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RESEARCH ARTICLE

DIFFICULT PREOPERATIVE DIAGNOSIS OF MULTIFOCAL PANCREATIC INTRAEPITHELIAL NEOPLASIA ARISING FROM LONG-STANDING BENIGN CYSTIC LESIONS: A CASE REPORT

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ABSTRACT

Pancreatic intraepithelial neoplasia is a premalignant tumor that arises from ductal epithelial cells of the pancreas. It is generally less than 5mm in size and affects individuals older than age of 50 years. Diagnostic studies used to visualize pancreatic cancers include computed tomography scan, magnetic resonant imaging, and abdominal ultrasound. Pancreatic intraepithelial neoplasia is not well visualized in these diagnostic imaging studies and thus it is difficult to diagnose without intraoperative tissue sampling. We present a case of multifocal pancreatic intraepithelial neoplasia originating from benign cystic lesions in the body and tail of pancreas, which was discovered postoperatively only, despite all the imaging modalities.

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INTRODUCTION

Pancreatic cysts are most commonly benign however some can have malignant nature. Benign cysts include serous cystadenoma whereas cysts that have malignant potential include pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). PanIN is a precancerous tumor that can lead to invasive pancreatic ductal adenocarcinoma (PDAC), which has a very poor prognosis[(1)], and is the 4th leading cause of cancer death in the United States[(2)]. PanIN is most commonly seen in patients older than 50 years of age [(3)]. They are usually small (<5mm) and they proliferate from ductal epithelium [(4)] but proliferation from other pancreatic cell types, such as acinar cells [(5)] is also a possibility. Genetic mutations in *Sox17* in acinar cells were shown to cause transformation to ductal epithelium, which gives PanIN a potential site to form. In addition, mutation in *Kras* gene transforms acinar cells into PanIN [(6)], which can later develop into PDAC. Transformation of PanIN into PDAC follows a few steps and these are classified as different grades. Grade I (PanIN-1) has low-grade dysplasia and shows mucinous hyperplasia; this is in contrast to Grade II (PanIN-2), which has moderate-grade dysplasia[(1)]. Grade III (PanIN-3) has the highest-grade dysplasia and is called carcinoma in situ. PanIN-3 has the highest potential to become invasive and become cancerous. This high risk of pancreatic cancer development makes it important to diagnose PanIN early in the course, which can be done with diagnostic imaging such as abdominal ultrasound, computed tomography scan or magnetic resonant imaging. However, imaging does not always clearly show PanIN formation[(7)].

CASE REPORT

A 69-year-old former smoker female with a past medical history of asymptomatic multiple small pancreatic cysts presented to the hospital 5 days ago for a possible surgical intervention. The patient has a past medical history of Type II diabetes, diverticulosis, chronic kidney disease, and hypertension.

Her past surgical history includes excision of multiple lower extremity neuromas, partial thyroidectomy due to papillary thyroid carcinoma, hysterectomy, appendectomy, and cholecystectomy. She also has a family history of colorectal cancer; patient's last colonoscopy was done 4 years ago. The benign cysts were incidentally found 6 years ago, and they were monitored with MRIs every year in a gastroenterology office clinic. The patient remained asymptomatic with no changes in cysts' size. The follow-up MRI taken 8 months ago showed no ductal dilation and small scattered cysts in the body and tail of pancreas, which were unchanged from the previous imaging performed a year ago. However, the report suggested diagnosis of either branch-duct intraductal papillary mucinous neoplasm (IPMN) or chronic pancreatitis. A month later, patient presented to the gastroenterology office to discuss the MRI findings but also had symptoms of generalized abdominal pain, acid reflux, and constipation. She was then sent to our hospital for further evaluation with an endoscopic ultrasound-guided fine-needle aspiration (EUS/FNA). The endosonographic report showed hypoechoic lesions suggestive of cysts in the pancreatic tail (Figure 1).

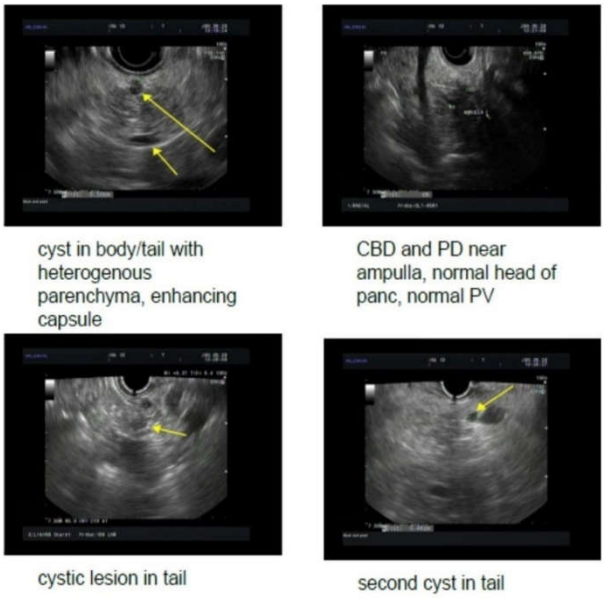

Figure 1. Endoscopic ultrasound guided fine-needle aspiration showing cysts in the body and tail of pancreas

Largest cyst was measured to be 5x5mm in maximal cross sectional diameter without obvious communication with the main pancreatic duct. The cytology report showed abundant clusters of neoplastic cells in the tail of pancreas with eosinophilic granular cytoplasm and round nuclei with conspicuous nucleoli. Differential diagnosis included acinic cell carcinoma and neuroendocrine neoplasm, which was found to be negative for synaptophysin (clone SP11), chromogranin (clone LK2H10), and trypsin by immunostains. Although immunostaining of the cells was able to rule out neuroendocrine tumor, it was unable to classify the specific type of neoplasm. The patient was then scheduled for the surgical removal of the distal portion of pancreas and possibly the spleen. During the procedure, en bloc distal pancreatectomy and splenectomy, partial omentectomy, and lysis of adhesions were performed. Pancreatic tissues resected from the body and tail during surgery were sent for pathologic evaluation, which showed focal microscopic acinar cystic transformation (ACT) and multifocal low-grade pancreatic intraepithelial neoplasia (PanIN).

DISCUSSION

Cystic pancreatic lesions are categorized as simple benign cysts and cystic neoplasms. Some of the cystic neoplasms are mucinous cystadenoma and intraductal papillary mucinous neoplasm (IPMN). Small-branch duct IPMN is usually found in asymptomatic patients with small cysts[8]. IPMN is grossly visible in contrast to PanIN, which is microscopically visible. Our patient was diagnosed with pancreatic cysts 6 years ago and was asymptomatic up until a few months ago. The latest MRI suggested a possible diagnosis of IPMN thus fine-needle aspiration for further investigation was needed. However, the final diagnosis was made after surgical intervention and it was PanIN. A case report published in 2015 also reported a patient with a history of benign pancreatic cysts that was diagnosed as IPMN preoperatively but was found to be PanIN postoperatively [1]. Thus, in the case of possible IPMN, PanIN should be kept as a differential diagnosis and further investigation should be done to rule out PanIN in order to reduce risk of pancreatic ductal adenocarcinoma development.

Patients with small benign cystic lesions present asymptomatically but when they become precancerous or cancerous, patients start having usually abdominal pain[1, 7]. Our patient's asymptomatic course lasted for years. Despite the MRI showing no changes compared to previous imagings, she became symptomatic with complains of abdominal pain and constipation, which clued some possible changes in the cysts. The decision of FNA was made to further investigate the pathology and the cytology report showed formation of possible acinic cell carcinoma. Although exceedingly rare, pancreatic cysts can undergo acinar differentiation and cause acinar cystic transformation (ACT); also referred to as acinar cell cystadenoma[9]. Finding ACT preoperatively might have led us to the final diagnosis as ACT, but then we would have missed the actual diagnosis of PanIN. Final diagnosis of multifocal PanIN and focal ACT in our patient shows the importance of diagnostic accuracy preoperatively. PanIN is a precancerous lesion that grow from ductal epithelium. Our patient had benign cystic lesions for years and development of PanIN now suggests the possibility of PanIN arising from benign pancreatic cysts. *Bansal S, et al.* reported that there might be some transformation of acinar cell cystadenoma (ACC) to PanIN, which gives the possibility of PanIN arising from ACC in our patient[9]. This might also be possible in our case but development of PanIN from ACC in 2 months is unlikely. Further information on how fast the transformation occurs is needed to make a final conclusion.

CONCLUSION

Benign cystic lesions might give rise to PanIN and yearly MRI screening is not sufficient to detect minor changes. An additive diagnostic test should be considered to increase the sensitivity of detecting minor changes since malignant transformation can be fatal.

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Abbreviations

Acinar cell cystadenoma: ACC
Acinar cystic transformation: ACT
Endoscopic ultrasound-guided fine-needle aspiration: EUS/FNA
Fine-needle aspiration: FNA
Intraductal papillary mucinous neoplasm: IPMN
Magnetic resonance imaging: MRI
Pancreatic ductal adenocarcinoma: PDAC
Pancreatic intraepithelial neoplasia: PanIN

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