Neuroendocrine Tumors of the Gallbladder

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Abstract

Similar to the hepatobiliary tract, the gallbladder is a well-known origin of diverse types of neuroendocrine tumors. Previously, most of these neoplasms were classified as carcinoid tumors, irrespective of their grade of malignancy and differentiation. Today, the same classifications as used as in other anatomical locations are employed for gallbladder neuroendocrine tumors. As malignant neuroendocrine neoplasms, including those that arise in the hepatobiliary tract, can metastasize, the distinction between primary and metastatic gallbladder lesions may be difficult. Generally, solitary lesions and those with an endoluminal growth may more commonly represent primary neoplasms. As in other locations, grading of neuroendocrine neoplasms of the gallbladder is performed in accordance with the ENETS scheme.

ICD-O codes
Neuroendocrine tumor (NET)
NET G1 (carcinoid) 8240/3
NET G2 8249/3
Neuroendocrine carcinoma (NEC) 8246/3
Large cell NEC 8013/3
Small cell NEC 8041/3
MANEC 8244/3

Introduction

As in other locations, including the ampullary region and the extrahepatic bile ducts, neuroendocrine tumors primary to the gallbladder were preferentially termed carcinoids or carcinoid tumors, irrespective of their grade of malignancy and differentiation. The term carcinoid is now reserved for well-differentiated neuroendocrine tumors, according to the 2010 WHO classification (NET G1), while other forms of neuroendocrine tumors are allocated to distinct entities that are different from carcinoids. The novel WHO classification defines neuroendocrine neoplasms of the gallbladder as neoplasms with neuroendocrine differentiation, including NET, neuroendocrine carcinoma (NEC), and mixed adenoneuroendocrine carcinoma (MANEC) (Komminoth et al. 2010).

Classification of Neuroendocrine Neoplasms

Following the widely employed 2000 WHO classification of neuroendocrine tumors, the novel 2010 classification introduced new categories and nomenclatures, summarized in Table 1. The designation "neuroendocrine" instead of "endocrine" is now adopted to indicate that cell lineages involved in the neoplastic process express neural markers. The term, neuroendocrine neoplasm, can be employed as a synonym of neuroendocrine tumor.

The difference between WDET and WDEC was defined according to staging features in the WHO classification. The novel category, NET G2, does not necessarily translate into WDEC of the WHO 2000 classification. NEC should not be termed, NET G3, as NET is per definition a well-differentiated neoplasm.

Grading of Neuroendocrine Neoplasms

As in other locations, grading of gallbladder neuroendocrine tumors is now performed in accordance to the ENETS scheme (Rindi et al. 2006, 2007). The criteria are listed in Table 2. Pillars for this proliferation-based grading system are the mitotic count and the proliferation fraction assessed through the Ki-67 index. This grading

Table 1 WHO classifications (2000 and 2010) of neuroendocrine neoplasms

WHO 2000	WHO 2010
1. Well-differentiated endocrine tumor (WDET)	1. NET G1 (carcinoid)
2. Well-differentiated endocrine carcinoma (WDEC)	2. NET G2
3. Poorly differentiated endocrine carcinoma/small cell carcinoma (PDEC)	3. NEC (large cell or small cell type)
4. Mixed exocrine-endocrine carcinoma (MEEC)	4. Mixed adenoneuroendocrine carcinoma (MANEC)
5. Tumor-like lesions (TLL)	5. Hyperplastic and preneoplastic

Table 2 ENETS grading of neuroendocrine tumors

G1: Mitotic count <2 per 10 HPF and/or < = 2 % Ki-67 index
G2: Mitotic count 2–20 per 10 HPF and/or 3–20 % Ki-67 index
G3: Mitotic count >20 per 10 HPF and/or >20 % Ki-67 index

requires mitotic counts in at least 50 high-power fields (HPF), 1 HPF representing 2 mm^2 of tissue. Grading may, therefore, be difficult or not reliable in very small biopsy samples. The determination of the Ki-67 index (MIB1 immunostaining) requires the analysis of 500–2,000 tumor cells assessed in areas of homogeneous and strongest nuclear labeling (so-called "hot spots"). In case differences in grade determination between mitotic count and Ki-67 index occur, it is proposed that the higher grade be assumed.

Staging Systems for Neuroendocrine Neoplasms of the Gallbladder

In contrast to other gastrointestinal sites harboring neuroendocrine tumors, there is still no proposal for a TNM/staging classification of neuroendocrine neoplasms of the gallbladder. It has therefore been suggested that, for definitely malignant neuroendocrine neoplasms of the gallbladder, and in particular for NEC, the TNM system used for gallbladder adenocarcinomas be employed. Table 3 shows the TNM7 staging system for cancers of the gallbladder.

Epidemiology

Neuroendocrine tumors of the gallbladder are rare lesions that represent only 0.5 % of all gallbladder tumors and 0.2 % of all gastrointestinal neuroendocrine neoplasms (MacDonald 1956). Well-differentiated NETs (carcinoids) have a lower age at presentation in comparison with other gallbladder tumors (Godwin 1975), while NECs occur in an older category of patients.

Table 3 TNM7 Staging system for malignant neoplasms of the gallbladder

T			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor invades the lamina propria or muscle layer		
T1a	Tumor invades the lamina propria		
T1b	Tumor invades the muscle layer		
T2	Tumor invades the perimuscular connective tissue, no extension beyond the serosa or into the liver		
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, e.g., stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts		
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures		
N			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

General Clinical and Imaging Features

NET located to the distal part of the gallbladder can cause obstruction and may thus be associated with acute cholecystitis. Acute cholecystitis has also been observed in carcinoid tumor metastatic to the gallbladder, in the absence of stones (Saxton 1983). Even though NETs can synthesize a wide array of endocrine/neuroendocrine peptides, hormonal syndromes caused by these neoplasms are rare and include Zollinger-Ellison syndrome (Bernades et al. 1972) and ACTH secretion

syndrome (Spence and Burns-Cox 1975). Abdominal sonography and CT at admission usually reveal either intramural gallbladder masses, polypoid lesions (Salimi and Sharafuddin 1995), or tumors protruding into the gallbladder lumen, the latter morphology being rather typical for NEC (Chuang et al. 1999). In high-grade tumors, liver invasion is often seen at imaging.

Biology of Disease

In regard to biology of disease and tumor disease progression, neuroendocrine neoplasms of the gallbladder can be divided into two major groups that markedly differ in regard to tumor aggressiveness. The first group consists of NET showing a wide spectrum of behavior ranging from relatively bland tumors to metastasizing lesions, while the second group, the NEC, invariably shows a highly malignant phenotype with rapid evolution and high morbidity and mortality. In the NET group, the risk of malignant behavior depends on tumor size and proliferative activity (grade). NETs measuring 0.3–0.5 cm usually do not develop metastases, while gallbladder NETs with a diameter exceeding 2 cm often invade the liver and/or produce metastases. The overall risk for NET to cause regional or distant metastases is estimated to be 44 % and 11 %, respectively, with a 5-year survival rate of 41 %, based on the SEER database (reviewed in Komminoth et al. 2010). Patients with the aggressive NEC exhibit signs of disseminated disease at the time point of diagnosis in 40–50 %. MANEC tumors are considered to behave similar to ordinary gallbladder adenocarcinomas.

Neuroendocrine Tumor G1 (NET G1; Carcinoid) and NET G2 of the Gallbladder

Introduction

Well-differentiated neuroendocrine tumors (NET G1 and NET G2) are rare tumors. The first case has been reported in 1929 (Joel 1929), and a recent listing of the SEER database has 278 cases of gallbladder NET. However, only a minority of well-differentiated (G1) NETs are listed in this database, suggesting that G1 lesions may be very rare in the gallbladder, most gallbladder neuroendocrine neoplasms belonging to aggressive lesions discussed below (Eltawil et al. 2010; Lee et al. 2010). The female/male ratio of gallbladder carcinoids was 2.4, and the mean age at diagnosis was 64.5 years (Albores-Saavedra et al. 2009). NET may be detected incidentally, in the setting of cholecystectomies performed for other reasons, or are diagnosed because they are symptomatic lesions.

Selected References (Bosse 1943; Barnes 1952; Lanza et al. 1965; Nizze 1973; Gaffney and Coyle 1978; Sommariva et al. 1988; Yamamoto et al. 1989; Mochizuki 1991; Betancourt et al. 1992; Naseer and Kabir 1992; Porter et al. 1992; Deehan et al. 1993; Khetan et al. 1995; Kawaguchi et al. 1996; Nishigami et al. 1996; Psathakis et al. 1996; Lovera et al. 1997; Machado et al. 1998; Kaiho et al. 1999; Yokoyama et al. 2000; Angelini et al. 2003; Ozawa et al. 2003; Arjaneyulu et al. 2007; Geo et al. 2007; Virzi et al. 2008; Baikoussis et al. 2009; Kanakala et al. 2009; Zou et al. 2010; Ghosh et al. 2011; Lee et al. 2011; Mezi et al. 2011).

In principle, symptomatic gallbladder NETs are indistinguishable from gallbladder cancer (Tewari et al. 2009), and the carcinoid syndrome is estimated to occur in only 1 % or less of patients (Salimi and Sharafuddin 1995). A minority of gallbladder NETs are associated with the production and eventual secretion of hormonal peptides, including pancreatic polypeptide, somatostatin, gastrin, or ghrelin (Tanaka et al. 1992; Heymann et al. 1997; Walter et al. 2009), sometimes associated with Zollinger-Ellison syndrome (Barone et al. 1992). Angiographically, gallbladder carcinoids are hypervascular lesions fed by a sometimes dilated and finely neovascularized cystic artery, and this hypervascular phenotype is recapitulated in hepatic metastases (Kitagawa et al. 1986). NET with a differentiation grade G1 or G2 may

probably and in part be translated in what was previously called typical carcinoid. In a group of 101 gallbladder tumors diagnosed as carcinoid, 81 cases were "typical" and 20 cases were "atypical" carcinoids, the latter containing less differentiated neoplasms (Soga 2003).

Only well-differentiated NETs of the gallbladder are expected to have a better prognosis (Iype et al. 2009). Some authors defined "variant endocrinomas" developing in the gallbladder. "Classical" carcinoids were different from the variant group by exhibiting a younger average age, a higher incidence of associated cholelithiasis, a higher incidence of small tumors 50 mm or less, a smaller average tumor size, and a lower rate of metastases (Soga 2003). For classical gallbladder carcinoids, the 10-year survival rate was 36 % (Albores-Saavedra et al. 2009).

Pathology

Macroscopically, NETs are nodular or polypoid tumors of whitish, yellow, or tan color. Part of the lesions show an infiltrative growth into the gallbladder wall at macroscopic examination already. The neoplasms are usually small, less than 2 cm diameter in most cases, but they may grow to sizes exceeding 5 cm. Early lesions that measure only a few mm may be missed at gross examination (Porter et al. 1992). Most NETs are solitary lesions, but rare instances of multifocality exist. Rarely, tumors appear as clearly pedunculated lesions with a well-identifiable stalk (Oku et al. 2008).

In "typical" carcinoid (NET G1), small "endocrine type", uniform cells are arranged in the form of anastomosing trabecular, solid, nested, or alveolar structures surrounded by a richly vascularized stroma. Some NETs show tubular structures. The cells exhibit a slightly eosinophilic cytoplasm and round to oval nuclei with inconspicuous nucleoli. NET G2 has more cellular and nuclear unrest, with more frequent deviation of nuclear size and shape from the round endocrine nuclei and more frequent mitotic figures (see the paragraph on grading). Grimelius staining is variably positive (Nishigami et al. 1996), but Fontana-Masson staining is usually negative.

Ultrastructurally, the neoplastic cells contain typical and sometimes numerous neurosecretory granules in the cytoplasm (Kaiho et al. 1999). Immunohistochemically, NETs are strongly reactive for chromogranin A, synaptophysin, neuron-specific enolase, and CD56/N-CAM. The tumors can express cytokeratins (AE17AE3 and CK7), serotonin, and several hormonal peptides, including somatostatin, gastrin, and pancreatic polypeptide (Kaiho et al. 1999; Zou et al. 2010; Mezi et al. 2011).

Variants of Gallbladder NET/Carcinoid Tumors

One variant of NET G1 is characterized by a composition of clear cells (lipid-rich/clear cell neuroendocrine tumor; clear cell NET G1). Similar to their counterparts occurring in the pancreas (Ordonez and Silva 1997; Hoang et al. 2001), which may occur in the setting of von Hippel-Lindau disease (Singh et al. 2006) or in MEN I (Fryer et al. 2012), clear cell tumors of neuroendocrine lineage of the gallbladder can develop in von Hippel-Lindau disease (Sinkre et al. 2001), but clear cell NET G1 of the gallbladder can occur in the absence of this genetic disorder (Konishi et al. 2003; Ishida et al. 2012). These tumors are composed of cells with a cytoplasm that contains lipid droplets and sometimes displays a foamy structure. The clear aspect of the neoplastic cells is not caused by glycogen accumulations, as PAS staining gives a negative result. Similar to ordinary carcinoids, clear cell NET G1 are immunoreactive for chromogranin A and synaptophysin and may also express several neuroendocrine peptides, including somatostatin, gastrin, and pancreatic polypeptide (Konishi et al. 2003). Clear cell NETs associated with von Hippel-Lindau disease, but not sporadic cases, are reactive for alpha-inhibin (Sinkre et al. 2001; Konishi et al. 2003; Ishida et al. 2012). A very rare variant of NET G1 is signet-ring cell carcinoid, characterized by a neoplastic proliferation of numerous signet-ring cells admixed with chromogranin A-positive clear cells (Papotti et al. 1990). Goblet cell adenocarcinoid has been found as a component of a composite tumor (Muto et al. 1984).

Neuroendocrine Carcinoma (NEC) of the Gallbladder

Introduction

Neuroendocrine carcinomas (NECs) of the gallbladder are rare neoplasms, and patients with such lesions have a poor prognosis. NECs exhibit early and often numerous locoregional lymph node metastases and distant metastases, in a first round frequently to the liver (Bosl et al. 1980; McLean and Pedersen 1991; Kumar et al. 1992; Yoshizumi et al. 1992; Mizukami et al. 1998; Bhutani et al. 2001). However, modern chemotherapy schemes can now result in long-term remission in part of patients (Mizukami et al. 1998; Shimono et al. 2009; Elahi et al. 2013).

Small Cell NEC (SCNEC)

Small cell neuroendocrine carcinomas (SCNECs) of the gallbladder represent the more common variant of NEC and share many features with their counterparts developing in other organs, particularly those in the lung (see above; paragraph on small cell carcinomas). Gallbladder small cell NECs were also termed oat cell carcinoma (Albores-Saavedra et al. 1984). The prevalence of SCNEC of the gallbladder is estimated to be 1–5 % of all gastrointestinal neuroendocrine neoplasms (Albores-Saavedra et al. 1984). Similar to SCNEC of the ampullary region, patients with gallbladder SCNEC are older at presentation than those with NET/carcinoids, with a median age at diagnosis of 65 years (in one study, 69 years; Maitra et al. 2001). There is a female preponderance (76 % are female), and the tumors are often associated with cholelithiasis (72 %).

Selected References (Cavazzana et al. 1991; Ron et al. 1992; Nishihara and Tsuneyoshi 1993; Muraina et al. 1996; Chuang et al. 1999; Moskal et al. 1999; Matsuo et al. 2000; Fujii et al. 2001; Maitra et al. 2001; Lane et al. 2002; Jun et al. 2006; Imai et al. 2008; Nishime et al. 2008; Uribe-Uribe et al. 2009; Lee et al. 2010; Nau et al. 2010; Ng et al. 2010; Mahipal and Gupta 2011; Benkel et al. 2012; Chen et al. 2014).

Similar to LCNEC, SCNECs are very aggressive lesions with poor outcome (Lee et al. 2010). Seventy-five percent of the tumors had metastasized or extended locally beyond the gallbladder at surgery (Maitra et al. 2001). In an analysis of 28 pure SCNEC and 8 MANEC containing SCNEC, the tumors metastasized to lymph nodes in 88 %, the liver in 88 %, the lung in 23 %, and the peritoneum in 19 % (Moskal et al. 1999). In an analysis of 12 patients, mean survival was 10.7 months, with a range of 3–25 months (Maitra et al. 2001). Similar to other small cell undifferentiated carcinomas, SCNECs are sometimes associated with paraneoplastic syndromes, e.g., hyponatremia (Ng et al. 2010) or sensory neuropathy (Uribe-Uribe et al. 2009).

Pathology

Macroscopy

Macroscopically, the tumors are usually bulky lesions of whitish to tan color that may protrude into the gallbladder lumen. In one study of 12 cases, the neoplasms had an average size of 3 cm (Maitra et al. 2001). On cut sections, the tumors have a fleshy consistency or are friable masses. The carcinomas have been described as ill-defined or nodular gray-white to whitish masses showing hemorrhagic necrosis (Chuang et al. 1999). The tumors are often large at the time point of diagnosis and show a propensity for submucosal growth (Albores-Saavedra et al. 1984). SCC may also present as small nodular lesions of the gallbladder, but even small tumors can metastasize to local lymph nodes (Uribe-Uribe et al. 2009), again a feature also known for SCC of the lungs

Histopathology

Histologically, SCNECs exhibit loosely cohesive tumor cells that diffusely infiltrate the gallbladder wall, may form sheets and cords, and can show

extensive lymphovascular invasion. The tumor cells are small to medium sized, mostly somewhat larger than quiescent small lymphocytes, i.e., like oat cells of lung carcinoma. Apart from round cells, spindled, fusiform, or polygonal cells also occur. The cytoplasm is scanty and slightly eosinophilic to amphophilic. The nuclei are ovoid, spindle shaped, or indented, with the characteristic "salt and pepper" chromatin structure with either no visible nucleoli or two to three small nucleoli. Characteristic nuclear "moulding" (also written "molding") is seen on high-power examination. Nuclear "moulding" is a helpful artifact due to the flexible nuclear membrane: the nucleus of one tumor cell appears to be bumping into another nucleus, causing the two nuclei to look like part of a jigsaw puzzle. Many and in part abnormal mitotic figures are noted, as well as apoptotic bodies and foci of necrosis. There may be tingible bodies reflecting phagocytosis of nuclear debris, and emperipolesis of apoptotic bodies may be found. Prominent necrosis is usually found, with accumulations of shadow cells. Similar to small cell carcinoma of the lung, the tumors display the diagnostically helpful nuclear "crushed" artifact caused by section preparation and may show the Azzopardi phenomenon, i.e., basophilic chromatin containing damaged DNA coating vessel walls following liberation of chromatin/DNA from dead cells (Albores-Saavedra et al. 1984; Takei et al. 2007; Nau et al. 2010). Part of SCNECs may show rosette-like structures and tubules. The latter should represent definitively less than 30 % of the tumor, otherwise MANEC has to be considered (see below). In a series of 12 patients, invasion of the muscularis propria and perimuscular connective tissue was detected in 90 % (Maitra et al. 2001). Association with intestinal metaplasia of the gallbladder mucosa has been found, with goblet cells, pseudopyloric glands, and Paneth cells (Kuwabara and Uda 1998). Argyrophilic cells may be found in the Grimelius stain (Iida and Tsutsumi 1992; Nishihara and Tsuneyoshi 1993).

In more than a quarter of cases, SCNEC is combined with adenocarcinoma, squamous cell carcinoma, or other types of carcinoma (Duan et al. 1991; Iida and Tsutsumi 1992; Nishihara et al. 1994; Okamoto et al. 2003; Mahipal and Gupta 2011). In the series of 12 patients published by Maitra et al. (2001), half of the cases were combined with other neoplasms. Four had foci of adenocarcinoma, one had a component of squamous cell carcinoma, and one had a focus of carcinosarcoma. Combined SCC and clear cell carcinoma of the gallbladder have been observed (Piana et al. 2002). Sarcomatoid carcinoma of the gallbladder was found to have an SCC component (Takahashi et al. 2004).

Ultrastructurally, neurosecretory-type cytoplasmic granules were detected (Cavazzana et al. 1991; Fujii et al. 2001). Immunohistochemically, the tumor cells express neuroendocrine lineage markers, above all synaptophysin and chromogranin A (Cavazzana et al. 1991; Chuang et al. 1999; Mahipal and Gupta 2011). Synaptophysin expression is usually diffuse, whereas chromogranin A tends to involve scattered cells. In some cases, focal reactivity for epithelial markers was detectable, including cytokeratins, EMA, and CEA (Cavazzana et al. 1991). SCNEC may express serotonin, but this is a rare feature. Relatively few tumors expressed neuroendocrine peptides, such as somatostatin, or ACTH. On a molecular level, 100 % of SCNEC of the gallbladder demonstrated inactivation of the pRB/p16 pathway, and 67 % of these tumors accumulated high levels of p53, while activating K-ras mutations were not found (Parwani et al. 2003).

Large Cell NEC

Among NECs of the gallbladder, the large cell variant (LCNEC) is the less common in comparison with its small cell counterpart (Papotti et al. 2000; Jun et al. 2006; Shimono et al. 2009; Furrukh et al. 2013; Okuyama et al. 2013; Samad et al. 2013). LCNEC has been found in association with anomalous union of the pancreaticobiliary duct (Yoon et al. 2009). Exceptionally, LCNECs were associated with paraneoplastic syndromes, e.g., Cushing's syndrome caused by

production of ACTH by the tumor (Lin et al. 2010).

Macroscopically, the tumors resemble the phenotype described for SCNEC. Histologically, the neoplasms display an organoid growth pattern and consist of large cells with an amphophilic or slightly eosinophilic cytoplasm and large vesicular nuclei with prominent nucleoli. These cells are arranged in a diffuse, solid, or focally nesting pattern. In fine-needle aspiration preparations, rosette-like structures may be encountered in a background showing extensive necrotic debris (Samad et al. 2013). In some tumors, the cell size is situated between large and small cells (intermediate cell NEC; ICNEC), a tumor not listed as such in the 2010 WHO classification. Immunohistochemically, the tumor cells are reactive for synaptophysin, chromogranin A (Okuyama et al. 2013), and at least part of the cells are reactive for epithelial markers (AE1/AE3; Samad et al. 2013). The proliferation fraction (Ki-67 index) is high or very high (Okuyama et al. 2013; Samad et al. 2013).

Mixed Adenoneuroendocrine Carcinoma (MANEC) of the Gallbladder

Introduction

In the 2010 WHO classification, mixed adenoneuroendocrine carcinomas (MANECs) are defined as composite neoplasms in which areas of adenocarcinoma or squamous cell carcinoma intermingle with areas of neuroendocrine tumor (NET) or neuroendocrine carcinoma (NEC), each component comprising at least 30 %, or exceeding 30 %, of the neoplasm. In the light of the different cell lineages involved, a role of stem cells has been proposed as a pathogenic mechanism (Paniz Mondolfi et al. 2011).

The first description of a gastrointestinal tumor with an exocrine and a neuroendocrine component dates in 1924 (Cordier 1924). Tumors having a synchronous presentation of adenocarcinoma and (neuro)endocrine components were previously called adenocarcinoid, a term first coined in 1978 based on tumors of the appendix (Warkel et al. 1978; Cooper and Warkel 1978). In 1987, Lewin suggested to classify such neoplasm into three different subtypes: collision tumors, combined tumors, and amphicrine tumors (Lewin 1987). According to the WHO classification of tumors, these lesions are now termed mixed adenoneuroendocrine carcinoma or MANEC (synonyms: adenoendocrine carcinoma; mixed/composite glandular-endocrine cell carcinoma; composite carcinomatous and carcinoid tumor; carcinoid tumor with adenocarcinomatous differentiation). The neuroendocrine components display features overlapping those described in pure NETs or NECs, being formed by solid and/or trabecular structures with argyrophilic cells that are immunoreactive for neuroendocrine markers. The identification in adenocarcinoma of scattered neuroendocrine cells by immunohistochemistry does not qualify for the definition of MANEC. The spectrum of lesions ranges from pure NE tumors to pure non-endocrine carcinomas, as discussed in a review as of 2006 (Volante et al. 2006), and MANECs form a distinct window in this spectrum. The nomenclature and classification of these tumors has recently been refined (La Rosa et al. 2012; Table 4). Gastrointestinal MANECs, including those of the gallbladder, can be stratified in different prognostic categories according to grade of malignancy of each component. High-grade malignant MANECs are malignant composite or combined tumors formed by an adenomatous or carcinomatous component and by a poorly differentiated (small, intermediate, or large cell type) neuroendocrine carcinoma. Intermediate-grade malignant MANEC includes mixed adenocarcinoma-neuroendocrine carcinoma and amphicrine carcinoma. The first category consists of adenocarcinoma, and the neuroendocrine component is represented by a

Table 4 Classification of MANEC and related tumors (La Rosa et al. 2012)

High-grade malignant MANEC
Intermediate-grade malignant MANEC
Mixed adenocarcinoma-neuroendocrine tumor (adenocarcinoma-NET)
Mixed adenoneuroendocrine tumor (MANET)
Adenoma-neuroendocrine tumor (adenoma-NET)

differentiated neuroendocrine tumor which can show grade 1 (NET G1) or grade 2 (NET G2) differentiation. Amphicrine carcinoma represents a peculiar neoplasm in which exocrine and neuroendocrine features are coexpressed by the same neoplastic cells. Mixed adenocarcinoma-neuroendocrine tumor (adenocarcinoma-NET) is a composite tumor consisting of areas of adenocarcinoma and areas of grade 1 or grade 2 NET (synonyms: mucin-producing carcinoid; composite carcinoid-adenocarcinoma, composite carcinoid tumor, mixed adenocarcinoid tumor, and composite glandular-neuroendocrine mixed tumor). Mixed adenoneuroendocrine tumors or MANETs include neoplasms formed by well-differentiated neuroendocrine and exocrine cells which behave in an indolent manner. Adenoma-neuroendocrine tumor (adenoma-NET) is a very rare neoplasm characterized by both an adenomatous and a NET component (synonym: glandular-carcinoid tumor). It has to be emphasized that adenocarcinoma having cells showing immunoreactivity for neuroendocrine markers (adenocarcinoma with neuroendocrine features) in the absence of neuroendocrine cells should not be classified as MANEC.

MANEC and similar lesions are rare primary tumors of the gallbladder, less than 30 cases having been reported.

Selected References (Wisniewski and Toker 1972; Ito et al. 1980; Wada et al. 1983; Kotake et al. 1984; Muto et al. 1984; Noda et al. 1989; Fish et al. 1990; Peraza et al. 1990; Duan et al. 1991; Olinici and Waslu 1991; Iida and Tsutsumi 1992; Ohmori et al. 1993; Nishihara et al. 1994; Resnick et al. 1994; Eriguchi et al. 2000; Yannakou et al. 2001; Piana et al. 2002; Shimizu et al. 2006; Sosnik and Sosnik 2006; Tsuchiya et al. 2006; Oshiro et al. 2008; Sato et al. 2010; Paniz Mondolfi et al. 2011; Harada et al. 2012; Rastogi et al. 2012; Russo et al. 2012).

The rarity of reported cases of MANEC may be related to the lack of immune-histochemical studies in older studies. Among 49 gallbladder cancers of a recent investigation using immunohistochemistry for neuroendocrine markers, a neuroendocrine component occupying more than 30 % of the entire tumor was found in 5/49 cases/10 % (Harada et al. 2012), MANECs develop without recognizable association with preexisting disease in the large majority of cases. In one patient, an association with pancreaticobiliary maljunction was found (Oshiro et al. 2008).

Clinical and Imaging Features

The clinical presentation of MANECs is nonspecific and mainly consists of upper abdominal pain and a right upper abdominal mass. Signs of carcinoid syndrome are lacking. In MANEC cases containing aggressive neuroendocrine components, chiefly small of large cell parts, patients may present with advanced stage disease and associated symptoms and signs of cancer disease, including weight loss and fever. MANECs with small cell NEC (SCNEC) and large cell NEC (LCNEC) components have a poor outcome, whereas the biology of disease in MANECs having a carcinoid component is dominated by the adenocarcinoma component of the tumor (La Rosa et al. 2012). Exceptionally, MANECs are associated with hormonal hypersecretion, e.g., pancreatic polypeptide (Marrano et al. 1999).

Pathology

Apart from solid and nodular tumors, MANECs of the gallbladder are relatively often endophytically growing lesions, with a polypoid pattern. On cut surfaces the tumors are grayish or white or whitish-yellow to tan, depending on the proportion of adenocarcinoma vs. neuroendocrine components. MANEC may be deeply invasive lesions, penetrating the entire gallbladder wall and even infiltrating the fossa and the liver substance proper.

The histology of MANEC is characterized by adenocarcinoma and neuroendocrine elements randomly distributed through the gallbladder wall, closely juxtaposed, but also with transitions between the two components. Several combinations of morphologies have been described

Table 5 Types of adenocarcinoma and neuroendocrine tumors combined in MANEC and mixed adenocarcinoma-NET of the gallbladder

Adenocarcinoma, carcinoid tumor	(Wisniewski and Toker 1972; Wada et al. 1983; Kotake et al. 1984; Noda et al. 1989)
Undifferentiated carcinoma, carcinoid tumor	(Ito et al. 1980)
Adenocarcinoma, signet-ring cell carcinoma, ICNEC	(Olinici and Waslu 1991)
Tubular adenocarcinoma, ICNEC	(Eriguchi et al. 2000; Yannakou et al. 2001)
Adenocarcinoma, SCNEC	(Duan et al. 1991; Iida and Tsutsumi 1992; Nishihara et al. 1994; Okamoto et al. 2003; Shimizu et al. 2006; Tsuchiya et al. 2006; Elahi et al. 2013)
Clear cell carcinoma, SCNEC	(Piana et al. 2002)
Mucinous adenocarcinoma, SCNEC, LCNEC	(Oshiro et al. 2008; Russo et al. 2012)
Tubular adenocarcinoma, LCNEC	(Sato et al. 2010)
Papillary adenocarcinoma, LCNEC	(Paniz Mondolfi et al. 2011)

LCNEC large cell neuroendocrine carcinoma, *SCNEC* small cell neuroendocrine carcinoma, *ICNEC* intermediate cell neuroendocrine carcinoma

(Table 5). The differentiation and mucin production patterns of the adenocarcinoma component vary considerably among cases, and some adenocarcinomas may only show florid neuroendocrine cell nests (Sakaki et al. 2000). The reticulin pattern differs between the two parts, being dense in adenocarcinoma and delicate in the neuroendocrine parts. MANEC may contain a component of goblet cell adenocarcinoid as a rare differentiation mode (Muto et al. 1984). Where the two components merge, so-called transitional tumor cells showing both histological and cytological features may be seen. In these areas, argyrophil granules and mucin can be found in the same cells (Wada et al. 1983). One MANEC showed extensive Paneth cell metaplasia (Sakakai et al. 2000). The adenoid component of a small cell NEC-type MANEC may only be manifest in the form of intestinal metaplasia (Kuwabara and Uda 1998). Some of the tumors show necrosis and/or fibrosis.

The tumors may be associated with erosion or ulceration of the overlying mucosa, and hyperplastic epithelial changes are sometimes seen in the adjacent intact mucosa. Ultrastructurally, individual tumor cells were shown to have overlapping features of neuroendocrine and glandular differentiation (Paniz Mondolfi et al. 2011).

The adenocarcinoma cells express a marker pattern typical of ordinary gallbladder adenocarcinoma, while neuroendocrine tumor cells are reactive for neuron-specific enolase (NSE), chromogranin A, and synaptophysin (Noda et al. 1989; Eriguchi et al. 2000; Shimizu et al. 2006; Tsuchiya et al. 2006; Sato et al. 2010). So-called transitional tumor cells display common immunoreactivity for CEA, cancer antigen 19-9, CK19, epithelial cell adhesion molecule, and CD117 (Paniz Mondolfi et al. 2011).

Pathogenic Pathways

The histogenesis of MANEC has not yet been clarified, but several hypotheses of their pathogenesis have been proposed. One view consists of the coincidental neoplastic change in two different cell lineages; the other suggests the involvement of a progenitor cell developing into an endocrine and a glandular cellular phenotype. The second hypothesis is sometimes favored owing to the fact that so-called transitional cells are detectable in part of the tumors.

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