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Cytological-Pathologic Correlation

Coexisting pancreatic serous cystadenoma and pancreatic ductal adenocarcinoma: A cytological-pathologic correlation with literature review☆

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ABSTRACT

Pancreatic serous cystadenoma (SCA) is a benign neoplastic lesion with a distinctive gross and microscopic appearance consisting of numerous thin-walled cysts lined by uniform epithelial cells with clear cytoplasm and small nuclei. The vast majority of serous cystadenomas are benign. Pancreatic SCA has rarely been reported in association with other pancreatic lesions. We present a challenging case in which a cystic and solid pancreatic mass was identified on imaging studies. FNA was performed and showed clusters of atypical cells with significant nuclear pleomorphism (> 4:1), disorganized, overlapping nuclei, and prominent nucleoli. The FNA diagnosis was positive for malignancy, consistent with adenocarcinoma. The patient underwent neoadjuvant therapy and pancreaticoduodenectomy. Final pathology showed a serous cystadenoma associated with small foci of high-grade PanIN. The lack of invasive adenocarcinoma in the resection specimen was most likely due to complete response of the tumor to neoadjuvant chemoradiation therapy, but it is also possible that only high-grade PanIN was present initially. To our knowledge, this is the first reported case of SCA and high grade PanIN/PDAC that was assessed by FNA. We discuss the cytologic differential diagnosis and how to avoid potential pitfalls highlighted by this case.

1. Introduction

Pancreatic lesions are being detected with increased frequency due to advances in imaging techniques. Establishing the correct diagnosis in these cases is imperative, as the appropriate treatment varies widely from observation to pancreatectomy based on the diagnosis [1]. Pancreatic lesions are often first recognized incidentally on computed tomography (CT) imaging [2]. However, diagnostic accuracy of cross sectional imaging studies for pancreatic cystic lesions is low [3]. Endoscopic ultrasound (EUS) provides high-resolution images, allowing for better evaluation of lesion morphology, relation to the pancreatic duct, and extent of spread; it also allows for fine needle aspiration (FNA) of the lesion. Cyst fluid can be used for chemical analysis and cytologic assessment [1,4-6]. FNA has high specificity and moderate sensitivity for diagnosis of pancreatic lesions. We present a rare case of microcystic serous cystadenoma occurring in association with pancreatic ductal adenocarcinoma and PanIN which was initially diagnosed on FNA. The case illustrates the importance of radiology-cytology correlation, but also highlights a potential pitfall in the interpretation of pancreatic FNAs.

2. Case report

The patient is a 75-year-old man with a history of prostatic adenocarcinoma treated with prostatectomy, hormonal therapy, and adjuvant radiation therapy. A pancreatic head lesion was incidentally identified on follow-up abdominal CT imaging and was further evaluated by magnetic resonance imaging (MRI). MRI showed a 6.8 × 5.7 × 4.6 cm well-demarcated lesion with a microcystic appearance and central calcifications abutting the portal vein. The pancreatic duct upstream from the mass was dilated up to 11 mm and the uninvolved pancreas showed atrophy. The imaging findings were initially interpreted as compatible with serous cystadenoma (SCA). Multiple liver and renal cysts were also identified.

EUS was performed and showed a mixed solid and cystic mass in the pancreatic head with poorly defined borders and evidence of invasion into the gastroduodenal artery and possible invasion into the portal vein. Aspirate fluid chemistries were not performed. Diff-Quik and

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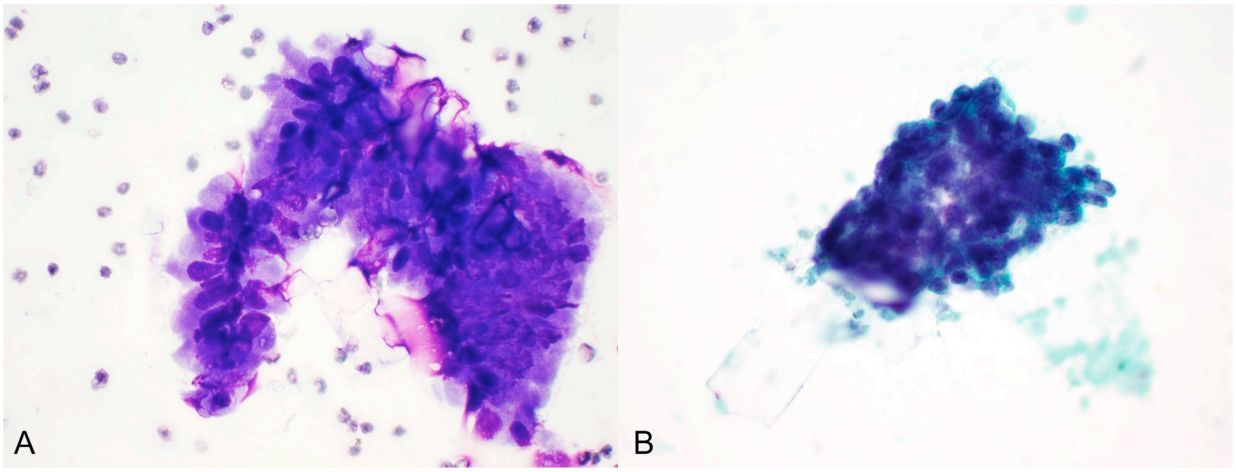

Fig. 1. A.) Fine needle aspirate with clusters of cells showing nuclear pleomorphism, disorganized, overlapping nuclei, and prominent nucleoli (Diff-Quik stain). B.) Occasional bland epithelial cell groups with scant cytoplasm and crystals suggestive of a long-standing cystic lesion were also noted (Papanicolaou stain).

Papanicolaou stained smears were prepared from the aspirated material and showed clusters of cells with significant nuclear pleomorphism (> 4:1 nuclear size variation), disorganized, overlapping nuclei, and prominent nucleoli (Fig. 1). Occasional bland epithelial cell groups with scant cytoplasm and crystals suggestive of a long-standing cystic lesion were also noted (Fig. 1). The FNA diagnosis was positive for malignancy, consistent with adenocarcinoma. At that time, the overall clinical impression was that this lesion was a pancreatic ductal adenocarcinoma arising within an IPMN in the pancreatic head. The patient was started on neoadjuvant chemotherapy with gemcitabine and paclitaxel and transitioned to neoadjuvant chemoradiation because the neoadjuvant chemotherapy was poorly tolerated. A follow-up CT scan after completion of neoadjuvant therapy showed a stable appearance of the tumor with complex cystic components, solid components, and central coarse calcifications with persistent dilation of the pancreatic duct up to 13 mm.

The patient underwent pancreaticoduodenectomy and the resection specimen showed a 6.0 × 5.5 × 3.5 cm spongy, multiloculated white-gray cystic lesion which entirely replaced the head of the pancreas (Fig. 2). The locules ranged from 0.1 to 1.2 cm in greatest dimension. A single 1.0 × 1.0 × 0.5 cm area in the center of the lesion had a white-gray appearance and was more solid. The entire cyst and all remaining pancreatic tissue were submitted for histologic examination. Histological sections were processed according to the standard processing algorithm and stained with hematoxylin and eosin. Microscopically, the lesion was composed of numerous closely packed cysts, and each cyst was lined by a single layer of uniform cuboidal cells with clear cytoplasm and small nuclei with dense chromatin. Focally, there were short papillae with fibrovascular cores projecting in to the cyst lumens. The papillae were lined by clear epithelial cells morphologically similar to the cyst lining cells. The stroma between the cysts was densely fibrotic with areas of hyalinization and calcification. Residual pancreatic islets and pancreatic acinar structures were embedded within the dense stroma. The background pancreas was atrophic. While most of the pancreatic ducts were unremarkable, several were lined by ductal cells with marked nuclear atypia, nuclear enlargement, hyperchromatic nuclei, prominent nucleoli, and loss of nuclear polarity. These areas also showed increased mitotic activity. Tufting and areas of architectural complexity were also seen (Fig. 3). The final diagnosis was microcystic serous cystadenoma and high-grade pancreatic intraepithelial neoplasia (PanIN) with no residual adenocarcinoma identified (complete treatment response to neoadjuvant therapy). Given the patient's history of two carcinomas (pancreas and prostate) and the association of pancreatic cystadenoma and renal cysts with von Hippel-Lindau syndrome, the Invitae Common Hereditary Cancers Panel was performed on a whole blood specimen from the patient. The panel uses next generation sequencing to analyze a panel of 46 genes commonly associated with cancer or cancer syndromes including the gene VHL (Invitae Corporation, San Francisco, CA). The results showed no pathogenic sequence variants or deletions/duplications in any of the genes analyzed.

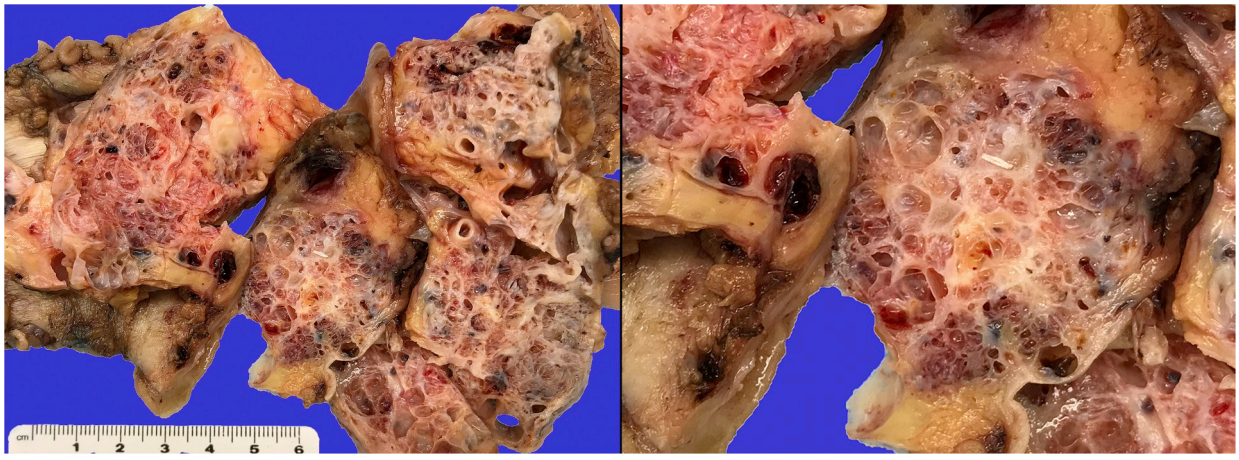

Fig. 2. Gross appearance of the lesion composed of numerous small cysts separated by thin septa.

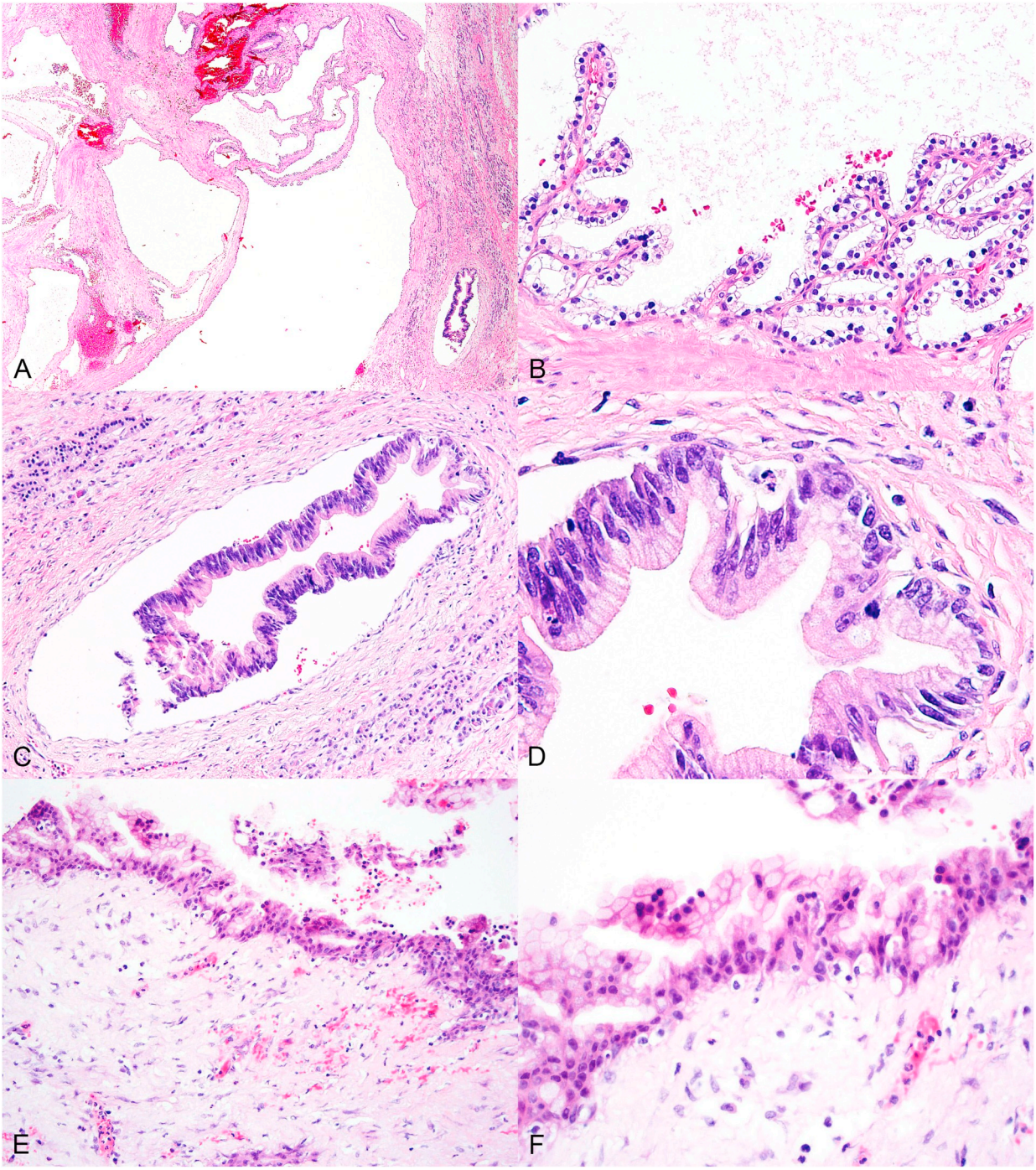

Fig. 3. Pancreaticoduodenectomy specimen. A.) Serous cystadenoma and adjacent area of PanIN. B.) Lining of serous cystadenoma with papillary area. C–F.) Ducts with PanIN showing nuclear atypia, mitotic activity, and architectural complexity.

3. Discussion

Serous cystadenoma is a benign neoplastic lesion which is most commonly found in female patients (3:1 female to male ratio) with a mean age of 58 yrs. It accounts for 32–39% of pancreatic cystic neoplasms [7]. SCA has a distinctive gross appearance consisting of numerous thin walled cysts giving the lesion a spongy appearance. The lesion classically contains a central scar, although this is only grossly identified in 16% of cases [8,9]. Microscopically, serous cystadenoma is composed of numerous small cysts lined by uniform flat to cuboidal epithelial cells with clear, glycogen-rich, cytoplasm and small nuclei with uniform chromatin [10]. The vast majority of serous cystadenomas are benign with only rare reports of malignant transformation [11-13]. The lesions require resection only if the diagnosis is uncertain, the patient is symptomatic, or they have characteristics that correlate with aggressive behavior (tumor location in the head of the pancreas and tumor size > 4 cm) [14,15].

Pancreatic SCA has rarely been reported in association with other types of pancreatic lesions. It is most commonly seen in combination with pancreatic neuroendocrine tumors [16-21]. Some of these cases have occurred in patients with von Hippel-Lindau disease. To our knowledge, eight cases of coexistent pancreatic serous cystadenoma and pancreatic ductal adenocarcinoma have been previously reported [22-27]. Additionally, several cases of serous cystadenoma with

associated PanIN have also been reported, including one case with high grade PanIN [28,29]. The results of FNA cytology have only been reported in a small number of these cases.

We present a challenging case in which a cystic and solid pancreatic mass was identified on imaging studies. The FNA was positive for adenocarcinoma, giving the overall clinical impression of an IPMN associated with invasive adenocarcinoma. The patient underwent neoadjuvant therapy and pancreaticoduodenectomy. Final pathology showed a serous cystadenoma associated with small foci of high-grade PanIN. The lack of invasive adenocarcinoma in the resection specimen is thought to be due to complete response of the tumor to neoadjuvant chemoradiation therapy, but it is also possible that only high-grade PanIN was present initially. To our knowledge, this is the first reported case of coexisting SCA and high grade PanIN/PDAC that was assessed by FNA. The case highlights two challenges in pancreas cytology: 1) accurate distinction between PanIN and adenocarcinoma on an aspirate specimen and 2) diagnosis of serous cystadenoma by FNA cytology. It also raises the question of whether the two lesions (SCA and high grade PanIN/PDAC) in our case occurred together by coincidence or if there is some relationship between the lesions.

PanIN has been recognized as a potential cause of false positive diagnosis of malignancy on pancreatic FNA. Chi et al. reported a series of false positive pancreatic FNAs in which two of the cases were caused by low grade PanIN. They compared the false positive aspirates with 12 true positive cases and concluded that the presence of at least 2 of 4 cytologic features (3 dimensional clusters with cell disorientation, isolated malignant cells, irregular nuclear contours in > 5% of atypical cell population, marked nuclear size variation > 4:1) should be used as minimal criteria for the diagnosis of adenocarcinoma [30]. Jarboe et al. reported four cases in which an FNA false positive diagnosis of malignancy was rendered. In each case, the resection specimen showed high-grade PanIN coexisting with other mass lesions (intraductal papillary mucinous neoplasms and neuroendocrine tumors) [31]. They note that while all four of the cases met the qualitative criteria for malignancy (morphologic features of atypia), only a small number of atypical cell groups were present and the cases most likely did not meet quantitative criteria for definite diagnosis of adenocarcinoma [31]. These two reports highlight the importance of fulfilling both the qualitative and quantitative criteria for a definite diagnosis of malignancy.

In addition to the scant lesional cellularity in the case that we presented, the case was further complicated by the lack of definite diagnostic cells of one of the two coexisting lesions (SCA) on the FNA specimen. The presence of these cells would have raised the possibility of coexisting lesions. Unfortunately, FNA of SCA is typically paucicellular. Lilo et al. showed that only 10% of resected SCAs that had a prior FNA contained diagnostic material in the aspirate specimen [32]. When present in cytology specimens, the epithelial cells of SCA are typically arranged in flat sheets and show round centrally placed nuclei with smooth nuclear contours, even chromatin and small nucleoli. The cytoplasm is often lost, but when present it is granular or clear/vacuolated with well-defined cell borders [33,34]. The presence of papillary fronds lined by cells typical of SCA has been reported in an aspirate of a SCA [35]. Our case showed papillary areas on histologic examination, however corresponding papillary structures were not identified in the cytology material. There should be no atypia, necrosis, or mitotic activity. Further difficulty can be encountered when the FNA includes contaminating background mucin from a transgastric aspiration. Close correlation between FNA and radiologic findings is imperative for an accurate diagnosis.

While coexisting tumors of the pancreas are rare, the reported cases raise the question of whether the development of the two coexisting lesions is purely coincidental or if there is an underlying relationship between the two lesions. It has been previously hypothesized that coexistence of PDAC and SCA could be due to a predisposing genetic abnormality in pancreatic exocrine cells that leads to development of both tumors [22,27]; this possibility needs further investigation. Another possibility is that the first tumor causes pancreatic duct obstruction and chronic pancreatitis which then predisposes to development of PanIN or PDAC. Andea et al. showed that PanIN occurs more frequently in pancreata with chronic pancreatitis or tumors other than PDAC than in normal pancreata. This supports the idea that the presence of pancreatic duct obstruction and chronic pancreatitis is related to an increased risk of developing PanIN [36]. The patient in the case we have reported had pancreatic duct dilation due to his SCA, which most likely caused chronic pancreatitis and predisposed the patient to developing PanIN/PDAC. Additional studies would be required to further investigate the etiology of these coexisting lesions. However, if mass lesions which cause duct obstruction do in fact raise the risk of development of PanIN, this is an additional reason to maintain strict quantitative criteria even in the presence of a mass lesion, as these patients could be at increased risk for having coexistent PanIN that could be detected on FNA and cause a false positive diagnosis of malignancy.

In conclusion, we present a case that illustrates the necessity of meeting both the quantitative and qualitative criteria for diagnosis of pancreatic malignancy by FNA. While interpretation of fine needle aspirate smears in the context of radiologic and laboratory findings is important, this can occasionally be misleading. At this time, the presence of a sufficient quantity of atypical cells in the smear is the only morphologic way to distinguish high grade PanIN from PDAC even in the presence of a mass lesion; as even the presence of a mass can be misleading in some cases. The presented case highlights a potential pitfall in fine needle aspiration of the pancreas when two lesions are present.

Declaration of Competing Interest

None.

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