



Thymic epithelial tumors diagnosis and management: the importance of an international multidisciplinary approach

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Malignant thymic epithelial tumors (TETs) include thymomas and thymic carcinomas. They are derived from neoplastic thymic epithelial cells growing in a microenvironment highly variable from a strong predominance of immature lymphoid T cells to very few mature T cells. The 2015 WHO Classification clarifies the architectural, cytological, phenotypical and molecular characteristics of the different histotypes (A, AB, B1, B2, B3, malpighian thymic carcinoma) (1). Nevertheless, as these tumors are rare, a pathologist will face only rare cases in its practice, except in heavy specialized centers. The diagnosis therefore is considered as difficult. In addition, in a minority of cases, consensus between experts concerning the histotype classification is difficult, as the pattern of tumors can be heterogeneous and could not fit perfectly with the classical histotype feature. Indeed, it is a combination of elementary lesions that allow to classify a TET in a definite subtype and differential criteria to allocate one case to one or the other subtype might be sometimes difficult (2). For example, for cases difficult to classify between B2 and B3, the best criteria considered as the most reproducible is that B2 is a “low power” blue tumor appearance (rich in lymphoid cells with dark nuclei) whereas B3 is a pink tumor (linked to the eosinophilic large cytoplasm of epithelial tumor cells). However, this criterion might be sometimes difficult to evaluate reproducibly between experts as being dependent on the intensity of staining technique, varying from laboratory to laboratory.

In this issue of *mediastinum*, Sigurdson *et al.* (3) reported a rare case of an 11 year-old girl with thymoma and submitted to the international tumor board organized by

the ITMIG (International Thymic Malignancy Interest Group), the questions of postoperative adjuvant therapy as well as follow up. As TET are very rare in children, it is important to discuss the management with adult teams, although taking into account the context of a pediatric tumor with the implication of a pediatric oncologist. Thymomas are rare at this age with sixteen children at the median age of 11 years registered in European Cooperative Study Group for Pediatric Rare tumors between 2000 and 2012 among French, Italian, German and Polish patients (4). At the same period, 20 patients with thymic carcinoma were diagnosed. Among the 16 thymomas, only two presented with myasthenia and the maximum diameter exceeded 5 cm in 10 out of 16 patients as in the case submitted to ITMIG. A majority of cases were diagnosed as B1 [10] or B2 thymoma (3 cases) and very rare cases as A [1] or AB [2] thymoma. Only two patients were metastatic at presentation and one patient only received radiotherapy.

In addition, to assign the correct histotype, the pathologist when dealing with a resection of the TET should also evaluate the stage that is crucial for the postoperative treatment. This stage is evaluated depending on the center either according only to pTNM/IASLC/ITMIG, 8th edition (5) and in some centers according also to Masaoka-Koga detailed by ITMIG (6). For the resection decision, the multidisciplinary approach with the oncologist, thoracic surgeon and radiologist is crucial to define the anatomy and the extension of the lesions. However, this is the thoracic surgeon during the resection that will confirm the extension of the lesion as well the macroscopic completeness of resection. A detailed surgical report is

crucial to allow a good macroscopy by the pathologist as well as an appropriate orientation of the surgical sample on a “mediastinal board” as recommended by ITMIG (6). Sutures and clips both on the attached structures (i.e., pericardium, mediastinal pleura, innominate vein, ...) and on the doubtful R1 areas (to really differentiate resection limit from dissection limit by the pathologist) are crucial.

The combination of stage and histotype is defining the postoperative strategy, and possibly the interest of PORT (postoperative radiotherapy). However, there is lack of strong evidence of the benefit of PORT on survival or relapses and lack of consensus between teams underlining the importance of multidisciplinary approach between the oncologists, the surgeons, the radiation oncologists, radiologists and pathologists.

In the observation by Sigurdson *et al.* (3), four slides were submitted for the diagnosis for a 6 cm tumor, to the tumor board. This might not reflect the full spectrum of the tumor often heterogeneous as one slide per one cm of tumor is generally recommended to take into account this heterogeneity. The tumor board confirmed the B2 subtype with invasion stage IIA (Masaoka Koga/ITMIG) and pT1aN0M0, stage I (IASLC). As this tumor was resected by VATS without thymectomy, a partial sternotomy was performed secondarily for the completion of the thymectomy, which is the standard for all the thymomas. Although in this tumor, scattered epithelial cells were present at the blue-ink margin, tumor board did not feel there was sufficient evidence of a R1 stage underlining the complexity of the evaluation of R Resection by the pathologist particularly if the surgeon did not underline using clips the resection vs the dissection area. This observation underlines the fact that “tumor into the ink” was not a proof that we were at a resection area on one hand and that scattered epithelial cells were not considered by the tumor board as tumor cells. Therefore, tumor board decided that it was a R0 resection, and that there was no clear guidelines to propose PORT to this patient, stage I (IASLC) (7), taking into account in addition the late toxicity of PORT in pediatric patients. Considering follow up, the international tumor board suggested to use MRI rather than CT-SCAN to diminish the cumulative radiation for this young girl. In addition, this international tumor board showed that some concepts well known in pediatric oncology such as seeding risk when discussing adjuvant therapy were not considered as a physiopathological process when considering adult TET.

From The French multidisciplinary tumor board to the

international level.

In France, the French Cancer Institute since 2012 supported the creation of a national network called RYTHMIC (Reseau Tumeurs Thymiques et Cancer) with a multidisciplinary tumor board twice a months through 14 regional expert centers and with systematic review of all pathology slides by a national network of expert pathologists with the help of surgical report (8). Due to the heterogeneity of the tumor, all the slides are digitalized to be able to evaluate the stage with the limits of not performing the macroscopy. Nevertheless it seems crucial to the network to be able to diagnose on slides the stage even if they did not perform the macroscopy. For each case, with the help of an internet-based software, two pathologists voted independently for stage and histotype and in cases of discrepancy, the panel of expert will review the cases at a bimonthly national pathology meeting. It appears in the French network that although histotype was often reproducible between experts, this was not the case for stage (both Masaoka Koga or 8th pTNM) underlining how difficult it might be to differentiate Masaoka I from IIA, IIB, even taking into account ITMIG detailed histopathology criteria. The network experience raised up also the difficulty in some slides to recognize mediastinal pleura and to diagnose invasion of mediastinal pleura. This was also the case on some slides for pericardial invasion or lung invasion. This observation underlined the importance of discussion between pathologists to reach an agreement particularly at the era of defining a new pTNM classification. Indeed, in the 8th pTNM classification, visceral pleural invasion without lung invasion was not mentioned and it was therefore difficult to assess whether we considered those cases as a stage I (pT1a) or III (pT3).

Our experience at our national level underlined the importance of an international multidisciplinary approach and led us to propose to the ITMIG the constitution of an international RYTHMIC/ITMIG pathology group in the aim of defining on slides, reproducible criteria to evaluate stage and resection status. The success of our project at this international level will help us to better define the treatment for our patients according to stage through potentially newly defined reproducible criteria and will help us as work has to be done for the next 9th pTNM staging for thymic tumors.

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