

Neuroendocrine Tumor (NET): Its Origin, Pathology & What Does it Catch!

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The **dispersed or diffuse neuroendocrine system (DNS)** is distributed in a wide variety of organs and tissues throughout the human body and is composed of cells that have the capability of producing biologically active neuroamines, neuropeptides, and related substances. These cells can be recognized as individual cells (e.g. skin, thyroid gland, gastrointestinal tract, bronchopulmonary tree) or small aggregates (e.g. CNS, peripheral nervous system, pituitary gland, pancreatic islets, pulmonary neuroendocrine bodies).

The cells of DNS have been recognized since 1870 for their characteristic histochemical reactions. At that time, their affinity to chromium salts was described by Heindenheim. Subsequent works by several investigators have highlighted many of their histological features, anatomic distribution and histochemical characteristics, most notably argyrophilia and argentaffinia. In addition, the cells are rich in glycolytic enzyme enolase, nonspecific esterases or cholinesterases. Ultrastructurally, they demonstrated a cytoplasm rich in membrane bound granules or so called “neurosecretory granules”. In 1968, Pearse, introduced the concept of **APUD system** to refer to the biochemical ability of the component cells for **Amine Precursor Uptake and Amino Acid Decarboxylase**. Pearse proposed that cells are of neural crest origin but the subsequent elegant embryological studies by Le Douarin & Le Lievere using the chick-quail chimera dispelled this notion and helped outline the embryological development of neural crest cells. Additional work in experimental animals and humans have proved that the origin, differentiation and renewal of the four main epithelial cells within the intestinal tract are of endodermal origin. Only adrenal medullary cells, thyroid C-cells and melanocytes are of neural crest origin but the pancreatic islet cells, pituitary gland, parathyroid gland and K (Kultichsky) cells are endodermal and not of neural crest origin.

These studies have demonstrated the phenotypic diversification and heterogeneity of neural crest cells, persistence of pluripotent precursors and the role of growth factors and cytokines in their differentiation. These features help to explain some of the noted findings in pathological conditions such as in neoplasms, multiplicity of some endocrine tumors and ectopic production of hormones.

Currently, there are several histochemical and immunohistochemical markers that can be used to identify these cells; these include enzymes (argyrophilic reactions), hormones, intermediate filaments (cytokeratins- CK20, CK7, CK18, neurofilament), cell adhesion molecules (neural cell adhesion molecule CD56, CD57 & CD59), neuron specific enolase, chromogranin A & B and synaptophysin. Staining for EGFR and PDGFR has been detected in variable percentages.

Neoplasms of ENS cells is an interesting and challenging chapter in pathology. Tumors of this system have been recognized long time ago and have been described under a variety of terms reflecting their characteristic morphological and functional features. First description of carcinoid tumor –“karzinoide tumoren des dunndarms” is attributed to **Oberndorfer in 1907**. Reflecting their common distribution in the gastrointestinal tract, pancreas and lung, William and Sandler introduced the terms foregut (respiratory tract, thymus, pancreas, stomach and proximal duodenum), midgut (jejunum, ileum, appendix and ascending colon), and hindgut (transverse and descending colon, rectum) carcinoid. Two WHO classifications have been introduced: the first in 1980 and more recently in 2000. The more recent classification emphasizes the endocrine characteristics of these tumors and proposes three major categories: 1) Well differentiated endocrine tumor (carcinoid), 2) well differentiated endocrine carcinoma (atypical carcinoid) and 3) poorly differentiated carcinoma (small cell carcinoma and large cell neuroendocrine carcinoma). The classification recognizes that in some cases, a mixed pattern occurs. Of interest in this scheme is the recognition of multiple endocrine neoplasia (MEN I, MEN IIA & IIB). Moreover, there is recognition of the wide morphological spectrum for these tumors ranging from epithelial, spindle shaped, neural-like, mucin producing and mixed cell components. They show selective immunostaining for chromogranin, synaptophysin and other markers. In the histological assessment and grading of these tumors, primary consideration is given to cellular atypia, mitotic index, nuclear pleomorphism and necrosis. Immunohistochemical staining for Ki-67 has been used for tumor grading: <2% Grade 1, 2-20% Grade 2 and >20% Grade 3.

Neuroendocrine tumors occur in any part of the body, especially the GI tract which is considered the largest endocrine organ in the body. These tumors are heterogeneous and are commonly associated with clinical syndromes. The differentiated forms are generally small and slow growing but show variable clinical behavior. The majority of these cells express somatostatin receptors. Endocrine tumors represent about 2% of malignant GI tumors; it is estimated that they occur at an annual rate of 25 per million and it affects mostly adults above the age of 50 years. They affect mostly the midgut, most commonly the small intestine followed by the appendix (seen in 1/300 appendectomies) and is incidentally discovered in 1/2500 proctoscopies. Other common organ sites include lung (25%) kidney/ovary <1%. Those associated with MEN I are predominantly foregut tumors.

It is not uncommon for these tumors to be metastatic at time of diagnosis and it may be difficult to recognize primary site (neuroendocrine unknown primary tumors). These account for an estimated 13%. Most express specific receptors for amines or peptides, e.g. somatostatin receptors. In these situations, greater reliance is on radiological and laboratory tests. In diagnosing neuroendocrine tumors, Octreoscan has high sensitivity and specificity in localization. Other useful studies include bone scan, F-fluorodeoxyglucose PET and serum chromogranin.

Carcinoid syndrome occurs in <10% patients with carcinoid tumours. The clinical features include episodic cutaneous flushes, abdominal cramps and diarrhea. Some patients have bronchospasm. The occurrence and severity are related to secretion of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA). They show elevated serum chromogranin levels in 56-100% and is observed with liver metastasis- majority from midgut, foregut (2-33%), hindgut (extremely rare). Peritoneal fibrosis is seen in about 50% of patients with abdominal pain or carcinoid syndrome. Cardiac valvulopathy has significant adverse prognostic feature. 10-30% have cardiac complications (tricuspid regurgitation & tricuspid stenosis. Cardiac valve abnormalities account for 1/3 of carcinoid-syndrome related deaths.

Prognosis of these tumors is variable and is dependent on the stage of the disease. Chemotherapy has taken advantage of the expression of somatostatin receptors on these tumors which are expressed in 80-90% of neuroendocrine tumors. Five different subtypes of somatostatin receptors have been recognized and targeted therapy relies on using somatostatin analogues which have longer half life than somatostatin, show selectivity in binding to specific subtypes, effective in suppressing hormonal secretion and have antiproliferative activity.

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