

# Successful Treatment of Solid-Pseudopapillary Tumor of the Pancreas with Multiple Liver Metastases

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## Key Words

Solid-papillary cystic tumor · Surgery · Liver metastases

## Abstract

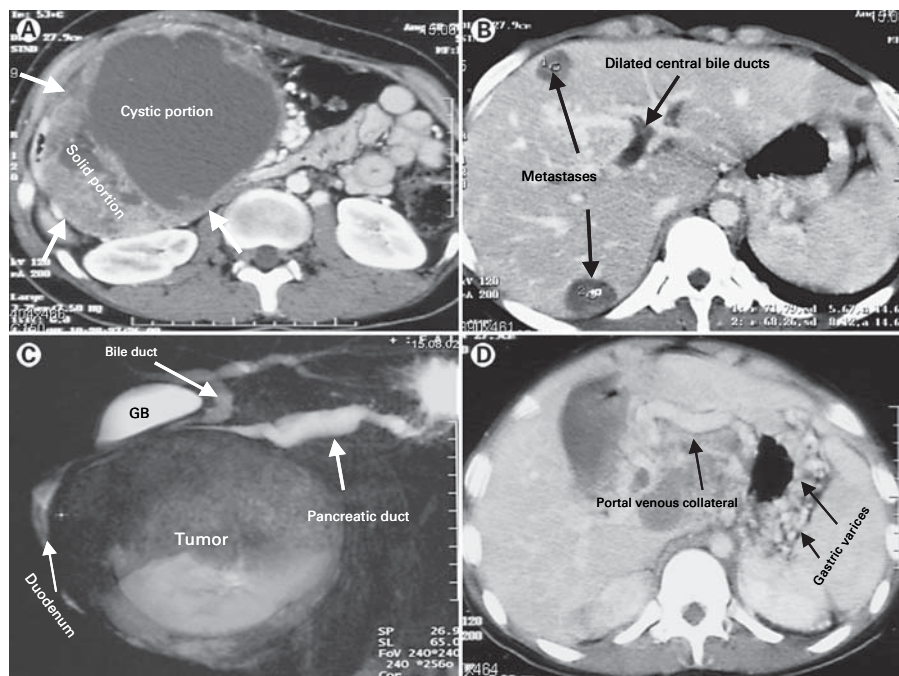
The solid-pseudopapillary tumor (SPT) is a very rare pancreatic neoplasm that predominantly affects young females. About 450 cases have been described in the world literature and approximately 20% of the reported patients were children. The occurrence of SPT with distant metastases in children is extremely rare with only two previously reported cases. We now report a 16-year-old Asian girl with a large SPT and synchronous multiple liver metastases who was successfully treated in a 2-step strategy, including initial pylorus-preserving partial duodenopancreatectomy, right hemicolectomy, resection and allografting of the portal vein and secondary resection of 12 liver metastases. The patient is disease free after a follow-up of 18 months after resection of the primary tumor, suggesting that an aggressive surgical treatment might also be justified for metastasized SPT.

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## Introduction

The solid-pseudopapillary tumor (SPT) of the pancreas is a rare cystic pancreatic neoplasm that accounts for only 1–2% of all exocrine pancreatic tumors [1]. This tumor was first described in 1959 by Frantz [2]. Synonyms include papillary epithelial neoplasm, papillary cystic neoplasm, solid-papillary neoplasm, solid-cystic neoplasm and low-grade papillary neoplasm of the pancreas [3]. To date, about 450 cases of SPT have been reported in the world literature [2–4]. SPT occurs predominantly in young women and female children and might have a predilection for individuals of Asian descent [5]. It is speculated that this tumor originates histogenetically from ductal cells [6], acinar cells [7] or primitive cells [8]. Thus, its histogenesis is still controversial. SPT is often asymptomatic until the tumor is large. It may then cause mild pain, vague gastrointestinal symptoms and rarely jaundice. Despite being locally aggressive, the prognosis tends to be good [9], local recurrence and metastases are unusual and have been reported to be particularly rare in children [5, 10]. In a recent review of 78 pediatric patients, only 1 child had liver metastases [10]. Surgical resection of the tumor is recommended whenever possible [11]. We now report the case of a 16-year-old Asian girl with a large SPT infiltrating the duodenal wall, the trans-

**Fig. 1.** CT and MRI of the abdomen. **A** A contrast-enhanced CT scan reveals a 15-cm-diameter well-defined mass (arrows) with solid and cystic portions arising from the pancreas with compression of surrounding abdominal structures. **B** Two hypodense hepatic lesions, dilation of central hepatic bile ducts, and cavernous portal collaterals in the porta hepatis are visualized in this transverse contrast-enhanced CT scan. **C** Coronal plane MRCP demonstrates the pancreatic head neoplasm with large cystic areas. The tumor compresses the distal common bile duct and pancreatic duct leading to dilation of the prestenotic biliary and pancreatic ductal system. Note also compression and displacement of the duodenum. **D** Venous phase contrast-enhanced CT shows multiple portal venous collaterals and gastric varices due to compression of the portal vein.



verse mesocolon, the portal and splenic veins, with synchronous multiple liver metastases who was treated successfully by an aggressive surgical approach in a 2-step strategy.

## Case Report

### Clinical History

At age 15, a girl living in Bangkok, Thailand, noticed swelling of her abdomen and intermittent abdominal pain without other gastrointestinal symptoms. Diagnostic work-up in Thailand revealed a 15-cm-sized cystic pancreatic tumor. In May 2001, the patient underwent explorative laparotomy in Bangkok that showed a large infiltrating tumor of the head of the pancreas with several liver metastases. The tumor was considered unresectable, but a biopsy was performed that showed an SPT based on the presence of characteristic light-microscopic features. The patient was referred to our hospital for the re-evaluation of the resectability of the tumor.

At admission in July 2002, the 16-year-old girl was in good general health and well nourished. A large tumor was visible and palpable in the upper abdomen. The patient complained of a slight abdominal pressure, but had no other gastrointestinal symptoms. A contrast-enhanced CT and MRI of the abdomen (including an MRCP, an MRA of the abdominal aorta, its visceral branches, and an MR portography) revealed a 14 × 12 cm cystic tumor of the pancreatic head with compression of the distal common bile duct and the pancreatic duct, occlusion of the portal vein and signs of portal hypertension with splenomegaly and pronounced vascular collaterals in the upper abdomen. In addition, at least 5 superficial

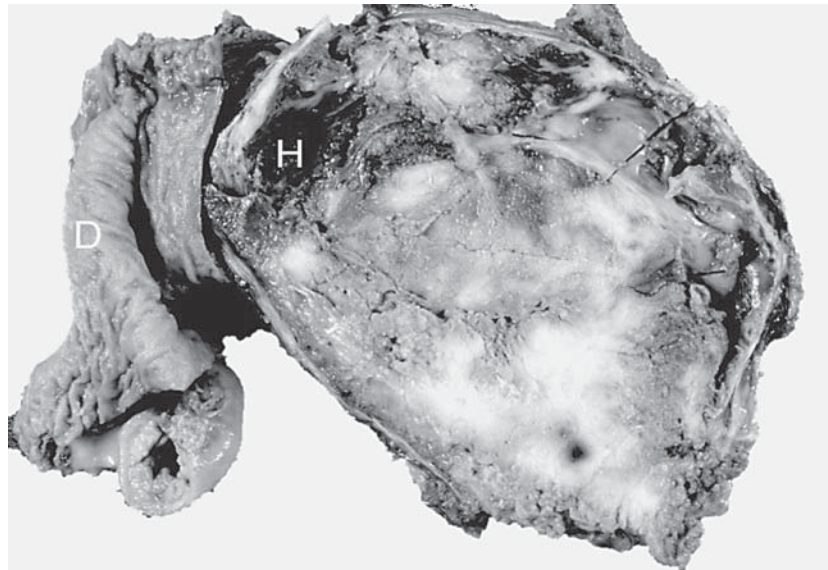
liver metastases with a size of up to 3 cm in diameter could be visualized in segments 2, 4, 5, 6 and 7 (fig. 1).

### Surgical Treatment and Follow-Up

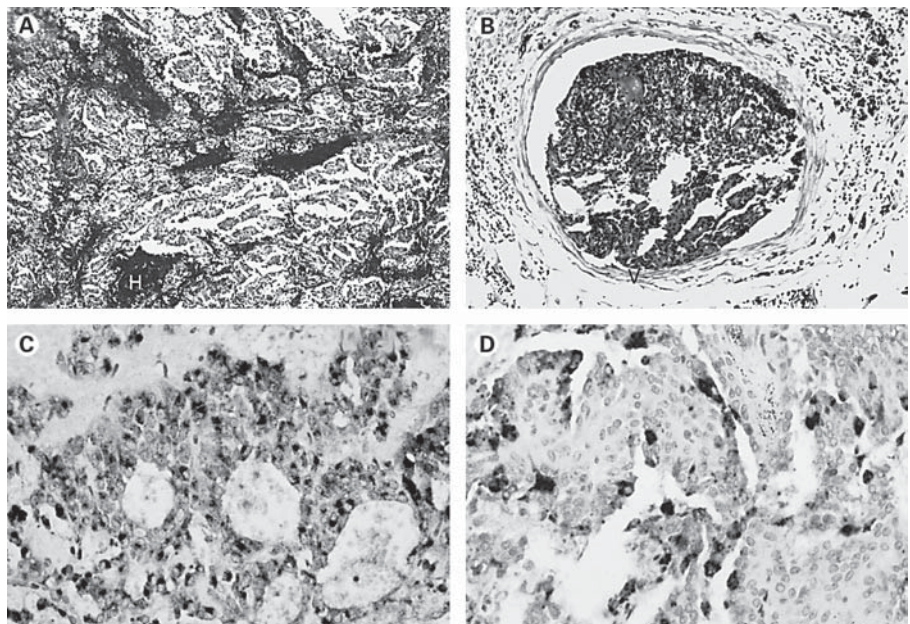
At explorative laparotomy, a 15-cm tumor of the head of the pancreas that infiltrated the duodenal wall as well as the right transverse mesocolon was noted. The tumor was surrounded by enlarged veins. The portal vein, the superior mesenteric and the splenic vein were compressed and infiltrated by the tumor. In the liver, a total of 5 metastases with diameters of up to 3 cm were palpable in segments 2, 4, 5, 6 and 7. During a 13-hour operation, the tumor was resected by a pylorus-preserving partial duodenopancreatectomy with resection of the portal vein and right hemicolectomy. The portal vein was allografted with an 8-mm dacron prosthesis, in which the splenic vein was re-implanted. The postoperative course was complicated by a leak of the hepato-jejunostomy which required surgical revision on postoperative day 7. The leakage had been oversewn and a T-drain was placed in the common hepatic duct. The patient recovered well after the revision and was discharged on postoperative day 36.

### Histopathology

The pathological investigation showed a large pancreas head tumor of 16 × 12 × 10 cm size demarcated by a firm capsule. Gross pathomorphology of the cut surface showed an inhomogeneous solid and partly hemorrhagic and cystic appearance (fig. 2). Microscopic examination demonstrated solid areas which were composed of monomorphous epithelioid cells with round to oval, occasionally indented nuclei lacking mitotic activity. The cytoplasm was partly eosinophilic and partly vacuolated and light. In PAS staining, the tumor cells were negative. Frequently, characteristic pseudopapillary formations were observed (fig. 3A). There



**Fig. 2.** The cut surface of the resected tumor of the pancreas shows inhomogeneous grey-white to brown solid areas as well as dark hemorrhagic (H) and cystic areas. Note demarcating fibrous capsule. D = Adjacent duodenum.



**Fig. 3.** Histologic (A, B; H&E staining) and immunohistochemical (C, D) findings of the tumor. **A** Survey micrograph showing pseudopapillary appearance and focal hemorrhage (H). **B** Tumor cone growing within a distended vein (V), indicating malignant behavior. **C** Immunostaining for  $\alpha_1$ -antichymotrypsin showing cytoplasmic plaque-like immunoreactivity in many tumor cells. **D**  $\alpha_1$ -Antitrypsin is strongly expressed in scattered tumor cells. In the negative areas, note the monomorphous round to oval nuclei of the tumor cells.

were regressive changes with focal hemorrhage, necrosis and deposition of cholesterol crystals. Some areas displayed extensive stromal fibrosis, with broad fibrous septa containing hemosiderin deposits.

By immunohistochemistry, vimentin staining was uniformly positive. In addition, there were positive reactions for  $\alpha_1$ -antichymotrypsin and  $\alpha_1$ -antitrypsin (fig. 3C, D). Strong immunoreactivity was detected for neuron-specific enolase. About 20% of the tumor cells revealed nuclear staining for the progesterone receptor while negative reactions were found for the estrogen receptor, various cytokeratins (pan-cytokeratin, CK7, CK18, CK20), chromogranin A, CD117 and inhibin. On the basis of these characteristic morphological and immunohistochemical findings, the diagnosis

of an SPT of the pancreas was confirmed. Ki67 staining demonstrated a low rate of proliferation, with less than 10% of positive nuclei.

Histopathological examinations also confirmed the invasive potential of the tumor as evidenced by a tumorous infiltration of the muscle layer of the duodenal wall and tumor deposits in the fatty tissue of mesentery of the transverse colon. Moreover, venous invasion was detected both in the submucosal layer of the resected ileum and in the mesenteriolum of the appendix (fig. 3B). Adjacent arteries showed polyarteritis nodosa-like changes with fibrinoid necrosis and nodular obliteration. All 33 peripancreatic and mesenteric lymph nodes were free of tumor. Biopsy of one of the liver metastases confirmed the metastasis of an SPT.

### Follow-Up

At the first and second follow-up examination 3 and 9 months postoperatively, an iron oxide MRI of the abdomen revealed neither recurrence of the tumor nor any signs of lymphadenopathy. It was noted that the liver metastases had decreased in number and size. At the third follow-up, 12 months after the tumor resection, a slight increase of the size of the liver metastases was noted on MRI. Therefore, we decided to suggest a third operation to resect the metastases. Based on intraoperative sonography 12 liver metastases with diameters ranging from 2 to 29 mm were visualized. As all metastases were located on the surface of the liver, all metastases could be removed by wedge resections. Intraoperatively, it could be demonstrated by color duplex sonography that both the portal vein allograft and the re-inserted splenic vein were patent. Histopathology confirmed 12 liver metastases of the SPT to have been resected with free margins.

Postoperatively, the patient developed a perihepatic abscess which was treated by percutaneous abscess drainage. The patient was discharged on postoperative day 19. The MRI scans 3 and 6 months after resection of the liver metastases showed no evidence of disease, neither in the liver nor in the original tumor bed.

### Discussion

The rare SPT is the most common pancreatic tumor in the Asian pediatric population. The yearly incidence for this group is about 0.01 per 100,000. The tumor occurs predominantly in young Asian women, between 15 and 35 years of age. Our patient fits into this group. Lack of specific clinical symptoms is typical for this tumor. Two thirds of the pediatric patients with SPT present with a mass in the upper abdomen that slowly enlarges; one third have abdominal discomfort. Jaundice has been reported as the presenting symptom in only 2 patients [4]. Our patient initially contacted her physician because she detected a mass in her upper abdomen without any other symptoms.

Histomorphologically, SPT contain both solid and pseudopapillary patterns, which give rise to the designation of solid-pseudopapillary pancreatic tumor. Other histopathological characteristics are regressive, hemorrhagic/cystic changes, that lead to the development of pseudocystic cavities. The SPT of our patient revealed all these typical features and the liver metastases were histologically identical to the primary tumor. Immunohistochemically, these tumors typically stain positive for vimentin, neuron-specific enolase,  $\alpha_1$ -antitrypsin and  $\alpha_1$ -antichymotrypsin [12, 13]. In our case, all the markers commonly found in SPT were detected and the immunostaining for Ki67 indicated a low proliferation rate. Epithelial markers such as cytokeratins are inconsistently expressed in SPT [13] and were absent in the present tumor.

The presence of progesterone receptor in SPT was not demonstrated in all cases. For instance Lam et al. [3] described a negative stain for progesterone receptor in 8 young Chinese patients, who did not exhibit metastases. On the other hand Zamboni et al. [14] analyzed progesterone receptor expression in 10 cases and suggested a correlation between high progesterone immunoreactivity and the absence of tumor invasion and metastases [14].

Our case supports this hypothesis, since the metastasized SPT had only a low immunoreactivity of 20% for the progesterone receptor.

The origin of this neoplasm is controversial. Ductal [6], exocrine [7] and endocrine [8] cells as well as primitive (stem) cells [13] have been hypothesized as the cells of origin of the tumor. However, the etiology of the tumor remains unknown. Apparently, a normal pancreatic cell exhibiting the immunophenotype of SPT does not exist. Recently, a relationship to the embryonal genital ridge and ovarian anlage was proposed [15]. Genetic and hormonal factors have been discussed because of sex specificity and the preference age [16, 17]. Whereas ductal pancreatic adenocarcinoma essentially never harbors an adenomatous polyposis coli/ $\beta$ -catenin gene mutation, alterations of the adenomatous polyposis coli/ $\beta$ -catenin pathway are present in 90% of SPT [18]. This finding suggests that pancreatic ductal adenocarcinoma and SPT progress genetically through two distinct pathways.

The diagnosis of SPT is often made only at laparotomy because of the lack of specificity of laboratory tests and imaging studies. In the literature, only 3 pediatric patients were diagnosed preoperatively [19]. In expert hands, fine needle aspiration cytology may reveal the diagnosis [20]. Common differential diagnoses include pancreatoblastoma, pancreatic pseudocyst or a nonfunctioning islet tumor [21].

Angioinvasion, perineural invasion and deep invasion into the surrounding tissue are distant metastases criteria of malignancy that predominantly occur in the liver. According to the recent review of Hong et al. [10], of 78 pediatric patients, only 1 child with SPT had synchronous liver metastases and 11 children revealed direct infiltration of adjacent structures by the tumor. From these 78 children with SPT, 10 patients survived more than 10 years and 21 survived more than 5 years. One patient died from distant metastases and 6 developed recurrences [5, 19].

However, metastases may occasionally develop with a latency of several years. Horisawa [22] reported a girl of 11 years of age who had local resection of an SPT in the

head of the pancreas. Ten years later, a local recurrence in the pancreatic head and 2 liver metastases were seen. Pancreaticoduodenectomy and enucleation of the metastatic lesions in the liver was performed. Six years after the second operation, the patient was well and free of disease [22]. Our patient had a malignant SPT with infiltrative tumor growth in the duodenum and transverse mesocolon, angioinvasion and synchronous liver metastases. A recent review of adult patients reported metastases and/or local recurrences after SPT resection in 55 of 374 cases (15%) [23]. In addition, it has been shown that long-term survival of up to 10 years can be achieved after tumor resection, even if residual disease remains [24, 25].

Since SPT has to be considered a low-grade malignant tumor, surgical resection remains the treatment of choice [9]. Cure could be achieved by tumor resection in more than 95% of patients reported in the literature. From the recent literature, it would appear that patients less than 15 years of age tend to have smaller tumors that only occasionally invade or metastasize. Of patients older than 20 years, a considerable number (up to 15%) will have metastases and some have been reported to have lost their lives at higher ages ranging from 36 to 60 years of age [10, 23]. This suggests, that these tumors arise in childhood and grow slowly but eventually will invade and metastasize. As a matter of fact, age has been identified to be the only significant prognostic factor in a recent analysis [5]. Together with the high recurrence rate reported for local excision and enucleation of tumors [5, 10, 19, 24, 25],

these observations support the concept of an early and aggressive surgical approach in young patients even for metastasized tumors to achieve the possibility of long-term survival or even cure [3, 5]. However, it is very important to achieve a definitive histological diagnosis before performing major surgery, since this would not be justified for other pancreatic tumors such as ductal adenocarcinoma.

In our case, we decided to proceed using an aggressive 2-step strategy. In the first step, the primary tumor was resected and in the second step 12 superficial liver metastases were resected. This experimental procedure led to a disease-free patient 18 months after resection of the primary tumor.

### Summary

SPT is a rare tumor that displays a low malignant potential in childhood. Distant metastases of SPT are extremely rare in children. SPT should be treated early and aggressively attempting complete resection of the tumor and its metastases. Long-term survival may be possible with such extensive surgery, which has to be proven by a large number of patients with adequate long-term follow-up. Given the relatively high risk for postoperative morbidity and even mortality, the indication has to be carefully evaluated and such procedures should remain reserved for specialized centers.

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