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The rare case of a cystic pancreatic neuroendocrine tumor

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ABSTRACT

The pancreatic neuroendocrine tumors (PanNETs) most commonly present as solid neoplasms; however, very rarely, they may present primarily as cystic neoplasms. Most of the cystic PanNETs are non-secreting tumors, and the radiological features are not well defined. Hence pre-operative diagnosis is usually challenging and the tumors are misdiagnosed as mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, serous cystic neoplasms, solid pseudopapillary neoplasms, and non-neoplastic cysts. However, the management depends on the accurate diagnosis of these cystic lesions, which poses a dilemma. Herein, we report the case of a cystic PanNET in the tail of the pancreas, which was clinically and radiologically misdiagnosed as a mucinous cystic neoplasm. This case is reported to highlight this issue to the medical community regarding the diagnostic difficulty in such rare non-functioning pancreatic neuroendocrine tumors.

Keywords
Pancreas; Neuroendocrine Tumors; Cysts, Pancreatic Intraductal Neoplasms

Pancreatic neuroendocrine tumors (PanNETs) are rare and constitute approximately 5% of the pancreatic neoplasm, with a prevalence of 0.2–2 cases per million persons per year.[1] Recent advances in radiographic and endoscopic imaging have improved their detection.[2] Previously, PanNETs were classified into functioning/syndromic NETs and nonfunctioning/non-syndromic NETs based on clinical syndromes owing to hormone hypersecretion. However, since 2017, the WHO classification of the PanNETs were based on their proliferative activity.[3] The majority of the PanNETs are nonfunctioning (30%–40%), which poses a great challenge in preoperative diagnosis. Radiological features are also often nonspecific; hence, preoperative diagnosis is hardly achieved. These tumors are mostly solid; however, they can—rarely—be cystic, which makes the preoperative diagnosis even more impossible.[4,5] The cystic change can be due to cystic degeneration in a large tumor, or tumor necrosis. Similar biological behavior and malignant potential between the solid and the cystic PanNETs might support this hypothesis. In larger series, it has been demonstrated that cystic PanNETs present in the lower stage with a lesser rate of lymph node and distal metastasis than their solid counterpart.[6,7] Ligneau et al.[8] published an extensive series comprising 50 cases of cystic PanNETs, most of which were non-functioning. Herein, we present the case of a cystic PanNET in a 48-year-old man who presented as a surgical emergency with severe abdominal pain, radiating to the back. The radiological evaluation depicted a cystic lesion in the tail of the pancreas.

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CASE REPORT

A 48-year-old male patient presented to the surgical emergency department with diffuse, colicky, abdominal pain and obstipation over the last 2 days. He denied fever or jaundice. His past medical history included diabetes mellitus, which was under control with oral hypoglycemic medication, and a similar pain crisis that started 2 weeks ago, which was relieved with oral analgesics prescribed by his GP. His physical examination was normal, except for the presence of diffuse abdominal tenderness. Biochemical and serological investigations were: serum lipase-63U/L (reference range [RR]; 0–160U/L), serum amylase-52U/L (RR up to 140U/L), serum chromogranin 85.35 ng/mL (RR <93 ng/mL) and serum gastrin 60.9pg/mL (RR <100 pg/mL). Random blood sugar and liver function tests were within normal limits. Endoscopic ultrasonography showed a normal pancreatic duct along with a cystic lesion of 3 × 2 cm in the tail of the pancreas, which was confirmed by upper abdominal ultrasonography. A contrast-enhanced computed tomography (CT) scan was subsequently done, which showed a well-defined cystic lesion in the tail of the pancreas with a small enhancing mural nodule (Figure 1A). The contrast-enhanced magnetic resonance imaging (MRI) characterized the lesion with a hyperintensity of the signal on T2-weighted images, and hypointensity on T1-weighted images with internal septations and an enhancing mural nodule (Figure 1B, C, and D).

The remaining pancreatic parenchyma was normal, and the pancreatic duct was not dilated. Based on the imaging study, a diagnosis of a cystic tumor of the

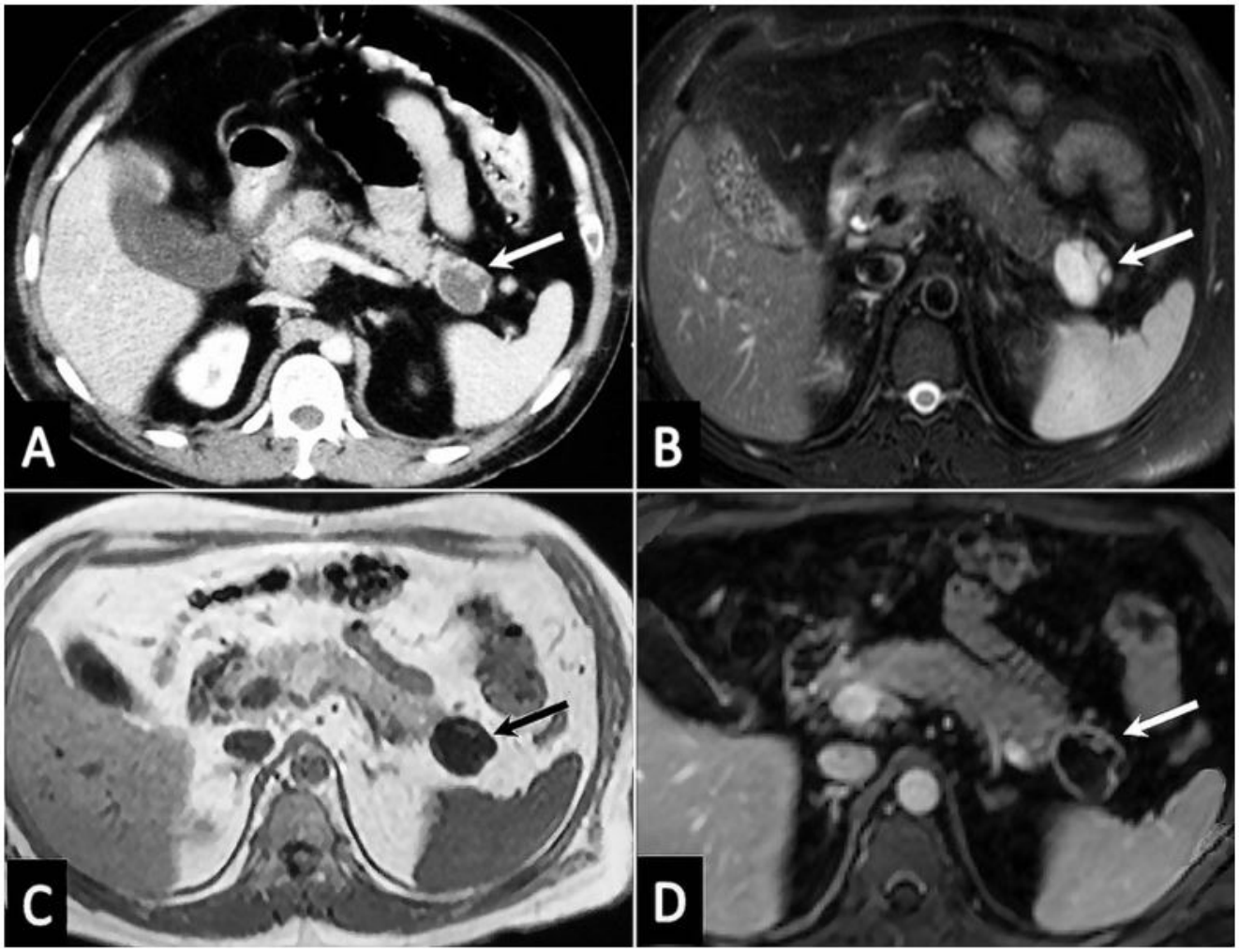

Figure 1. A – Axial contrast-enhanced computed tomography scan showing a cystic lesion in the tail of the pancreas (arrow) with a small mural nodule. Axial T2-weighted fat-saturated (**B**), axial T1-weighted (**C**), and axial contrast-enhanced (**D**) magnetic resonance images showing a cystic lesion (arrow) in the tail of the pancreas with internal septations and a mural nodule.

pancreas—possibly mucinous cystic neoplasm—was made. The patient was prepared for elective surgery. A distal pancreatectomy, splenectomy, and cholecystectomy were performed. Grossly, a well-circumscribed multi-cystic lesion measuring 3 × 2 × 1 cm was identified in the tail of the pancreas (Figure 2).

Histopathological examination of the cyst wall showed a fibrocollagenous cyst wall infiltrated by a tumor. The tumor cells were arranged in nests and ribbons, with a solid focal pattern, and were small, monomorphic with granular nuclear chromatin and abundant granular eosinophilic cytoplasm (Figures 3 and 4A). No atypical mitosis was identified. Further, immunohistochemistry showed positivity for synaptophysin (Figure 4B) and chromogranin (Figure 4C). The Ki-67 labeling index was 3% in the highest proliferating areas (Figure 4D). Based on these features, a diagnosis of neuroendocrine tumor Grade 2 with cystic change was suggested. The postoperative period was uneventful, and the patient was discharged on the fourth postoperative day. He remains under close follow-up and is currently doing well.

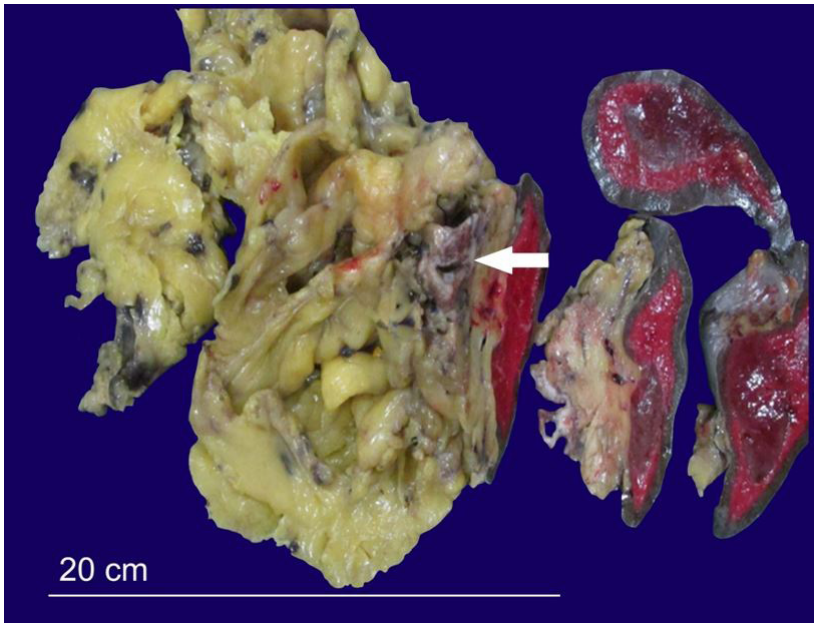

Figure 2. Gross appearance of the pancreatic tumor. A well-circumscribed cystic lesion measuring 3 × 2 × 1 cm is depicted in the tail of the pancreas.

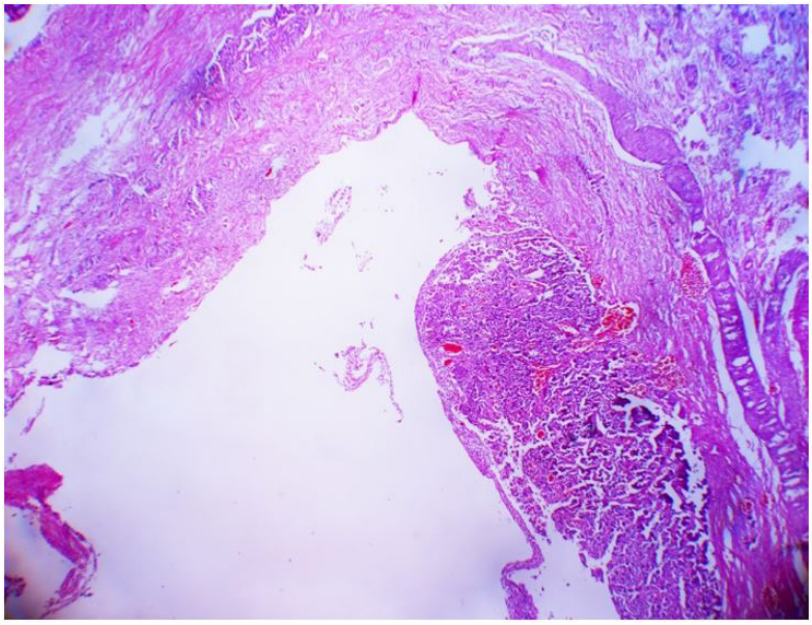

Figure 3. Photomicrograph of the cystic tumor showing a large cystic tumor with a focal lobular arrangement of tumor cells in the cyst wall (H&E, 4X).

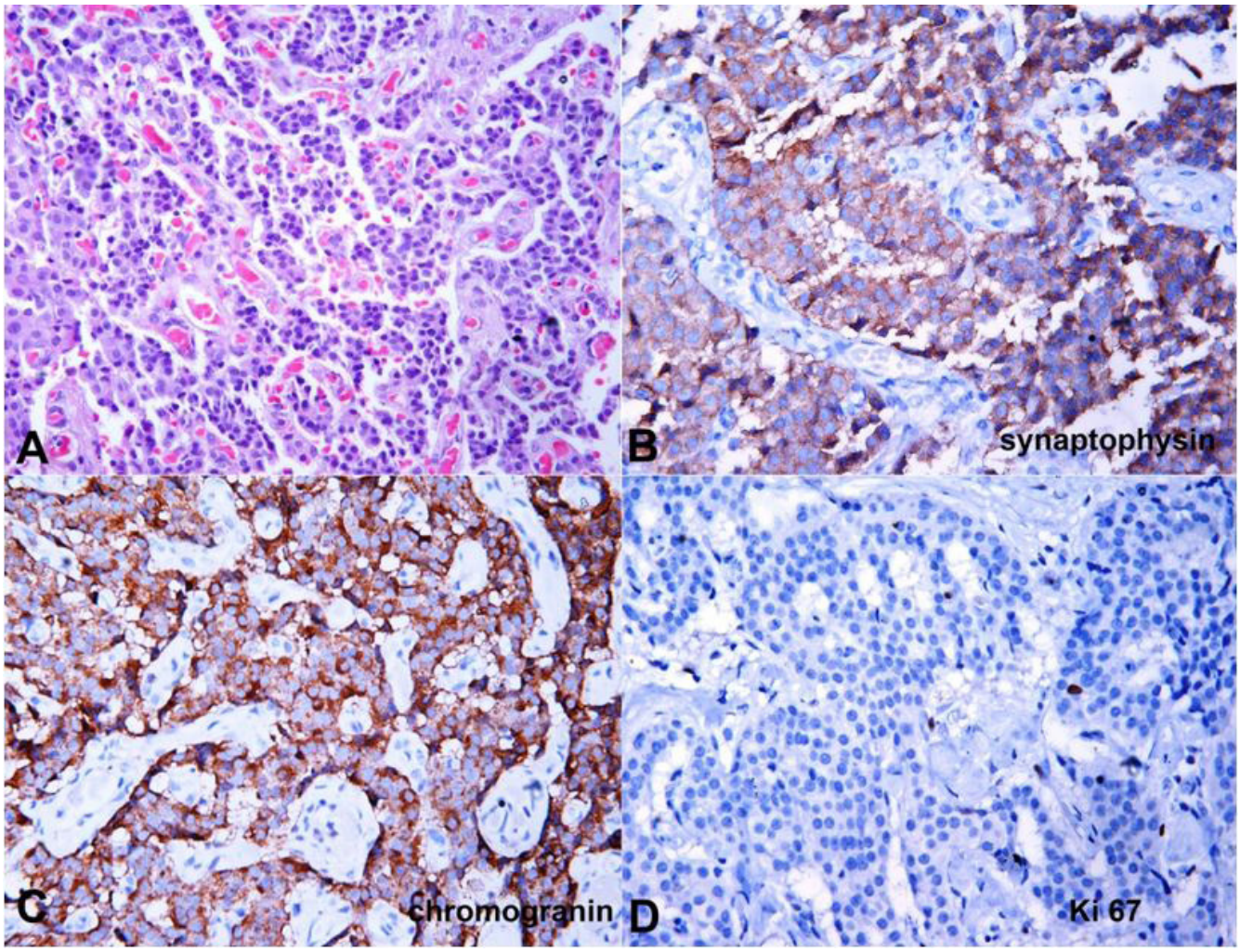

Figure 4. Photomicrographs of the tumor. **A** – Lobular arrangement of tumor cells (H&E, 40X); **B** – Immunopositivity for synaptophysin (40X); **C** – Immunopositivity for chromogranin (40X); **D** – Ki-67 labeling 3% (40X).

DISCUSSION

Since the first description of a cystic PanNET by Thigpen in 1940,[9] the debate on whether this is a separate entity or an NET with secondary degenerative changes remains unsolved. The cystic PanNET comprises only 2%–8% of all resected pancreatic cystic neoplasms.[10-12] Kamisawa et al.[13] proposed that the slow-growing PanNETs develop a fibrous capsule, which eventually restricts the tumor blood supply, resulting in infarction and necrosis, ultimately leading to the formation of the cyst. Iacono et al.[14] and Takeshita et al.[15] proposed that bleeding within this vascular tumor may be the reason behind the cyst formation. Buetow et al.[16] hypothesized that the presence of a cystic change or necrosis was correlated with the large tumor size (mean 7.9 cm), based on their series of 133 cases of PanNETs. In contrast, our index case presented a tumor size of 3.5 cm at its longest axis, and we did not identify any residual area of necrosis.

Cystic PanNETs can be sporadic, nonfunctioning, and solitary; they are discovered incidentally and seen in the sixth or seventh decade of life with a relatively equal sex distribution.[7,17] The tumors associated with MEN type 1 syndrome, occur in younger patients, are usually multiple, and glucagon-producing.[18] The cystic PanNETs were commonly identified in the pancreatic tail, whereas the solid counterparts are commonly found in the pancreatic head by Singhi et al.[4] Most of these cystic PanNETs have a single, thin-walled locule, which is centrally or eccentrically placed and is surrounded by a rim of neoplastic parenchyma. These cysts contain a clear-to-straw-colored fluid, while the larger cysts content is hemorrhagic. Like the index case, tumor necrosis, perineural or vascular invasion, regional lymph

node metastases, and synchronous distant metastases are not evident compared to solid PanNETs.[4] According to the American Joint Committee on Cancer's *Cancer Staging Manual* (7th edition)[19] prognostic staging system and the European Neuroendocrine Tumor Society, cystic PanNETs have a lower pathological stage and show low Ki-67 proliferation index compared to solid PanNETs. Precise preoperative diagnosis with conventional axial imaging, such as CT and MRI are challenging. The differential diagnoses considered in the literature comprise (i) mucinous cystic neoplasms; (ii) intraductal papillary mucinous neoplasms; (iii) serous cystic neoplasms; (iv) solid pseudopapillary neoplasms; (v) acinar cell carcinoma; and (vi) non-neoplastic cysts, including simple cysts and pseudocysts.[7,20] As the clinical management of different cystic neoplasms of the pancreas varies, preoperative diagnosis is of the utmost importance. In recent times newer diagnostic modalities, such as endoscopic ultrasound coupled with fine-needle aspiration, have been utilized in an attempt to preoperatively diagnose cystic pancreatic lesions. This new diagnostic modality not only renders the exact anatomical details of these lesions, but also enables the cytological, biochemical, and immunocytological analysis. Recently, a subset of tumors harboring mutations within the mammalian target of rapamycin pathway was identified. Everolimus, a TOR pathway inhibitor, has thus been shown to increase progression-free survival in a subset of PanNET patients.[21]

In summary, cystic PanNETs are a distinctive subgroup of PanNETs with unique clinical and pathologic features. Because of their cystic nature, these neoplasms often pose a diagnostic dilemma for the gastroenterologists, radiologists, and pathologists. Hence, awareness of this entity can aid the correct diagnosis. Upcoming genetic studies might also clarify new ways on the pathogenesis and possible treatment strategies for these neoplasms.

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