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Intraductal Papillary Squamous Neoplasm of the Pancreas: Cytologic-Histologic Correlation of a Novel Entity

Catherine E. Hagen, MD^a, Kathleen Christians, MD^b, Amanda Hopp, MD^c, Tamara Giorgadze, MD^c, Christopher P. Hartley, MD^a, Bryan Hunt, MD^c, Olca Basturk, MD^d, David Klimstra, MD^d

^aDepartment of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

^bDepartment of Surgical Oncology, Medical College of Wisconsin, Milwaukee, WI, USA

^cDepartment of Pathology, Medical College of Wisconsin, Milwaukee, WI, USA

^dDepartment of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

We correlate the cytologic and histologic features of a squamous-lined pancreatic cystic lesion with a complex papillary architecture and an associated *KRAS* mutation, which to our knowledge has not been previously described. A 69 year-old woman presented with intermittent left upper quadrant pain. CT imaging revealed a 1 cm solid lesion in the pancreatic tail with peripheral calcification. Endoscopic ultrasound-guided fine needle biopsy showed a proliferation of epithelial cells with fibrovascular cores. An immunohistochemical stain for p40 was positive in the lesional cells. A distal pancreatectomy revealed a unilocular, cystic, well-circumscribed, soft and friable mass measuring 1.0 × 1.0 × 0.8 cm. Histologically, the cyst was lined by nonkeratinizing stratified squamous epithelium with a complex papillary architecture, filling the cyst lumen. Molecular sequencing revealed a *KRAS G12V* missense mutation. While the lesion shared some histologic features with the previously described “squamous cyst of the pancreatic ducts”, the complex papillary architecture and presence of a *KRAS* mutation are unique to the entity we describe herein and we propose the name “intraductal papillary squamous neoplasm of the pancreas.” Reporting the cytomorphologic features of this novel entity may help in identification of similar lesions and understanding of the clinicopathologic significance.

Keywords

Pancreas cyst; squamous; *KRAS*; papillary; fine needle biopsy

Corresponding Author: Catherine Hagen, Mayo Clinic, Department of Laboratory Medicine and Pathology, 200 1st St. SW, Rochester, MN 55905, (ph) 507-284-9047, (fax) 507-284-1599, Hagen.catherine@mayo.edu.

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1.0 Introduction

Squamoid cyst of the pancreatic ducts was first described by Othmon and colleagues in 2007. Histologically characterized by a flat, non-keratinizing squamous or transitional epithelial lining, these intraductal pancreatic lesions lack papillae and are hypothesized to be non-neoplastic in nature, perhaps related to the incidental foci of squamous metaplasia commonly encountered in the smaller pancreatic ducts¹. We recently encountered a squamous-lined cystic lesion of the pancreas with a complex papillary architecture and an associated *KRAS* mutation, and to our knowledge such a lesion has not been described previously. Herein we describe the cytologic features of this novel entity and correlate with histologic features following distal pancreatectomy.

2.0 Case Summary

2.1 Clinical History

The patient was a 69 year-old Caucasian woman with a history of hypertension, gastroesophageal reflux, mitral valve prolapse, patent foramen ovale and hypothyroidism who presented to her primary care physician with intermittent left upper quadrant pain that had been occurring for several years. The pain was described as dull, with periods of sharpness and a burning sensation. Recently, the pain worsened and was associated with nausea and diarrhea. She was taking acid suppression and probiotics for a diagnosis of irritable bowel syndrome. CT imaging revealed a 1 cm solid lesion in the pancreatic tail with peripheral calcification believed to be consistent with a neuroendocrine tumor. Serum chromogranin was 488 (normal <98 ng/mL) and Ca 19-9 was 22 (normal = 0–35 Units/mL). Family history was significant for a father with mesothelioma and a sister with breast cancer. She underwent endoscopic ultrasound-guided fine needle biopsy (EUS-FNB) with SharkCore needle which revealed a hypoechoic solid mass in the pancreatic tail. As the lesion appeared solid, no cyst fluid analysis was performed. She was subsequently taken to the operating room and underwent robotic distal pancreatectomy, en bloc splenectomy, intraoperative ultrasound of the pancreas and microdissection of the splenic artery and vein. Her perioperative course was uneventful.

2.2 Cytologic Findings

The cytology specimen (EUS-FNB) showed a cellular proliferation of cohesive epithelial cells with fibrovascular cores. Many of the cells had eosinophilic to clear cytoplasm. An initial immunohistochemical staining panel revealed the lesional cells to be positive for pancytokeratin and CEA. Immunohistochemical stains for CD56, chromogranin, and synaptophysin were negative. An immunohistochemical stain for Beta-catenin showed normal membranous staining. The case was re-reviewed at our institution prior to the patient's surgical resection. Additional immunohistochemical stains were performed. CK7, CD10, and p40 were positive in the lesional cells. Immunohistochemical stains for PAX-8, CK20, GATA-3, Uroplakin, TTF-1, Inhibin, and CD117 were negative (Figure 1). Based on the morphologic appearance and immunohistochemical profile the diagnoses of invasive ductal adenocarcinoma, solid pseudopapillary neoplasm, and neuroendocrine tumor were

excluded. However, a definitive diagnosis was uncertain and a descriptive diagnosis was rendered.

2.3 Histologic Findings

Subsequently a distal pancreatectomy and splenectomy specimen was received for pathologic examination. Sectioning of the pancreas revealed a unilocular, cystic, well-circumscribed, soft and friable mass measuring $1.0 \times 1.0 \times 0.8$ cm. The background pancreas was grossly unremarkable. The entire mass and representative sections of the background pancreas were submitted for histologic examination.

Histologic sections of the resection specimen showed an intraductal well-circumscribed unilocular cystic lesion. The cyst was lined by nonkeratinizing stratified squamous epithelium which exhibited a complex papillary architecture, filling the duct lumen. In some areas, low columnar cells with basal nuclei and apical cytoplasmic snouts lined the luminal aspect of the squamous epithelium. Scattered extracellular mucin was present in gland-like intercellular spaces but no intracellular mucin was noted. There was no evidence of parakeratosis, a granular cell layer, lymphoid follicles, or skin appendages. There was no evidence of dysplasia or associated invasive carcinoma. An immunohistochemical stain for p40 was positive in the cyst lining cells and a mucicarmine stain highlighted the extracellular mucin. Sections of the background pancreas showed multiple clusters of smaller cystically dilated ducts lined by attenuated or simple squamous epithelium, representing foci of squamous metaplasia (Figure 2). There was no pancreatic intraepithelial neoplasia (PanIN) or other intraductal neoplasia.

2.4 Molecular Analysis

Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) was performed as previously described on a representative formalin fixed paraffin embedded tissue block of the cystic lesion. MSK-IMPACT is a hybridization capture-based next-generation sequencing assay that assesses the coding regions as well as selected promoter and intronic regions of 468 genes for mutations, amplifications, deletions, selected structural rearrangements, and microsatellite status against a patient's matched normal ^{2,3}.

Sequencing revealed a *KRAS G12V* missense mutation (allele frequency 0.34) as the only genomic abnormality. No mutations in *TP53*, *SMAD4*, or *CDKN2A* were detected and the lesion was microsatellite stable.

3.0 Discussion

The more frequent use of high quality imaging studies has led to the detection of incidental cystic lesions of the pancreas that would have otherwise gone clinically unnoticed. As such, surgeons and pathologists more frequently encounter cystic pancreatic lesions in their daily practice. Squamous-lined pancreatic cysts are relatively uncommon and include entities such as lymphoepithelial cysts, dermoid cysts, and epidermoid cysts in intrapancreatic heterotopic spleen, which each have distinctive histologic features. Lymphoepithelial cysts

are characterized by surrounding mature lymphoid tissue, dermoid cysts demonstrate skin adnexal structures, and epidermoid cysts are surrounded by splenic tissue ^{1,4}.

In 2007, Othman and colleagues described a series of six pancreatic cysts that they classified as “squamous cyst of pancreatic ducts.” These cysts were characterized as being small (median size 1.5 cm), unilocular, intraductal cysts with flat, transitional or non-keratinizing squamous epithelial lining and lacked the distinctive features of the above mentioned entities. Notably these cysts were devoid of papillary excrescences ¹. Since the initial description, seven additional cases have been reported in the literature, including a multifocal case (so called “squamous cystosis”) ^{5–9}. Othman et al. also described a similar incidental entity consisting of microcysts with squamous lining and mucoproteinaceous luminal secretions in 8% of pancreatectomy specimens. The combination of the findings led the authors to conclude that squamous cysts are non-neoplastic and arise as a result of localized obstruction with resulting pancreatic duct dilation and squamous metaplasia ¹.

Our entity shares some morphologic features with the previously described squamous cysts in that it was a unilocular, intraductal cyst with nonkeratinizing squamous epithelial lining. Additionally, the background pancreas showed squamous-lined microcysts similar to those described by Othman et al ¹. However, the epithelium of the lesion we describe was more proliferative with a complex papillary architecture. As such, we hypothesized the lesion may represent a squamous cyst with a superimposed papillary neoplasm. Detection of a *KRAS* mutation in the lesion further supported the neoplastic nature of the entity. To our knowledge, no molecular testing was performed on any of the previously described squamous cysts of the pancreas. Given the lack of associated dysplasia or carcinoma, the lesion in itself is likely benign. However, it is conceivable that it could serve as a precursor to more advanced neoplasia, and the natural course of such a lesion is yet to be seen.

Preoperative diagnosis of squamous-lined cysts in the pancreas remains a challenge both via imaging and cytology specimen interpretation. Many of the previously described squamous cysts were resected for suspicion of a mucinous tumor ^{1,5–9}. The cytologic features of squamous cysts have only been described in two prior cases and consisted predominantly of acellular eosinophilic proteinaceous debris ⁸. Likewise the preoperative differential diagnosis in our case included other diagnostic entities including pancreatic neuroendocrine tumor and solid pseudopapillary neoplasm. The cytology specimen for our case was cellular, consisting of epithelioid cells with evidence of squamous differentiation (p40 positive). However, evidence of squamous differentiation in a lesion with papillary architecture was somewhat puzzling and as such a definitive preoperative diagnosis could not be rendered. Reporting the cytologic features of this unique entity may help others establish an accurate preoperative diagnosis.

One possibility that we cannot exclude is that the lesion we describe represents an intraductal papillary mucinous neoplasm (IPMN) with extensive squamous metaplasia. While the lesion did show extracellular mucin, no intracellular mucin or mucinous dysplastic-type epithelium was identified. Squamous metaplasia of mucinous cystic neoplasms in the pancreas has rarely been described ^{10,11}. However, it would be unusual for an IPMN to undergo complete squamous metaplasia. Another intraductal neoplasm

that could be considered in the differential diagnosis is intraductal oncocytic papillary neoplasm (IOPN), which shares with intraductal papillary squamous neoplasm papillae lined by multiple layers of epithelium composed of polygonal cells with eosinophilic cytoplasm^{12,13}. However, IOPN lacks squamous differentiation and features distinctive cytoarchitecture, with intracellular and intraepithelial lumen formation and large nuclei with prominent nucleoli. IOPN also has characteristic gene fusions (DNAJB1-PRKACA, ATP1B1-PRKACA)¹⁴. We therefore believe the lesion we describe is a distinct entity which should clinically and histologically be distinguished from IPMN and IOPN, and we propose the name “intraductal papillary squamous neoplasm of the pancreas.” Reporting the cytomorphologic features of this entity may lead to identification of similar cases and ultimately a better understanding of the clinicopathologic significance.

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Highlights

- Cytologic-histologic correlation of a novel squamous-lined pancreatic cystic lesion with complex papillary architecture
- Fine needle biopsy cytology is compared to histology following distal pancreatectomy
- An associated KRAS mutation is identified
- The cytomorphologic differential diagnosis of such lesions is discussed

Figure 1:

Cytologic features. Cell block material from fine needle biopsy demonstrating papillary cores with epithelial lining (4x)(A). Higher power view of papillary core showing cells with evidence of squamous differentiation. The cells lack significant cytologic atypia and no mitotic activity is seen (40x)(B). Papinicolaou stain showing scattered squamous cells with abundant cytoplasm and smaller clusters of epithelial cells (40x) (C). Immunohistochemical stain for p40 showing nuclear staining in the epithelial cells (40x) (D).

Figure 2:

Histologic features of resection specimen. Low power view of cyst demonstrating circumscription and papillary cores filling the cyst lumen (2x) (A). Higher power view of cyst lining showing low columnar cells with basal nuclei and apical cytoplasmic snouts lining the luminal aspect of the squamous epithelium (20x)(B). Higher power view of papillary core demonstrating foci of extracellular mucin (20x)(C). Microscopic cysts in background pancreas lined by attenuated squamous lining and demonstrating eosinophilic luminal concretions (10x)(D).