

Mixed acinar-endocrine carcinoma of pancreas: a case report and brief review of the literature

Zhenzhen Liu^{1,2}
Chengyong Dong^{1,2}
Chengye Wang^{1,2}
Qinlong Liu¹
Deguang Sun¹
Liming Wang¹

¹Department of General Surgery, The Second Affiliated Hospital of Dalian Medical University, ²Dalian Medical University, Dalian, Liaoning Province, People's Republic of China

Abstract: Mixed acinar-endocrine carcinoma (MAEC) of the pancreas is a rare entity. We present a 65-year-old Chinese female who was admitted with jaundice and nagging epigastric pain with intermittent diarrhea for 1 month. She eventually underwent abdominal magnetic resonance imaging, which showed an 8×6 cm mass in the head of the pancreas and showed two abnormal lesions in the liver simultaneously. MAEC of the pancreas with synchronous hepatic metastasis was confirmed with immunohistochemistry after Whipple operation and hepatic partial resection of the lesions. Postoperative recovery of this patient was uneventful, and no evidence of recurrence or metastasis was observed after 12 months of follow-up. MAEC of pancreas is thought to be extremely rare and lack of typical clinical symptoms. The prognosis is poor overall, but early detection with complete resection may be beneficial to patients.

Keywords: acinar cell carcinoma, neuroendocrine carcinoma of pancreas, neuroendocrine carcinoma, pancreatic neoplasms

Introduction

Mixed acinar-endocrine carcinoma (MAEC) of the pancreas is a rare entity,¹ with 30 or so cases of pancreas MAEC reported in the English literature (Table S1). To date, its biological behaviors, the appropriate treatment modalities, and the overall prognosis remain unclear. Herein, we report a rare case of pancreas MAEC and present a brief literature review to contribute to the increased understanding of the clinical features of this disease.

Case report

The patient was a 65-year-old woman who presented with jaundice and nagging epigastric pain with intermittent diarrhea for 1 month. She denied fevers or chills, malaise, fatigue, or weight loss. She denied family history of pancreatic cancer and other cancers. She denied hepatitis B and other infectious diseases. Physical examination revealed that the sclera was mildly icteric and light tenderness could be felt under the xiphoid process, without rebound tenderness and muscle tension. There was a mass about 10 cm×7 cm around the navel, without a clear boundary between surrounding tissues, cystosolid, and no obvious abnormality was seen in the rest parts of the whole body. Laboratory tests revealed the following: aspartate aminotransferase (AST) 68.00 U/L (normal range 13–35 U/L); alanine transaminase (ALT) 138.00 U/L (normal range 7–40 U/L); total bilirubin 89.20 μmol/L (normal range 2–20 μmol/L); direct bilirubin 72.21 μmol/L (normal range 0–6 μmol/L); γ-glutamyltransferase (γ-GGT) 948.00 U/L (normal range 7–45 U/L); alkaline phosphatase (ALP) 494.00 U/L (normal range 50–135 U/L); and normal albumin, amylase, and glucose. Cancer antigen 19-9 (CA19-9), cancer antigen 125 (CA125), cancer antigen 153 (CA153),

Correspondence: Liming Wang
Department of General Surgery, The Second Affiliated Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian, Liaoning Province, 116027, People's Republic of China
Email wangbcc259@163.com

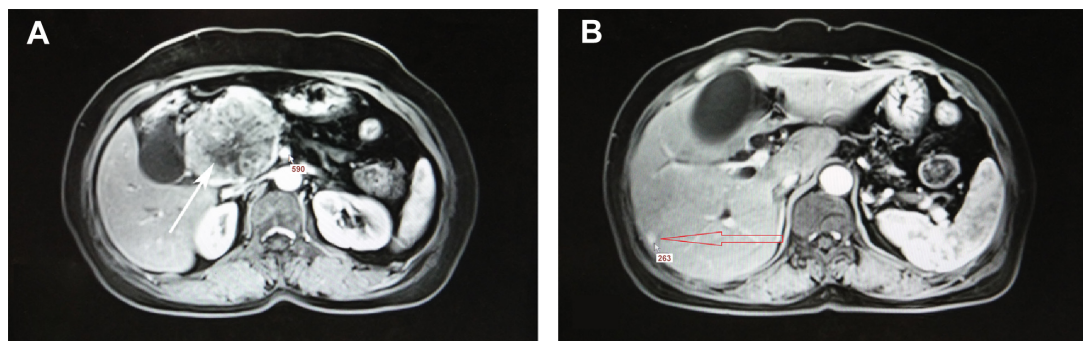


Figure 1 Abdominal enhanced magnetic resonance imaging with T1 findings.

Notes: (A) An 8×6 cm mass in the head of the pancreas (white arrow). (B) Liver metastasis from mixed acinar-endocrine carcinoma of the pancreas (red arrow).

and carcinoembryonic antigen (CEA) were normal. Alpha-fetoprotein (AFP) was 156.80 IU/mL (normal range 0.00–6.70 IU/mL). Chromogranin A level was 136 U/L (normal range 0–95 U/L in our hospital) and pancreatic polypeptide level was 307 ng/L (normal range 105–175 ng/L). The patient eventually underwent abdominal magnetic resonance imaging, which showed an 8×6 cm mass in the head of the pancreas and showed two abnormal lesions about 2×1 cm in the liver (Figure 1). Endoscopic ultrasound-guided fine-needle aspiration (FNA) of the mass was performed and its histopathology indicated pancreatic carcinoma. The patient then underwent pancreaticoduodenectomy (Whipple procedure) with tumor-free margins and negative lymph nodes. She underwent hepatic partial resection of the two lesions simultaneously. Pathological examination of the surgical specimen of pancreatic mass revealed a poorly circumscribed, elastic, soft, grayish-yellow section. Microscopically, the tumor cells had predominately solid and partly acinar morphology. The tumor measured 8 cm in the greatest dimension, extending into peripancreatic adipose tissue. It extended beyond the head of the pancreas but without the involvement of the celiac axis or the superior mesenteric vein or artery. Pathological examination of the surgical specimen of two liver abnormal lesions were confirmed as metastatic lesions of pancreatic mass. However, no regional lymph node metastasis was identified. Immunohistochemical staining of pancreatic mass was positive for trypsin and chymotrypsin, which indicated the tissue had an acinar component. Synaptophysin, chromogranin A, CD56, and neuron-specific enolase (NSE) were also positive for immunohistochemistry, suggesting that it had an endocrine component. Ki-67 had 10% positivity. Each component exceeded 25% of the tumor, and pathological diagnosis of MAEC was established (Figure 2). Microscopically, the tumor cells of liver metastasis had partly solid and partly acinar morphology. Immunohistochemical staining of liver metastasis was positive for trypsin and weakly positive

for synaptophysin, chromogranin A, and NSE (Figure 3). According to pathological analysis of primary MAEC of pancreas, the liver lesions showed a similar histological character to the primary pancreatic lesion, which suggested that the liver lesions derived from pancreatic metastatic lesions. After surgery, gastrin, glucagon, glucose, somatostatin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-hydroxytryptamine (serotonin) were detected, and all of these indicators were within normal limits. This might explain why the patient did not have clinical symptoms of abnormal hormone secretion, which is common in pancreatic neuroendocrine tumors. Moreover, she also underwent an octreotide scan after surgery which showed no evidence of uptake. However, the patient refused chemotherapy but wanted to accept regular checks. During the 12 months of follow-up, no evidence of recurrence or metastasis was observed.

Discussion

The pancreas is composed of exocrine and endocrine gland components, with the exocrine part comprising ductal and acinar cells, whereas the endocrine part is made up of endocrine cells. Pancreatic acinar cell carcinomas (ACCs) are uncommon, accounting for less than 2% of all pancreatic neoplasms,^{1,2} while pancreatic neuroendocrine tumors are less than 3% of all pancreatic neoplasms, without a significant sex predilection.³ However, ACCs have been found to show both ductal and endocrine differentiation.¹ Many researchers believe that MAEC of the pancreas is generally considered a variant of ACC.⁴ Pathological diagnosis of MAEC of the pancreas is based on these criteria: morphology of acinar and endocrine cells, and immunohistochemistry demonstrating both acinar markers (trypsin, chymotrypsin, lipase, and periodic acid–Schiff) and endocrine markers (chromogranin A, synaptophysin, CD56, NSE), at least 25%–30% for acinar markers and 25%–30% for endocrine

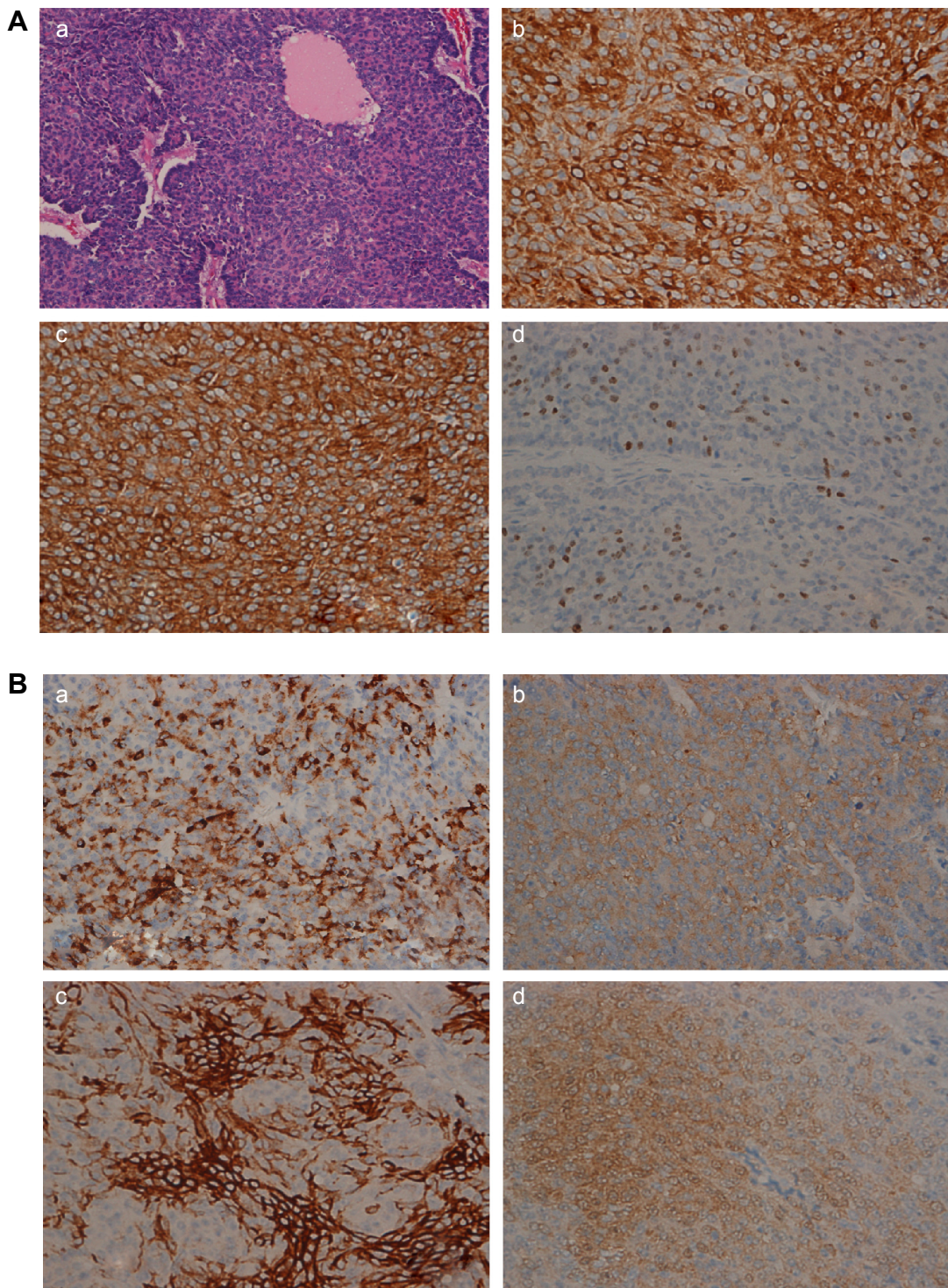


Figure 2 Histopathology of the pancreas tumor.

Notes: (A) (a) Hematoxylin–eosin image of the pancreas tumor (HEX200). (b) Immunohistochemistry of trypsin ($\times 400$, Abcam). (c) Immunohistochemistry of chymotrypsin ($\times 400$, Abcam). (d) Immunohistochemistry of Ki-67 ($\times 400$, Abcam [Cambridge, MA, USA]). (B) (a) Immunohistochemistry of chromogranin A ($\times 400$, Abcam) (b) Immunohistochemistry of synaptophysin ($\times 400$, Abcam). (c) Immunohistochemistry of CD56 ($\times 400$, Abcam). (d) Immunohistochemistry of neuron-specific enolase (NSE) ($\times 400$, Abcam).

markers.^{5,6} ACCs of the pancreas have been known to express endocrine markers as well in up to one-third of the cases, which are usually limited to a few scattered cells.^{2,7} Although pancreatic endocrine neoplasms and ACC are distinct entities, their pathological and morphological appearances are

sometimes extremely similar, and their components can be combined.⁸ When each component exceeds 25% of the tumor, the condition is defined as MAEC.⁶ However, little is known about MAEC because of its rarity.⁹ In MAEC, two different patterns of histopathologic structure have

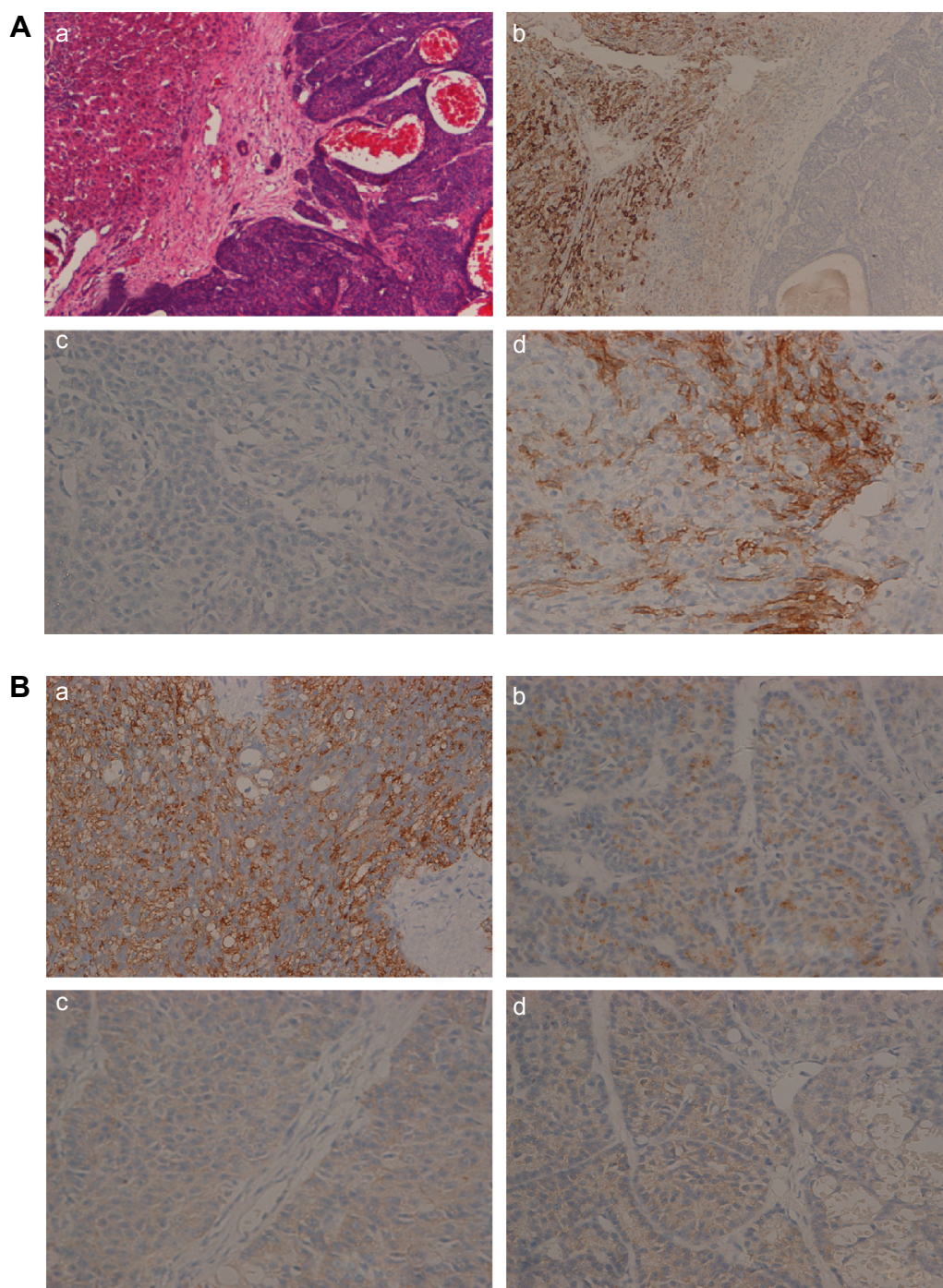


Figure 3 Histopathology of the liver metastasis.

Notes: (A) (a) Hematoxylin–eosin image of the liver metastasis (HEX100). Left is adjacent cancerous tissue and right is the liver metastasis. (b) Immunohistochemistry of hepatocyte paraffin I (Hep Par I) ($\times 100$, Dako). Adjacent cancerous tissue was positive for immunohistochemistry of Hep Par I and the liver metastasis was negative for the same. (c) The liver metastasis was negative for immunohistochemistry of Hep Par I ($\times 400$, Dako Denmark A/S, Glostrup, Denmark). (d) Immunohistochemistry of CD56 ($\times 400$, Abcam). (B) (a) Immunohistochemistry of trypsin ($\times 400$, Abcam), indicating that the tissue had an acinar component. (b) Immunohistochemistry of chromogranin A ($\times 400$, Abcam). (c) Immunohistochemistry of synaptophysin ($\times 400$, Abcam). (d) Immunohistochemistry of neuron-specific enolase (NSE) ($\times 400$, Abcam). Chromogranin A, synaptophysin, and NSE were weakly positive for immunohistochemistry, suggesting that the tissue of the liver metastasis had endocrine component.

been demonstrated. One is the coexistence of the acinar and endocrine components, and the other is their coexpression.¹⁰ The former consists of a histological segregation in the tumor differentiation.¹⁰ Each acinar and endocrine cellular component is entirely separate without intermingling.

The coexpression pattern consists of an admixture of both components, in which the neoplastic cells simultaneously show both acinar and endocrine differentiation.^{10,11} In our case, histology of the tumor presented with both acinar and endocrine differentiation and the neoplastic cells diffusely

expressed the acinar and endocrine markers (trypsin, chymotrypsin, chromogranin A, and synaptophysin), which indicated that tumor differentiation was towards both acinar and endocrine carcinomas.

MAEC of pancreas is an incredibly rare entity,¹ with only about 30 or so cases in the published English literature (Table S1). Based on these reported cases, 21 of all 35 patients with confirmed MAEC of the pancreas were male and the male:female ratio was 1.5:1.0, suggesting that MAEC of the pancreas affects both sexes. However, male patients may be more commonly affected, which is similar to ACC.⁸ The notion that MAEC of the pancreas mostly affects female patients^{4,11} may not hold true, which agrees with Yu et al.⁵ However, this may be incidental due to the small number of MAEC cases that have been reported. MAEC of pancreas is most commonly located at the head (18/35) and is often in middle-aged individuals (mean age of 60.9 years, except the 89-year-old patient [maximum value] and 6-year old patient [minimum value] were excluded when we calculated the mean age) (Table S1), which suggests MAECs of the pancreas should be considered in middle-aged patients with pancreatic head solid mass. In our case, the patient was no exception. The tumor size varied and the mean size was 6.95 cm in the greatest dimension. Abdominal pain and mass are common clinical manifestations in MAEC, but they are not a specific sign. In fact, the variable clinical behaviors of MAEC of the pancreas lack a reliable indicator so that we can detect the tumor early. In addition, all patients but one who presented with Zollinger-Ellison syndrome¹² did not exhibit hormone excess syndrome. Jaundice is relatively uncommon since MAEC is a well-circumscribed tumor and rarely invades surrounding tissue like the common bile duct, which could also be found in ACC.¹³ However, in our case, the patient was jaundiced because of tumor-mass effects.

The clinical diagnosis of MAEC of the pancreas remains a big challenge. The most common differential diagnoses of solid pancreatic mass are ductal carcinoma followed by neuroendocrine tumors.^{14,15} Other forms of solid pancreatic masses such as ACC, pancreatoblastomas, and solid pseudo-papillary neoplasms are also easily confused.^{16,17} Therefore, it is not surprising that the preoperative clinical diagnosis does not correctly identify MAEC of the pancreas.¹⁵ In our case, we conducted the endoscopic ultrasound-guided FNA of the pancreatic mass and it suggested pancreatic carcinoma. This may suggest the FNA still has some limitations for making a definite diagnosis.¹⁸ Therefore, the diagnosis of pancreas MAEC is mainly made by pathological analysis of the tumor morphology and immunohistochemical staining.

To our knowledge, about 15 sporadic single-case reports published over the last decade have explicitly recorded the quantification of acinar/endocrine components so that MAEC of the pancreas diagnosis could be verified⁵ (Table S1). As is shown in Table S1, trypsin, chymotrypsin, lipase, and periodic acid–Schiff were used for immunohistochemistry of acinar markers, while chromogranin A and synaptophysin were for endocrine markers.

Due to the small number of cases of MAEC reported, no standardized management protocol has been established. However, based on cases of MAEC reported on the current literature (Table S1), it is generally agreed that surgery is the prime treatment for the cases with resectable tumor.² Moreover, the large presenting tumor size and high Ki-67 index suggest that MAEC of the pancreas could grow rapidly if untreated. There also have been reports of patients benefiting from tumor debulking surgery and local and systemic antiproliferative therapy.⁷ The survival time of MAEC patients after surgical resection of the primary tumor varies. It was reported that there were only 21 of 35 cases of pancreas MAEC recording the survival time after surgical resection. The median overall survival time is about 12 months when the 21 cases are analyzed by the life table method, and the 12-month cumulative survival rate is 85%, as is shown in Table S2 and Figure S1. However, the overall survival of patients with ACC is reported to be from 18 to 19 months,¹⁹ which suggests that the prognosis of patients with MAEC shows lots of similarities to ACC.¹³ Moreover, the results of adjuvant chemotherapy and radiotherapy for MAEC have also been disappointing as well as ACC. Moreover, although many reports have shown that genetic alterations in the APC/ β -catenin pathway are common in ACC, we have little knowledge about the genetic alterations of MAEC since no researchers have reported it. Hence, we expect that the deep sequencing of MAEC can give us some hints about the genetic features of this rare tumor, which will definitely improve our understanding and treatment of this disease.²⁰

Conclusion

MAEC of the pancreas is an extremely rare tumor of the pancreas for which surgical resection remains a beneficial treatment. Patients need regular follow-up since it has a tendency of metastasis. There remains much uncertainty with MAEC because of the limited number of cases. Therefore, the accumulation of additional data from more cases is necessary to further elucidate this type of carcinoma and standardize optimal therapy.

Acknowledgment

Patient consent was obtained for this study.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 | Reported cases of mixed acinar-endocrine carcinoma in pancreas

| Case | Authors | Sex | Age (years) | Presentation | Location | Size ^a (cm) | Metastasis anterior ^b | Acinar marker | Endocrine markers | Morphology | Ki-67 | Treatment | Postoperative course | Metastasis posterior ^c | Year ^d |
|------|------------------------------|-----|-------------|-------------------------------------|----------|------------------------|----------------------------------|--|-------------------|---|---------|---|---|-----------------------------------|-------------------|
| 1 | Current study | F | 65 | Jaundice, epigastric pain, diarrhea | Head | 8 | Liver | Trypsin, chymotrypsin | CGA, SYN, NSE | Predominately solid and partly acinar | 10% | PD | 12 months without recurrence | N/A | 2015 |
| 2 | Yu et al ⁵ | M | 80 | Abdominal pain, early satiety | Head | 14 | Right kidney | Trypsin, chymotrypsin | CGA, SYN | Predominately solid and partly acinar | 53% | Splenectomy and debulking of the pancreatic mass and continued Sandostatin LAR and chemotherapy | Recurrence and metastasis; still alive at 3 years | Liver and right kidney | 2013 |
| 3 | Yu et al ⁵ | M | 89 | Melena | Head | 3.9 | No | Chymotrypsin | CGA, SYN | Predominately acinar and partly solid | 65% | Whipple procedure | Dead (2.5 months) after surgery due to complications | N/A | 2013 |
| 4 | Yu et al ⁵ | M | 60 | Abdominal pain | Head | 16 | No | Trypsin, chymotrypsin | CGA, SYN | Partly acinar and partly solid/trabecular | 65% | Subtotal colectomy, partial gastrectomy, and 70% pancreatectomy and chemotherapy | Recurrence and metastasis; dead (6 months) | Liver | 2013 |
| 5 | Yu et al ⁵ | M | 74 | Abdominal pain | Body | 10 | No | Trypsin, chymotrypsin | CGA, SYN | Predominately acinar | 10% | Neoadjuvant chemotherapy then underwent distal pancreatectomy and splenectomy and chemotherapy | Metastasis; still alive at 17 months | Wide metastasis | 2013 |
| 6 | Yu et al ⁵ | M | 59 | Fatigue, anorexia, jaundice | Head | 7.5 | No | Trypsin, chymotrypsin | CGA, SYN | Predominately solid | 30%–80% | Whipple procedure and adjuvant chemotherapy | Recurrence and 4 months metastasis; still alive at 7 months | Liver | 2013 |
| 7 | Ogbonna et al ⁷ | F | 57 | Epigastric pain | Body | 2.5 | No | Trypsin, chymotrypsin | CGA, SYN | Predominately solid | 40%–45% | Distal pancreatectomy and splenectomy and adjuvant chemotherapy | N/A | N/A | 2013 |
| 8 | Sullivan et al ¹⁸ | M | 75 | Liver transplant, multiple masses | Genu | 0.6 | Liver | PAS+ cyokeratin Trypsin, chymotrypsin | CGA, SYN | Half acinar component and half solid component | 40% | Chemotherapy | N/A | N/A | 2013 |
| 9 | Sullivan et al ¹⁸ | M | 51 | Acute pancreatitis | Body | 1.6 | No | Trypsin, chymotrypsin | CGA, SYN | Predominately solid | 7%–11% | Distal pancreatectomy | N/A | N/A | 2013 |
| 10 | Lee et al ⁶ | M | 66 | Vague midepigastic discomfort | Head | 3.1 | Liver | Trypsin, cyokeratin CAM 5.2 | CGA, SYN | and partly acinar Half acinar component and half solid component | 35% | Chemotherapy | Dead (21 months) | N/A | 2013 |

(Continued)

Table S1 (Continued)

| Case | Authors | Sex | Age (years) | Presentation | Location | Size ^a (cm) | Metastasis anterior ^b | Acinar marker | Endocrine markers | Morphology | Ki-67 | Treatment | Postoperative course | Metastasis posterior ^c | Year ^d |
|------|------------------------------|-----|-------------|---------------------------------------|---------------|------------------------|----------------------------------|---|--------------------------------------|--|-------|---|---|-----------------------------------|-------------------|
| 11 | Soubra et al ¹ | M | 52 | Epigastric pain, fatigue and jaundice | Head | 1.5 | No | Trypsin, chymotrypsin | CGA, SYN | Predominately solid and partly acinar | N/A | PD and chemotherapy | After 12 months recurrence, still alive 30 months | Liver | 2011 |
| 12 | Kobayashi et al ³ | M | 75 | Asymptomatic | Tail | 7 | No | Trypsin, PAS+ | CGA, SYN | Predominately acinar and partly solid | N/A | Distal pancreatectomy with lymph node dissection | 6 months without recurrence | N/A | 2010 |
| 13 | Chung et al ²² | F | 59 | Watery diarrhea | Tail | 8 | No | Trypsin, PAS+ | SYN | Half acinar component and half solid component | N/A | A partial pancreatectomy along with a splenectomy | N/A | N/A | 2010 |
| 14 | Kyriazi et al ² | M | 74 | Asymptomatic | Head | 12 | No | Trypsin, C56, CK7 | CGA, SYN | Predominately acinar | 80% | A modified Whipple procedure | Dead (21 months) | N/A | 2009 |
| 15 | Imaoka et al ¹⁰ | M | 80 | Generalized swollen lymph nodes | Head | 4 | No | Trypsin, chymotrypsin, lipase | CGA, SYN | and partly solid | N/A | Systemic chemotherapy and Whipple procedure | N/A | N/A | 2008 |
| 16 | Ohike et al ⁴ | M;F | 58.4 | N/A | N/A | 8.2 (n=2) | N/A | N/A | N/A | and partly solid | N/A | Surgery resection | N/A | N/A | 2004 |
| 17 | Mizuno et al ¹² | F | 67 | Zollinger-Ellison syndrome | Body | N/A | SMV | α -1-antitrypsin | CGA, SYN gastrin insulin | N/A | N/A | Chemotherapy | Dead (8 years) | Wide metastasis | 2001 |
| 18 | Skacel et al ²³ | M | 75 | N/A | Tail | 5.5 | No | Chymotrypsin α -1-antitrypsin | SYN | N/A | N/A | Surgery resection | 10 months without recurrence | N/A | 2000 |
| 19 | Skacel et al ²³ | M | 69 | N/A | Head | 10 | No | Chymotrypsin α -1-antitrypsin | SYN | N/A | N/A | Surgery resection | Dead | N/A | 2000 |
| 20 | Ogawa et al ²⁴ | M | 50 | Asymptomatic regular medical checkup | Head | 3 | No | PAS+ α -1-antichymotrypsin | CGA | Half acinar component and half solid component | N/A | A pylorus-preserving PD | 18 months without recurrence | N/A | 2000 |
| 21 | Frank et al ²⁵ | M | 61 | Abdominal pain, diarrhea, | Head and body | 4.9 | Liver | PAS+ Trypsinogen | NSE, CGA | Half acinar component and half solid component | N/A | PD, left hepatectomy, chemotherapy | Metastasis at 3 months; dead (2 years and 9 months) | Liver | 1998 |
| 22 | Shimoike et al ²⁶ | M | 28 | Convulsions | Tail | 3 | Liver | Trypsin α -1-antichymotrypsin | NSE, CGA | N/A | N/A | Biopsy and TAE, chemotherapy | Dead (10 months) | N/A | 1997 |
| 23 | Cho et al ²⁷ | F | 52 | Jaundice | Head | 6 | SMV | PAS+ amylase | NSE, CGA somatostatin and gastrin | Predominately solid and partly acinar | N/A | PD | Alive (1 year) | N/A | 1996 |
| 24 | Klimstra et al ¹¹ | M | 81 | Nausea, abdominal pain | Tail | 3 | No | Trypsin, chymotrypsin, lipase | CGA gastrin | Predominately acinar and partly solid | N/A | Surgery resection | Alive (3 months) | N/A | 1994 |
| 25 | Klimstra et al ¹¹ | M | 70 | Backaches, incidental mass | Multicentric | 10 | Lung, liver | Trypsin, chymotrypsin | CGA, CEA | Predominately solid and partly acinar | N/A | Surgery resection | Dead (3 months) | N/A | 1994 |

| | | | | | | | | | | | | | | | |
|----|------------------------------|---|----|-----------------|------|-----|----|-------------------------------|-----------------------------|--|-----|--|-----------------------------------|-------|------|
| 26 | Klimstra et al ¹¹ | F | 64 | Hematemesis | Head | 10 | No | Trypsin, lipase | CGA, SYN, somatostatin | Predominately solid and partly acinar | N/A | Biopsy and bypass | Dead (1 year and 6 months) | N/A | 1994 |
| 27 | Klimstra et al ¹¹ | F | 48 | Incidental mass | Tail | 11 | No | Trypsin, chymotrypsin, lipase | CGA, SYN, CEA | Predominately solid and partly acinar | N/A | Surgery resection | Alive with recurrence (12 months) | Liver | 1994 |
| 28 | Klimstra et al ¹¹ | F | 79 | Abdominal pain | Head | 10 | No | Trypsin, chymotrypsin, lipase | CGA, SYN | Predominately solid and partly acinar | N/A | Biopsy and bypass, chemotherapy, radiation | Alive (12 months) | N/A | 1994 |
| 29 | Ichijima et al ²⁸ | F | 6 | Abdominal mass | Tail | 8 | No | PAS+ | Tryptophan immunoperoxidase | N/A | N/A | Surgery resection | Alive (13 years) | N/A | 1985 |
| 30 | Ulich et al ²⁹ | F | 30 | Epigastric pain | Head | 9.3 | No | PAS+ lipase | Immunoperoxidase | Half acinar component and half solid component | N/A | PD | Alive (4 months) | N/A | 1982 |

Notes: ^aTumor size; ^bTreatment of anterior; ^cTreatment of posterior; ^dYear of publication.

Abbreviations: CEA, carcinoembryonic antigen; CGA, chromogranin A; F, female; M, male; N/A, not available; NSE, neuron-specific enolase; PAS, periodic acid-Schiff; PD, pancreaticoduodenectomy; SMV, superior mesenteric artery; SYN, synaptophysin; TAE, transcatheter arterial embolization.

Table S2 Life table showing survival time after surgery (months)^a

| Interval start time | Number entering interval | Number withdrawing during interval | Number exposed to risk | Number of terminal events | Proportion terminating | Proportion surviving | Proportion surviving end of interval | Proportion surviving at end of interval | Standard error of cumulative proportion surviving at end of interval | Probability density | Standard error of probability density | Hazard ratio | Standard error of hazard rate |
|---------------------|--------------------------|------------------------------------|------------------------|---------------------------|------------------------|----------------------|--------------------------------------|---|--|---------------------|---------------------------------------|--------------|-------------------------------|
| 0 | 21 | 0 | 21.000 | 0 | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 | 0.000 | 0.000 | 0.00 | 0.00 |
| 1 | 21 | 0 | 21.000 | 0 | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 | 0.000 | 0.000 | 0.00 | 0.00 |
| 2 | 21 | 0 | 21.000 | 0 | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 | 0.000 | 0.000 | 0.00 | 0.00 |
| 3 | 21 | 0 | 21.000 | 1 | 0.05 | 0.95 | 0.95 | 0.05 | 0.05 | 0.048 | 0.046 | 0.05 | 0.05 |
| 4 | 20 | 2 | 19.000 | 1 | 0.05 | 0.95 | 0.90 | 0.07 | 0.07 | 0.050 | 0.049 | 0.05 | 0.05 |
| 5 | 17 | 1 | 16.500 | 0 | 0.00 | 1.00 | 0.90 | 0.07 | 0.07 | 0.000 | 0.000 | 0.00 | 0.00 |
| 6 | 16 | 0 | 16.000 | 1 | 0.06 | 0.94 | 0.85 | 0.08 | 0.08 | 0.056 | 0.055 | 0.06 | 0.06 |
| 7 | 15 | 2 | 14.000 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |
| 8 | 13 | 0 | 13.000 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |
| 9 | 13 | 0 | 13.000 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |
| 10 | 13 | 1 | 12.500 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |
| 11 | 12 | 0 | 12.000 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |
| 12 | 12 | 12 | 6.000 | 0 | 0.00 | 1.00 | 0.85 | 0.08 | 0.08 | 0.000 | 0.000 | 0.00 | 0.00 |

Note: ^aThe median survival time is 12.00.

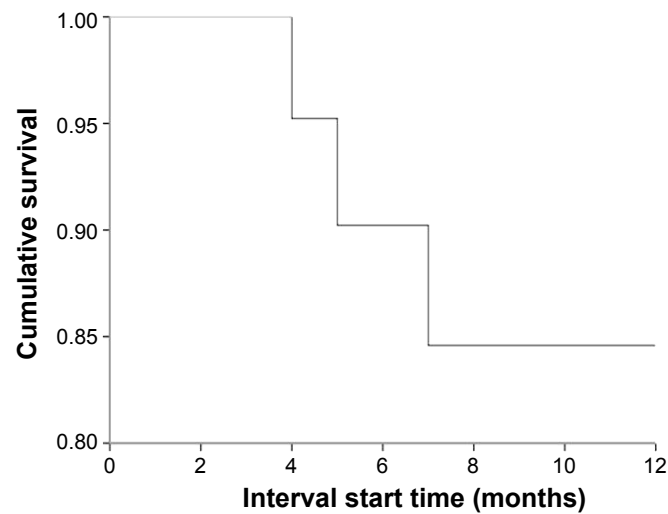


Figure S1 Survival curve for the patients after surgery.

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