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Case Report

Secondary glaucoma as initial manifestation of ring melanoma: a case report and review of literature

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Abstract: Melanomas account for over 70% of adult malignancies in the eye and occur primarily in the choroid. Melanomas rarely originate in the ciliary body, with an annual incidence of approximately 1.6 cases per million. While the incidence rate of these tumors is low, malignant melanomas metastasize at early stages of disease development and show poor prognoses. Malignant melanomas of the ciliary body are often deeply hidden and have complex clinical manifestations, which are easily misdiagnosed and affect the prognosis. Here, we report a case of monocular ciliary body melanoma in an elderly Asian woman. Using this case as an example, we perform a systematic review of the disease's clinical symptoms, signs, diagnoses, differential diagnoses, treatment and prognosis.

Keywords: Malignant melanoma, ciliary body, secondary glaucoma, ring malignant melanoma

Introduction

Malignant melanomas are highly malignant tumors that originate from the melanocytes. While the incidence rate of these tumors is low, malignant melanomas metastasize at early stages of disease development and show poor prognoses. Primary malignant melanomas of the skin are most common; however, the pigmented membrane tissue within the eye is also one of the primary sites for melanomas [1]. Malignant melanomas account for over 70% of the malignant tumors in the eye. Malignant melanomasare often distributed in a diffuse pattern in the choroid tissue. The majority of patients are diagnosed either due to decreased visual acuity or during conventional examination of the fundus [2]. Melanomas originating in the ciliary body or iris account for only 4%-10% of malignant melanomas in the eye, but these melanomas are often hidden and do not show clinical symptoms until a late stage, making them difficult to diagnose [3]. Once the melanoma is confirmed, the majority of patients have advanced stage diseases and a high rate of mortality. Therefore, the early detection and diagnosis of ciliary body melanomas is highly important. Here, we report the case of a malignant melanoma with secondary glaucoma as clinical manifestations.

Case presentation

The patient was a 76-year-old middle-aged Asian woman. She was admitted into the retinal surgery department of our hospital due to black patches observed on the surface of the left eye for over 30 years and increased visual blur for six months. Approximately 30 years ago, the patient was accidentally found to have dark brown patches on the left eye surface. There were no significant signs of congestion, pain or discomfort. Therefore, the patient did not receive specific treatment. Six months prior to admission, the patient noticed an increase in the number and size of the black patches on the left eye surface, accompanied by local mild hyperemia and pain. A local hospital diagnosed the case as conjunctivitis. The patient reported to our hospital after symptomatic treatment did not relieve the symptoms. The results of the visual inspection were OD = 20/20 and OS = 20/50, with no increase in the best corrected visual acuity. Intraocular pressure measure-

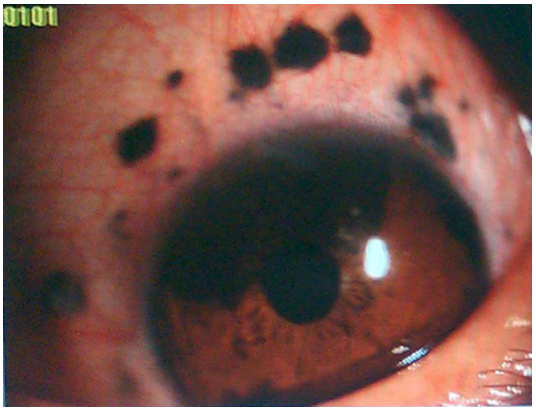

Figure 1. Slit lamp microscopy. Slit lamp microscopy showed a number of visible pigmentation patches of different sizes in the left eye. The surfaces of the patches were smooth and did not protrude from the ocular surface. There was no sign of bleeding or pannus and no significant necrosis. The left cornea was transparent, with no debris behind the cornea. The left anterior chamber depth was normal, with no aqueous flare or cells in suspension. There was a large fan-shaped area of visible pigmentation extending to the pupil of the left iris between the 10 o'clock to 2 o'clock positions, with no vasculature or necrotic tissue.

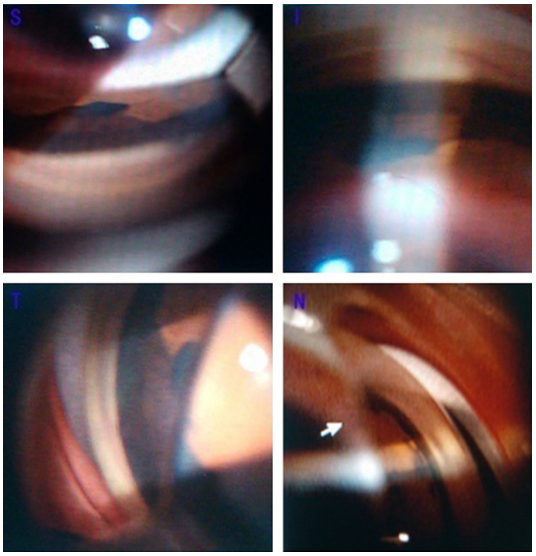

Figure 2. Gonioscopy. The gonioscopy showed: the left corner angle opened for 360 degrees; a large pigmentation jammed the angle; the trabecular meshwork structure was not clear; and the right angle was fully open.

ments were (Goldmann) OD = 14 mmHg and OS = 25 mmHg. The fundus contained glaucoma-like damage of the optic disc. The patient was transferred to the glaucoma clinic for further examinations. Slit lamp microscopy (**Figure 1**)

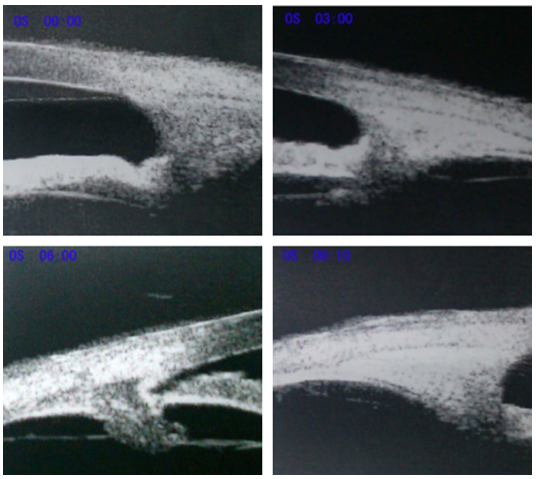

Figure 3. Ultrasound biomicroscopy. Ultrasound biomicroscopy (UBM): in addition to the bottom, the corner angles of every position were widened; the ciliary body was widened, thickened, and more echogenic; and part of the iris surface was also more echogenic.

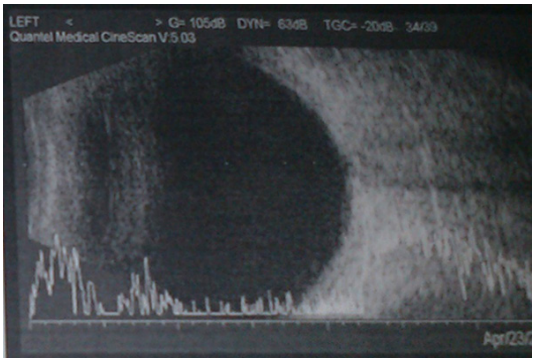

Figure 4. Ophthalmic A/B-mode ultrasound. Ophthalmic A/B-mode ultrasound showed that the vitreous and retina of both sides were normal.

showed a number of visible pigmentation patches of different sizes in the left eyeball. The surfaces of the patches were smooth and did not protrude from the ocular surface. There was no sign of bleeding or pannus and no significant necrosis. The left cornea was transparent, with no debris behind the cornea. The left anterior chamber depth was normal, with no aqueous flare or cells in suspension. There was a large fan-shaped area of visible pigmentation extending to the pupil of the left iris between the 10 o'clock to 2 o'clock positions, with no vasculature or necrotic tissue. The left lens was transparent, without opacity or cells in the anterior vitreous. Examination of the right anterior segment showed no abnormalities. The results of gonioscopy (**Figure 2**) were the

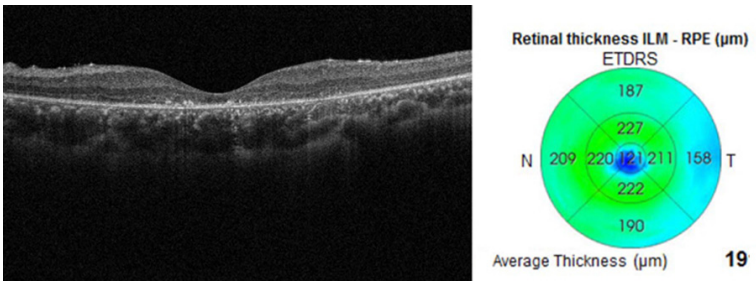

Figure 5. Retinal optical coherence tomography. Retinal optical coherence tomography (OCT) showed atrophy and thinning in the left macula and surrounding retina. There was limited protrusion of the pigment epithelium.

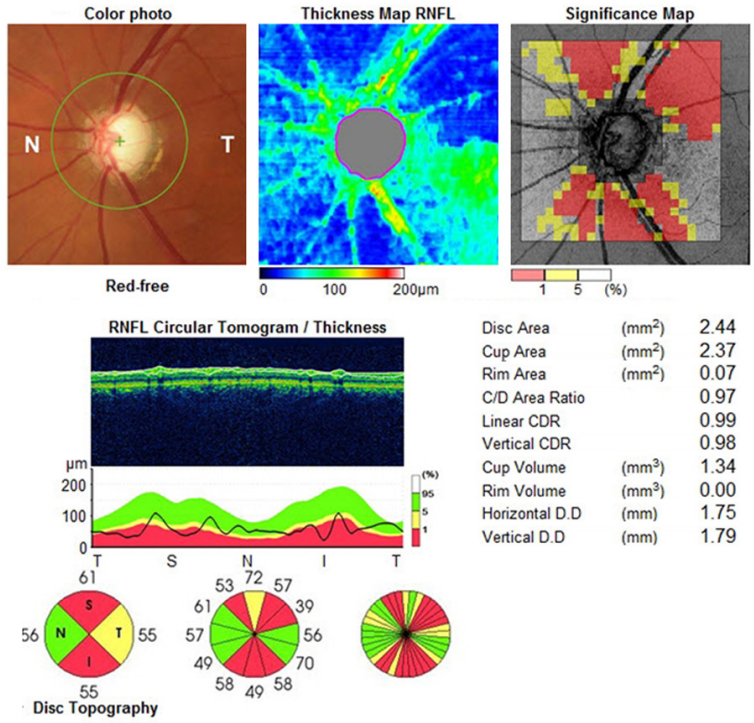

Figure 6. Disc OCT. Disc OCT showed that the nerve fiber layer was significantly thinner in the regions above and below the disc.

following: the left anterior chamber angle opened for 360 degrees; a large pigmentation jammed the angle; the trabecular meshwork structure was not clear; and the right angle was fully open. The dilated fundus examination indicated that: The C/D area ratio of left optic disc is over 0.9, and glaucoma-like damage was significant; the left retina was thin, with some areas showing the underlying choroidal vessels; and the right fundus was normal. The results of the ultrasound biomicroscopy (UBM) (**Figure 3**) were the followings: in addition to the bottom, the anterior chamber angle at each position were widened; the ciliary body was widened, thickened, and more echogenic, and part of the iris surface was also more echogenic. Ophthalmic A/B-mode ultrasound (**Figure 4**) showed that the vitreous and retina were normal bilaterally. Retinal optical coherence tomography (OCT) (**Figure 5**) showed atrophy and thinning in the left macula and surrounding retina. There was limited protrusion of the pigment epithelium. Disc OCT (**Figure 6**) showed that the nerve fiber layer was significantly thinner in the regions above and below the disc. Abdominal ultrasound, chest X-ray and cranial CT all showed no abnormality. The patient had no family history of cancer. The initial diagnosis was the following: 1. Suspected ciliary body melanoma; 2. Secondary glaucoma; 3. Choroidal melanoma retinopathy. One day post examination, the patient received a ciliary body biopsy and an iris biopsy, and pathological and immunohistochemistry analyses were continually conducted. These tests confirmed the diagnosis of a malignant melanoma (**Figure 7**). Four days after the diagnosis confirmation, the patient received enucleation of the left eye. The patient has been followed until the present (about two years), and no tumor cell dissemination or metastasis has been observed.

Discussion

In 1898, the Russian ophthalmologist Ewetsky reported a rare type of disseminated malignant melanoma with a primary site in the ciliary body [4]. This melanoma primarily originates in the ciliary body matrix, shown as multiple sites [5]. When the disease expands to a region covering more than six hour positions of the ciliary body and iris, it is called a ring malignant melanoma [6]. The incidence of ciliary body melanomas is

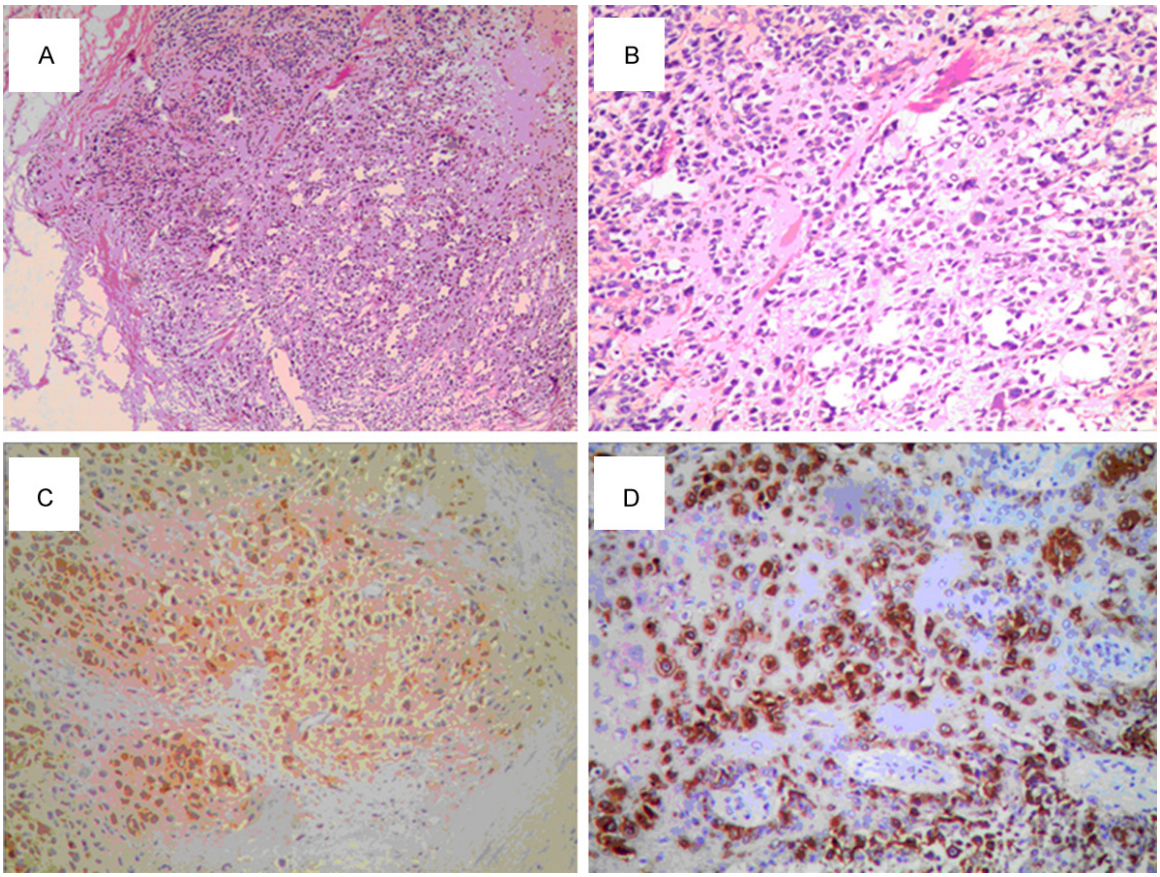

Figure 7. Pathological and immunohistochemistry analyses. A, B. Tumor consisted of malignant epithelial tumor cells and spindle cells with large amounts of acidophilic cytoplasm and prominent nucleoli (HE staining). C. Immunohistochemical staining for Melon A is positive (Original magnification ×100). D. Immunohistochemical staining for HMB-45 is positive (Original magnification ×100).

low, at less than 1.6 per million [1]. Aging is a risk factor for this disease. Although ciliary body melanomas primarily occur in patients over the age of 50, they are also occasionally reported in the younger population [7, 8]. Ciliary body melanoma occurs relatively often in the Caucasian population and has relatively low incidence in Asian or black populations. In addition, the incidence of the disease is similar for both genders and for both the left and right eyes. It is commonly observed in one eye and rarely observed in both eyes [1].

The clinical manifestations of ciliary body melanoma are diversity, depending on the location, size, growth pattern and biological behavior of the tumor. As the tumor volume increases, the tumor oppresses the lens, resulting in visible changes in the refractive status, lens dislocation, and turbidity, among others [9, 10]. When the tumor extends to the ciliary epithelial cells, it can decrease aqueous humor secretions and intraocular pressure [11]. When the tumor extends to the surface of the sclera, it can cause telangiectasia, redness and pain in the eye. A direct invasion into the anterior chamber angle or anterior displacement of the lens-iris diaphragm from posterior mass effect may cause secondary open-angle or closed-angle glaucoma [7, 12-15]. Tumor necrosis can cause hyphema, vitreous hemorrhage, retinal exudates and retinal detachment [16, 17].

Gonioscopy and UBM are important methods to determine the range of the tumor invasion. UBM examinations revealed that the angle widened at the 12 o'clock, 3 o'clock and 10 o'clock positions. The echo of the ciliary body widened and increased consistently with the range of the tumor invasion. However, gonioscopy detected melanoma cells accumulating in the corner and around the irisunder each view. The

gonioscopy range was wider than that of UBM; therefore, UBM cannot replace gonioscopy.

Interestingly, the patient showed obvious and diffusive optic nerve and macular atrophy. OCT results showed diffuse thinning of the retina and limited protrusions of the pigment epithelium. Despite a 25 mmHg IOP and a large difference in intraocular pressure compared to the contralateral eye, the OCT results cannot be fully explained by changes in glaucoma-induced optic nerve damage. Because the involvement of the outer retina was observed, we proposed a diagnosis of melanoma-associated retinopathy (MAR). MAR is a tumor immunoretinopathy [18, 19]. Currently, 15 different retinal antibodies have been found [20], including anti-bipolar cell antibody [21], anti-recoverin antibody, and anti-enolase antibody, among others. Studies have shown that the primary mechanisms of MAR include autoantibody-induced damage and death of retinal cells (bipolar cells and photoreceptor cells) [22, 23]. MAR fundus examinations show no obvious abnormalities at early stages. However, as the disease progresses, the retinal arteries narrow and the retina shows diffusive atrophy.

Secondary glaucoma is one of the most common complications of ciliary body melanoma. Seventeen percent of ciliary body melanomasare associated with elevated intraocular pressure (IOP) [24]. When the tumor located in the ciliary body increases in size, it pushes the crystal iris diaphragm forward, which may result in acute angle-closure glaucoma [7]. The tumor may also cause adhesions behind the pupil, leading to secondary acute angle closure. In addition, the diffuse tumor cells accumulate in the corner and the trabecular meshwork, blocking the outflow and increasing intraocular pressure [8, 14]. Ischemia and hypoxia can induce expression of vascular endothelial growth factor (VEGF), leading to neovascularization and humor circulation disorder. Acute intraocular pressure increases, caused by the rupture of neovascularization, have also been reported [16, 25].

The glaucoma caused by ciliary body melanomas is refractory glaucoma [8], which can be treated by relatively few types of anti-glaucoma drugs. Skalicky et al. [26] recommended treating this type of glaucoma with β receptor blockers, α-2 receptor agonists and carbonic anhydrase inhibitors. Because prostaglandin-like drugs increase the activity of matrix metalloproteinases and reducethe resistance of the aqueous humor outflow through the uveal scleral pathway, they can potentially increase the risk of tumor dissemination. When drugs are ineffective, glaucoma surgery is an option. Conventional glaucoma surgeries, including filtration surgery, aqueous humor drainage, and ciliary body destruction, among others, do not provide permanent control of intraocular pressure. Tumor cells can easily block aqueous humor outflow through the artificial channel. In addition, the surgery itself may accelerate tumor dissemination. Lee et al. reported two cases of patients receiving trabeculectomy and Molteno drainage tube implantation. IOPs were poorly controlled after the surgery. Finally, a patient died due to tumor dissemination [8]. Escalona-Benz et al. [7] and Othman et al. [25] also reported similar results. Girkin et al. [27] propose that filtration surgery and drainage tube implantation cannot be applied to ciliary body melanoma patients, as these procedures enable faster tumor metastasis and a reduction in difficulties. In addition, Piirtola et al. [28] reported that transscleral photocoagulation therapy can reduce IOP and the number of treatments for secondary glaucoma patients. This treatment strategy remains controversial, and there are two foci in the debate over this treatment. Firstly, it is unclear whether photocoagulation surgery will accelerate tumor spread and metastasis. Currently, there have been no randomized controlled trials assessing this topic. Secondly, ciliary body photocoagulation or cryotherapy can cause the regional death of tumor cells, to some extent, alleviating high intraocular pressure and prolonging the time before a correct diagnosis is made.

Notably, ciliary body melanomas have a high misdiagnosis rate during the initial diagnosis. This may be one of the reasons for the poor prognosis. At an early phase, the ciliary body melanoma can be easily misdiagnosed as primary angle-closure (open-angle) glaucoma because the major clinical manifestations of both diseases is intraocular hypertension. Thus, many patients received antiglaucomatous surgeries. However, the surgery itself cannot control IOP well and may even lead cancer cells to disseminate, thereby posing a threat to the patient's life. On one hand, the misdiagnosis is due to the hidden nature of the ciliary

body tumors. It is difficult to make an early diagnosis with conventional B-type ultrasound, gonioscopy or slit lamp examination. On the other hand, patients often have early mild visual impairments. If the contralateral eye shows symptoms, such as the presence of a shallow anterior chamber, or if there is a medical history or family history of glaucoma, the ophthalmologist is likely to make an incorrect diagnosis [7]. In the case study presented here, the black plaque on the surface of the patient's left eye had been known for more than 30 years, which led the ophthalmologist to quickly diagnose the patient with a melanoma. Notably, melanomas, under certain conditions, can transform into malignant melanomas. Escalona-Benzet al. also reported similar cases [7].

It is also worth noting that at some stages, ciliary body or iris malignant melanomas present similar clinical manifestations as those of corneal endothelial syndrome (ICE) [8]. Specifically, with the presence of disseminated tumor cells, the patient may show pigmentation, goniosynechia and refractory elevated IOP at the corneal endothelium and the angle. A corneal endothelial microscopy examination may show similar changes as those observed with ICE, thereby leading to misdiagnosis.

In summary, early malignant melanomas may have similar clinical manifestations as those of primary open-angle or closed-angle glaucoma. As the disease progresses, ICE syndrome-like symptoms may be present at the corneal endothelium, iris and anterior chamber angle. These non-specific symptoms could result in misdiagnosis, thereby interfering with prognosis. Therefore, for any patient, regardless of age or race, ophthalmologists should consider the possibility of ciliary body melanoma when observing unilateral, refractory increases in IOP coupled with asymmetric changes in anterior chamber depth, angle, iris color, pigment dispersion, or iris mass, among others. UBM is effective in the early diagnosis of ciliary body melanomas, but it cannot replace gonioscopy. Biopsy and immunohistochemistry results are the gold standards for the diagnosis of ciliary body melanomas. Because ciliary body melanomas tend to metastasize early and are highly malignant, once diagnosed, the patient should receive enucleation within a specified time frame, in addition to long-term follow-up care.

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Disclosure of conflict of interest

None.

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