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Endoscopic enucleation and clinicopathologic correlation of a small choroidal melanoma hiding massive extrascleral extension☆

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ABSTRACT

Purpose: To report the unusual case of a previously stable choroidal nevus, closely followed for over 15 years, which underwent malignant transformation into small choroidal melanoma with massive extrascleral extension.
Observations: A 67-year-old Caucasian female was referred to the Stanford Ocular Oncology Service with concern for malignant transformation of a previously stable choroidal nevus in her left eye. Her funduscopic examination demonstrated a dome-shaped choroidal lesion with overlying associated lipofuscin and subretinal fluid, consistent with a diagnosis of small choroidal melanoma. By B-scan ultrasonography, the lesion measured 8.0 × 6.0 mm in base and 2.1 mm in thickness. B-scan ultrasonography also disclosed an associated retroscleral mass, which appeared contiguous with the intraocular melanoma and was confirmed on subsequent orbital magnetic resonance imaging. A decision was made to proceed with enucleation. Under direct endoscopic visualization, the globe and extrascleral mass were fully isolated, mobilized, and removed *in toto*. At 24 months post-enucleation, the patient remains disease-free without evidence of systemic metastasis or local recurrence.
Conclusions/importance: This case describes a small choroidal melanoma hiding massive extrascleral extension, underscoring the value of B-scan ultrasonography. This case also describes the unique management of choroidal melanoma with extrascleral extension using endoscopic enucleation. Performing enucleation under direct endoscopic visualization ensures complete resection and prevents inadvertent transection of the extrascleral component.

1. Case report

A 67-year-old Caucasian female with no significant personal or family medical history was followed from 2004 to 2019 with serial fundus examination and photography of an asymptomatic and reportedly stable choroidal nevus of her left eye (OS) (Fig. 1A). In 2019, she became symptomatic with progressive metamorphopsia and blurred vision OS. Examination revealed concern for growth along the inferior border of the lesion (Fig. 1B), prompting further evaluation at a tertiary referral center by ocular oncology.

On examination at the tertiary referral center in late 2020, visual acuity measured 20/20 in the right eye (OD) and 20/25 OS. Examination of the anterior segment of both eyes and fundus OD was unremarkable. Fundoscopy OS revealed a dome-shaped elevation measuring 6.0 × 8.0 mm at base and extending inferiorly from the macula (Fig. 2A). Associated orange lipofuscin pigment and subretinal fluid were clinically visualized and later confirmed by fundus autofluorescence and optical coherence tomography (OCT) (Fig. 2B–D).

Transverse sections on B-scan ultrasonography revealed an intraocular dome-shaped choroidal mass with low internal reflectivity and thickness of 2.1 mm. B-scan also identified an associated retroscleral mass with low internal reflectivity, measuring 5.8 mm in width and 7.5 mm in thickness (Fig. 3A). Subsequently, high-resolution magnetic resonance imaging (MRI) of the orbits was obtained, confirming a thin intra-ocular component with associated T2 hyperintense intraconal mass. (Fig. 3B). The extraocular mass was well-circumscribed and abutting the optic nerve. Systemic work up, including positron emission tomography computed tomography (PET CT) scan, revealed no evidence of metastasis. Incidentally identified thyroid nodules were biopsied and found to be benign.

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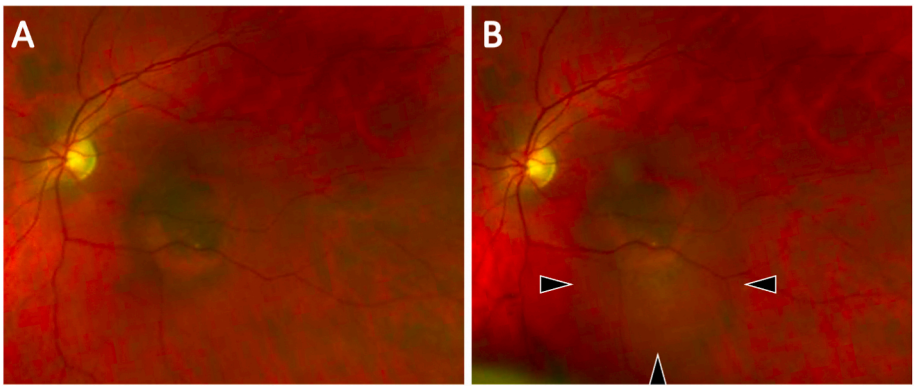

Fig. 1. Scanning laser ophthalmoscopy photographs from 2017 **(A)** reveals a stable choroidal nevus, which underwent malignant transformation in 2019 **(B)** along its inferior border, prompting ocular oncologic referral.

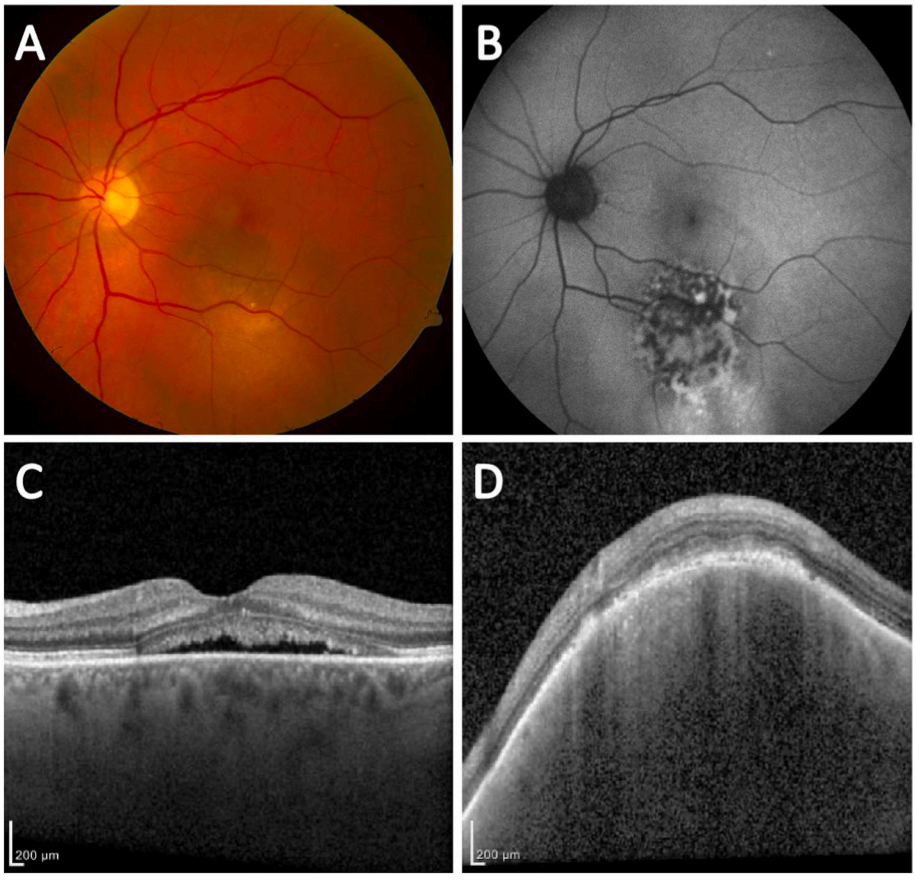

Fig. 2. Fundoscopy in 2020 **(A)** reveals an ovaloid dome-shaped elevation extending inferiorly from the macula. Overlying this elevation were the original choroidal nevus and a contiguous amelanotic choroidal mass. On fundus autofluorescence **(B)**, the inferior lesion demonstrates patchy hyper-autofluorescence, consistent with orange lipofuscin pigment and a diagnosis of melanoma. Enhanced depth imaging (EDI) OCT through the central fovea **(C)** shows edematous ("shaggy") photoreceptors overlying a pocket of subretinal fluid. EDI-OCT over the lesion **(D)** shows a dome-shaped choroidal mass with outer retinal disruption, shallow SRF, and moderate choroidal shadowing. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

A presumptive diagnosis of choroidal melanoma with massive extrascleral extension (ESE) was made. Given the extent of presumed ESE, treatment options including enucleation, exenteration, and radiation therapy were discussed. Ultimately, the patient elected to proceed with enucleation.

Given the posterior location of the extrascleral component in this case, and its proximity to the optic nerve, the decision was made to perform the enucleation under endoscopic visualization to avoid inadvertent transection of the extrascleral component with subsequent orbital seeding. Following isolation of the rectus muscles, an endoscope was inserted through the superior aspect of the orbit. Under endoscopic visualization, orbital fat was dissected using a hand-over-hand technique in all quadrants until the posterior sclera, optic nerve, and retrobulbar mass were fully isolated (Fig. 3C). Then, under direct visualization, the optic nerve was cross-clamped posterior to the mass and transected. The globe and extrascleral mass were removed *in toto* (Fig. 3D).

A fine-needle biopsy performed on the extrascleral portion was sent for gene expression profile testing (DecisionDx-UM, Castle Biosciences Inc, Friendswood, TX) and identified the tumor as Class 1A, conferring a favorable 5-year-metastasis risk of 2%. The remainder of the enucleation sample was analyzed by ocular pathology.

Histological evaluation of the enucleation sample (Fig. 4A) demonstrated an intraocular choroidal neoplasm with thickness of 1.7 mm and largest basal diameter (vertical) of 5.7 mm. The lateral intraocular component was comprised of melanoma cells in a dense spindle configuration, while the medial portion consisted mostly of pigment-laden macrophages resembling clear ("balloon") cells. The extrascleral

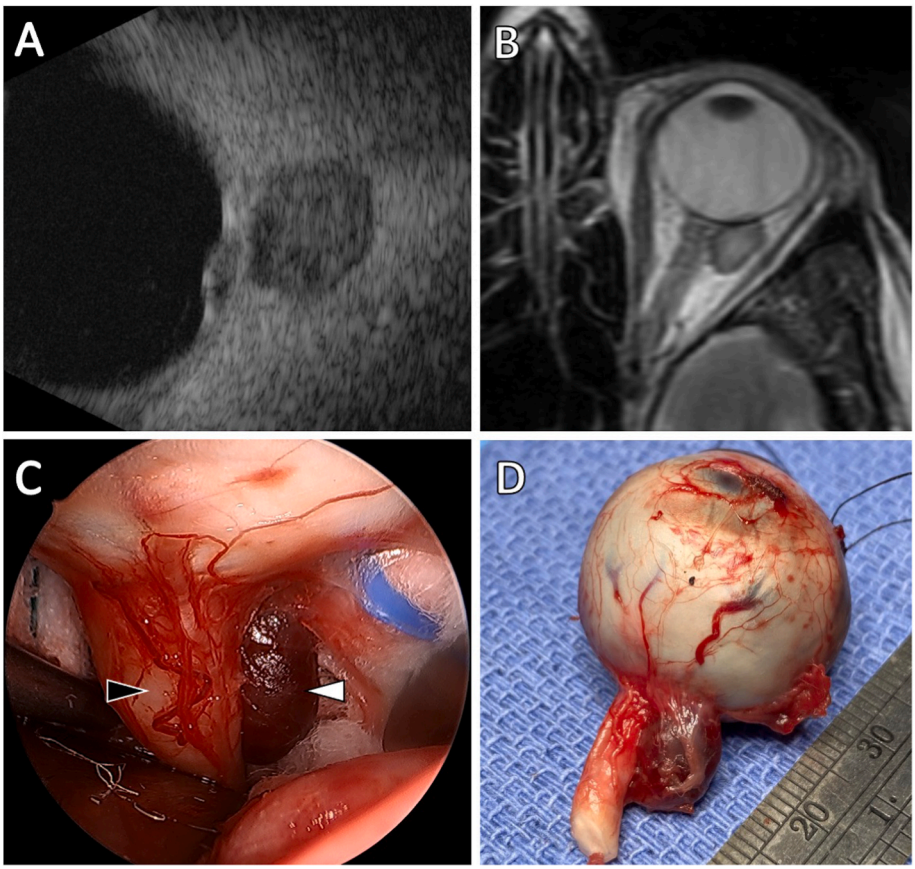

Fig. 3. Transverse section on B-scan ultrasonography **(A)** and magnetic resonance imaging **(B)** depict a small intraocular dome-shaped choroidal mass and an associated extrascleral mass. The pigmented extrascleral tumor **(white arrowhead)** abuts the nerve **(black arrowhead)** on endoscopic **(C)** and gross visualization **(D)**.

portion measured 10 mm × 5 mm x 5 mm and was surrounded by a fibrous pseudo-capsule. An extrascleral portion containing mostly spindle morphology was observed with resultant scleral bowing. There was possible seeding within orbital fat. Although full thickness transit of the sclera was not directly visualized, contiguous extension from the intraocular portion was highly suspected given extravascular envelopment of emissary vessels within the sclera (Fig. 4C and D). No optic nerve involvement was detected. The tumor was diffusely positive for Melan A stain and negative for PRAME. BAP-1 nuclear expression was retained. Ki-67 proliferation index was estimated at up to 4%.

Following enucleation, the patient received post-enucleation radiotherapy to the left orbit consisting of 60 Gy in 30 fractions.

The patient's disease has remained in remission for 24 months since enucleation. Continued surveillance is planned according to NCCN guidelines for low-risk uveal melanoma.

2. Discussion

This case illustrates the potential diagnostic challenge of differentiating choroidal nevus from small choroidal melanoma early in its natural course. Initially, the clinical characteristics of this small melanocytic choroidal lesion were more consistent with a nevus than small melanoma. The only high-risk feature present in this case was longstanding nevus-associated SRF since 2017. SRF can be observed in association with chronic nevi as a result of RPE dysfunction or choroidal neovascularization. In retrospect, the SRF observed in this case likely reflected vascular leakage from nascent melanoma[1,2] or mechanical compression of choroidal vasculature[3] by an undiagnosed extrascleral component. By the time the intraocular melanoma was recognized, extrascleral growth had likely already been underway for months to years based on melanoma doubling times.[4–6]

A complete work up of pigmented choroidal tumors should include B-scan ultrasonography, which might have led, in this case, to earlier detection of extrascleral extension (ESE) and thus a timelier diagnosis of melanoma. However, histopathological studies also indicate that B-scan ultrasonography has low sensitivity for detection of posterior ESE, identifying only 1 of 9 cases of histologically proven posterior ESE.[7,8] The authors estimate the ESE thickness must likely exceed 2 mm for reliable sonographic detection.[7,8] The true rate of ESE in uveal melanoma at time of diagnosis therefore likely exceeds the 5.8% reported by Shields et al. based on their clinical and ultrasonographic evaluation of 2135 patients with posterior choroidal melanomas.[9]

Classically, the presence of ESE has indicated a locally invasive pattern of growth and has been correlated with poor prognosis and metastatic death. ESE is more commonly seen in tumors with large basal size, anterior location, and cytogenetic abnormality (e.g. monosomy 3 status).[10] However, our case and others[11] show that ESE can occur in the absence of aggressive biological tumor behavior. In this case, the tumor was relatively small (largest basal diameter <8 mm, thickness 2.1 mm) and posteriorly located without ciliary body involvement. The tumor had relatively low-grade histopathologic features, including low mitotic activity by Ki-67 proliferation index and spindle A morphology. The tumor was characterized as class 1A, the lowest metastatic risk category, by gene expression profile (GEP) analysis, with negative PRAME expression, and retained BAP-1 expression. This constellation of clinicopathologic, histopathologic, and genetic features is highly suggestive of low metastatic risk.

It is conceivable that ESE may contain multiple subtypes defined by the pattern of extension. In our case, histological examination revealed likely contiguous tumor spread through posterior scleral emissary canals

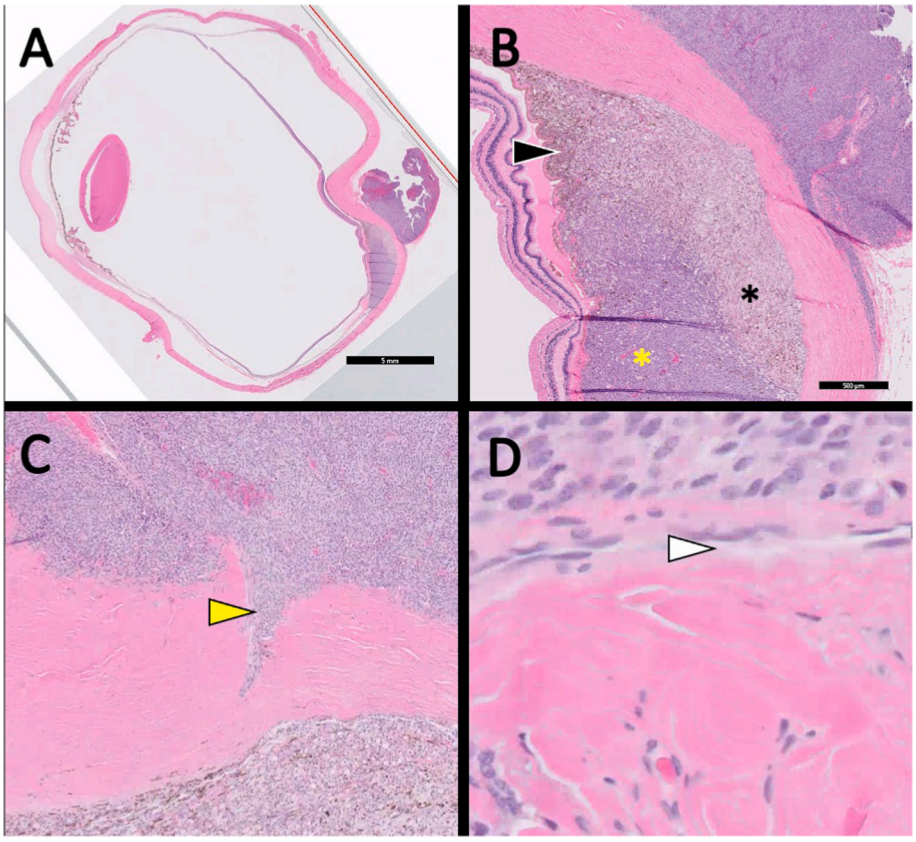

Fig. 4. Histological evaluation of the enucleation sample **(A)** shows a small intraocular tumor and artifactually fragmented extrascleral component. Low power microscopy **(B)** reveals an intraocular choroidal mass comprised of heavily pigmented melanocytes **(black arrowhead),** loosely arranged clear cells **(**black **asterisk)**, and denser melanoma cells in spindle A configuration **(yellow asterisk)**. High power microscopy reveals **(C)** presumed extension through a posterior scleral emissary canal. **(D)** Melanoma cells are seen tracking a scleral lumen **(white arrowhead)**. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and outer scleral layer infiltration. Notably, the scleral infiltration occurred horizontally (between scleral fiber layers) as opposed to vertically (through scleral fiber layers). These findings reflect a "pushing" pattern of tumor growth along a path of least resistance through tissue planes, as opposed to bona fide invasion through scleral layers. Other reports describe a similar pattern of growth in low-risk melanoma.[11]

The suggestion that ESE represents intraocular growth through a path of least resistance is supported by a large-scale study by Coupland et al. examining routes of ESE spread.[12] Coupland et al. report that the preferred route of extension — whether through aqueous drainage, venous, arterial, or neural channels — depended mostly on intraocular tumor location and hence the likelihood of tumor extension into the given scleral emissary canal. Tumors displayed no propensity to invade a specific type of channel independent of location.[12] Thus, factors such as large tumor size, anterior location, and monosomy 3 may rather reflect an intraocular tumor's ability to reach emissary canals than its innate propensity to invade such canals. In other words, while biologically aggressive tumors are more likely to exhibit ESE, ESE on its own is likely a poor surrogate for tumor behavior. Indeed, Damato et al. demonstrated that some conventional clinical risk factors, including ESE, lost prognostic significance with regards to metastatic risk when cytogenetic data were analyzed.[13]

Histological evaluation of the intraocular tumor also revealed the presence of a significant clear cell component. With an estimated prevalence of just 0.1%, this finding is rarely associated with choroidal melanoma.[14] Electron microscopy suggests these clear cells might represent altered melanocytes undergoing metamorphosis, with degeneration of intracellular melanosomes.[15] In our case, staining of the clear cell component with Melan A confirms this possibility. Clear cell presence has been associated with spontaneous melanoma regression, indicating a possible positive prognostic factor. This may also explain clear cell association with the depigmented zone of halo nevus,[16] a reported protective factor against malignant transformation.[1,2] Interestingly, the clear cells in our case also stained for CD163, which is a scavenger receptor marker specific to macrophages.

In summary, we present the case of a 67-year-old Caucasian female followed for 15 years for a stable and asymptomatic choroidal nevus. Further workup and imaging with B-scan ultrasonography, and MRI revealed massive ESE. The globe and extrascleral mass were enucleated *in toto*, and histological analysis demonstrated choroidal melanoma with extrascleral extension likely along the emissary vessels. Extrascleral extension especially through emissary vessels, in and of itself, might not portend poor prognosis, as molecular analysis suggests this malignancy is low risk.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

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References

1. Shields CL. Choroidal nevus transformation into melanoma: analysis of 2514 consecutive cases. *Arch Ophthalmol*. 2009;127(8):981–987.
2. Dalvin LA, Shields CL, Ancona-Lezama D, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. *Br J Ophthalmol*. 2018;103(10):1441–1447.
3. Yu MD, Dalvin LA, Ancona-Lezama D, et al. Choriocapillaris compression correlates with choroidal nevus–associated subretinal fluid: OCT analysis of 3431 cases. *Ophthalmol*. 2020;127(9):1273–1276.
4. Char DH. Uveal melanoma. *Arch Ophthalmol*. 1997;115(8):1014.
5. Sumich P. Choroidal nevi in a white population. *Arch Ophthalmol*. 1998;116(5):645.
6. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. *Ophthalmol*. 2005;112(10):1784–1789.
7. Burris CKH, Papastefanou VP, Thaung C, et al. Detection of extrascleral extension in uveal melanoma with histopathological correlation. *Orbit*. 2018;34(7):287–292.
8. Martin JA, Robertson DM. Extrascleral extension of choroidal melanoma diagnosed by ultrasound. *Ophthalmol*. 1983;90(12):1554–1559.
9. Shields JA, Shields CL. Massive orbital extension of posterior uveal melanomas. *Ophthalmic Plast Reconstr Surg*. 1991;7(4):238–251.
10. Affeldt JC, Minckler DS, Azen SP, Yeh L. Prognosis in uveal melanoma with extrascleral extension. *Arch Ophthalmol*. 1980;98(11):1975–1979.
11. Papadopoulou D, Moulin AP, Zografos L, Schalenbourg A. How would you manage this small melanocytic choroidal tumour? *Br J Ophthalmol*. 2012;96(12):1530.
12. Coupland SE, Campbell I, Damato B. Routes of extraocular extension of uveal melanoma. *Ophthalmol*. 2008;115(10):1778–1785.
13. Damato B, Eleuteri A, Fisher AC, et al. Artificial neural networks estimating survival probability after treatment of choroidal melanoma. *Ophthalmol*. 2008;115(9):1598–1607.
14. Grossniklaus HE, Albert DM, Green WR, et al. Clear cell differentiation in choroidal melanoma. *Arch Ophthalmol*. 1997;115(7):894.
15. Khalil MK. Balloon cell malignant melanoma of the choroid: ultrastructural studies. *Br J Ophthalmol*. 1983;67(9):579–584.
16. Hashimoto K. Ultrastructural studies of halo nevus. *Cancer*. 1974;34(5):1653–1666.