A Mixed Neuroendocrine/Non-Neuroendocrine Neoplasm Arising in the Background of Ulcerative Colitis: A Case Report and Review of the Literature

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Patient: Female, 57-year-old
Final Diagnosis: Mixed neuroendocrine non-neuroendocrine neoplasm • ulcerative colitis
Symptoms: Abdominal pain • distention • obstruction
Medication: —
Clinical Procedure: Laparoscopic diverting loop colostomy and colonic mass biopsy • open laparotomy and total colectomy with end ileostomy
Specialty: Surgery

Objective: Rare coexistence of disease or pathology
Background: Inflammatory bowel disease (IBD) is a chronic, potentially life-long, disorder, including ulcerative colitis (UC) and Crohn's disease (CD). Ulcerative colitis (UC) is an idiopathic chronic inflammatory disorder affecting the mucosa of the colon; it starts at the rectum and continues proximally in a continuous pattern to include up to the entire colon, called pancolitis. Patients with ulcerative colitis are at particularly higher risk of developing colorectal cancer (CRC) than the general population. Adenocarcinoma is the most common type of colorectal malignancy reported in the general population and IBD patients. One of the rarest types reported are the neuroendocrine neoplasms (NENs), which account for only 1% of all colorectal cancers, and it is very infrequent in IBD patients. Moreover, mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN) is a rare aggressive subtype of NENs that involves the colon in the background of an underlying chronic inflammatory process.

Case Report: A 57-year-old woman, known to have long-term cirrhosis and ulcerative colitis, came to the Emergency Department with a suspected large-bowel obstruction. Imaging (CT scan of the abdomen) showed an obstructive transverse colon mass along with multiple descending colon masses. Biopsy of the transverse tumor confirmed the diagnosis of mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN).

Conclusions: Although neuroendocrine tumors are rare, strong association exist between MiNENs and ulcerative colitis. Further studies and reports can help better understand the pathogenesis, diagnosis, management, and prognosis of these cases.

Keywords: Abdominal Pain • Colitis, Ulcerative • Colonic Neoplasms • Inflammatory Bowel Diseases • Neuroendocrine Tumors

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Background

Ulcerative colitis (UC) a subtype of inflammatory bowel disease (IBD). Ulcerative colitis (UC) is an idiopathic chronic inflammatory disorder affecting the mucosa of the colon, starts at the rectum and continuing proximally in a continuous pattern to include up to the entire colon, called pancolitis. Patients with ulcerative colitis are particularly more risk of developing colorectal cancer (CRC) than the general population, with an overall risk of 1.29 cases per 1000 IBD patients [1,2]. Among of the rarest types reported are the neuroendocrine neoplasms (NENs), which account for 1% of all colorectal cancers, and it is very infrequent in IBD patients. Moreover, mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN) is a rare aggressive subtype of NENs that involves the colon in the background of an underlying chronic inflammatory process [3]. With an incidence rate of of 1.16 cases per 1 000 000 individuals [4]. Notably, few case reports have been reported of IBD in relation to MINEN.

In this report we present such a case, with a thorough literature review.

Case Report

A 57-year-old woman presented to the Emergency Department with a 2-week history of abdominal pain and distension, associated with constipation alternating with loose bowel movements. In addition, the patient reported having constitutional symptoms of weight loss and poor oral intake during the past 2 years.

Twenty years ago, the patient had similar severe abdominal pain associated with diarrhea and rectal bleeding, where the medical team planned to do a colonoscopy due to a suspicion of inflammatory bowel disease. However, the patient refused to follow up, and was not started on any medical therapy. She denied having any similar episodes during this time period.

Upon examining the patient, she looked malnourished and dehydrated, but had normal vital signs. The abdomen was hugely distended, mildly tender, with shifting dullness on percussion.

Laboratory results during admission showed low hemoglobin (9.7 g/dL), sodium 117 mEq/L, and tumor markers only showed high CA-125 (233 U/mL) (normal level <35 U/mL). All other laboratory work-ups were unremarkable and within normal ranges.

Computed tomography (CT) of the abdomen and pelvis was done, which showed a distended large bowel with a cecal diameter of 8.5 cm, down to a short stricture, with one of 2 cm at the mid-transverse colon (Figure 1) and another colonic stricture span for around 5 cm at the distal descending colon (Figure 2). Also, there was a polypoid mass lesion involving the medial colonic wall just distal to descending colon (Figure 3). Signs of inflammation were noted, with irregular mucosal thickening, hyperenhancement, and paracolic fat stranding with lead pipe appearance of the colon suggesting IBD, particularly UC. Moreover, the liver was cirrhotic and showed innumerable hypo-dense micro-nodules with right hepatic vein thrombosis.

Further laboratory investigations were done for the patient’s cirrhotic liver, which revealed she had hepatitis C virus (HCV) and was categorized as Child- Pugh score B with ascites and hepatic vein thrombosis.

In this report we present such a case, with a thorough literature review.
Given the complexity of the patient’s presentation with the concurrent bowel obstruction and liver cirrhosis, she was not stable and required admission to the Intensive Care Unit (ICU). The plan at that time was to relieve the obstruction temporarily by diverting stoma and performing a biopsy the lesions to appropriately diagnose and stage the patient and optimize her clinical condition for definitive resection and proper planning of the extent of resection.

The pathological examination from the transverse colon mass biopsy demonstrated large cells with adenocarcinoma and neuroendocrine carcinoma morphology. Immunohistochemical staining showed that more than 50% of the tumor was positive for synaptophysin and CDX2, with a Ki67 index of 75%. Moreover, some tumor cells were 40% positive for CK20. Thus, the biopsy was suggestive of poorly-differentiated MiNEN in a background of active chronic colitis, confirming the diagnosis of UC.

Liver magnetic resonance imaging (MRI) was done for further evaluation of the suspicious lesions to exclude metastasis, which showed a redemonstration of the cirrhotic liver, with no concerning focal hepatic lesion.

During her hospital stay and given her co-morbid liver failure and the active colitis, the patient showed no significant improvement despite starting hydrocortisone along with supportive medical management. The case was discussed with the tumor board committee, and the decision was made to proceed with high-risk surgery for total colectomy, given the multiple malignant lesions on the transverse and descending colon in the background of ulcerative colitis. Upon exploring the abdomen, the colon was examined, showing 1 stricture at the transverse colon and another 2 masses at the descending colon. Total colectomy with end-ileostomy were then performed.

The pathologic examination of the surgical specimen showed a multifocal colonic tumor with 3 separate masses. The first mass was located at the transverse colon at the stricture area and showed MiNEN of poorly-differentiated neuroendocrine carcinoma with Ki67 more than 70% and signet cell carcinoma, poorly differentiated, within 1 mm from the serosal surface (Figure 4).

The other 2 masses were identified at the descending colon, and 1 of the masses had poorly-differentiated signet cell carcinoma (Figure 5), while the other mass was moderately differentiated adenocarcinoma (Figure 6). The pathologic final staging (pTNM, AJCC 8th Edition) was mpT3 N2b M0.

Postoperatively, the patient showed improvement in clinical condition. She was discharged from the ICU and was followed up by Hepatology regarding the liver cirrhosis.

The case was discussed again in the tumor board, and, due to the patient's comorbidities and performance status, she was considered to be high risk for adjuvant chemotherapy.

Two weeks after discharge, a follow-up examination at the clinic showed that the wounds were completely healed, and after tumor board and family discussion and full explanation of the patient's advanced condition, the patient and family agreed to continue only with palliative care.

After 6 months, the patient came back to the Emergency Department with severe fatigue and poor oral intake and was found to have severe electrolyte derangements, with severe hyponatremia (sodium level 118) and severe hyperkalemia (potassium level 7.1). After admission, medical and supportive management were started, but the patient died due to respiratory failure.

**Discussion**

NEN in the colon are rare neoplasms; they account for <1% of colorectal cancers and are extremely rare in the background of IBD. Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) is a very rare subtype of tumor that involves a combination of both adenocarcinoma and NEC [3]. NEN associated with UC are twice as common in males as in females, but our patient was a female. It is also known to have poor outcomes, secondary to high metastasis rates (>50% to the liver), and 1-year survival was reported to be 40% [5].

The association between IBD and NEN was reported only in 16 cases in the literature. However, the association between IBD and MiNEN was only reported in 3 cases [6-20].
**Figure 4.** Histopathology slides of the mid-transverse colon stricture (A, B) shows the poorly-differentiated neoplasms of the 2 components. (C, D) Cells shows positivity focally for synaptophysin and CD56. (Hematoxylin-eosin and IHC, original magnifications ×4 [A, B, and D] and ×20 [C]).

**Figure 5.** (A, B) Histopathology slides of the splenic flexure colon mass showing a poorly-differentiated carcinoma with signet ring cell morphology. (Hematoxylin-eosin, original magnifications ×4 [A] and ×40 [B]).
Our patient and 3 out of the other reported cases had an interesting pathological diagnosis of MiNEN, which is defined as the presence of ≥30% of adenocarcinomatous component of the tumor masses [8,11]. Strong staining for synaptophysin and positive Ki67 marker >70% were observed in almost all reported cases, which was similar to our finding [9,20]. Two of the reported cases were found to have rectal MiNEN and 1 was found to have a sigmoid colon MiNEN, while in the presented case a transverse colon MiNEN was found with 2 other masses in the descending colon: poorly-differentiated signet cell carcinoma and moderately differentiated adenocarcinoma [8,11].

MiNEN is regarded as a conceptual category of neoplasms rather than a specific diagnosis. Different types of MiNENs arise in different sites throughout the gastroenteropancreatic system [3]. Prognosis and treatment of MiNENs still are unclear, and no well-defined treatment strategy has been established. If resectable intermediate-grade MiNEN is found, surgery should be performed, but if distant metastasis is found, chemotherapy against both types should be started. High-grade MiNEN is the most commonly seen, as in our patient, and is considered the most aggressive type. Localized lesions without distant metastasis are treated with surgery and adjuvant chemotherapy, while systemic chemotherapy is used for distant metastasis [21,22]. According to the latest NCCN guidelines, MiNENs of the GI tract are considered to have poor prognosis and should be managed according to the adenocarcinoma of the colon and rectum guidelines [23].

Conclusions

After encountering this case and reviewing the literature, a clear association was identified and specific characteristics...
were found between MiNENs and UC. As it is considered rare, this would represent distinct disease features that require further evaluation. Further research studies with larger sample sizes would help to understand the pathogenesis, diagnosis, management, and prognosis.

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