An adolescent with uveal melanoma and *BAP1* tumor predisposition syndrome

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INTRODUCTION

BRCA1-associated protein-1 (BAP1) tumor predisposition syndrome (*BAP1*-TPDS) is an inherited cancer syndrome arising from pathogenic germline variations in *BAP1*. Affected individuals have increased risk for uveal melanoma, cutaneous melanoma, renal cell carcinoma, and malignant mesothelioma as well as characteristic benign cutaneous lesions (*BAP1*-inactivated nevi), basal cell carcinomas (BCCs), and other malignancies.[1-3] The full phenotypic neoplastic spectrum is still being investigated. We present the case of a 15-year-old girl with uveal melanoma leading to a diagnosis of *BAP1*-TPDS.

Abbreviations used:

BAP1: *BRCA1*-associated protein-1
BCC: basal cell carcinoma
TPDS: tumor predisposition syndrome

CASE REPORT

A 15-year-old girl presented to ophthalmology clinic with sudden onset of a stable grey line in the central vision of her left eye, accompanied by ipsilateral loss of peripheral vision. Clinical examination and ultrasound scan suggested ocular melanocytosis and choroidal melanoma. Enucleation and fine-needle aspiration of the choroidal lesion were performed. Pathologic evaluation found bilobed melanoma of the choroid surrounding the optic nerve with scleral invasion. Fine-needle aspiration of the choroidal lesion was submitted for gene expression profiling with a proprietary 15-gene panel and showed a high-risk molecular signature (class 2) with a higher risk for metastatic recurrence.[4]

Family history included mesothelioma in her paternal grandmother. One paternal great aunt had stomach cancer, and another had unknown ocular pathology requiring eye enucleation. Next Generation Sequence analysis of *BAP1* detected a germline, monoallelic single base substitution c.2188T>C, leading to loss of a stop codon, p.X730Arg. This variation, although not previously reported, was favored to be pathogenic, and *BAP1*-TPDS was diagnosed. Initial staging included computed tomography (thorax and abdomen) and magnetic resonance imaging (abdomen and brain); all were unremarkable for metastasis.

Dermatologic physical examination found several soft pink and pink-tan papules approximately 2-4 mm in size. Pathology of a representative lesion on the lateral canthus (Fig 1, *A*) showed a dome-shaped biphenotypic melanocytic lesion composed of epithelioid melanocytes with eosinophilic cytoplasmic centrally and ordinary common nevus peripherally (Fig 1, *B*). The epithelioid component was arranged in a cellular sheet-like growth forming an expansile nodule (Fig 1, *C*). Both components of the lesion were positive for $BRAF^{V600E}$. There was loss of nuclear *BAP1* expression within the epithelioid component (Fig 1, *D*). Ki-67/MART1 dual immunostain demonstrated a low proliferation index; p16 expression was retained. The findings were diagnostic for

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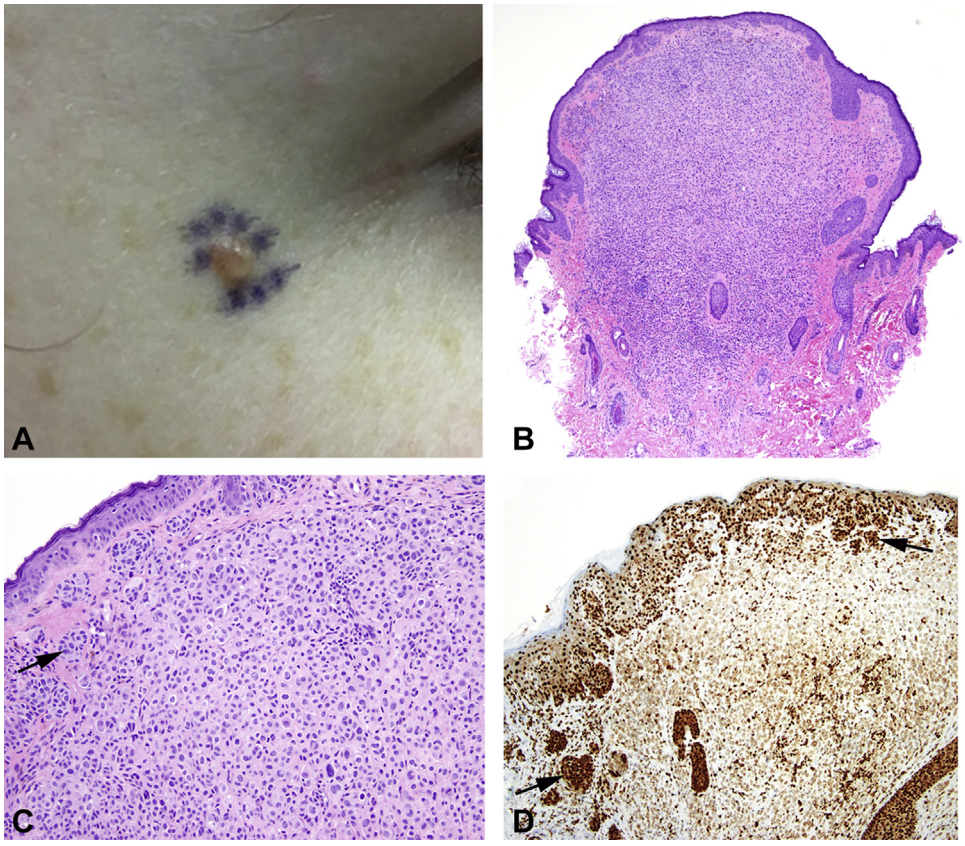

Fig 1. **A**, *BAP1*-TPDS. Clinical presentation of BAP1-inactivated nevus, right lateral canthus. **B**, Scanning magnification of *BAP1*-inactivated nevus shows dome-shaped to polypoid silhouette with increased cellularity centrally. **C**, *BAP1*-inactivated nevus shows ordinary nevus at periphery (*arrow*) merging with epithelioid component arranged in a cellular sheet-like configuration. **D**, *BAP1*-inactivated nevus shows retention of nuclear BAP1 staining in ordinary nevus component (*arrows*) and loss of BAP1 staining in epithelioid component. (**B** and **C**, Hematoxylin-eosin stain; **D**, BAP1 immunostain; original magnifications: **B**, ×40; **C** and **D**, ×200.)

BAP1-inactivated nevus. Removal of several of the patient's other cutaneous lesions also demonstrated histologic features consistent with *BAP1*-inactivated nevi.

The patient remains in active melanoma surveillance with annual dilated eye examinations with ophthalmologic imaging. Cancer geneticists guide her surveillance with other physicians. She undergoes physical examinations every 4 months with blood work including liver panel; annual computed tomography of the chest; abdominal imaging every 6 months, alternating ultrasound scan and magnetic resonance imaging; and total body skin examinations every 6 months with dermatology.

DISCUSSION

BAP1-TPDS is inherited in an autosomal dominant manner[3] and increases the risk of uveal melanoma, mesothelioma, cutaneous melanoma and clear cell renal cell carcinoma.[1,5-8] Additional dermatologic manifestations include *BAP1*-inactivated nevi, the most common lesion reported with *BAP1*-TPDS, and basal cell carcinoma.[9-11] However, the entire associated tumor spectrum is not well defined. Recent reports suggest that meningioma, cholangiocarcinoma, and potentially other cancers may be part of the *BAP1*-TPDS spectrum.[1,12,13]

Uveal melanoma is the most common type of malignancy reported with *BAP1*-TPDS, found in 24%-28% of documented cases.[1,2] Patients with germline *BAP1* pathogenic variants tend to have more aggressive class 2 tumors with increased risk for metastasis and poorer prognosis.[14] Median age of onset of uveal melanoma in *BAP1*-TPDS is in the 6th decade of life, with the earliest reported at age 16,[1,14,15] slightly older than our patient. Current recommendations suggest that screening for uveal melanoma should begin around age 11.[3]

In patients with *BAP1*-TPDS who underwent total body skin examinations, *BAP1*-inactivated nevi (also known as *BAP1*-inactivated melanocytic tumors, melanocytic *BAP1*—mutated atypical intradermal tumors, or BAPomas) were identified in 75% of patients and had a median age of detection of 32 years, which represent a significantly higher penetrance and younger age of onset compared with other *BAP1*-associated tumors.[2] These lesions appear as skin-colored to pink, dome-shaped or pedunculated papules 0.2-1 cm in diameter, often clinically indistinguishable from typical nevi; affected patients can have few or many of these lesions.[2] Dermoscopy findings can include structureless, pink-to-tan regions with or without irregular dots/globules, peripheral vessels or pigment network.[16]

Biopsy is required to diagnose *BAP1*-inactivated nevus. Histopathology usually finds a biphenotypic or combined, predominantly intradermal melanocytic lesion composed of varying components of ordinary nevus and larger epithelioid melanocytes with eosinophilic cytoplasm and distinct cytoplasmic borders. There may be considerable cytologic atypia and nuclear pleomorphism.[9,11] When there is high-grade atypia, the term *BAP1*-inactivated melanocytoma is recommended.[17] *BAP1* pathogenic variant status correlates well with protein expression on immunohistochemistry. Therefore, cells with loss of both alleles of *BAP1* will show negative staining for this protein, whereas those with monoallelic inactivation will still demonstrate nuclear staining with or without cytoplasmic staining.[2] Most tumors are also positive for $BRAF^{V600E}$ mutations.[9,11] It has been estimated that perhaps 10%-20% of patients with *BAP1*-inactivated nevi could have pathogenic germline variations in *BAP1*,[18,19] although prospective studies are warranted in this area.

Cutaneous melanomas have been reported in around 18%-19% of patients with known *BAP1* germline mutations.[1,2] Cutaneous melanomas tend to occur at an earlier age and may have poorer prognosis than sporadic melanomas.[14] Loss of BAP1 expression is seen in cutaneous melanomas diagnosed in both sporadic and *BAP1*-TPDS cases.[14,20] Melanoma can arise de novo or within a preexisting *BAP1*-inactivated nevus/melanocytoma. BCCs, found on chronic ultraviolet light—exposed skin, were recently added to the clinical spectrum of *BAP1*-TPDS. BCCs in these patients exhibit loss of BAP1 expression, whereas sporadic BCCs do not.[10]

Dermatologists are critically positioned to identify and care for patients with *BAP1*-TPDS given the high penetrance and early onset of *BAP1*-inactivated nevi and the high frequency of cutaneous melanomas in this population. To date, there are no evidence-based screening recommendations for detection of germline *BAP1* mutations. However, *BAP1*-TPDS should be suspected, and referral to cancer genetics suggested, in patients with 2 or more confirmed *BAP1*-TPDS tumors or one *BAP1*-TPDS tumor with a suggestive family history.[3] Patients with *BAP1*-TPDS should receive skin cancer education and regular skin examinations and, under the guidance of cancer genetics, should undergo screening for uveal melanoma, renal cell cancer, and other associated cancers.

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