The B3 / Thymic Carcinoma Borderland

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Introduction

Thymomas are considered rare neoplasms arising from thymic epithelium (fourth to fifth decades), without distinction of gender. One third of the patients has no symptoms, one third presents local symptoms and the remaining manifest on autoimmune disease at the time of the diagnosis\(^1\). Systemic symptoms, such as fever, anorexia, asthenia and weight loss are rare. In fact, thymomas are mostly accidental foundings during routine exams such as thoracic x-ray and 15% are linked to myasthenia gravis, preferentially in women and associated with WHO types AB, B2 and B3 thymomas\(^2\,^3\,^4\). Besides being the most frequent anterior mediastinal tumours, thymomas are reported as rare, below 1% of all adult cancers, with an incidence rate of 1-5/million population/year\(^3\). The majority of these thymic tumours are benign, as that the integrity of the thymic capsule in maintained; malign thymomas are defined as a neoplasm born in thymic epithelium that has latter invaded the capsule of the organ; metastatic presentation is not common\(^1\), and lungs (as other thoracic organs) and the liver are the most common hosts for metastases. The histological classification of primary thymic epithelial neoplasms has been changing due to the wide variety of
morphologic appearances that these tumours can display. Various classification schemes have been applied through the years, as those of Masaoka (1981), Muller Hermelink (1989), Suster-Moran (1999) and the actual WHO (2004) classifications, and there is still a lack of randomized clinical trials evaluating the prognosis of patients with thymomas and the effects of various treatment modalities.

The contemporaneous WHO 2004 classification has a straight correspondence with Muller Hermelink’s: WHO type A corresponds to medullary thymoma (spindle cell thymoma); type AB to mixed thymoma; type B1 to predominantly cortical thymoma (lymphocyte-rich thymoma); type B2 to cortical thymoma; and type B3 to well-differentiated thymic carcinoma (squamoid thymoma). The importance of the histopathologic subtype as an independent prognostic factor has varied in different studies, mostly due to a lack of concordance among pathologists by the use of a single classification scheme. The main purpose of the international classification introduced by WHO in 2004 was to provide a universal formula that would facilitate comparison among various terms from the already existing classifications.

However, it was not totally well succeeded, since today it still remains a source of discrepancy among different centres.

The thymus is a complex and in many ways mysterious organ as preneoplastic lesions and the pools of adult stem cells have not yet been substantialized to understand carcinogenesis and integrate the differential and intermingled phenotypes of thymic epithelial tumours as endoderm and ectoderm express their synergism. As much remains to be learned about thymus development, structure and function, many observers have suggested that reproducible cytoarchitectural classification is impossible. This is not comfortable for pathologists, who both want to understand
tumour morphology and improve the contribution to patient management and treatment\textsuperscript{22-25}.

**The B3 Thymoma**

WHO 2004 classification clearly characterizes types A, AB, B1, B2 and B3 thymomas, as well as a large group of thymic carcinomas exhibiting the most possible morphological patterns. Although criteria are short cut, in between all morphological aspects can be intermingled as huge thymomas are resected and a large number of sections are observed beyond those explored for cortical invasion. Also some cystic well defined areas are observed expressing epithelial hyperplasia and atypical cells may be present, raising the suspicion of pre-neoplastic lesions for thymomas, and we can also raise the question of inflammation and repair as triggering lymphomas or thymomas.

The B3 type thymoma raises no diagnostic concern when epithelial squamoid cells (WHO) form solid and large nests of cells maintaining the organotypic pattern of thymomas, separated by delicate stroma with lymphocytes superimposed. The illustrating case is typical - HUC 11574/08: 56 years old man presenting *myasthenia gravis* for one year - nuclear atypia is absent as nuclei maintain as small or large, clear and the granular chromatin aspect.

B3 type thymoma corresponds then to the thymic carcinoma once we despise the little presence of the lymphocytes as it happens in type A thymoma: in between, types AB, B1 and B2, raise with the high prevalence of lymphocytes.

As all histological types of thymomas can intermingle in routine observed cases, as mixed thymomas (beyond the recognized AB type) any other phenotype beyond the recognized A, AB, B1, B2 and B3, indicates another tumor, it means, a specific thymic «pure» carcinoma or a mixed carcinoma – thymoma.
Concerning B3 type thymoma, it pure incidence may become very low because when histopathology shows clear intercellular bridges and / or unicellular keratinisation or keratin pearls, the squamous cell carcinoma is defined. As atypical nuclei is not a criteria for thymomas, when present, without the other markers for epidermoid carcinoma, it becomes a poorly differentiated epidermoid carcinoma, with – mixed B3 type thymoma and epidermoid carcinoma or without type B3 thymoma.

Stem cells have been recalled to explain thymic epithelial tumors heterogeneity, as in any other organ, and studies have been developed to clear immunohistochemistry as a helpful tool. Even though, morphology alone stands the main argument to distinguish the different types of tumors and their different concomitant patterns, correlated with invasiveness of the thymic capsule (Masaoka staging). Uptake of F-18 FDG PET-CT in children and young adults thymic tumors and in thymic hyperplasia in patients after chemotherapy or with Graves' disease may differentiate thymic carcinoma from other thymic diseases, and thymoma from thymic hyperplasia as the intensity of FDG uptake is useful for predicting the grade of malignancy in thymic epithelial tumors without relationship with invasiveness (26).

Thymic new entities are raising either in epithelial as in soft tissue counterparts. Losses on 16q and 17p may be significant in the sequence from B2 to B3 and C thymomas, indicating events in the transition between development and progression of thymomas, gains on the long arm of chromosome 1 occur early in tumor development and are correlated with losses on 6p and 6q while losses on 16q and 17p appear to be late event and independent pathway leads to losses on 3p and 13q, which are closely correlated indicating developmental pathways probably from the same progenitor cell (27,28).
New entities approach as expertise and experience are provocative. "Corpuscular thymomas" are similar to WHO type B2 and B3 thymomas and described as rare, indolent and rarely associated with myasthenia gravis. As Hassall's corpuscles are uncommon in thymomas, when present may indicate medullary differentiation of WHO type B1-3 thymomas and also immature T cells were present (29).

Genetic data allowed the separation of thymic carcinomas from thymomas in WHO 2004 classification, still as a very heterogeneous group, comprising squamous cell carcinomas, basaloid carcinomas, mucoepidermoid carcinomas, lymphoepithelioma-like carcinomas, sarcomatoid carcinomas, biphasic metaplastic thymoma, clear cell carcinomas, adenocarcinomas, neuroendocrine carcinomas (and typical and atypical carcinoids), hepatoid carcinoma, carcinoma with t(15;19), undifferentiated carcinomas and other combined subtypes, mimicking morphology in other organs, expressing c-Kit immunohistochemically, mature lymphocytes and without incidence of myasthenia gravis. In that large nomenclature, thymic squamous cell carcinomas and lymphoepithelioma-like carcinomas appear now and then and immunohistochemical markers such as CD5, CD70, CD117, CD205, FOXN1 as well as chromosomal gains and losses help to distinguish epidermoid carcinoma from not only from thymomas but also from pulmonary epidermoid carcinomas. Suritinib as a tyrosine-kinase inhibitor is revealing a RECIST validated treatment for thymic carcinomas (30, 31).

Completeness of surgical tumour resection, thymic tumors Masaoka-Koga staging, chest imagiology reporting to help clear clarification of thymic thymomas / carcinomas to fulfil statistical comprehension and small biopsies interpretation in advanced stages, are the promising parameters defined by the ITMIG in the Journal of
Thoracic Oncology 6 (7) supplement, 2011, to begin with a normalized thymic tumor patients dealing.

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