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Case Report

Fever of unknown origin as a possible sign of malignancy? – Solid pseudopapillary neoplasm of the pancreas in a teenager: Case report with literature review

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Abstract

Introduction: Solid pseudopapillary neoplasm (SPN) of the pancreas is an exceedingly rare tumor, accounting for 0.2% to 2.7% of all pancreatic neoplasms, predominantly affecting young females.

Aim: The aim of this study is to highlight a rare presentation of SPN as persistent fever of unknown origin (FUO) without other significant symptoms, emphasizing the need to include pancreatic neoplasms in FUO differential diagnosis.

Case study: An 18-year-old female presented with persistent FUO without other significant symptoms. Initial laboratory tests were largely unremarkable except for mild anemia. Imaging studies revealed a well-defined mass in the tail of the pancreas measuring 5 × 5 × 6 cm. An ultrasound-guided core needle biopsy suggested SPN, characterized by monomorphic cells with minimal atypia and a specific immunophenotype. The patient underwent a distal pancreatectomy with splenectomy. Histopathological examination confirmed the diagnosis of SPN (pT3 pN0 LVI− PNI+), with clear surgical margins and no lymph node involvement. The postoperative course was uneventful, and follow-up examinations showed no signs of recurrence.

Results and discussion: This case underscores the importance of considering pancreatic neoplasms in the differential diagnosis of FUO, even in young patients. Early detection and surgical intervention are crucial for favorable outcomes.

Conclusions: SPN is a rare low-grade malignant tumor with good prognosis following surgical resection. Increased clinical awareness of its atypical presentations is essential for timely diagnosis and treatment.

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1. INTRODUCTION

Pancreatic tumors are heterogeneous neoplasms derived from multipotent exocrine or endocrine cells ranging from benign to malignant. Pancreatic cancer is the seventh leading cause of cancer-related mortality worldwide.[1] The vast majority of these neoplasms are pancreatic ductal adenocarcinomas (PDACs), accounting for over 90% of these tumors. In advanced stages, the 5-year survival rate is about 10%, rendering it one of the most formidable cancers in medical practice. The average age at diagnosis is around 65 years, while its incidence among adolescents is extremely rare.[1,2]

According to the World Health Organization data, the age-standardized incidence rate of pancreatic cancer among individuals aged 15–24 years is 0.06 per 100,000, with a mortality rate of 0.02 per 100,000. The overall risk of developing pancreatic malignant tumor is higher in men than in women.[3,4]

Thus, pancreatic tumors are extremely rare and establishing the correct diagnosis may pose a challenge due to a frequent lack of specific symptoms. The disease usually manifests itself as a leisurely growing abdominal mass that may incite abdominal discomfort or pain.[5,6]

This paper discusses a rare case of an 18-year-old female patient who initially presented with fever of unknown origin (FUO) and was subsequently found to have a solid pseudopapillary neoplasm (SPN) of the pancreas.

2. AIM

This case report aims to raise awareness of SPN of the pancreas presenting as FUO in adolescents, and to highlight the significance of comprehensive diagnostic evaluation, including early imaging, to guide appropriate surgical management.

3. CASE STUDY

An 18-year-old female patient, who had been under investigation for persistent FUO for nearly two months, presented to the Oncology Surgery Clinic with a mass in the tail of the pancreas, detected during a diagnostic ultrasound examination conducted to investigate her symptoms (Figure 1).

The patient's condition was stable with a consistent weight, good appetite, and a normal CA 19–9 level of 7.0 (reference range: <37 U/ml). Physical examination revealed a soft and non-tender abdomen without any palpable masses or pathological resistance. Her physiological functions were normal and she had no significant past medical or surgical history. The family history was notable for pancreatic cancer in a grand aunt. The patient had no allergies, denied substance use, and her gynecological history was unremarkable. Laboratory investigations showed mild anemia, with a hemoglobin level of 11.5 g/dL (reference range: 12.0–16.0 g/dL), hematocrit at 34.0% (reference range: 37.0–47.0%), and a red blood cell count of 4.15×10^{12}/L (reference range: $4.2–5.4 \times 10^{12}$/L). A computed tomography (CT) scan revealed a large $5 \times 5 \times 6$ mass in the tail of the pancreas (Figure 2). An ultrasound-guided core needle biopsy of the pancreatic mass was performed under local anesthesia using 40 mg of lignocaine in 10 mL of 0.9% sodium chloride solution. Three tissue specimens were obtained from the solid lesion measuring 5.3 cm in diameter. The results showed monomorphic cells with minimal nuclear atypia and an immunophenotype consistent with solid pseudopapillary neoplasm with no evidence of vascular involvement, the absence of metastatic lymph nodes, but the presence of perineural invasion (Figure 3). Accordingly, the neoplasm was classified as pT3 pN0 LVI(–) PNI(+).

Initial histopathological examination of the biopsy specimen included only a very small fragment of normal gastric

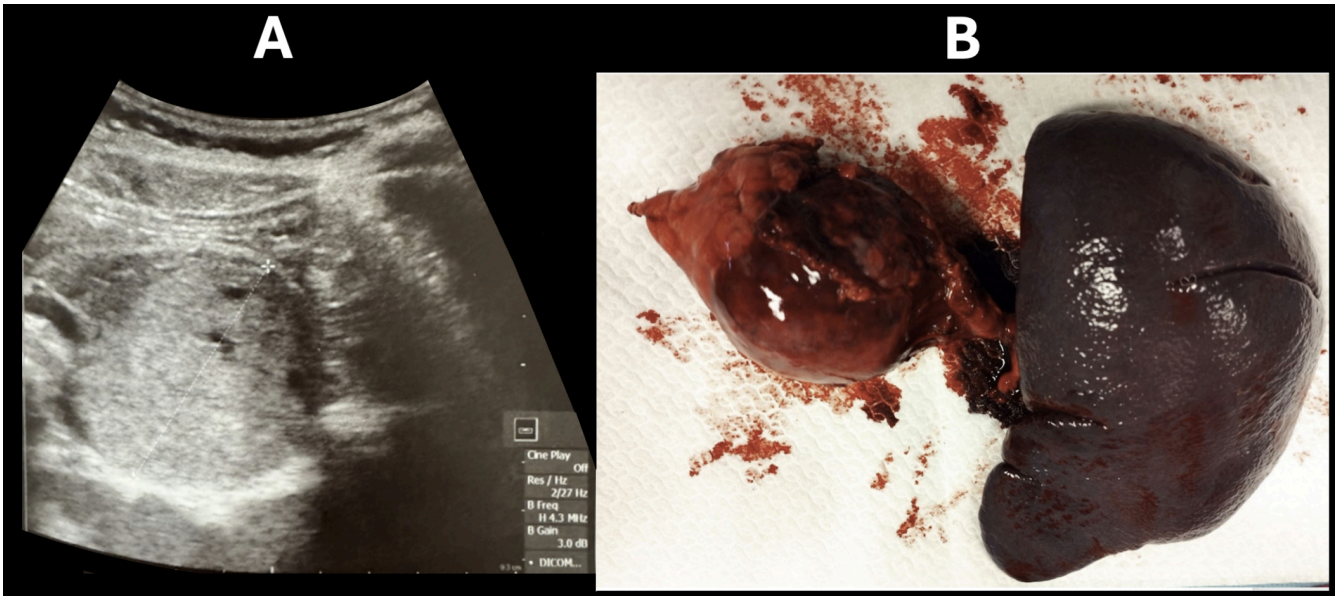

Figure 1. Ultrasound print of the SPN (A) and postoperative image showing the excised tumor and spleen (B).

mucosa with no evidence of neoplasm. Further analysis revealed fragments of a tumor composed of epithelioid cells forming solid patterns with minimal nuclear polymorphism and no mitotic activity. Immunohistochemical studies demonstrated that the tumor cells were positive for synaptophysin, SMAD4, progesterone receptor (PR), beta-catenin (nuclear and cytoplasmic expression), CD99 (dot-like pattern), and was negative for cytokeratin 7 (CK7), chromogranin A, and carcinoembryonic antigen (CEA). The Ki-67 proliferation index was less than 5%. These findings were consistent with a diagnosis of an SPN of the pancreas (ICD-O code 8452/3).

The patient was informed of the diagnosis and scheduled for distal pancreatectomy. Preoperative assessments, including updated laboratory tests, remained within acceptable ranges. She underwent a distal pancreatectomy with splenectomy. Intraoperative findings included a well-encapsulated, solid, pinkish tumor measuring 5 × 4.5 × 6 cm located in the distal pancreas. The tumor was resected with a 6 mm margin from the pancreatic parenchyma and a 0.2 mm margin distally, constituted by the connective tissue capsule. The spleen, measuring 10.5 × 8 × 5 cm, appeared macroscopically normal. A fragment of the splenorenal ligament was also removed, containing seven lymph nodes.

Postoperative histopathological examination confirmed the diagnosis of SPN. The tumor was classified as pT3 pN0 according to the TNM staging system. There was no lymphovascular invasion (LVI-negative), but perineural invasion (PNI-positive) was noted. Surgical margins were clear, with the narrowest being 6 mm from the pancreatic parenchyma and 0.2 mm distally. All seven examined lymph nodes were free of metastasis (0/7). The spleen showed normal histological architecture without focal lesions.

The patient's postoperative recovery was uneventful, and the fever resolved following surgery. Three months after the surgery, during a follow-up visit, she reported no symptoms or complaints. Physical examination revealed a soft, nontender abdomen without palpable masses or organomegaly. Physiological functions remained normal. She was advised to undergo a follow-up CT scan of the abdomen and pelvis to monitor for any signs of recurrence (Figure 2).

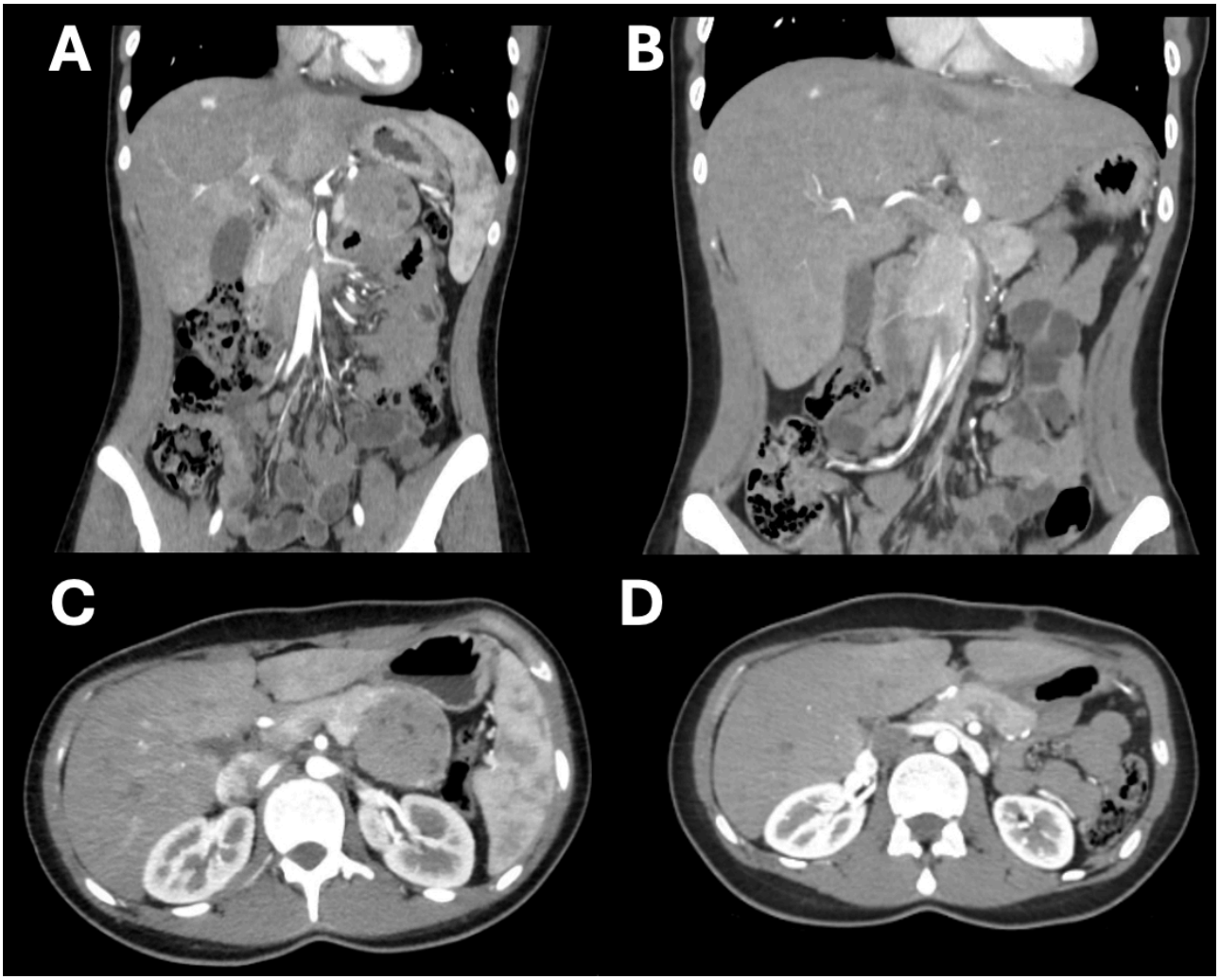

Figure 2. CT scan of the abdomen: (A) Coronal section showing a massive round mass in the tail of the pancreas; (B) Coronal section after the excision of the spleen and pancreatic tail; (C) Transverse section showing the tumor before surgery; (D) Transverse section after surgery.

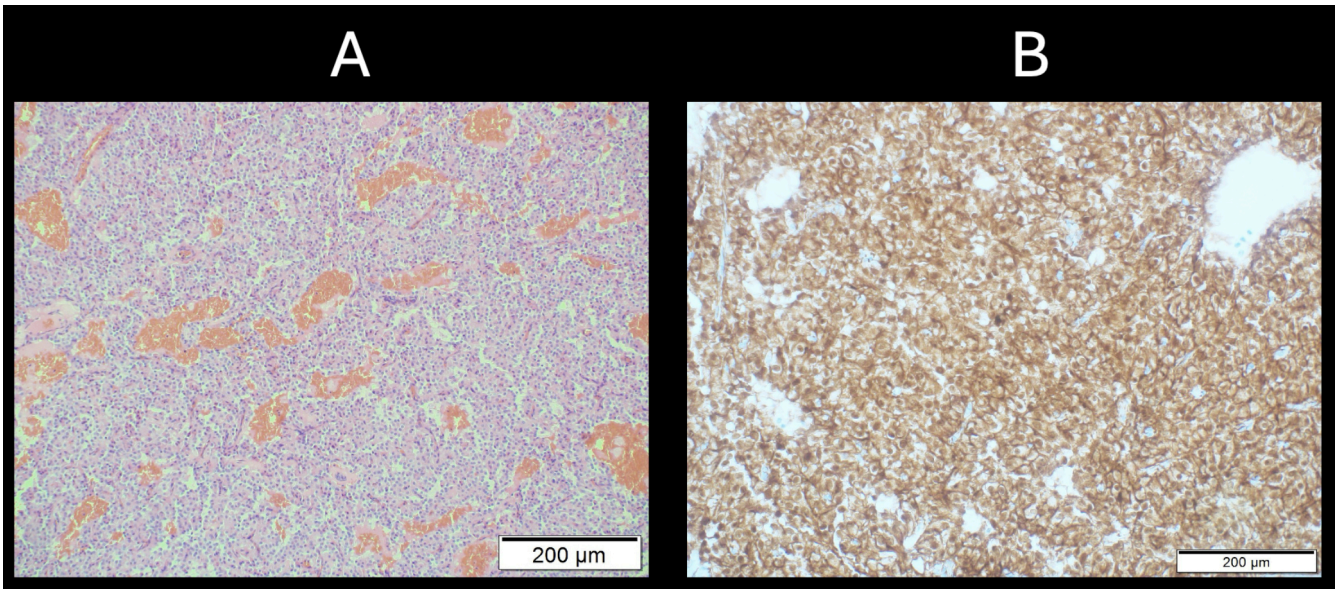

Figure 3. Histopathological image from biopsy: (A) Solid areas with focal pseudopapillary structures and hemorrhagic foci within the tumor, hematoxylin and eosin (H&E) staining, 100 × magnification; (B) Positive nuclear and cytoplasmic β-catenin expression in tumor cells, immunohistochemistry, 200 × magnification.

The patient maintains a good performance status and is currently under observation at the outpatient clinic.

4. RESULTS AND DISCUSSION

SPNs of the pancreas are extremely rare, accounting for only 0.2 to 2.7% of pancreatic tumors.[6] First described by Virginia Kneeland Frantz in 1959, they are commonly referred to as 'Frantz's tumor'.[7] The term "solid pseudopapillary tumor" reflects two main microscopic features: the presence of areas with a solid structure and pseudopapillary formations.

SPNs predominantly affect females under 35 years, with unclear roles of estrogen and progesterone in their development, despite identified hormone receptors. Papavramidis et al. reported a mean age of onset for SPNs of approximately 21.97 years, with a significant female predominance.[8]

Often asymptomatic, nearly half of SPNs are discovered incidentally during examinations for other pathologies. They are commonly found in various parts of the pancreas: 41.7% in the tail, 33.3% in the head, and 25% in the body of the pancreas.[9] A comprehensive review of 643 patients underscored abdominal pain as the most prevalent symptom, noted in 46.50% of cases. Patients also reported symptoms such as abdominal discomfort, dyspeptic disorders, bloating, and weight loss. Very rarely, it can also cause obstruction of the bile ducts, leading to mechanical jaundice. Fever was present in only 8% of the cases.[8]

The cases from the literature showing concomitant fever and SPNs in adult and pediatric patients were collected in Table 1.

The SPNs likely originate from pluripotent cells with both exocrine and endocrine differentiation potential. A characteristic feature is the somatic mutation of the β-catenin gene, present in about 95% of cases, causing nuclear, cytoplasmic, and excessive E-cadherin expression. Remarkably, SPNs require fewer mutations on average (~3) compared to PDACs, which averages 26–63 mutations, or acinar cell carcinoma (~131 mutations). Additionally, there is emerging evidence suggesting that conditions like familial adenomatous polyposis, may increase the risk of developing SPNs.[10]

Biochemical markers, such as CA 19–9, CA125, carcinoembryonic antigen, and α-fetoprotein typically yield normal results.[9] Imaging techniques including X-ray, ultrasonography, and CT play a central role, often revealing a well-defined mass with both solid and cystic components, lacking internal septations, hemorrhagic alterations within the lesion and a fibrous capsule, which may contain calcifications. CT typically shows a hypodense, round mass with peripheral solid parts enhancing after intravenous contrast administration. Ultrasonography displays iso- or hypoechoic lesions relative to normal pancreatic tissue.

The treatment of choice for SPNs is radical resection, if technically feasible.[11,12] In most studies, the tumor is considered a borderline malignant neoplasm with a favorable prognosis. Survival rates for patients with SPNs following radical surgery are high, with a 97% survival rate at 2 years and 95% at 5 years.[8,13] Incomplete resection of the tumor carries a high risk of local recurrence; however, even after radical removal, recurrences or metastases, primarily in the liver, are observed in 10–15% of cases, typically appearing 2 to 168 months postoperatively.[9]

Chemotherapy has limited efficacy, though isolated cases report a positive response to the treatment with cisplatin and 5-fluorouracil in adults with inoperable papillary-cystic tumors. Radiotherapy may be used to achieve local control in specific cases. It's worth noting that after a distal

Table 1. Case reports describing SPNs of the pancreas presenting with fever and related symptoms. The table outlines patient age and concomitant clinical features, including abdominal pain, discomfort, dyspeptic manifestations, bloating, and weight loss.

Case Report[ref]	Age	Fever	Abd. Pain	Abd. Discomfort	Dyspeptic Disorders	Bloating/ Distension	Weight Loss
Albuquerque, 2020[16]	13	+	+	–	+	–	+
Paramasivam, 2020[17]	22	+	+	–	+	–	+
Reppucci, 2019[18]	11	+	+ (persistent, generalized)	–	+ (emesis)	+ (dist.)	–
Tine, 2023[19]	24	+	+ (epigastric, RLQ)	+	+ (nausea)	–	–
Nai, 2015[20]	87	+	–	+	+ (vomiting, poor intake)	–	–
Fajardo Ponce, 2021[21]	11	+	+ (colicky)	–	+ (constipation)	–	+ (20 kg)
Klotz, 2013[22]	37	+ (38.8 °C)	+ (diffuse abdominal pain)	+	–	–	–

pancreatectomy, pseudocyst formation can sometimes be mistaken for a tumor recurrence.[8,13]

FUO is classically described as having a body temperature greater than 38.3 degrees Celsius lasting more than 3 weeks and an undetermined genesis after 1 week of hospitalization. Despite advances in diagnostics, approximately 25% of FUO cases remain without a definitive cause. Neoplasms are a significant etiological category, yet FUO is frequently overlooked, particularly in the absence of localized symptoms.[14,15]

This case emphasizes the need to consider neoplasms in the differential diagnosis of FUO. The patient's young age could pose a distraction, considering the incidence of cancer among people aged 15–19, despite that, in the case of FUO appearance, proper diagnostic workup should be conducted, including an active search for a possible malignancy.[14]

5. CONCLUSIONS

(1) Persistent FUO, especially in young women, should include pancreatic neoplasms, specifically solid pseudopapillary neoplasm in the differential diagnosis.
(2) Early abdominal imaging is critical when FUO lacks localizing features and can expeditiously reveal surgically curable pathology.
(3) Complete surgical resection of solid pseudopapillary neoplasm especially in early stages achieves excellent oncologic outcomes implicating the critical need for investigating the FUO etiology in each patient.

Informed consent
Informed consent was obtained from all participants included in the study.

Ethics approval
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Conflict of interest
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Data collection: WM
Data interpretation: JK-Z, MŁ, PJ, KK, JW, SK
Manuscript preparation: JK-Z, MŁ, PJ, KK, WM
Literature search: JK-Z, MŁ, PJ, KK

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