EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY
60th ANNUAL MEETING

Date of meeting: Valencia 2022, May 25th - May 28th

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Case number: 780/13

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CILIARY BODY MELANOCYTIC TUMOUR OF UNCERTAIN MALIGNANT POTENTIAL IN AN EYE WITH IRIS BICOLOR

Clinical history

A 71-year old woman was referred to the Clinic of Eye Diseases, University Clinical Centre of Serbia, in October 2013, because of darkly pigmented lesion at the left iris root noticed by local ophthalmologist on routine examination. She did not report any other past significant ocular problem except different colour of the left iris present since birth or early childhood.

On **examination**, visual acuity and intraocular pressure were as follows: right eye BCVA was 1.0, IOP=14 mmHg and left eye BCVA was 0.6-0.7, IOP=14 mmHg. Anterior segment slit-lamp examination of the right eye revealed only incipient cataract. Left eye anterior segment slit-lamp examination revealed a pigmented 6-7 mm in basal diameter iris root mass at 6–8 o'clock position displacing the iris root anteriorly. On the opposite side, there was pigmented (light brown) iris lesion present comprising upper temporal quadrant without angle involvement. Also, a sectoral cataract was noted. Episcleral sentinel vessels, signs of diffuse or sector ocular (or oculodermal) melanocytosis and pigment dispersion in chamber angle were absent. Fundus examination of both eyes were unremarkable, according to patient's age, with only mild dry AMD changes.

On **gonioscopic evaluation**, lower nasal quadrant (from 05:30-08:30 o'clock position) of the left anterior chamber angle was closed and affected by tumour, while others sectors were wide open with no pathological peculiarities.

Left eye **ultrasound biomicroscopy** (UBM) revealed a solid mass of the pars plicata region of the ciliary body, at the 6-8 o'clock position (at the lower nasal quadrant), with extension into the iris root, demonstrated lower internal reflectivity, and measuring 6,02x5,35 mm, with several intrinsic cysts (or multiple hollow cystlike cavities). On the contralateral side, at the upper temporal quadrant of the iris, there was a lesion of high internal reflectivity, measuring 0.47 mm in thickness, without anterior chamber angle involvement.

The patient's **past medical history** was significant only for well controlled arterial hypertension.

After the examination, **clinical differential diagnosis** was ciliary body melanoma (or melanocytoma) with displacement of iris root, and (congenital) sectorial iris simple heterochromia probably due to idiopathic/isolated segmental iris melanocytosis (or sector iris naevus) in the oposite quadrant of the ciliary body lesion.

Systemic examination revealed that a chest X-ray, abdominal/liver ultrasonography and laboratory liver function investigations (hepatogram) were in normal range.

It was decided to perform a **surgery** of the ciliary body mass, due to concern of possible melanoma, in a form of excisional biopsy (partial lamellar sclerocyclogonioiridectomy with further iridoplasty) accompanied with immediate sequential phacoemulsification with intraocular lens implantation, under local anesthesia. The postoperative course was more or less uneventful – IOP was in normal range, partial haemophthalmus was reabsorb during the next twelve months after the surgery, and after that the visual acuity was excellent. No additional adjuvant therapy was administered after the histopathological diagnosis was made. The patient was under regular six months follow-ups during the first four years and then annually, which also include abdominal/liver ultrasonography.

After a 9 years of **follow-up** period no signs of tumour recurrence or metastatic disease have been observed. On the last examination, in April 2022, the left eye visual acuity was 1.0 and the intraocular pressure of the left eye was 13 mmHg.

Ocular pathology

Gross examination:

Two biopsy specimens were sent for examination, first measuring 7x4x0,5-1 mm (tumour) and second measuring 1x1x<0,5 mm (suspicious scleral tissue from the outer scleral flap).

Light microscopy examination:

Microscopic inspection showed a highly cellular and moderately (in some areas heavily) pigmented neoplastic lesion confined mainly to the pars plicata region of the ciliary body which invaded trabecular meshwork and root of the iris. Tumor cells were arranged mainly in a back-to-back nesting or in a fascicular pattern with one or two sharply circumscribed nodules which stand out. In the apical or surface part of the pars plicata portion of the neoplasm there was a broad cohesive compactly arranged or a plaque-like portion of the lesion which was more intensily pigmented than the other parts of the tumour.

Tumour contained multiple cavities. The cavities occupied ~25% of the entire mass thickness on one section. The cavitations were either opticaly empty or contained erythrocytes, serous exudate, cellular debris or a few pigment-laden macrophages. Cystlike cavities near the tumor apex seems to have an endothelial or flattened epithelial lining of the inner walls. No areas of necrosis were observed.

Several cell types were recognized within eosinophilic, fiber-rich stromal component of lesion:

1. Non-pigmented large naevoid balloon-cells with abundant foamy cytoplasm.

2. Little or non-pigmented slender spindle-shaped cells with basophilic nucleus distributed in a striking fascicular manner in the outer portions of a naevoid neoplasm.
3. Plump fusiform shaped and dendritic cells, less intensely pigmented, with a somewhat larger nucleus and a slightly looser chromatin pattern.
4. Epitheloid mononucleated naevoid cells.
5. Plump, polyhedral or globular in shape cells with voluminous cytoplasm so heavily packed with melanin granules which obscure the nuclear details.
6. Scattered individual larger "pleomorphic" cells.

The ovoid or elongated nuclei of these cells contained either a finely even dispersed or vesicular or washed-out chromatin pattern or intranuclear vacuoles. The nucleoli were either absent or dot-like (punctate basophilic) in the majority of tumor cells but around 10% of the cells possessed high nuclear:cytoplasmic ratio and a relatively large nucleoli. Zero mitotic figures were counted in 40 high-power fields. Only one mitosis was found in one serial section of the whole specimen.

In the second biopsy specimen a small intrascleral emissarial nerve is surrounded by infiltrating tumour cells.

Immunohistochemistry revealed the following immunophenotype:
S100 +++ (strong; diffuse), Melan-A +++ (strong; diffuse), SOX-10 ++ (moderate; diffuse), Bcl-2 ++ (moderate; diffuse), HMB-45 + (weak to moderate; focal), Ki-67 + <1%.

Based on the histopathologic features/morphology, immunohistochemistry, and clinical data (examination, imaging and a 9 years of follow-up), a **diagnosis of ciliary body melanocytic cavitary tumour of uncertain (borderline) malignant potential in an eye with isolated sectorial iris heterochromia** was found to be most compatible. The other two differential diagnosis were either low-grade cavitary spindle-cell melanoma of the ciliary body arising from a ciliary body nevus (ciliary body nevus with early malignant change) or a (spindle-cell) ciliary body nevus with several intrinsic cysts.

Discussion

On clinical basis and with available ancillary tests, ciliary body naevi cannot be reliably differentiated from ciliary body melanoma. Clinical features of these lesions are not distinctive enough to distinguish them with certainty. Moreover, there are no available size criteria for ciliary body naevi in contrast to for example choroidal or even iris naevi. [1-9]

On the other hand, histological differentiation between spindle naevus cells and spindle melanoma cells is subtle and also can be difficult because there is a considerable morphologic overlap between benign and malignant melanocytic lesions. Immunohistochemistry aids in the distinction between various uveal melanocytic proliferations but sometimes findings may be inconclusive. Likewise, molecular/genetic background/profile is certainly helpful if it is not compromised by known limitations of use of tissues from formalin-fixed paraffin-embedded samples - DNA isolated from older tissue samples may be of lower quality, thus offering challenges with sequencing, the sequencing of which may yield artifactual mutation calls. [1-7, 9]

Involvement of the iris, extension onto the chamber angle or onto the back of the cornea or even extrascleral extension of the ciliary body melanocytic tumor should not be considered to be a sign of malignancy, as long as the cells continued to display the same benign cytologic characteristics. However, some pathologists might regard the presence of the small nucleoli as evidence of a spindle cell melanoma. [3-6, 9]

Different colours of a person's irises are called heterochromia. Few kinds of it we distinguish: complete (whole iris is affected), partial (part of one iris is a different colour than the rest of it) or central (there is an inner ring that is a different colour than the outer area of the iris). Also, we differentiate *heterochromia iriduum* (binocular heterochromia), a difference between the colour of the two irises, and *heterochromia iridis* (monocular heterochromia), when areas of the same iris are different in colour. Heterochromia, either binocular or monocular, may be congenital or acquired, and causes of it are quite numerous. [10-11]

Histologically, sectorial melanocytosis represents a hyperplasia and hypertrophy of the normally occurring bipolar or multipolar iris stromal melanocytes without a mass lesion effect. [12]

Therapy of melanocytic ciliary body lesions is individually tailored. Patient's concerns, in addition to clinical features, and also a surgeon's preference, regardless of presence or absence of tumor growth, usually determine the appropriate management. In this case we favored surgery over observation or radiation therapy.

According to the literature, to the best of my knowledge, this case of the ciliary body melanocitic cavitary neoplasm located at the opposite side from the isolated sectorial iris heterochromia is unique, regardless how we are designating this neoplasm - as naevus, melanocytic lesion with uncertain malignant potential or melanoma.

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