Duodenal neuroendocrine tumors

R Komminoth

Dept. of Pathology University of Zürich, Switzerland.

Frequency

Duodenal neuroendocrine tumors are still rarer than gastric neuroendocrine tumors and constitute between 1% and 1.5% of all gastrointestinal and ~2% of all neuroendocrine tumors (1). The proportion of neuroendocrine tumors among all duodenal malignancies is 1.6%.

Embryology

The embryogenesis of the endocrine cells of the digestive system has been the subject of considerable controversy. Initially, it was postulated that they are derived from the neural crest. However, the theory that most endocrine cells of the digestive system are derived from the endoderm is currently favored (2).

Classification

The nomenclature of the endocrine tumors of the digestive system is controversial. Some believe that the term “carcinoid” should be applied while others prefer the term “neuroendocrine tumors” for all neoplasms derived from the endocrine cells of the gut. Since they do not appear to be of neural origin, it could be argued that the term “neuroendocrine” is a misnomer. However, the prefix “neuro-” is appropriate if restricted to mean a common program of the synthesis of peptides, amines and certain antigens shared by the diffuse endocrine cells and neurons (3).

Well-differentiated endocrine tumor (carcinoid)

Benign behavior confined to mucosa-submucosa, < 1 cm paragangliocytic parangangioma confined to mucosa-submucosa, > 1 cm and/or angioinvasive

Uncertain behavior extending beyond submucosa or with metastases

Poorly differentiated endocrine carcinoma

High-grade malignant small or intermediate cell type

Hyperlasia

Enterochromaffin cell hyperplasia occurs in the small intestinal mucosa of patients with untreated gluten-sensitive enteropathy. This hyperplasia appears to be directly related to the severity of the disease and represents a nonspecific response to chronic mucosal inflammation and increased repair.

Neoplasms

Neuroendocrine neoplasms of the duodenum belong to the group of foregut tumors, which encompass neoplasms of the esophagus, stomach and duodenum, including those of the ampulla of Vater. They are generally similar to each other and to neuroendocrine tumors from other locations when conventional histological methods are used.

When light microscopy is used, foregut tumors may show several patterns, from clusters and sheets to ribbons and rosettes. These cells, as a rule, have a benign appearance, and mitoses are exceedingly rare. They are usually argyrophilic but on occasions may be argentaffin. Under the electron microscope, their secretory granules vary a good deal in appearance. In some tumor granules identical with those of the G, I, D or ECL cells are seen, whereas others contain small, ill-defined cytoplasmic granules.

Approximately half of all patients with neuroendocrine tumors of the duodenum present with endocrine symptoms, one-third with others contain small, ill-defined cytoplasmic granules.

Sporadic neuroendocrine tumors

Gastrinoma

Most extrapancreatic gastrin-producing tumors are found in the duodenal wall, often accompanied by the typical Zollinger-Ellison...
syndrome. These tumors can be extremely small and in one patient with the full-blown Zollinger-Ellison syndrome, a duodenal gastrinoma measuring 1.5 mm in diameter was discovered incidentally during gastroduodenal surgery (5). If occurring as multiple tumors, a multiple endocrine neoplasia (MEN) type I syndrome (see below) should be suspected.

Immunohistochemically, gastrinomas show the presence of gastrin as well as of other peptides, such as somatostatin, serotonin, pancreatic polypeptide and so on. With electron microscopy, the tumor cells can be seen to contain secretory granules of variable morphology, sometimes they are identical with those of the normal antral gastrin-producing (G)-cells and sometimes they are more similar to the so-called IG-cells and, on occasion, with more bizarre morphology.

**Somatostatinoma**

These tumors are found with a certain frequency in the duodenum, especially in the vicinity of the ampulla and sometimes coexisting with neurofibromatosis (~50%). These tumors are usually single and are rarely associated with the syndrome typically found in association with pancreatic somatostatinomas (diabetes mellitus, steatorrhea, cholelithiasis). Some duodenal somatostatinomas contain psammoma-like bodies that are positive for periodic acid-Schiff (6). However, such psammoma-like bodies are not specific for somatostatinomas and may also be found in other types of endocrine tumors. In most of somatostatinomas the only secretory product identified by immunohistochemistry has been somatostatin, although occasional cells containing gastrin, substance P and vasoactive intestinal polypeptide (VIP) are encountered. Sporadic tumors are more frequently multihormonal than those associated with neurofibromatosis. Ultrastructural analysis reveals typical D-cell granules in the cytoplasm of the neoplastic cells.

**Other types of neuroendocrine tumors**

These tumors can produce a variety of bioactive peptides and amines, such as parathyroid hormone, vasopressin, adrenocorticotropic hormone (ACTH) and calcitonin. Some show the corresponding humoral syndrome but most do not. Exceptional duodenal neuroendocrine tumors are associated with the typical “carcinoid syndrome”.

**Small-cell poorly differentiated carcinoma**

These highly malignant tumors occur in all portions of the gastrointestinal tract, including the duodenum. The majority of such tumors, however, which are analogous to the “oat-cell” carcinomas of the lung, are found in the esophagus. Immunohistochemistry demonstrates some peptides, most commonly calcitonin and ACTH, although one duodenal small-cell endocrine carcinoma expressed VIP production. The patient, however, did not have the typical “WDHA” (watery diarrhea, hypokalemia, achlorhydria) syndrome that accompanies most VIP-producing tumors elsewhere (7). Thus, virtually all these tumors are clinically “silent” and their biological behavior is similar to that of the small-cell tumors of the respiratory tract. They spread and metastasize very early and respond readily to multidrug chemotherapy.

**Mixed endocrine-exocrine tumors**

Occasional endocrine-appearing argentophilic cells are common in many digestive neoplasms. Although early reports suggested that the presence of endocrine cells in neoplasms does not influence prognosis, subsequent reports indicated that the existence of a significant neuroendocrine cell population might worsen such prognosis. The appellation of mixed or composite tumors is generally restricted to those entities containing at least 30-50% endocrine elements. Theoretically, such mixed or composite tumors can be divided into two categories: i) combination tumors, containing two distinct populations of cells, one with an endocrine and the other with an exocrine phenotype; and ii) amphoteric tumors, composed of a single population of cells, all simultaneously demonstrating exocrine and endocrine traits. Some tumors, however, may exhibit a multiplicity of cell types, including endocrine, exocrine and truly amphoteric. Immunohistochemical studies have revealed a variety of bioactive substances, including calcitonin, gastrin, serotonin and somatostatin.

One type of combination tumor is the adenocarcinoma or composite cell carcinoma. With light microscopy they present as ordinary glandular or tubulovillous carcinomas but on careful inspection at least one-third to one-half of their cells have endocrine characteristics. Another type of combination tumor is the variously called goblet cell carcinoid, mucinoid carcinoid, adenocarcinoid and crypt cell carcinoma. However, these tumors occur mainly in the appendix and rarely in the colon. An example of an amphoteric tumor is the so-called tubular carcinoid, which is characterized by the presence of tubules or glands, the cells of which are both argentophil and mucin-positive. An immunohistochemical analysis reveals the presence of glucagon immunoreactivity in their cells. These tubular carcinoids are simultaneously and strongly positive for carciinoembryonic antigen and for chromogranin A.

**Familial neuroendocrine tumors**

**Multiple endocrine neoplasia**

The Zollinger-Ellison syndrome commonly occurring in patients with MEN1 was thought for a long time to be due to multiple pancreatic gastrinomas. However, further studies have revealed that pancreatic gastrinomas are the exception in patients with MEN1, although their pancreas may be studded with tumors of varying sizes (8). Most MEN1 gastrinomas are instead located in the duodenum, where they form multiple tiny nodules (9). Although they are often smaller than 0.6 cm, they have frequently metastasized to the regional lymph nodes at the time of diagnosis. These lymph nodes may then be much larger than the primary tumors in the duodenum, which easily escape detection if not looked for carefully.

The MEN1 syndrome is associated with inherited mutations of the MEN1 gene, which codes for a new 660 amino acid protein (10). The MEN1 gene encompasses 10 exons and is approximately 9 kb long. The 2.8 kb mRNA is expressed not only in neuroendocrine tissues but also in a variety of other organs, indicating that MEN1 may play a role not only in the development of MEN1-associated tumors, but also in that of other tumors (11, 12). The function of the MEN1 protein is not yet known but it is speculated that it is involved in cellular control and that it represents a new type of tumor suppressor gene.

**Neurofibromatosis Recklinghausen**

Neurofibromatosis (NE), also called von Recklinghausen disease, is an autosomal dominant disorder (4:10,000) associated with mutations of the neurofibromatosis I (NFI) gene. The NE type I syndrome is characterized by cafe-au-lait spots and neurofibromatous skin tumors and is associated with many, variable, pleiotropic manifesta-
tions that may result in disfigurement and functional impairment. Other manifestations of the syndrome include neuroendocrine tumors of the duodenum (somatostatinomas) and pheochromocytomas.

Numerous mapping studies localized the NFI gene on the long arm of chromosome 17 near the centromere and led to cloning of the complete coding region (13). The NFI gene encodes an mRNA of 11-13 kb containing at least 59 exons. Four alternatively spliced NFI transcripts have been identified. NFI appears to be a tumor-suppressor gene. Its product, called neurofibromin, is a GTPase activating protein (GAP)-like polypeptide that appears to down-regulate the RAS oncogene. Over 80% of germline mutations appear to predict severe truncation of neurofibromin.

Somatostatinomas in neurofibromatosis patients are typically pure" tumors and exhibit psammoma bodies in approximately 66% of tumors. Metastatic disease is rare (27%) and mainly confined to lymph nodes (88%)

References
2. Andrew A, Kramer B, Rawdon RB. The origin of gut and pancreatic neuroen-
docrine (APUD) cells—the last word? J Pathol 1998; 186: 117-118.
5. Veesir S, Petras RE. Duodenal microgastrinoma producing the Zollinger-
7. Swanson PE, Dykoski D, Wick MR et al. Primary duodenal small-cell neu-
8. Pipeleers MM, Somers O, Willems G et al. Gastrinomas in the duodenum of patients with multiple endocrine neoplasia type I and the Zollinger-Ellison syn-
13. Marchuk DA, Saulino AM, Tavakkol R et al. cDNA cloning of the type I neu-

Gangliocytic paragangliomas of the duodenum

J. Lechago

Dept. of Pathology and Medicine, Baylor College of Medicine
and The Methodist Hospital, Houston, Texas, USA.

Introduction

Gangliocytic paragangliomas, also referred to as nonchromaffin paragangliomas or paraganglio-neuramas, are peculiar lesions com-posed of neuroendocrine epithelial cells, ganglionar neurons and sustentacular cells, which have been reported almost exclusively in the upper gut. Within the latter, they are found almost invariably in the duodenum, generally in the vicinity of the ampulla of Vater, although isolated reports of their presence in the jejunum have been made. Whereas these are virtually always isolated single lesions, there are sporadic reports of multiple lesions or of their association with duodenal adenocarcinoma, somatostatin-producing carcinoid tumor, patients with von Recklinghausen disease, or pancreatic rests.

Gangliocytic paragangliomas generally appear as submucosal masses that protrude into the lumen of the duodenum where they may obstruct or bleed as a consequence of their tendency to ulcerate. They generally measure between 1 and 3 cm in maximum diameter, although rare instances of lesions measuring 10 cm in maximum diameter have been recorded. They are more common in men than in women and their age of appearance ranges between the third and the ninth decade of life, with a peak incidence in the mid-fifties.

Histogenesis

In view of the diversity of the elements composing gangliocytic paragangliomas, some authors have proposed that these lesions represent a hamartomatous proliferation, perhaps originating from different embryonal layers during the formation and migration of the pancreatic primordia. However, the fact that a handful of such lesions has undergone malignant transformation and produced lymph node metastases argues in favor of a true neoplastic nature. Interestingly, in one of the reported cases of lymphatic spread, only the neuroendocrine epithelial elements were present in the metastasis. This finding suggests that, even if these lesions are originally developed from diverse origins, their epithelial neuroendocrine component is indeed capable of behaving as a neoplasia, and even with malignant potential.

Microscopic morphology

Light microscopy and histochesmy

Three cellular elements compose gangliocytic paragangliomas of the duodenum. Firstly, neuroendocrine cells with an epithelial appearance. These cells have a moderate amount of faintly granular eosinophilic or amphophilic cytoplasm and round to oval nuclei with delicate, stippled chromatin and generally inconspicuous nucleoli. They are clustered in variable patterns, mostly in so-called "Zellballen" like paragangliomas elsewhere, or in anastomosing ribbons like card-
ioid tumors. Grimelius' silver stain is generally positive, whereas only exceptionally they are positive for the argentaffin stains. Secondly, ganglion neurons, characterized by abundant cytoplasm with an irregular contour and large, vesicular nuclei endowed with prominent nucleoli. These cells are found interspersed among clusters of neuroendocrine cells or in close contact with them and their cytoplasm displays strong staining with cresyl violet, indicating the presence of Nissi substance. Apparent transitional forms between neuroendocrine and ganglion cells have been reported. Thirdly, Intersitial cells, representing Schwann cells, in contact with neurons...