Serous Cystadenocarcinoma of the Pancreas: Clinical Features and Management of a Rare Tumor

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Key Words

Cystic pancreatic neoplasms · Serous cystadenocarcinoma · Pancreatic cystadenoma · Metastatic cystic neoplasms of the pancreas

Abstract

Background/Aims: The vast majority of serous cystic neoplasms of the pancreas are benign, and small, asymptomatic lesions, which are generally managed with observation. However, some of these tumors may attain a large size and occasionally metastasize. **Methods:** In this study, we present a 78-year-old man with serous cystadenocarcinoma of the pancreas with liver metastases treated by distal pancreatectomy and liver ablation, who went on to develop new liver metastases 5 years after the initial operation. We perform a literature review to determine the number of these malignant neoplasms previously reported and to identify features associated with malignant lesions. **Results:** Literature reveals that metastatic serous cystadenocarcinomas of the pancreas are rare tumors, occurring in less than 3% of cases of serous cystic neoplasms. All malignant cases reported

have been in tumors >4 cm in size. **Conclusions:** Serous cystic neoplasms of the pancreas >4 cm have malignant potential and therefore should be considered for surgical management.

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Introduction

Serous neoplasms of the pancreas are generally considered to be benign, whereas mucin-producing cystic neoplasms have a well-established malignant potential. The first case of metastatic serous cystadenocarcinoma was documented by George et al. [1], and there has since been a growing body of evidence demonstrating the malignant potential of this neoplasm, including cases describing neural, vascular, or lymphatic invasion, direct invasion into surrounding structures, and distant metastasis [1–5]. Serous cystadenocarcinomas are exceedingly rare, with estimates of malignant conversion of cystadenomas ranging between 1 and 3%, and only 15 cases described to date [6, 7].

Fig. 1. Abdominal CT demonstrating a heterogeneous, 16 cm, multi-cystic mass replacing the body and tail of the pancreas with low attenuation areas, several small calcifications, and smooth lobulated margins.

In this study, we present a 78-year-old man with serous cystadenocarcinoma of the pancreas with liver metastases treated with distal pancreatectomy and liver ablation, who went on to develop new liver metastases 5 years after the initial operation. We also review the literature to help appreciate the rarity of this neoplasm and to identify features that are associated with malignancy.

Case Report

The patient is a 78-year-old male who was incidentally found to have a large pancreatic mass on chest CT done for a research study of COPD. An abdominal and pelvic CT was then performed, which revealed a 16 cm, multi-cystic mass with smooth, lobulated margins replacing the body and tail of the pancreas and causing occlusion of the splenic vein. The mass appeared heterogeneous with areas of focal enhancement, low attenuation areas, and several small nodular calcifications (fig. 1). There were left upper quadrant gastric varices, but no evidence of SMV or SMA involvement, nor direct invasion of the liver, spleen, or stomach. There was no sign of peritoneal nodules or ascites to suggest peritoneal carcinomatosis. However, 2 low-attenuation liver lesions were noted in the periphery of the liver, one measuring 5 cm in segment 7 (fig. 2) and the other 1 cm in segment 4, which were suspicious for metastasis.

Fig. 2. Abdominal CT demonstrating the larger of the 2 metastases in the periphery of the right hepatic lobe (black arrow), and the top of the primary lesion (white arrow).

A CT-guided core biopsy of the cystic lesion in the distal pancreas and the 5 cm liver lesion were then performed. The pancreatic tissue revealed a multicystic lesion with areas of thick, fibrous septae. The cysts were lined by attenuated cuboidal epithelium, which was predominantly in a single layer. The cells were relatively small in size with intermediate to low nucleus:cytoplasm ratio. The nuclei were oval with dense chromatin. Abundant clear cytoplasm was present and mitotic figures were not noted. The neoplastic cells were intensely positive for low molecular weight cytokeratin. CT-guided biopsy of the liver (fig. 3) was histologically identical to the accompanying pancreatic biopsies. Based on these findings, the diagnosis of serous cystadenocarcinoma of the pancreas with metastasis to the liver was made. Further workup included an endoscopic ultrasound, which revealed an irregular, microcystic mass with poorly defined borders, extending from the pancreatic neck to the tail.

The patient underwent distal pancreatectomy, splenectomy, cholecystectomy, and radiofrequency ablation of the 2 liver lesions. Operative exploration revealed a large, firm and multicystic mass extending from the neck of the pancreas to the spleen. The spleen also had abnormal-appearing lesions on it and these lesions resembled the pancreatic mass. The mass was found to be adherent to the transverse mesocolon. There was evidence of mass penetration through the mesocolon for which resection of a portion of the transverse mesocolon was performed. Intra-operative US revealed a large lesion in segment 7 of the liver, and 2 additional small lesions in segments 4-b and 5, near the porta hepatis. These lesions

Fig. 3. Metastatic serous cystadenocarcinoma to the liver (white arrow). The tumor is histologically identical to that in the pancreas and is indistinguishable from a typical serous cystadenoma. Benign hepatic parenchyma is present at right (black arrow; H&E, 200 $\times$).

Fig. 4. Aggressive histopathologic features in serous cystadenocarcinoma: **a** tumor (*) invades into the peripancreatic fat to encircle the splenic artery (H&E, whole mount). **b** Focus of perineural invasion, with nerve in the center and serous cystadenoma cells surrounding it (H&E, 400 $\times$). Otherwise, the cytoarchitecture of this tumor is indistinguishable from a typical serous cystadenoma.

were all treated with radiofrequency ablation with ultrasound guidance.

Postoperative pathology demonstrated a 15.5 $\times$ 12.0 $\times$ 10.5 cm bosselated, irregular red, white, and yellow mass. The mass was sectioned to reveal tan and red variegated cystic and solid cut surfaces, a 6 cm tan-yellow central scar, and tan fibrous soft tissue trabeculations throughout. Microscopic examination demon-

strated macro and micro-cystic structures lined by glycogen-rich clear cells arranged in a single cuboidal layer without atypia or mucin production. The cystic neoplasm was well-circumscribed with a fibrotic pseudocapsule composed of lamellated hyalinized connective tissue (fig. 4a). Rare foci of perineural invasion were noted (fig. 4b), while lymphovascular space invasion was not identified.

The patient was followed closely with CT scans of the abdomen and abdominal ultrasounds. An ultrasound performed 54 months postoperatively demonstrated a new liver lesion, and further evaluation with MRI revealed a total of 3 new liver lesions consistent with metastases (a $1.5 \times 1.6 \times 1.6$ cm lesion in segment 8, a $1.0 \times 1.2 \times 0.7$ cm subcapsular lesion in segment 6, and a 1.5×2.5 cm lesion in segment 5). A biopsy performed of one of these lesions demonstrated the same histology as that of the original primary tumor. He underwent open microwave ablation of these lesions with ventral hernia repair. A follow-up ultrasound 4 months and CT 10 months postoperatively revealed the ablation sites, but no new liver lesions. Unfortunately, an MRI performed 15 months after this second surgery revealed 9 new foci in the right lobe concerning for metastases, the largest lesion being 1.5 cm in size. The patient, now 84 years of age (6 years and 1 month after the first operation) and otherwise asymptomatic, elected to be observed at this time.

Methods

To identify previous reports of pancreatic serous cystadenocarcinoma, the PubMed database was searched using the keywords 'pancreas' and 'serous cystadenocarcinoma'. Bibliographies from these reports and existing reviews of the literature were also scrutinized to identify further relevant reports. Cases without documentation of malignancy and those that were considered duplicates were excluded.

Results

Twenty-nine articles were included in the analysis with a total of 35 cases described of metastatic or locally advanced pancreatic serous cystadenocarcinoma or cystadenoma. Case reports were then subdivided into 2 groups: those which included metastases to the liver, peritoneum, or lymph nodes (table 1) and those which exhibited local invasion only (table 2). Fifteen cases described distant metastases: 10 cases with liver metastases, 2 cases with liver and retroperitoneal metastases, one case with liver and peritoneal metastases, and one case with nodal metastases. One particularly aggressive case reported metastases to the lungs, bone marrow, adrenal glands, and lymph nodes [2]. In cases in which the primary lesion diameter was reported, all lesions were >4 cm, with a range 4–19 cm, with an average diameter of 11.75 cm.

Twenty cases did not describe metastasis, but did demonstrate signs of potentially aggressive behavior, such as neural, lymphatic, vascular or local invasion. These tumors had an average diameter of 8.9 cm (range 2.5–12 cm), and 9 of 10 lesions were >4 cm. The most common features seen in these locally advanced tumors were invasion into the spleen or soft tissues, perineural invasion, or vascular invasion.

Discussion

The diagnosis of cystadenocarcinoma is established by the clinical behavior of the neoplasm, which may include synchronous or metachronous distant metastases to the liver, peritoneum, or lymph nodes. This case represents the second in which the diagnosis of serous cystadenocarcinoma was made preoperatively, after Wasel et al. [8] described a case in which the diagnosis was also made by percutaneous biopsy. In this case and in the previous metastatic cases, there were no reliable histological or pathological characteristics seen in the primary tumor which allowed for differentiation of a malignant vs. benign neoplasm.

Local invasion, including vascular invasion, perineural invasion, or direct invasion into lymph nodes, spleen, duodenum, or stomach is not considered sufficient for the diagnosis of malignancy [9]. Rather, it has been suggested this locally aggressive behavior is indicative of increased proliferative ability and malignant potential [10]. In one review of 158 cases of resected serous cystic neoplasms, three were described as having 'locally aggressive disease' on histology; of these three, one went on to develop liver metastases 13 years after the initial operation was performed [6].

The rate of malignant transformation of asymptomatic lesions is very small, with estimates falling between 1 and 3% [6, 7]. Therefore, it is difficult to determine which cases of asymptomatic serous cystadenoma pose the highest risk of developing metastatic disease. Review of the literature demonstrates that all cases of metastatic serous cystadenocarcinoma had a diameter >4 cm (table 1). Tseng [11] suggested that resection of serous cystadenoma should be considered when the lesion has a diameter >4 cm or is symptomatic in good surgical candidates. A European expert consensus statement recommends that surgical intervention is indicated if the lesion is symptomatic; however, tumor size was not considered to be an important factor [12]. If surgical resection is indicated, procedures to remove pancreatic cystic lesions are generally well tolerated and have low mortality in high volume centers ($<1\%$) [13].

Review of the literature revealed 15 metastatic cases (table 1), although the patient described in Widmaier et al. [4] may have also been included in Schmidt-Rohlfing et al. [14], and the one described in Wu et al. [15] may have been also included in Galanis et al. [6] (since these studies derive from the same institutions). These cases demonstrate that even in the presence of initial or recurrent metastasis, the prognosis remains encouraging, with

Table 1. Characteristics of metastatic serous cystadenocarcinoma of the pancreas

Case	Author	Year	Size, cm	Age/sex	Presenting symptoms/signs	Metastases	Treatment	Follow-up
1	George et al. [1]	1989	11	70/M	GI bleeding from gastric varices	Liver metastases; local invasion of stomach, spleen	Distal pancreatectomy	Intraoperative death from blood loss
2	Friedman [5]	1990	19	74/F	Flank pain, weight loss, abdominal mass	Metastases to liver, lungs, bone, adrenal glands, and lymph nodes	None	Dead of disease
3	Okada et al. [23]	1991	12	63/F	Abdominal pain	Liver metastases 4 years postoperative	Distal pancreatectomy	Alive without recurrence 5 years postoperative
4	Yoshimi et al. [24]	1992	12	63/F	Left upper quadrant abdominal mass, epigastric pain	Liver metastases 3 years postoperative	Distal pancreatectomy and splenectomy Partial hepatectomy 4 years later	Alive without recurrence 6 years postoperative
5	Widmaier et al. [4]	1996	4	71/M	Elevated ALT/AST	Lymph node metastasis Perineural invasion	Pancreaticoduodenectomy	Alive without recurrence 1 year postoperative
6	Ishikawa et al. [25]	1998	12	63/F	Abdominal pain	Liver metastases 3 years postoperative	Distal pancreatectomy Partial hepatectomy	NS
7	Eriguchi et al. [26]	1998	16	56/F	Abdominal mass	Liver metastases; recurrent liver metastases 9 years postoperative	Splenectomy and distal pancreatectomy + microwave ablation; Partial resection and ablation of liver tumors 9 years later	Alive 10 years postoperative without additional recurrence
8	Wu et al. [15]	1999	NS	57/F	NS	Liver metastases; peritoneal metastases at second operation; diffuse liver metastases at last operation	Left lobe liver resection; pancreatectomy, cholecystectomy, splenectomy 8 years later; exploratory laparotomy and wedge liver biopsy 20 months later	NS
9	Strobel et al. [7]	2003	14	56/F	Abdominal pain, diarrhea, weight loss	Liver metastases	Pancreaticoduodenectomy	Alive without recurrence 3 years postoperative
10, 11	Galanis et al. [6]	2007	NS	NS	NS	(1) Liver metastases (2) Locally aggressive disease at operation; recurred 13 years later with liver and retroperitoneal metastases	(1, 2) Resection of pancreatic tumor	(1) Extensive growth 1 year later (2) NS
12	Franko et al. [16]	2008	5	68/F	Duodenal erosion, abdominal pain, anemia weight loss, weakness	Liver metastases 3 years post-biopsy of primary lesion	Palliative care	Expired from local tumor progression and metastatic disease 45 months after initial presentation
13	Bano et al. [20]	2011	7	62/M	Epigastric pain, vomiting, anorexia, weight loss, fatigue, palpable mass, jaundice	Liver metastases; duodenal invasion	Pancreaticoduodenectomy + microwave ablation, cystogastrostomy, choledochoduodenostomy, cholecystectomy	Alive without recurrence 1 year postoperative
14	Bramis et al. [21]	2012	17	86/F	Abdominal pain from pre-pyloric ulcer perforation	Liver metastases; invasion into the stomach	Inoperable	Died 1 month later due to unrelated problems
15	Wasel et al. [8]	2013	12	68/M	Incidental finding	Liver metastases; retroperitoneal metastases	4 months of neoadjuvant chemotherapy, then observation (no surgery)	Asymptomatic 1 year after diagnosis

NS = Not specified. Table adapted and modified from Wasel et al. [8].

Table 2. Characteristics of pancreatic serous cystadenoma with locally aggressive features

Case	Author	Year	Size, cm	Age/sex	Presenting symptoms/signs	Aggressive histologic features	Treatment	Follow-up
1	Kamei et al. [2]	1991	Multifocal, 10	72/F	Jaundice	Neural invasion; portal vein, bile duct obstruction (but not invasion)	Total pancreatectomy	NS
2	Ohta et al. [3]	1993	2.5	64/M	Incidental finding on CT	Vascular invasion	Enucleation of tumor	Alive without recurrence 9 months postoperative
3, 4	Siech et al. [27]	1998	NS	40, 75	NS	(1) Local infiltration (2) NS	Pancreaticoduodenectomy, total pancreatectomy	Early recurrence, NS
5	Abe et al. [28]	1998	12	71/F	Abdominal mass, fatigue, weight loss	Lymph node direct invasion, local invasion	Distal pancreatectomy, splenectomy	Alive without recurrence 2 years postoperative
6–9	Schmidt-Rohlfing et al. [14]	1998	NS	52–74	NS	(1) Local invasion of adrenal gland (2–4) NS	Distal pancreatectomy; total pancreatectomy; segmental resection; pancreaticoduodenectomy	NS
10, 11	Kimura and Makuuchi [29]	1999	5.3	53/F, 66/M	NS	(1, 2) Neural and stromal invasion	Distal pancreatectomy	(1, 2) Alive without recurrence 6 years postoperative
12	Horvath and Chabot [30]	1999	6	81/F	NS	NS*	Distal pancreatectomy + somatostatin	Alive 11 months postoperative
13	Matsumoto et al. [31]	2005	12	87/F	Abdominal mass	Colonic mesentery and splenic invasion	Distal pancreatectomy, splenectomy, colon resection	Alive without recurrence 10 months postoperative
14	Shintaku et al. [32]	2005	12	85/F	Incidental CT finding for stomach cancer preoperative	Splenic invasion; peripheral nerve invasion	Distal gastrectomy and distal pancreatectomy with splenectomy	Alive without recurrence 10 months postoperative
15	Friebe et al. [10]	2005	8	80/F	Abdominal pain, loss of appetite, weight loss	Splenic invasion	Distal pancreatectomy and splenectomy	Alive without recurrence 1 year postoperative
16	Gupta et al. [33]	2008	10	42/F	Abdominal mass, dyspepsia, abdominal pain, diarrhea, loss of appetite, weight loss	Focal invasion of cyst wall	Cyst removal with attached pancreas, spleen and colon	Alive without recurrence 2 years postoperative

Table 2. (continued)

Case	Author	Year	Size, cm	Age/sex	Presenting symptoms/signs	Aggressive histologic features	Treatment	Follow-up
17	King et al. [34]	2009	9	70/M	Duodenal ulcer, abdominal pain, upper GI bleeding	Duodenal, vascular, and neural invasion	Pancreaticoduodenectomy	Alive without recurrence 7 years postoperative
18	Vadala et al. [35]	2010	NS	74/M	NS	Portal vein invasion	Pancreaticoduodenectomy and portal vein thrombectomy	NS
19	Cho et al. [36]	2011	12	64/F	Hematochezia	Splenic invasion	Colon resection, distal pancreatectomy, splenectomy	NS
20	Rathore et al. [37]	2013	9	60/F	Abdominal pain	Vascular and soft tissue invasion	Pancreatectomy	NS
NS = Not specified. * Details not given other than cystadenocarcinoma. Table adapted and modified from Wasel et al. [8].								

several long-term survivors (including the patient described in the current case). In these series, however, the risk of malignant transformation and pathological growth should not be ignored, as the presumably benign lesions may progress to inoperability, metastasis, and patient mortality. Franko et al. [16] described such a case where a 5 cm serous cystadenoma was observed due to spleno-renal involvement; liver metastases developed 3 years after presentation, and the patient expired from local tumor progression 3 months after the diagnosis of metastatic disease was made.

Alternatives to surgical resection are limited, and there have been a limited number of reports of chemotherapy or radiotherapy for serous cystadenocarcinoma. Wasel et al. [8] reported giving 4 months of neoadjuvant chemotherapy to their patient without response (the specific regimen was not given), and the patient did not undergo operation. Experience with the more commonly malignant mucinous cystadenocarcinoma is also limited, with just a few reports. Björk Werner et al. [17] described 5 patients deemed to be unresectable being treated with gemcitabine-based regimens, with a mean survival of 11 months and a range of survival of 3–37 months. There has been one report of excellent response to gemcitabine-oxaliplatin, where the liver metastases disappeared with 13 cycles, allowing for primary tumor resection, and no recurrence at 22 months of follow-up [18]. Wood et al. [19] described 2 patients treated with 5-FU and radiotherapy with unresectable cystadenocarcinomas resulting in response, allowing for resection. These results may or may not be generalizable to patients with serous cystadenocarcinomas, but could be considered in cases thought to be unresectable.

The time elapsed from initial diagnosis of cystadenoma to the development of metastatic disease ranged from 3 months to 13 years [6, 20]. Long-term, consistent follow-up is imperative even with seemingly benign cases of serous cystadenoma. Bramis et al. [21] described a patient who was followed closely for 6 years, then lost to follow-up for 4 years, and finally presented with a perforated ulcer and a 17 cm inoperable mass.

Most cases of serous cystadenocarcinoma with metastatic disease had a slowly progressive clinical course, and the standard approach for small, asymptomatic lesions without concerning features on imaging (which include cyst >3 cm; thickened, enhancing walls; mural nodules; pancreatic duct diameter 5–9 mm, or abrupt change; and lymphadenopathy) is conservative management with close observation [22]. However, one unusually aggres-

sive case was reported by Wu et al. [15] after >8 years of indolent disease and close follow-up, where the entire liver parenchyma was replaced with diffuse metastatic disease over the course of 20 months.

All 15 cases of metastatic serous cystadenocarcinoma have been >4 cm in size (table 1), as have 16 out of 17 serous cystadenoma cases with documented local invasion (where sizes are given; table 2). Therefore, if a pancreatic serous cystadenoma exceeds 4 cm, it should be treated as if it has malignant potential. If the lesion is <4 cm, is as-

ymptomatic, and has no worrisome features of malignancy on imaging, it can be observed. All cases should be subject to prolonged follow-up, as metastatic disease may present many years after the initial resection. Particularly close follow-up is suggested in cases that involve patients who demonstrate signs of potentially aggressive behavior on surgical pathology, including local invasion, lymphovascular, or perineural invasion, as these signs are associated with increased metastatic potential.

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