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# Synchronous Occurrence of Advanced Neuroendocrine Carcinoma and Tubular Adenocarcinoma of the Rectum

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## Key Words

Neuroendocrine carcinoma · Small cell type · Tubular adenocarcinoma · Synchronous occurrence · Rectum

## Abstract

This report presents a rare case with the synchronous occurrence of advanced neuroendocrine carcinoma (NEC) and tubular adenocarcinoma of the rectum. A 52-year-old Japanese male presented with general fatigue and bloody stool. Endoscopic examination showed an ulcerated lesion of the lower rectum. The pathological diagnosis of biopsy specimens from this lesion indicated moderately differentiated adenocarcinoma. He was referred to the surgical outpatient clinic with advanced rectal cancer. Barium enema indicated two lesions in the upper and lower rectum. Computed tomography revealed multiple hepatic metastases. A low anterior resection was performed with lymph node dissection. The resected specimen indicated an elevated lesion with ulceration in the upper rectum and an ulcerated lesion in the lower rectum. Histopathological and immunohistochemical analyses revealed NEC from the upper rectum and moderately differentiated tubular adenocarcinoma from the lower rectum. These two lesions were completely separated from each other. Therefore, this case demonstrates the synchronous occurrence of advanced NEC and tubular adenocarcinoma in the rectum.

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## Introduction

Neuroendocrine carcinoma (NEC) of the rectum is rare with an aggressive behavior and poor prognosis in comparison to adenocarcinoma [1], even if diagnosed at an early stage [2]. The incidence of colorectal NEC is less than 0.1–0.2% among all kinds of colorectal cancer [3]. Patients with NEC have liver and lymph node involvement of between 65 and 80% at the time of diagnosis [1]. NEC is occasionally accompanied by adenocarcinoma in a single tumor of the gastrointestinal tract [4, 5]. Above all, colorectal NEC is occasionally associated with adenoma and/or adenocarcinoma in a single tumor [6]. However, the synchronous occurrence of NEC and tubular adenocarcinoma of the rectum is extremely rare.

This report presents a surgical case of the synchronous occurrence of advanced NEC and tubular adenocarcinoma in the rectum.

## Case Report

A 52-year-old Japanese male presented with general fatigue and bloody stool. Endoscopic examination revealed an ulcerated lesion of the lower rectum. The pathological diagnosis of biopsy specimens from this lesion indicated moderately differentiated adenocarcinoma. He was referred to the surgical outpatient clinic with advanced rectal cancer.

Laboratory data showed that he had a white blood cell count of 5,900/mm<sup>3</sup>, a hemoglobin of 14.8 g/dl, a hematocrit of 43.4%, a platelet count of 251,000/mm<sup>3</sup>, normal electrolytes as well as normal blood urea nitrogen levels and liver function. CEA was 12.3 ng/ml and CA19-9 was 27.2 U/ml. Digital examination of the rectum identified a hard tumor about 6.5 cm from the oral side of the anal verge.

Barium enema indicated two lesions in the upper and lower rectum (fig. 1a). One was an elevated lesion with ulceration in the upper rectum (fig. 1a, arrows), while the other was an ulcerated lesion in the lower rectum (fig. 1a, arrowheads). Computed tomography revealed a rectal mass (fig. 1b) and multiple hepatic metastases (fig. 1c). A low anterior resection with lymph node dissection was performed. The resected specimen had an elevated lesion with ulceration in the upper rectum (fig. 2, arrows) and an ulcerated lesion in the lower rectum (fig. 2, arrowheads). The carcinoma cells of both lesions had invaded through the serosa or adventitia of the rectal wall. There was lymphatic and venous invasion of the carcinoma cells in both lesions. Numerous regional lymph node metastases were also observed.

Histopathological examination with hematoxylin and eosin staining revealed NEC in the upper rectum (fig. 3a) and moderately differentiated tubular adenocarcinoma in the lower rectum (fig. 3b), and also showed that these two lesions were completely separated from each other. Immunohistochemical analyses indicated that many NEC cells were positive for synaptophysin (fig. 3c) and chromogranin A (fig. 3d), and all of the lymph nodes were metastasized from NEC. Serum NSE after the operation was highly elevated at 980 ng/ml.

An implantable port was created for intra-hepato-arterial chemotherapy, and the patient was discharged from the hospital on the 29th day after surgery. However, multiple hepatic metastases progressed rapidly and he died 2 months after the operation.

## Discussion

NEC is occasionally accompanied by adenocarcinoma in a single tumor of the gastrointestinal tract [4, 5]. Colorectal NEC is also occasionally accompanied by adenocarcinoma in a

single tumor [6]. Gastrointestinal NEC is morphologically classified into two subgroups: composite-type tumors, in which both components appear to be mixed haphazardly [5], and collision-type tumors, which are considered to be double tumors with a 'side by side' or 'one upon another' pattern [7, 8]. However, cases with the synchronous occurrence of advanced NEC and tubular adenocarcinoma at the different sites of the colorectum are extremely rare. The NEC mass in the current patient had no other component. Moreover, this case had completely separated lesions of NEC and tubular adenocarcinoma in the rectum even in histopathological examination.

NECs are subtyped into large cell and small cell types, according to the current WHO classification of gastroenteropancreatic neuroendocrine neoplasms [9]. The present case was diagnosed as NEC, small cell type. A combination of colorectal large cell NEC and adenocarcinoma is extremely rare, and only four cases have been reported [6, 10–12]. There are two reports of the synchronous occurrence of large cell NEC and adenocarcinoma at different sites of the colon [10, 11]. The other reports indicate two different components in one tumor [6, 12]. On the other hand, synchronous occurrence of small cell NEC and adenocarcinoma at different sites of the colon has not been reported in the English literature. However, in the Japanese literature two cases have been reported with synchronous occurrence of small cell NEC and adenocarcinoma in the colorectum [13, 14]. Therefore, the present case is thought to be extremely rare.

NEC of the gastrointestinal tract is an aggressive neoplasm, which has been reported to occur frequently with distant metastasis and carries a poor prognosis, even if diagnosed in the early stage [1, 2]. The median survival ranges from 6 to 12 months for treated patients and is only weeks for untreated patients [15]. Brenner et al. [15] reported a univariate analysis to show several factors such as performance status, weight loss, T stage, N and M status, TNM stage and extent of disease (limited disease vs. extended disease) to be significant prognostic factors. The 1-year survival rate of extended disease (29%) was significantly worse in comparison to that of limited disease (72%) [15].

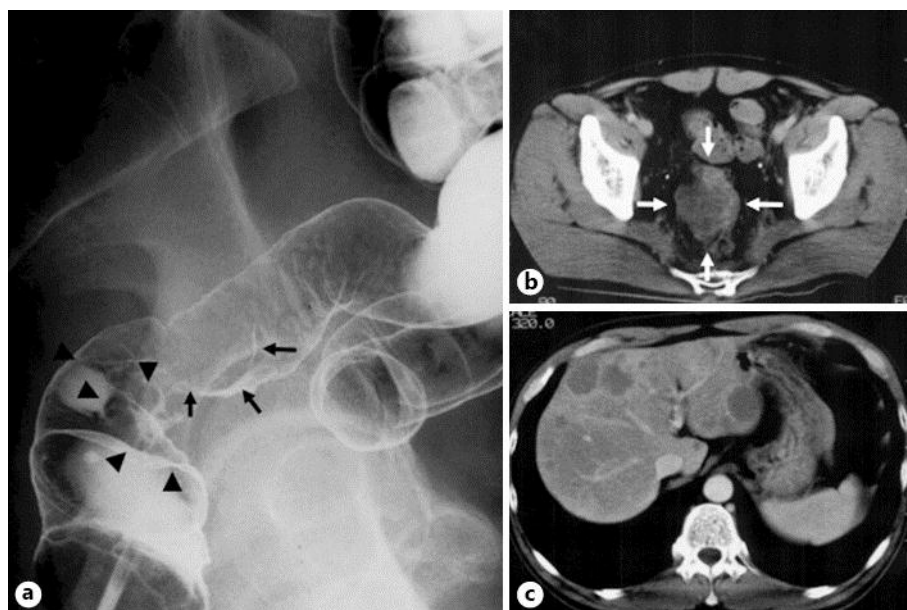
No standard treatment has been established for advanced or recurrent colorectal NEC. Chemotherapy for advanced colorectal NEC has been performed using many regimens such as cisplatin and 5-FU [2], cisplatin and 5-FU/leucovorin, cisplatin and etoposide, cisplatin and topotecan, carboplatin and etoposide, systemic infusion of mFLOFOX6 and bevacizumab. Though many chemotherapeutic agents have been used, no conclusions can be made regarding which regimen is most effective because of the limited number of patients. At any rate, multidisciplinary therapy might be needed for colorectal advanced NEC in the future because of its serious malignant potential.

In conclusion, this report presents a rare surgical case of synchronous occurrence of advanced NEC and tubular adenocarcinoma of the rectum.

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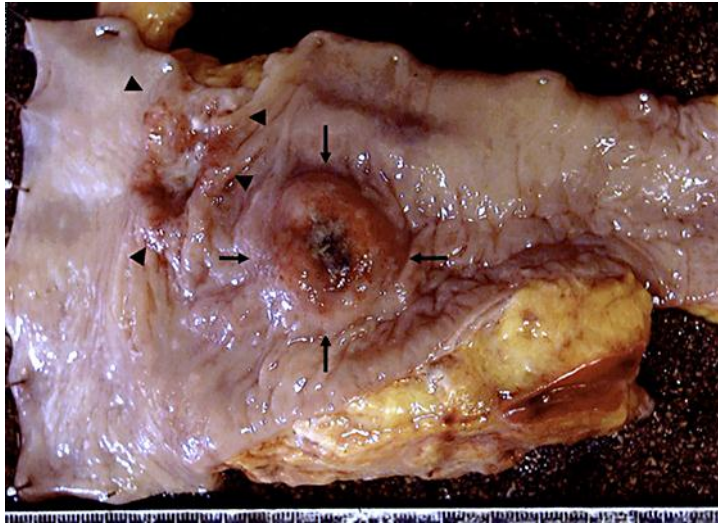
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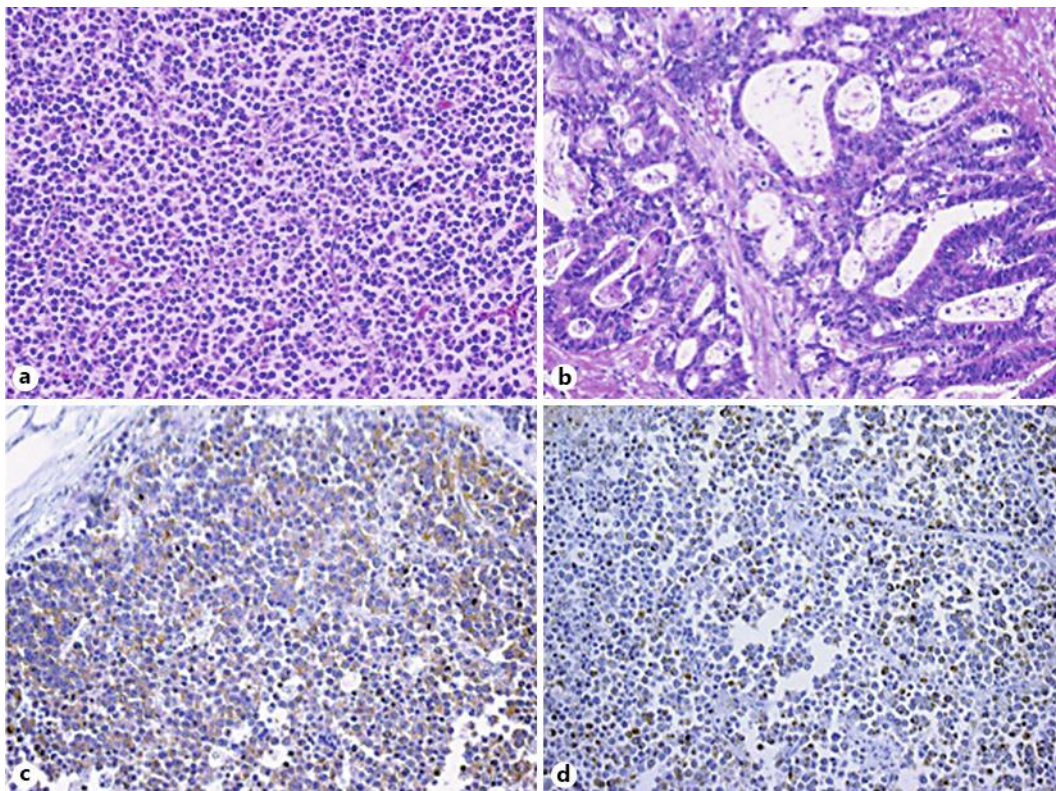


**Fig. 1.** Barium enema revealed two lesions in the upper rectum (a). One was an elevated lesion on the oral side (arrows) and the other was an ulcerated lesion on the anal side of the upper rectum (arrowheads). Computed tomography revealed a rectal mass (b) and multiple hepatic metastases (c).





**Fig. 2.** The surgical specimen revealed an elevated lesion with ulceration on the oral side of the upper rectum (arrows) and an ulcerated lesion on the anal side of the upper rectum (arrowheads).



**Fig. 3.** Histopathological examination with hematoxylin and eosin staining revealed NEC in the oral lesion from the upper rectum (**a**,  $\times 200$ ) and moderately differentiated tubular adenocarcinoma from the anal lesion on the upper rectum (**b**,  $\times 200$ ). Immunohistochemical analyses indicated that many NEC cells were positive for synaptophysin (**c**,  $\times 200$ ) and chromogranin A (**d**,  $\times 200$ ).