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Medullary Thyroid Carcinoma in the IARC/WHO Neuroendocrine Schema

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Medullary thyroid carcinoma (MTC) is a neuroendocrine neoplasm derived from the calcitonin-producing parafollicular C cells of the thyroid. Like other neuroendocrine cells, C cells can be hyperplastic in situations where there is physiological stimulation. They can also proliferate in patients with genetic predisposition to neuroendocrine neoplasia; early lesions, classified as "hyperplasia," are actually precursor lesions of transformed cells that give rise to progressive neoplasia known as MTC. A Linnaean classification would place most MTCs as epithelial well-differentiated neuroendocrine neoplasms (NENs), which are known as neuroendocrine tumors (NETs) in the most recent IARC/WHO schema [1].

In this issue of Endocrine Pathology, four papers advance our knowledge of this disease, providing the opportunity to reconsider the spectrum of these tumors, their classification, and their clinical management, as well as shedding light on the inconsistencies of current NEN classifications.

Because of their location within an endocrine gland, MTCs have not been widely included in discussions of NENs and they have escaped the concept of grading until recently. However, in the last two years, three papers have brought to the fore a proposal for grading of these tumors. An initial proposal was for a two-tiered grading system that defined high-grade MTCs as those with a mitotic count ≥ 5 mitoses per 10 high-power fields (HPF) and/or the presence of tumor necrosis [2]. A separate proposal was for a three-tiered grading system that defined low-grade MTCs as those with < 3 mitoses per 2 mm^2 (approximately equivalent to 10 HPF on many microscopes), a Ki67 labeling index $< 3\%$, and no necrosis; intermediate-grade MTCs as those with a mitotic count of 3–20 per 2 mm^2 or a Ki67 labeling index of 3–20% with no necrosis, or with low proliferative activity (mitoses or Ki67) but with necrosis; and high-grade MTCs as those with intermediate proliferative activity (3–20 mitoses per 2 mm^2 and/or 3–20% Ki67) with necrosis or high proliferative activity (> 20 mitoses per 2 mm^2 and/or $> 20\%$ Ki67) with or without necrosis [1, 3]. To address the discrepancy between these two contemporaneous proposals, the two groups collaborated on a multi-institution study of 327 MTC patients from five international medical centers that included the two original study cohorts; using extensive statistical analyses, they identified as the best system a two-tiered grading scheme, termed the International Medullary Thyroid Carcinoma Grading System (IMTCGS), in which high-grade tumors had at least one high-grade feature: a mitotic count ≥ 5 per 2 mm^2, a Ki67 labeling index $\geq 5\%$, or the presence of tumor necrosis [4]. IMTCGS grade was shown to be an independent predictor of recurrence-free and disease-specific survival in multivariate analyses that included most known prognostic parameters.

In this issue of Endocrine Pathology, Vissio et al. evaluate the clinical role of these systems in an independent cohort of 111 MTCs [5]. They report that necrosis alone correlates with tumor relapse; there was no correlation between recurrence and either measure of proliferation (mitotic count or Ki67 labeling index), but the combinations of all parameters according to all three grading systems showed the classification of "high-grade" MTCs as significantly associated with disease recurrence in all systems. Importantly, the IMTCGS was the only one that could predict disease-free survival with statistical significance, including in a subgroup of sporadic MTCs, however none of the three systems predicted overall survival in their validation cohort. In a separate paper, Williams et al. show good interobserver reproducibility of IMTCGS grade [6].

The cumulative findings raise questions about the grading of well differentiated epithelial NENs at various sites. While

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a three-tiered grading system has been long endorsed as the accepted approach for gastroenteropancreatic (GEP) NETs, the cut-off for the distinction between G1 and G2 was arbitrarily changed between the 4th and 5th editions of the WHO. There remain questions about the correct cut-offs for lung and thymic NETs, and in other tissues such as pituitary, cell type is more important than "grade." However, the need for consistency is exemplified by the not uncommon situation in which a metastatic epithelial NEN of unknown primary site is identified in a biopsy of liver, lymph node, bone, or other tissue. Indeed, one might reasonably question the need for a specific "grade"; most proliferation measures including mitotic counts and Ki67 labeling indices are continuous variables that clearly have limitations when cut-offs are applied. As an example, a GEP-NET with a Ki67 of 4% is not likely to have the same prognosis as a GEP-NET with a Ki67 of 19% but both are G2 tumors. Perhaps it is time to consider using these parameters as continuous variables without the artificial cut-offs that may provide statistical evidence but might well be misleading in an individual case.

Tumor proliferation and necrosis are not the only critical parameters in the prediction of outcome in MTCs. The impact of vascular invasion (angioinvasion) in the prediction tumor recurrence/metastasis [7] remained unexplored in most recent series that have focused on tumor grading. Moreover, the need for a "big-picture" approach to prognosis and management of patients is highlighted in the paper by Le et al. from Japan [8]. These authors collected 2526 MTC patients from the Surveillance, Epidemiology, and End Results (SEER) database who fulfilled their inclusion criteria to build a prognostic model. They developed a risk table including age, gender, tumor size, extrathyroidal extension, and lymph node metastasis. They arrived at a final model that identifies three risk groups of patients with significant differences in the risk of both metastasis and survival. This work further points out that pathology grading is not the only prognostic factor for patients with MTC, as is the case in other NENs.

Similar to the status of vascular invasion and grade, tumor subtyping seems to matter in dynamic risk stratification of MTC. An interesting case prompted a review of amphicrine MTCs by Khandakar et al. [9]. This review of the literature documents the rare cases that have been reported and uses the current case to characterize MUC expression profiles in this unusual entity. This paper raises the important subject of the distinction between mixed neuroendocrine and non-neuroendocrine neoplasms (MiNENs) composed of two populations of cells, as exemplified by mixed medullary and follicular/papillary carcinomas, and tumors with a homogeneous population of tumor cells that show dual differentiation, known as amphicrine tumors that express MUC1, MUC5AC, and MUC6.

In all this, there remains a fundamental challenge that has not been addressed. There are high-grade MTCs that resemble spindle cell or even small cell carcinomas. If we are to continue the effort to consolidate and unify all epithelial NENs in a single framework, we must also consider the importance of the word "carcinoma" in this context. How will we distinguish the poorly differentiated epithelial NENs that are true neuroendocrine carcinomas in the thyroid, and will we be able to implement a change in nomenclature to align C cell NETs of the thyroid into the NET terminology where the majority belong? Or do these tumors prove the fallacy of the current WHO proposal for this specific distinction that has been adopted with success in most other locations?

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Declarations

Competing Interests The authors declare no competing interests.

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