Journal of Clinical and Translational Pathology **2022** vol. 2(1) | 18–22
DOI: 10.14218/JCTP.2022.00008

Review Article

Differential Diagnosis of High-grade Neuroendocrine Neoplasms in the Digestive System

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Received: February 28, 2022 | **Revised:** March 7, 2022 | **Accepted:** March 8, 2022 | **Published:** March 18, 2022

Abstract

The current World Health Organization classification of neuroendocrine neoplasms of the digestive system separates these tumors into two major categories: well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. These two groups are considered fundamentally different tumors, with different molecular abnormalities, prognoses, and treatment strategies. The cornerstone of the classification is proliferative rate of the tumor cells, as assessed by mitotic rate and Ki-67 labeling index. However, the range of mitotic rate and Ki-67 labeling index overlaps between high-grade, well-differentiated neuroendocrine tumor and poorly differentiated neuroendocrine carcinoma. In order to accurately separate these two entities, a systematic approach is necessary, which includes attention to the morphology, accurate assessment of the proliferative rate, review of any additional pathology materials, judicial use of immunohistochemistry, and correlation with clinical features. With this approach, the majority of tumors can be correctly classified as either high-grade, well-differentiated neuroendocrine tumor or poorly differentiated neuroendocrine carcinoma. This review aimed to evaluate the current World Health Organization classification system for neuroendocrine neoplasms of the digestive system, focusing on the differentiation between well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas.

Citation of this article: Yang Z. Differential Diagnosis of High-grade Neuroendocrine Neoplasms in the Digestive System. J Clin Transl Pathol 2022;2(1):18–22. doi: 10.14218/JCTP.2022.00008.

Introduction

In the current (2019) World Health Organization (WHO) classification of neuroendocrine neoplasms (NENs) of the digestive system, NENs are separated into two major categories: well-differentiated neuroendocrine tumors (WDNET) and poorly differentiated neuroendocrine carcinomas (PDNEC, i.e., small cell carcinoma or large cell NEC). The former is further separated into three grades (G1/low, G2/intermediate, and G3/high) based on mitotic rate and/or Ki-67 labeling index (Table 1).[1] However, the range of mitotic rate (>20 mitoses/2mm^2) and Ki-67 labeling index (>20%) overlaps between WDNET G3 and PDNEC, thus creating confusion regarding how to differentiate these two types of high-grade NENs.

Both categories were lumped together as high-grade poorly differentiated neuroendocrine carcinoma (PDNEC) in the previous (2010) WHO classification.[2] Accumulating evidence suggested that these were fundamentally two different types of tumors with divergent molecular pathways,[3] and PDNEC showed much worse patient survival than WDNET G3.[3,4] Two studies conducted in Europe found that WDNET (or NEN with Ki-67 index <55%) responded poorly to platinum-based chemotherapy while showing longer survival than PDNEC (or NEN with Ki-67 index >55%).[5,6] Partially based on these studies, in the current National Comprehensive Cancer Network guidelines, the mainstay treatment for PDNEC is systemic platinum-based chemotherapy. For WDNET G3, the treatment is more diverse, and tumors with favorable biology (e.g. Ki-67 index <55%) are usually offered somatostatin analogue, peptide receptor radionuclide therapy, or inhibitors of mammalian target of rapamycin, similar to lower grade WDNET; while tumors with unfavorable biology (e.g. Ki-67 index ≥ 55%, rapid tumor growth, etc.) may be considered for systemic chemotherapy.[7] Thus from a clinical point of view, the distinction is very important for prognostication and optimal patient management.

This review focuses on a systematic approach for this critical differentiation, which includes assessment of morphology, proliferative rate, other pathology material, and use of selected immunohistochemical markers. This approach is usually sufficient to separate most tumors into one of these two categories.

Tumor morphology

Evaluation of NENs always starts from assessment of morphology based on routine hematoxylin and eosin (H&E) staining. WDNETs often show organoid architecture, such as acinar, trabecular, gyriform, nested, or peripheral pali-

Keywords: Neuroendocrine tumors; Neuroendocrine carcinoma; Pancreas; Small intestine.

Abbreviations: ATRX, alpha thalassemia/mental retardation syndrome X-linked; DAXX, death domain associated protein; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; PDNEC, poorly differentiated neuroendocrine carcinoma; Rb, retinoblastoma; SSTR, somatostatin receptor; WDNET, well-differentiated neuroendocrine tumor; WHO, World Health Organization.

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Table 1. Current World Health Organization classification of neuroendocrine neoplasms in the digestive system[1]

Terminology	Differentiation	Morphology	Grade	Mitotic rate (mitoses/2mm^2)	Ki-67 Index
NET, G1	Well-differentiated	Organoid pattern, rich capillary	Low	<2	<3%
NET, G2	Well-differentiated	Organoid pattern, rich capillary	Intermediate	2–20	3–20%
NET, G3	Well-differentiated	Organoid pattern, rich capillary	High	>20	>20%
SCNEC	Poorly differentiated	Diffuse/solid growth, tumor necrosis, high nuclear:cytoplasmic ratio, inconspicuous nucleoli	High	>20	>20%
LCNEC	Poorly differentiated	Diffuse/solid growth, tumor necrosis, abundant cytoplasm, large nuclei, vesicular chromatin, prominent nucleoli	High	>20	>20%
MiNEN	Well- or poorly differentiated		Variable	Variable	Variable

NET, neuroendocrine tumor; SCNEC, small cell neuroendocrine carcinoma; LCNEC, large cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm.

sading. The organoid architecture is typically maintained in WDNET G3, though there may be increased cellularity and more solid nests. The area between the tumor nests is usually rich in capillaries (Fig. 1a, Table 1). The tumor cells are more or less uniform, with the classic salt-and-pepper chromatin pattern.[8,9] Single cell tumor necrosis is common, and large areas of tumor necrosis are rare.[10]

In contrast, PDNECs often show diffuse or solid growth without forming any particular architectural pattern. A large area of tumor necrosis is more common. Small cell carcinoma has very high nuclear to cytoplasmic ratio with finely granular chromatin, while large cell neuroendocrine carcinoma shows more abundant cytoplasm, larger nuclei, with vesicular chromatin patterns and prominent nucleoli (Table 1). Pseudorosettes may also be present (Fig. 2a).[8,9]

Proliferative rate

Accurate assessment of proliferative rate (mitotic rate and Ki-67 labeling index) is the cornerstone of modern classification of NENs. It is recommended that tumor cell mitoses be counted in 10 mm^2 area (42 high-power fields with a 10×/22 mm eyepiece), and the total number of mitoses be divided by 5 to arrive at a mitotic rate per 2 mm^2.[8,11] Only the unequivocal mitotic figures should be counted, which excludes pyknotic nuclei, apoptotic bodies, and darkly stained nuclei. The mitosis-specific immunohistochemical marker, phosphohistone H3, was validated in a number of tumor types including pancreatic NET,[12,13] but this has not been widely used in routine practice. Ki-67 labeling index is expressed as a percentage of the positively stained nuclei.

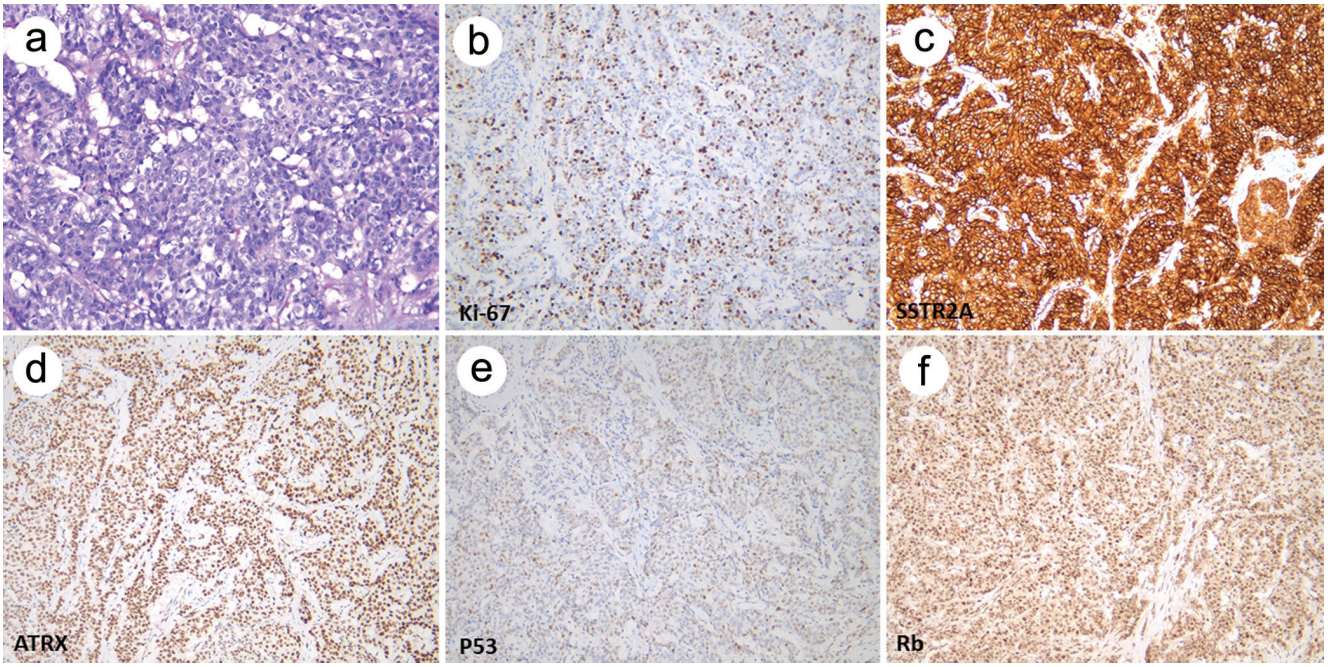

Fig. 1. High-grade (G3), well-differentiated pancreatic neuroendocrine tumor. (a) Hematoxylin and eosin staining of tumor showing an organoid pattern rich in capillaries (original magnification, 200×). (b) Ki-67 labeling of the tumor. (c) Immunohistochemical staining of somatostatin receptor 2A (SSTR2A). (d) Nuclear staining of alpha thalassemia/mental retardation syndrome X-linked (ATRX). (e) Weak, heterogeneous nuclear immunostaining pattern of p53, consistent with wild type p53. (f) Nuclear staining of retinoblastoma (Rb). (Immunohistochemistry, original magnification 100×).

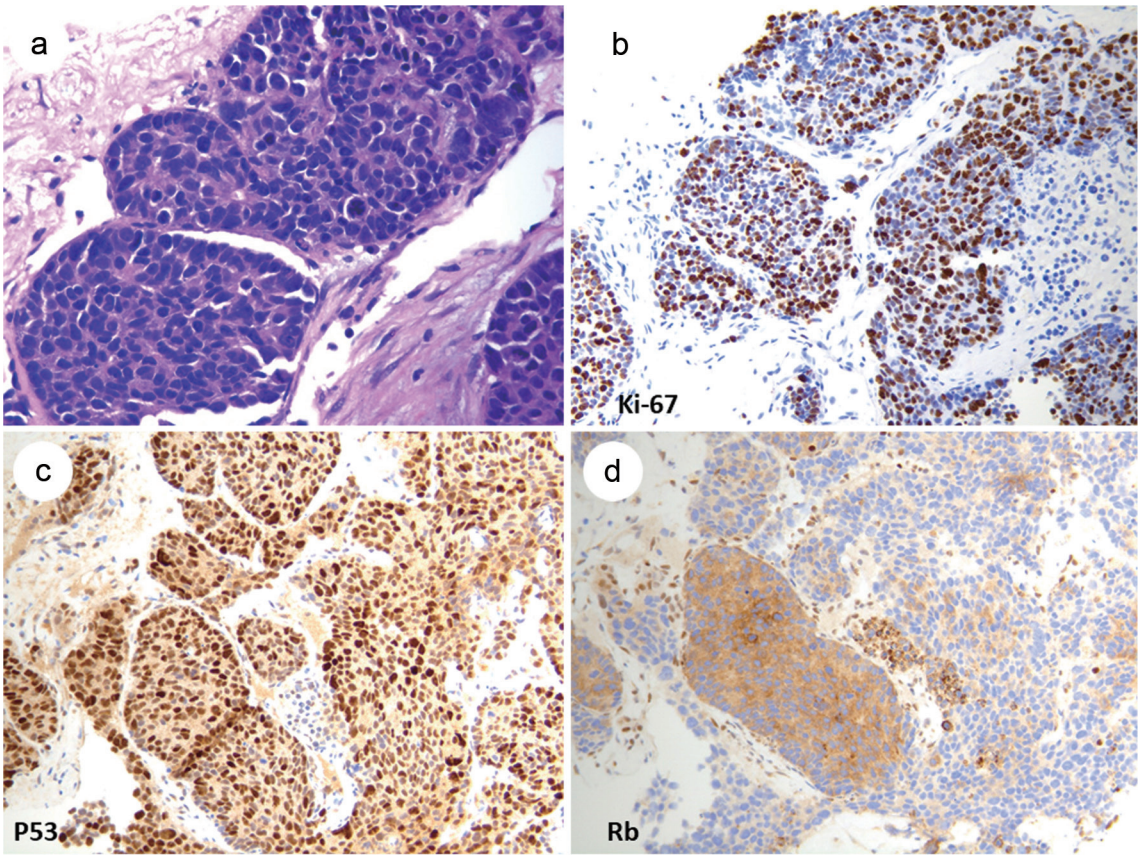

Fig. 2. Poorly differentiated, metastatic neuroendocrine carcinoma (large cell neuroendocrine carcinoma) in a liver biopsy. The patient had a history of colonic adenocarcinoma, now with widely metastatic disease. (a) Hematoxylin and eosin staining of the tumor showing solid nests with pseudorosettes and fibrotic stroma (original magnification, 400×). (b) Ki-67 labeling of the tumor. (c) Strong, diffuse nuclear immunostaining of p53, consistent with mutant p53. (d) Absence of nuclear Rb immunostaining. (Immunohistochemistry, original magnification 200×).

The WHO recommends counting at least 500–2,000 tumor cells in the highest labeling area (hot spot).[1] A comparison study concluded that counting by visual inspection (so-called "eyeballing"), though very quick, was not accurate. Unless an imaging analysis software is available, the authors recommended taking a color image, usually at intermediate power (20× objective), and manually counting on a paper printout.[8,14,15]

Despite the overlap of proliferative rate, which makes it a less reliable parameter, mitotic rates for WDNET G3 often fall into the G2 range (2-20/2 mm^2), thus was previously considered a mixed grade tumor, with Ki-67 index generally on the lower side (typically less than 55%) (Fig. 1b). PDNEC often shows a much higher mitotic rate (>20/2 mm^2) and Ki-67 index (>55%) (Fig. 2b).[4,16,17] A preliminary study found that a cutoff of 25 mitoses/2 mm^2 and Ki-67 index of 65% provides better separation between WDNET G3 and PDNEC.[18] The proliferative rate should be assessed in pretreatment specimens, and even in PDNEC, treated tumors may show deceptively low Ki-67 index.[19]

Previous or concurrent tumors

Intratumoral and intertumoral heterogeneity is a prominent feature of WDNETs, which show different tumor grades in different areas of the same tumor, as well as between primary and metastatic sites (lymph nodes, liver, etc.).[20–22] When WDNETs metastasize (usually to the liver), about one third show grade progression.[13] On the contrary, PDNECs generally maintain the high-grade features regardless of whether they are primary tumors or metastases. A subset of PDNEC belongs to the mixed neuroendocrine-non-neuroendocrine neoplasm category, with admixed adenocarcinoma or squamous cell carcinoma components.[17,23]

The above observations can be useful in the differentiation between WDNETs and PDNECs. When there is pronounced grade discrepancy in different areas of the same tumor, or between the primary tumor and metastatic site, or if there is a history of lower grade NET, a diagnosis of WDNET is favored. When there is a component of non-neuroendocrine carcinoma such as adenocarcinoma or squamous cell carcinoma from the same organ, a diagnosis of PDNEC is generally the rule.[16]

Ancillary immunohistochemical markers

Enormous progress has been made in our understanding of the molecular pathway of WDNETs in the pancreas. The multiple endocrine neoplasia type 1 (*MEN1*) gene plays a central role in the tumorigenesis of pancreatic WDNETs, and telomere maintenance genes, for example death domain associated protein (*DAXX*) and alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) are the most commonly mutated genes, occurring in more than 40% of cases.[24,25] Mutations in *DAXX* and *ATRX* are mutually exclusive, and are mostly frameshift mutations whose loss of

expression at the protein level can easily be detected by immunohistochemistry.[16,24] However, molecular changes in WDNETs of other organs are less well defined, and no reliable immunomarkers are available for routine use.

PDNECs of the pancreas show a very different spectrum of molecular abnormalities, and the most common changes involve the following proteins: p53, retinoblastoma (Rb), B-cell CLL/Lymphoma 2 (Bcl2), p16, Kirsten rat sarcoma virus oncogene homolog (KRAS), and mothers against decapentaplegic homolog 4 (SMAD4). These changes are similar to those seen in pancreatic adenocarcinoma though with slightly different frequency, but are rarely seen in WDNETs. This supports the concept that PDNEC and adenocarcinoma have a shared origin.[3,26] By immunohistochemistry, p53 missense mutations usually show diffuse, strong nuclear staining, and null mutations show complete loss of staining. Rb mutations generally show loss of nuclear expression. Similar changes are also observed in PDNECs of other organs.[26]

Thus, when a combination of morphology, proliferative rate, and review of other pathology material cannot distinguish between WDNET and PDNEC, especially in the pancreas, immunohistochemistry for DAXX, ATRX, p53 and Rb may be performed to aid in the differentiation. Loss of expression of either DAXX or ATRX in the pancreas supports a diagnosis of WDNET, though retained expression of both proteins does not exclude that diagnosis (Fig. 1d). Weak heterogeneous staining for p53 and retained nuclear expression of Rb is more typical of WDNET (Fig. 1e, f), while diffuse, strong or complete absence of p53 expression and/or loss of Rb expression supports a diagnosis of PDNECs (Fig. 2c, d).[16]

Somatostatin receptor (SSTR), whose expression can be detected by immunohistochemistry, octreotide scan, or PET/CT scan,[27] is often strongly expressed in WDNET (Fig. 1c) but shows much less staining in PDNEC.[18,28,29] As mentioned previously, there is no specific marker for gastrointestinal WDNET outside of pancreas, thus immunohistochemical staining for DAXX or ATRX plays no role in those cases. In non-pancreatic NENs, SSTR immunohistochemistry can be particularly helpful. Diffuse, strong SSTR expression supports a diagnosis of WDNET, while PDNEC often shows limited or negative expression. Similar to those in pancreas, non-pancreatic PDNECs also show frequent p53 mutation and/or Rb loss.[18,28,29]

Challenging scenarios

Using the above approach, Tang *et al*.[16] were able to correctly classify 32 of 33 pancreatic high-grade NENs, with the remaining one case as indeterminate. The challenges are mostly due to discordance between morphology and molecular changes. As previously mentioned, even for pancreatic WDNETs, loss of expression of DAXX or ATRX occurs in about 40% of cases, and there is no readily detectable immunomarker for the remaining (>50%) pancreatic WDNETs, as well as WDNETs of other organs.[24] In addition, there have been several reports that a small number of morphologically-classified WDNETs show aberrant staining patterns and gene mutations in p53 and/or Rb.[18,24,25,30,31] In those cases, a tentative diagnosis of high-grade NEN may be rendered, and patient management is generally driven by Ki-67 index and clinical parameters.[7]

Conclusions

Differentiation between WDNET and PDNEC requires a systematic approach to assess the morphology, proliferative rate, current or prior pathology specimens, along with judicious use of immunohistochemistry or molecular data. With this approach, the majority of cases can be correctly diagnosed as either WDNET or PDNEC. In the small number of indeterminate cases, a diagnosis of high-grade NEN with accurate determination of Ki-67 index may be sufficient for clinical management.

Acknowledgments

The author would like to thank members of the pathology department at the University of Pennsylvania, especially the GI pathology group, for their support and collegiality. This manuscript was presented during the 7th Chinese American Pathologists Association Diagnostic Course on September 12, 2021, via virtual format.

Funding

The author declares no financial support to this manuscript.

Conflict of interest

Dr. Yang has been an editorial board member of *Journal of Clinical and Translational Pathology* since May 2021. The author has no other conflicts of interest related to this publication.

Author contributions

Dr. Yang is the sole author of this article.

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