Editorial

Thymic epithelial tumors and paraneoplastic autoimmune syndromes

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Thymic epithelial tumors (TETs) are rare tumors of anterior mediastinum with an estimated incidence rate of 1–5 per million of the population per year (1). The group includes thymomas, thymic carcinomas and neuroendocrine tumors. They all derive from thymic epithelial cells and are malignant but they differ in morphology, biology and clinical course.

Thymomas are the most common in this group. They are tumors of a low or medium-grade malignancy and have usually long-term overall survival and progression free survival after complete resection (2). The current (2015) histological classification proposed by the World Health Organization divides thymomas into 5 main histological subtypes: A, AB, B1, B2 and B3. These vary in morphology of neoplastic epithelial cells and in the proportion of neoplastic cells and accompanying non-neoplastic immature (Tdt-positive) T-lymphocytes (thymocytes) (3).

Thymic carcinomas share a histological morphology and names with their extrathymic counterparts. They are highly aggressive tumors that should not be confused with thymomas due to their clearly inferior prognosis (4).

Neuroendocrine tumors of the thymus, i.e., carcinoids and neuroendocrine carcinomas (small cell carcinoma and large cell carcinoma), are extremely rare and are classified according to the criteria for neuroendocrine tumors of the lung (3).

One of the most characteristic and intriguing features of TETs and especially thymomas is the frequent coexistence with autoimmune disorders usually myasthenia gravis (MG) a neurological disorder caused by autoantibodies against components of a neuromuscular junction, which impair the neuromuscular transmission (5). Padda *et al.* in an analysis based on The International Thymic Malignancy Interest Group (ITMIG) database for TETs in a cohort of 6,297 patients found that 2,068 cases (32.8% of all TETs) were associated with MG (6). This percentage is in accordance with the results of other studies that usually report MG as 30–47% of TETs, with these nearly exclusively thymomas (7,8). On the other hand, 10–15% of patients with MG have a thymoma and the most common pathology in myasthenic thymus is a non-neoplastic follicular hyperplasia associated with occurrence of lymphoid follicles with germinal centers in the thymic parenchyma (5). Such pathology is also often found in the thymic tissue surrounding the tumor of thymoma patients. MG is by far the most common paraneoplastic autoimmune disease associated with thymic tumors but other disorders are also reported. The patients may manifest Lambert-Eaton myasthenic syndrome, acquired neuromyotonia (sometimes in form of Morvan's syndrome), encephalitis or myositis/dermatomyositis (9). Autoimmune rheumatic, hematological or other comorbidities, that may be isolated or coexist together, were also observed. The authors report the coexistence of systemic lupus erythematosus (SLE) (2–10% patients of thymomas), pure red cell aplasia (0.7–5%), hypogammaglobulinemia (0.2–5%), autoimmune hemolytic anemia, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, Hashimoto's thyroiditis, Graves' disease and pemphigus or autoimmune hepatitis (6,7,10). One of the most serious paraneoplastic syndromes is thymoma-associated multi-organ autoimmunity resembling graft-versus-host diseases involving liver, intestine or skin (11). The

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paraneoplastic symptoms usually precede thymic neoplasm but often both diseases occur simultaneously or autoimmune disorder is diagnosed after discovery of TET (7).

MG and other autoimmune disorders in the vast majority of cases are associated with thymomas predominantly of the B2 and/or B3 types (2,6-8). In one study the AB type was the most prevalent (12). Padda *et al.* found the type AB the most common morphology not associated with paraneoplastic symptoms (6) while other authors usually report type A (2,7). Thymomas are unique neoplasms because most of them preserve the ability of thymopoiesis, i.e., a process of maturation of $CD4^+$ and $CD8^+$ T lymphocytes specific for the normal thymus. However, due to the neoplastic transformation of thymic epithelial cells the maturation of lymphocytes is impaired resulting in exporting to the blood a large number of autoreactive T cells. The architecture of thymoma resembles the normal thymus gland but it is disorganized. Under normal conditions the medullary part of the thymus contains a certain number of myoid cells that express skeletal muscle cells receptors, but in thymomas the number is reduced or absent. Lymphocyte-rich areas of thymomas recall a distorted cortical part of the thymus (5). It was shown that neoplastic epithelial cells variably express epitopes of muscle antigens instead of the whole receptors. The expression modifies the phase of a positive selection of maturing thymocytes and generates the population of T cells that improperly recognizes the antigens (5). The decreased expression of human leukocyte antigen (HLA) class II detected on neoplastic cells as well as the characteristic for thymomas lack or deficiency of an autoimmune regulator (AIRE), a protein that plays an essential role in central tolerance by influencing the expression of autoantigens in the thymic medulla, impair a negative selection—the next step of T cell maturation (5). Ströbel *et al.* proved that there was a significant reduction of naïve $CD4^+$ T cells in the MG(–) thymomas in comparison to MG(+) tumors and control thymic tissue. Moreover, in some cases the authors detected the population of $CD4^+$ cells of peculiar phenotype similar to phenotype of dying lymphocytes in the process of apoptosis (13). It is possible that in MG(–) thymomas negative selection is efficient enough to reduce autoreactive T lymphocytes and to prevent the MG symptoms (13). The process is inefficient in MG(+) thymomas and mature autoreactive T cells are exported from the tumor microenvironment to the periphery and they stimulate B cells to production of autoantibodies (5,13).

In patients with thymoma-associated MG the main target for these autoantibodies is acetylcholine receptor (AChR) expressed in neuromuscular junction on skeletal muscle cells. Antigen-antibody reaction disturbs neuromuscular transmission and this results in the clinical manifestation of the disease. In exceptional cases there are found autoantibodies against another antigen, muscle specific kinase (MuSK) (5,14). There are also reported sero-negative cases, in which the target and a type of autoantibodies are still not known (5). In 70–90% of patients with thymoma-associated MG there are autoantibodies directed against striated muscle antigens, titin and ryanodine receptors (14), and, although their pathogenicity still requires an explanation, there are reports that these autoantibodies may be associated with more severe myasthenic symptoms (5,14). The whole process of autoimmunization and the reason for its focusing on muscle antigens still is not fully understood.

According to the guidance for management of MG established by Myasthenia Gravis Foundation of America and a panel of international experts an acetylcholinesterase inhibitor (pyridostigmine) that slows down the degradation of acetylcholine in neuromuscular junction is usually the initial treatment in most patients with MG (15). Corticosteroids, nonsteroidal immunosuppressive agents or thymectomy are other management options. Patients with life threatening myasthenic crisis require intravenous immunoglobulin or plasma exchange (15). A new therapeutic strategy for patients with refractory generalized MG and anti-AChR antibodies may be eculizumab, a monoclonal antibody that inhibits complement-mediated membrane damage in neuromuscular junction (16). A complement-mediated membrane attack is a result of processes induced by a reaction between autoantibodies and AChR with subsequent endocytosis and degradation of the receptors. A phase 3, randomized, double-blind, placebo-controlled study revealed no significant difference in change in the MG-Activities of Daily Living score between eculizumab and placebo, however, fewer number of MG exacerbations or admissions to hospital and reduce use of rescue medication was observed in the group of patients receiving eculizumab compared with the group receiving placebo (16). The role of anti-complement treatment in MG patients requires further investigations.

The majority of thymoma patients with MG also have neutralizing autoantibodies directed against cytokines: interleukin-12 (IL-12) and interferon-α (INF-α) (17). The production of these autoantibodies is associated with AIRE deficiency observed in thymomas and this impairs the function of an immune system predisposing a patient

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to chronic mucocutaneous candidiasis (18). Buckley *et al.* postulated that an assessment of a titer of anti-IL-12 and anti-INF-α antibodies in patients after thymoma treatment might enable the identification of a tumor relapse (17).

The most frequent antibodies found in patients with thymomas and autoimmune disorders affecting central nervous system (acquired neuromyotonia, Morvan's syndrome) are autoantibodies against voltage-gated potassium channels (VGKCs) (19,20). It was shown that the major target for anti-VGKCs antibodies is contactin-2 associated protein (Caspr2), a protein complexed with VGKCs that is expressed in the juxtaparanodes of myelinated axons (19,20). van Sonderen *et al.* in a cohort of 37 patients with Caspr2-antibody-associated diseases of central nervous system found thymomas as the most common malignancy (20).

In contrast to thymomas, the association between thymic carcinomas or thymic neuroendocrine tumors and autoimmune paraneoplastic symptoms remains questionable. Padda *et al.* reported that 6% of thymic carcinomas and 4% of neuroendocrine thymic tumors were associated with autoimmune disorders, however the authors admitted there was no central pathology review in the study that would verify histopathological diagnoses (6). Paraneoplastic symptoms in the course of thymic carcinomas were reported also in other studies (Filosso *et al.* 23%, Li *et al.* 12%) (8,21). However, Roden *et al.* pointed that interobserver agreement in the histopathological differentiation between B3 thymomas and thymic carcinomas might be poor, thus a proportion of thymomas might be misclassified as thymic carcinomas (4). The authors did not find any autoimmune disorder in the group of patients who had a definite histopathological diagnosis of thymic carcinoma. Zhu *et al.* in a group of 58 thymic carcinomas observed only one MG-associated case but it was a combined tumor containing both carcinoma and thymoma components (2). One should also remember that in older histopathological classifications (before 1999) B3 thymoma was named "well-differentiated thymic carcinoma" as well as that for short time thymic carcinomas were classified as "type C thymomas". Such changes in classifications produced confusion and might influence the interpretation of the results of the studies.

Thymopoiesis is not detected in thymic carcinomas and the lymphocytes infiltrating the tumor include mature T and B cells (5).

Paraneoplastic symptoms of neuroendocrine thymic tumors are usually the result of endocrine activity of neoplastic cells. Cushing syndrome is the most common disorder and may present as isolated disease or a component of multiple endocrine neoplasia type 1 (MEN 1) (22). Autoimmune diseases, including MG, are reported in the literature extremely rarely. Padda *et al.* in ITMIG database found 5 such cases: 1 typical and 1 atypical carcinoid and 3 poorly differentiated neuroendocrine carcinomas (6). In such controversial cases each diagnosis should be well documented and the central pathological review seems to be mandatory.

The prognostic relevance of paraneoplastic autoimmune diseases, especially MG, for the course of TETs is a frequent topic in the literature. Filosso *et al.* demonstrated that age, incomplete resection, higher stage of a disease (III–IV) and thymic carcinoma histology were negative prognostic variables for overall survival (8). MG at univariate analysis showed a slight protective effect but a multivariate model did not confirm the result. The authors postulated that MG-associated tumors presented a slightly better outcome, because the patients with neurological symptoms were under strict clinical and radiological observation and the tumors were detected at earlier stages of the disease (8). In a cohort analyzed by Padda *et al.* a MG-associated thymoma group also presented a higher rate of earlier stages of the disease and complete resections, however, in a multivariate model paraneoplastic autoimmune disorders were not an independent prognostic factor associated with overall survival or recurrence-free survival (6). The study showed that older age, carcinoma or neuroendocrine differentiation in histology, advance stage (III–IV), chemotherapy and macroscopically positive resection margin were factors independently correlated with a worse overall survival while radiotherapy and B1 histology were independent characteristics that improved this parameter (6). An unfavorable impact of chemotherapy was explained by its potential long-term toxicity (6), however this issue requires further investigations. The authors noted a trend for improved overall survival in a group of MG (+) thymic carcinomas (6) but because the histopathology of the tumors were not verified, there is a risk, that B3 or other thymomas could have been improperly enrolled into this group, thus affecting the results. Padda *et al.* analyzed survival in three 20-year spans and found significantly improved overall survival in the most recent time period in a group of patients with MG-associated thymomas. This probably reflects better efficacy of the current MG treatment (6,8). The opinions about significance of autoimmune paraneoplastic symptoms, usually MG, as an independent prognostic factor for thymoma course vary in the literature. A number of studies showed no such characteristic (2,12)

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but e.g., Tseng *et al.* demonstrated that MG was the positive independent prognostic factor for recurrence-free survival for completely resected tumors (23).

Surgery is the first step of the treatment of resectable TETs and it is often followed by radiotherapy or, less frequently, chemotherapy (24). The extent of resection depends on the stage of neoplastic disease and the concomitant MG. According to the current The International Association for the Study of Lung Cancer (IASLC) and ITMIG recommendations a complete thymectomy, including the tumor, thymic gland and perithymic fat tissue with locoregional lymphadenectomy is preferred (25). However, in the least advanced and non-myasthenic tumors thymomectomy (tumor resection without thymic tissue and mediastinal fat) may be taken into consideration (26). In myasthenic patients a complete thymectomy enables the achievement of not only a satisfactory oncological effect but also a long-term clinical improvement of myasthenic symptoms, reducing the need for immunosuppressive therapy (27). Padda *et al.* in their study noted that patients presenting paraneoplastic symptoms usually underwent a complete thymectomy, which was in concordance with the recommendations mentioned above, however, due to the lack of sufficient data about the severity of MG symptoms before and after treatment, the authors could not comment the efficacy of surgery for MG severity (6).

Paraneoplastic autoimmune diseases constitute one of the most interesting and intriguing facets of TETs. However, the rarity of these tumors hinders becoming acquainted with them and the development of the best therapeutic strategies. The proper management of patients requires a multispecialized approach and involves neurologists, surgeons, radiologists, pathologists and oncologists. The best method is a multi-institutional or even international cooperation in collecting, storing and analyzing data.

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