# Differential Diagnosis of Neuroendocrine Tumors

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## Introduction

Well-differentiated NETs are generally composed of a uniform population of oval, round, to polygonal cells with medium to moderate granular cytoplasm, "salt-to-pepper" chromatin pattern, and inconspicuous nucleoli. NET cells are usually growing in nodular, nested, organoid, trabecular, tubular, rosette, and pseudoglandular patterns. Microscopic foci of degenerative atypia can be seen. Degenerative nuclear atypia and pleomorphism could be seen occasionally and focally in any given tumor, even within grade 1 well-differentiated NETs. Attention should be made not to interpret these features to distinguish tumor grades or predicting prognosis [1–5]. These "pseudo-dysplastic foci" include enlarged nuclei and cell bodies, nuclear hyperchromasia, and smudgy chromatin texture. These seemingly alarming phenomena should not be interpreted as true dysplasia or features associated with higher-grade NETs. Focal whirling and spindling of tumor cells usually exists; however, none of the abovementioned histology has been proven clinically significant for disease progression and prognosis.

In NETs, the intervening and surrounding stroma is generally rich in vasculature and shows focal or diffuse hyalinization, which has been attributed to the deposition of hormonal secretion by these cells (see Fig. 1 in the chapter "Immunophenotypical

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Profile and Molecular Genetics of Neuroendocrine Tumors"). A special stain with Congo red could highlight the amyloid deposition. Dense fibrosis and abundant collagen deposition are also not infrequent. Occasional cases have been reported to contain foci of microcalcification (psammomatous calcification) and cartilaginous or osseous metaplasia. It should be noted that the presence of metaplastic tissue does not impact NET grades or prognosis.

One of the most import prognostic factors in NETs is the grade, which can be determined using the tumor proliferation index and presence/absence of necrosis. The tumor proliferation index can be assessed using the tumor nuclear labeling with Ki-67 or MIB-1. MIB-1 is a monoclonal antibody directed against a different epitope of the same proliferation-related antigen recognized by Ki-67 antibody [1, 3, 6, 7]. In pathology practice, counting tumor cell mitoses in 10 high-power fields cannot always be accomplished on biopsy material, when the tumor tissue is scant or contains only a few tumor cells. In these situations, Ki-67 proliferation index becomes an essential tool for determining neuroendocrine tumors grade. Ki-67 immunostain will decorate the nuclei of all cells present in the cell cycle between G1 and M phases [1, 3, 6, 7]. According to the current criteria, NETs are well differentiated and grade 1 if Ki-67 index is equal to or less than 2 % and grade 2 if the Ki-67 index is between 2 and 20 % (AJCC, seventh edition). One potential technical challenge and diagnostic pitfall is the presence of intratumoral and peritumoral lymphocytic infiltrates, which may determine a falsely high Ki-67 labeling rate. The nuclei of lymphocytic are Ki-67 positive and if they are counted in error as tumor cells will inevitably and falsely increase the Ki-67 proliferation index in a given tumor. One method to avoid this issue is the adoption of a double staining technique (we use the Ki-67/keratin cocktail where the Ki-67 antibody is labeled with a brown chromogen (peroxidase) and the cytokeratin antibody is labeled with a red chromogen (alkaline phosphatase)). This method will effectively eliminate the erroneous counting of interspersed lymphocytes within the NETs (the lymphocytes will be labeled with nuclear Ki-67 only and not with the cytoplasmic keratin signal). Optimal interpretation of the double immunostain requires the tissue to be well preserved and well processed. Significant crushing artifact may pose a great challenge when dealing with a mixture of dark brown-red signal coloring the smeared cells.

In high-grade (grade 3) neuroendocrine carcinoma (NEC), the malignant morphological features will include increased tumor proliferation rate (20 or more mitoses per 10 high-power fields, or a Ki-67 nuclear labeling index equal or more than 20 %), usually accompanied by frequent single cell apoptosis and/or confluent "geographic" necrosis, and an infiltrative growth pattern [1, 3, 6, 7]. Fragile, smudgy nuclei with molding and/or overlapping, irregularly bizarre nuclear shape and giant cells, as well as intermediate cell morphology are also identified frequently; the three latter features have been frequently observed in small cell carcinoma (SCC) among NECs [1, 3, 6–8]. Importantly, in our daily pathology practice, we have seen tumors that were morphologically well-differentiated neuroendocrine neoplasms, but demonstrated a higher than 20 % Ki-67 proliferation index and demonstrated an aggressive clinical course, while the mitotic count was well under 10 %. These peculiar tumors were seen especially in MEN 1 patients. Therefore, we suggest that mitotic rate alone may not

**Table 1** Differentiating neuroendocrine tumor from various adenocarcinomas

| NET (grades 1 and 2) | Adenocarcinoma |
|---|---|
| Bland cytology, maybe degenerative atypia | Dysplastic cytology |
| Chromogranin, synaptophysin, or CD56 positivity | Chromogranin and synaptophysin negative; focal weak signal can be seen in poorly differentiated tumors |
| Hyalinization, amyloid, and psammomatous calcification; no desmoplastic response | Desmoplastic response frequently present; invading adjacent stroma |
| 0–20 mitotic counts per 10 high-power fields | Mitotic figures frequent; atypical mitosis present |
| Nodules, cohesive nests, and strands; pushing boarders | Infiltrative, invasive, Indian files, destructive growth |
| Ki-67 usually between 0 and 20 % | Significantly higher Ki-67, usually well above 50 % |
| Mucicarmine and PAS-D both negative | Mucicarmine and PAS-D highlight intra- and extra-cytoplasmic mucin |

be an accurate measure of neuroendocrine tumor grade without determination of the Ki-67 proliferative index. One frequent challenge in GI pathology is to differentiate GI NETs from other morphologically similar entities. This chapter aims to cover the major differential diagnoses to consider when dealing with a possible GI NET. However, we cannot describe all of the possible scenarios that can be encountered in a daily pathology practice. Please refer to Table 1 for a summary of these entities.

## *Neuroendocrine Tumor Versus Adenocarcinoma*

When facing gastrointestinal NETs, we should be sure to eliminate the possibility of mimickers, which include both primary and secondary adenocarcinomas, and a spectrum of other entities. Histologically, NETs may grow in tubular, nodular, or pseudoglandular configurations that may mimic adenocarcinoma, either primary or metastatic [1, 3, 4, 7]. When differentiating an NET from a poorly differentiated adenocarcinoma, attention must be paid to the peculiar morphological, histochemical, and immunoprofile details. Making the correct diagnosis is of the outmost importance as it will impact therapy and the clinical management of the patient [3, 9].

Histochemically, adenocarcinomas produce mucin which is positive with a periodic acid–Schiff–diastase (PAS-D) special stain, and it will appear as either intracellular or extracellular bright red vacuoles. NETs are negative by PAS-D staining due to the lack of mucin production. Similarly, mucicarmine stain can also be used to highlight mucin in adenocarcinomas, and it will be negative in NETs. However, although specific, PAS-D and mucicarmine are not sensitive histochemical markers, and false-negative results are not infrequent, especially when dealing with a poorly differentiated adenocarcinoma. When assessing PAS-D and mucicarmine in these cases, it is important to examine the entire tumor because both stains can be positive only in focal areas or in rare tumor cells. Hence, histochemical stains alone may not be sufficient to detect a poorly differentiated adenocarcinoma. Histological and

immunohistochemical studies and detailed evaluation of the clinical history, radiological findings, and laboratory (i.e., 5-hydroxyindoleacetic acid or 5-HIAA levels in urine) and serological tests (i.e., serum chromogranin A levels) are all essential in reaching the correct diagnosis.

Immunohistochemically, adenocarcinomas and NETs are both positive for multiple cytokeratin markers (if not all of them), including pan-cytokeratin, GI, or pancreatobiliary-related markers, such as CK20, CK7, CK17, CK19, CK8/CK18, and MOC-31. Therefore, cytokeratin staining alone is not a suitable marker for neuroendocrine differentiation. It is important that at least one neuroendocrine marker be unequivocally positive in NET cells. Usually multiple positive markers are positive in low-grade NETs. The most frequently used are synaptophysin and chromogranin. CD56 and neuron-specific enolase (NSE) are also used frequently [1, 3, 4, 10, 11]. In addition, Ki-67 proliferation index is essential when grading NETs, but it can also aid in differentiating a low-grade NETs from adenocarcinoma [10–13]. Ki-67 positivity is within 20 % in low-grade NETs but always significantly higher in adenocarcinomas (usually between 50 and 90 %). A higher than 20 % proliferative index is also seen in neuroendocrine carcinomas, including both small cell carcinoma and large-cell NEC; but these two entities show distinct histological differences from adenocarcinoma. Other immunohistochemical markers such as gastrin, somatostatin, glucagon, insulin, histamine, and bradykinin are less frequently utilized [10–13]. Serological and laboratory markers, such as urine 5-HIAA, have mostly clinical significance It should also be kept in mind that occasionally, poorly differentiated adenocarcinomas can be focally and weakly positive for a neuroendocrine marker such as synaptophysin or chromogranin. This positivity, however, should be viewed as reflection of the poorly differentiated nature of the tumors, instead of an indication of neuroendocrine differentiation. Rarely, mixed adenocarcinoma and neuroendocrine carcinoma (MANEC) has been reported in the literature and encountered in practice; detailed inspection of the histological sections, PAS-D, and/or mucicarmine special staining, immunohistochemical staining for neuroendocrine markers, Ki-67 proliferation index, and clinical information can all aid in reaching the correct diagnosis [11, 14, 15]. Importantly, for a tumor to be classified as MANEC, each of the two components must represent at least 30 % of the total tumor. Clinically, MANEC behaves aggressively, and the consensus is to manage this malignancy as neuroendocrine carcinoma [15].

## *Neuroendocrine Tumors Versus Primary Tumors Originated in the Liver*

One frequently encountered clinical scenario is that of a patient presenting with liver nodule(s) and clinical suspicion of a primary neoplasm(s) of the liver (HCC, cholangiocarcinoma, or other hepatic types of tumor) which needs to be differentiated from a metastatic NET involving the liver. A large proportion of these lesions represent hepatocellular neoplasms including benign and dysplastic hepatocellular

lesions as well as hepatocellular carcinoma (HCC). One common feature of these primary hepatocellular lesions is that most of them are immunohistochemically positive for hepatocellular specific antigen (HepPar-1) and arginase, represented by a diffuse granular cytoplasmic labeling [16]. In the case of HCC, ancillary staining with alpha fetoprotein (AFP) (cytoplasmic labeling), glypican-3 (cytoplasmic and membranous labeling), polyclonal CEA (canalicular pattern), CD34 (sinusoidal pattern), and CD-10 (canalicular pattern) can all be used to differentiate HCC from NET. Clinically, HCC patients frequently show an elevated serum AFP levels; however, this is not always the case especially when dealing with a fibrolamellar type of HCC. On the other hand, hepatocellular adenoma and focal nodular hyperplasia are also positive for HepPar-1 and arginase, and a reticulin stain will highlight benign 1–2 cell thick hepatic plates in adenoma and focal nodular hyperplasia as compared to thick hepatocyte cords seen in HCC. Imaging study often can detect scar-like central areas in focal nodular hyperplasia, but this is not always the case. All these hepatocellular lesions are negative for neuroendocrine markers. Moreover, metastatic NETs to the liver usually express markers related to the site of origin, for example, NETs of colonic origin will stain for CDX-2 and CK20, those of pulmonary origin will be TTF-1 positive, and those deriving from a pancreatic primary will be PAX8 positive [17–19]. It should be noted that all high-grade neuroendocrine carcinoma may express TTF-1 regardless of the site of origin [8].

### *Neuroendocrine Tumors Versus Other Neoplasms*

Primary liver endothelial neoplasms including hemangioma, epithelioid hemangioendothelioma, and angiosarcoma can all be distinguished from NETs by morphological evaluation and essential immunostains for endothelial, epithelial, and neuroendocrine markers. Intrahepatic cholangiocarcinoma and most secondary adenocarcinomas involving the liver, such as metastatic pancreatobiliary, lung, and upper and lower GI tract adenocarcinomas, can be differentiated by histological evaluation, mucicarmine and PAS-D special stains, and immunostains for neuroendocrine markers, as mentioned above. In addition, comparison with previous biopsy or resection material, radiological findings, and related clinical history may clarify the diagnosis. Detailed review of clinical information and image findings will aid in forming a differential list, and additional confirmatory workup can help narrow down the differential.

### *Neuroendocrine Tumors Versus Solid Pseudopapillary Neoplasm (SPN) of the Pancreas*

SPN is a relatively rare entity which has been predominantly diagnosed in female patients [20], usually of young to middle age. Morphological distinction of NET and SPN, either grossly or microscopically, can be challenging. The typical

histological features of NET (i.e., organoid and pseudoglandular patterns) and of SPN (pseudopapillary fibrovascular core wrapped by bland-appearing neoplastic cells) may not be well preserved on the H&E-stained sections, due to sampling issue, tissue degeneration, or surgical-related change. Therefore, immunohistochemical workup becomes essential in discriminating one from the other. SPN expresses epithelial markers such as AEI/AE3 and CAM 5.2, although usually focally and weakly; SPN cells are usually immunohistochemically positive for CD56 and synaptophysin (patchy stain) but negative for chromogranin. Importantly, SPN shows abnormal beta-catenin expression (nuclear and cytoplasmic stain), a reflection of a mutation in CTNNB1 gene (cyclin-D1) which is invariably present in SPN [21]. SPN tumor cells express progesterone receptors, but not androgen receptors [20, 21], and galectin-3, which will help in differentiating SPN from pancreatic NET [22]. Of notice, both NET and SPN demonstrate low Ki-67 proliferative index, usually lower than 5 %, indicating a low growth potential for SPN.

### *Neuroendocrine Tumors Versus Paragangliomas*

NET cells are generally arranged in a nodular, nested, and trabecular pattern of growth, intermingled by subtle fibrovascular stroma. Cytologically NET cells display mild to moderately eosinophilic, clear, or finely granular cytoplasm and nuclei with a "salt-to-pepper" chromatin distribution pattern [3, 4, 23]. Paragangliomas (so-called extra-adrenal pheochromocytomas) are originated in the ganglia of the sympathetic nervous system in the body, known for their "zellballen" pattern of growth [24, 25]. Architecturally paragangliomas can mimic NETs in terms of nodular and nested growth pattern and rich vasculatures embedded within fibrovascular septa [24, 25]. In the presence of a metastatic tumor, it can be difficult to differentiate one entity from the other, and both NET and malignant paraganglioma are capable of metastasis. Immunohistochemistry may be helpful in this differential: paraganglioma contains sustentacular cells which are highlighted by S-100 stain, and paraganglioma is not labeled by cytokeratin.

### *Neuroendocrine Tumors Versus Nonepithelial Neoplasms*

Differentiating lymphomas, small blue cell tumors such as Ewing sarcoma, and desmoplastic small round cell tumor and malignant melanoma from NET may occasionally be difficult. Careful histological analysis, essential immunohistochemical study, and related molecular and genetic test(s) can aid in reaching the correct diagnosis. Noticeably, S-100 protein is frequently expressed by both NETs and NECs, and it should not be used in this differential. It is wise to test separate melanoma markers such as tyrosinase, Mitf, melan-A, and HMB-45. Desmoplastic small round cell tumor, a soft tissue sarcoma that usually occurs as masses in young adults and teenagers involving multiple organ sites, displays densely fibrotic stroma,

mimicking fibrovascular septa within NETs [26]. However, the clinical presentation, the clinical history, and both immunohistochemical and molecular studies are essential to identify this malignant and aggressive tumor which is typically positive for cytokeratins, desmin, epithelial membrane antigen, and vimentin [26]. Metastatic thyroid medullary carcinoma is immunohistochemically positive for neuroendocrine markers, but also for TTF-1, calcitonin, and CEA. These markers, in the presence or absence of a clinical history of primary medullary carcinoma, will help in reaching the correct diagnosis [27].

## *Determination of Origin for Metastatic NET*

One frequently encountered clinical scenario is a patient presenting with a diagnosis of metastatic NET, without a known primary site. Recent publications have indicated that while most NETs from small intestine (especially those from the terminal ileum) and appendix are positive for CDX-2, less than 20 % of NETs from the upper GI tract, including the stomach and duodenum, display CDX-2 labeling [18]. Rectal NETs show a CDX-2 labeling rate which is in between the two listed above. On the other hand, while a similar low percentage of pancreatic NETs are positive for CDX-2, around two-thirds of pancreatic NETs are positive for PAX-8 [17]. Interestingly, NETs from the duodenum show a similar rate of PAX-8 positivity. A metastatic low-grade NET from the lung is usually TTF-1 positive [19]. Of course, clinical history, imaging findings, and laboratory results are all required to generate a complete differential list and to reach a corrected diagnosis.

## *Neuroendocrine Tumors Versus Prostate Cancer*

Prostate cancer, especially when metastatic or when involving the rectum, can be misinterpreted as NET on small biopsies and on frozen section. The small prostatic acini, especially when confluent (tumors with high-grade Gleason score), may mimic an NET with nested growth pattern. To compound this problem is the fact that rectal NETs may express prostatic acid phosphatase (PAP). Also on a frozen section sample, the prominent nucleoli of prostatic carcinoma cells may be less prominent. The suspicion of prostate cancer in a male patient should prompt the pathologist to perform PSA immunostain when dealing with a tumor believed to be a NET.

Figure 1 and Tables 1 and 2 summarize features and tests that can help in differentiating an NET from its mimickers.

In summary, diagnosing an epithelial neoplasm as an NET, NEC, or other types of tumors (i.e., adenocarcinoma) is a frequently encountered event during a daily pathology practice. Please refer to Fig. 1 for the H&E images of the most relevant mimickers of NET and NEC. In addition, the attached Table 1 summarizes the major criteria that could be adopted when differentiating any given neuroendocrine neoplasm from its mimickers.

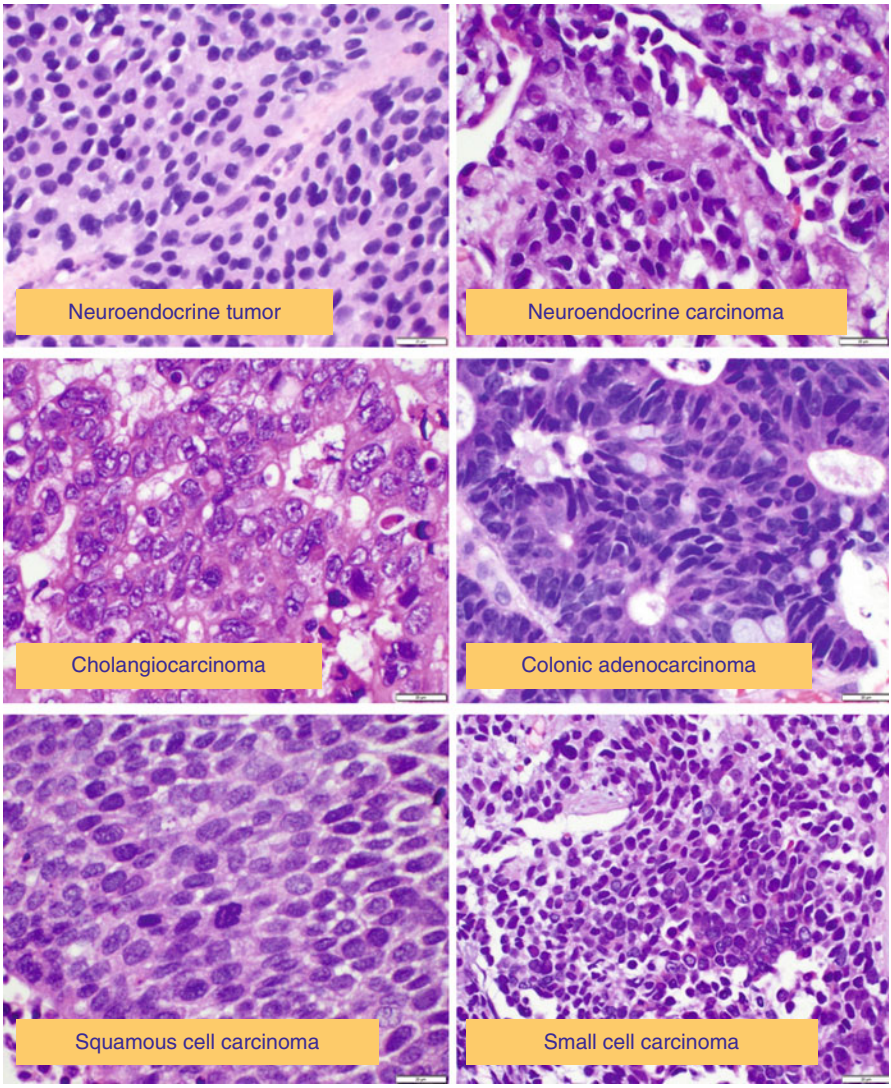


**Fig. 1** Neuroendocrine neoplasms and the most relevant mimickers (H&E sections, 40×)

**Table 2** Differentiating neuroendocrine neoplasms from various malignancies

| Neuroendocrine neoplasms | Frequent mimickers of neuroendocrine neoplasms |
|---|---|
| Neuroendocrine tumor | Bland cytology (NET grades 1 and 2); frank cytological atypia or infiltrative growth (NEC); positive neuroendocrine markers |
| Neuroendocrine carcinoma | |
| Adenocarcinoma from a spectrum of origins (GI and pancreatobiliary tract, lung, GYN, GU, and skin adnexal appendages) | A wide spectrum of cytological and architectural dysplasia; frequent mitoses and potentially necrosis; positive mucicarmine and PAS-D; negative neuroendocrine markers |
| Pancreatic acinar cell carcinoma (usually in senior patients, large tumor size, aggressive behavior with frequent mitoses) | Focal weak synaptophysin labeling; negative chromogranin; positive trypsin, chymotrypsin and Bcl-10, invading adjacent stroma with nuclear signal for beta-catenin |
| Pancreatic solid pseudopapillary neoplasm (SPN, mostly in middle-age female patients, located in pancreatic tail) | Positive CD10 and nuclear beta-catenin; focal synaptophysin; negative or focally label by cytokeratin; PAS-D (+) intracytoplasmic globules; positive alpha-1 antitrypsin |
| Malignant melanoma (usually with but occasionally without a clinical history of melanoma) | Markedly dysplastic morphology (monster cells), destructive growth; positive S-100, melan-A, Mitf, and tyrosinase; negative cytokeratin by IHC |
| Lymphoma (clinical history or frankly de novo diagnosis; a history or clinical evidence of lymphoma could give a way) | Discohesive clusters, nests, or sheets of atypical monomorphic lymphoid proliferation; positive for CD45 and lymphoma markers by IHC and flow cytometry; negative for cytokeratin and neuroendocrine markers |
| Ki-67 usually between 0 and 20 % for NET; >20 % for NEC | Significantly higher Ki-67 in various malignancies, usually at least 50 % (adenocarcinoma, acinar cell carcinoma, melanoma, and lymphoma); only 1–4 % for SPN |

## Abbreviations

| | |
|---|---|
| NET | Neuroendocrine tumor |
| NEC | Neuroendocrine carcinoma |
| NSE | Neuron-specific enolase |
| GI | Gastrointestinal |
| SCC | Small cell carcinoma |
| LCNEC | Large-cell neuroendocrine carcinoma |
| MANEC | Mixed adenoneuroendocrine carcinoma |
| SPN | Solid pseudopapillary neoplasm |

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