

Foschini MP, Eusebi V.

Divergent differentiation in endocrine and nonendocrine tumors of the skin.

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In the skin, endocrine tumors showing areas with nonendocrine features and nonendocrine tumors showing endocrine differentiation are present. (1) Neuroendocrine carcinomas with nonendocrine differentiation: Merkel cell carcinoma (MCC) of the skin has been frequently described in association with squamous cells carcinoma (SCC) which can arise separately (as synchronous or metachronous lesions) from MCC as well as closely intermixed. In the first event the possibility that the lesions are sustained by same causative factors (among which sun exposure is the most probable) is suggested. In cases of lesions closely intermixed the possibility of an origin from a common precursor is suggested. Furthermore, cases of MCC have been described to contain glandular, melanocytic, striated muscle, and lymphoepithelioma-like features. These latter findings further support the hypothesis of tumors showing divergent differentiations. (2) Nonendocrine tumors showing endocrine differentiation: Basal cell carcinoma (BCC) was the first cutaneous nonendocrine tumor described to contain neuroendocrine granules. Presence of endocrine features were subsequently confirmed with immunohistochemical studies. Endocrine features were then described in sweat gland apocrine and eccrine carcinomas. Endocrine elements present in BCC and in sweat gland carcinomas do not show morphological and immunohistochemical features of Merkel cells. Thus the possibility that these tumors develop an immature Merkel cell or a new type of endocrine cell of the skin is suggested. Tumors with follicular differentiation such as trichoblastomas and trichofolliculomas contain a high number of Merkel cells. As Merkel cells are numerous in hair follicles of human fetal skin, the possibility that these tumors recapitulate the human skin embryogenesis is suggested.

di Sant' Agnese PA.

Divergent neuroendocrine differentiation in prostatic carcinoma.

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A rich variety of neuroendocrine cells are present in the normal prostate gland. Prostatic carcinoma may show divergent differentiation towards a neuroendocrine phenotype in the form of neuroendocrine small cell carcinoma or carcinoid-like tumors. Much more common is focal neuroendocrine differentiation in prostatic adenocarcinoma which may be pronounced in approximately 10% of adenocarcinomas. The prognostic significance of focal neuroendocrine differentiation in prostatic carcinoma is controversial but current evidence suggests an influence on prognosis related to hormone resistant tumors and/or a role in the conversion to a hormonal resistant phenotype. Chromogranin A appears to be the best overall tissue and serum marker of neuroendocrine differentiation. Chromogranin A serum levels may be useful in the assessment of the emergence of and/or progression of hormone resistant cancer.

Brambilla E, Lantuejoul S, Sturm N.

Divergent differentiation in neuroendocrine lung tumors.

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The classification of neuroendocrine (NE) lung tumors has been revised in the 1999 World Health Organization (WHO) classification of lung tumors, allowing sharp morphological definition of typical versus atypical carcinoids, and atypical carcinoids versus large cell neuroendocrine carcinoma (LCNEC), a newly described class of high-grade NE lung tumors which differs from small-cell lung cancer by a large-cell phenotype. Divergent differentiation accounts for the high frequency of glandular differentiation with mucin production, and ultrastructural features in carcinoids and LCNEC, and low frequency of squamous differentiation in both LCNEC and SCLC. Specific NE markers (chromogranin, synaptophysin, neural cell adhesion molecule) and epithelial markers consistently negative in neuroendocrine components (cytokeratins 1, 5, 10, 14; epidermal growth factor (EGF)-receptor, human leukocyte antigen beta 2 (HLA-beta2) microglobuline) help to recognize divergent differentiation in NE tumors. At morphological level, divergent differentiation in NE tumors is recognized in WHO classification as variants: combined SCLC and combined LCNEC. The derivation of all lung tumors from a common endodermal stem cell and adoption of amine precursor uptake and decarboxylation properties by this endodermal stem cell explains divergent differentiation in NE lung tumors and the occurrence of NE subsets in NSCLC.

Sapino A, Righi L, Cassoni P, Papotti M, Pietribiasi F, Bussolati G.
Expression of the neuroendocrine phenotype in carcinomas of the breast.
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Neuroendocrine (NE) features are detectable in carcinomas of the breast either as scattered cells immunoreactive for NE markers in carcinoma of the usual type (NOS), or as special type of tumors where the vast majority of the cells display NE characteristics. The former type of lesions, whose biological and diagnostic significance is not clear yet, might reproduce the same phenomenon known to occur in carcinomas of the gastrointestinal tract and pancreas. In the present review we focus on the latter type of lesions, a spectrum of breast tumors largely composed of NE cells. These carcinomas, that we consider the "NE differentiated carcinomas of the breast," are here distinguished from "breast carcinomas NOS with NE differentiation." The diagnostic and histogenetic features of the various types of "NE differentiated carcinomas of the breast," their histological and cytological features and the role and value of ancillary diagnostic techniques, are reviewed. Data of the literature are discussed and related to a relatively large personal series. In addition, divergent differentiation in NE carcinomas of the breast, which is a relatively frequent phenomenon of diagnostic interest but of unknown significance (mainly involving mucinous intra- and extracellular production) is discussed.

Tischler AS.
Divergent differentiation in neuroendocrine tumors of the adrenal gland.
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Composite tumors of the adrenal medulla usually consist of pheochromocytoma admixed with ganglioneuroma or ganglioneuroblastoma. These neoplasms reflect phenotypic plasticity shown by primitive sympathetic cells and mature chromaffin cells in vitro. They may give rise to metastatic neuroblastoma in adults and may cause signs and symptoms attributable to both catecholamine and neuropeptide production. Schwann cells and sustentacular cells are typically numerous in these tumors but it is not known whether they are neoplastic. Immunohistochemical staining for catecholamine biosynthetic enzymes, secretory vesicle proteins and S-100 protein tends to recapitulate staining of the normal adrenal medulla or sympathetic ganglia. Sparsity of chromogranin A in the cell bodies of immature and mature neurons is a diagnostically useful characteristic.

Papotti M, Volante M, Komminoth P, Sobrinho-Simoes M, Bussolati G.
Thyroid carcinomas with mixed follicular and C-cell differentiation patterns.
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Divergent endocrine-neuroendocrine differentiation in thyroid carcinoma occurs in mixed medullary-follicular carcinomas (MMFC). Less than 40 cases of MMFC have been reported having highly heterogeneous patterns of growth. Classical medullary carcinoma areas may be intermingled with follicles or papillae or even oxyphilic and solid areas. Calcitonin and thyroglobulin are expressed in different cell populations. Presence of the latter suggests a potential usefulness of radioiodine treatment. The clinical behavior of MMFC does not differ from that of ordinary medullary carcinoma. The histogenesis of MMFC is controversial. The genetic analysis of the 2 neoplastic components showed that they are not derived from a common precursor, but rather display remarkable differences in the genetic profile (RET mutations and allelic losses). In addition, in some cases the follicular component was found to be oligo/polyclonal and therefore possibly hyperplastic rather than neoplastic. The follicular cells may have grown into the medullary carcinoma, after acquiring some molecular defect, being "hostage" of the true neoplastic (medullary) component.

Kloppel G.
Mixed exocrine-endocrine tumors of the pancreas.
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Neoplasms of the pancreas usually show either ductal, acinar, or endocrine differentiation. Mixed exocrine-endocrine pancreatic neoplasms, in which the endocrine component is significant and comprises one-third to one-half of the tumor tissue, are rare. Truly mixed tumors have to be distinguished from exocrine neoplasms with scattered endocrine cells. In ductal adenocarcinomas, the scattered endocrine cells seem to be nonneoplastic. In other malignancies such as acinar cell carcinoma and pancreatoblastoma, scattered endocrine cells most likely represent an integral component of the tumor.

Capella C, La Rosa S, Uccella S, Billo P, Cornaggia M.
Mixed endocrine-exocrine tumors of the gastrointestinal tract.

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Mixed endocrine-exocrine tumors of the gastrointestinal tract are rare neoplasms, which have been reported in the literature mainly as case reports and have been designated with a various and rather confusing terminology. In this review, on the basis of personally studied cases and of the analysis of cases reported in the literature, we have tried to identify types of mixed endocrine-exocrine tumors showing different clinicopathologic and biological characteristics. We have also tried to group the different clinicopathologic entities in prognostic classes which include: benign, low-grade, intermediate grade, and high-grade malignant mixed endocrine-exocrine tumors. The criteria for identifying the various types of mixed endocrine-exocrine tumors are extensively discussed.