Pulmonary neuroendocrine carcinomas—evidence for a spectrum of differentiation

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In this issue, Pelosi and colleagues present the results of a gene alteration analysis of a large series of pulmonary neuroendocrine carcinomas. This study provides molecular support for the concept that carcinoid tumors can transform into high-grade neuroendocrine carcinomas through the acquisition of additional molecular alterations. This concept challenges the current and widely held belief that carcinoid tumors are different histogenetic entities from the high-grade neuroendocrine carcinomas thereby denying the existence of any transitional forms.

Neuroendocrine carcinomas of the lung are a group of tumors that originate from the diffuse neuroendocrine system of the bronchopulmonary tree. These neoplasms have been the subject of intense debate for more than a century due to divergent opinions on the concept and classification of these tumors and their relation to biologic behavior. Hence, the literature to date contains numerous proposals for histopathologic classification. The current World Health Organization (WHO) Classification of Lung Tumors [1] separates pulmonary neuroendocrine carcinomas into four major categories based on a combination of tumor morphology, mitotic activity, and presence of necrosis: carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma, and small cell carcinoma. Clinically, these four categories translate into a three-tiered grading system with carcinoid tumor representing the low grade, atypical carcinoid tumor the intermediate grade, and large cell neuroendocrine carcinoma and small cell carcinoma the high-grade end of the malignant spectrum [1]. This prognostic categorization is reflected in the clinical management of the patients: while those with carcinoid tumor are

treated with surgery alone, individuals with atypical carcinoid often require additional systemic therapy and management of patients with high-grade tumors usually includes a combination of surgery and systemic therapy or systemic therapy alone [2]. Although the WHO classification of pulmonary neuroendocrine carcinomas is currently the most widely used system, this schema is not without controversy, largely due to the rigid diagnostic criteria applied to each category and problems with reproducibility and prognostic efficacy [3]. Additionally, current concepts of the pathogenesis of these tumors support the idea that carcinoid tumors are independent neoplasms that should not be considered progenitor lesions that can transform into high-grade tumors. This view is largely based on studies investigating the genomic landscape of these tumors, the results of which have revealed different mutational patterns in the carcinoid group compared to the high-grade tumors [4–6].

Contrary to that, the current study by Pelosi et al. provides evidence of widely shared genetic alterations across all subtypes of pulmonary neuroendocrine carcinomas supporting the concept that carcinoid tumors can progress towards high-grade lesions as a result of accumulation of genetic damage during tumor progression. Their results confirm that “secondary” high-grade neuroendocrine carcinomas can indeed arise from lower-grade progenitor lesions supporting similar observations in other organ systems. This finding elegantly underscores a number of important prior observations that would support this notion. For instance, tumors that by current diagnostic criteria are composed of more than one pattern or that show transitional forms within the same tumor mass have long been recognized in the literature [7, 8]. In addition, neoplasms that show low-grade morphologic features but have mitotic counts exceeding the specified cutoff have not only been described in other organ systems but are increasingly also observed in the lung [9]. In a similar manner, cases of pulmonary carcinoid tumors have been documented that show higher proliferation rates in their metastatic sites than in the primary tumor [10]. Furthermore, any practicing pathologist is only too aware of the diagnostic intricacies

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when it comes to distinguishing atypical carcinoid from large cell neuroendocrine carcinoma or separating large cell neuroendocrine carcinoma from small cell carcinoma in certain cases. All these examples seem to provide the morphologic basis in support of a concept of tumor transformation among this group of neoplasms.

The results of the analysis by Pelosi et al. also expose two other important issues. First, evidence of the ability of carcinoid tumors to transform into high-grade tumors raises concerns about the current terminology of pulmonary neuroendocrine carcinomas as stipulated by the WHO classification [1]. Use of outdated terminology such as “carcinoid tumor” and “atypical carcinoid tumor” to describe lesions that have at least low or intermediate grade malignant potential should best be avoided and replaced by a nomenclature highlighting their malignant nature, i.e., “low grade neuroendocrine carcinoma” and “intermediate grade neuroendocrine carcinoma”, respectively. Failure to do so will not only misguide clinicians but also give patients a false sense of security. Second, the current classification and grading of pulmonary neuroendocrine carcinomas according to the WHO schema (1) is suboptimal as it fails to appropriately classify a significant number of tumors that may not unequivocally fall into the existing categories. Misclassification of such tumors may result in adverse consequences for patient management and prognosis. Hence, a novel and more flexible approach, perhaps with greater emphasis on proliferative activity rather than cytologic detail to distinguish between tumor subtypes should be explored for use in future classifications.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

References

1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson A (eds) (2015) Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC Press, Lyon

2. Gridelli C, Rossi A, Airoma G, Bianco R, Costanzo R, Daniele B, Chiara GD, Grimaldi G, Intelli L, Maione P, Morabito A, Piantadosi FV, Riccardi F (2013) Treatment of pulmonary neuroendocrine tumours: state of the art and future developments. *Cancer Treat Rev* 39(5):466–472. <https://doi.org/10.1016/j.ctrv.2012.06.012>
3. Moran CA, Suster S, Coppola D, Wick MR (2009) Neuroendocrine carcinomas of the lung: a critical analysis. *Am J Clin Pathol* 131(2): 206–221. <https://doi.org/10.1309/AJCP9H10TMUCSKQW>
4. Fernandez-Cuesta L, Peifer M, Lu X, Sun R, Ozretić L, Seidel D, Zander T, Leenders F, George J, Müller C, Dahmen I, Pinther B, Bosco G, Konrad K, Altmüller J, Nürnberg P, Achter V, Lang U, Schneider PM, Bogus M, Soltermann A, Brustugun OT, Helland Å, Solberg S, Lund-Iversen M, Ansen S, Støelben E, Wright GM, Russell P, Wainer Z, Solomon B, Field JK, Hyde R, Davies MPA, Heukamp LC, Petersen I, Perner S, Lovly CM, Cappuzzo F, Travis WD, Wolf J, Vingron M, Brambilla E, Haas SA, Büttner R, Thomas RK (2014) Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. *Nat Commun* 5:3518. <https://doi.org/10.1038/ncomms4518>
5. Sampietro G, Tomasic G, Collini P, Biganzoli E, Boracchi P, Bidoli P, Pilotti S (2000) Gene product immunophenotyping of neuroendocrine lung tumors. No linking evidence between carcinoids and small-cell lung carcinomas suggested by multivariate statistical analysis. *Appl Immunohistochem Mol Morphol* 8(1):49–56. <https://doi.org/10.1097/00129039-200003000-00008>
6. Peifer M, Fernández-Cuesta L, Sos ML, et al (2012) Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* 44(10):1104–1110. <https://doi.org/10.1038/ng.2396>
7. Moran CA, Suster S (2000) Thymic neuroendocrine carcinomas with combined features ranging from well-differentiated (carcinoid) to small cell carcinoma. A clinicopathologic and immunohistochemical study of 11 cases. *Am J Clin Pathol* 113(3):345–350. <https://doi.org/10.1309/Q01U-60BL-VEV4-TWR1>
8. Fabbri A, Cossa M, Sonzogni A, Bidoli P, Canova S, Cortinovis D, Abbate MI, Calabrese F, Nannini N, Lunardi F, Rossi G, La Rosa S, Capella C, Tamborini E, Perrone F, Busico A, Capone I, Valeri B, Pastorino U, Albini A, Pelosi G (2017) Thymus neuroendocrine tumors with CTNNB1 gene mutations, disarrayed β -catenin expression, and dual intra-tumor Ki-67 labeling index compartmentalization challenge the concept of secondary high-grade neuroendocrine tumor: a paradigm shift. *Virchows Arch* 471(1):31–47. <https://doi.org/10.1007/s00428-017-2130-2>
9. Quinn AM, Chaturvedi A, Nonaka D (2017) High-grade neuroendocrine carcinoma of the lung with carcinoid morphology: a study of 12 cases. *Am J Surg Pathol* 41(2):263–270. <https://doi.org/10.1097/PAS.0000000000000767>
10. Desmeules P, Sabari J, Santos-Zabala ML, Litvak AM, Pietanza MC, Poirier JT, Rudin CM, Klimstra DS, Travis W, Rekhtman N (2017) Metastatic lung carcinoid tumors: evidence of proliferation rate progression at metastatic sites. *Mod Pathol* 30:475A