Acinar cell carcinoma of the pancreas presenting as diffuse pancreatic enlargement

Two case reports and literature review

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Abstract

Rationale: Pancreatic acinar cell carcinoma (ACC) is a rare malignant tumor of exocrine pancreas. It is typically a well-marginated large solid mass arising in a certain aspect of the pancreas. Diffuse involvement of ACC in the pancreas is very rare, and may simulate pancreatitis in radiological findings. We report 2 cases of ACC presenting as diffuse enlargement of the pancreas due to tumor involvement without formation of a distinct mass.

Patient concerns: The patients consisted of a 41-year-old man with weight loss and a 77-year-old man who was asymptomatic.

Diagnoses: Computed tomography (CT) and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT showed diffuse enlargement of the pancreas forming a sausage-like shape with homogenously increased FDG activity.

Interventions: Endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy of the pancreatic lesion was performed.

Outcomes: Histopathology results from the pancreas confirmed the diagnosis of pancreatic ACC.

Lessons: Because diffuse enlargement of the pancreas is a common imaging feature of pancreatitis, recognition of this rare morphologic pattern of ACC is important for radiological diagnosis of this tumor. Imaging is essential for detection and preoperative diagnosis of pancreatic neoplasms. The imaging features of ACC described previously include well-circumscribed large mass, usually exophytic, oval or round, with a varied degree of cystic components, and less intense enhancement than normal pancreas on postcontrast computed tomography (CT) and magnetic resonance (MR).\textsuperscript{13−7} Diffuse enlargement of the pancreas is rarely seen in the setting of pancreatic neoplasms unless in tumor-induced pancreatitis. We herein report 2 cases of pancreatic ACC showing diffuse enlargement of the pancreas due to extensive involvement of the tumor in the pancreas demonstrated in FDG PET/CT.

Keywords: FDG, pancreatic acinar cell carcinoma, positon emission tomography/computed tomography

1. Introduction

Pancreatic acinar cell carcinoma (ACC) is an uncommon malignancy of exocrine pancreas. It occurs mainly in adults, composed of relatively uniform neoplastic cells that are arranged in solid and acinar patterns with production of pancreatic exocrine enzymes.\textsuperscript{[1]} ACC of the pancreas may show different clinical symptoms, morphological features, and outcomes, which may give rise to difficulties in the clinical diagnosis of this tumor.\textsuperscript{[2]} Imaging is essential for detection and preoperative diagnosis of pancreatic neoplasms. The imaging features of ACC described previously include well-circumscribed large mass, usually exophytic, oval or round, with a varied degree of cystic components, and less intense enhancement than normal pancreas on postcontrast computed tomography (CT) and magnetic resonance (MR).\textsuperscript{[13−7]} Diffuse enlargement of the pancreas is rarely seen in the setting of pancreatic neoplasms unless in tumor-induced pancreatitis. We herein report 2 cases of pancreatic ACC showing diffuse enlargement of the pancreas due to extensive involvement of the tumor in the pancreas demonstrated in FDG PET/CT.

2. Case presentation

Ethical approval was waived by the institutional review board of our hospital, as this work is a retrospective case report.

2.1. Case 1

A previously healthy 41-year-old man presented with weight loss for 3 months. He denied nausea, diarrhea, abdominal pain, jaundice, or fever, and physical examination was normal. Abdominal ultrasonography disclosed diffuse enlargement of the pancreatic body and tail with hypoechoic echogenicity. CT confirmed enlargement of the pancreas, particularly in the pancreatic body and tail, with homogenously delayed enhancement after contrast administration. The pancreatic duct was not dilated. Serum amylase, lipase and IgG4 were within normal ranges, and CA19-9 and CA242 were 69.6 and 82.1U/mL, respectively. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/CT demonstrated homogenously increased FDG activity (SUVmax 3.5) in the enlarged, sausage-shaped pancreatic body and tail (Fig. 1A, B). Besides, a hypermetabolic
pulmonary nodule (SUVmax 2.1) with calcification and cavity change was also noted in the left upper lobe of the lung. According to the clinical and image findings, a pancreatic neoplasm could not be excluded, and the pulmonary nodule was considered a chronic inflammation. The patient then underwent endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) biopsy of the pancreatic lesion. The cytological examination showed degeneration of epithelial cells, but was negative for neoplastic cells. The patient declined surgery and was then discharged.

A follow-up 18F-FDG PET/CT was performed 5 months after the initial scan because the patient had persistent weight loss. PET/CT showed that the pancreas was obviously larger in size with more intense FDG uptake (SUVmax 4.3) (Fig. 1C). In addition, increased radioactivity was noted in the portal vein (SUVmax 3.9) (Fig. 1D). The previous pulmonary nodule in the left upper lobe diminished after antibiotic treatment. The repeated abdominal contrast-enhanced CT confirmed progressive enlargement of the pancreas, and the enhancement was inhomogenous with patches of hypoattenuating areas (Fig. 1E). The portal vein and its intrahepatic branch were dilated with multiple filling defects in the patent lumen (Fig. 1F). The follow-up images were indicative of pancreatic malignancy with tumor thrombus in the portal vein. The patient again underwent EUS with FNA biopsy and histological findings identified pancreatic ACC. The tumor cells contained PAS-positive cytoplasmic granules. In addition, immunohistochemical staining revealed tumor cells positive for AACT, AAT, and AE1/AE3, and negative for CgA, Syn, CD56, and Vimentin.

2.2. Case 2

A 77-year-old man without symptoms was referred to the hospital because diffuse enlargement of the pancreas had been accidentally found by abdominal ultrasonography in an outside hospital for 16 months. He denied abdominal pain, abdominal distention, nausea, diarrhea, loss of appetite, or weight loss during the course of disease. Serum amylase, lipase, IgG4, and tumor markers such as CEA, CA199, CA242 were within the normal limits. In contrast-enhanced CT, the whole pancreas was found to be diffusely swollen with a clear margin, forming a sausage-like shape. The enhancement was heterogeneous with multiple cystic areas in the diffusely enlarged pancreas (Fig. 2A). The pancreatic duct and the common bile duct were not dilated. 18F-FDG PET/CT showed significantly increased FDG uptake in the enlarged pancreas (SUVmax 9.4) that was diffusely distributed from the uncinate process to the tail of the pancreas (Fig. 2B, C). No other hypermetabolic lesion was detected. A EUS-guided FNA biopsy was performed and histological findings identified pancreatic ACC. The tumor cells contained PAS-positive cytoplasmic granules. In addition, immunohistochemical staining revealed tumor cells positive for AACT, AAT, and AE1/AE3, and negative for CgA, Syn, CD56, CD10, and Vimentin.

3. Discussion

Although the pancreas is composed predominantly of acinar cells, which are responsible for the production of digestive enzymes, the majority of pancreatic carcinomas are adenocarcinomas of ductal origin; ACC of the pancreas only represents 1% to 2% of neoplasms of the exocrine pancreas. Extensive studies of ACC have been carried out with detailed descriptions of its clinicopathologic features. Typically, ACC occurs during the fifth...
to seventh decades of life, with a male predilection.\[8-13\] Patients with ACC may be asymptomatic or may present clinically with nonspecific symptoms, such as abdominal pain, weight loss, nausea, or diarrhea.\[3,6,8,9,13\] Unlike pancreatic ductal adenocarcinoma, biliary obstruction and jaundice are infrequent presenting complaints,\[3,6-9\] because ACC generally push rather than infiltrate into adjacent structures.\[1\] On rare occasions, lipase hypersecretion syndrome, characterized by excessive lipase production with subcutaneous fat necrosis and polyarthralgia, occur in 10% to 15% of patients with ACC.\[1,3,8,9\] In our cases, 1 patient was asymptomatic and the other experienced weight loss without any other complaints, which is in concordance with previously published data. Lipase hypersecretion syndrome was absent in the case of our patients possibly due to its rarity.

Histopathologically, ACC has several architectural patterns of growth: an acinar pattern consisting of cells growing in well-formed acini, which is the most characteristic pattern; a solid pattern characterized by sheets and cords of tumor cells in a fibrovascular stroma. In rare instances, a trabecular arrangement or a gyriform appearance of tumor cells may be present.\[1,2,8,9,13\] The desmoplastic stroma characteristic with well-developed glandular structures of ductal adenocarcinomas is generally absent. The histological appearances of ACC sometimes closely mimic of pancreatic endocrine tumors. Therefore, immunohistochemistry is important for distinguishing ACC from other pancreatic neoplasms.\[2\] The diagnostic hallmark of ACC is the immunohistochemical demonstration of digestive enzymes of exocrine pancreas, such as trypsin, chymotrypsin, and lipase. Neuroendocrine markers are generally negative or only focally positive.\[1,8,9,13\] Cytokeratin stains are usually positive.\[13\] PAS staining after diastase digestion characteristically reveals PAS-positive granules corresponding to zymogen granules, which are detectable in greater than 90% of ACCs.\[8\] In our cases, both of the tumors were cytoplasmic positive for PAS. Immunohistochemically, they were positive for AAT and AACT, which are antibodies against trypsin and chymotrypsin, respectively. Syn and CgA, well-known immunohistochemical markers of neuroendocrine tumors, were negative in both cases. In addition, positive staining of AE1/AE3, which is an antibody cocktail against cytokeratin, and negative for CD56, CD10, and vimentin did provide evidence for distinguishing from solid pseudopapillary tumor. The ki67 index of the first case was 35%, which is in concordance with previous data demonstrating that the mean ki67 index was 32.21% in ACCs in a clinicopathologic study with 62 cases.\[13\] The above characteristics in the pathological specimens obtained from FNA biopsy in our cases were histologically compatible with ACC.

ACC may arise in any portion of the pancreas, but the pancreatic head seems to be the most common site.\[3,4,9,13,14\] Radiographically, ACCs are usually large, oval or round, exophytic, and well-margined mass arising from the pancreas on CT and MRI.\[3-6,14-19\] The mean dimension of the tumor is around 5 to 7 cm.\[3,6,7,14,19\] Central cystic component due to necrosis might be present within the tumor,\[3,4,6,7,14,15,17-19\] and the cystic areas might constitute more than 75% of the mass.\[15,6\] Some tumors also contain internal foci of calcifications,\[3,4,7,14,19\] while intratumoral hemorrhage is not frequently seen. The tumors typically enhance homogeneously or heterogeneously but less than surrounding pancreatic parenchyma.\[3,4,6,7,17-19\] Rarely, ACCs might be hypervascular in arterial phase imaging.\[15,20,21\] Unlike ductal adenocarcinoma, ACCs may not

Figure 2. (A) Arterial phase of contrast-enhanced CT showing diffuse enlargement of the pancreas with a clear margin, forming a sausage-like shape. The enhancement was heterogeneous in the pancreas with multiple hypodensening cystic areas. (B) Axial PET/CT fusion image revealing diffuse enlargement of the pancreas with markedly increased radioactivity. The SUVmax was 9.4 in the pancreas. (C) The maximum intensity projection of PET image demonstrating diffuse and intense FDG uptake involving the entire pancreas from the uncinate process to the pancreatic tail.
commonly cause pancreatic ductal dilation or common bile duct dilation.\[3,4,6,7,17-19\]

However, rather than presenting as a well-circumscribed mass such as typical ACCs, both tumors in our cases extended through the whole or the bulk of the pancreas that was demonstrated by FDG PET/CT, and replaced the pancreatic parenchyma to mimic the shape of the pancreas, which was referred to as a sausage-like shape without formation of a distinct mass. ACC involving the entire pancreas is very rare. In a clinicopathologic study of 62 ACCs of the pancreas, only 1 case involved the entire pancreas, while others were well-circumscribed mass in a certain aspect of the pancreas.\[13\] The possible explanation for this rare, but unique tumor shape in ACC might be intraductal growth of the tumor and spreading within the main pancreatic duct, which was first described by Hashimoto et al\[22\] in 2003. In their case report, the tumor formed a bulging intraductal mass in the main pancreatic duct with invasion and compression of the pancreatic parenchyma. CT and MR revealed a solid sausage-shaped intraductal tumor in the pancreas; however, the CT/MR images were not displayed in this paper.\[22\] Since then, the intraductal variant of ACC characterized by intraductal polypoid growth has been described in some studies with less than 30 cases in total.\[13,23-31\] The majority of those intraductal growing ACCs were intraductal mass with cystic dilatation of the pancreatic ducts, which closely resembles that of intraductal papillary mucinous neoplasms.\[23-25,27,28,31\] In some cases, ACCs with intraductal polypoid growth spread along the pancreatic ducts, filling the ducts and destroying the duct walls with invasion to the parenchyma, which contributes to the formation of a distinctive sausage-like gross tumor shape.\[22,26,29\] and that probably was the case in our patients.

In PET/CT, ACC of the pancreas are likely to demonstrate a high FDG uptake\[21,29,32-34\] in line with its relative aggressiveness. But sometimes the tumors may present weak FDG activity,\[33,35,36\] which might be due to cystic degeneration\[33\] or extensive and various degrees of clear cell change.\[16\] In our cases, increased FDG activity was demonstrated in both of the tumors with a wide range of SUVs (SUVmax 3.5–9.4) that is consistent with the literature. In addition, tumor thrombus from the upper portion of the superior mesenteric vein to the intrahepatic branch of the portal vein was also revealed on both PET/CT and contrast-enhanced CT in the first case. Pancreatic tumors are rarely accompanied by portal tumor thrombus, which is commonly demonstrated in hepatocellular carcinoma. There have been only a few case reports of ACC accompanying tumor thrombus in the portal vein, superior mesenteric vein, and splenic vein.\[3,5,6,7,29,37,38\] It is important to differentiate tumor thrombus from blood thrombus because therapeutic strategy and prognosis varies. In our case, although we could not obtain tissue from the tumor in the portal vein, the compatible FDG uptake of the thrombus with the primary tumor, and the contiguous nature of the extension from the pancreatic primary tumor support the conclusion of tumor thrombus.

The prognosis of ACC is considered better than that of ductal adenocarcinoma but worse than pancreatic endocrine tumors.\[10,12\] A previous study based on cancer registry database of 672 patients with ACC demonstrated that patients with ACCs have a mean overall survival of about 47 months with an overall 5-year survival of 42.5%, compared with 3.8% for ductal adenocarcinoma.\[11\] In our first case, the patient underwent 4 cycles of chemotherapy without surgical resection of the tumor, and he was alive with disease 19 months after detection of the tumor; however, follow-up data were not available in the second case. It is well established that surgical resection and the stage of ACC correlate significantly with survival. The 5-year survival rate in unresected ACC patients varied from 0% to 22%, with a median survival time of 3 to 25 months in different epidemiological studies, whereas resected ACC patients had higher 5-year survival rate of 36.2% to 71.6% and longer median survival time (27–123 months).\[10,12\] Interestingly, it has been suggested in a clinicopathological study with a small number of patients with ACCs that the intraductal polypoid growth pattern may be associated with less aggressive pathological features and higher disease-specific survival rates. The respective 5-year disease-specific survival rate was 85.7% for patients having ACC with intraductal polypoid growth, and 25% in the absence of intraductal growth.\[26\] The metabolic indices of the tumor derived from FDG PET/CT have been shown to be independent prognostic factors in many neoplasms, including pancreatic ductal adenocarcinoma.\[39-42\] However, there are not enough data for such study in ACC due to its rareness.

4. Conclusion

We have reported 2 cases of histologically proven ACC of the pancreas, which appeared as an uncommon sausage-like tumor shape involving the bulk or the entire pancreas depicted by FDG PET/CT without forming a distinct mass. This rare but unique tumor shape might be a feature for identification of pancreatic ACC, specifically that with intraductal growth and invasion to pancreatic parenchyma, although this pattern of growth was not histologically confirmed in our case. Awareness of this rare morphologic pattern in ACC is important so that diagnosis can be made correctly without delay.

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