Review Article

Overview of the pathology of thymic neuroendocrine tumors

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Abstract: In the last edition of WHO classification of tumors of the lung, pleura, thymus and heart, lung and thymic neuroendocrine tumors (NETs) have been incorporated into a separate new category of neuroendocrine neoplasms. Similarly, they were classified into low-grade typical carcinoids (TCs), intermediate-grade atypical carcinoids (ACs) and high-grade poorly differentiated neuroendocrine carcinomas (HGNECs) of the large and small cell types (LCNEC and SCLC), but contrary to lung, most thymic carcinoids are atypical. Different histotypes are distinguished based on morphological features; Ki67, however, can help to differentiate low and intermediate grade tumors from high grade neoplasms, especially on small biopsies. Although available data are limited, genomic profiles of thymic NETs seem similar to corresponding NETs of other locations, but *MEN1* alterations are more frequent in thymic carcinoids. *RB1*, *TP53* and *PTEN* mutations are frequent in HGNEC, as expected. Predictive biomarkers have not been extensively investigated in thymic NETs, but reported evidence suggests possible efficacy of targeted therapies against receptor tyrosine kinases and mTOR pathway. A better integration of lung, thymic, gastrointestinal and pancreatic NETs classifications, in terms of terminology and histological categories, is warranted.

Keywords: Neuroendocrine tumor (NET); carcinoid; thymus

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Definition

In the WHO classification of tumors of the lung, pleura, thymus and heart published in March 2015 (1), lung and thymic neuroendocrine tumors (NETs) have been incorporated into a new category of neuroendocrine neoplasms, and have been similarly classified into low-grade typical carcinoids (TCs), intermediate-grade atypical carcinoids (ACs) and high-grade poorly differentiated neuroendocrine carcinomas (HGNECs) of the large and small cell types (LCNEC and SCLC). Combined thymoma or thymic carcinoma and NET (usually high-grade NE carcinomas) rarely occur. It may be impossible to assess the exact origin of these tumors in the presence of large and centrally located NETs, infiltrating the mediastinal pleura and lung on one side and the mediastinal tissues (including thymus) on the other. In fact, no single marker of NET cells is absolutely specific to lung *versus* thymic derivation, or even versus mediastinal metastases of gastroenteropancreatic NETs (except for some hormonally active tumors).

Diagnostic criteria

At variance with lung carcinoids, primary thymic carcinoids are mostly ACs, being TCs extremely rare. As for their pulmonary counterpart, pure morphological criteria are the only appropriate tools for identifying the different histotypes, combining architectural (organoid versus diffuse growth) and cytological features (cell size, atypia, mitotic

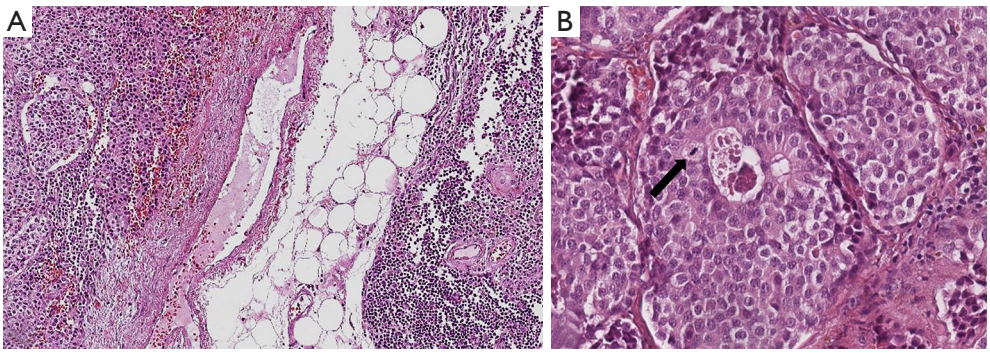

Figure 1 Hematoxylin and eosin (H&E) images of an atypical thymic carcinoid. (A) Low-power image (40×) showing an atypical thymic carcinoid next to non-neoplastic atrophic thymic parenchyma; (B) intermediate-power image (200×) showing a mitosis (arrow) close to focal necrosis.

count, necrosis) (*Figure 1A,B*). Apart from the two forms of carcinoids, LCNEC has been reclassified from the group of large cell carcinomas to the new group of NE neoplasms and is defined by large atypical cells, usually arranged in nests and trabecula, possibly forming rosette-like structures, and with irregular nuclei with granular chromatin and conspicuous nucleoli (2). Necrosis is often more extensive and mitotic count exceeds 10 per 10 high power fields even in cases that maintain a well differentiated/organoid morphology. Paraneoplastic symptoms due to abnormal hormones production, usually ACTH, are frequent and have been reported also in thymic LCNEC (3). Combined cases of thymoma or thymic carcinoma and NET are rarely observed in the thymus and are characterized by the coexistence of a NE component along with one of thymic tumor types. Since neuroendocrine differentiation in both thymomas and thymic carcinomas is possible (4,5), diagnosis of a coexisting neoplasm requires the identification of morphological features of both tumors (6-8). The pathogenesis of such combined thymic tumors is not fully understood, although genetic data from other locations (e.g., lung or pancreas) mostly showed a similar genetic profile in the two components, suggesting a divergent differentiation of a single neoplasia.

Most diagnostic difficulties derive from small biopsies or cytological samples, in which the scant amount of tumor cells may hamper a correct interpretation. While the definition of the NE nature may not be difficult, thanks to the demonstration of specific NE markers like synaptophysin and chromogranin, and the lack of high molecular weight cytokeratin expression in all NE tumors, regardless of their location, the definition of the histotype is less reliable in such materials, especially the separation of low-grade carcinoids from high-grade NE carcinomas. The data mentioned above, together with our clinical experience, suggest that the most useful diagnostic marker is Ki67 (as reported in the lung) (9). This marker maintains its nuclear distribution even in tumor areas with crushing artifacts, as commonly observed in biopsies, thus allowing to distinguish carcinoids from HGNEC.

There is no specific grading system for thymic neuroendocrine neoplasms and the prognostic value of lung NETs classification criteria in thymic lesions has not been demonstrated yet.

The literature data indicate that, although the evaluation of Ki67 proliferation index has not been officially incorporated in the WHO criteria for thymic NETs (nor for pulmonary NETs), it is a reliable and useful tool to predict their behavior. In fact, it has been proposed as an additional parameter (combined with the two "official" tools, i.e., mitotic count and necrosis) for grading lung NETs (10). Probably due to their rarity, a similar study for thymic NET grading has not been performed yet. Nevertheless, the proposed cutoffs of 4 and 25% for taking low-intermediate-high grade lung NETs apart, also seem to be applicable to thymic NE neoplasms.

Genetics

Although a large number of genetic studies on pulmonary NETs have recently been published, including NGS data (11,12), thymic NETs have been rarely addressed. In carcinoids, *RB1* and *TP53* mutations were uncommon, whereas *MEN1* mutations are known to occur in thymic NETs, along with *CDKN2A* alterations (13). High-grade carcinomas (LCNEC and SCLC) shared gene mutations

with similar tumors of other locations (e.g., lung), including *RB1*, *TP53*, *PTEN* (14), as well as amplifications of MYC gene (15). In a genetic study of 73 cases from multiple institutions, 13 TCs, 40 ACs, and 20 HGNECs were investigated. Chromosomal imbalances were identified at increasing mean numbers per tumor from 0.8 in TCs to 1.1 in AC cases, up to 4.7 in HGNECs (also the percentage of aberrant cases increased from 31%, to 44% and 75% in TCs, ACs and HGNECs, respectively). The most frequently detected genetic changes in both carcinoids and HGNECs were gains at the *MYC* gene locus (8q24) (15). Whole exome sequencing of a series of 9 thymic NETs with ectopic ACTH secretion syndrome identified three genes (*HRAS*, *PAK1* and *MEN1*) potentially involved in tumorigenesis (16).

Predictive biomarkers

Predictors of response to specific treatments (including mTOR pathway alterations, YY1 mutations and SSTR expression), as reported in pulmonary and gastroenteropancreatic NETs (17,18), have not been extensively investigated in thymic NETs, except for single case reports.

Response to treatment with receptor tyrosine kinases inhibitors (sunitinib and imatinib) has been reported in thymic NET (19,20). mTOR pathway inhibitors, such as everolimus, have shown efficacy in NET of multiple sites and seem promising also in thymic neuroendocrine neoplasms (21). Recently, expression of five potential predictive biomarkers (CD52, CD22, CD26, EG5 and IGF-1R) has been evaluated in a series of 5 thymic carcinoids identifying only rare expression of CD22 and EG5 (22).

Conclusions

Although the current classification of thymic NETs reflects tumor biology and it is prognostically relevant, accepted worldwide and familiar to clinicians, an improved homogenization or better integration of lung, thymic, gastrointestinal and pancreatic NET classifications would be highly welcome, at least in terms of terminology and histological categories.

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Footnote

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