Accuracy of pathologic diagnosis for thymic epithelial tumors: a brief report from an Italian reference Center

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Abstract

Objectives - Rare tumors are diagnostic challenges for pathologists. Consultation or referral to Centers with expertise is crucial for the right diagnosis. This is particularly true for Thymic Epithelial Tumors (TETs), whose treatment strategies vary according to histological subgroup. We aimed at evaluating the accuracy of TET pathologic characterization in an Italian reference Center.
Materials and methods - All the cases with diagnosis or suspicion of TETs, which underwent a pathological second opinion at Istituto Nazionale dei Tumori (INT), Milan, between 2015 and 2019 were retrospectively reviewed. All cases had been pathologically characterized through immunohistochemistry (IHC). Descriptive statistics were used for qualitative variables. Concordance was estimated through Cohen's kappa (k).
Results - Out of 278 cases of TETs diagnosed in INT, 72 were referred to INT for a pathologic revision. The INT revision changed the diagnosis in 41 cases (56.9%), with a potential therapeutic shift in 32 (44.4%). In particular, 20 cases of thymoma were reviewed as a different subtype of thymoma (19/20) or lymphoma (1/20); nine cases of thymic carcinoma were reviewed as thymoma. On the other hand, three cases of lung carcinoma were reviewed as thymic carcinoma (2/3) or thymoma (1); eight cases of carcinoma Not Otherwise Specified were reviewed as thymic carcinoma; one case of lymphoma was reviewed as thymoma. Concordance between pathologists was moderate for thymoma (74.7%, k 0.447), inferior for thymic carcinoma (60.5%, k 0.139).
Conclusion - A significant proportion of cases referred to INT for a presumptive TET received a different characterization. A potential shift in therapeutic indication was not rare. This underlines the importance for TETs to get a second pathological diagnosis by an expert pathologist and supports the need for networks on rare cancers.

Keywords: diagnosis; histology; networking; rare diseases; thymic epithelial tumors.

1. Introduction

Thymic Epithelial Tumors (TETs) are a heterogeneous group of rare entities, with a complex classification. Their annual incidence ranges from 1.3 and 3.2 cases per million. Most cases of TETs are thymomas, whose

incidence is 2.8/1,000,000/year. Thymic carcinomas are much rarer, with an estimated incidence <0.1/1,000,000/year [1,2].

The diagnosis and histological classification of TETs are based on World Health Organization (WHO) classification and International Thymic Malignancies Interest Group (ITMIG) consensus statement. According to these guidelines, TETs are divided into the following subgroups: thymoma (with subtypes A, A/B, B1, B2, B3) and thymic carcinoma. Mixed forms are also described. The histological characterization of TETs is based upon the morphology of epithelial cells, the architectural similarity to the normal thymus, and the proportion of lymphocytic infiltrate (the last two criteria both decreasing from type A to B3). Thymic carcinomas have mostly squamous histology, resembling similar carcinomas of other sites in terms of morphology and immunohistochemistry (IHC) [3,4]. Main histological attributes of each TET subtype are recapped in Supplementary figure 1.

The correct attribution of a TET to one of these categories and the differential diagnosis with other thoracic malignancies can be achieved with a limited panel of antibodies in most cases. In particular, cytokeratins, p63 or p40, and terminal deoxynucleotidyl transferase (TdT) are characteristic of thymomas, while KIT (CD117), CD5, GLUT1 and MUC1 are markers of thymic carcinoma [5]. Despite this general rule, the diagnosis and characterization of TETs are often difficult, also due to their rarity. Therefore, a histological revision in Centers with pathological expertise should be sought, whenever a case of TET is suspected.[6] Although most guidelines agree on this point, the pathologic second opinion is not a rule in real-life practice. We aimed at assessing the accuracy of TET diagnosis analyzing pathologic reviews done by an Italian reference Center, member of national and international networks of TET expert Institutions.

2. Material and methods

2.1 Study population

Among all patients accessing Istituto Nazionale dei Tumori (INT), Milan, Italy, for a possible TET between 2015 and 2019, we selected those who underwent a pathologic review. Clinical and pathological data were retrieved from the INT Institutional database.

2.2 Pathologic analysis

Each INT second look implied the execution of stainings for p40, CD5, CD117, GLUT-1, whenever not previously performed, according to ITMIG consensus and WHO reference book [2,3]. Additional stainings were sometimes performed at the pathologist's discretion, depending on the diagnostic challenge of the specific case. The final diagnosis was based on IHC pattern, morphological features and architecture of tumor epithelial cells, and quantification of lymphocyte infiltrate.

2.3 Statistical analysis

Descriptive statistics were used to report diagnoses. Fisher's exact test was applied to test association between categorical variables. The concordance rate between external and INT pathologists was described as the percentage of change. Each discordance was defined as either minor or major according to potential therapeutic shift, according to authors' judgement. Cohen's kappa was calculated for main diagnostic categories (thymoma regardless of subtype, thymic carcinoma) [7].

3. Results

Two hundred seventy-eight cases accessing INT for presumptive TETs or diagnosed with a TET at INT were identified. Seventy-two of them underwent a pathologic revision by the INT expert pathologist.

Disease stage was unknown in one of the 72 cases. Thirty-eight patients (53.5%) had an advanced stage disease (IVa-IVb according to Masaoka-Koga system) at the time of tissue collection. The remaining 33 patients (46.5%) had an initial or locally advanced stage disease (I-III according to Masaoka-Koga system), potentially amenable of surgery either as first therapeutic approach or after induction treatment.

The tissue specimen which was analyzed for the pathologic second look had been obtained through a percutaneous or endoscopic biopsy in 47 cases (65.3%), through a surgical intervention in the remaining 25 (34.7%). All the cases had histological specimens; no diagnoses were performed through citology.

INT pathologic revision changed the diagnosis in 41 (56.9%) cases, with a potential shift in therapeutic approach in 32 (44.4%) (Table 1). In particular, 20 cases of thymoma were reviewed as a different subtype of thymoma (19/20) or diffuse large B cell lymphoma (1/20); nine cases of thymic carcinoma were reviewed as thymoma. On the other hand, three cases of lung carcinoma were reviewed as thymic carcinoma (2/3) or thymoma (1); eight cases of carcinoma NOS were reviewed as thymic carcinoma; one case of lymphoblastic lymphoma was reviewed as thymoma.

No association emerged between TET stage (localized or advanced) and pathologic discordance (Odds Ratio [OR] 0.5000, 95% Confidence Interval [95%CI] 0.1907-1.3110; p=0.2285). Similarly, the nature of tissue sample (surgery or biopsy) was not associated to the likelihood of diagnostic change (OR 0.8254, 95%CI 0.3081-2.2120; p=0.8045).

Overall concordance among pathologists was moderate for the initial diagnosis of thymoma (74.7%, k 0.447), inferior for the initial diagnosis of thymic carcinoma (60.5%, k 0.139), as outlined in Figure 1.

Two paradigmatic cases of diagnostic shift are one diagnosed with thymoma type B2 after an initial diagnosis of lymphoma (Supplementary figure 2), and one diagnosed with thymoma type B3 after an initial diagnosis of thymic carcinoma (Supplementary figure 3).

4. Discussion

Rare cancers often constitute diagnostic challenges for inexperienced Centers, and this can lead to delays and/or misdiagnoses. Specific guidelines to drive treatment decisions are not available for many rare conditions, and their dissemination is rarely optimal. Therefore, the opportunity to receive the best care is not homogeneous across Institutions and Countries for patients with rare cancers [8-12].

TETs are an excellent example of these pitfalls, as they encompass a heterogeneous family of different conditions with a difficult diagnosis and a regular need for a multidisciplinary personalized approach [13]. Herein we present the experience of a high-volume Italian Institution, on the pathologic accuracy of TET diagnoses. The results demonstrated that the second revision by a dedicated/expert pathologist could change diagnosis in more than half of the cases. A potential consequent shift in therapeutic indications was not rare. In few patients, the revision implied a so radical change in diagnosis, that its omission could exclude them from a potentially curative treatment (e.g. the case diagnosed with lymphoma instead of thymoma), or induce to apply very aggressive treatments with poor likelihood of success (e.g. the case classified as lymphoblastic lymphoma instead of thymoma).

The role of pathologic second look has already been discussed for other rare cancers such as sarcoma. As an example, a large prospective analysis conducted in France and Italy showed an incidence of diagnostic change of 40% for all sarcoma histotypes, thus supporting the importance of systematic revisions [14].

Based on this and similar experiences, two strategies have been proposed to optimize rare cancer care. The first one is based on patients' referral to few Centers with multidisciplinary expertise. Although effective in reducing impropriety, this approach has the limitation of requiring patients' access to reference Institutions. The consequent "health migration" has a heavy burden in terms of quality of life and social cost. To address these points, the "hub-and-spoke model" has been formalized. It aims to make available to collaborating Institutions ("spokes") the expertise of a small number of reference "hubs", thus limiting patients' migration [8]. The "hub-and-spoke" system is difficult to realize, as it requires strong collaboration among healthcare providers and the creation of adequate infrastructures (e.g. web-based platforms for teleconsultation, virtual tissue/blood banks). However, it seems to conjugate standardization of care, with optimization of resources and patients' quality of life.

In the specific field of TETs, a previous work analyzed the topic of pathologic revisions and diagnostic accuracy. The authors from a large Estonian Center identified 49 TET patients, whose pathologic specimens were systematically sent to a French reference Institution with a high expertise in the disease. The concordance rate reported in this work was higher than in our case series, as the initial diagnosis was consistent with pathologic second look in 60% of cases, with only 16% of major changes [15]. The difference between the results may be attributed to the nature of the involved Centers, as the Estonian hospital was the largest oncologic Institution in that Country, as documented by the availability of a relatively large case series

of TETs. On the contrary, the cases we collected were unselected for origin and often came from general hospitals lacking any specific expertise on rare oncologic diseases.

Within the existing evidence on this topic, our study has the limitation of being conducted in a single Institution with a retrospective approach. Methods to obtain diagnosis were not standardized in a pre-defined protocol. Patients' follow-up is lacking in many cases. Nonetheless, the availability of a wide Institutional database of TETs let to collect a significant number of cases considering the rarity of the disease. Furthermore, the Institution has been appointed as a reference Center within the European Reference Network (ERN) dedicated to rare adult solid cancers (EURACAN), a virtual network of highly specialized healthcare providers promoted by the European Union with the purpose to coordinate research and share knowledge on rare cancers across Europe. The ERN appointment certifies the quality of the diagnostic and therapeutic process performed in INT.

In conclusion, the high rate of diagnostic discordance in the INT case series supports the role of pathologic expertise in obtaining the right diagnosis for TETs. This underlines the importance of networking to ease patients' access to a pathologic second look. National and international networks (e.g. ERN at a European level, the Italian collaborative group for ThYmic MalignanciEs [TYME] in Italy) will likely be crucial to guarantee broad access to high-quality care, making the "hub-and-spoke" model a reality.

5. References

[1] E.A. Engels, Epidemiology of thymoma and associated malignancies, J. Thorac. Oncol. 5 (2010) S260–S265. doi: 10.1097/JTO.0b013e3181f1f62d.

[2] G. Gatta, R. Capocaccia, L. Botta, et al, Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study, Lancet Oncol. 18 (2017) 1022–1039. doi: 10.1016/S1470-2045(17)30445-X.

[3] W.D. Travis, E. Brambilla, A.P. Burke, A. Marx, A. Nicholson, WHO classification of tumours of the lung, pleura, thymus and heart, 4th ed., WHO classification of tumours, vol. 7, IARC Lyon 2015, ISBN 9789283224365.

[4] A. Marx, P. Strobel, S.S. Badvel, et al, ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting, J. Thorac. Oncol. 9 (2014) 596-611. doi: 10.1097/JTO.0000000000000154.

[5] A.G. Nicholson, F. Detterbeck, A. Marx, et al, Dataset for reporting of thymic epithelial tumours: recommendations from the International Collaboration on Cancer Reporting (ICCR), Histopathology. 70 (2017) 522-538. doi: 10.1111/his.13099. doi: 10.1111/his.13099.

[6] N. Girard, E. Ruffini, A. Marx, C. Faivre-Finn, S. Peters, on behalf of the ESMO Guidelines, Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 26 (2015) v40-v55. doi: 10.1093/annonc/mdv277.

[7] I. Guggenmoos-Holzmann, The meaning of kappa: probabilistic concepts of reliability and validity revisited, J. Clin. Epidemiol. 49 (1996) 775-782. doi: 10.1016/0895-4356(96)00011-x.

[8] A.M. Frezza, A. Trama, J.Y. Blay, P.G. Casali, Networking in rare cancers: what was done, what's next, Eur. J. Surg. Oncol. 45 (2019) 16-18. doi: 10.1016/j.ejso.2018.03.030.

[9] G. Gatta, R. Capocaccia, L. Botta, et al, Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a ppulation-based study, Lancet Oncol. 18 (2017) 1022-1039. doi: 10.1016/S1470-2045(17)30445-X.

[10] S. Sandrucci, S. Naredi, S. Bonvalot, Centers of excellence or excellence networks: the surgical challenge and quality issues in rare cancers, Eur. J. Surg. Oncol. 45 (2019) 19-21. doi: 10.1016/j.ejso.2017.12.012.

[11] S. Mathoulin-Pélissier, K. Pritchard-Jones, Evidence-based data and rare cancers: the need for a new methodological approach in research and investigation, Eur. J. Surg. Oncol. 45 (2019) 22-30. doi: 10.1016/j.ejso.2018.02.015.

[12] G. Gatta, A. Trama, R. Capocaccia, RARECARENet Working Group, Epidemiology of rare cancers and inequalities in oncologic outcomes, Eur. J. Surg. Oncol. 45 (2019) 3-11. doi: 10.1016/j.ejso.2017.08.018.

[13] M. Imbimbo, M. Ottaviano, M. Vitali, et al, Best practices for the management of thymic epithelial tumors: a position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME), Cancer Treat. Rev. 71 (2018) 76-87. doi: 10.1016/j.ctrv.2018.10.001.

[14] I. Ray-Cocquard, M.C. Montesco, J.M. Coindre, et al, Sarcoma: concordance between initial diagnosis and centralized expert review in a population-based study within three European regions, Ann. Oncol. 23 (2012) 2442-2249. doi: 10.1093/annonc/mdr610.

[15] K. Oselin, N. Girard, K. Lepik, et al, Pathological discrepancies in the diagnosis of thymic epithelial tumors: the Tallinn-Lyon experience, J. Thor. Dis. 11 (2019) 456-464. doi: 10.21037/jtd.2018.12.123.

6. Figure legends

Figure 1. Discordance between external and INT0 pathologists, defined as either “major” or “minor” according to potential therapeutic shift as assessed by the authors.

Supplementary figure 1. TETs according to WHO classification, H&E staining. (A) Type A thymoma: spindle-shaped epithelial cells, very few mature lymphocytes interspersed, 200×. (B) Type AB thymoma: network of epithelial cells, with a variable lymphocyte content, mostly composed of immature T cells; scattered

hystiocytes with clear cell cytoplasm, 200×. (C) Type B1 thymoma: the most organotypic histotype of thymoma, with a loose network of epithelial cells mostly hidden by a high amount of lymphocytes of the immature cortical type, 100×. (D) Type B2 thymoma: a dense network of epithelial cells stands out on the lymphocyte background of the cortical type, 200×. (E) Type B3 thymoma: sheets of epithelial cells with few lymphocytes interspersed, usually of immature type; epithelial cells in palisades around vessels, 100×. (F) Thymic carcinoma: nests of poorly differentiated epithelial cells in a fibrous stroma, 200×.

Supplementary figure 2. A case of thymoma type B3, initially diagnosed as thymic carcinoma. (A) H&E staining, 200x. (B) Negative staining for CD5 in epithelial cells. (C) Positive staining for TdT.

Supplementary figure 3. A case of thymoma type B2, initially diagnosed as lymphoblastic lymphoma. (A) H&E staining, 200x. (B) Positive staining for p40, confirming the presence of epithelial cells. (C) Staining for TdT in lymphoid cells.