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CASE REPORT

Mixed neuroendocrine non-neuroendocrine neoplasm: a case report and review

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Abstract

Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) of the pancreas is a rare entity, and obtaining a preoperative diagnosis is difficult. We present a 70-year-old man in whom the possibility of MiNEN was successfully discovered preoperatively by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Immunostaining revealed positive results for the neuroendocrine markers chromogranin A and synaptophysin. We considered the possibility for MiNEN before surgery. He underwent distal pancreatectomy with splenectomy. Immunohistochemical examination of the tumor cells showed a wide range of positivity for trypsin as well as for chromogranin A and synaptophysin. Considering that ≥ 30% tumors ware positive for both acinar and neuroendocrine markers, the patient was diagnosed with MiNEN. MiNEN is a malignant tumor that requires early detection and treatment but is a rare disease for which no method has been established. We found that EUS-FNA and immunostaining are effective diagnostic methods for MiNEN.

Keywords Acinar cell carcinoma · Neuroendocrine carcinoma of pancreas · Neuroendocrine carcinoma · Pancreatic neoplasm · MiNEN

Abbreviations

ACC	Acinar cell adenocarcinoma
CEA	Carcinoembryonic antigen
CGA	Chromogranin A
MiNEN	Mixed neuroendocrine non-neuroendocrine neoplasm
N/A	Not available
NET	Neuroendocrine
NSE	Neuro-specific enolase
PAS	Periodic acid-Schiff
SYN	Synaptophysin
TAE	Transcatheter arterial embolization

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Introduction

Most pancreatic cancers fall into four distinct categories: ductal adenocarcinoma, intraductal papillary mucinous neoplasm with an associated invasive carcinoma, acinar cell carcinoma (ACC), and neuroendocrine neoplasm [1]. Among pancreatic cancers, pancreatic ACC is rarer than invasive pancreatic ductal carcinoma and is reported to account for < 1% of all pancreatic cancers [2]. Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN) is defined a mixture of exocrine and endocrine tumors of the pancreas in which ≥ 30% of the endocrine component is found in an exocrine cell carcinoma by the World Health Organization (WHO) classification system [1] However, it is well established that roughly one-third of ACCs express neuroendocrine markers. When neuroendocrine cells account for > 30% of the total tumor size, they are classified as MiNEN [1]. Herein, we present the case of a 70-year-old man who was diagnosed with MiNEN using endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and who then underwent distal pancreatectomy. He was diagnosed with MiNEN on histopathological examination same to the results of preoperative immunostaining. There have been about 40 reports on MiNEN in the past. Here we discuss the detailed

pathological features of MiNEN and the appropriate preoperative diagnosis using EUS-FNA. Due to its rarity, a treatment protocol for MiNEN has not yet been standardized. We also review the existing English literature here.

Case report

An asymptomatic 70-year-old man was referred to our hospital for examination after a pancreatic mass was identified on abdominal ultrasonography. Physical examination and laboratory test results were within normal ranges. Carcinoembryonic antigen level was 1.9 ng/mL and carbohydrate antigen 19–9 (CA19-9) was 16 U/mL, which did not increase thereafter. Serum neuron-specific enolase level was also normal. Computed tomography (CT) showed a contrast-enhanced mass with a diameter of 15 mm in the pancreatic tail (Fig. 1). Magnetic resonance imaging (MRI) showed a high-intensity mass lesion on diffusion-weighted images (Fig. 2). EUS showed a 17-mm-sized mass with an unclear boundary in the pancreatic tail. There was no capsule-like structure on the tumor margin, and the inside was hypoechoic. The central part of the tumor appeared necrotic with no echo (Fig. 3a). EUS-FNA was performed using a 22G EZ shot 3 plus. We performed two punctures in the mass during one session. Obtained specimens were subjected to tissue diagnosis after formalin fixation. The specimens revealed tumor tissues in which acidophilic cells with atypical polygonal shape formed vesicle nests and proliferated (Fig. 4). The hypoechoic region within the tumor represented cystic

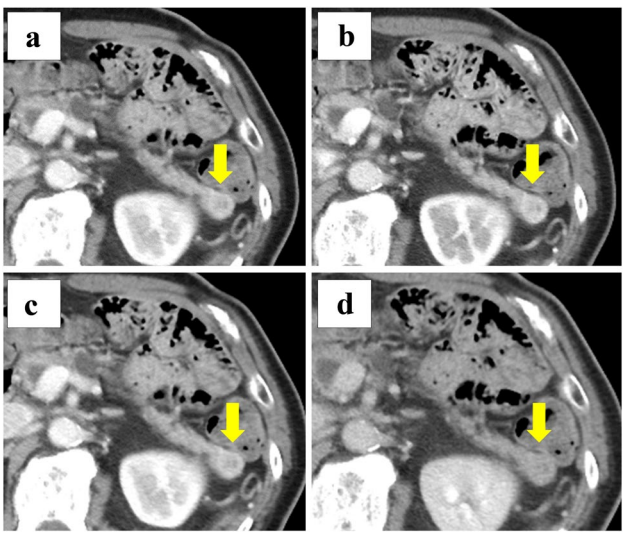

Fig. 1 **a** Contrast-enhanced axial CT scan during the arterial phase. The tail pancreas axis, which is approximately 15 mm in size, is replaced by a hyper-attenuating mass-like lesion (arrow). **b** Late arterial phase (arrow); **c** vein phase (arrow); **d** conflict phase (arrow)

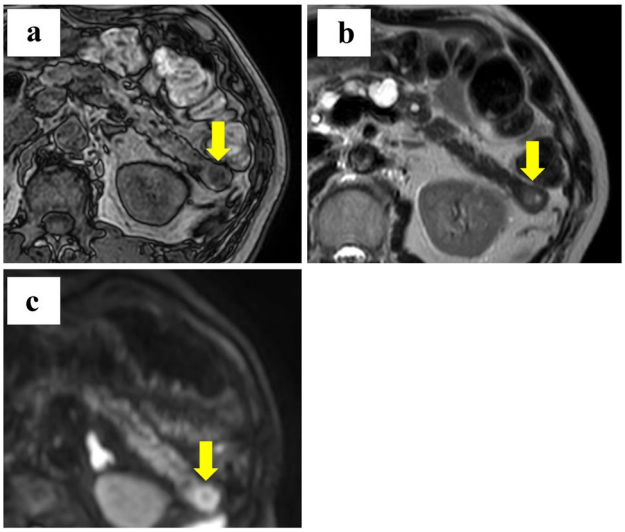

Fig. 2 **a** Contrast-enhanced T1-weighted axial MR image showing a heterogeneously hypointense tumor compared to the normal pancreas (arrow). **b** T2-weighted axial MR image showing a heterogeneously hyperintense mass compared to the normal pancreas (arrow). **c** A diffusion-weighted axial MR image showing a heterogeneously hyperintense mass compared to the normal pancreas (arrow)

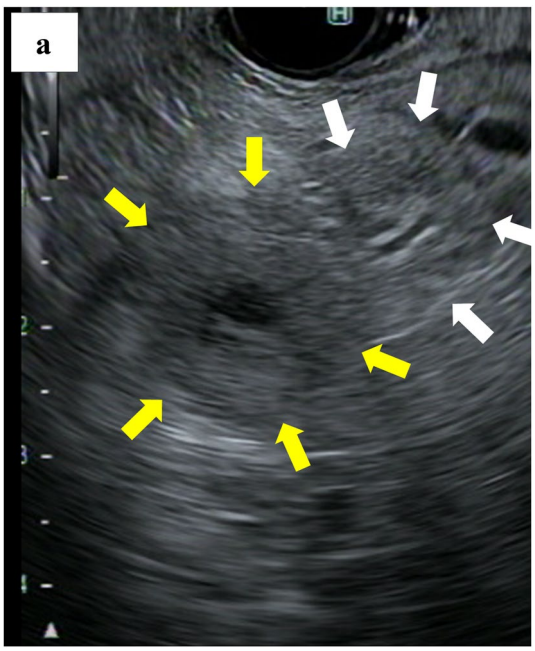

Fig. 3 **a** Endoscopic ultrasonography (EUS) by convex scope showing a 17-mm-sized hypoechoic mass with an unclear boundary in the pancreatic tail. The central part of the mass is accompanied by a non-echoic region (yellow arrow). The mass lesion has poor flow compared to normal pancreatic parenchyma (white arrow)

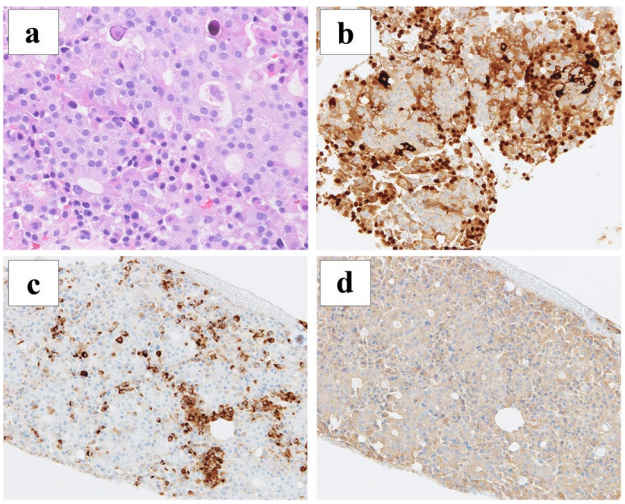

Fig. 4 Endoscopic ultrasound-fine-needle aspiration (EUS-FNA) histopathology. **a** Hematoxylin and eosin image of the pancreatic tumor (400×); **b** α1-anti-chymotrypsin (200×); **c** chromogranin A (200×); **d** synaptophysin (200×)

degeneration. There were no necrotic findings on pathological examination.

Immunostaining was positive for the acinar marker α1-anti-chymotrypsin and the neuroendocrine markers chromogranin A and synaptophysin. Because both acinar and neuroendocrine markers were positive, we suspected the possibility of MiNEN preoperatively (Fig. 5).

The patient underwent distal pancreatectomy with splenectomy. The resected tumor had a maximum size of 12 mm, with a well-circumscribed shape and focal cystic change of 5 mm. In the histological findings, the tumor showed two distinct cell populations: neuroendocrine and non-neuroendocrine components, which were critically different in morphological appearances as shown by hematoxylin and eosin staining and in the patterns of special staining and immunohistochemical staining. While about 60% of the cells in the tumor showed acinar, glandular, and solid patterns, representative of acinar cell carcinoma, the other cell population (about 40%) in the tumor showed trabecular, nest, and rosette structures, suggestive of neuroendocrine carcinoma. In the special staining and immunohistochemical analyses, the former cells were positive for both periodic acid-Schiff (PAS) and PAS with diastase digestion (D-PAS) and positive for alpha-chymotrypsin, while the latter cells were positive for chromogranin A, synaptophysin, and somatostatin receptor 2 (SSTR2), which are representative markers of neuroendocrine differentiation. The Ki-67 labeling index was 1%, indicating that the tumor cells were non-proliferative or low-grade. Considering all these findings, the tumor met the histopathological criteria of mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) with good differentiation (Fig. 6).

According to the Union Internationale Contre le Cancer classification 8th edition of pancreatic cancer, the following staging was established: pT1, CH0, S0, RP0, RV0, A0, PL0, PCM0, DPM0, R0, N0, M0, pStageI.

The postoperative course remained uneventful. The patient was not given adjuvant chemotherapy. The patient survives for 1 year after surgery without recurrence.

Discussion

The pancreas is composed of exocrine cells consisting of pancreatic duct epithelial cells, adenocytes, and endocrine island cells. Cancer of each cell type is termed pancreatic ductal carcinoma, pancreatic ACC, and pancreatic endocrine carcinoma, respectively. Some pancreatic tumors have both exocrine and endocrine tumors mixed or coexisting within the tumor [3]; these tumors are known as MiNEN of the pancreas. All cells that compose the pancreas embryologically originate from the pancreatic duct epithelial cells, which probably explains tumors in which endocrine and exocrine

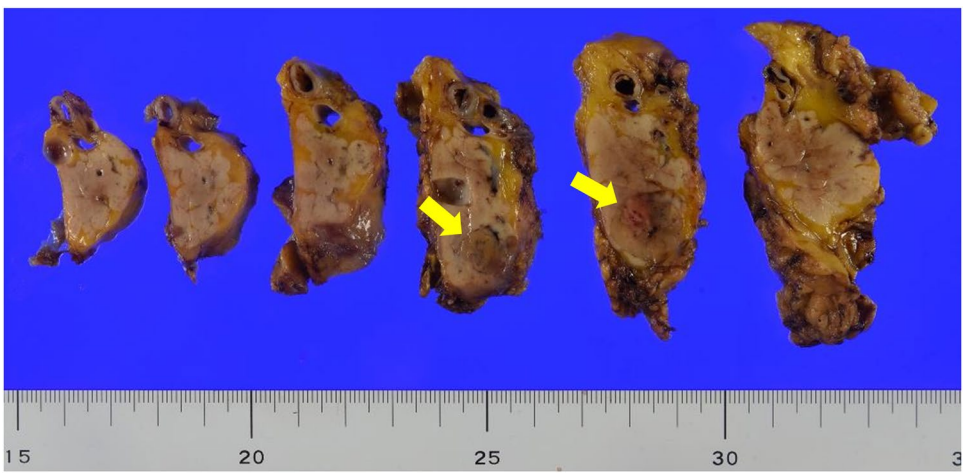

Fig. 5 Specimen: MiNEN (yellow arrow)

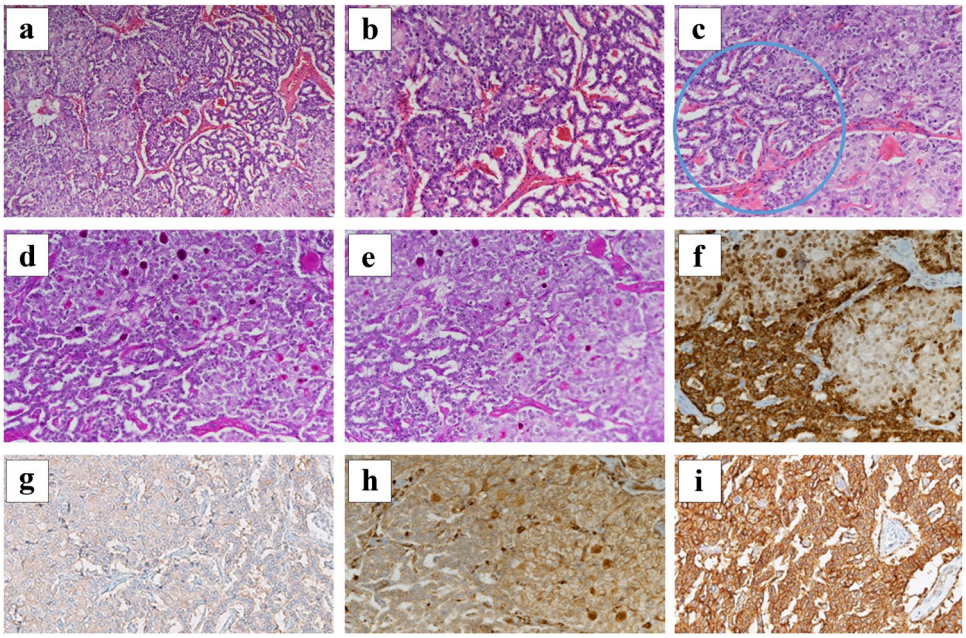

Fig. 6 Histopathological features of the MiNEN. **a**, **b** Hematoxylin and eosin image of the pancreatic tumor showing a trabecular, nest, and rosette-like structure and a sheet-like structure. Acinar cell carcinoma and NET (G1) components can be observed. The 2 components are closely attached. Combined/biphasic type (100×) (200×). **c** Transition between ACC components and NET components (×200). The inside of the blue circle is the NET component, and the others are the ACC components. **d** PAS stain (200×). **e** D-PAS stain (×200). **f** α1-anti-chymotrypsin (200×). **g** Immunostaining of the pancreatic tumor for chromogranin A (200×). Left side: The area where the cytoplasm is stained is the NET component; right side ACC area. h: SSTR2 (200×). i: synaptophysin (100×)

masses coexist [4]. The WHO Classification 2019 collectively refers to pancreatic and gastrointestinal tumors with endocrine properties as neuroendocrine neoplasms (NEN), which are roughly categorized into well-differentiated neuroendocrine tumors (neuroendocrine neoplasm: NET) and poorly differentiated neuroendocrine tumors (Neuroendocrine carcinoma: NEC), with NET classified into NET G1, NET G2, and NET G3 based on the number of nuclear fission and the Ki-67 index. The 2019 WHO classification defined MiNEN as tumors in which ≥ 30% of the endocrine component is found in an exocrine cell carcinoma. This definition has undergone several transitions until MiNEN appeared in the 2019 WHO classification as a general term that covers various pathological conditions that do not contain adenocarcinoma components and consist of ACC and NEN components. This review includes reports the investigated mixed adeno-neuroendocrine carcinoma (MANEC) based on the 2010 WHO classification. MiNEN (including MANEC) of the pancreas is rare, with only 40 cases in the published English literature (Table 1) [2–30]. We summarized the clinicopathological features in each report in this review.

In this case report, the mass had characteristics of both acinar and endocrine cells. These findings suggest that the mass was derived from acinar cells: (1) the glandular cell line had an acinar structure, (2) α1-antitrypsin was widely positive, and (3) synaptophysin was also positive. On the other hand, findings supporting that they were derived from endocrine cells were as follows: (1) chromogranin A was extensively positive (60%) and (2) synaptophysin was also positive. We accurately suspected the possibility of MiNEN preoperatively by immunostaining the sample collected with EUS-FNA. We then performed a prompt surgery.

Since MiNEN is rare and the number of cases is limited, diagnosing MiNEN before surgery is very difficult and the diagnostic method is also controversial. Many studies have reported the correct diagnosis rate with tissue diagnosis using EUS-FNA. The pathological diagnosis of pancreatic disease by EUS-FNA was first reported by Vilmann et al. [31]. According to Agarwal et al., the sensitivity, specificity, and accuracy rate of EUS-FNA for detecting pancreatic cancer is 89, 100, and 90%, respectively, and the sensitivity for detecting endocrine carcinoma is reported to be 77–93% [32]. Based on reported cases (Table 1), this suggests that the clinical diagnosis of pancreatic MiNEN remains a big challenge. Niiya et al. [29] reported several cases of successful preoperative diagnosis of MiNEN with EUS-FNA. Among these, a definitive diagnosis of tumors with size ≤ 11 mm was rare. All reports of successful MiNEN diagnosis preoperatively using EUS-FNA were stained for both acinar and neuroendocrine markers. However, cases in which MiNEN was not diagnosed were

Table 1 Reported cases of mixed acinar-neuroendocrine carcinoma in the pancreas (including MANEC)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
1	Thomas Ulich	F	30	The tumor consisted of cells with atypical nuclei, abundant eosinophilic cytoplasm. In the acinar areas, the nuclei of the cells were often basally situated. Rare mitoses. Delicate fibrovascular trabeculae separated groups of tumor cells	PAS + lipase	Immunoperoxidase	N/A	Adenocarcinoma + NET
2	Kunio Ichijima	F	6	The tumor showing acinar, tubular, solid pattern. The lumina contain homogeneous material	PAS + lipase	Tryptophan immunoperoxidas	N/A	ACC + NEN
3	David S.Klimstra	F	79	N/A	Trypsin,chymotripsin, lipase	CGA, SYN	N/A	ACC + NEN
4	David S.Klimstra	F	48	The tumour cells are solid sheets of small cells; focal irregular nests of cells contain more abundant clear cytoplasm	Trypsin,chymotrypsin, lipase	CGA, SYN, CEA	N/A	ACC + NEN
5	David S.Klimstra	F	64	N/A	Trypsin,lipaseT	CGA, SYN, somatostatin	N/A	ACC + NEN
6	David S.Klimstra	M	70	Solid and acinar growth patterns and basal nuclear palisading at the interface with the vessels	Trypsin,chymotrypsin	CGA, CEA	N/A	ACC + NEN
7	David S.Klimstra	M	81	The acinar cells are arranged in trabecular and acinar formations, with basally oriented nuclei, granular cytoplasm, prominent nucleoli. The endocrine cells are arranged in solid sheets	Trypsin,chymotrypsin, lipase	CGA gastrin	N/A	ACC + NEN
8	Kyung-Ja Cho	F	52	Solid nests of mildlu pleomorphic round to oval cells,sorrounded and separated by fibrovascular tissue. In some areas, the tumor cells showed acinar arrangement or gladular formation with eosinophilic secretory material	PAS + amylase	NSE, CGA somatostatin,gastrin	N/A	ACC + NEN

Table 1 (continued)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
9	Tomoko Shimoike	M	28	The neoplastic cells of the hepatic metastasis show eosinophilic cytoplasm and many mitoses. They have proliferated in solid sheets,with a fibrovascular stroma	Trypsinα-1-anti-chymotrypsin	NSE, CGA	N/A	ACC + NEN
10	Margareta Frank	M	61	The tumor was composed of polymorphis medium-sized to tall cuboid tumor cells arranged either in solid nests or in acinar stractures. Miotic figures were numer-ous. The cells revealed abundant eosinophiluc cytoplasm	PAS + Trypsinogen	NSE, CGA	N/A	ACC + NEN
11	Tomoko Ogawa	M	50	The tumor cells were arranged in solid nests and sheets, with focal acinar and gladu-lar stractures, and showed focal microcystic change	PAS + α-1-antitrypsin	CGA	N/A	ACC + NEN
12	Marek Skacel	M	69	The tumor cells contained large nuclei with single prominent nucleoli and abundant eosinophilic cytoplasm	Chymotropsin; α-1-antitrypsin; PAS + α-1-antitrypsin	SYN	N/A	ACC + NEN
13	Marek Skacel	M	75	The tumor grows in a solid-trabecular pattern, similar to an endocrine neoplasm	Chymotropsin; α-1-antitrypsin	SYN	N/A	ACC + NEN
14	Nobumasa Mizuno	F	67	The tumour cells was arranged in a rosset-like,solid and papillary pattern and had ensinophillic cytoplasm with atypia	α-1-antitrypsin	CGA, SYN gastrin insulin	N/A	ACC + NEN
15	Nobuyuki Ohike	M:F 2:4	58.4	Solid pattern (2 cases) mixed acinar-solid pattern (3 cases) scattered cell clusters the size of islets composed of cells with pale cytoplasm(1 case)	N/A	N/A	N/A	ACC + NEN

Table 1 (continued)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
16	Hiroshi Imaoka	M	80	The tumor showed round neoplastic cells with eosinophilic cytoplasm in irregularly shaped groups	Trypsin, chymotrypsin, lipase	CGA, SYN	N/A	ACC + NET
17	Maria A. Kytiazi	M	74	The tumor was multilobular, well circumscribed and fully encapsulated. Numerous neoplastic emboli were present in the vascular and lymphatic channels. Lymph nodes harboured metastases of the neoplasm	Trypsin, C56, CK7	CGA, SYN	80%	ACC + NET
18	Won Jung Chung	F	59	Hemorrhage and focal necrosis with cystic change throughout the tumor A lymphovascular invasion was observed	Trypsin, PAS +	SYN	N/A	ACC + NEN
19	Shinjiro Kobayashi	M	75	The tumor was whitish with a distinct border and had expansive and lobular growth. Tumor thrombus was observed in the pancreatic duct. Tumor cells include acinar and grandular stractures	Trypsin, PAS +	CGA, SYN	N/A	ACC + NEN
20	Ayman Soubra	M	52	75% of cells with endocrine differentiation(islet cells) and 25% with exocrine features (acinar), well differentiated	Trypsin, chymotripsin	CGA, SYN	N/A	ACC + NET
21	Lili Lee	M	66	The cell block showing clusters of these neoplastic cells. The neoplastic cells formed solid sheets and acinar stractures	Trypsin, chymotrypsin CAM5.2	CGA, SYN	35%	ACC + NET
22	Peggy S. Sullivan	M	51	The cells had round to oval nuclei with mild nuclear size variation, slightly irregular nuclear countours, salt-and-papper chromatin.The cytoplasm was scant and delicate	Trypsin, chymotripsin	CGA, SYN	7% ~ 11%	ACC + NET

Table 1 (continued)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
23	Peggy S. Sullivan	M	75	The cells had round to oval nuclei,moderate nuclear size variation, irregular and angulated nuclear contours, coarsely granular chromatin, frequent macronucleoli. The cytoplasm was moderate to abundant and delicate to granular	Trypsin, chymotripsin	CGA, SYN	40%	ACC + NET
24	Onyekachi Henry Ogbonna	F	57	Poorly circumscribed, mostly solid neoplasm with mixed aciner-neuroendocrine	Trypsin, chymotrypsin PAS + cytokeratin	CGA, SYN	40% ~ 45%	ACC + NET
25	Run Yu	M	59	The component exhibited more acidophilic cytoplasm, smaller nuclei, lower nuclei-cytoplasmic ratio and exhibited basophilic cytoplasm, larger nuclei, higher nuclei-cytoplasm ratio	Trypsin, chymotrypsin	CGA, SYN	30% ~ 80%	ACC + NET
26	Run Yu	M	74	The tumor cells were arranged in sheets and nests	Trypsin, chymotrypsin	CGA, SYN	10%	ACC + NET
27	Run Yu	M	60	The tumor consisted of both acinar and solid or trabecular growth patterns and showed extensive areas of necrosis and focal clear cell differentiation. The tumor cells had abundant eosinophilic sytoplasm and prominent nucleoli	Trypsin, chymotrypsin	CGA, SYN	65%	ACC + NET
28	Run Yu	M	89	The tumor consisted of predominately asinar and partly solid patterns and a high mitotic rate (10/10 HPF)	Chymotropsin	CGA, SYN	65%	ACC + NET
29	Run Yu	M	80	The tumor was composed of solid sheets and nests of tumor cells with focal acinar formation in a background of fibrotic stroma	Trypsin, chymotrypsin	CGA, SYN	53%	ACC + NEN
30	Kanemasa Yusuke	M	60	The unihorm neoplastic cells were mostly grouing in a solid pattern and partially in an acinar or tubular pattern	Trypsin	CGA	N/A	ACC + NEN

Table 1 (continued)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
31	Zhenzhen Liu	F	65	Predominantly solid and partly acinar morphology	Trypsin, chymotrypsin	CGA, SYN,NSE	10%	ACC + NET
32	Mark Jakobsen	F	62	The tumor was well-circumscribed and entirely encapsulated. The tumor cells in the cystic areas were arranged in an alomost acinar pattern. The size of nuclei varied	Chymotrypsin	SYN, CGA,CD56	22%	ACC + NET
33	Motokazu Sugimoto	M	48	N/A	Trypsin,chymotrypsin lipase,periodic acid-Schiff	CGA, SYN, CD56,NSE	10% ~ 20%	ACC + NET
34	Takeo Hara	F	45	The cellular neoplasm originating from the pancreatic oarenchyma. Many tumor cells grow in solid nests and include acinar and glandular stractures	Trypsin	CGA	N/A	ACC + NEN
35	Masataka Yokode	M	65	Tumour cells arranged in an acinar or trabecular architecture	bcl-10	CGA, SYN	55%	ACC + NEC
36	Anneleen de both	F	35	The solid areas alternating with tumor cells arranged into small acinar stractures	Chymotripsin	SYN	40%	ACC + NET
37	Alexander M.Strait	M	33	The tumor cells had enlarged nuclei with a high nuclear-to-cytoplasmic ratio, insonspicuous nucleoli,granular cytoplasm. Abundant neked nuclei were noted. Some nuclei exhibited salt and pepper chromatin	Trypsin,synaptophysin	CKAE1/3	40%	ACC + NET
38	Alexander M.Strait	M	66	Atypical epithelial cells with enlarged nuclei and high N:C ratios, arranged both singly and in loosely cohesive clusters. Some cells were plasmacytoid with prominient nucleoi, vesicular chromatin, and fine cytoplasmic granules	Trypsin,chymotrypsin, synaotophysin	CKAE1/3	N/A	ACC + NEN

Table 1 (continued)

Case	Authors	Sex	Age (years)	Clinicopathological features	Acinar marker	Endocrine markers	Ki-67	Mixed components
39	Fumitaka Niiya	M	72	The tumour cells was showed a small tumor cell with a round nucleus and a solid growth of an acinar/tubular stacture	bcl-10	CGA, SYN	N/A	ACC + NEN
40	Xiu Jun Tang	M	52	The tumoue cells was epithelioid cell tumor with poor differentiation in glandular or lamellar arrangement	Synaptophysin	CGA	50%	ACC + NEC
41	Current study	M	70	Acinar, glandular, and solid patterns the other had trabecular, nest, and rosette structures	α-1-anti-chymotrypsin, PAS PAS, D-PAS	CGA, SYN, Glucagon, SSTR2A, SSTR5	1%	ACC + NET

stained only for either acinar or neuroendocrine markers [29]. They suggested that thorough immunostaining can help diagnose MiNEN. We also successfully suspecting of MiNEN preoperatively by immunostaining acinar and neuroendocrine markers.

A previous study reported that patients with MiNEN had worse overall and recurrence-free survival than those with pancreatic neuroendocrine tumor (PanNETs), but no significant difference was found between the former group and those with ACCs [33]. ACCs presented more commonly with intraductal growth than MiNEN, whereas MiNENs more often have lymph node metastasis. Patients with MiNENs and ACCs have worse survival and display more aggressive behavior than those with PanNETs. Moreover, clinicopathological behavior of MiNENs resembles that of ACCs rather than that of PanNETs [33].

Hara et al. reported that the 1-year overall survival rate was 80% and that the 3-year overall survival rate was 60% in 16 patients who underwent surgery [25]. In addition, Yu et al. reported that the larger the tumor diameter and the higher the Ki-67 index, the faster the progression rate [20]. In this case, Ki-67 was low grade in 1%, so we did not administer adjuvant chemotherapy. Moreover, Kim et al. reported that the mean survival of MiNEN patients after surgical resection of the primary tumor is 10.5 months [33]. Therefore, detection of small MiNEN and complete surgical removal are essential to achieve a cure. These results support the need for improved accuracy in the preoperative diagnosis of MiNEN.

Due to the limited number of cases of MiNEN, no effective treatment for MiNEN has been established. However, surgical resection is often performed as a curative treatment. There have also been reports of patients benefiting from surgical tumor debulking and local and systemic antiproliferative therapy [21]. In addition, no treatment has been established for unresectable or recurrent cases, and there have been reports of transcatheter hepatic artery chemoembolization for liver metastasis [20]. Moreover, an effective chemotherapy regimen is yet to be established. Yokode et al. reported that some MiNENs show a good response to S-1 chemotherapy. A multidisciplinary approach with surgery is needed for patients with advanced cases of MiNEN [26].

Preoperative diagnosis of MiNEN is difficult and is often misdiagnosed as PanNET. PanNETs are often followed up, and there is a risk that MiNEN will be overlooked. Therefore, the detection of small MiNENs and their complete surgical removal is essential to achieve cure. MiNEN is a very rare tumor of the pancreas for which surgical resection remains the only established standard treatment. Continued identification and reporting of these cases should be encouraged with the goal to better understand the disease and standardize optimal therapy.

Further cases need to be accumulated to improve the preoperative diagnostic accuracy of MiNEN and to establish an effective treatment method.

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Author contributions SH drafted the manuscript. RY performed the pathological diagnosis and pathological analysis such as immunostaining. We believe that surgery, treatment, and pathological analysis have similar importance in this case report. Therefore, SH and RY are co-first authors. MH and TI supervised the preparation of the manuscript. YM performed the surgery. TN supervised the pathological diagnosis. TS and MH performed endoscopy and biopsy. MH reviewed and modified the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Sawako Hiroi, Rie Yamamoto, Michinori Hamaoka, Masakata Hoshino, Tamito Sasaki, Yasuhiro Matsugu, Takashi Nishisaka, Hideki Nakahara and Toshiyuki Itamoto declare that they have no conflict of interest.

Human Rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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