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Case Report

Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms of the Rectum: A Case Report

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Keywords

Mixed neuroendocrine-non-neuroendocrine neoplasms · Mixed epithelial endocrine neoplasms · Case report · Colorectal cancer

Abstract

Introduction: Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) represent roughly 1–2% of all colorectal malignancies. Given the rareness and heterogeneity of these mixed tumors, recognition and accurate diagnosis remain a challenge. In the absence of established guidelines, they are treated according to the standard of care for pure neuroendocrine carcinomas or adenocarcinomas from similar sites of origin. ***Case Presentation:*** We herein report a case of a rectal MiNEN in a 55-year-old male. He underwent colonoscopy for rectal bleeding and mucus emission, which revealed a vegetating lesion located approximately 8 cm from the anal verge, corresponding to a moderately differentiated low-grade adenocarcinoma of the rectum. Computed tomography scan and magnetic resonance imaging uncovered the presence of lung, lymph node, and subcutaneous implant metastases. The biopsy of the cutaneous implant showed neuroendocrine carcinoma Ki-67 90%. The patient underwent systemic chemotherapy. ***Conclusion:*** High-grade MiNEN tumors are the most commonly encountered in clinical practice and have an aggressive biological behavior. Little is known about the genetic drivers of this neoplasm and its pathogenesis remains controversial. Clinical and pathological awareness of this rare entity is a key step to design future targeted therapies and improve treatment options. The aim of this case report is to further our understanding regarding the clinical presentation, radiological features, pathology, management, and prognosis of MiNEN.

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Introduction

The term mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) was re-defined by the World Health Organization (WHO) in 2017 as the association of two types of components, a non-neuroendocrine (NNE) component and neuroendocrine (NE) tumor; each of them must account for at least 30% of the entire neoplasm and both components should be malignant. It must be underlined that this cutoff has been arbitrarily chosen. However, in the WHO classification of digestive tumors, no minimum percentage of either component has been specified in the definition of MiNENs [1].

Despite being described in all organs, mixed neoplasms have been better characterized in the digestive system, where they are called mixed adenoneuroendocrine carcinomas (MANECs). This terminology has not been accepted for mixed neoplasms originating from other sites [2].

Adenocarcinoma (ADC) is the non-NE component reported in over 90% of cases [3]. The NE component may be either a neuroendocrine carcinoma (NEC) or a neuroendocrine tumor (NET).

The NE component is classified according to the WHO 2019 classification of NETs into grades based on the differentiation and Ki-67 proliferative index [4]: Grade 1 tumors <3%; grade 2 between 3% and 20%; and grade 3 >20% (Table 1). Grade 3 NETs often have a Ki-67 index <60%, while the indices for NECs are typically >50–60%.

MiNEN has been classified into three grades (high, intermediate and low) according to the prognosis. High-grade MiNEN are the most common cases [5], combining NEC with ADC or adenoma. NEC is usually the most aggressive component.

Mixed tumors of the colon and rectum are frequently diagnosed incidentally. They account for about 1–2% of all colorectal malignancies according to the reported literature. Rectal MiNENs affect males most commonly (63.1%), and adults with a mean age of 61,9 years. Even though no risk factors have been identified, inflammatory bowel disease has been reported in association with MiNEN [6]. Molecular findings demonstrate that the NE and NNE components show an overlapping molecular background suggesting a monoclonal origin from a common precursor progenitor cell, and express generally as composite tumors [7, 8].

The prognosis of gastrointestinal high-grade MiNENs depends on the stage and type of neoplastic components, but usually seems to be indiscernible to that of NECs, meaning that the NEC component is the cornerstone of the prognosis [1]. Ki-67 may have a prognostic role when evaluated in the NE component of this high-grade MiNEN. In MANEC cases in which the NE component showed Ki-67 <55%, there was a better prognosis than with higher Ki-67 [9].

A study demonstrated that gastroenteropancreatic NECs and MANECs, in which the NE component is composed by NEC, which are associated with microsatellite instability (MSI), show better prognosis than neoplasms with a stable phenotype. In this way, MSI may be a valuable prognostic tool [10]. Nevertheless, for rectal NETs, a multiparametric approach evaluating Ki-67 with tumor size, lymphatic and vascular invasion, level of wall infiltration, and immunophenotype may be the best aid in identifying patients at higher risk of metastasis and tumor-related death [11].

Herein, we report a 55-year-old male case of a rectal MiNEN and reveal the challenges faced in managing this unique tumor. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538384).

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Table 1. Proposed grading of MiNENs

Grades	Neuroendocrine component	NEN component
Low	Well-differentiated NETs Grade 1: Ki-67 <3, MI <2/10HPF Grade 2: Ki-67 3-20, MI 2-20/10HPF	Adenoma
Intermediate	Well-differentiated NETs Grade 1: Ki-67 <3, MI <2 Grade 2: Ki-67 3-20, MI 2-20	ADC, mucinous carcinoma, signet ring cell carcinoma
High	Poorly differentiated NEC (small/large cell) Grade 3: Ki-67 >20 Anaplastic/undifferentiated	Adenoma, ADC, squamous cell carcinoma, adenosquamous carcinoma, mucinous carcinoma, signet ring cell carcinoma

Adapted from "Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs" WHO 2019 and Jacob et al. [4].

HPF, high-power field; MI, mitotic index; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

Case Report

A 55-year-old male presented with a medical history of typhoid fever at the age of 12 years and no surgical history of note. There was no relevant oncological family history. The patient reported occasional alcoholic habits and denied smoking and drug use. His usual medication consisted of vitamin D and B.

The patient presented to gastroenterology consultation with rectal bleeding and mucus emission in large quantities and, subsequently, increased frequency of intestinal transit, tape stools, and tenesmus. Anorectal exam was unremarkable, excluding hemorrhoids and anal fissures as a cause of bleeding. Fecal occult blood test was positive, and a colonoscopy was performed, revealing a voluminous vegetating lesion located approximately 8 cm from the anal verge. The histological report showed a moderately differentiated low-grade ADC of the rectum, with MLH1, MSH2, MSH6, and PMS2 expressions. KRAS mutation c.38G>A p.(Gly13Asp) was detected. Laboratory data ruled out anemia. The serum levels of tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9) were within normal ranges (CA 19–9 28.6 U/mL; CEA 0.7 ng/mL).

Computed tomography (CT) demonstrated several pulmonary micronodules, a right epiphrenic adenopathy, multiple necrotic subcutaneous nodules in proximity to the left semilunar line, along the anterior margin of the rectus abdominis and the oblique muscles of the abdominal wall with 33 mm, on the opposite side with 12 mm and adjacent to the right gluteus major muscle with 10 mm. Pelvic magnetic resonance imaging (MRI) depicted a large tumor involving the upper two thirds of the rectum starting 8.7 cm from the anal margin and extending over 6.2 cm. The lesion had an extramural necrotic component invading the mesorectal fascia. In the upper rectal lymphatic chain, at least one adenopathy was observed, measuring 15 × 7 mm. In the inferior mesenteric lymph node chain, small ganglia were identified. A cutaneous implant biopsy was performed and was compatible with NEC Ki-67 90%, positive for CK7 and synaptophysin and negative for CK 20, CDX2 and chromogranin; the scarcity of material did not allow further studies.

The patient presented at consultation with ECOG performance status 1 and mentioned 3 to 4 stools per day with decreased caliber and new skin implants for 2 weeks. On observation, three cutaneous implants were denoted: first implant in the left flank with a 3 cm diameter; second implant >1 cm; third implant in the right flank with a 2 cm diameter; no additional findings on physical examination.

Due to clinical presentation and after multidisciplinary team (MDT) discussion, the assumed diagnosis was 1 tumor with both ADC and NE components, presenting as an ADC of the middle/upper rectum with neuroendocrine differentiation, with Ki-67 of 90%, stage IV, due to cutaneous and probable lung and lymph node metastasis. Positron emission tomography-18F-fluorodeoxyglucose (PET-FDG) revealed hypermetabolism at the level of rectal neoplasia, probable superior right lateral-tracheal and aortic/pre-vertebral adenopathy at D12 level, pulmonary, hepatic and node/implant metastases next to the right psoas muscle and bilateral subcutaneous lesions in the abdominopelvic wall (shown in Fig. 1).

After MDT discussion, first-line chemotherapy (CHT) with cisplatin and etoposide was started. There was a clinical and imaging response with an overall decrease in subcutaneous implants, and a partial response was assumed. Therefore, he proceeded CHT, with hematologic toxicity (Grade 2 Neutropenia, according to Common Terminology Criteria for Adverse Events [CTCAE] v5.0), and was supported with granulocyte-colony stimulating factor. CHT was completed after 8 cycles, with a progression-free survival of a month and a half.

Two months after resuming CHT, he presented at an oncology consultation with neuropathic pain radiating from the left hip to the ipsilateral thigh for the last 15 days. A second CT was performed, revealing a new lytic lesion with cortical disruption in the L1 vertebral body, with a soft tissue mass in the left psoas muscle, new lung micronodular opacities, and volumetric reduction of several known lesions. MRI of the neuraxis did not identify an evident intracanal component or adjacent foraminal obliteration. The patient was admitted to a medical ward for pain control with corticotherapy and radiotherapy (total of 29.4 Gy [6 fractions of 4.9 Gy]). Biopsy of a bone lesion was performed to unravel which component was progressing. Metastasis of ADC was confirmed with CK20 and CDX2 expression, compatible with the rectal origin of the neoplasm. FoundationOne®Liquid CDx was performed and gene alterations in *KRAS* G13D (which favored resistance to cetuximab and panitumumab), *APC* E1306, R554, *FBXW7* R465H, *RB1* splice site 1420_1421 + 30del32, *SMARCA4* R973Q, and *TP53* C135F were revealed; Blood Tumor Mutational Burden – 6 Muts/Mb; elevated tumor fraction and MSI-high were not detected.

The patient started a second line of CHT with FOLFIRI. He repeated CT which showed rectal lesion progression with stability of other lesions and partial vertebral fractures of L3 and L4. Vertebroplasty was performed. Rectal biopsy was performed again, confirming the diagnosis of MiNEN, consisting of components of moderately differentiated ADC and NEC (synaptophysin + and Ki-67~70%) (shown in Fig. 2, 3, respectively).

Regarding the pain and rectal bleeding, the patient was submitted to palliative radiotherapy with 36 Gy (1 fraction of 8 Gy followed by 25 Gy: 5 fractions 5 Gy/day). After MDT, a colostomy was made due to a rectovesical fistulous tract. Due to disease progression and worsened performance status (ECOG PS-2), with a platinum-free interval of six and a half months, third-line therapy with weekly carboplatin and paclitaxel was initiated.

Bone pain worsened and disseminated cutaneous lesions appeared in the trunk, upper and lower limbs, some of them painful, as seen in Figure 4. Another neuraxis MRI was done: a recent fracture underlying L1 stood out, as well as new somatic collapses from L5, D8 to D11 and extensive metastasis of anterior and posterior paraspinal soft tissues.

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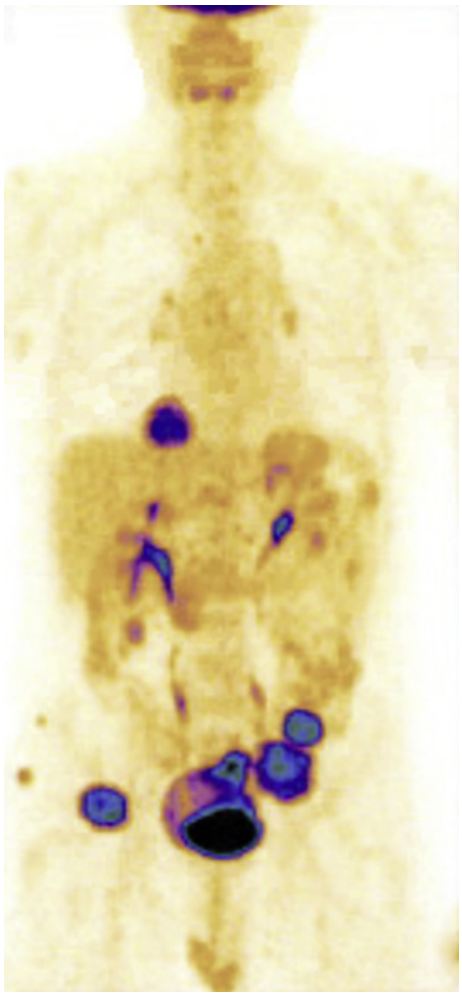

Fig. 1. PET-FDG scan.

The patient underwent another vertebroplasty and pain therapy optimization with palliative care team support. The clinical status deteriorated during hospitalization and he eventually died.

Discussion

This case report depicts a case of a rare neoplasm: rectal MiNEN. The definition of MiNEN neoplasms has been a matter of debate for a long time and different terms have been used. It is a conceptual term, not an entity and both NE and NNE components can show variable morphological features.

Depending on their components, MiNEN can be separated into different prognostic groups. According to several case reports, lymph node metastasis, distant metastasis, greater proportion of NE to non-NE component, and clinical stage III/IV were associated with poor prognosis [12].

The liver is the most common site of metastasis followed by the lung and distant lymph nodes [13]. The difficulty in managing MiNEN relies on it being a distinctive subgroup of NE neoplasms with limited treatment options and lack of standardized guidelines due to paucity of clinical trials.

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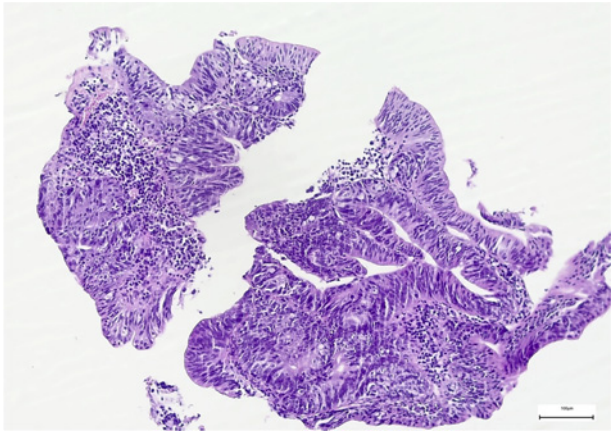

Fig. 2. ADC component: carcinoma forming glands, with complex architecture and fusion of glands, and scattered inflammatory cells. H&E, ×10.

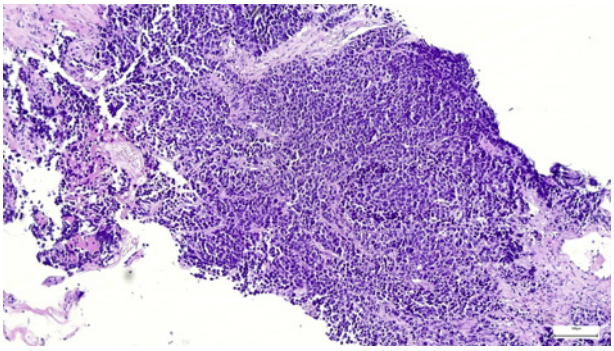

Fig. 3. Neuroendocrine component: sheets and sometimes vaguely organoid structures of small neoplastic cells with hyperchromasia and apoptotic bodies. H&E, ×10.

Surgery and adjuvant CHT should be considered in treating localized digestive MiNEN. The management of metastatic disease is controversial and should be based on the predominant histological component or address the more aggressive component within the tumor. MiNEN prognosis and management are generally based on the latter [14]. In such manner, the first-line treatment of metastatic disease may vary between platinum/etoposide and fluoropyrimidines in combination with oxaliplatin or irinotecan, depending on whether a NEC regimen or an ADC regimen is preferred, respectively [15]. In this case, CHT regimen of choice for NEC driven tumors with etoposide and cisplatin was started as first-line therapy. The most widely used NE markers are chromogranin A, synaptophysin, and CD56, while ADCs express carcinoembryonic antigen (CEA), CA 19–9, cytokeratins 7, 19, and AE 1/3 [16].

FDA has approved CA19-9 as a biomarker in routine management in pancreatic cancer but not in colorectal cancer (CRC) since its prognostic value remains controversial [17]. However, studies have suggested CA19-9 as an additional marker to determine the prognosis of CRC patients without elevated preoperative CEA [18]. As depicted in Graphic 1, the rising of CA19-9 level during first-line therapy was consistent with the ADC component progression.

There is no established second-line therapy, but FOLFIRI, FOLFOX, CAPTEM ± bevacizumab may be considered [19]. According to ESMO Guidelines, both FOLFIRI and FOLFOX are considered to be equally effective in the first-line treatment for unresectable metastatic colorectal cancer [20]. Taking everything into consideration, after ADC component progression, second-line therapy with FOLFIRI without bevacizumab, due to rectovesical fistulous tract, was started.

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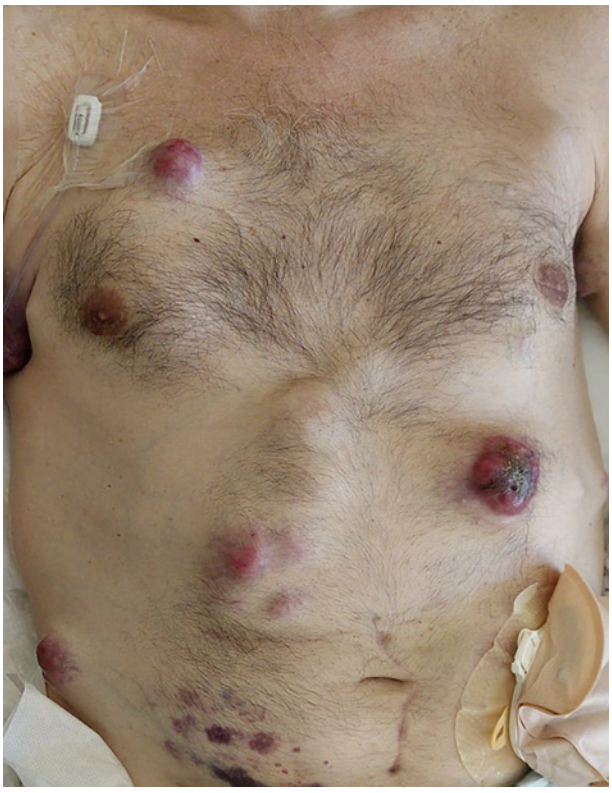

Fig. 4. Cutaneous metastasis.

The NE component's Ki-67 index likely determines the natural history of the disease; therefore, treatment should be generally directed at this component if it is high grade. In the first biopsy of the NE component, Ki-67 was 90%, which could be related with the aggressive nature of the MiNEN.

This case is an example of the challenge of treating a rare and aggressive neoplasm in a young patient. Moreover, it depicts the importance of palliative care in advanced disease management, in which the median overall survival is 11 months, such as local palliation of rectal symptoms with radiotherapy [21].

Based on studies, TP53 is the most common mutation in MiNEN, KRAS was detected in 11.9% of colorectal MiNEN, while the BRAF V600E mutation was found in 3.2% [22, 23]. Targeted therapeutic agents should be used in patients with advanced or metastatic MiNEN, taking into consideration the limited treatment options and potential benefit [4]. These may be considered after CHT. The better comprehension of these mixed carcinomas may lead to an improved understanding of other aspects of clonality in cancer [24].

Statement of Ethics

This study protocol was reviewed and approved by Comissão de Ética para a Saúde, from Centro Hospitalar Universitário de Lisboa Central, approval number 1455/2023. Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Filipa Verdasca made substantial contributions to the conception and design of the work and took the lead in drafting the article. Rita Ferreira contributed to the review of the writing. Inês Guerreiro played a crucial role in the review process, providing valuable input and suggestions and, additionally, participated in the drafting of the manuscript, demonstrating a commitment to its intellectual content. Ricardo Luz played a crucial role in the review process. Alexandra Montenegro, José Mendes, Ivánia Furtado, Rui Escaleira, Válter Fernandes, and Marta Seladas focused on reading and ensuring the integrity of the final version. Miguel Cristovão played a role in the accuracy of histopathologic descriptions and literature revision. Filipa Verdasca, Rita Ferreira, Inês Guerreiro, Ricardo Luz, Alexandra Montenegro, José Mendes, Ivánia Furtado, Rui Escaleira, Válter Fernandes, Marta Seladas, and Miguel Cristovão provided final approval of the version to be published and have agreed to be accountable for all aspects of the work, ensuring the accuracy and integrity of the entire manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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