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Mixed acinar-neuroendocrine carcinoma of the pancreas: a case report and a review

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Summary. A 62-year-old woman presented with abdominal discomfort. Imaging studies showed a tumor in the pancreatic tail. At contrast-enhanced CT and macroscopy, the tumor showed cystic, solid and hemorrhagic areas. Histologically, the tumor was well-circumscribed and entirely encapsulated. Some of the tumor cells in the cystic areas were reminiscent of acinar cells, and the majority was arranged in a solid growth pattern. Immunohistochemistry revealed >30% positivity for chymotrypsin, chromogranin A, synaptophysin, and CD56. The diagnosis of a mixed acinar-neuroendocrine carcinoma (MAEC) was made. Review of the English language literature revealed 44 previously published cases of resected MAECs. We found that, compared to pure acinar cell carcinoma, patients with MAEC have a slightly higher age and are less frequently males, as the male/female ratio was almost equal. The histogenesis of MAEC is still controversial. Due to the small number of cases it is at present not possible to define an evidence-based optimal treatment strategy for these patients.

Key words: Mixed acinar-neuroendocrine carcinoma, Pancreatic cancer, Acinar cell carcinoma, Immunohistochemistry

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Introduction

The majority of 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 (Fukushima et al., 2010). Acinar cell carcinoma is a rare tumor accounting for approximately 1% of pancreatic exocrine tumors (Klimstra et al., 2010). Although it is well established that roughly one-third of acinar cell carcinomas may express neuroendocrine markers (Klimstra et al., 1994; Ohike et al., 2004), their neuroendocrine component is usually limited to a few scattered cells. When the neuroendocrine cells exceed 30% of the tumor, it is classified as mixed acinar-neuroendocrine carcinoma (MAEC) (Fukushima et al., 2010). MAECs are exceedingly rare. We present a case of a 62-year-old woman who was treated with a left-sided pancreatic resection with the post-operative diagnosis of MAEC. Because it is not known whether MAECs have characteristic clinicopathological features that distinguish them from ACCs, we reviewed the existing literature.

Material and methods

Case report

A 62-year-old woman presented with abdominal discomfort over a one-month period. Pancreatic exocrine and endocrine symptoms were absent. The physical examination and blood tests were in the normal range,

serum amylase was 27 U/L preoperatively. Serum levels of AFP and NSE were not analyzed. She was referred for an abdominal ultrasound which showed a large, well-circumscribed tumor, measuring 5 cm in diameter and located in the pancreatic tail. Subsequent abdominal contrast-enhanced computed tomography (CT) of the abdomen (Fig. 1) and endoscopic ultrasound confirmed the findings, as both were indicative of a cystic or solid-pseudopapillary neoplasm. The patient underwent a left-sided pancreatic resection with splenectomy and postoperative adjuvant chemotherapy with gemcitabine targeting the ACC component. She is currently well, now 12 months after the operation, without evidence of recurrence.

Immunohistochemistry

The resection specimen was fixed in formalin and selected areas of interest were embedded in paraffin. 4 μm thick sections from these formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin & eosin. For immunohistochemistry, the sections were mounted on FLEX IHC slides (Dako, Glostrup, Denmark), dried at room temperature, and incubated at 60°C for 60 minutes before immunostaining. The immunohistochemical staining procedure was automated using the BenchMark Ultra immunostainer (Ventana Medical Systems, Tucson, AZ), with the OptiView-DAB detection kit (Ventana Medical Systems, Tucson, AZ). Primary antibodies, dilutions, incubation times and epitope retrieval procedures were as specified in Table 1. Nuclear counter staining was performed with the BenchMark Ultra instrument, using Hematoxylin II (Ventana Medical Systems, Tucson, AZ). Finally, slides were washed, dehydrated, and coverslipped using a Tissue-Tek Film coverslipper (Sakura, Alphen aan den Rijn, The Netherlands).

Electron microscopy

For the electron microscopic examination, tissue fragments of 1 mm^3 were cut with a scalpel from distinct areas in the relevant paraffin blocks chosen from the HE-stained sections. The tissue was then reprocessed using xylene dewaxing, specimen rehydration with ethanol, post-fixation in glutaraldehyde and then rehydrated before being infiltrated with epon. The hardened epon blocks were trimmed and sectioned into 1 μm slices with glass knifes attached to an ultramicrotome. These sections were then stained with Toluidine blue and examined with a light microscope in order to identify areas of interest. 6 nm sections were cut from these areas and mounted on a grid for electron microscopic examination.

Literature review

PubMed searches using the terms "mixed acinar-neuroendocrine carcinoma AND pancreas", "MAEC AND pancreas", "Mixed adeno-neuroendocrine carcinoma AND pancreas", "MANEC AND pancreas" and "acinar cell carcinoma AND pancreas" were performed. Moreover, we found relevant publications by cross referencing. All English language articles reporting cases with MAECs and giving at least age and sex of the patients were included in the review. Papers where the diagnosis of MAEC was based on cytology alone were excluded.

Results

Macroscopy

Macroscopically, a tumor in the pancreatic tail was observed, measuring 5.2 cm in largest diameter. The cut surface revealed a large cystic area, 2 cm in greatest dimension, and solid areas. The color was pale and fawn, interchanging with tan and dark-brown areas. Hemorrhage and degenerative cystic changes were also observed (Fig. 2).

Microscopy and immunohistochemistry

The tumor was well-circumscribed and entirely encapsulated. The tumor cells in the cystic areas were reminiscent of acinar cells, which focally were arranged in an almost acinar pattern (Fig. 3A). The size of their nuclei varied only slightly, and distinct nucleoli were present in some of them. At immunohistochemistry, more than 30% of these cells strongly expressed

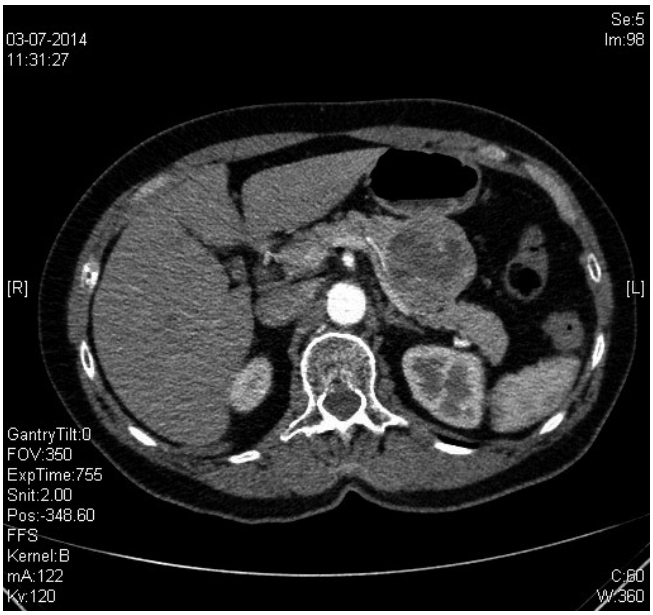

Fig. 1. Contrast-enhanced CT scan of the abdomen showing a well-circumscribed tumor with cystic areas in the pancreatic tail. There is no involvement of the lymph nodes.

Table 1. Antibodies used for immunohistochemical staining.

Antigen	Company	Clone	Code nr.	Dilution	Epitope retrieval	Incubation	Detection system
AFP	Dako	-	A0008	2000	CC1_32_100	16 min/36C	OptiView-DAB
Alpha-1 antitrypsin, Z-variant	Hycult Biotechnologie	2C1 (mouse), monoclonal	HM2289	200	CC1_32_95 + Protease 3/4 min.	16 min/36C	OptiView-DAB
BCL10	Dako	151	M7260	25	CC1_32_100	20 min/36C	OptiView-DAB
Beta catenin	BD Transduction Laboratories	14 (mouse), monoclonal	610153	500	CC1_48_100	32 min/36C	OptiView-DAB
Calretinin	Ventana Medical Systems	SP65 (rabbit), monoclonal	790-4467	RTU	CC1_32_100	12 min/36C	OptiView-DAB
CD10	Novocastra	56C6 (mouse), monoclonal	NCL-L-CD10-270	10	CC1_32_100	32 min/36C	OptiView-DAB
CD56	Cell Marque	MRQ-42 (rabbit), monoclonal	156R	500	CC1_32_100	32 min/36C	OptiView-DAB
CEA-mono	Zymed	Col-1, Carcinoembryonic Antigen (CD66e)	18-0057	200	CC1_32_100	32 min/36C	OptiView-DAB
Chromogranin A	Ventana Medical Systems	LK2H10 (Mouse), monoclonal	760-2519	RTU	CC1_24_100	24 min/36C	OptiView-DAB
Chymotrypsin	Acris Antibodies GmbH	4E1 (mouse), monoclonal	BM293	200	CC2_32_91	24 min/36C	OptiView-DAB
CK7	Ventana Medical Systems	SP52 (rabbit), monoclonal	790-4462	RTU	CC1_48_100	32 min/36C	OptiView-DAB
CK8	Epitomics	EP17 (rabbit), monoclonal	AC-0007	100	CC1_32_100	32 min/36C	OptiView-DAB
CK19	Ventana Medical Systems	A53-B/A2.26 (mouse), monoclonal	760-4281	RTU	CC1_32_100	32 min/36C	OptiView-DAB
CK20	Ventana Medical Systems	SP33 (rabbit), monoclonal	790-4431	RTU	CC1_32_100	12 min/36C	OptiView-DAB
Gastrin	Ventana Medical Systems	Polyclonal (rabbit)	760-2643	RTU	Protease 1/4 min.	16 min/36C	OptiView-DAB
Glucagon	Epitomics	EP74 (rabbit), monoclonal	AC-0074A	200	CC1_32_100	8 min./36C	OptiView-DAB
Insulin	NovoCastra	2D11-H5 (mouse), monoclonal	NCL-INSULIN	100	CC1_16_100	24 min/36C	OptiView-DAB
Ki67	Ventana Medical Systems	30-9 (rabbit), monoclonal	790-4286	RTU	CC1_48_100	12 min/36C	OptiView-DAB
NSE	Dako	BBS/NC/VI-H14 (mouse), monoclonal	M0873	1000	CC1_32_100	12 min/36C	OptiView-DAB
Serotonin	Dako	5HT-H209 (mouse), monoclonal	M0758	50	CC2_32_91	16 min/36C	OptiView-DAB
Somatostatin Receptor 2	Epitomics	EP149 (UMB1) (rabbit), monoclonal	AC-0162	400	CC1_32_100	32 min/36C	OptiView-DAB
Somatostatin	EuroProxima	B18-1 (rabbit), polyclonal	B18-1	10000	CC1_32_100	12 min/36C	OptiView-DAB
Synaptophysin	NovoCastra	27G12 (mouse), monoclonal	NCL-L-SYNAP-299	50	CC1_48_100	32 min/36C	OptiView-DAB
Trypsin	Chemicon-Millipore Internat. Inc.	MAB1482 (mouse), monoclonal	MAB1482	100	-	-	OptiView-DAB
Vimentin	Ventana Medical Systems	V9 (mouse), monoclonal	790-2917	RTU	CC1_32_100	16 min/36C	OptiView-DAB
VIP	EuroProxima	6-28 (rabbit), polyclonal	2263B34-1	1000	CC1_32_100	16 min/36C	OptiView-DAB

C, Celsius degrees; CC1, Cell Conditioning Solution 1 (pH 8.5) (Ventana Medical Systems); CC2, Cell Conditioning Solution 2 (pH 6.0) (Ventana Medical Systems); CCx,_minutes incubated_/ degrees Celcius; RTU, ready-to-use.

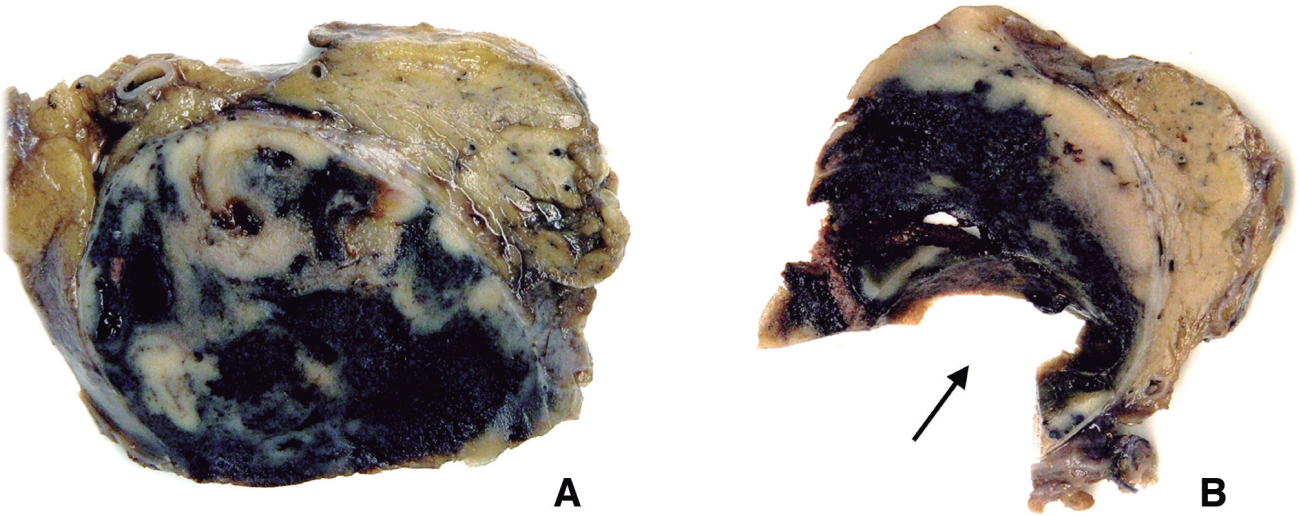

Fig. 2. The cut surface of the left-sided pancreatic resection specimen. **A.** Solid areas with a pale and fawn color interchanging with tan and dark-brown areas. **B.** Hemorrhage and degenerative cystic changes are also seen. A larger cystic area is shown (arrows).

chymotrypsin (Fig. 3B), and the neuroendocrine markers synaptophysin (Fig. 3C), chromogranin A and CD56. Also in the solid areas (Fig. 4A), the tumor cells expressed chymotrypsin (Fig. 4B) as well as synaptophysin (Fig. 4C), CD56, and chromogranin A. Scattered apoptotic tumor cells were seen. The stroma was very sparse and contained small vessels. A few scattered microcystic formations with hemorrhage were observed. Moreover, there were areas with hemosiderophages. Angioinvasion and perineural invasion were absent. Eight lymph nodes were examined microscopically and without metastases.

Immunohistochemistry revealed, in addition to the already mentioned markers, expression of CD10 and CK8. There was nuclear positivity for beta-catenin in a significant proportion of the tumor cells, especially in close proximity to smaller vessels, but positivity was diffusely present throughout the tumor (Fig. 4D). Trypsin (Fig. 4E) and BCL 10 (Fig. 4F) both showed a diffuse and strong positivity throughout the tumor. The Ki-67 index was 22%, classifying the neuroendocrine component as a grade 3 tumor, according to the WHO classification 2010 (Rindi et al., 2010). Distinct nucleoli as well as "salt and pepper" speckled nuclei were observed in some of the tumor cells (Fig. 5A). There was no expression of AFP, alpha-1 antitrypsin, calretinin, CEA-mono, CK7, CK19, CK20, gastrin, glucagon, insulin, NSE, serotonin, somatostatin, somatostatin receptor 2, vimentin, or VIP. Based on these findings, the diagnosis of a MAEC was made.

Electron microscopy

Ultrastructually, the tumor cells were of variable size

Table 2. Symptoms, age, sex, localization, treatment, follow up, and survival in the 45 published histological cases of MAECs.

Study	n	Symptoms	Age* [range], sex	Location, diameter* (cm) [range]	Type of surgery	Follow-up* in months [range]	Patients alive at time of publication
LaRosa et al., 2012 (USA, France, Japan, Italy)	12	Abdominal pain, weight loss	62.3 [37-88], 7M, 5F	4 head 1 head/body 1 body 1 body/tail 4 tail 1 † 8.8 cm [2.8-19.5]	NA	24.75 [6-111]	6
Ohike et al., 2004 (Germany)	6	Abdominal pain	51.3 [16-65], 2M, 4F	No predilection, 8.2 cm	NA	NA	NA
Klimstra et al., 1994 (USA)	5	Abdominal pain Incidental mass Hematemesis Incidental mass Abdominal pain	81M 70M 64F 48F 70F	Tail, 3 cm Multifocal, 10 cm Head, 10 cm Tail, 11 cm Head, 10 cm	NA NA Biopsy, bypass NA Biopsy, bypass	9.6 [3-18]	3
Yu et al., 2013 (USA)	5	Abdominal pain, dyspepsia Melena, weight loss Abdominal pain, diarrhea Abdominal pain, weight loss Anorexia, jaundice	80M 89M 60M 74M 59M	Head, 19 cm Head, 4.9 cm Head, 21 cm Body, 10 cm Head, 7.5 cm	Debulking with splenectomy Whipple's procedure CGP‡ Distal pancreatectomy with splenectomy Whipple's procedure	13.7 [2.5-36]§	3
Cho et al., 1996 (Korea)	1	Jaundice	52F	Uncinate process, 6 cm	Whipple's procedure	12	1
Chung et al., 2010 (Korea)	1	Watery diarrhea	59F	Tail, 8 cm	PPPD ll	NA	NA
Frank et al., 1998 (Germany)	1	Abdominal pain	61M	Head/body	Whipple's procedure	47	1
Ichijima et al., 1985 (Japan)	1	Asymptomatic	6F	Tail, 8 cm	Distal pancreatectomy	156	1
Imaoka et al., 2008 (Japan)	1	Lymphadenopathy	80M	Head, 4 cm	Whipple's procedure	NA	NA
Kobayashi et al., 2010 (Japan)	1	Asymptomatic	75M	Tail	Distal pancreatectomy	6	1
Kyriazi et al., 2009 (Greece)	1	Polyarthralgia	74M	Head, 12 cm	Whipple's procedure	3	1
Muramatsu et al., 2000 (Japan)	1	Weight loss	72M	Body to tail, 13 cm	Autopsy	3	0
Ogawa et al., 2000 (Japan)	1	Asymptomatic	50M	Head, 3 cm	PPPD	18	1
Ogbonna et al., 2013 (USA)	1	Abdominal pain	57F	Body, 2.5 cm	Pancreatectomy with splenectomy	0	1
Seth et al., 2008 (USA)	2	Abdominal pain	NA NA	NA, 12.5 cm NA, 4.5 cm	Distal pancreatectomy Pancreaticodoudenectomy	1 5	1 1
Shi et al., 2008 (China)	1	Whipple's triad	51F	Tail, 1.2 cm	Distal pancreatectomy	0	1
Soubra et al., 2011 (Lebanon)	1	Abdominal pain	52M	Head	Whipple's procedure	19	1
Ulich et al., 1982 (USA)	1	Asymptomatic	30F	Head, 5.8 cm	Whipple's procedure	0	1
Virlos et al., 2002 (UK)	1	Pruritus, weight loss	33M	Head, 3.5 cm	PPPD	15	1
Present case (Denmark)	1	Abdominal pain	62F	Tail, 5.2 cm	Pancreatectomy with splenectomy	12	1

NA, not available. * If more than one patient is reported, mean and [range] are given. † Information regarding tumor site for 1 patient was not available. ‡ CGP: Subtotal colectomy, partial gastrectomy, and 70% pancreatectomy. § 1 patient died of complications to surgery after 2.5 months. ll PPPD: Pylorus-preserving pancreaticoduodenectomy.

with a moderate to high amount of mitochondria, rough endoplasmatic reticulum (rER) and secretory granules (Fig. 5B). The secretory granules varied in size and had a homogeneous electron dense appearance and bore a resemblance to normal acinar secretory cells. The cytoplasm contained two distinct types of secretory

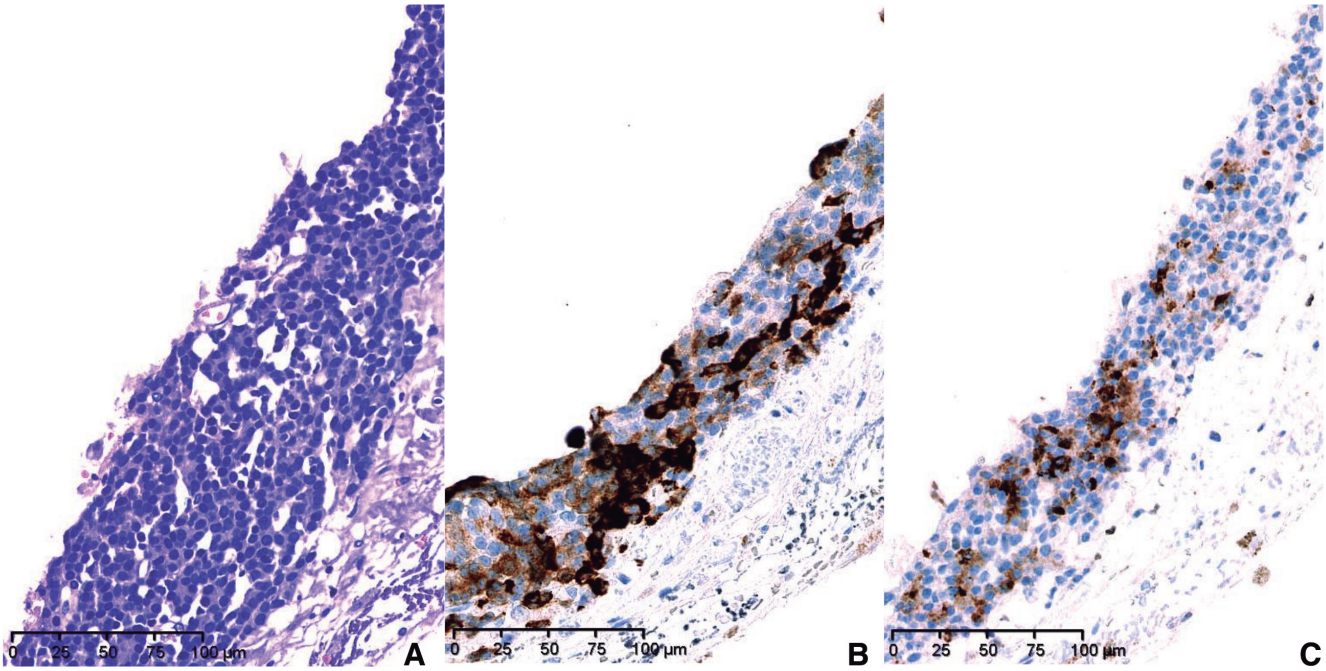

Fig. 3. Microscopic and immunohistochemical findings in the cystic part of pancreatic MAEC. **A.** Hematoxylin-eosin. **B.** Chymotrypsin. **C.** Synaptophysin.

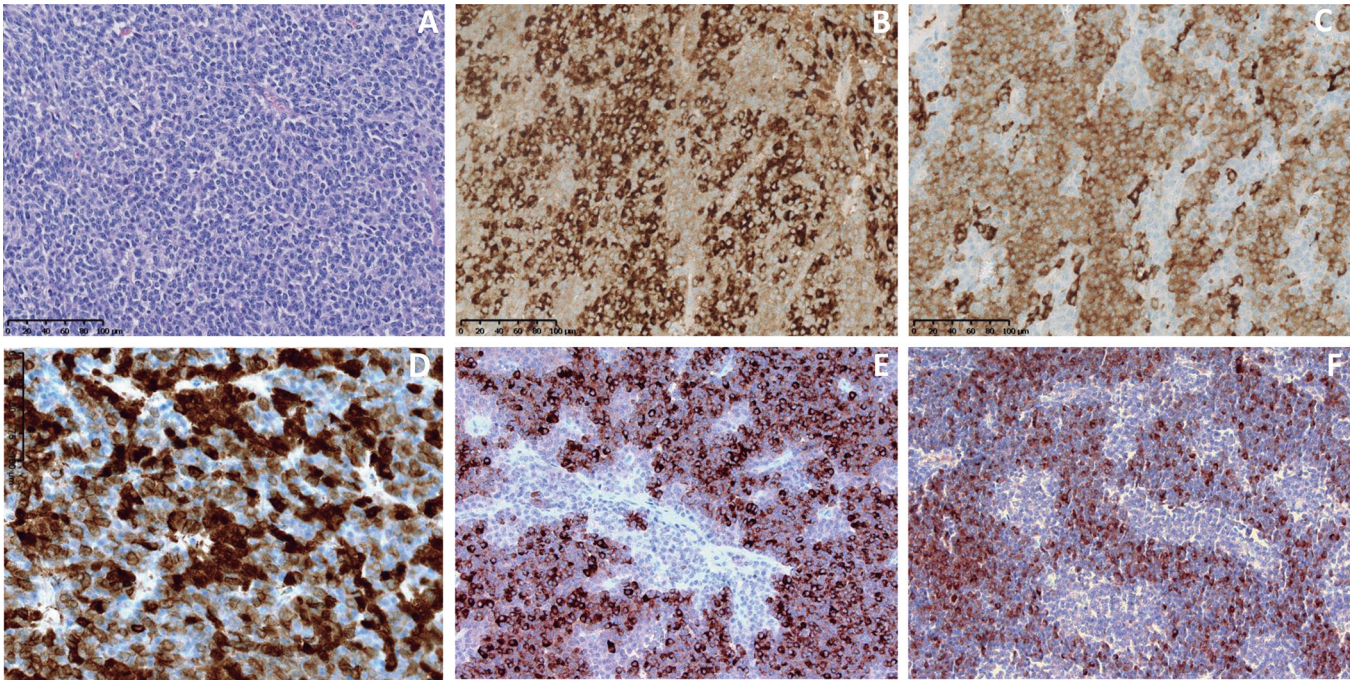

Fig. 4. Microscopic and immunohistochemical findings in a solid area of pancreatic MAEC. Immunohistochemically, the mixed nature of the carcinoma is illustrated with the following stains: **A:** Hematoxylin-eosin, **B:** Chymotrypsin, **C:** Synaptophysin, **D:** Beta-catenin, **E:** Trypsin, **F:** BCL10.

granules, with some cells containing larger (800 nm) and some cells containing smaller granules (100 nm), but most often the cells had intermediate features, with moderate amounts of rER and dispersed granules ranging 300-400 nm.

Literature review

A review of the English language literature revealed 44 previously reported cases of MAEC (Table 2). Including the present case, patients with MAEC are diagnosed at a mean age of 60.1 years (range 6-89 years). The male:female ratio is almost equal (56% men). Most tumors are located in the pancreatic head (51%), followed by the tail (37%). The mean diameter of the tumors is 8.2 cm (range 1.2-21 cm). The follow-up period ranged from 0 to 13 years. 26 of the 45 patients were alive at the end of the various follow-up periods.

Discussion

We present a case of pancreatic MAEC, an exceedingly rare tumor type in the pancreas, and review the existing English-language literature. Based on macroscopy and immunohistochemistry, solid-pseudopapillary neoplasia (SPN) represents one of the most important differential diagnoses of MAEC. SPNs are, however, predominantly found in young women, whereas our patient was 62 years old. Moreover, microscopically, the characteristic features of SPNs, such as pseudopapillary growth pattern, eosinophilic globules, foam cells, or longitudinal nuclear grooves, were not present. Instead, the tumor cells had mixed features of neuroendocrine and acinar cells. At immunohistochemistry, the strong positivity for BCL10, CK8, CK19, chromogranin A, chymotrypsin, trypsin, and synaptophysin clearly indicated a tumor with mixed features of ACC and NEC, as most of these markers usually are negative or only focally positive in SPN. On the other hand, markers often strongly expressed in SPN, such as alpha-1 antitrypsin, NSE, and progesterone receptor, were negative in the present case. Ultrastructually, the present case also had distinctive features, separating it further from SPN by the moderate to high amounts of mitochondria, rough endoplasmatic reticulum, and secretory granules, which are well known characteristics of secretory cells. The secretory granules varied in size and had a homogeneous, electron-dense appearance resembling acinar secretory cells, as described by others (Klimstra et al., 1994; Ichijima et al., 1985). Histologically and immunohistochemically, MAECs can show 3 different compositions: tumors with 1) separate acinar and neuroendocrine areas, 2) an admixture of neuroendocrine and acinar cells, or 3) a uniform but amphicrine cell population, showing neuroendocrine and acinar cytological features (Klimstra et al., 1992; Klöppel et al., 1996). In the present case, the cystic as well as the solid areas revealed an admixture of acinar as well as neuroendocrine features (Figs. 3, 4).

The histogenesis of MAECs is still unclear. Both exocrine and endocrine pancreatic cells are thought to originate from a multipotential precursor cell (Cho et al., 1996). The tumor cells may remain in a primitive state and produce immature hormones, but have such a low production that the vast majority of MAECs are nonfunctional (Ohike et al., 2004). Non-dysjunctional mitosis with dual differentiation or presence of amphicrine cells within the pancreas are two other theories regarding the histogenesis of MAECs (Lee et al., 2013).

A review of all previously published cases of MAECs (Table 2) showed that a few of these cases are based on cytology alone (Lee et al., 2013; Sullivan et al., 2013). The mean age of the resected patients with

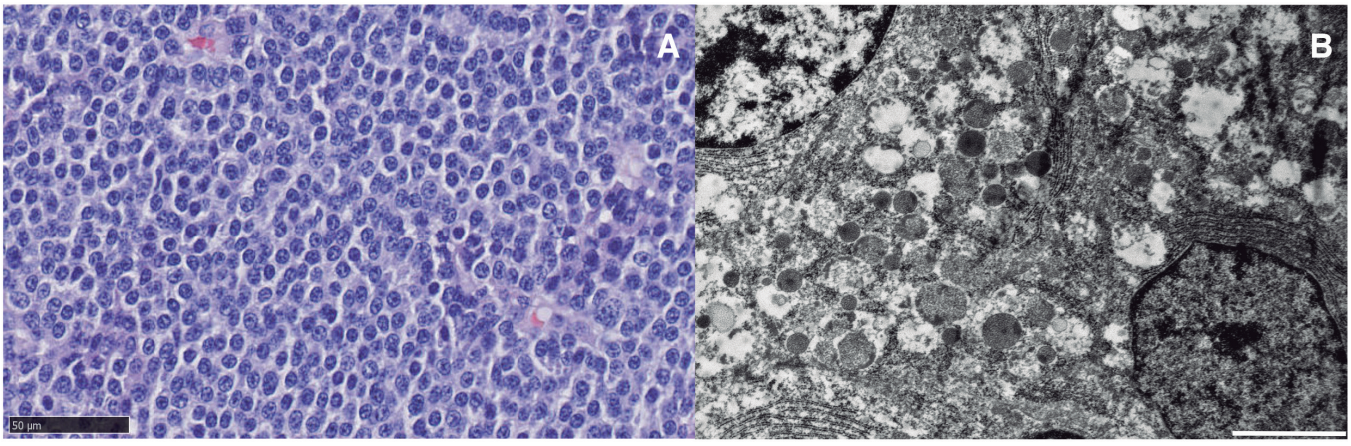

Fig. 5. Cytological and electron microscopic features of a pancreatic MAEC. **A.** A solid area where tumor cells have nuclei of uniform size is shown. Distinct nucleoli as well as "salt and pepper" speckled nuclei are observed in some of the tumor cells. **B.** Tumor cell with mixed ultrastructural features. Small, intermediate and larger granules are seen in close proximity to the rough endoplasmatic reticulum. Scale bar: 2000 nm.

MAECs fulfilling the inclusion criteria showed an almost equal age distribution (56% males). Considering the limited number of cases, our observation may well be coincidental, particularly because the early series by Klimstra and Ohike (Klimstra et al., 1994; Ohike et al., 2004) which, however, were included in our calculation, showed a female predominance. Interestingly, pure acinar cell carcinomas (ACC) show a male predilection by 3 to 1 (Klimstra et al., 2010; La Rosa et al., 2012).

MAECs have a dismal prognosis, with a median survival after surgical resection of approximately 24 months (La Rosa et al., 2012). In another study of 39 patients with histologically proven ACC, the median survival was 19 months for all patients, and surgery remained the best therapy for patients with resectable tumors (median survival of 36 months compared to 14 months) (Holen et al., 2002).These data indicate that MAECs may behave more aggressively than true ACCs, but larger-scale studies with a higher number of patients are needed to elucidate this further. However, ACCs have a high recurrence rate even after complete surgical resection, suggesting that micrometastases may be present in these patients at time of surgery (Holen et al., 2002). Chemotherapy and radiation therapy, however, do not usually improve the outcome significantly (Holen et al., 2002).

In conclusion, the present case of a pancreatic MAEC demonstrates the typical morphological, immunohistochemical and ultrastructural features of this rare tumor type. Our review of the previously published MAECs in the English-language literature establishes a slight male predominance in these tumors, which is contrary to previously reported small series.

Conflict of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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