

# A Case of Duodenal Neuroendocrine Carcinoma Treated with Amrubicin as Second-line Chemotherapy

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## ABSTRACT

We present the case of a Japanese man in his 60s with duodenal neuroendocrine carcinoma with distant metastases. Chemotherapy with irinotecan plus cisplatin was initiated as a first-line regimen. However, disease progression was observed after only two cycles. Therefore, amrubicin was administered as a second-line chemotherapy. The patient showed a long-term effect of amrubicin therapy, and the best response was a partial response after seven cycles. For duodenal neuroendocrine carcinoma, amrubicin therapy can be considered an effective treatment option as salvage chemotherapy.

**Key words:** duodenal neuroendocrine carcinoma – amrubicin - chemotherapy.

**Abbreviations:** AMR: amrubicin; CR: complete response; EP: etoposide/cisplatin; IP: irinotecan/cisplatin; NCCN: National Comprehensive Cancer Network; NEC: neuroendocrine carcinoma; PD: progressive disease; PR: partial response; SCLC: small-cell lung cancer.

## INTRODUCTION

Neuroendocrine carcinoma (NEC) of the gastrointestinal tract is rare, representing 0.1–1.0% of all gastrointestinal malignancies [1]. The esophagus is the most common primary site, accounting for approximately 50% of all gastrointestinal NEC cases. Duodenal NECs constitute 5% of gastrointestinal NECs. Most duodenal NECs occur in the papilla [2], therefore duodenal extra-ampullary NEC is extremely rare. In general, NEC displays an aggressive behavior; at least half of the patients have distant metastases at diagnosis [3]. Chemotherapy or chemoradiotherapy is performed for advanced NEC, and the regimen of chemotherapy is selected in the same way as for small-cell lung cancer (SCLC), which is clinicopathologically similar to NEC [4]. Therefore, as the first-line regimen, a

platinum-based combination, such as etoposide/cisplatin (EP) or irinotecan/cisplatin (IP) is chosen. However, a standard regimen has not been established, because evidence is lacking due to the very low incidence and poor prognosis of the disease. Consequently, evidence and available data are lacking even more for second-line than for first-line chemotherapy.

We present a case of NEC in the duodenal bulb with distant metastases. The patient was treated with an IP regimen as the first-line chemotherapy, but multiple bone metastases appeared after two cycles of IP therapy. Amrubicin (AMR) therapy was then initiated as second-line chemotherapy, achieving a partial response and an extended survival period.

## CASE REPORT

A Japanese man in his 60s presented to our hospital for upper abdominal pain. He had a history of hypertension and no contributory family history. Physical examination revealed slight abdominal tenderness. Laboratory studies showed a normal complete blood count and slightly elevated transaminase levels. Regarding the tumor marker studies, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were within normal limits, progastrin releasing-peptide was normal, but neuron-specific enolase (NSE) was elevated to 76.8 ng/mL (normal values  $\leq$  16.3 mg/ml). Computed tomography (CT) of the abdomen showed irregular wall thickness of the duodenum, lymphadenopathy at multiple sites in the abdomen, and multiple liver tumors (Fig.

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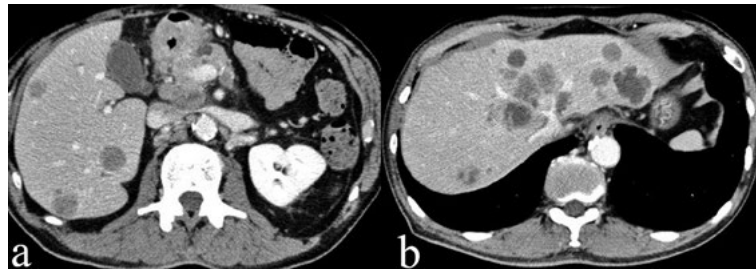
1). Endoscopy revealed duodenal stenosis and irregular tumors with ulcers from the duodenal bulb to the superior duodenal flexure (Fig. 2). Histopathological examination of endoscopic biopsy specimens showed small round, spindle-shaped atypical cells with scant cytoplasm and hyperchromatic nuclei (Fig. 3a). Immunohistochemically, the tumor cells demonstrated positive staining for chromogranin A, CD-56, and synaptophysin, which are diagnostic markers of NEC (Fig. 3). Therefore, we diagnosed duodenal NEC with distant metastases, and we initiated chemotherapy with IP according to the regimen used for SCLC. Cisplatin 60 mg/m<sup>2</sup> (day 1) plus irinotecan 60 mg/m<sup>2</sup> (days 1, 8, and 15) were infused as one cycle every 4 weeks. However, CT revealed multiple metastases of the bone after two cycles of IP therapy.

Amrubicin as second-line chemotherapy was administered intravenously at 40 mg/m<sup>2</sup> on days 1-3 every 3 weeks, but grade 3 neutropenia developed (Common Terminology Criteria for Adverse Events [CTCAE] ver. 4.0) after two cycles of AMR therapy. Therefore, the dosage was reduced to 35 mg/m<sup>2</sup> on days 1-3 every 4 weeks beginning with the third cycle. Thereafter, no adverse events worse than grade 2 were observed after reducing the dosage of AMR. After seven cycles of AMR therapy, CT showed that the metastases of the liver and lymph nodes around the duodenum were reduced and that the irregular

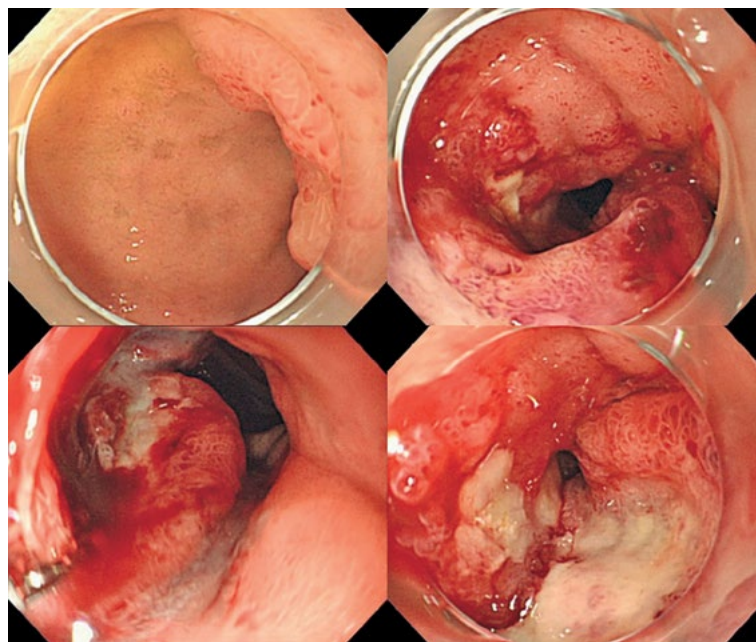
wall thickness of the duodenum had improved; thus, a partial response (PR) was obtained based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (Fig. 4). Although the patient's general condition was good, CT after 13 cycles of AMR therapy showed that the metastases of the liver and lymph nodes had increased. Therefore, carboplatin plus etoposide were administered as third-line chemotherapy. After one cycle of carboplatin plus etoposide therapy, the patient wished to discontinue chemotherapy. He died of disease progression 412 days after the initiation of AMR therapy, and 467 days after the first day of chemotherapy.

## DISCUSSION

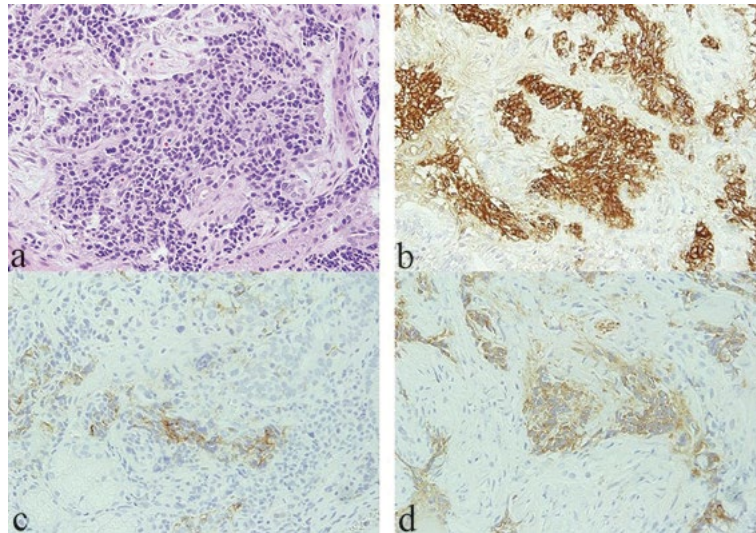
Gastrointestinal NEC is very rare and has a poor prognosis; therefore, standard therapy has not yet been established [1, 3]. Duodenal NEC is even rarer, and there is extremely little available clinical information on duodenal NEC [2]. In general, the regimen of chemotherapy is chosen in the same way as for SCLC, regardless of the primary site of the NEC, because NEC is clinico-pathologically similar to SCLC [4]. The National Comprehensive Cancer Network (NCCN) guideline generally recommends SCLC regimens for metastatic gastrointestinal NEC [5]. As a first-line regimen, a platinum-



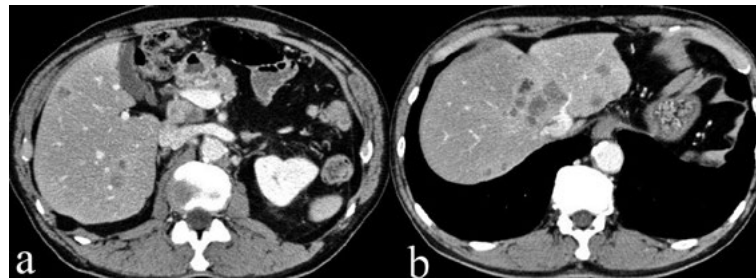
**Fig. 1.** Computed tomography: irregular wall thickness of the duodenum; enlarged lymph nodes around the duodenum (a); multiple tumors in the liver, considered to be metastases (b).



**Fig. 2.** Endoscopic aspect: irregular tumors with ulcers from the duodenal bulb to the superior duodenal flexure and duodenal stenosis.



**Fig. 3.** Histopathological examination of endoscopic biopsy specimens: small round, spindle-shaped atypical cells with scant cytoplasm and hyperchromatic nuclei (a). In immunohistochemistry, chromogranin A (b), CD-56 (c) and synaptophysin (d) were positive.



**Fig. 4.** After 7 cycles of amrubicin therapy, computed tomography revealed that the metastases of the liver and lymph nodes around the duodenum were reduced, and the irregular wall thickness of the duodenum was improved (a, b).

based combination, such as EP or IP therapy, is chosen [6-7]. In a study of Japanese SCLC patients, IP was reported to be more effective than EP [7]. In reports of gastrointestinal NEC treated with IP therapy, the median overall survival was 12.6–13.7 months [4, 8, 9]. In the present case, we selected the IP regimen as first-line chemotherapy. However, disease progression was observed after only two cycles of IP. Thus, the present case was categorized as “refractory-relapse”.

Amrubicin is a synthetic anthracycline, which shows potent topoisomerase II inhibition, and AMR has been used as a salvage-line regimen for SCLC [10, 11]. Although AMR is an anthracycline, cardiotoxicity is rarely observed. The most frequent and severe adverse event is bone marrow suppression. In a recent phase II and phase III study of SCLC patients treated with AMR as second-line chemotherapy, the median overall survival was 6–8.9 months [12-14]. However, there are very few reports of gastrointestinal NEC treated with AMR. To our knowledge, there are three case reports [15-17] and two case series [18, 19]. In the case reports, the primary sites were the stomach in two cases [15] and the esophagus in two cases [16, 17]. In two cases of gastric NEC, AMR was used as third-line chemotherapy in both patients. In one patient, AMR was stopped after only one cycle due to the hematologic toxicity, and no remarkable responses were achieved with AMR therapy in

the other patient [15]. In the case reports of esophageal NEC, the best responses were progressive disease (PD) in one case [16] and complete response (CR) in one case [17]. In a case series published in 2011 [18], five cases of gastrointestinal NEC (three in the esophagus, one in the anus, and one in the colon) were treated with AMR therapy as salvage chemotherapy. The best responses were CR in one case, PR in two, stable disease in one, and PD in one, and the median survival was 217 days. The most common adverse events greater than grade 3 were neutropenia (80%), anemia (60%), thrombocytopenia (20%), and febrile neutropenia (20%). In a case series published in 2015 [19], 13 cases of NEC of the digestive organs (including 2 cases of NEC in areas other than the gastrointestinal tract) were treated with AMR therapy as salvage chemotherapy. The primary sites were the stomach in six, the rectum in three, the esophagus in two, the liver in one, and the pancreas in one. The median overall survival was 215 days, and the most common severe adverse events (grades 3/4) were neutropenia (84.6%) and febrile neutropenia (30.8%). Amrubicin was expected to be an effective salvage therapy for gastrointestinal NEC, because treatment outcomes were obtained with AMR for SCLC in both case series. However, severe bone marrow suppression was also observed in the same way as in studies of SCLC. Thus, AMR requires close attention for the management



of adverse events. To the best of our knowledge, the present case is the first reported case of duodenal NEC treated with AMR therapy. The patient in the present case experienced long-term treatment effects of AMR, and the best response was a PR. Although grade 3 neutropenia was observed in the present case, no adverse events were observed after the dosage was reduced to 35 mg/m<sup>2</sup> on days 1–3 every 4 weeks. Thus, the patient's general condition was good, and his survival was extended with a satisfactory quality of life.

## CONCLUSION

As noted previously, a standard chemotherapy regimen for gastrointestinal NEC has not been established because gastrointestinal NECs are very rare and have a poor prognosis. Duodenal NEC is even rarer as gastrointestinal NECs. In the present case, AMR was effective for duodenal NEC with distant metastases, suggesting that it may be an effective salvage chemotherapy for duodenal NEC. As more cases of duodenal NEC accumulate, it is expected that the appropriate treatment and regimen will be established with a high level of evidence.

**Conflicts of interest:** No conflict to declare.

**Authors' contribution:** T.I. wrote the manuscript. T.M, H.N. and H.I. collected the patient's clinical data and searched literature data. F.O. and H.S. critically reviewed the manuscript.

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