Editorial Commentary

The characteristics and prognostic role of thymic epithelial tumors with paraneoplastic autoimmune syndromes

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Thymic epithelial tumors (TETs) are generally categorized as those that originate from thymic epithelial cells (thymoma and thymic carcinoma) and those that originate from neuroendocrine cells (thymic carcinoid, germ-cell tumor, and thymic cyst). Among the different types of TETs, this study specifically focused on thymoma, thymic cancer, and neuroendocrine tumors of the thymus (NETT) and examined the presence of paraneoplastic syndrome (PN/AI), specifically myasthenia gravis (MG), pure red cell aplasia (PRCA), and hypogammaglobulinemia, as comorbid autoimmune diseases (1). Padda *et al.* performed a retrospective analysis of patients with TETs and demonstrated that most patients had undergone surgical resection and 34% of those patients had PN/AI. The study is highly reliable as it used the largest database of TETs that is currently available in the world. However, as the authors state, MG was the most common PN/AI, with 96.5% (2,068/2,143) of patients with autoimmune syndromes having MG. In contrast, there were very few patients with PRCA and hypogammaglobulinemia, consisting of 2.2% and 0.6% of all patients with autoimmune syndromes, respectively. Thus, the study population mostly reflects the characteristics of those with TETs and TETs + MG, rather than TETs + PN/AI. Furthermore, 96.1% (2,061/2,143) of PN/AI (+) patients had thymoma while only 2.0% and 0.2% of PN/AI (+) patients had thymic cancer and NETT, respectively. Although the study did not compare the combinations of TETs with MG, PRCA, or hypogammaglobulinemia, the majority of patients likely were represented by those with thymoma or thymic cancer. Based on the WHO classification, Type B2 (37%) and Type AB (29.6%) thymomas were the most common in PN/AI (+) and PN/AI (–) patients, respectively. Based on pathological staging, 25.5% and 36.7% of patients in stage III or above had PN/AI (+) and PN/AI (–), respectively. Since most patients in advanced stages had PN/AI (–), the authors suggest that the symptoms associated with PN/AI enable early detection of TETs. The authors further performed multivariate analysis of clinical factors and demonstrated that PN/AI syndromes were associated with a younger age, type B1 thymoma, early-stage cancer, and increased rate of a complete resection status. They also examined the prognosis of patients and demonstrated that the presence of PN/AI syndromes was not independently associated with overall survival.

The extent of thymectomy, type of chemotherapy, and dose and location of irradiation determine the prognosis of patients with TETs after the treatment. At the same time, these factors will likely affect the treatment response and lead to the worsening of PN/AI syndromes, which may include acute exacerbation of MG, progression of anemia in patients with PRCA, and infections in patients with hypogammaglobulinemia due to immunosuppression. Thus, these factors may explain why the presence of PN/AI led to the early detection and subsequent resection of TETs but was not associated with the prognosis. While

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thymectomy leads to remission of MG, it is not as effective in other types of PN/AI; specifically, it is only effective for 25% of patients with PRCA and is also known to be less effective against hypogammaglobulinemia (2-4). Thus, in addition to surgery, chemotherapy, and radiation therapy for TET patients, treatments should also be developed specifically for PN/AI patients in order to improve the prognosis of patients with TETs and PN/AI. Among various types of TETs, thymic carcinoma is associated with a poor prognosis since it is usually in an advanced stage at the time of diagnosis and is also difficult to treat since it is rarely associated with PN/AI. It is questionable whether it was appropriate to include thymic carcinoma as one of the TETs in this study given that it is mostly characterized as squamous cell carcinoma. It is also distinct from other TETs in terms of treatment, as evidenced by a recent study demonstrating that immunotherapy is effective against thymic carcinoma (5).

Minimally-invasive surgery will likely dominate the surgical treatment options for TETs. However, surgery itself should be a careful option for patients with uncontrolled PN/AI, particularly severe MG, since general anesthesia and invasive surgical procedures could worsen the condition of PN/AI patients and lead to the development of pneumonia as a result of respiratory disturbance. Furthermore, many patients with PN/AI take steroids. As such, minimally-invasive procedures are preferable considering the impact on PN/AI during the perioperative period. In fact, uniportal video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) are currently performed for stage I and stage II patients with TETs around the world. Furthermore, non-intubated subxyphoid uniportal VATS, which does not involve the use of muscle relaxants, has also performed (6). This procedure may be a suitable option for TET patients with MG that is a disorder of neuromuscular transmission. Additional studies are needed to better understand TETs with PRCA or hypogammaglobulinemia given that they are uncommon and there is limited clinical evidence. Future studies should also focus on examining the treatment effects for TET patients with PN/AI, and to determine the most appropriate and minimally-invasive methods of total thymectomy in resectable cases. It is also necessary to better understand the characteristics of PN/AI patients for whom thymectomy is ineffective.

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Footnote

Conflicts of Interest: 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.

References

1. Padda SK, Yao X, Antonicelli A, et al. Paraneoplastic syndromes and Thymic Malignancies: An examination of the International Thymic Malignancy Interest Group Retrospective Database. J Thorac Oncol 2018;13:436-46.
2. Zeok JV, Todd EP, Dillon M, et al. The role of thymectomy in red cell aplasia. Ann Thorac Surg 1979;28:257-60.
3. Suster S, Rosai J. Thymic carcinoma, a clinicopathologic study of 60 cases. Cancer 1991;67:1025-32.
4. Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol 2018;19:347-55.
5. O'Sullivan KE, Ktraden US, Herbet AE, et al. A systematic review of robotic versus open and video assisted thoracoscopic surgery (VATS) approaches for thymectomy. Ann Cardiothorac Surg 2019;8:174-93.
6. Liu Z, Yang R, Sun Y. Non-intubated subxiphoid uniportal video-assisted thoracoscopic thymectomy. Interact Cardiovasc Thorac Surg 2019;29:742-5.

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