CASE REPORT

Coexistent poorly-differentiated neuroendocrine cell carcinoma and non-invasive well-differentiated adenocarcinoma in tubulovillous adenoma of the rectum : report of a case

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Abstract : A 74-years old man was referred to our hospital for treatment of a rectal mass. Colonoscopy revealed villous tumor covering all the lower rectal lumen. Biopsy yielded a diagnosis of adenoma. CT examination showed tumor shadows of the rectum and the liver. Pelvic MRI examination showed a 10.5×8×7 cm tumor with high signal intensity on the T2 weighted images in the rectum. Rectosigmoidectomy with lymph node dissection was performed with the diagnosis of rectal cancer that metastasized to the liver. Histological and immuno- histochemical features showed coexistent poorly-differentiated small cell neuroendocrine cell (NEC) carcinoma and non-invasive well-differentiated adenocarcinoma in tubulovillous adenoma. However the chemotherapy with FOLFOX and Bevacizumab was performed postoperatively, the patient died in cancer 3 months after surgery. Rectal poorly-differentiated NEC carcinomas are thought to be a tumor with a high malignant potential. Recently, the UICC TNM classifications of malignant tumors, 7th edition and the Guidelines for colorectal NEC tumors of European Neuroendocrine Tumor Society have been published. They would be evaluated, and effective multimodal therapy for NEC carcinomas should be established. J. Med. Invest. 57 : 338-344, August, 2010

Keywords **:** *neuroendocrine cell carcinoma, rectum, adenoendocrine cell carcinoma, small cell carcinoma*

INTRODUCTION

Colorectal poorly-differentiated (POR) neuroendocrine cell (NEC) carcinomas are rare aggressive neoplasm at this location, accounting for less than 1 percent of all colorectal malignant tumors (1-7). Furthermore, colorectal POR NEC carcinomas have very poor prognosis, and treatments of this carcinomas are very difficult (1-7). We herein report a coexistent POR NEC carcinoma and non-invasive well-differentiated (WELL) adenocarcinoma in villous adenoma of the rectum.

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CASE REPORT

A 74-years old man was admitted to our hospital in March 2009 after detection of a rectal mass during investigation for difficult defecation and diarrhea. Laboratory findings showed no abnormalities on peripheral blood and serum examination. Colonoscopy revealed villous tumor covering all the lower rectal lumen 4 cm from anal verge (Fig. 1). Biopsy

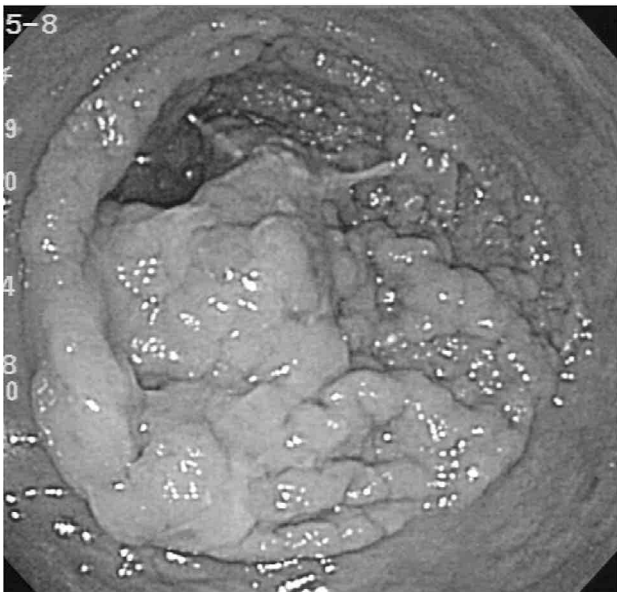

Fig. 1 : Colonoscopy revealed villous tumor covering all the lower rectal lumen 4 cm from anal verge.

yielded a diagnosis of adenoma. Abdominal computed tomography (CT) showed the low density tumor shadows of the rectum and the right hepatic lobe (Fig. 2). Pelvic magnetic resonance imaging on the T2 weighted images showed a large tumor with slight high signal intensity of 10.5×8×7 cm in the rectum (Fig. 3).

From the above findings, rectal cancer was considered most. Following a diagnosis of rectal cancer that metastasized to the liver, lapalotomy was performed. There were widespread liver metastasis and lymphadenopathy in the abdomen. No peritoneal dissemination was observed. Rectosigmoid resection with lymph node dissection and total mesorectal excision was performed. The resected specimens showed elevated villous tumor covering all the rectal lumen measuring 10.5×8 cm, in association with a type 2 tumor in the anterior side (Fig. 4). Histological features showed two different components. The elevated lesion consisted mainly of tubulovillous adenoma containing WELL adenocarcinoma confined to the mucosa (Fig. 5a). No conventional adenocarcinoma cells were observed into the submucosa, the muscularis propria or the subserosa. Whereas, the other type 2 tumor composed highly atypical small cells with hyperchromatic nuclei and scanty cytoplasm, in solid nests and trabeculae, resembling the features of small cell carcinoma of the lung. These small cells diffusely infiltrated the submucosa, the muscularis propria, the subserosa and the serosa. Nuclei were irregular in size and mitotic figures were frequently identified (Fig. 5b). Focal necroses were found. Severe lymphatic and vascular invasions, as well as lymph node metastasis, were observed. The type 2 small cell tumor was diagnosed pathologically as POR NEC carcinoma by immunohistochemical study using Chromogranin

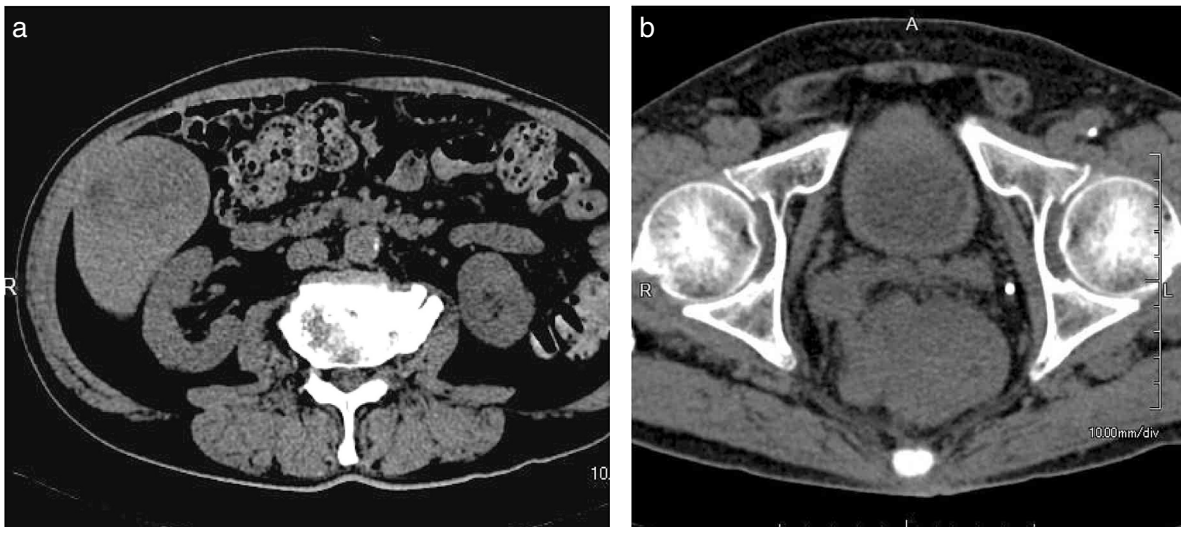

Fig. 2 : Abdominal computed tomography showed the low density tumor shadows of the rectum and the right hepatic lobe.

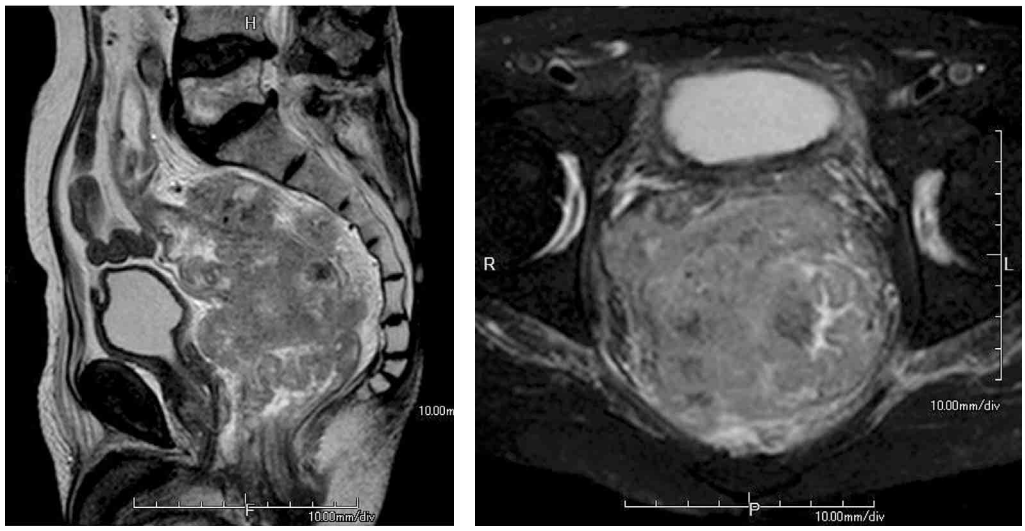

Fig. 3 : Pelvic magnetic resonance imaging on the T2 weighted images showed a large tumor with slight high signal intensity of 10.5×8×7 cm in the rectum.

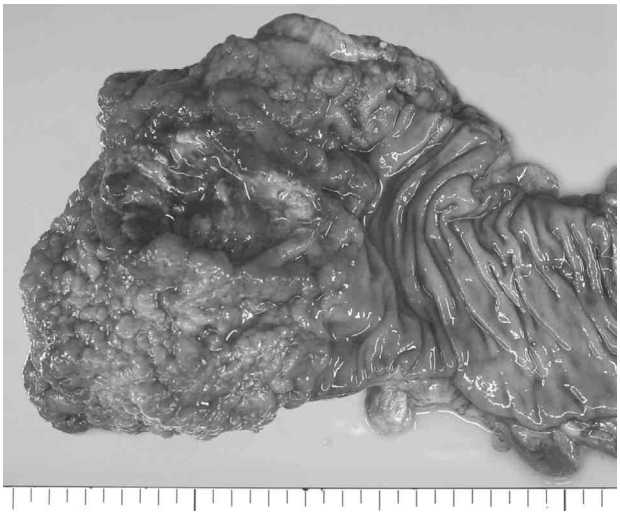

Fig. 4 : The resected specimens showed elevated villous tumor covering all the lower rectal lumen measuring 10.5×8 cm, in association with type 2 tumor in the anterior side.

A (Chr A) (Fig. 6a) and Synaptophysin (Fig. 6b). No immunoreactivity with LCA, CD3 or CD20 was seen. No transitional zone was observed between the adenocarcinoma in adenoma and the NEC carcinoma.

CT scan was performed 1 month after operation and made clear an increasing metastases focus in the liver (Fig. 7). The patient was given intravenous combination chemotherapy using Fluorouracil, Folinic acid, Oxaliplatin (FOLFOX) and Bevacizumab postoperatively. But his general condition turned worse by exacerbation of the cancer, he died in cancer 3 months after surgery.

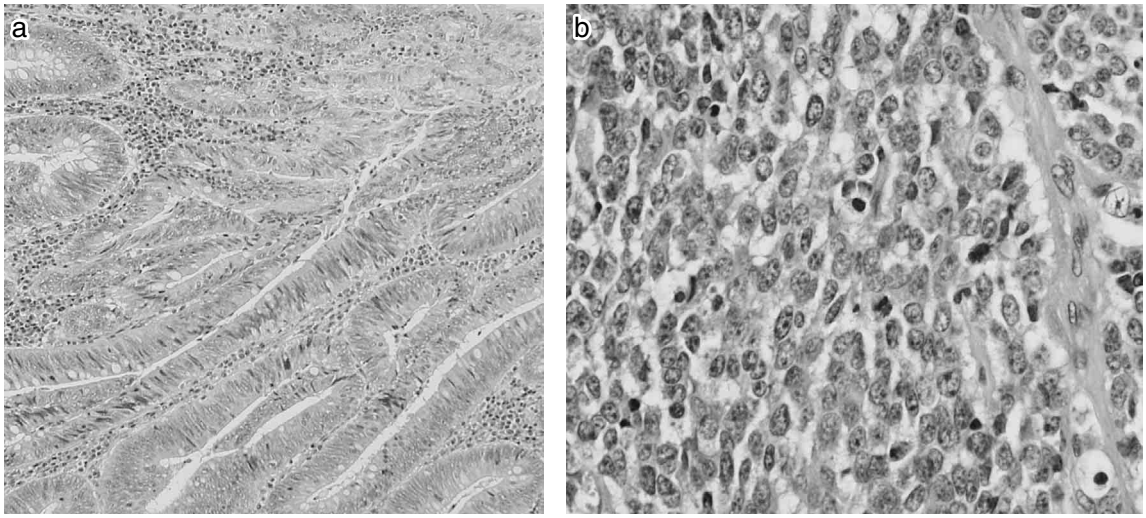

Fig. 5 : Histological features showed two different components. The elevated lesion consisted mainly of tublovillous adenoma containing well-differentiated adenocarcinoma confined to the mucosa (Fig. 5a) (H.E.×100). Nuclei of the NEC carcinoma cells were irregular in size and mitotic figures were frequently identified. Focal necroses were found (Fig. 5b) (H.E.×200).

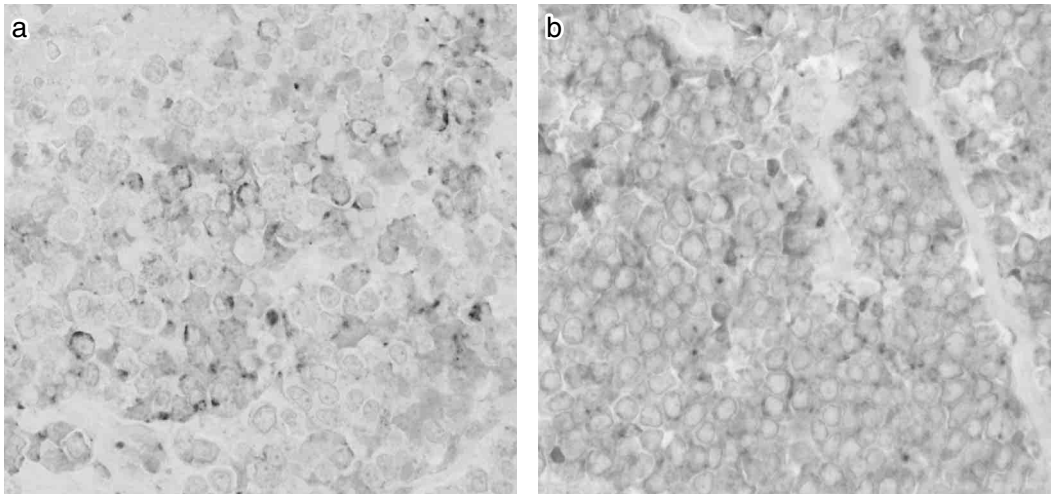

Fig. 6 : Immunohistochemical features. The NEC carcinoma cells are immunoreactive for (a) Chr A (×200) and (b) SNP (×200).

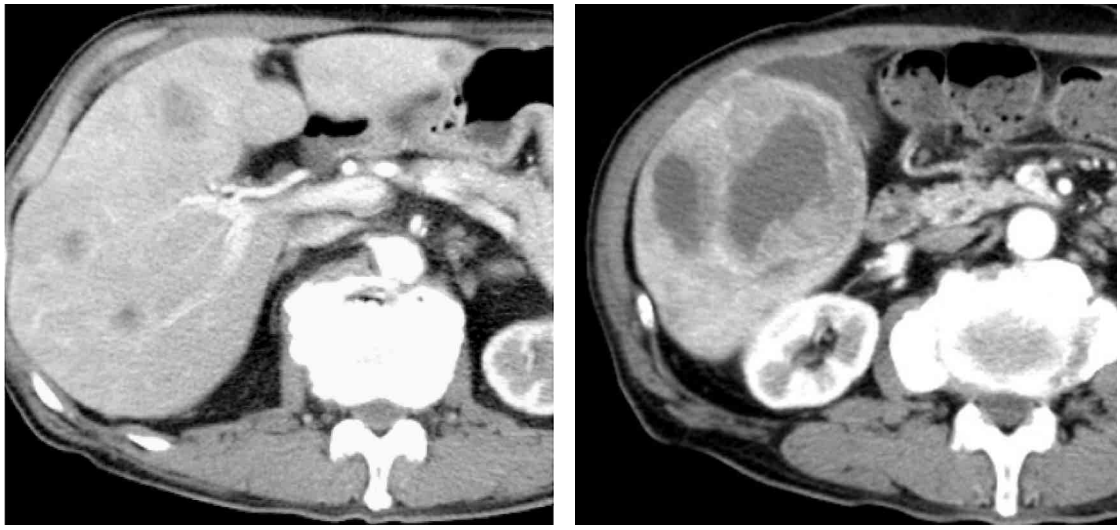

Fig. 7 : CT scan performed 1 month after operation found an increasing metastases focus in the liver.

DISCUSSION

The classification of gastrointestinal (GI) NEC tumors is controversial. The chapter of GI NEC tumors was deleted from latest World Health Organization (WHO) classification of the tumors of endocrine organs (8). Therefore, GI NEC carcinomas are classified in accordance with WHO classification of the tumors of the digestive system (9). However, it is thought that three following subgroups are easy to grasp the property of GI NEC tumors. In other words it is 1) WELL NEC tumors of benign or uncertain behavior, 2) WELL NEC carcinomas of low grade malignancy, so-called carcinoid tumor and 3) POR or undifferentiated NEC carcinomas of high grade malignancy. Furthermore, a dichotomous classification scheme, small cell vs. non-small cell including large cell, for POR NEC carcinomas of the GI tract has been present (10). Hence, our NEC tumor case is thought to be classified in POR small cell NEC carcinoma.

Colorectal POR NEC carcinomas are uncommon, comprising less than 1 percent of all colorectal malignancies. The first described series of colorectal small cell NEC carcinoma was reported in 1978 (11). In Japan, the first documented series of rectal POR NEC carcinoma was reported in 1984 (1). Since that initial Japanese description, a total 48 cases of rectal POR NEC carcinomas have been reported in Japan (12-15). Colorectal POR NEC carcinomas are sometimes associated with adenoma and/or adenocarcinoma (16, 17). Coexistent NEC carcinoma and adenocarcinoma is so-called adenoendocrine cell carcinoma. In Japan, there were 20 isolated reports describing rectal adenoendocrine cell carcinoma including our case (Table 1).

Table 1. Summary of 20 cases of rectal Adenoendocrine cell carcinoma in Japan

Age (year) (average)	Sex		Tumor size (mm) (average)	Liver meta		Treatment		Survival	
44~84	male	11	23~160	preope	9	surgery alone	8	6 month survival rate	50%
(58.4)	female	8	(56.7)	postope	6	surgery +CT± RT	9	1 year survival rate	30%
	unknown	1				best supportive care	2	3 year survival rate	15%
						other	1		

CT : chemotherapy
RT : radiotherapy

In our case, the NEC carcinoma was next to the non-invasive WELL adenocarcinoma in tubulovillous adenoma. The adenocarcinoma in adenoma located upper layer confined to the mucosa. On the other hand, the NEC carcinoma located lower layer. Each tumor of the adenocarcinoma in adenoma and the NEC carcinoma were two-tiered structure. The histogenesis of tumors containing both glandular and endocrine components is not fully elucidated. But according to the current histological and molecular studies, it has been considered that both NEC carcinoma and adenocarcinoma are derived from a multi-potential stem cell (18-21). Our case seems consistent with this theory by morphological feature.

Colorectal POR NEC carcinomas have very poor prognosis. The negative prognostic factors of gastroenteropancreatic NEC tumors such as expression of Chr A, high Ki-67 indexes, high mitotic rates, large size of the primary tumor and presence of metastasis have made clear (7, 22, 23). Our case had four negative prognostic factors mentioned above. A novel TNM classification including a Ki-67 index or mitotic index based grading system has been advocated by the European Neuroendocrine Tumor Society (ENTS) (24). According to this ENTS TNM classification, clinical stage of our case was T4 (invasion to the seminal vesicle and prostate), N1, M1 (liver), stage4. Whereas a new TNM classification, 7th edition has been published by International Union Against Cancer (UICC) (25). The GI NEC tumor is expressed as a new classification by this UICC TNM classification. However, the UICC TNM classification of the GI NEC tumors is only carcinoids. POR NEC carcinoma must be classified as GI carcinoma of small cell/large cell. So, clinical stage of our case was T4b (invasion to the seminal vesicle and prostate), N2b, M1a (liver), stage4A in accordance with update UICC TNM classification, 7th edition.

The medical treatment against colorectal POR NEC carcinomas is controversial. ENTS's Guidelines for the management of patient with colorectal NEC tumors recommend systemic chemotherapy using cisplatin/etoposide (26, 27). In Japan, the effective case with chemotherapy that used cisplatin/irinotecan against the rectal POR NEC cancer has been reported (28). In ASCO 2006, the outcome that the FOLFOX-4 regimen was well tolerated and effective in progressive malignant NEC carcinoma with increased proliferative potential was presented (29). Although there are some optional chemotherapy regimens for the advanced colorectal POR NEC carcimona, few prospective randomized chemotherapy studies is still being performed. For our case, we used FOLOX-6 and Bevacizumab being the drugs of choice currently prescribed for colorectal adenocarcinomas. The initial chemotherapy was done. But the general condition of the patient became worse because of increased liver metastases. The continuation of the chemotherapy became difficult. So, this resume was not able to be evaluated.

In conclusion, surgical resection and adjuvant chemotherapy will be necessary as main treatment of the colorectal POR NEC carcinoma. Effective multimodal therapy for NEC carcinoma should be established.

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