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Case report

Advanced gastric glandular-endocrine cell carcinoma with 1-year survival after gastrectomy

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Abstract

Primary gastric endocrine cell carcinoma (ECC) is extremely rare. In general, when it is advanced, gastric ECC causes extensive ulceration (type 2) and invades or metastasizes to other organs, frequently to the liver and sometimes to the lungs or bones, and carries a poor prognosis. We herein report a 67-year-old man with advanced gastric ECC of extensive-polypoid shape (type 1) but without distant metastasis, who underwent total gastrectomy and treatment with oral tegafur-uracil (UFT), and showed no sign of recurrence 1 year later.

Key words Endocrine cell carcinoma · Stomach · Polypoid type · Type 1

Introduction

Endocrine cell carcinoma (ECC) is rare in the gastrointestinal tract, accounting for about 1% of cancers in the esophagus, 0.2% in the colon, and 0.1%–0.4% in the stomach [1–3]. Gastric ECC shows various macroscopic types in the early stage [4], but in patients with advanced disease, the expansive-ulcerative type is seen in more than half of the patients and the polypoid type is a minority [5,6]. The biological behavior of gastric ECC is aggressive, as shown by frequent metastasis to liver and lymph nodes and the poor effectiveness of chemotherapy [4,5–7] (Table 1). Here, we report a patient with advanced gastric ECC of polypoid shape and large size, without any recurrence 1 year after gastrectomy.

Case report

A 67-year-old man, who had congenital hearing loss, diabetes mellitus, hypertension, and benign prostatic hypertrophy, was referred to our hospital because of a polypoid gastric lesion first detected at another hospital after a complaint of epigastric discomfort. On admission, there was no enlargement of any superficial lymph node. Peripheral blood showed moderate anemia (RBC, $343 \times 10^4/mm^3$; hemoglobin [Hb], 8.9 g/dl; hematocrit [Ht], 27.3%), and serum showed hypoalbuminemia (albumin, 3.4 g/dl), minimally high C-reactive protein (CRP; 1.4 mg/dl; normal range, <0.6 mg/dl), normal levels of tumor markers (alpha-fetoprotein [AFP], 1.8 ng/ml, carcinoembryonic antigen [CEA], 1.2 ng/ml, and carbohydrate antigen [CA]19-9, <10 U/ml) and various levels of gastrointestinal hormones — gastrin, 756 pg/ml; (normal range, 42–200 pg/ml); somatostatin, 23.0 pg/ml (normal range, 1–12 pg/ml); serotonin, 12.2 μg/dl (normal range, 10–30 μg/dl); glucagon, 43 pg/ml (normal range, 70–160 pg/ml); vasoactive intestinal peptide (VIP), <5 pg/ml (normal range, ≦100 pg/ml); insulin, 6 μU/ml (normal range, 3–18 μU/ml).

Gastric fluoroscopy (Fig. 1) showed a large polypoid lesion consisting of multiple irregularly shaped nodules extending from the cardia to the body. Gastric endoscopy (Fig. 2) showed a Type 1 (polypoid) lesion with an abrupt tumor margin and rough surface covered with whitish-yellowish exudate. The lesion was proven to be ECC by histological examination of a biopsy sample. Abdominal computed tomography (CT) (Fig. 3) showed an enhanced polypoid lesion and an enlarged lymph node adjacent to the posterior wall of the gastric body, but no liver metastasis.

Total gastrectomy (Fig. 4) and splenectomy was performed, without any complication. The surgical stage was IIIA (T3N1H0P0M0CY0) [48]. The histological diagnosis was gastric glandular-endocrine cell carcinoma, medullary-type, INFβ, ss, ly1, v2, n1 (#3), pm(−), dm(−), 10 × 8.5 cm, type 1, Post, UM [48]. A histological adenocarcinoma component was recognized in the continuity of the ECC component (Fig. 5a–c). Immunohistological staining of the ECC was strongly and

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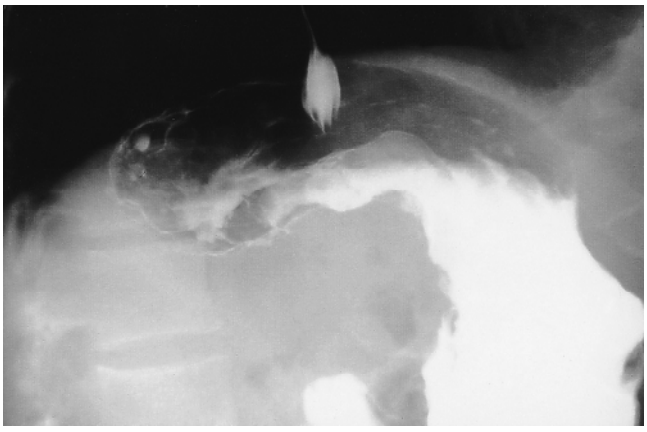

Fig. 1. Gastric fluoroscopy showed a large polypoid lesion, consisting of multiple irregularly shaped nodules, in the gastric cardia and body

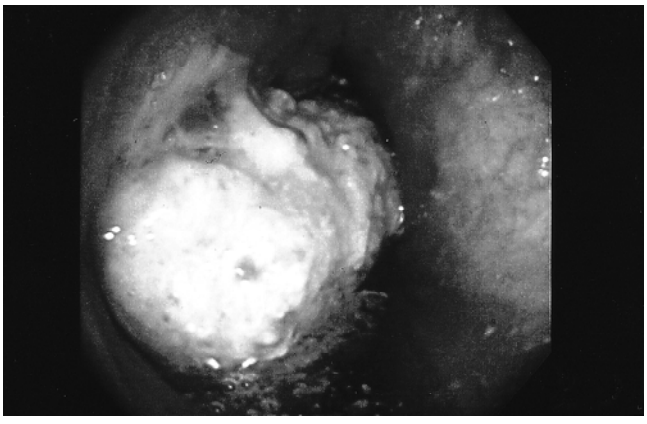

Fig. 2. Gastric endoscopy showed a polypoid lesion with an abrupt tumor margin and rough surface covered by a whitish-yellowish exudate

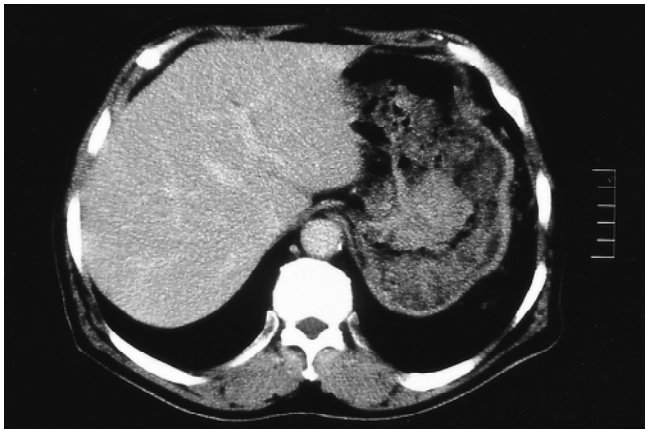

Fig. 3. Computed tomography demonstrated an enhanced polypoid lesion and an enlarged lymph node adjacent to the posterior wall of the gastric body, without liver metastasis

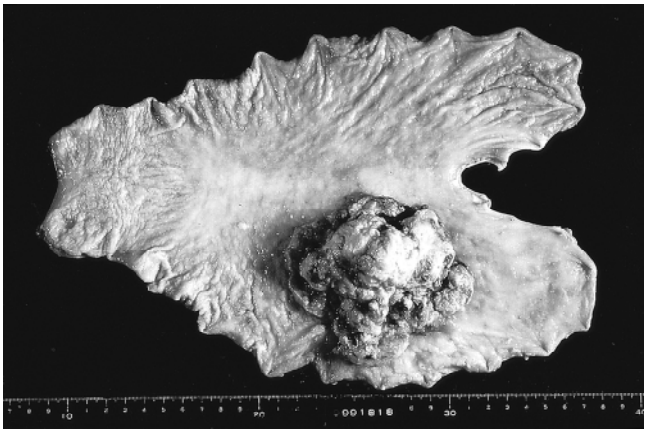

Fig. 4. Macroscopic view of resected stomach with a 10-cm rough polypoid lesion in the posterior wall of the gastric body and cardia

diffusely positive for Grimelius, chromogranin, neuron-specific enolase (NSE) (Fig. 5d), but negative for serotonin, gastrin, somatostatin, glucagon, insulin, pancreatic polypeptide, peptide YY, adrenocorticotropic hormone (ACTH), Fontana-Masson, MUC2, MUC5AC, and CD10. All of these immunostainings, except for Grimelius (focally positive) and CD10, were negative in the adenocarcinoma component. No hybrid cells, i.e., those with both adeno- and endocrine-cell characteristics, were recognized in the double-stained sections in which MUC2, MUC5AC, and CD10 were used for detecting adeno-characteristics and chromogranin and NSE were used for detecting endocrine characteristics. Immunostaining of p53 and Ki-67 [49] was strongly and diffusely positive in both the ECC and adenocarcinoma components. The yellowish-whitish exudate that covered the tumor surface consisted of necrotic cancer cells, inflammatory cells, and fibrin.

The patient did well in his postoperative course and was soon discharged, taking oral tegafur-uracil (UFT), 300 mg/day. One year after the operation, he was examined by abdominal CT scan, which showed no recurrence or liver metastasis.

Discussion

Early in the twentieth century, endocrine cell tumors were categorized as "carcinoid" because of their histological resemblance to carcinoma [50]. Later, carcinoids were histologically divided into four types (A to D) by Soga et al. [51]. In Japan, the category of gastric endo-

Table 1. Clinicopathological features of gastric endocrine cell carcinoma in the Japanese and English-language literature (1961–2001)

Case no.	Author	Year reported	Age/Sex	Location[a]	Size (cm)	Gross type[b]	Depth of invasion
Japanese literature							
1	Hayashi [8]	1980	69/M	U (Post)	6 × 6	Type 3	se
2	Kazato [9]	1983	77/M	M (Ant)	1 × 1	III + IIc	sm
3	Ushiyama [10]	1984	58/M	U	8 × 7 × 2.5	Type 1	se
4	Emi [11]	1984	60/M	M (Less)	3.1 × 2	Type 3	se
5	Terasawa [12]	1985	69/M	EGJ	3.5 × 3	Type 2	mp
6	Kaketani [13]	1987	58/M	L (Gre)	2.5 × 2.5	IIa + IIc	sm
7	″	″	69/F	ML (Less)	15 × 10 × 11.5	Type 2	se
8	Ishihara [14]	1988	75/M	RS	10 × 7 × 2.5	Type 3	si
9	Iwafuchi [15]	1989	73/M	RS (Ant)	9.5 × 4.5	IIb	se
10	Takeshita [16]	1990	51/M	M (Less)		IIC	sm
11	″	″	57/M	M (Ant)		Type 2	si
12	″	″	76/M	M (Less)		Type 3	si
13	Matsumoto [17]	1990	55/M	ML (Less)	6.5 × 6.0 × 1.4	Type 2	ss
14	Maeta [18]	1990	67/F	L (Less)	6 × 5	Type 2	
15	Kuhara [19]	1991	69/M	ML (Less)	13 × 12	Type 1 + 2	ss
16	Uesugi [20]	1991	64/M	L (Less)	2.6 × 2.5	Type 2	ss
17	Gotoh [21]	1992	48/M	M (Gre)			si
18	Katsuyama [22]	1992	73/M	L (Gre)	6 × 5	Type 3	si
19	Kamio [23]	1992	56/M	M (Less)		Type 5[c]	
20	″	″	80/M	RS (Post)		Type 1	
21	Nakamoto [24]	1992	79/M	L (Post)	7 × 6.5	Type 2	ss
22	Masuyama [25]	1994	69/M	U (Less)	7 × 6.5	Type 3	ss
23	Nagafuchi [26]	1994	57/M	L (Gre)	4.5 × 3.5 × 1.5	Type 2	si
24	Imamura [27]	1995	73/M	M (Post)	4 × 2.5	Type 1	mp
25	Maekawa [28]	1995	77/M	U (Gre)		Type 4	ss
26	Kodama [29]	1995	68/M	L (Gre)	2	Type 2	mp
27	Fudaba [30]	1996	55/M	L (Less)	12 × 8, 5 × 3	Type 3	
28	Inoue [31]	1996	64/M	L (Ant)		Type 2	
29	Sakai [32]	1997	31/M	ML		Type 5[c] (multiple)	
30	Hiramoto [33]	1998	58/M	L (Gre)		Type 3	
31	″	″	75/M	M (Ant)		Type 1	
32	″	″	63/M				
33	″	″	62/M	M (Post)		Type 3	
34	″	″	64/F	RS (Ant)		Type 1	
35	Iwasaki [34]	1998	58/M	M (Gre)		Type 3	
36	″	″	69/M	M (Gre)		Type 5	
37	Yamamoto [35]	1999	56/F	LM (Less)	4 × 4	Type 2	
English-language literature							
38	Christodoulopoulos [36]	1961	36/F	U (Post)	3.5 × 2.5 × 2		
39	″	″	75/F	L (Less)	2.3 × 1.8		
40	Vasudeo [37]	1965	45/F	L	6.5 × 5		mp
41	Brodman [38]	1968	66/F	U	10	Type 2	si
42	Parks [39]	1970	56/M	ML	16 × 8		

Metastasis			Operation[e]	Chemotherapy and other treatment	Prognosis[o]
Liver	N[d]	Other			
−	+		STD + DP	−	9d, death of other disease
−	+	−	SG	−	NM
+	+	Skin, bone, etc.	−	Radiation + ADM, MMC, MTX	2m, death
−	+		SG	−	6m, death
+	+		PG	TU[f] (orally), cyclophosphamide	4m, death
−	+		SG	−	2y, no recurrence
−	+	Abdominal wall, etc.	SG	MMC, 5-FU, ADM	5m, death
+	+	Lung	−	−	2m, death
+	+	Lt. adrenal	−	TU[f], Ubenimex	4m, death
		− → Brain	+ (method NM[o])	−	1y, death
+			−	−	4m, death
+			TG	−	2y, death
−	+	−	SG	MFC	3y, no recurrence
+	+	− → Peritoneum	−	CAI[g]: MMC, ADM→ MTX, 5-FU, MMC, leucovorin	3m, death
−	+	− → Lung	SG	−	2m, death
−	+	−	SG	−	8m, no recurrence
− → +	−	Mediastinum, etc.	SG	+ (menu: NM)	5m, death
− → +	+		SG	MMC, 5-FU, OK-432, 5 KE	2m, death
			TG	−	NM
			−	−	NM
− → +	−		SG	5-FU (orally)	17m, death
+	+	−	TG	Res[h]: 5-FU, OK-432 2 KE → 5-FU, TU[f] (orally), OK-432	7m, alive
−	+	−	SG	CDDP, etoposide → etoposide (orally)	8m, no reccurence
− → +	+		SG	−	2y, death
−	+	− → Peritoneum	TG	−	10m, death
−	+		SG	FA-CDDP	5m, alive
+	+	Peritoneum	Unresectable	MMC, 5-FU	9m, death
−	+		−	Carboplatin, etoposide	7m, death
		Bone	−	HDCT[i], PBSCT[j]	8m, alive
− → +	+	Peritoneum	SG	CDDP, 5-FU	6m, death
− → +	+		STG → PH	TU[f] (orally)	8m, alive
−	+		STG	CDDP, TU[f]	(period NM), alive
− → +	+		TG	TU[f]	4m, death
− → +			RRS	Lentinan, TU[f] + HAE[k]	7m, alive
+	−	−	−	CAP-PVP[l]	3m, death
+	−	−	−	CAP-PVP, TU[f]	10m, death
+			TG	Res[h]: CDDP, Tegafur suppo	4m, death
+			Simple excision	−	10m, alive
			SG		9d, death
−	+		SG	NM[p]	NM
−	+	Omentum	EG + Sp	−	3y 6m, alive
−	+	Omentum, pancreas, spleen	SG + Sp		2m, death

Table 1. *Continued*

Case no.	Author	Year reported	Age/Sex	Location[a]	Size (cm)	Gross type[b]	Depth of invasion
43	Matsusaka [1]	1976	54/M	L		Type 5[c]	mp
44	″	″	65/F	M (Less)	4 × 2.2	Type 2	ss
45	Chejfec [40]	1977	66/M	U	9 × 8 × 1		
46	″	″	79/M	(Gre)	15 × 9 × 7	Type 2	
47	Eimoto [41]	1980	66/M	U (Ant)	9 × 7.5 × 4	Type 2	si
48	Abrams [42]	1980	33/F	UML	0.2–4.5	I (multiple)	sm
49	Shibuya [43]	1985	54/M	L (Gre)			si
50	Fukuda [44]	1988	74/M		0.8	IIc	sm
51	Hussein [45]	1990	42/M	L (Less)	3	Type 2	si
52	O'Byrne [46]	1997	54/M	U			
53	Sato [47]	1997	74/M	U (Less)	5 × 4 × 1.5	Type 2	ss
54	Current patient	2001	67/M	M (Post)	10 × 8.5	Type 1	ss

SMT, Submucosal tumor; ADM, adriamycin; MMC, mitomycin C; MTX, methotrexate; 5-FU, 5-fluorouracil; CDDP, cisplatin; VCR, vincristine
[a] U, Upper-third stomach; M, middle stomach; L, lower third stomach; EGJ, esophgo-gastric junction; RS, remnant stomach; Ant, anterior wall; Post, posterior wall; Gre, greater curvature; Less, lesser curvature
[b] Japanese classification of gastric carcinoma
[c] SMT-like gross type
[d] Lymph node
[e] SG, Subtotal gastrectomy; TG, total gastrectomy; PS, pancreaticosplenectomy; STG, splenototal gastrectomy; PH, resection of left lateral lobe of the liver; RRS, resection of the remnant stomach; EG, esophagogastrectomy; Sp, splenectomy
[f] Tegafur-uracil
[g] Injection from celiac artery
[h] Using reservoir catheter
[i] High-dose chemotherapy with CDDP + etoposide + CPA + VCR
[j] Peripheral blood stem cell transplantation
[k] Embolization of hepatic artery
[l] CPA + ADM + VCR + CDDP + etoposide
[m] Cyclophosphamide + doxorubicin + VCR
[n] Cyclophosphamide + doxorubicin + etoposide
[o] Vincristine + chlorambucil + dexamethasone
[p] NM, Not metioned; d, day(s); m, month(s); y, year(s)

crine cell carcinoma (ECC) was reported by Matsusaka et al. [1]. Endocrine cell tumors of the stomach have been classified as "classical-type carcinoid" and "endocrine cell carcinoma" (ECC) [2], with different cell origin [4,52], biological behavior, and prognosis [3,4]. Iwafuchi et al. [4] reported that most early gastric ECCs (76%) were located in the deep mucosa or submucosa and were adjacent to coexisting instramucosal differentiated adenocarcinomas. In our patient, an adenocarcinoma component was recognized in continuity with the ECC, which suggests ordinary histological carcinogenesis of an ECC or glandular-ECC.

In the development of gastric endocrine cell tumor, possible factors are chronic hypergastrinemia due to type A gastritis [52], pernicious anemia [53], and long-term treatment with proton pump inhibitors (PPI) [54]. In our patient, although there was no history of pernicious anemia or PPI administration and no gastrin production in the tumor, the serum gastrin level was revealed to be high. Although the origin of this high level was unknown, this may have played an important role in the progression of the tumor, because most gastrointestinal hormones, except for somatostatin, promote the proliferation of both the gastrointestinal epithelium and of cancer [3].

To date, 37 cases have been reported in the Japanese literature and 16 in the English-language literature, in terms of clinicopathology, therapies, and/or prognosis of gastric ECC (Table 1). According to previous studies with clinicopathological analysis [5–7,44], the macroscopic appearance of gastric ECC varies in its early stage. However, when it is advanced, type 2 (tumor-ulcerative) is dominant and type 1 (fungating or polypoid), as in our patient, is less frequent [5,6]. Matsui et al. [6] hypothesized that a crater-like ulceration develops, probably due to rapid proliferation, and that only a few tumors maintain a polypoid appearance in the advanced stage.

Metastasis			Operation[e]	Chemotherapy and other treatment	Prognosis[o]
Liver	N[d]	Other			
+			SG	−	1 y, death
				−	5 y, alive
−	+		Unresectable	−	1 m, death
+	−		−	−	2 m, death
+	+	Peritoneum	Unresectable	5-FU, MMC	5 m, death
−	+		TG	−	82 m, alive
+	+	Retroperitonium, omentum, pelvis	Unresectable	−	1 m, death
− → +	+	−	TG	5-FU, OK-432	6 m, death
+	+	Omentum	SG	CAV[m] → CDDP, VP-16 → 3-deazaguanine	9 m, death
−			−	CDE[n] → carboplatin, MTX + CDE → VCD[o]	22 m, death
−	+	−	TG	Tegafur → MTX, CDDP, epirubicin, 5-FU	21 m, death
−	+	−	STG	TU[f] (orally)	1 y, no recurrence

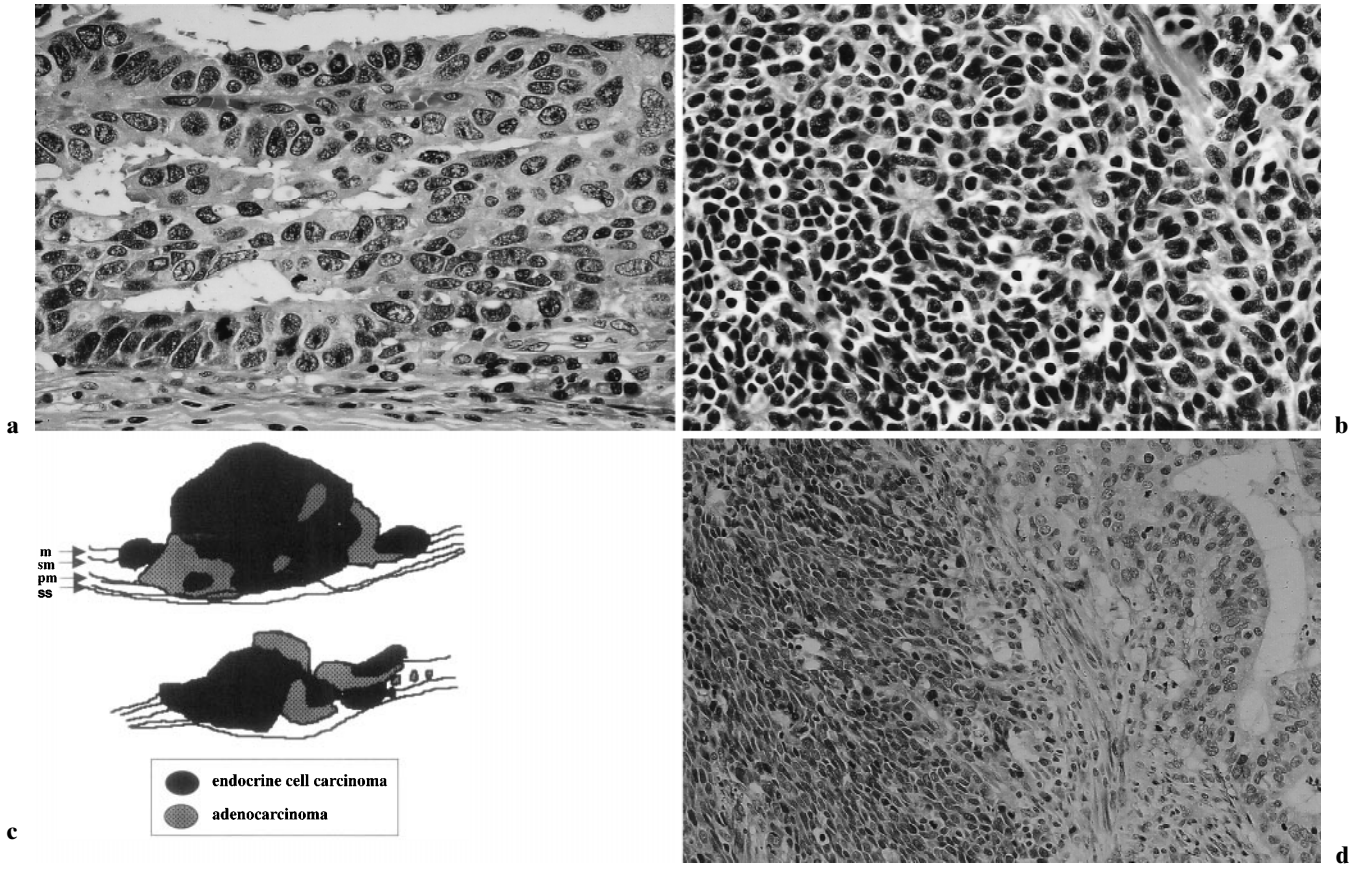

Fig. 5a–d. Histological findings of the tumor. This tumor consisted of components of **a** adenocarcinoma (×100) and **b** endocrine cell carcinoma (×100). **c** Schematic view of the main sections of the tumor. **d** Neuron-specific enolase (NSE) staining demonstrated strong positivity in the endocrine cell carcinoma component but not in the adenocarcinoma component (×50)

Concerning treatment, because of the tumor's aggressive biological characteristics, intensive chemotherapy, with or without operation, is recommended for gastric ECC at any stage [44]. Previously, several chemotherapeutic menus have been employed for gastric ECCs, but their effectiveness has been shown in only a few patients [32,46,55]. Sakai et al. [32] showed complete remission in a 31-year-old man with gastric ECC with multiple bone metastasis (case 29 in Table 1), with seven cycles of chemotherapy consisting of cisplatin (CDDP), etoposide, cyclophosphamide, epirubicin, and vincristine, followed by high-dose chemotherapy and peripheral blood cell transplantation. O'Byrne et al. [46] reported that a 54-year-old man with gastric ECC with severe epigastralgia and weight loss (case 52 in Table 1) was treated with six cycles of CDE (cyclophosphamide, doxorubicin, etoposide) chemotherapy, resulting in 11 months of complete remission. In patients with neuroendocrine carcinoma or undifferentiated small cell carcinoma, including lung small cell carcinoma and extrapulmonary small cell carcinoma, PE (cisplatin and etoposide) and CDE chemotherapies have been thought to be effective [56,57]. The tumor in our patient was resected curatively without distant metastsis, and this may explain the 1 year of survival in spite of the large tumor size and advanced stage. However, we thought it necessary to follow this patient carefully, because gastric ECCs show a high Ki-67 index, as in this patient [58], and some of them relapse after long intervals, such as 747 days [55].

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