



CASE REPORT

Mixed adenoneuroendocrine carcinoma (collision tumor) of the gastrointestinal tract: A case report

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Abstract

Mixed adenoneuroendocrine carcinomas (MANECs) of the colon are rare malignant neoplasms that mostly present at an advanced stage. MANECs can be classified as composite or collision tumors, but the neuroendocrine and exocrine component must both exceed 30% of the tumor mass. Collision tumors are composed of two distinct tumor components at the same site with a separate morphology and immunohistochemical pattern. The studies concerning MANECs are insufficient and the guidelines for the treatment of such tumors are lacking. We present a case of a 66-year-old female patient with a collision tumor of the sigmoid colon and metastases in the lymph nodes and liver.

Key words: Mixed adenoneuroendocrine carcinoma; collision tumor; colon; high-grade

1. Introduction

Mixed adenoneuroendocrine carcinomas (MANECs) are tumors containing glandular and neuroendocrine components. According to the World Health Organization (WHO) each component must constitute at least 30% of the tumor and be separately classified as carcinomas and graded [1,2]. The presence of neuroendocrine cells in gastrointestinal adenomas or adenocarcinomas is not rare, and can be immunohistochemically detected in up to 41% of colorectal adenocarcinomas. However, real MANECs, as defined by the WHO, are very rare and account for 3–9.6% of colorectal tumors [1-4]. MANECs are classified as collision or composite, depending on the pattern of the glandular and neuroendocrine component. Composite tumors, in which glandular and neuroendocrine cells are intermixed, are thought to arise from a single cell through multidirectional differentiation which has been confirmed by studies that showed shared genetic alterations in both components [4,5]. Collision tumors, in which both components are arranged side by side,

are traditionally believed to be biclonal and therefore considered independent tumors at the same site [2,4,6,7]. There are cases reporting lymph node metastases featuring glandular and neuroendocrine components, which puts this theory into question [2,6]. In this paper, we report a case of a 66-year-old patient with a collision tumor of the sigmoid colon with neuroendocrine metastases in two lymph nodes and the liver.

2. Case Report

A 66-year-old female presented with abdominal discomfort lasting a couple of days and blood in her stool. Medical history included a hysterectomy and adnexectomy. Abdominal exam revealed hypogastric tenderness and a post-operative scar. Abdominal ultrasound showed multiple isodense, hypodense, and hyperdense nodes (3 cm and less in diameter) in both lobes of the liver. Colonoscopy showed a tumor at the entrance of the sigmoid flexure. Histological examination of the biopsy specimen revealed high-grade epithelial dysplasia. Computed tomography showed a neoplasm up to 4.5 cm

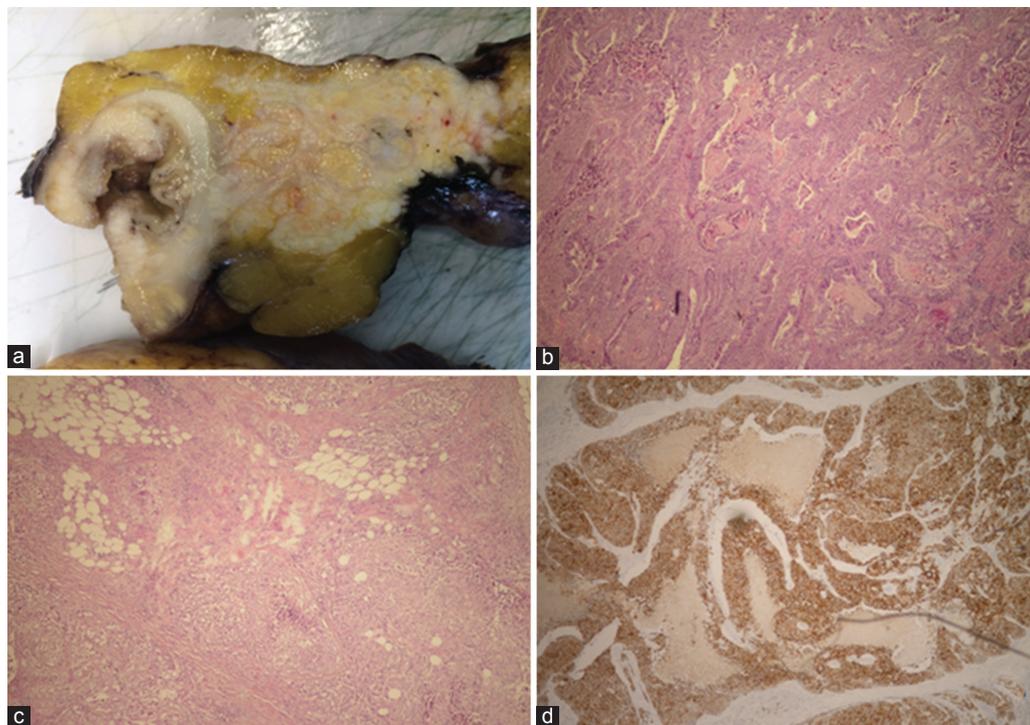


Figure 1. (a) Macroscopic findings: Cross-section of the ulcerated tumor (3.8 × 3.5 cm) and in the same location, a distinct tumor (4.5 cm) in the surrounding fatty tissue. Microscopic findings: (b) Low-grade adenocarcinoma, (c) high-grade neuroendocrine carcinoma showing solid nests and sheets of cells with abundant cytoplasm and vesicular nuclei with prominent nucleoli infiltrating the surrounding adipose tissue, and (d) immunohistochemistry for synaptophysin, positive in the neuroendocrine component

in largest diameter in the distal part of sigmoid colon spreading through the serosa and into the surrounding fatty tissue with possible metastasis in the left iliac bone and liver. Tumor markers carcinoembryonic antigen, carbohydrate antigen 15-3 (CA 15-3), and CA 19-9 were within normal range, and alpha-fetoprotein was increased (92.2 ug/L). A median laparotomy was performed and multiple metastatic nodes were found in the right and left lobes of the liver. A rectosigmoid colectomy was undertaken along with resection of the greater omentum, which adhered to the right abdominal wall. A biopsy specimen of the liver was taken.

Gross examination of the surgical specimen revealed an ulcerated tumor with raised edges (measuring 3.8 × 3.5 cm) that infiltrated the bowel wall. The tumor invaded adjacent adipose tissue measuring up to 4.5 cm (Figure 1a). In addition, two colonic polyps were found on the opposing sides of the tumor measuring 0.6 and 0.8 cm in largest diameter. Microscopic examination revealed two distinctive neoplasms with separate morphologies: An invasive, low-grade, gland forming carcinoma infiltrating the muscle wall (Figure 1b), and an invasive, and poorly differentiated high-grade NEC penetrating through the bowel wall into the surrounding fatty tissue (Figure 1c). Immunohistochemically the neuroendocrine component of the tumor was found to be strongly positive for synaptophysin (Figure 1d) and focally positive for chromogranin. The Ki-67 proliferation index was approximately 50%. Vascular and perineural invasion was found as well as numerous mitotic figures. Lymphocyte infiltration was scant. The macroscopically described polyps showed low-grade dysplasia. Cancer metastasis was found in 2 out of the 12 dissected regional lymph nodes (0.3-0.7 cm in diameter). The liver biopsy showed metastasis of the NEC. The histological and immunohistochemical findings were consistent with MANEC, collision tumor consisting of a low-grade adenocarcinoma (pT1N0M0) and high-grade NEC (pT3N1M1).

3. Discussion

Since MANECs are rare, it is difficult to predict their clinical behavior; however, it has been noticed that cases with a high-grade neuroendocrine component behave similarly to the pure high-grade NEC that are

very aggressive [2]. Even cases with a neuroendocrine component which comprises <30% of the tumor have reported metastases [2]. Some report that patients with gastrointestinal MANECs show a better survival than pure NECs, which seems to be connected to the higher stage of the pure NECs at presentation [4]. Colorectal high-grade MANECs usually present at an advanced stage with non-specific symptoms, often after they have already metastasized [3,5,7]. They can be associated with intussusception in adults as well as carcinoid syndrome; however, this has not been reported in literature [3,7-9]. They are macroscopically indistinguishable from colorectal carcinoma, and usually present as semicircular ulcerated stenotic lesions or prominent polypoid masses occupying the lumen on colonoscopy. Biopsy specimens should always be taken from different parts of the tumor to avoid misdiagnosis. The diagnosis is made microscopically on biopsy or resection specimens and confirmed by immunohistochemistry. Commonly used markers of neuroendocrine differentiation are chromogranin-A, synaptophysin, neuron-specific enolase, and CD56, of which at least two must be expressed for the tumor to be diagnosed as a high-grade MANEC [3,4]. Nevertheless, the neuroendocrine cells are not always immunoreactive for specific markers which can make diagnosis difficult [8]. Histologically, the poorly differentiated neuroendocrine component of MANEC can appear as small cell or large cell subtype, but this does not seem to be clinically relevant, unlike the mitotic count and Ki-67 proliferation index on which the WHO grading of neuroendocrine neoplasms of the gastrointestinal tract is based [1,2,8]. The other important prognostic factor, staging, depends on tumor size, invasion of the muscularis propria, lymphovascular invasion, invasion of adjacent organs, and the presence of metastases. The most common sites of metastasis are the lymph nodes and liver [2,7]. Aggressive behavior and histology of high-grade NEC are similar to small cell or large cell lung cancer so its treatment corresponds to the treatment of small cell lung cancer [3,4,8]. Curative resection is not an option for most high-grade metastatic neuroendocrine tumors of the gastrointestinal system. They show a high response rate to a combination of cisplatin (or carboplatin) and etoposide, even though the response duration is short and the overall survival is less than a year [2,5,9,10].

4. Conclusion

MANECs of the gastrointestinal tract usually have a poor prognosis due to their aggressive behavior and a high risk for metastases. Diagnosis is based on the tumor histology and confirmed by immunohistochemistry using specific neuroendocrine markers. Due to their rarity, the majority is presented as case reports, and the exact mechanism of their origin and optimal treatment strategies are not clear. It is generally believed that the more aggressive component should be taken into consideration when making decisions regarding treatment. Further research is necessary for a better understanding of these tumors and subsequently, their treatment.

Author's Contributions

BJ made the draft of the article, performed microscopic examination, acquired microscopic images. JŠ revised the draft, performed microscopic examination. IB revised the draft, acquired the data concerning patient medical history and macroscopic images. BK was involved in the conception of the case report and planning, he supervised the work and revised the draft. All authors provided critical feedback and helped shape the manuscript. All authors approve the final article.

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