Autopsy Case Reports

Editorial

Neuroendocrine neoplasms: a brief overview emphasizing gastroenteropancreatic tumors

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Neuroendocrine neoplasms are considered to be composed of cells with features similar to those of the normal diffuse neuroendocrine system (DNES) scattered throughout the body (e.g. gastroenteropancreatic [GEP], the enteroendocrine hormonal signaling system; respiratory and urogenital systems; paraganglia; adrenal medulla; skin; thymus; heart; middle ear; and other tissues). Despite being considered rare, neuroendocrine neoplasm incidence has been reported to be increasing, with increased survival duration over time, suggesting that neuroendocrine tumors (NETs) are more prevalent than previously reported.[1] The present overview addresses the main focus on DNES cells and the anatomic pathology features of neuroendocrine neoplasms that occur in GEP.

The recognition of GEP DNES seems to have started in the 19th century. In 1870, Heidenhain[2] reported the presence of chromaffin cells (EC), a term later introduced by Ciaccio,[3] in the gastric mucosa, probably the current gastric counterpart of the intestinal Enterochromaffin Cell: EC-Like (ECL) but it was Kultschitzky[4] who reported a seminal study describing EC in Lieberkühn crypts of the intestinal mucosa. Then, Feyrter[5] established the concept of a "diffuse" endocrine system (DNES) in the gastrointestinal mucosa. Neuroendocrine cells have been independently recognized by several authors and variably termed enterochromaffin cells, argentaffin and argyrophil "clear cells," enteroendocrine cells, and Kultschitzky cells. Pearse[6] recognized that neuroendocrine cells of the gut uptake 5-hydroxytryptophan, which is decarboxylated to 5-hydroxytryptamine. Rosai,[7] in a remarkable essay, presented claims favoring the endodermal origin of the GEP DNES, but pointed out that there was still evidence missing to definitively establish this possibility. The neuroendocrine cells express general markers of allegedly neuroendocrine differentiation (e.g. chromogranin and synaptophysin)—since a common phenotype does not mean a common histogenesis—and hormones according to site (e.g. a more "neural-like" differentiation in the larynx, lung, thymus, and thyroid; a more "epithelial-like" differentiation in the GEP system), and that an interplay seems to exist between these neuroendocrine cells and neural crest-derived nerve endings.

The first autopsy report of a GEP neuroendocrine neoplasm is ascribed to Langhans,[8] which was followed by reports of Lubarsch[9] and Ramson.[10] Of note, it seems probable that the first description of a carcinoid tumor was reported in the bronchus by Laennec.[11] The term "carcinoid" was established (1907) by Oberndofer,[12] who, in 1929,[13] confirmed the possibility

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that "karzinoide," meaning "carcinoma-like," might exhibit malignant features and metastasize.

Williams and Sandler[14] reported three distinct groups of GEP neuroendocrine neoplasms: foregut (intrathoracic, gastric, and duodenal), midgut (small intestine, appendix, and proximal colon), and hindgut (distal colon and rectum). In 2000, the WHO (reviewed by Klöppel et al.[15]) established the following categories based on the degree of differentiation: well-differentiated endocrine tumors (further classified into benign tumors and low-grade malignant tumors, based on the tumor size, mitotic rate, Ki-67 labeling index, lymphovascular invasion, and symptoms, in association with hormonal oversecretion), and poorly differentiated endocrine (small- and large-cell) carcinomas. The WHO 2010[16] classification established GEP neuroendocrine (well-and poorly-differentiated) neoplasms as malignant tumors, except for gangliocytic paraganglioma and pancreatic neuroendocrine microadenomas, which are considered to be benign tumors; and L-cell–type (glucagon-like peptide and peptide YY-producing) NETs and tubular carcinoids, as uncertain malignancies.

Well-differentiated NETs are reported to occur most frequently in GEP sites up to two-thirds (more in the small intestine, but variably according to different reports), a quarter in the bronchopulmonary system, and the remaining 10% scattered throughout the body. In contrast, neuroendocrine carcinomas occur predominantly in the bronchopulmonary system.[17]

There are GEP neuroendocrine neoplasms associated with hereditary syndromes[18] (e.g. multiple neuroendocrine neoplasia type 1 [MEN1], von Hippel-Lindau syndrome, neurofibromatosis 1, and tuberous sclerosis [TSC]), but most are considered sporadic. Well-differentiated sporadic pancreatic neuroendocrine neoplasms were reported to display a high frequency of mutations[19] in *MEN1*, *ATRX* (alpha thalassemia/mental retardation syndrome X-linked), and *DAXX* (death-domain associated protein), which seem to associate with better behavior; and low frequency mutations in genes of the mTOR (mammalian target of rapamycin) pathways, such as *PTEN* (phosphatase and tensin homolog), *TSC2*, and *PIC3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha). Interestingly, it seems that telomerase promoter mutations in pancreatic NETs are rare,[20] but mainly found in tumors from patients with hereditary syndromes. Strikingly, most of the molecular mechanisms of neuroendocrine neoplasms remain to be clarified.

The current staging of GEP neuroendocrine neoplasms is based on the proposals of the American Joint Committee on Cancer (AJCC)[21] and the European Neuroendocrine Tumor Society (ENETS).[22,23] The AJCC and ENETS staging for almost all gastrointestinal neuroendocrine neoplasms—those of the stomach, duodenum, ampulla, jejunum, ileum, and colon-rectum—are identical; whereas some differences exist in the T classification of the pancreatic and appendiceal neuroendocrine neoplasms between AJCC and ENETS staging.

GEP neuroendocrine neoplasms are graded[22,23] based on the mitotic count (MC)/10 high power fields (HPFs) and the Ki-67 proliferation index (Ki-67 LI), regardless of tumor size, extent, or location; a minimum of 50 HPFs (1 HPF = 2 mm^2) should be carefully evaluated to accurately determine the MC, and 500–2000 cells to determine the percentage of KI-67 LI. GEP neuroendocrine neoplasms are usually graded as (well-differentiated) G1 (MC < 2/10HPF and/or ≤ 2% Ki-67LI) and G2 (MC 2-20/10 HPF and/or 3-20% Ki-67 LI) NETs, and (poorly-differentiated, small or large cell) G3 neuroendocrine carcinomas (NECs; MC > 20/10HPF and/or > 20% Ki-67 LI). It is worth noting that there are reports[24] of "well-differentiated G3 neuroendocrine neoplasms" that seem to display less aggressive behavior than bona fide NECs.

It seems that up to 50% of NETs display synchronous or metacronous metastases after diagnosis (more common in poorly differentiated neoplasms), and appear to occur more frequently when the well-differentiated neuroendocrine primary neoplasm is located in the cecum or pancreas.[25] Most metastases of neuroendocrine neoplasms occur in the liver, lungs, and bone, and are much rarer in other sites[26] (e.g. brain, ear, ovary, breast, thyroid, pancreas, skin, adrenal glands, kidney, spleen, orbit, retroperitoneum, testis, and pituitary gland).

Conclusively, it seems that, as in the first medical identification of a GEP neuroendocrine neoplasm, autopsy studies are still very much justified[27] to clarify the pathogenesis of cancer in general, and of NETs in

particular, especially in unusual cases and/or in cases submitted to the new medical therapies of cancer.

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