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Case Report

Acinar Cell Carcinoma of the Pancreas with Gastric Metastasis: A Case Report and Literature Review

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Abstract

Background

Acinar cell carcinoma of the pancreas is a rare malignant epithelial tumor arising from the exocrine pancreas that represents about 1% of all pancreatic cancers. The natural history of this malignant neoplasm is poorly understood.

Case Summary

A 65 year-old Caucasian man presented with recurrent acute pancreatitis. Computed tomography found abnormal pancreatic duct dilatation extending distally from a segment of heterogenous enhancement in the genu of the pancreas. Endoscopic ultrasound with fine needle aspiration revealed a 1.7cm ill-defined mass in the genu of the pancreas. Cell block preparation from the cytology specimen was consistent with a pancreatic neoplasm to include acinar cell carcinoma of the pancreas (ACC). Exploratory laparotomy revealed a tumor in the genu of the pancreas and a 2 cm peripheral mass in the liver. Wedge resection of the liver mass was found to be morphologically and immunohistochemically similar to the pancreatic tumor, consistent with ACC. Systemic chemotherapy was initiated and approximately one year later the patient presented with hematemesis and anemia of acute blood loss. Esophago Gastro Duodenoscopy (EGD) revealed a 5 cm round, lobular, and friable mass located 3 cm from the gastroesophageal junction, spanning from the gastric cardia to the gastric body. Biopsy of the gastric mass was found to be histologically consistent with involvement by the patient's previously diagnosed ACC. Prior surveillance positron emission tomography - computed tomography did not detect gastric metastasis, and an EGD performed one year earlier was unremarkable.

Conclusion

The clinical presentation of acinar cell carcinoma of the pancreas (ACC) is generally non specific and the absence of ductal obstruction is characteristic. Metastasis is discovered in about half of patients at diagnosis, most commonly in the liver and regional lymph nodes. No cases of distant gastric metastasis have previously been described. Herein we report a novel case of ACC presenting with recurrent acute pancreatitis and later complicated by acute upper gastrointestinal bleeding secondary to gastric metastasis. The clinicopathology of ACC and gastric metastasis are both reviewed.

Keywords: Acinar Cell Carcinoma of the Pancreas; Gastric Metastasis; Hematemesis; Pancreatitis; Upper Gastrointestinal Bleeding.

Introduction

Acinar cell carcinoma of the pancreas (ACC) is a rare malignant epithelial neoplasm that represents less than 1% of all pancreatic cancers.1 Presenting signs and symptoms are usually nonspecific and may include abdominal pain, weight loss, nausea, and vomiting. Jaundice is an uncommon presenting sign in 0-21% of patients.2-8 Acute pancreatitis is the presentation in about 13% of cases,4 but is less frequently acknowledged in retrospective case series. Lipase hypersecretion syndrome, a paraneoplastic syndrome of panniculitis and polyarthralgia secondary to hyperlipasemia, is one of the rarest disease presentations described in 0-16% of cases. 2,4-6,8,9 Metastasis is detected in about 50% of cases at the time of diagnosis and is most commonly found in the liver and regional lymph nodes.3,6,9,10 Uncommon metastatic sites include the lung,4,8 bone,4 cervical lymph nodes,10 and ovary.11 We present a novel case of ACC presenting with recurrent acute pancreatitis

and later complicated by hematemesis due to distant metastasis to the stomach wall while on systemic chemotherapy. This is the first reported case of ACC with distant metastasis to the stomach.

Case Presentation

A 65 year-old Caucasian man with a history of stage IV (T1N0M1) ACC with known liver metastasis, tumor thrombus in the portal vein, deep venous thrombosis (DVT), and anemia of chronic disease presented with hematemesis. Exam revealed an alert and anxious man with relative hypotension and epigastric tenderness. Hemoglobin decreased to 7.3 from 8.7 mg/dL, and platelets remained stable at 104,000 / μL.

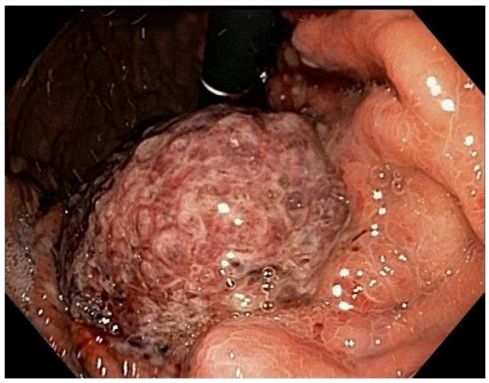

Figure 1: Endoscopic appearance of ACC gastric metastasis.

Esophago Ggastro Duodenoscopy (EGD) revealed a 5 centimeter (cm) round, lobular, and friable mass located 3 cm from the gastroesophageal junction, spanning from the gastric cardia to the gastric body (Fig. 1). Biopsy of the gastric mass was found to be histologically consistent with involvement by the patient's previously diagnosed pancreatic ACC (Fig. 2), including immunopositivity for alpha-1-antitrypsin (Fig. 3). No endoscopic or surgical intervention was performed and the patient was discharged in stable condition following blood transfusion. The patient died 1 month later due to unrelated complications from infection.

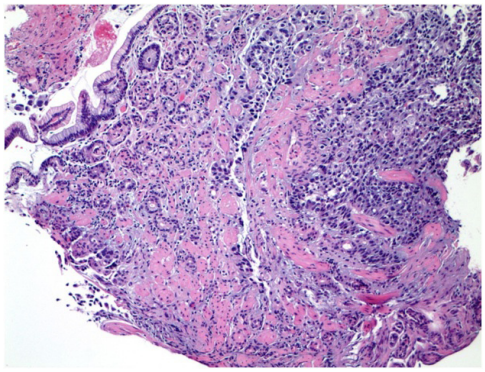

Figure 2: Histologic appearance of ACC gastric metastasis (H&E 10x). Infiltrative nests of tumor cells with enlarged hyperchromatic nuclei, small distinct nucleoli, and moderate eosinophilic cytoplasm. The cytoplasm is finely granular and occasional gland formations are seen.

Diagnosis of stage IV ACC was made 18 months before endoscopic detection of gastric metastasis. Recurrent acute pancreatitis was the patient's initial manifestation of underlying malignancy. The patient presented to our institution for evaluation of his sixth reported episode of pancreatitis spanning a 7 month period. Alcohol use was denied on history. Initial workup revealed a serum lipase of 1398 U/L, along with normal serum calcium and triglyceride levels. No gallstones were seen on ultrasonography. Medication list was reviewed and no culprits were identified. Serum IgG4 was unremarkable. A mechanical etiology was suspected after computed tomography (CT) found abnormal pancreatic duct dilatation to 10 millimeters (mm) extending distally from a 3.5 cm segment of heterogenous enhancement in the genu of the pancreas. Multiple low attenuation solid liver masses were also seen. Endoscopic ultrasound with fine needle aspiration (EUS-FNA) revealed a 1.7 cm ill-defined mass in the genu of the pancreas, with hypoechoic and heterogeneous echotexture. The FNA cytology revealed malignant cells with enlarged vesicular nuclei, prominent nucleoli, and moderate cytoplasm. On the cell block preparation, the tumor cells were found to be immunopositive for CK8/18, CK7 (25% of cells), alpha-1 antitrypsin, and inhibin (10% of cells), and immunonegative for synaptophysin, chromogranin, vimentin, CD10, PAX-8, and mucicarmine, with appropriate controls. These findings were consistent with a pancreatic neoplasm to include ACC, and excluded pancreatic neuroendocrine neoplasm. Exploratory laparotomy revealed a tumor in the genu of the pancreas and a 2 cm peripheral mass in segment 3 of the liver. A wedge resection of the liver mass was performed, and the tumor was found to be morphologically similar to the pancreatic tumor, with similar immunohistochemistry findings, consistent with ACC.

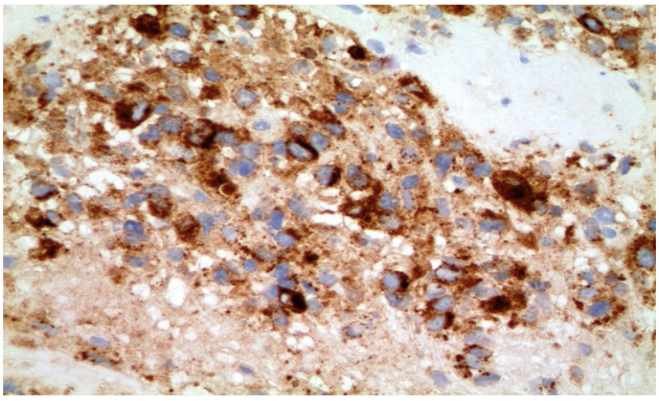

Figure 3: Immunohistologic appearance of ACC gastric metastasis (alpha-1 antitrypsin immunostain 40x). The tumor cells show cytoplasmic staining for alpha-1 antitrypsin.

The patient was initially treated with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). Transition to gemcitabine and paclitaxel occurred due to poor tolerance. A session of transcatheter arterial chemoembolization (TACE) using cisplatin was performed and then held due to development of sig-

nificant portal vein tumor thrombosis. Lastly, the patient received irinotecan with fluorouracil and folinic acid (FOLFIRI). While receiving FOLFIRI, hematemesis occurred and diagnosis of distant metastasis to the gastric cardia was made via EGD. Of note, regular surveillance positron emission tomography-computed tomography (PET-CT) did not detect gastric metastasis, and a previous EGD performed one year earlier was negative for malignancy.

Conclusions

Pancreatic cancers are almost entirely derived from the pancreatic epithelium, which is composed of endocrine (islet) and exocrine cells.12,13 The exocrine pancreas contains clusters of acinar cells that synthesize and release digestive proenzymes into a branching ductal system that converges into the main pancreatic duct. Acinar and ductal cells comprise 80% and 10%-15% of the gland volume, respectively.12-14 Islet cells contribute 1%-2% of the gland volume. Likewise, malignant neoplasms of the pancreas are about 95% exocrine and 1%-2% endocrine in origin. 12-14 Pancreatic ductal adenocarcinoma (PDAC) predominates and accounts for about 85% of malignant exocrine pancreatic neoplasms. 12 Among the remaining six main histologic types of malignant epithelial tumors arising from the exocrine pancreas, ACC is one of the rarest 15.

ACC represents about 1% of malignant exocrine pancreatic neoplasms.1,6,8,15-17 ACC is defined through its resemblance to normal pancreatic acinar cells by way of morphology and synthesis of pancreatic enzymes.3,8,10,15,16 The median age of diagnosis is the sixth or seventh decade of life.1,2,6,8,9,17 A male predominance is seen in most review studies,1,2,3,6,9 with the exception of a female preponderance (64%) reported in an institutional review study by Seth et al. Large population-based cohort comparisons of ACC to PDAC found that patients with ACC were significantly more likely to be male, Caucasian, and diagnosed at a younger age than patients with PDAC.1,17

Clinical features of ACC are usually nonspecific and secondary to locoregional mass effect.1,3,6,8,16 Abdominal pain is the most prevalent presenting symptom and may be accompanied by weight loss, nausea, and vomiting.1,3,5,6,8,9,16,17 Obstructive jaundice is uncommon, with prevalence reported as high as 21% in Seth et al. (prevalence of 0% in Wang et al., 6% in Tian et al., 7% in Raman et al., 9% in Tatli et al., 12% in Klimstra et al., 17% in Hsu et al.). Acute pancreatitis secondary to ACC was diagnosed in 13% of cases by Raman et al., and pancreatic duct dilatation was seen in 17% of cases in both Hsu et al. and Tian et al. Lipase hypersecretion syndrome is a rare presentation in less than or equal to 16% of cases in Klimstra et al. (prevalence of 0% in Raman et al., 0% in Seth et al., 0% in Wang et al., 8% in Holen et al., 9% in Tatli et al.). Hyperlipasemia mediates the effects of this paraneoplasticsyndrome, which generally occurs in the setting of hepatic metastasis or high primary tumor burden.10 Clinical manifestations include polyarthropathy and painful subcutaneous nodules from periarticular and subcutaneous fat necrosis (panniculitis). Lipase hypersecretion syndrome is the only specific disease presentation of ACC.

The absence of ductal obstruction is characteristic of, but not specific for, ACC.7 The pathophysiological explanation for the relative paucity of bile and pancreatic duct obstruction secondary to ACC is multifactorial. The main determinants are the derivative cell type and histopathologic behavior of ACC, as well as the geographic tendency of the primary tumor. PDAC, which is commonly associated with obstructive jaundice and pancreatitis, is a useful comparison to understand these concepts. First, ACC originates from the acinar cells as opposed to the intraductal epithelium in PDAC.3,7 Second, ACC exhibits exophytic (outward) growth and is often well-circumscribed;2,4,5,7,10 whereas, the tumor margins of PDAC are usually infiltrative.7 Third, ACC is less commonly found in the pancreatic head compared to PDAC. Two large population-based cohort studies comparing ACC to PDAC found that ACC occurs in the head in 28-42% of cases,1 versus 52-55% of PDAC cases.17 Even in cases of ACC that do arise in the head of the pancreas, ductal obstruction is the exception.2,4,6-8

The natural history of disease for ACC is more indolent than PDAC and more aggressive than typical pancreatic neuroendocrine tumors.9 Schmidt et al. and Wisnoski et al. found that patients with ACC are more likely to present with an earlier stage of disease, including less distant metastasis than patients with PDAC. Moreover, Schmidt et al. demonstrated a significantly greater stage-specific survival in ACC versus PDAC. As a result, surgical resection is more frequently performed in cases of ACC than PDAC.1,17 Long-term survival is greater in both operative and non-operative patients with ACC, and is independently predicted by younger age, lower grade tumors, and negative resection margins.1 Postoperative adjuvant therapy may improve outcome compared to resection of ACC alone.1,2

ACC carries a better prognosis than PDAC, but metastases at presentation are reported in approximately 50% of patients (7% in Raman et al., 33.5% in Schmidt et al., 46.4% in Wisnoski et al., 49% in Holen et al., 50% in Klimstra et al., 50% in Hsu et al.). After resection of the primary tumor, more than half of patients may develop recurrence (57% in Seth et al., 63.1% in Wang et al.). Metastasis confers the greatest impact on cancer-related morbidity and mortality.18 The most common sites of metastasis in cases of ACC include the liver and regional lymph nodes.3,4,6,9,10 Liver metastasis is likely favored via portal circulation. The hepatic microenvironment may also be well-suited for disseminated tumor cells from gastrointestinal tumors.18 Rare sites for ACC metastasis include the lung,4,8 bone,4 cervical lymph nodes,10 and ovary.11 Metastasis from direct tumor invasion can occur, especially

when the primary tumor approaches or exceeds 10 cm in diameter. Locoregional direct tumor invasion has been reported in the colon,5,19 duodenum,5,20 and twice in the stomach.5,20 Based on our review of the literature, ACC with distant metastasis to the stomach has not been described; therefore, our case is the first reported episode.

Metastatic tumors to the stomach are rare, with an incidence that is best determined from necroscopy series of solid malignant primary tumors (incidence of 0.7% per Green, 1.7% per Menuck and Amberg, 5.4% per Oda et al.). Gastric metastasis is usually found in patients with advanced disease of a known primary malignancy and is rarely the initial presentation of disease.21 Mechanisms of gastric metastasis include direct tumor invasion, hematogenous dissemination, lymphatic spread, and peritoneal dissemination.24 Clinical manifestations of gastric metastasis may include abdominal pain, dyspepsia, nausea, vomiting, and anemia from occult gastrointestinal bleeding. 21,23-25 Overt upper gastrointestinal bleeding is uncommon. 24 Clinical suspicion helps facilitate detection of gastric metastasis because nonspecific signs and symptoms may be confounded by the primary neoplasm and by the effects from treatment. EGD with biopsy is a reliable means for detection and confirmation of gastric metastases 23-25.

A recent review of 341 cases of gastric metastases by Namikawa&Hanazaki found that the most commonly associated primary tumors were breast cancer (27.9%), lung cancer (23.8%), esophageal cancer (19.1%), renal cell carcinoma (7.6%), and malignant melanoma (7%). 21,23-32 The high incidence of gastric metastases secondary to breast and lung cancers may reflect the high incidence of these tumors in the general population.24 The high incidence of gastric metastases from malignant melanoma may be due to high tropism for the gastrointestinal tract, since the incidence of melanoma is relatively low in the general population.28,33 Pancreatic cancer with gastric metastasis is reported in few studies, with an exception of Oda et al., who found two cases (1%) of gastric metastases among 209 autopsied cases of pancreatic primary tumors.

ACC is one of the rarest malignant epithelial tumors arising from the exocrine pancreas. Knowledge of the natural history of this neoplasm is limited to mostly small retrospective case series, although several large population-based cohorts do exist. Herein we present a case of ACC manifesting with recurrent pancreatitis and complicated by metachronous metastases to both the liver and gastric cardia, the latter while receiving systemic chemotherapy. Acute pancreatitis is an uncharacteristic presenting sign, and distant gastric metastasis has never before been documented in a case of ACC. Hematogenous dissemination was the likely mechanism of gastric metastasis in our patient. PET-CT failed to identify the presence of gastric metastasis prior to EGD, which was indicated for hematemesis with anemia of acute blood loss. Overt upper gastrointestinal bleeding secondary to metastatic ACC is a novel complication of an obscure disease, and this case highlights the clinical danger of gastric metastasis. Improving longevity in cancer patients may lead to an increased incidence of gastric metastases, including patients with uncommon malignancies. EGD remains a reliable means for detection of and possible intervention in cases of gastric metastases.

List of Abbreviations

ACC	Acinar Cell Carcinoma of the Pancreas
CT	Computed Tomography
DVT	Deep Venous Thrombosis
EGD	Esophagogastroduodenoscopy
EUS-FNA	Endoscopic Ultra Sound with Fine Needle Aspi ration
FOLFIRI	Irinotecan with Fluorouracil and Folinic Acid
FOLFIRINOX	5-Fluorouracil, Leucovorin, Irinotecan, and Oxaliplatin
PET-CT	Positron Emission Tomography - Computed Tomography
PDAC	Pancreatic Ductal Adenocarcinoma
TACE	Transcatheter Arterial Chemoembolization

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent (signature) was obtained from the patient who is the subject of our case report.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

OA and GR performed the EGD and discovered the gastric metastasis. HW performed the histological examination of the primary and metastatic tumors, and was a major contributor in writing the manuscript. MK, OA, HW, and GR analyzed and interpreted the patient data. MK, OA, and GR performed the literature review of ACC and gastric metastasis. All authors read and approved the final manuscript.

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