



## Cytological-Pathologic Correlation

Choroidal melanoma diagnosed by aspiration cytology: A case report with cyto-histologic correlation and review of the literature<sup>☆</sup>Daniel W. Abbott<sup>a</sup>, Kenneth Simons<sup>a,b</sup>, Tamara Giorgadze<sup>a,\*</sup><sup>a</sup> Department of Pathology, Medical College of Wisconsin, Milwaukee, WI, United States of America<sup>b</sup> Department of Ophthalmology and Visual Sciences, Medical College of Wisconsin, Milwaukee, WI, United States of America

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## ABSTRACT

Histologic and cytologic features of uveal melanomas have been well characterized; however, cytologic-histologic correlation has rarely been described in detail in the literature. A 50-year old female presented at our institution with an intraocular mass which was diagnosed as choroidal melanoma by aspiration cytology. The patient subsequently proceeded to enucleation, confirming the diagnosis. Cytology revealed epithelioid cells containing melanin pigment and only mild nuclear atypia. The enucleation specimen contained 90% epithelioid cells with similar cytomorphology and an additional 10% spindle cell component not observed in the aspiration cytology. In summary, we present a case of choroidal melanoma showing high concordance between cytologic and histologic morphologic features.

## 1. Introduction

Uveal melanoma is the most common primary intraocular malignancy, occurring most frequently in adult Caucasians around the 4th to 6th decades [1,2]. Ocular melanomas (including uveal and conjunctival) comprise around 5% of all melanoma diagnoses of which 85% arise in the uvea [3]. Uveal melanomas (melanomas arising from the iris, ciliary body, and choroid) are often not recognized until they become symptomatic and carry a variable prognosis that correlates with histomorphology [1,3].

While the application of cytology to the diagnosis of uveal melanomas has been well established in the literature, there are very few studies with detailed histologic-cytologic correlation [1,3]. Herein, we present a case report of a patient diagnosed with choroidal melanoma on cytology whose diagnosis was confirmed on subsequent enucleation.

## 2. Case summary

A 50-year old Hispanic female with no known prior medical history presented to a community ophthalmologist with a dense vitreous hemorrhage in the left eye following 1 ½ weeks of decreased vision and blurriness. By the time of clinical presentation, the patient had significant loss of vision in her left eye. Review of symptoms was non-contributory except for occasional headaches. Examination of the

ocular adnexa was unremarkable bilaterally. Extraocular muscles showed full range of motion bilaterally with no nystagmus. Pupils were equal, round, and reactive to light. Slit lamp examination was unremarkable except for mild bilateral cataracts. The right eye showed 20/40 visual acuity with confrontation fields full to finger counting, as well as a normal Amsler Grid evaluation. The left eye showed light perception only. Dilated fundus examination of the right eye was unremarkable while the left eye showed vitreous hemorrhage. A B-scan ultrasound of the left eye revealed the presence of a large subretinal mass with medium to high internal reflectivity. Visualization of the mass was compromised by the presence of hemorrhage.

The patient was subsequently referred to the Medical College of Wisconsin's Eye Institute for further evaluation of the lesion. A follow-up ultrasound of the left eye demonstrated a collar button-shaped choroidal mass adjacent to the optic nerve with persistent vitreous hemorrhage. Although the shape and internal reflectivity of the lesion were not entirely diagnostic, choroidal melanoma was high on the differential diagnosis. The possibility of performing an orbital MRI was discussed; however, the patient was self-paying and elected for observation and to return to the clinic in one month.

The patient showed no changes in symptoms at the follow-up visit. The ultrasound of the left eye obtained at this time was essentially unchanged. At this time, an MRI was obtained, which demonstrated a 6 × 5 × 5 mm choroidal-based mass involving the optic nerve at the

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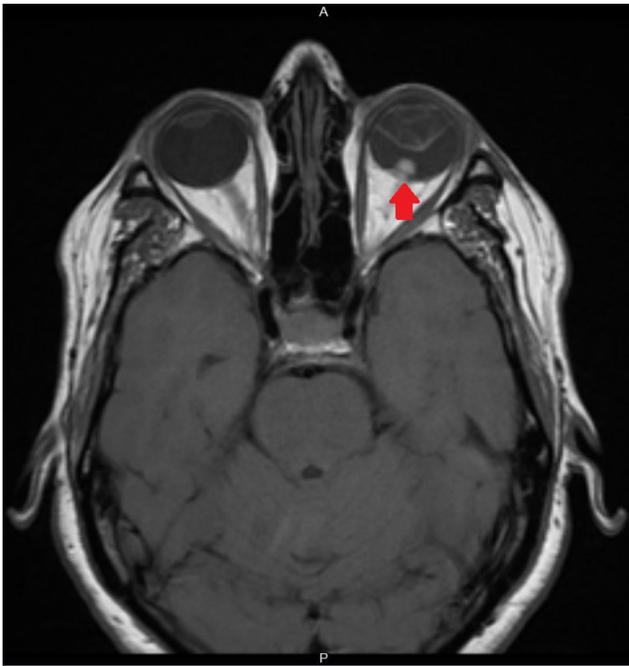


Fig. 1. MRI image showing the location of the lesion (tip of red arrow).

most posterior aspect, concerning for choroidal melanoma (Fig. 1).

In light of the MRI findings, the patient agreed to undergo a pars plana vitrectomy with intraocular mass visualization and sampling to confirm the diagnosis prior to enucleation. After removal of the hemorrhagic fluid, a chocolate-colored pedunculated mass was visualized using binocular indirect ophthalmoscopy (BIOM®). The mass was positioned over the optic nerve and obscured all of the retinal vessels. The top layer of the tumor was removed using a vitreous cutter, collected in a syringe, and sent to cytology.

The cytology laboratory received 5 ml of dark turbid fluid which grossly contained tissue fragments. Two cytospin slides stained with Papanicolaou (PAP) and DiffQuik (DQ) stains as well as a cell block were prepared. Microscopic evaluation revealed a highly cellular specimen with numerous malignant epithelioid cells containing cytoplasmic pigment. Nuclei showed only mild atypia without significant anisonucleosis or prominent nucleoli (Fig. 2; Diff-Quik, 100×). A melanoma cocktail immunostain with red chromogen highlighted the malignant cells, confirming the diagnosis of choroidal melanoma.

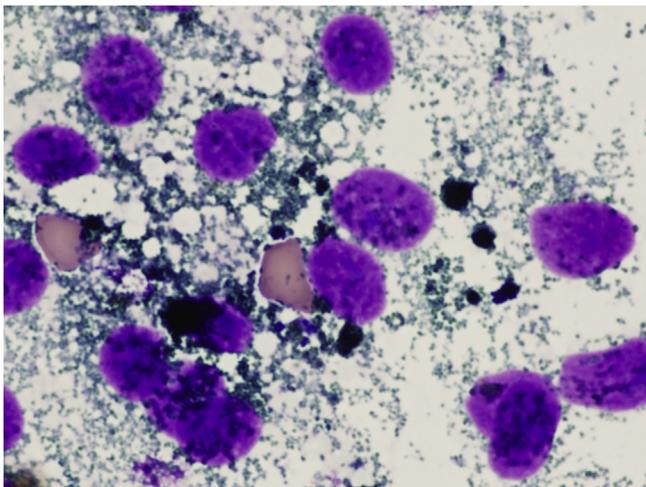


Fig. 2. Cytospin preparation from the intraocular mass sampling (Diff-Quik, 100×).

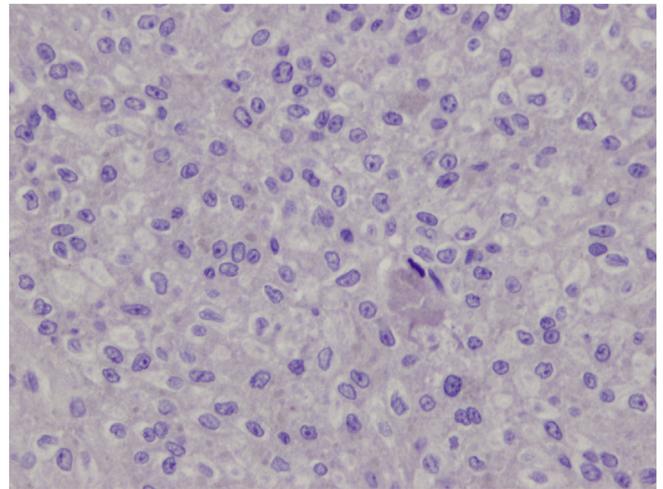


Fig. 3. Enucleation specimen (H + E bleached, 40×).

Within two weeks, the patient underwent enucleation. Gross examination of the eye revealed a black mushroom-shaped mass in the posterior globe attached at the optic disk region. Histologic evaluation revealed a mass composed of predominantly epithelioid cells (90%) with a minor spindle cell component. The mass had a greatest basal diameter of 9 mm and a greatest thickness of 7 mm without extraocular extension (AJCC tumor stage pT2a). Since much of the cytomorphology was obscured by melanin pigment, a bleached slide was prepared which showed epithelioid cytomorphology similar to that from the prior aspirate (Fig. 3; H + E bleached, 40×). All surgical resection margins were negative. Melanoma cocktail immunohistochemistry was positive. Fig. 4 shows slide scan cross-sections of the enucleation specimen unbleached (Fig. 4a), bleached (Fig. 4b), and with melanoma cocktail immunohistochemistry with a red chromogen (Fig. 4c). Molecular testing performed using DecisionDx®-UM and DecisionDx®-PRAME classified the tumor as class 1a and negative, respectively, conferring the lowest risk of metastasis. The patient was fitted for a prosthesis and was recovering well at three months post-enucleation.

### 3. Discussion

Uveal melanomas are relatively uncommon and are often not recognized until they present with symptoms, mainly retinal detachment or hemorrhage. These symptoms are non-specific and naturally carry a wide differential diagnosis that includes subretinal hemorrhage, choroidal hemangioma, metastasis, nevus, and other benign lesions [1]. A diagnosis of uveal melanoma carries significant morbidity even with a relatively good prognosis. Thus, the ability to recognize uveal melanomas in specimens containing limited diagnostic material is essential to proper direction of patient care.

Uveal melanomas fit into three morphologic categories: Spindle, epithelioid, or mixed. The spindle morphology is the most common and shows cytomorphology that is most similar to uveal melanocytes. This morphology is characterized by relatively bland cells with elongated cytoplasm and low-grade nuclear features [4]. The nuclei may show grooves and small inconspicuous nucleoli [3]. In contrast, epithelioid uveal melanomas contain plump, polyhedral cells with abundant cytoplasm and higher-grade nuclear features, including prominent nucleoli, intracytoplasmic invaginations, and inclusions. Of note, epithelioid melanomas typically show membranous expression of E-cadherin and Beta-catenin [5,6]. While the spindle cell morphology is the most commonly encountered morphology of primary tumors, the epithelioid morphology is more commonly observed in metastases. Mixed epithelioid/spindle melanomas are thought to represent a phenotypic point of transition. This diagnosis is subject to the most interobserver variability

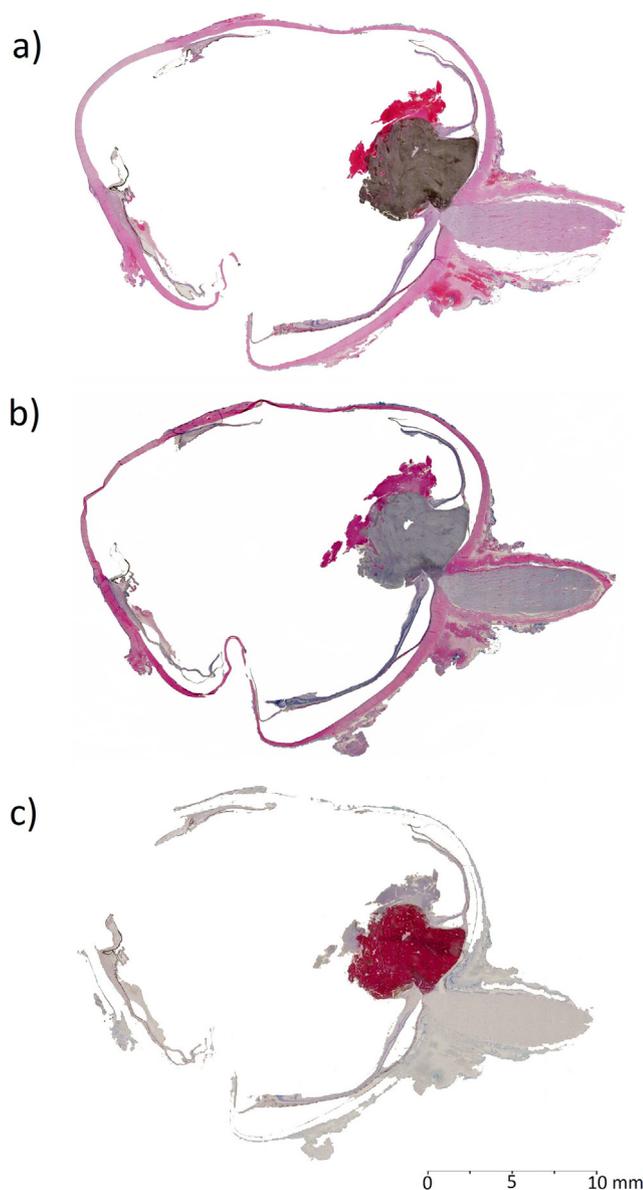


Fig. 4. Whole slide scan of the enucleation specimen showing a) H + E unbleached, b) H + E bleached, and c) melanoma cocktail immunohistochemistry.

[3].

Spindle uveal melanomas carry the best prognosis and are the least likely to metastasize with a 5-year survival of 90–95% [3,4]. Epithelioid melanomas carry the worst prognosis with a 5-year survival of 30–40% [3]. The mixed epithelioid/spindle morphology carries only a slightly better prognosis than the pure epithelioid type with a 40–50% 5-year survival. Due to the aggressive nature of epithelioid melanomas and the similarity in survival, it has been suggested that aspirates of mixed melanomas with more epithelioid cells be categorized as epithelioid [3].

Uveal melanomas arising in the choroid are the most common [3,4]. Choroidal melanomas tend to metastasize within five years of diagnosis and treatment, especially to the liver, and occult metastases are common. The tendency of choroidal melanomas to metastasize is in part due to their posterior uveal location and proximity to vasculature

[3]. Predictors of tumor behavior include size, necrosis, depth of tumor, scleral invasion, cytologic features, and cytogenetic changes, such as loss of chromosome 3 and gain of chromosome 8 [3,7]. While the difference in clinical behavior between epithelioid and spindle cell melanomas is well known, more recently these morphologies have been shown to have different gene expression profiles [3]. The epithelioid cell variant has been shown to demonstrate epithelium-like differentiation including cytokeratin, Beta-catenin, epithelial cell adhesion markers (CDH1), and epithelioid basement membrane markers (MACF1, SPARC). In addition, E-cadherin expression has been shown to relocate from the cytoplasm to the cell membrane, which is thought to represent a transition from neural-crest differentiation to epithelial-like differentiation which also correlates with more aggressive behavior [3].

To our knowledge, there is a single prior case report in the literature in which the correlation of cytology and histology was described in detail [1]. This case report described a 32 year old female presenting with an intraocular mass. Fine needle aspiration revealed a non-pigmented spindle cell lesion with relatively bland nuclear features, including occasional prominent nucleoli and nuclear grooves. The diagnosis was later confirmed on the enucleation specimen, which also showed spindle cells with bland nuclear morphology and few mitoses.

In contrast, our case showed mostly epithelioid morphology. However, like the previous case, the cytomorphology seen in the aspirate correlated well with that observed in the enucleation specimen. The enucleation specimen revealed an additional minor component of spindle cell morphology that was not represented in the aspirate, likely attributable to sampling. Like the aspirate, the enucleation specimen showed mild nuclear atypia with few mitoses. Abundant cytoplasmic melanin pigment was present within both samples, though it should be noted that most (80%) of uveal melanoma cases contain cytoplasmic melanin pigment [4].

In conclusion, our case shows cytomorphologic features on aspirate cytology that correlated well with those observed in the enucleation specimen, similar to the earlier findings of Kashyap et al [1]. Certainly more data is required to establish the extent to which cytomorphologic features can be correlated between aspirate cytology and enucleation histology; however, our institution does not have any other cytology cases on file diagnostic for uveal melanoma. Medina et al. did note a 100% correlation in 41 enucleated eyes; however, a detailed comparison of cytomorphology and histomorphology that included morphologic subtype was not included in this study [4]. Thus, a comparison of morphologic subtypes could likely be performed using cytology aspirate data and microscope slides from prior cases.

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