Squamoid Cyst of Pancreatic Ducts

A Case Series Describing Novel Immunohistochemistry, Cytology, and Quantitative Cyst Fluid Chemistry

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Squamous cyst of pancreatic ducts (SCPD) is a recently described benign entity originally reported by Othman et al1 as a series of 6 clinically manifested cases and 10 cases identified incidentally in resected specimens. A subsequent case series discusses the cytology and cyst fluid chemistry profiles in 2 SCPDs and describes morphologic and immunohistochemical features that have not been previously reported. Fine-needle aspiration of 2 SCPDs yielded acellular debris lacking mucin or exfoliated squamous cells. Two cysts had elevated fluid carcinoembryonic antigen (CEA) and amylase levels. Positive immunohistochemical staining included cytokeratin 5/6, pCEA, synaptophysin, and chromogranin (both focal). MUC2 and MUC5AC showed negativity in all cases, while PAX8 showed negative nuclear staining. An accurate preoperative diagnosis of SCPD is potentially difficult in the setting of elevated fluid CEA levels, and acellular cytology as a mucinous cyst cannot be confidently excluded.


Squamous cyst of pancreatic ducts (SCPD) is a recently described benign entity originally reported by Othman et al1 as a series of 6 clinically manifested cases and 10 cases identified incidentally in resected specimens. A subsequent case was reported in a letter to the editor 2 years following this publication.2 To our knowledge, these 17 cases comprise all that is written of this entity.

The morphologic features of the resected SCPDs have been well characterized in the prior reports.1,2 Briefly, SCPD is a unilocular cyst with a simple stratified squamous epithelial lining lacking a granular layer and superficial keratinization.1,2 Preresection qualitative cyst fluid chemistry profiles have only been reported in 2 cases and were not quantified.3 These cases had elevated carcinoembryonic antigen (CEA) levels, which led clinicians to the most common preoperative misdiagnosis of mucinous cysts.1 Microscopic features of material obtained via fine-needle aspiration (FNA) have not been described. Therefore, it is currently unclear if cytology can lead to a correct preoperative diagnosis, which would avoid unnecessary surgery, especially in an era when imaging is detecting increasing numbers of incidental benign pancreatic cysts.

We present a case series of 3 SCPDs diagnosed at our institution. Two lesions had preoperative FNA and quantitative cyst fluid analysis, and therefore represent the first cases in which cytologic features and quantitative fluid chemistry profiles are reported. In addition, 1 lesion had oncocytic features and another showed patchy neuroendocrine differentiation by immunohistochemistry, two characteristics not previously described.

Following discussion of these cases and brief review of the 17 previously reported clinically manifested cases, we hope to build on the clinicopathologic features of these benign but commonly misdiagnosed lesions.

REPORT OF CASES

Two men and 1 woman were identified. The first patient was a 74-year-old man being followed up with serial computed tomography (CT) scans for an abdominal aortic aneurysm. During surveillance, a thin-walled 1.6-cm cyst was seen in the body of the pancreas. The cyst grew to 2.0 cm during 4 years as documented on a follow-up magnetic resonance imaging scan (Figure 1, A). Serum amylase and lipase levels were normal. Endoscopic ultrasonography showed no communication with the normal-caliber pancreatic duct. Fine-needle aspiration yielded thin, clear serous fluid containing acellular eosinophilic proteinaceous debris (Figure 1, B). The cyst fluid CEA concentration was 565 ng/mL and amylase was 242 414 U/L. The elevated CEA level was concerning for a mucinous cyst, specifically an intraductal papillary mucinous neoplasm (IPMN), given the patient’s sex and the location of the cyst. Seven months later, a CT scan revealed interval cyst growth to 2.6 cm. Serum CEA and CA19-9 levels were normal. Because of its progressively increasing size, the cyst was resected.

The second patient was a 57-year-old man with a history of coronary artery disease and chest pain who received a CT scan as part of his diagnostic workup, which revealed multiple cysts in the head of the pancreas, the largest of which measured 4.0 cm. Serum amylase and lipase concentrations were normal and cyst fluid contained acellular eosinophilic proteinaceous fluid. Fine-needle aspiration of the 2.6-cm cyst yielded acellular eosinophilic proteinaceous debris, which led to the diagnosis of a mucinous cyst. The 2.6-cm cyst was resected. The third patient was a 79-year-old man who presented to his primary care physician with left upper quadrant abdominal pain. A CT scan demonstrated a 2.6-cm cystic lesion in the body of the pancreas. Serum amylase and lipase levels were normal. Endoscopic ultrasonography showed no communication with the normal-caliber pancreatic duct. Fine-needle aspiration yielded thin, clear serous fluid containing acellular eosinophilic proteinaceous debris. The cyst fluid CEA concentration was 134 ng/mL and amylase was 127 464 U/L. The elevated CEA level was concerning for a mucinous cyst, specifically a mucinous cyst of the pancreas. The 2.6-cm cyst was resected.

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270 Arch Pathol Lab Med—Vol 138, February 2014
Figure 1. In case 1, an abdominal magnetic resonance imaging scan revealed a simple cyst in the pancreatic body (A, arrow). Fine-needle aspiration of the cyst yielded acellular eosinophilic proteinaceous debris (B) (cell block). The cyst lining was composed of oncocytic cells with abundant eosinophilic cytoplasm and round uniform nuclei with prominent nucleoli (C). Immunohistochemical stains for p63 (D) and CK5/6 (D, inset) confirmed squamous differentiation. In case 2, the resected cyst was unilocular, had a thin wall, and lacked complex features such as septations and nodularity (E). The cyst lining consisted of squamous epithelium lacking a granular layer, parakeratosis, and superficial keratinization (F) (hematoxylin-eosin, original magnifications ×400 [B, C, and F]; original magnifications ×400 [D and inset]).
chemistry profiles were not determined. The pancreatic cyst was resected via a Whipple procedure. On pathologic evaluation, the pancreas had a 2.5-cm main duct, intestinal-type IPMN with low-grade dysplasia. Invasive carcinoma was not present. Elsewhere in the pancreatic head was a 1.0-cm simple cyst that proved to be a SCPD. The cyst did not communicate with the pancreatic duct. The cyst fluid was not described in the gross report and cyst fluid chemistry profiles were never determined.

The third patient was a 67-year-old woman who underwent enucleation of an incidentally discovered 4.5-cm pancreatic neck cyst, clinically thought to be a mucinous cyst. The cyst had been increasing in size for 4 years and was being followed up by serial imaging. An initial endoscopic ultrasound-guided FNA revealed a cyst fluid CEA concentration of 14 ng/mL and an amylase level of 207,000 U/L. Three years later, the fluid CEA level was elevated to 127 ng/mL while the amylase level decreased to 44,500 U/L. On both occasions the cyst fluid was serous and not viscous. Cytology revealed acellular eosinophilic proteinaceous debris similar to what was seen in case 1. Serum chemistry profiles were not determined.

MATERIALS AND METHODS

The clinicopathologic findings in 3 resected SCPDs from 3 patients at Yale New Haven Hospital (YNHH), New Haven, Connecticut, were evaluated. The analysis included review of serum and cyst fluid chemistry profiles, gross images, and gross reports. The morphology and immunohistochemical stains for all cases were reviewed. A literature review was conducted with documentation of similar clinicopathologic features of the clinically manifested cases. Immunohistochemical staining, including positive and negative controls, was performed on formalin-fixed, paraffin-embedded tissue for all cases according to the manufacturer’s instructions. The antibody sources are as follows: p63 (M7247, Dako, Carpinteria, California), CK5/6 (M7233, Dako), PAX8 (363A-18, Cell Marque, Rocklin, California), MUC2 (10RM134B, Fitzgerald, Concord, Massachusetts), GLUT1 (355A18, Cell Marque), Inhibin (M3609, Dako), Synaptophysin (M0776, Dako), Chromogranin (A0430, Dako), CK7 (M0718, Dako), CK20 (M7019, Dako), CK19 (M7019, Cell Marque), pCEA (N1503, Dako), and MUC5AC (10RM134B, Fitzgerald).

RESULTS

Pathologic Features

Case 1 deviated from the usual histologic appearance of these lesions as originally described by Othman et al. The epithelial lining in this case showed oncocytic features. The cells were characterized by abundant eosinophilic granular cytoplasm with round nuclei harboring prominent nucleoli (Figure 1, C). Squamous differentiation was demonstrated by strong diffuse expression of p63 (Figure 1, D) and cytokeratin (CK) 5/6 (Figure 1, D [inset]).

All cases were unilocular and the cyst walls were thin and smooth without nodules or excrescences, exemplified by the gross image of case 2 (Figure 1, E). Cases 2 and 3 demonstrated the typical stratified squamous epithelium. The epithelium lacked a granular layer, parakeratosis, and superficial keratinization (Figure 1, F). A thin bland rim of stromal fibrosis was present beneath the epithelium. The background pancreas was essentially normal with rare foci of atrophic acini adjacent to the cyst wall. There were no prominent lymphoid aggregates, ovarian stroma, or adnexal structures in the cyst wall.

Immunohistochemistry

We used the same stains first reported by Othman et al: p63, GLUT1, inhibin, CK7, CK19, and CK20. Cytokeratin 7, p63, and CK19 showed positivity in all of our cases. Inhibin showed negativity in all cases, while GLUT1 showed positivity in 2 cases (strong, full thickness).

We also used the following immunohistochemical stains not previously reported: intestinal mucin marker MUC2, gastric mucin marker MUC5AC, pCEA, synaptophysin, chromogranin, CK5/6, and PAX8, which has recently been described as having nuclear positivity in pancreatic neuroendocrine tumors. MUC2 and MUC5AC showed negativity in all 3 cases. PAX8 showed negative nuclear staining in all cases with variable cytoplasmic positivity, mostly weak. CK5/6 and pCEA had strongly positive staining in all 3 cases. Synaptophysin and chromogranin showed negativity in 2 cases. One case (case 3) had weak synaptophysin positivity in the superficial squamous layer and focal but strong chromogranin positivity scattered throughout the epithelial lining.

COMMENT

Our experience with SCPDs is similar to what has been reported previously. The average age of our patients was 66 years, while the average age of patients from all previously reported clinically manifested cases was 70 years (range, 52–80 years). Serum CEA concentration and CA19-9 concentration were normal in one of our patients and serum amylase and lipase levels were normal in 2 patients, consistent with normal serum chemistry profiles in all previously reported cases.

These benign cysts are often discovered incidentally and the most common diagnostic problem is the preoperative distinction from a mucinous cyst, usually a branched duct IPMN, given their tendency to be found in the head of the pancreas. This is an important distinction to make as mucinous cysts often require resection while SCPDs do not.

The most widely used tumor marker in differentiating nonmucinous from mucinous pancreatic cysts is cyst fluid CEA. A CEA level lower than 30 ng/mL has a sensitivity of 79% and specificity of 73% for diagnosing a nonmucinous cyst while levels greater than 192 ng/mL have adequate specificity for diagnosing a mucinous cyst. All SCPDs with measured CEA concentrations showed elevated levels at some point during their diagnostic workup. This includes 2 of our cases and 2 previously reported cases in which the levels were not quantified. Our cases are the first to quantify the values, underscoring that the level can be high enough to suggest a mucinous cyst if it is used in isolation to make a preoperative diagnosis. Some authors have proposed a fluid CEA cutoff of 800 ng/mL to improve diagnostic specificity of mucinous cysts. It is currently unknown if levels this high can be seen in SCPDs.

Unfortunately, in our 2 cases, cytology was not helpful in avoiding a misdiagnosis. Cytologic features revealed eosinophilic acellular proteinaceous debris (Figure 1, B), a finding that would be interpreted by many as unsatisfactory given the lack of diagnostic desquamated cyst-lining cells. In addition, similar cytologic findings are seen in pancreatic pseudocysts but these lesions typically have CEA levels that average 10 ng/mL and are not usually considered in the differential diagnosis of cysts with high fluid CEA levels. The reason for such high fluid CEA levels in a nonmucinous cyst is unclear but has also been reported in squamous epithelium–lined pancreatic lymphoepithelial cysts, with levels ranging from 45 to 112,830 ng/mL. The gross cyst fluid appearance in these lesions is similar to SCPD, though cytology can identify exfoliated squamous
cells in nearly half of cases, leading to a correct diagnosis.6 Our cases lacked exfoliated squamous cells, suggesting that a preoperative diagnosis may be elusive, though more cases must be studied to ultimately determine the diagnostic utility of FNA in these lesions.

The pathologic diagnosis of SCPDs in resected specimens is usually straightforward. Squamoid cysts of pancreatic ducts are commonly unilocular and are lined by a simple stratified layer of squamous epithelial cells lacking a superficial granular layer, parakeratosis, and keratinization. Other squamous epithelium–lined cysts that enter into the differential diagnosis include lymphoepithelial cysts, epidermoid cysts of intrapancreatic accessory spleen, and dermoid cysts. Lymphoepithelial cysts can be readily ruled out, as SCPDs lack dense lymphoid tissue in the cyst wall.9 Epidermoid cysts of intrapancreatic accessory spleen occur almost exclusively in the tail, are seen in younger patients (fourth decade of life), and are surrounded by splenic tissue, while dermoid cysts are also seen in younger patients (third decade of life) and have adrenal structures in their cyst walls.10

One novel morphologic feature noted in our case series was oncocytic differentiation (case 1). Oncocytic differentiation might raise the possibility of an intraductal oncocytotic papillary neoplasm, though this entity usually has a complex architecture and high-grade cytology, features not seen in SCPDs. Diagnostic uncertainty can be resolved by immunohistochemical positivity for squamous markers if necessary. Occasionally, serous oligocystic adenomas will enter into the differential diagnosis. These cysts may have an attenuated lining and therefore could resemble an attenuated SCPD. Negative staining for markers of serous differentiation, such as inhibin and GLUT1, will help rule out a serous cystadenoma.11 However, positive staining for GLUT1 was seen in 2 of our cases, and inhibin showed positivity in all cases reported by Othman et al.1 Thus, positivity with GLUT1 and inhibin does not rule out a SCPD and additional stains demonstrating squamous differentiation, such as p63 and CK5/6, would be helpful in arriving at the correct diagnosis.

Our study is the first to investigate other immunohistochemical markers not previously reported (MUC2, MUC5AC, synaptophysin, chromogranin, PAX8, and pCEA). All of our cases were negative for intestinal glycoprotein MUC2 and gastric glycoprotein MUC5AC. This observation, in combination with reported positivity for pancreatic intercalated duct marker MUC1 and centroacinar cell marker MUC6,12,13 supports the assertion of Othman et al1 that SCPD represents a cystic dilatation of the native pancreatic ducts rather than de novo cystic growth of epithelium foreign to the pancreas. We noted weak positivity for synaptophysin and focal but strong positivity for chromogranin in 1 case, suggesting a possible pitfall with cystic neuroendocrine tumor. Synaptophysin and chromogranin positivity have been documented in other squamous lesions,14 and therefore, focal positivity should not dissuade one from making the diagnosis of SCPD if the morphology and other staining results are supportive. Fortunately, PAX8, a nuclear marker recently described in pancreatic neuroendocrine tumors,15 showed negative nuclear staining in all of our cases, which may prove to be helpful in the face of neuroendocrine marker positivity.

In conclusion, with increased imaging for a variety of indications, SCPDs are becoming increasingly recognized and should be considered in the myriad of differential diagnoses of pancreatic cystic lesions. Elevated cyst fluid CEA levels often lead to a preoperative misdiagnosis of a mucinous cyst. Our case series adds to the body of literature by documenting quantified cyst fluid CEA levels. In 1 case, the level was high enough (565 ng/mL) to be considered relatively specific for a mucinous cyst.13 We are also the first to report FNA characteristics (or lack thereof), which so far cannot allow one to confidently make the correct diagnosis. These findings, in combination with those of the previously reported cases, suggest that the tools we currently use to differentiate SCPDs from mucinous cysts are inadequate. Squamoid cyst of pancreatic ducts remains a difficult diagnosis to make preoperatively and further studies are needed to identify specific clinical, radiologic, and laboratory characteristics that can accurately differentiate this lesion.

References