CASE REPORT

Multilocular Pancreatic Acinar Cystadenoma Containing Areas of Multifocal Branch-Duct Intraductal Papillary Mucinous Neoplasm

Sahil Bansal[1], Priya Iyer[2], June S Peng[2], Anthony T Stafford[2], Gareth Morris-Stiff[2], R Matthew Walsh[2], Shu-Yuan Xiao[3], Xiuli Liu[1]

[1]Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, OH
[2]Department of General Surgery, Digestive Disease Institute, Cleveland Clinic Foundation, Cleveland, OH
[3]Department of Pathology, University of Chicago, IL

ABSTRACT

Context Pancreatic acinar cystadenomas are rare cystic lesions that show acinar differentiation and follow a clinically benign course. Few previously reported acinar cystadenomas have demonstrated focal mucinous metaplasia. Although debatable, ACAs are considered to be neoplastic. **Case report** We present a case of a sixty-three-year-old man who underwent total pancreatectomy for a diffuse, multilocular acinar cystadenoma with multifocal branch-duct intraductal papillary mucinous neoplasm with moderate dysplasia. Histologically, the lesion was composed of variably sized cysts lined predominantly by cuboidal and focally flattened acinar cells with some cysts lined solely by mucinous epithelium. Overt evidence of acinar differentiation adjacent to the cysts was identified and composed of dilated and interconnected acini communicating with the cysts. Scattered mural nodules composed of acinar cells were present throughout the pancreas. There was no significant nuclear atypia or mitotic activity seen in the acinar component. Eosinophilic lamellated concretions, club-like pseudopapillae, and focal squamous metaplasia were noted in some cysts. In addition, focal metaplastic ossification and patchy minute foci of calcifications were present within the acinar cystadenoma. About 30% of the lesion showed areas of branch-duct intraductal papillary mucinous neoplasm with focal areas of moderate dysplasia. The residual pancreas contained multifocal areas of pancreatic intraepithelial neoplasia 1. **Conclusion** This finding supports the classification of multilocular acinar cystadenoma as a neoplastic lesion predisposing to both intraductal papillary mucinous neoplasm and pancreatic intraepithelial neoplasia. Although benign, complete resection may be needed for diffuse, multilocular lesions given the potential presence of dysplasia.

INTRODUCTION

Acinar cystadenoma (ACA) of the pancreas is a cystic lesion first described in 2002 [1], and was previously referred to as "cystic acinar transformation" of the pancreas [2]. Cysts of this entity are lined by epithelium with morphologic and immunohistochemical resemblance to pancreatic acinar cells. Approximately 40 cases have been reported in the English literature, with 10 cases in the largest case series by Khor *et al.* [3].

The reported cases of ACAs display a benign course, with no reports of recurrence or metastasis [1, 4-9]. It remains debatable whether ACAs are neoplastic or if they represent a non-neoplastic process as a developmental anomaly or glandular dilatation occur secondary to obstruction [1, 4-5, 9]. Limited molecular data suggest that multilocular ACAs, at least, are neoplastic lesions with multiple chromosomal gains [3].

We present an unusual case of a diffuse multilocular ACA with multiple areas harboring branch-duct intraductal papillary mucinous neoplasm (BD-IPMN). The lesion illustrated a clear transition from typical ACA areas to obvious IPMN-like regions where moderate dysplasia was noted. The adjacent residual pancreas showed multifocal pancreatic intraepithelial neoplasia 1 (PanIN 1). These features provide further evidence supporting a neoplastic nature of multilocular ACAs.

MATERIALS AND METHODS

The specimen included a pylorus-preserving pancreatoduodenectomy (PPPD) and subsequent completion pancreatectomy with splenectomy. A macroscopic examination was performed of the fresh specimens and they were subsequently fixed in 10% neutral buffered formalin and embedded in paraffin. Deparaffinized sections were stained with hematoxylin

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Abbreviations ACAs acinar cystadenomas; BD-IPMN branch-duct intraductal papillary mucinous neoplasm; PanIN 1 pancreatic intraepithelial neoplasia 1
Correspondence Xiuli Liu
Department of Anatomic Pathology
Cleveland Clinic Foundation9500 Euclid Avenue/L25|
Cleveland, Ohio 44195
Phone +216-445-8745
Fax + 216-445-6967
E-mail liux3@ccf.org

and eosin (h&e). Histochemical staining analysis for periodic acid-Schiff (PAS) with and without diastase pretreatment was performed. Immunohistochemical stains for cytokeratin 7, chromogranin A, synaptophysin, chymotrypsin, and Ki-67 were performed. The primary antibodies used are summarized in **Table 1**.

CASE REPORT

Clinical Presentation

A sixty-four-year-old male presented with painless jaundice and malaise. His medical history was significant for chronic lymphocytic leukemia, new onset diabetes, and hypertension. At presentation, he had a total bilirubin of 5.3 mg/dL (normal <1.5 mg/dL), alkaline phosphatase of 816 U/L (normal 40-150 U/L), alanine transaminase of 1313 U/L (normal 5-50 U/L), and aspartate aminotransferase of 645 U/L (normal 7-40 U/L). He underwent endoscopic retrograde cholangiopancreatography (ERCP) with placement of a common bile duct (CBD) stent; brushings were taken and were negative for malignancy. Computed tomography (CT) of the abdomen showed complete cystic replacement of the pancreas by innumerable thin-walled cysts, ranging in size from sub-centimeter to 2 cm in diameter **(Figure 1a)**, and a few areas of coarse calcification in the pancreatic head with no definite solid mass visualized **(Figure 1b)**.

Endoscopic ultrasound (EUS) was performed which demonstrated complete replacement of the pancreas with multiple thinly septated cysts without solid components, no visualized connections to the main pancreatic duct, and a 2 cm cyst was noted to be compressing the CBD in the pancreatic head. Fine needle aspiration (FNA) of two larger lesions was done; the fluid was negative for malignant cells and PAS staining was negative for mucin. Cyst fluid demonstrated elevated carcinoembryonic antigen (CEA) level of 470 ng/mL and a low amylase of 37 U/L.

The preoperative diagnosis was a mix-type IPMN and the patient was scheduled for a diagnostic laparoscopy, pancreatoduodenectomy with potential for completion pancreatectomy. On intraoperative examination, the entire pancreas was replaced by multiple cysts as expected **(Figure 1c)** and the patient underwent pancreatoduodenectomy. Frozen section examination of pancreatic duct margin identified atypical intraductal proliferation with acinar features and the patient underwent completion pancreatectomy and splenectomy. Post-operative recovery was unremarkable, and he showed no evidence of recurrence at 6 months follow-up.

Macroscopic Features

Macroscopic examination of the fresh specimen revealed the head of the pancreas to be almost completely replaced by a multilocular cystic lesion which measured 4.5 cm in maximal diameter. The lesion did not communicate with the main pancreatic duct, which itself was of normal caliber. No mucosal lesions were noted in the lumen of the main pancreatic duct. The distal pancreatic parenchymal margin was submitted for frozen section examination and was read as intraductal atypical proliferation with acinar features in branch ducts. As a result, distal pancreatectomy and splenectomy was performed. The distal pancreas showed a diffuse and near complete replacement of the pancreatic parenchyma by multilocular cysts that were continuous with the cystic lesion in the head of the pancreas. The lesion was characterized by numerous cysts which varied in size from less than one millimeter to several centimeters **(Figure 1d)**. The cystic lesions contained clear, watery fluid without obvious mucinous content noted. Many of the cysts had thick and fibrotic walls. No obvious papillary projections were seen in any cysts on gross examination. In the distal pancreas, a focal area of calcification and ossification was noted at the edge of the cystic lesion. Like the main pancreatic duct in the head of the pancreas, the main pancreatic duct in the distal pancreas did not show dilatation or mucosal abnormality (**Figure 1d**). There was only a minimal amount of tan and fibrotic pancreatic tissue present at the periphery of the pancreas, and no solid, infiltrating, or firm area was appreciated on macroscopic examination.

Histologic Features

The cystic lesion was well sampled with a total of 50 blocks submitted for examination. Histologically, the variably-sized cysts were lined by a single layer of epithelium, which varied from non-descriptive flattened/cuboidal epithelium to overt acinar differentiation (**Figure 2a**). There was focal squamous metaplasia noted as well (**Figure 2b**). Multiple IPMN-like areas composed of cysts solely lined by mucinous epithelium were scattered throughout the lesion **(Figure 2c)** and some of these areas harbored moderate dysplasia **(Figure 2d)**. The transition zone between acinar cell-lined cysts and IPMN-like regions consisted of glands lined by both acinar cells and mucinous epithelium either with abrupt transition or a region of nondescript flattened/ cuboidal cells **(Figure 2e, 2f)**.

Eosinophilic lamellated concretions were noted in the lumen of the cysts, which were lined by acinar cells **(Figure 2g)**. Multiple intracystic club-like projections were observed with fibrous stalks **(Figure 2h)**, as well as intracystic cellular nodules composed exclusively of acinar cells **(Figure 2i)**. In addition, mural nodules

Table 1. Primary antibodies used in this study.

Antigen	Clone/Antibody	Dilution	Source
Cytokeratin 7	Clone: OV-TL 12/30; catalong no.:M7018	1:40	Dako
Chromogranin A	Clone: DAK-A3; catalog no.: M0869	1:100	Dako
Synaptophysin	Clone: Snp88; catalog no.: AM363-10M	Prediluted	Biogenex
Chymotrypsin	Clone: 4E1; datasheet: 2100-0657	1:100	Serotec
Ki-67	Clone: 30-9; catalog no.: 790-4286	Prediluted	Ventana

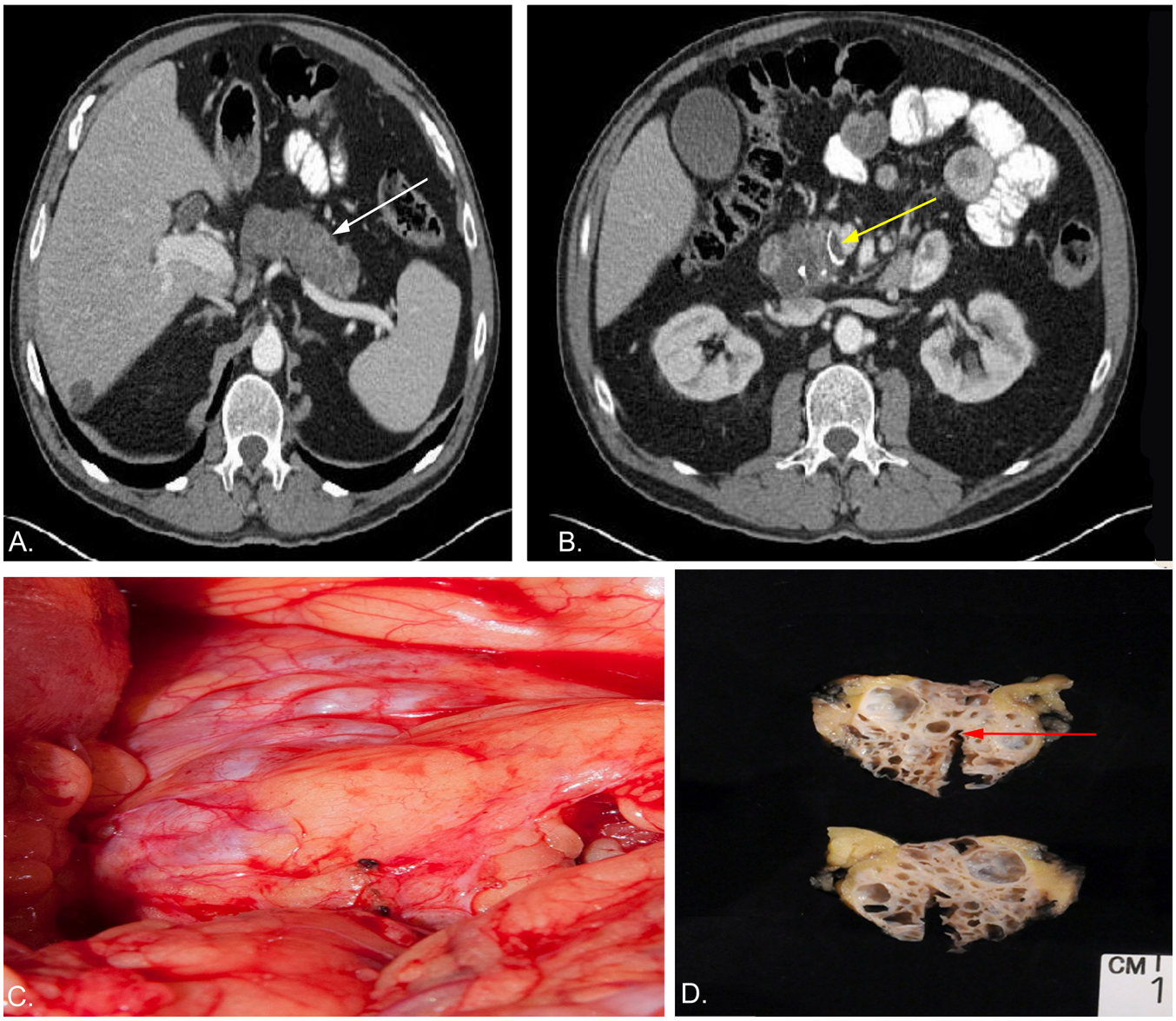

Figure 1. Computed tomography (CT) of the abdomen showing complete cystic replacement of the pancreas (**a,** multiple thin-walled cysts marked by arrow), and a few areas of coarse calcification in the pancreatic head with no definite solid mass **(b**, coarse calcification marked by arrow). Intraoperative examination demonstrating the entire pancreas was replaced by multiple cysts (**c**). The lesion consists of variably sized cysts with no obvious papillation or solid area. The main pancreatic duct was previously opened but is of normal caliber (marked with arrow) and shows no luminal lesions **(d)**

composed of acinar cells which formed a complex anastomosing pattern were identified adjacent to the lining epithelium **(Figure 2j)**. The acinar cells in the specimen which lined the cysts or formed intracystic or mural nodules lacked cytologic atypia, and mitotic figures were absent. There were rare mural nodules that contained islet cells in addition to acinar cells, but the majority lacked islet or ductal structures.

In some areas, the cyst walls were thick, fibrous, or hyalinized **(Figure 2k)**. No ovarian-like stroma was noted. A few cysts showed focal epithelial denudation with subsequent histiocytic reaction in the lumen and cyst wall. Multifocal calcification was noted in the mural nodules and one area showed metaplastic ossification.

A minimal amount of residual pancreatic parenchyma was present in the periphery, which showed fibrosis with cystic dilatation of pancreatic acini and pancreatic intraepithelial neoplasia 1 (PanIN 1) **(Figure 2l)**.

Histochemical properties and Immunophenotype

Periodic acid-Schiff stain with diastase pretreatment (PAS/D) revealed apical granules in cyst-lining acinar cells **(Figure 3a)**. Compared to normal acinar cells, the cyst-lining acinar cells had fewer, smaller, and paler eosinophilic apical granules. However, these granules were readily appreciable on the H&E stain **(Figures 3b)**.

The cyst-lining or mural nodule-forming acinar cells showed diffuse and strong immunoreactivity for cytokeratin 7 (CK7) **(Figure 3c)**, in contrast to the normal, non-lesional acinar cells, which were negative for CK7 **(Figure 3d)**. Immunoreactivity for chymotrypsin was present not only in cyst-lining acinar epithelium recognized on H&E staining (**Figure 3e**) but also in a portion of the cyst-lining nondescript flattened/cuboidal epithelium, confirming their acinar nature (**Figure 3f**). The lesional acinar cells were negative for chromogranin A **(Figure 3g)** and synaptophysin. Immunohistochemistry

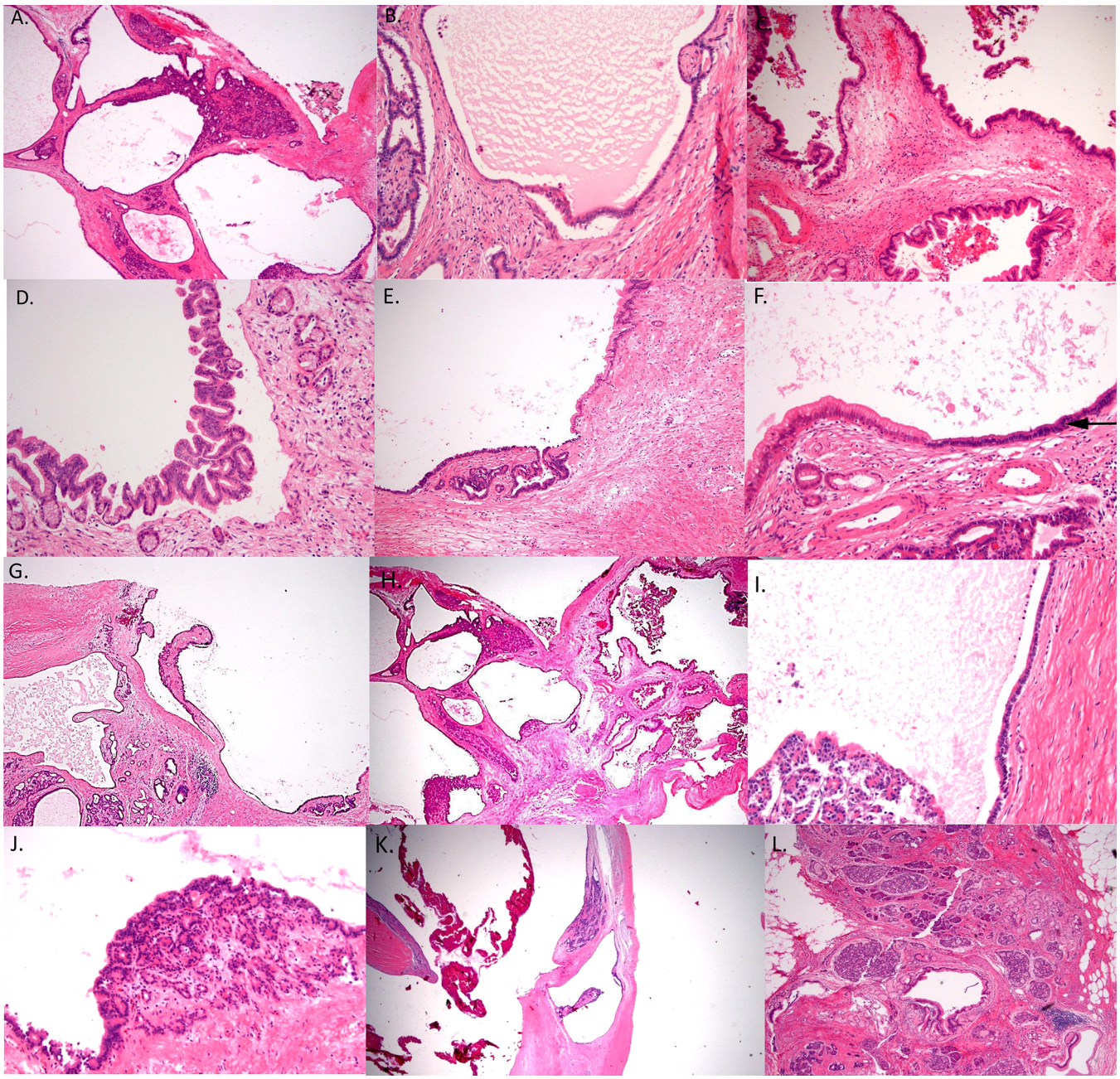

Figure 2. Histologic features of pancreatic acinar cystadenoma and background pancreas. The cysts are lined by nondescript flattened/cuboidal epithelium to cells with overt acinar differentiation (**a, h&e** stain, 40x) which may show focal squamous metaplasia (**b, h&e** stain, 100x). Multiple IPMN-like areas are scattered throughout the lesion (**c, h&e** stain, 100x) and with focal moderate dysplasia (d, h&e stain, 200x). The transitional zone of acinar cell-lined cysts and IPMN-like area can be abrupt (**e, h&e** stain, 20x) or through a region of nondescriptive flattened/cuboidal cells (**f, h&e** stain, 200x, non-descriptive cells marked by arrow). The cysts contain eosinophilic lamillated concretions (**g, h&e** stain, 40x) and may demonstrate intracystic club-like projections with a fibrous stalk (**h, h&e** stain, 20x). Intracytic cellular nodules or mural nodules consisting of acinar cells may be seen (**i&j, h&e** stain, 200x). The cystic wall may be hyalinized (**k, h&e**, 20x). The residual pancreas shows fibrosis, cystic dilatation of pancreatic acini, and pancreatic intraepithelial neoplasia (PanIN 1) (**l, h&e** stain, 40x).

for Ki-67 showed a low proliferation index (< 2%) in the cyst-lining and mural nodule-forming acinar cells and only focally increased Ki-67 labeling index in the IPMN-like areas **(Figure 3h)**.

DISCUSSION

Pancreatic acinar cystadenomas are rare pancreatic cystic lesions, with fewer than 40 cases described in the literature and only three case series reported to date, with the largest describing 10 cases [3]. The lesions occur in predominantly female patients with a wide range of ages at presentation, and a mean age between 40-50 years.

ACAs were initially described as non-neoplastic cysts of the pancreas and referred to as 'acinar cystic transformation' [2]. Subsequently the term 'acinar cell cystadenoma' was adopted [1], highlighting their neoplastic nature. ACAs are generally considered to be benign processes, and there have been no reports of malignant transformation [1, 4-9].

Pancreatic cysts lined by acinar epithelium, measuring < 0.5 cm are common incidental findings in pancreatic resections [10]. These cysts normally lack atypia and mitotic activity, and are termed 'retention cysts.' Singhi *et al.* [11] recently hypothesized that ACAs develop from non-neoplastic ballooning of acini evolving over multiple

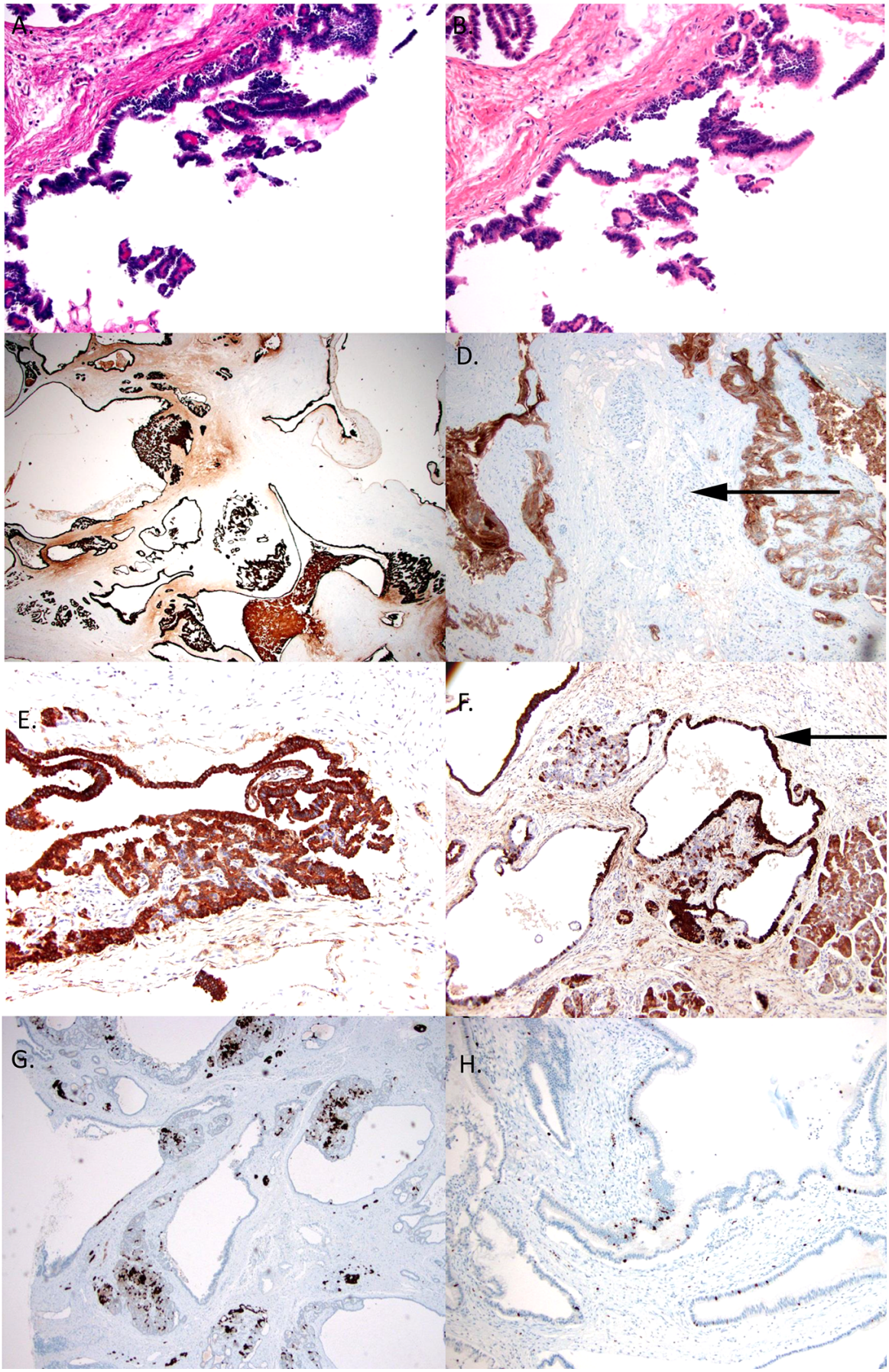

Figure 3. The cyst-lining acinar cells contain apical granules (**a,** periodic acid-Schiff stain with diastase pretreatment, 200x; **b. h&e** stain, 200x) and show immunoreactivity for CK7 (**c**, immunoperoxidase stain, 20x), in contrast to normal, non-lesional acinar cells which are negative for CK7 (**d**, immunoperoxidase stain, 100x, residual acini marked by arrow). Both cyst-lining acinar cells and nondescriptive flattened/cuboidal epithelium are positive for chymotrypsin (**e&f,** immunoperoxidase stain, 200x and 100x, respectively; **f,** non-descriptive epithelium marked by arrow). The acinar cells are negative for chromogranin a (**g,** immunoperoxidase stain, 40x). The Ki-67 labeling index is less than 2% in the cyst-lining acinar cells and only focally increases in the IPMN-like area (**h**, immunoperoxidase stain, 100x).

stages, eventually incorporating smaller ducts and then larger ducts. They further suggest that as these lesions increase in size, they form large coalescing cysts that are predominantly composed of acinar epithelium and intervening ductal epithelium. Although small incidental acinar cell cysts can represent retention cysts, the presence of a single large or multilocular ACA in an otherwise normal pancreas without duct obstruction, chronic inflammation, or fibrosis is more consistent with a neoplasm [1, 3,7].

To further address if ACAs result from a neoplastic process, Khor *et al.* performed array comparative genomic hybridization (aCGH) in one of their cases [3] and identified multiple chromosomal gains involving small (< 2.7 Mbp) regions on chromosomes 1p, 3p, 6p, 7q, 8, 10q, 11, 14, 20, and X. A few cancer-associated genes were involved in these low level copy gains, although no significant copy losses of cancer-associated genes were noted. The aCGH results suggest that ACAs display focal genomic copy number gains of cancer-associated genes, and thus should be considered as neoplasms.

The pathogenesis of ACAs is unclear. If ACAs truly arise from the acinar compartment, they would be expected to be negative for the marker CK7. In our case, the acinar epithelium of the ACA stained positive for CK7, which favors a transformative process. Our findings are in line with additional studies supporting a centroacinar compartment of this lesion [12-14]. Interestingly, the same origin has been postulated for ductal adenocarcinoma by acinar-ductal transdifferentiation and the development of PanIN as an intermediate step [15-16]. The presence of branch-duct IPMN and PanIN 1 in our case supports the idea that ACAs may develop from a multipotential cell within this compartment with the potential for differentiation along various lineages such as acinar cell, nondescript epithelium, and mucinous epithelium.

Preoperative diagnosis of ACAs is difficult. Of note, FNAs of two larger lesions in our case were negative for malignant cells and mucin but cyst fluid demonstrated an elevated CEA of 470 ng/mL. These seemingly discrepant results may have resulted from sampling from different area of the lesion, e.g. the sample used for mucin detection was from ACA and the sample tested for CEA and amylase was taken from the IPMN-like area.

In summary, we present a case of diffuse, multilocular ACA coexisting with a branch-duct intraductal papillary mucinous neoplasm harboring moderate dysplasia, in the setting of multifocal PanIN 1 in the residual pancreas. This case provides further evidence that multilocular ACA represents neoplastic lesion. Complete resection may be indicated if the lesion is diffuse and multilocular, or if dysplasia or carcinoma is suspected.

Conflict of interest

Authors declare to have no conflict of interest.

References

1. Albores-Saavedra J. Acinar cystadenoma of the pancreas: a previously undescribed tumor. Ann Diagn Pathol 2002; 6:113-5. [PMID: 12004359]

2. Kloppel G. Pseudocysts and other non-neoplastic cysts of the pancreas. Semin Diagn Pathol 2000; 17:7-15. [PMID: 10721803]

3. Khor T, Badizadegan K, Deshpande V. Acinar cystadenoma of the Pancreas: A Clinicopathologic study of 10 cases incluiding multilocular lesions with mural nodules. Am J Surg Pathol 2012; 36:1579-91. [PMID: 10721803]

4. Zamboni G, Terris B, Scarpa A, Kosmahl M, Capelli P, Klimstra DS, *et al*. Acinar cell cystadenoma of the pancreas: a new entity? Am J Surg Pathol 2002; 26:698-704. [PMID: 12023573]

5. Chatelain D, Paye F, Mourra N, Scoazec JY, Baudrimont M, Parc R, Flejou JF. Unilocular acinar cell cystadenoma of the pancreas an unusual acinar cell tumor. Am J Clin Pathol 2002; 118:211-4. [PMID: 12162680]

6. Couvelard A, Terris B, Hammel P, Palazzo L, Belghiti J, Lévy P *et al*.. [Acinar cystic transformation of the pancreas (or acinar cell cystadenoma), a rare and recently described entity]. Ann Pathol 2002; 22:397-400. [PMID: 12483157]

7. Gumus M, Ugras S, Algin O, Gundogdu H. Acinar cell cystadenoma (acinar cystic transformation) of the pancreas: the radiologic-pathologic features. Korean J Radiol 2011; 12:129-34. [PMID: 21228949]

8. McEvoy MP, Rich B, Klimstra D, Vakiani E, La Quaglia MP. Acinar cell cystadenoma of the pancreas in a 9-year-old boy. J Pediatr Surg 2010; 45:e7–9. [PMID: 2438912]

9. Pesci A, Castelli P, Facci E, Romano L, Zamboni G. Primary retroperitoneal acinar cell cystadenoma. Hum Pathol 2012; 43:446–50. [PMID: 21840569]

10. Oertel JE. The pancreas. Nonneoplastic alterations. Am J Surg Pathol 1989; 13(suppl 1):50–65. [PMID: 2699169]

11. Singhi AD, Norwood S, Liu T-C, Sharma R, Wolfgang CL, Schulick RD, *et al*. Acinar cell cystadenoma of the pancreas: a benign neoplasm or non-neoplastic ballooning of ducts? Am J Surg Pathol 2013; 37:1329-35. [PMID: 24076773]

12. Bouwens L. Cytokeratins and cell differentiation in the pancreas. J Pathol 1998; 184:234-9.[PMID: 9614373]

13. Klimstra D, Hruban RH, Pitman M. Pancreas. In: Mills SE, ed. Histology for Pathologists. Philadelphia: Lippincott Williams &Wilkins; 2006:705-20.

14. Kosmahl M, Wagner J, Peters K, Sipos B, Klöppel G. Serous cystic neoplasms of the pancreas: an immunohistochemical analysis revealing alpha inhibin, neuron-specific enolase, and MUC6 as new markers. Am J Surg Pathol 2004; 28:339-46. [PMID: 15104296]

15. Esposito I, Seiler C, Bergmann F, Kleeff J, Friess H, Schirmacher P. Hypothetical progression model of pancreatic cancer with origin in the centroacinar-acinar compartment. Pancreas 2007; 35:212-7. [PMID: 17895840]

16. Murtaugh LC, Leach SD. A case of mistaken identity? Nonductal origins of pancreatic “ductal” cancers. Cancer Cell 2007; 11:211-3. [PMID: 17349578]