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Melanomas of Unknown Primary May Have a Distinct Molecular Classification to Explain Differences in Patient Outcomes

Georgia M Beasley, MD MHSc

[1]Duke University

Although metastatic melanoma of unknown primary (MUP) is relatively uncommon, clinicians who routinely treat melanoma patients will encounter and manage patients with MUP as approximately 3–8% of all metastatic melanoma patients present with MUP. Historically, patients with MUP have been managed similarly to those with metastatic melanoma and a known primary (MKP). However, biologic observations differentiating MUP and MKP have been consistently reported including improved survival for patients with MUP compared to MKP patients with the same corresponding tumor stage.[1,2] Furthermore, patients with MUP may have increased response to immune checkpoint therapy compared to patients with MKP.[3] The biologic basis for these observations has largely consisted of hypotheses regarding immune mediated control of the primary tumor. However, in depth immunologic and tumor analysis is limited. In this issue of Annals of Surgical Oncology, De Andrade et al report on the "Multidisciplinary care of melanoma of unknown primary: Experience in the era of molecular profiling," which begins to investigate the unique molecular classification of tumors associated with clinical presentation of MUP.[4]

Importantly, the mutations reported in this article on MUP patients include activating BRAF and TERT promoter mutations, suggest that the MUPs in this study were consistent with a cutaneous origin. Similarly, in single genes assays for BRAF mutations in 42 patients, the 52% rate of BRAF mutations (n=22) appears similar to that cutaneous MKP. However, although a small sample size, the rates of V600E (55%) and V600K (27%) seem somewhat discordant with MKP where V600E makes up a larger majority activating mutations. Interestingly, V600K mutations appear to benefit less from BRAFi/MEKi therapy and often have a higher mutational load corresponding to improved response to immunotherapy.[5] Thus a higher rate of V600K mutations in MUP could explain improved response to immunotherapy. In addition to BRAF mutations, there may be differences in TERT promoter mutations seen in 46% (n=11) of patients with MUP in this study while TERT promoter mutations have been reported in 85% (45/53) of patients with metastatic melanoma and 33% (25 of 77) patients with primary melanoma.6 Although it is important to consider these differences may be the result of a small size and selection bias, the observed differences in

Corresponding author Duke University, Box 3118, Durham, NC 27710, 919-684-6858 fax, Georgia.beasley@duke.edu.

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disease outcomes for MUP and MKP suggest there may be underlying differences in the molecular composition of these 2 clinical entities that remain unknown. Molecular analysis could ultimately uncover key biologic determinants of tumor growth and proliferation unique to MUP.

Clinical observations are often the gateway to scientific discovery. MUP has been observed to have distinct biology from MKP in that multiple reports indicate improved prognosis for MUP patients compared to stage matched MKP patients. Defining a distinct signature of MUP would ultimately serve to better inform, treat, and manage patients presenting with MUP. There may be key differences in the molecular profile of tumors in MUP such that treatment strategies should vary for patients with MUP compared to MKP. De Andrade et al in this article have begun to explore these potential molecular differences between MUP and MKP. A larger cohort analysis of the molecular profile of patients with MUP is warranted.

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