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Metastatic Cutaneous Melanoma Presenting with Choroidal Metastasis Simulating Primary Uveal Melanoma

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Established Facts

- Cutaneous melanoma can rarely involve the eye and can even be the first presentation of metastasis.
- Enucleation provides effective palliation for a blind, painful eye with tumor burden.

Novel Insights

- It is not always possible to definitively distinguish cutaneous melanoma choroidal metastasis from uveal melanoma based on clinical exam, imaging studies, histopathology, and immunocytochemistry.
- Tumor genetic testing can help distinguish cutaneous versus primary uveal melanoma due to genetically distinct initiating mutations.

Keywords
Metastatic cutaneous melanoma · Ocular metastasis · Genetic testing

Abstract

Purpose: To report a case of metastatic cutaneous melanoma presenting with choroidal metastasis simulating primary uveal melanoma. ***Design:*** Case report. ***Method:*** Presentation of clinical, radiographic, histopathologic, and tumor genetic findings in a patient with cutaneous melanoma with choroidal metastasis. ***Results:*** A 50-year-old man with a remote history of stage 1A cutaneous melanoma presented with eye pain, peripheral vision loss, floaters, red eye, and choroidal mass that was originally diagnosed as a primary uveal melanoma at an outside institution; however, subsequent imaging and clinical evaluation demonstrated that this choroidal mass was the first manifestation of widely metastatic cutaneous melanoma (liver, pancreas, lung, bone, brain, and orbit lesions). Histopathologic analysis of the tumor after enucleation was consistent with cutaneous melanoma, and tumor genetic testing was positive for *BRAF* V600E mutation, confirming the choroidal lesion to be a cutaneous melanoma metastasis rather than a primary choroidal melanoma. ***Con-***

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clusions: Metastatic cutaneous melanoma to the orbit or globe occurs rarely. Tumor genetic testing may help differentiate metastatic cutaneous melanoma from primary uveal melanoma in cases where the diagnosis is uncertain, and can also inform therapy and prognostic counseling.

Introduction

Approximately 5% of patients with cutaneous melanoma develop distant metastases via lymphatic spread, most commonly to the lungs, liver skin, and brain, with the 5-year survival rate of approximately 22% [1]. Very rarely, metastatic cutaneous melanoma can involve the eye and orbit, accounting for less than 5% of all ocular and orbital metastases [1–5]. However, this may be an underestimate, as at least one-third of metastatic melanoma patients described in one autopsy study were found to have asymptomatic intraocular metastases [6].

In cases of metastatic cutaneous melanoma to the eye, the most common primary tumor location is the trunk, followed by the upper and lower extremities, and least commonly the head and neck [1]. Intraocular metastases are more common than extraocular metastases. The uvea is involved in approximately 75% of cases, but other reported sites include the orbit, retina, vitreous, optic nerve, conjunctiva, and anterior chamber [1]. Cutaneous melanoma choroidal metastases typically grow in a more rapid and aggressive manner than do primary uveal melanomas, and are often multifocal [1].

The typical presenting symptoms in patients with intraocular metastatic cutaneous melanoma include decreased vision, floaters, pain, and red eye. Patients may present with diplopia if the extraocular muscles are involved. Secondary ocular complications have been reported in more than half of all affected patients, including iris neovascularization, glaucoma, uveitis, and vitreous detachment or hemorrhage [1].

Case Report

A 50-year-old man presented with a 1-week history of new-onset right eye pain, peripheral vision loss, floaters, and red eye. He had developed new right eye irritation 3 weeks earlier, initially diagnosed as conjunctivitis and treated with topical antibiotics. His visual acuity was 20/30 in the right eye and 20/20 in the left eye. His right eye had mild injection and moderate chemosis. On dilated funduscopic exam, he was found to have a large, inferotemporal, amelanotic, dome-shaped choroidal lesion in the right eye (Fig. 1a). Aside from symmetric, 1+ nuclear sclerosis bilaterally, the remainder of the ophthalmic exam was unremarkable. B-scan ultrasound of the right eye showed a dome-shaped choroidal mass with low-intermediate internal reflectivity, measuring 11.56 by 12.5 mm, with 5 mm thickness and with associated serous retinal detachment inferiorly. This lesion was diagnosed as a primary uveal melanoma by his referring physician.

The patient's medical history was significant for stage 1A cutaneous melanoma 7 years prior (a nonulcerated, upper paraspinal cutaneous melanoma). Diagnostic biopsy at that time revealed a 0.89 mm Breslow depth with invasion limited to the papillary dermis (Clark's level III), and an intermediate mitotic rate. He underwent definitive management with a wide local full-thickness excision with 1 cm margins and a deep left axilla dissection with sentinel lymph node biopsy; two sentinel nodes were negative for melanoma. Given his negative biopsy, no further adjuvant treatment was required, and the patient was instructed to follow up every 3–4 months with Dermatology at an outside institution.

Within 3 weeks of ophthalmic presentation, the patient had no light perception vision in his right eye and complained of worsening ocular pain. CT imaging demonstrated pulmonary nodules, multiple liver masses, and a nodule in the dorsal pancreatic body, all presumed to be metastatic cutaneous melanoma. He underwent biopsy of a liver lesion and an abdominal subcutaneous nodule, and both were found to be metastatic melanoma. *BRAF* mutation testing performed on both lesions was positive for the *BRAF* V600E mutation. Immunohistochemistry staining of the hepatic lesion was diffusely positive for S100, HMB-45, and Melan-A, and approximately 5% of tumor cells also stained positive for PD1.

Repeat PET/CT imaging 3 weeks later revealed rapid interval progression with widespread metastatic disease, including the right choroidal lesion, multiple lung nodules increased in size and number, and numerous hepatic and skeletal lesions. Brain MRI revealed extensive intracranial disease (7 masses) consistent with metastatic melanoma within both cerebral hemispheres and the right cerebellar hemisphere. Mild vasogenic edema was noted associated with the right orbital lesion (enlarged globe measuring 3 × 2.8 × 2.5 cm), as well as a large vitreous detachment, extensive retrobulbar edema, and proptosis.

Whole-brain radiation therapy and palliative radiotherapy to the right orbit were initiated, during which time the patient presented to our center's Ocular Oncology and Medical Oncology services (70 days after his initial presentation). He had severe right eye pain and no light perception in the eye, as well as marked conjunctival injection with tortuous episcleral vessels, a dense cataract, iris rubeosis, and a poor view to the posterior segment. B-scan ultrasound demonstrated a highly elevated choroidal mass located posterior to the equator and extending into the periphery in the inferotemporal quadrant with medium to low, irregular internal reflectivity, with associated total retinal detachment with dense membranes and debris within the vitreal cavity. The tumor measured 21.4 × 19.7 mm with 13-mm thickness (Fig. 1b). Given the patient's late presentation to our Center with a blind painful eye, transretinal biopsy of the ocular lesion was not possible.

The patient elected for urgent enucleation after completing his radiation therapy. Histopathologic analysis of the globe revealed a large, amelanotic mass arising from the choroid measuring 12.5 by 20.0 mm in basal diameter with 13-mm thickness, extending into the subretinal space and associated with an exudative retinal detachment (Fig. 1c). No extraocular extension was noted. The cor-

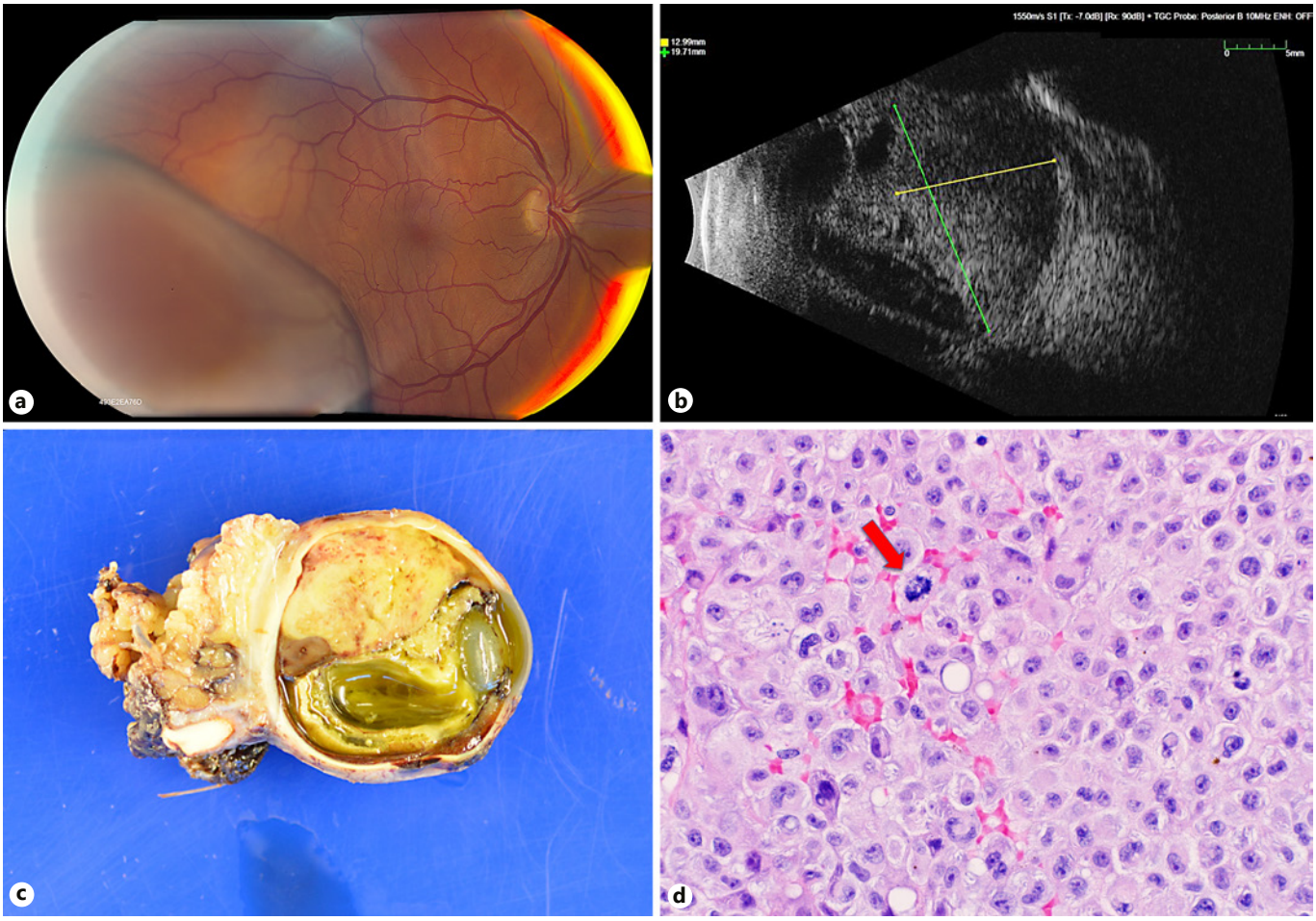

Fig. 1. a Dilated fundoscopic exam of the right eye at initial presentation, demonstrating a large, inferotemporal, amelanotic, dome-shaped choroidal lesion. **b** B-scan ultrasound showing highly elevated, dome-shaped choroidal mass with medium low internal reflectivity, exudative retinal detachment, and vitreous hemorrhage. **c** Pathology of the enucleated globe and orbital tissue posteriorly. A large, amelanotic choroidal mass with 12.5 × 20 mm basal diameter and 13-mm thickness, extending into the subretinal space with associated exudative retinal detachment. **d** Histopathology demonstrating epithelioid cells (red arrow) with high mitotic activity, seen in both metastatic cutaneous melanoma and uveal melanoma.

nea was diffusely opaque, and there were ischemic changes in the iris, ciliary body, and lens consistent with neovascular glaucoma.

On microscopic analysis (Fig. 1d), the tumor was composed of a few spindle-shaped and many epithelioid melanoma cells, mostly without pigment. Mib-1 staining was positive in up to 15% of the tumor cells in focal areas, and the tumor cells were also positive for HMB-45, SOX10, and MITF staining. Staining was negative for HepPar1, EMA, pancytokeratin, and CK7. The tumor invaded the retina, and the sclera beneath the tumor was edematous and infiltrated with inflammatory cells. A BRAF testing assay utilizing PCR revealed that the tumor was positive for the *BRAF* V600E mutation.

Systemic chemotherapy was initiated 2 days after enucleation with dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor). The patient passed away 3 months later from complications of metastatic disease.

Discussion

A cutaneous primary source is known at the time of diagnosis in nearly all cases of metastatic melanoma to the eye and orbit. However, in a large review of 93 cases, 2 patients had ocular metastasis as the first presentation of their systemic disease, as did this patient [1]. The mean interval between known primary cutaneous melanoma diagnosis and subsequent ocular metastasis was 3 years, and 72% of patients had ocular metastases within 5 years of initial diagnosis [1]. However, 16% of patients did not develop ocular metastasis for over 7 years from original diagnosis, as with this patient.

This case demonstrates that it is not always possible to definitively distinguish metastatic cutaneous melanoma from uveal melanoma based on initial clinical exam, ocular imaging studies, or histopathology and immunocytochemistry. This patient's choroidal metastasis was originally diagnosed as a primary uveal melanoma, although subsequently his clinical history of remote early stage cutaneous melanoma and imaging studies demonstrating widely metastatic disease made the diagnosis quite clear. Although not absolutely necessary in such cases, tumor genetic testing can often be helpful to confirm the diagnosis, since cutaneous and uveal melanomas have different genetic mutation profiles (with some rare reported exceptions). Cutaneous melanomas typically have activating mutations in *BRAF* (~50%) or *NRAS* (~15%) [7, 8], and loss of tumor suppressor genes such as *CDKN2A* and *PTEN*. In contrast, uveal melanomas typically lack *BRAF* mutations [9] and are characterized by activating mutations in *GNAQ* or *GNA11* and possible *BAP1* loss [10, 11] and monosomy 3, which increase the risk of metastasis [12]. This patient's choroidal tumor was positive for the same *BRAF* mutation detected in his liver metastasis, confirming the ocular lesion to be metastatic cutaneous melanoma.

Surgical resection and radiation therapy have historically been the primary methods of local treatment for extraocular metastatic cutaneous melanoma. Until the relatively recent development of several promising systemic immunotherapy agents, the management of widely disseminated and intraocular metastatic cutaneous melanoma has been more limited, focusing primarily on radiotherapy, enucleation, and efforts to preserve vision and quality of life. The mean survival after diagnosis of ocular metastases from cutaneous melanoma has been reported to be 7.3–8.8 months [1, 13], but these survival times are now likely underestimates given the subsequent development of effective systemic immunotherapies for metastatic cutaneous melanoma.

Statement of Ethics

The study complied with the guidelines for human studies. The subject gave informed consent for use of clinical images, and the case report was deemed exempt by the Institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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