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MANEC TUMOR OF RECTUM. A RARE CASE SERIES OF 3 PATIENTS AND A LITERATURE REVIEW

The term Mixed Adeno-Neuro-Endocrine Carcinoma (MANEC) was introduced in 2010 by the WHO Classification of Tumors of the Digestive System. It refers to a neoplasm with dual epithelial and neuroendocrine differentiation, each component representing at least 30% of the tumor. It is an uncommon tumor accounting for < 3% of all colon and rectum malignancies. We report three cases of this extremely rare MANEC of the rectum. All three cases presented with hematochezia, variable constipation, and abdominal pain. They were diagnosed and staged appropriately with colonoscopy, biopsy with immunohistochemistry, and imaging. They underwent an anterior resection with circular stapled anastomoses. Because of the low incidence of this histotype, we reviewed the clinical presentation, diagnostic characteristics, and treatment of MANEC of the colon and rectum.

Keywords: MANEC, rectum, adenocarcinoma, neuroendocrine carcinoma, colonoscopy.

The first description of a gastrointestinal tumor with exocrine and neuroendocrine components was published by Cordier in 1924 [1]. Since then, several cases have been reported under many different names including composite carcinoid, mucin-producing carcinoid, argentaffin cell adenocarcinoma, goblet cell carcinoid, adenocarcinoid, small cell undifferentiated carcinoma, and so on. The use of all these different names led to considerable confusion among clinicians, surgeons, gastroenterologists, and pathologists. In the 2000 WHO classification of endocrine tumors, such neoplasms were defined as mixed exocrine-endocrine tumors when each component represents at least 30% of the lesion [2]. The term mixed adenoneuroendocrine carcinoma (MANEC) was introduced by the World Health Organization in 2010 referring to a neoplasm with dual adenocarcinomatous and neuroendocrine differentiation, each component representing at least 30% of the tumor [3]. The diagnosis is mainly based on the tumor architecture, along with immunostaining/immunohistochemistry (IHC) using specific neuroendocrine and

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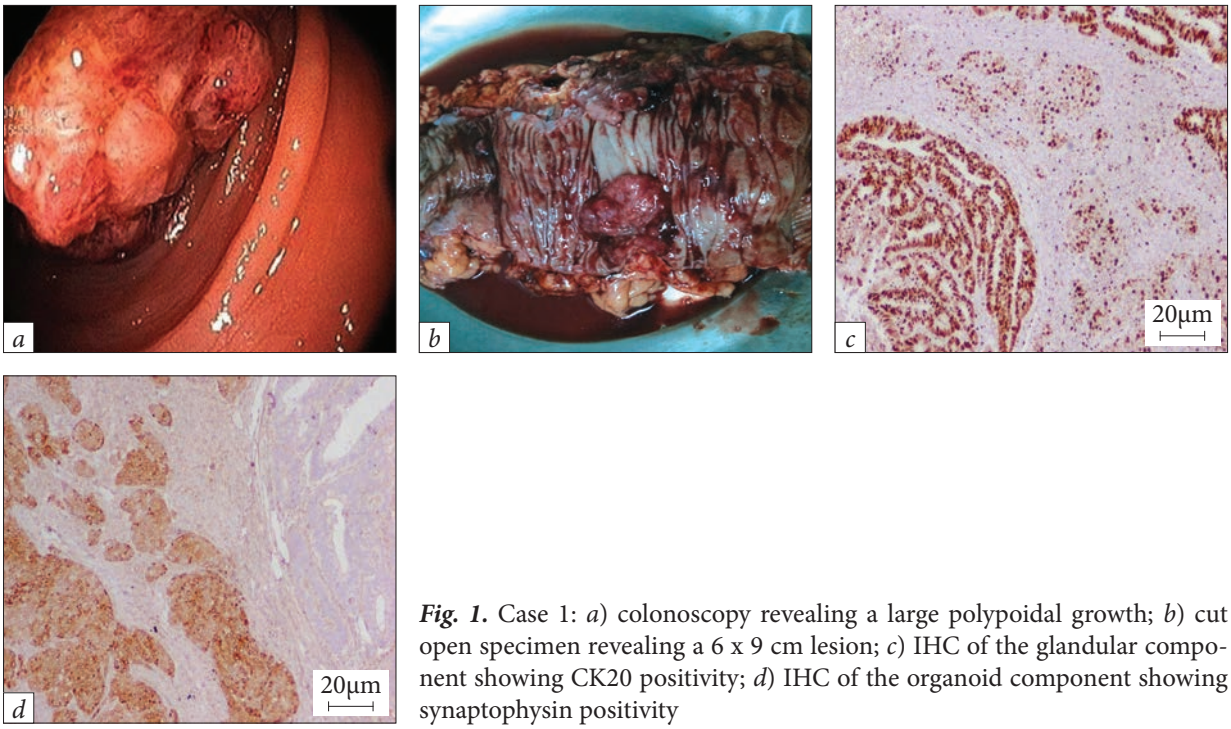

Fig. 1. Case 1: *a*) colonoscopy revealing a large polypoidal growth; *b*) cut open specimen revealing a 6 x 9 cm lesion; *c*) IHC of the glandular component showing CK20 positivity; *d*) IHC of the organoid component showing synaptophysin positivity

non-endocrine markers. MANEC has been described in several organs but is very rare [4]. We report three extremely rare cases of MANEC of the rectum and a review of the relevant literature.

Description of Cases

Case 1. A 34-year-old female presented to the surgery department with occasional constipation, abdominal pain, and hematochezia for 6 months. On physical examination, body temperature was 37.6 °C, heart rate was 88 bpm, blood pressure was 130/84 mmHg, and abdominal and digital rectal examinations were normal. A colonoscopy revealed a large polypoidal growth in the distal part of the sigmoid colon and rectosigmoid junction (Fig. 1, *a*). Multiple biopsies were taken from the lesion and histopathological examinations showed a moderately differentiated adenocarcinoma. The serum carcinoembryonic antigen (CEA) assay was 5.02 ng/ml. After appropriate staging with a CECT scan, the patient underwent a high anterior resection with regional lymph node dissection. A gross examination of the surgical specimen showed a 6 × 9 cm polypoidal tumor at the rectosigmoid region (Fig. 1, *b*). The final histopathological examination confirmed a high-grade MANEC diagnosis, with a pathologic stage of pT3N0M0. On IHC, the neoplastic glandular component showed positivity for CK20 (3+, > 90%), synaptophysin (3+, 1%—2%), chromogranin (3+, 1%—2%), and negativity for CD56 and Ki-67 (Fig. 1, *c*). The proliferative index was 70%. The neoplastic cells in the organoid component demonstrated positivity for synaptophysin (2+, > 90%), chromogranin (2—3+, > 90%), and negativity for CD56, Ki-67, and CK20 (Fig. 1, *d*). The proliferative index was 40%—50%. The case was discussed in the tumor board, and regular follow-up was advised as there were no apparent metastases. The patient has been on regular follow-up for 3 years and 9 months with no evidence of recurrence.

Case 2. A 66-year-old man was referred by the medical gastroenterology team for a suspected

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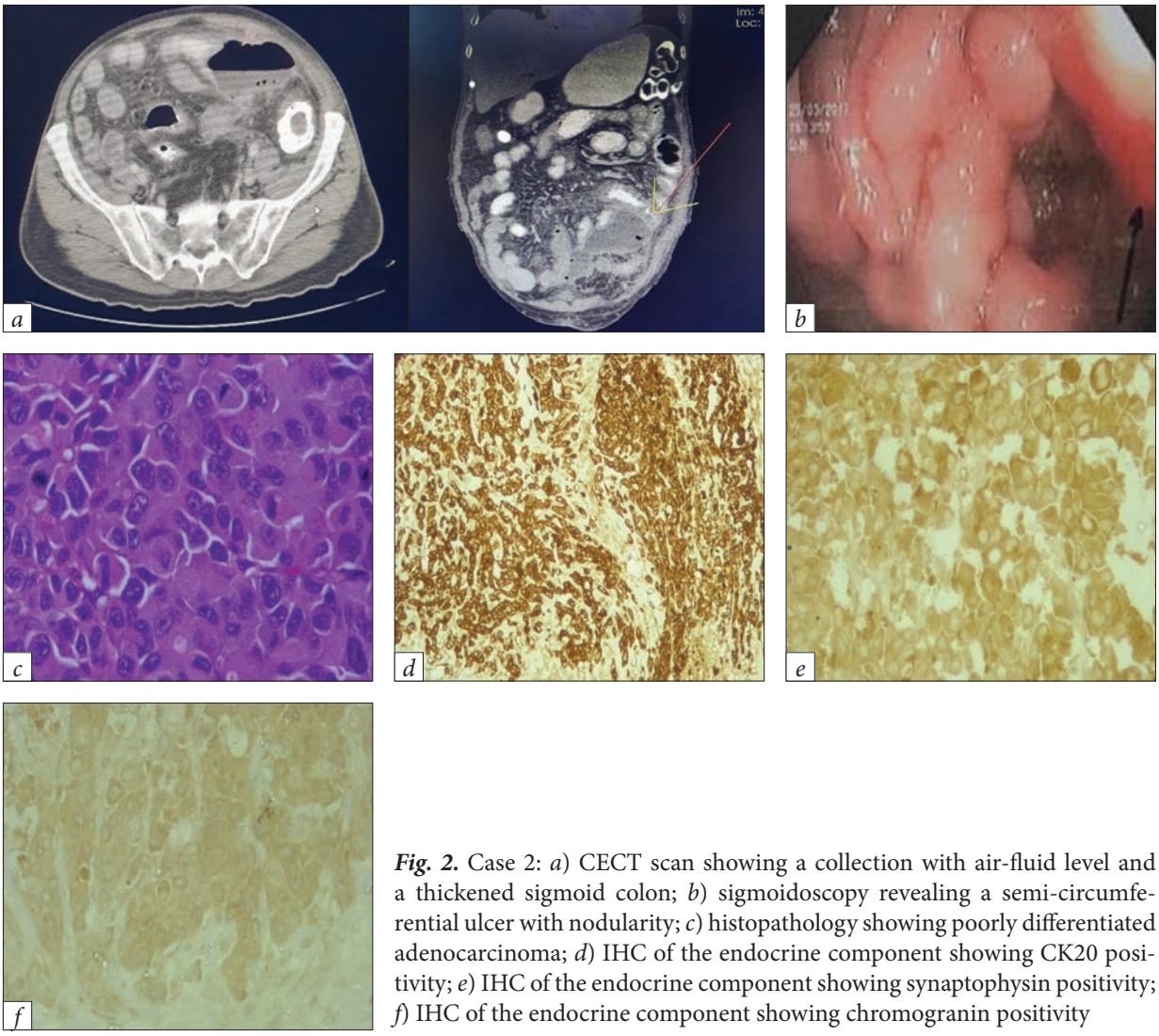

Fig. 2. Case 2: *a*) CECT scan showing a collection with air-fluid level and a thickened sigmoid colon; *b*) sigmoidoscopy revealing a semi-circumferential ulcer with nodularity; *c*) histopathology showing poorly differentiated adenocarcinoma; *d*) IHC of the endocrine component showing CK20 positivity; *e*) IHC of the endocrine component showing synaptophysin positivity; *f*) IHC of the endocrine component showing chromogranin positivity

sigmoid diverticular phlegmon treated initially conservatively. He had presented initially with constipation, lower abdominal pain, intermittent low-grade fever, and weight loss of 2 months. On physical examination, a body temperature was 38.9 °C, a heart rate of 108 bpm, and blood pressure 134/82 mmHg. The abdominal examination demonstrated local signs of peritonism and a vague tender mass in the left lumbar and iliac region. Blood reports showed a neutrophilic leucocytosis only. Contrast-enhanced computed tomography (CECT) scan showed a loculated collection with an internal air-fluid level (Fig. 2, *a*) measuring 11 × 4 × 4 cm in the left lumbar region along with a long segment thickening of the distal sigmoid colon suspecting a sealed-off sigmoid diverticular perforation (Fig. 2, *a*). The patient was treated with antibiotics and an interventional radiologist pigtailed the collection, following which he improved significantly. On close follow-up, the resolution of the mass was not as expected! So he underwent a sigmoidoscopy, which revealed a semi-circumferential ulcer with nodularity in the rectosigmoid region, and was biopsied (Fig. 2, *b*). Histopathological examinations revealed a poorly differentiated

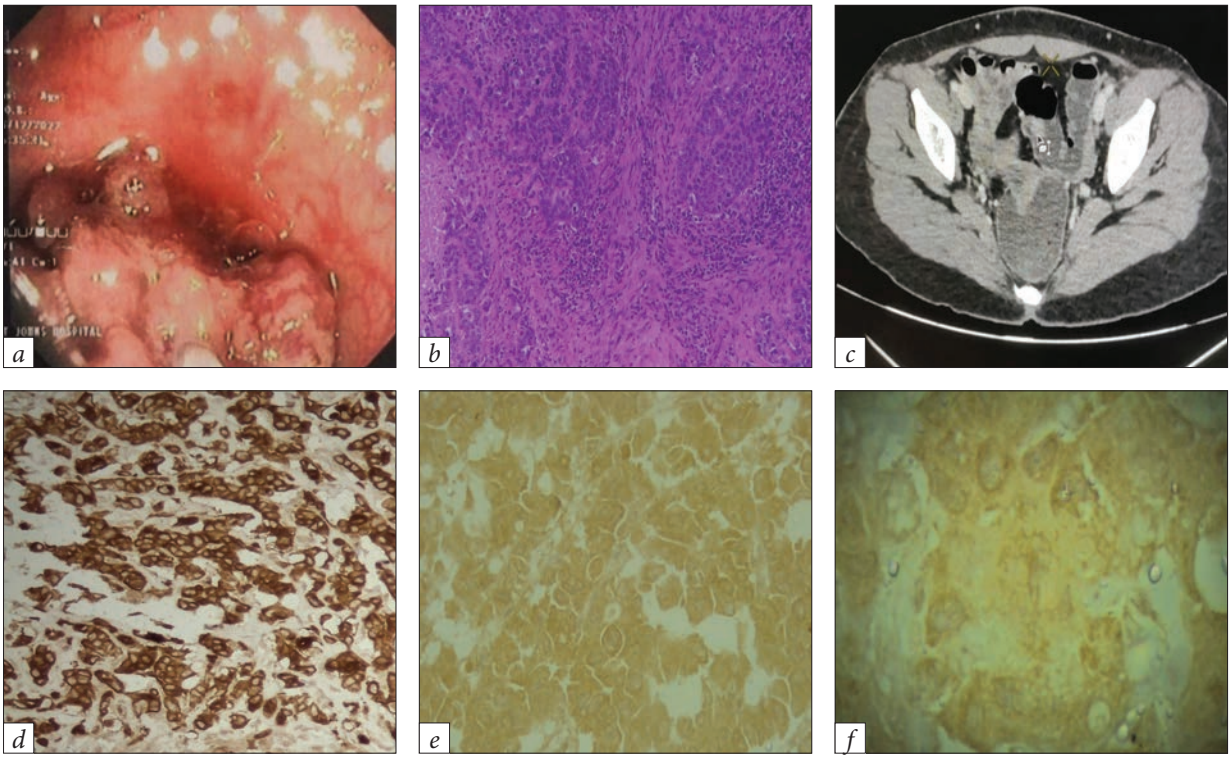

Fig. 3. Case 3: *a*) colonoscopy revealing a large sessile polyp in the recto-sigmoid region of the colon; *b*) final histopathology showing poorly differentiated adenocarcinoma; *c*) CECT scan showing a polypoidal lesion with post-contrast enhancement at the rectosigmoid region of the colon; *d*) IHC of the neuroendocrine component showing CK20 positivity; *e*) IHC of the neuroendocrine component showing synaptophysin positivity; *f*) IHC of the neuroendocrine component showing chromogranin positivity

adenocarcinoma (Fig. 2, *c*). The CEA level was 18.65 ng/ml. The patient underwent a high anterior resection with regional lymph node dissection. On IHC, the neoplastic cells showed diffuse positivity for CK20 (3+, > 20%, Fig. 2, *d*), synaptophysin (3+, 3%—5%, Fig. 2, *e*), chromogranin (3+, 4%—5%, Fig. 2, *f*), CD56 was equivocal, Ki-67 and CDX2 were not contributory. The final immunoprofile demonstrated a poorly differentiated adenocarcinoma with > 30% neuroendocrine component consistent with a diagnosis of MANEC, with a pathologic stage of pT3N2bM0. The case was discussed at the tumor board and was advised adjuvant chemotherapy. The patient underwent a FOLFOX4 regimen, unfortunately, during the 9th cycle, he developed severe neutropenic sepsis and succumbed.

Case 3. A 24-year-old female presented to the surgery clinic with intermittent hematochezia for 2 months. On physical examination, a body temperature was 37.4 °C, a heart rate of 80 bpm, and a blood pressure of 124/74 mm Hg. Abdominal, digital rectal, and proctoscopy examination was normal. A colonoscopy revealed a large 5 × 5.5 cm sessile polyp in the recto-sigmoid junction (Fig. 3, *a*), and multiple biopsies were taken. Histopathological examinations demonstrated a moderate well-differentiated adenocarcinoma and fragments revealing areas of low to high-grade dysplasia (Fig. 3, *b*). The serum carcinoembryonic antigen (CEA) level was 8 ng/ml. A staging CECT scan showed a loco-regional disease only (Fig. 3, *c*). She underwent a laparoscopic high anterior resection with regional

lymph node dissection. The final histopathological examination confirmed a poorly differentiated adenocarcinoma with a pathologic stage of pT2N0M0. IHC showed positivity for CK20 in 30% (Fig. 3, *d*), synaptophysin (Fig. 3, *e*), chromogranin (Fig. 3, *f*), and negativity for CD56 and CDX2. The proliferative index was 45%. The final diagnosis was MANEC. Our case was discussed at the tumor board, and, as it was an early disease, a regular follow-up was advised. This patient had a follow-up of 2 years and 5 months with no evidence of recurrence.

Discussion

Mixed adenoneuroendocrine carcinomas (MANEC) are rare tumors found in the gastrointestinal tract, especially the stomach, and even rarer in the colon and rectum. It was first described by Cordier in 1924 [1]. Neoplasms with dual adenocarcinomatous and neuroendocrine differentiation, each component representing ≥ 30% of the tumor, were referred to as MANEC [3]. The actual incidence of MANEC has not been well documented, and they account for < 3% of all colorectal tumors. They are commonly seen in the 5th or 6th decade of life with an M : F ratio of 1.5 : 1 [5]. Large series have not been reported to date, so further research is warranted. Indeed, the systematic application of immunohistochemical techniques to the study of gastrointestinal tumors has demonstrated that neuroendocrine cells occur rather frequently in non-endocrine neoplasms. Similarly, the presence of an exocrine component in gastrointestinal neuroendocrine neoplasms, especially in high-grade neuroendocrine carcinomas, has also been widely documented. There is a wide spectrum of such combinations of exocrine and neuroendocrine components, ranging from adenomas or carcinomas with interspersed neuroendocrine cells on the one end to classical neuroendocrine tumors with a focal exocrine component on the other end [6, 7]. MANEC has 2 distinct types: collision (side-by-side pattern) and composite (intermingled). Gastrointestinal MANECs can be stratified into prognostic categories based on the grade of malignancy of each component.

The MANEC can have a diverse range of clinical presentations. It can be clinically occult and difficult to diagnose [8] or highly aggressive with a high risk for distant metastases [9]. It is still unclear whether the glandular or the neuroendocrine component is the primary factor driving disease progression and metastases [5, 10]. However, some reports suggest that the neuroendocrine component drives the clinical behavior [11] while others have revealed that the exocrine component does [12]. MANEC composed of large neuroendocrine cells has better survival and clinical behavior compared to patients with non-large neuroendocrine cells (small-to-intermediate or mixed large-to-intermediate cells) [13]. Independent of the proportion of the neuroendocrine component, the associated carcinoid syndrome has not yet been reported in the literature; the serum level of tumor markers such as CEA, CA125, and CA19-9 are also normal [11]. However, identification of the neuroendocrine component in tubular adenocarcinomas is not easily performed because the neuroendocrine cells are not always immunoreactive for specific markers, with the reported rate of positivity being 60%—70% for chromogranin, 75%—90% for synaptophysin, and 50% for CD56 [11, 14, 15]. Diagnosis is mainly based on the tumor architecture, being completed by the immunostaining with specific neuroendocrine markers such as chromogranin, synaptophysin, CD56, and neuron-specific enolase (NSE), combined with the markers on non-endocrine differentiation such as keratin 7 (for gastric tumors) and keratin 20, CDX2, and carcinoembryonic antigen (CEA), respectively, for colorectal segments. The European Neuroendocrine Tumor Society's guidelines recommend 2 of 3 commonly used immunohistochemical neuroendocrine markers, such as chromogranin A (CgA), synaptophysin (Syn),

and CD56, should be positive to substantiate the neuroendocrine differentiation of MANEC [16]. Due to the rarity of this tumor, few aspects are known about its histogenesis, with most of the authors admitting its origin in a multipotent stem cell with bidirectional differentiation, opposite to collision tumors, in which a separate origin of the two components is supposed [11, 15, 17]. Because the poorly differentiated areas can also display positivity for synaptophysin in colorectal carcinomas [18], we tend to believe that it is not about a real multidirectional differentiation of a single neoplasm but rather a neuroendocrine phenotype of dedifferentiated areas of tubular adenocarcinoma. Clarifying this hypothesis could help identify the proper therapeutic management of these rare and highly malignant tumors, either as pure adenocarcinomas or neuroendocrine tumors.

The main modality in the treatment of MANEC is surgery with an R0 resection [19]. Following this adjuvant treatment with specific chemotherapy based on the histology (adenocarcinoma vs. neuroendocrine load) and staging should be considered due to their aggressive nature. This helps to reduce their recurrence and improves survival. However, specific guidelines have not been suggested by the National Comprehensive Cancer Network's guidelines for MANEC [19]. In our case series, one patient died following chemotherapy due to neutropenic sepsis and the other two patients did not receive chemotherapy due to their early stage. The overall survival rates of MANEC are poor compared to adenocarcinoma [13, 20].

The current literature on MANEC has limitations as most of the studies are case reports and series. Due to the rarity and unusual presentation, there are shortcomings in the data on large series. As a result, the conclusions on the optimal strategy for managing MANEC are variable and controversial. Therefore, it is crucial to gather more evidence on this disease and its management.

Tumor heterogeneity is a major challenge in oncology. MANEC of the rectum has a very common presentation with hematochezia along with non-specific imaging features. Therefore, histopathological examination with immune profile markers specific to neuroendocrine differentiation is necessary to confirm the diagnosis. This will enable an optimum multimodality treatment of these highly aggressive and rare tumors.

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Conflict of interest

None declared.

Consent for publication

Obtained from patients and next of kin as applicable.

Authors' contributions

All authors have contributed responsibility to this case report. ShG: data acquisition, interpretation, analysis, drafting of the article, final drafting, and approval of the manuscript. RG: data acquisition, drafting of the article, and approval of the manuscript. CP: a critical review of intellectual content, final drafting, and approval of the manuscript. SG: article design, critical review for intellectual content, final drafting, and approval of the manuscript.

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ПУХЛИНИ MANEC ПРЯМОЇ КИШКИ. СЕРІЯ РІДКІСНИХ ВИПАДКІВ У ТРЬОХ ХВОРИХ З ОГЛЯДОМ ЛІТЕРАТУРИ

Термін змішана аденонейроендокринна пухлина (MANEC) було запроваджено в 2010 р. у класифікації ВООЗ пухлин травної системи для новоутворень, що характеризуються двоспрямованим, епітеліальним та нейроендокринним, диференціюванням, причому кожний компонент складає щонайменше 30% пухлини. Це рідкісне новоутворення: на нього припадає менш ніж 3% всіх злоякісних пухлин товстої та прямої кишки. У повідомленні розглянуто три випадки вкрай рідкісної MANEC прямої кишки. В усіх випадках враховували наявність крові в калі, закрепи різного ступеню та біль у животі. Для діагностики та визначення стадії захворювання проводили колоноскопію, виконували біопсію з наступним імуногістохімічним дослідженням, а також застосовували методи візуалізації. Хворим проводили передню резекцію з циркулярним скобковим анастомозом. Зважаючи на низьку частоту таких випадків, ми наводимо стислий огляд літератури з даними клінічної та діагностичної характеристики цього захворювання та його лікування.

Ключові слова: MANEC, пряма кишка, аденокарцинома, нейроендокринна карцинома, колоноскопія.