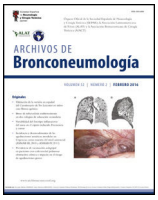
Arch Bronconeumol. 2019;55(5):235–236

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Thymoma. A Systemic Disease?☆

El timoma, ¿es una enfermedad sistémica?

Juan Carlos Trujillo-Reyes,* Elisabeth Martínez-Téllez, Josep Belda-Sanchis

Servicio de Cirugía Torácica, Hospital Universitari de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

The thymus is the primary lymphoid organ responsible for the maturation of T cells. During the early years of life, T cells are activated and, more importantly, inactivated within this gland, to achieve the correct level of central tolerance.[1,2]

Thymomas are tumors that develop in the thymus. They are rare, occurring with an incidence of 0.15 cases per 100 000 inhabitants.[3]

The publication of the new World Health Organization classification[4] has established that, despite being slow-growing, thymomas are malignant epithelial tumors. As such, when we are dealing with thymoma, we must abandon the concept of benignity.

The association of thymoma with certain autoimmune diseases is well known. Myasthenia gravis (MG), pure red cell aplasia, autoimmune encephalitis, hemolytic anemia, Good's syndrome, and autoimmune thyroiditis are some of the diseases that have been associated with this tumor.[4]

The coexistence of thymoma and MG is the most common and also the most studied. Around 15%–20% of patients with MG also have thymoma, and 35%–40% of patients with thymoma may develop MG.[5] Moreover, histological analysis of the mediastinal tissue in patients with MG has revealed that more than 80% of patients show thymic tissue abnormalities that are not thymoma, the most common being hyperplasia (70%).[6,7]

In some series, over 40% of patients with a diagnosis of thymoma have some type of associated autoimmune disease.[7] This association is probably underdiagnosed, and is in reality even higher. For this reason, when a patient is diagnosed with thymoma, additional examinations should be performed to rule out any such coexisting disease.

The association between thymoma and various diseses of autoimmune origin raises the following question: is it the thymoma that causes the immune changes or is the thymoma a manifestation of a common systemic involvement?

It has been difficult until now to define the role of the thymoma in autoimmunity due to the lack of uniform criteria in the published studies. Experience is scant and disperse due to the limited number of patients diagnosed in multiple institutions.

Interest in improving the diagnosis and treatment of these tumors has grown in recent years. In 2010, the creation of the International Thymic Malignancy Interest Group (ITMIG)[8] facilitated the development of an international database in which more than 10 800 diagnosed cases are registered. The initial analysis of this database led to the introduction of improvements in the diagnostic process, including the definition of immune system disorders in thymoma patients.[9]

The etiopathogenesis of the development of immune disorders in thymoma patients is an alteration in the glandular structure and reduced expression of the major histocompatibility complex class II and the T-cell autoimmune regulator gene.[9]

The combination of these changes leads to altered T cell maturation, a fact that may explain the relationship between these tumors and diseases dependent on T cell-mediated autoimmunity.

The finding of these changes in thymoma cells suggests that the tumor may be responsible for the development of concomitant autoimmune disease.

However, other data contradict this statement and suggest that thymoma is not the trigger but instead another manifestation of a common systemic alteration. The facts that support this latter hypothesis are the following:

1 How can we explain the development of autoimmune disease in cases in which thymoma is not diagnosed? This could be explained if changes seen in the thymocytes of the thymoma were observed in the thymic tissue cells of all patients with autoimmune disease, but this could not be demonstrated in series of patients with MG who underwent thymectomy without thymoma. This, then, suggests that other autoimmunity anomalies exist that are different from those observed in the thymocytes of the thymoma that cause the concomitant disease.
2 After thymectomy, one would expect partial or complete remission of the symptoms of concomitant disease after surgery, but the impact is very variable. Although patients with MG do show a greater response, the response of patients with autoimmune diseases other than MG is less significant.[7]
3 A link between thymoma and an increased risk of developing other extrathymic cancers has been described.[10] One of the prevailing theories is that immunosuppression generated by the thymocytes of the thymoma predisposes to the development of these neoplasms. More recent studies have questioned

☆ Please cite this article as: Trujillo-Reyes JC, Martínez-Téllez E, Belda-Sanchis J. El timoma, ¿es una enfermedad sistémica?. Arch Bronconeumol. 2019;55:235–236.

* Corresponding author.
E-mail address: jtrujillo@santpau.cat (J.C. Trujillo-Reyes).

1579-2129/Published by Elsevier España, S.L.U. on behalf of SEPAR.

this theory because thymoma sometimes is diagnosed after the extrathymic cancer. Changes in T cell maturation would already exist prior to the development of the thymoma and could be the origin of immunosuppression causing both neoplasms.[9]

The maturation that takes place in the thymic cortex is highly complex. The theories that explain the changes responsible for the development of autoimmune anomalies seem too simple. Autoimmunity activation pathways, as yet unknown, probably exist that could confirm that thymoma is another manifestation of a common immune alteration and not its trigger.

In any case, regardless of the pathogenic implications of thymoma in immune alterations and its association with various systemic autoimmune diseases, these tumors are considered nowadays to be malignant and treatment is multidisciplinary, surgery being the treatment of choice even in advanced stages. Tumor excision is indicated, or at least should be considered, in all cases, whether before induction treatment or after it, even if complete resection is not expected, as it offers better local disease control.

As we have seen, thymomas are rare tumors with a very special biology. Their etiopathogenesis is highly complex and seems to be best explained by viewing the tumor as part of a systemic alteration.

The low incidence of these tumors demands the creation of multicenter databases and multidisciplinary committees which, as far as possible, reflect the real situation of the disease in a specific environment, allow in-depth investigation of tumor biology, and improve the diagnostic-therapeutic practices employed.

Understanding thymomas as a manifestation of a systemic disease would pave the way to therapeutic studies based on cellular and genetic changes.

The possible autoimmune origin of thymoma suggests that it might be a tumor which is particularly sensitive to new lines of immunotherapy. Performing such studies might change current therapeutic strategies.

References

1. Miller JFAP. Revisiting thymus function. Front Immunol. 2014;5:411.
2. Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). Nat Rev Immunol. 2014;14:377–91.
3. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5:260–5.
4. Ströbel P, Marx A, Travis WD, Brambilla E, Burke A, Marx A, Nicholson A. Tumours of the thtymus. WHO classification of tumours of the lung, pleura, thymus and heart. 4th ed. Lyon: Published by the International Agency for Research on Cancer (IARC); 2015. p. 183–298.
5. Fujii Y. Thymus, thymoma and myasthenia gravis. Surg Today. 2013;43:461–6.
6. Evoli A, Lancaster E. Paraneoplastic disorders in thymoma patients. J Thorac Oncol. 2014;9:143–7.
7. Bernard C, Frih H, Pasquet F, Kerever S, Jamilloux Y, Tronc F, et al. Thymoma associated with autoimmune diseases: 85 cases and literature review. Autoimmun Rev. 2016;15:82–92.
8. Detterbeck FC. International thymic malignancies interest group. A way forward. J Thorac Oncol. 2010;5:365–70.
9. Weksler B, Lu B. Alterations of the immune system in thymic malignancies. J Thorac Oncol. 2014;9:137–42.
10. Souadjian JV, Silverstein MN, Titus JL. Thymoma and cancer. Cancer. 1968;22:1221–5.