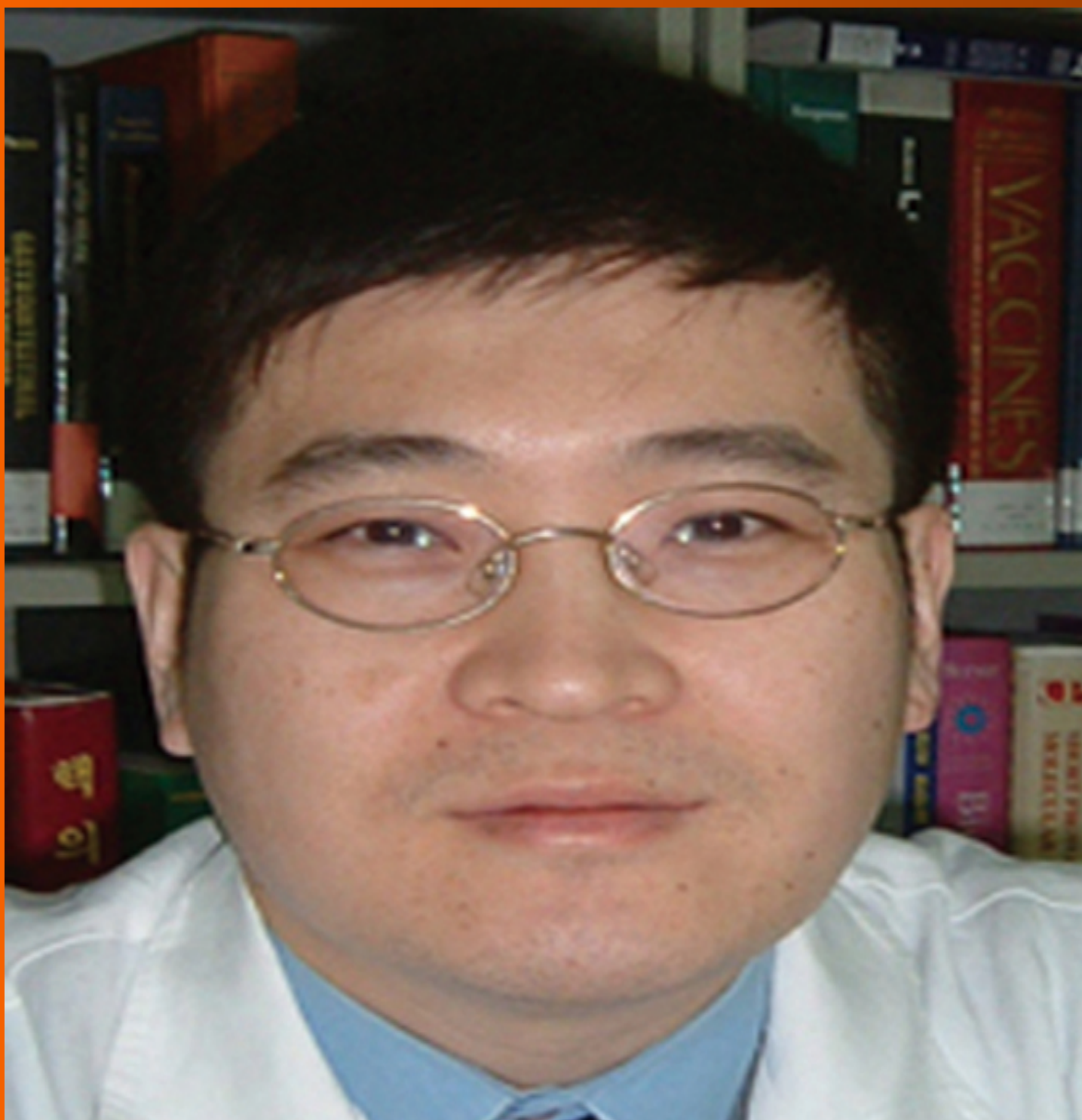


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## Colorectal neuroendocrine carcinoma: A case report and review of the literature

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**Author contributions:** Yoshida T, Kamimura K and Terai S wrote the manuscript; Hosaka K, Doumori K, Oka H and Fukuhara A collected data for review; Sato A, Watanabe S, Sato T and Tomidokoro T treated patients; all authors read and approved the final version of the manuscript.

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### Abstract

#### BACKGROUND

Colorectal neuroendocrine carcinoma (NEC) is a rare tumor that demonstrates aggressive growth pattern with ingrowth into the tract, metastasis to the other organs, and invasion to the surrounding organs; these clinical characteristics result in poor prognosis. Surgical resection appears as an effective approach; however, because it is difficult to accurately diagnose NEC during the early stage and owing to its aggressive growth pattern, development of a reliable standard chemotherapy regimen and management strategies are essential.

#### CASE SUMMARY

Here, we report the case of patient with NEC showing an aggressive growth pattern that resulted in the rupture of the tumor to the outside the colon after stenting of the internal colonic stenosis. In addition, the tumor invaded into the duodenum, thereby causing duodenal stenosis that required an additional stent in the duodenum. This aggressive growth pattern is one of the main features of the NEC that is different from adenocarcinoma. To clarify the clinical characteristics, we reviewed 60 recently reported cases, including data on tumor location, size, treatment, and prognosis.

#### CONCLUSION

We consider that the information presented here is of great significance for the diagnosis, treatment, and management of symptoms of the patients with NEC.

**Key words:** Neuroendocrine carcinoma; Colon; Colorectal mixed adenoneuroendocrine



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**Core tip:** The aggressive growth pattern of the rare tumor colorectal neuroendocrine carcinoma (NEC) results in the rapid growth into the tract, metastasis to the other organs, and invasion to the surrounding organs. The overall prognosis has been poor compared with invasive colon adenocarcinoma. The aggressive growth pattern of this tumor could result in the colonic stenosis, tumor rupture outside the colon, and invasion to the surrounding organs. Because of its rarity and poor prognosis, clinical information has not been yet summarized; we have summarized the information obtained from 60 cases reported to date. The information summarized in the present study would be of great importance to assist physicians for the diagnosis, treatment, and management of the symptoms of patients with NEC.

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## INTRODUCTION

Neuroendocrine carcinoma (NEC) of colon and rectum is a rare neuroendocrine tumor (NET) type that accounts for < 1% of all colorectal malignancies<sup>[1]</sup>. The clinical progression of NECs includes highly aggressive growth and rapid dissemination along with a high tendency for metastasis<sup>[2]</sup>. Moreover, these tumors could be detected at advanced stage<sup>[3]</sup>. The 3-year overall survival (OS) was estimated to be 5%–27%<sup>[1,4,5]</sup>, and response to chemotherapy was reported as the only predictive factor in patients with metastasis<sup>[1]</sup>. Because of its aggressive nature and high recurrence rate of the NEC, adjuvant chemotherapy constitutes a critical part of the treatment and significantly improves survival<sup>[4]</sup>. Although platinum-based regimens are widely used as first-line chemotherapy for the treatment of patients with advanced NEC, no standard regimen has yet been established. A previous study has reported that some cases who received chemotherapy showed the complete response (CR) or partial response (PR) to the advanced NEC; however, more than half of patients showed progressive response<sup>[6]</sup>.

Additionally, some NEC cases showed aggressive progression and outward growth with the invasion of surrounding tissues. These aggressive tumors lead to serious health issues such as colonic obstruction and internal organ exclusion. The management of such health issues is sometimes challenging; moreover, an appropriate therapeutic strategy has not yet been proposed because of rareness of the aggressive NEC.

Here, we attempted to present a patient with NEC that showed aggressive tumor progression. Although the patient received various therapeutic options, such as chemotherapy or intestinal self-expandable metallic stent, all those treatments have been unsuccessful yet.

## CASE PRESENTATION

### Chief complaints

A 55-year-old man was admitted to our hospital with a huge abdominal mass. He complained of palpable abdominal mass, while painless mass two months prior to the presentation.

### History of past illness

He had no significant history of past illness.

### Physical examination

Physical examination showed a palpable tumor and a relatively soft mass associating with poor movability in the right upper quadrant.

### Laboratory examinations

Laboratory findings showed an elevated white blood cell count (9740 / $\mu$ L), platelet count ( $37.3 \times 10^4$  / $\mu$ L), C-reactive protein (4.99 mg/dL), lactate dehydrogenase (328 IU/L), and hemoglobin level (9.4 g/dL). Carcinoembryonic antigen showed mild elevation of 9.5 ng/mL, while other tumor markers were in normal range (Table 1).

### Further progress, diagnosis, treatment and outcome

Abdominal contrast-enhanced computed tomography (CT) showed an irregularly shaped, 10 cm, as well as an enhanced mass in the transverse colon at the hepatic flexure (Figure 1A) and suspicious of metastatic tumors in the liver (Figure 1B). Colonoscopy showed the mass in the right transverse colon with significant stenosis (Figure 1C) due to submucosal elevation of the tumor (Figure 1D), while the lumen had a necrotic tissue (Figure 1E) evidenced by colonic enema with water-soluble contrast medium showing an irregular shape in the lumen of colon (Figure 1B). Following the mucosal biopsy for the histological analysis, a self-expandable metallic stent was successfully placed. However, the patient re-admitted to our hospital because of the sudden onset and severe abdominal pain at 5 days after the placement. The contrast-enhanced CT of the abdomen showed intraperitoneal free-air associated with the colon tumor (Figure 1F). The hematoxylin and eosin (HE) staining showed that the tumor cells were poorly differentiated (Figure 2A) with hemorrhage in the tumor (Figure 2B) and significantly stained positively for Synaptophysin (Figure 2C). In addition, Ki67 staining showed a highly proliferative pattern with the Ki67 index of 90% (Figure 2D).

## FINAL DIAGNOSIS

Based on these findings, the tumor was diagnosed with NEC, and the tumor showed perforation to the outside the colon probably due to the expandable growth of the tumor.

## TREATMENT

The tumor showed severe invasion to the surrounding tissues; therefore, it was considered to be curatively unresectable, and anastomosis between the ileum and left colon was surgically developed that followed by chemotherapy.

## OUTCOME AND FOLLOW-UP

Although the patient was treated with multiple chemotherapies, such as irinotecan + cisplatin (as the first-line therapy) and etoposide + carboplatin (as the second-line therapy); however, the tumor showed no significant response, and disease was rapidly progressed due to this invasive growth, in which the tumor induced the bile duct and duodenal obstruction by tumor progression. An additional stent for the duodenal stenosis was also placed; however, the appetite and general condition did not recover and he died 4 mo after the diagnosis.

## DISCUSSION

The World Health Organization classification, published in 2010, divides NETs of the digestive tracts into NET grade (G) 1, NET G2, and NECs, based on mitotic counts and the Ki-67 proliferation index, regardless of tumor size, extent, or location, and also the colorectal NEC is a rare tumor with the incidence rate of 0.1%<sup>[1]</sup>. In addition, NEC and colorectal mixed adenoneuroendocrine carcinoma (MANEC) revealed high-grade cancer cells evidenced by high level of Ki-67 index (> 20%). The advanced NEC typically associates with the expansive growth pattern similar to that associates with the stage II colon cancer, *i.e.*, yellowish ulcer and raised margin of non-neoplastic mucosa like submucosal tumor<sup>[6]</sup>. Colorectal NEC involves high malignant potential with poor differentiation and high invasiveness, while its prognosis is worse than colorectal adenocarcinoma. The median survival rate and relative survival (%) at 5 years of NEC and adenocarcinoma were 7.1–14.7 and 36.0 mo, and 8.0%–16.3% and

**Table 1 Results of laboratory investigation on the day of admission**

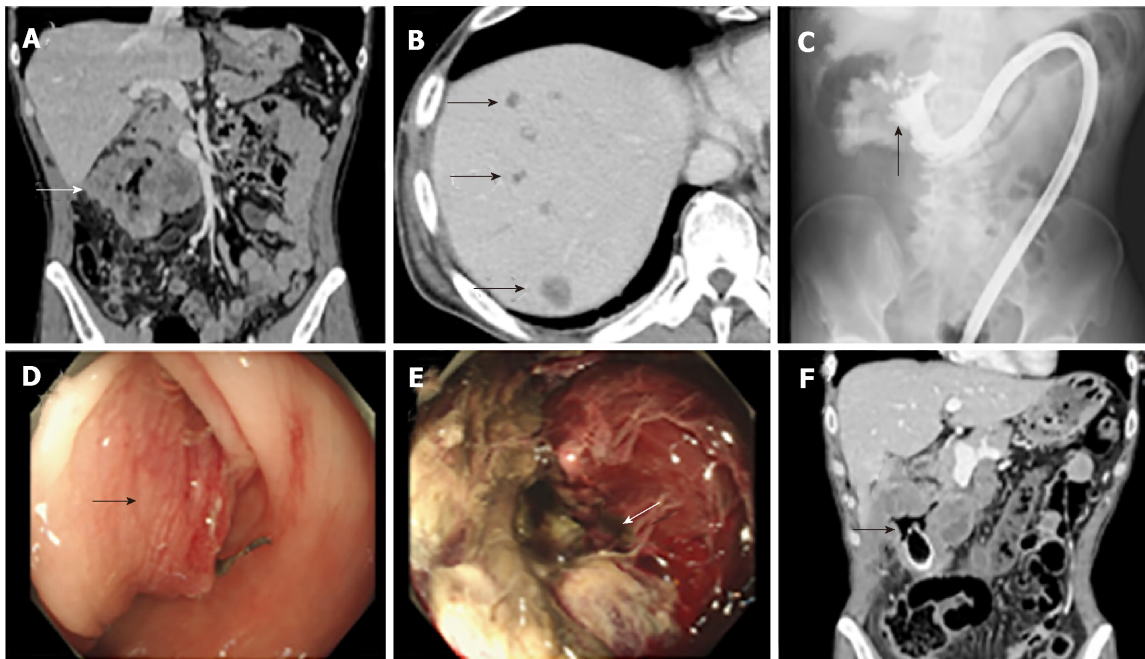
WBC	9740 / $\mu$ L
RBC	$344 \times 10^4$ / $\mu$ L
Hb	9.4 g/dL
Ht	29.1%
Plt	$37.3 \times 10^4$ / $\mu$ L
TP	6.7 g/dL
Alb	3.8 g/dL
BUN	12.3 mg/dL
Cre	0.85 mg/dL
AST	12 IU/L
ALT	9.0 IU/L
LDH	328 IU/L
ALP	166 IU/L
$\gamma$ -GTP	43 IU/L
T-bil	0.4 mg/dL
CRP	5.0 mg/dL
CEA	7.4 ng/mL
CA19-9	1.0 U/mL

WBC: White blood cells; Hb: Hemoglobin; Ht: Hematocrit; Plt: Platelet counts; TP: Total protein; Alb: Albumin; BUN: Blood urea nitrogen; Cre: Creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase;  $\gamma$ -GTP,  $\gamma$ -glutamyl transferase; T-bil: Total bilirubin; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

50.2%, respectively. In addition, MANEC showed significantly poor OS compared with adenocarcinoma<sup>[3]</sup>. Because of the aggressive progression, NEC was mainly detected at advanced stage in comparison with adenocarcinoma resulted in the fact that 57.9%–67.5% of NEC patients were initially diagnosed with the stage IV compared with the finding that 25.2% of cases with adenocarcinoma were diagnosed with stage IV<sup>[1,3,6]</sup>. These findings suggest that neuroendocrine differentiation is the cause of higher malignant potential and worse prognosis. Table 2 presents the characteristics of 59 cases with advances NEC and MANEC, while the terms “colon” and “neuroendocrine carcinoma” were searched in PubMed, and the available clinical information was summarized.

Although a reliable treatment guideline has not presented yet, chemo-therapy plays a key role in treatment of patients with advanced NEC. Platinum-based chemotherapy, as a therapeutic strategy, is often used and the response rate is 42% to NEC that is relatively lower than that of 67% for small cell lung cancer<sup>[6]</sup>. A previous study proposed the effectiveness of 5-fluorouracil (5-FU)-based chemotherapy<sup>[7]</sup>; however, as mentioned earlier, a standard regimen for NEC has not been developed yet. It has also been reported that a regimen for the MANEC, comprising neoplasms with both neuroendocrine carcinomatous and adenocarcinomatous components, depends on which component dominantly contributes. In the present research, the number of patients with NEC and MANEC was 44 and 13, and the mean age was 61.5 and 56.2 years old, respectively (other two patients were diagnosed as the combination of NEC with squamous cell carcinoma). Besides, 29 patients were died due to these tumors, while 15 patients were saved by treatment with tumor resection and chemotherapy. The OS of 48 patients who received the tumor resection was 19.2 mo, which was significantly higher than 3.4 mo belonged to 7 patients who did not undergo surgical resection. These results highly reveal that surgical resection is essential to prolong prognosis. However, a poor prognosis was observed in the majority of those patients because of the delayed diagnosis similar to our case, and we therefore were unable to perform the surgical treatment. To follow the chemotherapy, an effective stenting for the obstructive tumor is vital for treatment and also for quality of life (QOL) of the patients as significant rapid tumor progression in both inside and outside the colon are clinical features of NEC and may cause intestinal tract obstruction and also stenosis of the surrounding organs, including small intestine. The rapid growth resulted in the huge tumor upon the diagnoses, as our findings showed that the average diameter of NEC was 76.8 mm, and growth toward outside of the colon, outward invasion, which was observed in 42% of the patients,



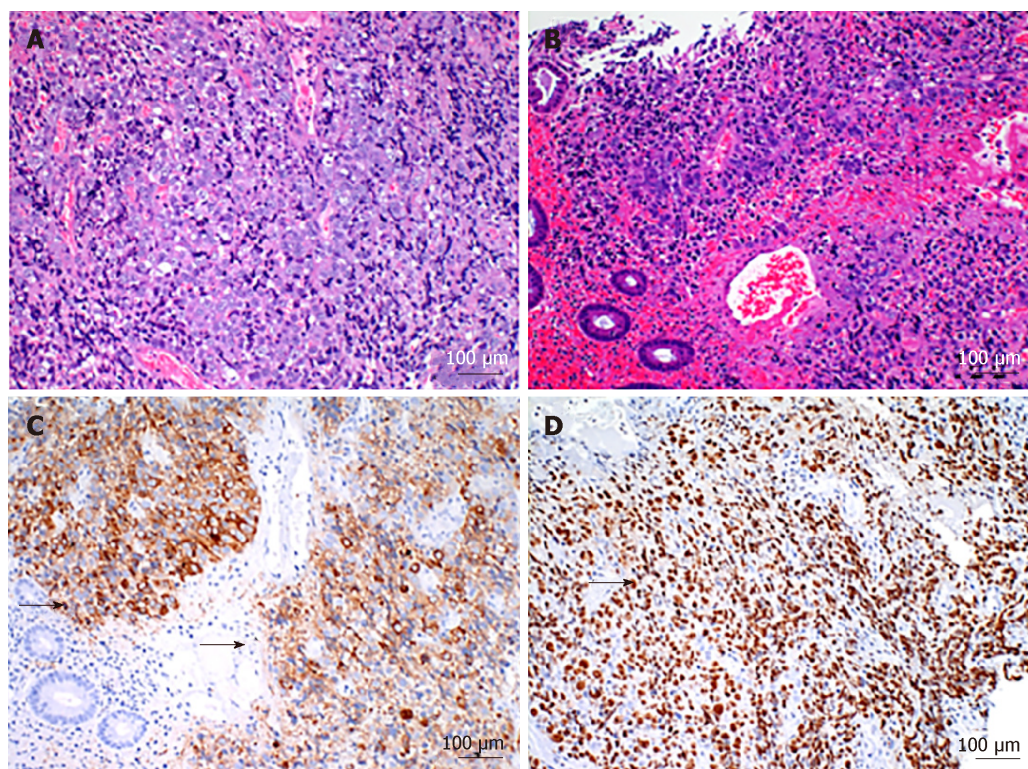


**Figure 1 Imaging findings.** A: Contrast-enhanced computed tomography (CT) of the abdomen shows an irregularly shaped and enhanced mass (10 cm) at the right colonic flexure. White arrow indicates the tumor; B: CT showed multiple low-density tumors in the liver with no enhancement effect. Black arrows indicate the tumors; C: Colonic enema with water-soluble contrast medium (Gastrografin®) shows an irregular shape in the lumen of colon. Black arrow indicates the stenotic and irregular lesion; D: Colonoscopy showed the mass in the right transverse colon with significant stenosis due to submucosal elevation of the tumor. Black arrow indicates the submucosal elevation; E: Colonoscopy showed the necrotic tissue in the lumen of the tumor. White arrow indicates the necrotic lesion; F: Perforation of the colon by stenting. Black arrow indicates the free-air and intratumoral air outside the stent.

and similar results reported by a previous study<sup>[5]</sup>. Importantly, MANEC, associating with a rapid growth pattern in NEC, showed 60% of outward growth, indicating that the higher growth rate of the tumor cells represents this aggressive and infiltrative growth pattern. In our case, colonic and duodenum self-expandable metallic stent (SEMS) were inserted for direct colonic obstruction and infiltrative growth toward the duodenum. Generally, stenting in the gastrointestinal tract for malignant obstruction due to the adenocarcinoma has been reported as an effective and safe strategy with the clinical success rate of 90.5%–95.5%, as well as an adverse event rate of 3.5%–7.6%<sup>[8–10]</sup>. In addition, it is extremely rare to find out the tumor perforation, following the stent placement with the rate of 2% that might occur at the necrotic tissue of the tumor<sup>[11]</sup>. The main reason of the tumor perforation following SEMS insertion in our case is likely due to the rapid growth of the NEC tumor cells at both inside and outside the colon, evidenced by the tumor necrosis appeared in the endoscopic findings and 90% of positive cells by Ki67 staining that led to the vulnerability of the mass structure. As successful induction of the chemotherapy could lead to the better survival period (Table 2), stenting is of great importance to manage the symptoms and QOL. The summary of the chemotherapy induced in the recent cases are summarized in Table 2<sup>[7,12–68]</sup>. As shown in Table 2, 24 NEC patients received platinum-based chemotherapy and 11 NEC patients received 5-FU-based chemotherapy as the first-line regimen. In particular, 9 MANEC patients received 5-FU-based chemotherapy, and only 1 patient received platinum-based chemotherapy, probably targeting the component of adenocarcinoma. The responses to the platinum-based and 5-FU-based chemotherapy were (CR, 2; PR, 7; stable disease (SD), 3; and progressive disease (PD), 11; and (CR, 0; PR, 3; SD, 2; and PD, 6), respectively. Therefore, development of an effective chemotherapy-based regimen is essential as well.

Consequently, exertion is essential to detect NEC in early stage, thereby the correct diagnosis is of great importance, while NEC and MANEC are frequently misdiagnosed as adenocarcinoma or another malignant tumor at the first imaging or histological study<sup>[5]</sup>. Thus, to diagnose accurately, detailed endoscopic observation and histological research are required. A study suggested that fluorodeoxyglucose positron emission tomography (FDG-PET) associates with high-sensitivity to tumor, as well as high-proliferation (*e.g.*, NEC)<sup>[12]</sup>, therefore FDG-PET is precious to diagnose tumor with clinical feature of NEC.

At present, early diagnosis followed by the surgical resection is the most favorable clinical course for better prognosis, and if impossible, careful making decision for



**Figure 2 Histological findings of the tumor.** A: Hematoxylin-eosin staining showed that the tumor cells were poorly differentiated; B: Complicated with the intratumoral bleeding; C: Tumor cells underwent immunohistochemical staining for Synaptophysin. Black arrows indicate the positively stained cells; D: A high proliferative fraction of immunohistochemical staining for Ki67 staining. Black arrows indicate the positively stained cells.

chemotherapy and stenting for obstruction is significant. Furthermore, NEC with higher cell proliferation not only may cause the intestinal obstruction, but also the invasive growth to the surrounding organs, leading to the tumor rupture after stenting inside the tract, thus careful consideration is essential for making a right clinical decision. In particular, the placement of stent needs to be highly taken into account as it is significantly different from the colorectal adenocarcinoma in terms of the cell growth pattern, and clinical characteristics.

## CONCLUSION

As a result, as the rapid growth pattern of NEC is difficult to be managed, early diagnosis and careful management with the understanding of the disease are essential. However, accumulated data related to this rare disease may assist physicians to effectively treat patients with the help of development of chemotherapy, stenting method, as well as upgrading medical devices. We hope that the results of the present study can enhance the information related to NEC and also help the scholars to better understand the disease.

Table 2 Summary of the cases reported to date

No.	Ref.	Year	Age	Gender	Diagnosis	Location	Size (mm x mm)	Positive for Ki-67 (%)	Stenosis (%)	Symptom of Obstruction	Invasion to Surrounding Tissue	Metastasis	Surgery	CT	RT	Chemotherapy	Response to Chemotherapy	Overall Survival (mo)
1	12	1996	65	F	ECC	A	150	N/A	100	+	-	+	-	+	-	P	PD	3
2	13	1998	70	M	ECC	R	80x55	N/A	60	-	-	+	+	+	-	P	PD	15
3	14	1999	54	F	MAE NC	S	60	N/A	N/A	-	+	+	+	+	-	F	N/A	N/A
4	14	1999	46	M	NEC	R	160x130x40	N/A	100	-	-	+	+	+	-	P	PD	8
5	15	2002	50	F	small cell carcinoma	R	45x55	N/A	50	-	-	+	+	+	-	P	CR	54, alive
6	16	2002	76	M	MAN EC	C	45x45x15	N/A	N/A	-	N/A	+	+	+	-	N/A	N/A	N/A
7	17	2002	67	F	small cell carcinoma	A	N/A	N/A	N/A	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	18	2003	61	F	ECC	R	N/A	N/A	60	-	+	+	+	+	-	P	PD	5
9	19	2004	78	M	ECC	R	47x43	N/A	60	-	-	+	+	+	-	P	PD	6
10	20	2004	38	M	NEC	T	100	N/A	100	+	+	-	+	+	-	P	PR	14
11	21	2004	79	M	MAN EC	R	30x20	N/A	30	-	-	+	+	+	+	F	PR	21, alive
12	22	2006	34	M	ECC	T	170x110	N/A	100	-	+	+	+	+	-	P	PD	8
13	23	2006	48	M	ECC	R	120x100	N/A	50	-	+	+	+	+	+	P	SD	24, alive
14	24	2006	62	M	NEC	A	45x25	N/A	60	-	+	+	+	+	-	F	PD	11
15	25	2006	71	M	NEC	D	40x50	N/A	50	-	-	+	+	+	-	F	PD	6
16	26	2007	53	M	NEC	R	32x27	40	30	-	+	+	+	+	-	P	PR	51
17	27	2007	45	M	ECC	C	42	N/A	50	-	-	+	+	+	+	P	PR	67
18	28	2007	44	F	MAN EC	T	80x75x50	N/A	100	N/A	N/A	+	+	+	-	N/A	N/A	N/A
19	29	2007	38	F	ECC	T	29x27	N/A	50	-	+	+	+	+	-	F	PD	9
20	30	2008	63	M	ECC	A	50x70	N/A	100	-	-	+	+	+	-	F	PD	41
21	31	2008	56	M	ECC	C	40x50	N/A	N/A	-	-	+	+	+	-	P	PD	6
22	7	2008	61	M	ECC	R	50	N/A	100	+	+	+	+	+	+	F	PR	50, alive
23	32	2009	79	F	ECC	S	115x35	N/A	100	+/-	+	+	+	+	-	P	SD	14, alive
24	33	2010	78	M	NEC	S	82x74	N/A	N/A	-	+	+	+	+	-	F	SD	10
25	34	2010	59	M	ECC	N/A	N/A	80	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A
26	35	2011	63	M	NEC	A	N/A	N/A	N/A	N/A	-	+	+	+	-	F	PR	11
27	36	2011	70	M	NEC	A	74x51	N/A	60	-	-	+	+	-	-	-	N/A	N/A
28	37	2011	74	F	NEC	A	N/A	90	100	+	-	+	+	-	-	-	N/A	1
29	38	2011	76	F	NEC	A	N/A	66.3	50	-	-	+	+	+	-	P	PR	27, alive
30	39	2012	54	M	MAN EC	R	30	N/A	50	-	N/A	N/A	+	+	-	F	N/A	N/A
31	40	2012	76	F	NEC	T	183x115	N/A	100	-	+	-	+	+	-	F	PD	42, alive
32	41	2012	74	F	NEC	A	N/A	75	30	-	-	+	-	+	-	P	PR	8
33	42	2012	57	F	NEC	N/A	N/A	80	30	-	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A
34	43	2012	81	F	NEC	C,A	N/A	N/A	100	N/A	N/A	+	+	-	-	-	N/A	6

35	44	2012	68	F	NEC	S	30	N/A	50	-	N/A	+	-	-	-	-	N/A	0.5
36	45	2013	51	M	NEC	R	N/A	N/A	50	-	-	+	+	+	-	F	PR	12, alive
37	46	2013	68	M	NEC	R	N/A	N/A	50	-	-	+	+	+	+	P	PR	7
38	47	2014	77	M	NEC	A	40x35	20-30	30	-	-	+	+	+	-	F	PD	8, alive
39	48	2014	71	M	MAN EC	T	70x45	25	80	+	-	+	+	+	-	F	PD	13
40	49	2014	48	M	MAN EC	S	N/A	N/A	100	+	+	+	+	+	+	F	PD	3
41	50	2014	63	F	NEC	A	N/A	60-70	100	+	-	+	+	+	-	P	PD	10
42	51	2014	39	M	MAN EC	T	N/A	80	50	-	-	+	+	+	-	F	PD	7
43	52	2014	55	F	MAN EC	A	N/A	N/A	30	-	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
44	53	2014	34	F	MAN EC	D	N/A	N/A	100	+	+	N/A	+	N/A	N/A	N/A	N/A	N/A
45	54	2015	74	F	MAN EC	C	70x18	<20	100	+	+	-	+	+	-	F	SD	10, alive
46	55	2015	44	M	NEC	A	170x110x80	N/A	100	+	+	-	+	+	-	P	SD	84, alive
47	56	2016	70	M	MAN EC	D	100	82.9	100	-	+	+	+	+	-	F	CR	30, alive
48	57	2016	48	F	NEC	S	93x40	>90	100	+/-	-	+	-	+	-	P	PR	2
49	58	2016	70	M	NEC	S	15	N/A	25	-	-	+	-	+	-	P	N/A	N/A
50	59	2016	67	M	NEC+ SCC	C	60x50	>40	100	+	+	+	+	+	-	P	PD	3
51	60	2017	49	F	ECC	T	100x100	N/A	100	-	+	-	+	-	-	-	N/A	10, alive
52	61	2017	60	M	NEC	Anus	20	90	N/A	-	-	+	-	+	-	N/A	PR	N/A
53	62	2017	68	M	MAN EC	A	30	75	30	-	-	-	+	+	-	P	SD	N/A
54	63	2017	32	M	MAN EC	C	80x55	N/A	70	+/-	-	+	+	+	-	F	SD	6, alive
55	64	2017	61	F	NEC	T	50	90	100	+	N/A	-	+	-	-	-	N/A	N/A
56	65	2018	74	M	NEC	S	60x50	90	100	-	+	+	+	+	-	F	SD	36, alive
57	66	2018	68	M	NEC+ SCC	D	35x35	80	100	+/-	-	+	+	+	-	P	PD	N/A
58	67	2018	40	F	NEC	R	45x36x44	N/A	50	-	N/A	+	-	+	+	P	CR	N/A
59	68	2018	77	M	ECC	T	N/A	N/A	100	+	-	+	+	-	-	-	N/A	2
60	N/A	Our Case	55	M	NEC	T	100x100	90	100	+	+	+	-	+	-	P	PD	4

F: Female; M: Male; ECC: Endocrine cell carcinoma; MANEC: Mixed adeno-neuroendocrine carcinoma; NEC: Neuroendocrine carcinoma; SCC: Squamous cell carcinoma; A: Ascending colon; R: Rectum; S: Sigmoid colon; C: Cecum; T: Transverse colon; D: Descending colon; P: Platinum-based chemotherapy; F: 5-fluorouracil-based regimen; PD: Progressive disease; CR: Complete response; SD: Stable disease; PR: Partial response.

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