Cutaneous Metastasis of Uveal Melanoma

Nicole Edmonds[1] ▪ Seth Martin, MD[2] ▪ R. Hal Flowers, MD[3]

A 65-year-old man presented to our dermatology clinic with a 1-week history of 2 new scalp lesions. He denied any associated pruritus or bleeding.

He had a medical history significant for hypertension and uveal melanoma with recent metastasis to the liver. His liver lesions were treated with microwave thermal ablation. The patient had been receiving carboplatin and paclitaxel chemotherapy for 3 months.

Physical examination

Two smooth, uniformly bluish-black papules were noted with surrounding telangiectasias on the posterior crown **(Figure)**, as well as 3 similar-appearing papules on the left hairline anterior to the ear. Initial differential diagnosis included metastatic or new primary melanoma, agminated blue nevi, and angiolymphohyperplasia with eosinophilia.

Diagnostic testing

Punch biopsy of one of the lesions on the left preauricular scalp revealed a malignant epithelioid melanocytic neoplasm with significant atypia, prominent nucleoli, and frequent mitoses, expanding from the dermis into the subcutis. Test results from the lesion cells were positive for Melan-A and programmed death-ligand 1 (PDL-1, 5% membranous staining) and negative for *BRAF*, consistent with a diagnosis of cutaneous metastasis of uveal melanoma.

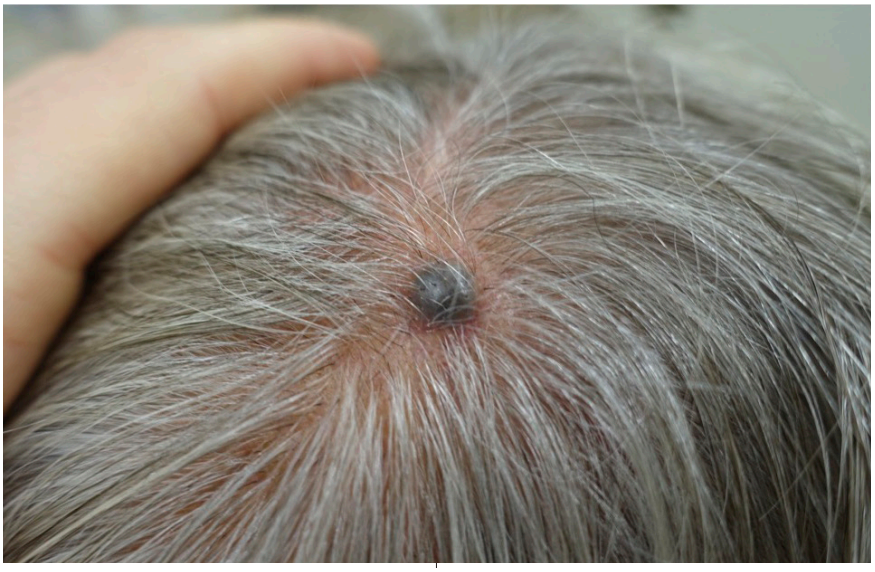

Figure. Smooth, uniformly bluish-black papule with surrounding telangiectasias on the posterior crown.

Treatment and management

The patient was started on an experimental combination immunotherapy regimen consisting of systemic administration of durvalumab, 1500 mg, every 1 month, as well as intratumoral injections of polyinosinic-polycytidylic acid and poly-L-lysine (poly-ICLC) and tremelimumab.

Discussion

Melanomas of the choroid, ciliary body, and iris are collectively known as uveal melanoma, with choroid melanoma being the most common.[1] Although

AFFILIATIONS:

[1]Medical Student, Department of Dermatology, University of Virginia School of Medicine, Charlottesville, Virginia

[2]Resident Physician, Department of Dermatology, University of Virginia School of Medicine, Charlottesville, Virginia

[3]Assistant Professor, Department of Dermatology, University of Virginia School of Medicine, Charlottesville, Virginia

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CORRESPONDENCE:

Nichole Edmonds, University of Virginia Health System, 1221 Lee Street, PO Box 800718, Charlottesville, VA 22903 (nle2fy@virginia.edu)

uveal melanomas are the most common intraocular tumors in adults, they represent only 3.1% of all melanomas.[1] The incidence of uveal melanoma varies from 0.1 to 8.6 per million population based on age, ethnicity, and latitude.[2] Risk factors for uveal melanoma are similar to cutaneous melanoma such as fair skin, light eye color, and inability to tan, as well as unique risk factors such as ocular or oculodermal melanocytosis; cutaneous, iris, or choroidal nevi; and *BRCA1*-associated protein 1 (BAP-1) mutations.[3] About 30% of patients with choroidal or ciliary body melanoma are asymptomatic at the time of presentation, but symptoms may include blurred vision, photopsia, floaters, visual field loss, visible tumor, pain, or metamorphopsia.[3] In comparison, melanomas of the iris are typically diagnosed earlier because associated iris color change and pupil distortion are easily identified by the patient.[3]

The diagnosis of uveal melanoma is based primarily on clinical examination with a slit lamp and indirect ophthalmoscopy together with ultrasonography of the eye.[3] Upon slit light examination, most posterior uveal melanomas appear dome-shaped, and 55% are pigmented, while 15% are nonpigmented and 30% are mixed.[3] Larger apical and basal dimensions are more likely seen in neoplastic lesions.[4] Upon indirect ophthalmoscopic examination, uveal melanomas exhibit subretinal fluid and orange pigment—termed lipofuscin—which arises from breakdown of the retina or tumor itself.[4] Benign lesions show evidence of drusen and pigment epithelial changes.[4] On ocular echography scan, melanomas exhibit low internal reflectivity and have an intrinsic acoustic quiet zone.[4] Other tests such as fluorescein angiography, gonioscopy, and optical coherence tomography can be conducted if the melanoma is not well visualized with the previously mentioned diagnostic tests.[3] A clinical biopsy is rarely necessary to make the diagnosis, although a prognostic biopsy can be performed to assess the tumor for genetics and the risk of future metastasis.[4]

While uveal melanomas and cutaneous melanomas are both derived from melanocytes, they differ both clinically and biologically. Cutaneous melanomas are usually associated with *BRAF* or *NRAS* mutations, while uveal melanomas are often found to have *GNAQ* or *GNA11* mutations.[5] Additionally, uveal melanomas have a worse prognosis, with almost 50% of uveal melanomas developing metastatic disease and 76% causing death within the year.[5,6] Metastasis of uveal melanoma is primarily hematogenous to the liver, lungs, bone, and skin.[6]

A paucity of data on treatment of uveal melanoma with metastasis to the skin has resulted in a lack of consensus on management approach to such cases. Checkpoint inhibitors such as antiprogrammed cell death protein 1 (PD-1, nivolumab) and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4, ipilimumab or tremelimumab) inhibitors are some of the most successful agents for cutaneous melanoma therapy, with success rates as high as 60% with combination therapy.[7] Unfortunately, the effect of this combination therapy on metastatic uveal melanomas has not been nearly as impressive.[7] PDL-1 inhibitors such as durvalumab, which was prescribed in this case, have demonstrated superior efficacy for inhibiting PD-1 binding compared with PD-1 inhibitors for the treatment of various malignancies.[8] However, this treatment for uveal melanoma specifically has never been studied.[8]

Patient outcome

Our patient demonstrated 5% membranous staining for PDL-1 and had good interval progression on durvalumab and tremelimumab initially, but ultimately this therapy could not halt his systemic disease. He developed progressive metastatic disease and died a few months later.

Conclusion

This case highlights the characteristic physical examination findings of cutaneous metastasis of melanoma. When the skin is the first site of metastasis/recurrence, early identification and histologic confirmation can expedite early referral to oncology. We also emphasize the importance of obtaining a thorough medical and surgical history when evaluating new cutaneous lesions in the dermatologist's office.

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