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Pathology and Nomenclature of Human Gastrointestinal Neuroendocrine (Carcinoid) Tumors and Related Lesions

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Abstract. The pathology and nomenclature of the neuroendocrine cell proliferations in the gut are reviewed. The neoplastic lesions are discussed within the light of a new classification system that attempts to consider the morphologic, functional, and biologic features of the tumors.

Endocrine tumors (thyroid tumors excluded) were once thought to be rarities. However, with increasing knowledge about the features of endocrine cells that give rise to tumors and the increasing ability to identify those cells in normal and pathologic states, it has become obvious that the spectrum of endocrine tumors is wider than assumed. The most important contribution to the pathology of endocrine tumors was the identification and definition of what is currently called the neuroendocrine cell system [1]. As defined today, this system includes all neuronal and endocrine cells that share a common phenotype characterized by simultaneous expression of certain marker proteins (i.e., general neuroendocrine markers) and cell type-specific regulatory peptides (i.e., peptide hormones, neurotransmitters, among others). Using these criteria, which require the application of immunocytochemistry, it has been recognized that neuroendocrine cells are involved in a wide variety of tumors including those that histologically lack the features of endocrine differentiation or arise in tissues that do not belong to the classic endocrine organs. Considering this reorientation of our understanding of the contribution of the endocrine cells to tumor pathology, we herein briefly review the morphologic spectrum and nomenclature of the gastrointestinal endocrine tumors, which are collectively known as carcinoids but are here termed neuroendocrine tumors. The reason for using the term neuroendocrine tumor will become obvious from the subsequent discussion.

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Nomenclature and Classification

Since the introduction of the term "carcinoid" by Oberndorfer in 1907 and the recognition of its endocrine nature by Gosset and Masson in 1914 using silver staining techniques, this name has been used to designate all endocrine tumors of the gastrointestinal tract displaying similar features. As comparable tumors were also found in other organs such as the lung, the term carcinoid finally was extended to a variety of endocrine neoplasms from different organs.

In 1963 Williams and Sandler [2] classified the gastrointestinal carcinoids on the basis of their embryogenesis into foregut carcinoids (stomach, pancreas, duodenum, upper jejunum), midgut carcinoids (lower jejunum, ileum, appendix, cecum), and hindgut carcinoids (colon and rectum). Although this categorization revealed for the first time some general clinicopathologic differences among the gastrointestinal carcinoids, its usefulness in practical diagnostic work has proved to be limited by its failure to characterize individual tumor entities with well defined histologic, cytologic, hormonal, and clinicopathologic profiles. This lack is particularly evident in the case of foregut tumors, which markedly differ in regard to morphology, function, and biology.

In 1980 the World Health Organization (WHO) classification of endocrine tumors applied the term carcinoid to all tumors of the diffuse endocrine system (synonymous with neuroendocrine cell system), excluding pancreatic endocrine tumor (islet cell tumor), medullary carcinoma of the thyroid, paraganglioma, small-cell lung carcinoma, and Merkel cell tumor of the skin. The carcinoids were then subdivided on the basis of various silver and other granule-staining techniques into (1) enterochromaffin (EC) cell carcinoids ("classic" carcinoids, "argentaffinomas"); (2) gastrin (G) cell carcinoids; and (3) other carcinoids. The broad use of the WHO terminology, however, has proved difficult and has often created confusion among pathologists and clinicians. This confusion is primarily due to the fact that the wide application of progressively refined techniques in pathology (i.e., the progress from hematoxylin-eosin stain to the methods of biochemistry, histochemistry, immunocytochemistry, and molecular biologic techniques) has revealed a great diversity among neuroendocrine

tumors. Thus tumors were identified as neuroendocrine neoplasms that lacked the histologic characteristics of endocrine differentiation but displayed neuroendocrine features when examined immunocytochemically. The historical term "carcinoid" has therefore become more and more inappropriate to encompass all neoplasms with neuroendocrine features [3].

Another problem in conjunction with the term carcinoid comes from the fact that the clinically characterized "carcinoid syndrome" mostly relates to a certain type of carcinoid, the EC cell carcinoid, which produces serotonin and substance P, whereas non-EC cell carcinoids are associated with other endocrine syndromes or are functionally silent.

Finally, there is a great deal of uncertainty among pathologists concerning the prognosis of the various "carcinoids" because the WHO classification only vaguely considers the biologic behavior of the neuroendocrine neoplasms.

For these reasons a number of investigators, including our group, proposed to replace the term "carcinoid" by the more uncommitting name "neuroendocrine tumor" [4–7]. This name includes the entire neuroendocrine tumor spectrum, with the classic carcinoid at one end and the undifferentiated carcinoma at the other. In addition, we proposed a new classification scheme that deals with all aspects of the pathology of neuroendocrine neoplasms [8]. The first principle is that the tumors are distinguished according to the site of origin. For the gastrointestinal neuroendocrine tumors, this rule implies that the tumors of the stomach, duodenum, jejunum-ileum, appendix, and colon-rectum are considered separately. The second principle is to subdivide the neoplasms into (I) tumors with benign behavior, (II) tumors with uncertain behavior (i.e., tumors that may behave benignly or as low-grade malignancies), (III) tumors with low grade malignant behavior, and finally (IV) high-grade malignant tumors. The main criteria for this biologic categorization are histologic differentiation, angioinvasion, direct invasion of neighboring organs, and the presence of metastases. An additional criterion is size, which has been established as a reliable prognostic parameter for a number of tumors. The third principle is to incorporate the hormonal function and various clinical associations of the neuroendocrine tumors into the classification, because these features appear to be related to the tumors' clinical behavior. Tumors causing an endocrine syndrome by uncontrolled secretion of a certain hormone have therefore been designated as "functioning," whereas those without a hormonal syndrome are called "nonfunctioning."

The new classification does not include neoplasms that have been termed mixed exocrine-endocrine or amphicrine tumors. Such tumors, which exhibit multiple lines of cellular differentiation, were first described in the appendix and were called goblet cell carcinoids. Recently, adenocarcinomas from different locations showing interspersed neuroendocrine cells have been reported in increasing numbers. These observations have given rise to a confusing array of names. In future it should therefore be attempted to define a simpler classification that separates truly mixed tumors (i.e., tumors in which the exocrine and endocrine cell populations are intimately mixed and the endocrine cell comprises about one-half of the tumor tissue) from tumors with a diffusely scattered subpopulation of neoplastic neuroendocrine cells and collision tumors. So far it seems that few tumors qualify as truly mixed (or composite), and most of the so-called mixed neoplasms belong to the group of tumors with only a small subpopulation of neuroendocrine cells. In general, mixed exocrine-endocrine neoplasms should be kept separate from neuroendocrine tumors because the biologic behavior of the former lesions appears to be dictated by the differentiation of the exocrine cell compartment.

Table 1. Neuroendocrine tumors of the stomach.

Benign: Nonfunctioning, well differentiated small tumor (up to 1 cm) within the mucosa-submucosa and without angioinvasion. Usually ECL cell tumors of the fundic mucosa associated with chronic atrophic gastritis (CAG) and hypergastrinemia.
Benign or low grade malignant: Nonfunctioning, well differentiated tumor within the mucosa-submucosa of intermediate size (> 1 up to 2 cm) without angioinvasion, or of small to intermediate size (up to 2 cm) with angioinvasion. (1) Usually ECL cell tumors of the fundic mucosa associated with CAG and hypergastrinemia. (2) Rarely MEN-I-associated or sporadic ECL cell tumors.
Low grade malignant[a]: (1) Nonfunctioning, well differentiated tumor of large size (> 2 cm) or extending beyond the submucosa. (a) Usually sporadic ECL cell tumors; rarely serotonin-producing tumors[b] or others. (b) Rarely MEN-I- or CAG-associated ECL cell tumors. (2) Functioning, well differentiated tumor of any size and extension. Sporadic gastrinoma, serotonin-producing tumor[b] or others.
High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate or small-cell carcinoma.

[a] If metastasis or gross invasion is present, the tumor should be called a low grade neuroendocrine carcinoma.
[b] Also called an EC cell tumor.

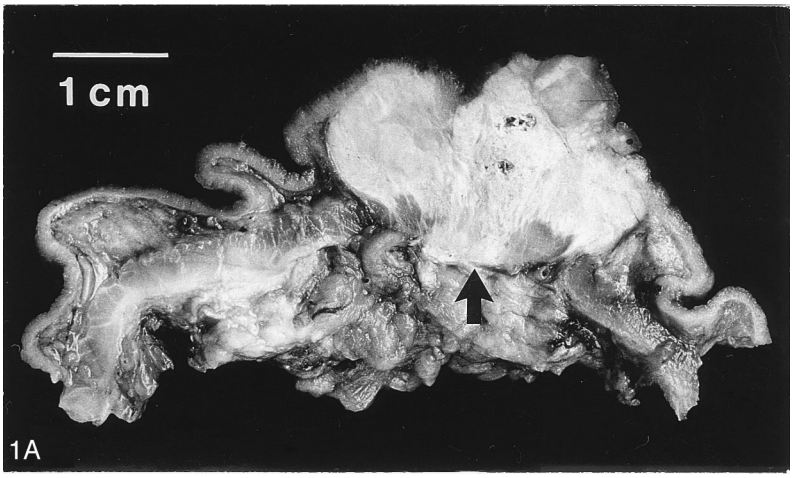
Esophageal Tumors

Neuroendocrine tumors primarily arising in the esophagus are rare. Because all tumors so far reported have shown the features of high grade undifferentiated carcinoma indistinguishable from small-cell carcinoma of the lung [5, 9, 10], no attempt has been made to stratify these tumors further. Some of the tumors display the combined features of small-cell carcinoma with either squamous or glandular differentiation [11]. Grossly, the tumors usually occur in the lower half of the esophagus and present as large fungating, ulcerating masses. Because of rapid dissemination the prognosis is poor.

Gastric Tumors

In the early studies by McDonald [12] and Godwin [13] gastric endocrine tumors accounted for only 3% of all neuroendocrine neoplasms of the gut. However, according to more recent investigations [14–16] it seems that their incidence is probably greater than previously recognized and may range between 11% and 41%. Likely this change is not a real increase in frequency but may be primarily due to the increased use of endoscopy in gastroenterology and our increased knowledge about these diseases.

The gastric neuroendocrine tumors may be stratified according to their association with certain forms of gastritis and other diseases [17–23] into tumors associated with hypergastrinemia and chronic atrophic gastritis (CAG) with or without pernicious anemia; tumors associated with the Zollinger-Ellison syndrome (ZES) in combination with the syndrome of multiple endocrine neoplasm type I (MEN-I); and tumors occurring as sporadic neoplasms. This distinction bears prognostic relevance, as tumors associated with CAG and MEN-I/ZES have a much better



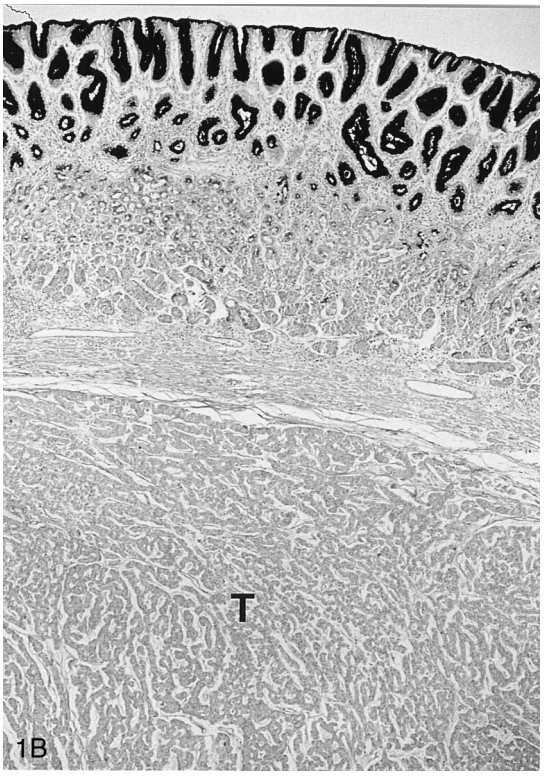


Fig. 1. A. Cross section through a sporadic nonfunctioning, well differentiated neuroendocrine carcinoma of the stomach. Arrow indicates invasion through the muscular layer. **B**. Microscopic section from this tumor (T) showing a well differentiated neuroendocrine carcinoma in the submucosa of the gastric fundus. (PAS. ×60)

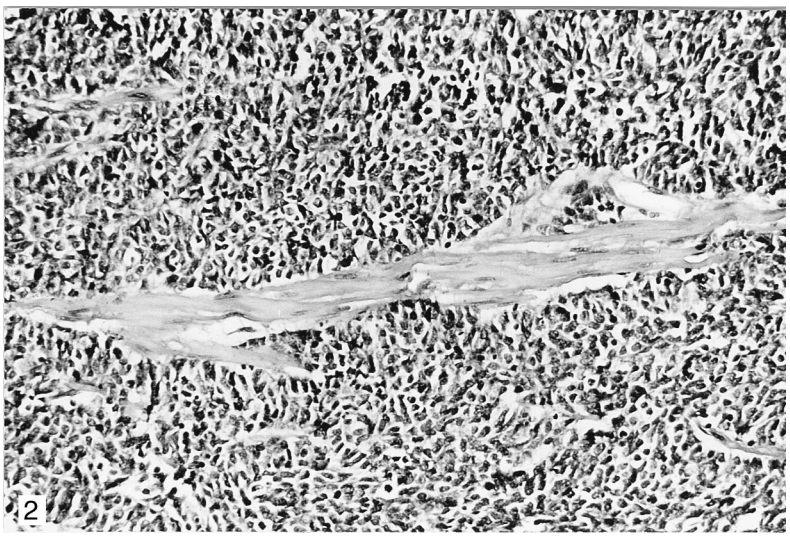


Fig. 2. Poorly differentiated neuroendocrine carcinoma of the stomach. (H & E. ×230)

prognosis than most of the sporadic tumors (for more details see Rindi et al., this issue). However, as size and histologic differentiation [17] seem to have even a greater impact on the prognosis, the classification presented in Table 1 is primarily based on the morphologic features of gastric neuroendocrine tumors.

Most gastric neuroendocrine tumors are small (< 1 cm in diameter), well differentiated, and confined to the mucosa and submucosa of the corpus-fundic region and the corpus-antral transition zone of the stomach. Grossly, they present as polypoid tumors. The benign behavior of these tumors is well documented by several clinicopathologic studies [17, 18, 21, 22, 24, 25]. They are composed mainly of enterochromaffin-like (ECL) cells, which are argyrophilic and have been shown to produce histamine. The tumors usually present as multiple growths ("carcinoidosis") in association with CAG of the corpus-fundus, which is due to autoimmune destruction of acidopeptic glands, resulting in the profound achlorhydria, hypergastrinemia, and commonly pernicious anemia. Because gastrin is trophic to the ECL cells [19, 22], the CAG-associated tumors, which comprise approximately two-thirds of all gastric neuroendocrine neoplasms, arise on a background of ECL cell hyperplasia (see later). In a series of 27 CAG-associated neuroendocrine tumors with a diameter up to 2 cm (mean diameter 0.7 cm), none of the tumors had metastasized [17], and a review of the literature revealed lymph node metastases in only 17 of 197 (8.6%) cases [17].

Few of the nonantral well differentiated neuroendocrine tumors arise in association with an end-stage *Helicobacter pylori* gastritis (HG) involving the corpus-fundus mucosa of the stomach in addition to the antrum [26]. Another rare background condition favoring the development of multiple ECL cell tumors is Zollinger-Ellison syndrome in the setting of MEN-I. With this condition, tumor-associated hypergastrinemia causes acidopeptic gland hypertrophy and promotes argyrophilic ECL cell hyperplasia, and the combined action of MEN-I-associated tumor suppressor gene loss and chronic hypergastrinemia seems to induce ECL cell tumors [20]. Both HG- and MEN-I/ZES-associated tumors are usually small (mean 0.5 cm; range 0.1–1.6 cm), but the MEN-I/ZES-associated tumors may show lymph node metastases [17, 20].

Well differentiated neuroendocrine tumors arising sporadically in the gastric mucosa—being > 2 cm (Fig. 1) or showing angioinvasion or deep stomach wall invasion—develop metastases in more than 60% of cases, with liver metastases in about 50% of cases [17]. The mean survival of patients with fatal cases was

about 2 to 4 years. Only a few of these tumors produce carcinoid syndrome of the classic, or "histamine," type [27]. These tumors comprise 20% of all gastric neuroendocrine tumors and present as solitary lesions. They may be composed of a mixture of endocrine cell types but are usually predominantly ECL cells. Tumors consisting of gastrin cells are rare and occur only in the antropyloric region [28].

Poorly differentiated neuroendocrine carcinomas of the stomach are composed mainly of intermediate-size cells rather than small cells (Fig. 2) and, like comparable tumors from other sites, have a poor prognosis, with three-fourths of the patients dying within 1 year from diagnosis owing to extensive metastatic disease [17, 23].

The above data indicate that, for well differentiated gastric neuoroendocrine tumors, size is probably the most important individual prognostic factor (Table 1). Tumors < 1 cm in diameter follow a benign course. The behavior of tumors > 1 cm and up to 2 cm, single or multiple, with or without associated CAG, MEN-I/ZES, and hypergastrinemia remains difficult to predict, although most of the cases so far investigated showed localized disease [15, 17, 24, 29]. Tumors > 2 cm in diameter must be considered malignant, as they frequently develop metastases. Poorly differentiated neuroendocrine carcinomas, regardless of their size, indicate a poor prognosis with a short survival time.

Table 2. Neuroendocrine tumors of the duodenum.

Benign: (1) Nonfunctioning, well differentiated small tumor (≤ 1 cm) within the mucosa-submucosa and without angioinvasion. Gastrin or serotonin-producing[a] tumors in the proximal duodenum. (2) Gangliocytic paraganglioma (any size; periampullary region).

Benign or low grade malignant: Nonfunctioning, well differentiated tumor within the mucosa-submucosa, of intermediate size ($>$ 1 to 2 cm) without angioinvasion or of small to intermediate size (up to 2 cm) with angioinvasion. (1) Serotonin-producing[a] tumors or others (any site). (2) Somatostatin-producing tumors (ampullary region) with or without Recklinghausen's disease.

Low grade malignant[b]: (1) Nonfunctioning, well differentiated large tumor ($>$ 2 cm) or extending beyond the submucosa. (a) Gastrin- or serotonin-producing[a] tumors (any site) and (b) somatostatin-producing tumors (ampullary region) with or without associated Recklinghausen's disease. (2) Functioning, well differentiated tumor of any size and extension. (a) Sporadic gastrinoma, serotonin-producing tumor[a] or others. (b) Hereditary MEN-I-associated gastrinoma, usually multiple.

High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate or small-cell carcinoma (usually ampullary region).

[a] Also called EC cell tumor.

[b] If metastasis or gross invasion is present, the tumor should be called a low grade neuroendocrine carcinoma.

Duodenal Tumors

The pathology and biology of the neuroendocrine tumors of the duodenum, which are less frequent (relative incidence 1–2%) than gastric neuroendocrine tumors, has been the subject of a number of investigations [30–42]. According to these studies five major types of neuroendocrine tumor can currently be distinguished in the duodenum: gastrin-producing tumors, somatostatin-producing tumors, gangliocytic paragangliomas, serotonin/calcitonin/PP-producing tumors, and poorly differentiated carcinomas. In contrast to the neuroendocrine tumors of the stomach, for which tumor size and the association with other diseases are the most important prognostic factors, the behavior of the neuroendocrine tumors of the duodenum is, in addition to size, strongly associated with their functional features (Table 2).

Gastrin-producing tumors are most frequent among the neuroendocrine duodenal tumors, representing more than 60% of all cases [31, 37]. Approximately one-third of the tumors are associated with a ZES (i.e. "functioning tumors"), which may be part of the MEN-I syndrome [35, 37]. On the other hand, all patients with sporadic ZES are considered, at least 40% of them (Klöppel, Marichal, and Dralle, unpublished observations) appear to have a duodenal gastrinoma, whereas in the remaining patients the tumor is found in the pancreas. In MEN-I patients with ZES, the incidence of duodenal gastrinoma is even higher and may reach 90% [6, 42]. Another characteristic of MEN-I-associated duodenal gastrinomas is their frequent multicentricity. Sporadic and MEN-I-associated duodenal gastrinomas reside preferentially in the first and second portions of the duodenum. Grossly, they present as small (< 1 cm) sessile submucosal nodules that are easily overlooked. Histologically, they show a trabecular or pseudorosette pattern. Although small, many of them, when functioning, have already metastasized to the regional lymph nodes at the time of diagnosis [42]. These lymph node metastases may be much larger than the primary lesions in the duodenum. Spread to the liver, however, is a rare and late event. According to these features most functioning gastrin cell tumors fall in the category of neuroendocrine tumors of the duodenum with low grade malignant behavior, either as sporadic gastrinoma or hereditary MEN-I-associated gastrinoma (Table 2). In contrast, most nonfunctioning gastrin-producing tumors show a benign behavior and are located in the duodenal bulb [37].

Somatostatin-producing tumors are second in frequency and account for 15% to 20% of all neuroendocrine tumors of the duodenum [30, 37]. They occur almost exclusively in the ampulla of Vater and present as bulky lesions. Histologically, they are characterized by a glandular pattern (Fig. 3) and the presence of psammoma bodies [30]. At the time of diagnosis most of them show invasion of the muscular layer and regional lymph node metastases. Although they stain strongly for somatostatin, they are nonfunctioning (i.e., not associated with a somatostatinoma syndrome), as it may be produced by their pancreatic counterparts. However, about one-third of the patients have an associated neurofibromatosis type 1 (von Recklinghausen's disease) [33, 37]. Because of their locally invasive pattern and their size, most somatastatin cell tumors fall into the category of nonfunctioning, well differentiated neoplasms with low grade malignant behavior (Table 2).

Third in frequency are the gangliocytic paragangliomas. They occur in the ampullary-periampullary region [32, 34, 39]. Histologically, they are characterized by their gangliocytic component; immunocytochemically, they express predominantly somatostatin and PP and are also positive for S-100. Although they are often large (> 2 cm) and may involve the muscularis propria, they usually behave benignly. Most of the gangliocytic paragangliomas therefore fall into the category of tumors with benign behavior (Table 2).

Duodenal neuroendocrine tumors producing serotonin or other hormones such as calcitonin and PP are rare. Outside of the

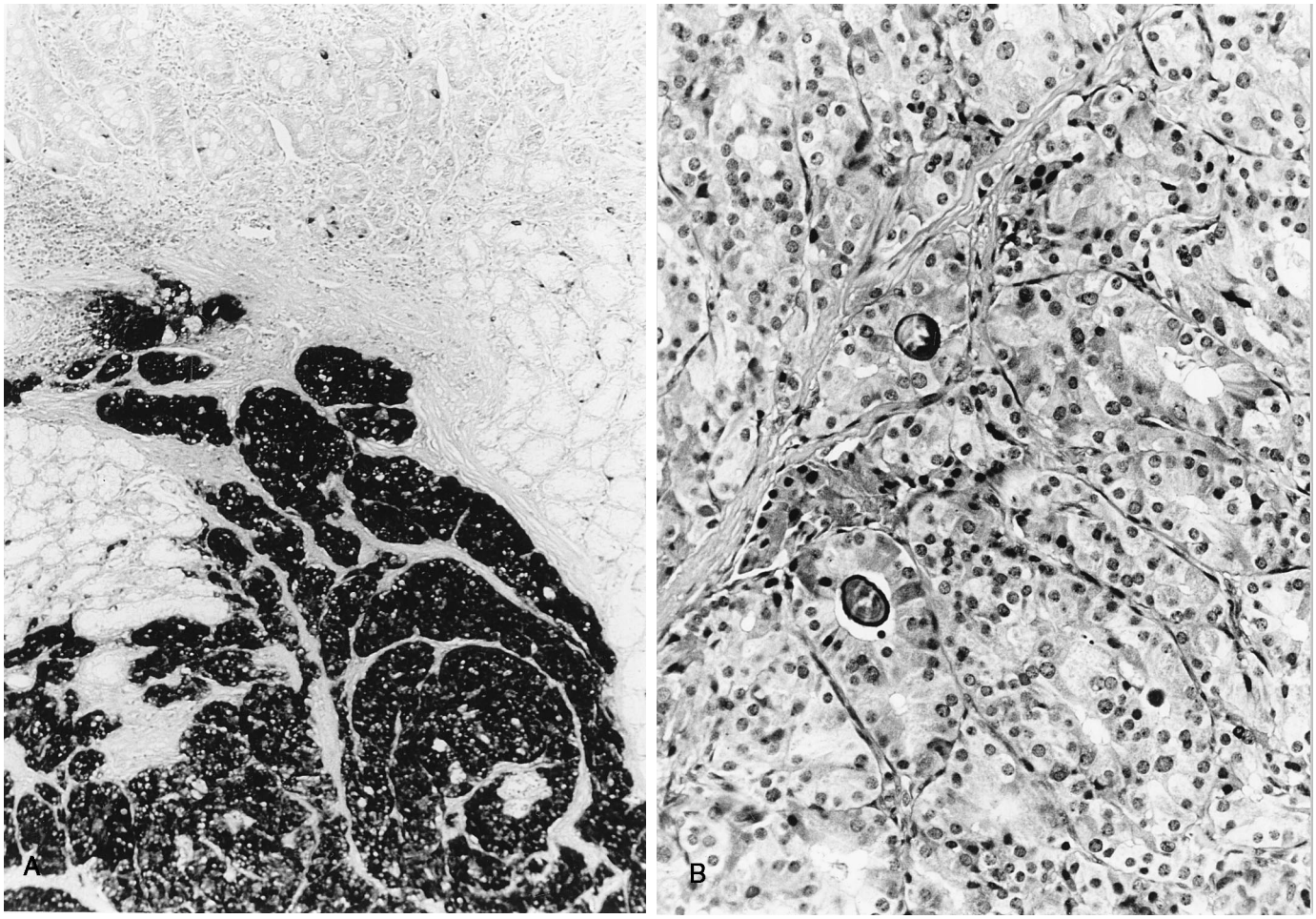


Fig. 3. Well differentiated neuroendocrine tumor from the duodenum, showing (**A**) intense immunostaining for somatostatin (×60) and (**B**) a trabecular-glandular pattern with psammoma bodies. (×250)

ampulla they are usually small and lack signs of infiltrative growth. The occurrence of a carcinoid syndrome is exceptional. Hence most of them represent nonfunctioning, well differentiated tumors with benign behavior (Table 2). A few of these tumors are found in the ampulla, and about half of these lesions fall into the category of tumors with low grade malignant behavior [40, 41] (Table 2).

Poorly differentiated neuroendocrine carcinomas are rare. Most occur in the ampulla of Vater [36, 38]. Histologically, they represent undifferentiated carcinomas of the intermediate-cell or small-cell type. The neuroendocrine nature of these highly malignant neoplasms is revealed only by their positivity for general neuroendocrine markers.

Jejunoileal Tumors

Neuroendocrine tumors of the jejunum and ileum account for 20% to 30% of all neuroendocrine neoplasms of the gut. Most of the tumors are of the classic "argentaffin" carcinoid type. They are composed of EC cells that produce serotonin and substance P

Table 3. Neuroendocrine tumors of the jejunum and ileum.

Benign: Nonfunctioning, well differentiated small tumor (≤ 1 cm) within the mucosa-submucosa but without angioinvasion. Usually serotonin-producing[a] tumors in the terminal ileum.

Benign or low grade malignant: Nonfunctioning, well differentiated tumor of intermediate size (> 1 up to 2 cm) but without angioinvasion or extension beyond the submucosa. Usually serotonin-producing[a] tumors of the terminal ileum.

Low grade malignant[b]: (1) Nonfunctioning, well differentiated large tumor (> 2 cm) or extending beyond the submucosa or angioinvasive (or both). Usually serotonin-producing[a] tumors of the terminal ileum.
(2) Functioning, well differentiated tumor of any size and extension.
(a) Serotonin-producing tumor[a] with carcinoid syndrome.[c]
(b) Sporadic gastrinoma (upper jejunum).

High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate or small-cell carcinoma.

[a] Also called an EC cell tumor.

[b] If metastasis or gross invasion are present, the tumor should be called a low grade neuroendocrine carcinoma.

[c] As serotonin is metabolized and inactivated by the liver, serotonin-secreting tumors of the gut produce a syndrome only if liver metastases are already present.

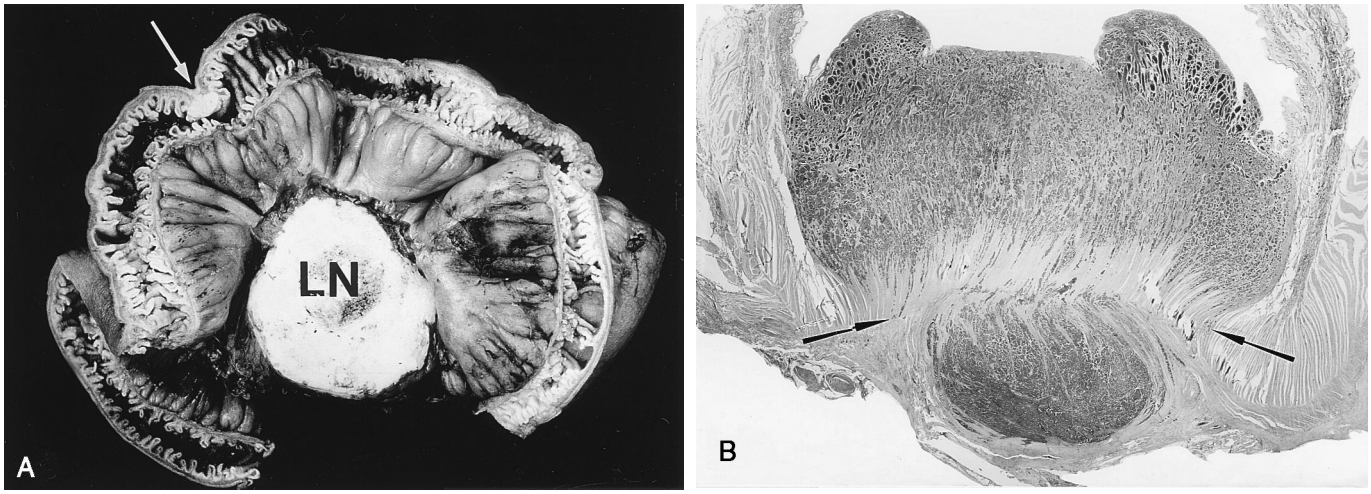


Fig. 4A. Well differentiated neuroendocrine carcinomas (arrow) of the ileum in a 64-year-old man with lymph node (LN) and liver metastases and carcinoid syndrome. **B**. Microscopic section of this tumor showing invasion of the muscular layer. (H & E. ×40)

[43–46]. Enteroglucagon/PP/PYY-producing tumors are exceptionally rare [46] (Table 3).

The serotonin- and substance P-producing neuroendocrine tumors occur preferentially in the second part of the ileum. Grossly, they appear as yellowish gray nodules in the submucosa, which protrudes into the lumen of the gut. Histologically, theyshow an insular pattern. If found at autopsy, they are usually small (up to 1 cm) and show no metastases. These tumors constitute the neoplasms with benign behavior (Table 3). In surgical series, which encompass the symptomatic cases, the tumors are > 1 cm and invade the mesentery, angulating and distorting the bowel wall. This bowel deformity is caused by contraction of desmoplastic tissue induced by the tumor. Clinically, it leads to intestinal obstruction. Tumors > 2 cm in diameter are almost all malignant (i.e., presenting with regional lymph node metastases) (Fig. 4). In up to 40% of patients there are multiple tumors. Approximately 20% of the malignant tumors are associated with carcinoid syndrome, which implies that these patients already have liver metastases. The tumors > 2 cm, extending beyond the submucosa, angioinvasive, and with a carcinoid syndrome comprise the category of low grade malignancies (Table 3).

Jejunal tumors or tumors occurring in Meckel's diverticulum are rare. Histologically, they show a trabecular pattern. Immunocytochemically, they more often stain for gastrin or somatostatin than for serotonin. Poorly differentiated neuroendocrine carcinomas are rare in the jejunum or ileum.

Table 4. Neuroendocrine tumors of the appendix.

Benign: Nonfunctioning, well differentiated small tumor (< 2 cm) without extension into the mesoappendix. (1) Usually serotonin-producing[a] tumors at the tip of the appendix. (2) Rarely enteroglucagon-producing tumors.[b]

Benign or low grade malignant: Nonfunctioning, well differentiated large tumor (> 2 cm) with extension into the mesoappendix. (1) Usually serotonin-producing[a] tumors at the tip of the appendix. (2) Rarely enteroglucagon-producing tumors.[b]

Low grade malignant[c]: Nonfunctioning, well differentiated large tumor (> 3 cm), with deep invasion into the mesoappendix. Serotonin-producing tumors.[a] (2) Functioning, well differentiated tumor of any size and extension. Serotonin-producing tumor[a] with carcinoid syndrome.[d]

High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate-cell or small-cell carcinoma.

[a] Also called an EC cell tumor.

[b] Also called L cell tumors, producing glucagon-, PP-, and PYY-related peptides.

[c] If metastases or gross invasion are present, the tumor should be called a low grade neuroendocrine carcinoma.

[d] As serotonin is metabolized and inactivated by the liver, serotonin-secreting tumors of the gut produce a syndrome only if liver metastases are present.

Appendiceal Tumors

Approximately 40% to 50% of gut neuroendocrine tumors are found in the appendix. As in the ileum, most tumors are classic "argentaffin" carcinoids composed of EC cells that produce serotonin and substance P [47–52]. Only a few are "nonargentaffin" L cell tumors that produce glicentin-related peptides (enteroglucagons) and PP-PYY [50, 52] (Table 4). The common EC cell tumor is usually an incidental finding. Most of them (70%) are located at the tip of the appendix, are rarely > 2 cm, and show an insular pattern [50]. These tumors appear to derive from subepithelial neuroendocrine complexes rather than from intraepithelial endocrine cells [47, 53]. This view is supported by the finding that S-100 protein-positive Schwann-like (sustentacular) cells are found as an integral component of appendiceal EC cell tumors, whereas these cells are lacking in ileal and colonic EC cell tumors, which probably develop from EC cells of the mucosal crypts [53].

The second, much less common group of appendiceal neuroendocrine tumors is composed of nonargentaffin L cell tumors that produce glicentin-related peptides (enteroglucagons) and PP/PYY. They have a trabecular growth pattern [51, 52].

Appendiceal neuroendocrine tumors have a good prognosis. The reported frequency of metastasis from these tumors lies between 1.4% and 8.8% [13, 54–59]. The tumors that metastasize usually are > 2.0 cm [49]. In an analysis of 414 cases from the

Table 5. Neuroendocrine tumors of the colon and rectum.

Benign: Nonfunctioning, well differentiated small tumor (< 2 cm) within the mucosa-submucosa and without angioinvasion. (1) Trabecular enteroglucagon-producing tumors,[a] usually in the rectum. (2) Serotonin-producing tumors,[b] usually in the cecum or colon.
Benign or low grade malignant: Nonfunctioning, well differentiated small tumor (< 2 cm) within the mucosa-submucosa but with angioinvasion. (1) Trabecular enteroglucagon-producing tumors,[a] usually in the rectum. (2) Serotonin-producing tumors,[b] usually in the cecum or colon.
Low grade malignant[c]: (1) Nonfunctioning, well differentiated large tumor (> 2 cm), sometimes extending beyond the submucosa. (a) Trabecular enteroglucagon-producing tumors,[a] usually in the rectum. (b) Serotonin-producing tumors,[b] usually in the cecum or colon. (2) Functioning, well differentiated tumor of any size and extension. Serotonin-producing tumor[b] with carcinoid syndrome.[d]
High grade malignant: Functioning or nonfunctioning poorly differentiated intermediate-cell or small-cell carcinoma.

[a] Also called L cell tumors, producing glucagon-, PP-, and PYY-related peptides.

[b] Also called an EC cell tumors.

[c] If metastasis or gross invasion is present, the tumor should be called a low grade neuroendocrine carcinoma.

[d] As serotonin is metabolized and inactivated by the liver, serotonin-secreting tumors of the gut produce a syndrome only if liver metastases are present.

literature, McGillivray et al. [60] found that tumor size > 2 cm and invasion of the mesoappendix were closely related to the presence of metastasis. In those patients with tumors < 2 cm, mesoappendiceal invasion was significantly associated with metastasis. The size of the tumor is thus clearly related to the risk of malignant behavior but cannot be relied on as the sole predictor of malignancy. Invasion of the mesoappendix is predictive of an increased risk of metastasis for carcinoid tumors of the appendix < 2 cm [54, 60]. Location of the tumors at the base of the appendix with involvement of the surgical margin requires at least a hemicolectomy to avoid residual tumor or subsequent recurrence [61].

The carcinoid syndrome is rarely observed in neuroendocrine tumors of the appendix. When it manifests, it is almost always associated with widespread metastases of the tumor, predominantly to the liver and retroperitoneum [58, 59].

Colorectal Tumors

In the colon and rectum, at least three types of neuroendocrine tumor have been identified: L cell tumors producing glicentin-related peptides and PP-PYY, EC cell tumors producing serotonin and substance P, and poorly differentiated (small-cell) carcinomas [62–68] (Table 5).

Well differentiated L cell tumors, which show a trabecular pattern, usually occur in the rectum and account for approximately 10% of all gut neuroendocrine tumors [52]. Grossly, they form small (< 1 cm), solitary, firm submucosal nodules that are movable. Immunocytochemically, they are positive for glucagon-29, glucagon-37, glicentin, proglucagon cryptic fragments, PYY, PP, and Pro-PP icosapeptide [69]. Small populations of serotonin, substance P, somatostatin, insulin, enkephalin, β-endorphin, neurotensin, human chorionic gonatropin (α-hCG), and motilin immunoreactive cells may also be found [69–73]. To date, there is only one report of a rectal trabecular neuroendocrine tumor in which motilin cells represented the prevailing cell population [74]. Size is the usual prognostic predictor of well differentiated neuroendocrine tumors of the rectum [75, 76]. Comparing "benign and malignant carcinoids," Peskin and Orloff [77] found that 9 of 10 rectal carcinoids with diameters > 2 cm were locally invasive with or without distant metastases. On the other hand, 14 of 15 carcinoids measuring < 2 cm in their largest diameters failed to show local invasion or metastasis. Bates [78] confirmed the relation between size and malignancy. Of 37 rectal neuroendocrine tumors that had metastasized, 78% were > 2 cm. Only 8% of the 115 lesions < 2 cm had developed metastases. The risk of a tumor < 1 cm metastasizing is estimated at 3% or less [79]. A rectal neuroendocrine tumor 1.0 to 1.9 cm in diameter carries a 7% to 11% risk of metastasizing [79, 80]. The presence of invasion of the muscularis propria has also been considered as an index of tumor aggressiveness [76]. For tumors of intermediate size (1.0–1.9 cm), Naunheim et al. [79] found that 46% of lesions with invasion of the muscularis propria metastasized.

The EC cell tumors of the classic "argentaffin" carcinoid type, with characteristic insular pattern and serotonin production, are rare in the rectum [81, 82]. These neoplasms are the most frequent type of neuroendocrine tumors in the colon, with greatest prevalence in the cecum [62]. The colonic neuroendocrine tumors are usually larger than well differentiated neuroendocrine tumors of the rectum. In the review of Berardi [62], the average size for colonic tumors with metastasis was 6.1 cm, whereas that of tumors without metastasis was 4.7 cm. In a series of seven colonic neuroendocrine tumors, Morgan et al. [75] found all tumors > 2 cm were associated with lymph node metastases and six with distant metastases. The carcinoid syndrome was present in 4 of 118 cases of neuroendocrine tumors of the colon in Berardi's series [62], and in all these cases the tumors had metastasized.

Poorly differentiated neuroendocrine carcinomas present as bulky, rapidly developing masses [63, 83]. Their distribution in the colorectum resembles that of conventional colonic adenocarcinomas. An origin for such neoplasms in conventional colonic adenomas has been described by Mills et al. [67]. Microscopically, the cells are of small to intermediate size and arranged in solid groups with extensive necrosis. The tumor cells are generally unreactive to antisera directed against gut hormones but are strongly positive for cytosolic neuroendocrine markers and epithelial antigens [68]. At the ultrastructural level, scattered small (100–250 μm) neurosecretory granules are observed [63, 68]. Clinically, there has been no hormonal syndrome in any of the patients reported so far. The prognosis is poor, and most patients die with widespread metastases within a few months (average survival 5 months [68]) of clinical presentation.

Precursor Lesions

ECL Cell Hyperplasia

To date only one type of hyperplastic change of gut neuroendocrine cells is known to precede tumor development: ECL cell hyperplasia of the fundic mucosa of the stomach, which has already been mentioned in conjunction with the well differentiated neuroendocrine tumors associated with prolonged hypergas-

trinemia [19, 84]. There is experimental and clinicopathologic evidence that gastrin may act as a trophic factor for ECL cells and stimulates their proliferation. Hypergastrinemia can be found not only in the presence of ZES but also autoimmune CAG causing pernicious anemia. In both instances the ECL cells increase in number, leading to hyperplasia. However, only in the case of autoimmune CAG does the simple, linear type of hyperplasia proceed to a micronodular pattern and eventually to an invasive well differentiated neuorendocrine tumor (see above). With ZES the situation is more complex. ZES patients who have a sporadic gastrinoma, in either the duodenum or pancreas, do not develop gastric ECL tumors, whereas the patients who have ZES as part of the MEN-I syndrome may present with such tumors. From these findings it has been concluded that prolonged hypergastrinemia leads to ECL cell hyperplasia but not to the progression of ECL cell hyperplasia to ECL cell tumors. The development of ECL cell tumors obviously requires additional factors, such as a particular genetic background, as in patients with MEN-I [20, 84].

G Cell Hyperplasia

G cell hyperplasia has been described as a primary (idiopathic) disease or as secondary to a known cause of hypergastrinemia [for reviews see 84–86]. Microscopically, primary and secondary antral G cell hyperplasias are identical and show increased numbers of G cells dispersed throughout the lower and middle thirds of the antral mucosa crypts. The diagnosis of G cell hyperplasia is based on a determination of the number of G cells expressed per unit length of mucosa [87].

Primary G cell hyperplasia is though to be a rare cause of gastric hyperacidity and recurrent ulcer disease due to persistent hypergastrinemia. Although a number of cases have been reported, few of them appear to be convincingly documented [84, 85, 86]. The fact that during the last 10 years only one additional report on a case of primary hypergastrinemia has been published [87] raises the question whether this disease condition has either vanished or did not exist at all. There is no ready answer to this question, but the issue should be reconsidered in the light of the increasing experience with microgastrinomas in the duodenum, which, although small, may be the origin of gastrin hypersecretion. Because many of these tumors are located in the first part of the duodenum, it could be that in cases of primary G cell hyperplasia in which hypergastrinemia was cured by antrectomy a part of the proximal duodenum was also removed that contained an occult microgastrinoma. The role of *H. pylori* has been stressed [88].

Secondary G cell hyperplasia has been reported in association with autoimmune CAG, iatrogenic exclusion of the antrum, posttruncal vagotomy syndrome, and long-term treatment with acid-blockers, hypercalcemia, acromegaly, and chronic uremia [for review see 84]. Neither primary nor secondary G cell hyperplasia seems to progress to a G cell tumor.

Other Endocrine Cell Hyperplasias

Celiac sprue and ulcerative colitis have been reported to be associated with increased numbers of EC and S cells [for review see 84]. These changes are probably due to a nonspecific reaction to chronic mucosal damage.

Conclusions

During the last decade our knowledge and understanding of neoplasms with neuroendocrine differentiation has increased. The classifications used to date, however, insufficiently consider all the newly established morphologic, functional, and biologic features of these tumors. We therefore propose new classifications of the neuroendocrine tumors of the lung, pancreas, stomach, duodenum, jejunum and ileum, appendix, and colorectum [8]. We focused here on neuroendocrine tumors of the gut, discussing their morphologic and prognostic features with respect to their classification as "benign," "benign or low grade malignant," "low grade malignant," and "malignant" neoplasms.

Résumé

Cet article revoit la pathologie et la classification des proliférations neuroendocrines de l'intestin. Les lésions néoplasiques sont passées en revue, compte tenu de la nouvelle classification qui prend en considération les aspects morphologiques, fonctionnels et biologiques de ces tumeurs.

Resumen

El presente artículo revisa la patología y la nomenclatura de las proliferaciones celulares neuroendocrinas en el intestino. Las lesiones neoplásicas son discutidas a la luz de un nuevo sistema de clasificación que intenta considerar las características morfológicas, funcionales y biológicas de los tumores.

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