Extended Abstract

Thymic carcinomas *vs.* lung carcinomas—pathologist's perspective: extended abstract

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A pathologist analyzing the sample obtained from mediastinal tumor often faces the problem of differentiation between thymic carcinoma (TC) and metastatic lung carcinoma (LC).

LCs are the third most common types of cancer (SEER database: 43.2/100,000 people) and the most common cause of death due to cancer. TCs are very rare (0.2/100,000 people), they are often not included into statistical databases, and the available data about their biology is still scant (1).

Both lungs and thymus develop from the endoderm but from its different segments. Lungs arise directly from the anterior foregut endoderm and the thymus develops more cranially from the endoderm of the third pharyngeal pouch. Both organs develop different, highly specialized epithelial cells. In the thymus multiple types of medullary and cortical epithelial cells necessary for proper thymocyte differentiation are found. Epithelial component of the lungs is constituted by a variety of bronchial cells and pneumocytes involved in gas exchange between the external environment and the cardiovascular system (2-4). All pulmonary and thymic epithelial cells can transform into carcinomas.

Despite different histology and embryological development, a microscopic morphology of TCs and LCs is often similar or even identical, e.g., morphology of squamous cell carcinomas (SqCC), majority of adenocarcinomas (ADC) and many other histological subtypes included into the current (2021) WHO histological classification (5). Thus morphology usually does not allow to establish the point of origin of a neoplasm.

Immunohistochemical reactions, used in routine histopathological diagnostics, may help to differentiate between TCs and LCs, however, they are not in a 100% specific or sensitive. The specificity depends on the tumor (poorly differentiated tumors may lose "typical" markers or may gain unusual immunophenotype) or on the clone of antibody used for the test, e.g., for the lung cancers [ADC or neuroendocrine tumors (NETs)] the clone 8G7G3/1 of TTF-1 is the most specific. The sensitivity may be affected by the tumor itself, the condition of neoplastic cells (e.g., necrotizing cells of SqCC quickly lose the expression of p40) and type of fixative used (nuclear reactions are weaker after fixation in alcohol—own observations).

SqCC is the most frequent subtype of TCs. Its etiology in the thymus is unknown and it is not associated with smoking, opposite to lung SqCC. The most useful and relatively the most specific immunohistochemical markers for thymic SqCC are CD5, co-expression of CD5 and CD117 and FOXN1. Other often used markers like CD117 alone, CD205 and PAX8 may be helpful but they can be also positive in some percentage of lung SqCC (6-11).

ADC is currently the most common subtype of LCs. The most important markers pathologists use to differentiate between thymic and lung ADC and to confirm pulmonary origin are TTF-1 and Napsin A. The CD5 and CD117 are not useful since in many thymic ADCs they are negative and, on the other hand, in some lung ADCs these reactions reveal positive results (6,7,10,11).

In many mediastinal masses, especially in some rare histological subtypes of carcinomas microscopic analysis does not allow to establish unequivocally the organ of origin, i.e., thymus vs. lung. Clear cell carcinoma often associated with distinct hyalinization of the stroma reveals in both organs squamous cell differentiation and, in many cases, the fusion of *EWSR1-ATF1* gene. Of note, in the thymus the tumor behaves aggressively with local recurrences and metastases while the pulmonary variant is regarded as low-

grade tumor and no recurrences has been reported (12,13). Lymphoepithelial carcinoma of both, thymus and lung, may be associated with *EBV* infection and both thymic and lung mucoepidermoid carcinoma may reveal *CRTC1-MAML2* gene fusion (14,15). In such cases and in all cases of carcinomas with negative immunohistochemical results the final decision, whether the tumor originates from the lung or from the thymus, requires radiological and clinical correlation.

Thymic and lung NETs, which in WHO classification are separated from the carcinomas and represent the distinct histological subgroups, pose the similar diagnostic problem for pathologists. Histological criteria for thymic and lung subtypes of NETs (typical and atypical carcinoids, large cell neuroendocrine carcinomas and small cell carcinomas) are the same (5). TTF-1 may be positive in both thymic and lung NETs and only PAX8 may help - if positive, it enforces the diagnosis of thymic NET. The differences in genetic alterations between thymic and lung NETs have been found, however, such tests are not widely available for pathologists, and they are not recommended by WHO classification for routine diagnostics (16-18).

Despite similar microscopic morphology, the biology of TCs and LCs differs importantly. This corresponds with availability of predictive biomarkers for these diseases. Currently in all advanced lung ADC it is mandatory to assess the *EGFR*, *ALK*, *ROS1* genes and it is recommended to test additionally *BRAF*, *MET*, *RET*, *NTRK-family*, *HER2*, *KRAS* genes. The mutations or rearrangements found in these genes may qualify the patient to relevant targeted therapies. Pathologists should also assess in all advanced lung non-small cell carcinomas the immunohistochemical expression of PD-L1. High expression (>50% positive neoplastic cells) is associated with higher probability of positive response to the treatment with some of the immune check-point inhibitors (11). There are not such recommendations for TCs since no clinically relevant biomarkers for these tumors have been established yet. The potential biomarkers (e.g., mutations in *KIT*, *PDGFRA*, *CDKN2A*, *FGFR3* genes or expression of mesothelin) are analyzed in many studies but their utility is still under evaluation. PD-L1 expression in many TCs is high, however, the efficiency and safety of the treatment with immune check-point inhibitors still require further analysis in clinical trials. The list of predictive biomarkers for LCs is growing but for TCs it is still under evaluation (19-22).

In conclusion, despite different biology, the morphology of TCs and LCs is often very similar so immunohistochemical differential diagnostics is required. However, it may not be sufficient to establish the point of origin of the tumor. The final diagnosis must be correlated with clinical data and radiological findings.

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