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Original Article

Coexisting Macular Hole and Uveal Melanoma: A Case Series and Literature Review

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Purpose: To report five cases of macular hole (MH) coexisting with uveal melanoma (UM) and review the literature.

Methods: Seventeen patients (5 new and 12 from previous reports) with coexisting MH and UM were reviewed. The patients were divided into two groups based on whether the MH was diagnosed before or after tumor treatment. The clinical features, pathogenesis, management options, and clinical outcomes were reviewed.

Results: Of 505 patients with UM in our institution, 5 (1.0%) had a concurrent MH in the ipsilateral eye. The 17 patients reviewed had a mean age of 63.9 years at the time of MH diagnosis. Of 16 patients with available data on sex, 11 (64.7%) were female. There were no major differences in the demographic or clinical data of the groups. Of the 15 known tumor locations, 6 (35.3%) were juxtapapillary or macular. In patients who developed MH after UM treatment, the durations from tumor treatment (radiotherapy or transpupillary thermotherapy) to MH diagnosis were 3 to 56 months (median, 8.5 months). MH surgery was performed in nine eyes, and hole closure was achieved in seven eyes with postoperative data. The mean visual acuity showed a tendency of improvement after surgery. No intraocular or extraocular tumor dissemination associated with surgery was observed.

Conclusions: MH is observed in approximately 1% of patients with UM, either before or after tumor treatment. Of patients with coexisting MH and UM, MH surgery appears to be safe and effective in those with stable tumors and visual potential.

Key Words: Choroidal melanoma, Macular hole, Uveal melanoma

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults although it is rare. Its incidence varies across ethnicities and regions, ranging from <1 to >9 per million population per year [1]. In the United States, the mean age-adjusted incidence of UM is 5.1 per million; the majority of cases (97.8%) affect the white population [2]. The incidence is relatively low in Asian countries, such as South Korea (0.4–1.1 per million per year)

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[3,4] and Japan (0.6 per million per year) [5].

The coexistence of a full-thickness macular hole (MH) and UM has been rarely reported. Uffer and Zografos [6] reported the first case of MH coexisting with UM and rhegmatogenous retinal detachment in 1997. A PubMed search revealed 11 more cases of UM with MH detected at the same time or that developed after tumor treatment (radiotherapy and/or transpupillary thermotherapy [TTT] or local resection) [6–14]. This suggests that the development of a tumor or tumor regression after treatment is associated with the development of MH. The present study analyzed previously reported cases of UM coexistent with MH and five new cases encountered at our institution.

Materials and Methods

Ethics statement

This retrospective observational case series was approved by the Institutional Review Board of Severance Hospital, with a waiver of informed consent (No. 4-2021-1085). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Study design

For the retrospective case series, the medical records of consecutive patients who were diagnosed with UM at our institution between June 1997 and March 2021 were reviewed. Of the 505 patients diagnosed with UM, 5 (1.0%) were diagnosed with MH. The clinical data of the five patients, including age, sex, ocular history, best-corrected visual acuities (BCVAs), tumor dimensions (measured by A- and B-scan ultrasonography), tumor location (macular, juxtapapillary, from arcade to equator, or anterior to equator), tumor treatment method, duration from tumor treatment to MH diagnosis, MH management, MH treatment outcome, follow-up duration, tumor recurrence, and distant metastasis, were retrieved. Every patient underwent a comprehensive ophthalmic examination, including fundus photography and spectral-domain optical coherence tomography (SD-OCT).

For the data collection of previously reported cases, reports of MH coexisting with UM published before December 2022 were retrieved from the PubMed search using the keyword "macular hole and melanoma." Additional articles were identified through a reference search.

Data from the present and previous cases were pooled and analyzed for the clinical features of MH coexisting with UM. Patients were categorized into two groups according to the order of MH diagnosis and tumor treatment. Group 1 included patients who presented with MH simultaneously or before UM treatment. Group 2 comprised patients who developed MH after UM treatment (TTT, radioactive plaque brachytherapy, and external beam radiotherapy). The demographic and clinical characteristics of the patients in the two groups were compared.

Statistical analysis

Results are presented as mean or median with standard deviation or interquartile range for quantitative variables and with absolute and relative frequencies for qualitative variables. The Snellen chart BCVA was converted to the logarithm of the minimum angle of resolution (logMAR). Fisher exact test was performed for discontinuous variables, and Mann-Whitney *U*-test was used for continuous variables. The Wilcoxon signed rank test was used to analyze the differences in VAs and tumor sizes before and after treatment. Spearman rank correlation analysis was performed to evaluate the association between tumor size and MH diameter. All data were analyzed using IBM SPSS ver. 25 (IBM Corp), and the level of statistical significance was set at the two-sided 5% level.

Results

Demographic and clinical characteristics

The present retrospective observational case series involved 12 patients from 10 previous case reports and series [6–15] and 5 new patients from our institution (Table 1). Table 2 presents the results of the combined analysis of the data from the present and previous cases. The mean age of the 17 included patients (5 men, 11 women, 1 not reported) at the time of MH diagnosis was 63.9 ± 14.4 years (range, 42–84 years). The tumor location was within the macular or juxtapapillary area in six patients (35.3%), from the arcade to the equator in seven (41.2%), within the area anterior to the equator in two (11.8%), and unknown in two

Table 1. Demographic and clinical characteristics of patients with MH coexistent with uveal melanoma in previous and present studies (n = 17)

Patient no.	Age (yr)	Sex	Tumor location	Initial basal tumor dimension (mm)	Initial tumor height (mm)	Initial BCVA	Previous treatment	MH diagnosis	Tumor treatment	Duration from tumor treatment to MH diagnosis (mon)	BCVA at the time of MH diagnosis	Tumor height at the time of MH diagnosis (mm)	MH diameter (μm)	MH repair surgery	MH closure	Time of FU after MH diagnosis (mon)	Final tumor height (mm)	Final BCVA	Tumor recurrence at final FU	Metastasis at final FU
1 (Uffer and Zografos [6])	71	Male	From arcade to equator	NA	13	HM	NA	Simultaneously	Enucleation	NA	HM	13	NA	SP enucleation	NA	NA	SP enucleation	SP enucleation	NA	NA
2 (Narang et al. [8])	45	Female	Macular area	10.2 × 9.1	4.7	20 / 1,200	NA	Simultaneously	TTT	NA	1 / 60	4.7	500	No	NA	6	3.1	20 / 1,200	NA	NA
3 (Gold et al. [10])	65	Female	From arcade to equator	16 × 14	2.4	20 / 400	NA	Simultaneously	I-125 plaque brachytherapy	NA	20 / 400	2.4	NA	Yes (PPV + ILMP)	Yes	NA	NA	20 / 400	NA	NA
4 (Gold et al. [10])	77	Female	Juxtapapillary	14 × 13	2.3	20 / 200	MH repair surgery, cataract surgery	Simultaneously	I-125 plaque brachytherapy	NA	20 / 200	2.3	NA	No	NA	36	Slightly involuted	20 / 200	NA	NA
5 (New)	74	Female	Anterior to equator	6.5 × 6.5	9.21	20 / 100	Cataract surgery, MH repair surgery	Before PUM diagnosis	CyberKnife	NA	NA	9.21	693.8	No	NA	5	NA	LP+	No	NA
6 (Balestrazzi et al. [11])	62	Female	Arcade to equator*	9.6 × 9.5	2.7	20 / 20	NA	After treatment	TTT	3	HM	2.2†	NA	Yes (PPV + ILMP)	Yes	1	No tumor elevation	20 / 80	NA	NA
7 (Shields et al. [15])	75	Female	Juxtapapillary	NA	NA	20 / 100	NA	After treatment	I-125 plaque brachytherapy	NA	NA	NA	NA	NA	NA	NA	16	FC	NA	NA
8 (McCannel and McCannel [9])	Relatively young	NA	NA	NA	NA	NA	NA	After treatment	I-125 plaque brachytherapy + PPV + SOI	6	NA	NA	NA	Yes (PPV)	Yes	NA	NA	NA	NA	NA
9 (Beykin et al. [14])	72	Female	NA	6.4 × 7.2	2.6	FC 30 cm	NA	After treatment	Plaque	3.5‡	FC 150 cm	NA	NA	Yes (PPV + MP)	Yes	18§	2	FC 30 cm	No	No
10 (Damato et al. [13])	45	Male	From arcade to equator	8 × NA	8	NA	NA	After treatment	Local resection	NA	NA	NA	NA	Yes (PPV)	No	NA	SP enucleation	SP enucleation	NA	NA
11 (Zhou et al. [12])	83	Male	From arcade to equator	5.9 × 5.7	4.1	20 / 17	NA	After radiotherapy	Stereotactic hypofragtionated radiotherapy	5	20 / 50	NA	232	Yes (PPV + ILMP)	Yes	6	NA	20 / 125	No	No
12 (New)	47	Female	From arcade to equator	7.5 × 6.9	4.99	20 / 20	None	After treatment	Ru-106 plaque brachytherapy, TTT	56	20 / 500	2.95	164.6	Yes (PPV + ILMP)	Yes	24	2.56	20 / 22	No	No
13 (New)	42	Female	Juxtapapillary	11.3 × 9.3	9.63	HM	None	After treatment	CyberKnife	11	HM	3.42	158.8	No	NA	19	2.32	HM	No	No
14 (New)	65	Male	Juxtapapillary	10 × 7.1	7.09	20 / 50	BRVO SP sector PRP	After treatment	Ru-106 plaque brachytherapy, TTT	15	LP–	6.3	147	No	NA	52	9.13	LP–	No	No
15 (New)	46	Female	From arcade to equator	6.6 × 6.3	3.58	20 / 25	None	After treatment	Ru-106 plaque brachytherapy	12	20 / 125	3.1	82.32	Yes (PPV + ILMP)	Yes	12	3.49	20 / 125	No	No
16 (Foster et al. [7])	84	Male	Anterior	7 × 6	3.5	NA	NA	NA	I-125 plaque brachytherapy	13‡	NA	2.2	NA	Yes (PPV + MP)	NA	3§	NA	NA	No	No
17 (Gold et al. [10])	70	Female	Juxtapapillary	16 × 14	5.8	20 / 200	I-125 plaque brachytherapy	Before PUM diagnosis	NA	NA	20 / 200	5.8	NA	No	NA	0	NA	NA	NA	Yes

Group 1, MH before UM treatment (patients 1–5). Group 2, MH after UM treatment (patients 6–15). Not included in either group due to lack of data, patients 16 and 17.
MH = macular hole; BCVA = best-corrected visual acuity; FU = follow-up; NA = not applicable or not reported; HM = hand movements; SP = status post; TTT = transpupillary thermotherapy; I-125 = iodine-125; PPV = pars plana vitrectomy; ILMP = internal limiting membrane peeling; PUM = posterior uveal melanoma; LP = light perception; FC = finger counting; SOI = silicone oil injection; MP = membrane peeling; Ru-106 = ruthenium-106; BRVO = branch retinal vein occlusion; PRP = panretinal photocoagulation.
*The tumor is located 7 mm superior to the optic disc, and it is assumed to be posterior to the equator; †Tumor height 2 months before the MH diagnosis; ‡Duration from tumor treatment to vitrectomy; §Duration of follow-up after vitrectomy.

patients (11.8%). The mean largest basal tumor dimension and height at the initial presentation were 9.6 mm (median, 9 mm; range, 5.9–16.0 mm) and 5.6 mm (median, 5 mm; range, 2.3–13.0 mm), respectively. For UM management, nine patients were treated with plaque brachytherapy (six plaque brachytherapy only, two with adjunctive TTT, one with vitrectomy and silicone oil tamponade). Three patients received external beam radiotherapy, and two patients were treated with TTT monotherapy. In one patient, MH was detected in the enucleated specimen.

Nine patients underwent MH repair surgery, and MH closure was achieved in seven eyes following surgery; closure was not achieved in one eye [13], and postoperative data were unavailable for another [7]. The MH remained closed for a mean follow-up of 12.2 months (n = 5; median, 12 months; range, 1–24 months) with no reported cases of intraocular or extraocular tumor dissemination. Overall, the mean VA showed a tendency of improvement after surgery; the initial and final mean logMAR VAs were 1.34 ± 0.87 and 0.72 ± 0.49, respectively (p = 0.285). Of the six

Table 2. Demographic and clinical characteristics of all patients (n = 17)

Characteristic	Value
Age (yr) (n =16)	63.9 ± 14.4 (42 to 84)
Sex	
Male	5 (29.4)
Female	11 (64.7)
Not reported	1 (5.9)
Tumor location	
Macular/juxtapapillary	6 (35.3)
From arcade to equator	7 (41.2)
Anterior to equator	2 (11.8)
Unknown	2 (11.8)
Initial largest basal tumor dimension (mm) (n = 14)	9.6 ± 3.5 (5.9 to 16.0)
Initial tumor height (mm) (n = 15)	5.6 ± 3.2 (2.3 to 13.0)
Initial BCVA (logMAR) (n = 14)	0.98 ± 1.00 (–0.07 to 2.70)
Tumor treatment	
Brachytherapy	9 (52.9)
External beam radiation therapy	3 (17.6)
Transpupillary thermotherapy	4 (23.5)
Local resection	1 (5.9)
Enucleation	1 (5.9)
BCVA at the time of MH diagnosis (logMAR) (n = 12)	1.82 ± 1.19 (0.40 to 4.70)
Tumor height at the time of MH diagnosis (mm) (n = 12)	4.8 ± 3.4 (2.2 to 13.0)
MH repair surgery	
Yes	9 (52.9)
No	6 (35.3)
Follow-up period after MH diagnosis (mon) (n = 12)	15.2 ± 15.8 (0 to 52)
Final tumor height (mm) (n = 7)	5.1 ± 5.0 (2 to 16)
Final BCVA (logMAR) (n = 12)	1.68 ± 1.36 (0.04 to 4.70)
Primary tumor recurrence	0 (0)
Systemic metastasis	1 (5.9)

Values are presented as mean ± standard deviation (range) or number (%).
BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; MH = macular hole.

eyes that did not undergo MH surgery, MH remained stable in five (patients 2, 4, 5, 13, and 14) during a mean follow-up duration of 23.6 months (median, 19 months; range, 5–52 months).

Local recurrence or distant metastasis of UM accompanying MH was not identified, except in a single patient (patient 17) with systemic metastasis to the liver. None of the five patients in our institute developed intraocular tumor dissemination or systemic metastasis during follow-up with a mean duration of 22.4 months (range, 5–52 months). Furthermore, surgery-related intraocular or extraocular tumor dissemination was not observed.

There were 5 patients in group 1 (patients 1–5), 10 patients in group 2 (patients 6–15), and 2 patients who were not included in either group due to lack of data (patients 16 and 17). There were no differences between groups 1 and 2

Table 3. Demographic and clinical characteristics of patients with MH and coexisting UM based on the order of MH diagnosis and tumor treatment (n = 15)

Characteristic	Group 1 (n = 5)	Group 2 (n = 10)	*p*-value*
Sex			>0.999
Male	1 (20.0)	3 (33.3)	
Female	4 (80.0)	6 (66.7)	
Age (yr)	66.4 ± 12.8	59.7 ± 15.2 (n = 9)	0.518
Tumor location			0.728
Macular/juxtapapillary	2 (40.0)	3 / 8 (37.5)	
From arcade to equator	2 (40.0)	5 / 8 (62.5)	
Anterior to equator	1 (20.0)	0 / 8 (0)	
Initial largest basal tumor dimension	11.7 ± 4.2 (n = 4)	8.2 ± 1.9 (n = 8)	0.154
Initial tumor height (mm)	6.3 ± 4.7	5.3 ± 2.6 (n = 8)	0.943
Initial BCVA (logMAR)	1.50 ± 0.78	0.65 ± 0.96 (n = 8)	0.093
Tumor treatment			0.818
Brachytherapy	2 (40.0)	6 (60.0)	
External beam radiotherapy	1 (20.0)	2 (20.0)	
Transpupillary thermotherapy	1 (20.0)	1 (10.0)	
Local resection	0 (0)	1 (10.0)	
Enucleation	1 (20.0)	0 (0)	
BCVA at the time of MH diagnosis (logMAR)	1.69 ± 0.74 (n = 4)	2.01 ± 1.47 (n = 7)	0.927
Tumor height at the time of MH diagnosis (mm)	6.3 ± 4.7	3.6 ± 1.6 (n = 5)	0.548
MH diameter (μm)	596.9 ± 137.0 (n = 2)	156.9 ± 53.3 (n = 5)	0.095
MH repair surgery			0.217
Yes	1 (20.0)	7 / 9 (77.8)	
No	4 (80.0)	2 / 9 (22.2)	
Follow-up period after MH diagnosis (mon)	15.7 ± 17.6 (n = 3)	18.9 ± 16.6 (n = 7)	0.667
Final tumor height (mm)	3.1 (n = 1)	5.9 ± 5.6 (n = 6)	>0.999
Final BCVA (logMAR)	1.94 ± 1.21 (n = 4)	1.55 ± 1.49 (n = 8)	0.461
Primary tumor recurrence	0 (0)	0 (0)	-
Systemic metastasis	0 (0)	0 (0)	-

Values are presented as number (%), mean ± standard deviation, or mean only. Group 1, MH before UM treatment (patients 1–5). Group 2, MH after UM treatment (patients 6–15).
MH = macular hole; UM = uveal melanoma; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.
*Fisher exact test was performed for discontinuous variables, and Mann-Whitney *U*-test was used for continuous variables.

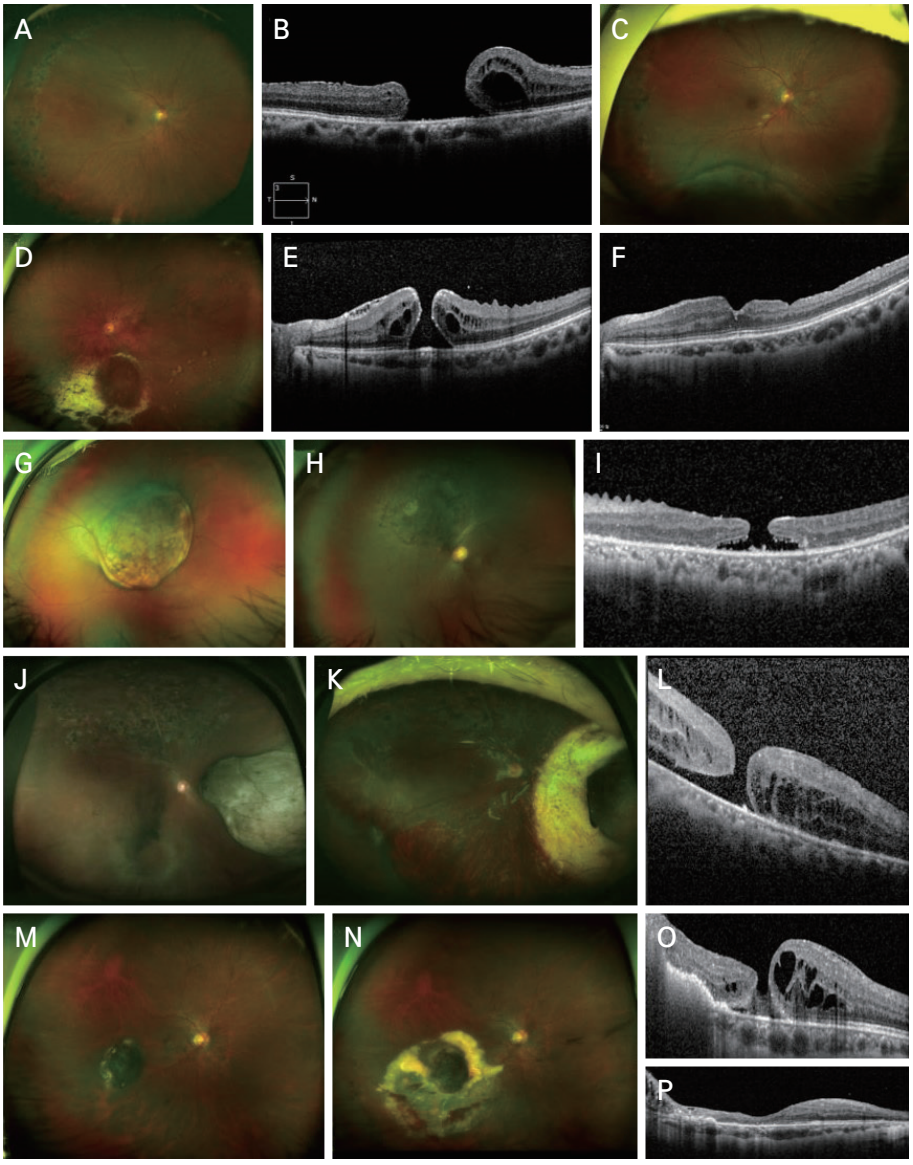

Fig. 1. Representative images of five patients with a macular hole (MH) coexistent with choroidal melanoma. (A–C) Case 1 (patient 5) in group 1. (A) Wide fundus photography and (B) optical coherence tomography (OCT) images from the previous hospital, 17 months prior to the initial visit at our initial institution, exhibiting chronic MH with no visible choroidal mass. (C) Wide fundus photograph from the initial visit at our institution showing an elevated, pigmented mass at the inferior area with surrounding serous retinal detachment with a chronic MH. (D–F) Case 2 (patient 12) in group 2. (D) Wide fundus photography and (E) OCT images at 56 months following brachytherapy, showing regressed choroidal melanoma below the inferior major arcade and a secondary MH with cystoid macular oedema in the left eye. (F) OCT image after pars plana vitrectomy with internal limiting membrane peeling and pneumatic tamponade using perfluoropropane (C_3F_8) gas, showing closed MH. (G–I) Case 3 (patient 13) in group 2. (G) Wide fundus photograph at the initial visit showing the presence of a large protruded choroidal mass superior nasal to the left optic disc obscuring macula. (H, I) Eleven months after radiotherapy, the tumor showed involutional stability with corresponding decrease in size, but the development of MH was observed. (J–L) Case 4 (patient 14) in group 2. (J) Wide fundus photograph from the initial visit showing the presence of a large protruding mass in the nasal juxtapapillary area with mild vitreous hemorrhage and previous sector panretinal photocoagulation scars at superior retina. The patient underwent ruthenium-106 plaque brachytherapy and thermotherapy followed by pars plana vitrectomy with lensectomy due to nonclearing vitreous hemorrhage and worsening cataract. Approximately 1 year later, additional vitrectomy was performed with retinectomy and silicone oil tamponade because of the development of exudative retinal detachment with proliferative vitreoretinopathy, and MH was noted under a surgical microscope in the operating field. (K, L) After surgery, the retina was attached, but the MH remained open. (M–P) Case 5 (patient 15) in group 2. (M) Wide fundus photograph from the initial visit showing a pigmented choroidal mass inferior temporal to the macula in the right eye. (N) Wide fundus photography at 12 months after brachytherapy reveals regressed choroidal melanoma with adjacent exudates and hemorrhages due to radiation retinopathy. (O) OCT image shows the full-thickness MH associated with cystic changes. (P) The MH is closed after pars plana vitrectomy with internal limiting membrane peeling and pneumatic tamponade with sulfur hexafluoride (SF_6) gas.

related to patient demographic and clinical data, including tumor size, VA at the time of MH diagnosis, and follow-up duration after MH diagnosis (Table 3).

In group 2, the duration from tumor treatment to MH diagnosis ranged from 3 to 56 months (median, 8.5 months; n = 8). The mean tumor height at the time of MH diagnosis was significantly lower than the mean height before treatment (3.59 ± 1.58 mm vs. 5.33 ± 2.61 mm, $p = 0.043$).

The analysis conducted on the subset of cases with available data on tumor size and MH diameter (seven eyes) revealed no significant correlation between the largest basal diameter of the tumor and the MH size ($p = 0.589$), or between tumor height and the MH size ($p = 0.645$). This suggests that tumor size, either in terms of basal diameter or height, does not appear to influence the development or size of the MH. However, the analysis was limited by the small sample size, and therefore, further studies with larger cohorts are needed to validate these findings and better understand the potential relationship between tumor size and MH development or size.

Group 1 (simultaneous UM and MH): case 1 (patient 5)

A 74-year-old woman presented with a large choroidal melanoma in her right eye. Her ocular history included cataract surgery 10 years earlier and a failed MH surgery 3 years earlier. There was no history of a choroidal mass in the records obtained from the previous hospital where she underwent MH surgery (Fig. 1A, 1B). At presentation, an elevated pigmented mass in the inferior fundus with surrounding serous retinal detachment was noted with a large, chronic MH (Fig. 1C). Ultrasonography revealed a mushroom-shaped choroidal mass with medium internal reflectivity; the largest basal diameter was 6.50 mm and the maximum tumor height was 9.21 mm. The mass was hypointense on T2-weighted magnetic resonance imaging and showed moderate ^{18}F-fluorodeoxyglucose uptake on positron emission tomography/computed tomography. CyberKnife radiotherapy (total dose to the tumor, 60 Gy) was delivered in four equal fractions.

Group 2 (MH after plaque brachytherapy or external beam irradiation of UM)

1) Case 2 (patient 12)

A 47-year-old woman presented with a mushroom-shaped choroidal melanoma just below the inferior arcade in her left eye with 20 / 20 vision. Ophthalmic findings of the fellow eye were unremarkable. The height and largest basal diameter of the tumor were 4.99 and 7.50 mm, respectively, and SD-OCT revealed a normal contour of the macula. She underwent ruthenium-106 plaque brachytherapy delivering 85 Gy to the tumor apex and 509.4 Gy to the sclera. One month after brachytherapy, TTT was performed twice at a 3-month interval as an adjunctive treatment. The tumor regressed well and was stable after treatment. Fifty-six months after brachytherapy, her VA decreased to 20 / 400. Fundus examination and OCT revealed a full-thickness MH (Fig. 1D, 1E). She subsequently underwent pars plana vitrectomy with internal limiting membrane peeling and pneumatic tamponade with 14% perfluoropropane (C_3F_8). The MH remained closed for 24 months after surgery, and her BCVA was 20 / 22 at the final visit (Fig. 1F). There has been no tumor recurrence or metastasis 24 months after MH repair.

2) Case 3 (patient 13)

A 42-year-old woman presented with a large mushroom-shaped juxtapapillary choroidal melanoma obscuring the optic disc and macula in her left eye (Fig. 1G). The height and largest basal diameter of the tumor were 9.63 and 11.30 mm, respectively, with a VA of hand motion. Transretinal biopsy (TRB) using a 25-gauge ocutome was performed, and CyberKnife radiotherapy with a total dose of 64 Gy was performed in four equal fractions. The tumor markedly decreased in size, with the largest basal diameter at 7.41 mm and height at 3.38 mm at 7 months after radiotherapy. At 11 months after radiotherapy, MH developed, but the VA persisted at hand motion (Fig. 1H, 1I). Due to the limited potential of visual gain, MH repair surgery was not recommended. Her most recent visit at 31 months after radiotherapy revealed no definite changes in the MH status and VA of hand motion, along with a stable tumor without metastasis.

3) Case 4 (patient 14)

A 65-year-old man presented with a large choroidal melanoma with the largest basal diameter of 10 mm and a height of 7.09 mm associated with mild vitreous hemorrhage in his right eye fundus (Fig. 1J). His ocular history included superior branch retinal vein occlusion treated with sector panretinal photocoagulation 10 years earlier.

SD-OCT revealed a relatively normal foveal contour. Ruthenium-106 plaque brachytherapy delivering 53.18 Gy to the tumor apex and 1,062 Gy to the sclera and adjunctive TTT (one session) were performed. After 2 months, the patient underwent pars plana vitrectomy with lensectomy due to a nonclearing vitreous hemorrhage and worsening cataract obscuring fundus details with VA of no light perception. The postoperative VA remained at light perception negative, presumably due to radiation optic neuropathy. Tumor regression was observed approximately 1 year later, but the patient developed exudative retinal detachment with proliferative vitreoretinopathy and underwent additional vitrectomy with retinectomy and silicone oil tamponade. MH was observed under a surgical microscope. After surgery, the retina was attached, but the MH remained open (Fig. 1K, 1L). Because the tumor was stable and there was no vision potential, MH repair surgery was not attempted. For 5 years, there was no tumor recurrence or metastasis.

4) Case 5 (patient 15)

A 46-year-old woman presented with choroidal melanoma just temporally inferior to the macula in her right eye with 20 / 25 vision (Fig. 1M). The height and largest basal diameter were 3.58 and 6.63 mm, respectively. SD-OCT revealed a lamellar hole with temporal cystoid macular edema. TRB was performed using a 25-gauge ocutome, and ruthenium-106 plaque brachytherapy delivering 92 Gy to the tumor apex and 319 Gy to the sclera was performed. Radiation retinopathy developed at 9 months after radiotherapy with a stable tumor. The patient received two intravitreal injections of bevacizumab (1.25 mg/0.05 mL) at an 8-week interval. At 12 months after radiotherapy, the patient complained of metamorphopsia with the development of MH (Fig. 1N, 1O). Subsequent vitrectomy with internal limiting membrane peeling and pneumatic tamponade with 20% sulfur hexafluoride (SF_6) resulted in hole closure (Fig. 1P). No local recurrence or distant metastasis occurred 24 months after brachytherapy and 12 months after MH surgery.

Discussion

There are limited reports in the literature on the diagnosis and management of UM with coexisting MH [7–15]. In this study, we analyzed the data of 5 new and 12 previously reported cases to identify the clinical characteristics and possible mechanisms of MH in eyes with UM. The prevalence of MH in eyes with UM in our cohort was 1.0%, which is higher than the prevalence of idiopathic MH, approximately 0.17% [16]. However, since this study evaluated the proportion of MH among UM patients within a single institution, and the data were not age- or sex-standardized to the general population, direct comparisons with prevalence rates are limited.

Two most relevant systemic risk factors of idiopathic MH include age of ≥65 years and female sex, accounting for 67% to 72% of cases [17–19]. In this study, among UM patients, the mean age at the time of MH diagnosis was 63.9 ± 14.4 years, and the female to male ratio was 2.2:1, similar to those observed in idiopathic MH. Although these two entities may coincidentally occur in the same eye, the observation that MH was found in 1% of eyes among 505 UM patients in this study suggests a potential association between the development of MH and UM. However, since female predilection is not prominent in UM, further studies are needed to investigate the risk of developing MH in female patients with UM. Moreover, UM tends to be larger and more posterior in men than in women [20], which can place more stress on the macular area and might lead to MH development in men rather than women.

Several mechanisms may account for the co-occurrence or development of MH in patients with untreated UM (group 1). The presumed pathogeneses include tangential retinal traction from the enlargement of the tumor, changes secondary to cystoid changes of the macula, or coincidence. Gold et al. [10] hypothesized that the MH may have developed as a result of the combination of tangential retinal traction from an enlarging mass, dehiscence of associated cystic macular changes, and lipid exudation in UM. In our case series, 13 of the 17 UM cases (76.5%) were located posterior to the equator. The proximity of the tumor and the macula may influence the retinal tractional forces as the tumor enlarges. Cystoid macular edema can occur in eyes with UM due to several factors, including the undetermined "toxic" effect of the tumor on the macula [6], increased capillary permeability secondary to inflammation [6,8], and microvascular abnormalities and damage to the external limiting membrane [8]. Foveal cysts may be the initial changes in the foveal structure that predisposes to

MH progression [21].

The pathogenesis of MH formation after tumor treatment (group 2) can be explained at several levels. First, MH may occur as a complication of the diagnostic procedures for UM. Transretinal or transscleral biopsy may be performed in UM to confirm the diagnosis or to obtain cytogenetic information. TRB has agreeable complication rates, but MH can occur as a postoperative complication [22]. Two patients (patients 13 and 15) in group 2 underwent TRB using an ocutome, and MH was diagnosed after 13 and 14 months, respectively. In some cases, vitrectomy and silicone oil tamponade were performed before or with radiation therapy in anticipation of the radiation-attenuating effect (patient 8) [9]. Although secondary MH formation after vitrectomy is a rare surgical complication (incidence rate, 0.24%–1.9%) [23], MH occurrence as a complication of vitrectomy cannot be ruled out.

Second, MH may occur as a complication of UM treatment. Radiation maculopathy can occur in 19.6% to 50% of patients after ruthenium-106 plaque [24–26] and in 85% of patients after external beam radiotherapy [27]. Macular cystic changes after radiation maculopathy may result in MH formation. In patient 15 in group 2, MH was diagnosed 3 months after the onset of radiation retinopathy. However, it remains whether the MH resulted from cystic changes related to radiation retinopathy. TTT using an infrared diode 810-nm laser is sometimes used to treat smaller UM or as an adjunctive therapy, which can cause retinal holes or tears if severe retinal atrophy or abnormal vitreoretinal adhesion develops in the laser-ablated area [28,29]. Balestrazzi et al. [11] reported the occurrence of MH and rhegmatogenous retinal detachment 3 months after TTT for choroidal melanoma, although it is uncertain whether MH occurred as a complication of TTT because the treated area was distant from the macula. In group 2, three patients (patients 6, 12, and 14) underwent TTT with or without plaque brachytherapy; however, the treated tumor was distant from the macula in all patients.

Third, MH may develop in association with tumor regression after treatment. The majority of UMs exhibit tumor regression after radiotherapy, usually during the first 2 years or so, before becoming stable [30]. In group 2 of this study, all patients with available data showed significant tumor regression after treatment (radioactive plaque brachytherapy or external beam radiotherapy and/or TTT) (p = 0.043). Significant tumor regression may induce changes in vitreoretinal traction forces, leading to MH formation. Six tumors (46.2%) were located in the juxtapapillary area close to the macula or macular area.

Moreover, MH formation may be associated with reduced choroidal thickness after tumor treatment. Lee et al. [31] reported that subfoveal choroidal thickness significantly decreased after ruthenium-106 brachytherapy in choroidal melanoma. The thinner choroid is implicated in the pathogenesis of idiopathic MH [32,33]. Thus, reduced choroidal thickness in treated UM may be associated with posttreatment MH formation, although the exact mechanism has yet to be determined.

The safety and effectiveness of the surgical repair of MH and the optimal duration of surgery remain to be elucidated. In this review, vitrectomy was performed in nine cases (52.9%), including seven previous cases [7,9–14] and two cases from our institute. The anatomical outcomes were favorable, with all patients with available data achieving successful hole closure after surgery. Among the six patients with available data, the mean VA showed a tendency to improve after surgery. Vitrectomy may rarely lead to intraocular or extrascleral tumor dissemination in UM [7], and MH surgery in stable tumors appears to be safe. No patient in the present study developed local tumor progression or extension after MH surgery. However, the benefits and risks of surgical management of MH should be carefully evaluated for patients with minimal visual potential.

This study has several limitations. First, its retrospective design and small sample size limit the statistical significance of our findings. Second, the proportion of MH among UM patients was derived from a single institution and was not standardized by age or sex to the general population, limiting direct comparisons with the prevalence of idiopathic MH. Third, the small sample size and the lack of comprehensive data on variables that could potentially influence MH development prevented statistical analyses aimed at identifying risk factors. These limitations underscore the need for future studies with larger cohorts and more detailed datasets to better understand MH development and to identify associated risk factors in the context of UM.

In conclusion, MH was observed in approximately 1% of UM patients both before and after tumor treatment, showing a higher prevalence compared to idiopathic MH in the general population. MH surgery appears to be safe and ef-

fective in selected patients. Therefore, in cases with stable tumors and visual potential, MH surgery could be carefully considered.

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