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Vulvar Melanoma with Isolated Metastasis to the Extraocular Muscles: Case Report and Brief Literature Review

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Abstract. *Background/Aim: Orbital metastasis of systemic cancer is exceedingly rare. This is a case report of a patient treated for locally recurrent vulvar melanoma who later presented with unilateral proptosis and was found to have an isolated biopsy-proven extraocular muscle metastasis. Patients and Methods: A 94-year-old female with locally recurrent vulvar melanoma presented with eye discomfort and blurry vision. Patient underwent histopathological, genetic, and imaging studies. Results: All prior work-up, including brain MRI and PET/CT, was negative for disease elsewhere from local recurrence. Orbital MRI demonstrated a mass involving the extraocular muscle, and immunohistochemistry staining of biopsy was consistent with metastasis. The patient underwent radiation therapy and tolerated treatment well. Conclusion: This is the first reported case of vulvar melanoma with extraocular muscle metastasis. The absence of findings on imaging as part of the staging work-up underscores the importance of considering extraocular muscle (EOM) metastasis as a differential for patients with vulvar melanoma who present with proptosis.*

Metastases to the orbit is exceedingly rare, occurring in 1-4.7% of patients with systemic cancer (1). Melanoma represents only 5 to 15% of all orbital metastases, and the most common primary sites are the skin, contralateral uveal tract, and unknown origin (1, 2). Vulvar melanoma represents 3 to 7% of melanomas in women (3). Here, we present the first case, to our knowledge, of a vulvar melanoma with an isolated metastasis to the extraocular muscle (EOM).

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Case Report

An 82-year old African American female presented with a two-month history of itchiness of the right vulva. She had a vulvar biopsy that revealed malignant melanoma at least 3.0 cm in depth. Right vulvar excision with sentinel lymph node biopsy revealed microscopically positive margins with zero out of nine nodes involved. She was offered a combination of chemotherapy and radiation therapy (RT), but she declined further treatment and instead opted for observation with close follow-up. However, she subsequently developed multiple local recurrences on the left vulva without distant metastasis. She underwent multiple resections, a course of adjuvant RT using high dose rate brachytherapy, and a course of ipilimumab.

The patient then presented again at 94-years of age, five years after the last recurrence, with complaint of right vulvar pruritis. Biopsy revealed recurrent right vulvar malignant melanoma. PET/CT and staging MRI of the brain revealed no other evidence of disease. Patient refused surgical excision. She opted for external beam RT of 50 Gy in 15 fractions.

One month following RT, the patient presented to the ED complaining of a three-week history of eye discomfort and blurry vision. On physical examination, visual acuity was 20/50 in her right eye and 20/400 in her left eye. Intraocular pressures were 14 mm in the right eye and 13 mm Hg in the left eye on primary gaze. Light reflexes and fields of vision were intact, but patient was found to have unilateral right eye proptosis with lateral outward displacement (Figure 1A and B).

Laboratory tests included complete blood cell count (CBC), iron studies, coagulation studies, basic metabolic panel, lactate dehydrogenase, and thyroid function tests. CBC revealed mild anemia and leukopenia consistent with her baseline levels. All other laboratory examinations were normal.

Orbital MRI revealed heterogenous hyperintensity of the right inferior rectus muscle on T1-weighted imaging, with a 2.0 cm mass in the anterior portion of the muscle (Figure 1C-1F).

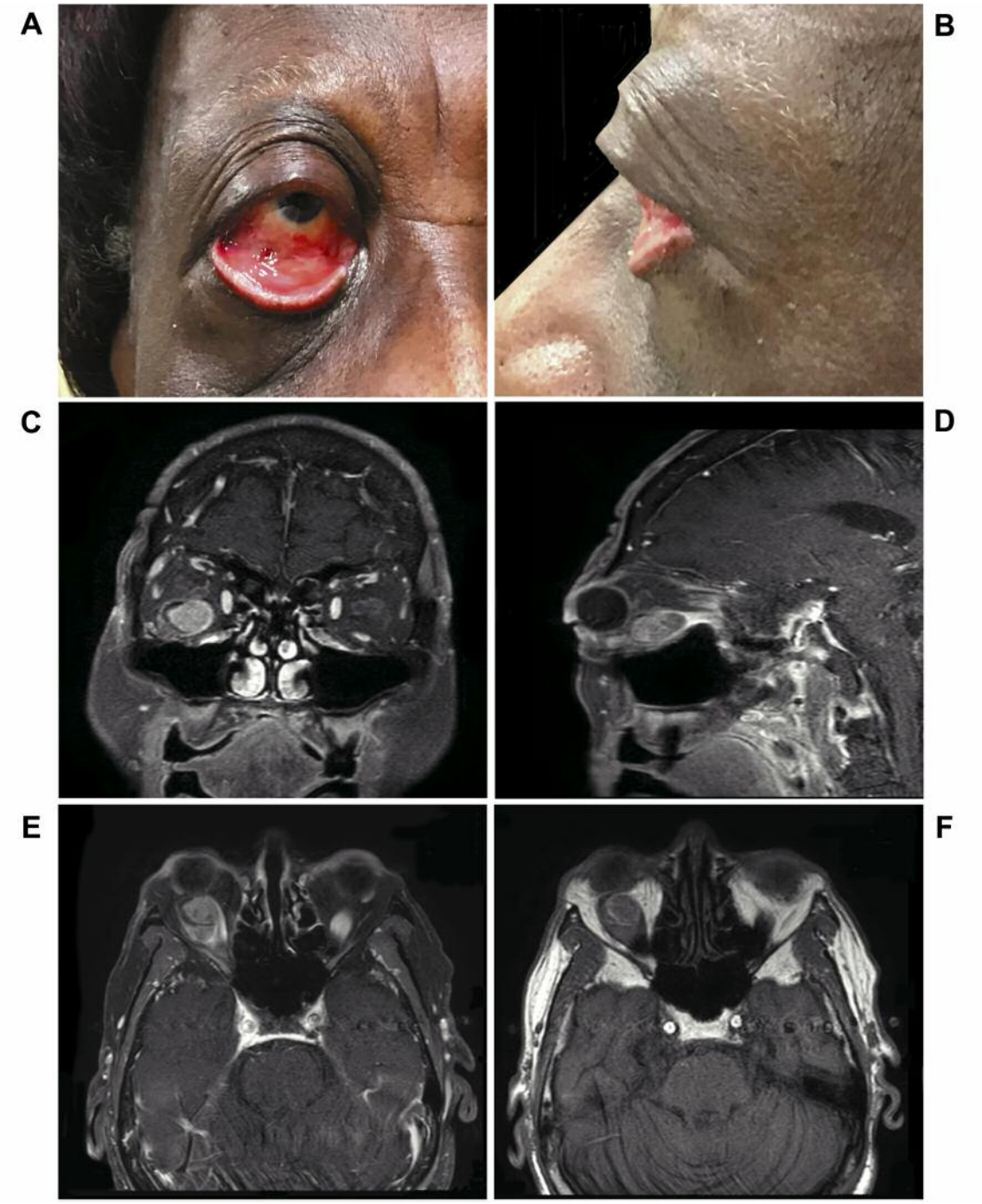

Figure 1. *Physical exam and Orbital MRI. Photograph of patient with right eye proptosis in frontal (A) and side (B) views. T1-weighted imaging with coronal view (C), sagittal view (D), axial view after contrast with fat suppression (E), and axial without contrast (F) showing heterogenous hyperintense lesion in the right inferior rectus muscle.*

T2-weighted imaging demonstrated hyperintensity in the intraconal fat directly adjacent to the posterior aspect of the right globe. CT scans of chest, abdomen, and pelvis demonstrated no masses.

Patient underwent orbitotomy and biopsy. Intraoperatively, the lesion was hyperpigmented and suspicious for melanoma. Immunohistochemical stain of biopsy tissue confirmed metastatic melanoma, showing

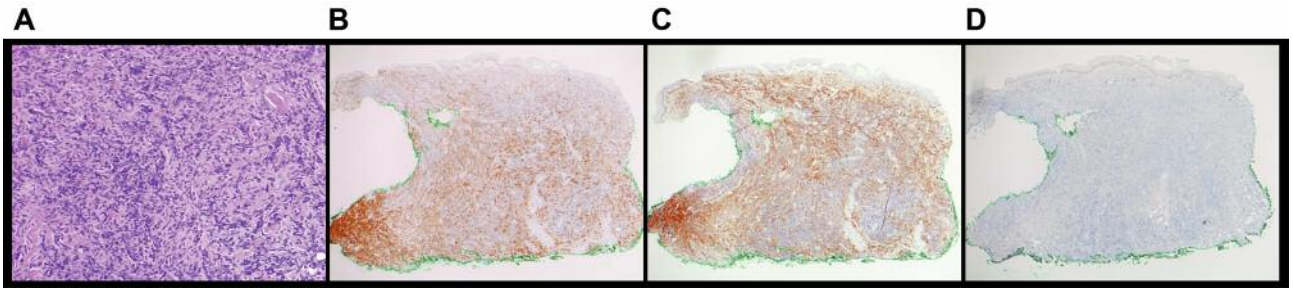

Figure 2. *H&E and immunohistochemical staining of orbital biopsy tissue showing metastatic melanoma of the vulva. Hematoxylin-eosin (H&E) magnified at ×40 (A). Immunohistochemical stains magnified at ×10: Melan-A (B), HMB-45 (C), S100 (D).*

neoplastic cells positive for Melan-A and HMB-45 and some positive for S100 (Figure 2).

Genetic mutation analyses were conducted on *NRAS* and *BRAF* genes. *NRAS* analysis evaluated for potential mutations in codons 12 and 13 on exon 2; 59, 60, and 61 on exon 3; and, 117 and 146 on exon 4. Codons 12, 13, 59, 60, and 146 were negative for mutations. However, results for codons 61 and 117 were inconclusive. *BRAF* gene mutation analysis was negative for V600E and V600K mutations on exon 15. *KIT* mutation analysis was inconclusive.

Given the patient's age and the high risk of morbidity, the patient was deemed to not be a good candidate for surgical resection or systemic immunotherapy. The patient decided to pursue palliative stereotactic body radiotherapy (SBRT) to relieve her worsening pain, proptosis, and vision. She received 7 Gy in 5 fractions and tolerated the treatment well. Proptosis reduced and eye closure became better. Extraocular movements improved but continued to be limited.

Discussion

Melanoma has since long been reported to metastasize to the orbit, but we believe that this is the first reported case of orbital metastasis from vulvar melanoma. Our case is further unusual in that there is only an isolated metastasis in the EOM.

Orbital metastases predominantly arise from carcinomas, primarily prostate and breast, but case series suggest that cutaneous melanoma accounts for 1.9-6% of all primary sites of orbital metastasis (1, 4). In contrast to the isolated metastasis in our patient, up to 89% with orbital metastases have at least one non-ocular distant metastasis (4). Orbital metastasis appears to occur in only advanced disease, particularly as autopsy evidence indicates that it is related to end-stage dissemination of melanoma prior to death (5).

Reports further suggest up to two-thirds of metastatic melanoma in the orbit occur in the intraocular region (4). However, when comparing metastatic patterns of different primary tumors, melanoma has a high propensity for spreading to EOMs. The distribution of metastatic melanoma in the orbit is in a 1:4:4 bone-fat-muscle ratio, whereas prostate cancer and breast cancer have a ratio of 4:1:0 and 1:3:2, respectively (6).

In accordance, there are four reports of metastatic melanoma with bilateral EOM involvement. Two cases include an unknown primary, one from skin, and one choroidal in origin (7, 8).

As in our patient, orbital MRI commonly shows EOMs with hyperintensity on T1-weighted images and relative hypointensity on T2-weighted images. Nonetheless, histopathological examination, immunohistochemistry staining, and genetic analysis of biopsy tissue should be pursued.

Recently, it has been established that vulvar melanoma is genetically similar to other mucosal melanomas, as they may have mutations in *NRAS* and *KIT* genes (9). *NRAS* mutations may be present in 12% of vulvar melanomas. *KIT* amplifications and mutations are also present in 12% and 18% of these tumors, respectively, and immunochemistry may detect moderate to strong KIT expression in up to 46% of patients. However, like our patient, *BRAF* mutations are virtually absent. Mutation presence can determine treatment options, such as imatinib in patients with mutations in *KIT* exons 13 and 17 (10-12).

The presence of EOM metastasis in our patient with melanoma of the vulva adds to the growing body of evidence that vulvar melanoma mimics the behavior of cutaneous and mucosal melanoma rather than vulvar carcinoma, which primarily consists of squamous cell carcinoma (SCC) (13). Vulvar SCC seldom has distant metastasis, with an observed rate of 5.1% (14). However, mucosal melanoma and cutaneous melanoma are aggressive and associated with high local and distant recurrence rates; they are also known to metastasize to any organ in the body (12, 14-16).

Investigators have found that FIGO classification of vulvar carcinoma is a poor predictor of recurrence and survival for vulvar melanoma (17). Instead, The American

Joint Committee on Cancer criteria for vulvar melanoma staging includes factors prognostic in cutaneous melanoma, including tumor thickness, Breslow depth, and nodal status. The evidence therefore suggests that vulvar melanoma has a pattern of metastatic spread similar to that of cutaneous melanoma, making an EOM metastasis, such as the one in our patient, a possible occurrence.

Conclusion

This is the first reported case of vulvar melanoma with metastasis to the extraocular muscles. Orbital metastasis should be part of the differential diagnoses in patients with a history of vulvar melanoma who present with unilateral proptosis or other visual complaints.

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