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Case Series

Pathology Section

Aggressive Metastatic Behaviour in Pancreatic Solid Pseudopapillary Neoplasm: A Series of Three Cases

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ABSTRACT

Solid Pseudopapillary Neoplasms (SPNs) of the pancreas are rare low-grade malignant tumours predominantly affecting young women. Although its malignant potential is low, metastases- particularly to the liver can occur. Hereby, the authors present three unusual cases of pancreatic SPN in varied age groups are being presented - in a 17-year-old, 50-year-old and a 37-year-old female of which the all three cases were diagnosed as malignant SPN with metastases. The first case presented with abdominal pain and unusually huge palpable mass of greatest dimension of 18 cm with liver and peritoneal metastasis. Histopathology demonstrated high mitotic activity (approx. 40/10 hpf), capsular invasion, peripancreatic fat invasion, and metastatic deposits in both the liver and peritoneum, confirming malignant SPN. The second case presented with multiple liver Space-Occupying-Lesions (SOLs) which on Ultrasound-guided Fine-Needle Aspiration Cytology (FNAC) showed characteristic cytological features of SPN. The patient had a past history of distal pancreatectomy for SPN three years back. The cytologic features were suggestive of metastatic recurrence of SPN occurring after three years of primary disease, although there was no evidence of any recurrent tumour in the previous operation site in pancreas. The third case had undergone resection of pancreatic SOL for SPN which measured a maximum dimension of 24 cm and showed peripancreatic lymph node metastasis. This case is one of the largest documented SPN reported in literature. The malignant nature of the three cases were on the basis of liver and peritoneal metastasis in the first case, liver metastasis in the second case and peripancreatic lymph node metastasis in the third case. The first patient underwent surgical resection with no adjuvant therapy initiated at the time of reporting. The second patient was referred for oncology evaluation for systemic management of her metastatic recurrence. The third patient had an uneventful postoperative recovery and is currently under close follow-up. These three cases highlight the variable clinical spectrum of SPN including aggressive metastatic behaviour, exceptionally large tumour dimensions, and late recurrences. They also underscore the indispensable role of histopathology and immunohistochemistry in accurate diagnosis, and the importance of long-term follow-up even after apparently complete resection.

Keywords: Cystic pancreatic lesion, Epithelial tumour, Hepatic metastasis, Pancreatic neoplasm, Wnt/beta-catenin pathway

INTRODUCTION

The SPN of the pancreas is a rare epithelial tumour accounting for approximately 1-2.7% of all exocrine pancreatic tumours [1]. First described by Frantz in 1959, it has been formally categorised by the World Health Organisation (WHO) as a distinct low-grade malignant epithelial neoplasm, separate from other pancreatic tumours and lesions [1]. The tumour demonstrates a marked predilection for young women, typically presenting in the second to fourth decade of life, and is associated with favourable outcomes following complete surgical resection [2,3]. Although the majority of SPNs follow an indolent clinical course, metastases- predominantly to the liver and peritoneum- occur in approximately 10-15% of cases [1,4]. Malignant SPN is histologically defined by the presence of local invasion or distant metastases, and a subset of tumours may harbour an undifferentiated component characterised by diffuse sheets of cells with increased nuclear atypia and elevated proliferative index [1,4]. Adverse prognostic features include large tumour size, lymphovascular invasion, perineural invasion, capsular breach, positive surgical margins, and elevated Ki-67 index. The immunohistochemical profile of SPN is characteristic and essential for diagnosis. Key markers include nuclear and cytoplasmic beta-catenin positivity (reflecting aberrant Wnt pathway activation), CD10, Progesterone Receptor (PR), vimentin, and Cyclin D1. Neuroendocrine markers such as chromogranin A are consistently negative, although focal synaptophysin positivity may be observed [5,6].

Hereby, the authors present three cases of pancreatic SPN occurring in females of different age groups are reported here, two of which demonstrated aggressive metastatic behaviour while the third case being unusually large had peripancreatic nodal metastasis. This series is also noteworthy for the exceptionally large tumour dimensions in all three patients. The cases have been presented to highlight the variable clinical and pathological spectrum of SPN, with emphasis on the clinicopathological and immunohistochemical features that aid in diagnosis and risk stratification. Reporting such cases is important to improve awareness of its variable clinical spectrum and malignant potential.

CASE SERIES

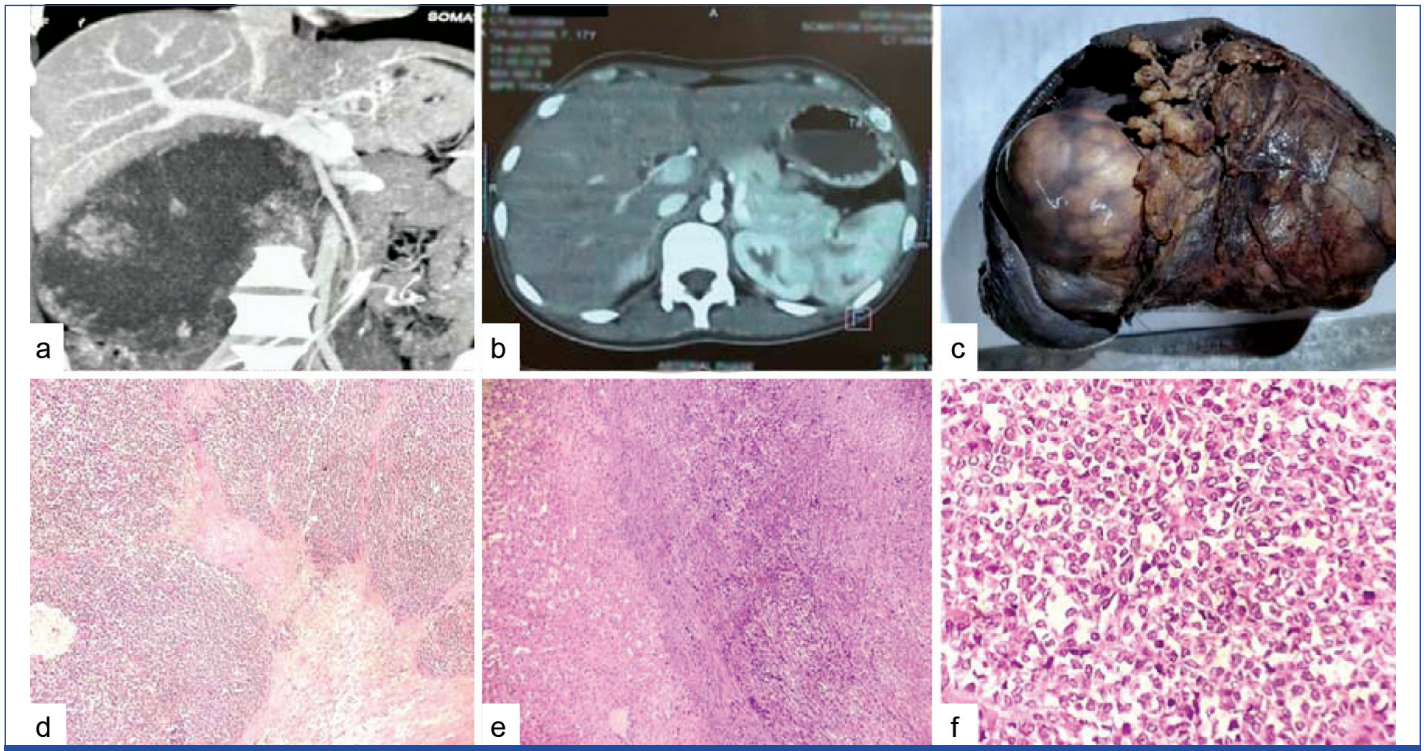
Case 1

A 17-year-old girl presented with progressive dull epigastric pain, mostly after food intake for last one year with early satiety, vomiting and weight loss for last five months. Physical examination revealed a firm, tender, non mobile mass in the epigastrium. There was no history of any jaundice. Laboratory findings included normal liver function tests with normal serum Cancer Antigen (CA) 19-9 and Carcinoembryonic Antigen (CEA) levels and negative beta-Human Chorionic Gonadotropin (β-hCG). Contrast-Enhanced Computed Tomography (CECT) scan of the abdomen revealed a large, well-circumscribed, heterogeneous mass in the pancreatic head region measuring 18×15 cm with areas of cystic degeneration and haemorrhage [Table/Fig-1a,b]. Multiple hypodense lesions were seen in both liver lobes. She underwent pancreatoduodenectomy (Whipple procedure) with resection of a segment of colon adhered to the duodenum and gallbladder along with wedge resection of a liver nodule. A small peritoneal nodule was also incidentally found intraoperatively, which was also resected and sent for histopathology.

On gross examination, the Whipple resection specimen measured 35×16×15 cm in aggregate, with an attached colonic segment of 17 cm. On cut sections, the pancreas showed a huge encapsulated mass measuring 18×17×15 cm [Table/Fig-1c] with solid and cystic areas and extensive areas of haemorrhage. On microscopy, the tumour was composed of poorly cohesive cells forming mostly solid sheets and focal areas showing pseudopapillary structures with delicate fibrovascular cores. Individual tumour cells showed oval nuclei, nuclear grooves, occasional nucleoli, moderate eosinophilic and clear cytoplasm with intracytoplasmic hyaline globules. Periodic Acid-Schiff with Diastase (PAS-D) was performed which demonstrated diastase resistant PAS positive nature of these hyaline globules. Mitoses were approximately 40/10 high-power fields (hpf)- a count notably elevated for SPN and corroborated with malignant transformation in this case. Capsular invasion and peripancreatic fat invasion were present. The liver nodules and peritoneal nodule showed presence of the tumour with similar morphology [Table/Fig-1d-f]. Lymphovascular invasion was identified. While perineural invasion was absent. Regional lymph nodes (n=4 examined) were free of metastasis. The resection margins were negative.

Case 2

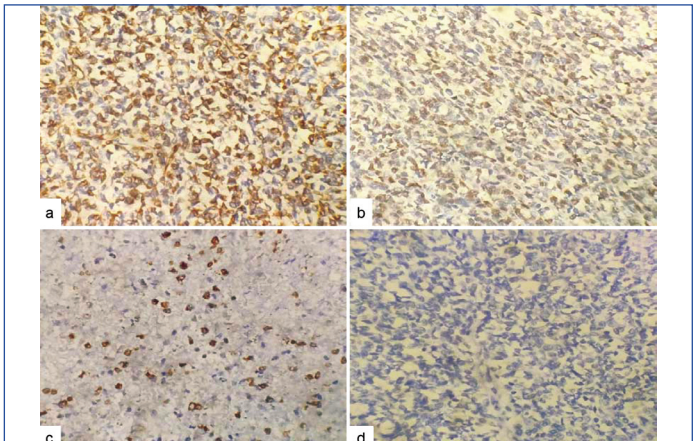
A 50-year-old woman presented with epigastric abdominal pain of three months duration. The pain was mild to moderate in intensity, dull aching, diffuse and continuous and relieved by oral analgesics. It was associated with recurrent vomiting and unintentional weight loss of approximately 5 kg over last six months. There was no history of any jaundice, gastrointestinal bleeding, fever, or co-morbid illnesses. On examination, the patient was haemodynamically stable. General and systemic examinations were unremarkable. Baseline laboratory investigations were within normal limits. Tumour markers were not elevated. An Ultrasonography (USG) and Computed Tomography (CT) scan of the abdomen revealed multiple hypodense SOLs in the liver- approximately six lesions with bilobar distribution, the largest measuring 4.2 cm in greatest dimension in segment VI [Table/Fig-3a]. An ultrasound-guided FNAC was done from the liver SOL, which showed a highly cellular at the time of reporting. The patient was placed on active surveillance with scheduled follow-up imaging at an interval of every six weeks.



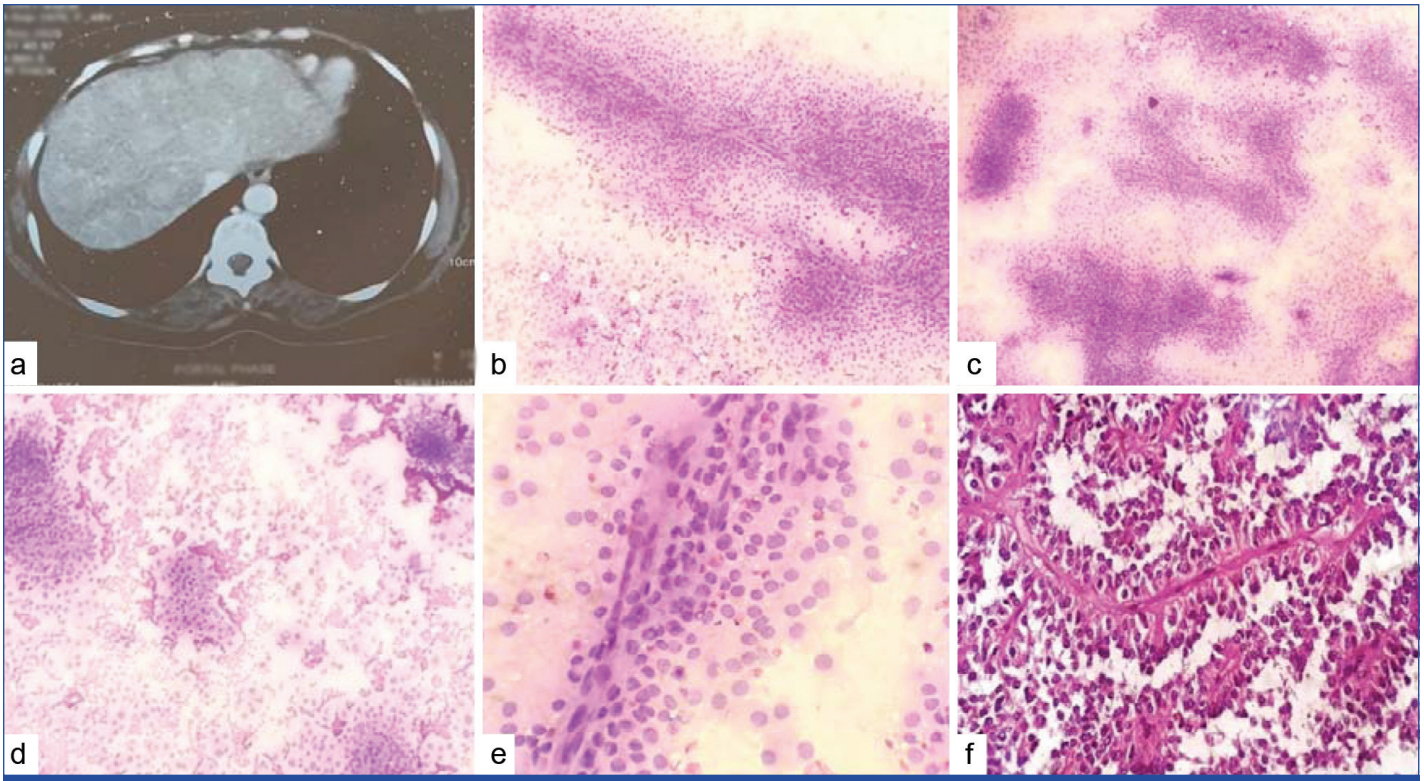
[Table/Fig-1]: a) Contrast-enhanced CT scan of the abdomen showing a large, well-circumscribed, heterogeneous mass in the pancreatic head region with small hypodense lesions; b) in the liver; c) Gross appearance of Whipple's pancreaticoduodenectomy specimen showing large encapsulated mass; d) The tumour characteristic solid appearance with capsular invasion (H&E, 10x); e) Liver metastasis by the tumour (H&E, 10x); f) High power image showing individual tumour cells with oval nuclei, nuclear grooves, occasional nucleoli and moderate eosinophilic to clear cytoplasm.

The histopathological differential diagnosis included SPN, well-differentiated pancreatic pancreatic Neuroendocrine Tumour (Pan NET), acinar cell carcinoma, and pancreatoblastoma. An immunohistochemical panel was selected accordingly. The tumour cells demonstrated strong nuclear and cytoplasmic positivity for beta-catenin positivity, vimentin, CD10, and PR expression. Chromogranin A, CK7, and CK20 were negative. Synaptophysin showed focal weak positivity- a recognised finding in a subset of SPNs and does not favour a neuroendocrine diagnosis in this context. Ki-67 proliferation index was 15% at hotspots [Table/Fig-2a-d]. The liver nodule and peritoneal nodule demonstrated tumour deposits with identical morphology.

A diagnosis of malignant SPN of the pancreas with synchronous liver and peritoneal metastasis was established on the basis of the above-mentioned findings. The patient was referred to the institutional oncology team for postoperative evaluation. In view of limited evidence for systemic therapy in SPN, no adjuvant chemotherapy or radiotherapy was administered to this patient



[Table/Fig-2]: Immunohistochemical profile of SPN: a) Strong nuclear and cytoplasmic beta-catenin positivity; b) Tumour cells positive for Vimentin; c) Tumour cells showing Ki67 positivity at hotspots; d) Tumour cells are negative for Chromogranin A immunostaining (40X).



[Table/Fig-3]: a) CT scan of the abdomen showing multiple hypodense lesions in the liver; b,c) USG-guided FNA done from liver showing characteristic cytological features of SPN with round to oval cells arranged in solid sheets with delicate papillary fronds with bland and uniform appearance with a moderate amount of cytoplasm; d) Tumour cells of SPN with sheets of benign hepatocytes in the centre; e) Fine papillae as seen in SPN with fibrovascular core; f) Micrograph of the tumour operated three years back with characteristic solid pseudopapillary pattern (H&E, 40x).

aspirate of round to oval cells arranged around fibrovascular structures with delicate papillary fronds. The tumour cells had a bland and uniform appearance with a moderate amount of cytoplasm with occasional interspersed hyaline globules [Table/Fig-3b-e]. The cytological differential diagnoses included metastatic SPN, well-differentiated NET, acinar cell carcinoma, and hepatocellular carcinoma. The morphological features, particularly the pseudopapillary arrangement of round to oval cells clinging on to fibrovascular cores and hyaline globules- were most consistent with a SPN. Features of NET like rosette-like pattern or structures and stippled nuclear chromatin were lacking.

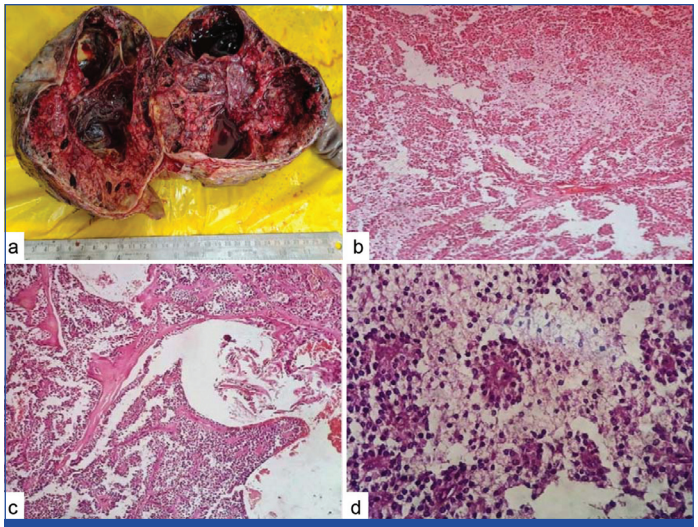
On further enquiry, she had an important past history of en bloc distal pancreatectomy with splenectomy, done for pancreatic SOL elsewhere about three years back. Her previous reports were traced and biopsy slides were retrieved and reviewed where we found that she was a diagnosed case of pancreatic SPN, involving the body and tail of the pancreas, with areas of necrosis and splenic vein thrombosis [Table/Fig-3f]. Margin status, lymphovascular invasion, perineural invasion, Ki-67 index, or lymph node status was not documented in the previous report and could not be retrospectively assessed. She had an interim disease-free life of three years. A repeat triphasic CT scan of the abdomen was also done but there was no evidence of any primary tumour in the pancreas or previous operation site.

A final diagnosis of metastatic SPN to the liver was made, representing late recurrence three years after an initial apparently complete resection, in the absence of any detectable pancreatic tumour on repeat imaging. The patient was referred for oncological evaluation. Surgical resection of liver metastases was considered; however, given the bilobar and multifocal nature of the metastatic deposits, surgery was not done in this patient. She was finally put on a combination chemotherapy of gemcitabine and cisplatin with close radiological follow-up.

Case 3

A 37-year-old woman presented with progressive abdominal swelling and distention with epigastric abdominal pain of six months duration. The pain was mild to moderate in intensity and dull aching in nature. The pain was relieved by intake of oral analgesics. It was associated with recurrent vomiting. There was no history of any weight loss. There was no history of any jaundice, gastrointestinal bleeding, fever, or co-morbid illnesses. On examination, the patient was haemodynamically stable. The abdomen was tender with a firm to hard palpable mass in the upper epigastrium. Baseline laboratory investigations were within normal limits. Serum CEA was mildly elevated at 6.8 ng/mL (normal <5 ng/mL); serum CA 19-9 was within normal limits. An USG of the upper abdomen revealed a huge intra-abdominal well-encapsulated SOL of mixed echogenicity, apparently originating from the pancreas. Triphasic CECT of the whole abdomen showed a large well circumscribed heterogeneous mass lesion measuring 24.0 cm in greatest dimension, arising from the body and tail of the pancreas, with internal areas of cystic degeneration and necro-haemorrhage. Regional lymph node enlargement was also reported around the pancreas.

The patient underwent distal pancreatectomy with splenectomy. On gross examination, there was a large well-encapsulated solid cystic mass with central necro-haemorrhage in the body of the pancreas measuring 24.0 x 19.0 x 17.0 cm. Extensive histologic sections were taken from the tumour. Microscopic examination showed a tumour composed of uniform round to oval cells admixed with capillary-sized blood vessels. Central areas showed cystic degeneration with tumour cells detaching from fibrovascular stalks, forming characteristic pseudopapillae. The stroma showed focal hyalinisation with infiltration by foamy macrophages. Lymphovascular invasion was present although capsular or perineural invasion were not identified. The stroma showed focal areas of hyalinisation with infiltration of foamy macrophages [Table/Fig-4a-d]. Given the characteristic morphology of the tumour, a diagnosis of SPN was made on histopathology. Immunohistochemistry was done in this case as well, which showed diffuse cytoplasmic positivity for beta-catenin and CD10 and negative immunostaining for CK7, CK20 and Synaptophysin. The tumour had adjacent peripancreatic lymph node metastasis in two out of nine lymph nodes. The postoperative course was uneventful. The patient was discharged and placed on six-monthly surveillance imaging.



[Table/Fig-4]: a) Gross appearance of the tumour showing solid cystic and necro-haemorrhagic areas; b-d) Characteristic cytology of SPN as seen in the third case with solid, pseudopapillary areas, cystic degeneration and infiltration by foamy histiocytes (H&E, 10x).

DISCUSSION

The SPN of the pancreas is a rare epithelial tumour with low malignant potential, showing a marked predilection for young female patients. Large systematic reviews and institutional series consistently report that SPN accounts for approximately 1-2.7% of pancreatic neoplasms, with increasing detection rates in recent years likely due to advances in imaging and heightened clinical awareness [5,6]. A significant proportion of cases are incidentally diagnosed, while symptomatic patients most commonly present with nonspecific abdominal pain or a palpable mass [5,7,8].

The three cases presented in this series are notable for their exceptionally large tumour dimensions, two cases demonstrating aggressive metastatic behaviour, and presentation across a broad age spectrum. This contrasts with the classic description of SPN as a tumour of adolescent and young adult females. Papavramidis T and Papavramidis S in their landmark review of 718 cases, reported a mean age at presentation of approximately 22 years [2]; so occurrence of SPN in a 50-year-old female is quite uncommon. Pontrelli A et al., in their systematic review noted that metastatic SPN represents a minority of cases with the liver being the predominant site [5]. The present series confirms this hepatic predilection and additionally documents peritoneal involvement in the first case which is also a rare occurrence.

The second case is more unique in the way that the patient had a disease-free period of three years after initial diagnosis, and relapsed later with metastatic recurrence in the liver without a detectable primary residual tumour. Late recurrences of SPN have been documented in the literature with intervals of up to several years between initial resection and relapse [7,9]. Lubezky N et al., similarly reported cases of late hepatic recurrence in a cohort with otherwise favourable long-term outcomes, reinforcing the need for extended postoperative surveillance [9]. The case also demonstrates the utility of image-guided cytology in confirming recurrence of SPN in the liver without requiring repeat surgical exploration.

The third case was unusually large in size with maximum dimension of 24.0 cm and had peripancreatic lymph node metastasis. Despite its huge size, this case only had metastasis in peripancreatic lymph nodes without any distant metastasis. This finding corroborates with the available literature, indicating that tumour size alone does not reliably predict metastatic behaviour, although it remains a recognised adverse prognostic factor in risk-stratification models [10].

Surgical resection remains the cornerstone of SPN management and is associated with excellent long-term outcomes. Margin-negative resection is curative in the majority of patients, with reported 5- and 10-year survival rates exceeding 90-95% [5,9]. Even in cases of locally advanced disease or limited metastasis, aggressive surgical management has been shown to provide durable disease control and prolonged survival [7,9]. Having said that, uncommon recurrences several years after initial diagnosis, that too as metastasis in the liver is very rare. Parenchyma-preserving procedures, including enucleation and central pancreatectomy, are increasingly utilised to minimise long-term endocrine and exocrine insufficiency. However, these approaches are associated with a higher incidence of postoperative pancreatic fistula compared with conventional resections, although overall morbidity and mortality remain low [5,6].

Despite its generally indolent nature, SPN demonstrates biological heterogeneity, and malignant behaviour in a small subset of patients. The adverse prognostic factors reported in literature include male sex, large tumour size, lymphovascular or perineural invasion, positive surgical margins, elevated Ki-67 proliferation index, and high-grade malignant transformation [5,8,10]. Recent large clinicopathological studies have proposed predictive risk models incorporating tumour size, lymphovascular invasion, and Ki-67 index to stratify patients according to recurrence risk and guide postoperative surveillance strategies [10]. Chen J et al., noted that high Ki-67 index and lymphovascular invasion were independent predictors of recurrence in their cohort of 210 patients [10]. The first case in this series showed an elevated Ki-67 of 15% seen which correlated with the aggressive nature of SPN as described.

The role of adjuvant therapy in SPN remains limited. Most studies report minimal benefit from chemotherapy or radiotherapy even in recurrent or metastatic disease [7,9]. Repeated surgical resection of recurrent or metastatic lesions has been associated with favourable outcomes, further reinforcing surgery as the primary therapeutic modality [7]. This series also underscores the importance of long-term follow-up in SPN, particularly for patients with high-risk pathological features.

CONCLUSION(S)

The SPN of the pancreas is a rare tumour with an excellent prognosis following complete surgical resection. While the majority of cases follow a benign clinical course, a small subset demonstrates aggressive behaviour as discussed in our first two cases, underscoring the importance of individualised surgical planning and risk-adapted follow-up. Further multicentre studies with standardised reporting and long-term follow-up are needed to refine prognostic models and optimise management algorithms.

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