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Pathology of neuroendocrine tumours

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1. ABSTRACT

Here we review the pathologic features of a specialized tumor subset, collectively referred to as neuroendocrine tumors. These tumors arise almost anywhere in the body but many issues regarding their diagnosis and classification remain to be settled. Recent technical improvements, have increased the rate of detection, and have contributed to better diagnosis and classification of these tumors.

2. INTRODUCTION

The evolution of the concept of the neuroendocrine cell and the definition of the neuroendocrine tumours (NET) are one of the most fascinating and only partially clarified issues in the literature. The identification of Kulchitsky's cells and the description of a special type of intestinal tumor, i.e. carcinoid, by Oberndorfer in the German literature in 1907, represent early scientific contributions to the elucidation of carcinoid tumours (1); few years later in 1914 Pierre Masson studying carcinoid tumours of the appendix observed that the neoplastic cells contained abundant secretory granules strongly stained with silver nitrate, and he showed that Kulchitsky's cells had the same features as the cells of carcinoid tumours (2). The work of Friedrich Feyrter and later Anthony Pearse established the concept of a diffuse endocrine cell system (3-4). NET arise from the neuroendocrine system, a diffuse system composed of the endocrine and the nervous systems interacting each other. More specifically, the endocrine system is primarily a network of glands producing hormones, along with cells that belong to the disseminated neuroendocrine system (DNS), scattered throughout other organs (5-6). As a matter of fact a wide variety of cells that are present in the central and peripheral nervous system and in many classic endocrine organs made the disseminated neuroendocrine cell system. Cells and tumours of the DNS may be divided in two principal groups: neural type, including

neuroblastoma, pheochromocytoma, and paraganglioma; and epithelial type which include carcinoid and NET from many sites.

3. PROBLEMS WITH TERMINOLOGY

The broad heterogeneity characterizing NET has posed problems regarding their correct classification. NET can develop in any organ or district of the body; most of them arise from the gastroenteropancreatic (GEP) district, hence the distinction in GEP and non-GEP neuroendocrine tumours previously referred to as carcinoids. They occur most frequently in the gastrointestinal system, where they are most common in the small intestine, appendix, and rectum, and in the bronchi as the most frequent extragastrointestinal site. NET are defined nowadays as endocrine tumors (ET), and they are divided into functional and non-functional tumours. Functional tumours are classified based upon the hormones they produce and the associated endocrine syndrome. The more common functional tumours are listed in table 1. Nonfunctioning tumours are either an incidental finding or are associated with an expanding mass (7). These two groups of NET are often histologically indistiguishable. Most NET are carcinoid, pheochromocytoma, medullary thyroid carcinoma, parathyroid tumors, and pituitary tumours. The rest of NET is composed of poorly differentiated tumours with a more aggressive behavior, including Merkel cell carcinoma. The new WHO classification, divided NET into the followings categories: 1. well-differentiated endocrine tumors, 2. well-differentiated endocrine carcinomas, formerly defined as carcinoids and malignant carcinoids respectively, 3. poorly differentiated endocrine carcinomas and 4. mixed exocrine–endocrine tumours on the basis of their location, tumor size, histologic features (angioinvasion and Ki-67 index), and biologic behavior. (8). This classification enables NET in the gastroenteropancreatic tract to be clearly diagnosed, but unfortunately this is not applied to lung tumours. The classification of NET of the lung is evolving and complex; they are currently classified in typical carcinoid, atypical carcinoid, small-cell lung carcinoma (SCLC), and large-cell neuroendocrine carcinoma (LCNEC) (9). Their separation rests primarily on mitotic rate and the presence or absence of necrosis, and, in the case of separating SCLC from LCNEC, cell morphology.
SCLC account for 20% to 25% of primary carcinomas of the lung and it is now widely acknowledged that they form the aggressive end of the spectrum of neuroendocrine lung tumours. Extrapulmonary small cell carcinomas in comparison are rare, however the clinical behavior of these tumours is generally aggressive, similar to their pulmonary counterparts (10).

Pretty nearly two thirds of all neuroendocrine tumors (NET) are located in the gastroenteropancreatic tract. They originate from the diffuse neuroendocrine cells distributed throughout the gut, and from the pancreatic islet cells. They usually produce bioactive substances and show immunoreactivity to neuroendocrine markers; based on their endocrine secretion, they are functional active or inactive. Functionally active NET present with clinical symptoms because of excessive hormone release from the tumor cells; examples of such events are insulinomas, gastrinomas, VIPomas, somatostatinomas , glucagonomas, ACTH producing tumours.

Finally, goblet cell carcinoid of the appendix is a distinct entity, it arise from a pluripotent cell with divergent neuroendocrine and mucinous differentiation. The dual endocrine and glandular differentiation has led to confusion in the nomenclature (adenocarcinoid, crypt cell carcinoma, and mucinous carcinoid. These tumours frequently have signet ring cell morphology. They are more similar to a adenocarcinoma of the colon, indeed they are widely invasive, with a high cellular proliferation rate and dysregulation of the cell cycle with up-regulation of cyclin Dl and p21, and down-regulation of p16 (11).

4. NEUROENDOCRINE TUMORS ARE NOW RECOGNIZED IN ALMOST ALL SITES IN THE BODY

The diverse extragastrointestinal sites where NET have been reported to occur are shown in table 2 (12-28).
Redarding the genital system, NETs are more common in the female than male genital tract; most are uterine small cell carcinomas or ovarian carcinoids. Most male genital tract NET are prostatic small cell carcinomas or testicular carcinoids. The prostate contains the largest number of neuroendocrine cells of any genitourinary organ. Most of these cells contain chromogranin A (Figure 1B) and serotonin (29). In histologically typical prostate adenocarcinoma, particular attention has been given to the presence of eosinophilic neuroendocrine cells which stained positively with chromogranin A. The term Paneth cell-like has been used to describe these neuroendocrine cells (30). More than ten years ago it has been demonstrated that androgen-deprivation therapy is associated with an increased number of neuroendocrine cells in hormonally treated prostate carcinoma (31).

5. DIAGNOSTIC CRITERIA AND IMMUNOHISTOCHEMICAL MARKERS

The hallmark of well-differentiated endocrine tumour is the presence of small cells containing regular, well-rounded nuclei, frequently arranged in a neuroendocrine growth pattern, i.e. well-defined nests of tumour cells separated by thin fibrovascular septa, or they show strands of tumour cells arranged in trabeculae, ribbons or festoons (Figure 1A).

Well-differentiated endocrine carcinomas share many of the features of the above described tumour, however they are distinguished by more pronounced cytologic atypia, increased mitotic activity and frequent foci of necrosis, and vascular invasion.

Poorly differentiated endocrine carcinomas represent the more aggressive end of the spectrum of NET, with significant morbidity and mortality, and one of the most common histological subtypes in the lung (Figure 2).

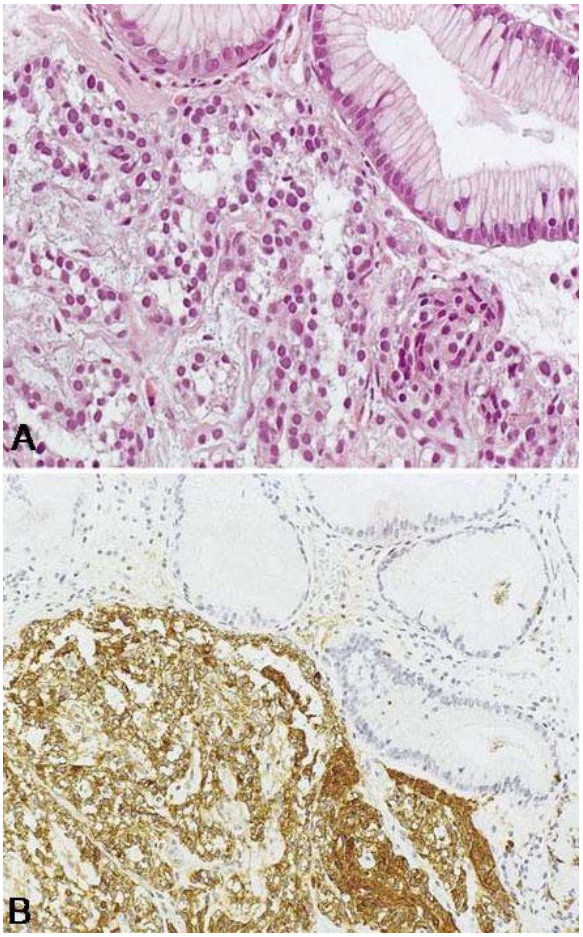

Figure 1. A) Nests of Well-differentiated endocrine tumour infiltrating gastric mucosa. B) The neoplastic cells are positively stained for chromogranin A, negative gastric gland are evident on top.

In these tumours the patterns of growth above described as ribbon-like, trabecular or festoons arrangement of tumour cells are rarely seen.

Merkel cell carcinoma deserves a mention apart, also called neuroendocrine carcinoma of the skin, most often develops in older people (Figure 3A). Long-term sun exposure or having a weak immune system may increase the risk of developing Merkel cell carcinoma. Because of its diffuse pattern of growth, and of its uniform small tumor cells, Merkel cell carcinoma is potentially mistaken for lymphoma. Histologically the dermis is diffusely involved by monotonous sheets of tumour cells, with a narrow band of intact papillary dermis (Figure 3B). The diagnosis of Merkel cell carcinoma can be reliably made even on cytological specimens obtained by fine needle aspiration biopsy (Figure 3C); the smears are usually highly cellular, the neoplastic cells have scanty cytoplasm, and the nuclei are round and vesicular, with a typically fine granular (dusty) chromatin and small multiple nucleoli often located in proximity of the nuclear membrane. High mitotic activity, and numerous apoptotic bodies are frequently seen (32).

The diagnosis of NET is a challenge even for pathologists dealing with cytological specimens, and in proper hands a reliable cytological diagnosis can be made (33-34).

5.1 Immunohistochemical markers

Immunohistochemically NET express positive reactions to neuroendocrine markers, including neuron specific enolase (NSE), synaptophysin, and chromogranin A (Figure 1B). NSE is a very sensitive, albeit no too specific marker for NET, reacting with some nonneuroendocrine tumours. NSE should be used only with other broad-spectrum markers of neuroendocrine cells in the diagnosis of NET.

Many endocrine tumours express somatostatin receptors, and very recently a scoring system for somatostatin receptor type 2A has been proposed in NET (35).

CD56 or neural cell adhesion molecule (NCAM) has become the antibody of choice in many laboratories being one of the most sensitive marker in this context (36-37).

The homeobox gene products such as thyroid transcription factor 1 (TTF1) and CDX-2 might be inappropriately expressed in NET.

CDX-2 expression can be highly specific in identifying NET of intestinal origin whereas TTF-1 expression could be helpful in identifying NET of pulmonary origin (38-39).
Immunohistochemically Merkel cell carcinoma shows immunoreactivity for both neuroendocrine and epithelial markers being positive for NSE, CD56, synaptophysin, chromogranin A, and showing a distinct perinuclear dot-like positivity for CK20 and neurofilaments (Figure 3D) (40).

It should be kept in mind that the immunohistochemical profiles are not specific for a particular NET, however the combination of the various antibodies can be helpful for diagnosis, prognosis, and therapy.

6. MOLECULAR FEATURES OF NET

The molecular pathogenesis of NET is still largely unknown. Recently authors underlined that the malignant progression of GEP endocrine tumors seems to be associated with complex allelotypes and chromosomal instability (41). More recently in a review of NET of the lung it has been suggested that a molecular classification of NET should be integrated to morphology, for a better definition of the different histological types and a more appropriate selection of the therapeutic strategy (42).

Hormones and neuropeptides may influence the activities of lymphoid organs and neuroendocrine cells.

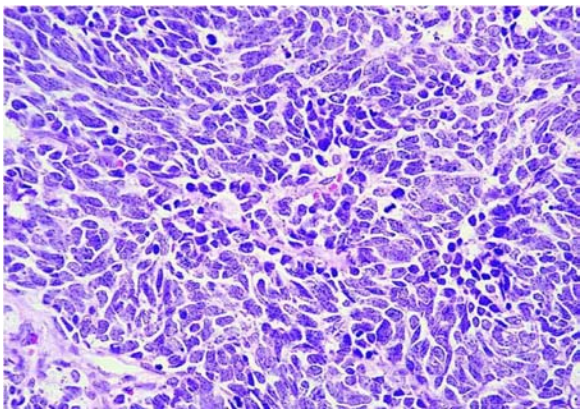

Figure 2. Poorly differentiated endocrine carcinoma with solid architecture and numerous mitoses.

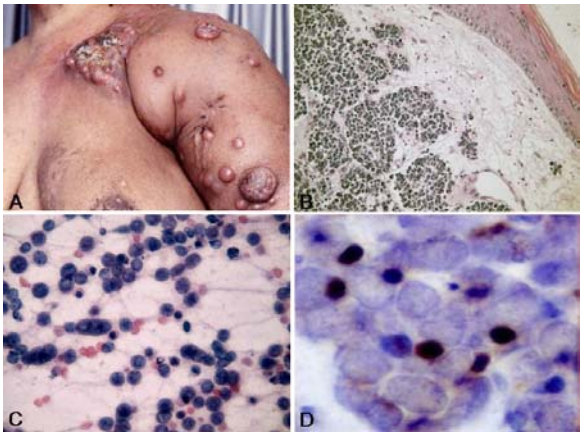

Figure 3. Composite figure of Merkel cell carcinoma. A) Classic clinical presentation. B) Monotonous sheets of tumour cells infiltrating the dermis. C) Aspirate of cutaneous nodule demonstrating loosely cohesive tumour cells. D) Immunoperoxidase stain showing neurofilament paranuclear dots in the tumour cells.

Table 1. Endocrine tumors

Carcinoid Tumors	Pancreatic Endocrine Tumors
Bronchial carcinoid	Insulinoma
Gastric carcinoid	Gastrinoma
Small intestine carcinoid	Somatostatinoma
Appendiceal carcinoid	Glucagonoma
Rectal carcinoid	VIPoma
	Non functioning ET

Table 2. Extragastrointestinal NET

Site	References
Liver and extrahepatic bile duct	12-13
Kidney	14
Bladder	15
Larynx	16-17
Lung	18-19
Breast	20
Pituitary gland	21
Thymus	22
Thyroid	23-24
Uterine cervix	25
Vagina	26
Ovary and fallopian tube	27-28

Somatostatin (SS) and cortistatin (CST) are two hormones sharing marked amino acidic sequence homology, as a result of a probable primordial gene duplication in chromosomes 3 and 1, respectively (43). The current literature supports a strong association between high level of SS expression and neuroendocrine tumours, including pituitary adenomas, endocrine pancreatic tumours, gastrointestinal and lung carcinoids, paragangliomas, pheochromocytomas, small cell carcinomas, Merkel cell carcinomas, neuroblastomas and medullary thyroid Carcinomas (44-46). While the role of SS in neoplastic conditions has been extensively studied, establishing the usefulness of SS analogs in the control of hormonal secretion and neoplastic growth in several neuroendocrine tumours, less clear remains the role of CST in the same tumours. Interestingly, in a very recently review, authors conclude that CST analog might open new interesting perspectives in the treatment of neuroendocrine tumours (43).

7. MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Multiple endocrine neoplasia (MEN) syndromes consist of 2 categories, MEN 1 and MEN 2. MEN 1 is a relatively uncommon inherited disease: individuals who inherit the gene for MEN 1. The endocrine glands most commonly affected by MEN 1 are the parathyroid, pancreas, and pituitary glands. (the endocrine glands which start with the letter "P"). Hyperparathyroidism is the most common manifestation of MEN 1, caused by hyperplasia of multiple parathyroid glands. Penetrance is almost 100% by age 50 years. In patients with MEN1, parathyroid hyperplasia or multiple adenomas occur in approximately 90–95%. (47). MEN 2 is a rare autosomal dominantly inherited familial cancer syndrome caused by RET proto-oncogene germline mutations. It is associated with an increased risk for medullary carcinoma of the thyroid (onset in early adulthood), pheochromocytoma and parathyroid adenoma/hyperplasia. Medullary thyroid carcinoma is a well-differentiated thyroid tumor that maintains the typical features of parafollicular C cells, and somatic RET mutations have been found in 40-50% of these tumours. Very recently authors demonstrated that point mutations in RET, at the germline level in (virtually all) MEN 2 patients and, at the somatic level, in about half of the sporadic cases, characterize medullary thyroid carcinoma, suggesting that these patients might benefit of novel treatments based on RET inhibition (48).

8. CONCLUSIONS AND PERSPECTIVE

Very recently authors, in evaluating the usefulness of WHO classification of NET for selecting an appropriate treatment, suggested that some clinicopathological parameters, i.e. the site of the primary tumour, liver involvement, high MIB-1 levels, and a long disease free survival could be important, although they conclude that the clinical and prognostic impact of each of these variables remains to be established (49).

Finally although at present the knowledge of the genetic background of NET may have not direct bearing on treatment and outcome, distinction on genetic analysis could become important to establish targeted therapeutic strategies for future treatment of neuroendocrine tumours.

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