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

Conflict of interests: there is no conflict of interests.

Financial disclosure: The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this study was supported by the Eye Cancer Foundation, Inc.

For citation: Finger P.T., Yin C.T., Pavlick A.C., Farhat N. Primary choroidal melanoma followed by two metachronous ipsilateral ocular metastases. Russian ophthalmological journal. 2022; 15 (1): 122-7. (In Russian). https://doi.org/10.21516/2072-0076-2022-15-1-122-127

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 лимфузлах. Системная иммунотерапия (ипилимумаб 3 мг/кг с ниволумабом 1 мг/кг внутривенно каждые 3 нед × 4 дозы) привела к рецессии внутриглазной опухоли, затем была назначена поддерживающая терапия ниволумабом.
Метастатическая меланома хориоидеи может развиваться через 10 лет после первого выявления хориоидальной меланомы. Заключение. Метастатическая меланома хориоидеи может после периода обследования в одном или другом глазе удалить провести диагностику меланомы. Затем, через 3 года после появления метастатической меланомы и через 2 мес после её второго метастаза в глаз, пациентка умерла. Это случилось через 2 года после первого выявления хориоидальной меланомы. 

Ключевые слова: метастазы; хориоидея; меланома; иммунотерапия; палладий-103; брахитерапия; метахронный; инсилатеральный

Конфликт интересов: отсутствует.

Прозрачность финансовой деятельности: авторы заявляют о финансовой поддержке исследования The Eye Cancer Foundation, Inc.

Для цитирования: Фингер П.Т., Йин К.Т., Павлик А.К., Фархат Н. Первичная меланома хориоидеи с двумя последующими метахронными инсилатеральными глазными метастазами. Российский офтальмологический журнал. 2022; 15(1): 122-7.

https://doi.org/10.21516/2072-0076-2022-15-1-122-127
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 expansive nodule formed of confluent nests

Fig. 1. Top: fundus photography reveals the darkly 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

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)
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...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 tumors 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,
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.

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

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Author’s contribution: Paul T. Finger — carried out provided patient care, initiated the research project, wrote, and reviewed the manuscript; Claire T. Yin — collected the data and wrote the manuscript; Anna C. Pavlick — provided medical oncology care and critically reviewed the manuscript; Nada Farhat — provided pathology images and analysis as well as critical review of the manuscript.

Originally received: 03.10.2021. Final revision: 16.10.2021. Accepted: 17.10.2021

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