Pathology of fore and midgut neuroendocrine tumours

Salvador J Diaz-Cano

Abstract

There is much confusion in both definition and practical issues among pathologists and clinicians alike for neuroendocrine tumours/carcinomas (NETs/NECs).

This review focuses the attention on key issues of foregut and midgut NET: pathological features (nomenclature, classification, diagnostic criteria, grading, staging, markers and prognosis), molecular genetics, and how to approach common problems in NET (multifocal vs multicentric, metastatic potential and prediction of primary site).

The value of the term *neuroendocrine* is related to its connotation of a particular phenotype or differentiation pattern. Accordingly, the NET nomenclature can be addressed by using any of the following groups of terms: (1) well-differentiated NET, well-differentiated NEC, or poorly differentiated NEC; or (2) NECs (grades I—III), indicating in an explanatory note the equivalent terminology, when appropriate. Ultimately, the use of specific NET terms remains a personal preference, but what is the most critical is the necessity that the terms will be understood by health professionals caring for patients and that the terms can be grouped and translated for epidemiologic and molecular studies that can offer unique targets for specific therapies.

Keywords foregut; gastrointestinal tract; midgut; molecular markers; neuroendocrine tumour; pathology

Brief statement on paper impact

Although neuroendocrine tumours (NETs) are relatively rare and they have been the object of numerous investigations, there is much confusion in its classification and definition by health professionals. This review focuses the attention on key issues of foregut and midgut NET: general pathological features (nomenclature, classification, diagnostic criteria, general grading, staging, markers and prognosis), molecular genetics of sporadic and familiar NETs, and how to approach common problems in NET (synchronic vs metachronic neoplasms, metastatic potential and prediction of primary site).

Ultimately, the use of specific terms for these neoplasms remains a personal preference, but what is the most critical is the necessity that the terms will be understood by health professionals caring for patients and that the terms can be grouped and translated for epidemiologic studies.

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Abbreviations: DNES, diffuse neuroendocrine system; GI, gastrointestinal; LOH, loss of heterozygosity; NE, neuroendocrine; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumours; PD-NEC, poorly differentiated neuroendocrine carcinoma; WD-NEC, well-differentiated neuroendocrine carcinoma; WD-NET, well-differentiated neuroendocrine tumour.

Introduction

The endocrine cells scattered throughout practically all organs with an epithelial lining constitute the so-called diffuse neuroendocrine system (DNES) that shares common biochemical and pathological properties. Currently, the DNES concept incorporates the 1970's ideas of Pearse, the paraneuron concept of Fujita, and observations of other investigators who have contributed to the development and evolution of an endocrine system that is not limited to a particular organ and stores its secretion in membrane-bound cytoplasmic granules. Although these cells and their tumours have the object of numerous investigations throughout the years, there is much confusion in both definition and practical issues among pathologists and clinicians alike.

Neuroendocrine tumours (NET) of the gastrointestinal (GI) tract have been classically classified according to embryological considerations.[1] Williams and Sandler proposed (1963) an embryologic classification of NETs based on their origins from foregut (stomach, duodenum, upper jejunum, and pancreas), midgut (lower jejunum, ileum, appendix, and cecum), and hindgut (colon and rectum) derivatives and demonstrated characteristic morphologic, histochemical, and immunohistochemical differences among the three groups. This classification offers correlation between the embryologic origin and the histologic pattern, argentaffin and diazo reaction, 5-hydroxy-tryptamine tumour content, urinary 5-hydroxy-indoleacetic acid, association with carcinoid syndrome, and metastasis to bone and skin. However, in the case of the foregut tumours, the usefulness of such a classification in practical diagnostic work is limited by its failure to characterize individual tumour entities with well-defined histological, hormonal, and/or clinicopathological profiles. After a brief embryological introduction, the present review will focus the attention on key issues of foregut and midgut NET: general pathological features (nomenclature, classification, diagnostic criteria, general grading, staging, markers and prognosis), molecular genetics of sporadic and familiar NE neoplasms, and how to approach common problems in NET (synchronic vs metachronic neoplasms, metastatic potential and prediction of primary site). Due to their special considerations, both lung and pancreatic NETs are not included in this review, except for specific issues related with its distinction from GI-NET.

Embryological and anatomical considerations

The story of the diffuse neuroendocrine system (DNES) started with the histological identification of chromaffin cells at the base of the normal bowel crypts by Kultschitsky (1897) and, pathologically, with the description of a peculiar little tumour of the small bowel and appendix with the terms of *small carcinoma* and *carcinoid tumour* by Lubarsch (1888) and Oberndorfer (1907), respectively. These cells were later revealed to share important biochemical pathways, symbolized by Pearse by the acronym APUD (Amine Precursor Uptake Decarboxylation),[2] which was suggested to express a common origin from the neural crest (a transient embryonal neural structure located at the junction of the neural tube and the dorsal ectoderm) already known to be the progenitor of autonomic ganglia and plexuses, paraganglia, and

melanocytes.[3] This theory was undermined by more rigorous experiments, in particularly the ingenious quail-chick chimeric model devised by LeDouarin (1974).

Currently, only ganglia, paraganglia, melanocytes, and thyroid C cells are considered neural crest derivatives,[3] while the other NE cells derive from the same local epithelial stem cells that give rise to all other epithelial cell types of the mucosa where these cells are located,[4] as Cheng and Leblond proposed for the small bowel mucosa (1974).[5] As a consequence, a substantial change in terminology has called into question the notions of NE cells and tumours. It has been proposed to drop the qualifier *neuro* from cells of non-neural derivations, and to call their tumours simply as *endocrine*; the pancreas is the best example of this approach, as sanctioned by the current WHO classification. Carrying this argument further, how can we explain the expression of thyroid transcription factor 1 by C-cell tumours or the existence of mixed follicular/papillary-medullary carcinomas? Although the current neurophobic tendency is true for certain locations, the neural crest derivation and the expression of neural markers are still valid. Despite these biological questions, the acronym NET is widely accepted and used clinically.

General pathological features

NETs occur in virtually all tissues and organs, including those that do not normally contain NE cells, and they may also occur as components of teratomas. These tumour cells, like their normal counterparts in the GI tract, express several antigens that are commonly expressed by neuronal elements and are commonly referred to as neuroendocrine markers (see this section below), independent of hormone production. It is for this reason that neuroendocrine is the preferred designation and the term NET is used in this review.

Specific trends in incidence for NETs of certain sites were identified, with a significant increase in the reported annual age-adjusted incidence of NETs from 1973 to 2004. The most common primary tumour site varied by race, with the lung being the most common in white patients, and the rectum being the most common in Asian/Pacific Islander, American Indian/Alaskan Native, and African American patients.[6] Among the most recently collected subset of data, sites that demonstrated the greatest NET incidence were the gastrointestinal tract (67.5%) and the bronchopulmonary system (25.3%). Within the gastrointestinal tract, most NETs occurred in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%). For all sites, age-adjusted incidence rates were highest in black males (4.48 per 100,000 per year). The best 5-year survival rates were recorded for patients with rectal (88.3%), bronchopulmonary (73.5%), and appendiceal (71.0%) carcinoids; these tumours exhibit invasive growth or metastatic spread in 3.9%, 27.5%, and 38.8% of patients, respectively. These findings bring into question the widely promulgated relative benignity of carcinoid disease. Certain NETs, such as those of the rectum, appear to be over-represented among the black and Asian populations within the United States, suggesting the role of genetics in the development of this intriguing disease.[7]

Nomenclature and terminology

The term karzinoid (carcinoid) meaning carcinoma-like was introduced by Oberndorfer to describe peculiar small intestine tumours that resembled cancers but had unusual clinical behaviour. This term has been applied differently by pathologists and clinicians: pathologists have traditionally classified well-differentiated endocrine tumours of the lung, gut and pancreas as "carcinoid tumours", while clinicians use the term to describe the syndrome caused by serotonin excess. It has also become apparent that "carcinoid tumours" in different locations within the GI tract are not necessarily equivalent and that they can display the full histopathological spectrum from very low-grade to high-grade malignancy. For these reasons the term "carcinoid" has been increasingly discouraged in favour of more precise terminology.

NETs may be associated with clinical syndromes due to the overproduction of biologically active amines or peptide hormones, while many others may be clinically silent. In the latter instances, amines or peptides often are demonstrable by immunohistochemical or other techniques. There is extensive overlap with pancreatic endocrine tumours, for example, somatostatin-producing cells are present in both, and during development gastrin is produced in the pancreas, so that any discussion of GI-NETs has implications for pancreatic NETs.

Before the advent of immunohistochemical analysis, the NET diagnosis most often relied on the use of fixatives containing chromate salts, histochemical stains, or electron microscopic examination. Certain intestinal endocrine cells and tumours show a positive chromaffin reaction, similar to that observed in the adrenal medulla and paraganglia. Silver stains of both argentaffin (Masson-Fontana) and argyrophil (Grimelius, Sevier-Munger) types also were used, although these staining sequences often produced inconsistent results. Other stains that had been used for the detection of NE cells included lead haematoxylin and toluidine blue or coriophosphine O following acid hydrolysis (masked metachromasia). With the exception of the Grimelius method, these stains are now used rarely in the workup of NETs. Electron microscopic examination was used extensively in the past to demonstrate secretory granules, but this approach has been largely replaced by immunohistochemical studies.

Classification

Given the wide array of NE cells, it is not surprising the lack of unified classification. The NET categorization is based on tumour size, angioinvasion, extent of organ-specific invasion, proliferation index, functional status/hormonal syndrome, and metastases to lymph nodes or liver.[8] Using these criteria, a site-independent NET classification system (Figure 1) considers[9,10]:

- Well-differentiated NET (WD-NET)
  - Benign
  - Uncertain malignant potential
- Well-differentiated neuroendocrine carcinoma (WD-NEC)—low-grade malignant
- Poorly differentiated neuroendocrine carcinoma (PD-NEC)—high-grade malignant

Well-differentiated, slowly growing GI-NETs and carcinomas, those that are also called carcinoids, which comprise a number of well-defined entities (e.g. gastrinomas, and others), are distinguished on the basis of their localization as well as their morphological and functional features. PD-NECs are composed of cells displaying high mitotic and Ki-67 indices, and few secretory granules, form a separate group not difficult to

