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A Case of Neuroendocrine Cell Carcinoma with Sigmoidovesical Fistula

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Key Words
Sigmoidovesical fistula · Neuroendocrine cell carcinoma · Chemotherapy · FOLFOX

Abstract
Colonic neuroendocrine cell carcinoma (NEC), which is a rare subtype of colon epithelial neoplasm, has been reported to show extremely aggressive characteristics with a 1-year survival rate of 20%. We report herein a resected case of NEC that manifested bacterial sepsis due to sigmoidovesical fistula. Staged surgery consisted of resecting the sigmoid colon and part of the bladder four weeks after construction of an ileostomy to alleviate septic shock. The resected specimen was histologically diagnosed as NEC invading the wall of the urinary bladder with metastasis to the regional lymph nodes. The patient underwent four cycles of FOLFOX after surgery for additional treatment of residual metastatic lymph nodes around the abdominal aorta diagnosed preoperatively. Although the patient showed stable disease measured by computed tomography scan for the first three months after surgery, he rejected additional chemotherapy thereafter, and died ten months after the initial admission due to progression of residual tumor in the urinary bladder as well as the lymph nodes. This is the first case report describing colonic NEC manifesting perforation into the urinary bladder. Although the optimal chemotherapeutic regimen for colonic NEC has not yet been established, FOLFOX may be one of the choices.

Introduction

Neuroendocrine cell carcinoma (NEC) of the colon, sometimes described as small cell carcinoma of the alimentary tract, is an extremely rare tumor, representing less than 1% of colonic cancers [1, 2]. Most patients are diagnosed at an advanced stage, presenting

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with clinical symptoms and macroscopic characteristics identical to colon adenocarcinoma. Because of its highly aggressive biological behavior, it progresses much faster than common adenocarcinoma of the colon, with early hemodynamic and lymphatic spread leading to a poor prognosis [1, 2]. Although previous reports have suggested that tumor resection with subsequent chemo-radiotherapy could be one of the favorable treatments, the optimal therapeutic protocol including chemotherapeutic regimen has not yet been established [3]. We report a rare case of NEC of the colon with sigmoidovesical fistula (SVF). Palliative resection of the tumor followed by chemotherapy using the FOLFOX regimen is considered feasible.

Case Report

A 78-year-old man was transported by ambulance to our hospital with complaints of severe lower abdominal pain, fecaluria and high fever. On admission, his body temperature was 38°C, heart rate was more than 100 beats/min, and blood pressure was 75 mm Hg, suggesting septic shock state. Laboratory data showed a white blood cell count of 15,100/mm^3 and a C-reactive protein level of 9.5 mg/dl. Urine sample contained significant amounts of white blood cells (100 counts/field), red blood cells (50–99 counts/field) and bacteria (3+), compatible with urinary tract infection. Abdominal computed tomography (CT) scan demonstrated a mass lesion at the sigmoid colon with marked inflammatory change around the urinary bladder (**fig. 1**). Bacterial sepsis due to urinary tract infection caused by the sigmoid colon tumor penetrating the urinary bladder was highly suspected, although direct visualization of SVF was not detected. Emergency surgery including ileostomy for fecal diversion and urethral catheterization (triple lumen, 24 French) was performed immediately. The clinical course after emergency surgery was good, and staged operation was planned after additional preoperative examination. Hypotonic gastrografin enema showed sigmoid colon stenosis without apparent findings of SVF. CT scan also showed sigmoid stenosis due to tumor-like mass. Colonoscopy was not performed in order to avoid relapse of pyelonephritis by pressure-induced enlargement of the SVF. Serum tumor markers, such as carcinoembryonic antigen and carbohydrate antigen 19-9, were within normal limits. Based on the diagnosis of sigmoid colon cancer with SVF, the patient underwent the second surgery for tumor removal four weeks after the initial surgery. Surgical findings showed a large solid tumor invading the bladder wall. Enlarged lymph nodes were found along the inferior mesenteric artery as well as the abdominal aorta. Sigmoidectomy with partial resection of the bladder with D2 lymph node dissection was carried out. The tumor in the sigmoid colon was 82 × 74 mm in size. Microscopic examination demonstrated that the tumor consisted of small round cells with nuclear atypia and had directly invaded and penetrated the bladder. Multiple lymph node metastases were also noted. Immunohistochemical examination demonstrated that more than 90% of the small cells were positive for CD56, which indicated a diagnosis of NEC of the sigmoid colon. The serum biomarker, neuronal-specific enolase specific for NEC, showed a high level of 31.9 ng/ml (cut-off level 12 ng/ml) even after the second surgery.

The patient underwent four cycles of chemotherapy intravenously which consisted of 5-fluorouracil (2,000 mg/m^2), levofolinate (200 mg/m^2) and oxaliplatin (85 mg/m^2) (FOLFOX regimen). Follow-up CT scan three months after the initiation of chemotherapy demonstrated that there was no change in the size of paraaortic lymph nodes (**fig. 2**). However, the patient refused to continue any additional treatment. Thereafter, the metastatic lymph nodes and local recurrent tumor grew rapidly and he died ten months after the second surgery.

Discussion

Colorectal NEC, which has been described as small cell carcinoma in the past, is an extremely rare histological type, representing 0.03–0.2% of all colorectal cancers [4, 5]. Morphological and biological aggressiveness similar to that of small cell carcinoma of the lung is its notable feature. Hung [1] reviewed 39 cases of small cell carcinoma of the colon and found that the 1-year survival rate was only 10% with a mean survival time of approximately 6 months. Most of the patients were diagnosed at an advanced stage. Radical resection at an early stage has been considered the only cure. However, the

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prognosis of these patients is sometimes dismal even when diagnosed at an early stage. Thus, further investigation with regard to its biology as well as therapeutic modality is warranted.

Systemic chemotherapy and/or radiation therapy have been therapeutic alternatives especially for advanced NEC, although there are no established standard regimens. Thirty-eight cases of advanced colorectal NEC treated with chemotherapy were reviewed in our literature survey using the key words 'neuroendocrine cell carcinoma', 'colon' and 'chemotherapy', to search the MEDLINE database between 1983 and 2008 (**table 1**) [3, 6–14]. We analyzed these 38 cases in addition to our case, and 24 and 15 cases showed liver and lymph node metastases. Regarding outcomes, 3 cases achieved complete response and 10 cases partial response, and the response rate including complete response, partial response and no change was 38%. Concerning the chemotherapeutic regimens, cisplatin (CDDP) was administered to 21 cases, and CPT-11 and etoposide were combined in 5 and 10 cases, respectively. These regimens were considered based on the current regimen of small cell carcinoma of the lung.

Recently several new regimens, such as FOLFOX and/or FOLFIRI, have been reported to show more favorable prognoses than conventional regimens for patients with common advanced or recurrent colorectal cancers, and the side effects were tolerable. Moreover, as the patient's renal function and digestive function were impaired, CDDP or CPT-11 was not indicated for systemic chemotherapy. Therefore, we treated our case using FOLFOX and obtained no change for three months without progression of either metastasized lymph nodes or local residual tumor. Sunose [15] also reported that liver metastasis showed a clinical response to the FOLFOX regimen. Although the results are still preliminary, sunitinib has been reported to be clinically effective for neuroendocrine cancer of the lung and pancreas [16, 17]. Combination treatment using chemotherapeutic and molecular targeting drugs may achieve a more favorable response. Multicenter clinical trials may be an efficient way of elucidating useful regimens especially for this rare type of cancer.

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Table 1. Reported cases of advanced colorectal NEC with metastases and the regimen used for chemotherapy and the response to treatment

Reference	Year	Location	Site of metastasis	Regimen	Response
6	2008	C	liver	CDDP+etoposide, 5-FU+CDDP+etoposide (HAI)	PD
7	2008	R	LN	CDDP+etoposide, CPT-11+CDDP	PR
8	2008	R	local invasion	IFL+radiation (preoperative therapy)	PR
18	2008	A	liver	5-FU+l-LV (HAI), CPT-11, FOLFOX6	PR
19	2007	R	local	CDDP+UFT	PD
20	2007	T	LN, P	CPT-11	PD
21	2007	C	liver	CDDP+CPT-11	CR
			LN, adrenal	CDDP+etoposide, cyclophosphamide+ doxorubicin+vincristine	PR
22	2007	R	LN, P	IFL	PD
9	2007	T	liver, LN	hepatectomy+chemotherapy (unknown)	CR
10	2006	R	liver	CDDP+etoposide	PD
		S	liver	FOLFIRI, TACE	PD
		R	liver, bone	5-FU+dacarbazine+epirubicin	PD
		R	liver, lung, LN	CDDP+etoposide	PR
		C	P	oral chemotherapy	PR
		R	liver	xeloda	PR
15	2006	R	local, liver	CDDP+CPT-11, IFL, FOLFOX4	PR, NC
23	2006	T	liver, P	CDDP+CPT-11	PD
24	2006	A	liver, LN	CDDP+5-FU (HAI)	PD
		D	liver, P	5-FU (HAI), 5-FU+l-LV	PD
25	2005	R	liver	5-FU, TS-1	PD
		R	liver	CDDP+5FU (HAI), FAM+CDDP	PD
26	2004	R	LN	CDDP+etoposide+paclitaxel	PR
27	2004	R	liver	CDDP+5-FU (HAI)+l-LV	PD
28	2004	T	local invasion	CDDP+CPT-11	CR
29	2003	R	liver, LN, local	CDDP+5-FU (HAI)	PD
11	2002	R	liver, bone, skin	unknown	PD
12	2002	A	liver	vincristin, etoposide, adriamycin, carboplatin, taxotere	PD
30	2002	R	liver, LN, local, bone, skin	CDDP+etoposide	PD
31	2002	R	LN	CDDP+etoposide	CR
13	2002	C	LN	unknown	lost to follow-up
		D	liver, LN, P	unknown	PD
2	1999	R	liver, LN, bone	CDDP+5-FU	PR
14	1999	S	liver, LN	5-FU+l-LV	PD
32	1998	R	liver, local	CDDP+etoposide	PD
33	1996	A	P	CDDP+etoposide+adriamycin	PD
34	1996	T	P	CDDP+5-FU	PD

A = Ascending colon; C = cecum; CDDP = cisplatin; CR = complete response; D = descending colon; FAM = 5-fluorouracil+adriamycin+mitomycin; HAI = hepatic arterial infusion; IFL = CPT-11+5-FU+LV; LN = lymph node; LV = leucovorin; NC = no change; P = peritoneum; PD = progressive disease; PR = partial response; R = rectum; S = sigmoid colon; T = transverse colon; TACE = transcatheter arterial chemoembolization.

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Fig. 1. CT scan demonstrated a mass lesion at the sigmoid colon with marked inflammatory change around the urinary bladder. There was an air density lesion in the wall of the bladder (arrow).

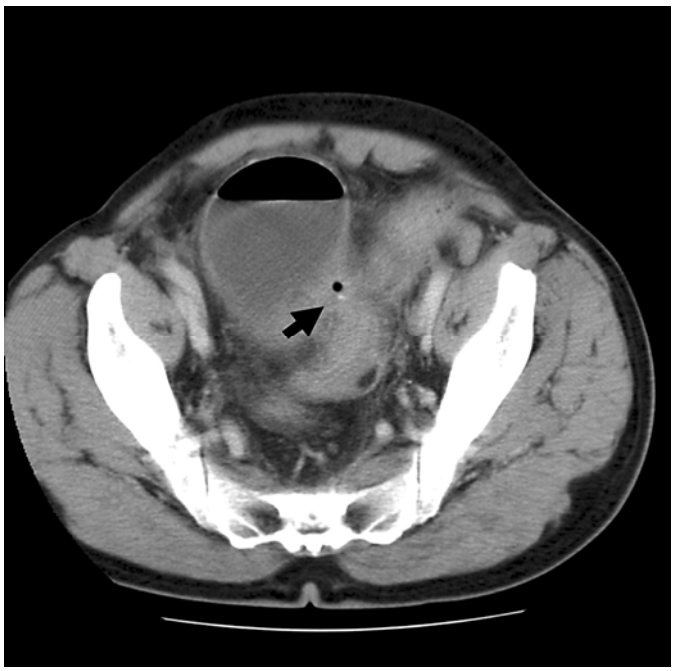
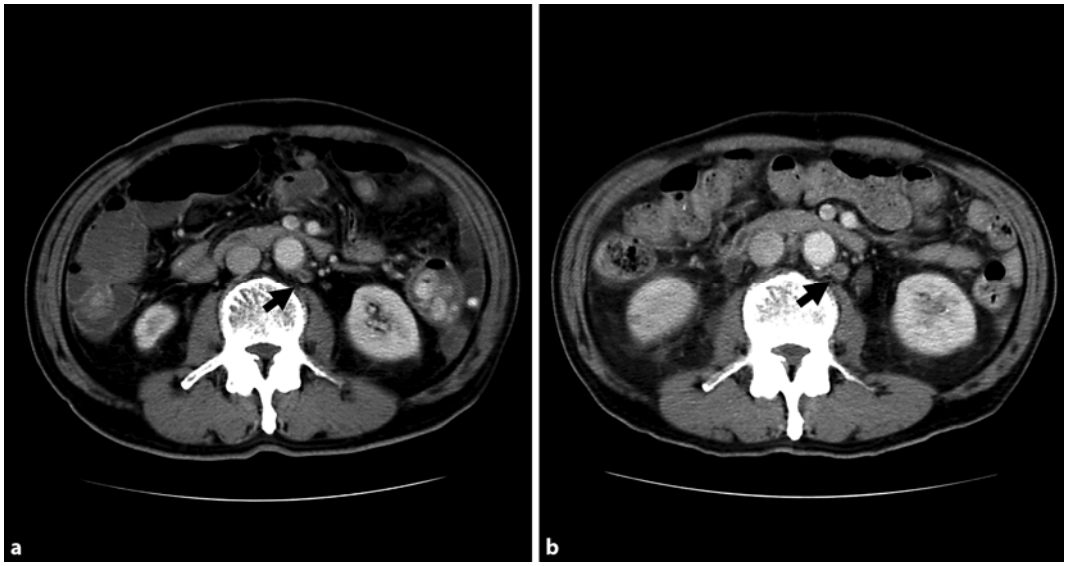


Fig. 2. Follow-up CT scan three months after the initiation of chemotherapy demonstrated no change in the size of the paraaortic lymph nodes. **a** Seven weeks after the first surgery, some paraaortic lymph nodes (arrow) demonstrated findings compatible with metastasis. **b** Three months after the initiation of chemotherapy, the size of these lymph nodes had not changed (arrow).



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