Rare pancreatic carcinosarcoma in a patient with medical history of esophageal cancer
A case report and literature review

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Abstract
Rationale: Pancreatic carcinosarcoma (PCS) is a very rare pancreatic cancer with an extremely poor prognosis. Interestingly, PCS can coexist with other metachronous malignant cancers. Here we report a case of PCS combined with esophageal cancer (EC).

Patient concerns: The patient was a 66-year-old man who presented with abdominal pain and progressive nausea. He had undergone esophagectomy for EC 5 years previously.

Diagnosis: Both EC and PCS were confirmed via postoperative pathological diagnosis.

Interventions: Owing to the patient’s previous esophagectomy for EC, pancreaticoduodenectomy for the PCS could not be performed. Instead, he underwent cholecystectomy with bile duct-jejunum Roux-en-Y anastomosis and radioactive seed implantation.

Outcomes: The patient is still alive for >1 year.

Lessons: To our knowledge, this is the first report of PCS combined with EC and thus of metachronous multiple primary carcinoma. A detailed literature review of the clinical and histologic features of PCS reveals important information about the epidemiology and biology of this rare disease.

Abbreviations: CEA = carcinoembryonic antigen, CK = cytokeratin, CT = computed tomography, EC = esophageal cancer, EMT = epithelial to mesenchymal transition, HE = hematoxylin and eosin, IHC = immunohistochemistry, MPC = multiple primary carcinoma, MRI = magnetic resonance imaging, PCS = pancreatic carcinosarcoma, SMA = smooth muscle actin.

Keywords: EC, MPC, pathological diagnosis, PCS

1. Introduction
Carcinosarcoma is a malignant tumor with a carcinomatous component and a sarcomatous component. Wiirchow,[1] a German pathologist, coined the term “carcinosarcoma” in 1864, when he microscopically observed a malignant tumor consisting of 2 different types of tumor cells. He believed that it was derived from 2 different tissues. Carcinosarcomas occur in an organ containing epithelial tissue and are most common in the genitourinary system, head and neck, and breasts. The epithelial component may be adenocarcinoma, squamous cell carcinoma, urothelial carcinoma, small cell carcinoma, or basal cell carcinoma, whereas the mesenchymal component can be fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, osteosarcoma, chondrosarcoma, or undifferentiated sarcoma. Pancreatic carcinosarcoma (PCS), which has been infrequently reported, is a very rare type of pancreatic cancer with an unclear tissue origin. It has a low survival rate owing to nonspecific clinical symptoms, rapid growth, and strong invasiveness.[2,3] Here we report a case of primary PCS. Interestingly, this tumor was also multiple primary carcinoma (MPC) because it was complicated by primary esophageal cancer (EC).

2. Case presentation
The patient was a 66-year-old man who complained of intermittent pain in the upper abdomen lasting for >5 months. The abdominal pain had recently worsened and was accompanied by progressive nausea for 6 days. The patient’s medical history included hepatitis B for half a year, but no smoking or alcoholism. He also underwent esophagectomy 5 years ago. A review of the esophagectomy records showed that the severed esophagus had a total length of 10 cm and a circumference of approximately 2 to 4 cm. There was an obvious ulcerous mass in the esophagus measuring about 1.5 × 1.0 × 0.7 cm with an inflammatory exudate at the bottom of the mass. Different-sized nest-like distributions of EC cells were seen under the microscope (Fig. 1A). A small amount of fibrous interstitium and infiltrative inflammatory cells was observed between the cancer nests, whose centers were full of keratin pearls (Fig. 1B). The squamous
The patient then underwent a comprehensive examination, which revealed jaundice in the sclera and skin, without pale conjunctiva. The abdomen was flat and soft, and there was no tenderness, rebound tenderness, muscle tension, or a palpable mass. Chest–abdomen computed tomography (CT) showed dilation of both intrahepatic bile ducts and pancreatic ducts, an enlarged gallbladder with a thickened wall, and significant expansion of the common bile duct, with an interruption at the lower end. Moreover, there were multiple irregularly shaped, low-density shadows in the soft tissue masses in the uncinate position of the pancreas (Fig. 2A). Biochemical items include albumin: 37.34g/L; total bilirubin: 25.9µmol/L; ALT: 164.2U/L; AST: 179.7U/L; GGT: 777.6U/L; sodium: 129mmol/L; chlorine: 93mmol/L; alkaline phosphatase: 444.1IU/L; and fasting blood glucose: 6.38mmol/L.

The patient was further examined via magnetic resonance imaging (MRI), which showed expansion of the intrahepatic bile duct, common hepatic duct, cystic duct, common bile duct, and pancreatic duct. The common bile duct and pancreatic duct were abruptly cut off at the pancreatic head. A 4.1 × 3.3 × 2.2 cm irregularly shaped mass with an unclear boundary was observed in the pancreatic head. MRI of the pancreatic mass showed an equal signal for T1 (Fig. 2B) and a slightly longer signal for T2 (Fig. 2C). Enhanced MRI revealed uneven progressive enhancement with flaky non-enhanced areas in the center (Fig. 2D). Hence, malignant lesions were highly likely.

2.1. Pathological studies

The jaundice of the skin and sclera worsened on the fourth day after admission. To relieve the obstructive jaundice, the patient underwent gallbladder puncture and catheter drainage under ultrasound guidance. Owing to his history of EC, pancreaticoduodenectomy could not be performed for the pancreatic head tumor; instead, he underwent cholecystectomy with bile duct–jejunum Roux-en-Y anastomosis and radioactive seed implantation. During the operation, an approximate 5.0 × 4.0 × 4.0 cm tumor was found in the pancreatic head; it had a low echo on B-mode ultrasonography. Five pieces of the mass were removed through the puncture in the pancreatic head and frozen for pathological diagnosis.

Hematoxylin–eosin (HE) staining showed that the tumor consisted of 2 morphologically distinct components. One component consisted of carcinoma cells infiltrating the pancreatic head with obvious proliferation of the fibrous tissue parenchyma; the cells were arranged into an irregularly shaped glandular tube or gland-like structure (Fig. 3A). The papillary structure protruded into the glandular cavity locally. There was a large amount of mucus both inside and outside the cancer cells, which were columnar or cuboidal. Most of the cytoplasm was transparent or eosinophilic. The nuclei were round or cuboidal and were located almost at the base of the cells. These morphological features were consistent with those of ductal adenocarcinoma. The second component consisted of pleomorphic tumor cells, which were long and spindle-shaped or polygonal and diffusely distributed around the glandular tube or gland-like structure and the small vessels (Fig. 3B). The nuclei had varying sizes and much heterogeneity and stained intensely with HE. Some giant nuclei were also detected. The cell cytoplasm was either transparent or eosinophilic. These morphological features are consistent with those of poorly differentiated sarcomas.
The 2 cellular components had different immunophenotypes as assessed via immunohistochemistry (IHC) using monoclonal antibodies to various markers. Cytokeratin (CK) 8, 18, and 19 and carcinoembryonic antigen (CEA) were expressed in the carcinomatous component, but not the sarcomatous component; a similar pattern was observed when an anti-pan CK antibody was used (Fig. 3C). Conversely, vimentin was expressed in the sarcomatous component but not the carcinomatous component (Fig. 3D). Owing to negative expression of smooth muscle actin (SMA), desmin, and S-100, undifferentiated sarcoma was difficult to identify. The rate of Ki-67 expression was 30% in the carcinomatous component and 20% in the sarcomatous component (Table 1). Therefore, both HE staining and IHC supported the diagnosis of PCS. The patient was discharged 7 days after surgery; 1 year after surgery (the time of this writing), he is still alive.

3. Discussion
Carcinosarcoma is defined by the World Health Organization as a rare malignancy consisting of closely mixed malignant epithelial and interstitial tissue. Each component has its own distinct immunohistochemical feature and ultrastructure. The origin of carcinosarcomas is not very clear at present, but there are several theories. The collision theory posits that the primary carcinoma and sarcoma arose from 2 different germ layers; initially adjacent, they merged during the process of growth and infiltration.[21,22] The interstitial induction theory suggests that the carcinomatous component induces the surrounding mesenchyme to develop reactive hyperplasia and atypia.[23] The polyclonal theory proposes that the tumors simultaneously originated from different stem cells and subsequently formed a complex tumor.[24] In the monoclonal theory, the carcinosarcoma is derived from totipotent...
stem cells with multipotent differentiation potential; during its development, multiple tissue components containing different germ layers are formed.\textsuperscript{[25]} Lastly, the epithelial to mesenchymal transition (EMT) theory postulates that owing to changes in cell morphology, behavior, and purpose during embryonic development, embryonic epithelial cells turn into mesenchymal cells.\textsuperscript{[26,27]} The number of researchers supporting the monoclonality theory increased in the late 1980s, and the EMT theory became popular in the mid-1990s. Both theories are most widely believed at present.

Carcinosarcomas mostly occur in the uterus, bladder, and lungs, but rarely in the pancreas. PCS has an extremely poor prognosis; the average survival rate of the 20 cases reviewed by document statistics is only about $10.8 \pm 1.96$ months. Most patients with PCS visit a hospital because of abdominal pain. Carcinosarcomas range from about 2.5 to 9.5 cm. Those in the pancreatic head are usually treated via pancreaticoduodenectomy, whereas those in the pancreatic tail are usually treated via distal pancreatectomy (Table 2).

### Table 1
Immunohistochemical results of pancreatic carcinosarcoma in this study.

|                | Carcinomatous component | Sarcomatous component |
|----------------|------------------------|----------------------|
| pan-CK         | +                      | −                    |
| CK8            | +                      | −                    |
| CK18           | +                      | −                    |
| CK19           | +                      | −                    |
| Vimentin       | −                      | +                    |
| CEA            | +                      | −                    |
| SMA            | −                      | −                    |
| Desmin         | −                      | −                    |
| S-100          | −                      | −                    |
| Ki-67          | 30%                    | 20%                 |

$−$ = negative, $+$ = positive, CEA = carcinoembryonic antigen, CK = cytokeratin, SMA = smooth muscle actin.
| Author                  | Age | Sex | Medical history                | Associated tumor                          | Symptom                          | Site and size            | Carcinomatous component | Sarcomatous component | Therapy                  | Survival |
|-------------------------|-----|-----|--------------------------------|------------------------------------------|-----------------------------------|--------------------------|-------------------------|------------------------|-------------------------|-----------|
| Our case                | 66  | F   | EC                             | EC (meta)                                | Abdominal pain, nausea, jaundice  | Pancreatic head; 5.0 x 4.0 x 4.0 cm | DAC                     | Undifferentiated        | Radioactive seed implantation | >1y       |
| Mszyco et al[4]         | 85  | F   | CAD, hypertension, hyperlipidemia | None                                     | Abdominal pain                    | Pancreatic head; 12 cm in greatest dimension | Undifferentiated        | MFH                    | PD                      | —         |
| Ruess et al[6] (2017)   | 73  | F   | None                           | Ovarian teratoma (meta), uterine leiomyoma (syn) | Abdominal pain, back pain         | Pancreatic body and tail; ... | MDAC                    | Spindle cells           | Gemcitabine, docetaxel, radiation therapy | 10 mo     |
| Li et al[5] (2017)      | 60  | M   | None                           | Spindle cells                           | Pancreatic tail; 4.7 x 3.5 cm      | Solid and pseudopapillary tumor | IPMC, PDAC              | Osteosarcoma, spindle cells | DP                      | —         |
| Shi et al[3] (2015)     | 74  | F   | None                           | None                                     | Pancreatic tail; 2.5 x 2.1 x 1.4 cm | Pancreatic head; ...             | DAC                     | Undifferentiated        | Gemcitabine              | —         |
| Barkatullah et al[4] (2005) | 67  | F   | Cholecystectomy                | None                                     | Pancreatic head; 2.5 x 2.5 x 2.0 cm | Mucin-producing epithelial cells | DAC                     | Spindle cells           | —                      | —         |
| Kim et al[15] (2011)    | 48  | M   | None                           | None                                     | Pancreatic tail; 3.5 x 2.5 x 1.5 cm | Duct-like, small cystic formations | Spindle cells           | PD                     | >20 mo                  | —         |
| Nakano et al[7] (2008)  | 82  | F   | Cholecystectomy                | None                                     | Anorexia, jaundice                 | Pancreatic head; ...             | DAC                     | Spindle cells           | —                      | 13 d      |
| Shen et al[18] (2010)   | 72  | F   | Atherosclerosis, acute pancreatitis | GIST (syn)                              | Abdominal pain, nausea             | Pancreatic head; 5.0 x 4.0 x 4.0 cm | DAC                     | MFH                    | —                      | 2 mo      |
| Wenig et al[9] (1997)   | 67  | M   | None                           | Acute pancreatitis                       | Abdominal pain                     | Pancreatic tail; 19 x 14 x 8.0 cm | MCN for all              | Spindle cells for all   | DP for all               | >1 y      |
| Wu et al[17] (2016)     | 76  | F   | —                              | None                                     | Abdominal pain, nausea             | Pancreatic tail; ...             | DAC                     | Spindle cells           | PD                      | 3 mo      |

**Legend:**
- AC = anaplastic carcinoma
- AITD = autoimmune thyroid diseases
- AML = angiomylipoma
- CAD = coronary artery disease
- DAC = ductal adenocarcinoma
- DP = distal pancreatectomy
- EC = esophageal cancer
- F = female
- GIST = gastrointestinal stromal tumour
- IPMC = intraductal papillary mucinous carcinoma
- M = male
- MCAC = mucinous cyst adenocarcinoma
- MCN = mucinous cystic neoplasm
- MDAC = moderately differentiated adenocarcinoma
- meta = metachronous
- MRH = malignant fibrous histiocytoma
- MS = metabolic syndrome
- PD = pancreatectoduodenectomy
- PDAC = poorly differentiated adenocarcinoma
- PVD = peripheral vascular disease
- RBD = recurrent brief depression
- RLS = restless legs syndrome
- SB = subarachnoid bleeding
- SC = squamous carcinoma
- syn = synchronous
Histologically, carcinosarcomas consist of 2 types of immunohistochemically and morphologically distinct components. Pan-CK is a marker for keratinized epithelium, stratified epithelium, and monolayer epithelium; hence, it identifies both epithelial and nonepithelial neoplasms.\[^{28,29}\] CK8 is a high molecular weight type B CK expressed in nonsquamous epithelium.\[^{30}\] CK18 is a low molecular weight type A CK expressed in several types of simple epithelium (e.g., glandular epithelium).\[^{31,32}\] CK19, the lowest molecular weight CK, is present in glandular epithelial cells, especially those in ductal epithelium.\[^{33}\] In our case, all CKs were expressed in the cytoplasm of the cancer cells that formed a glandular tubule structure. This indicates these cells were derived from the epithelial component, and supports the diagnosis of ductal adenocarcinoma. Vimentin is a cytoplasmic protein expressed in tumor cells originating in the mesenchyme but not the epithelium.\[^{34,35}\] In our study, the tumor cells in the interstitium and diffusely distributed around the glandular tubule structure and small vessels were highly positive for vimentin, thus suggesting that they were derived from mesenchymal cells. The lack of immunoreactivity to antibodies for SMA (a muscle marker), desmin (a muscle marker), and S-100 (a liposarcoma marker) excludes leiomyosarcomas, rhabdomyosarcomas, and liposarcomas,\[^{15}\] but does support a diagnosis of undifferentiated sarcoma. Just as our summary of case reports, most carcinosarcomas have a (ductal) adenocarcinoma as the carcinomatous component, whereas the sarcomatous component is usually described as a proliferation of malignant spindle cells (Table 2).

Among the 20 previously reported cases of PCS (Table 2), there were 4 with a medical history of pancreatitis and 2 with coronary artery disease, hypertension, diabetes, and cholecystectomy. The ovarian teratomas (previous or associated with a metachronous tumor) and uterine leiomyomas (associated with a synchronous tumor) reported by Salibay et al were benign tumors or angiomylipoma associated with metachronous tumor, according to Russ et al.\[^{5,6}\] Only Shen et al have described a pancreatic carcinosarcoma combined with a synchronous malignant gastrointestinal stromal tumor.\[^{18}\]

MPCs, 2 or more primary malignancies, can occur in the same or multiple tissues simultaneously or successively. Synchronous MPC is defined as the occurrence of the primary tumors at the same time or within 6 months, whereas metachronous MPC is defined as the occurrence of the primary tumors >6 months apart. As proposed by Billroth and revised by Warran,\[^{16}\] MPCs need to fulfill 4 criteria: (1) all tumors must be malignant; (2) each tumor exists independently from the others; (3) normal tissue is within a certain distance of the tumors; and (4) none of the tumors result from metastasis of the other tumors. In our case, the patient was diagnosed with well-differentiated squamous cell carcinoma of the esophagus 5 years before being diagnosed with PCS. Because our case supports all of the above conditions, we believe it describes metachronous MPC with both primary PCS and EC. To our knowledge, this is the first report of such a case.

Acknowledgments

We are very grateful to the patients who provided informed consent for publication of the case.

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References

[1] Bertram P, Treutner KH, Tietze L, et al. True carcinosarcoma of the colon. Langenbecks Arch Chir 1997;382:173–4.
[2] Del Chiaro M, Segersvard R, Lohr M, et al. Early detection and prevention of pancreatic cancer: is it really possible today? World J Gastroenterol 2014;20:1218–31.
[3] Huang T, Jiang SW, Qin L, et al. Expression and diagnostic value of HE4 in pancreatic adenocarcinoma. Int J Mol Sci 2015;16:2956–70.
[4] Mozyc S, Teng L, Annunziata J, et al. Pancreatic Carcinosarcoma: A Case Report Highlighting Computed Tomography Characteristics. Curr Probl Diagn Radiol 2017;46:342–5.
[5] Salibay CJ, Rewerska J, Gupta S, et al. Primary carcinosarcoma of the pancreas with CD10-positive sarcoma component. J Investig Med High Impact Case Rep 2017;5:1–4.
[6] Ruess DA, Kayser C, Neubauer J, et al. Carcinosarcoma of the pancreas. Pancreas 2017;46:1225–33.
[7] Li B, Liu Q, Chang X, et al. Pancreatic carcinosarcoma mimics malignant intraductal papillary mucinous neoplasm. Medicine 2017;96:e6961.
[8] Jia Z, Zhang K, Huang R, et al. Pancreatic carcinosarcoma with rare long-term survival. Medicine 2017;96:e5966.
[9] Gelos M, Behringer D, Philippou S, et al. Pancreatic carcinosarcoma. Case report of multimodal therapy and review of the literature. JOP 2008;9:50–5.
[10] Lee J, Hyan JI, Lee HS. A rare case of abdominal pain by pancreatic mass in a young female patient. Gastroenterology 2015;148:e3–5.
[11] Okamura J, Sekine S, Nara S, et al. Intraductal carcinosarcoma with a heterologous mesenchymal component originating in intraductal papillary-mucinous carcinoma (IPMC) of the pancreas with both carcinoma and osteosarcoma cells arising from IPMC cells. J Clin Pathol 2010;63:266–9.
[12] Hyun Seon K, Jin Il K, Minyoung J, et al. Pancreatic adenocarcinosarcoma of monoclonal origin: a case report. World J Gastroenterol 2014;20:12682–6.
[13] Shi HY, Xie J, Miao F. Pancreatic carcinosarcoma: first literature report on computed tomography imaging. World J Gastroenterol 2013;19:1357–61.
[14] Barkatullah SA, Deziel DJ, Jalake SM, et al. Pancreatic carcinosarcoma with unique triphasic histological pattern. Pancreas 2003;31:291–2.
[15] Kim HS, Joo SH, Yang DM, et al. Carcinosarcoma of the pancreas: a unique case with emphasis on metastatic transformation and the presence of undifferentiated pleomorphic high-grade sarcoma. J Gastrointestin Liver Dis 2011;20:197–200.
[16] Zhu WY, Liu TG, Zhu H. Long-term recurrence-free survival in a patient with pancreatic carcinosarcoma: a case report with a literature review. Med Oncol 2012;29:140–3.
[17] Nakano T, Sonobe H, Usui T, et al. Immunohistochemistry and K-ras sequence of pancreatic carcinosarcoma. Pathol Int 2008;58:672–7.
[18] Shen ZL, Wang S, Ye YJ, et al. Carcinosarcoma of pancreas with liver metastasis combined with gastrointestinal stromal tumour of the stomach: is there a good prognosis with the complete resection? Eur J Cancer Care (Engl) 2010;19:118–23.
[19] Wenig BM, Albores-Saavedra J, Butzow PC, et al. Pancreatic mucinous cystic neoplasm with sarcomatous stroma: a report of three cases. Am J Surg Pathol 1997;21:70–80.
[20] Watanabe M, Miura H. Mixed Osteoclastic/Pleomorphic-Type Giant Cell Tumor of the Pancreas with Ductal Adenocarcinoma: Mistochemical and Immunohistochemical Study. Pancreas 1996;15:201–8.
[21] Wada Y, Takami Y, Tateshi M, et al. Carcinosarcoma of the gallbladder: report of a case. Clin J Gastroenterol 2014;7:453–9.
[22] Kubota K, Kakuta Y, Kawamura S, et al. Undifferentiated spindle-cell carcinoma of the gallbladder: an immunohistochemical study. J Hepatobiliary Pancreat Surg 2006;13:468–71.
[23] Takubo K, Tsuchiya S, Nakagawa H, et al. Pseudoarcoma of the esophagus. Hum Pathol 1982;13:503–5.
[24] Gao SQ, Huang LD, Dai S, et al. Carcinosarcoma of the gallbladder: a case report and review of the literature. Int J Clin Exp Pathol 2015;8:7464–9.
[25] Thompson L, Chang B, Barsky SH. Monoclonal origins of malignant mixed tumors (carcinosarcomas) evidence for divergent his togenesis. Am J Surg Pathol 1996;20:277–85.
[26] Hugo H, Ackland ML, Blick T, et al. Epithelial-mesenchymal and mesenchyma—epithelial transitions in carcinoma progression. J Cell Physiol 2007;213:374–83.
[27] McCluggage WG. Malignant biphasic uterine tumors: carcinosarcomas or metaplastic carcinomas? J Clin Pathol 2002;55:321–5.
[28] Li H, Fu J, Xiu Y, et al. Diagnostic significance of combining telomerase activity with CYFRA21-1 level in differentiating malignant pleural effusion caused by lung cancer from benign pleural effusion. Zhongguo Fei Ai Za Zhi 2010;13:652–4.
[29] Fuchs E, Clevaland DW. A structural scaffolding of intermediate filaments in health and disease. Science 1998;279:514–9.
[30] Kriho VK, Yang HY, Moskal JR, et al. Kerat in expression in astrocytomas: an immunofluorescent and biochemical reassessment. Virchows Arch 1997;431:139–47.
[31] Fujisaki J, Shimoda T. Expression of cytokeratin subtypes in colorectal mucosa, adenoma, and carcinoma. Gastroenterol Jpn 1993;28:647–56.
[32] van Dorst EB, van Muijen GN, Litvinov SV, et al. The limited difference between keratin patterns of squamous cell carcinomas and adenocarcinomas is explicable by both cell lineage and state of differentiation of tumour cells. J Clin Pathol 1998;51:679–84.
[33] Jung YS, Lee KJ, Kim HJ, et al. Clinical significance of bone marrow micrometastasis detected by nested rt-PR for keratin-19 in breast cancer patients. Jpn J Clin Oncol 2003;33:167–72.
[34] Sarria AJ, Panini SR, Evans RM. A functional role for vimentin intermediate filaments in the metabolism of lipoprotein-derived cholesterol in human SW-13 cells. J Biol Chem 1992;267:19455–63.
[35] Leader M, Collins M, Patel J, et al. Vimentin: an evaluation of its role as a tumour marker. Histopathology 1987;11:63–72.
[36] Warren S, Gates O. Multiple primary malignant tumors: survey of the literature and a statistical study. Am J Cancer 1932;16:1358–414.