An update on the pathology of neuroendocrine tumors

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1. ABSTRACT

In this review, we highlight different aspects of a specialized tumor subset, neuroendocrine tumors. We discuss the terminology applied to these tumors, define their precancerous state, diagnostic criteria, immunohistochemical and molecular markers and finally the grading system that is currently applied to these subset of tumors.

2. INTRODUCTION

The concept of neuroendocrine cell has evolved over time together with the definition of neuroendocrine tumors (NET). These arise from diffuse neuroendocrine system (DNS), including the pituitary gland, C-cells of the thyroid, parathyroid glands, the endocrine pancreas, gastrointestinal neuroendocrine cells, adrenal medullary tissue, and other scattered neuroendocrine cells of the skin and bronchi, with common embryologic, morphologic and functional features (1). In 1907 Oberndorfer described, for the first time, a special intestinal tumor, the carcinoid, made of a particularcell type, identified by Kulchitsky in the same year (2). In 1914 Pierre Masson, studying carcinoid tumors of the appendix, observed that the neoplastic cells just like the neuroendocrine Kulchitsky cells contained abundant secretory granules strongly staining with silver nitrate (3). Later, Friedrich Feyrter and Anthony Pearse established the concept of a diffuse endocrine cells system, based on a common histochemical property summarized in the acronym "APUD", standing for "amine precursor uptake and decarboxylation" (4-6). Neuroendocrine is the interaction between the endocrine and the nervous system. Cells and tumors of the DNS may be divided in two main groups: neural type(neuroblastoma, pheocromocytoma and paraganglioma) and epithelial type (NET from many sites).

3. MATTER OF TERMINOLOGY

One of the most controversial and debated system of classification is represented by the group of the neuroendocrine tumors. The WHO classification system for gastrointestinal NET has changed in 2000, 2004 and 2010; to date the last classification (7) is a matter of argument. Certainly, the broad heterogeneity characterizing NET is one of the most important factor determining this changeability in nomenclature.

Already in 2000 the term carcinoid (carcinoma-like) had been abolished from the WHO classification (8-10) of gastrointestinal neuroendocrine tumors, because considered too "optimistic". The term neuroendocrine carcinoma was preferred and confirmed in 2004 (11). Every tumor that had demonstrated a malignant behavior (metastasis or gross local invasion) had to be called "carcinoma", even though it was well differentiated. The 2010 WHO classification of gastroenteropancreatic NET (GEP-NET) adopted the recommendations of the European Neuroendocrine Tumor Society, according to which the term carcinoma should be reserved to poorly differentiated neoplasms. At present, three categories for GEP-NET are recognized: 1. Neuroendocrine tumor, grade 1 (G1); 2. Neuroendocrine tumor, grade 2 (G2); 3. Neuroendocrine carcinoma, grade 3 (G3), including small cell carcinoma and large cell neuroendocrine carcinoma. This categorization is based on the mitotic activity and on mindbomb homolog 1 (MIB1/Ki-67) proliferative index (Table 1).

The term carcinoid persists within neuroendocrine tumors of the lung and thymus (2004 WHO classification) (12); they are currently classified in typical carcinoid, atypical carcinoid, small-cell lung carcinoma (SCLC), and large-cell neuroendocrine
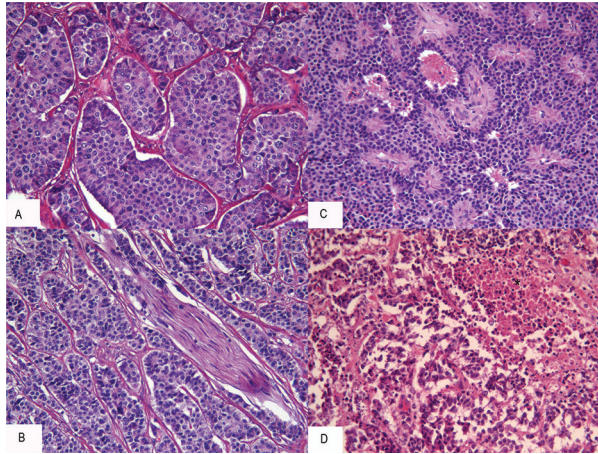
Figure 1. Morphologic patterns of well differentiated neuroendocrine tumors (G1): neoplastic cells are arranged in nests (A) or in pseudoglandular structures (C); sometimes perineural invasion can be observed (B). When the neoplasm is poorly differentiated (D), it is patternless and shows foci of necrosis (upper right corner). (H-E stain, 20x).

Table 1. Grading system of gastrointestinal NET

Grade	Gep-net (ENETS-WHO 2010)
Low	<2 mitoses/10HPF AND Ki67 index<3%
Intermediate	2-20 mitoses/10HPF OR Ki67 index=3-20%
High	>20 mitoses/10HPF OR Ki67>20%

Table 2. Grading system of NET of Lung and Thymus

Grade	Lung-Thymus (WHO 2004)
Low	<2 mitoses/10HPF AND No necrosis (Figure 6)
Intermediate	2-10 mitoses/10HPF OR Foci of necrosis
High	>10 mitoses/10HPF (Figure 7)

carcinoma (LCNEC). Their separation rests primarily on the mitotic rate and the presence or absence of necrosis and, in the case of separating SCLC from LCNEC, on cell morphology (Table 2). Very recently authors (13-15) reported a considerable interobserver variation in the histopathological classification of lung carcinoids, suggesting additional immunomarkers such as Ki-67 or orthopedia homeobox, to improve classification and prediction of prognosis.

4. NEUROENDOCRINE TUMORS ARE NOW RECOGNIZED IN ALMOST ALL SITES IN THE BODY

Most of NET arise from the gastroentero pancreatic (GEP) district, hence the distinction in GEP and non-GEP neuroendocrine tumors: among these, the most common sites are the appendix, ileum and rectum. Besides the pulmonary site, many different extragastrointestinal sites have been reported to occur (16-21).

Regarding the genital system, NET are more common in females; most are uterine small cell carcinomas or ovarian carcinoids (20-23). Most male genital tract NET are prostatic small cell carcinomas or testicular carcinoids. The prostate contains the largest number of neuroendocrine cells of any genitourinary organ. Most of these cells contain chromogranin A and serotonin (24). In histologically typical prostate adenocarcinoma, particular attention has been given to the presence of eosinophilic neuroendocrine cells which stained positively with chromogranine A. The term Paneth-like cells has been used to describe these neuroendocrine cells (25). Pure neuroendocrine prostate cancers are rare but extraordinarily aggressive, resistant to therapy and associated with poor survival (26-27). Small cell carcinoma of the prostate is a subtype of prostate cancer with unique clinical features and accounts for no more than 1% of all prostatic malignancies. They do not express androgen receptors (AR) or prostate specific antigen (PSA) (28-29). Tipically they are discovered at an advanced stage or as recurrences of castration-resistant adenocarcinoma following treatment with hormonal therapy (30-33).

Neuroendocrine tumors frequently metastatize to the liver, but the liver itself rarely is the site of a primary tumor. A review of the English literature in 2005 reported 95 cases of primary hepatic neuroendocrine tumors (34).

Merkel cell carcinoma (MCC) is the currently preferred term for a distinctive cutaneous malignancy belonging to the family of neuroendocrine tumors (35-37). It is an aggressive neoplasm that can cause distant metastasis to the lungs, liver, bones or to the regional lymph nodes (38). Occasionally, a morphologically and genetically typical MCC is found in a lymph node (most often inguinal), in the absence of a primary skin tumor (39,40). The diagnosis of Merkel cell carcinoma can even be reliably made on cytological specimens obtained by fine needle aspiration biopsy (41). This tumor seems to be associated with ultraviolet light exposure and with a recently discovered polyomavirus (42-44). In 2010, a consensus staging system for MCC was adopted worldwide (45).

5. DIAGNOSTIC CRITERIA AND IMMUNOHISTOCHEMICAL MARKERS

The hallmark of well differentiated neuroendocrine tumors is the presence of small cells with a granular eosinophilic cytoplasm and a well-rounded nucleus, arranged in a neuroendocrine pattern (well- defined nests of tumor cells separated by thin fibrovascular septa or strands of tumor cells arranged in trabeculae, ribbons, festoons) or even in pseudoglandular structures (Figure 1). An intermediate
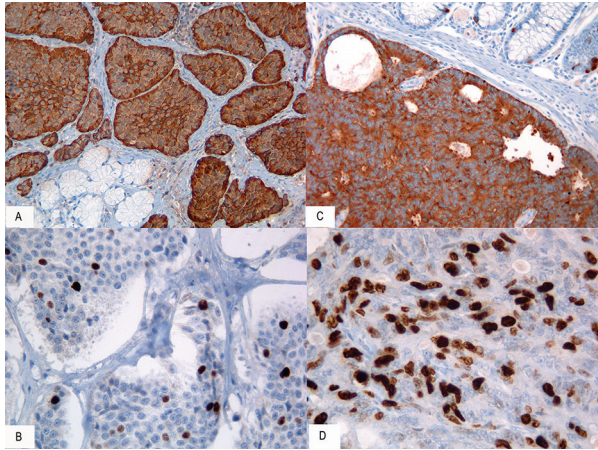
Figure 2. Immunohistochemistry: diffuse cytoplasmic reactivity for chromogranine A (A) and for synaptophysine (B). The cellular proliferation index Ki67 shows a nuclear signal: we observe positivity in 7% of neoplastic cells, in a case of NET G2 (B) and in 40% of neoplastic cells, in a NEC (G3).
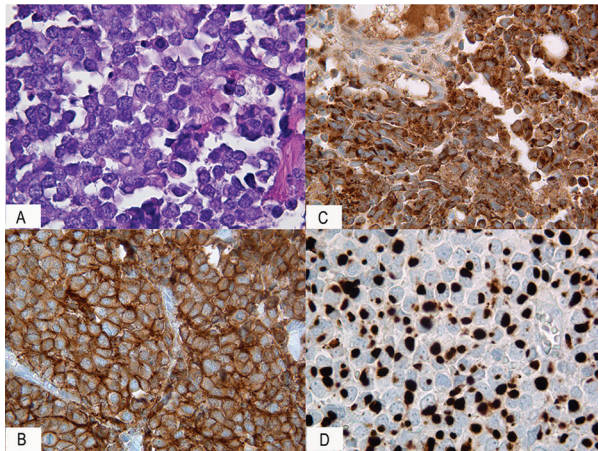
Figure 3. Merkel cell carcinoma. Medium sized cells, with a high nucleus/cytoplasm ratio and a solid pattern (A). In this case neoplastic cells are often characterized by intracytoplasmic globules. (H-E stain, 40x). Immunohistochemical evaluation reveals positivity for CD56 (B) and for chromogranine (C) and the typical dot-like reactivity for CK20 (D).

grade of differentiation implies a more pronounced cytologic atypia, an increased mitotic activity, frequent foci of necrosis, and perineural and vascular invasion. Finally, in poorly differentiated neuroendocrine carcinoma, the pattern of growth above described is rarely found.

For the diagnosis of NET immunohistochemical stains with the neuroendocrine markers synaptophysin and chromogranin A (Figures 2A&C, Figure 3) are mandatory (46). CD56 or neural adhesion molecule (NCAM) is the most sensitive neuroendocrine marker and it is preferred in supporting the diagnosis of small cell lung carcinoma, since around 25% of cases are negative

for both synaptophysin and chromogranin (47); however, in other sites it is excluded from the immunohistochemical panel because it lacks specificity.

The existence of immunohistochemical markers as prognosticators is still debated: for pancreatic NET CK19, CD117, CD99, CD44, p27, progesterone receptor (loss) and PTEN (loss) have proven to have adverse prognostic significance (48-55). Infact, progesteron receptor immunoreactivity has been showed to be significantly correlated with the absence of metastasis and lack of invasion into adjacent organs and large vessels (56,57). Clinically important is the performance of immunohistochemistry aimed to determine the primary site for NET presenting with metastases, since treatment options vary by primary location: TTF1 (58,59) is expressed in most pulmonary carcinoids (however, some high grade NEC can aberrantly express it) (55,56); CDX2 (Figure 4) is specific of intestinal, appendiceal and pancreatic origin (58,59,62); Islet 1 and PAX8 are found in pancreatic and rectal NET (63-65).

Sometimes tumors show the combination of different histological types and when both neuroendocrine and non-neuroendocrine components are conspicuous, representing at least 30% of the neoplastic tissue, tumors are classified as mixed exocrine-neuroendocrine carcinomas. The 2010 WHO classification has suggested this new entity, the mixed adenoneuroendocrine carcinoma (MANEC).

6. GRADING SYSTEM

The search for a predictor of outcome has been the aim of many important studies concerning NET. Actually the grade has the most relevant role in the classification system, more than the staging does.In thoracic NET (12) the grading system is based on mitotic count and on the presence/absence of necrosis while in the gastrointestinal tract (7), besides the mitotic activity (number of mitotic figures in 10 high-power microscopic fields), a quantitative immunohistochemical evaluation of the Ki67 labeling is performed (Figure 2 B&D). In general, the evaluation of the proliferation rate of the tumor is considered the most reliable predictor of outcome.

Ki67 is a nuclear protein of unknown function that is expressed only during the active phases of the cell cycle, but not in G0. The Ki67 usually correlates with the mitotic count and because a greater proportion of cells are labeled than those in mitosis, Ki67 is easier to quantify than the mitotic rate. The count can be visual (counting the number of positive cells on >2000 neoplastic cells in the most proliferative region-hot spot), can be an "eyeballed" estimate or can be based on digital image analysis. The first technique rests the most reliable and easiest to perform (66). When the mitotic count and the Ki67 are discordant it is recommended to assign the
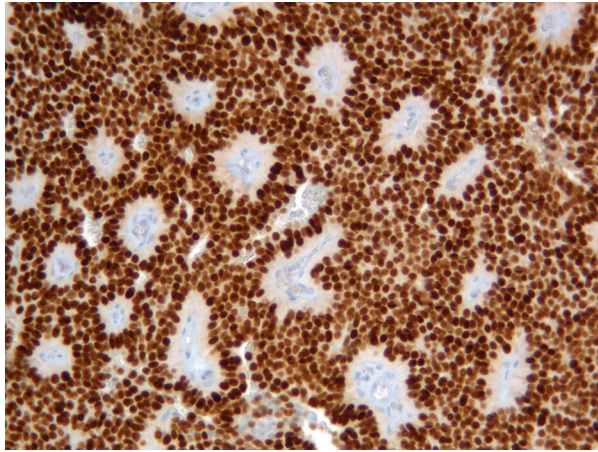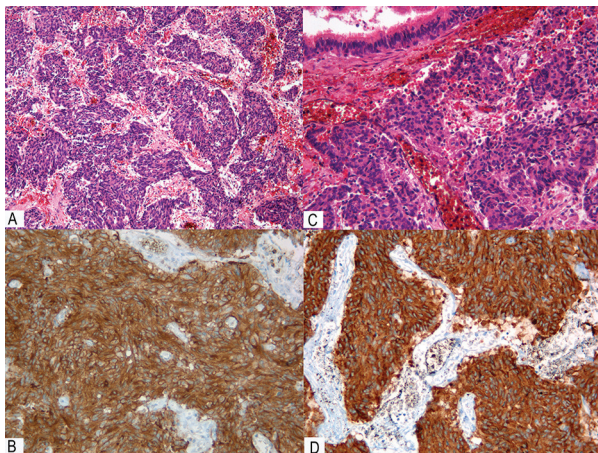
Figure 4. CDX2 nuclear positivity is helpful in identifying the primary site of a hepatic metastasis from NET (appendix or pancreas).
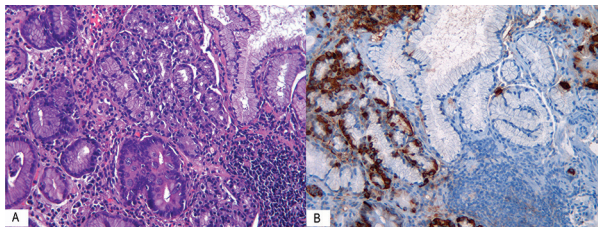
Figure 5. Pre-neoplastic lesions: in the context of a chronic atrophic gastritis, with intestinal metaplasia, linear hyperplasia of neuroendocrine cells can be observed (A: H-E stain, 10x; B: chromogranine stain).

Figure 6. Pulmonary carcinoid. A: H-E stain, 20x; C: H-E stain, 40x; immunoreactivity for CD56 (B) and for synaptophysin (D)

higher grade, but specific data justifying this approach do not exist. In a recent study (67), a group of pancreatic NET (G1-G2) has been revalued for the mitotic count and the immunolabeling of Ki67: 33% of mitotic grade 1 were WHO grade 2 by Ki67 proliferative index. Compared with concordant grade 1 tumors, grade discordant tumors were more likely to have metastasis to lymph nodes and to distant sites and there were few significant differences from tumors that were mitotic grade 2 and either Ki67 grade 1 or 2. This experience strongly suggests the importance of the Ki67 immunohistochemical marker as a prognostic factor. Another pitfall on the evaluation of Ki67 is caused by tumor heterogeneity, especially in well differentiated NET metastatic to the liver: usually the diagnosis is made on an ultrasound guided needle core biopsy which randomly samples the lesion without being targeted to regions that may show a higher proliferative rate. The greatest discrepancy is observed in NET of grade 2 (68,69). Over the course of the disease, the Ki67 Labeling Index in multiple neuroendocrine tumors seems to upgrade to a higher WHO class in a high percentage of cases: this evidence must be taken in consideration for the decision making of monitoring and treatment (70).

The category of neuroendocrine neoplasms of grade 3 includes all those cases in which mitotic index is over 20 figures/10HPF and/or Ki67 is >20%, that means a wide range of morphologic varieties. In order to characterize this large group of neoplasms, it would be desirable to also consider the grade of morphological differentiation, given that well differentiated NEC seem to have a better prognosis than large cell poorly differentiated one (thus excluding small cell carcinoma from NEC) (71). Future classification might consider the possibility of further splitting of G3 category into two subcategories.In another study on G3 NET (72), it was observed that only neuroendocrine carcinomas with a Ki67 index greater than 55% responded to platinum-based chemotherapy, whereas the tumors in the 20-55% range did not respond. This is a hot topic that requires a more consolidated experience with the new classification system (Who 2010), in order to draw conclusions (73).

7. PRE-NEOPLASTIC LESIONS

The best way to counteract neoplastic diseases is achieved with an early diagnosis or even acting on precursor lesions. In the contest of neuroendocrine neoplasms, very frequently is observed a sequence of cellular changes from hyperplasia to neoplasia, sometimes with the interposition of dysplasia, especially in presence of familial genetic syndromes.

The most fascinating precursor lesions are in the stomach. Gastric NET are divided into three types according to their association with other pathologies: type I, typically associated with autoimmune chronic atrophic gastritis (A-CAG), predominantly involving the corpus-fundus region; type II, associated with MEN-1 and Zollinger-Ellison syndrome; type III, sporadic, unassociated with any other pathology. Among these three typologies, the first two are frequently preceded by precursor enterochromaffin-like cells (ECL) hyperplasia.
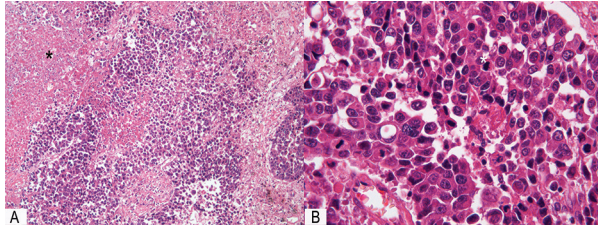
Figure 7. Large cell neuroendocrine carcinoma of the lung: the tumor shows areas of necrosis (* in A) and is composed of large cells with a vescicular nucleus and a conspicuous nucleolus and with a high mitotic activity (* in B). (A: H-E stain, 20x; B: H-E, 40x).

In the former, the trigger is the loss of parietal cells, consequence of the autoimmune reaction against the gastric mucosa, which causes the achlorhydria and then stimulates antral and duodenal gastrin-production. Gastrin, together with growth factors (TGFα and bFGF) and the antiapoptotic bcl-2 protein, have a trophic effect on ECL cells. In type II gastric NET, the hypergastrinaemia is due to a gastrin-producing NET, developing in the contest of MEN-1 syndrome. Whatever the pathogenesis, both types are preceded by a characteristic sequence hyperplasia-dysplasia-neoplasia and often debut in multiple forms (74-77). ECL hyperplasia is the presence of more than 5 cells/gland, at least 2 linear chains/mm (Figure 5) or one micronodule less than 150µm/mm. Enlargement and fusion of micronodules, microinvasion of the lamina propria or nodules associated with newly formed stroma are all features of dysplasia. This last condition is a high risk predictor of developing neoplasia (78,79): the evidence of invasion of the submucosa or a size exceeding 0.5 mm empowers the use of the term neoplasia (microtumors or microcarcinoids, if the nodule measures less than 5 mm).

MEN1 patients usually have a precursor lesion that is typically multifocal G cell and D cell hyperplasia. In the setting of this genetic syndrome, all somatic cells harbor a germline mutation in the MEN1 gene. While LOH (loss of heterozigosity) was not found in precursor lesions, it is detected in approximately 50% of MEN-1 related duodenal G cell NET; in the other cases other forms of mutations are found. Since the morphological aspect of hyperplastic lesions can be indistinguishable from tiny neoplastic one, molecular analysis can be of help in these cases (80).

The concept of preneoplastic neuroendocrine lesions in the lung is really more intricate, firstly because of the different embryologic origin of low grade and high grade lesions and then because central and peripheral tumors seem to have a different biology. The diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is an increase in number of individual PNECs (pulmonary neuroendocrine cells) or linear and nodular proliferations that may show bulging into the bronchial or bronchiolar lumen. When these proliferations break through the basement membrane and invade locally to form extraluminal aggregates of no more than 5mm in diameter, they are called tumorlets; this entity is considered benign even if somemetastatic cases have been described (81). PNEC is the first cell originating from the endoderm and takes part to the formation and differentiation of pulmonary epithelium during early developmental stages of the lung. They act as a chemoreceptor and can even form small aggregates termed neuroepithelial bodies, localized within the ciliated respiratory epithelium. DIPNECH is considered a premalignant precursor lesion that can give rise to a peripherally located pulmonary neuroendocrine tumor (12). DIPNECH must be distinguished from reactive PNEC hyperplasia (RPNECH), usually associated with fibroinflammatory pulmonary diseases (82,83).

8. MOLECULAR FEATURES OF NET

The increase in the incidence of NET, probably due to the improvement of diagnostic techniques, has been a source of inspiration for the advancement of knowledge about the molecular biology of these tumors.

In general, poorly differentiated, high grade carcinomas,represent aggressive cancers that have a different natural history and response to treatment, compared with well differentiated, low grade NETs, and are very heterogeneous in terms of morphology. Well-differentiated NET can be broadly subclassified as either carcinoid or pancreatic NET which have similar histologic characteristics but different biology and rate of response to therapy: pancreatic NET respond better than carcinoids to most therapeuticagents (84). Most of the information regarding the molecular profile of neuroendocrine tumors concern the pancreatic group; although most of them occur sporadically, they may arise in the context of four hereditary cancer syndromes (Multiple Endocrine Neoplasia type 1-MEN1, von Hippel-Lindau Disease-VHL, Neurofibromatosis Type 1-NF1, Tuberous Sclerosis-TS).

Several observations support the importance of the mTOR pathway in the pathogenesis of NET. mTOR (mammalian target of rapamycin) is an intracellular serine/threonine kinase regulating key cell functions involved in cell survival, proliferation and metabolism (85,86). It interacts with several proteins to form 2 multiprotein complexes (mTORC1 and mTORC2). When activated by growth factors and nutrients, mTORC1 phosphorylates the translational regulators of eukaryotic initiation factor 4E(eIF4E) binding protein 1 (4E-BP1) and S6 kinase1 (S6K1). These events lead to cell proliferation by promoting translation of specific mRNAs encoding proteins, regulating cell-cycle progression, angiogenesis, energy metabolism, and metastasis. Less is known about mTORC2. It also responds to growth factors signals

and, when active, mTORC2 regulates cell survival, cytoskeletal remodeling, and cell migration. It also serves to regulate the PI3K/AKT pathway via phosphorylation and activation of Akt. mTORC2 is not sensitive to rapamycin (87). mTOR is linked to the PI3K-Akt pathway by the tuberous sclerosis proteins TSC1 and TSC2, which act as a heterodimer that negatively regulates mTOR signaling. In response to insulin and other growth factors, TSC2 is phosporylated and inactivated by Akt, which then leads to mTOR activation (88).

The link between NET and mTOR is explained by the fact that the familiar cancer syndromes, previously appointed, are due to mutations in genes encoding proteins that lie upstream from mTOR (89). NF1 encodes the protein neurofibromin, which regulates TSC1 and TSC2: its loss leads to constitutive activation of mTOR and is associated with NET involving the ampulla of Vater and duodenum (90). Loss of function of TSC1 and TSC2 leads to mTOR activation in patients with tuberous sclerosis, which has been associated with pancreatic NET (91). Furthermore, whole exome sequencing analysis of sporadic pancreatic NET has identified somatic mutations in genes involved in the mTOR pathway, including PTEN, TS2, and PIK3CA, in 15% of cases (92). The knowledge of the involvement of this signaling pathway has resulted in the recent approval of a new therapy for pancreatic NET, i.e. the oral mTOR inhibitor (everolimus).

The exome sequencing approach identified, among patients with sporadic pancreatic NET, besides the mTOR pathway, other 2 key groups of somatic mutations, involving, respectively MEN1 and DAXX/ATRX: 45% have somatic inactivating mutations in MEN-1, which encodes menin, a component of a histone methyltransferase complex and 40% have mutations in genes encoding either of the two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain associated protein) and ATRX (alpha thalassemia/mental retardation syndrome X-linked). Clinically, these mutations seem to be associated with a better prognosis.

Recent evidences indicate that microRNA (93) contribute to tumor development and progression and may have diagnostic and prognostic value in several human malignancies: an investigation of global microRNA expression patterns in normal pancreas, pancreatic NET and acinar cell carcinoma showed that endocrine tumors are different from both the normal and exocrine tumors, suggesting that a specific set of microRNA is involved in NET tumorigenesis; they also showed that the overexpression of miRNA 21 is strongly associated with both a high Ki-67 proliferation index and the presence of liver metastasis. This finding may be useful in distinguishing tumors with different clinical behavior.

Bronchial carcinoids still lack of an effective treatment. Recently, *in vitro* studies (94) established that 62% of human bronchial carcinoids primary cultures respond to treatment with everolimus with a significant reduction in cell viability paralleled by apoptosis activation and that the novel PI3K/mTOR inhibitor NVB-BEZ235 is twice as potent as everolimus; this indicates that PI3K pathway plays an important role in the regulation of the proliferation of bronchial carcinoid cells. Knowledge regarding the biology of neuroendocrine tumors lies in a time of great revolution. Several working groups are considering the possibility of introducing the Ki67 value as a prognostic marker with cutoffs specifically generated for lung neuroendocrine tumors (95). All of these tumors have a common denominator, that is aderegulation of cell proliferation: this is why Ki67 turned-out to be a prognostic factor (96). However, comparative genomic hybridization studies and gene-expression profiling data reinforce the hypothesis that the carcinoids are biologically different from neuroendocrine carcinomas of the lung. Furthermore, a precursor lesion (DIPNECH) has only been observed in association with carcinoids and the occurrence of mixed tumors exclusively comprising high grade NE carcinomas also supports a different carcinogenesis for these tumors (83).

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