



Mixed Adenoneuroendocrine Carcinoma of the Small Bowel in a Patient with Crohn's Disease: A Case Report

크론병 환자에서 발생한 소장의 혼합 신경내분비선암: 증례 보고

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Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumor of the gastrointestinal tract that has both exocrine and neuroendocrine components. There are only 5 case reports about this combined tumor in the small bowel, arose in a background of long-standing Crohn's disease. Here, we report a case of small bowel MANEC in a 54-year-old male with Crohn's disease, who presented a heterogeneous enhancing, asymmetric small bowel wall thickening with small bowel obstruction and had a difficulty in differential diagnosis before surgery.

Index terms Crohn Disease; Intestinal Neoplasms; Neuroendocrine Tumors

INTRODUCTION

Mixed adenoneuroendocrine carcinoma (MANEC) was classified by the World Health Organization (WHO) in 2010 referring to a neoplasm with dual adenocarcinomatous and neuroendocrine differentiation. It is very rare malignancy of gastrointestinal tract and several cases were reported in the pancreas, colon, gallbladder, biliary tract, stomach, ampulla, cecum and esophagogastric junction, in order of frequency (1). But, there are only few reports in the small bowel, especially in Crohn's disease patient. Here, we report a case of MANEC of the small bowel in Crohn's disease patient.

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CASE REPORT

A 54-year-old male visited to our emergency room for abdominal pain and distension for 3 weeks. He had the diagnosis of Crohn's disease for 30 years, and the surgical history of the segmental resection of ileum for bowel obstruction and primary repair for enteric fistula. Bowel sound was absent on physical examination, and simple radiograph showed ileus (Fig. 1A). On initial laboratory examination, white blood cell count was 14080/ μ L with neutrophilia of 85% and the C-reactive protein was elevated to 5.3 mg/dL.

A dynamic phase contrast-enhanced abdominopelvic computed tomography (CT) was performed. CT examination revealed an asymmetric segmental wall thickening of jejunum (Fig. 1B, C). The thickened bowel showed heterogeneous enhancement with loss of normal layered pattern, and mesenteric fat stranding. Mild proximal small bowel dilatation also showed. And there were multiple enlarged mesenteric lymph nodes with central low density (Fig. 1B) and several ill-defined low density hepatic nodules in both lobes (Fig. 1B, C). And the thickened small bowel also showed hot uptake on 18 F-fluorodeoxyglucose positron emission tomography/CT (PET/CT) with maximal standardized uptake value 13.3 (Fig. 1D). We suspected adenocarcinoma of small bowel with metastatic lymphadenopathy and hepatic metastasis. Serum carcinoembryonic antigen was elevated (203.5 ng/mL) and other tumor markers, such as alpha fetoprotein and carbohydrate antigen 19-9 were within normal range.

We performed a ultrasonography-guided core needle biopsy on hepatic nodule and the initial pathology was an adenocarcinoma, probably metastasis from the small bowel carcinoma. The patient was treated with conservative therapy and discharged for further chemotherapy of the cancer.

2 weeks later, the patient came to our emergency department again for pneumoperitoneum. An emergency operation was done. And there were several perforation sites at small bowel, so we did a segmental resection of small bowel. On microscopy, the tumor revealed a classic adenocarcinoma component with glandular growth pattern as well as a neuroendocrine component on hematoxylin and eosin stain (Fig. 1E). And the neuroendocrine proportion showed positive reaction on chromogranin and synaptophysin immunohistochemical stain, while the glands of the adenocarcinoma component stain negative (Fig. 1F). The final pathology was a MANEC of small bowel. The patient underwent a conservative treatment after the surgery but was died after 2 months.

DISCUSSION

According to the WHO classification system published in 2010, neuroendocrine tumors in the digestive system were classified as neuroendocrine tumor grade 1, neuroendocrine tumor grade 2, neuroendocrine carcinoma, and MANEC. And MANEC is defined as having combined exocrine and neuroendocrine components, where each of these components composed at least 30% of the tumor (2). Also mixed exocrine and neuroendocrine tumor can be classified by morphological patterns of the two components; combined tumors (admixed of exocrine and neuroendocrine components within a single lesion, also known as intermingled tumors), collision tumors (two components occur in separate areas of the same lesion,

without admixture), or ampicrine tumors (two components are present in the same neoplastic cell) (3). And according to this classification, our case was a combined tumor.

Crohn's disease patients have a high risk of developing large and small bowel adenocarci-

Fig. 1. A 54-year-old man with mixed adenoneuroendocrine carcinoma of the small bowel.

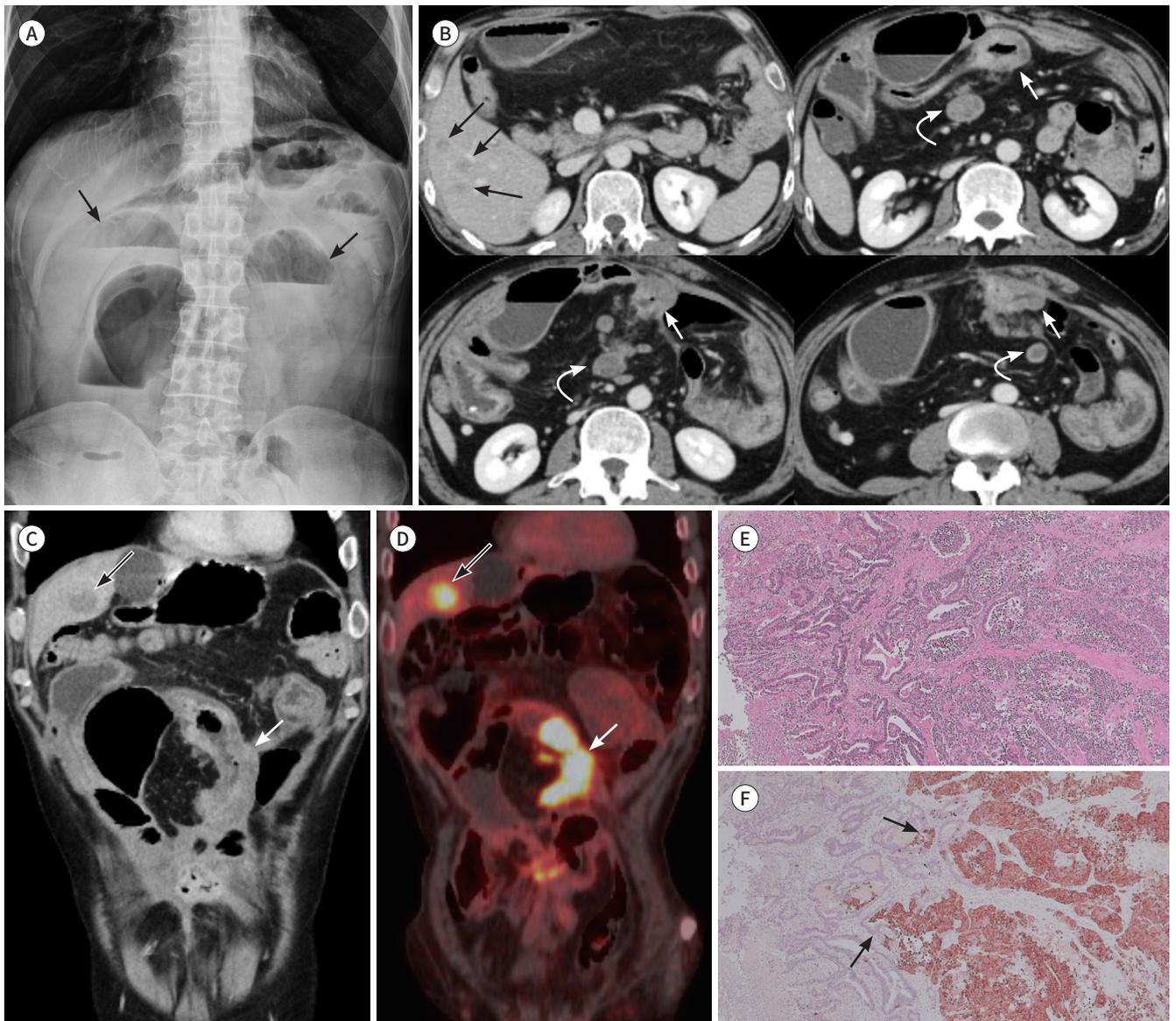
A. Simple radiograph, erect position. The radiograph shows multiple dilated small bowel loops with air-fluid levels (arrows).

B, C. Axial (**B**) and coronal (**C**) images in abdominopelvic CT. Asymmetric segmental wall thickening of small bowel is revealed in the mid-abdomen (white arrows). The thickened bowel shows heterogeneous enhancement and mesenteric fat stranding. The image also shows enlarged mesenteric lymph nodes with central low density (curved arrows) and ill-defined, low-density hepatic nodules (black arrows), suggesting metastasis.

D. PET/CT image shows increased FDG uptake in the thickened small bowel (white arrow) and hepatic nodules (black arrow) that appear on the CT scan.

E, F. Immunohistochemical staining of the tumor; H&E stain, $\times 40$ (**E**) and synaptophysin, $\times 40$ (**F**). On H&E staining, the tumor shows an adenocarcinoma component with a glandular growth pattern and a neuroendocrine component. The neuroendocrine component also shows a positive and diffuse reaction for synaptophysin (arrows). The tumor is consistent with a mixed adenoneuroendocrine carcinoma.

FDG = 18F-fluorodeoxyglucose, H&E = hematoxylin and eosin



noma compare to the general population. The relative incidence of small bowel adenocarcinoma in Crohn's disease is 3.4–66.7 fold higher than the general population. Similarly, they have an increased risk of developing neuroendocrine tumor of the gastrointestinal tract. Crohn's disease is associated with a 14.9 fold incidence of neuroendocrine tumor compare to incidental neuroendocrine tumor found in appendectomy specimen from healthy people. However, as most neuroendocrine tumors are found incidentally during surgery their true incidence in Crohn's disease is unknown (4, 5).

It is unclear whether there is a connection between the pathogenesis of Crohn's disease and carcinoid tumor. Some carcinoid tumors are found in colonic segments that are free from inflammation. This finding suggests that the development of neuroendocrine tumor in Crohn's disease may result from local inflammation and/or may be secondary to distant secretion of mediators (4, 5).

Simultaneous presence of neuroendocrine tumor and Crohn's disease is extremely rare, with 52 reported cases in the literature (5). And among them, only 5 cases of coexistent Crohn's disease and mixed adenoneuroendocrine tumor have been reported, as we know. Of the 5 cases, 1 case occurred in the cecum, and other 4 cases occurred in the terminal ileum. The most common clinical presentation of the small bowel mixed adenoneuroendocrine tumor is intestinal obstruction, similar to our case (5-7). However, these reports only focus on clinical and pathologic features.

Crohn's disease-related neuroendocrine tumor is very rare, so there are only little attention about imaging findings. It can present as a mural thickening associated with luminal narrowing and proximal dilatation, or a soft tissue mass on CT. In Boltin's case, the CT scan also shows a segment wall thickening and luminal narrowing of terminal ileum with proximal bowel dilatation (5, 8). However, Crohn's disease-related small bowel adenocarcinoma also shows similar image findings. Small bowel adenocarcinoma may present as 4 different patterns on CT, such as enhancing mass, long stenosis with heterogeneous submucosal layer and moderate enhancement, short and marked stenosis with resulting proximal small bowel dilatation, or sacculated small bowel loop with irregular and asymmetric circumferential thickening. Clearly visible mass can be detected only in 50% of the adenocarcinoma of Crohn's disease patient. Some cases show luminal narrowing and proximal bowel dilatation without visible mass on CT scan, similar to benign fibrotic or acute inflammatory stricture. So, it is very difficult to differential diagnose between benign stricture of Crohn's disease, Crohn's disease-related adenocarcinoma and neuroendocrine tumor in preoperatively (8, 9).

The optimal management of MANEC is largely unknown, due to its rarity. But, the more aggressive component of MANEC should be considered in treatment. MANEC containing a well differentiated neuroendocrine component and an adenocarcinoma component should be treated as adenocarcinoma. MANEC containing a poorly differentiated neuroendocrine component should be treated as neuroendocrine carcinoma (10). Also, the prognosis of MANEC depends on the grade of malignancy of each component.

In this report, we report a MANEC of the small bowel in Crohn's disease patient. Because of its rare incidence and non-specific image finding, it is difficult to diagnose MANEC before surgery. However, MANEC has different treatment and prognosis with other diseases. Therefore, we should understand the disease entity of MANEC so that appropriate treatment can

be done. And, this report will help to consider the possibility of MANEC when there is small bowel wall thickening with bowel obstruction or perforation on CT in Crohn's disease patients.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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크론병 환자에서 발생한 소장의 혼합 신경내분비선암: 증례 보고

김광민 · 배경은* · 김재형 · 정명자 · 김성희 · 김지영 · 김수현 · 이지혜 · 강미진 · 김태규

혼합 신경내분비선암은 외분비샘 그리고 신경내분비 요소를 모두 갖고 있는 위장관의 매우 드문 종양이다. 장기간 크론병을 앓았던 환자의 소장에서 이 혼합 종양이 발생한 경우는 5예의 증례 보고만이 있을 뿐이다. 이에 저자는 비균질하게 조영증강되는 비대칭적인 소장의 장벽비후와 소장폐색의 형태로 나타나, 수술 전 감별진단이 어려웠던 54세 크론병 환자에서 발생한 소장의 혼합 신경내분비선암의 증례를 보고하고자 한다.

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