

Nevus of Ota Associated With a Primary Uveal Melanoma and Intracranial Melanoma Metastasis

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PRACTICE POINTS

- Nevus of Ota is a hyperpigmented dermatosis that typically is distributed along the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve.
- *GNAQ* and *BAP1* mutations in patients with nevus of Ota confer a greater risk for malignant melanoma and metastatic progression.
- Ongoing ophthalmologic screening is paramount in patients with nevus of Ota and may prevent devastating sequelae.

Nevus of Ota is a blue, hyperpigmented, benign dermatosis of the skin and mucosae that most often occurs unilaterally in the distribution of the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve. Although uncommon, association with malignant melanoma is a complication that must be considered in the evaluation of patients with nevus of Ota. Mutations in the *GNAQ* and *BAP1* genes in patients with nevus of Ota place them at higher risk for malignant melanoma and metastasis. We report the case of a 29-year-old woman with a long-standing history of nevus of Ota who presented acutely with an intracranial melanoma as an extension of a primary uveal melanoma.

Cutis. 2018;102:E2-E4.

Nevus of Ota, originally referred to as nevus fusco-caeruleus ophthalmomaxillaris, initially was described in 1939 by Ota and Tanino.¹ It is a dermal melanocytic hamartoma arising from incomplete migration of neural crest melanocytes to the epidermis during

embryogenesis, resulting in nesting of subtle bands of dendritic melanocytes in the upper dermis. More common in Asians, Native Americans, and females, this hyperpigmented dermatosis most often is unilaterally distributed along the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve.² In some patients, nevus of Ota also is associated with ocular, orbital, and leptomeningeal melanocytosis. Approximately 15% of nevi of Ota have an activating guanine nucleotide-binding protein G(q) subunit alpha (*GNAQ*) or G protein subunit alpha 11 (*GNAQ*) mutation; 85% of uveal melanomas harbor one of these mutations.³ Although uncommon, neoplastic transformation with extension or metastasis to the brain has been reported in patients with nevus of Ota.⁴

We report the case of a 29-year-old woman with a long-standing history of nevus of Ota who presented acutely with an intracranial melanoma as an extension of a primary uveal melanoma.

Case Report

A 29-year-old woman with a history of a nevus of Ota involving the left inner canthus, eyelids, sclera, and superior malar cheek that had been present since birth presented to the emergency department with an acute onset of severe headache, blurred vision, and vomiting. Computed tomography (CT) and magnetic resonance imaging of the brain revealed a hemorrhagic mass in the left frontal lobe. Subsequent frontal craniotomy and resection revealed an intracranial melanoma.

Two weeks following surgery, the patient underwent magnetic resonance imaging and combined positron emission tomography and CT scans that demonstrated

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The authors report no conflict of interest.

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a fluorodeoxyglucose-avid left retro-orbital mass. Histopathology of a biopsy from the left retro-orbital mass that had been obtained intraoperatively demonstrated a pigmented, spindled to epithelioid neoplasm with areas of marked atypia and a high mitotic rate that was compatible with malignant melanoma (Figure 1). Intracranial biopsies were sent for genetic study and were found to harbor *GNAQ* (Q209P) and *BRCA1*-associated protein 1 (*BAP1*)(p.P324fs*11) mutations.

The patient was referred to dermatology by neurosurgery for evaluation of a suspected primary cutaneous melanoma. Biopsies of 2 blue papules that had appeared over the last 2 years within the nevus of Ota on the left medial canthus and left malar cheek (Figure 2) revealed cellular blue nevi (Figure 3). No primary cutaneous melanoma was identified. Based on the genetic profile described above and the presence of *GNAQ* and *BAP1* mutations, the patient was referred to ophthalmology. Inferotemporal darkening of the choroid, most likely consistent with a primary uveal melanoma, was discovered. The intracranial melanoma was thought to have arisen from the primary uveal melanoma.

The patient entered a clinical trial at an outside institution several weeks after initial presentation to our institution for treatment with a mitogen-activated protein kinase MEK1 inhibitor as well as radiation therapy. The patient was lost to follow-up.

Comment

It has been demonstrated that homozygous loss of *BAP1*, located on the chromosome 3p21.1 locus, allows for progression to metastatic disease in uveal melanoma. The *BAP1* gene codes for ubiquitin carboxyl-terminal hydrolase 7, which is involved in the removal of ubiquitin from proteins. This enzyme binds to *BRCA1* (*BRCA1*, DNA repair associated) via the RING (Really Interesting New Gene) finger domain and acts as a tumor suppressor.⁵ Biallelic *BAP1* mutations allow the transition to malignancy in concert with other mutations, such as *GNAQ*. Identification of a *BAP1* mutation may serve as a valuable diagnostic and future therapeutic target in uveal melanoma.

Currently, there are no drugs that directly target mutated *GNA11* and *GNAQ* proteins. Because aberrant *GNA11* and *GNAQ* proteins activate MEK1, several

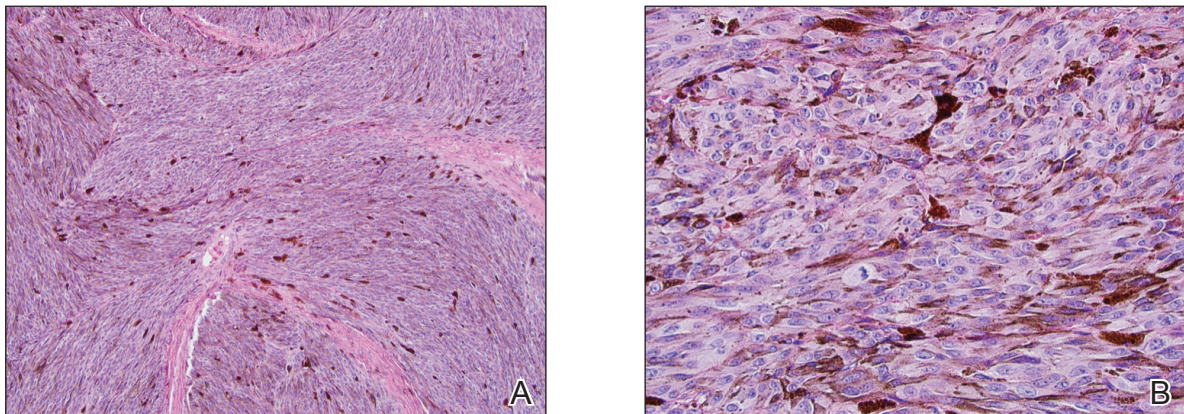


FIGURE 1. Histopathology of the intracranial biopsy. On low-power view, fascicles of atypical, pigmented, spindled to epithelioid melanocytes were noted (A)(H&E, original magnification $\times 10$). A higher-power view revealed increased mitotic activity (B)(H&E, original magnification $\times 40$). Findings were consistent with malignant melanoma.

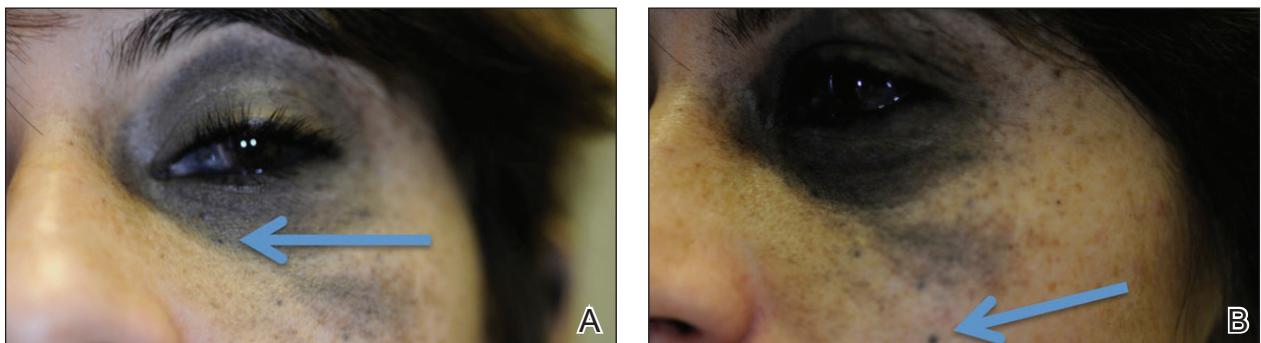


FIGURE 2. Nevus of Ota extending from the left medial canthus (A), encompassing the sclera and the malar cheek (B), containing the 2 papules that were biopsied (arrows).

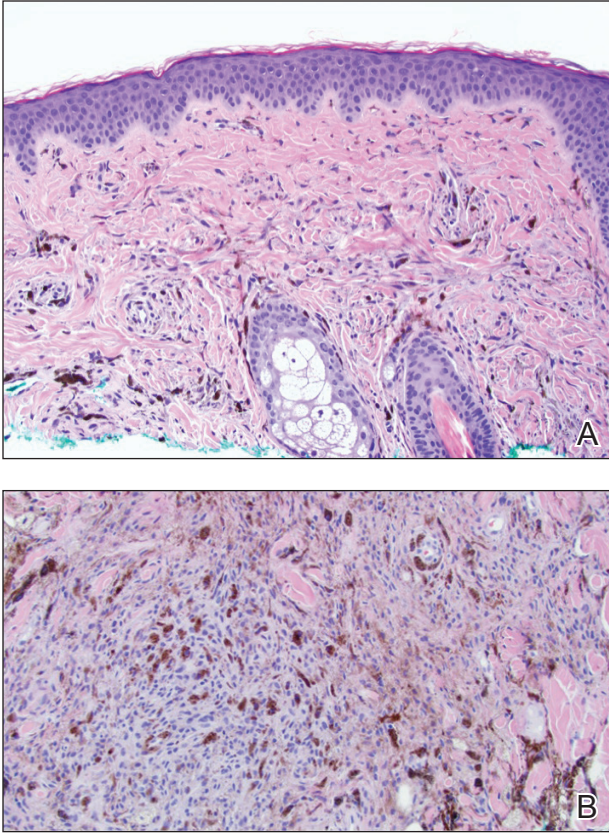


FIGURE 3. Punch biopsies of the left ear (A) and malar cheek (B) demonstrated bland, spindled, melanocytic proliferations with melanophages, consistent with cellular blue nevi (H&E, original magnifications $\times 10$ and $\times 40$).

MEK1 inhibitors are being tested with the hope of achieving indirect suppression of GNA11/GNAQ.⁶

We present a rare case of *BAP1* and *GNAQ* mutations in intracranial melanoma associated with nevus of Ota.

Although the uveal melanoma was not confirmed on histopathology, the clear mention of foci within the eye by ophthalmology, positron emission tomography–CT scan showing a fluorodeoxyglucose-avid left retro-orbital mass, and genetic studies of the intracranial biopsies were highly suggestive of a primary uveal melanoma.

Our case highlights the importance of ongoing ocular screening in patients with nevus of Ota, noting the possibility of malignant transformation. Furthermore, patients with nevus of Ota with ocular involvement may benefit from testing of *BAP1* protein expression by immunohistochemistry.⁷ Identification of *BAP1* and *GNAQ* mutations in patients with nevus of Ota place them at markedly higher risk for malignant melanoma. Therefore, dermatologic evaluation of patients with nevus of Ota should include a thorough review of the patient's history and skin examination as well as referral for ophthalmologic evaluation.

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