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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. Wirchow,[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 histocytoma, 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 $1.5 \times 1.0 \times 0.7$ 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

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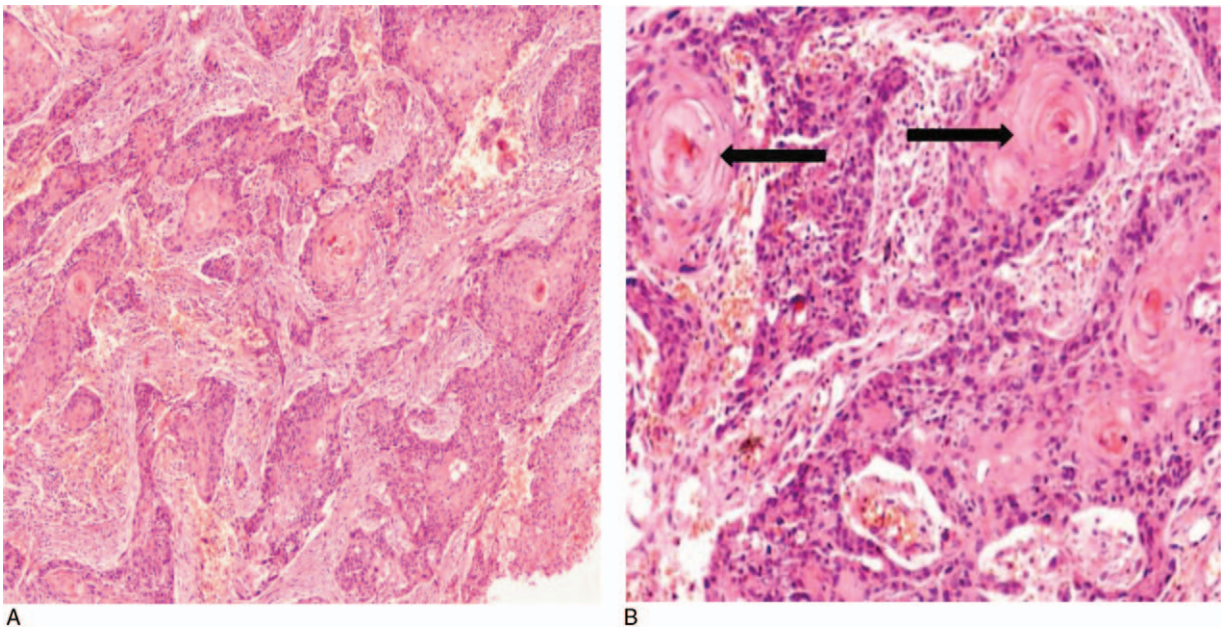

Figure 1. Hematoxylin–eosin (HE) staining of the esophageal cancer (EC). (A) The EC cells had a nest-like distribution. HE × 40. (B) Keratin pearls (arrows) were present in the centers of the nests. HE × 100.

epithelium was arranged hierarchically. The cancer cells were large, closely packed, and had eosinophilic cytoplasm. Under high magnification, an intercellular bridge between the cancer cells that infiltrated the submucosa of the esophagus was detected. These pathological results suggested a diagnosis of well-differentiated squamous cell carcinoma of the esophagus. The patient recovered well after surgery and was discharged 14 days thereafter.

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: 37.34 g/L; total bilirubin: 25.9 umol/L; ALT: 164.2 U/L; AST: 179.7 U/L; GGT: 777.6 U/L; sodium: 129 mmol/L; chlorine: 93mmol/L; alkaline phosphatase: 444.1 IU/L; and fasting blood glucose: 6.38 mmol/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 $4.1 \times 3.3 \times 2.2$ 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 $5.0 \times 4.0 \times 4.0$ 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.

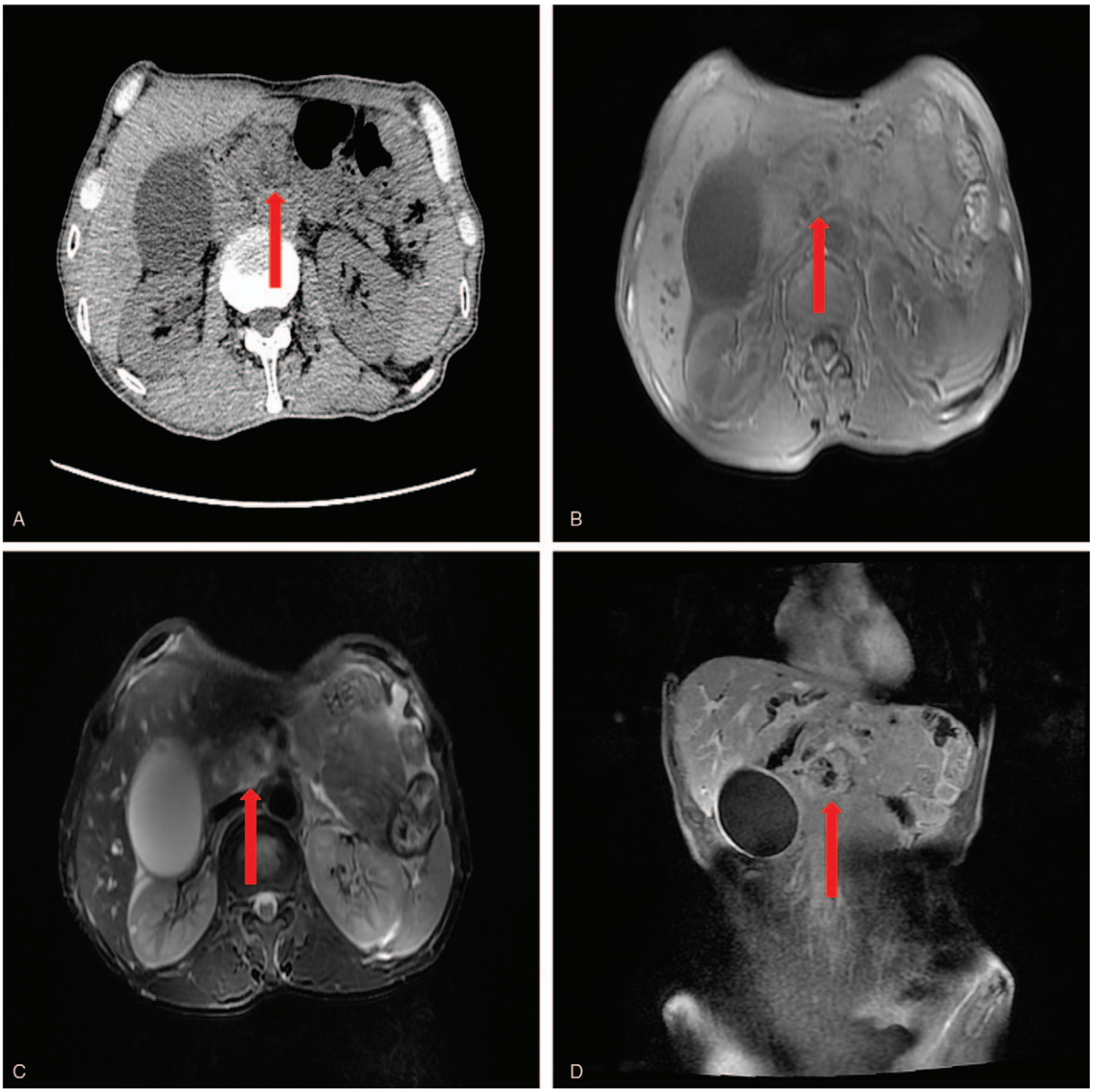

Figure 2. Chest-abdomen CT and MRI. (A) CT showed a soft tissue mass with multiple irregularly shaped, low-density shadows (arrow) in the uncinate region of the pancreas. MRI of the pancreatic mass showed an equal signal for T1 (B, arrow), and a slightly longer signal for T2 (C, arrow). (D) Enhanced MRI showed multiple nonenhanced areas in the pancreatic mass (arrow). CT = computed tomography, MRI = magnetic resonance imaging.

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

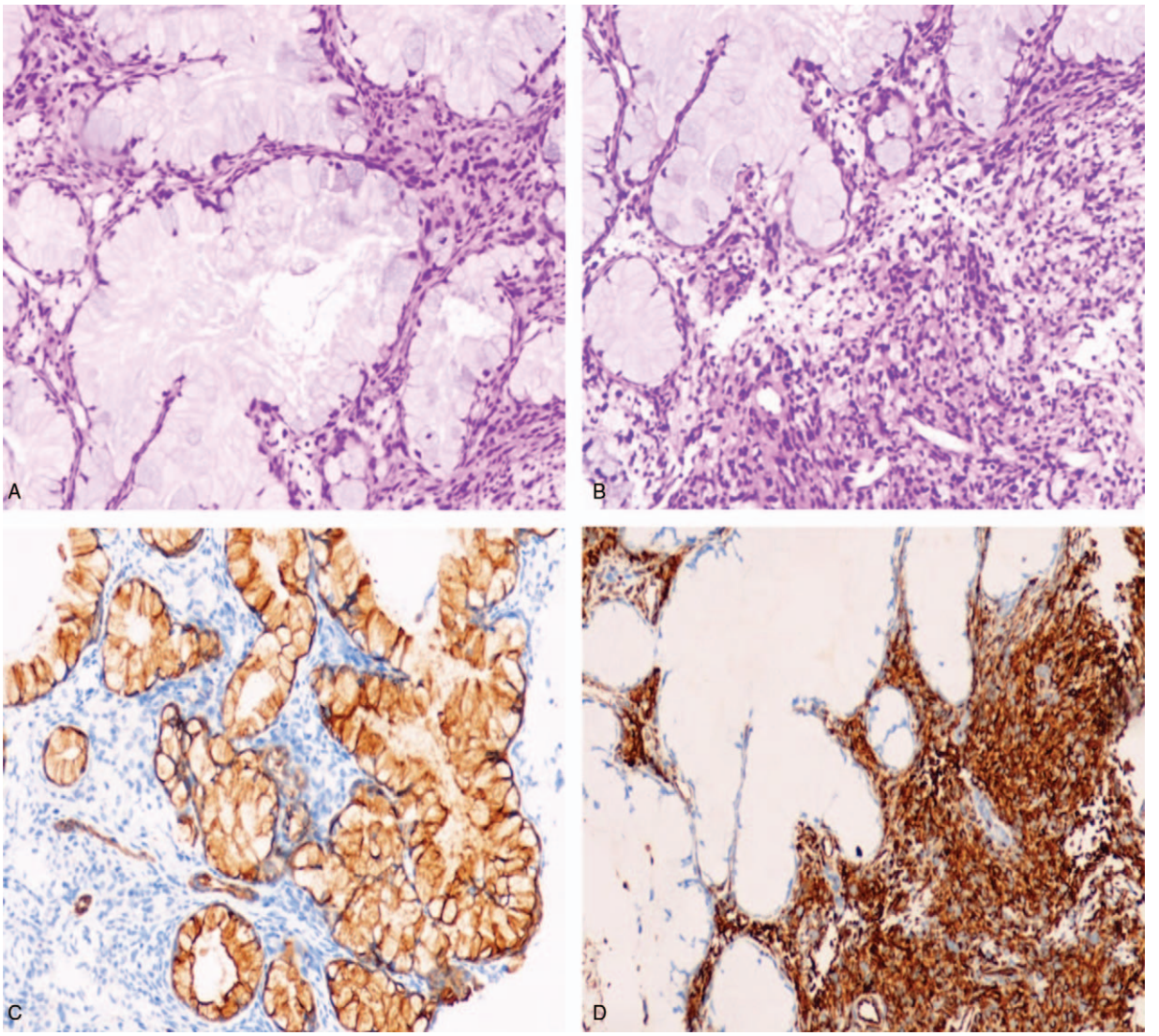

Figure 3. Hematoxylin–eosin (HE) staining and immunohistochemistry (IHC) of the pancreatic carcinosarcoma (PCS). (A) The carcinoma cells were arranged into an irregularly shaped glandular tube or gland-like structure. HE × 200. (B) The sarcoma cells were diffusely distributed around the glandular tube or gland-like structure and the small vessels. HE × 200. (C) Staining with an anti-pan cytokeratin (CK) antibody was positive in the carcinoma, but not the sarcoma. IHC × 200. (D) Vimentin was expressed in the sarcoma, but not the carcinoma. IHC × 200.

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.

stem cells with multipotent differentiation potential; during its development, multiple tissue components containing different germ layers are formed.[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.[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 ± 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 2

A detailed literature review of the clinical and histologic features of pancreatic carcinosarcoma.

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 × 4.0 × 4.0 cm	DAC	Undifferentiated	Radioactive seed implantation	>1y
Mszyco et al[4] (2017)	85	F	CAD, hypertension, hyperlipidemia	None	Abdominal pain	Pancreatic head; 12cm in greatest dimension	Undifferentiated	MFH	PD	—
Salibay et al[5] (2017)	49	M	Hypertension, pancreatitis, ovarian teratoma	Ovarian teratoma (meta), uterine leiomyoma (syn)	Abdominal pain, back pain	Pancreatic body and tail; _	MDAC	Spindle cells	Gemcitabine, docetaxel, radiation therapy	10 mo
Ruess et al[6] (2017)	73	F	AML, aneurysm, chronic pain, SB, AITD, RLS, RBD, MS, CAD	AML (meta)	Abdominal pain	Pancreatic head; 6.5 × 4.5 × 3.0 cm	DAC	Spindle cells	PD	4 mo
Li et al[7] (2017)	60	M	None	None	Abdominal palpable mass	Pancreatic head; 10 × 9.0 × 9.0 cm	Adenocarcinoma, SC	Cartilaginous and osteal differentiation	PD	>1 y
Jia et al[8] (2017)	44	M	Appendectomy, cholecystectomy	None	Jaundice	Pancreatic head; 3cm in diameter	MDAC	Spindle cells, osteosarcoma	PD, gemcitabine, raltitrexed	>31 mo
Gelos et al[9] (2008)	61	F	None	None	Anemia	Pancreatic head; 7.0 × 6.0 × 3.5 cm	MDAC	Spindle cells	PD	11 mo
Lee et al[10] (2015)	24	F	None	None	Abdominal pain	Pancreatic tail; 4.7 × 3.5 cm	Solid and pseudopapillary tumor	Spindle cells	DP	—
Okamura et al[11] (2010)	64	F	Diabetes	None	None	Pancreatic tail; 2.5 × 2.1 × 1.4 cm	IPMC, PDAC	Osteosarcoma, spindle cells	DP	>12 mo
Kim et al[12] (2011)	77	M	Diabetes	None	Poorly controlled blood sugar	Pancreatic head; 2.2 cm	DAC	Undifferentiated	Gemcitabine	—
Shi et al[13] (2015)	74	F	—	None	Acute calculous cholecystitis	Pancreatic tail; 5.0 × 4.0 × 2.0 cm	Mucin-producing epithelial cells	Spindle cells	DP	—
Barkatullah et al[14] (2005)	67	F	PVD	None	Abdominal pain	Pancreatic head; 2.5 × 2.5 × 2.0 cm	MDAC	Spindle cells	PD	8 mo
Kim et al[15] (2011)	48	M	None	None	None	Pancreatic tail; 3.5 × 2.5 × 1.5cm	MCAC; AC	Spindle cells	DP	4 mo
Zhu et al[16] (2012)	53	F	None	None	Abdominal pain	Pancreatic head; 5.0 × 4.0 × 3.0 cm	Duct-like, small cystic formations	Spindle cells	PD	>20 mo
Nakano et al[17] (2008)	82	F	Cholecystectomy	None	Anorexia, jaundice	Pancreatic head; 18×11×10 cm	DAC	Spindle cells	PD	13 d
Shen et al[18] (2010)	72	F	Atherosclerosis, acute pancreatitis	GIST (syn)	Abdominal pain, nausea	Pancreatic head; 5.0 × 4.0 × 4.0 cm	DAC	MFH	PD	2 mo
Wenig et al[19] (1997)	67	M	Acute pancreatitis	None	Abdominal pain	Pancreatic tail; 19 × 14 × 8.0 cm	MCN for all	Spindle cells for all	DP for all	15 mo
			Acute pancreatitis		Abdominal pain					>1 y
	48	F	Diabetes		—	Pancreatic tail; —				9 mo
	65	F				Pancreatic tail; 30 × 25 × 9.5 cm				
Watanabe et al[20] (1996)	76	F	—	None	Abdominal pain, nausea	Pancreatic head; 5cm in diameter	DAC	Spindle cells	PD	3 mo

AC = anaplastic carcinoma, AITD = autoimmune thyroid diseases, AML = angiomyolipoma, 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, MFH = malignant fibrous histiocytoma, MS = metabolic syndrome, PD = pancreaticoduodenectomy, 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 tube 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 tube 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 angiomyolipoma associated with metachronous tumor, according to Ruess et al.[5,6] Only Shen et al have described a pancreatic carcinosarcoma combined with a synchronous malignant gastrointestinal stromal tumor.[18]

MPC, 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,[36] 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.

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Author contributions

Conceptualization: Huanfen Zhao.
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Methodology: Yang Liu, Han Hao, Xiaowan Guo, Jieping Xu, Guona Zheng.
Writing – original draft: Yang Liu, Huanfen Zhao.
Writing – review and editing: Huanfen Zhao.

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