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ORIGINAL ARTICLE

Three Cases of Unusual Solid Pseudopapillary Tumors. Can Radiology and Histology Aid Decision-Making?

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ABSTRACT

Context Solid pseudopapillary tumors of the pancreas are generally considered to be of low malignant potential despite their often large size at presentation. The diagnosis of a solid pseudopapillary tumor depends on the characteristic histomorphology supported by immunohistochemistry. The tendency of some of these tumors to be locally aggressive and also to metastasize has been well recognized. It is not possible to predict the biologic behavior of these tumors based only on their morphology.

Methods The hospital database including the radiological records and histopathology of patients with metastatic solid pseudopapillary tumors, treated at the Tata Memorial Hospital between January 2006 and May 2007 were retrospectively reviewed.

Results The clinical details, radiological features and histopathology of three cases of unusually aggressive solid pseudopapillary tumors are presented.

Conclusions It is important to recognize that solid pseudopapillary tumors may present or recur as locally invasive as well as widely metastatic lesions. While clinical presentation and radiology demonstrate an aggressive disease, it may still be difficult to prove its malignant potential on conventional histomorphological grounds. In spite of the presence of local invasion and metastasis, long term survival is possible and complete excision should be attempted.

INTRODUCTION

Solid pseudopapillary tumors (SPTs) of the pancreas [1] or Frantz tumors [2] account for 0.13-2.7% of all pancreatic tumors [3, 4, 5, 6]. To date, approximately 718 cases have been reported in the literature [7, 8]. Owing to their indolent onset, they tend to become large in size prior to presentation. Despite this, surgery has always been recommended as the main modality of treatment for these tumors [9, 10]. Complete surgical excision with a clear margin of normal pancreatic tissue is usually curative [11].

About 15% of SPTs are known to metastasize [12]. It is not possible to predict the biologic behavior of these tumors based only on their morphology. The bizarre presentation of such tumors may often confound diagnosis. Histologic criteria which would help predict the biological potential of SPTs are not well-established. Further, due to the rarity of the tumor which is associated with a good prognosis, it has been difficult to establish criteria based on conventional histo-morphology which would be predictive of the aggressive behavior. SPTs with conventional histology can recur locally and also metastasize. This feature justifies the term ‘a tumor of uncertain malignant potential’ commonly coined for SPTs. SPTs exhibiting

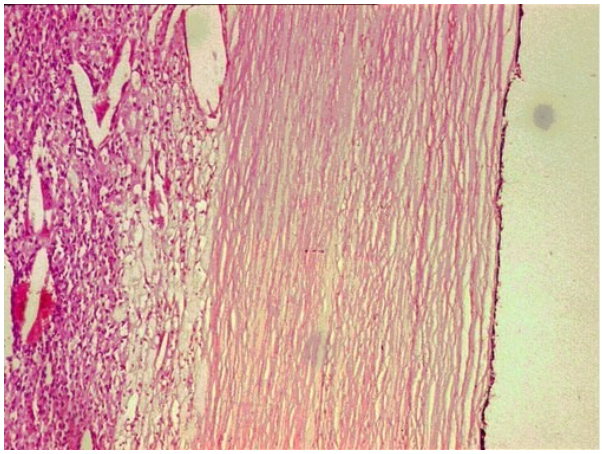

Figure 1. Histology of the previously resected solid pseudopapillary tumor of the pancreas in Case 1. An encapsulated tumor shows mostly solid areas composed of bland cells. Cholesterol crystals are seen. (H&E stain 10x)

the obvious histologic features of malignancy described above can be labeled as 'solid pseudopapillary carcinoma'.

Although the majority of these tumors arise in the pancreas, SPTs have also been found in ectopic pancreatic tissue in the mesocolon, retro-peritoneum, omentum, and the liver [13, 14, 15], mimicking metastatic SPTs. This has been attributed to heterotopy in patients demonstrating SPTs in the mesocolon [16].

We present our experience with three middle-aged female patients who presented to our hospital with highly metastatic malignancies. Two of the three patients had a prior history of surgery for pancreatic neoplasms. Our motive for presenting this series was to highlight the bizarre nature of the clinical and radiological presentation of SPTs and to stress the need for obtaining histological confirmation even in widely metastatic tumors with their epicenter in the pancreas since a complete resection in these patients (whenever feasible) has been reported to be associated with prolonged survival.

METHODS

The hospital database, including the radiological records of patients with metastatic SPTs, proven pathologically, and treated at the Tata Memorial Hospital between January 2006 and May 2007 were retrospectively reviewed.

RESULTS

The clinical details and radiological features of three patients with pathologically proven SPTs of uncertain malignant potential are presented below.

Case 1

A 40-year-old female presented complaining of pain in the epigastrium, constipation and vomiting. She had undergone a distal pancreatosplenectomy 6 years previously for a pancreatic tail neoplasm. The histopathological review of the previously resected pancreatic tumor specimen showed an encapsulated tumor composed of papillae formed by fibrovascular tissue. The cells lining the papillae were uniform and small with regular, bland nuclei. Mitotic activity was absent. Small areas of necrosis and hemorrhage were seen. Cholesterol crystals were evident focally (Figure 1). The features were those of a typical solid pseudopapillary tumor of the pancreas.

Clinical examination revealed a scar from previous surgery as well as a hard fixed mass in the left hypochondrium.

Computed tomography (CT) imaging (Figure 2) revealed a large homogeneous solid mass

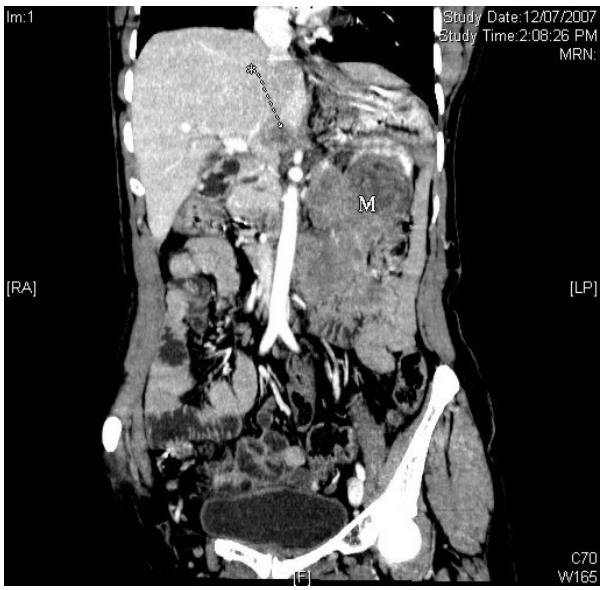

Figure 2. Coronal reformat obtained on a 16 slice multidetector computed tomography scanner showing caudate lobe metastasis (*) and the recurrent SPT in the left kidney and adjacent retroperitoneum and mesentery (M).

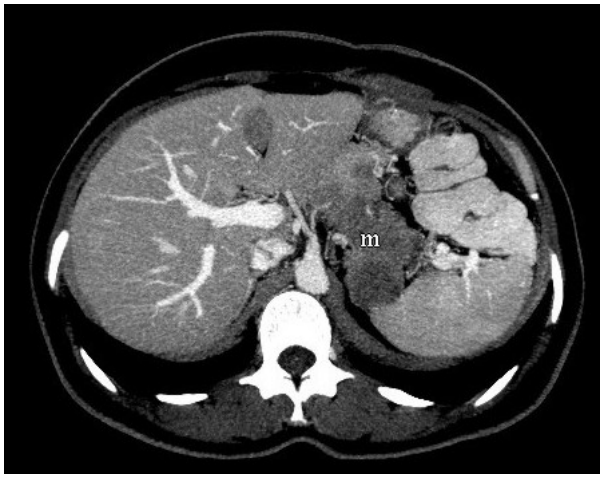

Figure 3. Axial post-contrast CT section showing an irregular solid mass arising from the body of the pancreas encasing and narrowing the splenic artery.

of 7.8x8x5.7 cm in the left anterior pararenal space invading the anterior parenchyma of the left kidney and also infiltrating one of the proximal jejunal loops along its posterior wall. No cystic component or calcification was evident. Multiple enlarged nodes were seen in the adjacent mesentery. The caudate lobe of the liver also showed a hypodense, poorly-enhanced lesion measuring 2.4x1.7 cm suggestive of metastasis. The caudal location of the tumor (in relation to the pancreatic tail region) adjacent to the left kidney favored a diagnosis of primary exophytic renal tumor.

Guided FNA of the lesion resulted in a report of 'an epithelial tumor with papillary configuration'; this further demonstrated the inability to differentiate between a papillary renal cell carcinoma and an SPT of the pancreas. An image-guided biopsy of the 'renal' tumor was done essentially to differentiate between a second primary tumor in the kidney and a recurrence of an SPT of the pancreas. Histology of the biopsy showed features remarkably similar to the previously resected pancreatic tumor as described above. There were no cytological features suggesting malignancy such as cellular atypia, the presence of mitoses or vascular invasion. In addition to papillary renal cell carcinoma, neuroendocrine carcinoma was also considered as a differential diagnosis. Immunohistochemistry revealed the tumor cells to be focally positive for the antibodies to vimentin, neuron specific enolase, CD10 and synaptophysin while they were negative for cytokeratin, epithelial membrane antigen and chromogranin. The Mindbomb homolog 1 (MIB1) labeling index was 2%. Based on these features, the diagnosis of recurrence of an SPT of the pancreas was established.

Despite the involvement of the root of the mesentery on imaging, and keeping in mind the histopathology of an SPT, the patient underwent exploratory surgery with intent to cure. However, we were unable to obtain a complete resection. She is alive at a follow-up of 7 months.

Case 2

A 50-year-old female presented complaining of pain in the abdomen and weight loss. She had had abdominal surgery for a pancreatic mass 9 years previously. A review of the histopathology indicated a benign SPT. Clinical examination revealed an ill-defined mass in the left hypochondrium.

CT imaging (Figure 3) revealed an irregular soft tissue mass in the region of the pancreatic tail with focal adherence to the stomach, spleen and left kidney. A hypodense lesion seen in segment VI of the right lobe of the liver was confirmed as a metastasis. Imaging features suggested an aggressive retro-peritoneal tumor with no specific features suggestive of a solid papillary epithelial neoplasm.

Owing to a long disease-free interval, the possibility of an unrelated retroperitoneal tumor was entertained. An image-guided biopsy showed a tumor with epithelial morphology composed of a predominant papillary pattern. The papillae were formed by fibrovascular tissue. The cells lining the papillae were uniform and small with regular, bland nuclei. Mitotic activity was absent. There was no necrosis or hemorrhage (Figure 4). The features were those of a typical solid pseudopapillary tumor of the pancreas. Due to the unusually aggressive behavior of this tumor compared to a conventional SPT, the differential diagnosis of a neuroendocrine carcinoma was considered. Sarcoma was clearly ruled out due to the epithelial

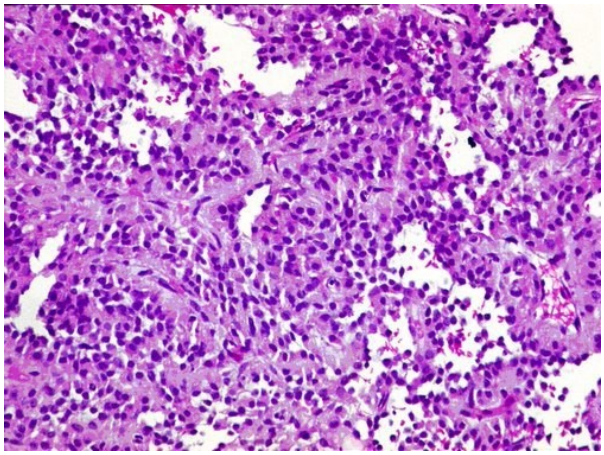

Figure 4. Histology of the recurrent tumor in Case 2 showing the features of a conventional solid pseudopapillary tumor of the pancreas. Papillary fronds with fibrous septae are lined by monotonous cells. Cellular atypia and mitoses are not evident. (H&E stain 20x)

morphology. Immunohistochemistry was carried out which revealed the tumor cells to be positive for antibodies to vimentin, CD10, neuron specific enolase and only focally for cytokeratin and synaptophysin. The MIB1 labeling index was 1%. The presence of a prominent 'pseudopapillary' architecture, bland cellular features in conjunction with the above-mentioned immunohistochemistry profile, helped in confirming a diagnosis of recurrent solid pseudopapillary tumor of the pancreas. The patient underwent exploratory surgery with the aim of carrying out a complete resection. However, the main tumor mass was adherent to the great vessels and hence only debulking surgery was performed. She is alive at a follow-up of 10 months.

Case 3

A 42-year-old female presented complaining of pain in the right side with weight loss. Clinical examination revealed a fixed mass arising in the retroperitoneum in the region of the epigastrium and right hypochondrium.
CT imaging (Figures 5 and 6) showed a large solid mass, 9.7x8.4x7.6 cm in size, arising from the posterior part of the pancreatic head and infiltrating the second part of the duodenum. The biliary tree was dilated. The mass encased the inferior vena cava with resultant thrombosis. The superior mesenteric vessels were not involved. There was further extension with infiltration of the right adrenal and anterior parenchyma of the right kidney. Diagnostic imaging showed pancreatic adenocarcinoma or adenocarcinoma of the duodenum. A differential diagnosis of SPT was not considered as there were no characteristic imaging appearances to suggest it.

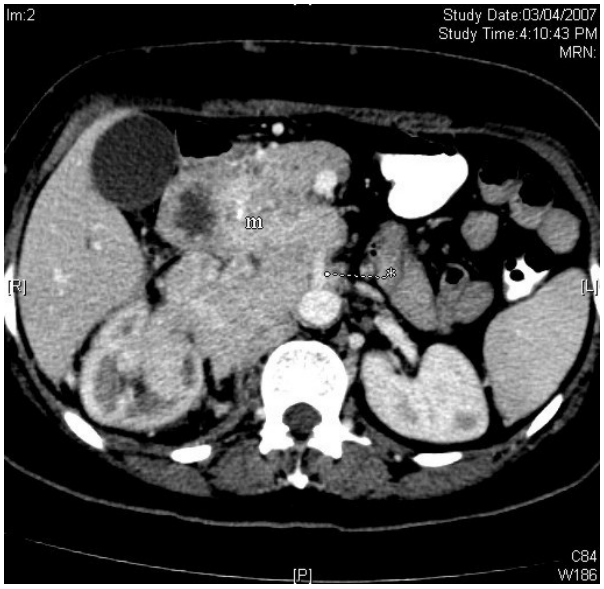

Figure 5. Axial post-contrast CT section showing a large mass (m) in the pancreatic head infiltrating the duodenum and encasing the superior mesenteric artery (*).

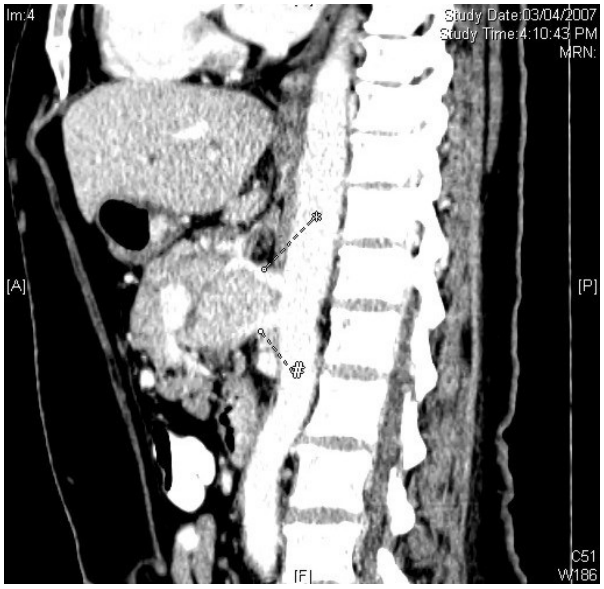

Figure 6. Sagittal reformation obtained on a 16 slice CT scanner showing a pancreatic head mass encasing the origins of both the celiac axis (*) and superior mesenteric artery (#).

FNA cytology of the metastatic lesion in the liver was interpreted as metastasis of a low grade adenocarcinoma. However, subsequent image-guided biopsy showed features strikingly similar to those described in Cases 1 and 2. Taking into consideration the highly invasive nature of this tumor, the differential diagnosis was again a neuroendocrine carcinoma. However, immunohistochemistry showed the tumor cells to express focal positivity for the antibodies to vimentin, synaptophysin and neuron specific enolase while they were negative for cytokeratin (Figure 7), epithelial membrane antigen and chromogranin. The MIB1 labeling index was 2%. These features helped in arriving at a diagnosis of an SPT of the pancreas. The fact that imaging demonstrated the epicenter of the tumor to be in the pancreas also helped to exclude other malignancies such as those of renal origin.

Symptomatic care was advised as exploratory surgery was considered unlikely to yield a complete resection. She was alive at a follow-up of 4 months. However, for the last 5 months, she has been lost to follow-up.

DISCUSSION

SPTs are usually seen in young females of non-Caucasian ethnicity. Owing to its indolent development, these tumors attain a large size prior to presentation. The clinical presentation is usually non-specific with the occasional patient complaining of a mass in the abdomen when the tumor attains a large size.

The classical radiological features of SPTs have been described in the literature [17, 18, 19].

Ultrasonography shows the tumor as a well-defined mass consisting of solid as well as cystic components. CT imaging reveals large solid-cystic masses in the pancreas with peripheral capsule formation, typically located in the tail of the pancreas but also seen in the head/body. The cystic parts are centrally located while the peripheral parts are solid. There is enhancement of the solid parts. Fluid-debris levels may be present in the cystic components due to hemorrhage. The cystic parts may show multiple septations. Calcification may be present in the mass. Magnetic resonance imaging shows similar well-encapsulated solid cystic masses with enhancement of the solid parts. T1-weighted MR images may reveal hyperintense internal signal characteristics which are secondary to hemorrhage. T2-weighted images show heterogeneous high signal intensity and, on post gadolinium imaging, there is progressive heterogeneous peripheral contrast enhance-ement. The capsule is seen as a hypointense rim on both T1- and T2-weighted images.

A preoperative diagnosis is still difficult because of similar findings among the various cystic lesions. The tumor may also present as an entirely solid mass. A review of the records in a series of 14 patients revealed that SPTs were suspected preoperatively in only half of the cases [20]. A preoperative diagnosis may be achieved by imaging-guided fine needle aspiration biopsy.

The pathologic features of SPTs are well-documented. These neoplasms are large (ranging from 6 to 15 cm), round, solitary and often fluctuating. They are encapsulated and well-demarcated from the surrounding pancreas and other organs. The occurrence of multiple tumors is very rare. When sectioned, SPTs are partly cystic and partly solid, the proportion of the solid/cystic areas varying in each tumor. A conspicuous feature of SPTs is the presence of hemorrhage and necrosis. Microscopically, most SPTs show a variable

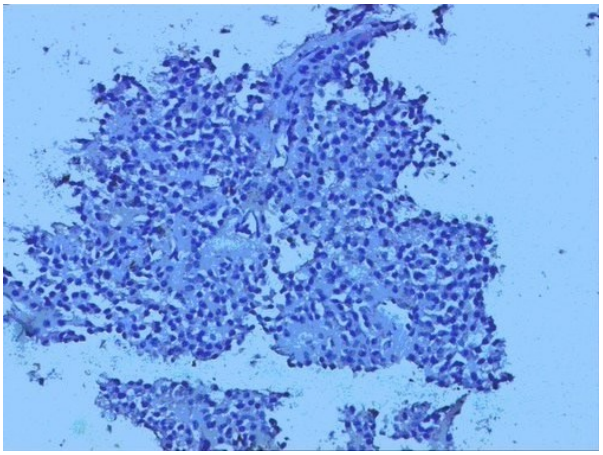

Figure 7. A negative immunostain of the antibody to cytokeratin in Case 3. (20x)

admixture of solid monomorphous growth and the ‘pseudopapillary‘ areas characteristic of this tumor. The papillary fronds show central fibrous septae lined by cells exhibiting ‘epithelial’ morphology. They are monomorphous and lack cytological atypia. Areas of necrosis and hemorrhage are commonly found but do not warrant a diagnosis of malignancy. Foci of calcifications, sheets of foamy macrophages and the presence of cholesterol crystals are additional features. The vasculature can be very conspicuous [21]. Histologically, the closest differential diagnosis is a neuroendocrine tumor (NET) of the pancreas. A monotonous cell population combined with prominent vasculature can be mistaken as a NET. NETs usually lack the widespread degenerative features and, hence, also lack pseudopapillary growth. Immunohistochemistry is helpful in making the distinction. SPTs demonstrate a distinct immunophenotype. Although they are classified under epithelial tumors of the pancreas, they usually do not express epithelial markers such as cytokeratin and epithelial membrane antigen. A small percentage of cases express cytokeratin and epithelial membrane antigen, however only focally. NETs, on the other hand, express cytokeratin strongly and diffusely. Vimentin, alpha-1-antitrypsin and alpha-1-antichymotrypsin are consistently positive in SPTs whereas they are negative in NETs. Synaptophysin positivity is commonly seen in SPTs similar to NETs. Chromogranin, however, is negative. A wide panel of immunostains should be used when distinguishing between these two entities. SPTs can be confused with other pancreatic pathologies such as pleomorphic carcinoma, inflammatory pseudocyst, non-functioning islet cell tumor, cystic fibrosis, hemangioma, lymphangioma, pancreatoblastoma and acinar cell carcinoma. Acinar cell carcinoma occurs more commonly in male patients, shows ill-defined margins, lacks pseudopapillary changes and expresses immunostaining for pancreatic enzymes and cytokeratins. Pancreatoblastoma is a childhood tumor; it lacks a prominent pseudopapillary pattern and does not express vimentin [22]. In all three of our cases, neuroendocrine carcinoma was excluded because of negative or only focal (Case 2) staining for cytokeratin associated with positive staining for vimentin, synaptophysin and neuron specific enolase. Chromogranin was negative in all cases. The MIB1 proliferation index did not exceed 2% in any of the cases.

Due to the unusual presentation and radiological findings, a differential diagnosis of papillary carcinoma of the kidney was also considered in Case 1. The presence of ‘pseudopapillae’ lined by monotonous cells with moderate eosinophilic cytoplasm, positive immunostains for vimentin, synaptophysin, neuron specific enolase associated with negative staining for cytokeratin and epithelial membrane antigen indicated the diagnosis of an SPT.

The origin of SPTs remains controversial. The predominantly young female distribution of this tumor led to suggestions that estrogen and progesterone hormones may have a role in its pathogenesis [23, 24]. The other contrasting hypothesis is based on the discovery of undifferentiated stem cell markers which suggest that it may develop from a pleuripotent stem cell [25] with multipotential differentiation [26]. In fact, SPTs express epithelial, mesenchymal, exocrine and endocrine features, and their cells may originate from the ductular-centroacinar cell compartment which, during embryogenesis, is thought to give rise to exocrine and endocrine cells [27]. However, the lack of clear-cut terminal differentiation into either acinar or endocrine cells, the cytological features, the low proliferative activity and malignancy are not consistent with a stem cell origin [28].

Kosmahl *et al*. [29] hypothesized that SPTs may actually be derived from genital ridge/ovarian anlage-related cells which were attached to the pancreatic tissue during early embryogenesis. However, the fact that SPTs can occur in males without sex hormone defects as well as the inability to identify an ovarian cell which exactly corresponds to the immunohistochemical pattern of SPT cells coupled with the apparent lack of ovarian

tumors having a strong similarity to SPTs has led to serious doubts about this concept [30].

Though uncommon, metastases can occur in patients with primary SPTs, although the mean reported interval is 8.5 years [31]. Metastases usually occur in the liver, regional lymph nodes, mesentery, omentum, and peritoneum. A more aggressive form of SPTs has been described with a different age and sex distribution [32]. Lam *et al*. reviewed over 400 cases of SPTs [4]. Sixty-six of the 452 SPTs in this review were found to be malignant (defined as having evidence of metastases or invasion of adjacent structures). Patients with malignant SPTs were older and were more often male. Most of the patients reviewed were non-Caucasians. The calculated 5-year survival rate was 97% with a mean follow-up of 38 months. Other authors have also reported that patients who suffered late fatal metastases were over 36 years of age at initial diagnosis [33, 34]. Histologically, the presence of necrosis and vascular invasion may indicate a more aggressive tumor. Although the histological criteria of malignancy are not clearly established, angioinvasion, perineural invasion or deep invasion into the adjacent pancreatic tissue or other organs is associated with malignant behavior. Nishihara *et al*. have compared the histological features of three metastasizing and non-metastasizing SPTs and found that venous invasion, nuclear atypia, mitotic activity and the presence of necrobiotic cells were associated with malignancy [35]. Kang *et al*. have found local invasion of the peripancreatic tissue to be the most frequent malignant pathological feature in 11 cases of malignant SPTs out of a total of 33. They also found that a tumor size of greater than 5 cm was a significant factor in predicting SPTs with malignant potential [36]. In their series of 34 patients, Tang *et al*. described two patients who died from aggressive disease which showed a diffuse growth pattern, extensive tumor necrosis, significant nuclear atypia, an unusually high mitotic rate and, in one case, sarcomatoid carcinoma. However, 5 out of 34 cases (15%) of SPT in the same study developed liver metastasis and showed conventional histological features [12]. Martin *et al*. found microscopic margin positivity, local invasion and a size of more than 5 cm not to be significant predictors of survival [28]. However, other authors have reported benign histological appearances of this tumor, despite the fact that local invasion of the surrounding tissues occurred in 16% and liver metastases in 7% [37]. This finding emphasizes that the typical histology of an SPT may not always indicate its biological potential. All three of our cases are examples of the above problem. Cases 1 and 2 recurred locally and also developed liver metastasis after a prolonged interval following primary resection. In spite of the aggressive behavior in the form of wide local invasion and liver metastases, the histology of the recurrent tumor was that of a conventional, typical SPT. No features of malignancy such as cellular atypia, vascular invasion or mitotic activity were seen. Moreover, in Case 1, the histology of the primary tumor resembled the recurrent tumor. Case 3 was an example of an SPT which was widely invasive and also metastatic at presentation. Also in this case, the histology showed a ‘typical SPT’. This finding in all three of our cases further justifies the term ‘lesions of uncertain malignant potential’ which has been coined for SPTs. The cases showing frank histologic features of malignancy should be labeled as ‘solid pseudopapillary carcinoma’ and are expected to behave much more aggressively.

It has been suggested that while attempting to prognosticate the tumor, other clinico-radiological parameters, such as patients over 40 years of age, male gender, septations and multilocularity seen on CT should raise the clinical suspicion of a malignant SPT [38].

In our series, the patients were 40-year-olds or older and all three were female. However, in Case 1 with the recurrent tumor, the patient was 34 years old when the primary tumor was detected. Imaging records of the primary disease prior to surgery were not available in the two cases of recurrent SPTs, but imaging of the recurrent tumor revealed an infiltrative disease pattern. The tumors in all three cases were solid without any cystic components.

There was invasion of the surrounding organs including thrombosis of the inferior vena cava. Liver metastases were noted in two of the three cases. Two cases recurred in the pancreatic bed/pancreas while the third had an epicenter away from the pancreatic bed and in the anterior renal parenchyma. An imaging differential diagnosis of SPT in this case was suggested only in view of the previous histopathology.

The last few years have witnessed some interesting research to better understand the pathophysiology of SPTs. A lot of this work has focused on the Wnt signal transduction pathway and especially on its components, viz. beta-catenin and E-cadherin [39, 40, 41]. An understanding of this aggressive behavior can be explained based on the proposed mechanism by Tang *et al*. [41]. According to them, mutations of beta-catenin lead to nuclear localization. This, along with the loss of E-cadherin, leads to the loss of cell-cell adhesions and consequently results in the pseudopapillary appearance. This can also explain the tendency for dissemination. We believe that additional work on this, and other related molecular pathways, will not only help explain the pathophysiology, but may even provide us with markers that may be used to determine aggressiveness thereby providing a better delineation of the entity of the carcinoma and lesions of uncertain malignant potential.

However, even patients with unresectable tumors, with local recurrence as well as liver and peritoneal metastases, are known to have a good prognosis with long-term survival [37, 42] as was also seen in our series. The presence of metastasis at first diagnosis does not exclude primary surgery because clinical benefits are associated with tumor resection. Complete resection of both the primary tumor and the metastases has been recommended if possible. The prognosis for metastatic disease has been reported as favorable in the pediatric age group, but poor for those over 40 years of age [43]. Salvia *et al*. [44] followed 31 patients over a period extending from 12 to 229 months (median 58 months) and found no evidence of recurrences/metastases. Nevertheless, SPTs can recur locally and metastasize after surgery at any age as is seen in our series. Nagri *et al*. [45] has reported a case of a 65-year-old white female with metastasis to the liver four years after a Whipple's resection for an SPT of the pancreas.

While there do exist reports of aggressive surgery with fair outcomes in patients with these tumors, unfortunately, in the patients in our series, the location of the tumor deposits precluded a complete resection. As seen above, SPTs of the pancreas can present in a bizarre, widely-metastatic fashion and yet lack the histological features of a solid pseudopapillary carcinoma. A complete resection of such tumors (whenever feasible) can result in prolonged survival in these patients unlike adenocarcinomas of other solid organs in the body where surgery would not be considered.

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Keywords Cysts; Neoplasm Metastasis; Neoplasms; Pancreas; Pancreatic Neoplasms

Abbreviations MIB1: mindbomb homolog 1; NET: neuroendocrine tumor; SPT: solid-pseudopapillary tumor

Conflict of interest The authors have no potential conflicts of interest

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