Case report

Iris melanoma with ciliary body infiltration presenting as a presumed chronic unilateral inflammatory glaucoma. The challenges of iris tumor biopsy assessment

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Uveal melanoma is the most common primary malignancy of the eye in adults. It may involve the choroid and ciliary body, and in only 2-3% of cases it involves the iris.
We present a case of a 56-year-old patient with a 6-year history of unilateral, inflammatory, refractory glaucoma of the right eye. Due to acquired heterochromia and heterogeneous thickness of the iris, iris melanoma was suspected, but the incisional biopsy did not confirm the diagnosis. In the next months, the lesion enlarged and the eye globe was enucleated. Histopathological examination revealed an iridociliary melanoma with annular growth pattern.

Key words: iris melanoma, ring melanoma, iris biopsy, unilateral glaucoma.

Introduction

Uveal melanoma is the most common primary malignancy of the eye in adults [1]. 97-98% of uveal melanomas involve the choroid and ciliary body, while only 2-3% are confined to the iris [2]. Among them 0.3% were reported to be ring melanomas of the ciliary body [3]. Ring melanoma involves a diffuse and circumferential growth pattern of the tumor around the ciliary body that was first described by Ewetzky in 1898 [3]. With the annular growth, lack of obvious tumor mass and non-specific symptoms, the diagnosis is usually challenging.

We present a patient with a 6-year history of a unilateral inflammatory glaucoma that eventually was diagnosed as ring melanoma. The growing tumor was undetectable for a clinician for a long time and the primarily performed iris biopsy revealed no tumor pathology.

Case report

A 56-year-old woman with acquired heterochromia was referred to the Glaucoma Service at our Department due to unilateral secondary glaucoma of the right eye refractory to treatment. According to the patient's history, heterochromia of the right iris occurred six years before. At the same time the patient was diagnosed with inflammatory glaucoma following two episodes of acute anterior uveitis. She had a history of a trabeculectomy 2 years earlier, cyclocryotherapy a year ago and ExPress Mini-shunt implantation 2 weeks prior to admission. Despite previous surgeries and maximal topical therapy, the patient maintained high intraocular pressure in

the right eye. Family history was negative for glaucoma. The patient denied any ocular traumas in the past. She was treated for systemic hypertension, but otherwise was healthy.

At presentation, the vision was 20/20 in the right eye and 20/20 in the left, otherwise healthy eye. The intraocular pressure (IOP) was 43 mmHg in the right eye on maximal topical therapy and 11 mmHg in the fellow eye. In anterior biomicroscopy, significant heterochromia could be noted – the right iris was brown and the left one was light blue (Fig. 1A, B). The cornea was slightly dimmed peripherally and 2 sclerocorneal sutures could be seen at 1.00 and 10.00 clock hours, respectively. The anterior chamber was unevenly shallow, especially in the nasal part where the iris was thickened. The patient was aphakic and iridectomy was present in the inferior part of the iris. The pupillary margin was irregular with some iridocapsular synechiae in the superior part (Fig. 1A). On gonioscopy, the angle was narrow in all quadrants (0 to 1 on the Shaffer scale) with numerous iridocorneal synechiae.

The intracameral part of ExPress Mini-shunt was visible in the superonasal quadrant of the angle, but the filtration was not active and the conjunctival bleb had not formed. No Krukenberg spindle was detected. On fundoscopy, the right optic disc was cupped. The anterior segment and retinal fundus of the left eye appeared normal. In the ultrabiomicroscopy (UBM) with the use of a 40 MHz probe (Eyecubed V 4.0, Ellex), the signs of iridocorneal synechiae were confirmed but no specific tumor mass was identified (Fig. 1C).

Due to a clinical suspicion of iris melanoma with iridocorneal angle infiltration, surgical incisional biopsy (SIB) of the iris was performed. During the procedure the corneal tunnel incision at 10 o'clock was made and 2 iris samples were taken at 2 and 6 o'clock. The histopathology report following the procedure revealed numerous epithelioid, moderately atypical melanocytes with no mitotic activity. The morphology of the lesion did not support clinical diagnosis of iris or ring melanoma (Fig. 2). Due to clinical ambiguity and the patient's complaints of a painful eye, enucleation was offered but was declined by the patient. Transscleral cyclocryoapplication was performed twice in order to lower the intraocular pres-

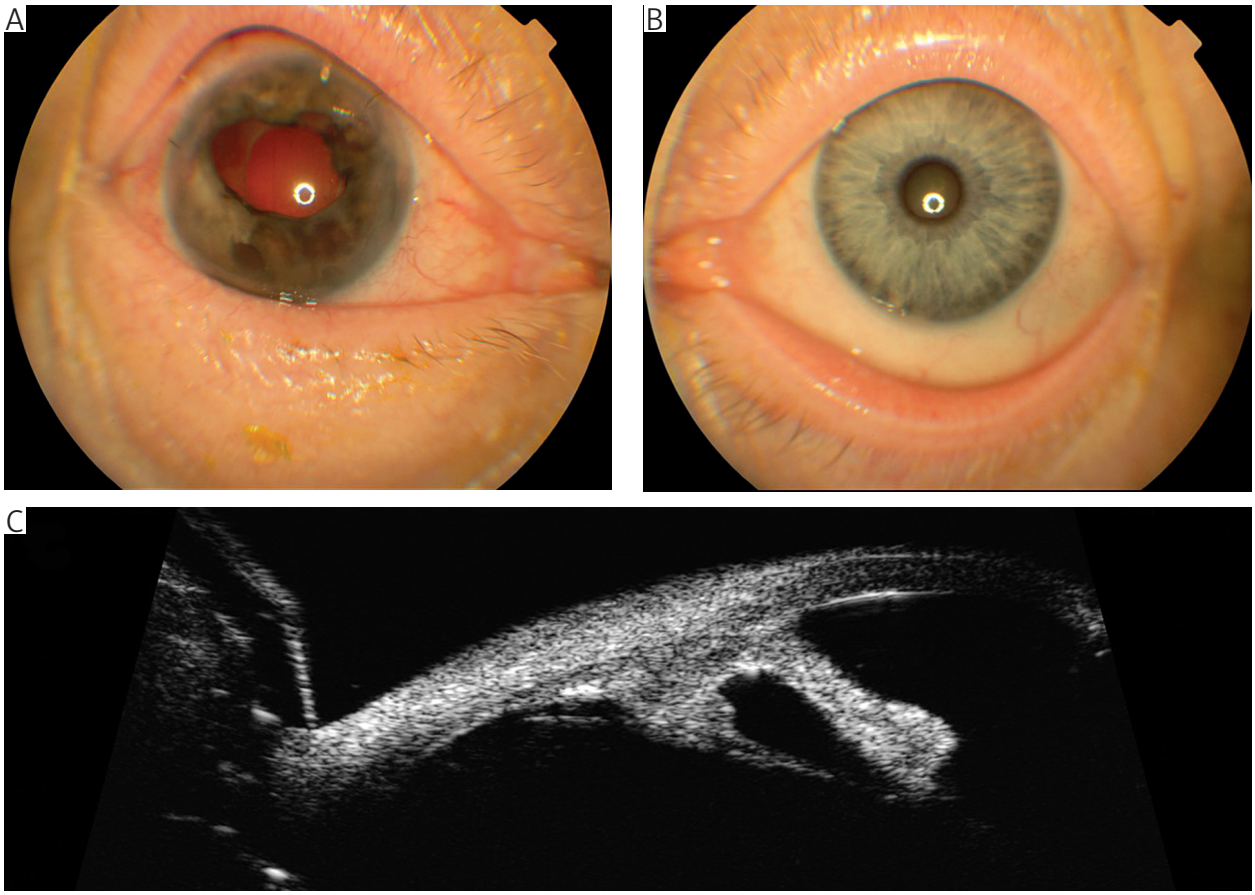

Fig. 1. A) Anterior segment of the right eye at presentation. Diffuse conjunctival irritation, iris heterochromia as well as the irregular pupil and iridocorneal synechiae on 1 o'clock, iridectomy on 6.30 o'clock and capsular phimosis are visible; B) Anterior segment of the left eye; C) UBM, longitudinal scan of the elevated and thickened part of the iris showing iridocorneal adhesion and no evidence of ciliary body tumor

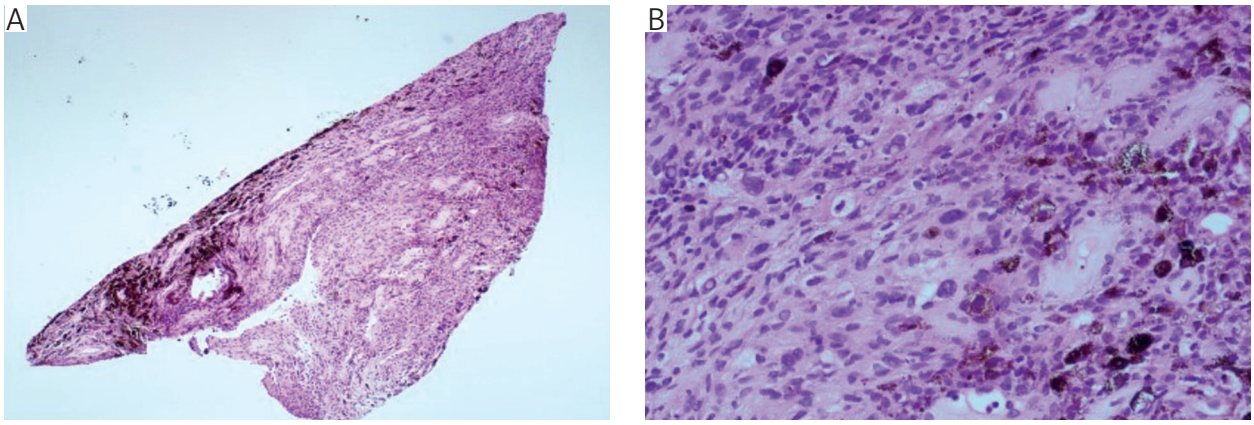

Fig. 2. Sections of the iris biopsy specimen. Epithelioid cells and pigment are visible, however, no mitoses seen with and only moderate cellular atypia (HE, A: 4 ×, B: 20 ×)

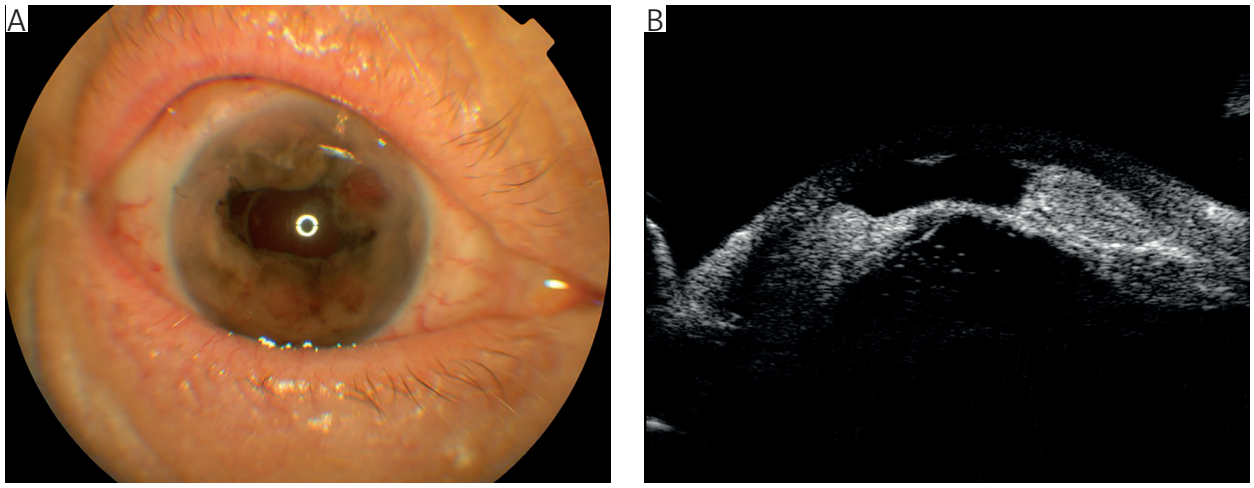

Fig. 3. A) Anterior segment of the right eye 9 months post biopsy. Significant tissue growth visible on the entire surface of the iris; B) UBM central scan on 12 o'clock. The image indicates a clear extension of the lesion, which now covers virtually the entire iridocorneal angle circumference

sure, then the patient was followed up on a monthly basis.

Nine months later, increased thickness of the iris and more shallow anterior chamber were noted on biomicroscopy. UBM was performed and showed almost 360 degrees circumferential growth of the hypoechogenic mass involving the iris, iridocorneal angle and the ciliary body (Fig. 3). Based on an earlier histopathological examination, lesion progression and clinical features of the tumor, the clinical diagnosis of iridociliary melanoma with annular growth was made.

Due to the infiltration of the iridocorneal angle and history of ExPress implantation, the lesion was not eligible for brachytherapy and the patient underwent enucleation with orbital implant insertion. Histopathological examination of the enucleated globe confirmed the diagnosis of ciliary body melanoma with annular ciliary body involvement and maximum tumor size of 13 × 15 mm (Fig. 4). The melanoma was of mixed cellularity but with a predominance of epithelioid cells (75/25). The mitotic activity was described as 38 mitoses per 40 high power fields (HPF). No sclera or optic nerve infiltration in histopathologic examination was found. Two years after surgery the patient is free from metastases and local recurrence.

Discussion

We present a rare case of primary iris melanoma infiltrating the whole circumference of the ciliary body that mimicked inflammatory glaucoma for years. Due to unspecific symptoms, no tumor mass visible in ancillary clinical tests and histopathological examination of the lesion sample, the tumor diagnosis was made after a long time of observation.

On the clinical background, the differential diagnosis for this case would be iris nevus, unilateral glaucoma, congenital iris heterochromia, ocular siderosis, Cogan-Reese syndrome, and Fuchs uveitis. Other

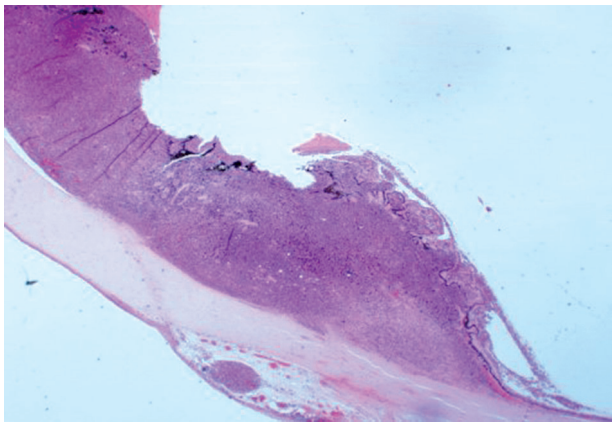

Fig. 4. Histopathological picture of the ciliary body in the enucleation specimen. The infiltration with melanoma cells is clearly visible (HE, 1.25 ×)

ciliary body tumors such as cysts, adenomas, and melanocytomas were excluded based on the histopathology report following enucleation that excludes other conditions leading to angle obstruction.

Ring melanoma of the ciliary body is a tumor of circumferential growth pattern that covers at least 6 clock hours [3]. It accounts for about 0.3% of choroidal melanomas with metastatic potential of 52% in 5 years [3]. In the case we report, it was difficult to assess whether the iris melanoma had primarily infiltrated the angle or vice versa. However, in view of the acquired heterochromia followed by long-term secondary glaucoma refractory to treatment, it can be assumed that primarily the melanoma originated from the iris and then secondarily spread to the ciliary body. Multifocal iris thickening and relatively slow course of the disease also confirm this hypothesis. For a long period of time no obvious tumor mass was revealed, but, of note, both iris melanomas and anterior chamber melanomas with diffuse growth pattern are very difficult to detect by ultrasound in early stages, and the diagnosis is based mainly on clinical examination including gonioscopy [3].

Clinical symptoms of ring melanoma can mimic both pigmentary glaucoma [6] and anterior uveitis [7]. Our patient was unsuccessfully treated for unilateral inflammatory glaucoma following the episodes of anterior uveitis. The presence of inflammatory cells in the aqueous humor and its tyndallization have already been reported in iris melanomas though [7]. According to the literature, most of the undiagnosed ring melanomas were initially incorrectly treated as pigmentary glaucoma [6, 8]. It is therefore necessary to thoroughly investigate the causes of each secondary glaucoma occurring unilaterally.

There are reports of tumor re-growth or dissemination after surgical procedures, mainly glaucoma filtering surgery [9, 10]. Demirci *et al*., based on an analysis of 14 cases of ring melanomas of the anterior chamber, suggested that these have a worse prognosis than other types of melanomas due to the presence of melanoma cells in Schlemm's canal, which may increase the risk of dissemination by blood vessels [11].

Early diagnosis of a tumor that is presenting a diffused growth pattern could mainly be made after a biopsy. Iris lesions can be biopsied in various ways: iridectomy with total excision of the lesion (excisional biopsy), fine needle aspiration biopsy (FNAB) [12] or small gauge vitrector-assisted biopsy [13]. For the pathologist the key issue is to identify such features as cytoplasmic melanin and spindle cell presence [12]. Immunohistochemistry both for epithelial and melanoma markers such as S100 and HMB45 is often useful when diagnostic doubts occur, especially in amelanotic tumors with the predominance of epithelioid cells [12].

FNAB with a 25 to 30 gauge needle is commonly used and seems to be a safe method of obtaining material for histopathological examination; however, it requires cooperation with an experienced cytologist [14]. Low cellularity and the fact that it samples the surface of the lesion only are common problems in FNAB or incisional biopsies. Mudhar *et al*. published data suggesting the presence of some tumor-modulatory factors in the anterior chamber that may influence the tumor cells and select better differentiated, less aggressive cell populations [15]. Therefore it might be important to collect samples containing material from deeper parts of the tumor. Some alternatives to FNAB have been presented to date, such as trans-corneal Rycroft cannula aspiration, which combines the advantage of microinvasiveness with taking a sufficiently large and deep sample [16].

In our patient an incisional biopsy was made. In the obtained samples many atypical epithelioid cells were found, but with the lack of mitotic activity not allowing for the diagnosis of a malignant tumor. The equivocal histopathological diagnosis could be caused by both too superficial material collection and the lack of immunohistochemical tests.

Iris tumors are insidious – they show relatively low aggressiveness and their histopathological picture may suggest a benign proliferative process for a long time. Ring melanomas are usually advanced at the time of diagnosis, mainly because of difficulties in identifying the mass of the tumor in regular examination and its ability to imitate the symptoms of other ocular diseases. Unilateral glaucoma refractory to treatment coexisting with heterochromia of the iris and symptoms of uveitis should always arouse the suspicion of intraocular pressure elevation secondary to iridocorneal infiltration.

Conclusions

This case shows the complexity and difficulty of the clinical diagnostic process in cases of a special

type of iris melanoma. In a case of insidious and diffuse tumor growth pattern, the tumor mass is not evident at first. In order to properly assess a patient regardless of the results of the paucicellular material like iris tumor biopsy, close cooperation between the pathologist and clinician is required to make a final diagnosis.

The authors declare no conflicts of interests.

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