A Well-Differentiated Grade-3 Neuroendocrine Tumor in the Ascending Colon: A Case Report

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Patient: Male, 60-year-old
Final Diagnosis: Colon mass • neuroendocrine tumor G3
Symptoms: Altered bowel habit • anemia
Medication: —
Clinical Procedure: Rt HemiColectomy
Specialty: Oncology • Surgery

Objective: Rare coexistence of disease or pathology
Background: Gastrointestinal neuroendocrine tumors (NETs) are indolent hormone-secreting pathologic illnesses that can occur throughout the whole digestive tract. They are classified by site and grade. Colon neuroendocrine neoplasm (NEN) is an unusual histologic finding that needs to be further investigated. Well-differentiated (WD) Grade-3 (G3) is a new category of NEN that falls between neuroendocrine tumor (NET) and neuroendocrine carcinoma (NEC).

Case Report: A 60-year-old man with a past medical history of diabetes mellitus presented with severe anemia and significant weight loss. Tumor markers (CEA and CA 19.9) were unremarkable. Colonoscopy showed a large fungating mass in the proximal part of the ascending colon. Biopsy results suggested colonic adenocarcinoma. Contrast-enhanced computed tomography of the chest, abdomen, and pelvis demonstrated a 5×5 cm ascending colon mass with few locoregional lymph nodes and no distant metastasis. A laparoscopic right hemicolectomy performed and histopathologic examination revealed T4N1, WD-NET G3. Postoperative completion work-up was done. Chromogranin-A was in the normal range and nuclear scans (PET and gallium 68) showed no abnormal uptake or residual disease. Extensive review, expert opinion, and multidisciplinary meetings failed to establish guidelines for adjuvant therapy due to the paucity of data in the literature.

Conclusions: Well-differentiated grade 3 NETs of the ascending colon is a rare finding in a rare disease. This entity of NENs is an unmet medical issue on the border between NET and NEC that remains a matter of great debate in terms of establishing an accurate diagnosis and outlining proper management.

Keywords: Carcinoma, Neuroendocrine • Colonic Neoplasms • Neuroendocrine Tumors

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Background

Neuroendocrine tumors (NETs) are a group of tumors with diverse biological behaviors that can be found in a variety of locations. They are usually composed of cells that release hormones into the blood in response to a signal from the nervous system. Colon NETs are extremely rare tumors of the intestine [1]. They are derived from the enterochromaffin cells of the gut [2]. WHO 2010 initially classified neuroendocrine neoplasms according to their histopathology and grading as well-differentiated neuroendocrine tumor (WD-NET) or poorly-differentiated neuroendocrine carcinoma (PD-NEC) [3]. Recently, a proportion of NETs was encountered, presenting a number of mitosis or Ki-67 index higher than 20% with a well-differentiated morphology calling for a new subset well-differentiated neuroendocrine tumor, Grade 3 (WD-NET G-3). Management of this ambiguous group is not yet standardized due to the paucity of data.

We describe the case of a WD-NET G-3 of the ascending colon that was managed surgically with no adjuvant therapy due to a lack of clear consensus in the literature.

Case Report

A 60-year-old man with a past medical history of diabetes mellitus, presented with severe constipation associated with iron-deficiency anemia and significant weight loss (15 kg in 3-4 months). The physical examination noted a pale, thin man with a palpable RLQ mass. General laboratory tests revealed only a low Hb and MCV. Colonoscopy showed a large fungating irregular mass at the junction between the cecum and the ascending colon, nearly obstructing the lumen. Histopathology showed the mass was moderately differentiated, likely arising from serrated adenoma. Carcinoembryonic antigen (CEA) tumor marker was normal. Staging contrast-enhanced computed tomography scan of the chest, abdomen, and pelvis demonstrated a 5×5 cm mass in the ascending colon (Figure 1) with no distant metastases.

He underwent an oncological laparoscopic right hemicolectomy (Figure 2). Histopathologic examination revealed a 5×5 cm, irregular, unifocal, circumferential, hard mass in the ascending colon, extending to the visceral peritoneum, with no microscopical tumor perforation (Figures 3, 4). All margins were uninvolved by the tumor. Perineural invasion was present and lymphovascular invasion was absent. Six out of 33 lymph nodes were positive. Processing of the slides demonstrated well-differentiated NET with mitotic rate >20% and Ki-67 index 60% (Figure 5). Immunohistochemistry (IHC) was positive for synaptophysin and chromogranin B and negative for the other stains (Figure 6).

The report summary was Stage IIIB T4N1 WD G3 NET colon.

His hospital stay was marked with postoperative ileus that was managed conservatively. A multidisciplinary meeting recommended completion work-up, which showed a normal chromogranin-A level and no detection of any pathological uptake on Gallium 68 DOTANOC PET and Fluorine 18 FDG PET scans.

After a thorough review of the literature and repeated consultation of experts, our MDT meeting elected not to proceed with adjuvant therapy. This decision was reached because of the locoregional extent of the disease and the lack of consensus in the medical literature to support adjuvant therapy.

Periodic PET and CECT and tumor markers were done every 3 months for the first year of surveillance, then repeated annually according to the ENETS. The 3-year follow-up noted disease-free survival and absence of any abnormal clinical symptoms.

Figure 1. Enhanced CT scan, axial and coronal cuts showing a large ascending colon mass (arrows).
Colon NENs are epithelial neoplasms with predominant neuroendocrine differentiation. They arise from Kulchitsky cells and are usually found within the crypts of Lieberkuhn. Historically, they have been referred to as APUD (amine precursor uptake and decarboxylation) cells and their related tumors as APUDomas [2]. Electron microscopy has demonstrated these precursor cells to contain membrane-bound secretory granules, which have been found to contain over 40 different hormones and biogenic amines [2].

The etiology is still not clear. Most tumors appear sporadic; some causes are familial as a part of MEN syndrome (Wermer) and others are genetic. Loss of gene on chromosome 18q or gene inactivation on chromosome 11q can be related to early genesis of midgut NET [4].

The colon is the least common site of intestinal NENs, and their incidence is less than 0.015 per 100 000. It has a peak in the seventh decade and female bias of 2:1 [5]. In 1963 William and Sandler classified gastrointestinal NETs according to embryologic site of origin into foregut, midgut, and hindgut. Colon NETs are divided into proximal colon (midgut supplied by the superior mesenteric artery) and distal colon (hindgut supplied by the inferior mesenteric artery) (Table 1) [6].
Colon NETs occur more in the proximal colon, and they have worse prognosis than those in other parts of the large intestine. Due to the larger diameter of the proximal colon, they have a female predilection and usually present late in the 7th decade, with an average size at diagnosis of 5 cm [7]. Carcinoid syndrome manifests in only 5% of patients, but 60% of them have metastatic or complicated disease and 5% have disseminated seeding at presentation. One series noted that 80% of patients with midgut tumors demonstrated significant mesenteric fibrosis at the time of surgery for intestinal obstruction [8]. Our patient had an ascending colon NET that presented with partial obstruction, anemia, and significant weight loss. Fortunately, no metastases or carcinoid syndrome was noted at the time of diagnosis, but he had mild mesenteric fibrosis.

Colonic NENs are staged similarly to rectal NENs based on pTNM classification of the American Joint Committee on Cancer (AJCC) 8th edition, 2017 [9]. However, Modlin et al [10] studied a large series that was identified by the Surveillance, Epidemiology, and End Results (SEER) database program of the National Cancer Institute. It compared colonic to rectal NENs, and showed a remarkable difference between them in terms of size; ones in the rectum are usually are smaller and can be removed endoscopically rather than surgically. Colon NETs tend to be more aggressive than rectal ones and have worse prognosis [10]. Our case was locally advanced, demonstrating a large mass in the ascending colon protruding through the serosa to the visceral peritoneum, with 6 out of 33 lymph nodes involved, T4N1 Stage IIIB.

The unified grading scheme of NENs is centered on mitoses and ki-67 index. Low grade (G1) is mitoses ≤2/2 mm² and ki-67 index < 3%. Intermediate grade (G2) is mitoses 2-20 mm² or ki-67 index 3-20%. High grade (G3) is >20/2 mm² or ki-67 index > 20%.

Figure 5. Ki-67 index expression reaching up to 60% in tumor cells. (A) Ki-67 index (20×). (B) Ki-67 index (40×).

Figure 6. Immunohistochemistry staining in tumor cells. (A) Chromogranin B positivity. (B) Synaptophysin positivity.
index >20%. The mitotic count should be evaluated in a 2-mm² hotspot area, roughly equivalent to 10 HPF with a 40× objective lens [11-13]. The terminology of NENs has evolved based on morphology and proliferative rate over the past 2 decades to reflect a separation into 2 major categories: WD-NET and PD NEC. According to the latest WHO classification 2019, WD NETs are not homogenous. In addition, a small number of WD NENs have a high proliferative rate with WD morphology; this subset is called WD-NET G-3 [13].

This entity is a recently named NENS that represents a number of mitosis or Ki-67 index higher than 20% and well-differentiated cytoarchitectural features [13]. They account for 6% of all NETs and they are usually located in the stomach and pancreas. A few cases have been reported in the colon [14]. This category falls between WD-NET and PD NEC in terms of treatment and prognosis. The disease outcome is intermediate between WD-G2 and NEC. Usually, WD G1 and G2 are easily diagnosed by pathologists, but confusion can occur when Ki-67 is above 20% and overdiagnosis to NEC can also be observed. Expert opinion is crucial for better distinction between these 2 types of proliferation (Table 1) [15,16]. In our patient, a second opinion was sought from the Kuwait Cancer Control Center (KCCC), and they confirmed our diagnosis of Ki-67 60% WD G-3.

About 40% of PD NECs cases contain non-neuroendocrine components, including adenocarcinoma, signet ring cell carcinoma, and, rarely, squamous cell carcinoma. If both components exceed 30%, then it is called mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN) [13]. Historically, they were referred to as mixed adenoneuroendocrine carcinomas (MANEC) [12]. Our patient initially was diagnosed by colonoscopy as having adenocarcinoma, but after colonic resection, the tumor was confirmed to be WD-NET G-3. IHC was attained for both specimens, and precise comparison by several expert pathologists revealed a consistent pathology.

WD-NET G-3 appears to be nonfunctioning in 75% of cases, and colonic carcinoid syndrome is also rarely observed [8,14]. Our patient denied any carcinoid manifestation and IHC was negative for the majority of markers except for chromogranin B and synaptophysin. Tumor markers were all within normal range. In non-metastatic neoplasms, ENET and NANET guidelines recommend a surgical resection for localized NEN, irrespective of tumor grading [13,17]. Coriat et al [18] implemented a platinum-based chemotherapy regimen for pancreatic WD G-3 based on Ki-67 percentage; less than 55% to use the same treatment protocol as WD G1-2 and if above 55% to be managed as a NEC. He also noted in his study that prognosis is considered intermediate between NET G-2 and NEC [19]. According to our literature review, there are no clear data that suggest a benefit of adjuvant therapy after curative-intent surgery. There are also no data concerning the efficacy of neoadjuvant chemotherapy for locally advanced or technically unresectable tumors [20]. Colon NET G-3 is a very rare finding and it usually follows the general NET G-3 category treatment recommendations according to the stage of the disease: somatostatin analogs, chemoembolization, chemotherapy, and peptide receptor radionuclide therapy (PRRTs). Our patient had a large but resectable ascending colon tumor and no metastases; consequently, he was managed surgically with no adjuvant chemotherapy.

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Galium 68 DOTATATE and Fluorine-18 FDG PET scans are increasingly used in NETs. DOTATATE is usually the primary scan that is

### Table 1. Comparison between WD-NET G-3 and NEC [15,16].

| Features                        | NET, G3                       | NEC                           |
|--------------------------------|-------------------------------|-------------------------------|
| **Morphology**                 |                               |                               |
| Differentiation                | Well-differentiated           | Poorly-differentiated         |
| Pattern of arrangement         | Organoid, nests, trabecular, insular | Diffuse sheets of either small or large cells |
| Nuclei                         | Round, oval with "salt & pepper" chromatin, inconspicuous nucleoli | Atypical, pleomorphic          |
| Cytoplasm                      | Eosinophilic                  | Basophilic                    |
| Apoptosis                      | +/-                           | ++                            |
| Necrosis                       | +/-                           | +++                           |
| **Immunohistochemistry**       |                               |                               |
| **Ki-67 index**                | >20% (up to 50%)              | >20% (usually more than 70%)  |
| Neuroendocrine markers         | ++                            | + weak                        |

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used to assess slow-growing NETs and low-grade disease with better prognosis. FDG avidity is associated with more aggressive tumors with high-grade disease and worse prognosis [18]. According to Bailey et al, integrated Dual tracer FDG/DOTATATE PET is a promising tool for whole-body molecular NET biopsy and may also be a predictive biomarker in subjects being considered for PRRT by Lutetium Lu-177 [21]. In Kuwait, we do not have the dual tracer PET. We performed DOTATATE and FDG separately after surgery and both showed no abnormal uptake.

According to ENETS consensus, the follow-up of G-3 NET is similar to that of G-3 NEC. CT or MRI with CgA is advised every 3 months during the first year, then FDG and serotonin receptor PET is recommended annually. Colonoscopy is indicated in case of any symptoms [22].

Management of NET G-3 is not yet standardized because of lack of data. In a non-metastatic setting, international guidelines recommend surgical resection, regardless of tumor grading. For metastatic lesions, chemotherapy is the main treatment, with a similar regimen as NET G-2. Sunitinib has also shown some positive results in a small sample of patients, but this needs confirmation. Peptide receptor radionuclide therapy (PRRT) and immunotherapy could be future available treatments after ongoing studies [23].

**Conclusions**

NET G-3 is a new histopathological subset that falls between NET and NEC. The paucity of available data on this entity indicates the importance of specialized meetings, MDT approach, and NEN expert opinion. There is a need for larger studies with long-term follow-up.

**Declaration of Figures’ Authenticity**

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