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Clinical Implications of Real-Time Integrative Sequencing in Management of Patients with Suspected Germline BAP1 Mutations

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INTRODUCTION

The BAP (BRCA associated protein) gene encodes the BAP-1 enzyme that catalyzes de-ubiquitination of protein substrates involved in cell cycle regulation, cell differentiation and cell death. BAP1 exhibits tumor suppressor activity, and a heterozygous germline mutation in this gene has been implicated in the development of tumor predisposition syndrome (TPDS). BAP1 associated TPDS is inherited in an autosomal dominant fashion and affected individuals are at high-risk for development of several tumors including malignant mesothelioma, lung adenocarcinoma, uveal melanoma and cutaneous melanoma. In this report, we present the case of a patient with recurrent metastatic melanoma who was subsequently found to have a pathogenic germline BAP1 and somatic BRAF mutation by clinical genomic sequencing. This finding led to a change in cancer surveillance recommendations for the patient, as well as other family members. (OMIM 603089, OMIM 614327)

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CASE REPORT

A 16-year-old female presented with a right sided post auricular skin tag. She had first noted it at 10 years of age but presented with a several month history of increasing size, pruritus and pain. She underwent biopsy and curettage of the lesion, which demonstrated superficial spreading type melanoma, Breslow depth 0.6 centimeters, Clark level 4. She subsequently underwent wide local excision and sentinel node biopsy with 2 out of 3 nodes being positive. Given the positive nodes, she underwent a right posterolateral neck dissection and all 53 lymph nodes were negative for involvement by melanoma. A CT scan of her neck, thorax, abdomen and pelvis was negative for any evidence of disease elsewhere. A whole body PET scan was likewise negative. She was treated with adjuvant high dose interferon-B and completed approximately four months of therapy. Due to significant side effects including febrile reactions and depression, the treatment was discontinued. Approximately one year following diagnosis, she was found to have a metastatic right occipital lymph node lesion. This was subsequently resected with negative tumor margins and further metastatic workup including brain MRI and whole body PET were negative. She subsequently received three adjuvant cycles of dacarbazine, vinblastine, and cisplatin at outside institution. She is currently over two years out from treatment completion and remains in remission without any evidence of recurrent disease. A detailed family history obtained at the time of enrollment, was significant for multiple malignancies (see Figure 1), including a maternal history of ovarian cancer diagnosed at age 44 years prior to melanoma diagnosis of her daughter. Mom had been seen in a cancer genetics clinic for her ovarian cancer at young age and had undergone a standard of care BRCA1 and BRCA2 testing (sequencing, as well as duplication/deletion analysis), which had failed to detect any mutation and mom was not advised to pursue any further testing herself or screening for family members.

At the time of her diagnosis, our patient was enrolled on a prospective integrative clinical sequencing trial (*PEDS-MIONCOSEQ*) and underwent paired tumor/normal whole exome DNA sequencing (WES) and tumor transcriptome sequencing (RNA-Seq) to better understand the biological basis of her melanoma. Specifics of the sequencing procedure and bioinformatics analysis have been described previously (1). Sequencing revealed a somatic BRAF (V600E) point mutation, as well as a BAP1 (p. D567X) germline pathogenic variant. Based on these findings, she was recommended to have a detailed ophthalmology examination to rule out uveal melanoma and family genetic screening was recommended for her 2 siblings and parents to rule out BAP1 associated TPDS. Four months after her diagnosis of melanoma, her mom was diagnosed with a second malignancy in form of peritoneal mesothelioma.

DISCUSSION

There were an estimated 87,110 new cases of cutaneous melanomas in the United States in 2017 (American Cancer Society). Melanoma is difficult to treat and is becoming increasingly prevalent being the fifth most common cancer diagnosed in men, and the seventh most common in women (2). These cases are typically spontaneous and related to occasional extreme sun exposure and UV radiation damage to the skin. This damage results in somatic mutations to genes, one of the most common being BRAF V600E, which is

involved in 40-60% of melanomas (3). In addition to spontaneous somatic mutations, heterozygous germline mutations to a tumor suppressor gene such as BAP1 and the subsequent development of TPDS can also be involved in development of melanoma. In these cases, tumors are the result of a second hit to the tumor suppressor gene and the elimination of the remaining wild type allele (4). A population-based study of melanoma cases in the UK revealed that <1% exhibited the germline BAP1 mutation (5). However, this gene has high penetrance, with malignancy developing in 69.74% of carriers and nearly all individuals with germline BAP1 mutations develop malignancies by age 55. These malignancies include uveal melanoma, cutaneous melanoma, malignant mesothelioma, lung adenocarcinoma and renal cell carcinoma. As is the case with other familial cancer syndromes, these malignancies may develop at a younger age than in the general population (6). The earliest reported case of cutaneous melanoma related to BAP1 mutations prior to this case was at the age of 25 (7).

Given her young age at initial presentation, family history of cancer, and recurrence of melanoma, our patient was enrolled in an integrative clinical sequencing to determine the specific genomic aberrations of her tumor. This sequencing revealed a somatic BRAF mutation that could be exploited with targeted therapy if needed in the future. Further, a germline BAP1 mutation (p. D567X) was identified. The presence of both a somatic BRAF mutation and germline BAP1 mutation have been implicated in cutaneous melanoma (4). Identification of specific, previously identified mutations allows for early screening of related malignancies, screening for family members and genetic counseling. While evidence based management has not yet been established, Rai et al. 2016 proposed recommendations for families with germline BAP1 mutations. Uveal melanoma should be screened with yearly dilated eye exams beginning at age 11. Cutaneous melanoma should be monitored with yearly full body skin exams by a dermatologist beginning at age 20. There are no specific recommendations regarding screening for malignant mesothelioma and renal cell carcinoma, but yearly physical exams and yearly abdominal ultrasounds or an MRI every 2 years were suggested as possible strategies for early detection of these cancers respectively (7).

In our case, evidence of confirmed germline BAP1 mutation led to screening for uveal melanoma by ophthalmology and close monitoring for cutaneous melanoma for the patient as well genetic screening for other family members. Early detection and local treatment of these tumors is curative when detected early and often fatal with metastatic disease (6). For uveal melanomas, prognosis worsens with initial treatment failure, large tumor size, and increased age, further highlighting the importance of early screening (8). Furthermore, the risk of metastasis in these tumors is different, thus impacting overall prognosis.

The integration of clinical sequencing as a tool to guide management in pediatric cancer patients is feasible and can identify actionable targets for therapy (9). Moreover, our case highlights the fact that integrative clinical sequencing can identify germline mutations in patients and families that were previously not considered high risk for TPDS by standard, detailed family history (1, 9). Prospective integrative sequencing for pediatric cancer patients, irrespective of their family history of malignancy, may identify pathogenic

germline mutations and may improve outcomes and treatment related morbidity by early diagnosis of malignancy.

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FIGURE 1.
Pedigree outlining family history of malignancy.