

Primary Malignant Melanoma of the Middle Ear

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PRACTICE POINTS

- Primary malignant melanoma of the middle ear is rare and has poor prognosis.
- Distant metastasis, including cutaneous metastasis, results from primary middle ear melanoma.

To the Editor:

An 82-year-old man presented to our dermatology clinic for a total-body skin examination due to a recently diagnosed primary melanoma of the left middle ear. He reported pain of the left ear and water behind the left eardrum of 1 year's duration. An otorhinolaryngologist performed surgery due to the severe mastoiditis. A biopsy of the contents of the left middle ear revealed malignant melanoma. Positron emission tomography-computed tomography revealed the mass was mainly located in the anterior aspect of the left middle ear with suspicion of tumor extension into the bony portion of the eustachian tube. No other disease was present. Prior to presentation to dermatology, gross excision of the left middle ear with removal of additional melanoma was confirmed by biopsy, and further analysis revealed v-Raf murine sarcoma viral oncogene (*BRAF*) was not detected while cellular proto-oncogene receptor kinase (*KIT*) mutation was detected on exon 13p (K642E).

The patient had no family history of melanoma. He never smoked and did not have contact with hazardous material. Initial examination at our clinic revealed

no other suspicious pigmented lesions. After additional negative workup by the oncologist, the patient was presented to the tumor board, and postoperative radiotherapy was recommended to improve local control. Eight months after the patient's initial diagnosis of the primary middle ear melanoma, a computed tomography-guided right lung biopsy showed metastatic melanoma. After various treatment modalities were discussed with the patient and his family, he was started on pembrolizumab. After 6 months on pembrolizumab, the patient developed autoimmune pneumonitis and pembrolizumab was discontinued. The patient elected to discontinue treatment and died 6 months later.

Malignant melanoma with primary involvement of the middle ear and mastoid mucosa rarely has been reported.¹⁻³ Primary malignant melanoma of the middle ear mucosa is difficult to diagnose clinically. Difficulty and delay in diagnosis occur because of the location and frequent lack of pathognomonic symptoms of the disease.² A comprehensive literature review by Maxwell et al³ in 2018 of the 10 reported primary middle ear mucosal melanomas found that patients most commonly presented with otorrhea, aural fullness, and hearing loss. Less common symptoms included otalgia, tinnitus, and facial weakness. Clinical examination revealed patients presented with serous otitis and/or a visible mass within the middle ear or external auditory canal. These melanomas demonstrated particularly poor outcomes, with 70% mortality, 20% local recurrence, and 50% distant metastasis. Distant metastases that occurred with primary middle ear mucosal melanoma include lung, liver, intraparotid, abdomen, and cutaneous metastasis.³

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The specific pathophysiologic factors underlying the development of primary malignant melanoma of the middle ear mucosa are not known.² The middle ear and its components develop from the first and second pharyngeal arches.⁴ Melanocyte precursors from the neural crest migrate during the seventh or eighth week of embryogenesis. These precursors migrate to the epidermis, various mucosal epithelial, hair follicles, dermis, retina, uveal tract, leptomeninges, inner ear, and other tissues.⁵ The ossicles of the middle ear develop from the neural crest⁶ and remain in the mesenchyme until the eighth month, when the surrounding tissue dissolves.⁴ Cutaneous melanomas arise from the malignant transformation of melanocytes in the skin of neural crest lineage. Noncutaneous melanomas are hypothesized to arise from melanoblasts migrating to noncutaneous organs after neural crest cells undergo an epithelial-mesenchymal translation.⁷

Melanoma 5-year survival rates vary based on the melanoma disease stage: 98% for stage 1, 90% for stage 2, 70% for stage 3, and 10% for stage 4. Although early-stage disease mainly is treated with surgery, advanced and unresectable disease is managed with different therapeutic options, including BRAF inhibitors such as vemurafenib, dabrafenib mesylate, and encorafenib; immune checkpoint inhibitors such as ipilimumab, nivolumab, and pembrolizumab; and oncolytic virus such as talimogene laherparepvec.^{8,9}

Ninety percent of melanomas are of cutaneous origin. Extracutaneous melanomas may be derived from the uvea, leptomeninges, mucous membranes, and gastrointestinal tract.¹⁰ Mucosal melanomas are rare and represent only approximately 1% of all melanomas.¹¹ In order of frequency, primary mucosal melanomas include the head and neck, anorectal region, vulvovaginal region, and urinary tract. UV radiation exposure is an important risk factor for cutaneous melanoma but has not been associated with the development of mucosal melanoma.⁷ In 2019, Altieri et al¹¹ analyzed 1824 cases of mucosal melanoma and found that anatomic site influences survival because mucosal melanomas in the most occult anatomic sites—spinal/central nervous system, lung and pleura, liver, and pancreas—have the worst prognosis, likely because they have already metastasized by the time they are diagnosed. Due to their occult anatomic location and lack of early presenting signs and symptoms, mucosal melanomas are difficult to diagnose at an early stage, resulting in a poorer prognosis compared with cutaneous melanomas. The most important prognostic indicator for cutaneous melanomas of tumor thickness (ie, Breslow depth) provides less prognostic value for patients with mucosal melanoma. Limitations also include the lack of a standardized staging system for mucosal melanoma, but Altieri et al¹¹ found that poorer survival in patients with mucosal melanoma was observed in relation to stage based on the clinical and pathologic tumor-node-metastasis staging system of the Surveillance,

Epidemiology, and End Results program. An aggregate 5-year survival estimate of patients diagnosed with mucosal melanoma is 28%, underscoring that mucosal melanoma is an aggressive melanoma that carries a poor prognosis and warrants a more aggressive treatment approach at the time of diagnosis.¹¹

Common treatment of primary middle ear mucosal melanoma involves a multimodality therapy including surgical oncological resection for most patients. Currently, radiation is in use for adjuvant treatment and definitive therapy in unresectable tumors or patients who are poor surgical candidates. Malignant melanoma traditionally was considered radioresistant, yet considerable variability in responsiveness has been observed both within and between tumors. Although there are no defined indications for adjuvant therapy, it is often administered in advanced or recurrent cases and those with positive or close margins. Chemotherapy generally is reserved for patients with systemic disease. The chemotherapeutic agents that have been used in the treatment of patients with melanoma of the middle ear include the alkylating agents dacarbazine, cisplatin, nimustine, paclitaxel, and temozolomide. Also, chemotherapeutic agents that have been reported in the treatment of melanoma of the middle ear include tamoxifen, the selective estrogen receptor inhibitor, and interferon. Most recently, programmed cell death protein 1 inhibitors pembrolizumab and nivolumab have been used in the treatment of middle ear melanoma. Outcomes remain poor with a high rate of mortality. Novel immunotherapeutic agents combined with adjuvant radiotherapy have been proposed to improve disease control and survival rates.³

Data on systemic therapies for mucosal melanomas are limited due to the rarity of the disease. Even with the development of novel therapies, outcomes remain poor for mucosal melanomas, and additional treatment strategies are needed. Although proto-oncogene *BRAF* mutations occur in 50% to 70% of cutaneous melanomas, these mutations are rare in mucosal melanomas.³ In mucosal melanomas, activating mutations of the cell receptor *KIT* are identified more frequently.⁷ Alterations in proto-oncogene *KIT* have been found in acral, mucosal, and cutaneous melanoma. *KIT* mutations were found on exons 11 and 13.¹² Variability in the biology of *KIT* is suggested. Treatment of melanomas with the *KIT* mutations with tyrosine inhibitors imatinib and nilotinib have shown variable benefits.¹⁰ In a 2019 study of 44 patients with mucosal melanoma, Moya-Plana et al¹³ found that in cases of unresectable and/or metastatic disease, immunotherapy with pembrolizumab had a better benefit-risk ratio than immune treatment with ipilimumab, a cytotoxic T-cell lymphocyte-associated protein 4 inhibitor.

Primary malignant melanoma of the middle ear is unusual and difficult to diagnose clinically. These melanomas have a poor prognosis and can have distant metastasis including cutaneous metastasis. We present

this case to emphasize the need to be aware that melanoma can arise in the middle ear.

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