

CASE REPORT

Pancreatic Carcinosarcoma. Case Report of Multimodal Therapy and Review of the Literature

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ABSTRACT

Context Carcinosarcoma (malignant mixed tumor) is a rare variant of a pancreatic neoplasm having a dismal prognosis; very few clinical data and treatment options have been published. Unlike adenocarcinoma of the pancreas, there is nothing specific in the literature for this variant regarding postoperative treatment with chemotherapeutic agents.

Case report We report the case of a 61-year-old woman presenting with anemia. Examination revealed a mass in the pancreatic head and she underwent a partial pancreaticoduodenectomy. Histopathological examination revealed a pancreatic neoplasm with both adenomatous as well as sarcomatous characteristics. Postoperatively, the patient was treated with gemcitabine and was in a good health for 9 months. Three follow-up CT scans were done, showing complete remission. Eleven months postoperatively, the patient died from a recurrence.

Conclusion Carcinosarcoma of the pancreas is a very rare disease having a dismal prognosis. In addition to reviewing the literature on this entity, we present the first published case where gemcitabine was administered as a treatment modality in combination with surgery.

INTRODUCTION

Carcinosarcoma of the pancreas is a rare entity comprising a small subset of all pancreatic neoplasms. The histogenesis is unclear. To our knowledge, nine cases of this entity have been published so far [1, 2, 3, 4, 5, 6, 7]. Diagnosis is usually established by immunohistochemical examination of the resected specimen. Prognosis is limited to several months after resection [1, 2, 3, 4, 5, 6, 7]. We present the case of a 61-year-old female patient, who underwent a partial pancreaticoduodenectomy and was treated postoperatively with gemcitabine as chemotherapeutic agent. We review the current literature on this rare type of neoplasia, considering histopathological and clinical features.

CASE REPORT

A 61-year-old white female was admitted to our hospital suffering from anemia. Her past medical history was not significant. She had no nausea nor hematemesis or dark stools. Laboratory investigation revealed a hemoglobin value of 5.0 g/dL (reference range: 12-16 g/dL). Other laboratory tests including liver enzymes, alkaline phosphatase and bilirubin were within the normal range. Esophagogastroduodenoscopy revealed a lesion within the duodenum, located orally to the papilla of Vater. An abdominal computed tomography scan showed a mass in the head

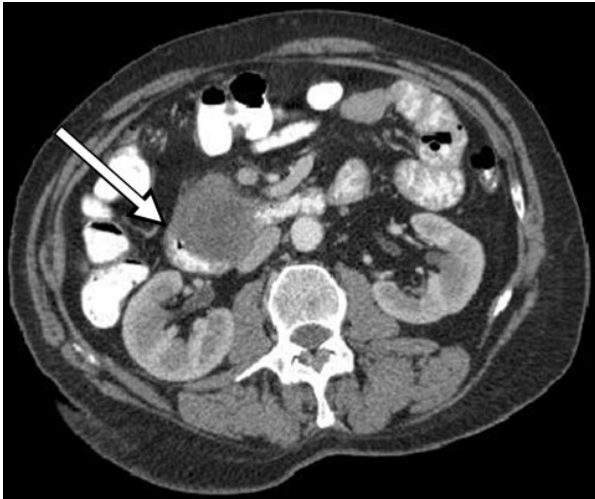


Figure 1. Axial contrast-enhanced CT image of the pancreas. A low-density mass is present (arrow) which involves the head of the pancreas.

of the pancreas with infiltration of the duodenum (Figure 1). A radical pancreaticoduodenectomy using the Whipple procedure was performed with two hepaticojejunostomies due to the presence of an aberrant bile duct.

Pathological Studies

The pathological specimen was composed of the head of the pancreas, a portion of the stomach and the duodenum, the distal portion of the common bile duct, an aberrant bile duct and the gallbladder. On gross examination, the head of the pancreas revealed an exophytically-growing tumor localized in the duodenum 1 cm orally to the papilla of Vater measuring 7x6x3.5 cm. Moreover, an extraluminal growing tumor localized 3 cm distally from the oral resection margin, 2 cm in diameter, was detected in the stomach.

Paraffin-embedded sections of formalin-fixed tissue were studied by routine morphological histology using hematoxylin-eosin staining. Immunohistochemistry was performed applying monoclonal antibodies to CK7, pan-cytokeratin, CK20, vimentin, PDGF, CD117, CD34, beta-HCG, CD31 and Ki-67.

Microscopically, the tumor yielded two components. The first one was a moderately differentiated adenocarcinoma (Figure 2a). The second component showed poorly differentiated solid tissue with a focally bizarre configuration of the nuclei (Figure

2b). Both components infiltrated the peripancreatic fat with extension to the resection margin, yielding an R1 situation. One of eight peripancreatic lymph nodes showed a metastasis of the adenoid component. None of the perigastric lymph nodes were malignant. The resection margins of the pancreatic body, the common bile ducts, the stomach, the duodenum and the pancreatic duct were free from malignant cells. Immunohistochemically, the epithelial component was strongly reactive for antibodies to CK7 and pan-cytokeratin (Figure 2a). A moderate reaction was detected for the antibody to CK20. The sarcomatoid component was negative for all CK-antibodies, but strongly reactive for the antibody to vimentin (Figure 2b). Spindle cells were found in the stomach tumor. Immunohistochemically, they were moderately positive for the antibody to

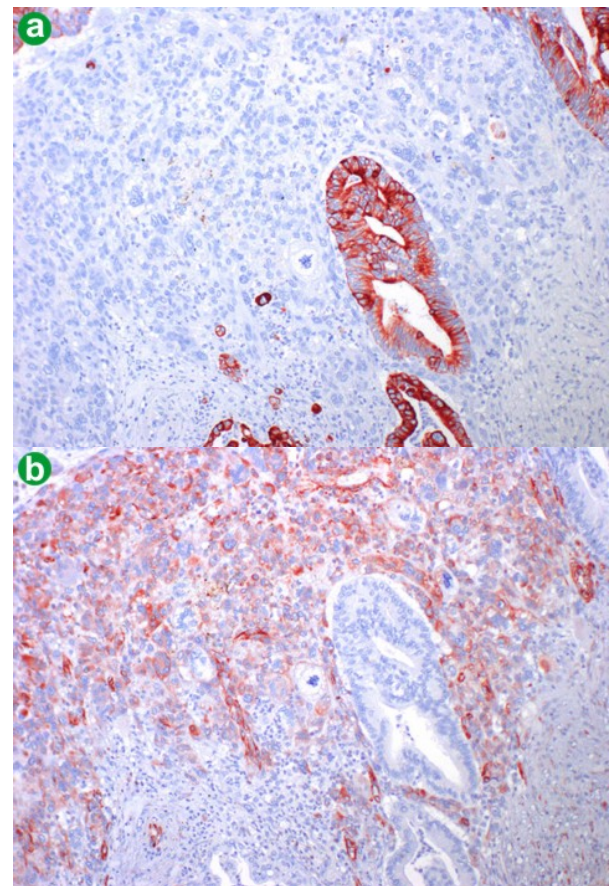


Figure 2. Immunohistochemical staining of the pancreatic tumor. **a.** Section with antibody against cytokeratin demonstrating the epithelial component. **b.** Section with antibody against vimentin demonstrating the sarcomatous component.

platelet-derived growth factor (PDGF). Ten percent of the tumor cells were strongly positive for Ki-67. All cells of this tumor were negative for CD117 (Table 1). The immunohistological features of this tumor were concordant with the growth of a benign gastrointestinal stromal tumor.

Clinical Course

On the first postoperative day, biliary liquid appeared via the abdominal drain. The patient underwent relaparotomy. Macroscopically, a minimal insufficiency within the terminolateral hepaticojejunostomy was visible. The anastomosis to the aberrant bile duct was sufficient. As no major insufficiency was detected and no obvious technical problem was present, we decided to protect both anastomoses by means of intraoperative stenting using endoscopic cholangiography in a random fashion. An inspectoral jejunal stoma of the descending sling was applied. Due to atonia and a prolonged need for supportive parenteral substitution of volume and weakness, she was in hospital for 6 weeks. After complete healing of anastomoses, the stoma was reconnected during the hospital stay 5 weeks postoperatively. One week later, the patient was discharged. After implantation of a venous port system, additional therapy with gemcitabine was initialized 8 weeks postoperatively. Due to postoperative complications, the start of the chemotherapy was delayed by approximately 2 weeks. Six cycles of gemcitabine with a dose of 1,000 mg/cm² were used and finished 7 months

postoperatively. The patient was well for about 9 months after surgery and tolerated chemotherapy without problems and without evidence of disease. Three follow-up abdominal and chest CT scans were done 2, 4, and 8 months postoperatively, showing no signs of tumor recurrence. Four months after stopping gemcitabine (11 months postoperatively), she was readmitted to our hospital with diffuse abdominal pain and anemia (hemoglobin 6.0 g/dL). An abdominal CT showed a huge mass consistent with a peritoneal carcinosis. The differential diagnosis was a hematoma. To definitively clarify the uncertain situation, a relaparotomy was performed, and a diffuse intraperitoneal tumor mass in the upper abdomen was detected. The patient died 2 days postoperatively.

DISCUSSION

Carcinosarcomas (malignant mixed tumors) are rare neoplasms, predominantly located in the uterus [8]. They are histologically characterized by a carcinomatous and a sarcomatous component. Immunohistochemical diagnosis is established by reactivity of the carcinomatous and sarcomatous elements to cytokeratin and vimentin, respectively. Carcinosarcomas must be differentiated from sarcomatoid carcinomas, which immunohistochemically show only cytokeratin reactivity and are therefore considered to be true carcinomas. However, they have to be separated from epithelioid sarcomas which are defined as sarcomas as they lack cytokeratin reactivity [9]. So far,

Table 1. Applied antibodies and staining intensities.

Antibody against	Epithelial component	Sarcomatous component	Stomach tumor
CK7	Strong staining	No staining	Not done
CK20	Moderate staining	No staining	Not done
CD117	Not done	Not done	No staining
Pan-cytokeratin	Strong staining	No staining	No staining
Vimentin	No staining	Strong staining	No staining
PDGF	Not done	Not done	Moderate staining
Ki-67	No staining	No staining	Strong staining

PDGF: platelet-derived growth factor

only a handful of cases reporting true pancreatic carcinosarcomas have been published and the prognosis appears limited with an average postoperative survival time of 6 months [1, 2, 3, 4, 5, 6, 7]. As a differential diagnosis, a metastasis of a mixed malignant ovarian Mullerian tumor may be considered, as described previously [10]. A gynecological primary tumor could be excluded in our case. Remarkably, an independent benign gastrointestinal stromal tumor localized 3 cm distant from the oral resection margin was detected in the stomach of our patient.

The origin of mixed carcinosarcomas is unknown. It has been postulated that these neoplasms represent cellular elements derived from two different histologic origins proliferating in one tumor [9]. In contrast, van den Berg *et al.* suggest a monoclonal origin with subsequent divergence of the neoplastic epithelial and sarcomatous portions [11]. Yamakazi proposed that carcinosarcomas begin growing as adenocarcinomas and later accumulate genetic alterations with consequent transformation into carcinosarcomas having two different histological patterns [5].

As detailed in Table 2, the cellular composition of the sarcomatous components varies. Wenig *et al.* report an association of pancreatic mucinous cystic neoplasms with sarcomatous stroma. They describe three cases of pancreatic mucinous cystic

neoplasms with sarcomatous stroma making the latter component responsible for their aggressive clinical behavior. Only one of the three patients was alive one year after surgical therapy [3]. Also in the latest publication regarding pancreatic carcinosarcoma [7], a mucinous cystadenocarcinoma containing sarcomatous components was found. The patient, treated by pylorus-preserving pancreaticoduodenectomy, died 4 months after therapy from metastatic disease to the liver and the peritoneum. In contrast to these data, our patient had no cystic components in her pancreatic tumor. In several reports, the sarcomatous component of the mixed neoplasms was composed of osteoclastic giant cells [2, 6, 12]. We could not detect such cellular components in our case. Millis *et al.* [1] found leiomyosarcomatous areas in regions of the tumor under examination. Moreover, they made the observation that the carcinomatous and sarcomatous areas of differentiation showed a polar distribution within the tumor. In contrast to this finding, the invasion front in our case consisted of epithelioid as well as sarcomatous cells. An Darvishian *et al.* were the first to describe a true pancreatic carcinosarcoma composed of adenocarcinoma and a malignant fibrous histiocytoma [4].

In our case, a residual tumor was detected in the caudal resection margin. After an interdisciplinary discussion held by the tumor

Table 2. Clinical and histological characteristics of published cases.

Author	Age	Gender	Predominant histology of non-epithelial component	Mucinous cystic component	Survival (months)
Millis <i>et al.</i> [1]	50	Female	Leiomyosarcoma	No	3
Watanabe <i>et al.</i> [2]	76	Male	Osteoclastic giant cells; pleomorphic giant cells	No	3
Wenig <i>et al.</i> [3]	48	Female	Spindle-shaped stroma, (rhabdoid)	Yes	12
Wenig <i>et al.</i> [3]	65	Female	Spindle-shaped stroma	Yes	9
Wenig <i>et al.</i> [3]	67	Male	Spindle-shaped stroma	Yes	15
Darvishian <i>et al.</i> [4]	74	Male	Malignant fibrous histiocytoma	No	- ^a
Yamazaki [5]	90	Male	Spindle-shaped stroma	No	- ^b
Barkatullah <i>et al.</i> [6]	67	Female	Spindle-shaped stroma; osteoclastic giant cells	No	8
Bloomston <i>et al.</i> [7]	67	Female	Spindle-shaped stroma	Yes	4

^a Alive and well 4 months after the surgery

^b Autopsy case report

board and a second opinion (Prof. Issels, Munich, Germany), we recommended gemcitabine therapy. This drug has gained importance in the treatment of pancreatic adenocarcinoma in a neoadjuvant as well as in an adjuvant setting. In adjuvantly-treated patients who underwent resection for pancreatic cancer with curative intent, it delays the development of disease progression [13]. Gemcitabine in combination with cisplatin has been associated with a high resection rate and improved survival in the neoadjuvant setting in a preliminary study [14].

In summary, we present the first case with a rare manifestation of an incompletely resected carcinosarcoma of the pancreas submitted to treatment with gemcitabine as systemic postoperative therapy. Though appearing to be a feasible treatment option, the patient died 11 months postoperatively from recurrent disease.

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Keywords Carcinosarcoma; Combined Modality Therapy; gemcitabine; Mixed Tumor, Malignant; Pancreas

Abbreviations PDGF: platelet-derived growth factor

Conflict of interest The authors have no potential conflicts of interest

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