

Conversion Surgery for Metastatic Pancreatic Mucinous Carcinoma Responsive to Systemic Chemotherapy with Modified FOLFIRINOX: A Case Report

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We report a case of metastatic pancreatic-head mucinous carcinoma (with multiple lymph node and bone metastases) and review the relevant literature. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was useful for diagnosis, and a satisfactory outcome was achieved after systemic chemotherapy with FOLFIRINOX followed by resection of the primary lesion as conversion surgery. The patient was a 55-year-old man. Hematological findings included elevated serum tumor marker levels: CEA 12.7 ng/mL, DUPAN-2 400 U/mL. Findings from several imaging modalities and EUS-FNA confirmed a clinicopathological diagnosis of metastatic pancreatic mucinous carcinoma with multiple bone and lymph node metastases. Five courses of modified FOLFIRINOX (*m*-FFX) were given as systemic chemotherapy, which had an antitumor effect. Subtotal stomach-preserving pancreaticoduodenectomy and extensive lymph-node dissection were thus performed. Histopathological analysis showed invasive ductal carcinoma, muc (pT3, pN1b, cM1). After surgery, the clinical course was notable for the absence of complications. Tegafur/gimeracil/oteracil (S-1) was started as maintenance adjuvant chemotherapy postoperatively, and no disease progression has been observed at 10 months after surgery.

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Key words: pancreatic mucinous carcinoma, modified FOLFIRINOX, conversion surgery

Introduction

We report a case of metastatic pancreatic-head mucinous carcinoma (with multiple lymph node and bone metastases) and review the literature. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was useful for diagnosis, and a satisfactory outcome was achieved by using systemic chemotherapy with modified FOLFIRINOX followed by resection of the primary lesion as conserving surgery.

Case

A 55-year-old man with abdominal distention and low

back pain visited a local gastroenterologist in 2017. A 5-cm hypoechoic tumorous lesion was detected in the pancreatic head region via abdominal ultrasound examination, and the patient was referred to our hospital for further examination and treatment.

Hematological findings: No bone marrow suppression was detected.

Biochemical findings showed slight elevations: LDH 588 IU/L, ALP 495 IU/L, and AMY 228 IU/L. There were elevated serum tumor marker levels of CEA 12.7 ng/mL and DUPAN-2 400 U/mL, but CA 19-9 was within the normal range, at 20.8 U/mL. There was no evidence of

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Fig. 1 CT and MRCP

- a, b: The pancreatic head tumor and metastases to adjacent lymph nodes on enhanced abdominal CT.
 c: MRCP showing a mass involving the head of the pancreas and adjacent lymph nodes.

diabetes.

Abdominal CT image: A heterogeneous clearly demarcated 50-mm tumorous lesion was detected in the head of the pancreas. The main pancreatic duct was dilated in the tail of the pancreas because of retraction associated with the lesion. Lymph node enlargement was observed as an extensive mass involving the pancreatic head region and the upper mesenteric and bilateral para-aortic regions (Fig. 1a and b).

MRCP detected a mass of 52 × 50 × 100 mm involving the head of the pancreas. Mild distention due to retraction was observed in the peripheral main pancreatic duct, although there was no continuity with the tumor (Fig. 1c).

PET-CT: FDG accumulation was observed in the pancreatic head tumor, mesenteric lymph nodes, and lymph nodes in the para-aortic regions, as well as in the left scapula, vertebral column, sternum, pelvic bone, and bilateral ribs as multiple bone findings (Fig. 2).

EUS-FNA: An oval hypoechoic tumorous lesion (51 ×

40 mm), with posterior echo enhancement, was detected in the head of the pancreas and formed a mass with adjacent lymph nodes. The tumor was enclosed in a capsule, and the internal echo revealed a mixture of solid and microcystic aggregate-like components—a so-called “sponge-like” structure (Fig. 3a and b). Aspiration cytology and biopsy were performed (Fig. 3c).

After definitive histological diagnosis of mucinous carcinoma (Fig. 4), the patient received a clinicopathological diagnosis of metastatic pancreatic head mucinous carcinoma with multiple bone and lymph node metastases. The choices for systemic chemotherapy included FOLFIRINOX¹ and combination therapy with gemcitabine and nab-paclitaxel (GEMNAB)^{2,3}; we chose FOLFIRINOX as the primary chemotherapeutic regimen.

Regimen Management

In accordance with the hematological and non-hematological toxicity grading scales for Japanese⁴, a total of five courses of modified FOLFIRINOX (*m*-FFX: 5-

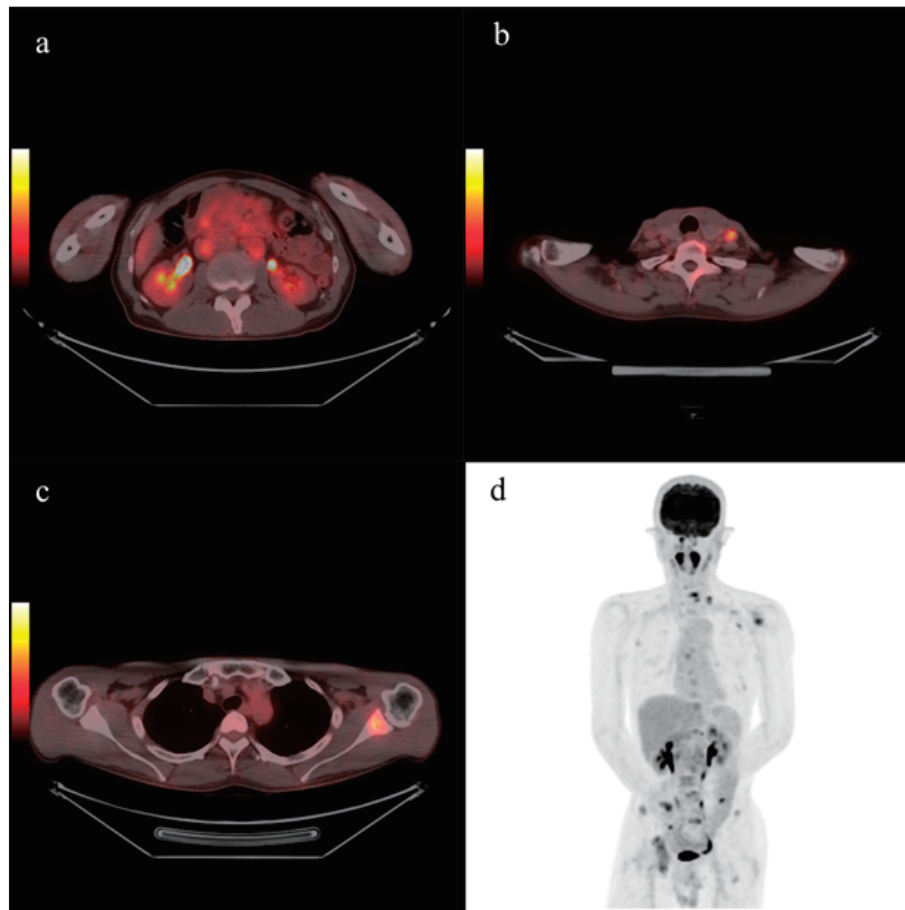


Fig. 2 PET-CT

- a: The pancreatic head tumor, mesenteric lymph nodes, and lymph nodes in the para-aortic regions.
 b: Left supraclavicular lymph node (Virchow's) metastasis.
 c: Left scapular metastasis.
 d: Multiple bone metastases.

fluorouracil 2,400 mg/m² on 46-h infusion, leucovorin 400 mg/m² div, irinotecan 150 mg/m² div, oxaliplatin 85 mg/m² div) was administered every 2 weeks⁵⁶, along with zoledronic acid 4 mg/day, every 4 weeks, to assist in treating bone metastases. Hematological adverse events included neutropenia, anemia, and thrombocytopenia (grade 1), and non-hematological toxicities included general malaise and loss of appetite (maximum, grade 2), as evaluated by NCI-CTC version 2.0 scores. The treatment was well-tolerated in this patient.

As for treatment outcome, contrast-enhanced CT and PET-CT images obtained at completion of five courses showed decreases in the size of the primary (32 × 25 mm) and lymph node metastatic lesions, as evaluated by RECIST criteria, and in the amounts of FDG aggregates (clinical partial response: cPR). Moreover, treatment of bone metastases achieved a clinical complete response (cCR), as no FDG uptake was seen on PET-CT (Fig. 5).

Serum levels of LDH, ALP, CEA, and DUPAN-2 were lower (183 IU/L, 315 IU/L, 3.8 ng/mL, and 240 U/mL, respectively) than baseline levels at the first visit.

Clinical Course

The expansive growth pattern of the tumor, including the lymph node metastatic lesions, suggested that wide resection of the tumor including the primary lesion might yield excellent short-term and good long-term outcomes. The patient was therefore scheduled for surgery after completion of the five courses of *m*-FFX. Subtotal stomach-preserving pancreaticoduodenectomy and extensive lymph node dissection were performed.

The operation time was 508 minutes, and the amount of blood loss was 308 mL. The resected specimen showed a tumor 38 × 30 mm in diameter in the head of the pancreas. Colloidal mucus was observed inside the tumor, and yellowish-white solid components were detected on

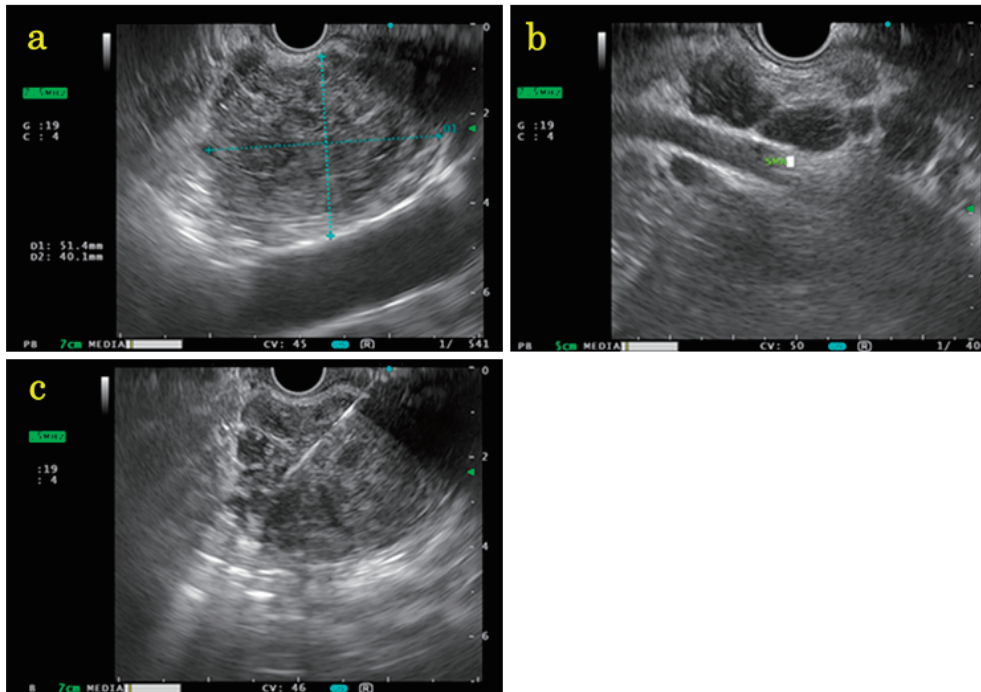


Fig. 3 EUS

- a: The pancreatic head tumor (51 × 40 mm) enclosed in a capsule; internal echo revealing a mixture of solid and microcystic aggregate-like components.
- b: Metastasis to adjacent lymph nodes.
- c: EUS-FNA.

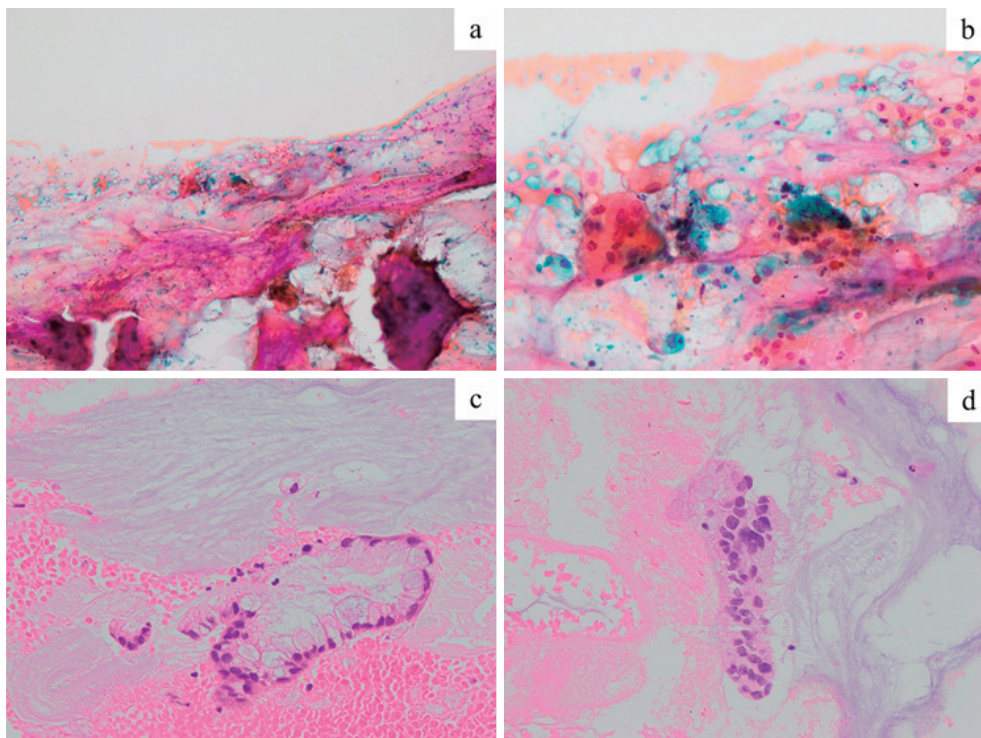


Fig. 4 Pathological results of EUS-FNA: diagnosis of mucinous carcinoma.
a, b: Tumor cells stained with Papanicolaou stain (a: ×20, b: ×100).
c, d: Biopsy tissue stained with hematoxylin-eosin (c: ×100, d: ×400).

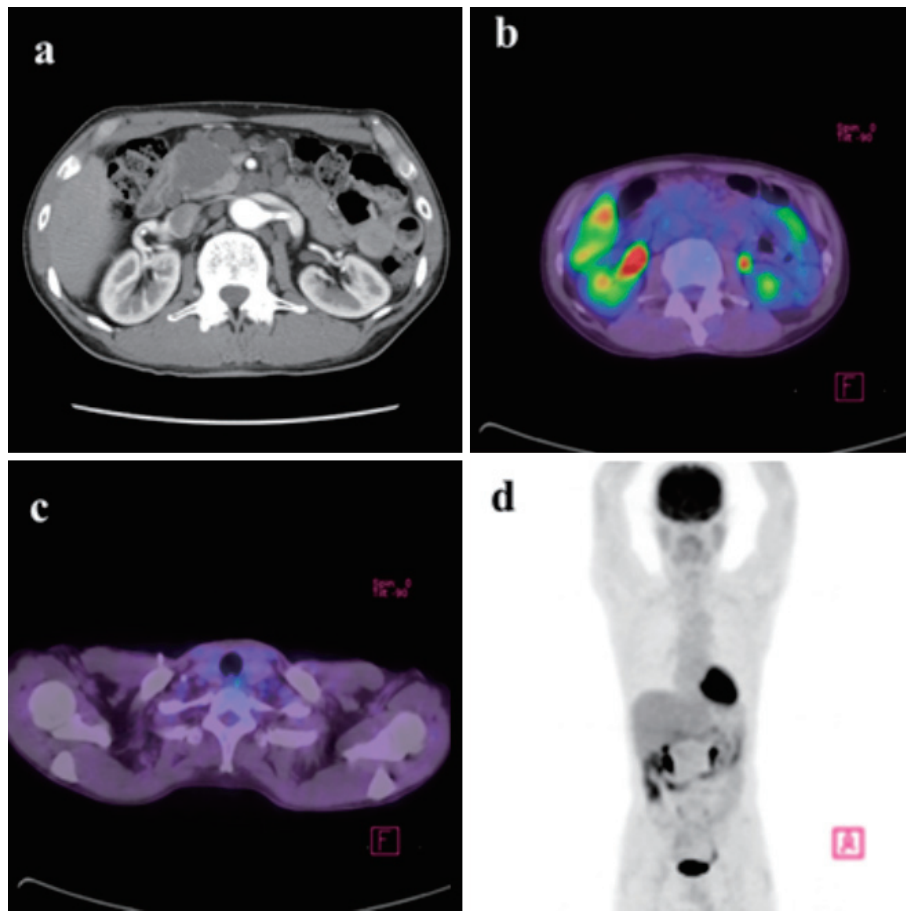


Fig. 5 CT and PET-CT (after completion of five courses of *m*-FFX)
 a: CT imaging revealing reductions in the size of the primary tumor and multiple lymph node metastases (cPR).
 b, c: Amount of FDG aggregates was reduced in the pancreatic tumor and multi-region lymph nodes.
 d: Bone metastases: absence of FDG uptake indicates cCR.

the margins of the tumor and between the mucous lakes (Fig. 6a and b).

Histopathological findings revealed formation of mucous lakes with abundant mucus production and a few free-floating cancer cells inside the mucus (Fig. 6c and d). Invasion of the duodenal muscularis propria was also observed. The final diagnosis was Ph, TS3 (pT3), invasive ductal carcinoma, muc, int, INFb, ly1, v1, ne1, pCH0, pDU1, pRP0, pPV0, pA0, pPL1, pPCM0, pBCM0, pDPM0, pN1b (22/38), and cM1. The histological outcome was grade 1b, according to Evans' criteria.

No complications were reported postoperatively, and the patient was discharged from the hospital on Day 23. Serum CEA and DUPAN-2 levels further decreased to normal levels (1.8 ng/mL and 48 U/mL, respectively).

Tegafur/gimeracil/oteracil (S-1) 120 mg/day administered for 2 weeks and followed by a 1-week withdrawal period was selected as maintenance adjuvant chemother-

apy on Day 40 postoperatively. At this writing, 10 months after surgery, the patient is alive and shows no signs of disease progression.

The patient provided informed consent for us to publish this case report.

Discussion

According to the Japanese "General Rules for the Study of Pancreatic Cancer, 7th edition", pancreatic mucinous carcinoma is a type of invasive ductal carcinoma and is rare (about 1.3% of pancreatic epithelial tumor cases in Japan). Pathological characteristics of this carcinoma include marked mucus production (leading to formation of mucous lakes), fibrotic changes around individual mucous lakes and the entire tumor lesion, and cancer cells with various degrees of differentiation on the margins and inside the mucinous lakes⁷⁻¹⁵. According to these guidelines, mucinous cancer is diagnosed if more than

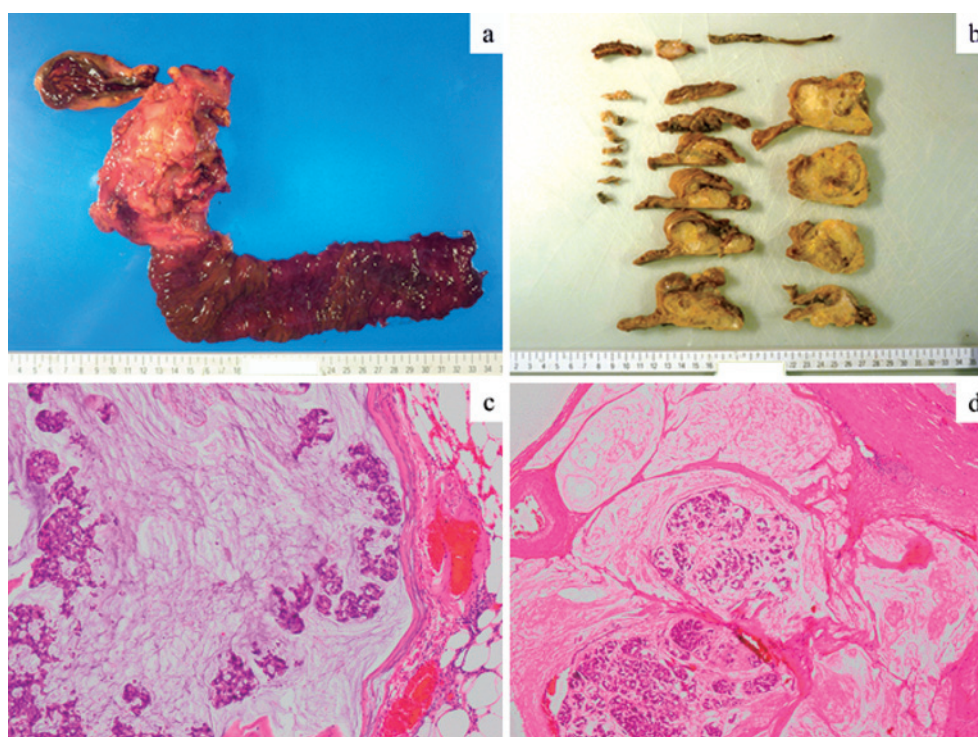


Fig. 6 Histopathological findings.

a, b: Macroscopic views: 50 × 32 mm tumor (head of the pancreas).

c, d: Microscopic views: formation of mucous lakes with abundant mucus production and existence of a very small number of free-floating cancer cells inside the mucus.

80% of the entire tumor lesion is occupied by mucinous lakes.

Tumor metastasis was observed in the present patient. Therefore, systemic chemotherapy was selected as the treatment regimen, and FOLFIRINOX¹ and GEMNAB^{2,16} were considered as first-line therapies. On the basis of previous reports on other mucus-producing cancers, we selected FOLFIRINOX, a regimen containing a platinum-based agent (oxaliplatin). After completion of five courses of this regimen, a clinical complete response (cCR) was achieved for bone metastases, and a partial response was achieved for the primary lesion and lymph node metastases. This satisfactory clinical course enabled conversion surgery. Our results indicate that this treatment regimen was appropriate¹⁷⁻¹⁹.

It is unclear if conversion surgery is indicated for metastatic pancreatic carcinoma. Several previous studies reported that the rate of conversion surgery for unresectable pancreatic carcinoma after FOLFIRINOX was 20% to 50%^{5,16,19}, but the quality of evidence was low. As of 2018, numerous studies have reported that tumor resection after systemic chemotherapy-so-called neoadjuvant chemotherapy (NAC)-can increase time to recurrence and survival time¹⁷⁻²⁰, as compared with provisional surgery, in cases of locally advanced pancreatic carcinoma.

The quality of evidence for this strategy is high, when studies from all countries are considered¹⁷⁻²⁰. Nevertheless, concerns remain regarding conversion surgery for unresectable pancreatic carcinomas, including those classified as stage IVb.

The present adjuvant chemotherapy regimen was similar to those selected for ordinary pancreatic carcinomas. The "Clinical Guidelines for the Management of Pancreatic Cancer" issued by the Japan Pancreas Society, recommends that S-1 be given for 6 months, as reported by Uesaka et al²¹. It is not known if pyrimidine fluoride agents are effective for treatment of mucinous carcinoma, as in the present case; nevertheless, we chose S-1 for our patient, because of concerns regarding tolerability. Because pancreatic carcinoma is rare histologically, evidence regarding optimal treatment is insufficient.

No previous study has reported conversion surgery for metastatic pancreatic mucinous carcinoma. Therefore, our patient is being followed carefully, to identify any prognostic differences from usual invasive ductal carcinoma.

In conclusion, conversion surgery is possible for patients with metastatic pancreatic carcinoma but depends on the clinical course of systemic multidisciplinary therapy.

Conflict of Interest: None.

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