

Short Course 14

Divergent differentiation in endocrine tumors

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Tumor heterogeneity has been recognized and well accepted by pathologists for a long time, but has only recently been brought to general attention because of related genetic and therapeutic implications. In endocrine tumors, detection of divergent differentiation carries several histogenetic, diagnostic and prognostic problems. The short course organized by the ESP working group on endocrine pathology will focus on such problems as they relate to tumors arising in different organs. The second part of the meeting will be devoted to discussion of selected posters on endocrine pathology.

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Mixed exocrine-endocrine tumors of the gastrointestinal tract

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Although the exocrine and endocrine components of the pancreas are morphologically and functionally distinct, they may become mixed within pancreatic tumors. The existence of such tumors suggests that neoplastic cells of the pancreas may, in principle, have the potential for dual differentiation, reflecting the common embryologic origin of the two components of the pancreas. While it is rare to see exocrine elements within endocrine tumors, the occurrence of endocrine cells in exocrine neoplasms of the pancreas is rather common. The endocrine cells are identified on the basis of their staining properties with silver preparations, their ultrastructural appearance and, in particular, their immunocytochemical features. In the diagnosis of mixed exocrine-endocrine tumors of the pancreas, two categories have to be distinguished.

The first category includes those exocrine tumors in which the endocrine component is limited to scattered individual cells. The second category is defined as truly mixed exocrine-endocrine tumors. In these tumors the endocrine component is significant and should comprise at least one-third to one-half of the tumor tissue. Mixed exocrine-endocrine tumors of the pancreas are rare. They include mixed ductal-endocrine carcinoma and mixed acinar-endocrine carcinoma. Tumors that may show scattered individual cells are ductal adenocarcinomas, intraductal papillary-mucinous tumors, mucinous-cystic tumors, acinar cell carcinomas and pancreatoblastomas.

Mixed ductal-endocrine carcinoma

This tumor consists of ductal and endocrine cells, which are intimately admixed in the primary tumor as well as in its metastases. The ductal differentiation is defined by mucin production and by the presence of a duct-type marker such as carcinoembryonic antigen (CEA). The endocrine cells are characterized by the presence of general endocrine markers and hormonal products. Biologically, mixed ductal-endocrine carcinoma behaves like the usual ductal

adenocarcinoma. This tumor is also referred to as mixed carcinoid-adenocarcinoma or mucinous carcinoid tumor. Mixed ductal-endocrine carcinomas are exceptionally rare in the pancreas. So far, only a few examples that appear to fulfill the criteria given above have been reported in the literature. Tumors that are composed of two topographically separate components (*i.e.*, collision tumors) are by definition not included in the mixed ductal-endocrine category.

Mixed acinar-endocrine carcinoma

This tumor shows a mixture of endocrine and acinar cells. It may also exhibit cells with ampicrine features (*i.e.*, the presence of endocrine and acinar cell characteristics). The acinar differentiation is defined by the production of pancreatic enzymes such as trypsin or lipase. In addition, the acinar cells may express pancreatic stone protein. Biologically, mixed acinar-endocrine carcinomas behave like the usual acinar cell carcinoma. The neoplasm has also been reported under the name acinar-endocrine cell tumor.

Exocrine tumors with scattered individual endocrine cells

Scattered endocrine cells are present in up to 79% of otherwise typical ductal adenocarcinomas. They also occur in up to 40% of acinar cell carcinomas and may occasionally be seen in pancreatoblastomas. Scattered endocrine cells have also been reported in intraductal-papillary mucinous tumors and in mucinous-cystic tumors.

Ductal adenocarcinomas with scattered endocrine cells

These carcinomas should be clearly distinguished from mixed ductal-endocrine carcinomas. Scattered endocrine cells associated with neoplastic glands seem to be particularly frequent in well-differentiated tumors, where they are either lined up along the base of the neoplastic ductal structures or lie between the neoplastic columnar cells. Immunocytochemically, all four islet hormones, as well as amylin (IAPP), serotonin and occasionally gastrin, have been identified in these cells. In the dorsal head region of the pancreas, which is rich in pancreatic polypeptide cells, most of the tumor-associated endocrine cells produce pancreatic polypeptide. Scattered endocrine cells in ductal adenocarcinoma might be neoplastic, considering their close association with neoplastic glands. Usually, however, the metastases of such tumors lack the endocrine cell population seen in the primary tumor. At least some of these cells may therefore represent non-neoplastic rather than true neoplastic endocrine cells. It is