>Black^[20]. Based on its racial orientation, it may be possible to differentiate intraocular leiomyoma from melanoma. However, no definitive conclusions can be drawn due to the limitations of the small sample.

Location According to the summary, the posterior choroid leiomyomas were found to be most frequently located in the temporal quadrant (11/15), followed by the subnasal quadrant (3/15), then the supranasal quadrant (1/15), which may be due to the more widely ramified temporal artery. In contrast, choroidal melanomas did not have a quadrant predilection. Their margins were usually within 3 mm of the disc^[21]. Thus, it takes posterior choroidal leiomyomas longer time to invade the macula since the appearance of visual impairment depends on the location and growth rate of the tumor.

Imaging Examinations

Magnetic resonance imaging and computed tomography

In all of these cases, the intraocular leiomyomas were hyperintense on T1-weighted images (T1-WI) and markedly hypointense on T2-WI, with intense enhancement. They were isointense to the brain on both T1-WI and T2-WI, as in previous studies. In computed tomography (CT), they all showed high density with enhancement. These features are not specific to uveal melanoma and they have also been observed in other common intraocular tumors such as retinoblastoma and retinal or choroidal hemangioma^[11,22-24]. Therefore, the MRI and the CT scan alone cannot be used to identify two of them.

Fundus fluorescence angiography and indocyanine green angiography

FA and ICGA can show the tumoral vessels below the retinal vasculature. However, they are not sufficient to identify choroidal malignant melanoma and leiomyoma. Both of them showed filling in the early stages and hyper-

fluorescence with prominent leakage in the late phase. In addition, there were two cases had reported the “dual-circulation” pattern^[7,13], which could also be observed in 60% of malignant melanomas^[17]. The “dual circulation” pattern would appear on FFA when the tumor grows large enough to break through Bruch’s membrane, symbolizing secondary choroidal vascularization in tumors^[20].

Ultrasonography Ultrasonography can provide the size and internal characteristics of tumors. On conventional ultrasound, most choroidal leiomyomas showed a well-defined, dome-shaped choroidal mass with moderate to low reflectivity and abundant blood flow. However, they were indistinguishable from choroidal melanoma. CEUS allows dynamic observation of the tumor, obtaining its perfusion pattern and quantitative diagnostic parameters^[25-26]. By comparing and analyzing the perfusion status with that of the surrounding normal tissue, the nature of the occupying lesion can be initially determined. The accuracy of CEUS, MRI and their combination in diagnosing uveal melanoma was 93.7%, 90.5% and 100%, respectively^[25-27]. In this article, we first describe the characteristics of a choroidal leiomyoma detected by CEUS. It was suspected to be a benign hemangioma based on the rapid wash-in and slow wash-out pattern, similar to that observed in uterine leiomyomas^[28]. In the case of benign tumors, the fast wash-in/slow wash-out pattern was predominant due to the poor blood supply. While choroidal hemangiomas show slow wash-in and wash-out pattern due to slower blood flow in their thin-walled vessels^[26]. In contrast, choroidal melanoma primarily exhibits a rapid wash-in and wash-out pattern due to its unique vascular structures, such as vascular rings and arteriovenous fistulas, which provide adequate circulation and nutrition^[25-27].

Furthermore, the transparency of the refractive interstitium of the eye does not interfere with CEUS. Allergy testing is not required because the contrast agent is cleared by the pulmonary circulation. It has no nephrotoxicity and does not interact with the thyroid gland. Therefore, it is safe for children and has been used for the diagnosis of other organ diseases such as heart, liver, kidney, thyroid, *etc*^[29-32]. Besides tissue imaging, targeted acoustic contrast agents with diagnostic and therapeutic effects are investigated. All of the above gives CEUS a considerable potential for clinical application^[33]. Therefore, CEUS can be a resolving technique when retinal/choroidal detachment and intraocular masses cannot be diagnosed by conventional ultrasonography^[34].

Pathology and Immunohistochemistry

Pathological observations Without evidence of mitosis, uveal leiomyomas usually show spindle cell bundles and oval nuclei arranged in intersecting fascicles. And the mesectodermal type has both muscle and neuronal features, similar to some

neuronal tumors such as gliomas and paragangliomas^[21,35]. In contrast, malignant uveal melanoma has more histological features due to the diversity of cell types^[36-37]. Light microscopic examination can provide us with a preliminary view of the tumor, but a precise diagnosis depends on IHC.

Immunohistochemistry Since 1989, IHC has been used for further clarification of the nature of mesectodermal leiomyomas^[38]. The smooth muscle actin (SMA), vimentin, HMB-45, S-100, desmin, and epithelial membrane antigen (EMA) were commonly detected in the previous cases. All cases in summary were positive for SMA and muscle-specific actin (MSA), while they were negative for HMB-45, Melan-A, and EMA. Most were negative to S-100 and glial fibrillary acidic protein (GFAP), and positive to Desmin and CD56. The current case covered more immune molecules than before. For example, the tumor was positive for CD34, indicating its vascularity, consistent with the diagnosis of benign hemangioma using CEUS^[39]. CD34-positive leiomyomas were rarely reported, which were considered harmful in malignant melanoma and may be associated with aggressive tumor behavior. It was often used to calculate microvascular density in uveal tumors and is also an indicator of mortality^[40]. The 2% positive Ki-67 reaction in this case also indicated that the tumor was benign and had a low proliferative capacity. Together with cell morphology and positive neural [CD56, neuron-specific enolase (NSE)] and muscle (Desmin, Caldesmon) markers, it was further diagnosed as mesectodermal leiomyoma. On the other hand, Melan-A, HMB45 and SOX10 were the most frequently used markers for the identification of uveal melanoma^[41]. With the molecules described above, the differentiation and diagnosis of uveal melanoma and choroidal leiomyoma could almost be done. And clinicians can select relevant molecules to explore the tumor heterogeneity.

TREATMENT

Treatment mainly depends on the type of tumor. It aims to control tumor growth, prolong the patient’s survival and protect vision. For malignant tumors, enucleation or removal of the eye would be considered. However, this may raise some questions. Only five cases in this review were treated with local excision. During follow-up, patients’ vision recurred at different levels depending on tumor size and surgical difficulty. In recent years, vitrectomy for intraocular tumors has become more popular. It allows the tumor to be removed locally and improve patients’ quality of life. It can preserve the patient’s eye and vision. The technique has been described in detail in the past. Some doctors have further modified the surgery, such as partial transscleral sclerectomy combined with microinvasive vitrectomy and ocular reconstruction^[42]. And internal resection or endoresection combined with pars plana vitrectomy for posterior choroidal tumors has been proposed

as an alternative to radiotherapy or enucleation^[43]. However, performing a successful procedure can also be a challenge to the surgeon's experience and skills. The most common intraoperative risks are vitreous hemorrhage and the main postoperative risks are mainly hemorrhage, retinal detachment, cataract, proliferative vitreoretinopathy and poor visual recovery^[42]. In addition, there is a risk of seeding in the case of malignant melanoma^[42,44]. Other therapies include radiotherapy and close follow-up. Radiation therapy can be used as an alternative to resection or local excision. However, there was evidence of tumor recurrence and growth after radiotherapy, and the outcome was unsatisfactory^[45].

CONCLUSION

In this review we present more details about choroidal leiomyomas and something new different from previous described. These include their racial orientation, gender, and quadrant preference, as well as richer IHC markers. The preoperative differentiation of choroidal leiomyoma from amelanotic choroidal melanoma remains a clinical challenge. And the final pathologic examination is still the gold standard for the diagnosis. However, we still strive to make an accurate diagnosis before surgery. As the fifth case reporting posterior choroidal mesectodermal leiomyoma, CEUS was used for the first time to aid in the differential diagnosis. It can be helpful when an intraocular tumor is suspected to be benign or malignant. Especially when it's confined to the choroid.

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