Case Report: Germline BAP1 Mutation

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Introduction

BRA1-Associated Protein 1 (BAP1) plays an important role in the regulation of a number of cellular processes involved in tumor suppression. Inheritance of a germline mutation in the gene encoding BAP1 results in a syndrome characterized by distinct melanocytic tumors and a predisposition to several malignancies.

Case Report

- A 37 yo male with a history of significant actinic damage, basal cell carcinoma and squamous cell carcinoma presented for a full body skin exam. He had no specific complaints.
- Family history was remarkable for his father having died of mesothelioma.
- A 6mm red-brown papule under the left chin (Figure A), present for an unknown duration, was discovered on exam. Clinical impression was an irritated intradermal nevus or an atypical nevus and a shave biopsy of the lesion was performed.
- Histopathologic diagnosis proved challenging as the specimen demonstrated features of both an atypical Spitz nevus and an atypical nevus and a shave biopsy of the lesion was performed.
- Special stains were performed (Figures C,D,E and F)
- Additional tests, including genomic studies were performed (Table 1)
- After review by multiple dermatopathologists specializing in melanocytic tumors a diagnosis of a "paleo" dermal melanocytic proliferation with desmocytic and Spitzoid features, consistent with a melanoma of at least 1.3mm depth," was agreed upon.
- The lesion was excised with 1cm margins. A sentinel lymph node biopsy was performed and 2 of 3 of nodes in the right neck were positive for melanoma.
- A PET/CT following the SLNB revealed bilateral upper cervical lymphadenopathy.
- Completion dissection was only performed on the right neck given the morbidity associated with bilateral neck dissection.
- No additional positive nodes were found.
- A 6 month follow-up scan revealed a mass on the left kidney, which was removed via robotic partial nephrectomy and found to be a clear cell renal cell carcinoma.
- Two years following the initial melanoma diagnosis a suspicious red-brown papule on the left upper back was discovered and biopsied.
- Microscopic examination revealed a bland atypical melanocytic proliferation, with both large epithelioid and small, bland appearing melanocytes. (Figure G)
- No unusual cytogenetic or fluorescence in situ hybridization abnormality (chromosome 11)
- Comparative Genomic Hybridization Chromosomal abnormalities: 3,9,10
- The patient was diagnosed with a germline BAP1 mutation and is now followed closely at our clinic and at university based melanoma and oncology clinics.

Clinical and Histologic Findings

A. Grom red-brown papule, under left chin.
B. Dermal proliferation of atypical melanocytes.
C. Enlarged melanocytes with abundant eosinophilic cytoplasm and nuclear pleomorphism.
D. Ki-67 = low proliferative index for dermal melanocytes.
E. FISH = strong staining within enlarged dermal melanocytes.
F. Large epithelioid melanocytes adjacent to a population of minute, bland appearing melanocytes.

Additional Tests

- BAP1 Testing
- Fluorescence In Situ Hybridization
- Comparative Genomic Hybridization
- Chromosomal abnormalities: 3,9,10

Discussion

- BRCA-associated protein 1 (BAP1) is a member of the ubiquitin carboxy-terminal hydrolase (UCH) system, which is involved in several important cellular functions.
- Somatic mutations of BAP1 have been discovered in a number of malignancies, including uveal melanoma (UM), cutaneous melanoma (CM), renal cell carcinoma (RCC), mesothelioma (MM), breast cancer, small cell and non-small cell lung cancers, cholangiocarcinoma and perhaps many more that have yet to be elucidated.
- Uveal melanoma, in particular, is associated with a high rate of BAP1 mutation, with as many as 47% harboring mutations.
- Mutations in the BAP1 gene may be inherited in an autosomal dominant fashion, predisposing individuals to several malignancies, including UM, CM, mesothelioma, RCC, and basal cell carcinoma.
- Germline BAP1 mutations appear to be associated with a distinct melanocytic tumor.
- Clinical appearance of these lesions are consistently described as flesh-toned to reddish-brown, well circumscribed, dome-shaped or pedunculated papules.
- Characteristic morphologic features include dermal aggregates of large, epithelioid melanocytes with abundant cytoplasm and nuclear pleomorphism.
- These appear in the first two decades of life and then increase in number, with some individuals having more than 50. Despite this, there are far fewer cases of cutaneous melanoma relative to the number of these tumors, thus they are thought to rarely evolve into melanoma.

Conclusion

- Dermatologists and dermatopathologists play an important role in the identification of patients with a number of inherited cancer syndromes, many of which initially present with cutaneous manifestations.
- Increased awareness of this syndrome will facilitate earlier recognition of affected patients, allowing for more appropriate management, such as increased surveillance for associated malignancies and genetic counseling.

References