Hereditary melanoma: Update on syndromes and management

Emerging melanoma cancer complexes and genetic counseling

Efthymia Soura, MD,[a] Philip J. Eliades, BS,[b,c] Kristen Shannon, MS,[d] Alexander J. Stratigos, MD, PhD,[a] and Hensin Tsao, MD, PhD[b,d]

Athens, Greece, and Boston, Massachusetts

Learning objectives

After completing this learning activity, participants should be able to describe algorithms used to assess patients with possible melanoma tumor syndromes (MTS), explain the genetic basis of MTS predisposition, in light of novel susceptibility genes identified recently in genomic studies; discuss the role of genetic testing and genetic counseling in patients with MTS; and determine when it is appropriate to refer patients with MTS.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors

The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners

The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Recent advances in cancer genomics have enabled the discovery of many cancer-predisposing genes that are being used to classify new familial melanoma/cancer syndromes. In addition to *CDKN2A* and *CDK4*, germline variants in *TERT*, *MITF*, and *BAP1* have been added to the list of genes harboring melanoma-predisposing mutations. These newer entities may have escaped earlier description in part because of more advanced technologies now being used and in part because of their mixed cancer phenotype as opposed to a melanoma-focused syndrome. Dermatologists should be aware of (and be able to recognize) the clinical signs in high-risk patients in different contexts. Personal and family histories of cancer should always be sought in patients with multiple nevi or a positive history for melanoma, and should be updated annually. Various features that are unique to specific disorders, such as the appearance of melanocytic BAP1-mutated atypical intradermal tumors in cases of BAP1 melanoma syndrome, should also be recognized early. These patients should be offered regular screenings with the use of dermoscopy and total body photography, as needed. More importantly, referral to other specialists may be needed if a risk for internal malignancy is suspected. It is important to have in mind that these patients tend to develop multiple melanomas, along with various internal organ malignancies, often at younger ages; a multidisciplinary approach to their cancer screening and treatment is ideal. (J Am Acad Dermatol 2016;74:411-20.)

Key words: BAP1; familial melanoma syndrome; melanoma genetics; MITF; mixed cancer syndromes; PTEN; TERT.

From the 1st Department of Dermatology,[a] University Clinic, "Andreas Sygros" Hospital, Athens; Department of Dermatology,[b] Wellman Center for Photomedicine, Massachusetts General Hospital, Boston; Tufts University School of Medicine,[c] Boston; and the Melanoma Genetics Program/MGH Cancer Center,[d] Massachusetts General Hospital, Boston.

Supported by National Institutes of Health grant K24 CA149202 (Dr Tsao) and by the generous donors to Massachusetts General Hospital on behalf of melanoma research.

Conflicts of interest: None declared.

Accepted for publication August 3, 2015.

Reprints not available from the authors.

Correspondence to: Hensin Tsao, MD, PhD, Massachusetts General Hospital and Harvard Medical School, Wellman Center for Photomedicine, Edwards 211, 50 Blossom St, Boston, MA 02114-2696. E-mail: htsao@partners.org.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.08.037

Date of release: March 2016

Expiration date: March 2019

GENERAL CONSIDERATIONS FOR EMERGING MELANOMA CANCER COMPLEXES

Key point

- **A number of melanoma susceptibility genes have been discovered in recent years, including mutations in BAP1, MITF, shelterin complex, and PTEN**

During the last few years, sequencing efforts in the field of melanoma research have led to a number of scientific breakthroughs, including the elucidation of unknown molecular pathways and the discovery of new susceptibility genes. These discoveries hold great value because they may assist in the identification of possible molecular therapeutic targets or could serve as biomarkers for melanoma development and progression. Although the identification of new susceptibility genes may shed a light on the complexity of the genetic landscape of melanoma, how these genes influence patient phenotypes has not been determined. Overall, it is estimated that about 10% of melanoma patients present with a positive family history for melanoma.[1] However, true hereditary melanoma syndromes are much rarer. Patients often present with early onset melanomas, multiple primary melanomas, and a family history that features multiple cases of melanoma in several generations on one side of the family.[2] In addition, a number of those patients (and their families) may present with other internal organ malignancies. These patients fall under the category of "mixed cancer syndrome" patients, where melanoma may appear in the context of a more general predisposition for malignancy. Familial atypical multiple mole melanoma syndrome is one of the most comprehensively described melanoma tumor syndromes. However, in recent years, mutations in BRCA1-associated protein 1 (BAP1), shelterin complex, microphthalmia-associated transcription factor (MITF), and phosphatase and tensin homolog (PTEN) have also been associated with melanoma and internal organ cancers. Part II of this continuing medical education article summarizes the current knowledge of these emerging cancer complexes, their pathogenetic mechanisms, and the known data regarding patient phenotypes. We also provide information regarding the management of these patients.

BAP1 TUMOR SYNDROME

Key points

- **BAP1 tumor syndrome is associated with the appearance of cutaneous melanoma, uveal melanoma, and various internal malignancies**
- **Up to 67% of patients with BAP1 cancer complex present with multiple melanocytic BAP1-mutated atypical intradermal tumors**
- **Patients presenting with metastatic uveal melanomas or concurrent uveal and cutaneous melanomas have a higher possibility of exhibiting BAP1 mutations compared to other patients with melanoma**

Somatic mutations of *BAP1* were first described in 26 of 31 aggressive (class 2) cases of uveal melanoma (UM).[3,4] Subsequently, germline *BAP1* mutations were also reported in multicancer families. *C*utaneous/*o*cular *m*elanomas, *m*elanocytic proliferations, and *o*ther internal *n*eoplasms are a part of the BAP1 cancer complex, and the term COMMON syndrome has therefore been proposed.[5] This cancer complex is phenotypically characterized by the appearance of clinically benign but histologically aggressive melanocytic skin tumors (Fig 1, *A* and *B*) at a young age, along with a high incidence of mesothelioma, UM, cutaneous melanoma, and possibly other cancers at older ages. Although a single germline *BAP1* mutation was reported in the original paper by Harbour et al,[4] the association of germline *BAP1* mutations with a multitude of cancers was independently described in families with UM and mesothelioma[6] and in kindreds with both UM and cutaneous melanoma.[7]

Aspects of the pathogenesis of BAP1 tumor syndrome

BAP1 is located on chromosome 3 (3p21.3), and it encodes the 90-kDa BAP1 protein (Fig 2, *A*). Enzymatically, BAP1 has an ubiquitin carboxy-terminal hydrolase domain, suggesting that it serves as an intracellular deubiquitinase.[8] Ubiquitin groups are small peptides used to posttranslationally modify proteins in order to target them for degradation by proteosomes or to regulate its function. BAP1 has roles in many important cellular processes, including cell division, gene expression, signal transduction, protein trafficking, dsDNA repair, and DNA repair regulation, among others.[8,9] The pathogenetic mechanisms through which *BAP1* mutations (ie, rearrangements, homozygous deletions, and missense mutations) directly or indirectly promote melanomagenesis have not been fully elucidated. Some authors have suggested that patients with the mutation may exhibit altered patterns of gene expression through histone 2A modification[10] or impaired DNA damage repair in response to ultraviolet light (UV)–induced damage.[8] However, the role of UV radiation in the appearance of UM is debatable.[11] BAP1 is also a UV-inducible substrate of