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Primary choroidal melanoma followed by two metachronous ipsilateral ocular metastases

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Purpose. *To describe two ipsilateral, metachronous, ocular choroidal melanoma metastases.* ***Material and methods.*** *A 64-year-old choroidal melanoma patient was initially treated with palladium-103 ophthalmic plaque brachytherapy which induced local control of the primary cancer. Seven years later, ophthalmic findings of a second, ipsilateral, discrete choroidal melanoma prompted restaging which revealed new hepatic and nodal metastases. Systemic immunotherapy (ipilimumab 3 mg/kg with nivolumab 1 mg/kg IV every 3 weeks × 4 doses) resulted in intraocular tumor regression and was followed by maintenance nivolumab 480 mg IV every 4 weeks with follow-up ophthalmic examinations.* ***Results.*** *Three years after initiation of systemic immunotherapy, the patient was found to have a second ipsilateral local recurrence of choroidal melanoma. It presented with retinal detachment, uveitis, and optic neuritis. Then, due to its anterior uveal location, extrascleral tumor extension was amenable to a diagnostic biopsy. Overall, 3 years after onset of metastatic uveal melanoma and 2 months after her second ocular metastasis, the patient died. This was 10 years after the initial diagnosis of choroidal melanoma.* ***Conclusions.*** *Metastatic choroidal melanoma can present twice in the same eye as the primary tumor. Ophthalmic and systemic examinations allowed for immunotherapy to affect initial systemic regression, vision sparing, and globe salvage.*

Keywords: metastasis; choroidal; melanoma; immunotherapy; palladium-103; plaque; brachytherapy; metachronous; ipsilateral
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Первичная меланома хориоидеи с двумя последующими метахронными ипсилатеральными глазными метастазами

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Цель *работы — описать клинический случай меланомы хориоидеи с двумя ипсилатеральными метахронными метастазами.* ***Материал и методы.*** *64-летней пациентке с меланомой хориоидеи была проведена брахитерапия офтальмологических бляшек с палладием-103, в результате которой был достигнут локальный контроль первичного рака. Семь лет спустя была обнаружена вторая ипсилатеральная дискретная меланома хориоидеи, что обусловило повторное обследование, которое выявило метастазы в печени и лимфоузлах. Системная иммунотерапия (ипилимумаб 3 мг/кг с ниволумабом 1 мг/кг внутривенно каждые 3 нед × 4 дозы) привела к регрессии внутриглазной опухоли, затем была назначена поддерживающая терапия ниволумабом*

480 мг внутривенно каждые 4 нед с последующим офтальмологическим обследованием. ***Результаты.*** *Через 3 года после начала системной иммунотерапии у пациентки был выявлен еще один ипсилатеральный локальный рецидив меланомы хориоидеи. Он проявлялся отслойкой сетчатки, увеитом и невритом зрительного нерва. Благодаря переднему увеальному расположению и экстрасклеральному прорастанию опухоли удалось провести диагностическую биопсию. Затем, через 3 года после появления метастатической увеальной меланомы и через 2 мес после ее второго метастаза в глаз, пациентка умерла. Это случилось через 10 лет после первого выявления хориоидальной меланомы.* ***Заключение.*** *Метастатическая меланома хориоидеи может дважды обнаруживаться в одном и том же глазу в виде первичной опухоли. Офтальмологическое и системное обследование дало возможность провести иммунотерапию, способствовавшую системной регрессии заболевания, сохранению зрения и глазного яблока.*

Ключевые слова: метастазы; хориоидея; меланома; иммунотерапия; палладий-103; брахитерапия; метахронный; ипсилатеральный
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Primary uveal melanoma presents as a solitary unifocal tumor with a North American incidence of 6 cases per million per year [1]. Bilateral uveal melanomas are much less common, in fact H. Shammas and R. Watzke [2] estimated a lifetime prevalence of 1 in 50 million, or a single case of bilateral uveal melanoma every 18 years in the United States. Unilateral multifocal uveal melanomas have been reported in the context of ocular or oculodermal melanocytosis and retino-invasive melanoma [1, 3–5]. The latter was defined as primary tumor-seed invasion of the retina at a non-contiguous location [5]. In these cases, an ipsilateral multifocal uveal melanoma was not diagnosed at presentation and there should be no evidence of systemic metastatic disease. Then, should second, ipsilateral intraocular melanoma present, the differential diagnosis should include recurrence, a second primary tumor, or intraocular metastasis.

Metastasis from primary uveal melanoma metastasis typically manifests within 5 years and rarely more than 10 years following treatment [1, 6]. The most commonly reported areas to which uveal melanoma metastasizes are: liver (95%), lungs (24%), bone (16%), and skin (11%) [1, 6]. However, reports on patients presenting with Stage-IV uveal melanoma suggests that whole-body imaging [e.g. positron-emission tomography / computed tomography (PET/CT)] will more likely to reveal extrahepatic metastatic disease and that patients with larger American Joint Committee on Cancer (AJCC) T-size uveal melanomas were more likely to present at Stage-IV [7–11]. While the incidence of ipsilateral ocular metastasis is unknown; there exist reported cases where a second independent primary tumor or an intraocular metastasis occurred [12–17].

PURPOSE of this work is to describe the clinical case of two ipsilateral, metachronous, ocular choroidal melanoma metastases.

MATERIAL AND METHODS

Ethics Committee Statement. Patient permission was obtained to publish this patient's health care information. Thus, this work conforms to the Tenets of the Declaration of Helsinki and the Health Insurance Privacy and Portability Act of The United States of America.

In this case, a patient with choroidal melanoma presented with both ipsilateral uveal and systemic metastasis 7.5 years after radiation-plaque induced local control of her primary tumor. All recurrent disease was controlled with immunotherapy for 3 years until the patient presented again with an additional ipsilateral uveal metastasis with anterior extrascleral extension. Systemic restaging revealed new hepatic and nodal metastases and an episcleral biopsy confirmed the second ipsilateral choroidal melanoma metastasis.

The Primary Choroidal Melanoma. In 2010, a 63-year-old female was referred to The New York Eye Cancer Center for evaluation of a choroidal mass in her left eye. Ophthalmic oncology evaluation revealed a best corrected visual acuity of 20/25, an intraocular pressure of 17 mm Hg and no anterior segment manifestation of tumor. Indirect ophthalmoscopy revealed a dome-shaped, melanotic melanoma with a secondary exudative retinal detachment in the supertemporal quadrant. 20 MHz B-scan ultrasound imaging was used to measure basal tumor dimensions of 8.6 × 7.8 mm and an apical height of 2.4 mm. Thus, the tumor was clinically diagnosed as an AJCC T1-sized choroidal melanoma [10]. Systemic staging with PET/CT was negative for metastatic disease. Palladium-103 (^{103}Pd) ophthalmic plaque brachytherapy was employed followed by delimiting laser around the tumor's inferior margins [18]. At 10 months status post plaque brachytherapy, an inactive appearing tumor residual had stabilized at 1.5 mm in apical height. Systemic surveillance for metastatic disease involved abdominal magnetic resonance imaging (MRI) scans every 6 months for the first 5 years, then at yearly intervals [1].

The First Ipsilateral Ocular Metastasis. At 7.5 years after treatment and 7 months after her last abdominal imaging study, indirect ophthalmoscopy revealed a new, discrete choroidal melanoma in the ipsilateral eye (Figure 1).

Ultrasonography revealed moderate internal reflectivity and measured tumor dimensions of 6.6 mm (height) and 14.5×12.3 mm (base). Discovery of the new tumor prompted restaging with PET/CT which revealed several fluorodeoxyglucose (FDG) avid low attenuation liver tumors. The left hepatic lobe exhibited 1 tumor with a specific uptake value (SUV) of 4.9, and dimensions 2.0 × 1.3 cm. Three tumors were noted in the right hepatic lobe, with an SUV of 4.0, and dimensions of 1.0 × 0.8 cm, an SUV of 4.5, and dimensions of 2.0 × 1.2 cm, and an SUV of 6.6, and dimensions 0.6 × 0.5 cm respectively. A liver biopsy confirmed the diagnosis of GNA11 mutated, metastatic melanoma. The diagnosis of systemic uveal melanoma affirmed the diagnosis of choroidal metastasis and therefore, ocular treatment was deferred to systemic immunotherapy. Systemic treatment involved induction with a combination ipilimumab (3mg/kg) and nivolumab (1mg/kg) intravenous (IV) every 3 weeks for 4 cycles, followed by maintenance every 4 weeks with nivolumab (480 mg, IV). After both induction therapy with ipilimumab and nivolumab and after 8 weeks of nivolumab maintenance, follow-up radiographic imaging demonstrated a significant shrinkage of all metastatic sites, including the eye. Of note, a recent phase II trial of ipilimumab and nivolumab followed by nivolumab maintenance demonstrated an overall response rate of 18% [19]. After 14 months of systemic immunotherapy, ultrasound imaging

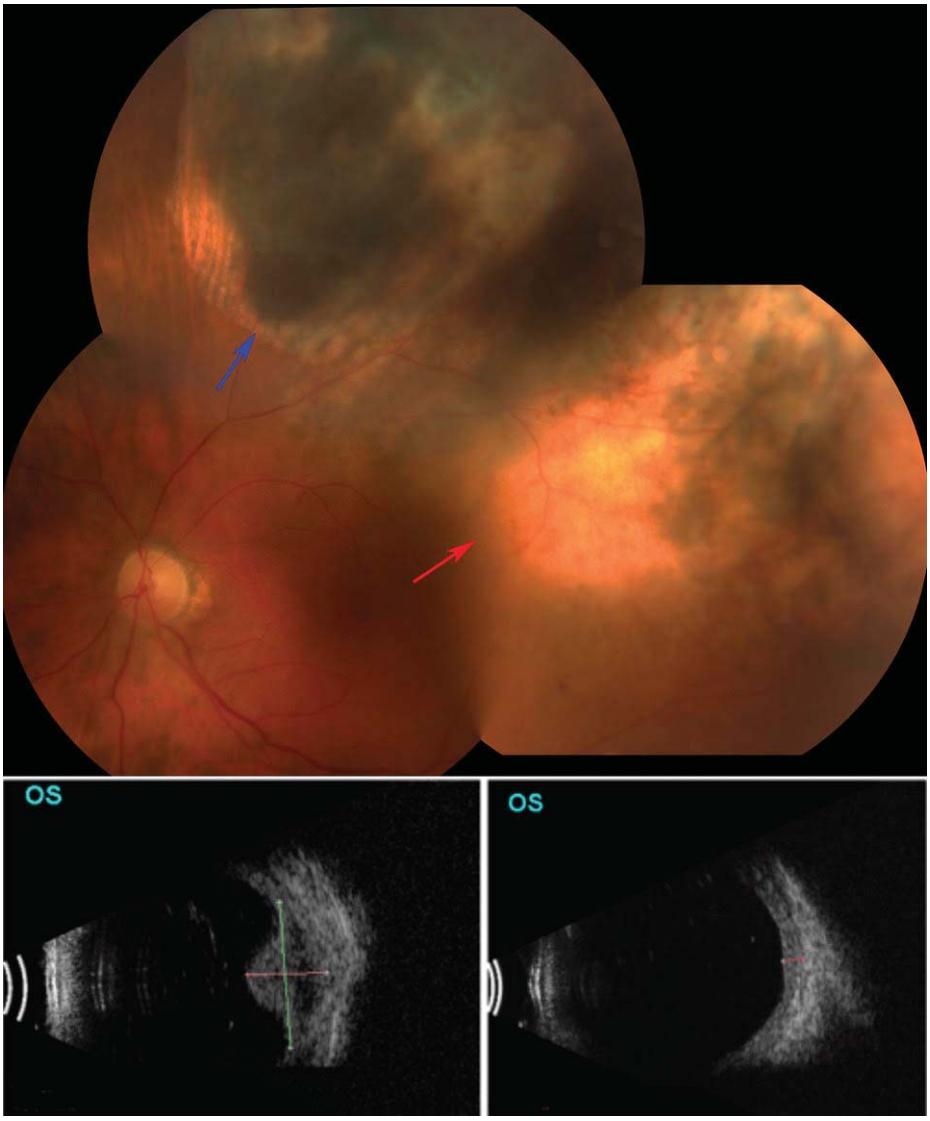

Fig. 1. Top: fundus photography reveals the darky pigmented regressed primary choroidal melanoma (blue arrow) and a new metastatic pigmented choroidal melanoma (red arrow). Bottom left: ultrasonographic images of the choroidal metastatic tumor in the left eye at the 2:30 o'clock meridian. Bottom right: ultrasound imaging at 14 months after systemic immunotherapy demonstrates tumor regression (measured from 6.6 mm to 1.5 mm in apical height). Local control of the first metastatic lesion was noted throughout follow up

Рис. 1. Вверху: на фотографии глазного дна видна темная пигментированная регрессирующая первичная меланома хориоидеи (синяя стрелка) и новая метастатическая пигментированная меланома хориоидеи (красная стрелка). Внизу слева: УЗИ новой метастатической опухоли хориоидеи в левом глазу на меридиане 2,5 ч. Внизу справа: УЗИ через 14 мес после системной иммунотерапии демонстрирует регрессию опухоли (с 6,6 до 1,5 мм в апикальной высоте). Состояние глаза после первого метастатического поражения контролировалось на протяжении всего периода наблюдения

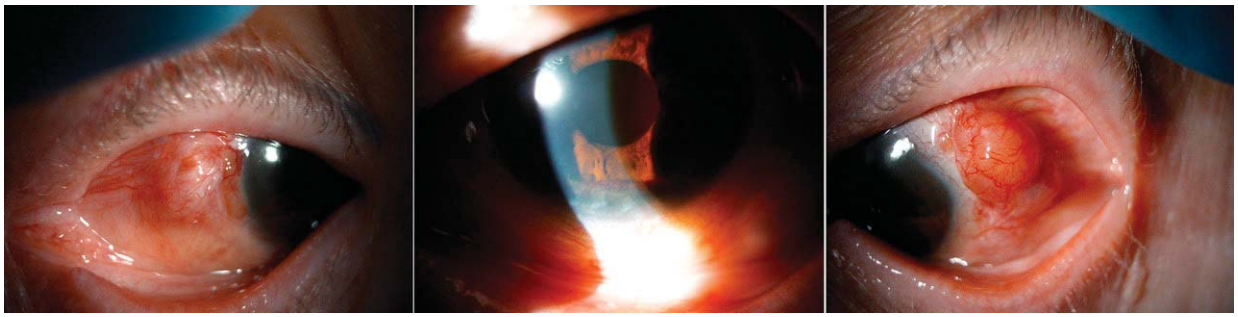

Fig. 2. Slit-lamp photographs at presentation of the second, ipsilateral metastasis. Center: a combination of tumor and blood fill 20% of the inferior anterior chamber. Left and Right: images reveal multiple epibulbar, extrascleral metastatic uveal melanomas. The superotemporal tumor was chosen for biopsy (see Figure 4)

Рис. 2. Фотографии с щелевой лампой второго ипсилатерального метастаза. В центре: опухоль и кровь заполняют 20% нижней части передней камеры. Слева и справа: видны множественные эпибульбарные экстрасклеральные метастатические увеальные меланомы. Для биопсии была выбрана верхневисочная опухоль (см. рис. 4)

revealed regression, then stabilization of the choroidal metastasis. The metastasis tumor height changed from 6.6 to 1.5 mm without any additional local intervention (Figure 1, bottom right).

The Second Ipsilateral Ocular Metastasis. Three years after initiation of immunotherapy, new epibulbar tumors and a pigmented hyphema were noted (Figure 2).

High frequency ultrasound imaging revealed that a ring-like anterior metastatic melanoma was separate from both the primary and first metastatic posterior choroidal tumors (Figure 3).

Biopsy of the temporal subconjunctival tumor revealed malignant melanoma (Figure 4). Histomorphologic features of the tumor shows an expansile nodule formed of confluent nests

of tumor cells underlying a thinned conjunctival epithelium containing mucocytes. Tumor nests are formed of epithelioid cells with vesicular cytoplasm, hyperchromatic nuclei with prominent, cherry-red macronucleoli, and numerous mitotic figures. Immunohistochemical studies show positive and strong labeling for SOX-10, HMB45, Mel-A and a KI-67 labeling index of approximately 60%.

Two months later, our patient died of hepatic-failure related to metastatic uveal melanoma. This was 10-years after the initial diagnosis of choroidal melanoma.

DISCUSSION

This rare case teaches that it was possible for a primary uveal melanoma tumor to twice metastasize to the same eye. This event was made possible (in part) due to successful systemic tumor suppression with immunotherapy. Prior cases of metachronous ipsilateral uveal melanomas often cannot determine whether the second melanoma is a second primary tumor or an intraocular metastasis. Retino-invasive choroidal melanomas are considered multifocal, due to intraocular seeding, transretinal seeding of the primary tumor [15]. Therefore, differentiation of unilateral multifocal uveal melanoma from ipsilateral uveal melanoma metastasis largely rests upon the timing of clinical presentation of the intraocular tumors and as they relate to the detection of synchronous systemic metastasis.

At the time of our patient's first ipsilateral metastasis we found hepatic and nodal metastases. Confirmatory liver biopsy demonstrated a GNA11-mutated melanoma. Both the systemic and intraocular metastases synchronously responded to systemic immunotherapy. This evidence confirmed that the first secondary intraocular tumor was metastatic [12]. Others might suggest that metastasis is a stochastic and time-dependent process, and thus intraocular and distant metastasis may not occur simultaneously, particularly in cases of ocular melanosis, the Nevus of Ota and dysplastic nevus syndrome [1, 4].

This case uniquely demonstrates that a second ipsilateral late local recurrence can follow successful local treatment of the primary and ipsilateral metastatic ocular melanoma. Evidence of successful local control of our patient's primary tumor include: the lack of growth local growth over 7-years follow-up as well as our centers' near-real-time measured and published outcome data (see https://eyecancer.com/results) [20]. This continually updated doctor reported outcome (DRO) data has shown that as of the writing of this case report, our methods of radiation plaque treatment has resulted in a very high, 99.7% local tumor control rate [21]. This is not the same for all centers. The AJCC Ophthalmic Oncology Task Force registry found that local tumor recurrence (failure of local control) was associated with a significantly higher risk of systemic metastasis. Of 3217 patients with posterior uveal melanoma at a median follow-up of 3.7 years, 152 (4.7%) experienced local recurrence [22]. Furthermore, local tumor recurrence increased the risk of systemic metastasis by a hazard ratio (HR) of 6.28 (95% CI, 4.4–8.9; $p < 0.001$). In addition, local recurrence events were detected up to 9.8 years after primary treatment [22].

Chemotherapy, immunotherapy, or liver-directed treatments for uveal melanoma metastasis may prolong life, but do not typically prevent cancer related death [1, 6, 19, 23]. This contrasts to recent improvements in immunotherapy outcomes for patients with metastatic cutaneous melanoma. This difference has been thought to be partially related to genetic differences between these two types of melanomas. For example, mutations in the GNAQ or GNA11 genes are common in uveal but not in cutaneous melanoma [23–26]. Conversely, BRAF and NRAS are common in cutaneous melanoma but extremely rare in uveal melanoma [24–27]. These differences highlight the lack of similarity between these two tumors as demonstrated by their different response to immunotherapy. In our case, the first ipsilateral and synchronous systemic metastases was found to respond to immunotherapy as it induced a dramatic, durable reduction of the metastatic intraocular tumor size as well as 3-years of local metastasis control. However,

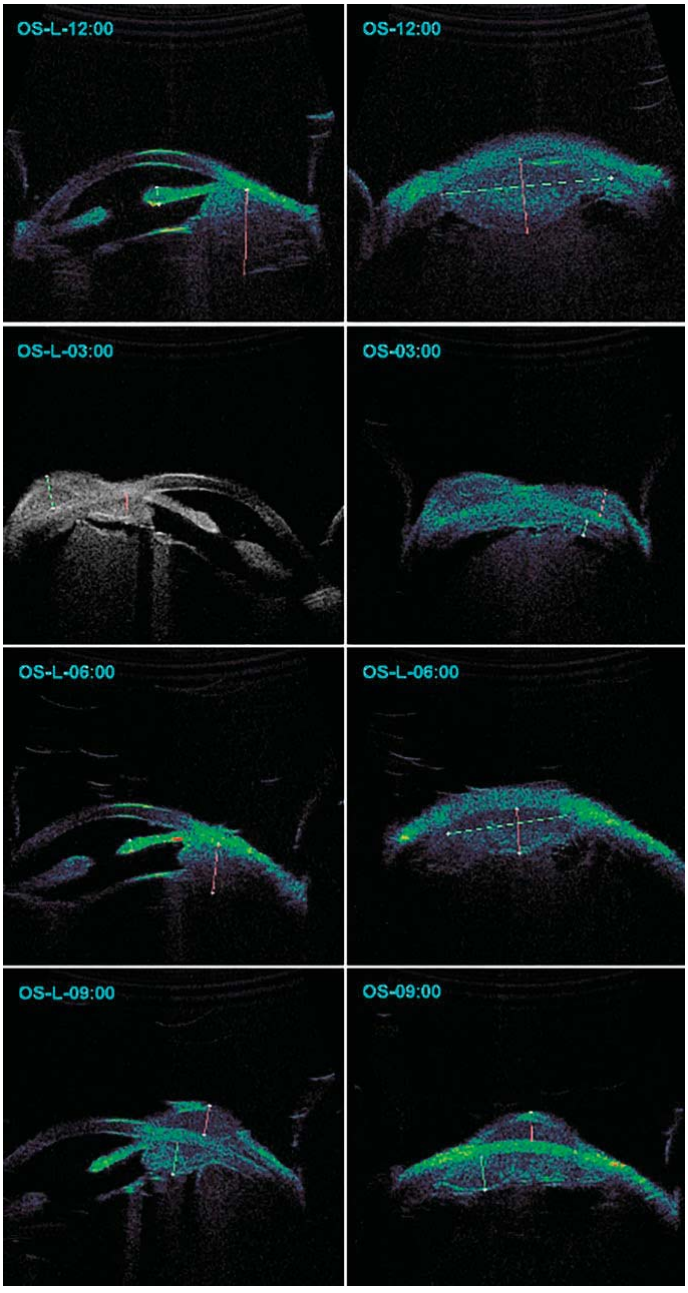

Fig. 3. A 35 MHz high-frequency ultrasound examination was performed in movie mode. Selected still images were recorded and collected at sequential clock hours (12:00, 3:00, 6:00 and 9:00). They reveal the tumor's anterior, ring configuration, multiple epibulbar extrascleral extensions as well as the tumors moderately to low internal reflectivity (inside and outside the eye)

Рис. 3. Высокочастотное ультразвуковое исследование с частотой 35 МГц было выполнено в режиме видеосъемки. Выбранные статические изображения были записаны и собраны в последовательные изображения на отдельных меридианах (12:00, 3:00, 6:00 и 9:00). Они выявляют переднюю кольцевую конфигурацию опухоли, множественные эпибульбарные экстрасклеральные расширения, а также опухоли со средней или низкой внутренней отражательной способностью (внутри и снаружи глаза)

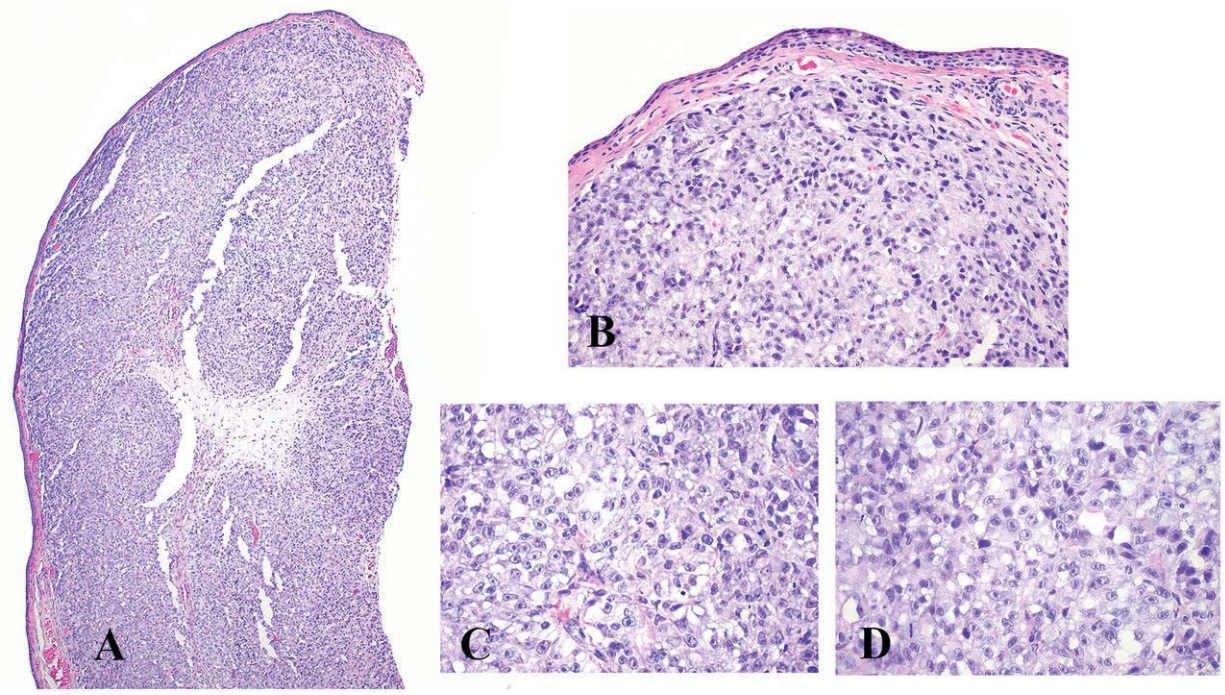

Fig. 4. Histopathologic evaluation of the temporal nodule shave biopsy was performed. A — low magnification image shows a nodule of malignant melanoma cells arranged in a sheet-like, confluent pattern (H&E; × 20). B — a thin rim of conjunctival mucosa with mucocytes is seen overlying the tumor (H&E; × 40). C — higher magnification shows tumor cells are round shaped with vesicular cytoplasm, hyperchromatic nuclei, and prominent nucleoli. D — numerous mitotic figures are seen throughout the tumor (H&E; × 40)

Рис. 2. Проведена гистологическая оценка бритвенной биопсии височного узелка. A — изображение с малым увеличением показывает узелок клеток злокачественной меланомы, расположенных в виде листообразного, сливающегося паттерна (H&E; × 20). B — над опухолью виден тонкий ободок слизистой оболочки конъюнктивы с мукоцитами (H&E; × 40). C — большее увеличение показывает, что опухолевые клетки имеют округлую форму с везикулярной цитоплазмой, гиперхромными ядрами и выступающими ядрышками. D — по всей опухоли видны многочисленные митотические фигуры (H&E; × 40)

it was not ultimately capable of preventing a second ipsilateral metastasis or preservation of life.

CONCLUSIONS

This case demonstrates the possibility of two metachronous choroidal melanoma metastases to the same eye. The primary choroidal melanoma exhibited excellent local control for all 10 years after 103Pd plaque brachytherapy. The first intraocular metastasis was located separate from the primary melanoma. The second intraocular metastasis presented as an anterior uveal tumor with extra scleral extension. This case thus emphasizes the importance of both ophthalmic and systemic periodic surveys during long-term metastatic surveillance of uveal melanoma patients.

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