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BRIEF REPORT

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Retinal pigment epithelium adenoma in vitreous fluid cytology

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Abstract

Ocular cytology specimens are relatively uncommon, adding to the difficulty of their evaluation by cytopathologists. While melanomas account for a majority of primary intraocular pigmented lesions, other diagnostic considerations must be included in the differential. This brief report highlights a case of a pigmented ocular lesion in a 24-year-old man and key morphologic, immunohistochemical, and clinical differences between melanoma, melanocytoma, choroidal nevus, and retinal pigment epithelium (RPE) adenoma.

KEYWORDS

retinal pigment adenoma, melanoma, melanocytoma, choroidal nevus, vitreous fluid

1 | INTRODUCTION

Pathology specimens from ocular sites are typically paucicellular, as only a small amount of material can be extracted without significant detriment to patients, which primes evaluation of these specimens by cytology. Fine-needle aspiration (FNA) is commonly utilized for initial evaluation of ocular lesions and can be useful in guiding appropriate clinical management.[1] FNA is particularly useful in cases where there is diagnostic uncertainty and a microscopic diagnosis is required to make a therapeutic decision, a patient refuses treatment without a definitive diagnosis, or tissue is needed for prognostication. However, the rarity of these specimens and the inexperience of many pathologists in the diagnosis of ocular lesions make these cases exceptionally challenging.

The most common primary intraocular neoplasm encountered in adults is melanoma. The sensitivity of cytology in detecting ocular melanomas ranges from 90% to 100%[2,3] with a specificity of 98%.[3] While large confirmed melanomas can lead to enucleation, other smaller melanomas may be treated with radiation therapy. In patients with carcinomas of other sites, it is important to rule out metastasis, as metastatic carcinomas involving the eye are typically treated with radiation. Fortunately, morphology on cytologic specimens often allows for the differentiation of melanomas from most carcinomas, which often display cohesive clusters. However, other benign pigmented ocular lesions are more difficult to distinguish from melanoma and may lead to false-positive diagnoses. The following case report highlights diagnostic considerations of intraocular pigmented retinal lesions on cytology.

2 | CASE REPORT

A 24-year-old African-American man presents with persistent right-sided cloudy vision for a week prior to presentation. Initial evaluation by ultrasound, fluorescein angiogram, and dilated fundus exam identified a right ciliary tumor. Echographic examination of the right eye identified a 7.8 mm irregular lesion with internal vascularity that extended from the ciliary body into the posterior segment and numerous pigmented vitreous seeds.

A FNA of the vitreous fluid was processed into a ThinPrep slide and cell block. The aspirate material was moderately cellular (Figure 1) but the cell block material had insufficient cellularity for evaluation. On higher power evaluation, cells characterized by an abundant amount of cytoplasm containing brown-pigmented granules that often obscured evaluation of nuclear features were arranged singly and in occasional loosely cohesive clusters. Scattered cells in which the nuclei were not completely obscured showed bland nuclei with round and smooth nuclear contours, even granular chromatin distribution, and inconspicuous nucleoli (Figure 2A-C). Although the presence of melanin was concerning for melanoma, the lack of atypia gave rise to the possibility of other less common pigmented ocular lesions including melanocytoma and retinal pigmented epithelium adenoma. Given the clinical concern and possibility for melanoma, the patient underwent surgical excision of the 1.0 cm ocular mass, which ultimately revealed RPE adenoma. The tumor emanated from the RPE and was characterized by heavily pigmented neoplastic cells with bland nuclei arranged in cords and

FIGURE 1 Moderately cellular ThinPrep slide preparation of vitreous fluid (ThinPrep, 10×) [Color figure can be viewed at wileyonlinelibrary.com]

trabeculae separated by fibrous septae (Figure 3A-B). There was no overt pleomorphism or ciliary body, adjacent retinal, or scleral invasion.

3 | DISCUSSION/CONCLUSION

As stated previously, the most frequently encountered intraocular neoplasm is melanoma.[1] Melanomas are typically rich cellular cytology specimens of epithelioid and/or spindled cells. Epithelioid melanomas are characterized by poorly cohesive, round, and pleomorphic cells with coarse chromatin distribution and prominent macronucleoli. Spindled melanomas, in contrast, display loosely cohesive groups of spindled cells with finely distributed chromatin, small nucleoli, and occasional nuclear grooves.[4] Cytoplasmic pigment granules can range from fine to coarse and are helpful diagnostic features of melanomas. However, not all cells with cytoplasmic pigment granules are melanomas. The differential of epithelioid intraocular pigmented lesions includes but is not limited to a melanoma, nevus, melanocytoma, and, as in the case presented, RPE adenoma (Table 1).

Choroidal nevi are typically small, but can present as larger lesions that mimic melanomas. However, on cytologic evaluation, these nevi commonly present as cohesive cells, rather than the singly dispersed cells in melanomas.[5] Additionally, choroidal nevi, even larger ones, lack the coarse chromatin distribution and prominent nucleoli that are characteristic of melanomas.[1] Nevi of the iris can be particularly difficult to distinguish from melanomas on morphology alone as they can also display large, round nuclei, coarse chromatin distribution, and prominent nucleoli.[6] However, in both choroidal and iris locations, the clinical picture of a slow-growing lesion is more in keeping with a nevus, which differs from the prototypical rapid progression and growth of melanomas.

Melanocytomas are rare, low-grade pigmented tumors that account for <0.1% of CNS tumors. They are commonly located in proximity to the optic disc but can also be located in the iris, ciliary body, choroid, or conjunctiva. Clinically, they appear as deeply pigmented lesions with few visual symptoms.[7] Microscopically, these lesions are composed of large cells with low nuclear-to-cytoplasmic ratios that display small, bland, round to ovoid nuclei and abundant cytoplasm. The cells frequently are densely pigmented and the abundance of cytoplasmic granules often obscures nuclear details. Mitotic

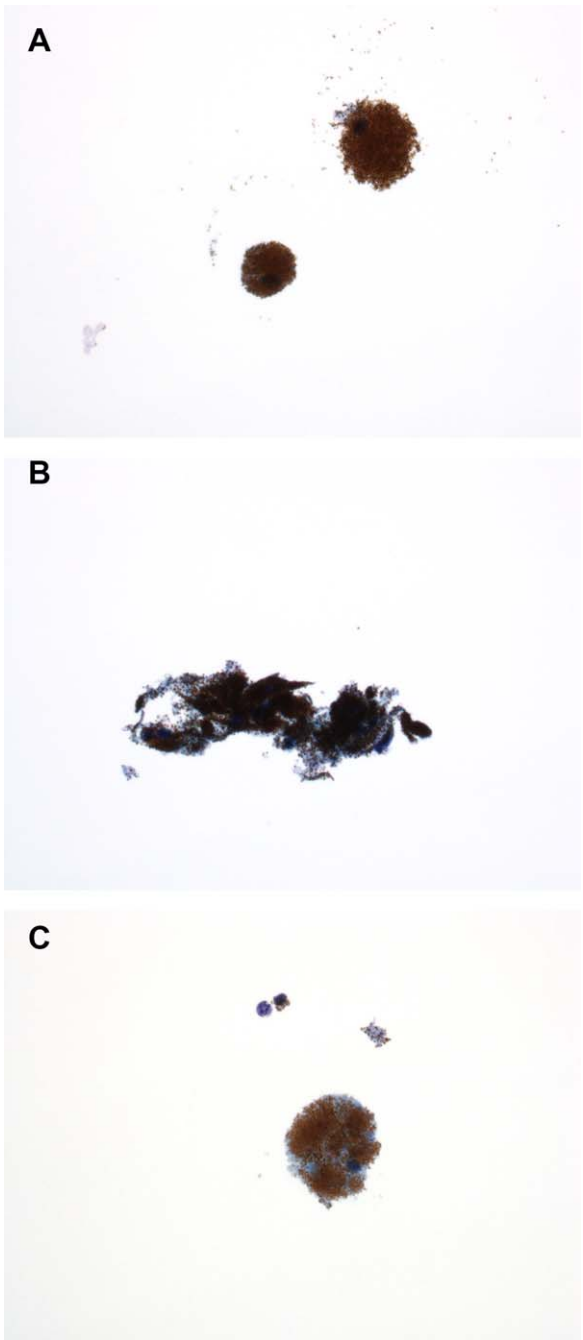

FIGURE 2 A, Singly dispersed cells with an abundant amount of cytoplasm filled with dark brown pigmented granules (ThinPrep, 40×). B, Pigmented cells were also occasionally arranged in loosely cohesive cell clusters (ThinPrep, 40×). C, In cells where the cytoplasmic pigment did not completely obscure nuclear features, small, round nuclei with smooth contours and inconspicuous nucleoli were identified (ThinPrep, 40×) [Color figure can be viewed at wileyonlinelibrary.com]

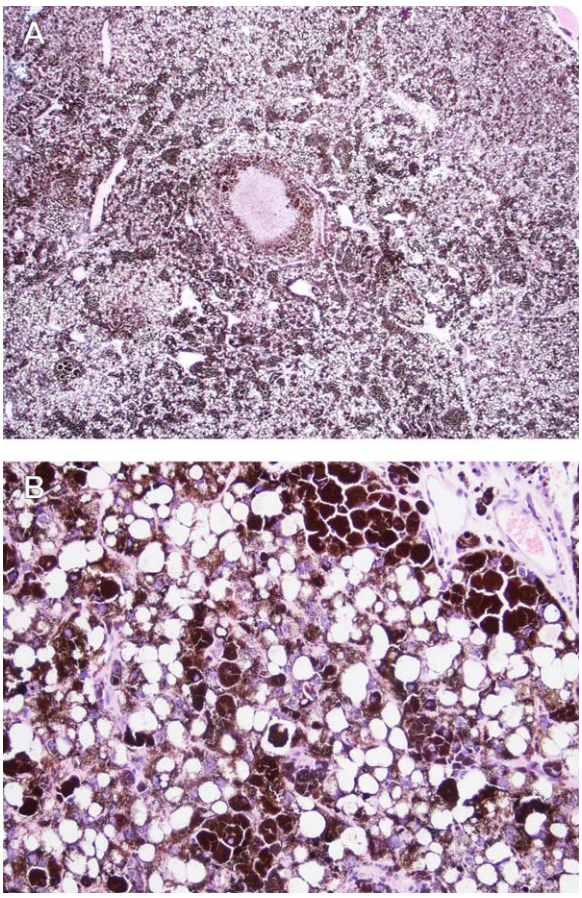

FIGURE 3 A, Cords and trabeculae of neoplastic pigmented cells separated by fibrous septae (H&E, 2×). B, Neoplastic cells with eccentrically placed bland nuclei, smooth nuclear contours, and variably distinct nucleoli show densely pigmented cytoplasm that obscures nuclear features. Some neoplastic cells show intracellular vacuoles (H&E, 20×) [Color figure can be viewed at wileyonlinelibrary.com]

figures, necrosis, and pleomorphism, which often are apparent in melanomas, are not present.

Retinal pigment epithelial cells can proliferate as a result of retinal tears and detachments (in which case macrophages, fibroblasts, myofibroblasts, and vitreous cells are seen), but can also be seen in benign neoplasms such as RPE adenomas. RPE adenomas are uncommon and may clinically mimic the appearance of ocular melanomas.[8] They frequently present as pigmented nodular lesions with abrupt elevation in adults lacking a history of ocular trauma or inflammation. On cytology, these lesions display round cells with eccentrically placed round to ovoid nuclei and abundant granular cytoplasm. There is usually mild nuclear and nucleolar size variation and large melanosomes. A subset of these lesions, particularly those in the anterior region of the retinal pigment epithelium, can display cytoplasmic vacuolation secondary to the accumulation of hyaluronidase resistant acid mucopolysaccharides.[8,9] However, in contrast to many epithelioid melanomas, exuberant nuclear pleomorphism is not a characteristic finding.[9] Rare mitoses can be identified, but are not numerous. In cytologic cases with exuberant nuclear pleomorphism, multiple nucleoli, and abundant mitoses, a RPE adenocarcinoma may be considered. However, definitive differentiation between RPE adenomas and adenocarcinomas can be exceedingly difficult on cytologic examination alone.

In cases where there is sufficient cellularity for cell block production, immunohistochemistry can be a helpful tool in differentiating pigmented ocular lesions. Melanomas are positive for S100, HMB-45, Melan-A, and SOX-10. RPE adenomas, in contrast, are positive for EMA, S100, NSE, and synaptophysin and are negative for HMB-45 and Melan-A. While the immunoprofile of melanocytomas are similar to melanomas Ki-67 would denote the lower proliferation index of a melanocytoma. The combination of bland morphologic features, dense cytoplasmic granularity of cells obscuring visualization of nuclei, and low mitotic index would be suggestive of a melanocytoma.

The differentiation of these ocular lesions can have a significant impact in patient management. Melanomas are frequently treated by enucleation, while benign lesions such as RPE adenomas and nevi may be treated conservatively by means of observation, local resection, and, possibly, radiation therapy. While melanocytomas may also be treated conservatively, they are commonly resected due to their tendency to grow and increase intraocular pressure. Given the overall infrequency of these samples and the clinical weight of diagnoses of ocular lesions, it is important to interpret morphologic features within the clinical context, emphasizing the importance of close communication between pathologists and clinicians.

TABLE 1 Gross, cytologic, and immunohistochemical features of pigmented ocular lesions

	Melanoma	Melanocytoma	Choroidal nevus	Retinal pigmented epithelial adenoma
Gross features	· Pigmented · Poorly circumscribed	· Deeply pigmented · Dome-shaped or sessile · Well-circumscribed	· Pigmented · Small (typically <0.5 cm)	· Deeply pigmented (dark grey to black); occasionally nonpigmented · Nodular growth with abrupt elevation from normal retinal pigmented epithelium
Cytologic features	· Discohesive · Prominent nucleoli · Coarse chromatin distribution · Nuclear pleomorphism · Fine to coarse cytoplasmic pigment granules · Necrosis · Numerous mitoses	· Discohesive · Small, round to ovoid nuclei · Indistinct nucleoli · Abundant cytoplasm with numerous cytoplasmic pigment granules · Rare mitoses · Lacks pleomorphism	· Cohesive cell clusters · Indistinct nucleoli · Granular chromatin distribution · Fine to coarse cytoplasmic pigment granules · Rare mitoses	· Discohesive and loosely cohesive cell clusters · Epithelioid and/or spindled neoplastic cells · Mild nuclear and nucleolar size variation · Large melanosomes · Rare mitoses · May have vacuolated cytoplasm
Immunohistochemical profile	*Positive* S100 HMB-45 Melan-A MiTF-1 SOX-10	*Positive* S100 HMB-45 Melan-A	*Positive* S100 MiTF-1 NSE *Negative* HMB-45 Melan-A	*Positive* S100 EMA Cytokeratin NSE Synaptophysin *Negative* HMB-45 Melan-A

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

None.

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