



Contents lists available at ScienceDirect

## International Journal of Surgery Case Reports

journal homepage: [www.casereports.com](http://www.casereports.com)

# Report of two cases of large cell neuroendocrine carcinoma of duodenal ampulla with contrasting outcomes following pancreaticoduodenectomy according to the use of adjuvant chemotherapy



Naoya Imamura, Atsushi Nanashima\*, Masahide Hiyoshi, Yoshiro Fujii

Division of Hepato-Biliary-Pancreas Surgery and Department of Surgery, University of Miyazaki Faculty of Medicine, 5200 Kihara Kiyotake, Miyazaki, Japan

## ARTICLE INFO

### Article history:

Received 28 October 2016

Received in revised form 13 January 2017

Accepted 14 January 2017

Available online 17 January 2017

### Keywords:

Duodenal ampulla

Neuroendocrine carcinoma

Large cell type

Mixed adenocarcinoma

Pancreaticoduodenectomy

Adjuvant chemotherapy

## ABSTRACT

**INTRODUCTION:** Large-cell neuroendocrine carcinoma (LCNEC) in the duodenal ampulla of Vater is a rare malignant tumor, with frequent postoperative recurrence and poor prognosis even following complete resection. Effective adjuvant chemotherapy is expected to offer longer survival.

**PRESENTATION OF CASE:** We present two patients with LCNEC accompanied by components of tubular adenocarcinoma/adenoma in the duodenal ampulla of Vater who underwent pancreaticoduodenectomy (PD), resulting in longer survival of 1 patient. The first patient was an 81-year-old man in whom a 14-mm protruding solid tumor of the ampulla was observed. Pylorus-preserving PD (PPPD) was performed for the diagnosis of adenocarcinoma of the ampulla, and the final histological diagnosis of the resected specimen was LCNEC with an adenoma component. The patient showed a liver metastasis 4 months after surgery and died of carcinoma after 11 months. The second patient was a 72-year-old man with a 24-mm ulcerative solid tumor of the ampulla. PPPD was also performed in this patient, and the final histological diagnosis was LCNEC with mixed adenocarcinoma component (21%). Adjuvant chemotherapy of cisplatin and etoposide was administered, and the patient survived without tumor relapse for 24 months after surgery.

**CONCLUSION:** In the surgical treatment of LCNEC of the ampulla showing malignant behaviour, an accurate preoperative diagnosis and effective adjuvant chemotherapy after curative resection are necessary for longer survival.

© 2017 The Author(s). Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Neuroendocrine carcinoma (NEC) of the duodenal ampulla of Vater is one of the types of neuroendocrine tumors (NET G1 and G2, NEC, and mixed adenoneuroendocrine carcinoma [MANEC]) that was classified by the diagnostic criteria of the World Health Organization (WHO) classification in 2010 [1]. NEC is characterized as large-cell NEC (LCNEC) and small-cell NEC by histological findings. The prevalence of NET in the ampulla is less than 5% of all duodenal malignancies and only 0.3% of the NET of the entire digestive tract [2–6]. Among NET in the ampulla, LCNEC is extremely rare; only a few examples and small case series are documented in the English literature [1–16]. Because LCNEC of the ampulla is very rare, its

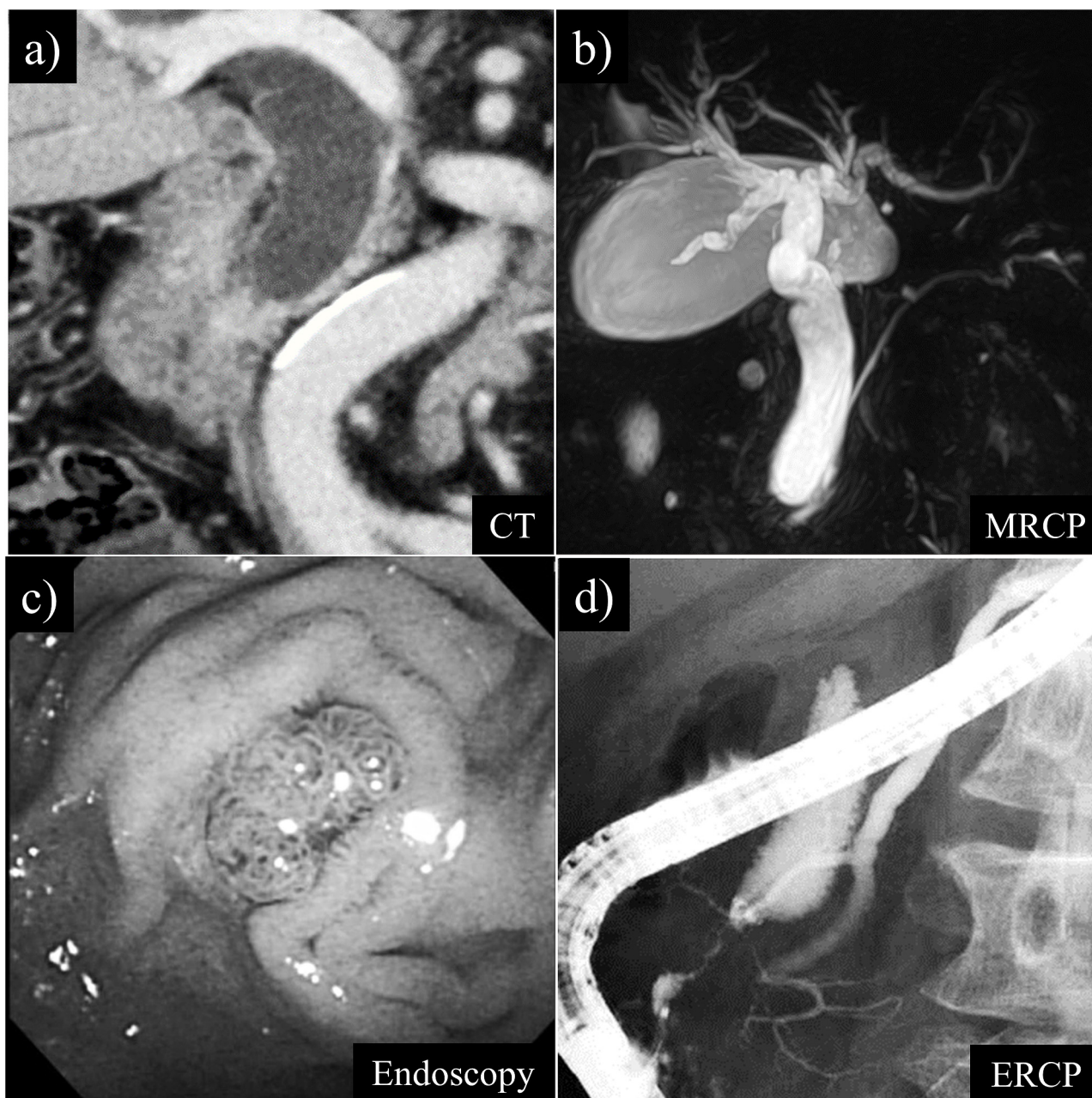
clinical features and treatment strategy are not well established. Preoperative diagnosis by imaging or endoscopic biopsy is often difficult [6,7]. The prognosis in patients with this disease is very poor and the prevalence of postoperative tumor relapse is very high in patients in whom liver metastasis is predominant [3–6,8–10]. To obtain a better patient prognosis after surgery, adequate and effective adjuvant chemotherapy is necessary. We recently encountered two contrasting cases of LCNEC accompanied by components of tubular adenocarcinoma/adenoma in the duodenal ampulla of Vater in which the patients underwent radical pancreaticoduodenectomy (PD).

## 2. Presentation of cases

The first patient was an 81-year-old man with no clinical symptoms. Increase in the values of hepatobiliary parameters were found at the medical health checkup. The laboratory data showed increased levels of total bilirubin (7.1 mg/dl; normal range <1.0), aspartate aminotransferase (110 IU/L; normal range <30), alanine

\* Corresponding author at: Division of Hepato-Biliary-Pancreas Surgery and Department of Surgery, University of Miyazaki Faculty of Medicine, 5200 Kihara Kiyotake, Miyazaki, 889–1692, Japan.

E-mail address: [a.nanashima@med.miyazaki-u.ac.jp](mailto:a.nanashima@med.miyazaki-u.ac.jp) (A. Nanashima).

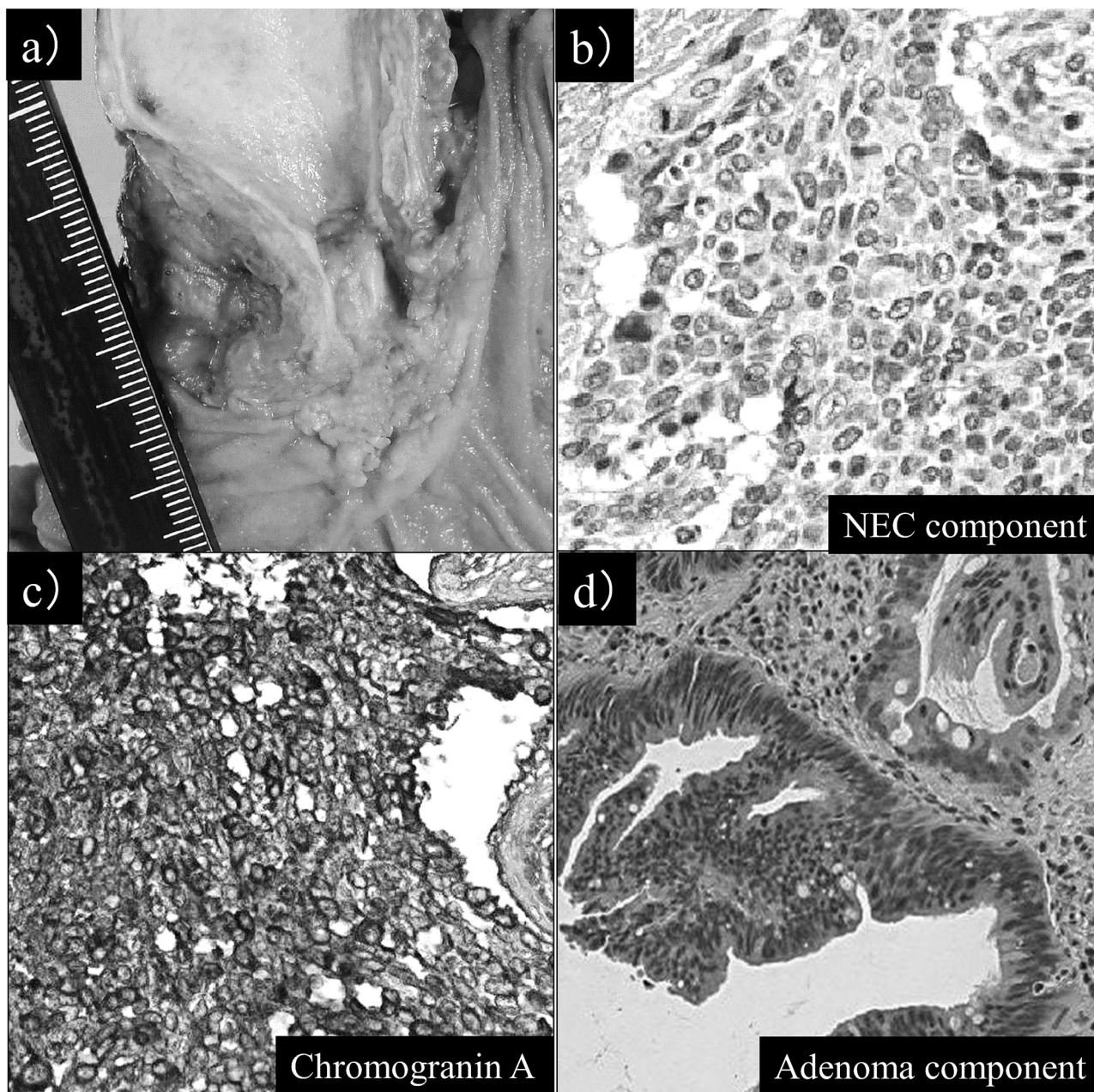


**Fig. 1.** a) Abdominal CT scan and b) MRCP revealed a 1.4-cm tumor of the ampulla of Vater, which obstructed the entire bile duct in the first case. c) Gross appearance of the ampullary tumor by endoscopy. (d) ERCP showed the biliary obstruction and stricture of the bile duct.

aminotransferase (223 IU/L; normal range <42) and alkaline phosphatase levels (1117 IU/L; normal range <322). Tumor markers of carcinoembryonic antigen (CEA) and CA19-9 were increased to 5.3 ng/mL (normal range <5) and 81.3 U/mL (normal range <37), respectively. Fig. 1a and b shows the obstructive dilatation of the bile duct and tumor lesion observed in the ampulla of Vater on abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP), respectively. Fig. 1c and d shows a 14-mm irregular protruding tumor lesion at the ampulla by the duodenal endoscopy and the resulting biliary stricture as indicated by endoscopic retrograde cholangiopancreatography (ERCP), respectively. Preoperative biopsy of the tumor revealed suspected poorly differentiated adenocarcinoma. Radical pylorus-preserving PD (PPPD) with regional lymph node dissection was performed. The resected specimen showed an ampullary protruding tumor infiltrating the duodenum, pancreas, and lower bile

duct (Fig. 2a). Lymph node metastases were not found. Atypical cells with hyperchromatic nuclei proliferated in solid or sheets in which the mitotic index was increased to 32 per 10 high-power fields and the MIB-1 index by Ki67 stain was high at 89% (Fig. 2b). Specimens were diffusely positive for both synaptophysin and chromogranin A staining (Fig. 2c), which represented poor differentiation and LCNEC. The tissue around the tumor cells showed papillary adenoma (Fig. 2d). The patient did not undergo adjuvant chemotherapy. However, multiple liver metastases were observed within 4 months postoperatively, and the patient died of this disease 11 months after surgery.

The second patient was a 72-year-old man with liver dysfunction diagnosed during follow-up for diabetes and hypertension. The laboratory data showed an increase in hemoglobin A1c to 6.6% (normal range <6), with other data almost within the normal ranges. CEA and CA19-9 levels were within the normal range at



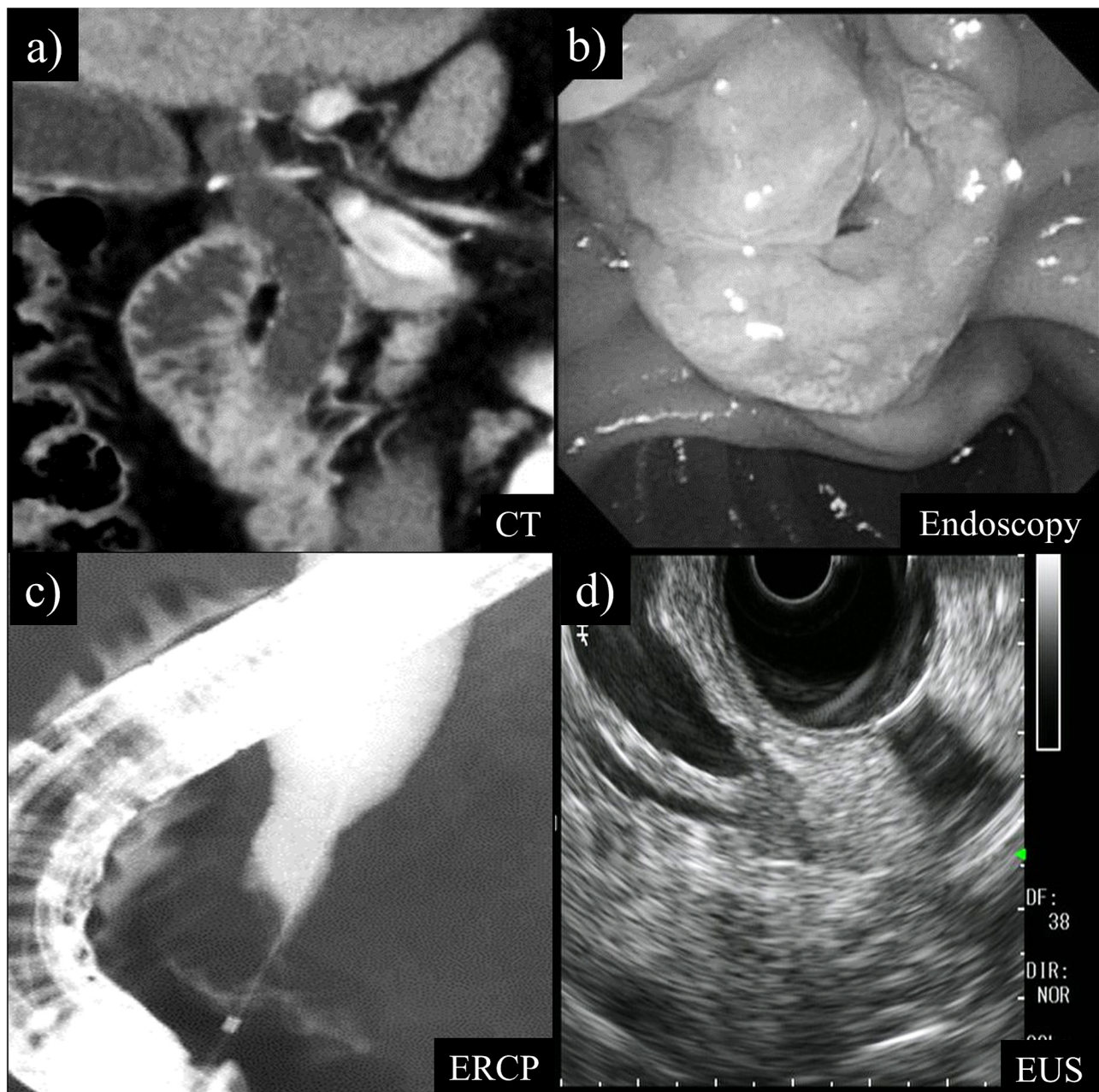
**Fig. 2.** a) Gross appearance of the resected tumor in the first case showed a protruding tumor at the ampulla of Vater infiltrating the duodenum and pancreas. Histological findings of the tumor: b) hematoxylin-eosin (HE) stain showed round and oval atypical cells in the NEC component, c) chromogranin A stain, and d) coexistence of an adenoma component.

2.6 ng/mL and 10.9 U/mL, respectively. Fig. 3a shows the obstructive dilatation of the bile duct and the tumor lesion as observed in the ampulla of Vater on abdominal CT. Fig. 3b–d shows a 24-mm irregular ulcerative tumor lesion at the ampulla by duodenal endoscopy that was shown to infiltrate into both the pancreas parenchyma and the lower bile duct by endoscopic ultrasonography (EUS) and ERCP, respectively. Preoperative biopsy of the tumor showed a mixed component of tubular adenocarcinoma and NEC by immunostaining as shown in Fig. 4a–d. Radical PPPD with regional lymph node dissection was performed. The resected specimen showed an ampullary protruding tumor infiltrating the duodenum, pancreas, and lower bile duct (Fig. 5a). One lymph node surrounding the pancreas head was confirmed as a metastasis. As observed in the biopsy specimen, atypical cells with hyperchromatic nuclei predominantly proliferated in solid or sheets in which the mitotic

index was increased to 32 per 10 high power fields and the MIB-1 index by Ki67 staining was high at 67% (Fig. 5b). Similar to that observed in case 1, both were diffusely positive for synaptophysin and chromogranin A staining, which represented poor differentiation and LCNEC (Fig. 5c). Furthermore, well-differentiated tubular adenocarcinoma was observed in 21% of the tumor area (Fig. 5d). The patient underwent adjuvant chemotherapy with etoposide plus cisplatin for 4 months according to the regimen for small cell lung carcinoma. The patient survived without tumor relapse for 24 months after surgery.

### 3. Discussion

We report here the case of two patients with LCNEC in the duodenal ampulla of Vater, which were extremely rare malignancies



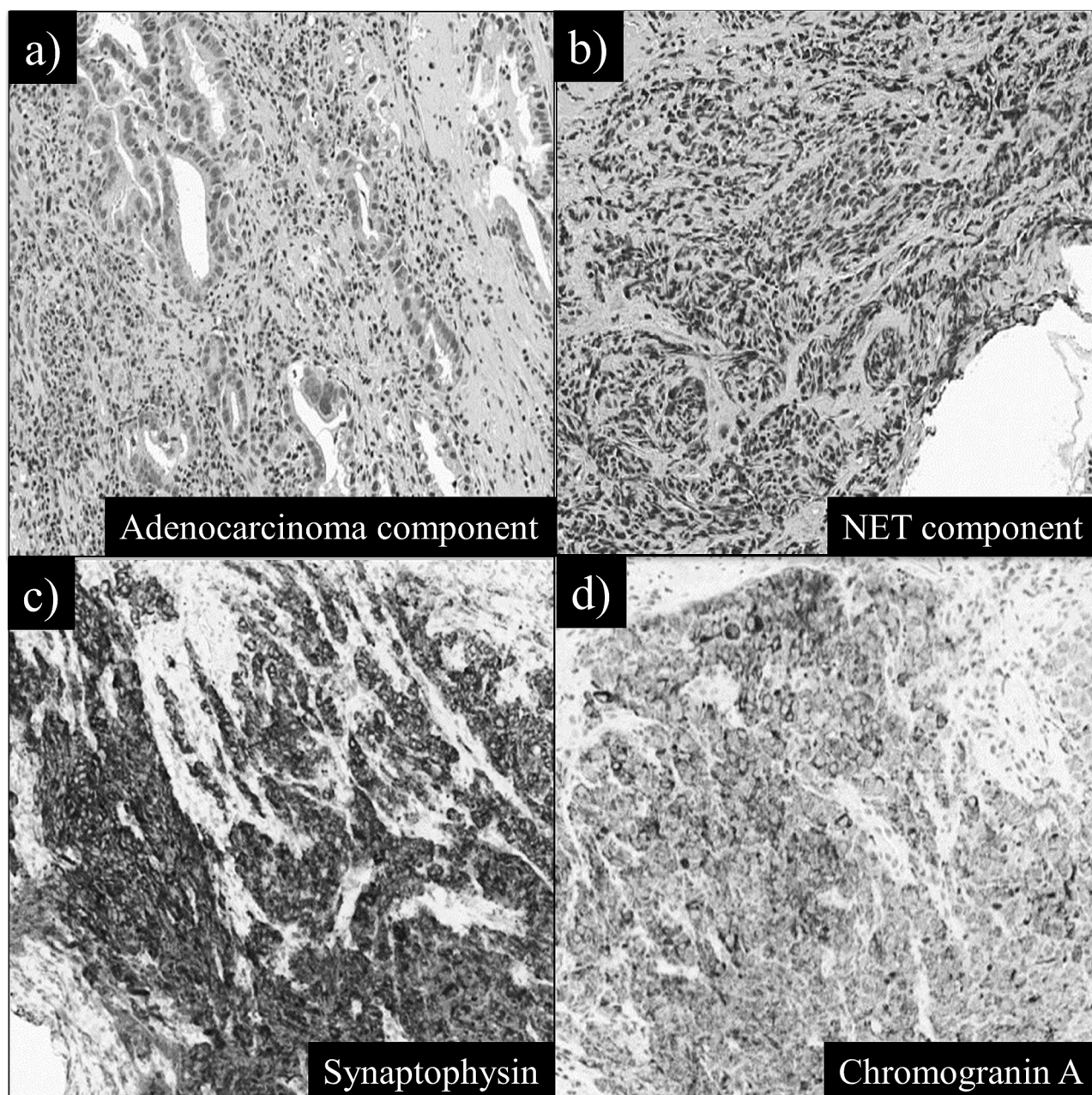
**Fig. 3.** a) Abdominal CT scan revealed a 2.4-cm tumor of the ampulla of Vater, which obstructed the entire bile duct in the second case. b) Gross appearance of the ulcerative tumor at the ampulla of Vater by endoscopy. (c) ERCP showed the biliary obstruction and infiltration of the tumor, and d) EUS revealed a tumor of the ampulla of Vater, which infiltrated into the pancreas and bile duct.

with aggressive behaviour. NET of the ampulla account for 2–8% of ampullary neoplasms, and almost all NET are classified as NET G1 and G2, with NEC being very rare [2–6,8,11–13]. Among 6081 malignant neoplasms of the ampulla, NET was reported in 139 cases in a US population-based study from the National Cancer Institute's Surveillance, Epidemiology, and End Results data from 1973 to 2006 [2]. Further, LCNEC is extremely rare, comprising only 4% (6/139) of the ampullary NET reported in that study. Some individual case reports and small series of LCNEC have been documented [1–16]. Beggs et al. studied a pooled analysis of previously published reports of LCNEC cases in 2012 and collected only 20 patients [8].

NEC has been reported often in concomitant observation with adenoma, adenocarcinoma, and other malignancy components [2,3,8–12]. MANEC is classified by WHO when the rate of mixed,

adenocarcinoma components is over 30% [1]. The rate of adenocarcinoma components in our present second case was less than 30%, different from MANEC, and thus was diagnosed as LCNEC. Our first patient had coexistence of LCNEC and adenoma, and the second patient had coexistence of LCNEC and adenocarcinoma. The associations with NEC and other neoplasms such as adenocarcinoma suggest a common initial carcinogenesis from the same multipoint stem cell [3,12,17].

A correct preoperative diagnosis of NET of the ampulla is difficult. The rate of accurate preoperative diagnosis of NET of the ampulla was reported to be below 30% [5–7,13] because patients with NET present with clinical symptoms and imaging similar to that of adenocarcinoma of ampulla. Furthermore, many of the tumor cells are located in the submucosa and are difficult to be detected in biopsy specimens. Most patients might be

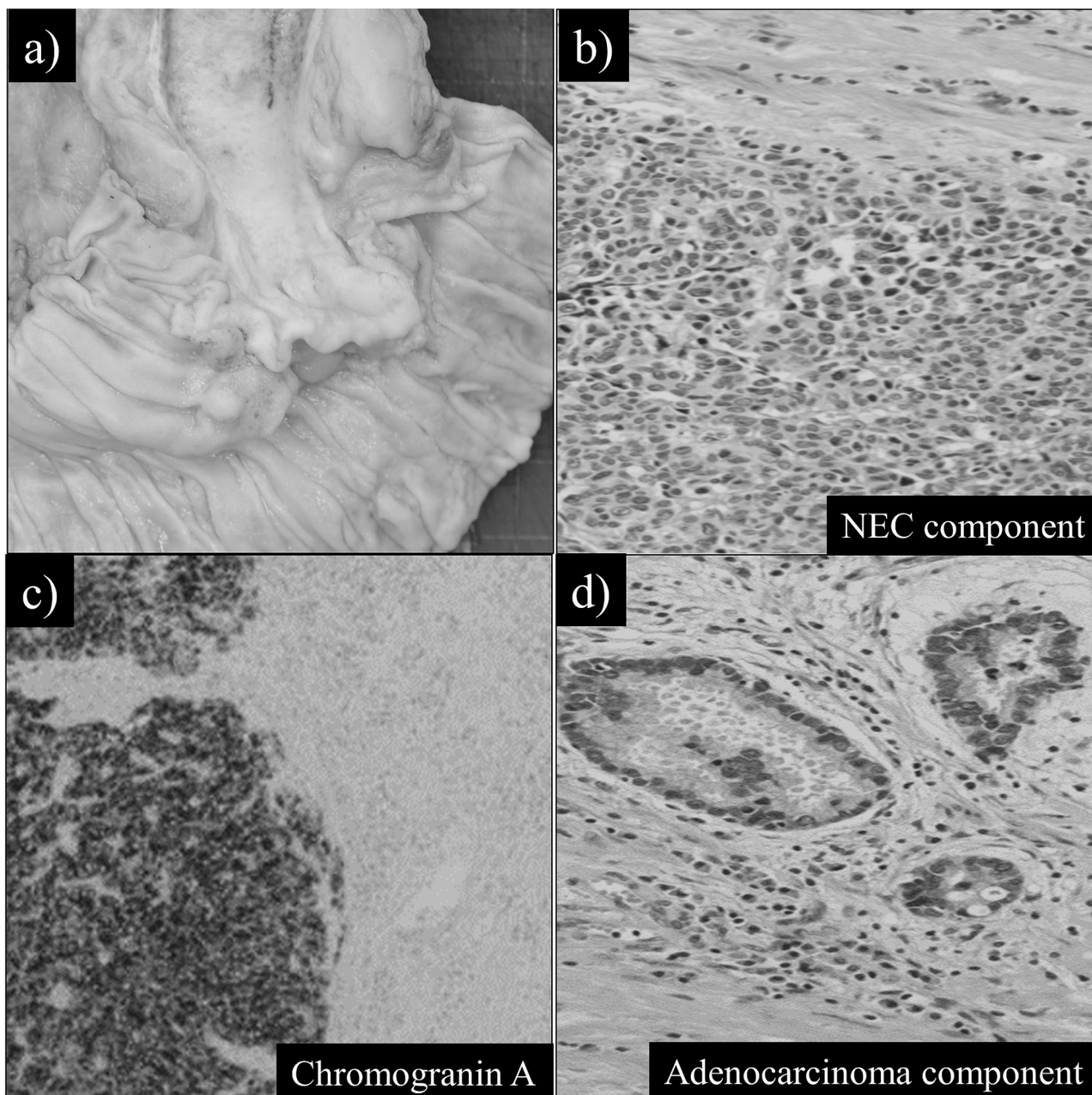


**Fig. 4.** Biopsy specimen under endoscopy in the second case. a) HE stain showed adenocarcinoma and b) NET tissue. Immunohistochemical findings: staining was positive for c) synaptophysin and d) chromogranin A.

asymptomatic or show indefinite symptoms, and liver dysfunction due to biliary obstruction is possible as observed in our two patients. Symptomatic NET showing carcinoid syndrome is rare [3,4]. Detailed and adequate preoperative examinations such as endoscopy, EUS, ERCP, CT, and MRI are necessary to determine the range of tumor infiltration. Furthermore, histological examination with immunostaining of specimens obtained by endoscopic or EUS-guided biopsy is necessary to define the treatment strategy noted in our patients [4,6,14].

NEC of the ampulla behaves aggressively, and the prognosis is poor [2,3,5,6,8–10,14–16]. LCNEC of the ampulla has a tendency for distant metastasis, and almost all patients die of the disease after less than one or two years despite curative surgery [8]. Early development of metastases is frequent as seen in our first case. A radical operation such as PD with extended lymphadenectomy should be scheduled first even in patients with a small-sized tumor

as noted in our patients and previous reports because of the high potential for malignancy [2,4,6,7]. Local resection such as endoscopic papillectomy is a limited indication for patients unable to tolerate surgery [4]. After a radical operation such as PD, however, patient prognosis remains poor, and more effective adjuvant therapy is needed [8,14]. Adjuvant chemotherapy has been reported previously, which comprises an etoposide plus cisplatin regimen for small lung cell carcinoma [18]. In Japan, another regimen, cisplatin plus irinotecan or S-1, was recently attempted [12,19]. Use of such adjuvant chemotherapy after radical operation enable long survival of some patients without tumor relapse [19]. By comparing our first and second patients, the significance of adjuvant chemotherapy after surgery could be expected by considering the two outcomes although we have no additional evidence for this. Because an administration protocol for adjuvant chemotherapy after surgery is not definitely decided for LCNEC, a future clini-



**Fig. 5.** a) Gross appearance of the resected tumor in the second case showed a protruding and ulcerative tumor at the ampulla of Vater infiltrating the duodenum and pancreas. Histological and immunohistochemical findings of the tumor: b) HE stain showed the NEC component, c) staining was positive for chromogranin A, and d) HE stain showed the adenocarcinoma component.

cal trial with a large number of patients is expected worldwide. In this report, we would like to emphasize the importance of adequate surgery and adjuvant chemotherapy for LCNEC of ampulla. This work has been reported in line with the SCARE criteria [20].

#### 4. Conclusion

We report two patients of LCNEC of the ampulla accompanied by tubular adenocarcinoma/adenoma components, which is very rare. Preoperative detail imaging examinations and the accompanying detailed histological examination were useful to diagnose NEC and to decide the adequate indication of radical operation such as PD with lymphadenectomy. The patient outcomes after radical surgery differed between these two patients because of the use of adjuvant chemotherapy in the second patient. Therefore, we believe

that adequately extended radical resection and additional adjuvant chemotherapy are necessary to provide longer survival to patients with LCNEC of the ampulla.

#### Conflict of interest

None.

#### Funding

None.

#### Ethical approval

This case report is not research study.

That is not applicable in this case report.

#### Authors' contributions

Naoya Imamura: Attending physician, who wrote of the paper.  
 Atsushi Nanashima: Editor, contributor, and supervisor.  
 Masahide Hiyoshi: Attending physician.  
 Yoshiro Fujii: Attending physician.

#### Consent

Informed consent was obtained from patients for being included in the study.

#### Research studies

This case report is not research study.  
 That is not applicable in this case report.

#### Guarantor

The guarantor is Atsushi Nanashima.

#### References

- [1] F.T. Bossman, F. Carneiro, R.H. Hruban, N.D. Treise, WHO Classification of Tumors of the Digestive System, 4th ed., IARC Press, Lyon, 2010.
- [2] J. Albores-Saavedra, A. Hart, F. Chablé-Montero, D.E. Henson, Carcinoids and high-grade neuroendocrine carcinomas of the ampulla of vater: a comparative analysis of 139 cases from the surveillance, epidemiology, and end results program—a population based study, *Arch. Pathol. Lab. Med.* 134 (2010) 1692–1696.
- [3] H. Nassar, J. Albores-Saavedra, D.S. Klimstra, High-grade neuroendocrine carcinoma of the ampulla of vater: a clinicopathologic and immunohistochemical analysis of 14 cases, *Am. J. Surg. Pathol.* 29 (2005) 588–594.
- [4] G.D. De Palma, S. Masone, S. Siciliano, F. Maione, J. Falletti, G. Mansueto, et al., Endocrine carcinoma of the major papilla: report of two cases and review of the literature, *Surg. Oncol.* 19 (2010) 235–242.
- [5] E. Selvakumar, V. Vimalraj, S. Rajendran, T.G. Balachandar, D.G. Kannan, S. Jeswanth, et al., Large cell neuroendocrine carcinoma of the ampulla of Vater, *Hepatobiliary Pancreat. Dis. Int.* 5 (2006) 465–467.
- [6] E. Selvakumar, S. Rajendran, T.G. Balachandar, D.G. Kannan, S. Jeswanth, P. Ravichandran, et al., Neuroendocrine carcinoma of the ampulla of Vater: a clinicopathologic evaluation, *Hepatobiliary Pancreat. Dis. Int.* 7 (2008) 422–425.
- [7] M. Hartel, M.N. Wente, F. Bergmann, J. Schmidt, M.W. Büchler, H. Friess, Large-cell neuroendocrine carcinoma of the major duodenal papilla: case report, *Gastrointest. Endosc.* 60 (2004) 838–841.
- [8] R.E. Beggs, M.E. Kelly, O. Eltayeb, P. Crotty, R. McDermott, P.F. Ridgway, Large cell neuroendocrine carcinoma of the ampulla of Vater, *JOP* 13 (2012) 470–475.
- [9] S.H. Liu, S.H. Tsay, Coexistence of large cell neuroendocrine carcinoma and adenocarcinoma of the ampulla of vater, *J. Chin. Med. Assoc.* 71 (2008) 536–540.
- [10] S.P. Cheng, T.L. Yang, K.M. Chang, C.L. Liu, Large cell neuroendocrine carcinoma of the ampulla of Vater with glandular differentiation, *J. Clin. Pathol.* 57 (2004) 1098–1100.
- [11] J.A. Musialik, M.J. Kohut, T. Marek, A. Wodolazski, M. Hartleb, Composite neuroendocrine and adenomatous carcinoma of the papilla of Vater, *World J. Gastroenterol.* 15 (2009) 4199–4200.
- [12] Y. Sunose, T. Ogawa, H. Itoh, T. Andoh, N. Tomizawa, T. Tanaka, et al., Large cell neuroendocrine carcinoma of the ampulla of vater with adenocarcinoma and squamous cell carcinoma components, *Jpn. J. Clin. Oncol.* 41 (2011) 434–439.
- [13] M. Jayant, R. Punia, R. Kaushik, R. Sharma, A. Sachdev, N.K. Nadkarni, et al., Neuroendocrine tumors of the ampulla of vater: presentation, pathology and prognosis, *JOP* 13 (2012) 263–267.
- [14] S.S. Huang, Y.J. Jan, S.B. Cheng, D.C. Yeh, C.C. Wu, T.J. Liu, et al., Large cell neuroendocrine carcinoma of the ampulla of vater: report of a case, *Surg. Today* 36 (2006) 1032–1035.
- [15] Z. Stojic, D. Brasanac, D. Bilanovic, O. Mitrovic, R. Stevanovic, I. Boricic, Large-cell neuroendocrine carcinoma of the ampulla of Vater, *Med. Oncol.* 27 (2010) 1144–1148.
- [16] A. Cavazza, M. Gallo, R. Valcavi, L. De Marco, G. Gardini, Large cell neuroendocrine carcinoma of the ampulla of vater, *Arch. Pathol. Lab. Med.* 127 (2003) 221–223.
- [17] A.O. Vortmeyer, I.A. Lubensky, M.J. Merino, C.Y. Wang, T. Pham, E.E. Furth, et al., Concordance of genetic alterations in poorly differentiated colorectal neuroendocrine carcinomas and associated adenocarcinomas, *J. Natl. Cancer Inst.* 89 (1997) 1448–1453.
- [18] J.R. Strosberg, D. Coppola, D.S. Klimstra, A.T. Phan, M.H. Kulke, G.A. Wiseman, et al., The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (High-Grade) extrapulmonary neuroendocrine carcinomas, *Pancreas* 39 (2010) 799–800.
- [19] N. Hashimoto, K. Hoshino, M. Nakamura, I. Takeyoshi, A case of adenoendocrine cell carcinoma of the papilla of Vater free from disease for 39 months after the surgery, *J. Jpn. Surg. Assoc.* 72 (2011) 1132–1136 (Japanese with English Abstract).
- [20] R.A. Agha, A.J. Fowler, A. Saetta, I. Barai, S. Rajmohan, D.P. Orgill, For the SCARE group: the SCARE statement: consensus-based surgical case report guidelines, *Int. J. Surg.* 34 (2016) 180–186.

#### Open Access

This article is published Open Access at [sciedirect.com](http://sciedirect.com). It is distributed under the [IJSCR Supplemental terms and conditions](#), which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.