American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e934798
DOI: 10.12659/AJCR.934798

Received: 2021.09.15
Accepted: 2021.10.26
Available online: 2021.11.10
Published: 2021.12.21

Repeated Resection for Recurrent Metastatic Solid Pseudopapillary Neoplasm of the Pancreas

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Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Financial support: None declared
Conflict of interest: None declared

Patient: Female, 49-year-old
Final Diagnosis: Solid pseudopapillary neoplasm
Symptoms: Jaundice and right upper abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Pathology • Surgery

Objective: Rare disease

Background: Solid pseudopapillary neoplasm (SPN) accounts for 1.0% to 2.0% of all pancreatic neoplasms. SPN generally has good prognosis after surgery; however, 10% to 15% of patients have local recurrence or distant metastasis. There have been a few reports of successful surgical resection of isolated recurrent tumors after radical resection and sporadic reports of multiple metastasectomies. Herein, we present a case of recurrent SPN treated by repeated surgeries.

Case Report: A 49-year-old woman was referred to our hospital with jaundice and right upper abdominal pain. Computed tomography (CT) scanning revealed a 73×43-mm heterogeneous mass in the pancreatic head. We performed a pancreatoduodenectomy and diagnosed SPN. The patient was discharged without any complications and was followed up by CT once every 6 to 12 months. Six years later, a 15×15-mm tumor was detected in Couinaud segment VI of the liver. A liver biopsy showed a pathological match to the pancreatic tumor. We performed a partial hepatectomy, and the pathology report confirmed metastatic SPN. At 8 and 10 years after the initial surgery, the patient underwent further partial hepatectomies for confirmed solitary liver metastases of SPN. The Ki-67 index increased for each metastasis identified (initial tumor, 1.88%; 6 years, 7.38%; 8 years, 5.53%; 10 years, 11.22%). No further masses were detected, and the patient survived more than 10 years following surgery.

Conclusions: Despite histological transformation to high-grade malignant disease, repeated aggressive surgical resection led to long-term survival in our patient with SPN.

Keywords: Liver Neoplasms • Neoplasm Metastasis • Pancreatic Neoplasms • Pathology, Surgical • Recurrence

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/934798

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Background

Solid pseudopapillary neoplasm (SPN) of the pancreas is relatively rare, representing only 1.0% to 2.0% of all pancreatic neoplasms. With advances in imaging systems, the number of diagnosed SPN has been increasing dramatically over the past decade [1]. Radical surgical resection is the mainstay of treatment for SPN, for which the estimated 5-year survival rate is 96.7% [2]. Therefore, pancreatic SPN is widely considered a benign disease. However, 10% to 15% of cases are reportedly aggressive and lead to local invasion and/or metastases, and many cases have synchronous metastasis at the time of presentation [3,4].

There are a few reports in the literature on the successful surgical resection of asynchronous metastasis of SPN following initial radical resection [4-6]. Conversely, reports of outcomes in patients who have required multiple metastasectomies are sporadic. We present a patient who successfully underwent 3 separate liver resections for SPN following the initial radical resection.

Case Report

A 49-year-old woman was referred to our Sapporo City Hospital, a tertiary care hospital, with jaundice for 3 days and right upper abdominal pain. The patient had no family history of chronic illness or other disorders. A physical examination revealed no remarkable findings. Laboratory data showed abnormally elevated levels of total bilirubin (5.8 mg/dL), aspartate aminotransferase (185 U/L), alanine aminotransferase (322 U/L), alkaline phosphatase (1450 U/L), and γ-glutamyltransferase (1028 U/L). The serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within the normal ranges. Computed tomography (CT) scanning and magnetic resonance imaging revealed a 73×43-mm heterogeneous mass in the pancreatic head, which led us to strongly suspect SPN in the pancreas (**Figure 1**). The patient underwent endoscopic nasobiliary drainage to lessen jaundice. Examination of a bile specimen did not reveal any signs of malignancy. We performed a pancreatoduodenectomy in which an 85×60×50-mm tumor with negative margins and only capsular infiltration was resected. Gross pathological assessment revealed mainly hemorrhage and necrosis.

Microscopically, the diagnosis of SPN was made based on the morphological features: bleeding and necrotic components were mixed on the cut surface, and it had a typical pseudopapillary architecture. The tumor cells showed an increased nuclear cytoplasmic ratio and cellularity. The Ki-67 index of the tumor was 1.88%. Immunohistochemical staining of the same specimen was positive for β-catenin and CD10, which supported

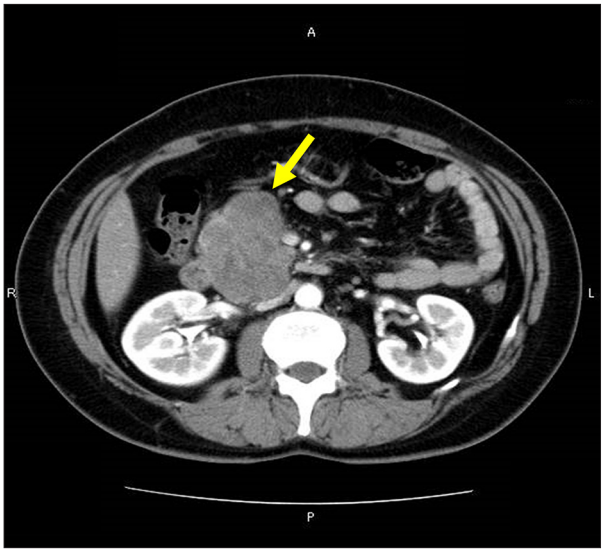

Figure 1. Comuputed tomography showing a 73×43-mm heterogeneous mass (thick arrow) in the pancreatic head.

the diagnosis (**Figure 2**). There was no lymphovascular or perineural invasion. There patient's clinical course was uneventful until the day of discharge. We planned to perform a physical examination, blood test, and CT scan at 6-month intervals for the first 3 years after surgery, and after that, we planned to perform them yearly.

Six years after the initial surgery, a routine follow-up CT scan detected a 15×15-mm well-defined tumor further in the later stage in Couinaud segment VI of the liver, which was growing over time. We suspected tumor recurrence and performed a liver biopsy to differentiate from other tumors. The pathological appearance of the biopsy specimen was similar to that of the pancreatic tumor. Partial hepatectomy was performed, and pathology confirmed the presence of recurrent metastatic SPN. The patient was discharged home 14 days after surgery without complications. We changed the follow-up plan to perform a physical examination, blood test, and CT scan every 6 months. Further metastatic tumors were found in the liver at 98 and 113 months after the initial surgery, for which the patient underwent repeated partial hepatectomies. We found that the Ki-67 index increased every time metastasis occurred, namely 1.88%, 7.38%, 5.53%, and 11.22%, respectively (**Figure 3**). The patient developed no further metastases and was alive at the time of reporting, which was 14 years following initial surgery.

Discussion

SPN is classified as a low-grade, malignant epithelial tumor with uncertain cellular differentiation in the 2010 World Health Organization classification. SPN usually develops in young

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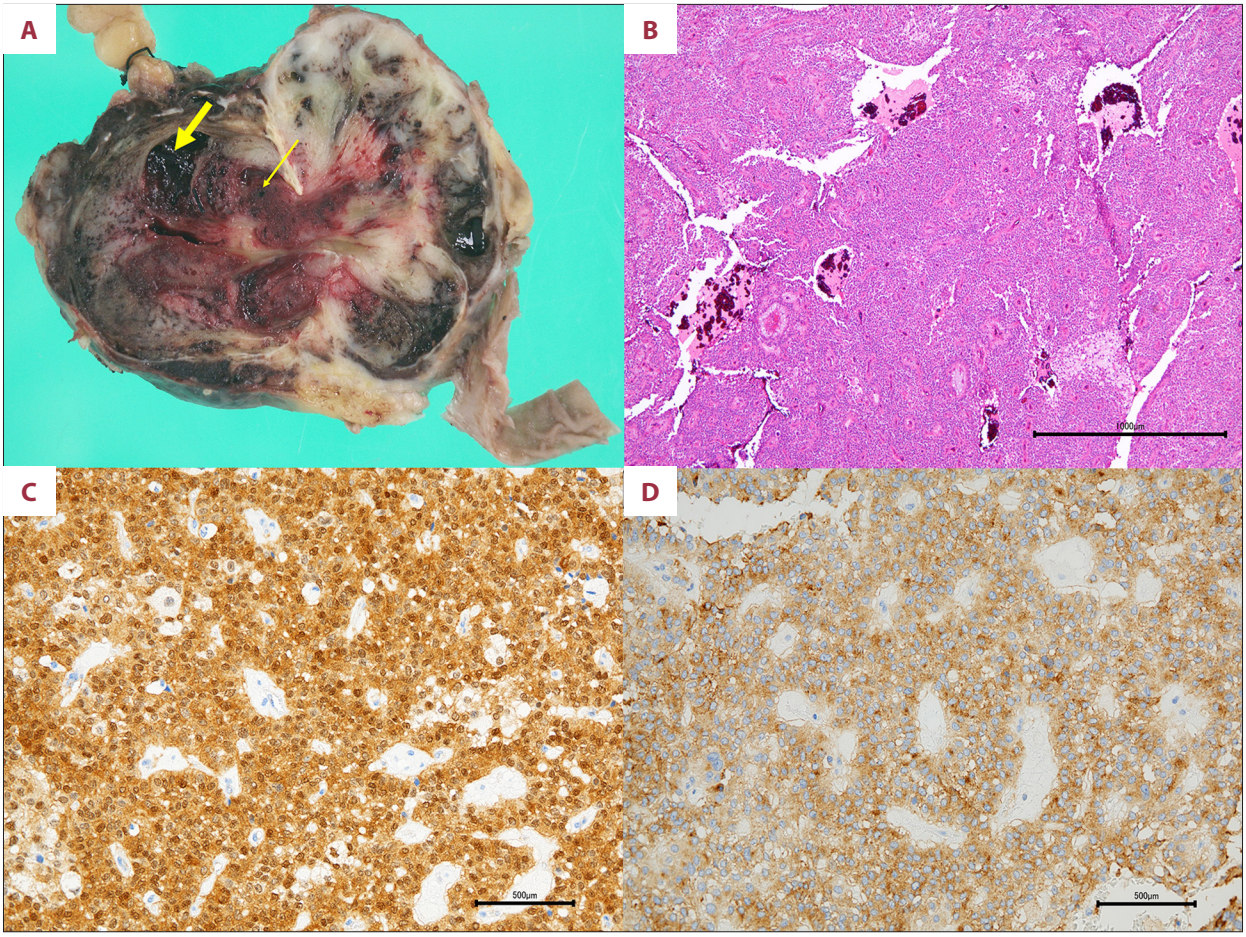

Figure 2. Characteristics of the primary tumor. (**A**) Macroscopic appearance of solid pseudopapillary tumor of the pancreas, showing mainly hemorrhage (thin arrow) and necrosis (thick arrow). (**B**) Image demonstrates an atypical pseudopapillary architecture. (**C**) The tumor shows positive staining for β-catenin. (**D**) The tumor shows positive staining for CD10.

women in the second or third decade of life and is associated with a good prognosis. However, the 10% to 15% of aggressive cases are associated with a lower survival rate than nonaggressive cases and have 5-year and 10-year survival rates of 71.1% and 65.5%, respectively [7]. The factors that lead to recurrence, metastasis, and unfavorable outcomes in patients with SPN remain unclear. Some studies suggest that the following pathological characteristics are associated with tumor aggression: a solid/diffuse growth pattern with extensive tumor necrosis, a high mitotic rate (>15 mitoses per 50 high-power fields), pancreatic parenchymal invasion, capsular invasion, extrapancreatic invasion, angioinvasion, nodal metastasis, and Ki-67 index >4% [8-10]. However, Kim et al found no significant correlations between angioinvasion, perineural invasion, or moderate nuclear pleomorphism and malignant tumor behavior, yet they also noted that the absence of these pathological findings does not exclude aggressive behavior [11]. Our patient, in whom only capsule infiltration was found following radical resection, had aggressive disease with recurrent metastasis. Interestingly, Watanabe et al showed that clinically aggressive SPNs have been associated with advanced patient age and this is more likely to reflect a period of tumor growth before resection [12]. As mentioned above, SPN is common in young women, but our patient was 49 years old at first presentation.

The most common sites of metastasis are the liver, regional lymph nodes, mesentery, omentum, and peritoneum [13]. In the literature, the mean time to recurrence is 50.5 months, which highlights the importance of long-term close observation after operative resection [14], although a consensus on the duration of follow-up has not been reached. There is no consensus regarding chemotherapy and radiotherapy for SPN, but there have been a few reports about the effectiveness of chemotherapy and radiotherapy for SPN [15,16]; therefore, these modalities might be considered as alternative approaches when surgery is not possible. Surgical resection of metastatic lesions is associated with prolonged survival [17]. This was evident in our case, where we observed an uneventful patient survival after repeated surgical resection for metastatic lesions.

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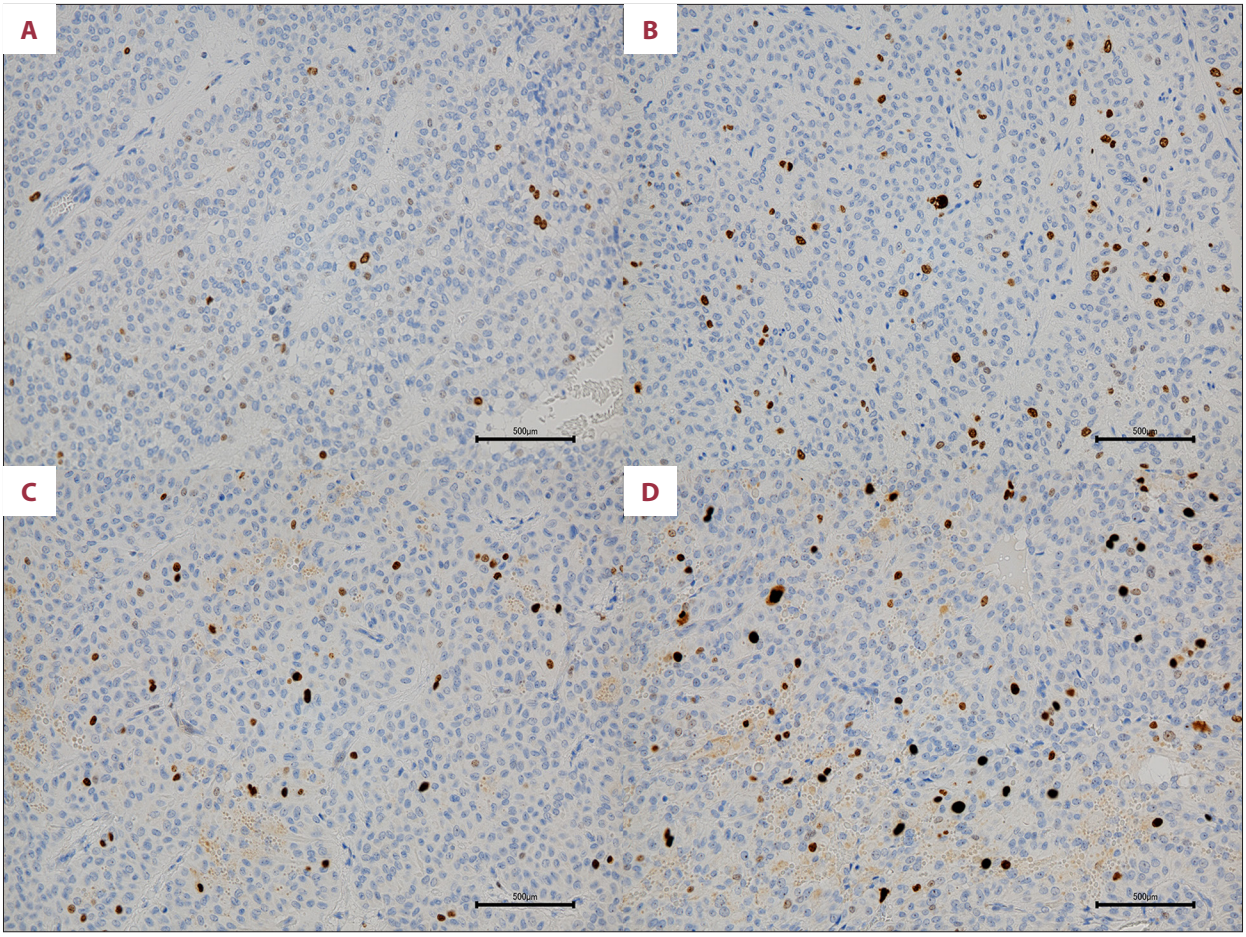

Figure 3. Changes in Ki-67 labeling index, showing an overall increasing trend. (**A**) Primary tumor. (**B**) Specimen resected at second surgery. (**C**) Specimen resected at third surgery. (**D**) Specimen resected at fourth surgery.

A few reports about successful surgical resection for isolated recurrences of SPN following radical resection exist, but cases involving multiple metastasectomies are rare [18,19]. Interestingly, in the present case, the intervals between recurrences of metastases were shortened as the Ki-67 index increased. To the best of our knowledge, this is the first report showing the relationship between the Ki-67 index and recurrences of metastases over time in a patient with SPN. Watanabe et al suggested that SPN can histologically transform from low-grade to high-grade malignancy [12]. Kim et al noted an association between an elevated Ki-67 index and development of distant metastasis [10]. Our findings support the increasing degree of malignancy with recurrent SPN metastases.

Conclusions

SPN is widely viewed as a low-grade malignant disease with favorable prognosis owing to the high success rate of surgical treatment. However, SPN can histologically transform to high-grade malignant disease that gives rise to recurrent metastasis. Aggressive surgical resection for repeated recurrent metastatic SPN can improve long-term survival. Further studies of SPN focusing on histological transformation are required to understand this enigmatic disease subtype more clearly.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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