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BAP1 Tumor Predisposition Syndrome

BAP1 tumor predisposition syndrome (*BAP1*-TPDS) is caused by mutations in the *BAP1* gene and is associated with increased risks for cancers such as uveal melanoma, malignant mesothelioma, cutaneous melanoma and renal cell carcinoma. Most individuals with a *BAP1* mutation develop multiple non-cancerous cutaneous lesions-melanocytic neoplasms that resemble atypical Spitz tumors and dermal nevi but are clinically, histologically and genetically different. It has been estimated that up to 85% of individuals with a mutation will develop cancer by 65 years of age, and an earlier age of onset for cancer has been observed compared to comparable cancers in the general population.[1]

There are currently no national consensus guidelines for the management and screening of individuals with *BAP1* mutations. However, some surveillance and management guidelines have been proposed as outlined below. A summary of the cancer risks, non-cancer features and general management guidelines based on the current literature is included below for your information. Mutations in *BAP1* have been recently described, and our understanding of the lifetime risks, types of cancers and management recommendations for individuals with *BAP1* mutations will evolve over time.

BAP1-TPDS Risks and Management Recommendations

Uveal Melanoma: Uveal melanoma (UM) has been reported 31% of individuals with *BAP1*-TPDS. The median age of onset in individuals with *BAP1*-TPDS is 51 years, but has been reported as early as 16 years.[1,2] UM tends to be more aggressive with a higher risk for metastasis compared to UM that occurs in the general population.

- Surveillance:
  - Annual dilated eye examinations with ophthalmic imaging by an ocular oncologist beginning at age 11
  - If UM is diagnosed, consider "high risk" patient monitoring protocol for systematic metastatic surveillance (e.g., liver-directed imaging every 3-6 months, pulmonary imaging every 6-12 months)
- Treatment: Due to aggressiveness of *BAP1*-related UM, all UMs should be managed as the more aggressive tumors (i.e., class 2 by expression profiling and those with monosomy 3)
- Prevention:
  - Arc welding has been associated with increased risks of UM, and should be avoided if possible
  - There are no data regarding the benefit of sunglasses for UM risk reduction

Malignant Mesothelioma: Malignant mesothelioma (MMe) has been reported in 22% of patients with *BAP1*-TPDS. The median age of onset is significantly earlier than the general population (55 v. 58 years, respectively). Both pleural and peritoneal MMe have been reported, with the majority of peritoneal MMe occurring in women. [1,2]

- Surveillance: No consensus surveillance modalities exist at this time, however the following have been proposed:
  - Annual physical examinations recommended. Evaluation should include assessment for chest pain, cough, fever, shortness of breath, dysphagia, hoarseness, weight loss, fever, upper body and face edema (chest mesothelioma) and abdominal pain, ascites, nausea, vomiting, and/or constipation (peritoneal mesothelioma). Annual physical examination is recommended to look for signs of pleurisy (pleural inflammation), peritonitis, ascites and/or pleural effusion.

    - If an abdominal MRI is to be performed as recommended for renal cancer surveillance, consider evaluation of the peritoneum and pleura as well
- Prevention: Asbestos exposure and smoking exposure should be avoided

Cutaneous Melanoma and Basal Cell Carcinoma: Cutaneous melanoma has been reported in 13% of patients with *BAP1*-TPDS. The median age of onset is earlier than the general population (46 v. 58 years, respectively). Basal cell carcinomas are also associated with *BAP1*-TPDS, exact risks remain unclear. Multiple primary cutaneous melanomas and basal cell carcinomas are common.[1, 2]

- Surveillance/Prevention:
    - Annual full-body skin exams beginning at age 20 years
    - Skin self-exam following ABCDE characteristics of melanoma
- Prevention:
    - Limiting of sun exposure
    - Regular use of sunscreen and protective clothing

Clear Cell Renal Cell Carcinoma: Clear cell renal cell carcinoma (ccRCC) has been reported in 10% of patients with *BAP1*-TPDS. The median age of onset is earlier than the general population (47 v. 64 years, respectively). These tumors tend to be higher grade at diagnosis compared to those not associated with *BAP1* mutations.[1,2]

- Surveillance:
    - Consider annual abdominal ultrasound
    - Consider MRI every 2 years
    - Consider annual urinalysis

Atypical Spitz tumors (ASTs): *BAP1*-TPDS is associated with atypical Spitz tumors (ASTs), a distinct subset of benign skin lesions of the head and neck, trunk, and limbs. This is the most common feature of *BAP1*-TPDs, found in an estimated 72% of affected individuals.[1] These tumors are also referred to as nevoid melanoma-like melanocytic proliferations (NEMPP), melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITS), and BAPoma.[2] *BAP1*-related dermal lesions usually present in childhood or adolescence and are clinically stable with a low risk of malignancy, however some reports have shown transformation to malignant melanoma and basal cell carcinoma. These tumors are characterized by biallelic inactivation of *BAP1* and frequent *BRAF* V600E mutation. Evaluation for ASTs should be included as part of the annual skin exams for skin cancer, as outlined above. If ASTs are detected, *BRAF* mutation testing and immunostaining for *BAP1* should be performed.[1]

Other Cancer Risks: There is some evidence suggesting that *BAP1* mutations are associated with increased risks for breast cancer, cholangiocarcinoma, melanoma, neuroendocrine tumors, non-small cell lung cancer, and thyroid cancer.[2] Further study is needed to clarify these associations. Currently, there are no consensus management guidelines for these cancers in individuals with *BAP1.* Individuals with *BAP1*-TPDS are encouraged to discuss these cancer risks, along with family history and personal risk factors, to establish an appropriate surveillance regimen.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have up to a 50% chance to have the familial *BAP1* mutation. Second-degree relatives (i.e. nieces/nephews, aunts/uncles, and grandparents) have up to a 25% chance to have the familial mutation.

- The risk for cancer with a *BAP1* mutation is not 100% and as such, individuals may develop one cancer, more than one cancer, or none at all and the types of *BAP1*-related tumors can vary among different members of the same family.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Rai, K., Pilarski, R., Cebulla, C.M., & Abdel-Rahman, M.H. Comprehensive review of *BAP1* tumor predisposition syndrome with report of two new cases. *Clinical Genetics*. 2016;89(3):285-294.
2. Pilarski R, Rai K, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK390611/