Multiple Epithelioid Spitz Nevi or Tumors With Loss of BAP1 Expression

A Clue to a Hereditary Tumor Syndrome

Klaus J. Busam, MD; Michelle Wanna, MD; Thomas Wiesner, MD

Importance: Recently, a group of melanocytic tumors with loss of BAP1 expression has been described. The lesions may occur sporadically or as part of a familial cancer syndrome. They have distinct histopathologic features characterized by a nevuslike silhouette and cytologic composition of large epithelioid melanocytes with oval vesicular nuclei, distinct nucleoli, and abundant cytoplasm. The large melanocytes are immunohistochemically characterized by loss of nuclear labeling for BAP1.

Observations: We describe a 21-year-old patient with multiple combined melanocytic proliferations composed of both a nevus component with strong BAP1 expression and a large epithelioid melanocyte population with loss of BAP1 expression. The occurrence of multiple BAP1 loss melanocytic lesions raised concerns about a possible germline mutation. Sequence analysis of DNA from lesional and nonlesional skin confirmed a BAP1 germline mutation.

Conclusions and Relevance: The presence of multiple clinically banal–appearing melanocytic lesions with childhood onset suggests that the combined lesions with BAP1 loss large epithelioid melanocytes described herein are probably combined nevi. Our findings also illustrate how the detection of a histopathologically distinct melanocytic lesion, coupled with knowledge of its possible association with a hereditary tumor syndrome, can lead to the suspicion and confirmation of a germline mutation.
aminations to detect tumors in an early or premalignant state.

REPORT OF A CASE

CLINICAL FINDINGS

A 21-year-old college student was seen by one of us (M.W.) for evaluation of multiple scalp nodules present since childhood, which were continuing to enlarge and were occasionally pruritic. Nevi of the right fifth toe, right cheek, and right antihelix were also increasing in size. He had a history of atypical nevus of the chest at age 12 years. His family history was negative for atypical nevi or melanoma. Five firm dome-shaped and polypoid pink nodules (0.8-1.2 cm) were identified on the scalp (Figure 1). The right cheek and antihelix had 0.5-cm dome-shaped pink papules. The right fifth toe had a 0.4-cm medium-brown macule with a central dome-shaped papule. None of the lesions had previously been biopsied. Biopsy specimens of the scalp and fifth toe were submitted for review. Subsequently, the scalp and toe lesions were excised; a biopsy of the right ear was performed, and an additional scalp lesion was excised.

HISTOPATHOLOGIC FINDINGS

The lesions from the right cheek, antihelix, and scalp were compound albeit predominantly of intradermal melanocytic proliferation. All were combined lesions composed of large epithelioid melanocytes with a second minor population of small melanocytes. The nuclei of the large melanocytes were 2 to 3 times the size of the nuclei of epidermal keratinocytes and adjacent small “ordinary” melanocytes. The enlarged melanocyte nuclei had smooth nuclear contours and displayed an open chromatin pattern and distinct nucleoli.

The histopathologic findings are shown on the excisional specimen from the scalp lesion; the lesion had a polypoid nodular silhouette (Figure 2). Most of the melanocytes were large epithelioid in appearance and formed a central nodule. The small melanocytes were predominantly at the periphery but also were admixed as a minor population in the center of the lesion. There was an associated mild lymphocytic infiltrate. A few multinucleated melanocytes were present.

IMMUNOHISTOCHEMICAL FINDINGS

Because of the cytologic resemblance with previously seen $BAP1^\text{loss}/BRAF^\text{V600E}$ melanocytic tumors, sections of the tumors were immunohistochemically analyzed for $BAP1$ expression. The large epithelioid melanocytes lacked nuclear labeling for $BAP1$ (Figure 3). In contrast, the population of small epithelioid melanocytes showed nuclear $BAP1$ staining. All nonlesional cells (epithelial, stromal, and inflammatory cells) were also immunoreactive for $BAP1$.

MUTATIONS AND DELETIONS OF $BAP1$

To distinguish somatic mutations from germline mutations, $BAP1$ was sequenced using both a lesional tissue sample as well as the tip of a skin ellipse with no lesional melanocytes. The tumor tissue showed a $BRAF^{V600E}$ mutation and a frameshift mutation of $BAP1$ (c.214del, p.172L*6), resulting in a truncation of the protein (Figure 4). In the sequencing electropherogram of the tumor, the signal intensity of the mutated $BAP1$ allele was stronger than the signal intensity of the wild-type $BAP1$ allele, indicating that the neoplastic cells had lost the re-
sidual wild-type BAP1 allele through a second event (e.g., loss of chromosome 3, the locus of the BAP1 gene). The adjacent normal tissue showed the same BAP1 frameshift mutation and no BRAFV600E mutation. In the sequencing electropherogram of the adjacent normal tissue, the signal intensities of the mutated BAP1 allele and the wild-type BAP1 allele were equally strong, indicating that adjacent normal cells have one mutated and one wild-type BAP1 allele (heterozygous BAP1 germline mutation).

COMMENT

Several acquired mutations have been identified in melanocytic nevi and melanomas, including BRAF (common acquired nevi and superficial spreading melanoma11–13), KIT (acral and mucosal melanoma, as well as melanomas on chronically sun-damaged skin16,17), HRAS (subset of Spitz nevi18), and GNAQ and GNA11 (blue nevi and uveal melanoma19,20). Recently, mutations and losses involving the BAP1 gene have been found in a lesion in the spectrum of atypical Spitz tumors,6,7 a heterogeneous group of melanocytic neoplasms sharing some resemblance with Spitz nevi but also displaying atypical features overlapping with melanoma. The BAP1 protein functions as a deubiquitination enzyme and is located in the nucleus. BAP1 mutations also have an important role in uveal melanoma and mesothelioma.21,22

The melanocytic tumors have a distinct histopathologic appearance and molecular profile characterized by BRAFV600E mutations and loss of BAP1 expression.6 In most cases, BAP1 loss is somatically acquired, but multiple tumors tend to be associated with a germline mutation of BAP1. Both sporadic tumors and melanocytic skin tumors associated with BAP1 germline mutations share the following similar distinct histopathologic features: multinucleate or giant cells, enlarged round or oval nuclei with vesicular chromatin and variably conspicuous nucleoli, and plump epithelioid cells with amphophilic cytoplasm and well-demarcated cytoplasmic borders.5,7 Furthermore, an associated lymphocytic infiltrate is commonly found.

Although limited follow-up information is available on the BAP1loss/BRAFV600E Spitz tumors, preliminary evidence suggests that most lesions are clinically indolent and likely represent combined spitzoid melanocytic nevi. However, until more long-term follow-up data are re-
ported, conservative complete excision seems prudent for patients with an isolated individual lesion. For patients with multiple lesions, genetic counseling (including testing for germline mutations) and clinical follow-up observation is recommended, with surgical intervention when a change is noted.

Figure 3. Immunophenotype. A, A nodular proliferation of predominantly large epithelioid melanocytes with a few scattered lymphocytes is surrounded by conventional small melanocytes (arrow). B, The large melanocytes lack labeling for BAP1 expression, while the nuclei of small melanocytes (arrow) and nonmelanocytic normal cells (keratinocytes and lymphocytes) are immunoreactive (red chromogen). C, The small epithelioid melanocytes (original magnification ×200) show strong nuclear labeling for BAP1 expression (inset). D, Although lymphocytes are immunoreactive, the large epithelioid melanocytes (original magnification ×200) fail to label for BAP1 expression (inset).

Figure 4. Mutation analysis. BAP1 is mutated in both normal tissue (skin ellipse with no lesion) and tumor cells. Only tumor cells show the BRAFV600E mutation.
Germline mutations of BAP1 predispose (with varying degrees of penetrance) to the development of various tumors, including melanocytic skin lesions, uveal and cutaneous melanoma, and mesothelioma.\textsuperscript{7,14,15,21} Although the incidence of BAP1 germline mutations in the general population is unknown, a recent study\textsuperscript{23} reported BAP1 germline mutations in 4 of 100 patients (4.0%) with ocular melanoma and in 3 of 200 patients (1.5%) with a family history of cutaneous melanoma. Adal patients with BAP1 mutations have been reported with positive sentinel lymph nodes in children and teenagers, and comparison with historically unambiguous and lethal melanomas.\textsuperscript{7,14,15,21} In each family, the patient described herein reports a family history of gastric cancer.

In conclusion, we describe the occurrence of multiple combined BAP1\textsuperscript{cohort}/BRAF\textsuperscript{cohort} melanocytic lesions in a young man. To our knowledge, the clinical constellation of multiple papules or polyoid nodules present since childhood has not been previously reported and supports the impression of clinically indolent or benign lesions. The histopathologic features favor a combined melanocytic nevus composed of BAP1-expressing common nevus cells and an epithelioid (spitzoid) component with loss of BAP1 expression. Finally, because genetic analysis was prompted by the knowledge of one of us (K.J.B.) about the association of distinct cytologic features with loss of BAP1 expression, the case also illustrates how phenotypic findings can lead to the diagnosis of a hereditary tumor syndrome and BAP1 germline mutations. Patients with this hereditary tumor syndrome may benefit from individualized screening and management strategies.

Accepted for Publication: October 3, 2012.
Correspondence: Klaus J. Busam, MD, Department of Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (busamk@mskcc.org).

Author Contributions: Drs Busam, Wanna, and Wiesner had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Busam. Acquisition of data: Busam, Wanna, and Wiesner. Analysis and interpretation of data: Busam, Wanna, and Wiesner. Drafting of the manuscript: Busam, Wanna, and Wiesner. Administrative, technical, and material support: Busam. Study supervision: Busam and Wiesner.

Conflict of Interest Disclosures: None reported.

REFERENCES