Letter to the Editor

Harnessing the power of multi-institutional databases to improve the understanding and treatment of thymic epithelial tumors

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Despite the significant advances in our understanding of thymic epithelial tumors (TETs), many questions regarding the pathogenesis and optimal treatment of TETs remain unanswered. The last few years have seen the development of several large thymic datasets to help answer critical questions for the treatment of TETs. The International Thymic Malignancy Interest Group (ITMIG) (1) database combines elements of national databases, including the European Society of Thoracic Surgeons (ESTS) (2) and Chinese Alliance for Research in Thymomas (ChART) (3), and joins other collaborators, including Japanese Association for Research on the Thymus (JART) (4) and Korean Association for Research on the Thymus (KART) (5), to enhance focused efforts for this disease. In spite of these efforts, the datasets are inherently limited by both the data fields collected and their retrospective nature.

Chief among the questions in TETs is the relationship between paraneoplastic/autoimmune syndromes (PN/AI) and prognosis. This has been the subject of considerable debate in the literature, as there are conflicting results among studies. The most common and most frequently studied PN/AI syndrome is myasthenia gravis (MG). The ITMIG retrospective database study (n=6,097) found an association between the presence of PN/AI syndromes (~97% MG) and favorable prognostic factors such as female sex, young age, early stage and complete resection status; however, in a multivariate analysis, PN/AI syndromes were not an independent prognostic factor for recurrence-free or overall survival (6). Our data is in line with a multicenter study from Italy that examined 797 patients with TETs (375 of whom had MG) and showed MG was associated with improved overall survival in a univariate analysis but not in a multivariate analysis (7). Similarly, the ChART database showed that MG was associated with improved overall survival in univariate but not multivariate analysis (3). Conversely, the ESTS cohort found that in a multivariate analysis, MG was associated with a lower cumulative incidence of recurrence although there was no significant association between MG and overall survival (2).

As explained by Cavalcante *et al.*, the favorable association between PN/AI syndromes and improved outcomes seen in our study and others is likely related to earlier diagnosis of TET (and therefore higher likelihood of early stage disease and complete resection) as well as more intensive clinical follow-up (8). It has been well established that stage and resection status are important prognostic factors in TETs (2-4). However, this may not be the entire story, as in the ITMIG study, there are clear demographic differences between patients with PN/AI syndromes compared to those without PN/AI syndromes (i.e., younger, female, European). This suggests that these autoimmune phenomenon are more than just a harbinger of malignancy, but may, as Joseph *et al.* note, represent a different disease entirely (9). While our understanding of

the relationship between PN/AI syndromes and TETs is still being elucidated, what we do know from the literature to date is that the presence of advanced stage (III or IV) disease, thymic carcinoma histotype and older age are negative prognostic factors for patients with TETs (2,6).

With much work still to be done for patients with TETs, we turn our attention to how we can optimize our currently available tools. The strength of the ITMIG database is its geographic breadth (56 institutions in 15 countries) and number of patients (7,795) (1). As a result, this introduces regional differences in patient management, surveillance and reporting. However, we feel the ITMIG cohort is representative of the TET population as the demographics and histotypes reported in this database mirror those seen in practice and are not significantly discrepant from existing literature. Currently, ITMIG is focused on the development of its prospective database, which will expand the breadth of clinical information as well as allow for standardization of data collection. The prospective database will address several weaknesses seen in the retrospective database with implementation of a virtual tumor bank to include pathologic slides and incorporation of detailed radiographic features across imaging platforms. The database will also collect information on chemotherapy and radiation details, cause of death, and outcomes of PN/AI syndromes. Already this dataset has facilitated answering the important clinical question of the role of positron emission tomography in the pre-operative management of patients with TETs (10).

As we move into the era of routine next generation sequencing (NGS) of tumor samples, it will be imperative to incorporate this information into databases as well. There have been numerous molecular abnormalities identified in TETs through NGS such as mutations in *EGFR*, *mTOR*, *TP53*, *HRAS*, *NRAS*, *GTF2I*, *c-KIT* and *PI3K* yet there is limited data on strategies to effectively target these mutations (11-13). The largest molecular analysis to date has been done through The Cancer Genome Atlas with whole exome sequencing performed on 117 TET tumor samples. This analysis revealed four molecular subsets of TETs which correlated well to WHO histologic classification and which also potentially present a target for future drug development (12). Moreover, this analysis revealed markers (i.e., aneuploidy, muscle autoantigens) which may potentially identify patients at risk for autoimmunity. This has significant implications for treatment, especially as we search for ways to safely deliver immunotherapy to these patients in the advanced unresectable setting. Given the mainstay of treatment is surgical for resectable TETs, analysis of archival or even fresh tumor samples with application of multi-omics platforms will expand our understanding of these tumors, along with the relationship of these findings to patient outcomes and autoimmunity. A database incorporating information on genomic aberrations in combination with harnessing the power of computational modeling of genetic information (14) will be a powerful tool in understanding TETs and developing future therapies.

In summary, our knowledge of TETs has expanded greatly over the last few years due in large part to the development of international databases. Although these datasets have inherent bias and other limitations, they provide great insight into this rare disease. Future work should be undertaken to strengthen these resources through the addition of biologic data as well as development of TET preclinical models (13) to help guide the development of novel agents.

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Footnote

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