Int J Clin Exp Med 2016;9(10):19826-19830
www.ijcem.com /ISSN:1940-5901/IJCEM0028744

Original Article

Clinical-pathological features and therapeutic strategies of malignant solid pseudopapillary tumor of the pancreas: cases report

Hao Zhang, Lu-Pin Xu, Qi Xie, Hong-Kun Zhou, Xiao-Pin Mei, Qin-Jiang Yu, Hao-Qiang Cao

Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jiaxing, Zhejiang, P. R. China

Received March 20, 2015; Accepted June 12, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: We retrospectively describe two patients with pathological proved solid pseudopapillary carcinomas. One was a young woman admitted because of ultrasound evidence of pancreatic tumor. Imaging studies indicated that the tumor was well encapsulated and contained cystic degeneration. A distal pancreatectomy with splenectomy was performed and a final diagnosis of SPT with local angioinvasion and perineural invasion were made. The patient was well without recurrence and metastases 5 years after the surgery. The other case was an old man with an aggressive course resulting in huge abdominal mass and retroperitoneal metastases. A distal pancreatectomy with splenectomy and lymphatic dissection was performed. The primary and metastastic tumor showed similar pseudopapillary and trabecular structure. The patient died of progressive disease at 10 months after operation. Our 2 cases experience and related literature indicate that the majority of malignant SPT is indolent and exhibit good prognosis after tumor resection. However, for those clinically aggressive lesions, there are still lack of effective predictive diagnosis modalities and curative treatment methods. Further research is required to find additional genes in the pathogenesis of these subgroup tumors, and find related molecular markers to predict of metastasis and prognosis.

Keywords: Solid pseudopapillary tumor of the pancreas, pancreatic neoplasm, surgical treatment

Introduction

Solid pseudopapillary tumor of the pancreas (SPT) is uncommon and "enigmatic" pancreatic neoplasm accounting for approximately 2-6% of all exocrine tumors of the pancreas. Frantz first described it in 1959. Up till now, more than 700 cases have been reported in English literatures, under various terms such as solid and cystic tumor, solid and papillary epithelial neoplasm, papillary-cystic neoplasm, papillary cystic epithelial neoplasm, papillary-cystic tumor, and Franz tumor [1-4]. Despite its favorable prognosis, there are still a small number of cases occurred after curative resection or developed metastases. For these malignant patients, preoperative diagnosis is often inaccurate and treatment strategies remain controversial. The present study reviewed 2 patients with malignant SPT managed in our institution and designed to define the clinical features, diagnosis and treatment strategies of this particularly rare disease.

Case reports

Case 1

A 23-year-old female patient with no medical history was admitted because of ultrasound evidence of pancreatic tumor found during a routine medical check. Physical examination was unremarkable. Abdominal ultrasound examination revealed a global mass of mixed echogenicity in the body of the pancreas, and the capsule appeared to be irregular. CT scan of the abdomen showed a well defined heterogeneous mass containing cystic and solid portions in **Figure 1A**. Tumor markers were within normal limits, as were as serum and urine amylase. Fine needle aspiration biopsy results indicated SPT of the pancreas. Laparotomy showed a 3.4 cm×2.8 cm mass arising from the body of the pancreas, performed distal pancreatectomy with splenectomy. The cut surface had a grayish white solid portion with interning cystic space in **Figure 1C**. Histologically, the tumor

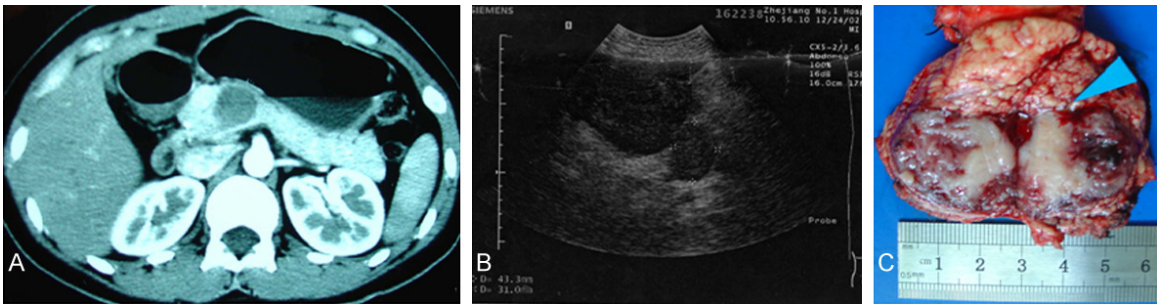

Figure 1. A: Contrast-enhanced CT scan shows a well-encapsulated mass with mixed attenuation. B: Abdominal ultrasound shows a hypo echoic mass in the epigastrium and a similar lesion in the retroperitoneal cavity. C: Photograph of gross surgical specimen shows heterogeneous appearance consisting of solid, cystic, and hemorrhagic components.

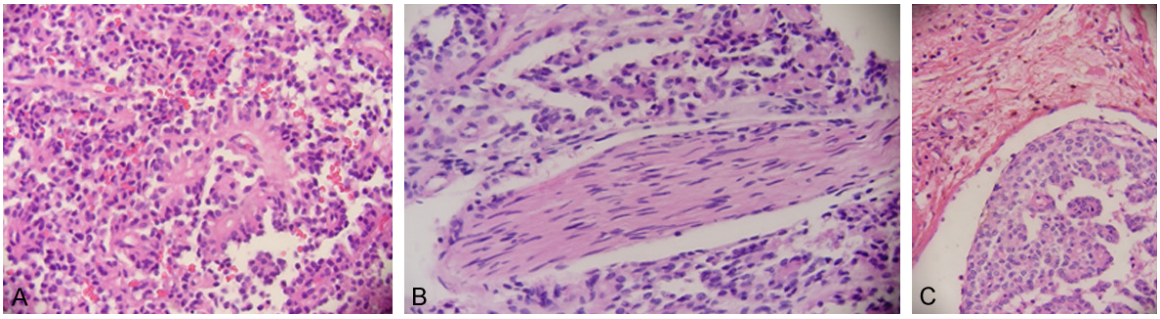

Figure 2. A: Photomicrograph indicates characteristic pseudopapillary architecture (HE×400). B: Perineural invasion (HE×400). C: Angioinvasion (HE×400).

was composed of nests of epithelial cells with a solid pseudopapillary cystic and trabecular pattern in **Figure 2A**. The capsule was focally incomplete. Perineural invasion and local angioinvasion were proved microscopically in **Figure 2B** and **2C**. The 5 years follow up detected no tumor recurrence, no signs of endocrine or exocrine insufficiency.

Case 2

A 68-year-old male was admitted with a 2-month history of epigastria pain. On examination, there was a huge firm, nontender mass in the upper abdomen. Abdominal ultrasound showed an 11.3×7.3 cm^2 hypo echoic mass in region of the left hepatic lobe and a 4.3×3.1 cm^2 similar lesion in the retroperitoneal cavity in **Figure 1B**. Abdominal CT scan reported a 10.5×7.1 cm^2 well defined hypo-dense heterogeneous mass in the left hepatic lobe that displaced pancreas inferiorly and laterally, and a 4.5×2.5 cm^2 similar mass behind the spleen artery. All blood tests including tumor markers and urine and blood amylase were normal. After B-us guided fine needle biopsy was carried out, a distal pancreatectomy with splenectomy and lymphatic dissection was performed. At operation, a large mass originated from the pancreas body and attached to left hepatic lobe and gastric was detected. Cut section shows solid and cystic components, both with extensive hemorrhagic degeneration. Microscopically, the primary and metastastic tumor showed similar pseudopapillary and trabecular structure. The patient was given 3 cycles of gemcitabine chemotherapy on 1 g/m^2 dosage postoperatively. He died of progressive disease at 10 month after operation.

Discussion

SPT is a rare exocrine pancreatic tumor, which is well known for its predilection in young women and indolent biologic behavior. In the last 10 years, there has been a steady increase in the number of this disease. An apparent rise in incidence is probably the result of a better awareness and recognition of its pathology. Although the follow-up of a large number of cases has shown that the majority of SPT are benign, however, SPTs generally appear low

grade malignant potential and a small number of cases recur or develop metastases after resection. According to the WHO classification, SPT have been divided into two categories: 1. solid-pseudopapillary neoplasm with borderline malignant potential; 2. solid-pseudopapillary carcinomas. Criteria which distinguish potentially malignant tumors and which are classified as 'SPT carcinoma' is: 1. angioinvasion; 2. perineural invasion; 3. deep invasion of the surrounding pancreatic parenchyma [1, 3].

Most of the cumulative reviews reported that approximately 15% of adults and 13% of children SPT were malignant, with a significant increase in elderly and male patients [2, 4]. In reviewing the clinical data from our hospital during the period of 2006-2014 years, we identified 19 patients with SPT who performed operation and pathologic examination, and encountered two patients who fit the diagnosis criteria of SPT carcinoma. Between the two malignant patients, one was an older man who died of tumor recurrence ten months after operation.

Just like benign SPT, most of the malignant SPT clinical presentation is usually nonspecific. Abdominal discomfort or mild upper abdominal pain is the most common symptoms, followed by a gradually enlarging abdominal mass and compression signs related to the large size of the tumor. Some patients are completely asymptomatic, just as one of the patients the present study reported, who revealed the tumor incidentally after imaging study and routine physical examination. Less commonly, some patients may exhibit a rapidly progressive clinical course. Tang et al reported two clinically aggressive SPT patients who demonstrated clinical presentations less than 2 weeks before admission to hospital, and died at the 6 and 16 month respectively after operation [5]. So it should be kept in mind that SPT may take such an aggressive clinical course, although majority of them are usually benign in nature.

The imaging studies such as CT or MR usually demonstrates a well encapsulated and circumscribed retroperitoneal cavity mass, with varying solid and cystic components owing to hemorrhagic degeneration. Following contrast material administration, enhancing solid areas are typically noted peripherally, whereas cystic spaces are usually more centrally located [6, 7]. Ultrasonographically, the tumor is well-encapsulated, homogeneous or heterogeneous, composed with solid echogenic and cystic hypoechogenic components [8]. For metastases, the most common site is the liver; which may be confirmed as several well-defined and scattered hypo or mixed density lesions at CT, less commonly, adjacent organs such as gastric, spleen and colon or vessels such as portal vein and superior mesenteric vessels are invaded, which presented a firm connection between the tumor and circumscribed organ, or vessels encasement. Lymph nodes larger than 1 cm can always be shown in CT or MR scan [9, 10]. Although overt metastases may be demonstrated at imaging examinations, microscopic local and vascular invasion are still beyond the resolution of most cross-sectional imaging studies. Some authors advocate preoperative endoscopic ultrasonography guided fine-needle aspiration biopsy for preoperative identifying the tumor [11, 12], but this may not be accepted by others because of possible tumor cell spread, so further research is needed to detect minimal metastases preoperatively.

The pathologic diagnosis of SPT is mainly based on the well-defined solid and cystic structure and characteristic pseudopapillary feature under microscopic examination. Although the tumor developed distant metastases and deep extrapancreatic invasion, vascular or perineural invasion is designated as SPT carcinoma, Tang et al reported that extrapancreatic invasion, vascular or perineural invasion did not seem to have a significant impact on the behavior of SPTs. Even with distant metastatic disease, patients were clinically stable for years [13]. To date, there are still no consensus pathological factors for predicting metastatic and recurrent potential, especially for those patients presented a more aggressive clinical course. A number of previous reports indicated that significant cellular polymorphism, nuclear atypia, as well as increased mitotic activity were useful histologic parameters to detect the malignant potential of SPTs [14], but in a large series of studies including more than 100 cases indicated that most of the above criteria failed to demonstrate a statistical difference between nonmetastasizing and metastatic tumors. Recently, some histological features such as extensive necrosis, nuclear atypia, and high mitotic rate and sarcomatoid areas have been suggested to be associated with aggressive behavior [5, 15]. So for those patients, if there is such a finding in the surgical specimen, an intensive follow up should be advised to

evaluate the efficacy of treatment and to supervise local recurrence and distant metastases.

Most current treatment recommendations support surgical resection whenever possible, targeting complete resection of both the primary tumor and the metastases [16-18]. For those lesions confined in the pancreas, achievement of clear surgical margins is important to prevent recurrence. Extensive lymphatic dissection or more radical local approaches are not indicated; for those had distant metastasis, the presence of metastasis does not exclude primary surgery because of the clinical benefits associated with tumor resection. Specifically, when liver metastases were present, operative excisions (lobectomies or enucleations) or even liver transplantation were used in most patients [5, 19]. Invasion to the portal vein or superior mesenteric vessels should not be included as a criterion for nonresectability of these pancreatic neoplasms, and resection of the portal vein with curative intent is indicated if macroscopic clearance can be achieved, resulting in a good long-term survival [20]. In patients with unresectable disease there is no consensus on treatment. Maffuz et al reported an aggressive patient with an unresectable SPT was treated with chemotherapy, and finally surgical resection [21]. Hassan et al reported a 2-step strategy to resect a huge SPT tumor of the head of the pancreas which metastasized to liver and infiltrated portal vein, duodenal wall and right transverse mesocolon. In the first step, the primary tumor was resected and in the second step, multiple superficial liver metastases were resected [22]. These reports provide other approaches to the treatment of unresectable SPT.

Experience with adjuvant therapy has been used only in a small number of patients because the resectability rate for SPT is so high. Many different regimens of chemotherapy had been used with variant demonstration of response and no current chemotherapy regimens are considered standard in the treatment of this tumor [23]. Radiotherapy have been proved ineffective despite the report by Fried and colleagues of a single case successfully treated with radiation [24].

Genetic events contributing to the development and malignant transformation of SPTs are unknown. Abraham and colleagues found that alteration of the adenomatous polyposis coli (APC)/beta catenin pathway and deregulated expression of cell cycle-associated protein as over-expression of cyclin D1 and cyclin D3 can be observed in SPT, these were obviously different from the generic changes involved in conventional pancreatic carcinomas which usually exhibited k-ras and p53 mutation [25]. Additionally, Tanaka and colleagues found that Wnt signaling with β-catenin mutations played important role in the tumor genesis of SPT [26]. These results could provide a crucial clue to understanding of the developmental process of this neoplasm.

In summary, the majority of malignant SPT is indolent and exhibit good prognosis after oncological resection. However, for those clinically aggressive lesions, we still lack of effective predictive diagnosis modalities and curative treatment methods. So, for complete understanding and overcoming this disease, further research is required to find additional genes in the pathogenesis of this tumor, and find related molecular markers to predict of metastasis and prognosis.

Acknowledgements

The work was supported by the following project's financial support: Jiaxing Science and Technology Projects (grant No. 2013AY21042-5); Jiaxing Science and Technology innovation team projects (grant No. 2013-03); and major projects of Zhejiang Province on the transformation of the appropriate technical achievements of primary health care (grant No. 2013T301-12 and 2013T301-15).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hao Zhang, Department of Hepatobiliary and Pancreatic Surgery, The First Hospital of Jiaxing, 1882 Zhong-Huan South Road, Jiaxing 314001, Zhejiang, P. R. China. Tel: +86-573-82519999; Fax: +86-573-82083006; E-mail: changgung1@163.com

References

[1] Estrella JS, Li L, Rashid A, Wang H, Katz MH, Fleming JB, Abbruzzese JL and Wang H. Solid pseudopapillary neoplasm of the pancreas: clinicopathologic and survival analyses of 64 cases from a single institution. Am J Surg Pathol 2014; 38: 147-157.

[2] Lam KY, Lo CY and Fan ST. Pancreatic solid-cystic-papillary tumor: clinicopathologic features in eight patients from Hong Kong and review of the literature. World J Surg 1999; 23: 1045-1050.

[3] Santini D, Poli F and Lega S. Solid-papillary tumors of the pancreas: histopathology. JOP 2006; 7: 131-136.
[4] Yu P, Cheng X, Du Y, Yang L, Xu Z, Yin W, Zhong Z, Wang X, Xu H and Hu C. Solid Pseudopapillary Neoplasms of the Pancreas: a 19-Year Multicenter Experience in China. J Gastrointest Surg 2015; 19: 1433-1440.
[5] Tang LH, Aydin H, Brennan MF and Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol 2005; 29: 512-519.
[6] Miao F, Zhan Y, Wang XY, Wang DB, Chen KM, Tang AR and Jiang H. CT manifestations and features of solid cystic tumors of the pancreas. Hepatobiliary Pancreat Dis Int 2002; 1: 465-468.
[7] Cantisani V, Mortele KJ, Levy A, Glickman JN, Ricci P, Passariello R, Ros PR and Silverman SG. MR imaging features of solid pseudopapillary tumor of the pancreas in adult and pediatric patients. AJR Am J Roentgenol 2003; 181: 395-401.
[8] Lee DH, Yi BH, Lim JW and Ko YT. Sonographic findings of solid and papillary epithelial neoplasm of the pancreas. J Ultrasound Med 2001; 20: 1229-1232.
[9] Yin Q, Wang M, Wang C, Wu Z, Yuan F, Chen K, Tang Y, Zhao X and Miao F. Differentiation between benign and malignant solid pseudopapillary tumor of the pancreas by MDCT. Eur J Radiol 2012; 81: 3010-3018.
[10] Chung YE, Kim MJ, Choi JY, Lim JS, Hong HS, Kim YC, Cho HJ, Kim KA and Choi SY. Differentiation of benign and malignant solid pseudopapillary neoplasms of the pancreas. J Comput Assist Tomogr 2009; 33: 689-694.
[11] Master SS and Savides TJ. Diagnosis of solid-pseudopapillary neoplasm of the pancreas by EUS-guided FNA. Gastrointest Endosc 2003; 57: 965-968.
[12] Mergener K, Detweiler SE and Traverso LW. Solid pseudopapillary tumor of the pancreas: diagnosis by EUS-guided fine-needle aspiration. Endoscopy 2003; 35: 1083-1084.
[13] Martin RC, Klimstra DS, Brennan MF and Conlon KC. Solid-pseudopapillary tumor of the pancreas: a surgical enigma? Ann Surg Oncol 2002; 9: 35-40.
[14] Nishihara K, Nagoshi M, Tsuneyoshi M, Yamaguchi K and Hayashi I. Papillary cystic tumors of the pancreas. Assessment of their malignant potential. Cancer 1993; 71: 82-92.
[15] Reindl BA, Lynch DW and Jassim AD. Aggressive variant of a solid pseudopapillary neoplasm: a case report and literature review. Arch Pathol Lab Med 2014; 138: 974-978.
[16] Casadei R, Santini D, Calculli L, Pezzilli R, Zanini N and Minni F. Pancreatic solid-cystic papillary tumor: clinical features, imaging findings and operative management. JOP 2006; 7: 137-144.
[17] Chen X, Zhou GW, Zhou HJ, Peng CH and Li HW. Diagnosis and treatment of solid-pseudopapillary tumors of the pancreas. Hepatobiliary Pancreat Dis Int 2005; 4: 456-459.
[18] Wang WB, Zhang TP, Sun MQ, Peng Z, Chen G and Zhao YP. Solid pseudopapillary tumor of the pancreas with liver metastasis: Clinical features and management. Eur J Surg Oncol 2014; 40: 1572-1577.
[19] Lagiewska B, Pacholczyk M, Lisik W, Cichocki A, Nawrocki G, Trzebicki J and Chmura A. Liver transplantation for nonresectable metastatic solid pseudopapillary pancreatic cancer. Ann Transplant 2013; 18: 651-653.
[20] Alexandrescu DT, O'Boyle K, Feliz A, Fueg A and Wiernik PH. Metastatic solid-pseudopapillary tumour of the pancreas: clinico-biological correlates and management. Clin Oncol (R Coll Radiol) 2005; 17: 358-363.
[21] Maffuz A, Bustamante Fde T, Silva JA and Torres-Vargas S. Preoperative gemcitabine for unresectable, solid pseudopapillary tumour of the pancreas. Lancet Oncol 2005; 6: 185-186.
[22] Hansson B, Hubens G, Hagendorens M, Deprettere A, Colpaert C and Eyskens E. Frantz's tumour of the pancreas presenting as a post-traumatic pancreatic pseudocyst. Acta Chir Belg 1999; 99: 82-84.
[23] Tajima H, Takamura H, Kitagawa H, Nakayama A, Shoji M, Watanabe T, Tsukada T, Nakanuma S, Okamoto K, Sakai S, Kinoshita J, Makino I, Nakamura K, Hayashi H, Oyama K, Inokuchi M, Nakagawara H, Miyashita T, Ninomiya I, Fushida S, Fujimura T, Wakayama T, Iseki S, Ikeda H and Ohta T. Multiple liver metastases of pancreatic solid pseudopapillary tumor treated with resection following chemotherapy and transcatheter arterial embolization: A case report. Oncol Lett 2015; 9: 1733-1738.
[24] Fried P, Cooper J, Balthazar E, Fazzini E and Newall J. A role for radiotherapy in the treatment of solid and papillary neoplasms of the pancreas. Cancer 1985; 56: 2783-2785.
[25] Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT and Hruban RH. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 2002; 160: 1361-1369.
[26] Tanaka Y, Kato K, Notohara K, Hojo H, Ijiri R, Miyake T, Nagahara N, Sasaki F, Kitagawa N, Nakatani Y and Kobayashi Y. Frequent beta-catenin mutation and cytoplasmic/nuclear accumulation in pancreatic solid-pseudopapillary neoplasm. Cancer Res 2001; 61: 8401-8404.