Dermatopathology quiz: A dome-shaped papule on the cheek

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The 43-year-old woman was evaluated for a 0.4 cm erythematous, dome shaped papule on her left cheek. Clinically, an irritated or atypical nevus was suspected, and a shave biopsy of the lesion was performed.

Histopathological sections revealed a compound, biphasic melanocytic neoplasm composed of both banal appearing nevus cells [Figure 1], and a second population of epithelioid melanocytes forming large dermal aggregates [Figures 2 and 3]. While the conventional component of the neoplasm demonstrated evidence of maturation and dispersion with descent into the dermis, the epithelioid component was monomorphic throughout and showed no evidence of maturation. An Elastic Van Gieson (EVG) stain showed retained elastic fibers within the epithelioid nests. A BRCA1 associated protein-1 (BAP1) immunohistochemical stain mirrored the dichotomous morphology, with nuclear staining in the conventional-appearing nevus cells and the absence of nuclear staining in the epithelioid cells [Figure 4]. Strong p16 staining was noted in the epithelioid component [Figure 5].

The most likely diagnosis is:

A. Malignant melanoma arising in a congenital nevus
B. Epithelioid Spitz nevus
C. Wiesner nevus
D. Metastatic, familial uveal melanoma involving a nevus
E. Balloon-cell change in a congenital nevus.

ANSWER: C. Wiesner nevus

DISCUSSION

Wiesner nevus is a benign epithelioid nevus with BAP1 mutation that represents a morphologically and genetically distinct variant in the spectrum of epithelioid Spitz nevi.[1] Clinically, the lesion typically presents as a skin colored or reddish-brown, well-circumscribed, dome-shaped papule. Alternatively, it may present as either rapid growth or pigmentary change within a preexisting nevus.[2] The lesions can arise as either isolated, sporadic lesions or as part of an autosomal dominant syndrome of familial uveal melanoma and benign cutaneous Weisner nevi (cutaneous BAPomas).[3]

Histopathologically, routine hematoxylin and eosin stained sections of benign epithelioid nevi with BAP1 loss are characteristically biphasic in appearance with one component composed of dermal nests of epithelioid cells. Specifically, these are larger melanocytes with nuclei that are round to oval with open vesicular chromatin and distinct nucleoli and abundant amphophilic cytoplasm. In general, this cell population is surrounded by a second population of smaller, more banal appearing melanocytes.[4] Lack of maturation, reverse maturation, cytologic atypia with large hyperchromatic nuclei, and rare mitotic activity have all been reported in these nevi, separating them from other Spitz nevi.[5] At the molecular level, Wiesner nevi demonstrates biallelic loss of BAP1 via BAP1 germline mutation, in the familial cases, or postzygotic somatic mutation, in the sporadic nevi. The microscopic correlate to this molecular anomaly is the immunohistochemical loss of nuclear expression of BAP1 in the epithelioid cells.[2] It is important to note that in a subset of these nevi a clumped-perinuclear staining

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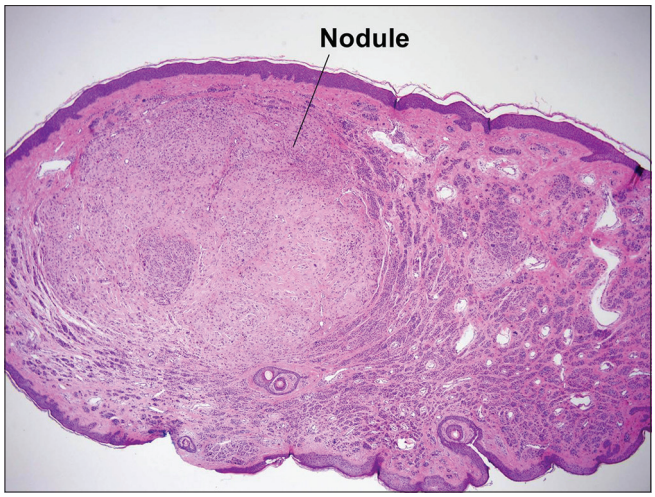

Figure 1: A large nodule of epithelioid melanocytes is embedded among small banal nevus cells

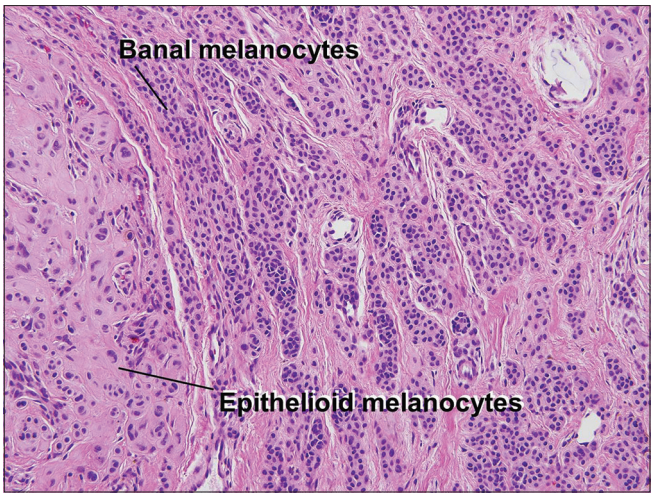

Figure 2: The epithelioid nodule is sharply circumscribed and the transition between the two populations is abrupt

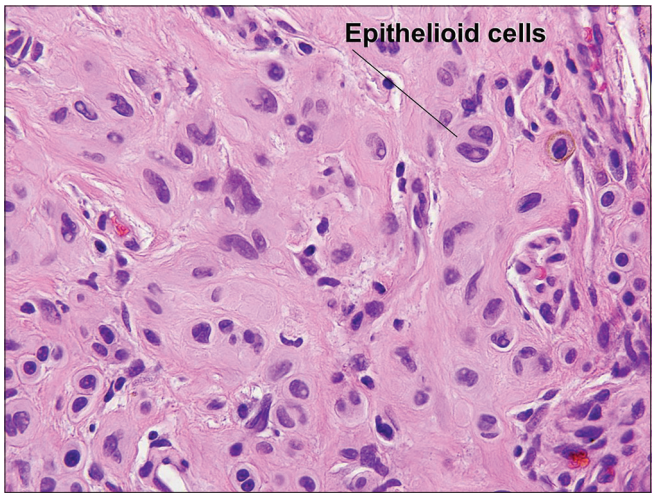

Figure 3: The nuclei of the epithelioid cells are hyperchromatic and pleomorphic. They are unlike the vesicular nuclei with prominent central nucleoli noted in Spitz nevi

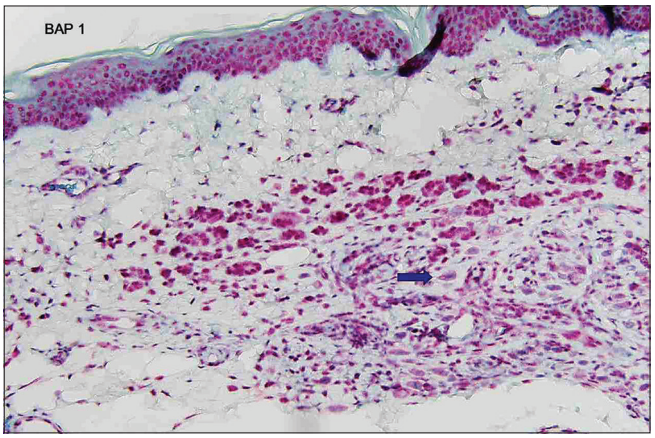

Figure 4: Nuclear BRCA1 Associated Protein-1 is expressed normally in the banal nevus population, but lost in the epithelioid population

pattern was reported suggesting an abnormal localization of a nonfunctional or dysfunctional protein.[6]

Differentiating benign epithelioid nevi with BAP1 loss from other entities in the differential diagnosis can be challenging. Epithelioid cells in Spitz nevus can show similar histologic features, but the absence of other characteristic features of a Spitz can be helpful in distinguishing between the two entities. Specifically, Spitz nevi typically demonstrate epidermal hyperplasia, hypergranulosis, clefting around junctional melanocytic nests and Kamino bodies. Spitz nevi mature and disperse with descent into the dermis, whereas Weisner nevi do not. At the molecular level, Wiesner nevi frequently have BRAF mutation in addition to the characteristic BAP1 mutation, a genetic finding absent in Spitz nevi.[2]

Melanoma arising out of a preexisting nevus is the most important differential diagnosis of benign epithelioid nevi with BAP1 loss.[7] Both melanomas associated with congenital nevi and Wiesner nevi are biphasic neoplasms in which one cellular component is significantly larger and more atypical than the other. There are, however, clues present on routine hematoxylin and eosin stained sections that favor one diagnosis over the other. Whereas, Wiesner nevi maintain a nevoid growth pattern that does not displace dermal connective tissue, melanomas demonstrate an invasive pattern in which tumor stroma typically displaces normal dermal collagen and elastic fibers. Furthermore, Wiesner nevi only rarely have mitotic figures, whereas melanomas frequently have multiple cells in mitosis. Special stains may also help assess the growth pattern and proliferation fraction of a given neoplasm. Staining for dermal elastic fibers with an EVG stain can help identify elastic tissue that has been displaced (or “bulldozed”), by melanoma tumor stroma.[8] A dual differentiation and proliferation marker combination such as the Mart-1/Ki-67 double stain may also help distinguish the two entities. Ki-67 proliferation index <10% favors a diagnosis of melanoma.[9] When other findings are

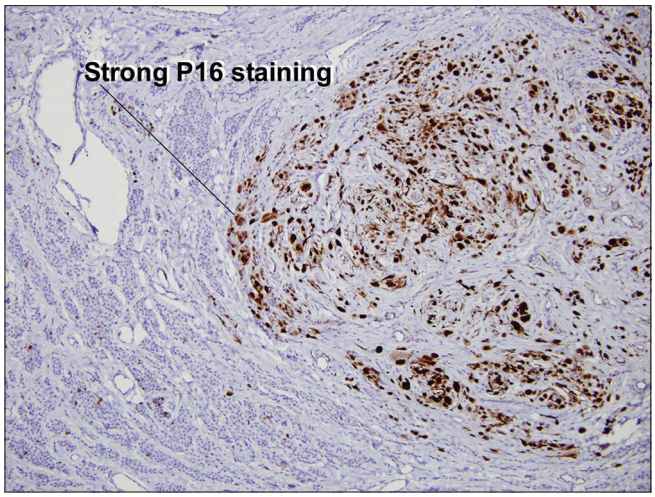

Figure 5: The epithelioid cells strongly express p16

equivocal, fluorescence *in situ* hybridization or comparative genomic hybridization can also be useful in distinguishing Wiesner nevus from melanoma.[5]

BRCA1 associated protein 1 is a tumor suppressor protein, which has a role in control of cell cycle progression at the G1/S check point, and its loss was found to have a role in tumor-genesis.[6] The increased susceptibility to develop uveal melanoma, mesothelioma, and renal cell carcinoma in patients with a germline mutation of BAP1is well documented.[2] However, sporadic BAP1-mutated nevi also occur in the absence of other evidence of a tumor syndrome.

Data until date suggests that Wiesner nevi are benign lesions that mimic melanoma arising in conjunction with a preexisting nevus.[9] As long-term follow-up is limited, complete excision of isolated lesions is recommended by some authors. Patients with multiple lesions should be offered genetic counseling to address both inherited tumor susceptibility in offspring and to enhance early tumor detection and intervention.[1]

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Conflicts of interest

There are no conflicts of interest.

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