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Metastatic Mixed Adeno-Neuroendocrine Carcinoma of the Colon to the Liver with Multiple Peritoneal Deposits: A Case Report

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Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 48-year-old
Final Diagnosis: Poorly differentiated mixed adenoneuroendocrine tumor of the colon
Symptoms: Abdominal pain • fatigue • weight loss
Medication: Azathioprine
Clinical Procedure: Colonoscopy
Specialty: Oncology • Pathology • Surgery





Objective: Rare disease
Background: Metastatic mixed adeno-neuroendocrine carcinoma (MANEC) is a rare malignancy. It is characterized by the presence of both neuroendocrine and epithelial components, each of which constitute at least 30% of the lesion to establish the diagnosis.

Case Report: A 48-year-old man presented with a 1-month history of right upper-quadrant pain and unintentional weight loss of 18 kg. He was also complaining of constipation and fatigue for 6 days. The initial diagnosis from a referring hospital was colon cancer with liver metastasis based on a computed tomography (CT) scan of the chest, abdomen and pelvis. After re-evaluation at our hospital, the scan revealed multiple peritoneal deposits in addition to the previously reported findings. A colonoscopy and biopsy were performed, after which the histopathological examination demonstrated a mixed poorly differentiated large cell neuroendocrine carcinoma and adenocarcinoma. Based on the imaging and histopathology reports, he was diagnosed with a poorly differentiated MANEC of the colon with liver metastasis and multiple peritoneal deposits. His lesions were deemed unresectable, and he was referred to the oncology department for palliative care. There he received a total of 9 cycles of cisplatin and etoposide for 8 months. His CT scan showed a regression of the primary tumor indicating a good response to chemotherapy. The patient is still following up with his medical oncologist.

Conclusions: Although it is rare, MANEC is a complex neoplasm that requires a high index of suspicion to diagnose due to its nonspecific presentation. It is confirmed through histopathology and immunohistochemistry of the tumor biopsy. Imaging is performed for staging, with most patients presenting at advanced stages with metastases. The only curative option is complete surgical resection of both the primary and metastatic lesion. Many cases, however, are regarded as unresectable and are referred for palliative treatment.

Keywords: Adenocarcinoma • Carcinoma, Neuroendocrine • Colorectal Neoplasms • Neoplasm Metastasis • Neoplasms, Complex and Mixed • Peritoneal Neoplasms

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Background

Neuroendocrine carcinoma of the lower gastrointestinal tract is a rare entity. Interestingly, neuroendocrine carcinoma can co-exist with adenocarcinoma within the same tumor, forming a mixed adeno-neuroendocrine carcinoma (MANEC). The first case of MANEC was described in the literature as “karzinoide” (“carcinoma-like”) by the German physician and pathologist, Oberndorfer in 1907 [1]. However, it was not until 1924 that the first definition of a gastrointestinal tumor of both exocrine and neuroendocrine components was published by Cordier in the Archives of Internal Medicine [2]. Only recently, in 2010, the World Health Organization (WHO) recognized MANEC as a very rare gastrointestinal tumor [3] characterized by the presence of a neuroendocrine and an epithelial component, each of which accounting for at least 30% of the lesion [4]. MANEC is most commonly encountered in the esophagus [5], stomach [6,7], appendix [8], gallbladder [9,10], and pancreas [11]. Other sites, such as the colon [12-17] and duodenum, are rare [18]. This pathology accounts for about 3-9.6% of all colorectal cancers. The right colon is the most common location of MANEC within the colon (56%), followed by the left colon and transverse colon [16]. Here, we report a case of metastatic MANEC of the colon that progressed rapidly to involve the liver bilobularly with multiple peritoneal deposits.

Case Report

We report a case of a 48-year-old man, known to have diabetes mellitus, on an oral hypoglycemic agent, who also had ulcerative colitis which was controlled with Azathioprine, with no history of flare-ups in the past six years. However, he was not compliant with his follow-up appointments and colonoscopies. The patient was referred to our hospital with complaints of moderate pain in the right upper-quadrant area for 1 month. The pain was intermittent, not increased with fatty meals nor radiating to the back. He also gave a history of fatigue, constipation for 6 days prior to his presentation, and weight loss of approximately 18 kg over a 1-month period. He denied any history of nausea or vomiting, anorexia, rectal bleeding, gallstones, or jaundice. He also denied any history of smoking or alcohol intake. His past surgical history was unremarkable, neither was his past family history, with the exception of his father who was known to have lung cancer. Upon general physical examination, the patient was not in pain and had no pallor or jaundice. He was vitally stable and afebrile. His abdomen was soft, not tender or distended, and a palpable mass was felt in the epigastric region. A rectal examination revealed an empty rectum. Results of laboratory investigations, including tumor markers, were all within normal ranges. A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis was performed at the referring hospital, and

it showed a segment of circumferential wall thickening affecting the proximal descending colon, 6.3 cm long, with a maximum wall thickness of 1.6 cm. Peri-colonic fat stranding and multifocal regional nodules and lymph nodes were identified. Multiple peritoneal deposits were seen, and the largest deposit was seen along the mesenteric margin, measuring 4.9×3 cm. There was no definitive involvement of adjacent structures. There were innumerable hypovascular ring-enhancing hepatic masses scattered in both lobes involving all liver segments, and the largest was located at segment 4b, measuring 8.1 cm. There was also necrotic lymphadenopathy seen at the gastrohepatic ligament. The lungs were clear, with no suspicious pulmonary nodules (Figure 1A, 1B). A full colonoscopy showed circumferential wall thickening, from which a biopsy was taken, and stenting over the area of the thickening secondary to the tumor was done (Figure 2A, 2B).

Histopathological examination of the descending colon biopsy demonstrated dual morphologies in which a predominant component comprised of tumor cells arranged in nested, organoid, and rosette-like growth patterns with a focal area of solid sheet associated with brisk mitotic activity estimated at 30 mitotic figures per 10 high-powered fields (Figure 3A). The second minor component (30%) exhibited intermingled malignant glandular structures morphologically consistent with adenocarcinoma (Figure 3B). The predominant component was diffusely positive for Pancytokeratin (AE1/AE3) and Synaptophysin and negative for Chromogranin immunohistochemical stains, whereas adenocarcinoma was negative for the neuroendocrine markers (Figure 3C, 3D). The Ki-67 proliferative index in neuroendocrine carcinoma is estimated at more than 90% by manual quantitative assessment (Figure 3E). The diagnosis was compatible with mixed poorly differentiated neuroendocrine carcinoma of large cell type and adenocarcinoma.

The patient was therefore diagnosed with metastatic poorly differentiated MANEC of the colon, which was deemed unresectable. It had metastasized to the liver with multiple peritoneal deposits based on radiological and histopathological findings. The patient was referred to the medical oncology department, where he received a total of 9 cycles of cisplatin and etoposide. The CT scan showed a good response to chemotherapy, with regression of the primary tumor, liver, and bony metastasis. However, he later developed right retinal vein thrombosis. The patient is currently following up with his medical oncologist for further chemotherapy.

Discussion

Owing to the dual histological origin of MANEC, its clinical behavior is different from that of adenocarcinoma or neuroendocrine carcinoma [19]. Since these tumors present with

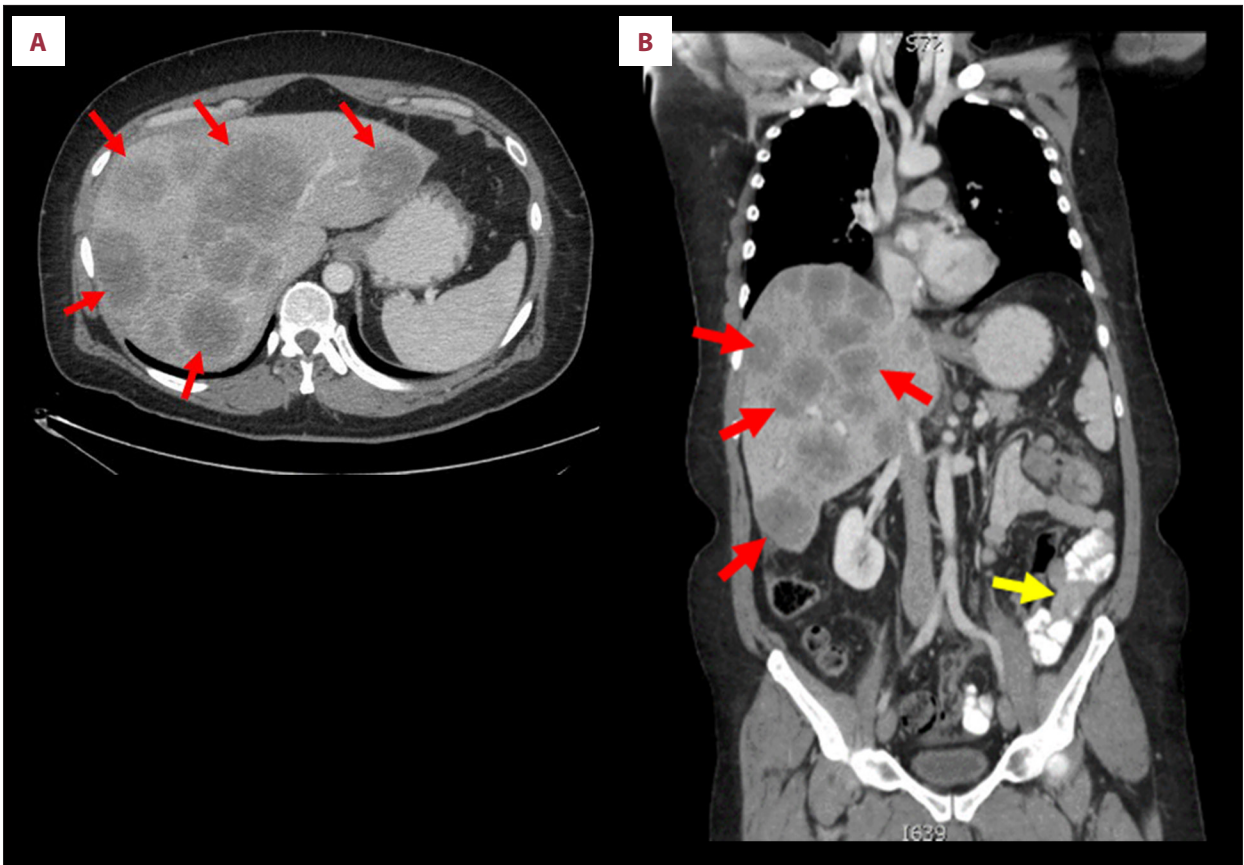


Figure 1. CT of chest, abdomen, and pelvis in (A) an axial cut and (B) in a coronal cut showing circumferential descending colon wall thickening (yellow arrow) and innumerable hypovascular ring-enhancing hepatic masses scattered in both lobes involving all liver segments (red arrows).

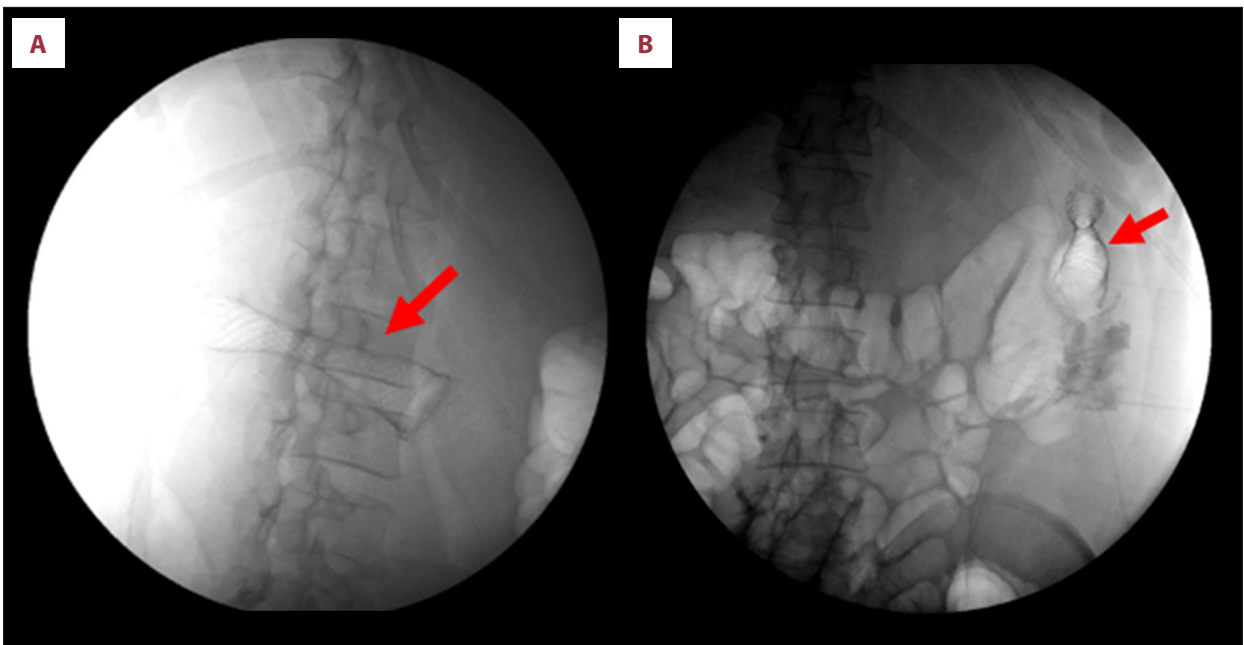


Figure 2. (A, B) X-ray post-endoscopic stenting of the site of colonic wall thickening (red arrows).

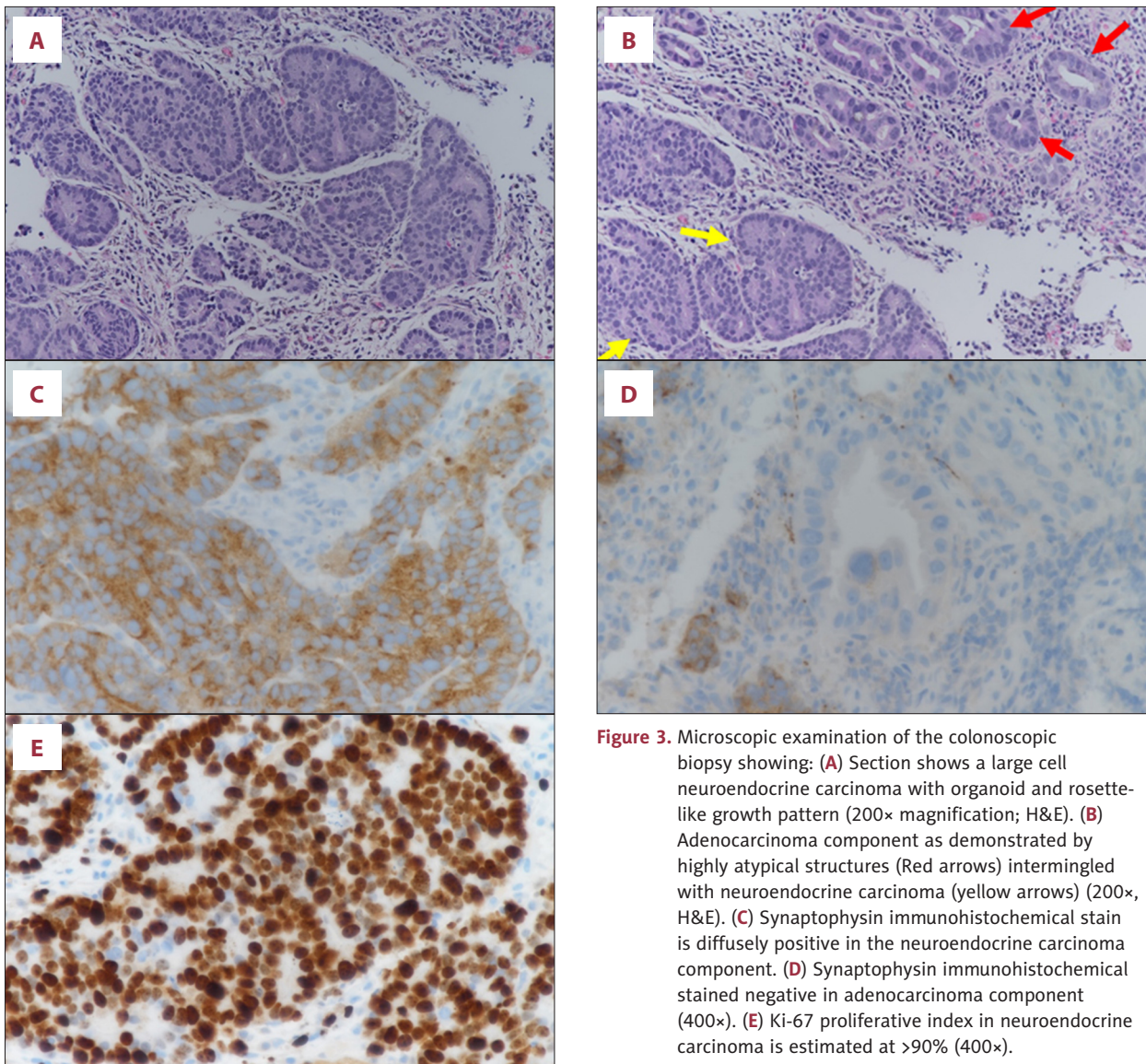


Figure 3. Microscopic examination of the colonoscopic biopsy showing: **(A)** Section shows a large cell neuroendocrine carcinoma with organoid and rosette-like growth pattern (200× magnification; H&E). **(B)** Adenocarcinoma component as demonstrated by highly atypical structures (Red arrows) intermingled with neuroendocrine carcinoma (yellow arrows) (200×, H&E). **(C)** Synaptophysin immunohistochemical stain is diffusely positive in the neuroendocrine carcinoma component. **(D)** Synaptophysin immunohistochemical stained negative in adenocarcinoma component (400×). **(E)** Ki-67 proliferative index in neuroendocrine carcinoma is estimated at >90% (400×).

nonspecific symptoms, they are usually found incidentally [20]. MANEC typically presents at advanced stages, acting as an aggressive tumor. Endoscopically, it appears semicircular with deep ulceration or as a fungating tumor occupying the lumen. However, it is often difficult to distinguish from colorectal adenocarcinoma based on endoscopic appearance alone due to their structural similarity [19]. Therefore, it is crucial that biopsies be obtained for histopathological examination and immunohistochemical staining to diagnose and grade the pathology [20]. The WHO recommends that each histological component be graded separately [3,21]. Furthermore, the European Neuroendocrine Tumor Society (ENETS) guidelines recommend a few immunohistochemical neuroendocrine markers, such as Synaptophysin and Chromogranin A [3] and CDX2, for the diagnosis of colorectal adenocarcinoma [22]. For staging, the National Comprehensive Cancer Network (NCCN)

recommends multiphase technique CT or MRI with i.v. contrast of the chest, abdomen, and pelvis as baseline imaging for patients suspected to have distant metastases, with a sensitivity of 66% to 96.3%. Intestinal neuroendocrine tumors most commonly metastasize to regional/mesenteric lymph nodes, the liver and bone [23]. F-fluorodeoxyglucose positron emission tomography is another modality for the detection of nodal involvement with neuroendocrine tumors, but its sensitivity in colorectal adenocarcinoma and neuroendocrine tumors is considered low, at 42.9% and 33%, respectively [19]. In our patient, a CT scan with i.v. contrast of the abdomen revealed innumerable bilobular hepatic lesions involving all liver segments and large peritoneal deposits.

It is proposed that in most MANEC cases, only one histologic component metastasizes. Hence, a biopsy of distant metastasis

should be performed before starting systemic treatment [19,24]. Biopsies of metastatic sites may not reveal both tumor components and may deceptively lead to a diagnosis of pure neuroendocrine carcinoma or adenocarcinoma [24]. Since the colon biopsy in our patient was predominantly large cell neuroendocrine carcinoma, which is notorious for its aggressiveness and high metastatic potential [20], it is very likely to be the culprit of the hepatic lesions, although no biopsy was collected from the liver to confirm this. Wang et al demonstrated a relationship between the size of the primary tumor and the presence of metastatic lesions, regardless of whether the metastasis is to lymph nodes or to distant organs, with primary tumors of more than 2 cm being 2 times more likely to have metastatic lesions [25].

Somatostatin receptor scintigraphy is also effective for the detection of the neuroendocrine carcinoma component in target lesions. It was reported that 69% of high-grade neuroendocrine tumors exhibit positive somatostatin receptor (SSTR) scintigraphy findings [19].

Due to the rarity of this complex neoplasm and the continuous revision of its treatment in the literature, managing patients with MANEC remains inconsistent and dependent on therapeutic regimens used for neuroendocrine carcinoma and adenocarcinomas [20]. The clinical practice guidelines of the ENETS recommend that the management of MANEC should follow the standard of care for pure grade III neuroendocrine carcinoma since it is the most commonly poorly differentiated and predominant component of MANEC, both in primary tumors and distant metastases. Moreover, other authors suggested treating the most aggressive component of MANEC, which is the most poorly differentiated component of the lesion, regardless of whether it is the neuroendocrine or exocrine component. Interestingly, recent molecular and genetic studies on MANEC have discovered shared molecular vulnerabilities between the 2 components, suggesting a potential role for targeted treatments against both components and overcoming the long-standing issue of their differential sensitivity to chemotherapy and or chemo-radiotherapy [24]. However, the NCCN guidelines state that the only curative option is a complete surgical resection of both the primary tumor and metastases. Unfortunately, the majority of patients diagnosed with colorectal cancer have unresectable metastatic liver disease. Those with liver-limited unresectable disease where critical structures are involved are increasingly considered for neoadjuvant chemotherapy in an attempt to regress the metastatic lesions and convert them to a resectable status. However, if there are many metastatic sites, it becomes unlikely to achieve R0 resection simply on the basis of a favorable response to chemotherapy [26]. Due to the bilobular hepatic involvement and multiple peritoneal deposits, the present case was deemed unresectable. This is because the probability that chemotherapy alone will completely

eradicate metastatic deposits is quite low. Such cases should be regarded as having unresectable disease that is not amenable to conversion therapy, as in this patient.

Since MANEC is a rapidly progressive and highly proliferative tumor, the prognosis is generally considered to be poor compared to that of patients with colorectal carcinoma. The 1-year survival rate is 58-76% and the median survival time for patients with liver metastasis is 7.5 months [27]. Colorectal MANECs appear to be aggressive, as 67% of patients in a large case series of appendicular and colonic MANECs presented at stage IV disease, and 41% had nodal metastases. The overall survival in this group was found to be less than that of pure neuroendocrine tumors at a median of 9 months [28]. In addition, a prospective analysis was conducted on the 9 patients diagnosed with MANEC of the colon and rectum and reported by the National Cancer Institute in Lithuania over a 10-year period. Five of these patients had distant metastases. Six patients underwent R0 resection and 6 underwent chemotherapy. The results demonstrated poor survival, as 4 patients (44%) died after a median follow-up of 12.5 months [29].

Ulcerative colitis and Crohn's disease are recognized for their predisposition to colorectal adenocarcinoma. The anatomic extent and duration of disease are considered independent risk factors for the development of colorectal cancer [30,31]. Adenocarcinoma is considered the most common colorectal epithelial malignancy associated with ulcerative colitis. As for non-epithelial malignancies, lymphomas and sarcomas represent the largest group of tumors reported in association with inflammatory bowel disease (IBD), especially in immunosuppressed patients. However, neuroendocrine tumors other than carcinoids may also be associated with IBD, although they are infrequently described in this setting. Two cases were reported of patients aged 35 and 77 years, with a disease duration of 11 years and 27 years, respectively. The first patient underwent surgical resection and followed by chemotherapy with cisplatin and etoposide and radiotherapy, then developed multiple liver metastases 1 year after surgery and died 15 months after diagnosis. The other patient was scheduled to receive neoadjuvant therapy. Both neuroendocrine tumors in these patients arose in the mild left-sided ulcerative colitis, but the patients differed in age and disease duration, which raises the question of whether these carcinomas are incidental in the background of IBD or if there is a real, yet rare, association between IBD and these tumors [30]. The pathophysiology proposed involves multipotent stem cells with bidirectional differentiation, but the exact mechanism for the development of this neoplasm in the setting of IBD is still not clear [20].

Conclusions

Although it is rare, MANEC is a complex neoplasm that requires a high index of suspicion to diagnose. It typically presents with nonspecific symptoms and may be found incidentally. The diagnosis is confirmed through histopathological examination and immunohistochemical staining after biopsy collection. Imaging is performed to stage the disease and localize the sites of metastases since most cases present at advanced stages. The only curative option is complete surgical resection of both the primary and metastatic lesion. Unfortunately, however, the majority of cases have unresectable liver disease. In such cases, neoadjuvant therapy may be tried to regress the tumor to a resectable status; but if there are many metastatic lesions, the patient is usually referred for palliative care. There is still no clear correlation between MANEC and ulcerative colitis.

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Conflicts of interest

None.