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Review

Neuroendocrine neoplasms of the duodenum, ampullary region, jejunum and ileum

Massimo Milione[1], Paola Parente[2], Federica Grillo[3,4], Giuseppe Zamboni[5], Luca Mastracci[3,4], Carlo Capella[6], Matteo Fassan[7], Alessandro Vanoli[8]

[1] 1st Pathology Division, Department of Pathology and Laboratory Medicine Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2] Unit of Pathology, Fondazione IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, FG, Italy; [3] Anatomic Pathology, Department of Surgical Sciences and Integrated Diagnostics, University of Genova, Italy; [4] Ospedale Policlinico San Martino IRCCS, Genova, Italy; [5] Department of Diagnostic and Public Health, Section of Pathology, University of Verona, Verona, Italy; [6] Department of Medicine and Surgery, University of Insubria, Varese, Italy; [7] Surgical Pathology and Cytopathology Unit, Department of Medicine (DIMED), University of Padova, Padova, Italy; [8] Anatomic Pathology Unit, Department of Molecular Medicine, University of Pavia and Fondazione IRCCS San Matteo Hospital, Pavia, Italy

Summary
Neuroendocrine neoplasms of the small intestine are some of the most frequently occurring along the gastrointestinal tract, even though their incidence is extremely variable according to specific sites. Jejunal-ileal neuroendocrine neoplasms account for about 27% of gastrointestinal NETs making them the second most frequent NET type. The aim of this review is to classify all tumors following the WHO 2019 classification and to describe their pathologic differences and peculiarities.

Key words: ampulla, MiNEN, NEC, NET, neuroendocrine neoplasms, small intestine, Jejunal-ileal neuroendocrine neoplasms

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Correspondence
Alessandro Vanoli
Anatomic Pathology Unit, Department of Molecular Medicine, University of Pavia, and IRCCS San Matteo Hospital, via Carlo Forlanini 16, 27100 Pavia, Italy
Tel. + 0382 523056
Fax: +0382 525866
E-mail: alessandro.vanoli@unipv.it

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Neuroendocrine neoplasms of the duodenum and ampullary region

Introduction

Duodenal neuroendocrine neoplasms (Duo-NENs) are uncommon, accounting for about 4% of all gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [1,2]. They include ampullary NENs, which arise within or around the major or minor papilla/ampulla and extra-ampullary NENs. Their incidence is increasing, likely due to improved diagnostic techniques.

Clinical presentation

Patients with Duo-NENs may present with abdominal pain, jaundice, bleeding or anemia [3]; however, many nonfunctioning neuroendocrine tumors (NETs) are discovered incidentally. Zollinger-Ellison syndrome due to a gastrinoma may occur, sometimes in the setting of multiple endocrine neoplasia type 1 (MEN1) syndrome, whereas somatostatinoma or carcinoid syndrome are extremely rare.

Subtypes

They include well-differentiated duodenal NETs (Duo-NETs), gangliocytic paragangliomas, poorly differentiated neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs).

Duo-NETs

Duo-NETs are graded according to the WHO proliferative criteria as G1, G2 and G3; most Duo-NETs (66-80%) are low-grade (G1) tumors, while grade 3 NETs are very rare.

Three main clinico-pathologic subtypes of Duo-NETs have been described [4] (Tab. I):

a **Gastrinoma** (i.e. functioning gastrin-producing NETs). This tumor subtype is, by definition, associated with Zollinger-Ellison syndrome and characterized by gastrin expression of neoplastic cells. Duodenal gastrinomas usually show a well-defined trabecular pattern, with frequent vascular pseudorosettes (Fig. 1). About 30% of duodenal gastrinomas arise in patients with MEN1 syndrome; MEN1-associated gastrinomas are often coupled with diffuse hyperplastic gastrin and somatostatin cell changes and multicentric gastrin-producing micro-NETs [5]. Despite their usually small size (0.7-0.8 cm), gastrinomas are more frequently associated with lymph node metastases in comparison with non-functioning gastrin-expressing Duo-NETs [6].

b **Ampullary-type somatostatin-producing NETs (AS-NETs),** also known as "somatostatinoma", despite the frequent lack of an associated hyperfunctioning clinical syndrome. They are characterized by a more or less prominent tubulo-acinar/pseudoglandular pattern of growth, often with psammoma bodies, and extensive (more than 50% of tumor cells) somatostatin reactivity (Fig. 2). AS-NETs represent the most common histologic subtype among NETs of the major and minor papilla/ampulla regions [4,7]; they can, however, be occasionally found in the extra-ampullary duodenum. A fraction of such neoplasms occur in patients with neurofibromatosis type 1 and they show a biallelic inactivation of *NF1* gene [8]. In addition to reactivity for general neuroendocrine markers and somatostatin, AS-NETs are, as a rule, positive for

Table I. Features of the main histologic subtypes of duodenal neuroendocrine neoplasms.

	Gastrinoma	Ampullary-type somatostatin-producing neuroendocrine tumor	Ordinary non-functioning neuroendocrine tumor	Gangliocytic paraganglioma	Neuroendocrine carcinoma
Age at diagnosis	5th decade	5th decade	6th decade	6th decade	7th decade
Hyperfunctional syndrome	Always (Zollinger-Ellison syndrome)	Rare (somatostatinoma syndrome)	No (by definition)	No	Rare (paraneoplastic syndromes)
Predisposing hereditary syndromes	Multiple endocrine neoplasia type 1 (less than 50%)	Neurofibromatosis type 1 (>10%), Pacak-Zhuang syndrome (rare)	Multiple endocrine neoplasia type 1 (rare)	Neurofibromatosis type 1 (rare)	No
Preferential location	First duodenal portion	Major/minor ampullary region	First duodenal portion	Major/minor ampullary region	Major ampulla region
Predominant histologic pattern	Trabecular	Tubulo-acinar/glandular	Nested/trabecular	Triphasic: paraganglioid+spindle cells+ganglion-like cells	Solid/diffuse (poorly differentiated)
Extensive (> 50%) somatostatin expression	No	Yes (by definition)	Rare	Frequent	No/very rare
Gastrin expression	Yes (by definition)	Rare (few cells)	Frequent	No	No/rare cells
Pancreatic polypeptide expression	No/rare cells	No/rare cells	No/rare cells	Frequent	No/rare cells
Type 2A somatostatin receptor expression	Frequent	Rare	Frequent	Frequent	Rare
Size > 1 cm	Rare	Frequent	Rare	Frequent	Frequent
Lymph node metastasis	Frequent	Frequent	Uncommon	Uncommon	Very frequent
Distant metastasis	Rare	Rare	Rare	Extremely rare	Frequent
Prognosis (after resection)	Good	Good	Good	Good	Bad

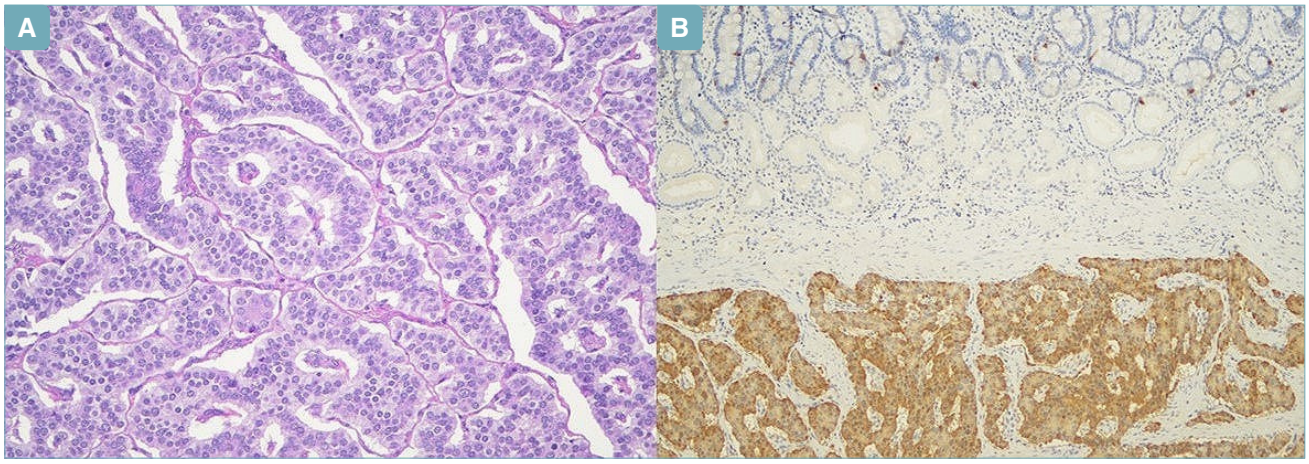

Figure 1. A duodenal gastrinoma, showing a trabecular pattern, with vascular pseudorosettes (A, hematoxylin and eosin), and tumor cell reactivity for gastrin (B, gastrin immunostaining). Note also the presence of gastrin-positive cells in normal duodenal mucosa overlying the neoplasm.

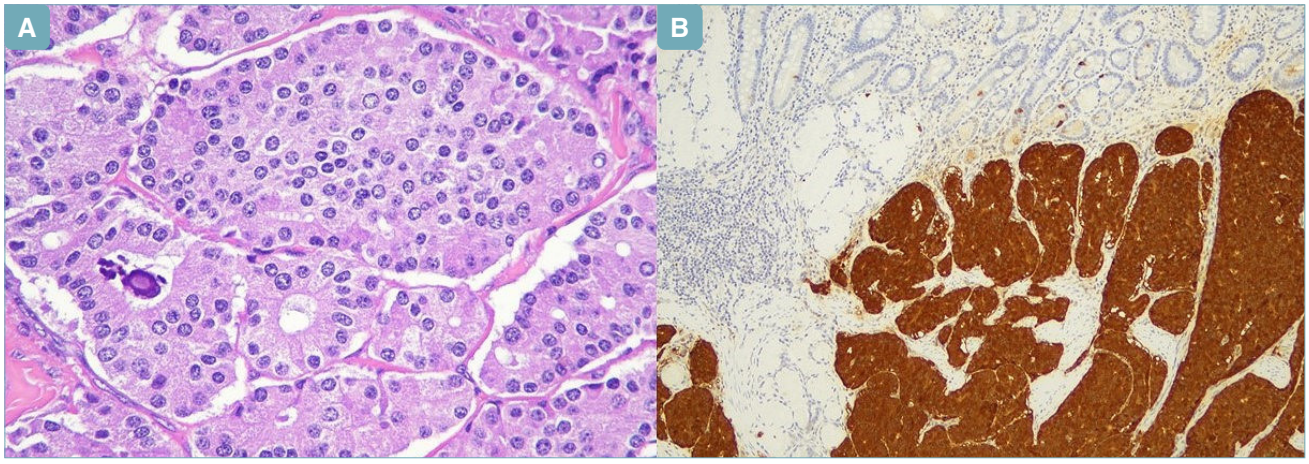

Figure 2. An ampullary-type somatostatin-producing neuroendocrine tumor, showing tubulo-acinar structures with psammoma bodies in a solid/trabecular architectural background (A, hematoxylin and eosin), and extensive somatostatin expression by tumor cells (B, somatostatin immunostaining).

MUC1/EMA, frequently reactive for cytokeratin 7 and negative for type 2A somatostatin receptors [4]. Although AS-NETs are significantly larger (median size: 1.8-2.5 cm) and have a higher lymph node metastatic rate (about 50% of cases) than ordinary non-functioning, mostly extra-ampullary, Duo-NETs, they display an indolent behavior, even when metastatic to the liver. Differential diagnosis with duodenal or ampullary adenocarcinomas is therefore of utmost clinical importance. In contrast to AS-NETs, adenocarcinomas show higher nuclear atypia and mitotic activity, absence of psammoma bodies, and negativity (or only focal positivity) for general neuroendocrine markers and somatostatin. It should also be recalled that duodenal NECs and gangliocytic paragangliomas may also express somatostatin; however, their cellular and architectural features allow a straightforward distinction from AS-NETs.

c **Ordinary non-functioning NETs.** The remaining Duo-NETs showing the "canonical" NET organoid architecture (nests, trabeculae, ribbons) and, in addition to general neuroendocrine markers, variable expression of gastrin or, less frequent-

ly, somatostatin [2] account for the vast majority of extra-ampullary Duo-NETs. Gastrin-producing Duo-NETs are more frequently detected in the first portion of the duodenum. Worthy of note is that enterochromaffin-cell serotonin-expressing NETs are exceptionally rare in the duodenum, in comparison with the jejunum or ileum. In Duo-NETs, risk factors for lymph node metastasis encompass tumor size, invasion of muscularis propria or beyond, lymphovascular invasion, and grade (2 or 3), while independent prognostic factors include tumor stage, tumor size (patients with tumors of 2 cm in diameter or larger have worse outcome) and lymphovascular invasion [4].

Gangliocytic paragangliomas

Gangliocytic paraganglioma represents a rare and distinct tumor type, which is almost always located in the ampullary region. It is characterized by a triphasic morphology, i.e. i) an epithelioid, paraganglioma-like neuroendocrine component (reactive for general neuroendocrine markers and, frequently, for cytokeratins, somatostatin, pancreatic polypeptide and progesterone receptors), ii) a Shwannian-like spindle cell component (reactive for S100 protein and SOX10 and often for synaptophysin), and iii) a ganglion-like cell component (reactive for synaptophysin and, sometimes, for somatostatin, S100 or cytokeratins) [4,9,10]. The three components may be variably intermingled. Despite their often pseudo-infiltrative pattern, gangliocytic paraganglioma is considered a very-low-grade tumor, with uncommon metastases, essentially to loco-regional lymph nodes. It should be mainly distinguished from Duo-NETs, especially from AS-NETs, which display a greater metastatic potential, and from true paragangliomas, gastrointestinal stromal tumors and ganglioneuroma. In addition to the typical triphasic histology, immunohistochemistry for progesterone receptor and pancreatic polypeptide may help distinguish gangliocytic paraganglioma from Duo-NET [9]. Recently, Mamilla et al conclude that gangliocytic paragangliomas have a NET-like [9] immunoprofile but differ from ordinary paragangliomas, almost all of which are cytokeratin-negative[10]. Gastrointestinal stromal tumors have a different immunophenotype, while ganglioneuroma lacks the epithelioid component.

Duodenal NECs

They are by definition high-grade NENs. Histologically, NECs are arranged in poorly formed trabeculae, large and confluent nests or sheet-like growths, similar to those described in the lung or remaining gastroenteropancreatic tract. Most duodenal NECs arise around the major ampulla [11,12], where they form large and invasive masses (median size: 2.5 cm). They may be separated histologically in two variants: small cell NECs and large cell NECs. Duodenal NECs, regardless of histologic variant, are generally associated with an advanced stage and a worse prognosis [4,12]. More than half of ampullary NECs show loss of Retinoblastoma (RB1) expression, which may be helpful to support the diagnosis of NEC (versus a NET G3) in challenging cases, while p53 overexpression occurs in about 30% of cases [12].

Duodenal MiNENs

Few ampullary MiNENs, composed of a NEC component combined with an adenocarcinoma component, each of which accounting for at least 30% of neoplastic growth, have been described and most display aggressive behavior [12].

Neuroendocrine neoplasms of the jejunum and ileum

Introduction

Jejunal-ileal neuroendocrine neoplasms (Je-Ile NENs) are almost exclusively represented by well differentiated serotonin producing enterochromaffin cell neuroendocrine tumors (EC cell-NETs) of the terminal ileum. They account for about 27% of gastrointestinal NETs making them the second most frequent NET type [13]. The remaining Je-Ile NENs are mostly represented by NETs producing gastrin (especially in the jejunum) [14]. Poorly differentiated NECs and MiNENs represent rare entities.

Clinical presentation

About half of Je-Ile EC cell NET patients are asymptomatic and their tumors are incidentally detected. Patients can be asymptomatic even if they may show high serum neuroendocrine markers, urinary 5-hydroxyindoleacetic acid (5-HIAA) and liver metastases. Primary tumor identification, in presence of liver metastases may be difficult due to small size of primary tumor, limitations of endoscopy and standard imaging techniques. Cases with symptoms present with crampy abdominal pain, due to intestinal obstruction and/or ischemia. The “carcinoid syndrome”, characterized by cutaneous flushing, diarrhea, bronchospasms and fibrous thickening of endocardium and valves of right heart, occurs only when liver metastases are present and is detected in at most 10% patients.

Subtypes

These are represented by WD Je-Ile NET, NECs and MiNENs.

1 Je-Ile NETs

Je-Ile NETs are graded according to the WHO proliferative criteria as G1, G2 and G3. Most Je-Ile NETs are low grade; grade 3 NETs are rare. Two Je-Ile NET clinico-pathologic subtypes have been reported:

a EC cell NETs

Pathology and Immunohistochemistry: they are mostly located in the distal ileum, only 11% in the jejunum and rarely they are found in Meckel's diverticulum. EC cell NETs are multiple (2-100 tumors) in about one third of cases and in familial cases. Tumor size is usually small, ranging from 1 to 2 cm. These NETs appear as firm white-yellow mucosal-submucosal nodules with intact or minimally eroded overlying mucosa. Muscular wall and peritoneal infiltration is frequent and consists either of extensive peritoneal fibrosis caused by fibroblastic growth factors produced by the tumor or by metastatic lymph nodes fused together. EC cell NETs are composed of solid rounded nests (Fig. 3A) of closely packed tumor cells, often showing peripher-

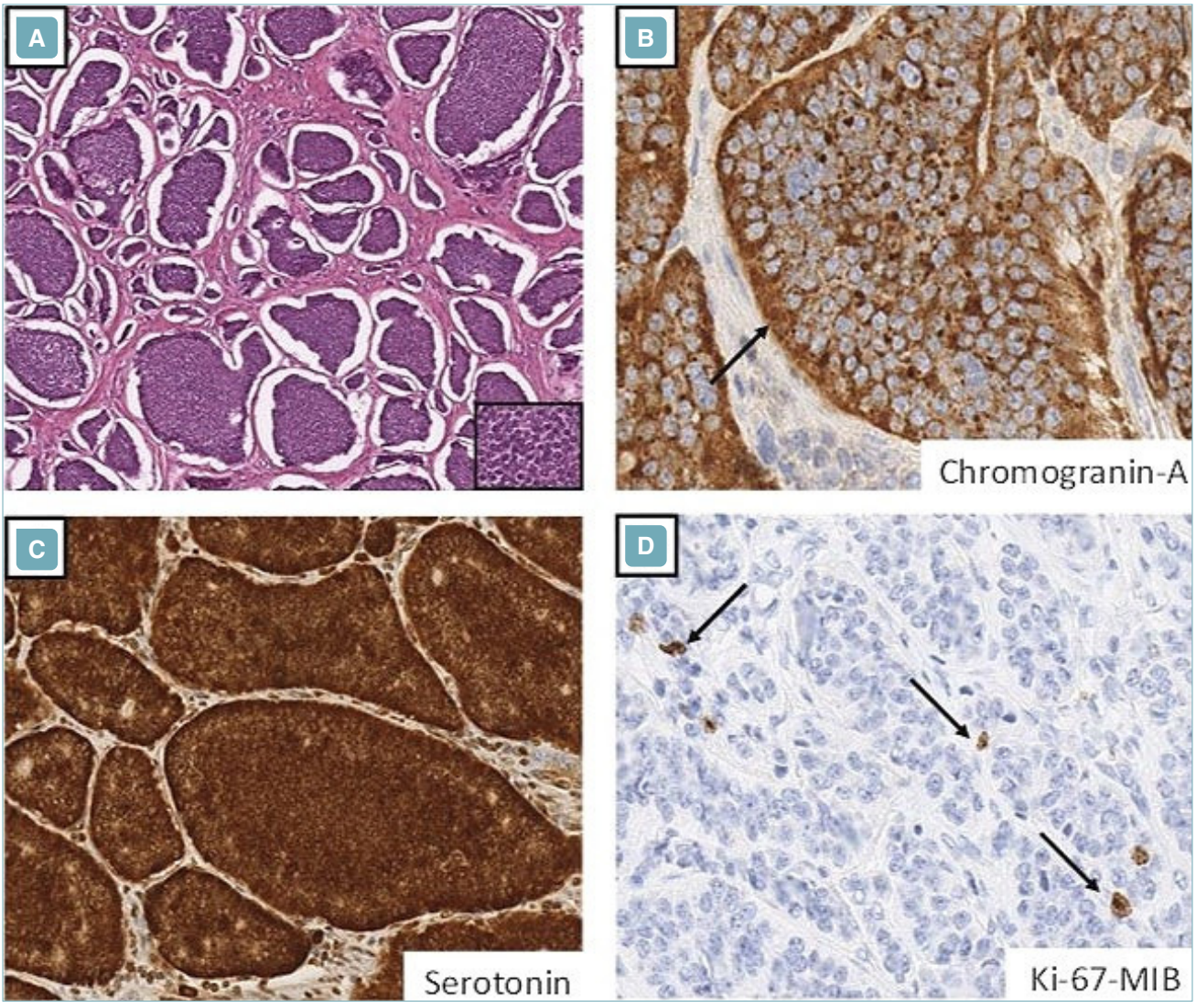

Figure 3. EC-cell ileal well differentiated neuroendocrine tumor. (A) The tumor cells are arranged in rounded solid nests. (B) Diffuse immunoreactivity of tumor cells for Chromogranin A with peculiar basal reinforcement (arrows). (C) Immunostain for serotonin confirms the diagnosis of EC cell NET. (D) Rare nuclei are positive for Ki-67.

al reinforcement with eosinophilic secretory granules. Cribriform, glandular-like and rosette-type structures are also frequently observed. Tumor cells are uniform with little or no pleomorphism and mitotic activity is null or low in most of the cases (0 to 2/2 mm2), which classifies these tumors as G1. Lymphovascular and perineural invasion are frequently observed. In addition to reactivity for general neuroendocrine markers (Fig. 3B) and serotonin (Fig. 3C), EC-cell NETs express CDX2 and type 2A somatostatin receptors.
Ki-67 proliferative index is very low (0-2%) (Fig. 3D) in most cases classified as G1 but may be more than 2% in some that are classified as G2 and more than 20% in few cases classified as G3.
Molecular findings: genetically Je-Ile EC cell NETs are characterized by lack of changes in *K-Ras*, *p53* and *DNA mismatch repair*, frequent whole chromosome/whole arm losses, low mutation rate in the genome and high percentage of epigenetic changes. Various studies reported loss of one copy of chromosome 18, with a percentage of 44-100%[15]; however there is no definitive evidence for driver genes in the regions involved. Gain of chromosome 14 is mainly detected in progressed and metastatic lesions and indicates an unfavorable prognosis [15]. The most frequent genetic mutation affecting *CDKN1B* (in ~8% of tumors) has no immediate detectable impact on clinical phenotype or outcome. Compared to genetic mutations, epigenetic alterations are more frequent and recurrent in EC cell NETs. More than half EC-cell NET display *CPG* island methylation phenotype and significant epigenetic dysregulation [16]. Based on an integrated genomic analysis, including DNA methylation, gene expression and copy number variance (CNV), three molecular subgroups associated with significant difference in progression free survival after surgical resection have been identified [16]. No established risk factors have been identified for sporadic Je-Ile EC-cell NET. Familial cases of Je-Ile EC-cell NETs, representing about 3% of patients harboring Je-Ile NETs are distinguishable from sporadic cases for their multiple synchronous tumors [17]. The IPMK gene was found to be mutated in only one family compared to 32 other families with multiple EC cell Je-Ile NETs showing wild type *IPMK* gene.
Prognostic factors: well differentiated Je-Ile NETs, which typically include G1 tumors but rarely may be G2 or G3 NETs, must be staged according to the UICC staging system (TNM classification of malignant tumors eight edition) [18]. The majority (> 60%) of patients with EC cell Je-Ile NETs present with metastatic disease. Metastases are principally located in regional lymph nodes and the liver [19]. Notwithstanding this, patients with advanced disease show prolonged survival related to the very low proliferative rate of these tumors. The 5-year overall survival rate of patients with localized disease is 70-100% while that of patients with distant metastases is 35-60%. Long term recurrence rate is roughly 50% [20]. The risk of recurrence is increased in patients with nodal metastases, mesenteric invasion, lympho-vascular invasion and perineural invasion.

b Heterogeneous group of Je-Ile NETs

This group comprises the subgroup of trabecular G1 NETs expressing gastrin, located in the jejunum, sharing the same general behavior as their duodenal counterpart, and a second subgroup represented by jejunal non-hormone expressing NETs, most of large size and locally invasive and frequently of G2 or G3 grade, located in the upper jejunum [14].

2 Je-Ile NECs

They are by definition high-grade malignant Je-Ile NENs and show poorly formed trabeculae, large and confluent nests or sheet-like growths similar to those previously described. Very few cases of this neoplasm have been reported [21].

3 Je-Ile MiNEN

As far as we know no well described cases of Je-Ile MiNEN have been reported so far [22].

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