possible that the growth and arrangement of endocrine cells in the vicinity of tumor cells is influenced by factors released by the neoplastic cells.

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Mixed exocrine-endocrine tumors of the gastrointestinal tract

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In 1927, Hamperl must have been one of the first to notice the presence of endocrine cells in adenocarcinomas of the gastrointestinal tract (1). Since then, numerous studies have demonstrated the occurrence of endocrine cells in carcinomas of almost any site of the gastrointestinal tract. Conversely, exocrine differentiation is found in typical endocrine tumors of the gut. Endocrine cells have been found in 13% of gastric carcinomas (2) and in about 5-10% of all colorectal cancers (3). They are absent or are very rare in pure squamous cell carcinomas of the esophagus, although they are present in adenocarcinomas, especially in those associated with Barrett's metaplasia. The cells are generally argyrophil and contain the same hormones as those found in gastric adenocarcinomas, including serotonin, gastrin, somatostatin and glucagon (4). Endocrine cells occur more frequently in mucopeptide- or intestinal-cell than in foveolar-cell carcinomas of the stomach and more often in diffuse rather than in glandular carcinomas (5, 6). In most cases, the types of endocrine cell are consistent with the types of exocrine cell: both occur in the normal mucosa mimicked by the tumor growth. No apparent change of tumor prognosis or biological behavior has been detected in most of these neoplasms, compared with histologically equivalent tumors of the same area lacking endocrine cells (7). Their endocrine component, however, may well explain some signs of clinical hyperfunction, reported in association with ordinary carcinoma, such as skin melanosis associated with melanocyte-stimulating hormone-producing gastric adenocarcinoma (8) and Gushing's syndrome associated with adrenocorticotropic hormone-producing undifferentiated carcinoma of the colon showing multidirectional neuroendocrine, exocrine and squamous differentiation (9).

Amphicrine cells, containing both endocrine and exocrine granules in their cytoplasm as a result of simultaneous differentiation toward endocrine and exocrine lines, have been described in adenocarcinomas of the esophagus, stomach, intestine and appendix (10).

Another known lesion is the mixed endocrine-exocrine tumor, in which the endocrine component forms at least one-third to half of the tumor tissue, either intimately and diffusely admixed with the nonendocrine component (combined tumor) or occurring in distinct areas of the same tumor (composite tumor).

Combined tumors

In gastric combined tumors the endocrine cells (including serotonin, enterochromaffin-like endocrine cells, gastrin and somatostatin cells) are mainly associated with diffuse type scirrhous and mucin-producing growths (11). In these tumors, the endocrine component expresses either pepsinogen II, indicating mucopeptic differentiation, or intestinal crypt markers (5).

Abundant endocrine cells are less frequently detected in well-differentiated intestinal adenocarcinomas (4, 7). Some authors have observed diffuse-type goblet cell carcinomas, with or without signet-ring cells, showing numerous endocrine cells (12). These tumors, which have been reported in association with ulcerative colitis (13), may represent the more malignant counterpart of the so-called goblet cell carcinoid (14) or crypt cell carcinoma (15), generally found in the appendix and rarely in the ileum (16), duodenum (17), periampullary region (18) or colon (19). The appendiceal goblet cell carcinoid is a low-grade tumor, composed of small nests and microglands formed by goblet, columnar, lysozyme-producing exocrine cells as well as by endocrine cells of EC-, L- or D-type. Goblet cell carcinoids of the appendix are seen less commonly than conventional carcinoids. The mean age at presentation is 58 years and it is slightly more common in males. In most cases, this tumor is not recognized macroscopically. In other cases the tumor forms nodules or areas of thickening of the appendiceal wall and in 22% of cases, tumor spread extends beyond the appendix, with evidence of both lymphatic and transcelomatic spread and detection of metastases in the peritoneum, ileocolic lymph nodes or ovary at the time of first diagnosis (20, 21). Goblet cell carcinoids tend to be more aggressive than ordinary appendiceal carcinoids but less aggressive than adenocarcinomas arising in the same site, with a 5-year survival rate of approximately 80% (22).

Composite tumors

Composite adenocarcinoma-carcinoid or glandular-carcinoid tumors have been observed in the esophagus (23), stomach (24), ampulla of Vater (25), small intestine (26) and colon (27). Using appropriate immunohistochemical markers and ultrastructural investigation, the endocrine component of composite tumors can be distinguished from trabecular and solid-medullary carcinomas showing areas with peripheral palisading or basaloid patterns which mimic an endocrine tumor but which lack the histochemical and ultrastructural features of true endocrine differentiation. Prognosis of composite tumors depends on the stage and grade of the exocrine or undifferentiated carcinomatous component of the lesion.

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Divergent differentiation in neuroendocrine lung tumors

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The classification of neuroendocrine lung tumors has been revisited in the latest edition of *World Health Organization Histological Typing of Lung and Pleural Tumors* (1). The concept of neuroendocrine lung tumors has been refined by the recognition of large cell neuroendocrine carcinoma (LCNEO) and by the modification of the criteria for atypical carcinoids.

Classification of neuroendocrine luna tumors

Spectrum of neuroendocrine oroliferations

Neuroendocrine lung tumors encompass one spectrum of a distinct subset of tumors, sharing certain morphological, ultrastructural, immunohistochemical and molecular characteristics, which sustain their neuroendocrine phenotype. Tumors with neuroendocrine morphology on light microscopy display organoid nesting, palisading, trabecular and rosette-like structures and include a three-grade spectrum of low-grade typical carcinoids, intermediate grade atypical carcinoid, high-grade LONEC and small cell lung carcinoma (SOLO). They all display the presence of neurosecretory granules at electron microscopy as well as immunohistochemical neuroendocrine markers, the most useful for pathological diagnosis being chromogranin, synaptophysin and neural cell adhesion molecules. The most important criteria for distinguishing between typical and atypical carcinoids and LONEC are mitotic activity and necrosis. A mitotic count of 2-10 mitosis per 2 mm2/10.HPF distinguishes atypical from typical carcinoids, whereas a mitotic count of 11 or more mitoses per 2 mm2 separates LONEC and SOLO from atypical carcinoids. The second important criteria is necrosis, which is absent in typical carcinoid focal or punctate in atypical carcinoid (eliminating typical carcinoid) and abundant and infarct-like in LONEC and SCLC.

In addition to these classical types of neuroendocrine lung tumors, the spectrum of neuroendocrine proliferations and neoplasms in the lung include a hyperplastic state: neuroendocrine cell hyperplasia and tumorlets occur in the context of associated fibrosis or chronic inflammation (bronchiectasia) or as a preinvasive state (provisional), occuring adjacent to carcinoids, or even isolated from them and called diffuse idiopatic neuroendocrine hyperplasia.

Divergent differentiation in neuroendrocrine lung tumors

Large cell neuroendocrine carcinoma is a category of tumors differing from carcinoids and small cell lung carcinoma but still showing neuroendocrine morphology and markers. These large-cell neuroendocrine carcinomas are the lung neuroendocrine tumors, which display the most frequent divergent differentiation (more than 50%). The most frequent type of divergent differentiation in large cell neuroendocrine carcinoma consists of glandular features with mucin secretion.

Apart from tumors with neuroendocrine morphology, which have been described and properly classified in the World Health Organization (WHO) classification, a subgroup of non-small-cell lung carcinoma (NSLOL) with neuroendocrine differentiation is recognized, although it is not considered as a separate category for histologic classification, essentially because of lack of clinical significance. This obviously defines a category of lung tumors (5-10%) which lacks neuroendocrine morphology but in which immunohistochemical (or ultrastructural) evidence of neuroendocrine differentiation can be demonstrated. A continuous spectrum of malignant tumors from pure LONEC and combined LONEC (with another non-component), to NSOLO with neuroendocrine differentiation emerges, which complicates tumor classification and diagnosis (2).

Obviously, neuroendocrine lung tumor does not escape from the paradigm of multidirectional differentiation, which was stressed long ago in lung tumors (3-9). Evidence of both epithelial (non-neuroendocrine) differentiation in classical neuroendocrine tumors and of neuroendocrine differentiation in non-neuroendocrine tumors has been provided. Mucins are identified in about half of all cardnoids and LONEC. Divergent non-neuroendocrine differentiation toward adenocarcinomatous or squamous differentiation occurs in SOLO spontaneously at the morphological level in a subset of 5% of SOLO (the so-called combined SOLO) and at the level of ultrastructure and immunohistochemistry (mucins and neurosecretory granules) in 20% of them. The increasing frequency of these divergent specializations in SOLO has been demonstrated after therapy (or by induction or selection mechanisms), which have made the post-therapy diagnosis difficult (10). Ultrastructural studies have demonstrated the presence of neuroendocrine granules in association with other specialized differentiation signs (mucus, microvilli, tonofilaments) in a large number of NSOLO and especially in large-cell (undifferentiated) carcinoma (11-13).

A common endocrine stem cell for lung tumors

Finally, neuroendocrine lung tumors appear to be epithelial tumors characterized by their preferential neuroendocrine differentiation but susceptible to following multidirectional differentiation pathways, as indicated by the occurrence in the same tumor cell cytoplasm (although rare) of neuroendocrine granules, mucin granules,