Article type: Commentary

NOTES

Ref 1: [add details at production]

COMMENTARY

JP 22 August 2018 Ms. No. 18/40-Commentary

Refining the ever-evolving molecular landscape of spitzoid melanocytic neoplasms

DOI: xx [add details at production]

Linked Article: Farah *et al*. *Br J Dermatol* 2018; **xxx**:xxx–xxx. [add details at production]

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Funding sources

No external funding.

Conflicts of interest

None to declare.

In this issue, Farah *et al*. reported a case of spitzoid melanoma with morphological characteristics of an *ALK*-rearranged spitzoid neoplasm and copy number gain, rather than rearrangement, of the *ALK* gene.[1] This case is interesting in that it demonstrates a novel mechanism by which *ALK* may be activated in spitzoid melanoma. It also expands the spectrum of *ALK* alterations associated with the plexiform spitzoid phenotype, namely intersecting fascicles of amelanotic fusiform melanocytes. The authors additionally provided a concise overview of the different types of *ALK* alterations that have been

identified in spitzoid neoplasms. In this modern era, where molecular data continue to accumulate at fast pace, this article serves as a timely and up-to-date guide to this subject. It is now known that approximately 50% of spitzoid lesions harbour kinase fusion of *ALK*, *BRAF*, *ROS1*, *RET*, *NTRK1* or *MET*.[2] Such fusions result in constitutive activation of oncogenic signalling pathways and ultimately proliferation of melanocytes. Of these kinases, *BRAF* is the most extensively studied in the realm of melanocytic lesions, and a myriad of activating alterations (point mutation, amplification and gene rearrangement) has been identified.[3] Our insight into *ALK* alterations in melanocytic lesions is following a similar path, where various activation mechanisms such as copy number gain and alternative transcription initiation are being increasingly recognized after the initial description of gene rearrangement.[1,4]

Besides kinases, a number of other genes (*HRAS*, *CDKN2A*, *BAP1* and *TERT*) are implicated in the pathogenesis of spitzoid neoplasms.[5] Many of these genetic changes are associated with a unique histomorphology and/or immunophenotype which may be used as surrogates of these changes, thereby streamlining the diagnostic process. The case illustrated by Farah *et al*. is an excellent example in which a plexiform spitzoid morphology raised consideration for an *ALK*-rearranged spitzoid melanoma, and prompted ALK immunohistochemistry and fluorescence *in situ* hybridization which led to the finding of *ALK* copy number gain.[1] Other well-known genotype–phenotype correlations include *BAP1*-inactivated atypical Spitz naevus/tumour and *HRAS* mutation/amplification in desmoplastic Spitz naevus, both of which are typically associated with an indolent behaviour in contrast to those with homozygous *CDKN2A* deletion or *TERT* promoter mutation.[5]

As our understanding of the molecular underpinnings of spitzoid neoplasms continues to evolve, additional genes of interest may emerge, possibly implicating new mechanisms of neoplastic transformation. Refining the different modes of genetic alteration will likely prove important in diagnostic classification, as well as predicting prognosis and response to targeted therapy.

Acknowledgments

The author would like to thank Dr Paul W. Harms (Departments of Pathology and Dermatology, University of Michigan, U.S.A.) for his critical review of this commentary.

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