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Mechanisms of Optic Nerve Invasion in Primary Choroidal Melanoma

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Keywords

Choroidal melanoma · Enucleation · Optic nerve invasion · Peripapillary melanoma · Retinal invasion · Vitreous seeding

Abstract

Aim: The aim of this study was to assess morphological risk factors associated with optic nerve invasion of choroidal melanoma and to identify possible mechanisms of optic nerve invasion. ***Methods:*** Medical charts and histology slides of patients with primary choroidal melanoma who were treated by enucleation/exenteration and whose pathology showed optic nerve invasion were reviewed. ***Results:*** Twenty-one patients (mean age: 65.67 ± 14.72 years) with primary uveal melanoma arising from the choroid were included in this analysis. A peripapillary location was present in 86% of the cases. Four types of optic nerve invasion were identified: transvitreal invasion (10%); retinal invasion (23%); direct peripapillary invasion (57%); and a combined mechanism (10%). Optic nerve invasion was prelaminar in 67%, laminar in 10%, and retrolaminar in 23% of the cases. Significantly higher largest basal diameter ($p = 0.021$) and tumor thickness values ($p = 0.017$) and higher rates of vortex vein ($p = 0.022$) and retinal invasion ($p = 0.007$) were observed in the transvitreal/retinal invasion groups when compared to the direct peripapillary invasion group. ***Conclusions:*** A peripapillary tumor location was the most common mechanism of optic nerve invasion of choroidal melanoma. In 43% of the cases, other mechanisms including transvitreal and retinal invasion resulted in optic nerve invasion.

Introduction

Uveal melanoma is the most frequent primary intraocular malignancy in adults. It can affect any part of the uveal tract, but choroidal melanoma is predominant, while iris and ciliary body melanomas are less common [1]. Optic nerve invasion is rare, having been described in 0.6–6.9% of uveal melanoma cases treated with enucleation [2–5]. Optic nerve invasion has been associated with poor prognosis and higher melanoma-related mortality [4, 6]. In rare cases, the melanoma cells may extend to the optic chiasm and cause a visual field defect in the contralateral eye [7, 8].

Infiltration of the optic nerve has been seen in 5–80.8% of eyes when the uveal melanoma is located adjacent to the optic nerve head [3, 4]. Loss of light perception was reported to be a sign of optic nerve invasion [7]. Infiltra-

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tion of the optic nerve has also been associated with elevated intraocular pressure, non-spindle cell type, and juxtapapillary location [3, 4, 9]. However, the optic nerve exhibits features that may protect against invasion, such as its unique blood supply and its surrounding dense fibrous coat [10].

In the current study, we addressed morphological risk factors associated with optic nerve invasion of choroidal melanoma and identified possible mechanisms of optic nerve invasion.

Patients and Methods

The medical charts and histology slides of patients with primary choroidal melanoma who were treated by enucleation or exenteration and accessioned into the L.F. Montgomery Ophthalmic Pathology Laboratory, Emory Eye Center, between January 1997 and October 2016 and whose pathology showed invasion of the optic nerve were reviewed. Patients with the melanoma confined to the iris and/or with ciliary body melanoma were excluded. The patient data evaluated included age and sex. The clinicopathological features evaluated included intraocular pressure, pretreatment modality, tumor location, largest basal diameter (LBD), tumor thickness, histopathologic tumor cell type, scleral invasion, extrascleral extension at the time of surgery, rupture of Bruch's membrane, necrosis, mitotic activity, vitreous seeding or hemorrhage, and emissary canal, vortex vein, and retinal invasion. The study followed the tenets of the Declaration of Helsinki and was approved by the Emory University Institutional Review Board.

Histology

Enucleation/exenteration specimens were immediately fixed in formalin (10%) and embedded in paraffin. Five-micrometer-thick pupil-optic nerve sections that included the center of the melanoma were mounted on glass slides; then the sections were deparaffinized with xylene and rehydrated through a graded series of ethanol and distilled water. The sections were stained with hematoxylin and eosin (H&E) and periodic-acid Schiff, and bleached sections were stained with H&E according to routine protocols. The slides were evaluated qualitatively and quantitatively with a light microscope (Olympus BHTU; Olympus, Tokyo, Japan). The tumor was considered necrotic when >50% of the tumor was necrotic. The cell type (spindle, mixed, or epithelioid), LBD, and thickness were recorded. The growth pattern of the tumor with regard to optic nerve invasion was determined (i.e., peripapillary tumor, transvitreal tumor, retinal invasion, or a combination of these growth patterns).

Data Analysis

Statistical analysis was carried out with SPSS for Windows (version 22.0) and MedCalc (version 14.8.1) statistical software. The normality of data was tested using the Kolmogorov-Smirnov test. If normality was rejected, a nonparametric test was performed. For continuous variables, data are expressed as mean ± SD and 95% CI for the mean. Comparisons between 2 variables were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for binomial variables. A p value of <0.05 is considered statistically significant.

Table 1. Mechanisms of optic nerve invasion of primary choroidal melanoma

I.	Transvitreal invasion	
	A.	Dispersion of viable melanoma cells into the vitreous body
	B.	Extravasation of malignant cells through the adjacent retinal vessels into the vitreous body or migration of melanoma cells with vitreous hemorrhage
II.	Retinal invasion	
	A.	Neuroretinal tumor spread after rupturing Bruch's membrane
	B.	Spreading of malignant cells on the inner retinal surface
III.	Peripapillary invasion	
	A.	Tumor extension between the end of Bruch's membrane and the border tissue
	B.	Extension of the tumor through the border tissue
IV.	Combined mechanism	

Results

Twenty-one patients (13 males, 8 females) with primary uveal melanoma arising from the choroid treated with enucleation (20 cases) or exenteration (1 case) with histologic optic nerve invasion were included in this analysis. The mean age was 65.67 ± 14.72 years (ranging from 39 to 90 years). The histologic cell type was mixed in 76% (16/21), epithelioid in 14% (3/21), and of the spindle type in 10% (2/21) of the cases. The mean LBD was 14.04 ± 7.11 mm (95% CI: 10.81–17.28) and the mean tumor thickness was 8.18 ± 5.00 mm (95% CI: 5.90–10.45). A peripapillary location was present in 86% (18/21) of the cases, the ciliary body was involved in 19% of the cases (4/21), and diffuse tumor growth was documented in 1 case. In 67% (14/21) of the cases, the tumor had ruptured through Bruch's membrane, and retinal invasion was seen in 43% (9/21). Vitreous seeding of melanoma cells was observed in 2 cases, and vitreous hemorrhage was also found in 10% (2/21). In 24% of the cases (5/21), the tumor was necrotic and there were 0–5 mitotic figures present in 40 high-power fields in the tumors.

The 4 types of optic nerve invasion were identified as shown in Table 1 and Figures 1–6. Transvitreal invasion was seen in 10% (2/21) (Fig. 1, 2), retinal invasion in 23% (5/21) (Fig. 3, 4), direct peripapillary invasion in 57% (12/21) (Fig. 5, 6), and a combined mechanism in 10%

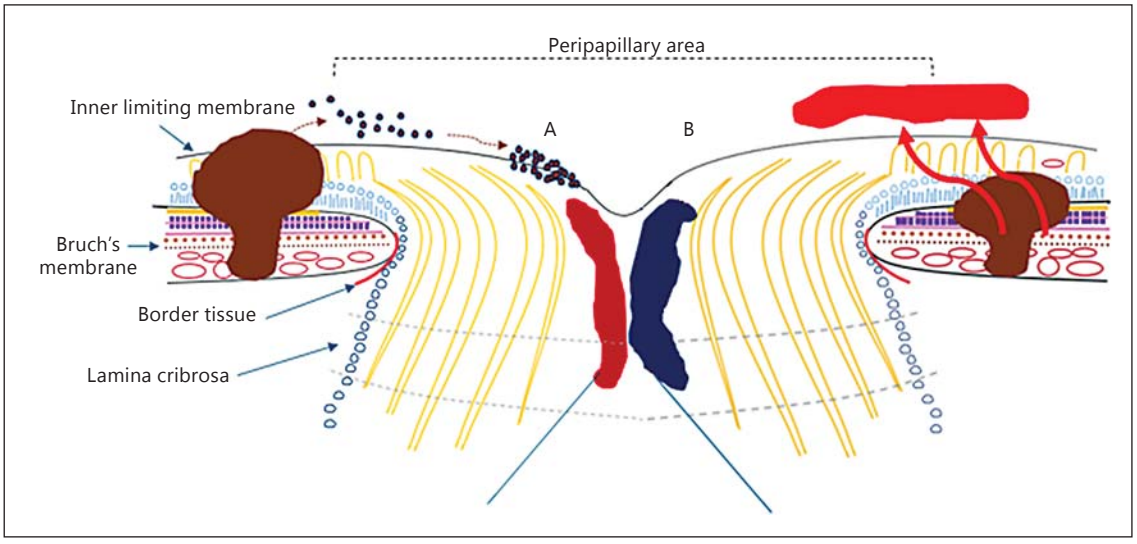

Fig. 1. Mechanism of transvitreal optic nerve invasion of choroidal melanoma. This mechanism involves the melanoma breaking through Bruch's membrane, with melanoma cell invasion into the vitreous and seeding of the optic nerve head. The melanoma may also cause vitreous hemorrhage.

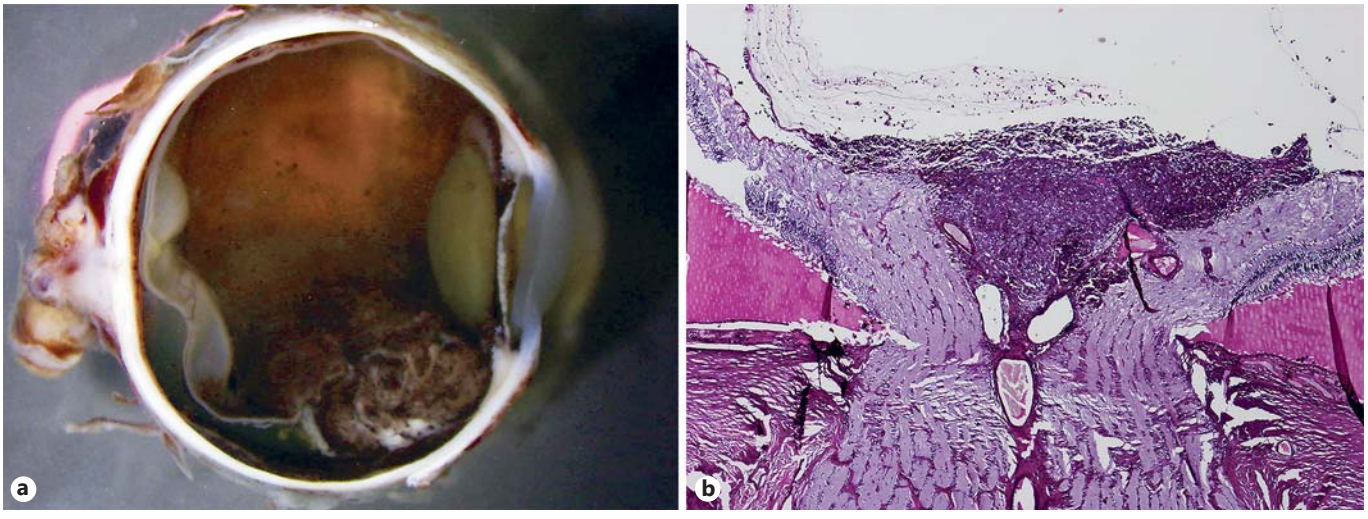

Fig. 2. Optic nerve invasion of melanoma cells dispersed from the surface of a peripheral melanoma arising adjacent to the ora serrata. **a** Gross photo. **b** Photomicrograph. Periodic-acid Schiff. ×5.

(2/21) of the cases. Scleral invasion was present in 91% (19/21), emissary canal invasion was seen in 33% (7/21), and extrascleral extension was found in 29% (6/21) of the specimens. Vortex vein invasion was present in 14% (3/21). An elevated intraocular pressure was reported in 4 patients (19%). One patient had previously been treated with transpupillary thermotherapy, and 2 patients had had prior plaque brachytherapy.

Invasion Pattern

We observed direct peripapillary optic nerve invasion in 57% (12/21) of our cases. In 43% (9/21), other mechanisms played a role, including transvitreal spread and/or retinal invasion. Optic nerve invasion was prelaminar in 75% (9/12) and 56% (5/9), laminar in 8% (1/12) and 11% (1/9), and retrolaminar in 17% (2/12) and 33% (3/9) in the peripapillary and the transvitreal/retinal invasion

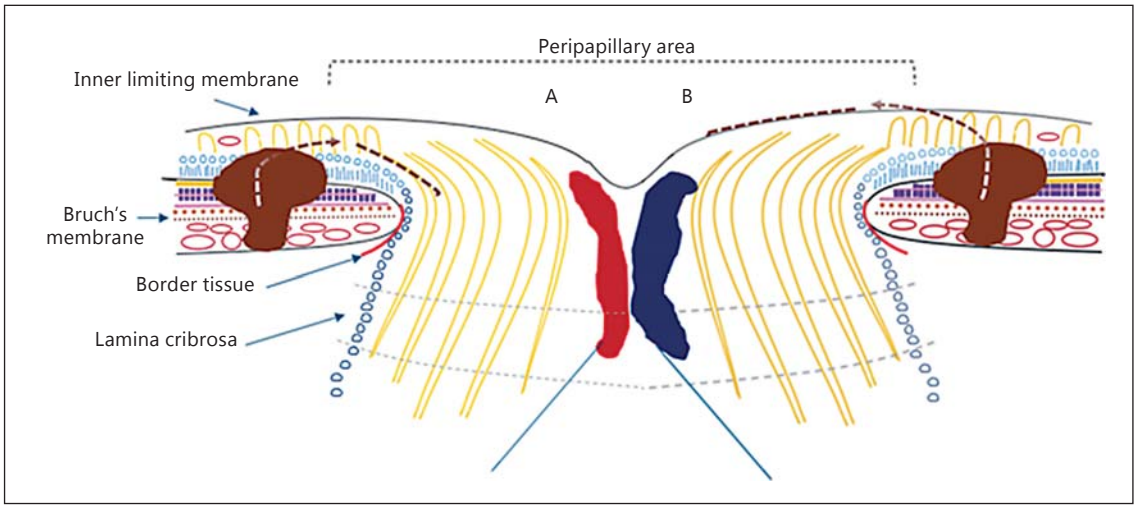

Fig. 3. Mechanism of retinal invasion-related optic nerve invasion of the melanoma. The choroidal melanoma (left) may directly invade the retina, and the intraretinal melanoma may extend into the optic nerve head. Alternatively (right), the melanoma may invade through the retina, and melanoma cells spread along the inner limiting membrane to the optic nerve head.

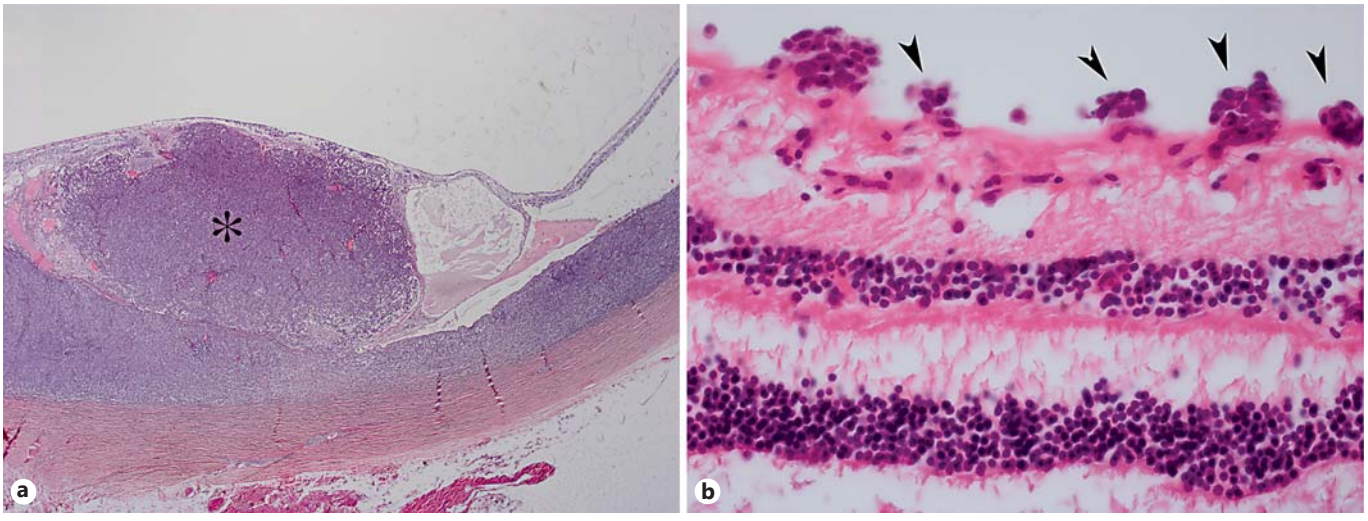

Fig. 4. a Retinal invasion (*) after breaking through Bruch's membrane. H&E; bleached. ×5. **b** Choroidal melanoma cells (arrowheads) spreading along the inner limiting membrane after retinal invasion. H&E. ×100.

group, respectively. Table 2 shows the clinicopathological characteristics of melanomas with peripapillary versus transvitreal and/or retinal invasion. In the peripapillary group, the cell type was mixed in 67% (8/12), epithelioid in 25% (3/12), and of the spindle type in 8% (1/12) of the cases. In melanomas with transvitreal/retinal invasion, the cell type was mixed in 89% (8/9) and of the spindle type in 11% (1/9) of the cases. A statistically significant difference was disclosed between the 2 groups in LBD ($p = 0.021$), tumor thickness ($p = 0.017$), and vortex vein ($p = 0.022$) and retinal invasion ($p = 0.007$). Elevated intraocular pressure was found in 1 case (8%) in the peripapillary group and in 3 cases (33%) in the transvitreal/retinal invasion group.

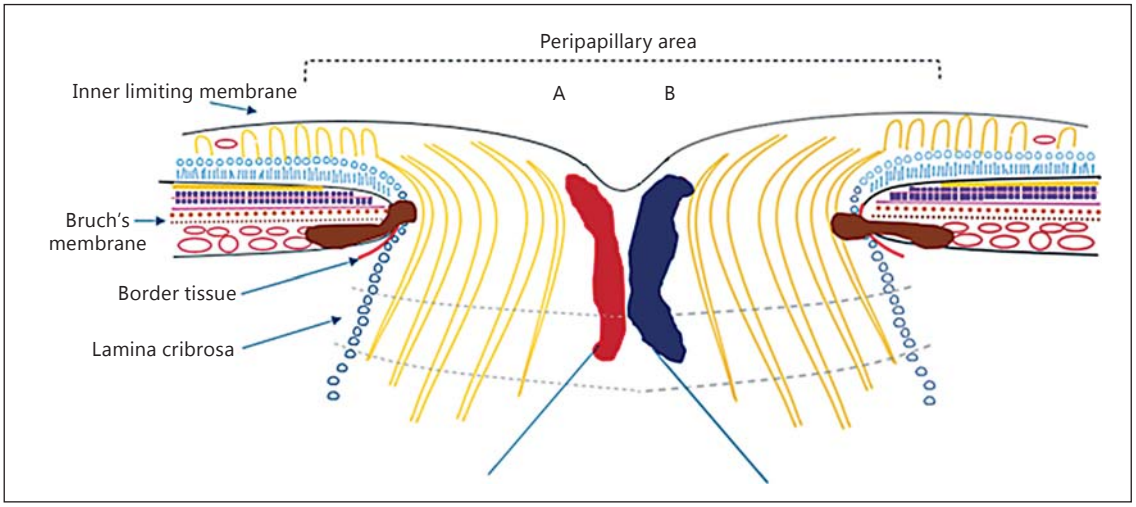

Fig. 5. Mechanism of peripapillary invasion of choroidal melanoma into the optic nerve head. Left: the melanoma invades along the edge of Bruch's membrane into the prelaminar optic nerve. Right: the melanoma extends directly through the border tissue into the laminar level of the optic nerve.

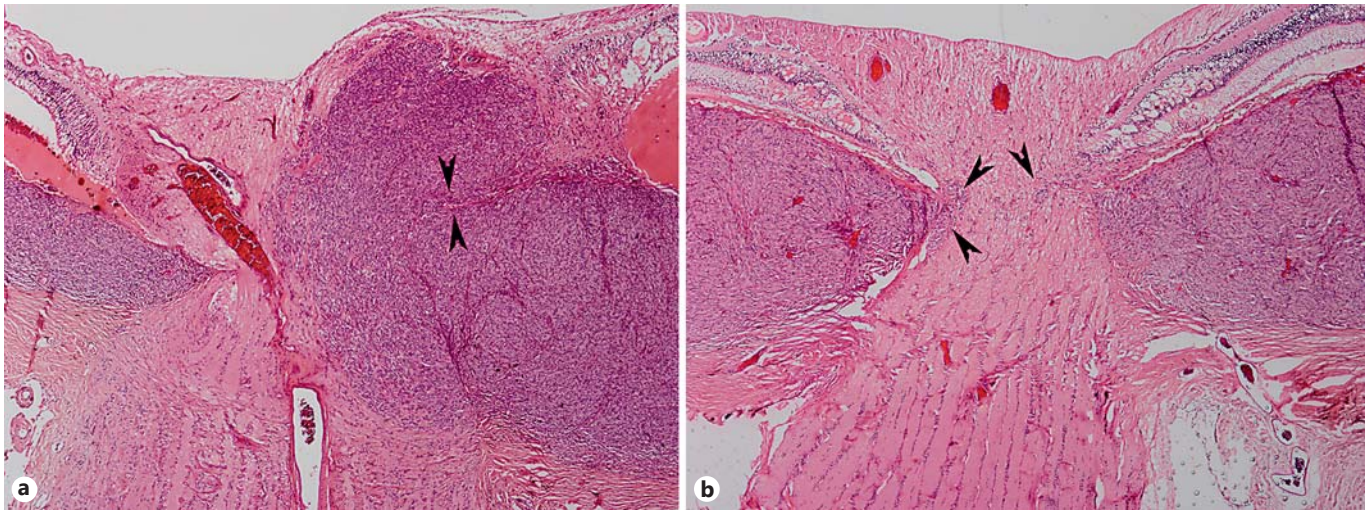

Fig. 6. a Peripapillary choroidal melanoma spread between the end of Bruch's membrane (arrowheads) and the border tissue into the optic nerve. H&E. ×10. **b** Microscopic image of choroidal melanoma. Direct invasion (arrowheads) into the optic nerve through the border tissue. H&E. ×10.

Invasion of the Lamina Cribrosa

Optic nerve invasion was prelaminar in 67% (14/21), laminar in 10% (2/21), and retrolaminar in 23% (5/21) of the cases. In the exenteration specimen, the tumor extended through the optic nerve to the surgical margin. Table 3 summarizes the clinicopathological features of the melanomas with prelaminar and laminar/retrolaminar invasion. In the prelaminar group, the cell type was mixed in 79% (11/14), epithelioid in 14% (2/14), and of the spindle type in 7% (1/14) of the cases. In the melanomas with laminar/retrolaminar invasion, the cell type was mixed in 71% (5/7), epithelioid in 14% (1/7), and of the spindle type in 14% (1/7) of the cases. Ninety-three percent (13/14) of the prelaminar melanomas and 71% (5/7)

Table 2. Clinicopathological features of choroidal melanomas with peripapillary versus transvitreal and/or retinal invasion

	Peripapillary invasion (n = 12)	Transvitreal and/or retinal invasion (n = 9)	p^1
Age (min–max), years	63.58±16.30 (39–90)	68.44±12.69 (56–89)	0.477
LBD (95% CI), mm	10.85±4.99 (7.68–14.02)	18.30±7.52 (12.52–24.08)	0.021
Tumor thickness (95% CI), mm	5.91±3.85 (3.46–8.35)	11.20±4.92 (7.42–14.98)	0.017
Mitotic activity (95% CI), /40 HPF	2.17±1.27 (1.36–2.97)	2.43±1.90 (0.67–4.19)	0.826
BM rupture	50 (6/12)	89 (8/9)	0.083
Vortex vein invasion	0 (0/12)	44 (4/9)	0.022
Retinal invasion	25 (3/12)	89 (8/9)	0.007
Emissary canal invasion	33 (4/12)	33 (3/9)	0.524
Scleral invasion	83 (10/12)	100 (9/9)	0.294
Extrascleral extension	25 (3/12)	33 (3/9)	0.701
Necrotic	8 (1/12)	44 (4/9)	0.315

Values are presented as mean ± SD or % (n/N) unless specified otherwise. LBD, largest basal diameter; HPF, high-power fields; BM, Bruch's membrane. [1] Mann-Whitney U test for continuous variables; Fisher's exact test for binomial variables.

Table 3. Clinicopathological features of choroidal melanomas with prelaminar versus laminar/retrolaminar optic nerve invasion

	Prelaminar invasion (n = 14)	Laminar/retrolaminar invasion (n = 7)	p^1
Age (min–max), years	62.21±12.99 (39–90)	72.57±16.52 (48–89)	0.205
LBD (95% CI), mm	12.42±5.41 (9.30–15.55)	17.29±9.30 (8.68–25.89)	0.433
Tumor thickness (95% CI), mm	6.76±4.34 (4.26–9.27)	11.0±5.35 (6.05–15.95)	0.061
Mitotic activity (95% CI), /40 HPF	2.00±1.29 (1.22–2.78)	2.83±1.83 (0.91–4.76)	0.274
BM rupture	57 (8/14)	86 (6/7)	0.225
Vortex vein invasion	0 (0/14)	57 (4/7)	0.013
Retinal invasion	43 (6/14)	71 (5/7)	0.247
Emissary canal invasion	29 (4/14)	43 (3/7)	0.544
Scleral invasion	86 (12/14)	100 (7/7)	0.391
Extrascleral extension	14 (2/14)	57 (4/7)	0.096
Necrotic	7 (1/14)	57 (4/7)	0.021

Values are presented as mean ± SD or % (n/N) unless specified otherwise. LBD, largest basal diameter; HPF, high-power fields; BM, Bruch's membrane. [1] Mann-Whitney U test for continuous variables; Fisher's exact test for binomial variables.

of the laminar/retrolaminar melanomas occurred in a peripapillary location. The breakdown of optic nerve invasion according to growth pattern showed the following results: transvitreal in 7% (1/14) of the prelaminar group versus 14% (1/7) of the laminar/retrolaminar group; retinal invasion in 21% (3/14) versus 29% (2/7); peripapillary in 64% (9/14) versus 43% (3/7); and combined in 7% (1/14) versus 14% (1/7). There was a statistically significant difference between the prelaminar and the laminar/retrolaminar group associated with vortex vein invasion (p = 0.013) and tumor necrosis (p = 0.021). Elevated intraocular pressure was observed in 4 cases (29%) in the prelaminar group and in no patients in the laminar/retrolaminar invasion group.

Discussion

Lindegaard et al. [11] evaluated 157 enucleated eyes and reported 4 different mechanisms for uveal melanomas to invade the optic nerve. Invasion of the tumor through the border tissue of Elschnig was an infrequent mechanism in that case series; extension of the tumor between the termination of Bruch's membrane and the border tissue of Elschnig into the optic nerve head was found to be a simple mechanical expansion of a growing tumor. Direct extension via this tissue was the most common mechanism in our study. Neuroretinal spread was associated with retrolaminar optic nerve invasion in their study, and tumor spread along the inner limiting membrane was found in only 1 case [11]. Invasion via the retina and vitreous was less common in our study, likely due to the rarity of uveal melanoma invading these structures.

In our study, 21 primary choroidal melanomas with histologically proven invasion of the optic nerve were identified between 1997 and 2016. Based on our findings, 4 mechanisms of optic nerve invasion of choroidal melanoma were identified. A peripapillary location was present in 86% of our cases, and direct peripapillary invasion was the most common mechanism of optic nerve invasion. A large histopathologic evaluation of uveal melanoma eyes enucleated from the Collaborative Ocular Melanoma Study (COMS) reported that 16.7% of the melanomas presented in a juxtapapillary location and 39.6% of those specimens showed optic nerve invasion, of which 1.1% extended beyond the lamina cribrosa [5].

Tumor size (LBD and thickness) is one of the most important clinical prognostic features of uveal melanoma [12]. The COMS Report No. 6 showed significantly greater invasion of the retina, vitreous, vortex veins, and tumor vessels and rupture of Bruch's membrane when the tumor was >10 mm in thickness, or >16 mm in LBD and ≥2 mm in thickness [5]. Our analysis included relatively larger choroidal melanomas with a mean LBD of 14.04 ± 7.11 mm and a mean thickness of 8.18 ± 5.00 mm. Bruch's membrane was ruptured less frequently (67% of the cases) in our series than in the COMS (88% of the cases) [5]. Cell type is generally considered to be the most potent single predictor of outcome [13]. Histologic examination showed a mixed cell type in 76%, an epithelioid type in 14%, and a spindle cell type in 10% of our cases. Microscopic scleral extension and emissary canal invasion have been reported in 10–40% of enucleated uveal melanoma eyes [14, 15]. Interestingly, we found a high percentage of scleral invasion in our cases (91% of all cases), and we detected emissary canal invasion in 33% and extrascleral extension in 29% of the eyes in our study. Tumor invasion within the sclera was less frequent in the COMS report (57.3% of the medium-sized tumors and 54.8% of the large tumors) [5]. Font et al. [16] reported extraocular extension of uveal melanomas in 39% of their cases. We found the following mechanisms of scleral invasion: direct invasion (11 cases); superficial scleral invasion (7 cases); perivascular emissary canal invasion (1 case); and intrascleral vortex vein combined with superficial direct scleral invasion (1 case). The sclera was necrotic in 1 case (the exenteration specimen).

Shammas and Blodi [3] reviewed 26 cases of peripapillary melanoma, and in 80.8% the tumor extended into the optic nerve or its sheaths. They observed that tumor necrosis, retinal invasion, glaucoma, and cell type (mixed or epithelioid) influenced the extension of melanoma cells along the optic nerve [3]. Melanoma cells extended into the subarachnoidal space in 46% (12) of their cases [3]. In our study, tumor cells extended beyond the surgical margin in 1 case; no other tumor was found to spread along the optic nerve sheaths. Optic nerve invasion was prelaminar in 67% and laminar/retrolaminar in 33% of our cases. Significant differences between prelaminar and laminar/retrolaminar invasion in our study correlated with vortex vein invasion and tumor necrosis, with laminar/retrolaminar invasion being more likely if there was vortex vein or tumor necrosis.

According to histopathologic studies following enucleation of uveal melanoma, retinal invasion occurs in 23–59% of cases [3, 5, 17, 18]. We observed retinal invasion of choroidal melanoma in 43% of our cases, and in 23% of these cases retinal invasion was the primary mechanism leading to optic nerve invasion. In enucleation specimens with retinal invasion, dispersed melanoma cells may form a malignant preretinal pigmented membrane [19]. We also observed uveal melanoma cells spreading along the inner limiting membrane and reaching the optic nerve head. We classified this growth pattern as a subclass of retinal invasion. It has been postulated that retinal invasion is more likely to occur when the tumor arises adjacent to the ora serrata or peripapillary choroid, where the retina and choroid are tightly adherent [20]. We also support the role of the unique structure of Bruch's membrane at its ora serrata and peripapillary terminations, making it predispose to retinal invasion [21, 22]. Retinal invasion has prognostically been shown to increase the risk for tumor recurrence but not for metastasis or death [23].

Based on our findings, we postulate 2 mechanisms explaining transvitreal melanoma spread: (1) viable mela-

noma cells from the surface of the tumor might be able to disperse to the vitreous after the tumor has ruptured Bruch's membrane, or (2) extravasation of malignant cells may also occur through the retinal vessels adjacent to the tumor or melanoma cells may migrate with vitreous hemorrhage to the vitreous body [24, 25]. These cells tend to invade the optic nerve head and the optic nerve beyond the lamina cribrosa. Spencer [6] reported 10 uveal melanomas (8 choroidal, 2 iris and ciliary body melanomas) with intravitreal spreading of tumor cells showing optic nerve invasion. This type of spreading is thought to be associated with more malignant melanoma cell types, particularly with those in which necrosis or hemorrhage has been found [6]. Elevated intraocular pressure is assumed to enhance dispersed viable tumor cells to adhere to and invade the optic nerve [3, 6].

Kivelä and Summanen [26] defined retinoinvasive uveal melanoma as a single entity showing similarities with metastatic cancers to the retina. Interestingly, the same mechanism of both retinal invasion and transvitreal spread has been observed in cancers that metastasize to the retina and vitreous [27–31]. Moreover, a recent article reported a case of metastatic cutaneous melanoma to the vitreous and retina with optic nerve head involvement [27]. The explanation for this phenomenon was that the melanoma cells could pass into the retinal circulation [28] or gain access to the vitreous directly through the pars plana [29]. Jaissle et al. [30] reported isolated vitreous metastasis of a cutaneous malignant melanoma case and postulated that tumor cells might pass into the retrohyaloid space with a spontaneous epiretinal hemorrhage.

In conclusion, we observed 4 mechanisms of optic nerve invasion of primary choroidal melanoma. The peripapillary tumor location was the most prevalent in our series. However, a peripapillary location may not be the only predisposing factor for optic nerve invasion of choroidal melanoma. In 43% of the cases, other mechanisms were involved, including transvitreal spread and retinal invasion. Tumor infiltration into adjacent tissues is a characteristic of aggressive tumor behavior. Significantly higher LBD and tumor thickness measurements, as well as higher rates of vortex vein and retinal invasion, were observed in the transvitreal and retinal spread type group compared to the peripapillary invasion type group. Transvitreal and retinal spread of choroidal melanoma showed similar mechanisms of spread to those in metastatic cancers to the retina and vitreous. Choroidal melanomas exhibiting these growth patterns may have aggressive phenotypes similar to vitreoretinal metastasis from systemic cancers, having poor prognosis [11, 31]. In contrast, most peripapillary melanomas with optic nerve involvement show mechanical expansion of the choroidal mass rather than an aggressive infiltrative growth pattern [11].

Acknowledgement

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Statement of Ethics

The study followed the tenets of the Declaration of Helsinki and was approved by the Emory University Institutional Review Board.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Shields CL, Kels JG, Shields JA: Melanoma of the eye: revealing hidden secrets, one at a time. Clin Dermatol 2015;33:183–196.
2 Wilder HC, Paul EV: Malignant melanoma of the choroid and ciliary body: a study of 2,535 cases. Milit Surg 1951;109:370–378.
3 Shammas HF, Blodi FC: Peripapillary choroidal melanomas. Extension along the optic nerve and its sheaths. Arch Ophthalmol 1978; 96:440–445.
4 Lindegaard J, Isager P, Prause JU, Heegaard S: Optic nerve invasion of uveal melanoma: clinical characteristics and metastatic pattern. Invest Ophthalmol Vis Sci 2006;47:3268–3275.
5 Histopathologic characteristics of uveal melanomas in eyes enucleated from the Collaborative Ocular Melanoma Study. COMS Report No. 6. Am J Ophthalmol 1998;125:745–766.
6 Spencer WH: Optic nerve extension of intraocular neoplasms. Am J Ophthalmol 1975;80: 465–471.
7 Shields CL, Shields JA, Yarian DL, Augsburger JJ: Intracranial extension of choroidal melanoma via the optic nerve. Br J Ophthalmol 1987;71:172–176.
8 Abdellatief A, Pulido JS, Bartley GB, Salomao DR, Quinn TA: Uveal melanoma extension to the optic chiasm. Retin Cases Brief Rep 2016; 10:1–5.
9 Chess J, Albert DM, Bellows AR, Dallow R: Uveal melanoma: case report of extension through the optic nerve to the surgical margin in the orbital apex. Br J Ophthalmol 1984;68: 272–275.
10 Othman IS: Ophthalmic Pathology Interactive with Clinical Correlation. Kugler, Amsterdam, 2009, pp 201–243.

11 Lindegaard J, Isager P, Prause JU, Heegaard S: Optic nerve invasion of uveal melanoma. APMIS 2007;115:1–16.
12 Kaliki S, Shields CL, Shields JA: Uveal melanoma: estimating prognosis. Indian J Ophthalmol 2015;63:93–102.
13 McLean IW: Prognostic features of uveal melanoma. Ophthalmol Clin North Am 1995;8:143–153.
14 Shammas HF, Blodi FC: Orbital extension of choroidal and ciliary body melanomas. Arch Ophthalmol 1977;95:2002–2005.
15 Sambuelli R, Luna JD, Reviglio VE, Aoki A, Juarez CP: Small choroidal melanoma with massive extraocular extension: invasion through posterior scleral emissary channels. Int Ophthalmol 2001;24:213–218.
16 Font R, Spaulding A, Zimmerman L: Diffuse malignant melanoma of the uveal tract: a clinicopathologic report of 54 cases. Trans Am Acad Ophthalmol Otolaryngol 1968;72:877–895.
17 Jensen OA: Malignant melanomas of the uvea in Denmark 1943–1952. A clinical, histopathological, and prognostic study. Acta Ophthalmol (Copenh) 1963;43(suppl 75):1–220.
18 Davies WS: Malignant melanomas of the choroid and ciliary body. A clinicopathologic study. Am J Ophthalmol 1963;55:541–546.
19 Eagle RC Jr, Shields JA: Pseudoretinitis pigmentosa secondary to preretinal malignant melanoma cells. Retina 1982;2:51–55.
20 Daicker B: Melanosis retinae et papillae durch transretinal in den Glaskörper eingebrochenes malignes Aderhautmelanom. Ophthalmologica 1973;166:460–471.
21 Hogan MJ, Alvarado JA, Weddell JE: Histology of the Human Eye. An Atlas and Textbook. Philadelphia, Saunders, 1971, pp 328–363.
22 Schraermeyer U, Addicks K, Kociok N, Esser P, Heimann K: Capillaries are present in Bruch's membrane at the ora serrata in the human eye. Invest Ophthalmol Vis Sci 1998;39:1076–1084.
23 Gündüz K, Shields CL, Shields JA, Cater J, Freire JE, Brady LW: Radiation complications and tumor control after plaque radiotherapy of choroidal melanoma with macular involvement. Am J Ophthalmol 1999;127:579–589.
24 Gündüz K, Shields JA, Shields CL, Eagle RC Jr: Cutaneous melanoma metastatic to the vitreous cavity. Ophthalmology 1998;105:600–605.
25 Spraul CW, Martin DF, Hagler WS, Grossniklaus HE: Cytology of metastatic cutaneous melanoma to the vitreous and retina. Retina 1996;16:328–332.
26 Kivelä T, Summanen P: Retinoinvasive malignant melanoma of the uvea. Br J Ophthalmol 1997;81:691–697.
27 Breazzano MP, Barker-Griffith AE: Features of cutaneous malignant melanoma metastatic to the retina and vitreous. Ocul Oncol Pathol 2015;2:80–85.
28 Cole EL, Zakov ZN, Meisler DM: Cutaneous malignant melanoma. Arch Ophthalmol 1986;104:98–101.
29 Rosenberg C, Finger PT: Cutaneous malignant melanoma metastatic to the eye, lids, and orbit. Surv Ophthalmol 2008;53:187–202.
30 Jaissle GB, Szurman P, Rohrbach JM, Gelisken F, Bartz-Schmidt KU: A case of cutaneous melanoma metastatic to the vitreous cavity: possible pathomechanism and review of the literature. Graefes Arch Clin Exp Ophthalmol 2007;245:733–740.
31 Shields CL, McMahon JF, Atalay HT, Hasanreisoglu M, Shields JA: Retinal metastasis from systemic cancer in 8 cases. JAMA Ophthalmol 2014;132:1303–1308.