INTRODUCTION

First identified in 1987[1], the receptor tyrosine kinase KIT gene has become the subject of intense investigation in melanoma research, as binding of the KIT ligand leads to activation of the receptor, which then participates in a variety of downstream signal transduction pathways, including MAP (mitogen-activated protein) kinase [2]. Point mutations and other genomic alterations in select exons of KIT (Figure 1) have been identified in distinctive subsets of melanomas: those involving acral skin, otherwise known as acral lentiginous melanomas, and mucosal melanomas [2].

The pathogenesis of melanoma from a benign melanocytic nevus to a dysplastic nevus has not been discussed, particularly in relevance to atypical acral nevi. In the current study, a greater proportion of acral nevi with atypia exhibited immunohistochemical positivity with CKIT versus those without atypia (82 versus 76%), suggesting that expression of CKIT may be of utility as a biomarker. However, we noted that the differences between the two groups did not achieve statistical significance, although a trend was observed in that approximately 50% of acral nevi with mild atypia exhibited immunohistochemical positivity with CKIT versus 100% of those with moderate and severe atypia.

Evidence regarding correlation between KIT mutation and immunohistochemical expression of CKIT is somewhat conflicting [5-7]. Data from Torres-Cabala et al. suggests that CKIT expression could be utilized as a negative predictor of KIT mutation, with cases staining >50% exhibiting KIT mutations and those staining <10% exhibiting wildtype. However, Curtain et al. found that all 3 cases of acral melanoma with KIT mutations stained positive for CKIT, suggesting an apparent positive correlation, while Ashida et al. found that 1 out of 2 cases of acral melanoma with KIT mutations stained positive for KIT, suggesting no apparent correlation. We found positive staining (11% or more) with CKIT 82% of acral nevi with atypia and in 76% of cases without atypia. However, no cases in either group demonstrated abnormalities in "hotspots" frequently associated with point mutations in acral melanomas. Thus, our findings argue against the utility of immunohistochemical expression of CKIT as a method of prioritizing cases for KIT genotyping.

Two mutually exclusive paradigms exist on the basis of our findings. The first model favors the existence of perhaps two distinct evolutionary paths to melanoma – one that appears to be KIT-mediated and another that is yet to be defined. This is best supported by the frequency of KIT mutations in acral melanomas which ranges anywhere between 9 to 23%. Thus, the fact that a large proportion of acral melanomas do not harbor a KIT mutation lends credence to the latter path. Further in support of this are findings from the current study indicating an absence of oncogenic KIT in all atypical acral nevi. The absence of the same in new without atypia further suggests that the KIT mutation may not necessarily be an initiating event in melanogenesis. The second model is perhaps more controversial and challenges the very existence of a precursor lesion.

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