Editorial

Specific mutations in thymic epithelial tumors

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Comment on: Petrini I, Meltzer PS, Kim IK, *et al*. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 2014;46:844-9.

Received: 31 August 2017; Accepted: 12 October 2017; Published: 03 November 2017.

doi: 10.21037/med.2017.10.07

View this article at: http://dx.doi.org/10.21037/med.2017.10.07

Thymic epithelial tumors (TETs) are the most common primary neoplasms of the anterior mediastinum (1). The mortality of TETs except for thymic carcinoma is not very high (2), and the growth speed is not very aggressive compared with other malignancies. The standard therapy for TETs is surgical resection, and the prognosis of the thymoma patients who receive complete resection is quite good. However, therapeutic strategies for advanced or relapsed cases of TET are controversial.

Radiation therapy and chemotherapy are recommended for advanced or relapsed TET patients who cannot undergo surgical resection. For type B1 and B2 TETs, steroid pulse therapy has achieved symptom relief by decreasing the tumor size in advanced or relapsed cases (3). Steroid pulse therapy is sometimes effective as neo-adjuvant therapy for reducing the size of large tumors.

We occasionally have difficulty selecting the appropriate chemotherapeutic regimen and timing to start the therapy for recurrent or advanced cases of TET. The drugs and regimens used for TETs fall under lung cancer treatment and are not specific for TETs. It is difficult to plan a randomized study for chemotherapy regimens because of the rarity of TETs, and the therapeutic strategy depends on the regimens for lung cancer or previously experienced strategies based on a case report. It is also difficult to identify the target mutation associated with effective therapy for TETs because of the rarity of such patients.

A number of efforts have been made to identify the tumorigenesis target genes and develop treatment strategies specific to TETs. However, genomic analyses are limited to only a few cancer genes, such as *EGFR*, *HER2*, *Kit*, *KRAS* and *TP53* (4-8). The rarity of TETs is strongly associated with the limited number of studies on these lesions.

Progress has recently been made in genetic variant research, and it is now possible to detect oncogenic driver mutations to take advantage in the development of therapeutic drugs for lung cancer (*EGFR* and *ALK*) (9,10). The accumulation of mutational and amplification data and the development of techniques for whole-exome sequencing and next-generation sequencing (NGS) have led to the identification of specific mutations of rare malignant tumors using the tumor tissues from only a few cases. Whole-exome sequencing and NGS have contributed to the analysis of rare disease like TETs, and these studies have helped us craft an ideal therapeutic strategy based on a genetic analysis of only a few patients.

Reports of genetic analyses for TETs are few in number, and fewer patients are enrolled in these studies than in those for other malignancies. The difficulties associated with quickly gathering tumor tissues in the fresh-frozen condition in a short period of time prevent planning studies on TETs. It is therefore ideal to investigate tissues from a small number of patients in order to identify targetable or oncogenic driver mutations by whole-exome sequencing or NGS. An additional evaluation to select candidate mutations should then be performed using formalin-fixed tissues to determine whether or not the found mutation is recurrent in TETs.

Genetic alterations and the etiology of TETs are also evaluated to clarify the most effective targeted therapies for patients with TETs. Petrini *et al.* (11) detected a missense mutation (chromosome 7 c.74146970T>A) in *GTF2I* at a high frequency in type A thymomas by analyzing 28 TETs using NGS. They also clarified that thymic carcinomas carried a

higher number of mutations than thymoma and identified several somatic mutations in thymic carcinomas, including *TP53*, *CYLD*, *CDKN2A*, *BAP1* and *PBRM1*. A NGS analysis is particularly useful for rare malignancies because it can identify novel mutations in each malignant tumor. Using a similar method, we detected 25 candidate mutations in 24 genes in an analysis of 12 cases of thymic squamous cell carcinoma (12). However, the comprehensive cancer panel that we used didn't include *GTF2I* as a cancer gene.

The *GTF2I* mutation was first reported as a recurrent mutation in 82% of type A and 74% of type AB thymomas but in only 8% of thymic carcinoma (11). This missense mutation in *GTF2I* has been repeatedly shown in other studies (13,14). Feng *et al.* (13) reported the clinicopathological relevance of the *GTF2I* mutation in TETs. A total of 124 of 296 (41.9%) patients harbored the *GTF2I* mutation, and its mutation was observed in 20 (87.0%) type A and 70 (78.7%) type AB thymomas but in only 7.7% thymic carcinomas. Lee *et al.* (14) also reported that the *GTF2I* mutation was the most commonly identified gene mutation in TETs (46 of 120, 38%). The presence of a *GTF2I* mutation correlated with a better survival.

When conducting studies on TETs, samples should be divided into thymoma and thymic carcinoma. The prognosis and pathologic status of thymoma are different from thymic carcinoma (15,16). Furthermore, the tumorigenesis of thymic carcinoma is completely different from that of thymoma. We detected high heterogeneity of thymic carcinoma in a NGS study of 12 thymic carcinoma cases (12). This is helpful for understanding the tumorigenesis and crafting therapies for thymoma and thymic carcinoma. In order to connect the specific missense mutation in *GTF2I* to a specific therapy, we must recognize that the *GTF2I* gene is not an oncogene but a tumor suppressor gene, just like *TP53*. The functional analysis and the delivery of recombinant adeno-associated viruses-based *GTF2I* gene therapy was studied for better understanding the pathophysiologic mechanisms of Williams-Beuren syndrome (17,18). However, further investigation should be performed in order to clarify the biological effect of the mutant *GTF2I* in TETs. An analysis of the mutant *GTF2I* may be useful to find the novel mechanisms of thymic tumor development and lead to the development of novel therapies.

We should also investigate thymic carcinoma, which is richer in mutations and copy number aberrations than thymoma. In the analysis of thymic carcinoma gene mutations, the most common mutations were those of tumor suppressor genes, including *TP53*, *CYLD* and *CDKN2A* (11,12), which are difficult to target for drug therapy. As possible targets for therapy for thymic carcinoma, we identified mutations in six tyrosine kinase genes (*KIT*, *DDR2*, *PDGFRA*, *ROS1*, *IGF1R*). The mutation status of thymic carcinoma is highly heterogeneous, so we must perform functional analyses of each mutations in order to clarify the molecular mechanism underlying tumorigenesis and explore the targeted therapeutic drugs.

Identifying recurrent mutations in TETs will aid in the diagnostic assessment of TETs and facilitate the development of tumorigenesis classifications and therapeutic strategies, including novel effective therapy. More studies involving greater numbers of TET cases and deeper investigations into the molecular mechanisms involving suspected TET tumorigenesis genes to clarify specific gene mutations and amplification will be needed in order to connect our understanding of TETs to the development of therapy for TET patients.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Qiangling Sun (The Central Laboratory in Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/med.2017.10.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med.2017.10.07
Cite this article as: Okuda K, Moriyama S, Haneda H, Kawano O, Nakanishi R. Specific mutations in thymic epithelial tumors. Mediastinum 2017;1:16.