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Case Report

Analysis of Gastric Carcinoma With Neuroendocrine Character

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The clinical significance of gastric adenocarcinoma with neuroendocrine differentiation is unclear because of its rarity. The aim of this study was to suggest a treatment strategy for this tumor. A total of 10 resected gastric tumors with neuroendocrine character, including 3 neuroendocrine carcinomas (NECs) and 7 adenocarcinomas with neuroendocrine differentiation, were retrospectively reviewed regarding tumor characteristics and therapeutic outcomes. The gastric adenocarcinomas with neuroendocrine differentiation had high rates of lymph node metastasis and vessel invasion, and showed the poor prognoses as NEC. The median survival time (MST) was 13 months. Preoperative and postoperative chemotherapy tended to prolong the MST compared with operation alone (112.5 versus 5 months; $P = 0.058$). Moreover, chemotherapy for postoperative recurrence significantly contributed to improving prognosis (MST, 15 versus 7 months; $P = 0.025$). Gastric adenocarcinoma with neuroendocrine differentiation had equivalently high potential malignancy as NEC. More aggressive treatment should be considered for this tumor according to NEC.

Key words: Gastric cancer – Neuroendocrine carcinoma – Adenocarcinoma with neuroendocrine differentiation

According to World Health Organization (WHO) classification in 2010,[1] a tumor is diagnosed as neuroendocrine carcinoma (NEC) if more than 70% of the cells show neuroendocrine character. In cases of up to 30%, the tumor is defined as adenocarcinoma with neuroendocrine differentiation (NED). An adenocarcinoma with 30% to 70% of neuroendocrine component is called mixed adenoneuroendocrine carcinoma. The gastric NEC was 0.1% to 0.4% of all gastric carcinoma,[2] and NEC was

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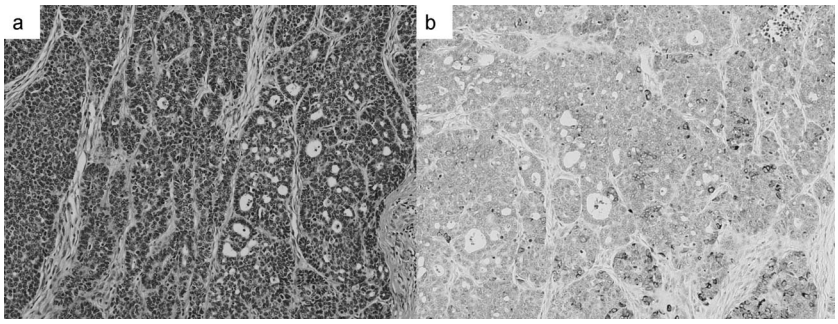

Fig. 1 (a) Adenocarcinoma with NED contains both adenocarcinoma and neuroendocrine component. In addition, the latter was less than 30% of each tumor (hematoxylin-eosin, ×100). (b) Tumor cells with NED were positive for synaptophysin (×100).

recognized as a poor-prognosis tumor. Chiba *et al*[2] reported that both lymphatic and vascular invasion were observed in more than 80% of NECs, and the median survival time (MST) of patients with gastric NEC was reported to be 8 to 13.3 months.[3,4] Their property seemed to be detected, so the National Comprehensive Cancer Network (NCCN) guidelines for NEC[5] were separated from those for conventional gastric adenocarcinoma.[6]

The prognoses of patients with NED component were known to be worse than those for typical adenocarcinoma in esophagus,[7] colon,[8] or prostate.[9] Recently, gastric adenocarcinoma with NED has been also reported to have unfavorable outcomes.[10] However, the treatment strategy for NED in gastric adenocarcinoma was not established yet. The patients with resectable gastric NEC usually underwent operation and chemotherapy. Although the chemotherapy regimen for small cell lung carcinoma is recommended for gastric NEC in the NCCN guideline,[5] several reports recently showed the efficacy of the regimens for conventional gastric adenocarcinoma, such as S1, cisplatin (CDDP), or irinotecan (CPT).[11] Therefore, we compared cases of NEC and adenocarcinomas with NED, to demonstrate the character of NED and to propose a treatment strategy for the tumor type.

Patients and Methods

Patients

This study included 10 patients who underwent operation for their gastric cancer with neuroendocrine character at the Kobe University Hospital between January 1998 and December 2013. All patients signed an informed consent form regarding the analysis of tissue specimens collected during operation.

Clinicopathologic data, operation procedures, and patient outcomes were extracted from the medical chart, operation records, and pathologic reports. The two types of tumor, including NEC and adenocarcinoma with NED, were compared based on the following factors: tumor status, surgical results, chemotherapeutic outcomes, and follow-up data.

The pathologic specimens were examined and assessed using the Union for International Cancer Control classification.[12] The definition of adenocarcinoma with NED was: (1) the neuroendocrine component was less than 30% of the tumor (Fig. 1a), and (2) tumor cells were positive for chromogranin A or synaptophysin (Fig. 1b). The effect of preoperative therapy was judged on the basis of the modified tumor regression grade (mTRG).[13] That score was briefly evaluated as follows: mTRG1 corresponded to the absence of tumor cells and replacement by abundant fibrosis or infarctlike necrosis (ILN); mTRG2 corresponded to rare residual tumor cells scattered throughout abundant fibrosis or ILN; mTRG3 corresponded to more residual tumor cells throughout predominant fibrosis or ILN; mTRG4 corresponded to a large amount of tumor cells predominating over fibrosis or ILN; and TRG5 corresponded to tumor cells without any fibrosis or ILN.

Statistical analysis

The statistical analysis was conducted using JMP 11 (SAS Institute Inc, Cary, North Carolina). A χ^2 test was used to assess the relationships between histologic types and patient or tumor characteristics. Recurrence-free survival (RFS) and overall survival (OS) were calculated with the Kaplan-Meier method and were analyzed using a log-rank test. A significant difference was defined as $P < 0.05$.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. Eight patients were male, and the median age was

Table 1 Patient characteristics

	Value
Age, y, median (range)	69 (56–75)
Sex, male/female, n	8/2
Depth of tumor invasion (T) (1/2/3/4), n	2/4/3/1
Lymph node metastasis (N) (0/1/2/3), n	3/6/0/1
Distant metastasis (M) (0/1), n	6/4
Stage (I /II/III/IV), n	2/3/1/4
Lymphatic invasion (0/1/2/3), n	3/3/2/2
Venous invasion (0/1/2/3), n	2/2/1/5
RFS, mo, median (range)	4.5 (1–165)
OS, mo, median (range)	13 (2–165)

69 years (range, 56–73 years). Eight tumors invaded more than the muscularis propria. A total of 7 patients had lymph node involvement, and 5 were classified more than stage III. Seven patients relapsed after operation. The MST of all patients after operation was 13 months.

Relationship between histologic type and prognosis

The 10 patients were subdivided into NEC (n = 3) and adenocarcinoma with NED (n = 7). Mixed adenoneuroendocrine carcinoma was not found. The lymphatic infiltration was more severe in NEC ($P = 0.015$), whereas there was no significant difference between 2 types of tumors in other factors, including T category, N category, M category, stage, and venous infiltration. A total of 2 patients with NEC and 5 with adenocarcinoma with NED had recurrence after operations. The median RFS rates of NEC and adenocarcinoma with NED were similar (2 versus 5 months), and their MSTs were also close (15 versus 11 months). Based on these results, adenocarcinoma with NED might have as aggressive a behavior as NEC.

Relationship between therapeutic approach and prognosis

A total of 2 patients were treated with preoperative and postoperative chemotherapy, and 5 underwent postoperative chemotherapy only. On the other hand, 3 patients did not receive chemotherapy for their entire course (Table 2). The chemotherapeutic regimens used were mostly those for conventional gastric adenocarcinoma, such as 5-fluorouracil (5-FU) with CDDP, S1, or CPT with CDDP. The response evaluations of preoperative chemotherapy were mTRG5 and mTRG2, respectively (Table 2).

Chemotherapy did not improve RFS, whereas it had some impact on survival. The MST with

Table 2 Clinical course of patients

No.	Age, y	Sex	Histology	Stage	Operation	Preoperative chemotherapy	mTRG	Postoperative chemotherapy	Recurrence	RFS, mo	Chemotherapy after recurrence	OS, mo	Prognosis
1	71	M	NEC	IIIA	PD + colectomy	—		5-FU + CDDP	—	104	—	104	Dead
2	68	F	NEC	IV	TG	—		—	+	2	—	2	Alive
3	66	M	NEC	IV	TG	—		CPT + CDDP	+	1	S1 + DCT	15	Alive
4	72	M	NED	IV	TG	DXR+ VCR+ CPA	2	DXR+ VCR+ CPA	—	165	—	165	Dead
5	66	M	NED	II	DG	—		—	+	4	—	5	Dead
6	58	M	NED	II	DG	CDDP + ETP	5	S1	+	19	PCT, CPT, AMR, RT	60	Alive
7	75	M	NED	IV	DG	—		CPT + CDDP	+	1	CPT, S1, PCT	25	Dead
8	56	M	NED	II	DG	—		S1	+	5	CPT, CDDP + RT	11	Alive
9	73	M	NED	IB	TG	—		—	+	4	Cap + trastuzumab	6	Alive
10	70	F	NED	IA	DG	—		—	—	7	—	7	Alive

AMR, amrubicin; Cap; capecitabine; CPA, cyclophosphamide; CPT, irinotecan; DCT, docetaxel; DG, distal gastrectomy; DXR, doxorubicin; ETP, etoposide; PCT, paclitaxel; PD, pancreatoduodenectomy; RT, radiotherapy; TG, total gastrectomy; VCR, vincristine.

chemotherapy, regardless of the timing, was longer than that without any chemotherapy (25 versus 5 months; $P = 0.061$). The combination of preoperative and postoperative chemotherapy provided the elongation of MST in comparison with operation alone (112.5 versus 5 months; $P = 0.058$). However, postoperative chemotherapy before recurrence alone could not improve survival. In addition, 2 patients who received chemotherapy after recurrence had significantly longer survival than 5 patients who did not receive chemotherapy (15 versus 7 months; $P = 0.025$). These results showed that chemotherapy, especially after recurrence, seemed to improve the prognosis of patients with gastric tumor with neuroendocrine character.

Discussion

NEC has been known to originate in dedifferentiation from adenocarcinoma,[14] and analysis about adenocarcinoma with NED made it clear that cells in such tumor proceeded from the same stem cells, whether cells showed NED or not.[15] Therefore, the NED component seems to result from the same dedifferentiation process as NEC. In the present study, the patients with NED had a process equally poor as those with NEC. Thus, we considered that highly aggressive treatment according to NEC would be needed for the patients who had NED cells within their cancer tissue, even in small amounts.

Recent reports showed that chemotherapy led to long-term survival in NEC patients.[4,16] For resectable NEC, operation and a chemotherapy regimen used for small cell lung carcinoma (CDDP or carboplatin and etoposide), with or without radiotherapy, are advised.[5] However, in that guideline, it was not precise (1) what staging of patients could be treated with chemotherapy, or (2) when the chemotherapy should be done. The description about NED could not be detected either.

The first problem is who should receive the chemotherapy. The NCCN guideline on gastric cancer recommends preoperative chemotherapy for the tumors that invade deeper than T2, and postoperative chemotherapy for a stage more extensive than stage IB.[6] Chemotherapy for early-stage NEC may be a reasonable suggestion, because NEC has a high potential of malignancy. The patients with NED should be also targeted, because patient no. 9, with pT1 and stage IB disease, had a recurrence within a short time in this study.

The second problem is when patients are forecasted to undergo postoperative chemotherapy. Chemotherapy tended to elongate survival. Described circumstantially, chemotherapy for recurrence significantly improved prognoses, and preoperative and postoperative chemotherapy tended to prolong OS. In our reports, the patients who underwent chemotherapy, especially preoperative and postoperative regimens, like patient nos. 4 and 6, became long-term survivors. Therefore, we suggest that patients with NED should be aggressively considered for preoperative and postoperative chemotherapy as well as NEC. Although patient nos. 4 and 6 were fortunately able to have received diagnosis prior to operation, this is rare, because the NED component resides partially in general and not always close to the tumor surface. Thus, it is probably difficult to perform preoperative chemotherapy in all cases with NED and NEC. Even in that case, we might well be able to improve the patient's outcome by taking a second best way, which means chemotherapy after the recurrence. Close follow-up is obviously needed. Although chemotherapy in the early postoperative period may improve survival, it was not presented in this study.

Some problems are still under debate, such as the mTRG grade of preoperative chemotherapy or the regimen of chemotherapy. As we stated above, preoperative chemotherapy may lead to better prognosis, like for patient nos. 4 and 6. Although the therapeutic effect for patient no. 4 was remarkable, that of no. 6 was, by contrast, limited. Moreover, in spite of the recommendation from the NCCN, the regimens for conventional gastric cancer were undertaken in Japan.[4] From our patient no. 1 or several reports,[10,16] those regimens sometimes seem to be effective. With the objective of RFS, and impact of postoperative chemotherapy, we need further investigation.

In conclusion, gastric adenocarcinoma with NED should be equally treated as NEC because of its potential malignancy. For these cases, preoperative and postoperative chemotherapy might be performed, if malignant cells with NED were diagnosed preoperatively. And chemotherapy after recurrence is also recommended.

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