"De novo" Appearance of a Choroidal Melanoma During 5 Years' Follow-up for CHRPE

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„De-novo"-Erscheinen eines Aderhautmelanoms während des 5-Jahres-Follow-ups einer kongenitalen Hypertrophie des retinalen Pigmentepithels

Introduction

Uveal melanoma, the most common primary intraocular malignancy in adults, has an incidence of about 6 new cases per million per year in Caucasians [1, 2]. The choroid is the most frequent localization (85–91%), whereas the ciliary body or the iris are affected in only 9–15% of cases. Its pathogenesis is not yet clearly understood. Relative risk factors are a fair skin, light eye color, ocular or oculodermal melanocytosis, and the presence of a cutaneous, iris, or choroidal nevus. It is associated with BAP1 or BRCA1 mutation carriers [2].

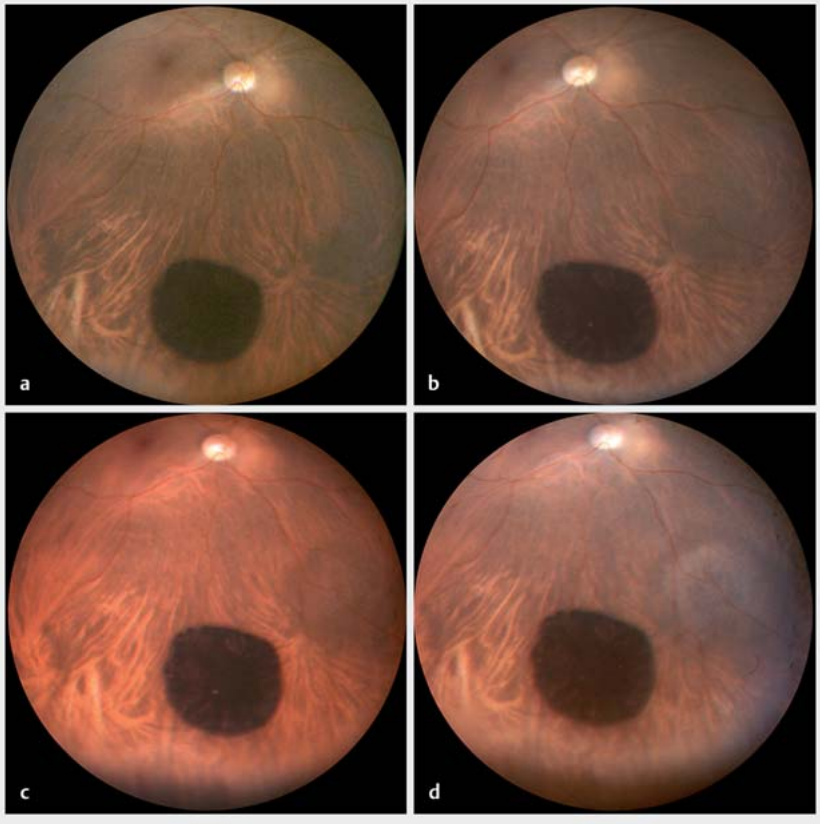
The question whether posterior uveal melanomas arise from preexisting nevi, or "de novo", has been an object of controversy, as the appearance and initial evolution of this rare fundus tumor occur asymptomatically, invisible to the patient. The first "proof" of the possible malignant transformation of nevi into melanoma was provided in 1967 by Yanoff and Zimmermann, who published a histopathological study on 100 uveal melanomas, in 73 of which they had observed the presence of "nevus cells" at the base of the tumor [3]. They concluded that "most malignant melanomas arise from pre-existing nevi". However, their conclusion lost its basis when Albert, in 1974, described "nevus-like" structures in experimental choroidal melanomas in laboratory animals [4], advancing the concept that melanomas also arise "de novo". Numerous studies have investigated the malignant transformation of presumed choroidal nevi and its risk factors [5, 6]. However, documented proof of a "de novo" genesis of a choroidal melanoma is rare [7, 8].

Growth of malignant tumors is exponential, and tumor doubling times (TDT) of choroidal melanomas, managed with observation, were observed to vary from 292 to 128 days in fusiform and mixed-cell melanomas, respectively, with the former and latter corresponding relatively more likely to "nevus" and "de novo" originating melanomas [9].

The aim of this report is to present the exceptional case of a "de novo" choroidal melanoma whose appearance and exponential growth were incidentally documented on serial color fundus pictures while monitoring the patient for another condition.

Case Report

A 46-year-old, white, Italian female consulted the Polyclinic at the Jules-Gonin Eye Hospital (Lausanne, CH) with complaints related to a decompensated exo-



▶ **Fig. 1** **a–d** Panoramic fundus photos (Panoret-1000) taken during periodic follow-up of an inferior CHRPE (RE), which remained stable. Coincidental "de novo" appearance, with exponential growth, of an adjacent melanoma in the nasal inferior choroid at presentation (**a**) and two years (**b**), four years (**c**) and five years (**d**) after initial presentation.

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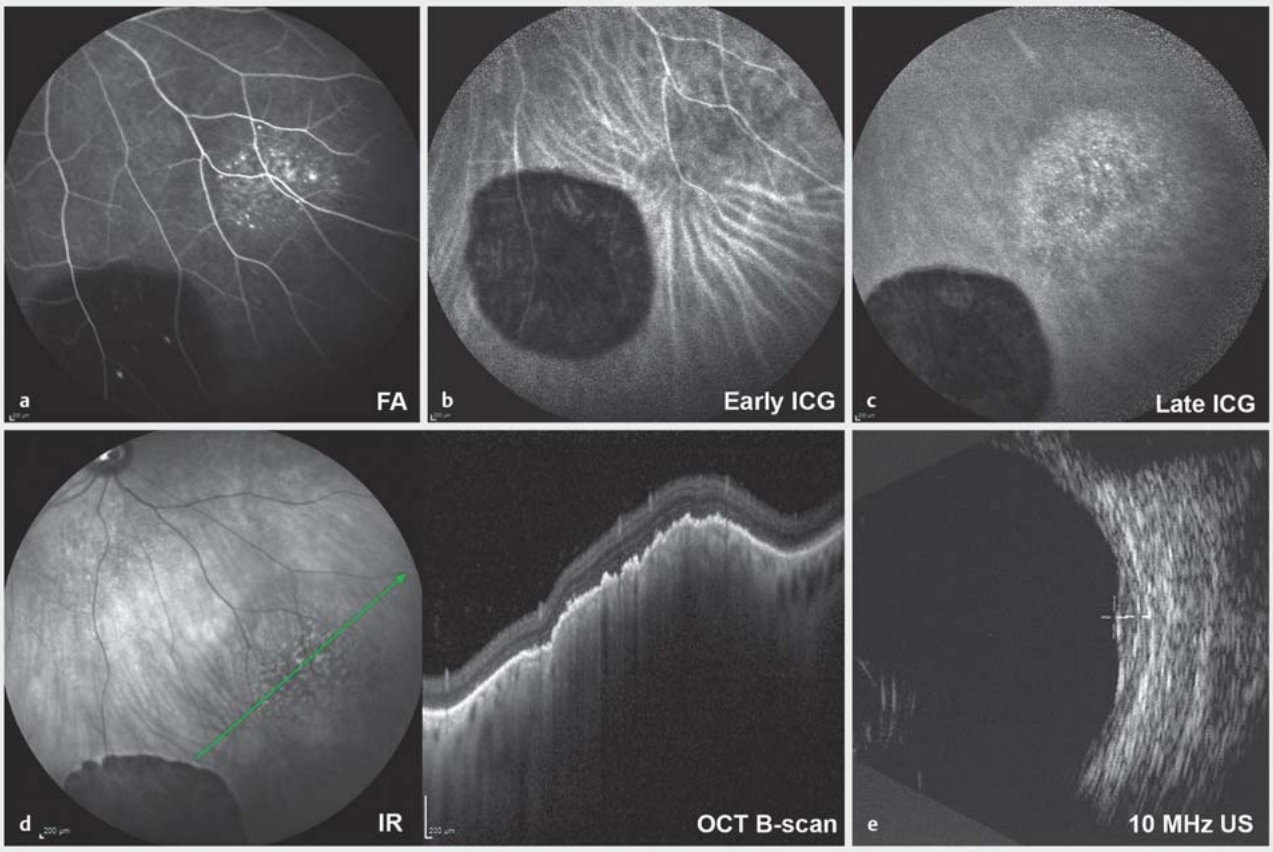

▶ **Fig. 2** Ancillary examinations in a small "de novo" choroidal melanoma (**a–d:** Spectralis; Heidelberg Engineering, Heidelberg, Germany). **a** On FA, pinpoints appear at the tumor's surface. **b, c** On ICG-A, the mass provokes an early masking defect (**b**), followed by a late hyper-cyanescence (**c**). **d** On OCT B-scan, the overlying retina shows no signs of chronicity; there is no subretinal fluid. **e** Tumor thickness is 1.6 mm on 10 MHz B-scan ultrasonography

phoria. Systemic history was unremarkable. Best-corrected Snellen visual acuity was 1.0, with a correction for mild myopic astigmatism OU. Intraocular pressure was 11 mmHg OU. She had a routine fundus examination and was found to present a congenital hypertrophy of the retinal pigmented epithelium (CHRPE) in her right eye (▶ **Fig. 1a**). Being informed of its minimal risk of malignant transformation into RPE (retinal pigment epithelium) adenocarcinoma [10], the patient solicited periodic fundus examinations, including color fundus photography (▶ **Fig. 1b, c**). Five years later, a second grey brown lesion was discovered in the adjacent nasal choroid (▶ **Fig. 1d**), with a thickness of 1.6 mm on 10 MHz B-scan ultrasonography (▶ **Fig. 2e**). A retrospective analysis of the fundus pictures (▶ **Fig. 1**) illustrated the emergence, with exponential growth, of a pigmented choroidal tumor. On fluorescein angiography (FA), pinpoints could be observed at the surface of the lesion (▶ **Fig. 2a**). During indocyanine green angiography (ICG-A), the mass first provoked a relative masking defect, and subsequently a late hyper-cyanescence (▶ **Fig. 2b, c**). On B-scan optical coherence tomography (OCT), there was no perilesional fluid. The overlying retina did not show any signs of a chronic "trophic" degeneration (▶ **Fig. 2d**), such as the loss of its layered structure, outer segment atrophy, or intraretinal cysts, which are often observed in association with an aged choroidal nevus. The diagnosis of a "de novo" choroidal melanoma was made. Conservative brachytherapy with a ruthenium plaque was proposed. The patient opted to be treated in her own country and was lost to follow-up.

Discussion

We describe a rare case where serial panoramic fundus photography, because of a CHRPE, coincidentally documented the "de novo" appearance of a peripheral choroidal melanoma over a period of 5 years.

The percentage of choroidal melanomas arising "de novo" is not known. A literature search, using PubMed/Medline databases from 1988 to 2021, with the key words "de novo" AND "choroidal melanoma", revealed only 2 similar cases. In 1988, before the era of panoramic fundus photography, Sahel et al. was the first to describe the "de novo" occurrence of a large peripapillary melanoma arising in a 71-year-old female screened 16 months previously for diabetic retinopathy. While on the initial color fundus and FA pictures no pigmented le-

sion can be seen at the posterior pole, the patient presented less than 1.5 year later with loss of vision, a cataract obscuring fundus view, and a 11-mm thick mushroom shaped lesion on B-scan ultrasonography. The patient was treated with enucleation. The implications as to the then presumed slow growth rate of choroidal melanoma and presence of precursor lesions are consequently discussed and questioned by the author [7]. Aleksidze et al. reported arguably the second case in 2015 of a 22-year-old white male, in whom at the age of 10 a "presumed freckle" had been observed, which was photo documented for the first time at the age of 15. Interestingly, despite the diagnosis of a "freckle" and not a "nevus", the lesion had been observed periodically, with proof of growth and the clinical diagnosis of a small macular melanoma 12 years after initial fundus examination. Iodine plaque therapy was performed [8]. Compared with these two cases, our report benefits from modern fundus imaging techniques, and provides, for the first time, doubtless and high-quality photographic proof of the fact that and how a choroidal melanoma can develop "de novo".

"Multimodal imaging is now an indispensable tool in ocular oncology for better definition of intraocular tumor features and surrounding tissue alterations," confirmed the Shields et al. in their recent article on risk factors for transformation of 2355 choroidal nevi into melanoma [5]. These risk factors, including tumor thickness > 2 mm, subretinal fluid, visual acuity of 20/50 or worse, detection of orange pigment, ultrasound acoustic hollowness, and tumor diameter > 5 mm, add up to a cumulative "risk" score [11]. Interestingly, only the tumor's diameter (> 5 mm or ~ 4DD) can be identified as a positive risk factor on the fundus photo (▶ **Fig. 1 d**). The pinpoints observed on the invasive, and therefore less accessible, FA are the only other risk factor revealed by multimodal imaging of this "de novo" melanoma. While proposing their MOLES model for analyzing pigmented lesions, Roelofs et al. stated that de novo melanomas might initially present with a low MOLES score and therefore be misdiagnosed. In our case, even if the resident (▶ **Fig. 1 c**) had noted the second lesion, its MOLES score would have been at most 2 (1 point for diameter of 3–4 DD and 1 point for unsure enlargement with regard to the first presentation (▶ **Fig. 1 b**) [6].

Conclusion

To the best of our knowledge, this case report provides, for the first time, doubtless and high-quality serial panoramic photographic proof of "de novo" appearance and development of a choroidal melanoma. On multimodal fundus imaging, this "de novo" melanoma did not present the usual risk factors, well known for the evaluation of melanomas arising from pre-existing nevi.

Conflict of Interest

The authors declare that they have no conflict of interest.

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