COSA NENs guidelines

Chapter 2: Histopathology of Gastroenteropancreatic Neuroendocrine Neoplasms

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Practice Points

1. Classification of gastroenteropancreatic neuroendocrine neoplasms (NENs) has been standardised.
2. A well differentiated NEN is called a neuroendocrine tumour (NET) and a poorly differentiated NEN a neuroendocrine carcinoma (NEC).
3. Morphology of NENs is usually characteristic, but with some exceptions.
4. NETs need to be graded G1, G2 or G3 based on proliferation indices.
5. The Ki-67 index should be calculated by a manual count – eyeball 'guesstimates' are inaccurate.
6. NECs are by definition high grade.
7. Immunohistochemistry is chiefly required for confirmation of neuroendocrine differentiation, Ki-67 estimation and exclusion of differential diagnoses.
8. NET G3 and NEC are separate diseases with different molecular signatures.
9. Gastric NETs must be typed by the pathologist due to major differences in prognosis and treatment algorithms.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of uncommon epithelial or neuroectodermal neoplasms, characterised by variable differentiation towards neuroendocrine cells, and including well differentiated neuroendocrine tumours (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed tumours with neuroendocrine and non-neuroendocrine differentiation. They occur at many sites throughout the body. Historically, differences in terminology and classification schema at different sites have caused confusion, but recent changes in classifications aim to reduce inconsistency. This review pertains to gastroenteropancreatic NENs, including tumours previously known as carcinoid tumours of the gastrointestinal tract and pancreatic islet cell tumours.

Classification

The current classification of digestive system neuroendocrine neoplasms published in the WHO Classification of Tumours: Digestive System Tumours (5th ed, 2019) (a), shown in Table 1, is based on a common classification framework for neuroendocrine neoplasms proposed following a consensus conference held at the International Agency for Research on Cancer (IARC) in November 2017 (b). This consensus conference based its recommendations largely on the previously published WHO Classification of Tumours of Endocrine Organs (4th ed, 2017) which had refined the classification of pancreatic NENs.

NETs are divided into 3 grades, based on mitotic rate and Ki-67 index. The pancreatic and digestive system classifications are the same - endocrine pancreas is treated in Endocrine Tumours in the WHO classification series.

Terminology	Differentiation	Grade	Mitotic count[a] (mitoses/2mm2)	Ki-67 index[a]
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3-20%
NET, G3		High	>20	>20%
NEC, small cell type (SMNEC)	Poorly differentiated	High[b]	>20	>20%
NEC, large cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated[c]	Variable[c]	Variable	Variable

Table 1: WHO classification of neuroendocrine neoplasms of the digestive system and pancreas (a)(kk). LCNEC, large cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCNEC, small cell neuroendocrine carcinoma.

[a]Mitotic counts are to be expressed as the number of mitoses/2mm^2 (equalling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2mm^2 (i.e. in a total area of 10mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hotspots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category.

[b]Poorly differentiated NECs are not formally graded but are considered high-grade by definition.

[c]In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately. In the WHO classification, the minor component must be ≥30% for this term to be used.

Changes from previous classification

A major change from previous classifications (WHO 2010, ENETS 2012) is the creation of a category of G3 NET, distinct from NEC. Under the 2010 WHO classification, all NENs with a Ki-67 index greater than 20% (G3) were classified as NECs (c). However, recent data suggests that the G3 group is, in fact, heterogeneous, including both morphologically well differentiated NETs with a high Ki-67 index, as well as poorly differentiated NECs, with differing morphology, molecular features and behaviour (d)(e)(f). The distinction between these groups is discussed further below.

The Ki-67 threshold for defining G1 NET was also modified; in the current classification this threshold is <3%, compared with ≤2% in previous classifications.

Histopathology of GEP-NETs

NETs of the gastrointestinal tract and pancreas have a similar appearance, generally comprising circumscribed, cellular tumours composed of a uniform population of cells with round to ovoid nuclei, "salt-and-pepper" chromatin, and granular eosinophilic cytoplasm, arranged forming nests, trabeculae, glands or acini, or solid sheets. The tumour morphology is similar in tumours from different sites, with rare exceptions; for example, glandular architecture and psammoma bodies are seen in somatostatin-producing NETs of duodenal origin, insular architecture in EC-cell serotonin-producing NETs of ileum, and trabecular architecture in L-cell NETs of rectum (g)(h).

The morphology of NETs is usually distinctive, but difficulties in diagnosis may arise in the uncommon tumours with variant morphologies, such as those showing cystic, papillary or angiomatoid architecture, or spindle cell, rhabdoid, clear cell or oncocytic cytology (g)(i). The differential diagnosis is discussed further below, in conjunction with immunohistochemistry.

Grading

The grading system for NETs is a 3-tiered system, based on assessment of cell proliferation within the tumour, using both the mitotic rate and the Ki-67 proliferation index.

Mitotic count is performed in "hot spots", the most mitotically active areas of the tumour, identified at scanning magnification. Ideally, at least 50 high power fields to a total area of at least 10mm^2 is counted, and the count expressed as a rate per 2 mm^2(a). Variables in assessment of mitotic count include acceptance of what constitutes a mitotic figure, amount of tumour present, tumour cellularity, and differences in fixation, section thickness, and staining between laboratories (j).

Ki-67 is a nuclear protein, expressed during G1, S and G2 phases of the mitotic cycle, and widely used as a marker of cell proliferation (k). The Ki-67 index of tumour cells is also assessed in "hot spots", or areas of tumour with the most frequent Ki-67 reactive tumour cells (a). Any discernible nuclear reactivity should be scored (l), and at least 500 tumour cells should be counted (a). Counting may be performed manually, on a printed or digital image, or with the use of an eyepiece grid with cell counter. Estimating the Ki-67 index, also known as "eye-balling", is not recommended, owing to inaccurate and unreliable results. Digital image analysis has been shown to be useful, but availability is currently limited and can be confounded by inflammatory cell infiltrates. (m)(n)

Tumours can show discordance in the grade based upon the mitotic rate and the Ki-67 index. In these instances, is recommended that the higher grade (usually the Ki-67 index) be assigned (a)(o).

Grading may be difficult (or even impossible) in small biopsy or cytology cell block samples. There may be an insufficient quantity of tumour to follow the processes described above, the tumour cells may be dispersed (making "hot spots" impossible to identify), or the tumour may be distorted by crush or diathermy artefact hindering counting. Grading on cytology samples may underestimate the grade, in comparison with surgical resection specimens (p). Correlation with functional imaging studies may facilitate more accurate grading by directing sampling of critical areas.

Molecular Pathology of NETs

A number of molecular changes are described in pancreatic NETs. Approximately 40% show inactivating mutations of the death domain-associated protein gene (*DAXX*) or ATR-X gene (*ATRX*), both of which encode proteins involved in chromatin remodeling, and loss of nuclear expression of DAXX or ATRX may be demonstrated with immunohistochemistry. These mutations are associated with alternative lengthening of telomeres (ALT), which can be identified by fluorescence *in-situ* hybridization (e)(q)(r). Loss of *DAXX* or *ATRX* has been associated with adverse outcome.(s) Pancreatic NETs may also show somatic inactivation of the *MEN1* gene in approximately 40% of cases, and mutations in genes in the mTOR pathway, including *PTEN*, *TSC1* and *TSC2*, are seen in approximately 14% of panNETs,(q)(r) In 10-20% of cases, pancreatic NETs are associated with hereditary syndromes, including multiple endocrine neoplasia type 1 (*MEN1* gene), von Hippel-Lindau syndrome (*VHL* gene), tuberous sclerosis (*TSC1* and *TSC2* genes) and neurofibromatosis type 1 (*NF1* gene).(a)(t)

Small intestinal NETs generally show a paucity of somatic mutations, but alterations may be seen in *SMAD* genes involved in the TGF-beta pathway, genes in the mTOR pathway or the SRC oncogene.(u)

Immunohistochemistry

Immunohistochemistry has a number of roles in diagnosis, grading and classification of NENs.

1. Cytokeratins: NETs almost always express cytokeratins, especially keratin 8 and keratin 18, detected with broad spectrum and low molecular weight cytokeratins (eg AE1/AE3, CAM5.2), but are usually negative for cytokeratin 7 and cytokeratin 20 (l). An absence of cytokeratin expression should raise the possibility of alternative diagnoses, such as paraganglioma.

2. Neuroendocrine markers: A number of neuroendocrine markers are commonly used. Chromogranin A is a very specific marker, but may be negative in rectal, L-cell appendiceal and gastrin-expressing NETs.(l) Synaptophysin is more sensitive, but less specific. Both chromogranin and synaptophysin are regarded as mandatory in the ENETS Consensus Guidelines.(v) CD56 (NCAM) and neuron specific enolase (NSE) are less reliable, but may be useful in some cases.(j) More recently, insulinoma-associated protein (INSM1) has been used in the diagnosis of GEP NETs, with lower sensitivity but higher specificity than synaptophysin and chromogranin, and potential use in grading.(l)(w)(x).

3. Ki-67: Immunohistochemistry for Ki-67 is an essential component of grading in NETs, as described above. It may also be useful diagnostically in certain situations, such as distinguishing NET from NEC on a small, crushed biopsy.

4. Hormone expression: Immunohistochemistry for various peptide hormones has been used to correlate with clinical hormonal syndromes, but is not always useful.(g)(v) Immunohistochemistry for serotonin, insulin, glucagon, somatostatin, gastrin and calcitonin is generally reliable, while VIP and PP are less often used.

5. Site of origin: Immunohistochemistry may assist in determining the site of origin of a NET, particularly in the context of metastatic disease. Commonly used markers include PAX8 or ISL1 expression for pancreatic NETs, and serotonin, CDX2 or SATB2 for small intestinal and appendiceal NETs.(l)(y)(z)(aa)(bb)

6. Somatostatin receptors: The majority of GEP NETs express somatostatin receptors (SSTRs), of which there are 5 subtypes.(aa)(cc) Somatostatin receptor subtype 2A (SSTR2A) expression can be used to correlate with functional imaging (e.g. Ga68-DOTATATE), and predict response to somatostatin analogue therapy or peptide receptor radionuclide therapy.(dd) SSTR expression may assist in discrimination between NETs and NECs, which uncommonly express SSTR.(l)(ee)

7. Molecular surrogates: Loss of expression of ATRX or DAXX, as mentioned above, is seen in approximately 40% of pancreatic NET, and is associated with reduced survival.(s)(ff). This finding may provide support for a diagnosis of G3 NET, as opposed to NEC.(e) In contrast, abnormal nuclear p53 expression (either over expression or loss), loss of Rb1 expression and bcl2 over expression favour a diagnosis of NEC, rather than NET.(e)(q)(ee)

8. Differential diagnosis: Immunohistochemistry may be helpful in excluding other diagnostic considerations. For example, bcl10 and trypsin are markers of pancreatic acinar cell carcinoma, while LEF1 and nuclear beta-catenin may be used as markers of solid pseudopapillary neoplasm of the pancreas, both of which may enter the differential diagnosis of a pancreatic NET.

Distinction of NET G3 from NEC

The distinction between well differentiated NET G3 and NEC has become important, given the significantly better clinical outcome and different therapeutic approach(d), but can be challenging, particularly on small biopsies.(gg)

Pancreatic NECs, both small cell and large cell carcinoma, show similar genetic features, with common mutations in *TP53*, *RB1*, *KRAS* and *SMAD4*, similar to those seen in pancreatic ductal adenocarcinoma.(a)(e)(hh) In contrast, inactivating mutations in *DAXX* and *ATRX* are seen in approximately 40% of NETs, but are rare in NECs (e). As mentioned above, immunohistochemistry may be useful as a surrogate for these molecular markers (see Table 2).

Most high grade NENs of the GIT are NECs, with mutations in *TP53* and *RB1* and, in the colon, *APC,* similar to those seen in adenocarcinomas (ii)(jj).

NET	**NEC**
p53 normal pattern	p53 abnormal pattern
Rb1 preserved	Rb1 loss
Loss of expression of DAXX or ATRX (for pancreatic NET)	Preserved expression of DAXX and ATRX
SSTR2A positive	SSTR2A negative

Table 2: Immunohistochemistry useful in distinguishing NET from NEC. These patterns are typical but not present in all cases.

Typing of NENs

Gastric NETs need to be classified by type as well as being graded. This is because there are marked differences in pathogenesis, prognosis and treatment algorithms between the types. Type 1 occurs in the context of autoimmune gastritis, type 2 in Zollinger-Ellison syndrome (duodenal or pancreatic gastrinoma) and type III in the absence of hypergastrinaemia.

Feature	Type 1 ECL-cell NET	Type 2 ECL-cell NET	Type 3 NET
M:F ratio	0.4:1	1:1	2.8:1
Relative frequency	80-90%	5-7%	10-15%
Hypergastinaemia	Yes	Yes	No
Antral G-cell hyperplasia	Yes	No	No
Acid secretion	Low or absent	High	Normal
Background mucosa	Atrophic gastritis	Parietal cell hypertrophy/hyperplasia	No specific change
ECL-cell proliferation	Yes	Yes	No
Grading	G1 G2 (rare) G3 (exceptional)	G1 G2 (rare)	G1 (rare) G2 G3 (rare)
Staging	I-II: 95% III: 4% IV: 1%	I-II: 70% III: 20% IV: 10%	I-II: 38% III: 32% IV: 30%
Metastasis rate	1-3%	10-30%	50%
5-year survival rate	~100%	60-90%	<50%

Table 3: Key clinicopathological features of gastric neuroendocrine tumour (NET) types 1, 2 and 3. (a)

As can be seen from the Table, type 1 disease is essentially benign. Type 1 and 2 tumours occur in the gastric fundus and body while type 3 tumours can occur anywhere in the stomach.

In assessing these patients, it is important that sufficient biopsies are taken from the stomach at endoscopy to assess gastric fundus, body and antrum, as well as biopsies from any tumour. Neuroendocrine markers are required on fundus and body biopsies and gastrin immunohistochemistry on antral biopsies to assess ECL-cell proliferation and G-cell hyperplasia respectively.

Another cause of hypergastrinaemia leading to neuroendocrine hyperplasia is proton pump inhibitors. The NETs that arise in this setting most resemble type 1 in that they reduce acid production leading to hypergastrinaemia and ECL-cell hyperplasia. However, there are relatively few cases reported in the literature considering the extent of PPI use in the community. Incidence seems rare, or perhaps it is only now that this type of ECL-cell NET is being recognised. In a 2020 study, the prognosis of 38 cases was much better than a control group of 28 type 3 cases.(mm,ll)

Other intestinal and pancreatic NENs are generally not formally typed by pathologists. Hormone immunohistochemistry has a limited role in the routine reporting of pancreatic NETs but can be done on specific clinical request. Functioning pancreatic NETs are classified on the basis of clinical features and elevated hormone levels, not on the basis of positive immunohistochemistry.(nn)

Conclusion

The diagnosis of gastro-entero-pancreatic neuroendocrine tumours may be challenging. Adherence to the current classification and grading is recommended, where possible. Ongoing developments in immunohistochemistry and the understanding of the molecular basis of NENs assist pathologists in accurate diagnosis, thereby supporting optimal management of patients.

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