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**Nonfunctional pancreatic neuroendocrine tumours misdiagnosed as autoimmune pancreatitis: A case report and review of literature**

Lin ZQ *et al*. Nonfunctional PNETs misdiagnosed as AIP

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**Abstract**

BACKGROUND

Nonfunctional pancreatic neuroendocrine tumours are difficult to diagnose in the early stage of disease due to a lack of clinical symptoms, but they can rarely manifest as autoimmune pancreatitis. Autoimmune pancreatitis is an uncommon disease that may cause recurrent acute pancreatitis and is therefore often regarded as a special type of chronic pancreatitis.

CASE SUMMARY

We report a case of a 42-year-old female who had nonspecific upper abdominal pain for 4 years and radiological abnormalities of the pancreas that mimicked autoimmune pancreatitis. The symptoms and pancreatic imaging did not improve following 1 year of steroid therapy. Finally, pancreatic biopsy was performed through endoscopic ultrasonography-guided fine-needle aspiration biopsy, and nonfunctional pancreatic neuroendocrine tumours were ultimately diagnosed. Pancreatectomy has resolved her symptoms.

CONCLUSION

Therefore, the differentiation of nonfunctional pancreatic neuroendocrine tumours from autoimmune pancreatitis is very important, although it is rare. We propose that endoscopic ultrasonography-guided fine-needle aspiration biopsy should be performed if imaging characteristics are equivocal or the diagnosis is in question.

**Key Words:** Pancreatic neuroendocrine tumour; Nonfunctional pancreatic neuroendocrine tumour; Autoimmune pancreatitis; Endoscopic ultrasonography-guided fine needle aspiration biopsy; Case report

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**Core Tip:** We report a case of a 42-year-old female patient who suffered from nonfunctional pancreatic neuroendocrine tumours but was misdiagnosed for 4 years. After the 3-year follow-up, she was misdiagnosed with autoimmune pancreatitis through radiography and underwent 1 year of corticosteroid therapy. However, her symptoms worsened. Biopsy *via* endoscopic ultrasonography-guided fine needle aspiration biopsy made a correct diagnosis of nonfunctional pancreatic neuroendocrine tumours, and pancreatectomy resolved the symptoms. Therefore, we propose that endoscopic ultrasonography-guided fine needle aspiration biopsy should be performed if imaging characteristics are equivocal or the diagnosis is in question.

**INTRODUCTION**

Pancreatic neuroendocrine tumours (PNETs) are uncommon and account for 1%-2% of all pancreatic neoplasms[[1](#_ENREF_1)], with annual worldwide incidences of approximately 3.2 cases per million in 2003 and 8 cases per million in 2012[[2](#_ENREF_2)]. PNETs are composed of both functional and nonfunctional PNETs. Functioning PNETs are often characterized by symptoms caused by hormone secretion, such as hypoglycaemia, multiple peptic ulcers, and diarrhoea, which enable early diagnosis. Nonfunctional PNETs are difficult to diagnose in the early stage due to a lack of typical clinical symptoms. Autoimmune pancreatitis (AIP) is also a rare disease that may cause recurrent acute pancreatitis and is recognized as a special type of chronic pancreatitis[[3](#_ENREF_3" \o "Nagpal, 2018 #21)]. Although many guidelines and management strategies for AIP have been developed and published in recent years, it is clinically difficult to differentiate between AIP and pancreatic cancer, especially with diffusely enlarged pancreatic tumours. Here, we report a case of pancreatic endocrine neoplasm that was misdiagnosed as AIP for many years.

**CASE PRESENTATION**

***Chief complaints***

A 42-year-old female suffered from nonspecific upper abdominal pain for 4 years, without fever or weight loss. The patient’s symptoms had worsened for 1 year.

***History of present illness***

When the patient first suffered from upper abdominal pain, she was diagnosed with chronic gastritis and treated with stomach-protective drugs for 6 mo, with no significant relief. Due to her nonspecific upper abdominal pain, the patient underwent abdominal magnetic resonance imaging (MRI) every year from 2015 to 2017. MRI demonstrated diffuse pancreatic enlargement, expansion of the main pancreatic duct, enhancement of the parenchyma, no obvious mass and clear peripancreatic fat space. No obvious abnormalities were found in the liver, gallbladder, spleen or kidneys (Figure 1A-C). She was then diagnosed with chronic pancreatitis and received pancreatic enzyme replacement therapy, which did improve her symptoms. Since then, her symptoms appeared recurrently and were relieved with oral enzyme supplementation. One year ago, her abdominal pain was aggravated, and she experienced jaundice, at which time she was diagnosed with “autoimmune pancreatitis” at a local hospital. After taking methylprednisolone tablets and ursodeoxycholic acid, her condition was slightly improved and maintained with methylprednisolone 16 mg/d for 1 year until she was admitted to our hospital when her symptoms worsened.

***History of past illness***

The patient was a healthy person without diabetes, hypertension or other underlying diseases.

***Personal and family history***

The patient had no family history.

***Physical examination***

Physical examination showed slight abdominal tenderness, no rebound tenderness and no tension.

***Laboratory examinations***

For further diagnosis and treatment, we performed a series of laboratory and imaging examinations. Liver function tests, such as serum alanine aminotransferase and aspartate transaminase, were slightly above normal limits (alanine aminotransferase, 100 IU/L and aspartate transaminase, 89 IU/L). However, amylase and lipase were within normal limits. The serum immunoglobulin G4 (IgG4) level was normal at 0.217 g/L (0.035-1.500 g/L), and the antinuclear antibody spectrum was negative. Serum tumour markers, including carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9), were high, at 4.21 ng/mL (normal < 3.4 ng/mL) and 153.2 U/mL (normal < 22 U/mL), respectively. Retrospective analysis of the results of laboratory tests of the patient from 2016 to 2018 found that alanine aminotransferase and aspartate transaminase were slightly higher than normal, fluctuating at approximately 100-150 IU/L and 70-100 IU/L, respectively. Her CA19-9 was becoming increasingly elevated (from 38.20 to 153.2 U/mL). IgG4 was negative from 2016 to 2018. The patient’s fasting blood sugar levels were normal.

***Imaging examinations***

MRI (Figure 2A) at this admission showed a lesion at the head of the pancreas with sausage-like diffuse enlargement; gallbladder and common bile duct enlargement (common bile duct diameter: 2.0 cm) were also present. Suspicious lymph nodes and additional liver metastasis were not found. Compared with previous images, pancreatic enlargement progressed. Enlarged gallbladder without lithiasis or thick wall and dilation of the main pancreatic duct due to an oval mass located in the head of the pancreas, which was well defined. Abdominal multi-detector computed tomography (MDCT) also revealed similar findings to MRI, and no substantial space occupying lesion was found (Figure 2B). Although imaging showed diffuse enlargement of the pancreas, the head of the pancreas was predominant and heterogeneous. The patient had dull upper abdominal pain with jaundice only once and never suffered from acute pancreatitis. After 1 year of steroid therapy, pancreatic enlargement showed no change, and CA19-9 increased every year. We doubted the original AIP diagnosis and considered the possibility of a pancreatic tumour. Then we performed abdominal endoscopic ultrasonography (EUS). It confirmed the diffuse enlargement of the pancreas. However, the nature of the enlargement remains unknown. EUS-guided fine needle aspiration biopsy (EUS-FNA/FNB) was performed from the pancreas head.

**FINAL DIAGNOSIS**

The pathological examination showed tumour cells. Immunohistochemistry (IHC) of EUS-FNA/FNB demonstrated chromogranin A (CgA) (+), synaptophysin (+), pan-cytokeratin (+), Ki-67 (MIB-1) (approximately 10%+), somatostatin (-), gastrin (-), insulin (-), glucagon (-) and IgG4 (-) (Figure 3). According to the World Health Organization classification[[4](#_ENREF_4" \o "Rindi, 2018 #9)], pancreatic neuroendocrine tumour was diagnosed.

**TREATMENT**

Methylprednisolone treatment was stopped for 1 mo, and pancreatectomy was arranged. Before pancreatectomy, computed tomography angiography was undertaken to establish whether the lesion had invaded the vascular structures. The computed tomography angiography showed tumour lesions in the head of the pancreas. The gallbladder was still enlarged, and the maximum diameter of the common bile duct reached 3.4 cm with the upper segment compressed and narrowed. The porta hepatis and intrahepatic bile ducts were all significantly dilated. The main portal vein was slightly dilated with a diameter of approximately 2.0 cm. There was local compression of the portal vein, and the splenic vein and right renal artery and vein were all narrowed, accompanied by multiple tortuous blood vessels shadowed around the stomach and spleen portal area.

The patient finally underwent total pancreatectomy on 28November 2018, and no hepatic metastasis was found. IHC showed CgA (+), synaptophysin (+), pan-cytokeratin (+), CD56 (+), CK7 (+), CK20 (+), Ki-67 (MIB-1) (+, 3%-7%), epithelial membrane antigen (-), CD10 (-), D2-40 (-), inhibin (-), somatostatin (-), gastrin (-), insulin (-) and glucagon (-) (Figure 4), which is compatible with a neuroendocrine tumour (Grade 2) according to the World Health Organization classification[[4](#_ENREF_4)]. Combined with the patient’s symptoms, these findings support the diagnosis of nonfunctional PNET.

**OUTCOME AND FOLLOW-UP**

The patient recovered well after the operation and required long-term oral pancreatin enteric-coated capsules.

**DISCUSSION**

Here, we first report a case of nonfunctional PNET misdiagnosed as AIP for many years. Most previous studies showed that AIP [mimicked neuroendocrine tumours or pancreatic cancer[[5](#_ENREF_5),[6](#_ENREF_6)].](https://pubmed.ncbi.nlm.nih.gov/22423237/) To avoid misdiagnosis and delay the timing of the operation, differentiation of nonfunctional PNETs from AIP is very important, although it is rare. The clinician should attach importance to this evaluation.

Nonfunctional PNETs are defined by the absence of hormone hypersecretion syndrome[[1](#_ENREF_1" \o "Howe, 2020 #32),[7](#_ENREF_7)]. Some recent studies have indicated that approximately 60%-90% of PNETs are nonfunctional and are generally diagnosed at late stages due to the lack of typical clinical symptoms[8,9]. A multicentre observational study showed that 32% of nonfunctional PNETs had liver metastases at first diagnosis[[10](#_ENREF_10" \o "Zerbi, 2010 #10)], and other studies showed that 60% presented distant metastases and usually hepatic metastases[[11](#_ENREF_11)]. The 5-year survival rate of nonfunctional PNETs is 43%, and the median overall survival of nonfunctional PNETs is 38%[[7](#_ENREF_7" \o "Falconi, 2012 #14)]. Hepatic metastasis is a major predictor of poor survival[[12](#_ENREF_12" \o "Mignon, 2000 #15)]. If symptoms appear, the common symptoms are abdominal pain (35%-78%), weight loss (20%-35%) and anorexia and nausea (45%), while intra-abdominal bleeding (4%-20%), jaundice (17%-50%) or palpable masses are less common (7%-40%)[[13-15](#_ENREF_13" \o "Matthews, 2000 #11)]. The positivity of synaptophysin and CgA by IHC indicates neuroendocrine origin[[7](#_ENREF_7" \o "Falconi, 2012 #14)]. Based on proliferation assessed by mitotic count and Ki-67 index from the 2018 World Health Organization classification, PNETs were divided into three tiers (G1, G2 and G3)[[4](#_ENREF_4)], and this patient was G2.

AIP is a special form of chronic pancreatitis and has a low incidence[[3](#_ENREF_3" \o "Nagpal, 2018 #21)]. Recently one study showed AIP has an annual incidence rate of 3.1 per 100000 persons in Japan[[16](#_ENREF_16" \o "Masamune, 2020 #48)]. The clinical manifestation of AIP is not severe abdominal pain, but it is often seen in acute pancreatitis or acute exacerbation of chronic pancreatitis. Some AIP patients suffer only mild or almost no abdominal pain[[17](#_ENREF_17" \o "Kamisawa, 2005 #31),[18](#_ENREF_18)]. Approximately 33%-59% of AIP patients have obstructive jaundice, 15% of them have back pain or weight loss, and 15% of patients have no symptoms[[19](#_ENREF_19" \o "Okazaki, 2010 #33)]. Therefore, it is difficult to distinguish AIP from nonfunctional PNET in terms of symptoms. The whole course of this case we presented here was manifested only by atypical abdominal pain and one occurrence of jaundice, without weight loss or onset of acute pancreatitis. All of these factors make diagnosis difficult.

Recently, the development of high-quality imaging techniques has led to increased incidental diagnoses of nonfunctional PNETs[[20](#_ENREF_20" \o "Lee, 2017 #16),[21](#_ENREF_21)]. MDCT usually shows circumscribed hypervascular solid masses that rarely obstruct the pancreatic duct. Smaller lesions are usually homogeneous, and larger lesions are more likely to have heterogeneous enhancement[[7](#_ENREF_7" \o "Falconi, 2012 #14)]. Diffusion-weighted imaging MRI may be more sensitive than MDCT for detecting smaller lesions and liver metastases, which often show lower signal intensity than normal pancreatic tissue in fat-suppressed T1-weighted images and high signal intensity on T2-weighted images[[7](#_ENREF_7),[22](#_ENREF_22),[23](#_ENREF_23)]. Abdominal characteristic MDCT images of AIP normally show diffuse enlargement of the pancreas, referred to as sausage-shaped, with delayed enhancement and with a band-like structure that appears to surround all or part of the lesions, termed a “capsule-like rim”[[24](#_ENREF_24)], which may be present in only approximately 30%-40% of AIP patients[[25](#_ENREF_25)]. MRI for AIP includes diffuse hypointensity on T1-weighted images and slight hyperintensity on T2-weighted images[[3](#_ENREF_3" \o "Nagpal, 2018 #21)]. Compared with MDCT scans, MRI provides better tissue contrast and plays an important role in the diagnosis of AIP[[26](#_ENREF_26" \o "Takahashi, 2020 #23)].

It is difficult to distinguish nonfunctional PNETs from AIP due to the lack of typical imaging changes and liver metastasis, especially large diffuse swelling in this case. MDCT showed only a diffusely enlarged pancreas, especially in the head of the pancreas, and no typical “capsule-like rim.” MRI of the patient in 2015 showed a diffusely enlarged pancreas, and it seemed to have a ‘‘capsule-like rim’’ of a peripancreatic lesion, though not a typical one. Swollen pancreas showed a higher signal than the liver in T2-weighted images (Figure 1A). There were no significant changes during 2016 and 2017, and misdiagnosis based on conventional pancreatic imaging seems unavoidable.

Somatostatin receptor scintigraphy is a whole-body functional imaging method with 111indium isotope-labelled pentetreotide and shows significantly higher sensitivity than CT/MRI[[27](#_ENREF_27" \o "Schillaci, 2003 #28)]. Recently, newer functional imaging studies utilizing positron emission tomography with 68Ga and 18F-DOPA have shown promising results that may be superior to conventional somatostatin receptor scintigraphy[[28](#_ENREF_28" \o "Cloyd, 2015 #29),[29](#_ENREF_29)]. The North American Neuroendocrine Tumour Society Consensus recommends that somatostatin receptor-positron emission tomography imaging should replace 111indium-pentetreotide scanning[[1](#_ENREF_1" \o "Howe, 2020 #32)] for identifying primary tumours and the extent of metastatic disease. However, these functional imaging techniques were not applied to this case.

CgA is a commonly used biomarker present in both tumours and blood for diagnosis in a fraction of nonfunctional PNETs and when evaluating response to therapy[[30](#_ENREF_30" \o "Falconi, 2016 #17)]. CgA is a glycoprotein, similar to secretory granulosin, present in secretory granules that store peptide hormones and catecholamines throughout the neuroendocrine system. However, CgA is also elevated in chronic renal or liver failure or patients treated with proton-pump inhibitors[[28](#_ENREF_28" \o "Cloyd, 2015 #29),[31](#_ENREF_31)]. Another controversial biomarker is pancreatic polypeptide, which may be useful for the early detection of pancreatic tumours in multiple endocrine neoplasia type 1[[7](#_ENREF_7)]. However, CgA and pancreatic polypeptide were not tested in this patient. IgG4, a biomarker for type 1 AIP[[3](#_ENREF_3" \o "Nagpal, 2018 #21)], was tested, but the levels were not high in this patient. In contrast, the serum CA19-9 level continued to increase in this case and is an important tumour biomarker for the early diagnosis of pancreatic cancer[[32](#_ENREF_32" \o "Wang, 2014 #19),[33](#_ENREF_33)]. The progressive increases in these tumour markers may prompt physicians to highly suspect the possibility of pancreatic tumours, but further investigation is required.

In fact, ultrasound (US) is a first-line examination for abdominal discomfort. However, the operator-sensitive modality is highly subjective, leading to wide variation regarding sensitivity and specificity. Only a mean of 39% (range 17%–79%) of PNETs were detected[[34](#_ENREF_34" \o "Sundin, 2009 #37)]. The recent new technology of contrast-enhanced US, which can allow continuous evaluation of tumour enhancement patterns in the arterial, venous, and late phases, has led to improvement in the diagnostic capabilities, especially in the detection of liver metastases[[34](#_ENREF_34),[35](#_ENREF_35)]. EUS can obtain the histological characteristics of gastrointestinal hierarchical structure and ultrasound images of the surrounding organs and is recognized as one of the most important preoperative procedures in the evaluation and management of PNETs[[36](#_ENREF_36),[37](#_ENREF_37)]. First, EUS can detect lesions smaller than 2 cm to 3 cm in diameter, which are not often detected by CT[[38](#_ENREF_38" \o "Khashab, 2011 #45)]. In many systematic reviews, EUS identified PNETs in over 90% of cases[[34](#_ENREF_34" \o "Sundin, 2009 #37),[39](#_ENREF_39)]. More importantly, tissue specimens can be obtained by FNA through EUS. For this case, the patient was in a long-term outpatient follow-up in another department of our hospital, and MRI was performed every year since 2015. To have a better comparison, we considered MRI review. Therefore, the patient did not undergo a basal US examination first.

For lesions in the biliopancreatic region suggested by imaging, multidirectional and comprehensive analysis combined with an evaluation of clinical symptoms is needed. We should not ignore the suggestive role of imaging. Without any clinical symptoms, pancreatic enlargement is often found by imaging physical examination, such as intraductal papillary mucinous neoplasm[[40](#_ENREF_40" \o "Qin, 2021 #47)]. One study showed the case of a patient with nonfunctioning well-differentiated neuroendocrine carcinoma of the head of the pancreas associated with extrahepatic cholangiocarcinoma by MRI and confirmed by surgery[[41](#_ENREF_41" \o "Maurea, 2011 #44)]. In this case, EUS was ultimately selected according to the imaging changes of MRI over the years.

The pancreatic tissue was obtained by EUS-FNA/FNB, and nonfunctional PNETs were ultimately confirmed by IHC in this case. EUS-FNA/FNB is a safe, less traumatic and more valuable technique for the detection, localization and diagnosis of identified lesions by imaging. EUS-FNA/FNB not only has higher sensitivity for PNETs but also detects lesions ranging from 4 cm to 10 cm[[34](#_ENREF_34),[42](#_ENREF_42)] and provides additional information (*e.g.*, distance from the main pancreatic duct and the Ki-67 proliferation index) for proper therapeutic management[[43](#_ENREF_43)].

**CONCLUSION**

In summary, we report a nonfunctional PNET misdiagnosed as AIP. If imaging characteristics are equivocal or if the diagnosis is in question, EUS-FNA/FNB should be performed as soon as possible to confirm the diagnosis and to avoid delaying treatment.

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**Footnotes**

**Informed consent statement:** This study was reviewed and approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University [No. 2021(407)]. The Patient was not required to provide informed consent because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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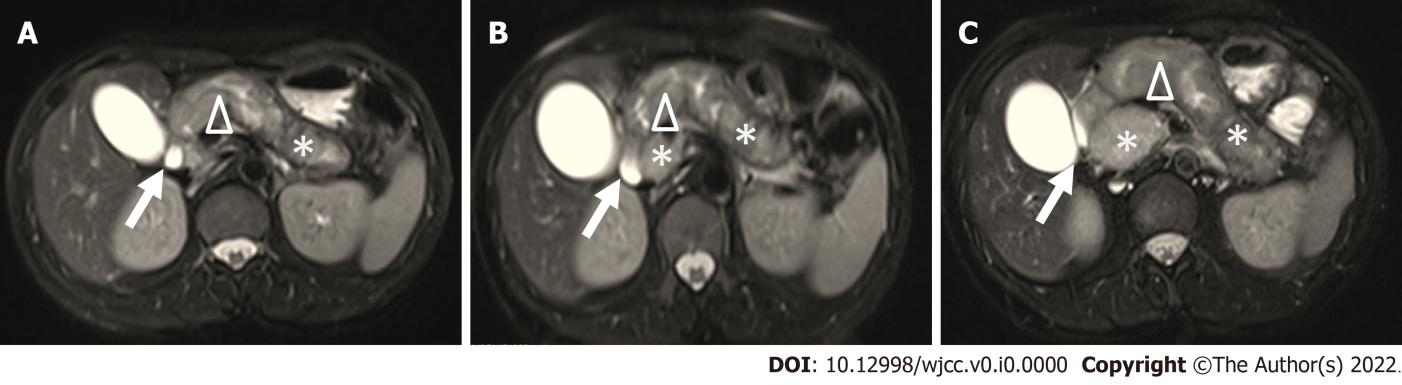
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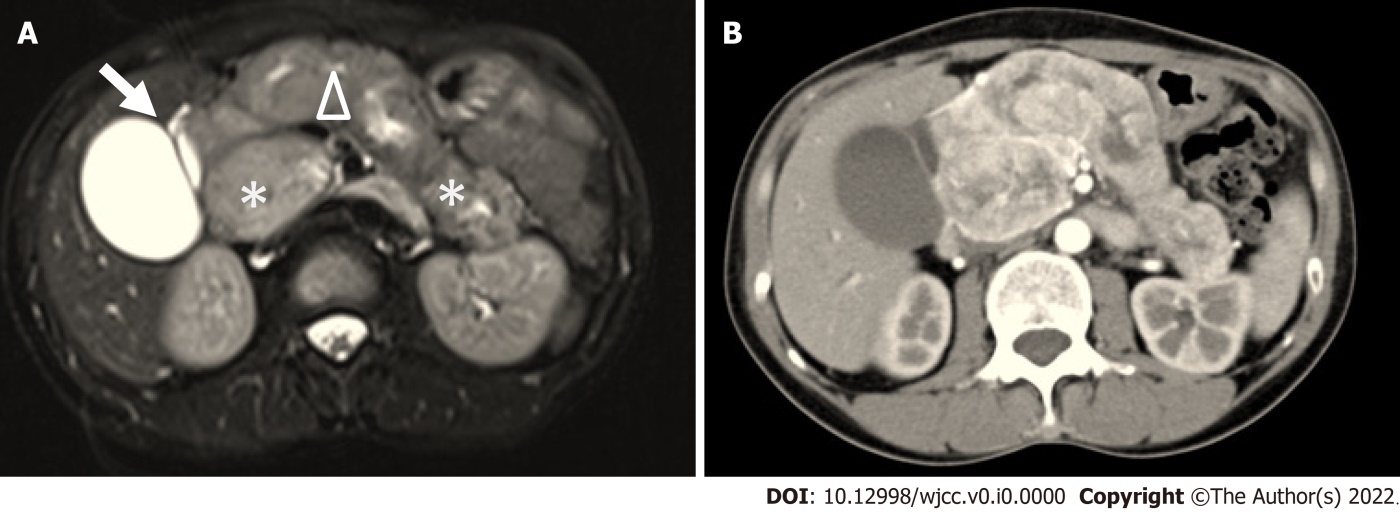
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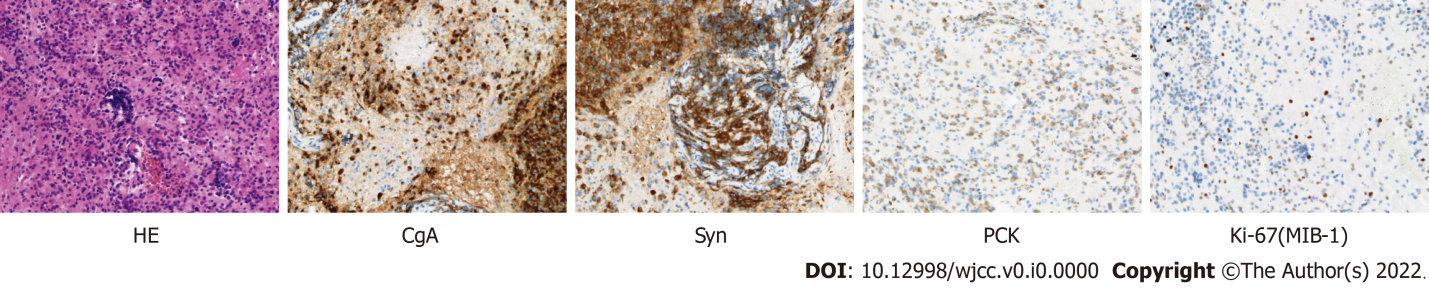
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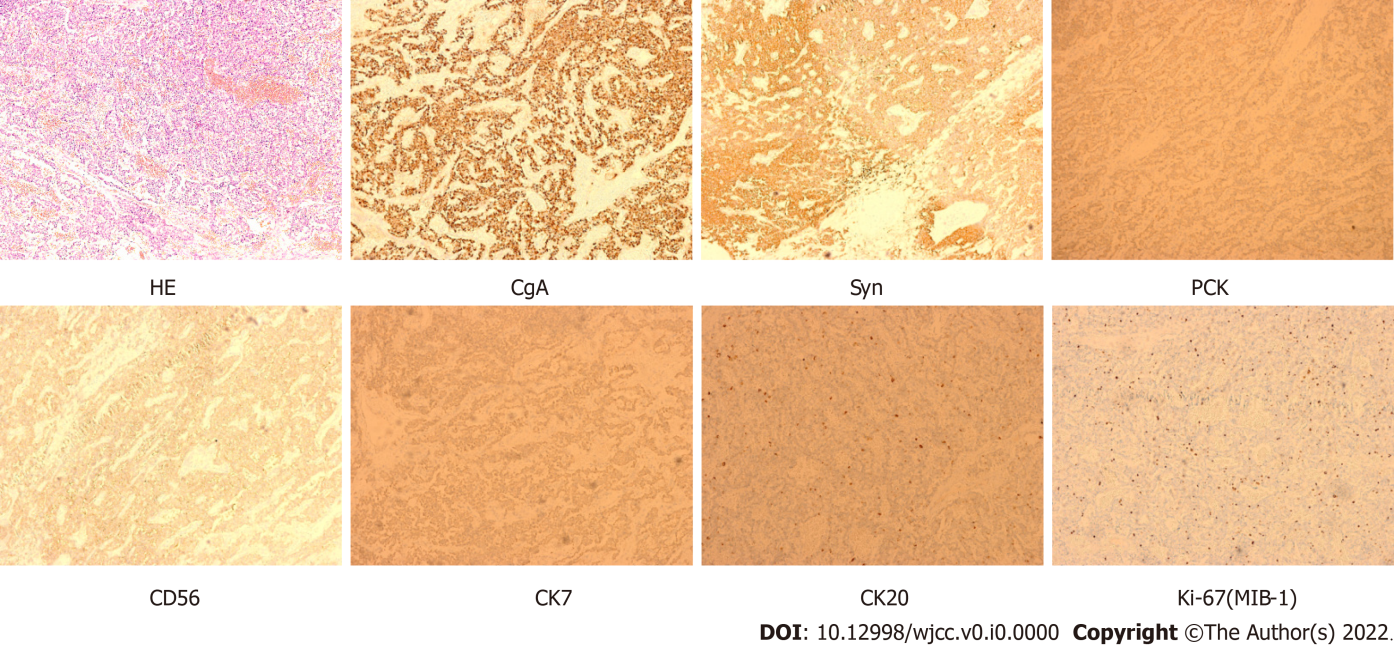
**Figure 1 Abdominal magnetic resonance imaging from 2015 to 2017.** A: Magnetic resonance imaging (MRI) in 2015. Axial post-contrast T2-weighted fat saturated MRI in pancreatic phase showed enlarged pancreas with diffuse homogenous enhancement (\*). The main pancreatic duct (triangle) and common bile duct (arrow) appear slightly dilated; B: MRI in 2016. Axial post-contrast T2-weighted fat saturated MRI in pancreatic phase showed enlarged pancreas with diffuse homogenous enhancement (\*). The main pancreatic duct (triangle) appeared irregularly dilated, and the common bile duct showed mild dilatation (arrow); C: MRI in 2017. Axial post-contrast T2-weighted fat saturated MRI in pancreatic phase showed enlarged pancreas with diffuse homogenous enhancement (\*). The head of the pancreas showed obvious swelling (\*). The main pancreatic duct (triangle) appeared irregularly expanded, and the common bile duct showed compression (arrow).



**Figure 2 Abdominal imaging in 2018.** A: Abdominal magnetic resonance imaging. Axial post-contrast T2-weighted fat saturated magnetic resonance imaging in pancreatic phase showed enlarged pancreas with diffuse uneven homogenous enhancement and sausage-like diffuse enlargement, especially in the pancreatic head (\*). The main pancreatic duct (triangle) appeared irregularly dilated. The gallbladder and common bile duct showed compression (arrow); B: Multi-detector computed tomography. Axial post-contrast arterial phase in pancreatic phase showed no substantial space occupying lesion.



**Figure 3 Immunohistochemical imaging of the pancreas from endoscopic ultrasonography-guided fine needle biopsy.** Hematoxylin and eosin stain showed pancreatic tissue (× 200); immunohistochemical staining showed chromogranin A (+), synaptophysin (+), pan-cytokeratin (+) and Ki-67 (MIB-1) (about 10%+) in the pancreatic tissue by endoscopic ultrasonography-guided fine needle biopsy. (× 200). HE: Hematoxylin and eosin; CgA: Chromogranin A; Syn: Synaptophysin; PCK: Pan-cytokeratin.



**Figure 4 Immunohistochemical imaging of the pancreas from pancreatectomy.** Hematoxylin and eosin stain showed pancreatic tissue (× 200). immunohistochemical staining showed chromogranin A (+), synaptophysin (+), pan-cytokeratin (+), CD56 (+), CK7 (+), CK20 (+) and Ki-67 (MIB-1) (+, 3%-7%), (× 200). HE: Hematoxylin and eosin; CgA: Chromogranin A; Syn: Synaptophysin; PCK: Pan-cytokeratin.