

Mixed adenoneuroendocrine carcinoma: case report

Carcinoma adenoneuroendocrino mixto: reporte de caso

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Abstract

Introducción: Mixed adenoneuroendocrine carcinoma is a rare tumor of the gastrointestinal tract with double differentiation into adenomatous and neuroendocrine carcinoma, each component with at least 30%. **Case report:** A 60-year-old female with acute abdominal pain. Surgical treatment was decided, finding a tumor at the level of the cecum and ascending colon, a right hemicolectomy and ileostomy were performed. **Discussion:** Mixed adenoneuroendocrine carcinoma can appear in various organs. They are highly malignant tumors, with a high risk of metastasis. **Conclusions:** These tumors do not present symptoms or specific radiological or laboratory findings; diagnosis depends on postoperative histopathological and immunohistochemical studies.

Keywords: Mixed adenoneuroendocrine carcinoma. Adenocarcinomatous differentiation. Neuroendocrine differentiation. Colorectal cancer.

Resumen

Introducción: El carcinoma adenoneuroendocrino mixto es un tumor raro del tracto gastrointestinal con doble diferenciación en carcinoma adenomatoso y neuroendocrino, cada componente con al menos el 30%. **Caso clínico:** Mujer de 60 años con cuadro de dolor abdominal agudo. Se decide tratamiento quirúrgico, encontrando un tumor a nivel de ciego y colon ascendente, y se realizan hemicolectomía derecha e ileostomía. **Discusión:** El carcinoma adenoneuroendocrino mixto puede aparecer en diversos órganos. Son tumores muy malignos, con alto riesgo de metástasis. **Conclusiones:** Estos tumores no presentan síntomas ni hallazgos radiológicos o de laboratorio específicos; el diagnóstico depende de estudios histopatológicos e inmunohistoquímicos posoperatorios.

Palabras clave: Carcinoma adenoneuroendocrino mixto. Diferenciación adenocarcinomatosa. Diferenciación neuroendocrina. Cáncer colorrectal.

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Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare GI tract tumor with dual adenocarcinomatous and neuroendocrine differentiation, with each component representing at least 30% of the tumor¹. Although rare, these tumors exhibit aggressive behavior and generally indicate a poor prognosis. Standardizing treatment for MANECs has historically been challenging due to a lack of diagnostic histological classification. Due to its rarity, current treatment recommendations for mixed adenoneuroendocrine carcinoma are based on limited data and generally follow guidelines for treating adenocarcinomas and neuroendocrine neoplasms². Uncertainty about the efficacy of available local and systemic treatment strategies complicates management. Even patients with limited local disease have relatively short life expectancy. In 2010, the World Health Organization (WHO) formally recognized this rare condition as a specific entity for colon cancer, aiming to better specify treatment options in the future³. MANECs represent 3% up to 9.6% of all colorectal cancers, and only 8 cases in the cecum have been reported to date, making the following case exceptionally rare⁴.

We present the case of a 60-year-old woman with acute abdominal symptoms who underwent surgery for acute appendicitis and was incidentally found to have a tumor in the cecum and ascending colon, later identified by pathology as MANEC.

Case report

A 60-year-old woman with a history of type 2 diabetes mellitus and systemic arterial hypertension, with no surgical history, presented with acute colicky pain in the right hypochondrium, scoring 7/10 on the pain scale, radiating to the lower right quadrant, along with abdominal distension, nausea, and 3 episodes of vomiting with gastro-food content, without exacerbating or relieving factors. In the last 12 hours, the pain became sharp, scoring 10/10 on the pain scale, localized in the right iliac fossa. On physical examination, the patient was neurologically intact, cardiopulmonary system unremarkable, and abdomen distended due to adipose tissue, with increased peristalsis in intensity and frequency. Pain was present on palpation in the right hypochondrium and right iliac fossa; Murphy's sign was negative, McBurney's sign positive, with a palpable mass approximately 5 cm × 5 cm in the right iliac fossa, mobile, unattached to deep planes, and of firm consistency;

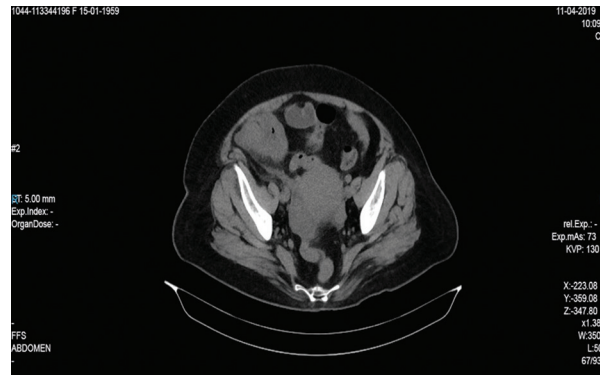


Figure 1. Simple-phase abdominal CT, axial view, showing an apparently cecum-dependent tumor (circle).



Figure 2. Simple-phase abdominal CT, transverse view, showing an apparently cecum dependent tumor (circle).

otherwise, findings were unremarkable. Lab test results: white blood cells $12.67 \times 10^3/\mu\text{L}$, hemoglobin 14.1 g/dL, hematocrit 44.2%, platelets $367 \times 10^3/\text{mm}^3$, neutrophils 82%, glucose 24.2 mg/dL, urea 32.4 mg/dL, BUN 15.0 mg/dL, creatinine 1.0 mg/dL, sodium 137.0 mmol/L, potassium 4.6 mmol/L, chloride 98.8 mmol/L, total bilirubin 0.18 mg/dL, direct bilirubin 0.44 mg/dL, indirect bilirubin 0.26 mg/dL, LDH 357 U/L, AST 15.5 U/L, ALT 10.5 U/L, alkaline phosphatase 107 U/L, CEA 2.13 ng/mL, CA-125 87.2 U/mL, and AFP 3.54 U/mL. Abdominal CT in simple phase revealed an image suggestive of complicated retrocecal acute appendicitis, with pronounced inflammatory changes and free fluid in the pelvic cavity, with nodular thickening of the cecal wall and multiple ileocecal and retroperitoneal lymph nodes (para-aortic, interaortic-caval, and retrocaval), the largest measuring 17 mm, possibly due to contiguous inflammatory process, though underlying colon lesions could not be ruled out (Figs. 1 and 2). Open surgical treatment was performed, revealing a tumor in the cecum and ascending

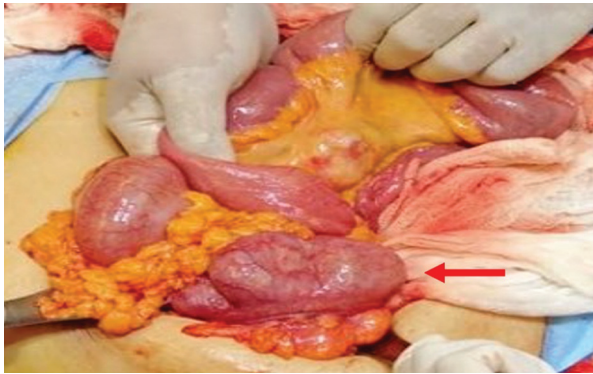


Figure 3. Tumor originating from the cecum obtained via exploratory laparotomy (arrow).



Figure 4. Surgical specimen obtained from right hemicolectomy and distal ileectomy.

colon, approximately 10 cm in size, of firm consistency, with inflammatory tissue and perforation in the mid-third, with fecal matter in the cavity, as well as an acute phase II process in the appendix. A right hemicolectomy and ileostomy were performed, and the specimen was sent for pathology. A half-inch laminar drain was placed towards the pelvic cavity, emerging in the lower right quadrant (Figs. 3 and 4).

Following surgery, the patient was sent to general surgery for 24-hour fasting, with functional ileostomy and a well-healed surgical wound. She received antibiotic therapy: metronidazole 500 mg IV every 8 hours for 14 days and ertapenem 1 g IV every 24 hours for 7 days. Oral intake was initiated and tolerated well, with output from the ileostomy. Pathology report: moderately differentiated adenocarcinoma with histological features of grade 2 moderately differentiated mixed adenoneuroendocrine carcinoma; acute, ulcerated, abscessed, transmural appendicitis in the postileal appendix (Figs. 5 and 6). Immunohistochemistry: intact MLH-1, intact MSH-6, positive CD56, positive synaptophysin, intact MSH-2,



Figure 5. Product of hemicolectomy and distal ileostomy, with postileal appendix (circle). A neoplastic lesion is visible in the ileum mucosa, ileocecal valve, and cecum.

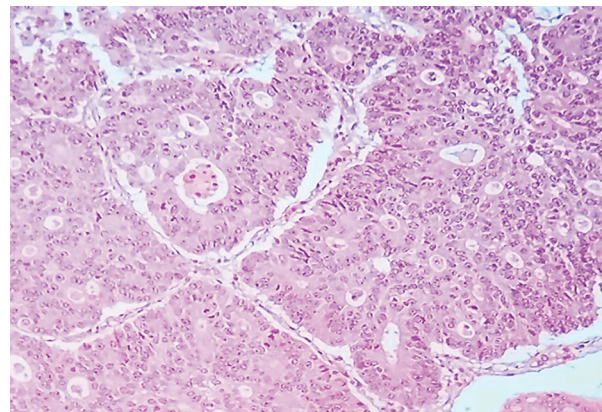


Figure 6. Neoplastic proliferation with insular pattern, suggesting neuroendocrine differentiation.

intact PMS-2, and positive chromogranin. Postoperative treatment included analgesic therapy with celecoxib 100 mg orally every 12 hours for 14 days, diclofenac 100 mg orally every 12 hours for 7 days, and prokinetic therapy with cinitapride 1 mg orally every 8 hours for 30 days. The patient was referred to medical oncology, where she is currently under follow-up and being evaluated for chemotherapy initiation.

Discussion

MANECs in the GI tract can appear in various organs, such as the esophagus, stomach, and colon, though

they are more common in the rectum⁵⁻⁷. Regardless of tumor location and stage, MANECs appear to be highly malignant tumors with a high risk of distant metastasis. Aggressiveness seems to depend on the endocrine component, regardless of its proportion². Diagnosis is primarily based on the tumor cytology and architecture, confirmed through immunostaining with specific neuroendocrine markers, such as chromogranin, synaptophysin, and CD56 (for the neuroendocrine component), along with non-endocrine differentiation markers, such as keratin 7. It remains unclear whether MANEC is biologically closer to neuroendocrine tumors or adenocarcinomas; however, it is an extremely rare tumor, with most cases presented in isolated reports⁵. These tumors did not exhibit specific symptoms, nor did radiological or lab test results reveal unique findings; thus, diagnosis relies on postoperative histopathological and immunohistochemical studies⁸. Due to its rarity, little is known about the origin and best therapeutic options. Recent WHO recommendations suggest that MANEC should be treated as an adenocarcinoma; however, recent evidence suggests that treatment should be based on the more aggressive histological component⁹. MANECs require complex management, including patient-specific chemotherapy based on the tumor histology. The only therapeutic strategy for MANEC is complete surgical resection (R0 resection) of both primary tumors and metastases. Due to its aggressive nature and high recurrence rate, adjuvant chemotherapy is critical to treatment and significantly improves survival¹⁰. MANECs consist of 2 clearly distinct components (adenocarcinomatous and neuroendocrine) that respond differently to chemotherapy. As a result, selecting appropriate chemotherapy for both the primary tumor and distant metastases remains one of the most complex and challenging aspects of treating patients with MANEC^{11,12}. In our case, the patient presented with nonspecific acute abdominal symptoms primarily related to an acute appendicular condition; however, physical examination revealed an apparently unrelated mass, and tomography identified a tumor originating from the colon, leading to surgical intervention. Histopathological analysis subsequently revealed the tumor type.

Conclusions

Due to their rarity, significant debate continues around MANEC treatment. These tumors present no specific symptoms or radiological or laboratory findings, so diagnosis relies on postoperative histopathological and immunohistochemical studies. Due to the nonspecific symptoms,

highly aggressive nature, and metastatic potential of these tumors, physicians must remain aware of MANEC in their differential diagnoses. The literature on MANEC remains limited, primarily based on isolated case reports. Clear guidelines for diagnosis, surgical management, and follow-up criteria have yet to be established.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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