Multiple Cutaneous Melanomas and Clinically Atypical Moles in a Patient With a Novel Germline BAP1 Mutation

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Case Report/Case Series

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everal kindreds having germline BAP1 mutations with a propensity for uveal and cutaneous melanomas and other internal malignancies have been described.1-4 BAP1 mutation carriers often develop crops of small (<10 mm) orange-red translucent papules, plaques, or nodules, typically located on the torso or the scalp.2 Histologically, these BAP1-deficient tumors (BDTs) consist of conventional nevus cells and a second population of epithelioid cells with spitzoid cytomorphology occupying the dermis.3 These spitzoid cells show a large pale eosinophilic cytoplasm and may be highly atypical. However, these lesions lack other features of Spitz nevi such as epidermal hyperplasia, Kamino bodies, clefting, or spindle-shaped melanocytes.3,5 Cytogenetically, BDTs in these patients often exhibit allelic loss on chromosome 3p21 at the BAP1 locus.3 These same combined melanocytic tumors may also occur sporadically.5

Patients with germline mutations in BAP1 have an increased risk for internal cancers such as mesothelioma, lung adenocarcinoma, meningiomas, and renal cell carcinoma, indicating that BAP1 inactivation leads to a mixed cancer phenotype.2,4,6 Some researchers have suggested that the constellation of cutaneous or ocular melanomas, atypical melanocytic proliferations, and other internal neoplasms should be termed COMMON syndrome to distinguish it from familial atypical multiple mole melanoma or from dysplastic nevus syndrome.1 In the latter, patients exhibit a high cutaneous melanoma risk but lack an apparent ocular melanoma risk. Moreover, individuals with familial atypical multiple mole melanoma have a large number of dysplastic nevi, which are histologically distinct from BDTs. Familial atypical multiple mole melanoma kindreds have also been shown to harbor inactivating germline events in CDKN2A (OMIM 600160) or activating mutations in CDK4 (OMIM 123829) and are at an increased risk for pancreatic cancer,7 which is seen less often in COMMON syndrome. We describe a new kindred with a novel germline mutation in BAP1 in which the proband phenotypically has dysplastic nevi, BDTs, and multiple conventional superficial spreading melanomas (SSMs).

OBSERVATIONS

We describe a 53-year-old man who was initially seen in 2003 with dysplastic nevus syndrome, multiple atypical melanocytic proliferations showing loss of immunostaining for BAP1, and 7 cutaneous melanomas. Germline testing was performed in the proband, his 16-year-old son, and his 13-year-old daughter, revealing a germline mutation in the BAP1 gene (c.592G>T, p.Glu198X) in the proband and in his 16-year-old son. CDKN2A and CDK4 genes were wild type. No members of this kindred reported a history of uveal melanoma.

CONCLUSIONS AND RELEVANCE

To our knowledge, this is the first report of a patient with multiple melanomas, dysplastic nevus syndrome, and an inactivating germline BAP1 mutation. The coexistence of dysplastic nevus syndrome and a BAP1 germline mutation extends the spectrum of the BAP1 tumor predisposition syndrome and may confer a greater risk for cutaneous melanomas.

IMPORTANCE

Several kindreds having germline BAP1 mutations with a propensity for uveal and cutaneous melanomas and other internal malignancies have been described. However, clinically atypical moles have not been previously recognized as a component of this syndrome, to our knowledge. We describe the first kindred to date with a germline mutation in BAP1 associated with multiple cutaneous melanomas and classic dysplastic nevus syndrome.

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tory included 7 cutaneous melanomas. One was a nodular melanoma, and 6 were SSMs with typical intraepidermal changes of melanoma, including extensive pagetoid and lentiginous growth (Figure 2). All 6 SSMs were reviewed by our histopathologist (P.G.), while the nodular melanoma was part of his medical history and was not available for our review. In all 6 SSMs, the cells were epithelioid but lacked spitzoid cytomorphology. The patient also had several biopsy specimens of dysplastic nevi (Figure 1) and 13 biopsy specimens of classic BDTs (Figure 3). BAP1 (C-4, 1:400; Santa Cruz Biotechnology) and BRAF V600E (VE1, 1:100; Spring Bioscience) immunostains were performed in the SSMs and in 6 BDTs on an autostainer (Leica BOND-MAX; Leica Biosystems) using a kit (DS9390, Polymer Refine Red Detection; Leica Biosystems). All 6 SSMs were negative for immunostaining for BRAF V600E. Two SSMs were also evaluated for BRAF (OMIM 164757) mutation using a test (cobas 4800 BRAF V600E; Roche), and were both negative. All 6 cases also showed loss of nuclear immunostaining for BAP1 antibodies (Figure 2). Six of the BDT cases were also evaluated by immunohistochemistry for BRAF V600E mutation, with 3 positive and 3 negative results. One of these negative cases was tested using the mutation test (cobas 4800 BRAF V600E), confirming the negative result. All the BDTs showed loss of nuclear BAP1 immunostaining.

One of the melanomas involved a sentinel lymph node, but the complete lymph node dissection was negative. Computed tomographic scans and blood test results suggested no evidence of further metastatic disease. The patient was given interferon alfa but tolerated the therapy for only 1½ months because of dysgeusia and palmoplantar paresthesias. He has had ophthalmologic examinations every 6 months for the last 2 years, which have revealed no evidence of uveal melanoma.

The proband’s family history was significant in that the patient’s mother died of lung adenocarcinoma. He denied any personal or family history of pancreatic cancer or additional cutaneous or uveal melanomas. The patient has a 16-year-old son who also had a BDT.

After obtaining approval from the Northwestern University Cancer Center and the Northwestern University Institutional Review Board and following receipt of written informed consent from the patient and his son and daughter, DNA was extracted from the paraffin-embedded blocks of one of the proband’s BDTs and from one SSM, as well as from his saliva and the saliva of his 16-year-old son and 13-year-old daughter. Sanger sequencing was performed to analyze the germline DNA for BAP1, CDKN2A, and CDK4 mutations. The proband and his son had identical germline nonsense mutations in BAP1 (c.592G>T, p.Glu198X) (Figure 4C and D). One
of the patient’s BDTs also showed loss of heterozygosity at BAP1 (Figure 4A), with loss of the wild-type allele. Analysis of a melanoma from the same patient demonstrated the presence of the germline mutation, while the other allele was wild type (Figure 4B). There were no germline CDKN2A or CDK4 mutations.

### Tissue Preparation and Analysis

The tissues were mounted on positively charged slides and allowed to dry in an oven. The slides were dewaxed on the autostainer. BAP1 immunohistochemistry was performed on the autostainer with a high-pH retrieval for 20 minutes. For detection of the antibody, an alkaline phosphatase–based chromagen was used with the kit (Polymer Refine Red Detection). Tumors were scored as positive or negative depending on whether or not their nuclei immunostained with BAP1. The BRAF V600E immunostain was also performed on the autostainer using a low-pH retrieval for 20 minutes, followed by detection using the kit (Polymer Refine Red Detection). The BRAF mutation was detected using DNA extracted from formalin-fixed paraffin-embedded tissue with the mutation test (cobas 4800 BRAF V600), performed according to the manufacturer’s protocol.

### Discussion

Multiple cutaneous melanomas have been associated with mutations in different genes (eg, CDKN2A or CDK4). Germ-line variants in BAP1 have an increased susceptibility for different malignancies, with cancers appearing earlier than sporadic cases. These malignancies include uveal melanoma.
and (less frequently) cutaneous melanoma, as well as other
cancers.8 To our knowledge, this is the first report of a
patient with dysplastic nevus syndrome and an inactivating
germline BAP1 mutation.

While all the SSMs from our patient demonstrated loss of
BAP1 expression, none of them were found to have a BRAF
mutation by polymerase chain reaction or by immunostain-
ing. Conversely, 3 of the 6 BDTs that were evaluated for a
BRAFV600E mutation were positive. Hence, there may be dis-
tinct tumorigenic pathways in patients with constitutive
BAP1 inactivation. If the cooperating driver mutation is
BRAFV600E, the melanocytic proliferation may more likely
evolve into a characteristic BDT. This is supported by another
recent study8 in which a high concordance between nuclear
BAP1 loss and BRAFV600E expression was reported. On the
other hand, if a cooperating driver mutation is an oncogenic
hit other than BRAFV600E, there may be a higher likelihood of
melanoma considering that none of our patient’s SSMs had a
BRAF mutation, although this model is speculative. Never-
theless, 3 of our 6 BDTs tested did not have a BRAF mutation.
Therefore, BDTs can develop in the context of other potential
oncogenic stimuli.

To our knowledge, the p.Glu198X is a novel germline BAP1
mutation, although this mutation has been observed in an un-
related tumor specimen.10 The BAPI protein is a tumor sup-
pressor that acts as a ubiquitin carboxyl-terminal hydrolase
functioning as a deubiquitinizing enzyme. It is a binding part-
ner to BRCA1 (OMIM 113705),11 as well as to other transcrip-
tion factors such as HCFI,12 and is implicated in DNA damage
repair and regulation of apoptosis, senescence, and cell cycle
regulation.8 BAP1 also interacts with ataxia telangiectasia mu-
tated and ataxia telangiectasia and Rad3-related proteins,
which regulate the DNA damage induced by UV radiation.\(^8\)

Therefore, mutations in \textit{BAP1} could increase the susceptibility to UV radiation and the risk for melanomas.\(^8\) \textit{BRAF} mutations have been identified in melanomas resulting from intense intermittent bouts of UV exposure.\(^12\)

This case also illustrates the importance of histopathology in guiding patient management. Patients with BDTs should undergo a thorough review of their family history as it pertains to all cancers. Lesional skin biopsy specimens may be screened for \textit{BAP1} loss by immunohistochemistry. It is thought that loss of nuclear expression correlates with absence of \textit{BAP1} function.

### Conclusions

Identification of this germline \textit{BAP1} mutation in a patient with a constellation of multiple cancers and multiple atypical melanocytic tumors expands the cutaneous phenotype of the \textit{BAP1} tumor predisposition syndrome. To date, most reports suggest a favorable prognosis for BDTs and \textit{BAP1}-deficient Spitz tumors,\(^13\) including the patient described herein. We speculate that the presence of a \textit{BAP1} germline mutation in a patient who phenotypically has dysplastic nevus syndrome may result in a considerable increased risk for cutaneous melanomas. However, further research is needed to determine if the \textit{BAP1} germline mutation increases the risk of cutaneous melanoma beyond the dysplastic nevus phenotype alone. Although no formal guidelines exist for patients with germline \textit{BAP1} alterations, strict sun protection and regular dermatologic and ophthalmologic evaluations are advisable.

**Figure 4. Electropherogram Showing a Nonsense Mutation in Exon 8 in the \textit{BAP1} Gene**

A-C. In the proband, the mutation was found in the DNA from a \textit{BAP1}-deficient tumor (A), a melanoma (B), and the saliva (C), thereby demonstrating germline origination. D. The same mutation was identified in the saliva of the patient’s 16-year-old son.