A man in his early 50s presented to our department for a skin cancer screening examination. He was generally healthy with no personal history of skin or other cancers. His family history was notable for the fact that his mother died from metastatic ocular melanoma. He had no particular concerns on his skin. Physical examination revealed a 2.5 cm soft, skin-colored nodule on the right plantar foot. (Fig. 1a) He reported this nodule had been present since childhood and was biopsied in the distant past, with the results showing a benign nevus. An excisional biopsy was performed for histopathologic evaluation (Fig. 1b). By immunohistochemical analysis, there was negative staining for nuclear expression of BRCA1 associated protein-1 (BAP1) (Fig. 1c). Genetic testing revealed a heterozygous, pathogenic, truncating, germline BAP1 variant.

What is your diagnosis? See next page for answer.

Fig. 1. (a) A large, soft, skin-colored nodule on the right plantar foot. (b) Histopathology: asymmetric, predominantly intradermal, melanocytic proliferation composed of nests and sheets of epithelioid melanocytes with large, pleomorphic nuclei and light eosinophilic cytoplasm (hematoxylin and eosin (H&E), original magnification × 2.5). (c) Negative immunohistochemical stain for BRCA1 associated protein-1 (BAP1) (original magnification ×20).
A Large Skin-colored Nodule on the Plantar Foot: A Commentary


Diagnosis: Melanoma associated with germline BAP1 mutation

BAP1 is a nuclear deubiquitinating enzyme that functions as a tumor suppressor via its role in DNA damage repair (1). Identification of a cutaneous melanoma with germline BAP1 mutation confirms the diagnosis of the BAP1 cancer syndrome. This is a rare autosomal dominant genetic syndrome typified by the development of mesotheliomas and uveal melanomas. Less commonly, cutaneous melanomas, various types of carcinomas – mostly from the kidney and gallbladder – sarcomas, and brain tumors can arise as well (2). The mechanism by which these seemingly disparate malignancies arise in the setting of a germline BAP1 mutation remains poorly understood. Nevertheless, it likely depends on multiple factors including the tissue in which the second BAP1 allele is inactivated, the mechanism of inactivation of the second BAP1 allele, the functional consequences of a particular BAP1 mutation, environmental exposures, and concurrent mutations (1). Nearly all carriers of germline BAP1 mutations develop at least one malignancy by age 55, and 18% develop cutaneous melanoma (3).

Patients with BAP1 cancer syndrome develop several, distinct, melanocytic neoplasms. These are raised, pink or tan, dome-shaped, benign lesions that have been referred to in the literature as “melanocytic BAP1-mutated atypical intradermal tumors/MBAITs” or “BAPomas” (2). Histologically, these lesions have large melanocytes with superficial and deep mitotic activity, leading them to be labeled “atypical Spitz tumors” given their resemblance to Spitz nevi (2). Nevertheless, MBAITs are molecularly distinct from true atypical Spitzoid neoplasms, with comparative genomic hybridization (CGH) revealing the former have genetic aberrations at chromosome 3p21 (BAP1 locus), whereas the latter show aberrations at 6q23, 6p25, 8q24, 9p21, and/ or 11q13 that influence the risk of aggressive behavior (4).

REFERENCES