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A Perforated Colonic Neuroendocrine Tumor with Liver Metastasis: A Case Report and Literature Review

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 57
Final Diagnosis: High grade and invasive colonic neuroendocrine carcinoma
Symptoms: Abdomen distension
Medication: —
Clinical Procedure: Subtotal colectomy and ileostomy creation
Specialty: Surgery





Objective: Unusual clinical course
Background: Neuroendocrine neoplasms (NENs) originate from cells of the endocrine and nervous systems, and they are rarely encountered in colorectal cases with no specific symptoms. The incidence and prevalence of NENs of the large bowel are increasing. Malignant colonic types are known to have poor diagnosis. The mean age of colonic NENs is the seventh decade, and the risk of NENs is increased 4-fold with affected first-degree family members.

Case Report: A 57-year-old male patient presented to our Emergency Department with a 5-day history of severe generalized abdominal pain associated with worsening abdominal distension, history of night sweats, and weight loss. A CT scan of the abdomen and pelvis demonstrated a large heterogeneously enhancing neoplastic mass lesion involving the splenic flexure of the colon surrounded by fat stranding with a small contained leak, in addition to multiple metastatic hypodense focal hepatic lesions. Multiple lymph nodes under 1 cm in size were also noted. The patient underwent exploratory laparotomy, subtotal colectomy, ileostomy creation, and washout. The histopathological exam revealed high-grade invasive colonic neuroendocrine carcinoma, which was pT4N2bM1c, while the peritoneal lesion was metastatic carcinoma. The patient was then referred to the multidisciplinary tumor board.

Conclusions: Unusual presentation of neuroendocrine tumors is shown to be expected. Since colorectal NECs are rare, highly aggressive diseases and usually discovered very late, individualization of management, as well as additional research, is required.

MeSH Keywords: Carcinoma, Neuroendocrine • Colonic Neoplasms • Liver Neoplasms • Neuroendocrine Tumors

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Background

Neuroendocrine tumors (NETs), also known as neuroendocrine neoplasms (NENs) or carcinoid tumors ('karzinoide' or carcinoma-like), are mostly rare benign neoplasms that originate from cells of the endocrine and nervous systems, but with malignant neoplasms present [1]. NETs are found predominantly in the gastrointestinal tract and account for only about 0.5% of all newly diagnosed cancers [2].

In recent decades, the incidence and prevalence of NETs, especially those of the large bowel, have been increasing (colonic and rectal NENs account for 7.8% and 13.7%, respectively), which is mostly explained by advances in classification and a better diagnostic approach [3,4]. Colonic and rectal NETs are different entities, as malignant colonic types are known to have a more aggressive course, higher grade, and poor differentiation [5,6]. The mean age of onset of colonic NET is 63.3–70 years. Usually, the diagnosis is late, mostly a result of locating a tumor; it is most common in females and usually affects the cecum area of the ascending colon. Signs and symptoms of bowel obstruction are the most common presentation, and the percentage of local disease compared to metastasis is 45% and 16–40%, respectively [4,7].

High-grade neuroendocrine tumors, also known as neuroendocrine carcinoma (NEC), are malignant epithelial tumors with evidence of neuroendocrine differentiation based on light microscopic, ultrastructural, or immunohistochemical evaluation. Although NECs of the colon and rectum are rarer than the other NETs, they are extremely aggressive neoplasms with a high mortality rate and account for 0.1–3.9% of all colorectal malignancies [8–10]. The risk of NETs increases 4-fold when first-degree family members are affected. Synchronous neoplasms account for 13% of cases [3,4,7].

To the best of our knowledge, we report the first case of a perforated colonic neuroendocrine tumor.

Case Report

A 57-year-old Saudi male patient (body mass index: 41 kg/m²), who was not previously known to have any medical illness, presented to the Emergency Department at King Saud University Medical City, with a 5-day history of severe generalized abdominal pain, mainly in the epigastrium, pressure-like in nature, aggravated by lying down on his side, with no alleviating factors, associated with abdominal distension, progressively getting worse in the past few days, shortness of breath at rest, orthopnea and wheezing, history of night sweats, and intentional weight loss of around 4 kilograms in the last month. The patient denied any history of decreased appetite, vomiting,

nausea, change in bowel habits, melena, hematochezia, Hx of trauma to the abdomen, any alcohol ingestion, history of blood transfusion, illicit drug use, or family history of gastroenterology malignancies.

Upon examination, the patient exhibited pain and distress, and was conscious and fully oriented. There was no cervical lymphadenopathy. The abdomen was distended, with epigastric tenderness. The fluid thrill was positive and organomegaly could not be assessed. The patient was vitally stable (T: 37°C (oral), RR: 20, BP: 116/72, SpO₂: 98%) but had leukocytosis (32.500×10⁹/L), mainly neutrophils and monocytes, markedly high ESR (118 mm/hr) and CRP (173 mg/L), slightly elevated lactic acid (2.1 mmol/L), and hypoalbuminemia (14.25 gm/L). Initially, serum chromogranin A and CgA were not performed as it was an emergency case and a neuroendocrine neoplasm was not suspected; these were subsequently requested but were not available in our institution. CT of the abdomen and pelvis demonstrated a large heterogeneously enhancing neoplastic mass lesion involving the splenic flexure of the colon surrounded by fat stranding, with a small contained leak just inferior to the mass lesion, and no signs of bowel obstruction. There were large loculated ascites in the abdomen, with scalloping of the liver surface. Multiple metastatic hypodense focal hepatic lesions were present as well. Multiple lymph nodes less than 1 cm in size were also noted (Figures 1–3). CT of the chest demonstrated bilateral pleural effusion small on the left and moderate on the right, with basal lung atelectasis and no lung nodules.

The patient was taken to the operating room as category one as he was diagnosed with a bowel perforation. He underwent exploratory laparotomy, subtotal colectomy, and ileostomy creation and washout. We placed 3 drains with closure en bloc. A 65-cm specimen and a peritoneal nodule were sent for the histopathological exam. The intraoperative finding was 1.5 liter of pus, multiple pockets of pus, phlegmon involving the stomach and large bowel, multiple peritoneal neoplastic deposits, and carcinomatosis of stomach, liver, and spleen. The patient was shifted to the surgical intensive care unit, intubated on inotropic support and placed on meropenem and fluconazole, as later cultures showed heavy growth of *Streptococcus anginosus* and scant growth of *Escherichia coli*. The patient was progressively improving. On day 5 after the operation, the patient was shifted to the general surgical ward. He was vitally stable and was able to eat and walk, and we continued providing post-operative care and management.

Grossly, the first specimen consisted of 1 piece of colon (ileum, cecum, right colon, and left colon) measuring 65.0 cm in length, showing extensive exudate all around the colon, with 1 tumor showing a constricting fungating surface with autolytic changes. The appendix was not grossly found. Both surgical margins

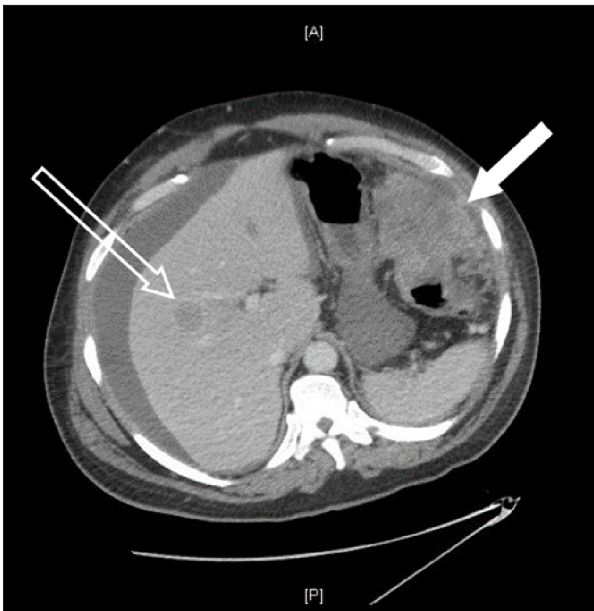


Figure 1. A contrast-enhanced CT scan of the abdomen (axial image) showing a large lobulated soft tissue mass adherent to the splenic flexure, with focal colonic wall thickening (solid arrow). The size of the tumor lesion is 9×7 cm. A focal metastatic lesion is seen in the liver (non-solid arrow), with loculated ascites.



Figure 2. Coronal CT scan of the abdomen showing loculated ascetic fluid with scalloping of the liver surface indicating malignant ascites (solid arrow). No signs of bowel obstruction.

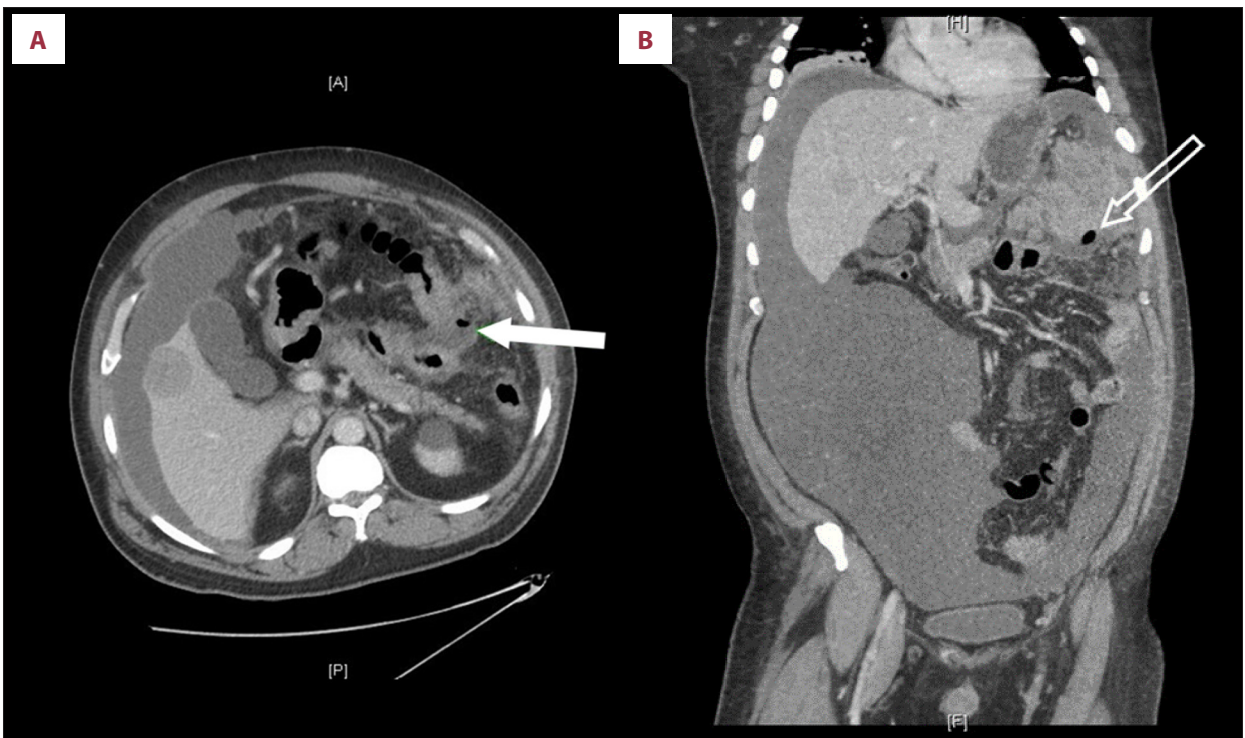


Figure 3. (A, B) A contrast enhanced CT scan of the abdomen in axial and coronal images showing small loculated fluid collection at the inferior aspect of the colonic mass (solid arrow) with tiny gas pockets (non-solid arrow) indicating concealed perforation.

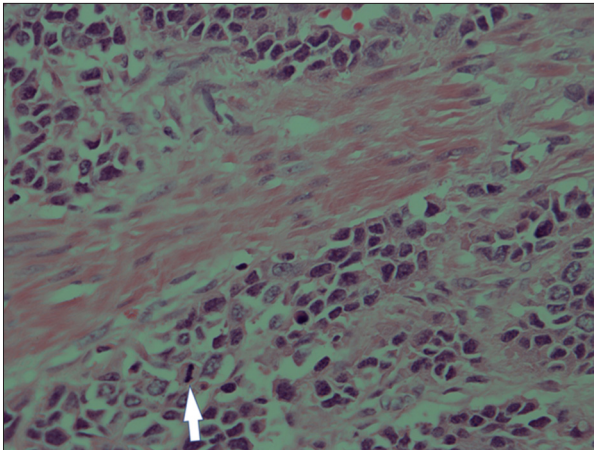


Figure 4. Poorly differentiated neuroendocrine carcinoma infiltrating smooth muscle cells. Note the granular nuclear chromatin (H/E stain $\times 400$) (solid arrow).

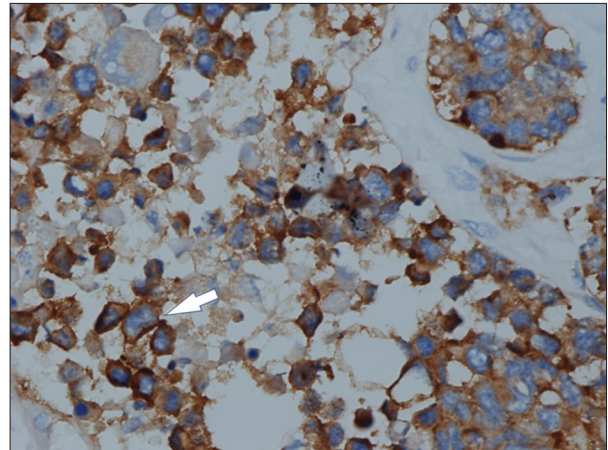


Figure 6. Neuroendocrine tumor cells showing strong positive cytoplasmic and membranous staining with synaptophysin (H/E stain $\times 600$) (solid arrow).

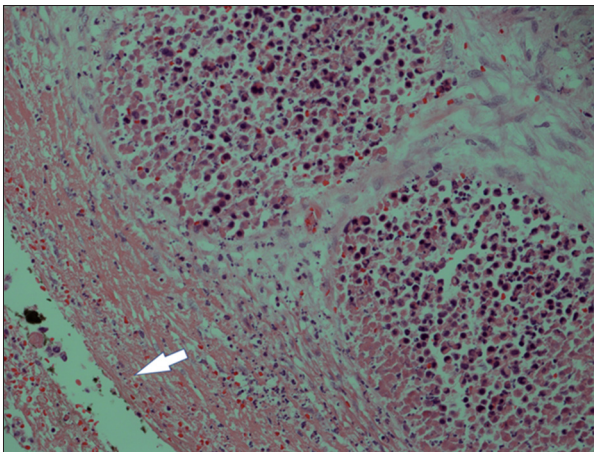


Figure 5. Necrotic neuroendocrine carcinoma adjacent to an area of bowel perforation lined by necrotic and fibrinous material (H/E stain $\times 200$) (solid arrow).

appeared to be tumor-free away from both surgical margins. The splenic flexure tumor measured 10.0 cm in the greatest dimension, and it was 0.1 cm from the serosa and 3.0 cm from the soft tissue margin and circumferential radial margin. It was diagnosed as a high-grade and invasive colonic neuroendocrine carcinoma. The mitotic index was more than 20/10 HPF with lymphovascular invasion, but perineural invasion could not be determined. There were 10 tumor deposits in the pericolic fat, with metastases to 9 out of 10 lymph nodes. Tumor staging was pT4 N2b M1c. Immunohistochemical staining was performed and showed that the tumor cells were positive for synaptophysin, Pan-CK, CD56, and CD117 (indicating poor prognosis). The proliferation marker (Ki-67) showed $>90\%$ positive nuclear staining.

The second specimen (peritoneal lesion) consisted of 2 pieces of irregular gray-brown tissue measuring $1.8 \times 0.9 \times 0.5$ cm, which was diagnosed as metastatic carcinoma (Figures 4–6).

Histopathological examination of the splenic flexure mass revealed high-grade and invasive colonic neuroendocrine carcinoma that was pT4N2bM1c, while the peritoneal lesion was metastatic carcinoma. Immunohistochemical staining was performed. The patient was referred to the multidisciplinary tumor board for proper assessment and management.

Discussion

Enterochromaffin (EC) and L cells are considered to be the origin of colorectal NETs, as EC cells secrete serotonin and they are typically located in the ascending colon, while the remaining part of the colon and rectum has L cells, secreting glucagon-like peptide (GLP) and YY peptide [6]. Colorectal neuroendocrine carcinomas are problematic for colorectal surgeons as they are highly malignant and have the lowest 5-year survival rate of all the gastrointestinal NENs. The ascending colon is the most common part to be affected by NECs, which account for approximately 75% of all colorectal NECs. Colorectal NECs are highly malignant neoplasms. Compared to metastatic extrapulmonary NECs, metastatic pulmonary NECs have a worse outcome [3,4,11].

Approximately 30% of cases of colonic NENs are metastasized to the lymph nodes, mesentery, peritoneum, and liver at time of diagnosis. This usually begins as polyps and then ends up with advanced stage seen at the time of diagnosis as exophytic tumors, which will be diagnosed as NEC or mixed neoplasms (MINENs) [3,7]. Broecker, based on a single-institution experience of over 15 years, found that colonic NETs have more aggressive clinicopathologic features and worse outcomes compared with rectal NETs [12]. The metastasis in our case was similar to that reported in most studies, but Lokesh reported a higher rate (54%) of bone metastasis [11].

Unfortunately, carcinoid syndrome symptoms are rarely observed with NETs (<5%). There are no specific symptoms associated with colonic neuroendocrine neoplasms, as they mainly mimic adenocarcinoma, but patients usually present with changes in bowel movements (mostly diarrhea) and, in advanced stage, may present with abdominal pain, weight loss, and palpable lesions in the abdominal cavity. Anemic symptoms may occur as a result of gastrointestinal blood loss. There is no diagnostic blood marker for colorectal NENs, but there is a role for serum chromogranin A and CgA concentration. Signs of bowel obstruction or perforation mandate surgical intervention but, to the best of our knowledge, there are no case reports in the literature on perforated colonic neuroendocrine tumors, as they are rarely perforated [3,13,14].

The WHO classification of NETs used in staging was announced in 1980 followed by multiple modifications (in 2000 and again in 2010), and the last modification was announced in 2017. The NENs were classified into 3 main grades. Grade 1 NET has a mitotic count of less than 2 per 10 high-power fields (HPFs) and/or a Ki67 index equal to or less than 2%. Grade 2 NET has a mitotic count of 2–10 per 10 HPFs and/or a Ki67 index between 3% and 20%. Grade 3 NEC has a mitotic count of more than 20 per 10 HPFs and/or a Ki67 index of more than 20%. Multiple studies have demonstrated a very strong association between Ki67 level (equal to or more than 55% vs. less than 55%) and the survival in patients with NEC [11,15].

Surgical choices for colonic NENs include resampling of colonic adenocarcinoma. Lymph node resection depends on the presence or absence of metastasis. Therefore, colonic NET with no evidence of distant metastasis indicates lymphadenectomy, while palliative resection with regional lymphadenectomy is recommended for patients with distant metastases (usually to the liver), or maximal cytoreduction of the tumor as a last resort, since most patients present at an advanced stage with poor performance status. A multi-organ excision, including the oncological resection of the involved colon, is recommended in case of invasion of near-by structures [7,9].

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Patients who do not receive chemotherapy tend to have a very short median survival of only about 1 month. As these tumors morphologically and biologically resemble bronchogenic small cell carcinoma, the platinum with etoposide (EP) regimen has been the standard therapy for advanced NECs, but more randomized control trials are needed to assess the validity. Capecitabine, streptozotocin, 5-fluorouracil, doxorubicin, and temozolomide are considered as other options [16,17].

Depending on the size of the primary tumor, histological grade, and clinical stage, the 5-year survival rate of patients with colonic tumors ranges from 40% to 70%. The mean survival time for patients with locally advanced lesions is 261 months, but it decreases when it is associated with regional lymph node metastases (36 months) or distant metastases (5 months) [3,4,7].

Conclusions

The incidence of NETs is progressively increasing, and unusual presentation is common. We report the first case of a perforated colonic neuroendocrine tumor managed by subtotal colectomy and ileostomy creation. Since colorectal NECs are rare, highly aggressive diseases (especially colonic type), and are usually discovered very late, individualization of management and additional research are needed.

Acknowledgement

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Conflicts of interest

None.

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