Letter to the Editor

# Primary malignant melanoma of esophagus shared similar genetic characters with both cutaneous and oral mucosal melanoma

**Jingjing Li[1], Shi Yan[2], Nan Wu[2]**

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Laboratory of Genetics, [2]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute, Beijing 100146, China

*Correspondence to:* Nan Wu, MD. Department of Thoracic Surgery II, Peking University Cancer Hospital & Institute. No. 52, Fucheng Avenue, Haidian District, Beijing 100142, China. Email: nanwu@bjmu.edu.cn.

*Response to:* Krauthammer M. Unraveling the etiology of primary malignant melanoma of the esophagus. J Thorac Dis 2018;10:S1074-5.

Submitted Apr 27, 2018. Accepted for publication May 15, 2018.
doi: 10.21037/jtd.2018.05.158
**View this article at:** http://dx.doi.org/10.21037/jtd.2018.05.158

We read with interest of the letter to the editor by Dr. Krauthammer. We appreciate the author for sharing his experiences in melanoma genome research, especially his insights into different melanoma subtypes. Primary malignant melanoma of esophagus (PMME) is subtype of mucosal melanoma, just like other subtypes of mucosal melanoma, it was difficult to make sure whether it was a primary mucosal melanoma or a metastasis site which originated from a cutaneous site. Sometimes, the original primary melanoma may be disappeared or hard to be identified. Mutation signature profiling could provide hints to infer what a tumor may experience during its carcinogenic process. In our reported PMME case, a smoking related signature (C>A preference) was found to be the main mutation signature, rather than C>T mutation which is related to UV exposure and found to be ubiquitous in UV caused melanoma. In two recent published studies, oral melanoma genome present both C>A and C>T mutation spectrum (1), anal and vulvar melanoma show a non-descript profile (2), which reflect that oral and esophagus melanoma may experience similar carcinogenesis process caused by similar inducer. As the C>A signature was defined as a result of smoking, it is difficult to explain why it appeared in non-smoker's genome. We use multiregional method to analysis the potential evolution history of this PMME case, and interestingly, we found that the C>T and C>A signature dominated in different tumor evolutionary stages. Most truck mutations had C>T transitions while branch mutations prefer C>A transition. Based on this fact, we could not build a relationship with lung cancer although it also posed a $KRAS^{G13D}$ mutation. Furthermore, there is possibility that this "primary esophagus site" may be a result of cutaneous melanoma metastasis from somewhere in the body, because the initial mutation signature is C>T. C>T transition at CpG sites may also be caused by spontaneous deamination of 5-methyl-cytosine, which increased with age (3,4). However, as Dr. Krauthammer suggested, it needs to take together oral and esophagus melanoma to figure out whether they had distinct molecular features from other melanoma or even other mucosal melanoma.

We agree with Dr. Krauthammer that this PMME case may heavily disordered in MAPK pathway. $BRAF^{H574Q}$ is not a typical $BRAF^{V600E}$ which is a hot spot mutation in skin melanoma, but recently study have proved this site to be a drug sensitive mutation. KRAS mutation is seldom reported in cutaneous melanoma, however, in limited reported PMME cases, there was a case with $KRAS^{G12S}$ mutation (5). $NF1^{L626I}$ is predicted as a benign mutation, and it only presented in the clade2, so whether it is as important in PMME as in cutaneous melanoma is not clear yet. *BRAF* and *NRAS* gene aberration are significant drive gene and in cutaneous melanoma but distributed mutually exclusive, while NF1 was identified as a third melanoma class (6). Respected upon above facts, although this PMME case presents distinct BRAF, RAS and NF1 point mutations, it is still having some cutaneous melanoma features.

With more mucosal melanoma samples sequenced, it is important to combine data from each individual study and refine the genomic landscape of this minority melanoma. By comparative analysis inside and outside subtypes of mucosal

melanoma, we could understand the genetic essence of melanoma and translate them to melanoma precision medicine.

## Acknowledgements

*Funding*: This work was supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of special funding support (grant number XMLX201841); Beijing Municipal Science & Technology Commission (No. Z161100000516063).

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References

1. Lyu J, Song Z, Chen J, et al. Whole-exome sequencing of oral mucosal melanoma reveals mutational profile and therapeutic targets. J Pathol 2018;244:358-66.
2. Hintzsche JD, Gorden NT, Amato CM, et al. Whole-exome sequencing identifies recurrent SF3B1 R625 mutation and comutation of NF1 and KIT in mucosal melanoma. Melanoma Res 2017;27:189-99.
3. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Deciphering signatures of mutational processes operative in human cancer. Cell Rep 2013;3:246-59.
4. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.
5. Sanlorenzo M, Ribero S, Osella Abate S, et al. Genetic mutations in primary malignant melanoma of the esophagus: case report and literature review. G Ital Dermatol Venereol 2015. [Epub ahead of print].
6. Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. Nat Genet 2015;47:996-1002.

**Cite this article as:** Li J, Yan S, Wu N. Primary malignant melanoma of esophagus shared similar genetic characters with both cutaneous and oral mucosal melanoma. J Thorac Dis 2018;10(Suppl 17):S2095-S2096. doi: 10.21037/jtd.2018.05.158

 