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CLINICAL CASE REPORT

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GNA11 Mutation in a Patient With Cutaneous Origin Melanoma

A Case Report

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Abstract: The rapid advances in the molecular biology and genetics have improved the understanding of molecular pathogenesis of v-Raf murine sarcoma viral oncogene homolog B *(BRAF)*, feline sarcoma viral oncogene v-kit *(KIT)*, and neuroblastoma v-Ras oncogene homolog *(NRAS)* mutant melanomas with the subsequent development of targeted therapeutic agents. However, only limited data are available for melanoma harboring other somatic than *BRAF*, *KIT*, and *NRAS* mutations. Mutations in guanine nucleotide-binding protein Q polypeptide *(GNAQ)* and guanine nucleotide-binding protein alpha-11 *(GNA11),* alpha subunits of heterotrimeric G proteins, constitutively activate mitogen-activated protein kinase (MAPK) pathway in uveal melanoma. However, there are no reports of *GNA11* mutations in cutaneous melanomas.

A 48-year-old woman was diagnosed with cutaneous nodular melanoma on the left scalp. Mutation analysis of the tumor revealed a *GNA11 Q209L* mutation. There was no evidence of uveal melanoma or malignant blue nevus in ophthalmologic exam, imaging studies, and pathology review.

To our knowledge, this is the first case report to demonstrate cutaneous origin melanoma harboring a *GNA11 Q209L* mutation.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartame aminotransferase, BRAF = v-Raf murine sarcoma viral oncogene homolog B, CT = computed tomography, FDG = fluorodeoxyglucose, GNA11 = guanine nucleotide-binding protein alpha-11, GNAQ = guanine nucleotide-binding protein Q polypeptide, Gy = Gray, H&E = hematoxylin and eosin, KIT = feline sarcoma viral oncogene v-kit, MAPK = mitogen-activated protein kinase, MRI = magnetic resonance imaging, NRAS = neuroblastoma v-Ras oncogene homolog, PET-CT = positron emission tomography – computed tomography, PV-10 = intralesional Rose Bengal disodium 10%.

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IRB approval and Consent and IRB approval IRB approval was not necessary for this case report as it did not involve a methodical collection or analysis of data. A consent for publication was mailed to the patient's last known address. No response was received at the time of this publication.
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INTRODUCTION

Melanoma is the most aggressive skin cancer and the main cause of skin cancer-related death. The incidence of melanoma has been increasing in the last several decades, and an estimated 73,870 patients will be diagnosed with melanoma and 9940 patients will die of melanoma in 2015.[1] Early stage melanoma is surgically curable; however, treatment for advanced melanoma remains quite challenging. The discovery of *BRAF* mutations in melanoma and the development of BRAF inhibitors have changed the landscape of advanced melanoma treatment. With the remarkable success of targeted therapy in *BRAFV600* mutant melanoma, extensive research efforts have been made to discover targetable somatic mutations other than *BRAF* in melanoma. The rapid advances in the molecular and genetic analysis of melanoma with the extensive research efforts have improved the understanding of clinicopathologic features of *BRAF*, *KIT*, and *NRAS* mutations in melanoma, which helps with development of targeted therapeutic agents. Approximately 70% of cutaneous melanomas harbor 1 of the 3 mutations.[2,3] However, only limited data about mutations are available for the other 30% of cutaneous melanoma. Therefore, further mutation studies are needed to understand molecular pathogenesis and identify therapeutic targets.

GNAQ and *GNA11* are alpha subunits of heterotrimeric G proteins which couple 7-pass transmembrane domain receptors to intracellular signaling pathways.[4] The mutations of *GNAQ/GNA11* have been reported exclusively in primary uveal melanoma and they are critical for the development and progression of uveal melanoma by activation of the mitogen-activated protein kinase (MAPK) pathway.[5–7] Although *GNAQ/GNA11* mutations are not rare in benign and malignant blue nevus,[7] *GNA11* mutations have never been reported in patients with cutaneous melanoma. Here, we report a patient with cutaneous origin melanoma harboring *GNA11* mutation.

Case Presentation

A healthy 48-year-old Caucasian woman with no significant past medical history was diagnosed with a 4.4 mm, Clark level IV, nodular melanoma without ulceration on the left scalp in August of 2009. Subsequently, she underwent a wide local excision of the primary melanoma and sentinel node biopsy in the left neck, which revealed 4 positive lymph nodes for metastatic melanoma. A left neck node dissection was performed along with a left superficial parotidectomy. Zero of 49 lymph nodes dissected contained melanoma and her final stage was classified as T4aN3M0, Stage IIIC. She received adjuvant radiation to the left neck with 30 Gray (Gy) in 5 fractions

without adjuvant systemic therapy. She remained in her usual state of health, with no significant comorbidities until August of 2011, when she was found to have a new 2 cm metastatic lesion in the inferior right liver, for which she received 2 doses of biochemotherapy (cisplatin, dacarbazine, interferon, interleukin-2, and vinblastine) without significant shrinkage of the metastatic lesion. Subsequently, she received 4 doses of combination of ipilmumab (3 mg/kg) and nivolumab (1 mg/kg), followed by 4 doses of nivolumab (1 mg/kg) with near complete response. Unfortunately, the treatment was complicated by autoimmune hypophysitis, grade IV liver toxicity, and grade III colitis. The highest alanine aminotransferase (ALT) level was 1197 Units/L and aspartate aminotransferase (AST) was 727 Units/L with normal bilirubin level. Initially, her symptoms and liver enzymes improved with high-dose intravenous steroid for 2 days, followed by oral prednisone 120 mg daily. When she started steroid taper, liver enzymes were elevated again. Thus, she restarted high-dose intravenous steroid and mycophenolate 1000 mg twice a day. After 3 months of steroid taper, she was placed on a maintenance physiologic dose of steroid. She was completely off steroid after 8 months. The liver lesion remained stable until August of 2013, when she had progression on positron emission tomography-computed tomography (PET-CT) (Figure 1), for which she underwent a wedge resection with harvest of tumor infiltrating lymphocytes in November of 2013. The pathology of the resected liver lesion confirmed metastatic melanoma (Figure 1). A molecular analysis of the liver lesion revealed a *GNA11* mutation with wild-type *BRAF*, wild-type *KIT*, and wild-type *NRAS* genes. A *GNA11* mutation was detected in codon 209, exon 5 of the gene that would change the encoded amino acid from glutamine to leucine (*Q209L*) (Figure 2). As *GNA11* mutations have been reported in uveal melanoma frequently, extensive ophthalmology exams and a magnetic resonance imaging (MRI) of the brain were performed, which revealed no evidence of uveal melanoma (Figure 3). A follow-up computed tomography (CT) of the body revealed new metastatic lesions in the liver and the lung in January of 2014, and she received intratumoral injection of intralesional Rose Bengal disodium 10% (PV-10) on a clinical trial into 2 of the metastatic liver lesions with further progression of the liver and lung lesions. Subsequently, she received 4 cycles of high-dose interleukin-2 treatment from April to July of 2014 without significant hepatotoxicity or colitis. Unfortunately, a CT scan of the body revealed progression of lung lesions and a new subcutaneous mass in the right deltoid muscle area. She started treatment with pembrolizumab in September of 2014. Due to further disease progression of lung and liver lesions and multiple new subcutaneous, peritoneal, and retroperitoneal nodules after 3 doses of pembrolizumab, she received adoptive T cell therapy with 2 cycles of high-dose interleukin-2 on a clinical trial. Her treatment was complicated by grade III hepatotoxicity ([ALT]:

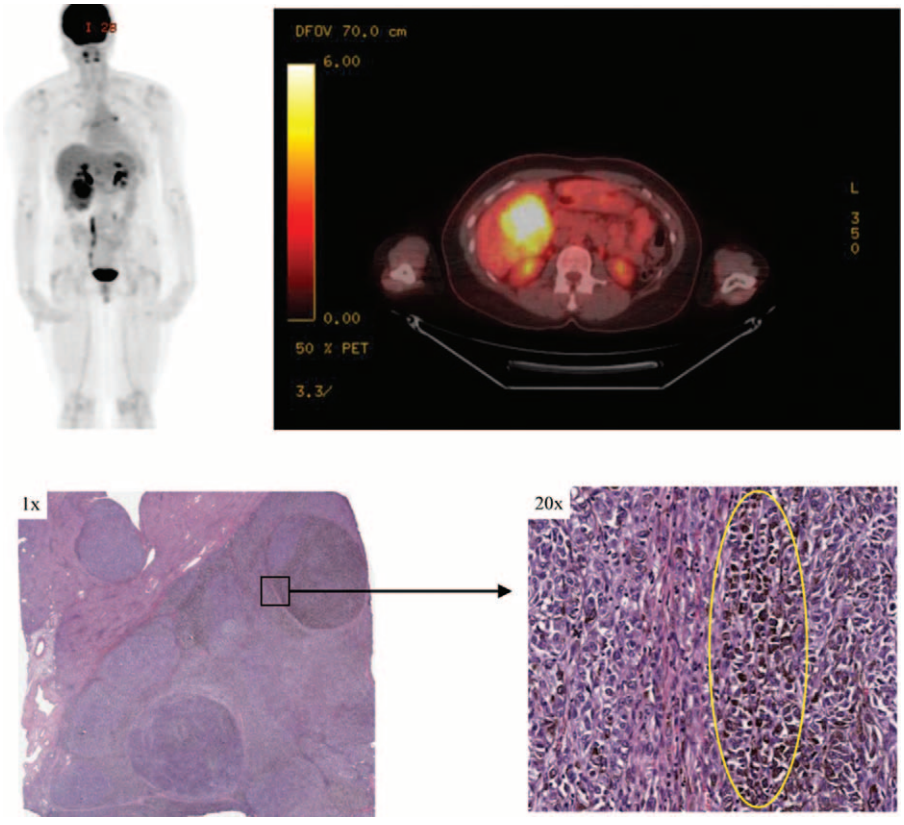

FIGURE 1. (A) Positron emission tomography-computed tomography (PET-CT) shows fluorodeoxyglucose (FDG) uptake in the liver. (B) Hematoxylin and eosin (H&E) stained sections of a metastatic liver lesion. H&E demonstrates dark brown pigmentation (circle) consistent with metastatic melanoma. FDG = fluorodeoxyglucose, H&E = hematoxylin and eosin, PET-CT = positron emission tomography-computed tomography.

FIGURE 2. Molecular analysis of the metastatic liver lesion. Sequencing of exon 5 of guanine nucleotide-binding protein alpha-11 (*GNA11*) revealed the mutation of glutamine (CAG; Q) to leucine (CTG; L) at codon 209 (Q209L) in the patient's tumor.

510). However, the toxicity completely resolved after discontinuation of interleukin-2 without any steroid. At the time of this manuscript draft, she has stable disease status.

DISCUSSION

GNAQ and *GNA11* are G protein coupled receptor alpha subunits encoding Gq and G11 proteins, respectively.[4] G proteins are composed of 3 subunits: alpha, beta, and gamma. Upon ligand binding, the alpha subunit is dissociated from the beta and gamma subunits to release GDP and bind to GTP, which activates the downstream pathway such as the MAPK pathway. The activation is terminated by an intrinsic GTPase of alpha subunit. *GNAQ* or *GNA11* mutations occur at either exon 4 *R183* or exon 5 *Q209* mostly, and these hotspot mutations are considered driver mutations in uveal melanoma by blocking intrinsic GTPase activity and activating downstream pathways constitutively.[7] In our patient, *GNA11 Q209L* mutation was detected by a next-generation sequencing platform.

Most cutaneous melanomas (up to 70%) have a dysregulated MAPK pathway via *BRAF* (50%) or *NRAS* mutations (15–20%), which promote uncontrolled proliferation and growth.[8,9] However, cutaneous melanomas rarely harbor *GNAQ/GNA11* mutations which were reported in primary uveal melanoma at a frequency up to 80%.[7] As liver is the predominant site of metastasis in most patients with uveal melanoma,[10] and the patient had metastatic disease in liver, it is conceivable our patient had primary uveal melanoma. However, it is unlikely as the dilated ophthalmologic examinations and multiple imaging studies demonstrated no evidence of primary uveal melanoma.

Although *GNAQ* mutation has been reported in 1 case of cutaneous melanoma,[7] there are no reports of *GNA11* mutation in cutaneous melanoma to our knowledge. Recently, *GNA11 R183C* mutation has been identified in 1 cutaneous origin melanoma cell line.[11] However, it is not clear whether the original cutaneous melanoma sample harbors *GNA11* mutation as several studies have demonstrated significant genomic difference between cancer cell lines and original tissue samples.[12–15] In addition, Griewank et al reported abnormally high frequency of *BRAF V600E* mutations in uveal melanoma cell lines; suggesting contamination in laboratories that handle both cutaneous and uveal melanoma samples;[16] furthermore, multiple studies failed to identify *BRAF* mutations in original uveal melanoma tissue,[17–19] which also suggests genomic difference between melanoma cell lines and original melanoma tissues.

Another possibility is that our patient has malignant blue nevus as *GNAQ/GNA11* mutations have been described in benign and malignant blue nevus.[6,7] However, her melanoma did not contain a component of common blue nevus or pigmented dendritic cells histologically, which is a feature of malignant blue nevus.

Previously, an increase in frequency of *GNA11* mutations from primary to metastatic uveal melanomas has been reported.[7] Thus, it is hypothetical that the *GNA11* mutation might have developed during tumor progression in our patient. Unfortunately, the *GNA11* mutation test of the primary lesion and metastatic lymph nodes was not performed due to insufficient samples.

As *GNAQ/GNA11* mutations are associated with activation of the MAPK pathway similar to *BRAF* and *NRAS* mutations, and a selective MEK inhibitor has demonstrated activity in metastatic uveal melanoma with *GNAQ/GNA11* mutations in a Phase II clinical trial,[20] the patient might have experienced clinical benefit from an MEK inhibitor. However, she was not treated with any MAPK pathway inhibiting agents to date.

There is no data regarding any effects of *GNAQ/11* mutations on *BRAF* or *NRAS* mutations, which are the most common oncogenic mutations in cutaneous melanomas. However, it is possible that mutations in *GNAQ/11*, *BRAF*, or *NRAS* are mutually exclusive similar to *BRAF* and *NRAS* mutations as co-mutations of *GNAQ/11* and *BRAF* or *NRAS* have not been reported,[16,21] and all these mutations activate the same MAPK pathway.

CONCLUSION

As far as we are aware, our case is the first documented cutaneous origin melanoma harboring a *GNA11* mutation. This case suggests that somatic gene mutation analysis of melanoma may give us a better understanding of genetic change of melanoma and exploration of therapeutic implications. The upcoming Cancer Genome Atlas in Cutaneous Melanoma will shed light on the presence and diversity of mutations in the melanoma population.

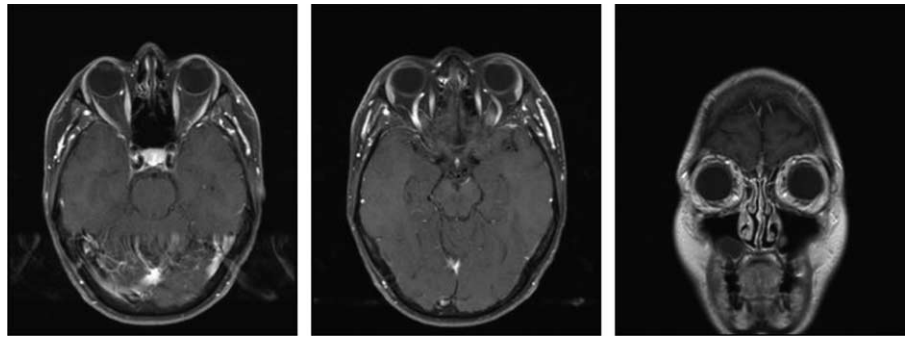

FIGURE 3. Magnetic resonance imaging (MRI) of the brain shows no evidence of uveal lesions.

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