



Mixed neuroendocrine nonneuroendocrine neoplasms of the pancreas: a case report and literature review of pancreatic mixed neuroendocrine nonneuroendocrine neoplasm

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Abstract: A 36-year-old woman underwent left lateral hepatic lobectomy and tumor enucleation of the pancreatic head due to the diagnosis of mixed neuroendocrine nonneuroendocrine neoplasms (MiNENs). Her past medical history revealed an ill-defined mass in the pancreatic uncinate (approximately 1 cm in size) and liver nodules in segment II, suggesting a pancreatic neuroendocrine tumor (pNET) and liver metastases. After the operation, pathological examination showed that the lesion in the pancreas was MiNEN. The neuroendocrine component consisted of grade 1 (G1) NETs, and the nonneuroendocrine part was well-differentiated adenocarcinoma. Additionally, in hepatic lesions, the type of pancreaticobiliary duct in moderately differentiated adenocarcinoma indicated the source of tumor cells. We present the following case in accordance with the CARE reporting checklist. MiNENs of the pancreas are extremely rare and heterogeneous malignancies. Owing to the rarity of pancreatic MiNEN, no structured guidelines on preoperative diagnostics, therapy and follow-up exist thus far. Thus, problems in differential diagnosis and appropriate therapy may arise when treating suspected MiNEN patients. We performed a rigorous search on pancreatic MiNEN via PubMed and Web of Science. In total, 167 studies were identified, and 28 cases in 15 studies about pancreatic MiNEN were assessed. All the available information was listed and fully discussed.

Keywords: Mixed neuroendocrine nonneuroendocrine neoplasm (MiNEN); pancreas; pancreatic mixed neuroendocrine nonneuroendocrine neoplasm; case report

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Introduction

Mixed neuroendocrine nonneuroendocrine neoplasm (MiNEN) in the pancreas is an extremely rare and heterogeneous malignancy. In 1987, the first classification

of mixed neoplasms with neuroendocrine and nonneuroendocrine components was proposed by Lewin (1). Thirteen years later, Capella *et al.* (2), attempted to standardize the terminology of digestive mixed neoplasms

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and provide a prognostic classification. In the same year, the World Health Organization (WHO) decided to introduce the 'mixed exocrine-endocrine tumor (MEEC)' to define neoplasms consisting of a nonneuroendocrine (exocrine) component and a neuroendocrine component, and the 30% cutoff value for each component was also defined. In 2010, 'MEEC' was replaced by 'mixed adeno-neuroendocrine carcinomas (MANECs)' by the WHO because of the wider real spectrum of mixed neoplasms in the digestive tract, while the cutoff remained. MANEC failed to adequately convey the morphological and biological heterogeneity of digestive mixed neoplasms, so the WHO reclassified MANEC to MiNEN in 2017 (3,4).

MiNENs are defined as mixed neoplasms with both neuroendocrine and nonneuroendocrine components, in which either component represents at least 30% of the lesion. MiNEN are generally thought to have an aggressive nature and to be associated with poor prognosis (5). While MiNEN have been found in several organs (e.g., stomach, intestines, pancreas, biliary tract, appendix, and cervix), the pancreas and gastrointestinal tract are the most common places they are usually found (4,6). In this study, we report a patient with small (~1 cm) primary pancreatic MiNEN with liver metastasis constituted by adenocarcinoma. Informed consent was obtained from the patient. A review of the English literature about pancreatic MiNEN was performed via PubMed (MEDLINE) and Web of Science with a rigorous search strategy (see [Appendix 1](#)). All abstracts, studies, and citations obtained were carefully reviewed by two investigators. In total, 167 articles were identified, and 28 cases in 15 studies about pancreatic MiNEN were assessed, listed, and fully discussed. We present the following case in accordance with the CARE reporting checklist (available at <https://dx.doi.org/10.21037/gs-21-564>).

Case presentation

A 36-year-old woman was admitted to a local hospital due to an ill-defined mass in the pancreatic uncinata (approximately 1 cm in size) and liver nodules in segment II during a regular medical check-up. Further laboratory examination showed a slightly elevated serum carbohydrate antigen 19-9 (CA19-9) level (41.30 U/mL; normal value <37.0 U/mL) but normal AFP and CEA level. She did not present with abdominal pain and distension, nausea, vomiting, diarrhea, or hypoglycemia.

For further treatment, she was referred to our hospital. Enhanced computed tomography (CT) of the abdomen

revealed a markedly enhanced lesion (1.0 cm × 0.9 cm) in the pancreatic head (*Figure 1A*) and a low-density lesion with slight enhancement on the periphery in the liver (*Figure 1B*). The patient underwent abdominal magnetic resonance imaging (MRI) for further evaluation. The MRI revealed a focal nodule with obvious enhancement in the pancreatic head (*Figure 1C*). In the left hepatic lobe, an irregular nodule was found, approximately 17 mm, with edge intensification in the arterial phase, hypointensity in the T1-weighted image (T1WI) and a relatively low apparent diffusion coefficient (ADC) value (*Figure 1D*). According to CT and MR examination, the lesion of the pancreatic head was considered a neuroendocrine tumor (NET), while the nature of the liver was unclear. The majority of pNETs express somatostatin receptors (SSTRs) on cell surfaces, especially in well-differentiated tumors (G1 or G2) with a low Ki-67 index; thus, gallium-68 TATE positron emission tomography/CT (68-Ga-TATE-PET/CT) was considered to assess SSTR expression (7). Then, 68-Ga-TATE-PET/CT was performed and it revealed increased focal TATE uptake in the head of the pancreas (SUV_{max} = 8.5) and no increased TATE uptake in the slightly hypodense lesion of the left liver (*Figure 2*), which confirmed our previous diagnosis of the pancreatic lesion. After a multidisciplinary team (MDT) meeting, liver biopsy was suggested to determine the nature of the lesion. The pathology turned out to be adenocarcinoma.

As previously mentioned, NETs (G1 and G2) normally express SSTR on the cell surface, while the SSTR decreases when tumors become less differentiated and more aggressive. With the decline in SSTR expression, cell glucose utilization increases (8). In ¹⁸F-fluorodeoxyglucose PET/CT (18-F-FDG-PET/CT) images, FDG, as a glucose analog, could visualize glucose metabolic activity. Since the primary lesion was unknown, 18-F-FDG PET/CT was also performed, which showed elevated FDG uptake only in the lesion of the left liver lobe (SUV_{max} = 6.2). Gastroscopy and colonoscopy, as well as gynecological examinations, were then performed to look for possible primary lesions. However, no abnormalities were found.

After another MDT meeting and communication with the patient, we performed a laparoscopic exploration on 8th May 2021. Pancreatic head nodules and hepatic nodules in segment II were found. No peritoneal metastasis was observed. Thus, the patient underwent left lateral hepatic lobectomy and tumor enucleation of the pancreatic head via laparoscopy.

Postoperative pathological examination showed

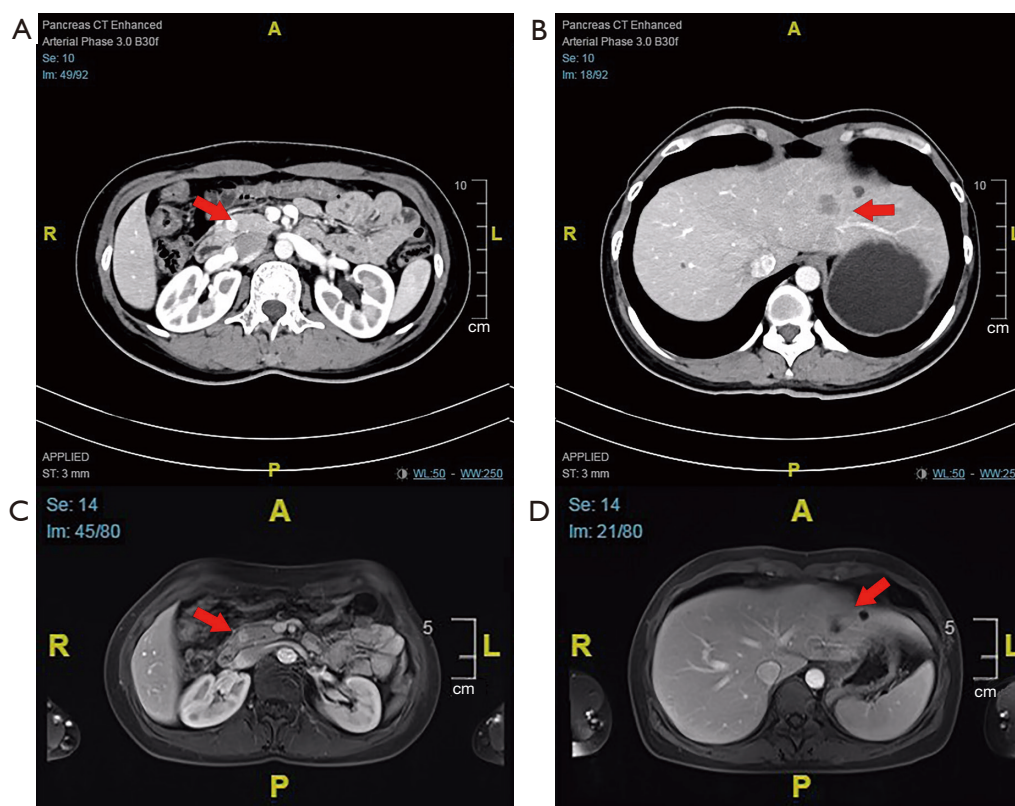


Figure 1 CT scan and MRI. (A) The enhanced CT scan reveals a markedly enhanced lesion in the pancreatic head (1.0 cm \times 0.9 cm). (B) A low-density lesion with slightly enhanced on the periphery of liver in the enhanced CT imaging. (C) MRI revealed a focal nodule with obvious enhancement in the pancreatic head. (D) A nodule (approximately 17 mm) with edge intensifying in arterial phase was found in in the left hepatic lobe on MRI. The arrows indicate the primary tumor in the head of pancreas and the metastatic liver lesion, respectively. CT, computed tomography; MRI, magnetic resonance imaging.

that the hepatic lesions were moderately differentiated adenocarcinoma with a type of pancreaticobiliary duct, while the pancreatic lesion were MiNENs (*Figure 3*). The neuroendocrine component consisted of grade 1 (G1) NETs, and the nonneuroendocrine part was a well-differentiated adenocarcinoma. According to hematoxylin and eosin (HE) staining, the composition of adenocarcinoma accounted for approximately 30%. The neuroendocrine part was immunohistochemically positive for cytokeratin-multi-AE1-AE3 (AE1/AE3), synaptophysin, chromogranin A, insulinoma-associated protein 1 and SSTR type 2 and negative for SSTR type 3. In addition, Ki67 index was approximately 2%. These features indicated NET, G1. Moreover, the hepatic lesions showed moderately differentiated adenocarcinoma with a type of pancreaticobiliary duct. Immunohistochemical results were positive for cytokeratin 7 and cytokeratin 19, but negative

for anti-CDX2 antibody (CDX2-88) and special AT-rich sequence binding protein 2 (SATB2). Due to the presence of liver metastasis, chemotherapy was given. Clinical course of the patient was shown in *Figure 4*.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

MiNENs of the pancreas are extremely rare and heterogeneous malignancies. Based on previous studies,

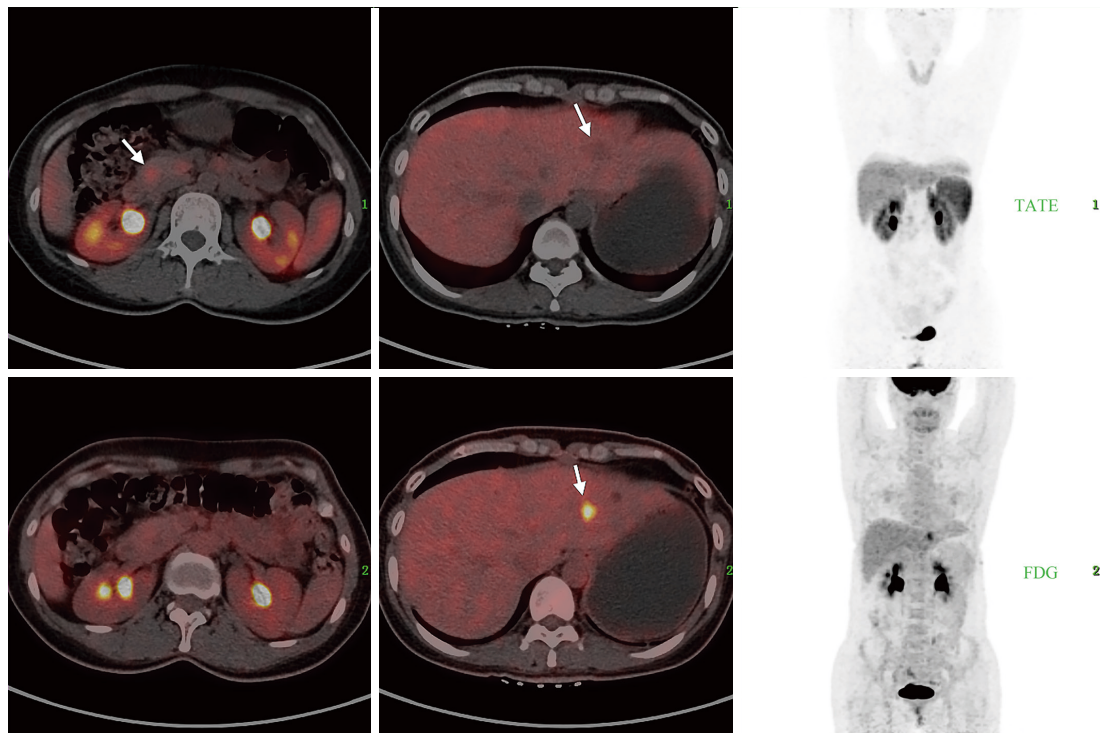


Figure 2 PET/CT scans using ^{68}Ga -TATE and ^{18}F -FDG. The arrows indicate the primary tumor in the head of pancreas and the metastatic liver lesion, respectively. PET/CT, positron emission tomography/computed tomography.

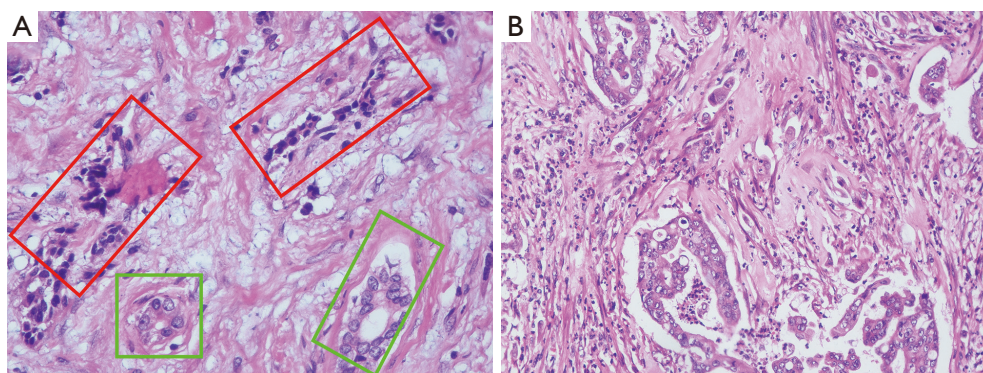


Figure 3 Histopathological findings. (A) The tissue of pancreatic lesion stained with HE (field of view: 10×40). The neuroendocrine component consisting of neuroendocrine tumor and nonneuroendocrine part consisting of adenocarcinoma are in the red-framed and light green-framed areas, respectively. (B) The tissue of hepatic lesion stained with HE (field of view: 10×20). HE, hematoxylin and eosin.

albeit limited and conflicting, MiNEN is an aggressive entity with a high-grade neuroendocrine component in most cases and is associated with poor survival outcomes similar to those of pure neuroendocrine carcinomas (NECs) (9,10). However, in our case, the neuroendocrine component was G1 NETs, which are rarer. Due to the rarity of this diagnosis, evidence from the literature on MiNENs

is almost exclusively derived from case reports and small retrospective series. With inadequate published data, the epidemiology, prognosis, and best therapeutic management of patients with MiNEN remain unknown.

We performed a rigorous search on pancreatic MiNEN cases via PubMed and Web of Science (last search on 14th August 2021). In total, 167 studies were identified

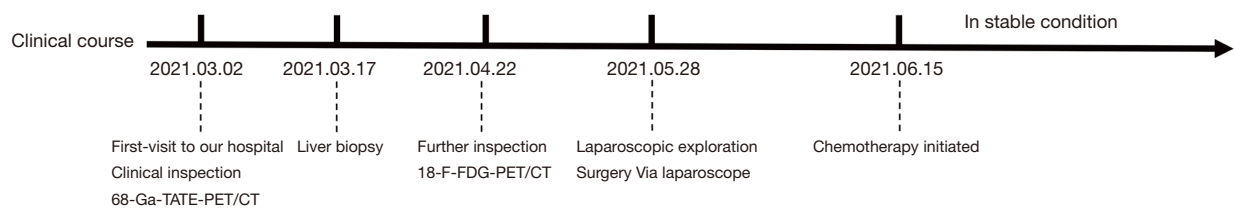


Figure 4 Clinical course of the patient. PET/CT, positron emission tomography/computed tomography.

(66 from PubMed and 101 from Web of Science). After removing duplications, 101 articles underwent title and abstract assessment, of which 34 articles were admitted to the full text screen. An additional related study was found and enrolled while screening the reference lists. Eventually, 28 cases in 15 studies about pancreatic MiNEN were assessed (Table 1). The studies yielded, patient age which ranged from 30 to 82 years (average age was 61.2 years) and the male to female ratio was 3:1. According to the table, MiNEN were located variably in all parts of the pancreas (10 in the head, 5 in the body, 3 in the tail, 7 in the ampulla of Vater and 3 in the uncinata process of the pancreas). Among them, 11 patients presented with metastatic lesions, and 8 of them had liver metastases. While most patients resorted to surgery, unresectable patients received chemotherapy as the main treatment.

Pancreatic MiNEN could arise in any part of the pancreas; for the histogenesis of pancreatic MiNEN, various hypotheses have been proposed. Some studies suggested that associated neuroendocrine and nonneuroendocrine neoplasms in the pancreas may arise from totipotent pancreatic stem cells in the pancreatic duct and islets, while other reporters assumed that dysfunction of numerous tumor suppressor genes resulted in different types of malignancy of MiNEN (13,25-27). In 2014, Scardoni *et al.* (28), suggested a monoclonal origin of the two MiNEN (MANCE) components of the gastrointestinal tract based on next-generation sequencing. In a recent study by Schiavo Lena *et al.* (12), they reported a case of pancreatic mixed intraductal papillary mucinous neoplasm-NET and confirmed the true mixed nature of both components based on the same molecular alterations (*KRAS*, *GNAS*, and *CDKN2A* mutations, and the amplification of the *CCND1* gene).

In MiNEN, acinar adenocarcinoma as a nonneuroendocrine component has been reported more frequently in the literature, while ductal adenocarcinoma as a component has rarely been reported. In most digestive MiNENs, the neuroendocrine component is represented

by NEC, and accordingly, the patient's outcome is ominous (29,30). In pancreatic MiNENs, mixed ductal-NEC (the main type of adeno-NEC) and mixed acinar-NEC are two main entities (29). A previous study reported that digestive NECs and adenocarcinomas share similar genetic mutation landscapes, suggesting a monoclonal origin of the two MiNEN components (28). Interestingly, this MiNEN case we reported consisted of well-differentiated NETs and adenocarcinoma, but the evolutionary relationship between NETs and adenocarcinoma is still unclear, and whether NETs can transcend NECs to evolve into adenomas also demands further research. Therefore, the next-generation sequencing data for this case are being processed, and our team is committed to solving these problems.

For pancreatic adeno-MiNEN, Yang *et al.* (5), performed a Chinese single-center study on pancreatic neuroendocrine neoplasms (pNEN) over a study period of 10 years (2002–2012) and showed a frequency of 5.5% (6 of 110) adeno-MiNEN out of all pNEN patients resected at the center. In the study of Nießen *et al.* (11), found that the occurrence of adeno-MiNEN was 0.2% (8 of 3,580) of all pancreatic resections for pancreatic tumors and 1.4% (8 of 570) of all resected pNEN over a study period of 19 years (2001–2019). For pancreatic acinar-MiNEN, Pokrzywa *et al.* (30), found that 515 of 57,804 patients resected for pancreatic malignancy had pancreatic acinar-MiNEN via American National Cancer Base, with an incidence of 0.9% over ten years (2004–2014). Similarly, in the cohort of Nießen *et al.* (11), the frequency of acinar-MiNEN was 0.8% (5 of 570) of all resected pNENs and 0.14% (5 of 3,580 patients) of pancreatic resections for pancreatic tumors from 2001 to 2019.

Pancreatic MiNEN usually present nonspecific symptoms due to local tumor growth and/or metastatic dissemination, leading to difficulty in diagnosis. HE-stained sections served for the morphological identification of both neuroendocrine and nonneuroendocrine components. Immunohistochemistry is mandatory to test the nature of the neuroendocrine component, which is also recommended to evaluate the subtype of the nonneuroendocrine

Table 1 Review of the literature: MiNENs of pancreas

N	A	G	Tumor location	Diagnostic basis	Nonneuro/neuro component	Metastasis	Metastatic component	Surgery	Chem	Reference
1	63	m	panc. head	Surgical specimen	n.a. adeno/G3 NEC	n	-	PD	y	(11)
2	71	m	panc. body	Surgical specimen	G3 adeno/G3 NET	n	-	DP	y	(11)
3	73	m	The ampulla of Vater	Surgical specimen	G2 adeno/G3 NET	n	-	PD	y	(11)
4	77	f	panc. body	Surgical specimen	G3 adeno/G1 NET	n	-	TP	y	(11)
5	62	m	panc. head	Surgical specimen	G2 adeno/G3 NET	n	-	PD	y	(11)
6	64	m	panc. head	Surgical specimen	G2 adeno/G3 NET	y [#]	n.a.	PD	y	(11)
7	82	m	The ampulla of Vater	Surgical specimen	G2 adeno/G3 NEC	n	-	PD	n	(11)
8	64	f	panc. body	Surgical specimen	G2 acinar/G3 NEC	n	-	DP	y	(11)
9	43	m	panc. tail	Surgical specimen	n.a. acinar/G2 NET	y [#]	n.a.	DP & rHH	n	(11)
10	30	f	panc. tail	Surgical specimen	n.a. acinar/G2 NET	n	-	DP	y	(11)
11	53	m	panc. head	Surgical specimen	n.a. acinar/G2 NET	y [#]	n.a.	PD	y	(11)
12	56	m	panc. head	Surgical specimen	IPMN/G2 NET	n	-	PD	n.a.	(12)
13	81	m	panc. head	Surgical specimen	G1-G2 adeno/G1 NET	n	-	PD	yes	(13)
14	67	f	panc. body	Surgical specimen	G1 adeno/G1 NET	n	-	PD	n.a.	(14)
15	57	m	The ampulla of Vater	Surgical specimen	G2 adeno/SCNEC	n	-	PD	n	(15)
16	52	m	panc. head	Surgical specimen	n.a. adeno/n.a. NEC	n	-	TP	n.a.	(16)
17	33	m	Uncinate process of the pancreas	EUS-FNA specimen	n.a.	y [#]	n.a.	Whipple procedure & hepatic mass resection	y	(17)
18	66	m	panc. tail	EUS-FNA specimen	G1 acinar/n.a.	y [*]	n.a.	n [*]	y	(17)
19	60	m	panc. head	EUS-FNA specimen	n.a. adeno/n.a. NEC	y [#]	Neuro component	n [*]	y	(18)
20	69	m	The ampulla of Vater	Surgical specimen	G2 adeno/LCNEC	n	-	PD	n	(19)
21	60	m	The ampulla of Vater	EUS-FNA specimen	n.a. adeno/SCNEC	y [*]	n.a.	n [*]	n.a.	(19)
22	57	f	panc. body	Surgical specimen	acinar/n.a.	n	-	DP & S	y	(20)
23	66	m	Uncinate process of the pancreas	EUS-FNA specimen	acinar/n.a.	y [#]	Nonneuro & neuro component	n [*]	y	(21)
24	63	m	panc. head	Surgical specimen	G1-2 adeno/n.a.	y [*]	n.a.	PD	y	(22)

Table 1 (continued)

Table 1 (continued)

N	A	G	Tumor location	Diagnostic basis	Nonneuro/neuro component	Metastasis	Metastatic component	Surgery	Chem	Reference
25	43	f	The ampulla of Vater	Surgical specimen	G3 adeno/n.a.	n	-	PD	y	(23)
26	60	f	The ampulla of Vater	Surgical specimen	G3 adeno/n.a.	n	-	PD	y	(23)
27	78	m	Uncinate process of the pancreas	EUS-FNA specimen	n.a./n.a. NET	y [#]	Neuro component	n*	y	(24)
28	66	m	panc. head	Surgical specimen	G1 adeno/SCNEC	y*	Nonneuro or neuro component	PD	y	(25)

N, number; A, age; G, sex; Chem, chemotherapy; f, female; m, male; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; n.a., information not available; adeno, adenocarcinoma; acinar, acinar carcinoma; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; IPMN, intraductal papillary mucinous neoplasm; SCNEC, small cell neuroendocrine carcinoma; LCNEC, large cell neuroendocrine carcinoma; y*, lymph node metastasis; y[#], liver metastasis; TP, total pancreatectomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; rHH, right hemihepatectomy; n*, not suitable for surgery or unresectable; S, splenectomy; y, yes; n, no.

part in MiNEN. Histopathological examination with immunohistochemistry of surgically resected specimens is the gold standard to confirm MiNEN; most patients were previously suspected to have pancreatic tumors or pNEN, and the final diagnosis of MiNEN was made based on the pathological evaluation of surgical specimens (11-13,15,16,19,20,22,23,25). Preoperative diagnosis was rarely established, and only a few cases reported had been diagnosed through preoperative biopsy with endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) specimens (17-19,21,24). Recently, EUS-FNA, a minimally invasive technique for histological diagnoses, has been widely used to diagnose pancreatic tumors, and several reports have used it for preoperative diagnosis in pancreatic MiNEN. However, it is not used in all MiNEN cases and should be carefully considered before use because it has high negative predictive value and fails to access the whole tumor to diagnose MiNEN (13).

The management and treatment of pancreatic MiNEN patients are without uniform standards. Usually, patients undergo surgery (normally R0 resection), and adjuvant chemotherapy is probably arranged after surgery (13). However, it is unclear whether to focus on both components or the major component. La Rosa *et al.* (4), suggested that treatment for MiNEN should be based on the dominant component because the clinical outcome is usually determined by the more aggressive cell type of such mixed tumor. This opinion was shared by most investigators and clinicians.

For prognosis in adeno-MiNEN, Yang *et al.* (5), reported on 6 adeno-MiNEN patients with a median survival of 15.3 months. In the literature with ten surgically resected gastroenteropancreatic adeno-MiNEN patients, the median follow-up duration was 15 months (range, 3–51 months) (31). According to the data from Nießen *et al.* (11), among 13 patients with MiNEN, the 5-year overall survival (OS) rate in all MiNEN was 40%, and the 5-year survival rate was 58% in adeno-MiNEN compared to matched pNEN (48%) and ductal adenocarcinomas (36%). For acinar-MiNEN, Kim *et al.* (32), compared 20 acinar cell carcinomas (ACCs) and 13 acinar MiNEN to a cohort of 269 well-differentiated pancreatic neuroendocrine tumors (pNETs). The study indicated that patients with acinar MiNEN had worse overall (P<0.001) recurrence-free survival (P<0.001) than those with pNETs, with a 5-year OS rate of 46.7%. Similarly, in the study of Pokrzywa *et al.* (30), the median OS and 5-year OS rates were 26.8 months and 37%, respectively, based on the evaluation of 515 acinar MiNEN

patients between 2004 and 2014. In the cohort of Nießen *et al.* (11), median and 5-year OS were lower for acinar-MiNEN than in previous literature, 17 months and 20%, respectively.

In conclusion, we report a new case of MiNEN with liver metastases. Based on our case and the literature that we reviewed, MiNENs represent an extremely rare diagnosis. Due to diagnostic limitations and insufficient scientific data, their prevalence might be largely underestimated. Preoperative diagnosis is difficult without specific symptoms and radiological features. Thus, the possibility of MiNEN should be considered when abnormal pancreatic lesions are detected.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://dx.doi.org/10.21037/gs-21-564>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/gs-21-564>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case

report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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