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Liver Transplantation for Metastases From Solid Pseudopapillary Tumor of the Pancreas: A Case Report and Review of Literature

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Solid pseudopapillary tumor (SPT) is a rare pancreatic tumor with relatively indolent course.¹ In some aggressive cases, metastasis to the liver is seen but is mostly manageable with surgical resection. For unresectable metastasis, due to ineffectiveness of other therapeutic modalities, transplantation becomes occasionally necessary in selected cases.² We describe our experience with liver transplantation (LT) for recurrent unresectable SPT and discuss the existing literature. A written informed consent was taken from our patient.

CASE

A 31-y-old lady presented with a left upper quadrant mass. Imaging showed a well-circumscribed heterogeneous mass arising from body-tail of the pancreas, measuring 17 cm (cranio-caudal) × 15 cm (transverse) × 8 cm (antero-posterior) and almost entirely replacing the pancreas. There was a thrombus in the splenic vein and portal vein (PV) but no nodal or distant metastasis (Figure 1A). Computerized tomography-guided biopsy histologically confirmed SPT and the multidisciplinary team agreed that surgery was her best option. Total pancreatectomy, en bloc right hemicolectomy with superior mesenteric vein, and PV resection with deceased donor vein reconstruction were done. After an uneventful postoperative course, she was discharged on

day 6. Histopathology confirmed SPT with extensive vascular and perineural invasion (Figure 1B and C), 1 of 51 regional lymph nodes positive and positive vascular margin. Immunohistochemistry (IHC) was positive for vimentin, CD10, beta-catenin (Figure 1D), synaptophysin, and A1 antitrypsin, and Ki-67 index was 10%–20%.

Imaging 2 wk after her surgery showed a right intrahepatic PV thrombus with the suggestion of tumor thrombus. She was kept on surveillance and anticoagulation continued. A subsequent computerized tomography showed retraction of right PV thrombus and atrophy of right lobe. Fluoro-deoxy-glucose positron emission tomography (FDG-PET) showed no uptake within the thrombus, but we decided on a right hepatectomy because of the high likelihood of a tumor thrombus. Histology confirmed tumor thrombus in right PV and its branches and additionally, a solitary 8-mm SPT deposit in S5, with R0 resection. Adjuvant Gemcitabine + Capecitabine chemotherapy was commenced because of high risk of recurrence.

Six cycles of chemotherapy were completed. The PV graft stenosed necessitated transhepatic stenting with a covered metal stent. Eighteen months after the primary surgery, surveillance imaging showed multifocal recurrence in the remnant left lobe unsuitable for ablation/resection (Figure 2A). In view of no of extrahepatic disease and limited other therapeutic options, the case was discussed for consideration of an LT based on the limited published literature reporting good long-term outcomes.^{2–6} Since this was not a conventional listing indication, per protocol, a national appeal was made and with consensus from other centers, the patient was listed for LT.

Following 6 mo on the waiting list with stable intrahepatic disease (9 lesions) and no extrahepatic recurrence, she finally received an LT from a deceased donor. Intraoperatively, multiple liver nodules were noted without any extrahepatic disease. There was dense fibrotic tissue around the hepatic artery. The stent-bearing segment of previous stenosed PV graft was removed and a further interposition iliac vein graft was used on superior mesenteric vein stump for PV inflow. Operation lasted for 8 h and blood loss was 4 liters. The explant liver had metastases with macroscopic vascular invasion in intrahepatic PV branches (Figure 2B–D), whereas the extrahepatic PV graft with stent had no residual tumor. Ki-67 index was 5% and 5 extrahepatic lymph nodes were nonmetastatic. She was given standard steroid induction and maintenance with tacrolimus monotherapy with a plan for intensive surveillance (we do not use mammalian target of rapamycin inhibitors or

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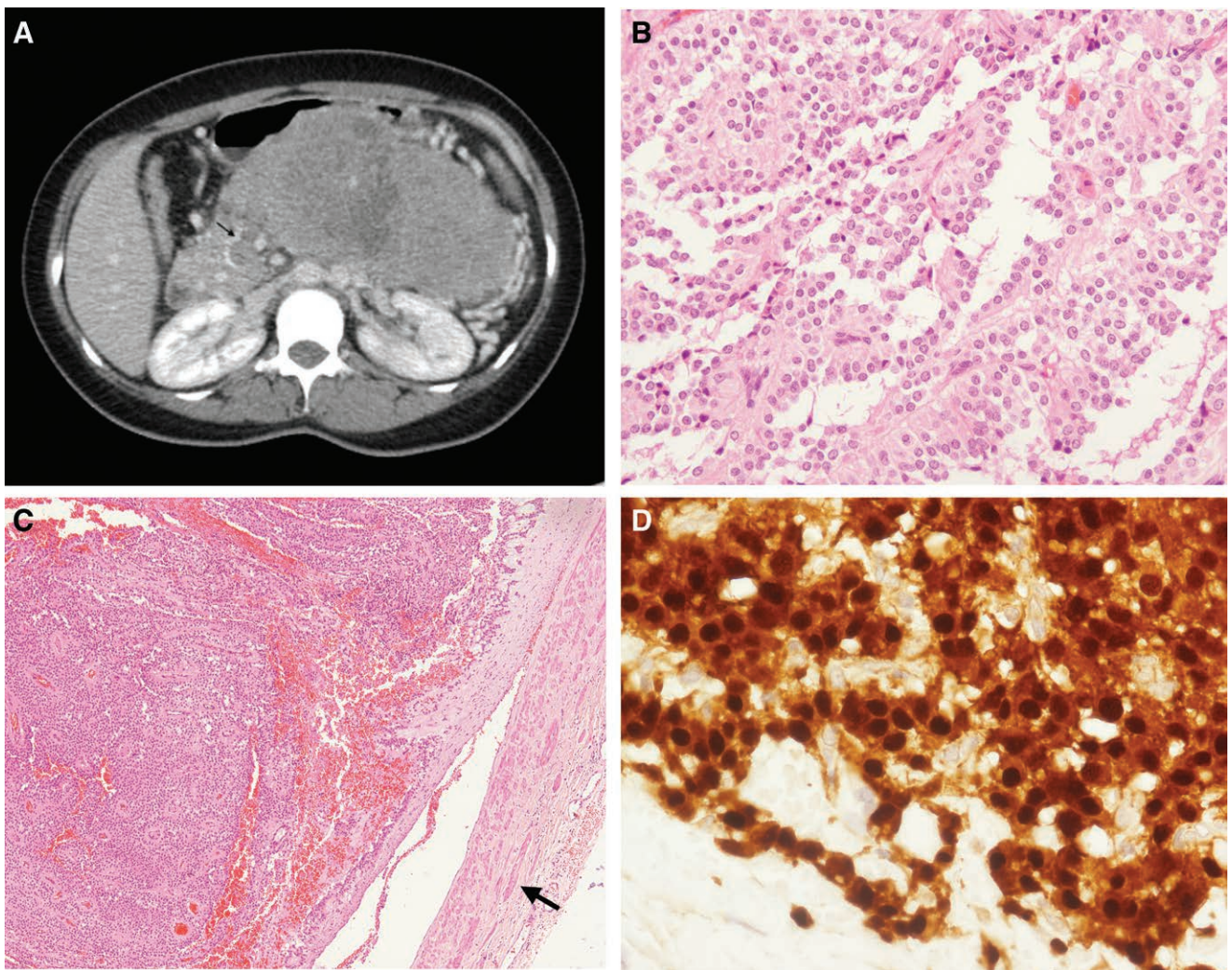


FIGURE 1. Primary tumor. A, CT showing the primary and PV thrombus (arrow). B, The tumor consists of polygonal cells with clear cytoplasm and round nuclei arranged in a pseudopapillary pattern. Magnification $\times 200$. C, Tumor thrombus in the PV (arrow, PV wall). Magnification $\times 40$. D, Immunostaining for beta-catenin shows the diffuse nuclear and cytoplasmic expression. Magnification $\times 400$. CT, computerized tomography; PV, portal vein.

adjuvant post-LT chemotherapy in our unit protocol). Fifteen months following her transplant now, she remains tumor free.

DISCUSSION AND REVIEW OF LITERATURE

SPT (previously termed as solid pseudopapillary epithelial neoplasms)⁵ is a rare pancreatic neoplasm whose histological appearance is unlike any other. The malignant potential of this tumor is low and can only be confirmed in the presence of metastases. Classically, these tumors are seen in young women in the third and fourth decade of their lives, of predominantly African or Asian ethnicity, and grow to substantial sizes before presenting with symptoms related to mass effect. Radiological appearance is that of well encapsulated heterogeneous mass with solid and cystic components (due to central necrosis). Solid components of most SPTs are markedly FDG avid on FDG-PET, this frequently helps in early diagnosis of distant metastasis.⁷ In atypical cases, endoscopic ultrasound-guided biopsy can be done where in negative carcinoembryonic antigen, papillary appearance, bland and uniform-looking tumor, and IHC will help in making a definitive diagnosis. Ki-67 score is typically low (1%–2%) and mitotic

figures are rare particularly at the benign end of the disease spectrum. IHC is positive for B-catenin, A1-antitrypsin and antichymotrypsin, vimentin, and androgen and progesterone receptors. Common differentials are neuroendocrine and acinar cell tumors.⁸ Extrapaneatic SPTs are exceedingly rare.

Up to 20% of SPTs can be malignant.⁹ Tumor size, vascular invasion, capsular infiltration, cellular polymorphism, Ki-67 index, Galectin-3, or lymphatic metastasis may all indicate an aggressive tumor, but only a recurrence or distant metastasis can truly determine malignant potential.^{10–12} The local recurrence rate is low (<10% after 5 y of resection).¹³ Due to the indolent behavior of these tumors, metastasis usually occurs late, 8 to 15.8 y after complete resection of the primary, due to long diploid DNA doubling time.¹⁴ Most metastasis occurs in the liver; recurrences in lungs, bone, and peritoneum are very rare. Five-year disease-free survival of >95% is noted among surgically resected primary SPTs.¹⁵ With aggressive SPTs (ie, metastasis, recurrence, or “deep tissue invasion”), the 5-y disease-free survival dropped to 26.8% in a study.¹⁶

Complete surgical tumor extirpation is the only curative option for SPTs as they are resistant to chemotherapy or radiotherapy. Enucleation is feasible in small tumors, whereas

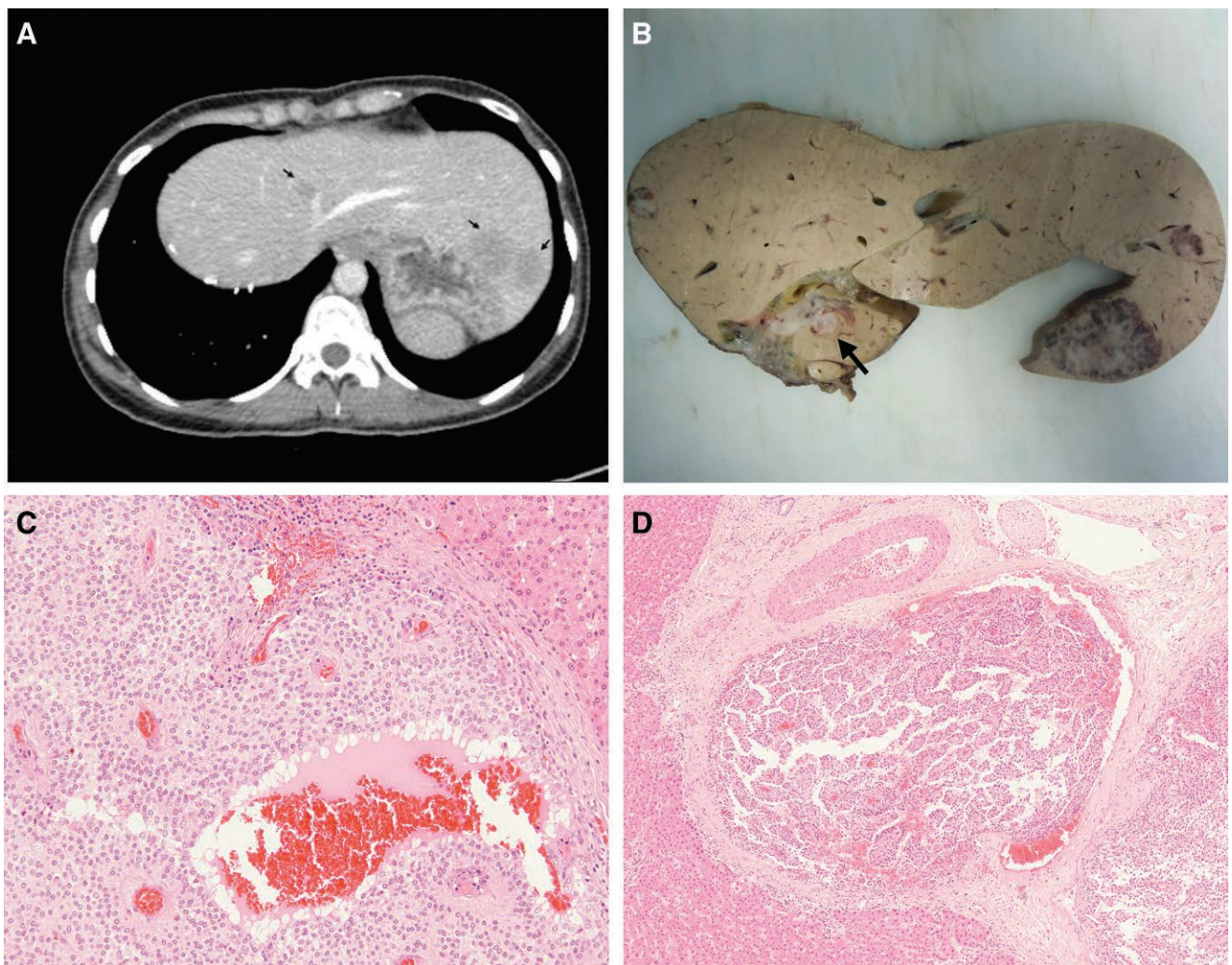


FIGURE 2. Metastases in the liver. A, Multiple recurrence nodules in remnant (arrows). B, The explanted liver shows a tumor thrombus in the left portal vein (arrow). Multiple metastatic deposits are also present in the liver parenchyma. Magnification $\times 100$. C, A metastatic deposit in the liver parenchyma. Magnification $\times 100$. D, Tumor thrombus in a portal vein branch. Magnification $\times 40$.

pancreatectomy is often needed for many. These tumors are known to displace surrounding structures, but since many patients present late with large palpable lesions, invasion of adjacent structures is not uncommon and may necessitate en bloc resection. Although venous reconstructions are commonly performed, unresectability of the primary is mostly due to extensive vascular involvement. Anecdotal reports of Gemcitabine-based neoadjuvant chemotherapy¹⁷⁻¹⁹ exist in the literature for downstaging the tumor. The role of adjuvant therapy is similarly limited and is determined on a case-to-case basis, the agent best determined by the receptor expression pattern.²⁰

Liver Transplantation for SPT Metastasis

The first description of LT for SPT metastasis was given by Sumida et al² in 2007. Left lobe living donor LT was performed for synchronous unresectable SPT metastasis (as a second stage procedure after a distal pancreatectomy) in an adolescent girl. Basing their decision to transplant on good outcomes in slow-growing tumors, they reported recurrence-free survival at 2 y after the transplant. No systemic therapy was employed in this case. Subsequent reports have described 5 more instances of LT for SPT metastasis (Table 1).³⁻⁶ Common to all these reports is the excellent case selection

by ensuring absence of extrahepatic disease and a period of observation after detection of liver metastasis. Use of systemic or local ablative therapies despite their limited efficacy may be warranted to prolong survival or delay the need for transplant (8 y in a report).⁴ Immunosuppression regimen does not need any change and mammalian target of rapamycin inhibitors can be used as per the unit protocol. None of the reported studies used any form of adjuvant chemotherapy after transplantation as is the usual case. One of the studies reported peripancreatic and celiac lymph node recurrence within a year of surgery, which was managed with resection and radiotherapy keeping her in good general condition for many years.⁶ The longest recurrence-free survival reported after LT is 5 y but since late recurrences can occur, follow-up for >10 y is necessary.

Decision making in our case was especially challenging due to a much larger primary necessitating total pancreatectomy, venous invasion, lymph node metastasis, high Ki-67 index, and the subsequent intrahepatic tumor thrombus. A pragmatic approach using systemic chemotherapy and a period of observation while monitoring for extrahepatic disease were hence employed to ensure good biology. The extent of previous surgery, degree of postoperative adhesions, and presence of PV stent increased the technical difficulty of the transplantation.

TABLE 1.**Reported cases of LT for SPT in literature**

Authors	Case	Presentation	Other therapy	LT	Last follow-up
Sumida et al ² 2007	14/F	8.5 cm primary distal pancreas and synchronous liver metastasis	–	Left lobe LDLT, 4 mo after primary resection	DFS 2 y
Kocman et al ³ 2008	20/F	Metachronous liver metastasis 3 y after distal pancreatectomy	–	Right lobe LDLT	DFS 2 y
Dovigo et al ⁴ 2011	44/F	Metachronous liver metastasis 3 y after distal pancreatectomy	Intra-arterial chemotherapy with 5-FU, Cisplatin, and Adriamycin in 3 sessions over first 2 y; arterial embolization; 2nd line Gemcitabine + Erlotinib followed by maintenance Erlotinib. Total duration of therapy 8 y	Deceased donor LT, 11 y after resection of primary	DFS 9 mo
Łągiewska et al ⁵ 2013	31/F	Distal pancreas lesion with unresectable liver metastasis	–	Deceased donor LT, 2 y after resection of primary	DFS 5 y
Wójciak et al ⁶ 2018	51/F	Distal pancreas primary, unresectable, lesional biopsy reported as neuroendocrine cancer based on IHC expression and Ki-67 index was 15%. Chemotherapy with 5-FU, leucovorin and dacarbazine followed by distal pancreatectomy at referral center revealed SPT. Liver metastasis noted 6 mo after resection of primary	–	Deceased donor LT, 2 y after resection of primary	Lymph node recurrence (celiac, lesser curvature, peripancreatic) after 1 y. Excision biopsies, switch to mTOR inhibitor-based immunosuppression, radiotherapy for nodal recurrence in celiac and SMA territory DFS 1 y; OS 4 y
Our case	31/F	17 cm primary almost entirely replacing the pancreas with PV tumor thrombus treated with total pancreatectomy and venous resection, Ki-67 index was 20%. Right hepatectomy for liver metastasis and right portal vein thrombosis 3 mo later. Multiple liver metastasis after 18 mo of primary resection and adjuvant chemotherapy	Adjuvant chemotherapy Gemcitabine and Capecitabine, 6 cycles after right hepatectomy	Deceased donor LT with SMV interposition graft, 2 y after resection of primary	DFS 15 mo

– means treatment not given.

DFS, disease-free survival; F, female; IHC, immunohistochemistry; LDLT, living donor LT; LT, liver transplantation; mTOR, mammalian target of rapamycin; OS, overall survival; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SPT, solid pseudopapillary tumor.

CONCLUSIONS

Surgical resection remains the gold standard therapy for SPT liver metastases. In the rare event of unresectable liver metastasis, with no extrahepatic disease, LT could be considered as a therapeutic option due to paucity of other available therapies.

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