Editorial

Paraneoplastic autoimmune diseases in patients with thymic malignancies: a favorable, but not independent, prognostic factor

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Thymomas and thymic carcinomas are rare epithelial tumors of thymus (TETs) associated with paraneoplastic autoimmune (PN/AI) disorders, including myasthenia gravis (MG), pure red cell aplasia, hypogammaglobulinemia, encephalitis, and acquired neuromyotonia (1,2). Patients affected by these disorders are usually screened for thymoma at diagnosis, and they frequently improve with thymoma treatment (2).

Thymomas are the most common mediastinal tumors; they are slow-growing and locally invasive neoplasms of thymic epithelial cells, showing high variability in histological and biological features. The World Health Organization (WHO) classification recognizes type A, AB, B1, B2 and B3 thymomas, based on lymphocyte content and epithelial cell features (3,4). Type B2 thymoma is the histological diagnosis most frequently associated with MG (4,5). Thymic carcinomas are less prevalent but more aggressive than thymomas, being characterized by frequent disease recurrence and metastases, and presenting as a large, locally aggressive lesion which makes difficult complete resection (1).

MG is the PN/AI disease most frequently associated with TETs, being present in approximately 30–45% of thymoma patients (1,5,6); conversely, up to 30% of MG patients show a thymoma (4,5). MG is an autoimmune disorder affecting neuromuscular junction, caused in most patients by the abnormal production of anti-acetylcholine receptor (AChR) autoantibodies (7). Thymomatous MG patients usually present generalized muscle involvement with more severe disease, lower rates of complete stable remission, and resistance to treatments than MG patients without thymoma (8,9). Along with anti-AChR antibodies, MG thymoma patients frequently have anti-actin, -myosin, -titin and -ryanodine receptor autoantibodies, which are thought to develop as a consequence of central self-tolerance failure and selective autosensitization against muscle antigens expressed within thymoma (5,7,8,10). Specifically, altered autoantigen presentation, abnormal T cell selection, failure in regulatory T cell generation and autoantigen-specific T cell export are postulated intra-tumorous mechanisms, not mutually exclusive, driving autoreactivity in thymoma-associated MG (11). Thymoma defective epithelial expression of autoimmune regulator (AIRE) and major histocompatibility complex class II molecules, and the absence of myoid cells expressing muscle antigens are considered crucial for linking thymoma to autoimmunity (11). These pathological features could explain the high frequency of autoimmune phenomena in patients bearing thymoma compared to those with other types of cancer, in particular the high liaison with MG (6). In addition, thymoma cells spontaneously produce anti-IFNα and anti-IL-12 autoantibodies, suggesting that the microenvironment of the tumor is prone to develop an autoimmune reaction (12).

Padda and collaborators (13) performed a useful and comprehensive review of the data from the multi-continent International Thymic Malignancy Interest Group (ITMIG) retrospective database (14). Their attempts were focused on the identification of prognostic clinical and tumor biomarkers from TET patients with and without PN/AI diseases and, in particular, to establish whether the presence of a PN/AI disease is a good prognostic factor in these

patients.

Data from 6,297 patients with pathological diagnosis of thymomas (86%), thymic carcinomas (12%), and neuroendocrine thymic tumors (2%), were revised; they included 2,143 patients with and 4,154 patients without PN/AI diseases. Almost all patients (99%) underwent thymectomy. Moreover, most of the PN/AI (+) patients were affected by MG (96.5%), and were predominantly female and younger compared to PN/AI (–) patients. This observation is in line with the gender/female bias in autoimmune diseases, including MG, and possibly with the age-related thymic function regression, which is associated with a decline in naïve T cell output (15,16). The WHO histological thymoma type most commonly found in PN/AI (+) patients was B2, whereas the type more represented in the PN/AI (–) group was AB. In addition, PN/AI (+) patients had a higher proportion of early tumor stage I–II, compared to the PN/AI (–) group, for which the pathologic stage was mainly represented by advanced stage II–IVB.

Cumulative incidence of recurrence (CIR) was lower in the PN/AI (+) compared to the PN/AI (–) group, when considering the overall TET population; this difference was not significant when TETs were stratified in thymomas and thymic carcinomas, or on the basis of the pathologic tumor stage, but it was maintained as significant when only patients with MG where included in the analysis.

In line with the CIR decrease, the overall survival (OS) was significantly increased in PN/AI (+) compared to PN/AI (–) patients, both when PN/AI diseases were considered all together, and when only MG patients where included in the analysis. The OS in PN/AI (+) versus PN/AI (–) patients was also significantly greater in the thymoma group, whereas in the thymic carcinoma group there was a trend for improved OS in the PN/AI (+) patients. For patients with carcinoma, additional factors, along with PN/AI diseases, may be important co-factors for improved OS, including tumor size and stage, and particularly complete/partial resection. Improved survival in the PN/AI (+) group was also significantly different compared to the PN/AI (–) group in advanced stage III and IVB subgroups (13). All these data indicate that PN/AI disease presence is a favorable prognostic factor for TETs. However, using a multivariate model, PN/AI disorders were not independently associated with clinical outcomes of recurrence-free survival (RFS) and OS. As expected, since PN/AI diseases were mostly represented by MG (96%), similar data were obtained both when considering PN/AI disorders all together, and when only MG was considered as PN/AI disorder. Clinical features, other than PN/AI diseases, were found to be independently associated with increased/decreased recurrence or worsened/improved OS: (I) older age, carcinoma and neuroendocrine thymic tumor (NETT) histology, advanced stages, and R2 resection status were independently associated with both increased recurrence and worse of OS; (II) Asian ethnicity was independently associated with decreased recurrence; (III) curative radiation was independently associated with decreased recurrence and improved OS; (IV) WHO B1 type was an independent factor associated with increased OS (13), although morphology data should be interpreted with caution due to inter-observer variation and changes in histological TET subtyping criteria over time (3). Consider the overall data, the PN/AI syndrome impact on CIR decrease and improved OS may be closely related to the increased proportion of younger patients among PN/AI (+) patients, and to the higher rate of total thymectomy and complete R0 resections in these patients compared to PN/AI (–) patients. Moreover, PN/AI (+) group had a lower proportion of thymic carcinoma and a higher proportion of early stage I–II disease, compared to the PN/AI (–) group. TET pathologic stage may be critically linked to favorable prognosis in TET patients with PN/AI diseases. Indeed, tumor stage (i.e., stages I and II) and completeness of resection were good prognostic factors for both recurrence and survival in previous multivariate analyses (17). In MG patients radical thymectomy is a therapeutic option whose aim is to increase clinical remission. Such a goal is supported by the results of the recent international randomized trial by Wolfe and colleagues on extended transsternal thymectomy combined with prednisone in non-thymomatous MG (18). This trial compared extended transsternal thymectomy plus alternate-day prednisone with alternate-day prednisone alone, and demonstrated that MG patients in the thymectomy group had a lower time-weighted average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone. Moreover, thymectomized patients had a lower average requirement for alternate-day prednisone, and a lower percentage of them required immunosuppression with azathioprine or was hospitalized for exacerbations compared to the prednisone-only group (18). These data indicated that thymectomy improved clinical outcomes over a 3-year period in patients with non-thymomatous MG.

We recently analyzed the efficacy of thymectomy in MG patients by evaluating the achievement of remission or pharmacologic remission 2 years after surgery in patients

submitted to video-assisted thoracoscopic extended thymectomy (VATET) or to extended transsternal thymectomy (T-3b) (19). Our study, which utilized the propensity score (PS) modelling to compare the outcome of MG patients submitted to VATET or T-3b techniques, provided Class IV evidence that VATET is more effective than T-3b for MG patients (19). Indeed, we showed that 68.9% of MG patients in the VATET-group reached the pharmacologic remission/remission status compared to 34.4% of T-3b-group patients; patients who underwent VATET had a lower INCB-MG score and had less muscle fatigability than those subjected to T-3b (19), clinical features that might influence the different proportion of positive outcomes between the two procedures.

The comparative analysis of the NIH MGTX trial (18) with the PS study (19) revealed major methodological differences: (I) the PS study, which included also thymomatous MG patients, compared two surgical procedures providing evidence for a beneficial effect of thymectomy, and this beneficial effect was demonstrated also when thymoma cases were excluded, thus suggesting that tumor was not necessarily a prognostic negative factor (19); (II) the NIH MGTX trial was "de facto" a pharmacological trial in which the "variable" thymectomy was weighted to evaluate different clinical outcomes in MG (18). However, even if a direct comparison between these two studies cannot be performed, both of them support the beneficial effect of thymectomy.

In non-MG patients with early stage thymoma, a multi-institutional propensity-matched study, which stratified for partial and total thymectomy, showed comparable results considering recurrence as an outcome (20). In this study partial thymectomy showed better perioperative outcomes, suggesting that this surgical approach may be a treatment option for early-stage thymoma patients without MG (20).

Among factors affecting OS, chemotherapy may be a negative one as it may worse PN/AI diseases or cause tumor-unrelated complications due to the toxic effects of chemotherapy agents.

Previous studies on the prognostic role of PN/AI diseases for TETs produced contrasting data (21-23). MG was not associated with a better survival in the study of Lee and collaborators (21). On the contrary, pre-operative absence of MG was found to be an independent predictor of lower OS by Wilkins and colleagues (22); Mineo and colleagues reported a significant correlation between MG and higher rates of disease recurrence not affecting survival (23).

The discrepancy among results from different studies may be due to different variables, such as use of different outcome measures, different statistical analyses (e.g., use or not of a multivariate modeling), differences in the clinical features of patients (e.g., receiving or not radiotherapy or chemotherapy). Regarding outcome in thymic malignancies, RFS and OS, employed by Padda and colleagues (13), are probably the best measures. However, it should be considered that many patients might die for causes unrelated to thymoma. Hence, adopting thymoma-specific survival outcome should be the best outcome measurement, since OS and thymoma-specific survival may give different results. In the analysis performed by Padda and colleagues (13), data on the causes of death are missing, strongly limiting the evaluation of the impact of PN/AI diseases, and related treatments, on thymoma OS/death. Data on the outcome of MG in the thymectomized patients, helpful to relate MG improvement or worsening with the risk of recurrence, are also missing. Another limitation of the study of Padda and colleagues (13) is that autoimmune disorders may have been underestimated, due to the surgical orientation of the ITMIG database. Nevertheless, it should be recognized that this study is one of the largest studies examining PN/AI diseases in TET patients, using a worldwide database, whose limitations are those intrinsic to retrospective databases. The application of a multivariate model is another important advantage of the Padda's analyses. It is interesting to stress that previous studies based on national databases provide results in line with those reported by Padda and colleagues (13). A recent study of Wang and collaborators, who analysed data from the Chinese Alliance for Research in Thymomas (ChART) registry, showed that MG is not an independent prognostic factor for the discovery of thymoma, and that the survival of thymoma patients was improved when MG was present, particularly in late stage patients (24). Another study by Ruffini and collaborators, which was based on the examination of the European Society of Thoracic Surgeons (ESTS) database, demonstrated, in a multivariate model, that incomplete resection and carcinoma histology have a significant impact in increasing tumor recurrence and reducing survival; moreover, non-MG patients had higher risk of recurrence (25).

The favorable impact of PN/AI disorders, particularly MG, on survival of thymoma patients may be mainly related to early diagnosis of the tumor, making higher the chance of an early complete resection; other favorable factors are the less aggressive histologic types and more intensive clinical follow-up, including early diagnosis of recurrences,

early detection of comorbidities, and treatments which may modulate cancer development. The latter considerations fit with the observation that OS was significantly improved in the PN/AI (+) patients followed-up in the most recent times (years 1991–2012) compared to years 1951–1970, or 1971–1990 (13), suggesting that a better outcome in thymoma patients with MG may be linked to improved care in more recent years. Moreover, common immunosuppressive therapeutic agents used for MG treatment could positively influence tumor recurrence and survival of patients.

In summary, data by Padda and collaborators (13) are clinically relevant. Indeed, they not only reinforce previous knowledge on factors affecting recurrence and survival in patients with TETs, but also provide new insights on the association and prognostic role of PN/AI disorders for TETs. Furthermore, this article highlights the importance and the clinical need of large databases, which include rare tumors and rare diseases: in this study thymic tumors and MG. Indeed, comprehensive clinical analyses will be feasible only by the availability of country-based registries sharing clinico-biological data. In this respect, the next challenge for international databases and large-scale multicenter studies will be to combine clinical and epidemiological features with biological data from high-throughput multi-omics analyses, which are able to disclose highly predictive and prognostic molecular markers. This could be fundamental for significantly improving prognostic stratification and clinical management of TET patients.

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Footnote

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