Review

Neuroendocrine neoplasms of the appendix, colon and rectum

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Conflict of interest
The Authors declare no conflict of interest.

Summary

Neuroendocrine neoplasms of the appendix, colon and rectum are classified according to the most recent WHO classification as neuroendocrine tumors (NET), neuroendocrine carcinomas (NEC) and mixed neuroendocrine-non neuroendocrine neoplasms (MiNENs). NECs and MiNENs are aggressive neoplasms requiring multimodal treatment strategies. By contrast, NETs are, in most cases, indolent lesions occurring as incidental findings in the appendix or as polyps in the rectum. While most appendiceal and rectal NETs are considered relatively non-aggressive neoplasms, a few cases, may show a more aggressive clinical course. Unfortunately, clinical/pathological characteristics to select patients at high risk of recurrence/metastases are poorly consolidated. Diagnosis is generally easy and supported by the combination of morphology and immunohistochemistry. Differential diagnostic problems are for NECs/MiNENs with poorly differentiated adenocarcinomas, when immunohistochemical neuroendocrine markers are not obviously positive, whereas for NETs they are represented by the rare appendiceal tubular and clear cell variants (which may be confused with non-neuroendocrine cancers) and rectal L-cell tumors which may be chromogranin negative and prostatic marker positive.

Key words: appendix, colon, rectum, neuroendocrine, tumor

Introduction

Neuroendocrine neoplasms (NEN) of the appendix, colon and rectum are primary epithelial neoplasms showing morphologic and immunophenotypic signs of neuroendocrine differentiation. They are classified using the WHO 2019 scheme, as neuroendocrine tumors (NET), neuroendocrine carcinomas (NEC) and mixed neuroendocrine-non neuroendocrine neoplasms (MiNEN) [1]. Whereas NECs and MiNENs are aggressive neoplasms that are generally diagnosed at advanced stage and require multimodal treatment strategies, NETs may be relatively indolent (such as in the appendix and rectum) or behave more aggressively (such as the colon). With regards to neuroendocrine neoplasms of the colon and those of the rectum, though often grouped together, these neoplasms show vastly different incidences (though both are on the rise), geographical distribution, treatment, histopathology and behavior.

Neuroendocrine neoplasms of the appendix

Neuroendocrine neoplasms of the appendix are some of the most frequent neuroendocrine tumors which may be encountered by the practicing pathologist. Whereas NECs and MiNENs are aggressive neoplasms that require extensive surgery if possible, appendiceal NETs are mostly cured by appendectomy alone. The parameters which identify the minority of appendiceal NET cases at risk for aggressive disease outcome are, however, not well-assessed, though they have an important impact in the definition of the clinical management of patients, including indications for right hemicolectomy and/or medical therapy. Data on prognostic parameters in appendiceal NETs are largely retrospective and frequently discordant, therefore recommendations and guidelines are heterogeneous and in part controversial, as discussed below.

CLINICAL PRESENTATION

The incidence of appendiceal NENs is difficult to assess, due to heterogeneous inclusion criteria in epidemiological studies. NETs are by far more common than NECs and MiNENs, and account for up to 70% of all appendiceal neoplasms and represent the fifth most frequent gastrointestinal NET. They are a frequent occurrence in appendectomy specimens, up to nearly 2% in a recent study. The great majority of appendiceal NETs are discovered incidentally at the tip of the appendix. When located in the mid or proximal portion, they may cause obstruction and appendicitis. The occurrence of functional tumors, characterized by the onset of carcinoid syndrome, is very rare and associated with metastatic spread. The prognosis of NETs is excellent with more than 90% survival probability at 10 years and an overall risk of metastases of < 10%. The clinical outcome is apparently even better in the pediatric population with extremely high survival rates, irrespective of the presence of putative adverse features and of type of surgical treatment [2]. NECs and MiNENs are aggressive neoplasms with a biological and clinical behavior similar to those of the colon. Specific data on appendiceal NECs and MiNENs, are, however, scarce. In a recent study, appendiceal MiNENs were associated with a worse prognosis compared to pure NENs (including NECs) but better than adenocarcinoma, but this difference was lost in advanced stage disease [3].

SUBTYPES

Definition and classification

As also stated above, according to the most recent WHO classification of gastrointestinal tumors, NENs in the appendix are subdivided into NETs, NECs and MiNENs (Tab. I). Whereas NECs are high grade by definition, NETs are further subdivided into G1, G2 and G3 according to the mitotic index and Ki-67 proliferative index. WHO 2019 rules for grading gastrointestinal NENs are described elsewhere in this issue and those in the appendix have no additional specific indications.

Pathology

Appendiceal NETs (A-NETs) appear as whitish nodules at macroscopy. They may be either well demarcated or infiltrative, but may be easily missed at gross specimen handling if of small size. It is therefore recommended to embed the appendiceal tip in total, in all cases. Histologic findings are typical of well differentiated neuroendocrine lesions, with nests or trabeculae of uniform polygonal cells. Stromal fibrosis is frequent. Tumor borders can be well demarcated or show infiltrative growth often composed of isolated cells. Infiltration may be limited to the muscular wall of the appendix or extend to the subserosa and/or the adipose tissue of the mesoappendix (Fig. 1). Perforation of the serosal surface or direct infiltration of the cecum or other adjacent structures are rare. Perineural invasion is rare but vascular invasion is not infrequent; however, when occurring in small thin-walled lymphatics or capillaries, they should be distinguished from artifacts caused by shrinkage of tumor cell islets detaching from the surrounding stroma. More than 80% of cases

Table I. Types of neuroendocrine neoplasms of the appendix.

WHO 2019 histological types	Grading groups	Sub-types	Hormone production
NET	G1	EC-cell type	Serotonin
	G2 G3	L-cell Type	GLP1, other proglucagon peptides
NEC	High grade by definition	Small cell-type Large cell-type	//
MiNEN	As for definition, each component to be graded independently	Mixed adenocarcinoma-NET Mixed adenocarcinoma-NEC	//

NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-non neuroendocrine neoplasms.
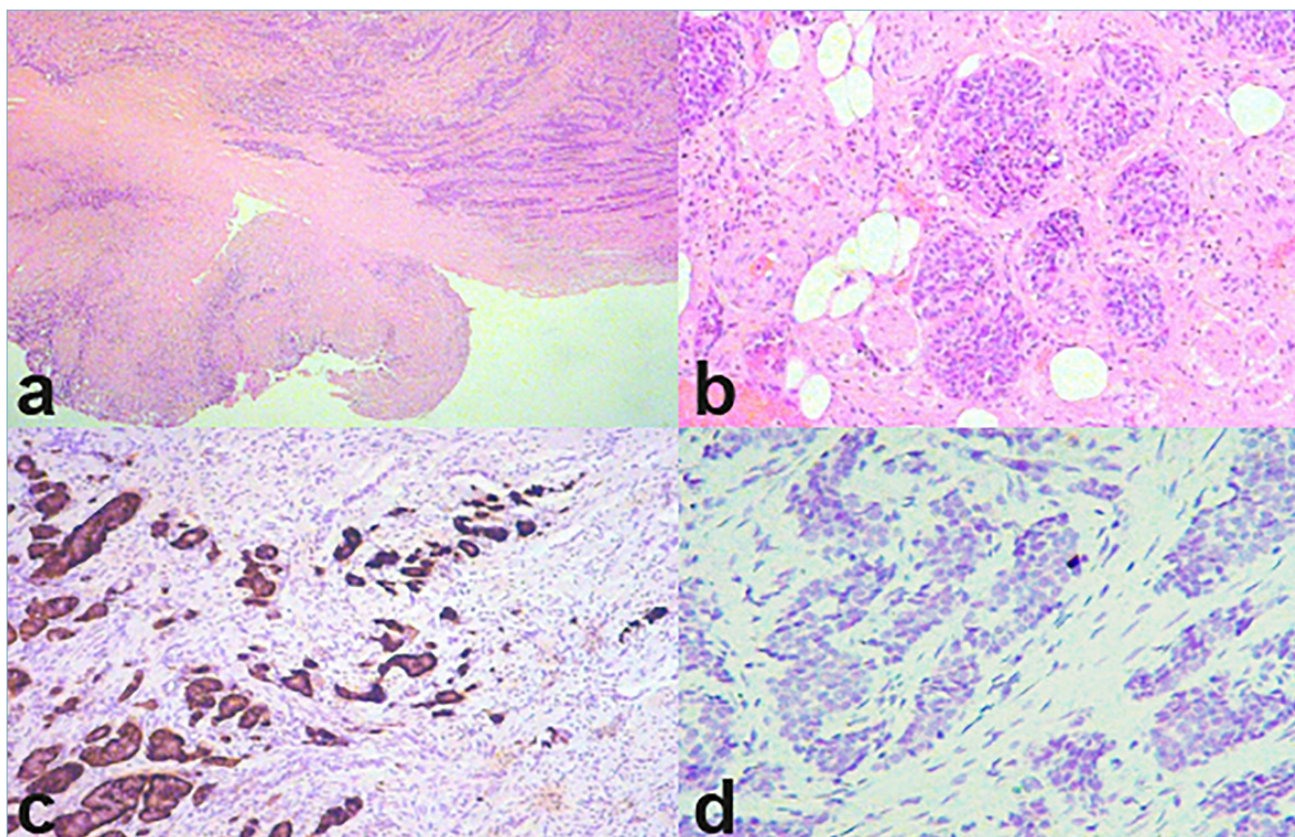
Figure 1. Neuroendocrine tumor of the appendix associated with acute appendicitis (a), with invasion of the mesoappendix (b), infiltrative growth, highlighted by chromogranin A immunohistochemical staining (c), but with low mitotic and proliferative index (Ki-67 staining) coding for G1 tumor grade (d).

are G1 and G3 NETs are exceptional. Mitotic count is therefore usually very low and Ki-67 proliferation index is less than 2% in the great majority of cases, independently of the depth of invasion of the tumor. Two major biological types are encountered, although they do not possess distinct clinical behavior. The EC-cell type, the most frequent and typical, produces serotonin, whereas the L-cell type, characterized by a more prominent trabecular arrangement, produces GLP-1 or other proglucagon-derived peptides.

NECs are morphologically identical to their colonic counterpart and are subdivided in small and large cell types, although specific literature descriptions of appendiceal NECs are missing due to their extreme rarity.

MiNENs are mixed neoplasms showing, by morphology and immunohistochemistry, both neuroendocrine and non-neuroendocrine components, and each component should be (arbitrarily) present in at least 30% of the whole lesion and should be graded individually. The non-neuroendocrine component corresponds, in almost all cases, to an adenocarcinoma, of mucinous or non-mucinous type. The neuroendocrine component can be either of the NET or NEC type, thus defining the adenocarcinoma-NET and adenocarcinoma-NEC subtypes of appendiceal MiNENs, respectively.

It is important to remember that the so-called goblet cell carcinoid, once classified as a mixed form of appendiceal NENs, is now included into the group of appendiceal adenocarcinomas and will not be discussed in this brief overview.

Staging. According to AJCC/UICC/WHO staging systems [1], NECs and MiNENs are staged as for adenocarcinomas. A-NETs are staged based on the size and depth of invasion into:

T1: ≤ 2 cm;

T2: > 2 and ≤ 4 cm;

T3: > 4 cm or subserosal or mesoappendix invasion, irrespective of the size of the tumor;

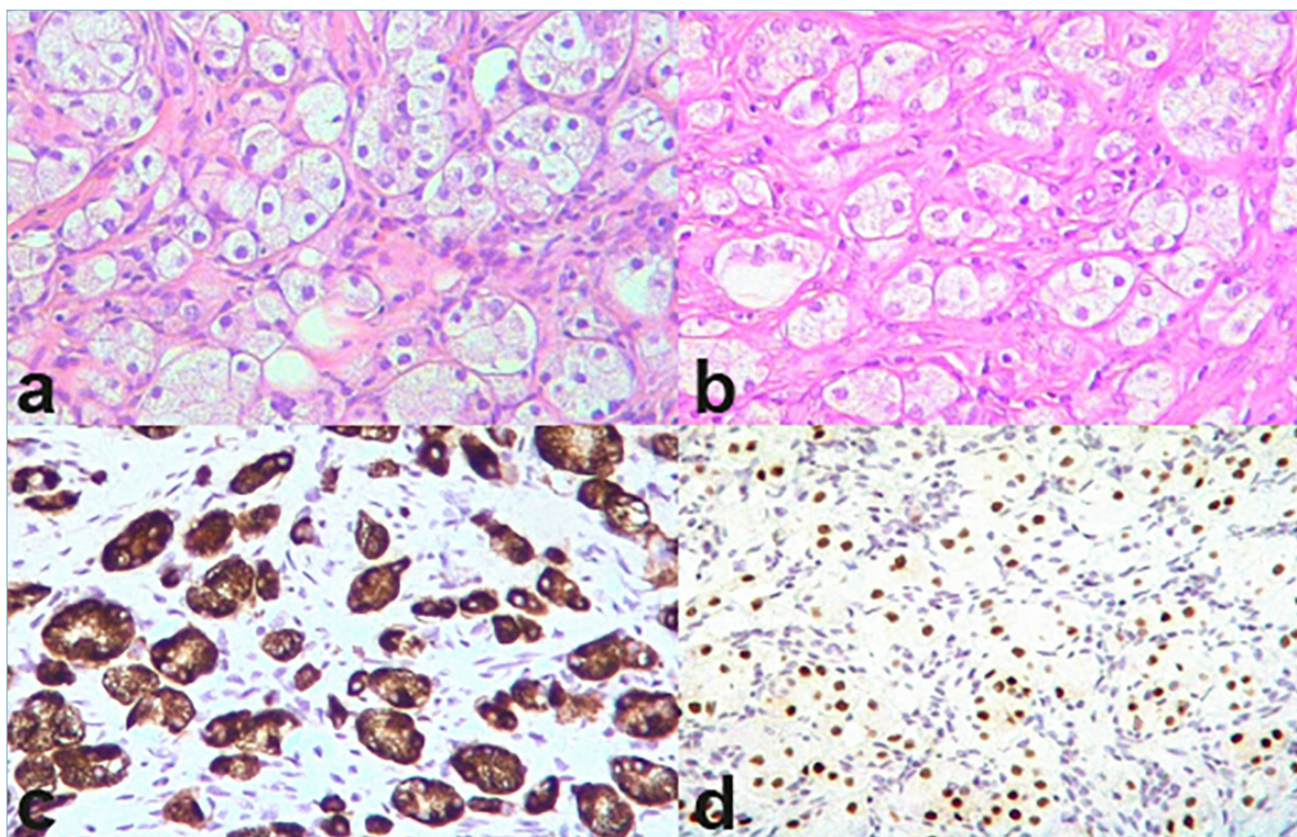T4: serosal perforation or direct invasion of adjacent organs or structures.

Figure 2. Neuroendocrine tumor of the appendix, clear cell variant, with clear granular cells (a) negative for PAS staining (b) and with diffuse granular positivity for chromogranin A (c) and nuclear positivity for CDX-2 (d).

Despite the majority of cases being of less than 2 cm in size, a relatively high proportion of cases are diagnosed, even when incidental, as stage pT3 due to the frequent occurrence of invasion outside the muscular wall [4].

Pathological variants. Variants of A-NETs include the tubular and the lipid-rich (clear cell) variant. The tubular variant is composed of cuboidal/columnar cells with basally oriented nuclei arranged in small glandular structures. They usually are of the L-cell by type. The clear cell variant is characterized by nests of clear cells with a foamy cytoplasmic appearance, related to lipid accumulation [5] which does not stain for PAS (Fig. 2). Most cases are of the EC-cell type and produce serotonin.

Prognostic parameters. Specific data on prognostic parameters in NECs and MiNENs are very scarce and stage IV disease seems the only relevant parameter to identify aggressive disease. The prognostic impact of clinical and pathological parameters in NETs has been more extensively investigated, but a great variability of results is observed with special reference to the identification of independent factors when tested at multivariable analysis. In a recent study, size > 15 mm, presence of lympho-vascular invasion and G2 grade have been identified as independent indicators for the presence of lymph node metastases [6], but only the latter two were identified in a similar study [7] and neither tumor grade nor tumor size were associated with disease-related survival in another study [8]. All these discrepancies reflect the high heterogeneity of study planning and case selection, which are the major biases of retrospective studies and are the cause of different indications to surgical treatment in different national and international guidelines. Whereas size > 2 cm is uniformly quoted as a strong indicator, other parameters in cases ≤ 2 cm in size, such as location at the base of the appendix, R1 resection status, lymph-vascular invasion, invasion of the mesoappendix (including extension > 3 mm) and G2 tumor grade, are heterogeneously considered [4] and recommendation for subsequent right hemicolectomy after appendectomy is to be discussed in an appropriate multidisciplinary setting. All these parameters

Table II. Essential and desirable parameters to be included in the pathological report*.

Essential parameters	Additional parameters

- WHO tumor type (NET, NEC, MiNEN)
  If NEC, large cell or small cell type
  NET variant, if present
	- NET Type (EC-cell, L-cell)

- WHO tumor grade (G1, G2, G3) for NET	- Mitotic index as absolute value (x2mm^2)
- Location (base, body, tip)	- Ki-67 index as absolute value (%)
- Size (mm)	- If present, extent of subserosa/mesoappendix invasion (mm)
- Depth of invasion (submucosa, muscolaris propria, subserosa, mesoappendix, adjacent structures)	- In case of R0 resection, distance to the closest margin
- Visceral peritoneum perforation (present/absent)	- In the presence of vascular invasion, describe if lymphatic or blood vessels and if intramural or extramural
- Lymphovascular invasion (present/absent)	- In the presence of perineurial invasion, describe if intramural or extramural and if close to the resection margins
- Perineural invasion (present/absent)	- In the presence of positive lymph nodes, describe the presence or absence of extra nodal extension
- Lymph node status (# examined nodes and, if positive, # positive nodes)	- Hormone or hormone receptor immunohistochemistry
- R status, and if R1 positive margin description (proximal, radial, mesenteric in case of appendectomy, proximal, mesenteric and distal in case of right hemicolectomy)	
- pTNM stage (AJCC/WHO/UICC)	
- Immunohistochemical markers performed and results (pan-neuroendocrine markers and Ki-67 mandatory)	

*: the table reflects authors' opinion, only, and is partly based on the protocol for the examination of specimens from patients with neuroendocrine tumors of the appendix, College of American Pathologists, posting date February 2020; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; MiNEN: mixed neuroendocrine-non-neuroendocrine neoplasms.

therefore have to be mentioned in the pathology report (Tab. II) to provide the best description of each individual case and serve as collective data for further clinical decision-making.

Immunohistochemistry

A-NETs are positive for conventional pan-neuroendocrine markers, such as chromogranin A and synaptophysin, although the former may be negative in L-cell type as for similar tumors in the rectal location. In NECs, and the neuroendocrine component of MiNEN, neuroendocrine markers may be negative or focally positive, therefore a panel – and not individual markers, only – should be used for an appropriate diagnostic procedure. Neuroendocrine phenotype-associated transcription factors, such as INSM1, are also usually positive in both NETs and NECs. S100 positive sustentacular cells are often present. Detection of hormone peptides or receptors (such as somatostatin receptors) is not mandatory for diagnostic purposes.

Molecular findings

Specific molecular data in appendiceal NEC and MiNENs are not available. With regards to A-NETs, two recent papers analyzed small series of cases by means of next generation sequencing with different results. In three cases, analyzed using a > 400 gene panel, no molecular alteration including mutations or copy number variations, were identified [9], whereas in another study using targeted-next generation sequencing of 50 genes, 4 of 5 cases presented more than 1 mutation, including *TP53*, *PTEN*, *SMAD4* and *EGFR* [10].

Differential diagnosis

A-NETs are easily recognizable based on typical morphological features of a well differentiated neuroendocrine neoplasm and appropriate immunohistochemistry easily confirm the diagnosis. Diagnostic pitfalls may be represented by uncommon variants, such as the tubular and clear cell types. The former may resemble an exocrine neoplasm (with special reference to goblet cell carcinoid which expresses neuroendocrine markers to-

gether with mucin production), whereas the latter should be distinguished from other clear cell neoplasms such as goblet cell carcinoid, granular cell tumor, or metastatic ovarian/uterine neoplasms and renal cell carcinoma. NECs should be distinguished from high grade adenocarcinomas with predominant solid growth, and sometimes the focal positivity for neuroendocrine markers may pose problems in the differential diagnosis.

Neuroendocrine neoplasms of the colon

CLINICAL PRESENTATION

Colonic-NENs represent approximately 5-7% of all well differentiated gastroenteropancreatic neuroendocrine tumors but 25% of all gastroenteropancreatic neuroendocrine carcinomas. Mean age is 65 years and clinical presentation is similar to that of colonic adenocarcinomas. Indeed, diagnosis is usually either at biopsy of mass or after surgical resection and most patients show advanced stage at diagnosis.

SUBTYPES

Definition and classification

Colonic NENs share the same classification as other gastroenteropancreatic neuroendocrine neoplasms [1] and should be classified as: well differentiated neuroendocrine tumours of the colon (C-NETs) – G1/G2/G3, poorly differentiated neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non neuroendocrine neoplasms (MiNENs).

Pathology

C-NETs (35% of colonic NENs) typically show enterochromaffin (EC)-cell features (insular architecture, serotonin production and CDX2 positivity). At diagnosis, about 30-40% are metastatic to the liver, nodes, mesentery and peritoneum. Indeed, C-NETs have a worse prognosis compared to rectal NETs and one of the lowest median survival rates of all NETs (5-year survival rates according to stage are: 80% for stage I or II; 50% for stage III, 10% for stage IV) [11].
C-NECs (45% of colonic NENs) can be found in the right and left colon and represent about a half of all colonic NENs but only 0.6% of colorectal cancers as a whole. Morphologically they are more often of large cell type, characterized by large sheets with ample areas of necrosis (Fig. 3a).
The colon is the most frequent site for **MiNENs** [12] and they often show a combined or collision type interface between components with the mixed adenoma/adenocarcinoma–NEC type being most often identified at histology (Fig. 3b-d) [13].

Immunohistochemical and molecular markers

Colonic NENs express general neuroendocrine markers such as synaptophysin, chromogranin A (which may be absent in NECs), neuron-specific enolase and CD56. C-NECs and MiNENs show microsatellite instability in approximately 15% of tumors [13].

Differential diagnosis

C-NETs are usually easily identified at histology. Colonic NECs and MiNENs, on the other hand, similarly to other sites, require thorough diagnostic workup and immunopanels for their distinction from solid, poorly differentiated adenocarcinoma.

Neuroendocrine neoplasms of the rectum

CLINICAL PRESENTATION

The SEER database has shown a 10-fold increase in the past 35 years of rectal NETs probably due to a true rise in incidence and as a consequence of better and more numerous colonoscopies with widespread use of screening endoscopy for detecting colorectal cancers. What is interesting is that there are important differences in incidence between countries. In Europe and the USA, for example, rectal NETs are between 5 and 27% of all gastrointestinal NETs while in Korea and Japan, incidence of rectal NETs is as high as 60% of all gastrointestinal NETs. Differences in classification, database compilation, colonoscopic screening programmes as well as possible ethnic diversities probably underlie this geographic variability [14].
Mean age at presentation is 55-60 years and diagnosis is often incidental during screening colonoscopy, though symptoms can include anal discomfort/pain, blood in stools and change in bowel habits. Some of these neoplasms are found in patients with long-standing inflammatory bowel disease. Most rectal NENs are small polypoid lesions that appear as even, beige colored bulges of the mucosa, 5 to 10 cm above the dentate line. Lesions are often submitted to pathology following polypectomy, however major issues which are still open include the optimal type of endoscopic resection, management of such lesions after endoscopic resection and when other surgical strategies (including surgical resection) are warranted.

SUBTYPES

Definition and classification

Rectal NENs include the overwhelmingly more frequent well differentiated rectal neuroendocrine tumors (R-NETs) and the rare, poorly differentiated NECs and
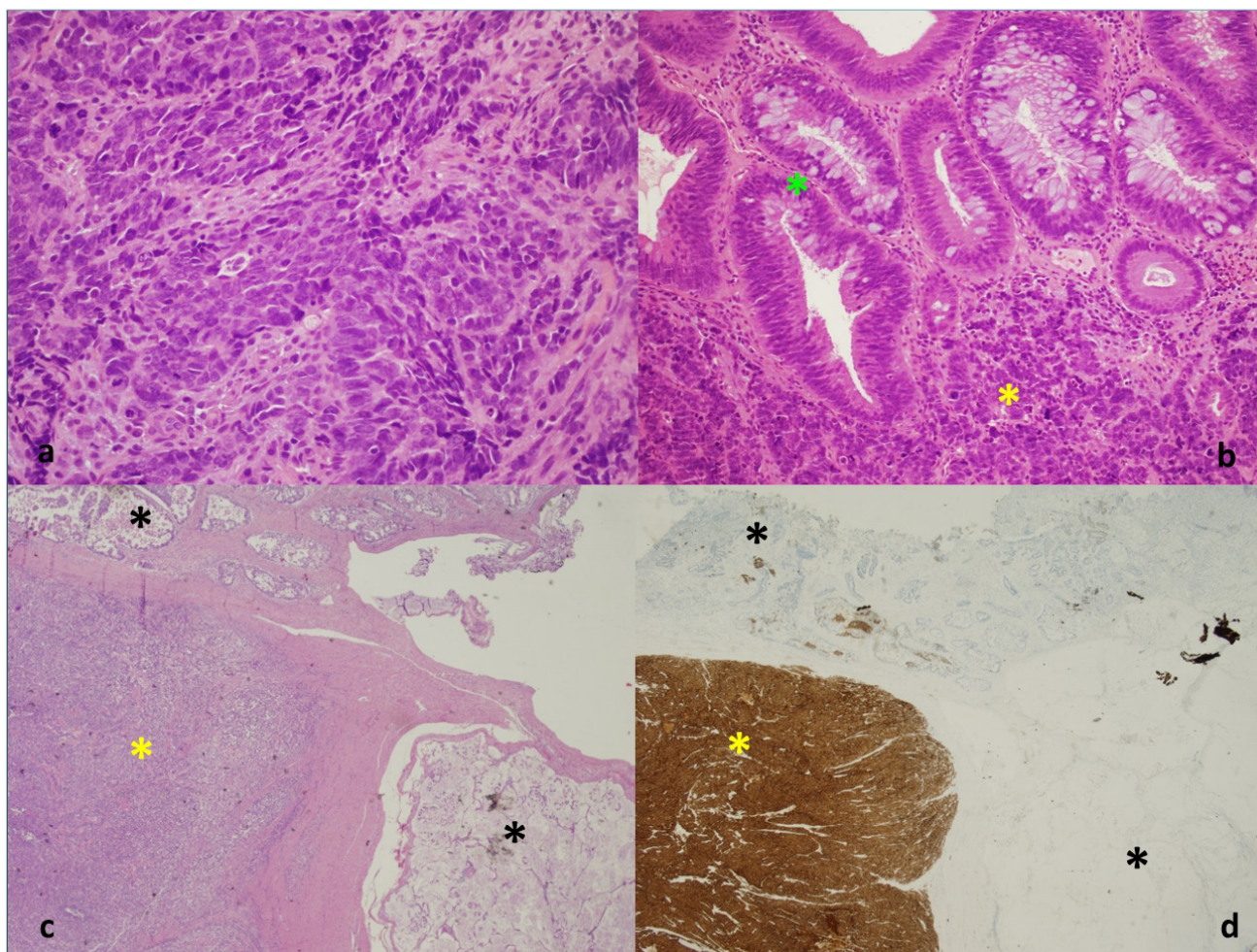
Figure 3. Poorly differentiated neuroendocrine carcinoma of the colon (a). Mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN) (b) with poorly differentiated neuroendocrine component (yellow asterisk) and adenomatous component (green asterisk). Mixed neuroendocrine-non neuroendocrine neoplasm (MiNEN) with poorly differentiated neuroendocrine component (yellow asterisk) and adenocarcinoma with evident mucin production (black asterisk) (c). Synatophysin of MiNEN (d) showing diffuse expression in the neuroendocrine component (yellow asterisk) and no expression in the adenocarcinomatous areas (black asterisk).

MiNENs[1]. Further sub-classification is possible for R-NETs: they can either be L-cell (PP/PYY producing) tumors or EC-cell (serotonin producing) tumors.

Pathology

L-cell R-NETs are the most frequent type (sometimes they may also be encountered in the distal sigmoid); lesions are generally small (75-88% are < 1 cm) and superficial and show a ribbon-like, trabecular or pseudo-glandular architecture with bland cytology (Fig. 4). **EC-cell R-NETs** share morphologic characteristics with the more frequent small intestinal/colonic counterparts.

Staging and prognosis

Perhaps the most important aspects which must be highlighted in R-NETs are prognostic and management issues. Most R-NETs show indolent behavior, with better long-term outcomes (overall 5-year survival rate of 74-88%) than NETs at other sites and require conservative management. However, a small percentage (10-20%) may metastasize to regional lymph nodes and beyond. The most important factor in therapeutic strategy (whether to limit treatment to endoscopic resection or perform radical surgery) is the risk of lymph node metastasis and this is dependent on various factors: tumor size (< 10 mm - risk of
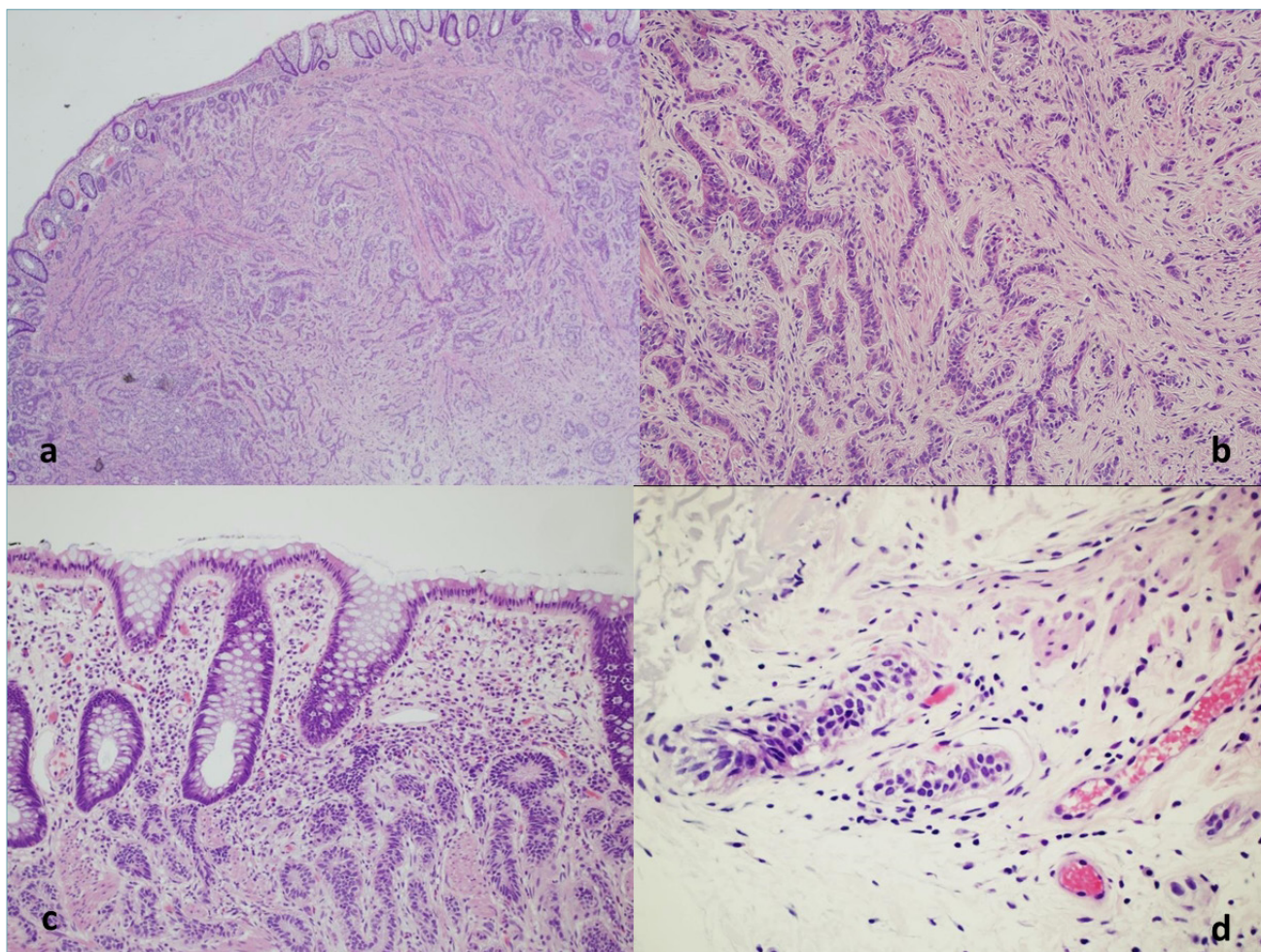
Figure 4. Rectal well differentiated neuroendocrine tumor L-cell type (a). Ribbon-like and festooned architecture of cytologically bland cells (b). L-cell rectal NET with pseudo-glandular architecture and overlying mucosa (c). Lympho-vascular invasion is an important prognostic factor (d).

nodal metastases is < 2%; 1-2 cm gray zone - risk of nodal metastases is 10-15%; > 2 cm - risk of nodal metastases is 60-80% and require surgery) [15]; depth of invasion (T1 versus T2 - muscularis propria) [16]; resection margin (complete *vs* incomplete resection); grade (G1 vs G2 vs G3); non L-cell origin which shows worse prognosis [17]; and lympho-vascular invasion [18].

Characteristics of NECs and MiNENs of the rectum are similar to those of the colon and elsewhere, though rectal NECs are often small cell, morphologically.

Immunohistochemical and molecular markers

L-cell R-NETs are positive for general neuroendocrine markers however they may be chromogranin A negative, as they often produce chromogranin B which is not detected by most common anti-chromogranin antibodies. They do not produce serotonin and are negative for the intestinal marker CDX2 however they do produce, and can be stained for, glucagon-like peptides (GLP1) and/or peptide YY (PYY)/pancreatic polypeptide (PP), similarly to appendiceal counterparts. As not all pathology laboratories have these stains, L-cell origin can be convincingly inferred by CDX2 and serotonin negativity. Apart from chromogranin A negativity, other potential staining pitfalls include a 70% positivity for prostatic acid phosphatase (PAP).

EC-cell R-NETs show overlapping immunohistochemical features to those of small intestinal origin (chromogranin A, nuclear CDX2 and serotonin positivity) while R-NECs and MiNENs overlap those of other sites.

Differential diagnosis

While differential diagnosis is not a major problem in localized disease, unusual immunostaining patterns may cause confusion in the metastatic setting. Indeed, L-cell R-NETs express pancreatic markers such as Islet-1 (ISL1) and PAX8 which may lead the unsuspecting pathologist awry. Recent studies have shown that special AT-rich sequence binding protein-2 (*SATB2*) [19], a transcription factor binding protein, is specific for NETs of rectal (and appendiceal) origin while it is not expressed in pancreatic/duodenal NETs.

Conclusions

Appendiceal, colonic and rectal neuroendocrine neoplasms require accurate pathologic classification. In particular, appendiceal and rectal NETs require thorough knowledge of criteria which are necessary for correct patient management. Indeed, though gray areas still abound, it is only though an accurate and reproducible classification system that more scientifically robust studies will aid in patient selection for diverse treatment options.

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