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Review

Introduction to neuroendocrine neoplasms of the digestive system: definition and classification

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Summary

Neoplasms characterized by the expression of markers of neuroendocrine differentiation in neoplastic cells are defined neuroendocrine. This broad definition comprises tumors found at different sites of the body with similar morphology but different behavior and genetic background. From a clinical standpoint neuroendocrine neoplasms may be functioning, when they give rise to unregulated secretion of hormones. Functioning tumors account for about one-third of neuroendocrine neoplasms. From a pathological standpoint neuroendocrine neoplasm are classified by cancer category, cancer families/classes, cancer types, cancer grade and cancer stage. The category identifies the cancer major trait and thus defined as neuroendocrine neoplasia (NEN) to comprise all families/classes of neuroendocrine cancer. The cancer family/types are neuroendocrine tumors (NET) as well differentiated, and neuroendocrine carcinoma (NEC) as poorly differentiated forms. Cancer grade, based on proliferation measure by mitotic count and Ki-67%, and cancer stage, based on tumor size and invasion (T), node deposits (N) and distant metastases (M), complete the pathological classification. Site-specific differences are the rule. Still missing is a genetic classification tool to complement current pathological descriptors.

Key words: neuroendocrine neoplasia, NEN, NET, NEC, Ki-67%

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Introduction

Neuroendocrine neoplasms represent a category of neoplasms defined by neuroendocrine differentiation, at histology based on positive immunolabelling for chromogranin A and synaptophysin. Neuroendocrine neoplasms may arise anywhere in the body either from endocrine organs, nerve structures or from the so-called diffuse neuroendocrine system. More than half are found in the gastro-entero-pancreatic (GEP) tract and, though relatively rare, their incidence has been steadily increasing in the last three decades [1,2]. GEP neuroendocrine neoplasms are a distinct though heterogenous cancer category when considering their clinical behavior, morphology, specific types of cells involved, biological and genetic features. The classification of neuroendocrine neoplasms evolved along the last two decades to reflect our increased understanding of this disease including clinical and pathological classifications.

Classification principles

Clinical classification

Clinically NENs are separated into functioning and non-functioning.

Functioning neoplasms are less frequent, accounting for about one-third of GEP neuroendocrine neoplasms [2]. Functioning neuroendocrine neoplasms are characterized by specific clinical symptoms defined by unregulated hormonal production (e.g. hyper-insulinemic hypoglycemia determined by insulinoma). The largest fraction of functioning neoplasm account for well differentiated neoplasm, though paraneoplastic endocrine syndromes may associate with poorly differentiated forms. Non-functioning neuroendocrine neoplasms are more frequent composed of by tumor cells sometimes expressing hormones at immunohistochemistry but unable of unregulated release. Similar to any other epithelial neoplasms, clinical symptoms are determined by the effects of tumor mass and growth, including mucosal erosion, wall/nearby organs invasion and metastatic deposition [3], in turn reflecting tumor cell biology.

The distinction between functioning and non-functioning neoplasms is virtually impossible based on histology and may only be defined by clinical symptoms and blood tests. When considering well differentiated neoplasms, tumor cell types composing both functioning and non-functioning neuroendocrine neoplasms usually follow the physiological distribution of their non-neoplastic counterpart (e.g. enterochromaffin-like cells in gastric neuroendocrine neoplasms, somatostatin-producing D cells in duodenum and pancreatic neuroendocrine neoplasms).

Pathological classification

The pathological classification includes the definitions of cancer category, cancer families/classes, cancer types, cancer grade and cancer stage (Tab. I) [4]. Malignancy is implicit.

Cancer category

The category is defined as neuroendocrine neoplasia (NEN) to comprise all families/classes of neuroendocrine cancer. Neuroendocrine is defined when at least two markers of neuroendocrine differentiation (e.g. chromogranin A and synaptophysin) are both expressed in the vast majority of neoplastic cells. In case only a fraction of at least 30% of cancer cells are neuroendocrine in nature, the cancer category is defined as Mixed NEuroendocrine non-neuroendocrine Neoplasia (MiNEN).

Cancer families/classes

The class distinction is based on morphology and separates neuroendocrine neoplasms into well and poorly differentiated forms (WHO 2000) [5]. The well differentiated neoplasms are currently defined as neuroendocrine tumors (NET) and poorly differentiated neoplasms as neuroendocrine carcinoma (NEC) [6]. At histology NETs substantially reproduce the structural (when present) and cytological features of their non-neoplastic counterparts. NETs are characterized by an “organoid” structure (so defined as resembling Langerhans islets), variably organized in nests, trabeculae and acini made by epithelial cells with usually monomorphic nuclei, rare mitoses, in the absence of, or with only focal (spotty), necrosis (Fig. 1. A-E). The morphology of NETs overlaps at different anatomical sites of the digestive system. The site of origin may be defined only by the use of immunohistochemistry for site-specific transcription factors and/or hormones. Nonetheless, some growth patterns are more often observed for certain cell types at specific anatomical sites (e.g. solid islets for serotonin-producing enterochromaffin cell tumors of the small intestine).

The poorly differentiated neuroendocrine neoplasms, NECs, are characterized by the disorderly solid proliferation of severely atypical cells, with abundant/diffuse necrosis and evident, often atypical, mitoses (Fig. 1 F-J). Two variants are described: the small cell type characterized by large nuclei with salt and pepper chromatin and a thin rim of cytoplasm (i.e. high nucleus/cytoplasm ratio) and the large cell type with large nuclei with prominent nucleoli, salt and pepper chromatin and abundant cytoplasm.

Cancer types

In the digestive system, the NEN types overlap the Family/Class definitions, i.e. NET and NEC. At other anatomical site this may not be the case, e.g. in the lung well differentiated NENs are defined as carcinoid [7]. Variants are foreseen, e.g. the clear cell or cystic subtypes in pancreas NET.

Cancer grade

The current WHO classifications [6,8] adopt a three-tiers grading system (G1-G3) for NET. NEC are by default G3, the grade being not to be specified to avoid confusion vs NET G3 (Fig. 1). The currently adopted grading system for NETs is based on proliferation assessment with incremental ranges of mitosis and Ki67 index (Tab. I). This tool directly stems from the European Neuroendocrine Tumor Society (ENETS) proposal [9,10] that proved of prognostic significance and for this reason was subsequently adopted by WHO in 2010 [11]. The present grading system allows the identification of a NEN subgroup with a well differentiated morphology and G3 proliferative values, isolating the most aggressive NET (Fig. 1). NET G3 display significant differences when compared to NEC in somatostatin receptor expression (diffuse in NET, almost absent in NEC)

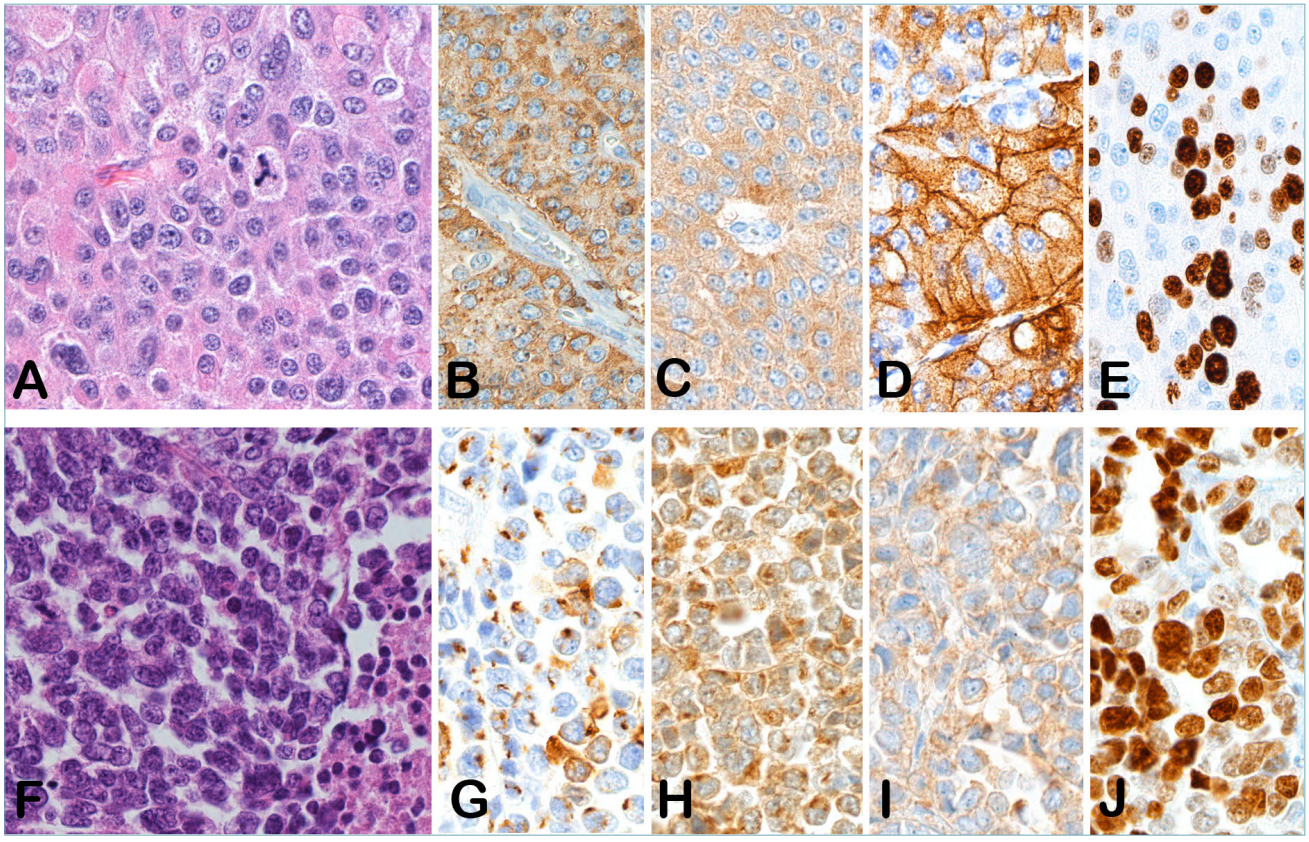

Figure 1. NET and NEC in the stomach: examples of high-grade NET G3 (A-E) and NEC (F-J). The NET G3 shows solid structure, in absence of necrosis in this case, and is made by relatively monomorphic cells with abundant cytoplasm, mildly irregular nuclei and moderate/severe atypia, atypical mitosis (A, center of the micrograph), intense immunoreactivity for chromogranin A (B), synaptophysin (C), somatostatin receptor type 2 (D) and high Ki-67 nuclear labelling (E, about 40%).The NEC, small cell type, shows a solid structure with abundant necrosis (F, lower right corner), and is made by severely atypical cells of medium-small size with scarce cytoplasm (G, AE1/AE2 dotted cytokeratin expression), diffuse chromogranin A (H, note some dots), synaptophysin (I) and sharply elevated Ki-67 nuclear labelling (J, about 90%). A, F H&E; B-E and G-J immunoperoxidase; magnification 400x.

Table I. Neuroendocrine Cancer Classification

Category	Type	Grade	Ki-67%[a]	Mitosis[b]	Stage
NEN	NET	G1	≤3	< 2	NET-specific & site-dependent
		G2	3-20	2-20	
		G3	> 20	> 20	
	NEC	G3	> 20	> 20	non-NE cancer & site-dependent
MiNEN[c]	na[c]	na[c]	na[c]	na[c]	non-NE cancer & site-dependent

NEN: neuroendocrine neoplasia; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; MiNEN: mixed neuroendocrine non-neuroendocrine neoplasm; non-NE: non-neuroendocrine; na: not available. [a] MIB1 clone, nuclear expression in % of cells in areas of highest labelling; [b] per $2mm^2$; [c] since non neuroendocrine pure, typing and grading of MiNEN are done for the neuroendocrine component as here described and for the non-neuroendocrine component according to the specific cancer category that is observed (adenocarcinoma or squamous cell carcinoma) [6].

prognosis (better in NET and invariably dismal in NEC) and in responsiveness to platinum-based chemotherapy (absent in NET, usually present in NEC).

Cancer stage

The Tumor Node Metastasis (TNM) staging tools are for NETs only and site-specific [12]. Developed following

the ENETS proposals [9,10], these are based on NET size and/or invasion for T definition, on the presence of one or more (depending on site) node deposits for N and on pathological evidence of distant metastases for M. NET staging tools differ from those adopted for the other digestive cancer which otherwise are to be used for NEC [6]. MiNEN are assimilated to non-neuroendocrine cancer and are staged according to the corresponding non-neuroendocrine cancer staging tools depending on site.

Conclusions

The current NEN classification and its pathological grading and staging tools are built to emphasize the profound difference existing between NET and NEC families. This distinction well mirrors differences in genetic background. NETs show a low number of gene alterations, low mutational burden and almost no involvement of classic cancer drivers, while NECs show a high degree of gene abnormality, most often involving classical drivers including *TP53* and *Rb*. Still missing is a genetic tool that may effectively complement or even surrogate the proven efficacy of current pathological descriptors.

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