OPEN ACCESS – CASE REPORT

A Case Report on Carcinosarcoma of the Pancreas with a Concise Literature Review

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ABSTRACT

Carcinosarcoma is a rare neoplasm that most commonly affects the uterus. In the pancreas, fewer than thirty cases are reported worldwide. We present a 47-year-old female with epigastric pain, and jaundice. Histopathology revealed a pancreatic head mass showing a biphasic tumor composed of seventy percent Pancreatic Ductal Adenocarcinoma, and thirty percent High Grade Sarcoma with immunohistochemistry using Pancytokeratin, Vimentin, Desmin, S-100, Smooth Muscle Actin, CD34, and Ki-67.

Key words: pancreatic carcinosarcoma, pancreas, carcinosarcoma, immunohistochemistry, surgical pathology, diagnosis

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INTRODUCTION

The most common pancreatic tumor is ductal adenocarcinoma. Undifferentiated carcinoma is one of its subtypes, and it has three distinct patterns: anaplastic undifferentiated carcinoma, sarcomatoid undifferentiated carcinoma, and carcinosarcoma. Carcinosarcoma is a biphasic tumor with epithelial and mesenchymal components. Each component should account for at least 30% of the tumor. Furthermore, the epithelial and mesenchymal components should be immunophenotypically distinct.[1] The incidence of carcinosarcoma in the pancreas is not well established. The *Surveillance, Epidemiology, and End Results (SEER) program* documented fewer than 30 cases worldwide.[2] In a 6-year institutional review at Zhejiang University in China, only 9 carcinosarcomas were identified among 1,824 cases of pancreatic ductal adenocarcinoma.[3] The purpose of this paper is to show the gross, histology, and immunohistochemistry profile of a case of pancreatic carcinosarcoma with multiple nodal metastases and to review the literature.

CASE

A 47-year-old female presented with epigastric pain, followed by jaundice, rash, acholic stools, and tea-colored urine. On blood examination, the patient had elevated liver enzymes and bilirubin levels. Imaging revealed the following findings: biliary obstruction due to a pancreatic head mass showing primary neoplasm features, mass effect on the duodenum and distal common bile duct, several cystic lesions at the pancreatic body and tail, and prominent lymph nodes (Figure 1). Whipple's procedure and superior mesenteric vein anastomosis were performed, and the patient was discharged stable after 8 days.

The gross examination of the pancreatic head exhibited an ill-defined, soft to firm, tan-yellow, solid mass which measured 8 x 7 x 5 cm. The areas near the anterior surface revealed a solid, tan-pink to cream-white, homogenous, smooth, and firm surface. The mass was located near the pancreatic parenchymal margin, posterior resection

margin, and anterior pancreatic surface, and it enfolded the common bile duct. An ulceration measuring 3 x 1 cm ran from the mass to the duodenum. The common hepatic duct, duodenojejunal resection margins, and ampulla of Vater were far from the mass. There were increased numbers of peripancreatic lymph nodes (Figure 2).

The morphology revealed a biphasic tumor with pancreatic ductal adenocarcinoma comprising 70% of the mass. These are composed of irregularly shaped, cystically-dilated, tubular, cribriform, and haphazardly arranged glands. The neoplastic cells had large, moderately pleomorphic, hyperchromatic to vesicular nuclei, coarse

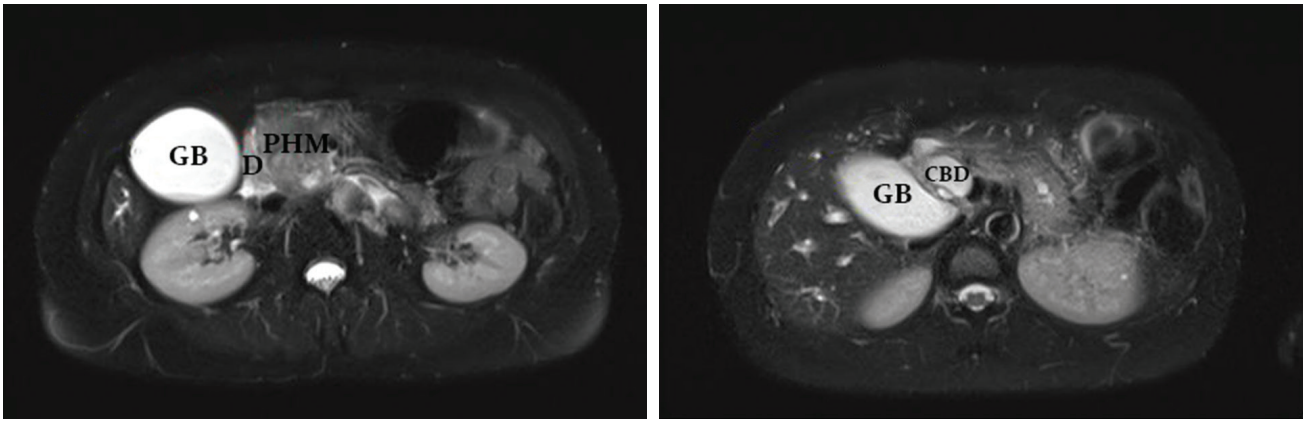

Figure 1. Magnetic Resonance Imaging of pancreatic carcinosarcoma cross-sectional view. CBD indicates common bile duct; D, duodenum; GB, gallbladder; PHM, pancreatic head mass.

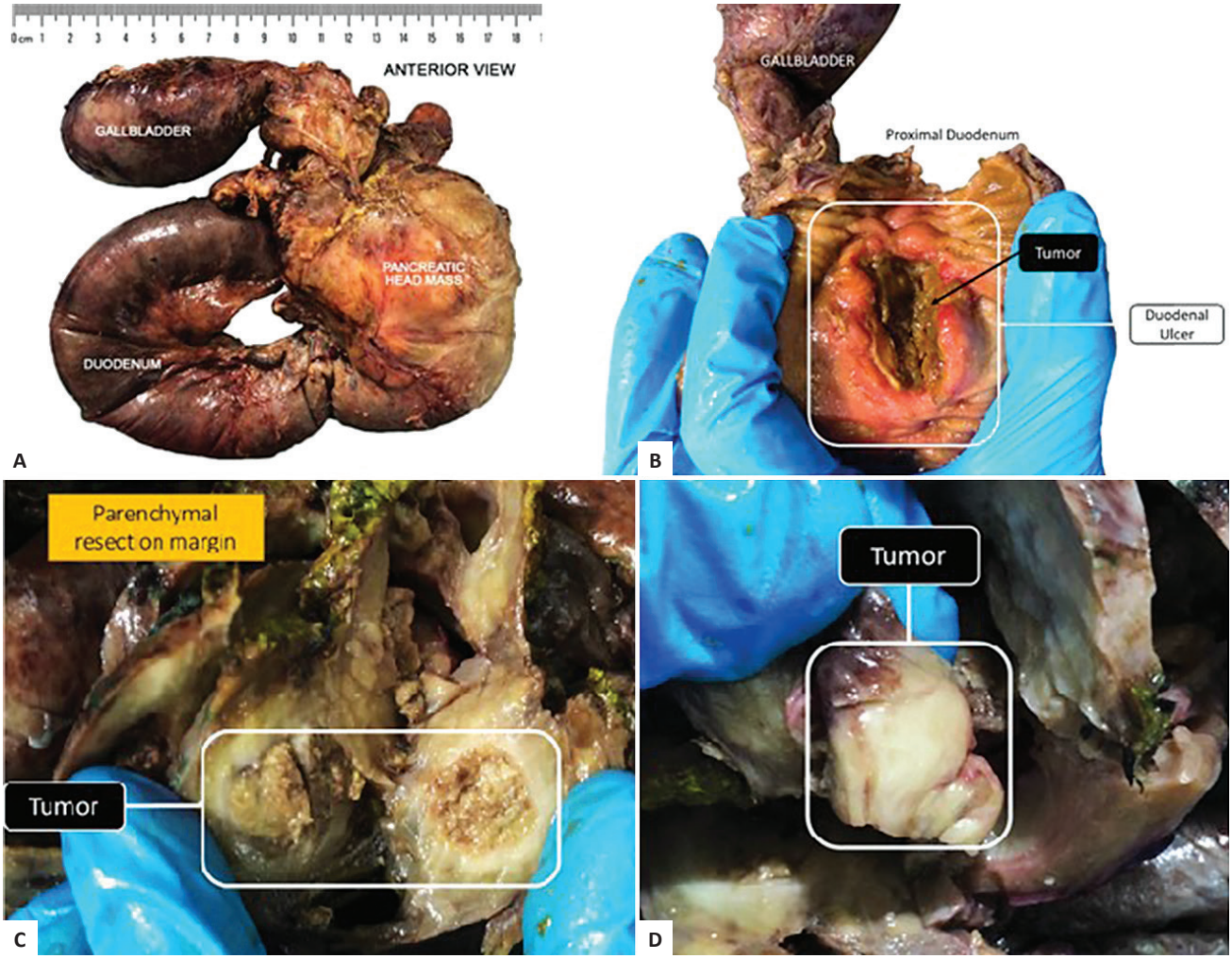

Figure 2. Gross appearance of pancreatic carcinosarcoma. **(A)** The entire pancreaticoduodenectomy specimen with a large pancreatic head mass attached to the duodenum. **(B)** Pancreatic carcinosarcoma is ulcerating the duodenum. **(C)** Cut surface of ill-defined and rough pancreatic carcinosarcoma. **(D)** Solid and homogenous cut surface near the anterior pancreatic surface.

chromatin, prominent nucleoli, and scant to ample eosinophilic cytoplasm. There is desmoplastic stroma and perineural invasion. The intermixed sarcomatous component accounted for 30% of the mass. These are composed of sheets of spindle-shaped cells characterized by large, pleomorphic, vesicular nuclei, coarse chromatin, inconspicuous nucleoli, and scant to abundant eosinophilic cytoplasm. The cells were arranged in a haphazard, herring-bone, and whirling pattern. There was a note of background basophilia, numerous mitotic figures (57 per 10 high power fields), and foci with necrosis and multinucleated giant cells (Figure 3).

The tumor invaded the duodenum, lymphatic vessels, and two peripancreatic lymph nodes. Intraductal papillary mucinous neoplasm with columnar epithelial lining was also evident.

Immunohistochemistry studies revealed a carcinomatous component with positive, strong Pancytokeratin expression and focal Vimentin expression. On the other hand, sarcomatous components expressed Vimentin while being negative for Pancytokeratin, and other mesenchymal markers, S-100, Smooth muscle actin (SMA), Desmin, and CD34. Ki-67 was high in both components (Figure 4 and Table 1). CD68 highlighted the multinucleated giant cells (GC). Hence, a diagnosis of Pancreatic Carcinosarcoma was made.

The management plan was implemented which included 12 cycles of gemcitabine and oxaliplatin. In the interim of chemotherapy, five months post-operatively, thickening and stranding of the mesentery, as well as multiple mesenteric nodularities, were seen on a triple-phase CT scan. Afterwards, eleven months post-operatively, the entire abdomen was filled with heterogeneous echoes with septations and loculations. After sixteen months, the following lesions were observed. A heterogeneously enhancing cystic mass in the pancreatic tail, as well as several calcified and non-calcified parenchymal nodules in both lungs, developed. The radiologic considerations were mesenteric carcinomatosis, tumor recurrence, and pulmonary metastases. However, no additional biopsies and cytology procedures were performed to confirm the diagnosis of metastasis. Instead, palliative care was selected as a treatment option.

Table 1. Immunohistochemistry studies done for the case

Immunohistochemical stain	Carcinomatous component	Sarcomatous component
Pancytokeratin	+	-
Vimentin	+ (Focal)	+
S-100	-	-
Desmin	-	-
SMA	-	-
CD34	-	-
Ki-67	50-60 %	60-70 %

DISCUSSION

Carcinosarcomas are rare biphasic tumors that frequently affect the female genital tract, but can occasionally occur

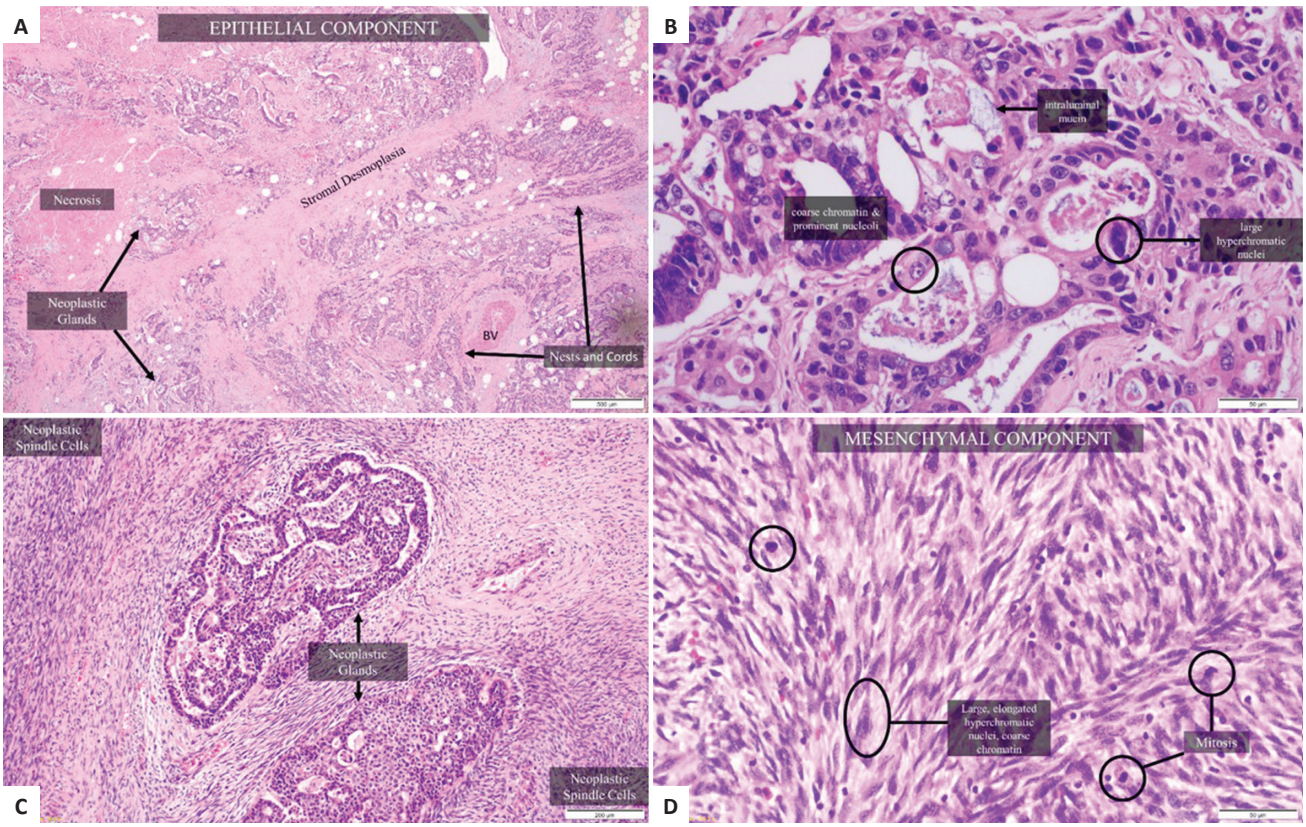

Figure 3. Hematoxylin and eosin-stained histologic sections of pancreatic carcinosarcoma. **(A)** Scanner view and **(B)** high power magnification of the carcinomatous component (CC) showing ductal adenocarcinoma (x40) and (x400). **(C)** Mosaic pattern of CC and sarcomatous component (SC) (x100). **(D)** High power magnification of SC showing neoplastic spindle cells with mitotic figures (x400).

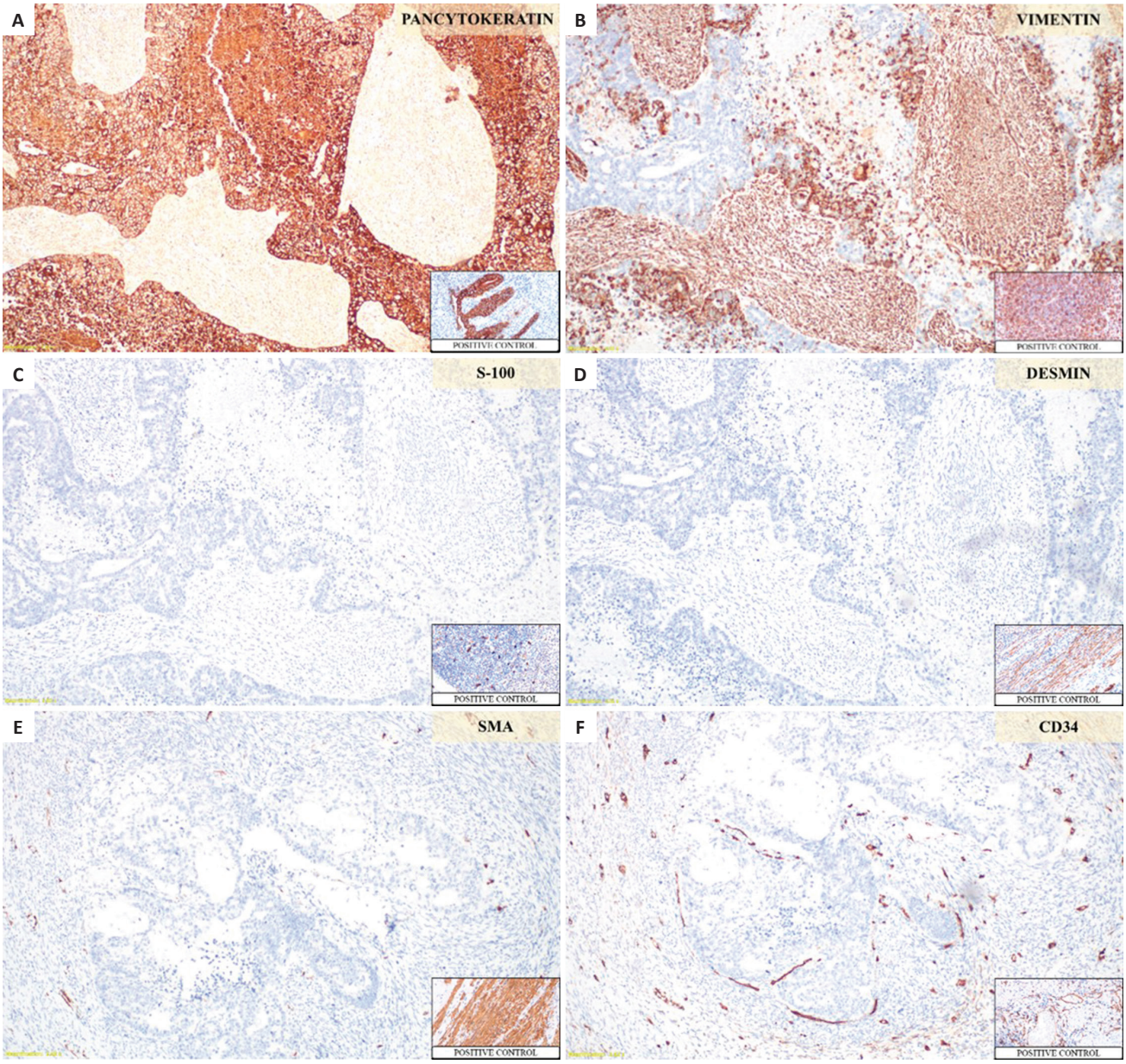

Figure 4. Immunohistochemical findings of pancreatic carcinosarcoma. **(A)** Cytokeratin highlights the carcinomatous component (CC) and negative staining of the sarcomatous component (SC) (x100). **(B)** Vimentin highlighting the SC and non-specific expression in the CC (x100). **(C)**, **(D)**, **(E)**, and **(F)** show negative staining on both CC and CC using S-100, Desmin, Smooth muscle actin (SMA), and CD34, respectively (x100).

in the prostate, urinary tract, head and neck, and gastrointestinal system, including the pancreas. The histogenesis of these tumors is still undefined. The following theories are considered: 1) Collision: wherein two independent malignancies are colliding in one organ, 2) Combination: both components are derived from an early mutation of a single multipotent cell, 3) Conversion: explaining that epithelial tumors undergo metaplastic transformation into mesenchymal tumors; and 4) Composition: describing that the mesenchymal component is a stromal response to the epithelial tumor.[4]

Genomic analysis of microdissected tissues showed consistent KRAS mutations on both carcinomatous and sarcomatous components, with single-nucleotide mutations, c.35G>A and c.35G>T at codon 12 and codon 34.[3-8] KRAS Q61H and TP53 Q100X mutations are also recently discovered to be present in both components.[3] In a case series by Ruess, molecular analysis of these tumors revealed that pancreatic carcinosarcomas are of monoclonal origin. KRAS mutation is a distinctive driver mutation in pancreatic ductal adenocarcinoma. Because of the similarities in KRAS mutations, it is postulated that pancreatic carcinosarcoma originated from pancreatic ductal adenocarcinoma. As explained by the authors, these findings may support the conversion theory of epithelial-mesenchymal transition (EMT). This would also justify WHO's classification of pancreatic carcinosarcoma as a subtype of pancreatic ductal adenocarcinoma.[4] Moreover, Nakano supported the idea that KRAS mutation in

codon 12 elicited the adenocarcinoma, and mutation in codon 34 induced the sarcomatous transformation.[8] Unfortunately, limited cases had molecular studies to verify the definite pathogenesis.

The majority of the cases documented worldwide had Ductal Adenocarcinoma (76%), few Mucinous Cystadenocarcinoma (13%), Adenosquamous Carcinoma (3%), Intraductal Papillary Mucinous Carcinoma with Invasive Adenocarcinoma (3%) and Adenocarcinoma with Squamous areas (3%) for the epithelial component. On the other hand, complex undifferentiated mesenchymal components are reported. They are described as spindled cells without explicit comment on their malignancy (27%), others are referred to be malignant but without definite diagnosis or differentiation (17%). One case is described as a High-Grade Spindle Cell with focal Chondrosarcoma and myogenic differentiation (3%). In several cases, a specific diagnosis is rendered: Malignant fibrous histiocytoma/ Undifferentiated Pleomorphic Sarcoma / Pleomorphic Spindle Cell Sarcoma (MFH/UPS/PSCS) (27%), MFH/UPS with Osteosarcoma (13%), Leiomyosarcoma (3%), Osteosarcoma (7%) and Embryonal Rhabdomyosarcoma (3%) (Table 2).[1-15]

Immunohistochemistry with Pancytokeratin and Vimentin demonstrated the distinction between the epithelial and mesenchymal components. The other epithelial markers with positive expression are CAM 5.2, Epithelial Membrane Antigen (EMA), Carcinoembryonic Antigen (CEA), Cytokeratin 7 (CK7), and Cytokeratin 19 (CK19). Contrary to most, the given case showed focal expression to Vimentin. Reported cases also exhibited focal expression to Smooth Muscle Actin (SMA) and Desmin in the mesenchymal component.[5] Ki-67 as a proliferation index ranged from 2-60% and 2-75% in the carcinomatous and sarcomatous components, respectively. High-grade sarcoma is identified given the necrosis, high mitoses, and nuclear atypia. Common involvement of the duodenum, peripancreatic soft tissues, lymph nodes, and liver metastasis were identified.[9]

Treatment options included surgery with or without the addition of chemotherapy. Although data on better prognosis with the benefit of chemotherapy is inadequate, analysis in a small population showed significance. Likewise, a locally advanced or metastatic pancreatic cancer warrants the use of adjunct systemic therapy. FOLFIRINOX is the recommended treatment regimen in the usual Pancreatic Ductal Adenocarcinoma, and Gemcitabine is an alternative therapy for patients with poor performance status and unable to tolerate toxic side effects.[16] Given the limited reported cases of Pancreatic Carcinosarcomas, no standard treatment has been established. The possible option is to offer Gemcitabine, as it may also target the sarcomatous component.[17] However, EMT was associated to Gemcitabine resistance. Wang provided molecular evidence of this association. The study demonstrated that Notch-2 and its ligand, Jagged-1, are upregulated in Gemcitabine-resistant cells linking it to the epithelial-mesenchymal transition phenotype.[18] The overall survival has a mean of 15 months and 14 days in 25 cases (Table 2).[1-15]

CONCLUSION

A case of pancreatic carcinosarcoma with extension to the duodenum and nodal metastases is presented. Pancreatic ductal adenocarcinoma and High-grade sarcoma are documented with immunohistochemical studies. Characterization of these tumors is essential as it influences treatment plan, behavior and prognosis.

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ETHICAL CONSIDERATION

Patient consent was obtained before the submission of the manuscript.

STATEMENT OF AUTHORSHIP

Both authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

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Table 2. Published case reports of carcinosarcoma

	Author	Age/Sex	Symptom	Localization and extent	Size (mm)	CC	IHC on CC									SC	IHC on SC									LN	KRAS and TP53 mutation	Teatment	Survival (months) Recurrence
							CK	Vimentin	S-100	Desmin	Myogenin	SMA	CD34	CD68	Ki-67		CK	Vimentin	S-100	Desmin	Myogenin	SMA	CD34	CD68	Ki-67				
1	***Our case***	47/F	Abdominal pain, jaundice	Head to duodenum	80	PDAC	+	+F	-	-	ND	-	-	+GC	50-60%	High Grade Sarcoma	-	+	-	-	ND	-	-	+GC	60-70%	2/35		S/p pylorus preserving whipples, end to end anastomosis of SMV S/p chemotherapy (GemOx) x 12 cycles	> 10 Peritoneal carcinomatosis, Stage IV
2	***Li, et al.*** [3]	60/M	Abdominal pain	Tail	75	PDAC	+	-	ND	ND	ND	ND	ND	ND	ND	Undifferentiated spindle cells (7/9); MFH and Osteosarcoma (2/9)	-	+	ND	ND	ND	ND	ND	ND	ND	0/19		Total pancreatectomy	2 Liver at 1 month
3		66/M	Painless jaundice	Head	40		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	0/27		Whipple, Gemcitabine plus Nab-paclitaxel	11 Liver at 3 months
4		69/M	Incidental finding	Head	25		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	3/33		Whipple, FOLFIRINOX	19 LN at 13 months
5		56/F	RUQ pain, jaundice	Head	100		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	5/30		Total pancreatectomy	39 Liver at 3 months
6		51/F	Epigastric pain, jaundice	Head	45		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	0/22		Whipple, Gemcitabine	17 Liver at 10 months
7		48/F	Epigastric pain	Tail	80		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	2/24		Total pancreatectomy	NA NA
8		67/F	Epigastric pain	Head	64		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	6/6		Whipple	4 Liver at 3 months
9		59/M	Abdominal pain	Head	53		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	3/21		Whipple	NA NA
10		49/M	Abdominal pain	Body	80		+	-	ND	ND	ND	ND	ND	ND	ND		-	+	ND	ND	ND	ND	ND	ND	ND	38/42		Distal pancreatectomy	NA NA
11	***Liu, et al.*** [10]	66/F	Abdominal pain, nausea, jaundice	Head	50	PDAC	+	-	-	-	ND	-	ND	ND	30%	Undifferentiated Sarcoma	-	+	-	-	ND	-	ND	ND	20%	NA		Cholecystectomy with bile ductjejunum, Roux-en-Y anastomosis, radioactive seed implantation	> 12 NA
12	***Still, et al.*** [2]	59/F	Abdominal pain, nausea and emesis	Head to duodenum, main pancreatic duct and intrapancreatic bile duct	25	Moderately Differentiated Adenocarcinoma	+ F	NA	NA	NA	NA	NA	NA	NA	NA	High Grade Spindle Cell with focal chondrosarcoma and myogenic differentiation	NA	NA	NA	+F	-	NA	NA	NA	NA	2/28		Pancreaticoduodenectomy, Neoadjuvant trial (6 cycles of FOLFIRINOX-Oxaliplatin, Irinotecan, Fluorouracil and Leucovorin), Chemotherapy with gemcitabine and paclitaxel	13 NA
13	***Salibay, et al.*** [11]	49/M	Abdominal pain	Body/tail	NA	Moderately Differentiated Adenocarcinoma	+	ND	ND	-	-	-	ND	ND	50%	High Grade Spindle Cell Sarcoma	-	ND	ND	+F	-	+F	ND	ND	50%	1/1		Total abdominal hysterectomy with right salpingo-oophorectomy and exploration of the pancreatic mass, Pancreatic biopsy, hepatodochal lymphadenectomy, gemcitabine and docetaxel with no response, followed by ifosfamide and Adriamycin with progression	10 NA
14	***Ruess, et al.*** [4]	73/F	Epigastric pain	Head to periadipose tissue	42	PDAC	+	-	-	ND	ND	ND	ND	ND	15%	Malignant mesenchymal component with undifferentiated spindle-shaped cells	+F	+	+F	ND	ND	ND	ND	ND	50-60%	0/17	exon 2 of KRAS gene with c.35G>A substitution leading to a p.G12D mutation on CC and SC	Pancreaticoduodenectomy	4 NA
15	***Jia, et al.*** [9]	44/F	Abdominal pain and jaundice	Head to peripadipose tissues	30	Moderately Differentiated Adenocarcinoma	ND	-	ND	ND	ND	ND	ND	ND	ND	Osteosarcoma	-	+	ND	ND	ND	ND	ND	ND	ND	3/18		Whipple, gemcitabine and raltitrexed	>31 NA
16	***Bai, et al.*** [5]	71/M	General symptoms of abdominal pain, jaundice, nausea, vominting, anemia, weight loss or incidental finding	Head	50	PDAC	+	-	ND	-	ND	-	ND	-	35 %	MFH/UPS + Osteosarcoma, focally	+F	+	ND	-	ND	ND	ND	-	35%	0/20	c.35G>A on both components	Pancreaticoduodenectomy, Splenectomy, Postoperative chemotherapy	11 Tumor recurrence or metastasis at 9 months
17		49/M		Head	50	PDAC	+	-	ND	-	ND	-	ND	-	15%	Osteosarcoma + MFH/ UPS	-	+	ND	-	ND	ND	ND	GC+	20%	0/1	c.35G>A on both components	Pancreaticoduodenectomy, Postoperative chemotherapy	39 NA
18		74/M		Head	80	PDAC	+	-	ND	-	-	-	ND	-	50%	PSCS	-	+	ND	-	-	-	ND	F+	60%	0/5	c.35G>T on both components	Pancreaticoduodenectomy	10 Tumor recurrence or metastasis at 9 months
19		38/M		Body/tail	160	MCAC	+	-	ND	-	ND	-	ND	-	25%	PSCS	-	+	ND	-	ND	ND	ND	GC+	20%	NA	KRAS c.35G>T on both components	Distal Pancreatectomy, Splenectomy, Gamma kinfe Radiosurgery, Postoperative chemotherapy	NA Tumor recurrence or metastasis at 26 months
20		67/M		Head	35	PDAC	+	-	ND	-	-	-	ND	ND	ND	ERMS	-	+	ND	+P	-	-	ND	ND	ND	NA		Pancreaticoduodenectomy, Postoperative chemotherapy	47 NA
21		60/F		Body/tail	75	MCAC	+	-	ND	-	ND	ND	ND	-	ND	MFH/UPS	-	+	ND	ND	ND	ND	ND	+GC	ND	NA		Pancreaticoduodenectomy	15 Tumor recurrence or metastasis at 12 months
22		75/F		Head	45	PDAC	+	-	ND	-	ND	-	ND	-	ND	PSCS	-	+	ND	-	ND	ND	ND	-	ND	0/10		Pancreaticoduodenectomy, Traditional Chinese medical herbal treatment	29 NA
23		59/M		Body/tail	55	PDAC	+	-	ND	-	ND	ND	ND	ND	20%	MFH/UPS	-	+	ND	ND	ND	ND	ND	ND	20%	NA	KRAS c.35G>A on both components	Pancreaticoduodenectomy, Splenectomy, Postoperative chemotherapy	17 NA
24	***Shi, et al.*** [12]	74/F	Incidental finding	Tail	50	MCAC	+	-	ND	ND	ND	ND	ND	ND	ND	Malignant spindle cells	-	+	ND	ND	ND	ND	ND	ND	ND	NA		Distal pancreatectomy, Splenectomy	NA NA
25	***Cicy, et al.*** [13]	50/M	Abdominal pain	Head	60	Adenocarcinoma	+	-	ND	ND	ND	ND	ND	ND	ND	PSCS	ND	+	-	-	ND	+	-	ND	Low	0/9		Whipple pancreaticoduodenectomy	> 47 days NA
26	***Oymaci, et al.*** [14]	48/M	Epigastric pain	Head to duodenum and periadipose tissue	35	PDAC	+	-	-	-	-	-	-	-	2%	High grade pleomorphic spindle cells	-	+	-	-	-	+F	-	-	2%	2/16		Extended pancreaticoduodenectomy	20 days NA
27	***Palaniappan, et al.*** [15]	46/M	Jaundice	Head to duodenum	30	Adenosquamous Carcinoma	+	-	-	-	ND	-	ND	-	High	Leiomyosarcoma	-	+	-	-	ND	+	ND	NS	High	0/5		Pancreatoduodenectomy, Gemcitabine	>28 NA
28	***Kim, et al.*** [6]	48/M	Incidental finding	Tail	70	MCAC	+	+ F	-	-	-	-	-	-	ND	MFH/UPS	-	+	-	-	-	-	-	-	ND	4/15	G to A transition at codon 12 of K-ras gene	Distal pancreatectomy with splenectomy and colonic segmental resection, Gemcitabine	4 Liver and peritoneum
29	***Okamura, et al.*** [7]	64/F	Incidental finding	Tail	35	IPMC with Invasive adenocarcinoma	+	ND	ND	ND	ND	ND	ND	+ GC	ND	Osteosarcoma with heterologous components	ND	+	ND	ND	ND	ND	ND	ND	ND	NA	KRAS (G35A mutation in exon 1) abd TP53 (T337A mutation in exon 4) in both components	Distal pancreatectomy, Gemcitabine	>12 NA
30	***Nakano, et al.*** [8]	82/F	Hypochondralgia, jaundice	Head to duodenum and transverse mesocolon	180	Adenocarcinoma with focal squamous areas	+	-	ND	-	-	-	ND	ND	ND	PSCS	+	+	-	-	ND	-	ND	ND	ND	NA	G to A transition at codon 12 and 34 on both components	Radical pancreatoduodenectomy with partial resection of the transverse colon	13 days NA

CC, Carcinomatous Component; CK, Cytokeratin; F, Focal; GC, Giant Cells; IHC, Immunohistochemical Stain; IPMC, Intraductal Papillary Mucinous Carcinoma; MCAC, Mucinous Cystadenocarcinoma; MFH, Malignant Fibrous Histiocytoma; MFH/UPS, Malignant Fibrous Histiocytoma / Undifferentiated Pleomorphic Sarcoma; NA, Not available; ND, Not determined; NS, Non-specific; PDAC, Pancreatic Ductal Adenocarcinoma; PSCS, Pleomorphic Spindle Cell Sarcoma; SC, Sarcomatous Component; SMA, Smooth Muscle Actin

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