



# Relationship between thymic epithelial tumors and autoimmune disorders

Tomoyuki Hishida

Division of Thoracic Surgery, Department of Surgery, Keio University School of Medicine, Tokyo, Japan

*Correspondence to:* Tomoyuki Hishida, MD. Division of Thoracic Surgery, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Email: thishida@nifty.com.

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Thymus is a primary lymphoid organ associated with T-cell development (1,2). The most important role of the thymus is the induction of immune self-tolerance by the positive and negative selection of T cells that prevent self-harm or autoimmunity (2). In 1672, the England doctor, Thomas Willis reported the first clinical description of a disease that was characterized by severe distal muscle weakness (3). One hundred years later, this disease was named myasthenia gravis (MG). In 1960, Simpson proposed that MG was caused by autoantibodies to muscle striations (4), and MG was elucidated to be caused by autoantibodies directed against the acetylcholine receptor in the neuromuscular junction of skeletal muscles. Although the precise underlying mechanisms are still unknown, it has been suggested that a defective negative selection of T cells in thymoma appears to be the key feature associated with the development of autoimmunity (5,6). It is well known that thymoma is associated with several autoimmune disorders other than MG, however, clinical manifestations of coexisting autoimmune disorders are still not understood due to the lack of a large study.

A recent article by Padda *et al.* evaluated the clinical features and survival of patients with thymic epithelial tumors harboring paraneoplastic and autoimmune (PN/AI) disorders by using a large retrospective cohort of 6,670 patients in the International Thymic Malignancy Interest Group (ITMIG) database (7). The ITMIG database was essentially a surgical database (98.3% of the patients underwent surgery). The data were collected from around the world; most of the subjects were from Asian countries other than Japan (41.9%), followed by Europe (32.6%) and

North America (24.7%). In this multicontinent database study, 34% of the cohort showed PN/AI disorders, and MG accounted for 97% of the reported PN/AI disorders. PN/AI disorders were associated with younger age, female sex, type B2 thymoma, earlier TNM stage, increased rate of total thymectomy and complete R0 resection, and tended to show a better outcome in terms of recurrence and survival rates. In multivariate analyses, the presence of PN/AI disorders was not an independent prognostic factor associated with either recurrence-free survival or overall survival.

The current results basically confirmed previous regional database studies, including those by the European Society of Thoracic Surgeons (ESTS) (8), the Japanese Association for Research on the Thymus (JART) (9), and the Chinese Alliance for Research in Thymomas (ChART) (10). In retrospective database studies, the presence of a selection bias, no central review of pathology, and no uniform follow-up protocol limit the ability to draw definitive conclusions of survival data irrespective of the sample size. However, these similar results imply that the presence of autoimmune disorders (mainly represented by MG) does not preclude surgical indication for thymic epithelial tumors. Nakajima and associates analyzed a total of 2,638 patients in the JART database and reported that even the severity of MG, as expressed by the MG Foundation of America (MGFA) classification, did not affect overall survival (OS) (9). An aggressive surgical procedure can be considered for thymic epithelial tumors suitable for resection irrespective of the concomitant autoimmune disorder status. The current results provided an important contribution to clarify the prognostic value of coexisting autoimmune

disorders in thymic epithelial tumors. At the same time, some questions might be raised about information that cannot be obtained from the current retrospective database. First, there is no systematic information on postoperative morbidity. Thymic epithelial tumor patients with autoimmune disorders frequently receive systemic steroid preoperatively, and usually undergo thymectomy via sternotomy. It might be beneficial if safety and morbidity information was available, especially for patients receiving sternotomy. Second, although most patients underwent surgical resection, there is no information available regarding the outcome of concomitant autoimmune disorders in the postoperative course. Was thymectomy effective for coexisting autoimmune disorders? In how many and what kind of patient was the remission of autoimmune disorders achieved after thymectomy? Did progression or new onset of autoimmune disorders occur? Progression or new onset of autoimmune disorders has also been reported after thymectomy and even systemic therapy (11-13). Currently, the use of immune checkpoint inhibitors has attracted interest in the setting of unresectable and refractory thymic epithelial tumors. In a phase II trial assessing pembrolizumab, at most 15% of patients presented with new-onset or severe immune-related events leading to treatment withdrawal (14). Serial checkup of the immunological profile should be considered for future studies of thymic epithelial tumors. Further prospective studies including not only surgical cases but also non-surgical cases are warranted to monitor autoimmune disorders during the treatment of thymic epithelial tumors.

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