Published in final edited form as:
Hum Pathol. 2010 April ; 41(4): 513–521. doi:10.1016/j.humpath.2009.05.017.

Mucinous Nonneoplastic Cyst of the Pancreas: Apomucin Phenotype Distinguishes this Entity from Intraductal Papillary Mucinous Neoplasm

Wenqing Cao, MD[*,1], **Brain P Adley, MD**[*,1], **Jie Liao, MD**[1], **Xiaoqi Lin, MD, PhD**[1], **Mark Talamonti, MD**[2], **David J Bentrem, MD**[2], **M Sambasiva Rao, MD**[1], and **Guang-Yu Yang, MD, PhD**[1]

[1]Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States

[2]Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States

Summary

Mucinous nonneoplastic cyst of the pancreas is a newly described and rare cystic lesion with unknown histogenesis. It is defined as a cystic lesion lined with mucinous epithelium, supported by hypocellular stroma and not communicating with the pancreatic ducts. It is very challenging to differentiate this lesion from other cystic mucinous neoplasms of the pancreas such as branch duct intraductal papillary mucinous neoplasm by morphology. In this study, a total of 436 pancreatic specimens resected between 2002 and 2007 in our institution were reviewed. 15 (3.4%, 15/436) mucinous nonneoplastic cyst were identified. They included 3 males and 12 females, with a median age of 60 years. 46% cases (7/15) occurred in pancreatic head, 27% (4/15) in neck, 7% (1/15) in body and 20% (3/15) in tail. The size of lesions ranged from 0.5-3.5 cm in greatest dimension. In the majority of cases (12/15, 80%), mucinous nonneoplastic cyst were associated or adjacent to acinar-ductal mucinous metaplasia. These morphologic data indicate that mucinous nonneoplastic cyst is not really a rare disease and may originate from acinar-duct mucinous metaplasia histogenestically. Furthermore, apomucin immunostains of mucinous nonneoplastic cyst showed: MUC1 expressed in 27% (4/15) cases; MUC5AC in 67% (10/15 cases); MUC2 was were negative in all cases. Whereas IPMN (n=17: 5 main duct type; 12 branch duct type) showed focal and weak MUC1 positivity in 18% (3/17) cases; MUC2 positivity in 71% (12/17) cases; all IPMN (17/17) were MUC5AC positive. The clonality assay with the HUMARA gene revealed that the MNC were of polyclonal origin. For the first time, using HUMARA assay, we demonstrate the nonneoplastic nature of these cysts, and further characterize morphological and immunophenotypic properties that allow differentiation from intraductal papillary mucinous neooplasm.

Name and address for correspondence and reprint to: Guang-Yu Yang, MD., Ph.D., Department of Pathology, Northwestern University, Feinberg School of Medicine, 303 E. Chicago Avenue, Chicago, IL 60611, Fax: 312-503-0647, Tel: 312-503-0645, g-yang@northwestern.edu Or Sambasiva M Rao MD, Department of Pathology, Northwestern University, Feinberg School of Medicine, 303 E. Chicago Avenue, Chicago, IL 60611, s-rao@northwestern.edu.
*These two authors contribute equally.

Keywords

mucinous nonneoplastic cyst; mucin phenotype; clonality; IPMN

1. Introduction

Mucinous cystic lesions of the pancreas include neoplastic entities such as mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) and ductal adenocarcinomas with cystic features that have been well defined and studied [1-3], and nonneoplastic lesions such as retention cyst and a recently described mucinous nonneoplastic cyst (MNC) [3-7].

MNC was first described by Kosmahl et al. in 2002. They included 5 cases in the original study [5]. Later Kosmahl and others reported on 6 more cases [4,6,8]. In the recently published Armed Forces institute of Pathology (AFIP)-tumor of the pancreas, this lesion is designated as simple cyst with tall columnar mucinous lining, and is alternatively regarded as retention cysts involved with low grade PanIN [9]. Morphologically, MNC are solitary and isolated unilocular or multilocular mucinous cystic lesions lined by single layer of cuboidal to columnar mucinous epithelium, supported by hypocellular stroma and not communicating with pancreatic ducts [5]. Obviously, this lesion differs from MCN by the lack of ovarian type stroma, and from main duct IPMN by the absence of communication with the pancreatic duct. However, the morphologic distinction of this lesion with branch duct IPMN, particularly benign branch duct IPMN could be difficult and challenging.

The classification of these cystic lesions of MNC by Kosmahl et al is based on absence of dysplastic morphologic features and no recurrence or malignant transformation after 2 years' median follow up[5]. At present, several polymorphic genes in the X chromosome are commonly used for clonality assay, including HUMARA [10,11]. HUMARA gene contains a CAG repeat unit (micro-satellite marker) with high frequency of heterozygosity. With predigested DNA using a methylation sensitive enzyme to cleave the unmethylated allele in active X chromosome, PCR-based amplification of polymorphic allele has been established and successfully used for determining the clonal status of micro-dissected cells [11].

In this study, we identified 15 MNC out of 436 resected pancreatic lesions during a period of 5 years. Clinical and pathological features, apomucin phenotypes and clonality were studied to further characterize this lesion.

2. Materials and Methods

2.1. Patients

Out of 436 resected pancreatic specimens between 2002 and 2007 at our institution, 15 cases of MNC and 17 cases of IPMN (5 main duct type, 12 branched duct type) were identified and included in this study. The criteria for the diagnosis of MNC are: 1) no connection to the main or secondary pancreatic duct by radiology and/ or gross examination; 2) no ovarian type supporting stroma; and 3) lined by mucinous epithelium with basally located nuclei and no cytologic atypia. The diagnosis and classification of IPMN are based on principal criteria defined by the WHO classification. Clinical information for all patients was obtained from the clinical database and surgical pathology reports.

2.2. Radiology

All MNC and IPMN patients in this study had at least one radiologic test (CT scan, MRI) prior to the surgery. Information such as cyst size, location, presence or absence of connection with

main or branch pancreatic duct and presence or absence of dilatation of pancreatic duct were obtained from radiology report.

2.3. EUS-FNA Cytology and cyst fluid CEA analysis

Ten MNC and 4 IPMN had endoscopic ultrasound guided fine needle aspiration (EUS-FNA) prior to surgical resection. The FNA specimens were analyzed for: background (mucinous or necrotic), cellularity (hypercellular or scant cellular), architecture (honeycombed flat sheets or papillary clusters), nuclear features (membrane, chromatin, pleomorphism, nucleoli) and fibrotic stroma. These features were reported as either present or absent (1 or 0). In addition, cyst fluid carcinoembryonic antigen (CEA) concentrations in 10 MNC were measured by specific immunoassay.

2.4. Special stain and immunohistochemistry

Representative paraffin sections from MNC and IPMN were selected and stained with PAS and immunohistochemically stained with MUC1 (Santa-Cruz Biotechnology), MUC2 (Santa-Cruz Biotechnology), MUC5AC (Chemicon International), and Ki-67 (Ventana) monoclonal antibodies using ABC immunoperoxidase procedure. Briefly, 5μm paraffin sections were deparaffinized and followed by microwave antigen retrieval. The rest of the procedure was done in automatic Ventana Benchmark Immunostainer. Appropriate positive and negative controls were used for each antibody. Immunostains were analyzed semi-quantitatively for specifically stained membrane and cytoplasm.

Compared with the proper negative control and positive control, intense brown membrane and cytoplasmic staining was scored as positive. The frequency and location of the labeled cells were evaluated and scored as '-' no staining or background staining, '+' mild specific staining of mucinous cells, '++' moderate staining of mucinous cells, and '+++' the most intense staining.

2.5. PCR-based clonality analysis with the HUMARA gene

The mucinous cystic epithelial cells from six cases of female patients were microdissected and harvested. High molecular weight DNA from each mucinous cyst was extracted with proteinase K/ phenol-chloroform method. The DNA from each cyst was digested with 30 U of methylation sensitive *HpaII* enzyme at 37°C overnight. Clonal assay was performed using a PCR-based analysis of the HUMARA gene according to the established method.

Following PCR amplification, only undigested (methylated / inactive) allele is amplified. Therefore, polymorphic HUMARA allele ratio of digested DNA (two allele band density ratio) was obtained. The cell population was classified as monoclonal when the ratio was either less than 0.33 or more than 3.

3. Results

3.1. Clinical findings

The clinical features of 15 MNC are summarized in table1. They included 3 males and 12 females, with a median age of 60 years (range, 22 to73 years). 46% (7/15) of the cysts were found incidentally, whereas other patients presented with various symptoms including abdominal pain/discomfort in 40% (6/15) of cases; polyuria 7% (1/15) and loss of appetite 7% (1/15) cases. Most patients (80%, 12/15) did not have other gastrointestinal disease.

Three patients had concurrent disease, one with gastric carcinoma, one with ampullary carcinoma and one with small islet cell tumor. Radiologically, none of 15 NMC showed definitive connection to main or branch pancreatic duct (Figure 1A, 1B). For all MNC cases,

the decision for surgery was based on combined features such as size, location, family history, mucinous nature of the disease and fluid CEA level. 7 patients underwent pancreaticoduodenectomy (Whipple's resection); 1 total pancreatectomy; 2 central pancreatectomy and 5 distal pancreatectomy.

Patients were followed at Northwestern Memorial Hospital for 2 to 42 months; none of them had recurrent disease or progression to malignancy during the follow-up period.

3.2. Pathological findings

Forty-six percent (7/15) MNC cases occurred in pancreatic head, 27% (4/15) in neck, 7% (1/15) in body and 20% (3/15) in tail. 11 patients had a single cystic lesion, whereas 4 patients had multiple cystic lesions. The size of cysts ranged from 0.5-3.5 cm in greatest dimension. In 9 cases the cysts were unilocular, 6 were multilocular (Figure 1A and Figure 1B). None of the cysts demonstrated gross connection with main or large branch pancreatic duct (Figure 1A-1D). The cystic contents were mucinous in 9 cases, serous/clear in 5 cases and hemorrhagic in 1 case.

EUS-FNA samples from these cysts were interpreted as: negative (benign mucinous cells, normal ductal cells, intestinal epithelium) in 4 cases, indeterminate (glandular cells with mucinous features and extracellular mucin, metaplasia vs. Mucinous neoplasm) in 1 case, suspicious (extracellular mucin, mucinous epithelium with mild atypia, atypical ductal cells) in 4 cases and mucinous neoplasm (sheets of mucinous epithelium with atypia, small papillary structures, loss of polarity) in 1 case (Figure 2A). In contrast, in 4 IPMN, cytological interpretation was reactive ductal cells (1 case), and neoplastic cells (sheets of mucinous epithelium, papillary clusters, and atypical cells) in 3 cases (Figure 2B). CEA concentration in cyst fluid for 10 MNCs showed levels ranging from 507 ng/ml to 7000 ng/ml.

Histologically, all 15 MNC cysts were lined by cuboidal to columnar type of mucinous epithelium. The nuclei of the lining epithelium were round to oval, uniform and showed no atypia or mitotic activity (Figure 3A and 3B). The cyst walls contained sparse cellular fibrous tissue in all cases (Figure 3C).

Acinar-ductal mucinous metaplasia (ADMM) is a type of lesion commonly seen in chronic pancreatitis and pancreatic parenchyma adjacent to ductal carcinoma. It defines as mucinous metaplastic epithelial change occurred in the terminal ducts adjacent to acini; morphologically, it is commonly identified as mucinous metaplastic epithelia mixed with acinar cells in the pancreatic lobules. In the present study, the majority of MNC (12/15, 80%) were associated or had adjacent acinar-ductal mucinous metaplasia (Figure 3D). In our serious, 9 cases the adjacent pancreatic tissue was unremarkable, 2 cases showed focal atrophy, 1 case showed focal peripancreatic fat necrosis, 3 cases had focal PanIN1 or PanIN2.

3.3 Apomucin phenotypes in MNC

All MNC showed positive PAS staining confirming the mucin production in these lesions (data not shown). Apomucin phenotypes in these cystic mucinous lesions were analyzed immunohistochemiscally. MUC1 was expressed only in 27% (4/15 cases) MNC. They showed focal and weak membranous/cytoplasmic staining (Figure 4A). MUC2 was negative in all cases (Fig. 4D). MUC5AC was positive in 67% (10/15) cases with strong cytoplasmic staining pattern (Figure 4G). This apomucin profile was very similar to the adjacent acinar-ductal mucinous metaplasia (Figure 4C, 4F and 4I).

3.4. Distinct Apomucin phenotypes and high Ki-67 proliferation in IPMN compared to MNC

To compare apomucin phenotypes between MNC and IPMN, 17 IPMN (5 main duct IPMN: 1 benign, 2 borderline, 2 carcinoma in situ and 12 branch-duct IPMN: 7 benign, 4 borderline, 1 carcinoma in situ) were further analyzed immunohistochemically for apomucin phenotypes. The most distinct apomucin in IPMN was MUC2 that 5/5 main duct and 7/12 branch-duct IPMN (4 benign, 2 borderline, 1 carcinoma in situ) MUC 2 showed mostly diffuse staining pattern in mucinous neoplastic cells (Figure 4E). MUC5AC was positive in 100% of IPMN (Figure 4H); While MUC1was positive only in 25% branch-duct IPMN (all borderline), all 5 main duct IPMN were negative (Figure 4B). Overall both main and branch duct IPMN showed expression of MUC2, MUC5AC and MUC1 in71%, 100% and 18% respectively. When subclassifying IPMN based on the mucin profile, two cases were focal MUC1 positive, MUC2 negative and MUC5AC positive indicating pancreatobiliary/ oncocytic types; 12 showed focal to diffuse MUC2 positivity, MUC5AC positive but MUC1 negative (intestinal type) and 3 cases showed MUC5AC positive but MUC1 and MUC2 negative (gastric type).

In addition, Ki-67 index for IPMN was 5% to 80% (mean 19.26+/- 4.0), whereas for MNC was 1% to 10% (mean 3.367 +/- 0.65). P value was < 0.0001 (Figure 5A and 5B).

3.5. Clonality analysis using HUMARA gene

To further characterize the nature of mucinous cystic lesion, six female patients with pancreatic mucinous cysts were analyzed for HUMARA gene using PCR-based clonality analysis. The results showed four of 6 cases were polymorphic/informative HUMARA gene. The two cases with non-informative HUMARA gene exhibited single allele with and without *Hpa II* digestion. Of four informative cases, two alleles of HUMARA gene following PCR amplification were still existent with *Hpa II* digestion, indicating their polyclonal nature, as showed in Figure 6.

4. Discussion

Most common neoplastic mucinous cystic lesions in the pancreas are MCN and IPMN, both of which have malignant potential.[1,2,12-14]. Therefore, the clinical management of MCN and main duct IPMN tends to be aggressive and usually involves surgery [1,15-17]. However, studies have found that branch duct IPMN especially small ones (<3cm) tends to have a much lower risk of malignant transformation and may be managed by nonoperative surveillance [15,16],. The molecular basis for the different behavior of main and branch duct IPMN is not clear.

A recently described mucinous nonneoplastic cyst, not a well recognized entity, shares many clinical and radiological features with MCN and IPMN; and it also raises a question if all or some of branch duct IPMN is a non-neoplastic process. Recognition of this lesion is clinically important since the management and prognosis are different from other neoplastic mucinous lesions. In this study, we further characterized MNC using morphological, immunohistochemical and biochemical parameters using 15 cases.

Terminology of MNC is another concern. As the nature of this MNC lesion is mucin productive and cystic lesion with non-neoplastic feature, it should be called mucinous non-neoplastic cyst (MNC). There is another entity in the literature called retention cyst that may share some of similarity with MNC; but retention cyst may also cover some nonmucinous cysts.

The incidence of MNC at our institution in 436 resected specimens was 3.4%. This is slightly higher than Kosmahl's report (2.1%) [3], probably due to different patient population in different medical centers. Like Kosmahl and others, we also found MNC in both men and women with a slightly preponderance in women (F: M =4:1). In our study, MNC were found

in wide age groups (22 to 73 years) but tended to be more common in patients older than 50 years (87%, 13/15). MNC are randomly distributed in the pancreas and may present as a unilocular or multilocular cyst. Most patients (73%) presented with single lesion; 27% presented with multiple cysts. The size of the cysts was usually small (0.5 to 3.5cm). The clinical presentations of MNC patients were nonspecific and include abdominal discomfort, pain, loss of appetite and increased frequency of urination. Radiologically, MNC did not communicate with the main or branch pancreatic duct, but could not be distinguished from other cystic lesion like MCN.

EUS-FNA evaluation of pancreatic cystic fluid has evolved as the initial diagnostic approach in all cystic lesions of the pancreas [1,14,18-22]. In our study, 10 of 15 cases had EUS-FNA and all showed extracellular mucin or mucinous epithelium confirming mucinous nature of these cysts. The cytomorphologic features of MNC are usually bland compared with IPMN which commonly show sheets of mucinous epithelium and papillary structures. Rarely, mild atypia or small sheets of mucinous epithelium may present in MNC fluid and make it difficult to distinguish from other neoplastic mucinous cystic lesions especially benign MCN and IPMN.

Cyst fluid analysis for pancreatic enzymes and different tumor markers has been suggested as a diagnostic tool in the differentiation of different cystic lesions of the pancreas [1,23-25]. Although a tremendous variability has been reported in the levels of these markers in neoplastic and nonneoplastic cysts, certain cutoffs are believed to provide high specificity. For example, amylase < 250 ng/ml and CEA > 800 ng/ml exclude a pseudocyst, and CEA < 5 ng/ml and CA19-9 < 37 excludes a mucinous cyst [1]. Increased cystic fluid CEA levels have been found in IPMN and MCN [1,23-25]. Recent studies have suggested extracellular mucin and fluid CEA levels greater than 300ng/mL are considered very sensitive and specific for neoplastic mucinous cyst [24]. However, studies have also found that cyst fluid CEA level can not differentiate between malignant and premalignant cyst, therefore is not predictive for malignancy [1]. In our study, cyst fluid CEA levels measured in 10 cases were all higher than 500 ng/ml, in which 5 cases were higher than 3000ng/ml. Our data further confirm the association of CEA with mucinous differentiation. However, the occasional high CEA level observed in MNC suggested that CEA level alone is not a reliable marker for neoplasia or malignancy. Using immunohistochemistry, Brunner et al [4] have demonstrated CEA staining in MNC. But CEA production in MNC is not associated with cytologic atypia or grading of the lesions.

Histological features of MNC were similar in our cases to other reported cases. Unilocular and some multilocular MNC were lined by a single layer of cuboidal to columnar mucinous epithelium; whereas in four multilocular and one unilocular MNC focal papillary features and multilayered epithelium were seen. No cytological atypia, pleomorphism or mitotic activity was seen. Cysts typically were surrounded by sparse fibrous tissue without any specific type of stroma. Interestingly, in the majority of our MNC (80%), the adjacent pancreatic tissue showed acinar ductal mucinous metaplasia, which is a metaplastic lesion commonly seen in chronic pancreatitis and normal pancreatic tissue adjacent to ductal adenocarcinoma. Previously, we have shown that acinar ductal mucionous metaplasia of pancreas arose from centroacinar cells (CAC, pancreatic stem/progenitor cells). The close association of MNC with acinar ductal mucinous metaplasia suggests that MNC may develop from and share the same pathway as acinar ductal mucinous metaplasia.

In previous studies of MNC, expression of MUC1 and MUC5AC was reported in 1/6 and 5/6 cases, respectively. Expression of MUC2 was not observed [4,5]. In this study, focal and weak MUC1 positivity in 27% cases; and moderate to strong MUC5AC expression in 67% cases was observed. None of our cases was positive for MUC2. This apomucin profile was also very

similar to the adjacent acinar-ductal mucinous metaplasia, further suggesting the possible origin of MNC from acinar ductal mucinous metaplasia.

For the first time we confirmed the nonneoplastic nature of the MNC using HUMARA clonality analysis. Kosmahl et al proposed that these cystic lesions are nonneoplastic based on morphological features and lack of recurrence or malignant transformation in 2 years median follow-up [5]. Benign IPMN and MCN can show very bland cytology with no mitosis. And the recurrence of the benign IPMN and MCN usually depends on surgical resection margins and if the lesion was completely excised, it may not recur in up to 5 years [1]. Our clonality assay indicated the polyclonal origin of the cystic epithelial cells, providing a strong experimental evidence of their nonneoplastic nature.

It is important to distinguish this lesion from MNC, MCN and IPMN for proper clinical management. Main duct IPMN are easy to separate from MNC or MCN by radiological studies. The MCN exclusively occurred in female patients, commonly in the pancreatic tail and, importantly, show ovarian type stroma, making it relatively easy to be distinguished from MNC. Distinction between MNC and benign branch duct IPMN may be extremely difficult due to the overlapping clinicopathological features. We compared the mucin profile of MNC with main and branch-duct IPMN, and found the majority of IPMN (100% main duct, 58% branch duct) were MUC2 positive, whereas all MNC were MUC2 negative. Therefore, MUC2 may be used as a biological marker in cases when differentiation of MNC and IPMN is difficult. On the other hand, for branch duct IPMN there were 42% cases showing no MUC2 expression. Thus, it raises the possibility of nonneoplastic nature of these lesions and this remains to be investigated further.

In summary, our results indicate that MNC are rare cystic lesions in the pancreas, commonly associated with adjacent acinar-ductal mucinous metaplasia and share similar mucin profile, suggesting the possible origin from acinar-ductal mucinous metaplasia. The polyclonal nature demonstrated by clonality analysis further supports our hypothesis that these lesions are non-neoplastic. Furthermore, MUC2 may serve as unique biomarker to differentiate MNC from branched duct IPMN.

Acknowledgments

This study was partially supported by NIH R21 CA122514 grant.

References

1. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol 2007;102(10):2339–49. [PubMed: 17764489]
2. Adsay NV. Cystic neoplasia of the pancreas: pathology and biology. J Gastrointest Surg 2008;12(3): 401–4. [PubMed: 17957438]
3. Kosmahl M, Pauser U, Peters K, Sipos B, Lüttges J, Kremer B, Klöppel G. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch 2004;445(2):168–78. [PubMed: 15185076]
4. Brunner A, Ladurner R, Kosmahl M, Mikuz G, Tzankov A. Mucinous nonneoplastic cyst of the pancreas accompanied by non-parasitic asymptomatic liver cysts. Virchows Arch 2004;444(5):482–4. [PubMed: 15045587]
5. Kosmahl M, Egawa N, Schroder S, Carneiro F, Luttges J, Kloppel G. Mucinous nonneoplastic cyst of the pancreas: a novel nonneoplastic cystic change? Mod Pathol 2002;15(2):154–8. [PubMed: 11850544]
6. Goh BK, Tan YM, Tan PH, Ooi LL. Mucinous nonneoplastic cyst of the pancreas: a truly novel pathological entity? World J Gastroenterol 2005;11(13):2045–7. [PubMed: 15801005]

7. Goh BK, Tan YM, Chung YF, Chow PK, Ong HS, Lim DT, Wong WK, Ooi LL. Non-neoplastic cystic and cystic-like lesions of the pancreas: may mimic pancreatic cystic neoplasms. ANZ J Surg 2006;76 (5):325–31. [PubMed: 16768691]
8. Kosmahl M, Pauser U, Peters K, Sipos B, Luttges J, Kremer B, Kloppel G. Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch 2004;445(2):168–78. [PubMed: 15185076]
9. Hruban, Ralph H.; P, MB.; Klimstra, David S. Tumors of the pancreas. Hahn, KS., editor. Washington DC: American Registry of Pathology; 2007. p. 358-360.
10. Uchida T, Ohashi H, Aoki E, Nakahara Y, Hotta T, Murate T, Saito H, Kinoshita T. Clonality analysis by methylation-specific PCR for the human androgenreceptor gene (HUMARA-MSP). Leukemia 2000;14(1):207–12. [PubMed: 10637497]
11. Kubota T, Nonoyama S, Tonoki H, Masuno M, Imaizumi K, Kojima M, Wakui K, Shimadzu M, Fukushima Y. A new assay for the analysis of X-chromosome inactivation based on methylation-specific PCR. Hum Genet 1999;104(1):49–55. [PubMed: 10071192]
12. Takaori K. Current understanding of precursors to pancreatic cancer. J Hepatobiliary Pancreat Surg 2007;14(3):217–23. [PubMed: 17520195]
13. Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. N Engl J Med 2004;351(12):1218–26. [PubMed: 15371579]
14. Zhai J, Sarkar R, Ylagan L. Pancreatic mucinous lesions: a retrospective analysis with cytohistological correlation. Diagn Cytopathol 2006;34(11):724–30. [PubMed: 17041953]
15. Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. J Gastrointest Surg 2008;12 (4):645–50. [PubMed: 18097728]
16. Lévy P, Jouannaud V, O'Toole D, Couvelard A, Vullierme MP, Palazzo L, Aubert A, Ponsot P, Sauvanet A, Maire F, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. Clin Gastroenterol Hepatol 2006;4(4):460–8. [PubMed: 16616351]
17. Yasuda H, Takada T, Amano H, Yoshida M. Surgery for mucin-producing pancreatic tumor. Hepatogastroenterology 1998;45(24):2009–15. [PubMed: 9951855]

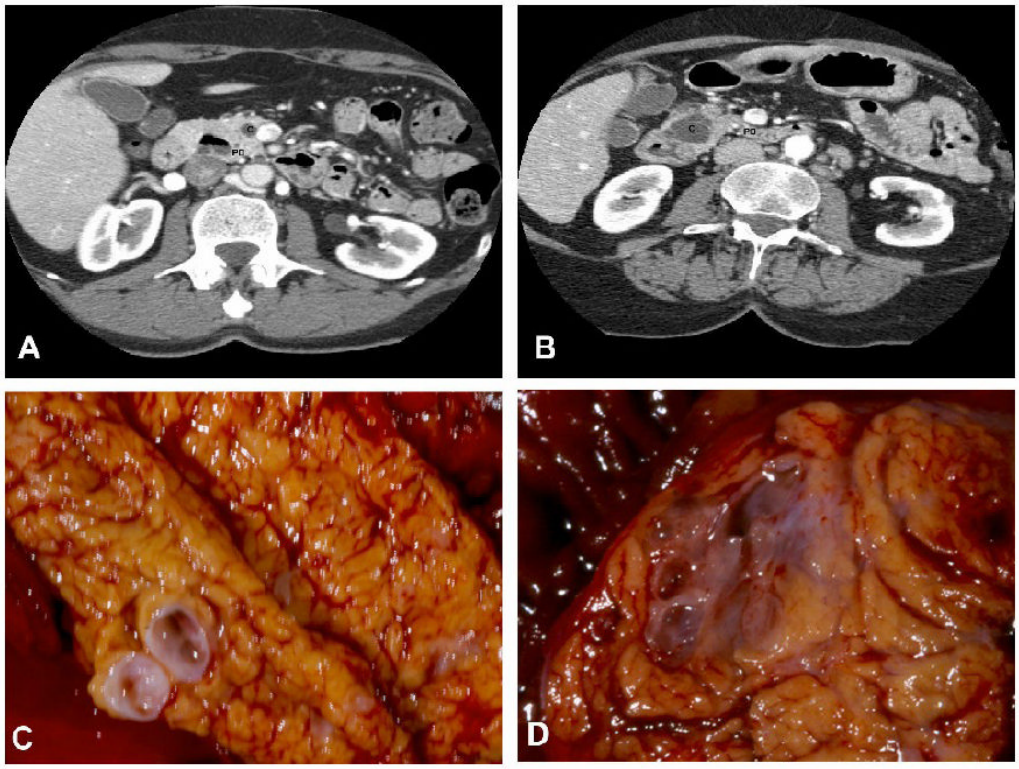

Figure 1. CT scans and gross photos of mucinous nonneoplastic cyst of the pancreas

A, C: unilocuar cyst and B, D: multilocular cyst with no definitive connection with pancreatic duct. (in the photos A and B: C indicates MNC; PD indicates pancreatic duct)

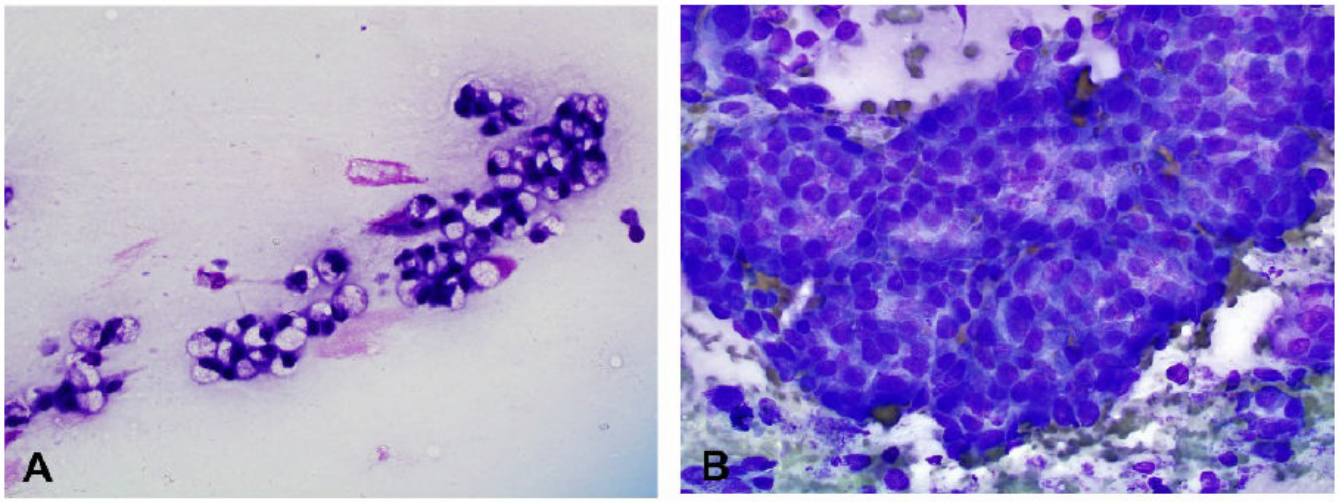

Figure 2. Cytomorphological features of the MNC and IPMN

A: MNC with bland mucinous cells and no cytological atypia (Diff quick stain, 400X); B: IPMN with sheets of mucinous epithelium, papillary structures and mild nuclear atypia. (Diff quick stain, 400X)

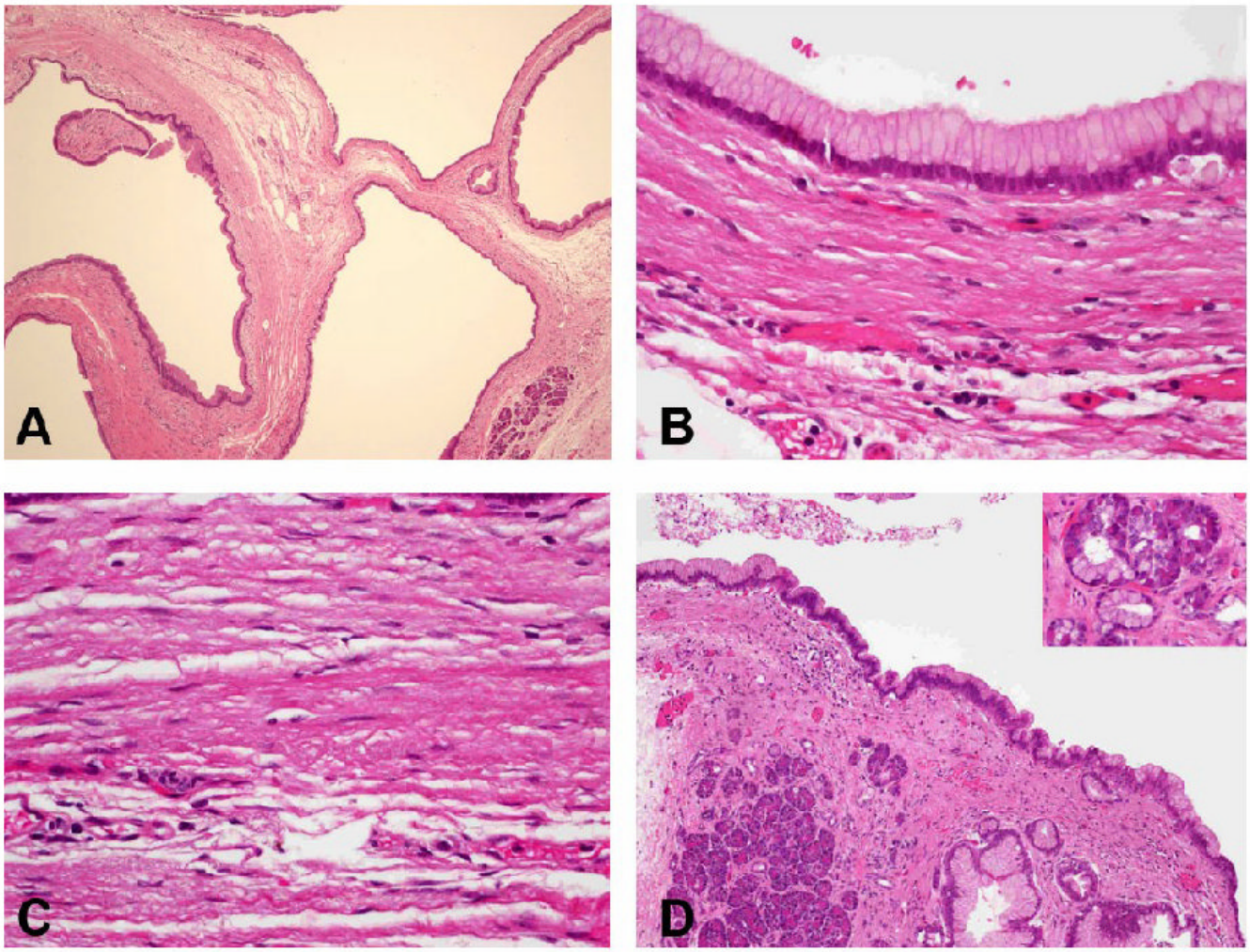

Figure 3. Histological features of MNC

A: Multilocular cysts lined by single layer of cuboidal / columnar mucinous epithelium (H&E, 100X); B: the epithelium show no cytological atypia or mitosis (H&E, 200X); C: hypocellular fibrotic stoma (H&E, 400X); D: mucinous cysts associated with acinar-ductal mucinous metaplasia (H&E, 100X).

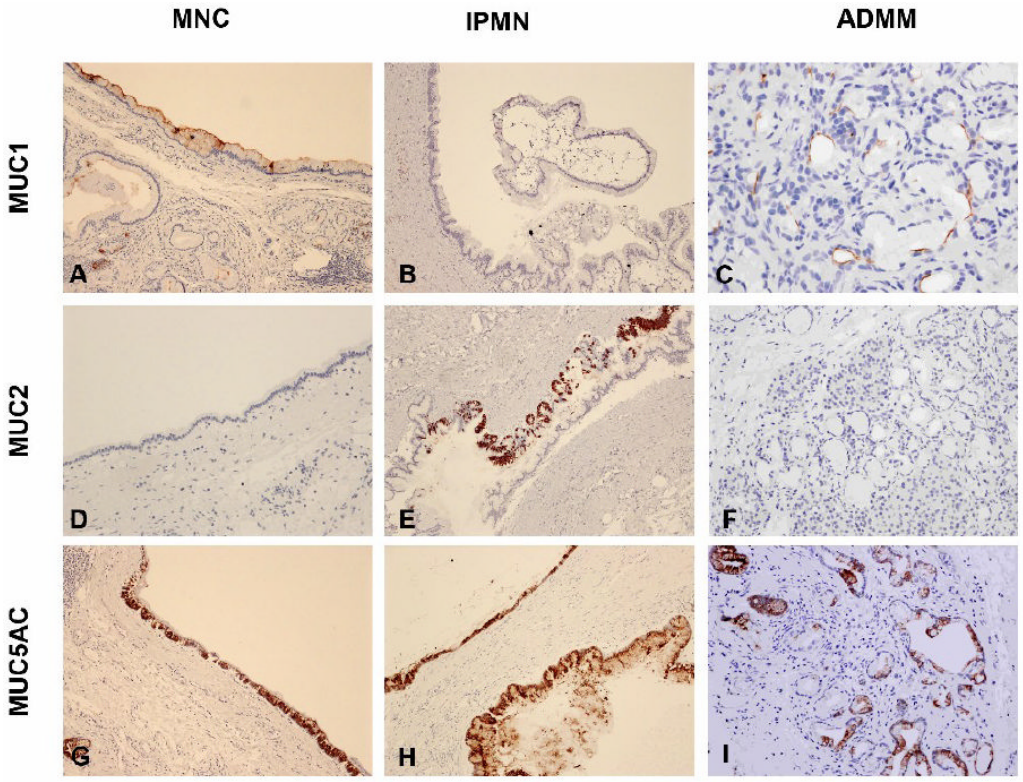

Figure 4. Comparison of Apomucin profiles of MNC, IPMN and ADMM

A, D, G: MNC (MUC1 29%, MUC2 0%, MUC5AC 65%); B, E, H: IPMN (MUC1 18%, MUC2 70%, MUC5AC 100%); C, F, I: ADMM (MUC1 19%, MUC2 0%, MUC5AC 48%).

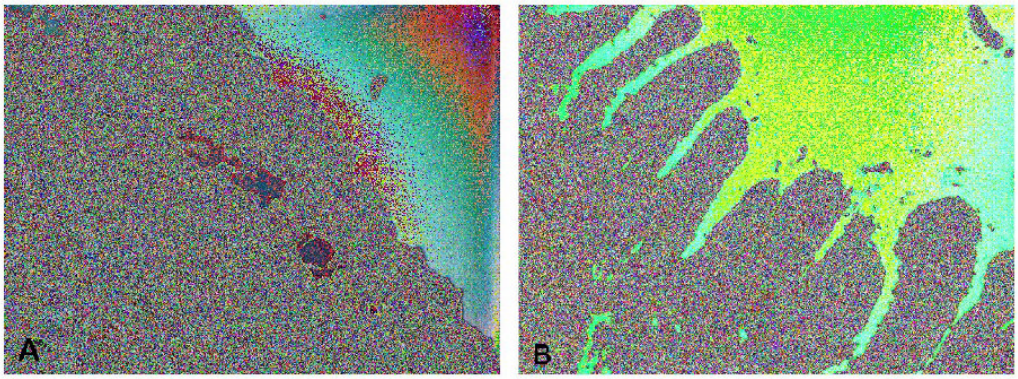

Figure 5. Ki67 labeled proliferation index in MNC and IPMN
A: MNC; B: IPMN.

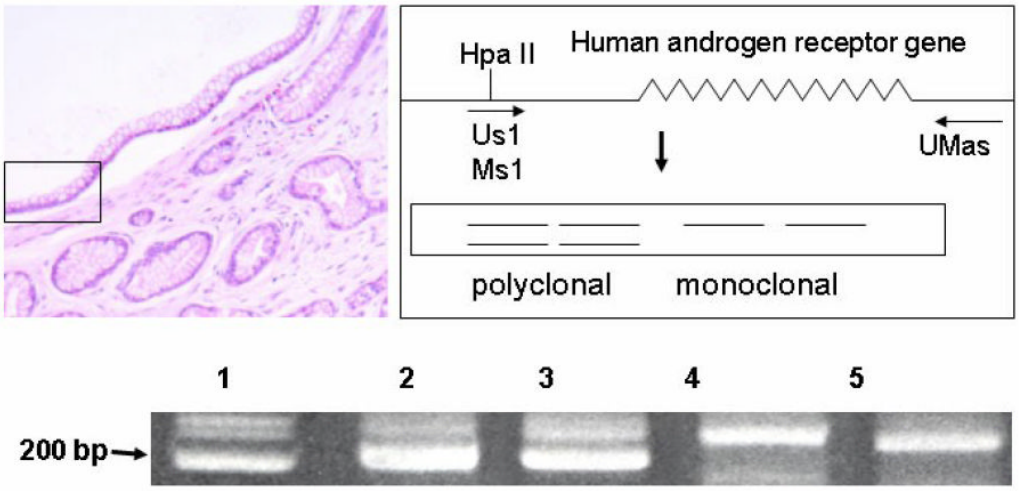

Figure 6. PCR based Clonality assay using HUMARA gene

Lane 1: Molecular marker; Lane 2 & 3, informative case of HUMARA gene showing polymorphic two alleles (Lane 2: genomic DNA extracted from mucinous cystic epithelial cells without *Hpa II* enzyme digestion before PCR amplification of HUMARA gene, and Lane 3: genomic DNA with *Hpa II* enzyme digestion). Lane 4 & 5, non-informative case of HUMARA gene showing a single allele (Lane 4, without *Hpa II* enzyme digestion, and Lane 5, with *Hpa II* enzyme digestion).

Table 1

Clinical and pathological features of 15 mucinous nonneoplastic cysts of the pancreas.

Case#	Age/sex	Symptoms	Location	Cyst/fluid	Size	Cytology	Fluid CEA (ng/ml)	Surgical procedure
1	56F	abdominal pain	head	Unilocular / clear	1.3 cm	suspicious	N/A	Whipple's resection
2	70M	none	tail	Unilocular / mucoid	1.3 cm	N/A	N/A	Distal pancreatectomy
3	72M	none	head	Multilocular / mucoid	1.6 cm	suspicious	5488	Whipple's resection
4	56F	none	Body/tail	Unilocular / hemorrgic	2 cm	suspicious	5975	Distal pancreatectomy
5	60F	none	head	Multilocular / clear	2 cm	N/A	4482	Whipple's resection
6	66F	none	head	Multilocular / clear	1.1 cm	negative	985	Whipple's resection
7	66F	Loss of appetite	head	Unilocular / serous	1.1 cm	N/A	N/A	Whipple's resection
8	49F	none	neck	Unilocular / mucoid	1 cm	N/A	1581	Central pancreatectomy
9	73F	none	head	Multilocular / mucoid	0.9~ 3.5cm	indeterminate	507	Total pancreatectomy
10	53F	abdominal pain	head	unilocular (2) / mucoid	0.4 and 1.0 cm	mucinous cystic neoplasm	3875	Whipple's resection
11	20F	abdominal pain	tail	multilocular / mucoid	2.2 cm	negative	2184	Distal pancreatectomy
12	66F	abdominal pain	tail	unilocular / clear	1.2 cm	negative	545	Distal pancreatectomy
13	66M	abdominal discomfort	neck	Multilocular / mucoid	1.5 cm	suspicious	2433	Central pancreatectomy
14	57F	polyuria	head	Unilocular / mucoid	1.4 cm	N/A	773	Whipple's resection
15	64F	abdominal discomfort	tail	Unilocular / seroux	2.5 cm	negative	7000	Distal pancreatectomy