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CASE REPORT CRSLS

Mixed Adeno-Neuroendocrine Neoplasms: Two Cases, One Institution

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ABSTRACT

Epithelial tumors with neuroendocrine and nonendocrine components constitute the rare yet aggressive entity of neoplasms of the gastro-entero-pancreatic tract. These tumors were first named "mixed adeno-neuroendocrine carcinomas" (MANECs) by the World Health Organization in 2010 and in 2017 renamed "mixed neuroendocrine non-neuroendocrine neoplasms" (MiNENs). Combined adenocarcinoma and neuroendocrine carcinoma neoplasms are a rare occurrence within the gastrointestinal tract. In this report, we describe two separate cases of mixed rectal adeno-neuroendocrine carcinomas and their treatment. We describe two cases at one institution of mixed neuroendocrine non-neuroendocrine rectal neoplasms. Given the rarity of diagnosis and inconsistencies in both nomenclature and treatment recommendations in the literature, mixed adeno-neuroendocrine carcinoma epidemiology and prognosis are not yet fully understood. Future prospective trials with a focus in management of MiNENs will offer valuable insight into these rare mixed carcinomas.

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INTRODUCTION

Combined adenocarcinoma and neuroendocrine carcinoma neoplasms are a rare occurrence within the gastrointestinal tract. They are particularly aggressive neoplasms with confusing nomenclature and inconsistent recommendations for treatment. In this report, we describe two separate cases of mixed rectal adeno-neuroendocrine carcinomas.

Case Descriptions

The first patient, a 47-year-old female with a past medical history of uterine fibroids and hyperlipidemia, presented to the gastrointestinal service with new complaints of bright red blood per rectum with cramping relieved with defecation. She underwent a colonoscopy demonstrating medium internal hemorrhoids, multiple sessile and pedunculated polyps diffusely throughout the large intestine measuring between 10 to 15 mm in size, and a 3-cm ulcerated mass in the proximal rectum approximately 12 cm from the anus. Specimen from her colonoscopy resulted as adenomatous colonic mucosa with high-grade dysplasia and foci suspicious for carcinoma (**Figure 1**).

Positron emission tomography/computed tomography (PET/CT) was completed for staging which demonstrated hypermetabolic activity within the high rectal neoplasm with associated right ovarian involvement. Two liver nodules were noted: a 5.2-cm nodule in segment 5 of the liver and a 3.8-cm nodule in segment 6. CT chest and magnetic resonance (MR) image of the abdomen and pelvis were later performed confirming metastasis to two liver segments without chest involvement and small perirectal lymph node. Thus, her staging was denoted a clinical stage 4 adenocarcinoma diagnosis (T4, N1, M1). Liver biopsy of the two nodules seen on PET/CT was performed and demonstrated high grade

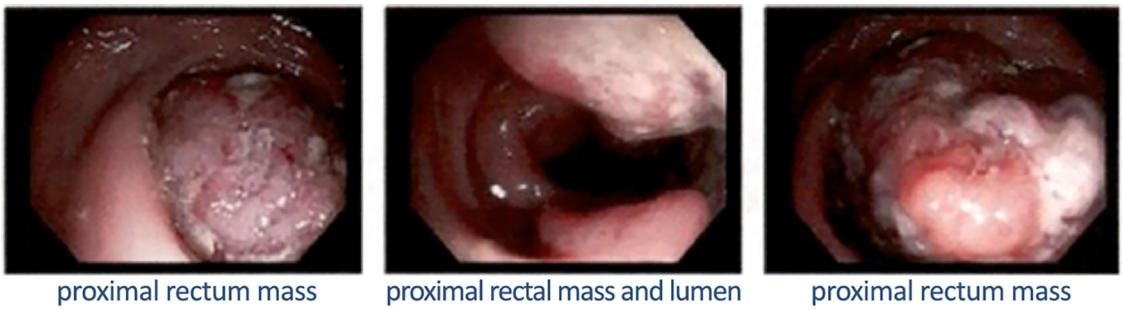

Figure 1. Rectal mass seen on colonoscopy.

neuroendocrine carcinoma. Pre-operative carcinoembryonic antigen test was normal at 1.5.

The patient completed eight rounds of 5-fluorouracil and oxaliplatin (FOLFOX) chemotherapy pre-operatively with significant tumor size reduction. She underwent an exploratory laparotomy with total abdominal hysterectomy, bilateral salpingo-oopherectomy, low anterior resection and hepatic lobectomies of segments 5 and 6. Subsequent pathology revealed benign findings of the uterus, cervix, bilateral fallopian tubes and ovaries. Liver specimen demonstrated high grade neuroendocrine carcinoma in addition to cavernous hemangioma. Specimen obtained from the rectosigmoid junction also demonstrated a 5.5-cm mass of high-grade neuroendocrine carcinoma with dissection mucin pools suggestive of treated adenocarcinoma. Two of six lymph nodes were positive and resection margins of the recto-sigmoid mass were negative. She returned six months after her index operation with a new abdominal wall nodule with biopsy confirming high grade neuroendocrine carcinoma. Her case was discussed by the multidisciplinary tumor board and she was started on folinic acid, fluorouracil, and irinotecan (FOLFIRI) and bevacizumab for her rectal cancer recurrence.

The second patient, a 69-year-old male with medical history significant for hypertension and diverticulitis, presented to his primary care physician for an annual check-up. He was noted to have a prostate-specific antigen (PSA) level of 146 ng/mL. He was asymptomatic except for a slow urinary stream at night and nocturia two to three times nightly. He denied any weight loss, appetite loss, and change in bowel habits or hematochezia. Given the elevated PSA, he underwent a prostate biopsy demonstrating a Gleason score of 7 and adenocarcinoma in 3% of the right and left bases. Screening colonoscopy was performed, revealing a midrectal polyp with moderately to poorly differentiated invasive adenocarcinoma and focal neuroendocrine differentiation. Pelvic MR imaging noted T3N+ rectal cancer of midrectum approximately 4.6 cm in length with clear colorectal margins and no sphincter involvement. A prostate tumor was also noted in the right posterior base along with osseous metastasis in the right iliac bone, acetabulum and right inferior pubic ramus. PET scan confirmed hypermetabolic uptake in the rectal mass, mesorectal lymph nodes, prostate and pelvic bones (**Figure 2**).

Ultimate staging revealed stage IV adenocarcinoma of the prostate (T3, Nx, M1) and stage 3 (T3, N+Mx) adenocarcinoma with focal neuroendocrine diagnosis of the rectum. Colonoscopy biopsies of the rectal mass revealed invasive adenocarcinoma with focal neuroendocrine differentiation arising in a tubulovillous adenoma. The tumor was synaptophysin positive and chromogranin negative.

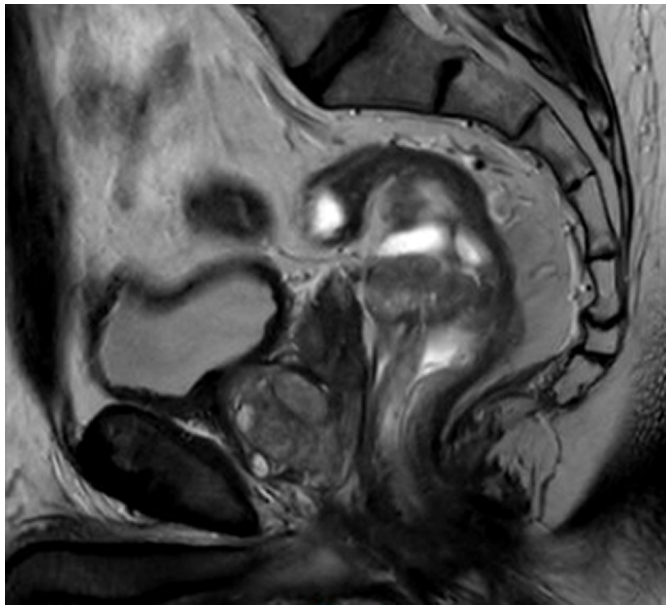

Figure 2. Sagittal view of rectal tumor on magnetic resonance imaging.

The patient underwent a robotic-assisted low anterior resection with laparoscopic assistance and a liver biopsy due to concern for diffuse metastasis in the liver. Liver biopsy revealed metastatic adenocarcinoma with neuroendocrine differentiation consistent with metastasis from primary rectal carcinoma. The resected portion of colon solely revealed a sessile tubulovillous adenoma of the rectum with focal high-grade dysplasia status post neoadjuvant chemo-radiation (FOLFOX), without adenocarcinoma or neuroendocrine involvement. However, 4 of 14 lymph nodes were positive for metastatic adenocarcinoma with neuroendocrine differentiation. The pathologic staging post treatment was T0, N2a, M1a.

The patient subsequently began androgen deprivation therapy along with a course of FOLFOX chemotherapy. This was followed with capecitabine and concurrent prostate and rectal radiation. He unfortunately died two years after diagnosis due to his disease progress.

DISCUSSION

Epithelial tumors with neuroendocrine and nonendocrine components constitute the rare yet aggressive entity of neoplasms of the gastro-entero-pancreatic tract (GEP). These tumors, termed "mixed neuroendocrine non-neuroendocrine neoplasms" (MiNENs) by the World Health Organization, consist of both neuro-endocrine and exocrine histology.[1,2] Per the definition, both the adenocarcinoma and neuroendocrine components of the tumors must each represent at least 30% of the tumor make-up and each must be malignant in nature.

The most extensive retrospective study in literature was performed by Friezzerio by analyzing data from five European Centers from January 1, 2010 to August 31, 2019. They reported that the incidence of MiNENs was said to be below 0.01/100,000 cases per annum.[3] Tissue biopsy, via formal surgical resection, is essential for diagnosis to quantitatively define the neuroendocrine and non-neuroendocrine components. Moreover, immunohistochemical analysis is typically leveraged.[4]

The aggressive behavior and poor survival outcome of MiNEN are attributed to the neuro-endocrine component of neoplasm, while adenocarcinoma is the most common secondary component.[4] The European Neuroendocrine Tumor Society (ENETS) clinical practice guidelines recommend that pure, grade 3 neuroendocrine carcinoma (NEC) should guide the management of MANEC, since the neuroendocrine component in MANEC is the most poorly differentiated and predominant. This is evident in both the primary tumors and in distant metastatic sites. Alternatively, when the exocrine component is the dominant or least differentiated histology, some clinicians recommend adopting treatment guidelines for adenocarcinomas from the same site of origin.[4]

Secondary to the rarity of diagnosis, the limited published data, and inconsistent terminology, the epidemiology, standardized management guidelines, and prognosis for MiNENs remain unknown. Friezzerio et al. reported the median overall survival of affected patients varies across the retrospective series, ranging between 10 to 78 months.[3] Proposed treatment guidelines for MiNENs are based on the tumor stage and whether or not the neoplasm is primary or recurrent.[4] If an adeno-neuroendocrine carcinoma is localized and resectable, then curative surgery is always preferred. Treatment therapy should be guided by the most dominant and aggressive histological component. Evidence for support of neoadjuvant chemotherapy in the treatment of MiNENs is limited. Neoadjuvant chemotherapy can be offered for MiNENs in an attempt to target the adenocarcinoma component of the tumor, likely more frequently considered in tumors comprised of a larger adenocarcinoma component. However, the use of neoadjuvant chemotherapy to prevent or delay relapse of the neuroendocrine component of MiNENs is not currently supported by data. When both components are equally represented and aggressive in the tumor, treatment is selected based on the pure neuroendocrine component which is the driving force of metastatic behavior. If a patient develops advanced recurrent disease after the initial curative treatment, the patient should be restaged by performing a tissue biopsy and relevant imaging. Currently, literature advocates for adjuvant chemotherapy after surgical excision in most colorectal MiNENs to reduce relapse and recurrence.[5]

Moving forward, prospective trials will be invaluable for establishing a more standardized approach to the management of MiNENs. Given the rarity of diagnosis and inconsistencies in both nomenclature and treatment recommendations evident in the literature, mixed adeno-neuroendocrine carcinoma epidemiology and prognosis is not yet fully understood. Future prospective trials with a focus in management of MiNENs will offer invaluable insight into these rare mixed carcinomas.

References:

1. Bosman FT. *WHO classification of tumours of the digestive system.* 4th ed. *Vol.* 3. Lyon, France: International Agency for Research on Cancer, 2010.

2. Cree IA. *WHO classification of tumours of the digestive system.* 5th ed. Lyon, France: International Agency for Research on Cancer, 2019.

3. Frizziero M, Wang X, Chakrabarty B, et al. Retrospective study on mixed neuroendocrine non-neuroendocrine neoplasms from five European centres. *World J Gastroenterol.* 2019;25(39):5991–6005.

4. La Rosa S, Sessa F, Uccella S. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs): unifying the concept of a heterogeneous group of Neoplasms. *Endocr Pathol.* 2016;27(4):284–311.

5. Paspala A, Machairas N, Prodromidou A, et al. Manage-ment of manec of the colon and rectum: a comprehensive review of the literature. *Mol Clin Oncol.* 2018;9(2):219–222.