Uveal Melanoma Metastatic to the Cavernous Sinus: A Case Report

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Abstract **: A woman in her early 50s previously treated 7 years prior with iodine-125 plaque brachytherapy without a biopsy for gene expression profiling for uveal melanoma in the left eye presented with a 3-week history of intermittent diplopia and headache. Ophthalmic examination was significant for limitation in left eye upward gaze; otherwise, examination revealed a stable, regressed tumor in the left eye, and normal vision, pressure, and pupils in both eyes. Neuroimaging showed a left cavernous sinus lesion, suggestive of a meningioma. Excisional biopsy revealed metastatic melanoma. The patient was treated with radiotherapy, and her diplopia resolved. Slight enlargement of the lesion was noted on neuroimaging 20 months later, and was treated with stereotactic radiosurgery. Serial neuroimaging in the following 6 months did not reveal any recurrences or new metastases. This case demonstrates the importance of investigating persistent diplopia in a patient with a history of uveal melanoma, and the possibility of metastases occurring in organs besides the liver or lung.**

Although rare, uveal melanoma is the most common primary intraocular malignancy in adults.[1] The vast majority of uveal melanomas arise in the choroid, and less commonly in the iris and ciliary body.[1] Despite recent advances in local disease control, the mean 5-year survival rate has been almost unchanged since 1973.[1,2] In fact, survival rates continue to drop drastically once metastasis is found, with a mean survival of only a few months with metastatic disease.[3] Considering the dismal outcomes associated with metastasis, many investigators are exploring different methods for genetic analysis of uveal melanoma and its impact on prognosis, as well as developing new targeted treatment strategies for metastatic disease.[4]

Despite the lack of an effective therapy for metastatic uveal melanoma, most ocular oncologists recommend systemic screening at regular intervals,[5] generally determined by the genetic profile of the tumor. Uveal melanomas spread hematogenously, most commonly to the liver and lungs, which are the usual sites of screening, followed by bone, skin, and subcutaneous tissue.[3] In rare cases, they can spread lymphatically through invasion of the conjunctiva by extraocular extension.[6] Other unusual sites of metastasis that have been reported include the brain, ipsilateral orbit, contralateral eye or orbit, and maxillofacial bones.[3] Most patients with metastasis usually have metastases to several sites, and most patients will have at least liver involvement as well.[3] In this report, we present a case of choroidal melanoma treated with brachytherapy that developed isolated metastasis to the cavernous sinus, which to our knowledge has not been reported previously. The research methods used in this report adhere to the ethical principles outlined in the Declaration of Helsinki as amended in 2013. Collection and evaluation of protected patient health information was compliant with the Health Information Portability and Accountability Act.

CASE PRESENTATION

A woman in her early 50s presented for follow-up examination to the Duke Eye Center 7 years after iodine-125 plaque brachytherapy treatment of a left eye choroidal melanoma (T1bN0M0). At initial diagnosis, extended fundoscopy revealed an elevated, melanocytic lesion without orange pigment or subretinal fluid (Fig. 1A). On B-scan ultrasonography, the lesion had low-to-medium internal reflectivity with a largest basal diameter of 10 mm and a thickness of 3.5 mm (Fig. 1B). Treatment had resulted in regression of the tumor (Fig. 1C,D), and systemic screening had not revealed any evidence of metastatic disease in the chest, abdomen, or pelvis. Her medical history was otherwise significant for basal cell carcinoma in her leg, high-grade cervical dysplasia, and severe migraine. At her visit, she complained of 3 weeks of intermittent vertical diplopia worse on right-upward gaze, associated with self-reported left eye ptosis and dryness. She also reported a headache not relieved by her usual migraine therapy. Five months before presentation, she was evaluated in the Duke University Emergency Department for a severe headache associated with horizontal binocular diplopia. She was diagnosed with sphenoid sinusitis, and her symptoms resolved with oral antibiotics and steroids.

On examination, her vision was 20/20 in both eyes, intraocular pressures were normal bilaterally, and pupils were equal, round, and reactive to light. Motility exam revealed mild limitation in left eye upward gaze, and nystagmus with rightward and upward eye movements. Left eye examination showed a stable regressed tumor with no signs of radiation retinopathy, maculopathy, or neuropathy.

MRI of the orbits and brain showed a heterogeneously enhancing mass in the anterior aspect of the left cavernous sinus extending into the left superior orbital fissure and left optic canal. The presentation and imaging findings were suggestive of a meningioma, and the patient elected surgical resection. A left pterional craniotomy and subtotal surgical resection of the lesion was performed. Histological examination disclosed melanoma composed mostly of spindle-shaped cells forming fascicles (Fig. 2A). Many of the tumor cells contained melanin, and the neoplastic cells were intensely immunoreactive using a cocktail of antibodies to the melanoma markers MART-1 (Melan-A) and HMB-45 (Fig. 2B), weakly to moderately intense and focally reactive using antibodies to S100 protein (Fig. 2C), and the tumor cells were nonreactive to a cocktail of antibodies to low- and high-weight cytokeratins (Fig. 2D). Next-generation sequencing revealed mutations in *GNA11* (c.626A>T; p.Gln209Leu), but no mutations in *BRAF*, *NRAS*, or *KIT* were detected. The patient was diagnosed with choroidal melanoma metastatic to the left cavernous sinus. She completed 5 sessions of 5 Gy hypofractionated stereotactic radiotherapy to the left cavernous sinus, after which her diplopia resolved. Serial brain imaging and whole-body PET/CT scans showed a stable lesion in the cavernous sinus and left orbital apex. No other recurrence or new metastasis was noted until 20 months later when very slight enlargement was found in both the cavernous sinus and orbital apex tumors. She was treated with 27 Gy stereotactic radiosurgery for the cavernous sinus/orbital apex lesion, and serial neuroimaging over the past 6 months has demonstrated stability.

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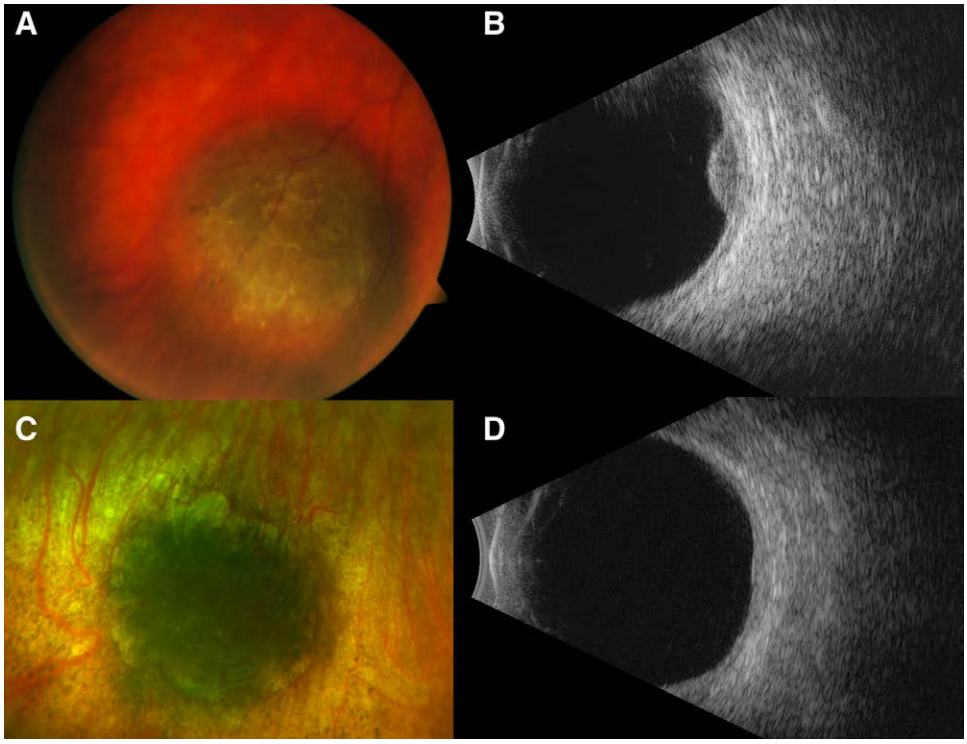

FIG. 1. Fundus photographs and B-scan ultrasonography showing the choroidal melanoma upon presentation (**A** and **B**) and 7 years after treatment (**C** and **D**), respectively. Post-treatment, there is evidence of complete tumor regression with chorioretinal atrophy on exam (**C**) and flattening on ultrasound (**D**).

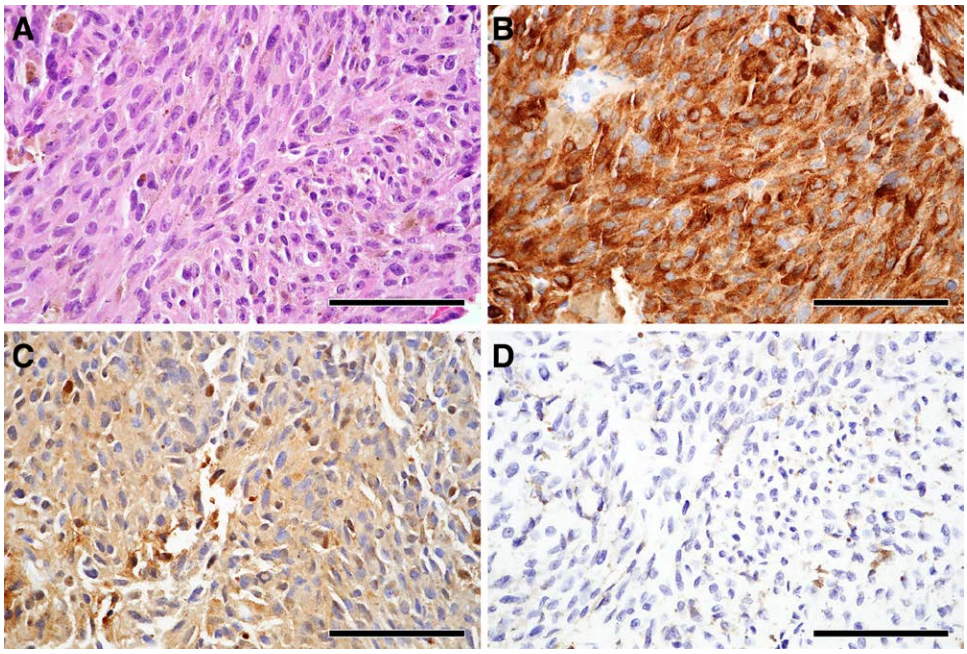

FIG. 2. The cavernous sinus tumor was composed of spindle-shaped cells organized in fascicles, with fine granules of melanin visible in many of the tumor cells (**A**; hematoxylin & eosin). The tumor cells stained intensely positive using a cocktail of antibodies to MART-1 and HMB-45 (**B**) and stained weakly to moderately positive using antibodies to S100 protein (**C**). The tumor cells lacked immunoreactivity using a cocktail of antibodies to low- and high molecular weight cytokeratins (**D**; all photomicrographs are at the same magnification; bar = 100 μm). The brown pigment in **D** is melanin within the tumor cells.

DISCUSSION

This is the first reported case of uveal melanoma metastatic to the cavernous sinus. Typically, cavernous sinus lesions cause ophthalmoplegia often associated with pain, and diplopia is a common presenting symptom.[7] On physical exam, decreased sensation in the trigeminal area distribution can be noted.[8] The differential

for cavernous sinus lesions is broad and includes inflammatory, infectious, vascular, traumatic, and neoplastic etiologies.

Neoplastic lesions in the cavernous sinus can result from contiguous spread of locally invasive cancers of the nasopharynx or head and neck, and less commonly from metastatic spread of more distant cancers through the hematogenous or lymphatic routes.[8] Neoplasms that are known to metastasize to the cavernous sinus include breast and lung cancers; rare instances of gastrointestinal, renal, and thyroid cancer spread to the cavernous sinus have been reported as well.[8] Although there is no reported case of uveal melanoma spreading to the cavernous sinus, a case of cutaneous melanoma manifesting initially as cavernous sinus syndrome secondary to metastasis was reported.[9] That patient presented in a similar way to our patient with double vision, ptosis, and severe headache. Two other cases of cutaneous melanoma metastasis to the cavernous sinus have been reported, one in the Japanese literature,[9] and another in a patient presenting with Parkinson's syndrome.[10] Neuroimaging using MRI can be used to detect cavernous sinus lesions; however, in some cases, it is not specific enough to identify the correct etiology.[7] Cavernous sinus metastatic lesions can be mistaken for benign tumors, including meningiomas, as in our case, or even pituitary adenomas.[11]

In our patient, the cavernous sinus was the first and only site of metastasis 7 years after diagnosis and treatment of the primary choroidal melanoma. The risk of uveal melanoma metastasis depends on several factors, including tumor morphology, pathology, and genetic analysis.[4] Loss of chromosome 3, and gain of 8q gene signatures have been associated with increased risk of metastasis.[4] More recently, a gene expression profile test that classifies uveal melanomas as low-risk (class 1) and high-risk (class 2) has been developed.[4] Class 2 tumors have been found to be associated with inactivating mutations in the BRCA 1-associated protein 1. In the case of our patient, gene expression profile class is unknown since gene expression profile analysis was not routinely performed at our center at the time of her diagnosis in 2010.

Since this is the first reported case of cavernous sinus metastasis of uveal melanoma, it is difficult to predict the prognosis; however, in general, prognosis in uveal melanoma is poor after detection of metastasis, with an average median survival time of only 1.25 years.[3] The lack of liver involvement, which is seen in only 11% of patients with metastatic disease,[3] could be indicative of better prognosis. Since completing her radiotherapy course, the patient has been followed up with regular metastasis screening, including yearly chest and abdominal imaging, and MRI of the orbit and brain every 3–4 months; no new metastatic lesions have been identified thus far.

This case demonstrates the importance of investigating diplopia when it occurs in patients with a history of uveal melanoma. In our case, the patient had intermittent double vision with changing patterns. Diplopia in uveal melanoma patients who receive brachytherapy is not uncommon and is most commonly secondary to strabismus resulting from plaque brachytherapy. Sometimes, the plaque is placed under or between extraocular muscles, which can result in muscle damage or displacement[12]; there is even evidence that ultrastructural changes in extraocular muscles occur, most notably a focal decrease in muscle tissue with increase in fibroblasts and collagen.[13] Strabismus can also be due to sensory deviations secondary to decreased visual acuity from radiation retinopathy or optic neuropathy, and this can present years after therapy.[12] However, this case demonstrates that the threshold to investigate the cause of diplopia by ordering neuroimaging in patients with uveal melanoma should still be low, especially in the context of progression or changes in the pattern of diplopia, as this might suggest the presence of an ongoing pathology such as a compressive lesion.[14] This is especially true when there is an unusual quick progression of symptoms and atypical imaging findings.[8]

A limitation of our report is that without tissue diagnosis of the primary choroidal melanoma, we cannot definitively determine that the cavernous lesion is a metastasis of that tumor. However, the diagnosis of uveal melanoma is a clinical one, and there is a general trend in decreased histopathologic confirmation of the diagnosis.[1] Moreover, the next-generation sequencing panel results, which revealed mutations in *GNA11*, and none in *BRAF* and *KIT*, are consistent with melanoma of uveal origin as opposed to cutaneous origin.[4] In fact, GNAQ/11 mutations are frequently found in UM and are thought to be early events in the malignant transformation of nevi.[15,16] Finally, the patient was investigated for other primary tumors like skin melanoma, and all investigations were negative. Therefore, with the previous clinical diagnosis of uveal melanoma, the histopathology and genetic profile of the biopsied lesion typical of uveal melanoma, and in the absence of other primary tumors, the case is most compatible with primary uveal melanoma metastatic to the cavernous sinus.

REFERENCES

1. Mahendraraj KLCS, Lee I, Chamberlain RS. Trends in incidence, survival, and management of uveal melanoma: a population-based study of 7,516 patients from the surveillance, epidemiology, and end results database (1973–2012). *Clinical Ophthalmology* 2016;10:2113–2119.
2. Diener-West M, Earle JD, Fine SL, et al.; Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS report No. 18. *Arch Ophthalmol* 2001;119:969–982.
3. Diener-West M, Reynolds SM, Agugliaro DJ, et al.; Collaborative Ocular Melanoma Study Group. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: collaborative ocular melanoma study group report no. 26. *Arch Ophthalmol* 2005;123:1639–43.
4. Seider MI, Mruthyunjaya P. Molecular prognostics for uveal melanoma. *Retina* 2018;38:211–219.
5. Simpson E, Gallie B, Laperrierre N, et al. The American brachytherapy society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy*. 2014;13:1–14.
6. Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes: report of two cases. *Retina* 2000;20:76–79.
7. Fernández S, Godino O, Martínez-Yélamos S, et al. Cavernous sinus syndrome: a series of 126 patients. *Medicine (Baltimore)* 2007;86:278–81.
8. Post MJ, Mendez DR, Kline LB, et al. Metastatic disease to the cavernous sinus: clinical syndrome and CT diagnosis. *J Comput Assist Tomogr* 1985;9:115–20.
9. Harkness KA, Manford MR. Metastatic malignant melanoma presenting as a cavernous sinus syndrome. *J Neurol* 2004;251:224–5.
10. Dryden SC, Kudrna JJ, Thompson BN, Patel RB, Choudhri AF, Ditta LC. Metastatic malignant melanoma to the cavernous sinus: a case of recurrent disease presenting as Parkinson syndrome (published ahead of print on Janaury 14, 2020). *J Neuroophthalmol* 2020. doi: 10.1097/WNO.0000000000000886.
11. Jacob S, Pye E, Hbahbih M, et al. Rapidly progressive bilateral ophthalmoplegia and enlarging sellar mass caused by amelanotic melanoma. *J Neuroophthalmol* 2006;26:49–50.
12. Dawson E, Sagoo MS, Mehta JS, et al. Strabismus in adults with uveal melanoma following episcleral plaque brachytherapy. *J AAPOS* 2007;11:584–8.
13. Kïratlï H, Yïlmaz PT, Sargon M. Ultrastructural alterations in extraocular muscles following iodine-125 brachytherapy for uveal melanoma. *Strabismus* 2007;15:103–109.
14. Danchaivijitr C, Kennard C. Diplopia and eye movement disorders. *J Neurol Neurosurg Psychiatry*. 2004;75(suppl 4):iv24–iv31.
15. Vader MJC, Madigan MC, Versluis M, et al. GNAQ and GNA11 mutations and downstream YAP activation in choroidal nevi. *Br J Cancer* 2017;117:884–7.
16. Bakhoum MF, Esmaeli B. Molecular characteristics of uveal melanoma: insights from the cancer genome atlas (TCGA) project. *Cancers (Basel)*. 2019;11:1061.