Published in final edited form as:
Am J Surg Pathol. 2010 March ; 34(3): 364–370. doi:10.1097/PAS.0b013e3181cf8bb6.

Preferential Expression of MUC6 in Oncocytic and Pancreatobiliary Types of Intraductal Papillary Neoplasms Highlights a Pyloropancreatic Pathway, Distinct From the Intestinal Pathway, in Pancreatic Carcinogenesis

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Abstract

The expression of different MUC glycoproteins has helped define cellular lineage in variety of pancreatic neoplasms, and has helped identify distinct carcinogenic pathways such as the intestinal pathway characterized by diffuse/strong MUC2/CDX2 expression in intestinal-type intraductal papillary mucinous neoplasms (IPMNs) and their associated colloid carcinomas (CCs). In this study, the expression profile of MUC6, a pyloric-type mucin, was investigated in both preinvasive and invasive pancreatic neoplasia. Florid papillary ("in-situ") components of 9 intraductal oncocytic papillary neoplasms (IOPNs), 24 IPMNs, and 7 mucinous cystic neoplasms (MCNs), were analyzed immunohistochemically for MUC6 expression, as were 15 PanINs, 112 usual invasive ductal adenocarcinomas (DAs), and 14 CCs. In PanINs, MUC6 expression was limited to the very early areas of PanIN-1A that typically have pyloric features. Expression was lost in later stages. Similarly, in IOPNs or IPMNs or MCNs, MUC6 expression was detectable in the cystic or flat areas that have pyloric-like histology. However, in the more advanced (papillary) components of these neoplasms, MUC6 expression was mostly limited to the "cuboidal-cell" but was not seen in the "columnar-cell" phenotype: there was diffuse or strong expression in 8/9 IOPN and, relatively weaker but consistent expression in all 6/6 pancreatobiliary-type IPMNs; whereas virtually no expression in villous or intestinal-type IPMNs. The 7/8 gastric or foveolar-type IPMNs were also negative; in the single case with positivity, the labeling was limited to high-grade dysplastic areas. Interestingly, the papillae in MCNs were also mostly negative. Among invasive carcinomas, 39/112 DAs and only 1/14CC expressed MUC6. In DA, the expression did not correlate with survival (P=0.94), or any of the markers of aggressiveness: more than 2-cm tumor size (P=0.76), positive surgical margins (P=0.27), lymph node metastasis (P=0.82), or high grade (P=0.08). In conclusion: (1) The expression of MUC6 in oncocytic and pancreatobiliary-

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This study was presented in part at the annual meeting of the United States and Canadian Academy of Pathology in Atlanta, GA, February 2006.

type neoplasms but not in villous or intestinal-type neoplasms supports the presence of a pyloropancreatic pathway distinct from the MUC2/CDX2 expressing intestinal pathway in intraductal papillary neoplasia. (2) MUC6 expression is present in the earliest (nonpapillary) form of any type of preinvasive neoplasia regardless of whether it is PanIN or IOPN or IPMN or MCN suggesting that these entities may share some characteristics early on, but evolve along divergent pathways as they progress.

Keywords

MUC6; pancreas; intraductal; intraductal papillary mucinous neoplasm; mucinous cystic neoplasm; papilla; pyloric; intestinal

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The MUC glycoproteins are a highly heterogeneous group with differential expression profile in different organs, and highly variable physiologic functions depending on the type and location. For example, MUC1, also called mammary-type mucin, maintains lumen formation and has an inhibitory role in cell-stroma interaction. It is expressed widely in the luminal surface of tubular structures in a variety of organs. In epithelial neoplasms of the same organs, expression of MUC1 is also quite common, and has been found to be a marker of aggressive behavior, presumably in part related to its inhibitory role of cell-stroma interactions.[16] In contrast, MUC2, also known as intestinal-type mucin, is normally expressed almost exclusively in goblet-cells, and is generally confined to adenocarcinomas with intestinal differentiation. MUC2 gene has also been shown to have tumor suppressor activities, and its expression in a neoplasm is generally regarded as a good prognostic sign.[25,26]

In the pancreas, the diffuse and strong expression of MUC2 and its upstream regulator CDX2 (responsible for intestinal programming) has been found to be mostly limited to villous or intestinal-type papillae of intraductal papillary mucinous neoplasms (IPMNs), and among invasive carcinomas, to colloid carcinomas (CCs), which also often arise in association with villous or intestinal-type IPMNs.[4] This has led to the identification of an indolent “intestinal pathway” in pancreatic carcinogenesis, distinct from the conventional PanIN-to-ductal adenocarcinoma pathway characterized by MUC1 expression. It has been postulated that MUC2 and CDX2, are not only epiphenomenon, but they also play a key role in driving the neoplastic transformation toward an intestinal lineage, and that MUC2, which had also been called “gel-forming” mucin, has a role both in the morphogenesis of CCs (“gelatinous-carcinoma”) and in its indolent behavior.[2,3]

Characterization of these biologically-distinct pathways by their MUC expression profiles suggests that further investigation of the patterns of expression of the other MUC types will be fruitful. MUC6, pyloric-type mucin, is one such candidate. It seems to be an important molecule in foregut differentiation of cells and has been implicated in gastric and pancreatic carcinogenesis. [8,13,17,22] Furthermore, MUC6 seems to be regulated by key molecules such as Sp and NFkB that have been known to have important roles in pancreatic tumorigenesis. [11,19]

Recently, Nakamura and Yonezawa et al have investigated the expression profile of MUC6 in biliary tract neoplasms, and they have found that MUC6 expression is mostly limited to what they regarded as “cuboidal-cell” phenotype, and not seen in “columnar-cell” phenotype.[15,20] In addition, in a relatively small number of IPMNs, they have shown distinct patterns of MUC6 expression among different types of IPMNs as well.[14]

In this study, we carried out a systematic analysis of MUC6 expression profile in a large number of various types of preinvasive and invasive neoplasms that occur in the pancreas with the purpose of further elucidating the patterns of MUC6 expression in different tumor types in this organ.

MATERIALS AND METHODS

Cases

Histologic sections of florid papillary nodules from 9 intraductal oncocytic papillary neoplasms (IOPNs), 24 IPMNs, and 7 mucinous cystic neoplasms (MCNs), and 15 PanINs, 112 usual invasive ductal adenocarcinomas (DAs), and 14 CCs of the pancreas were retrieved from the files of Wayne State University and The Karmanos Cancer Institute, Memorial Sloan-Kettering Cancer Center, The Johns Hopkins University, and Verona University.

Subclassification of Intraductal Neoplasms

Histopathologically, the intraductal neoplasms were classified into 4 groups as earlier described.[1,4,5,15,20,25]

IOPN—Complex arborizing papillae lined by relatively monotonous cuboidal cells with oncocytic morphology (abundant acidophilic granular cytoplasm, cuboidal nuclei, and single prominent nucleoli) that exhibit the characteristic intraepithelial lumen formation some of which are multicell size.[1]

Pancreatobiliary-type IPMN—This is characterized by complex papillae, lined by cuboidal cells with variable degrees of pleomorphism and atypia, and high nucleo-cytoplasmic ratio.

These 2 types (1 and 2), together, match to the “cuboidal-cell” type, proposed by Yonezawa et al for the bile ducts tumors[20] or “compact” and “clear-cell” phenotype, earlier used by the same group in the pancreas.[15,25]

Villous or Intestinal-type IPMN—This shows villous architecture with long finger-like projections without complex branching, very similar to colonic villous adenomas. These villi are lined by pseudostratified columnar cells that have variable amounts of mucin in the apical cytoplasm and cigar-shaped nuclei with coarse chromatin and small, if any, nucleoli, also similar to villous adenomas.

This type matches the “columnar-cell” type, proposed by Yonezawa et al for the bile ducts tumors[20] or “villous dark-cell” type, earlier designated by the same group in the pancreas.[15,25]

Gastric or Foveolar-type IPMN (In Addition Known as “Clear-cell” Type IPMN[15,25])—This is composed of papillae lined by tall columnar cells with abundant pale supranuclear mucin, some with acidophilia, creating a pattern reminiscent of gastric foveolar epithelium. At their base, these papillae often have glandular elements very similar to gastric pyloric type glands.

The lining of cystic (nonpapillary) component of any IPMN subtype has cells morphologically very similar to the lining cells of gastric-type papillae; thus this is also referred as “null-cell” type by some authors.[12]

Immunohistochemical Labeling for MUC6

Tissue sections were deparaffinized; solution of EZ-Prep (Ventana no.950-101) was applied. Sections then were rinsed with reaction buffer (Ventana no. 950-300). Antigen retrieval was carried out with Ventana CC2 (Citrate Buffer), after which endogenous peroxidase was blocked with inhibitor solution (Ventana DAB Detection Kit no. 760 to 2021). Sections were then rinsed in reaction buffer. A 100 μL of MUC6 (Novocastra Lyophilized Mouse Monoclonal Antibody MUC-6 Glycoprotein; 1:80) antibody was manually applied to slides and incubated for 26 minutes at 37°C. The excess antibody was washed off, after which biotinylated antimouse secondary antibody was applied and incubated for 8 minutes at 37°C. After rinsing the sections again, avidin or streptavidin-enzyme conjugate was applied for 8 minutes. Chromogenic substrate was then applied.

To further exclude the possibility of false positivity with a biotinylated antigen, MUC6 immunostaining was also carried out with biotin blockage. Separately, to rule out a cross reaction with a mitochondrial antigen (after the results showed intense labeling in oncocytic tumors), MUC6 was also applied to 6 oncocytoma of the kidney and none of them showed labeling.

The labeling was scored for both the extent and the intensity. The extent was recorded semiquantitatively as the percentage of the cells that showed labeling: negative (<10% of the cells), focal (10% to 50% of the cells), and diffuse (>50% of the cells). The intensity was graded as negative, weak, or strong.

Cystic and papillary components of the noninvasive neoplasms were evaluated and scored separately. The results were also compared with known prognostic parameters and survival of DA (for comparative analysis the data were arbitrarily divided into 3 groups: negative, focal or weak, and diffuse or strong).

Statistical Analysis

Pearson χ^2 was used for comparison of MUC6 expression in different types of the papilla. Pearson method was used to assess correlation of MUC6 expression with tumor size (≤2 cm vs. >2 cm) and grade in DA. χ^2 was used to assess correlation with margin status (positive vs. negative) and lymph node (positive vs. negative). For survival analysis, Cox proportional hazard method was used.

RESULTS

Normal Pancreas (Fig. 1)

In normal tissue, MUC6 was expressed in the intercalated ducts of the pancreas, in the small pancreatic tributary ducts with pyloric features, and in Brunner glands of the duodenum, but not in the intralobular and interlobular ducts, nor in the islets. Focal granular labeling was also noted in some acini.

Noninvasive Lesions

PanINs (Fig. 2)—Only a minority of PanINs expressed MUC6 and the expression was mostly confined to the areas with pyloric features (earlier called mucinous hypertrophy) in PanIN1A (5/11). MUC6 expression was seen at very low frequency in PanIN1B (2/11) and lost in PanIN2 (0/10) and PanIN3 (0/9).

Cystic (Nonpapillary, Flat) Components of IOPNs, IPMNs, and MCNs—MUC6 was expressed fairly consistently in the cystic areas in which the epithelium showed glandular arrangement forming pyloric-like glands. The same type of labeling was also

noted fairly consistently in the basal aspects of the papillary regions; however, the expression in the papillae growing on top was different (See below) (Fig. 3A).

Papillary Components of IOPNs, IPMNs, and MCNs (Table 1)—MUC6 expression was mostly limited to the "cuboidal-cell" variants of IPMN but was not seen in the "columnar-cell" phenotype (Fig. 3B): Oncocytic-type papillae showed diffuse and strong MUC6 expression in 8 of 9 IOPNs (Fig. 3C) and focal and weak expression in 1 of 9. IPMNs with pancreatobiliary-type papillae also consistently expressed MUC6, but the degree of expression was less intense than in the oncocytic examples with the exception of 1 case (Fig. 3D).

MUC6 expression was very infrequent in columnar-cell type papillae: Only 1 of 10 villous or intestinal and 1 of 8 gastric or foveolar-type IPMNs showed labeling, which was focal and weak (another gastric or foveolar-type IPMN revealed focal staining in the basolateral cytoplasmic compartment of some cells covering the papillae; however apical compartment of these cells was negative). The singular gastric or foveolar-type that was positive displayed labeling only in the areas with highgrade dysplastic changes but not in lesser grade areas (Figs. 3E, F).

Interestingly, the papillae in MCNs were also mostly negative (Fig. 3G). Only 1 of 7 MCN showed focal and weak expression.

Invasive Lesions

DAs (Fig. 3H)—Out of 112 DAs studied, 39 (35%) labeled with antibodies to MUC6 (focal or weak in 28, diffuse or strong in 11). The expression did not correlate with survival (P=0.94), or any of the markers of aggressiveness: tumor size (P=0.76), positive surgical margins (P=0.27), or lymph node status (P=0.82), although there was a trend with higher MUC6 expression and higher grade (P=0.08).

CCs—Only 1 of 14 (7%) CC focally and weakly expressed this marker. For comparison, 14 cases of CC of the breast were also analyzed and all showed strong positive labeling.

DISCUSSION

Our findings reveal that, among papillary intraductal neoplasia of the pancreas, there is a pyloropancreatic pathway distinct from the intestinal pathway. This pathway is represented in IOPNs and pancreatobiliary-type IPMNs, which, together, match to the "cuboidal-cell" category, proposed by Yonezawa for the bile duct tumors.[20] Therefore, it is possible to classify intraductal papillary neoplasia into 3 groups based on different lineages (Fig. 4) (1) Villous or intestinal group that has "columnar-cell" pattern, and the expression profile of MUC1−/MUC2+/CDX2+/MUC6−, (2) Pyloro or pancreatic group, characterized by the "cuboidal-cell" pattern and MUC6 expression, which can be further subdivided into 2 subsets: (2A) Oncocytic: MUC1−variable/MUC2+variable/CDX2−/MUC6+ and (2B) Pancreatobiliary: MUC1+/MUC2−/CDX2−/MUC6−weak+. Of note, emerging evidence suggests that the socalled intraductal tubular and tubulopapillary neoplasms of the pancreas are also often MUC6 positive,[6,9] in addition to MUC1, and thus may be a close relative of the latter category, but this will require further analysis to verify.

This study also supports the notion that the earliest form of neoplastic transformation in the pancreatic ductal epithelium shows common characteristics, regardless of the tumor type, whether it is in PanIN or IOPN/IPMN/MCNs. In all of these, the earliest (metaplasticlike) areas are typically either MUC5AC-positive (foveolar-type mucin expression) as has been shown in several publications[17,18,21,24] or MUC6-positive (pyloric-type mucin expression)

as found in this study. This is in support of a shared “null” cell type that shows gastriclike features, upon which other metaplastic or neoplastic pathways develop and new lineages emerge as the neoplasm progresses into more papillary and advanced forms of dysplasia.

It is tempting to speculate that the associations elucidated in this study and discussed above are in fact morphologic and immunophenotypic reflections of deeper and more basic genetic molecular alterations that play a key pathogenetic role in the progression of these tumors, and their biologic behavior. Data in the literature suggest that NFκB and Sp families of genes may be candidate regulators of MUC6 transcription.[11,19] Both NFκB and Sp families have been also implicated in pancreatic carcinogenesis.[23,27] It has also been shown that pseudopyloric gland phenotype, including MUC6 expression, is associated with gastric carcinogenesis.[19] More importantly it has been known that MUC6 transcription is inducible by PDX1 that is an important determinant of cellular lineage for organs of foregut endoderm,[10] in particular, of pancreatic differentiation. Thus, it is not surprising that MUC6 expression is shared by early neoplastic changes in different types of preinvasive neoplasia in this organ. Furthermore, the MUC6-expressing pyloropancreatic pathway suggested by this study may be a manifestation of the NFκB induced subset that is biologically closer to the gastro or pancreatic carcinogenesis than the metaplastic intestinal type. Thus, it should not be surprising that invasive carcinomas seen in pancreatobiliary-type IPMNs are more commonly of the conventional ductal type. Of note, invasive carcinomas seen in association with intraductal tubular or tubulopapillary neoplasms, which seems to be another example of MUC6 pathway, are also of the ductal (tubular) type. This is in contrast with CCs,[4] the typical invasive carcinoma arising in villous-intestinal IPMNs (ie, MUC2 or CDX2 pathway). The lack of MUC6 in colloid type invasive carcinomas of the pancreas also supports the rather mutually exclusive nature of these pathways.

This study also lends additional support to the noncommittal (undetermined) nature of the papillary in situ neoplasia arising in MCNs. These often show chimeric morphology that is difficult to classify either as villous-intestinal (columnar-cell) or pancreatobiliary (cuboidal-cell) (Fig. 5). These MCN papillae also seem to lack commitment to one of the established cell lineages defined by the patterns of MUC expression as well: Diffuse MUC2 or CDX2 expression is virtually not seen[7] and this study shows that these do not necessarily belong to the pyloropancreatic pathway either, because they also lack MUC6. This brings up the etiopathogenetic question of whether exposure to external milieu as in the case of intraductal neoplasia is a triggering factor in the advancement of early neoplasia into one of either villous/intestinal or pyloropancreatic pathways, whereas MCNs, which do not communicate with the ducts and thus not connected to external mileu, are not exposed to the same triggering factors.

In conclusion, MUC6 expression in papillary in situ neoplasms of the pancreas may serve as a marker of a pyloropancreatic pathway separate from the diffuse MUC2/CDX2 expressing intestinal lineage earlier characterized. [4] In addition, this study supports the notion that earliest (nonpapillary) form of any type of preinvasive neoplasia, whether IOPN, IPMN, or MCN, and to a lesser degree even in PanINs, may share gastric-like characteristics (showing MUC5AC or MUC6), but evolve along divergent pathways as they progress.

Acknowledgments

This study is supported in part by the National Cancer Institute Specialized Program in Research Excellence (SPORE) CA101936 in Pancreas Cancer (PAR-02-068) and in part by the Georgia Cancer Coalition Distinguished Cancer Clinicians and Scientists Program.

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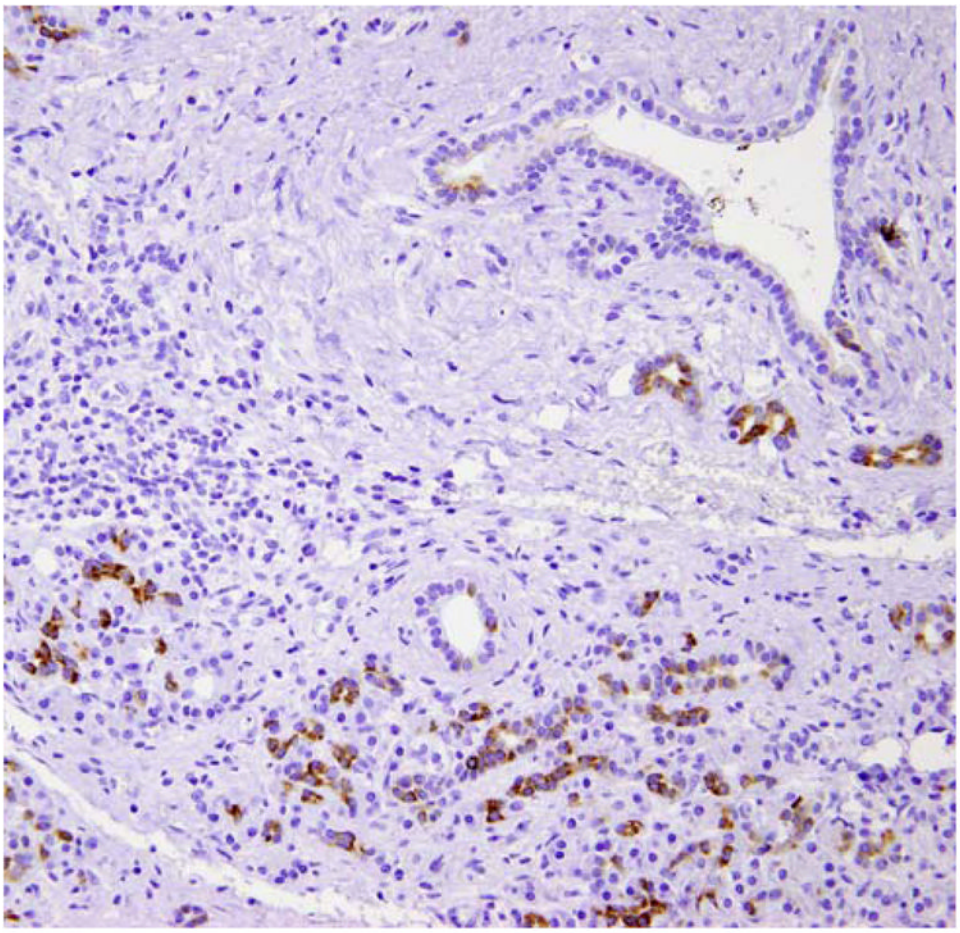

FIGURE 1.
In normal pancreas, MUC6 was expressed in the intercalated ducts and in the small tributary ducts, but not in the intralobular and interlobular ducts, nor in the islets.

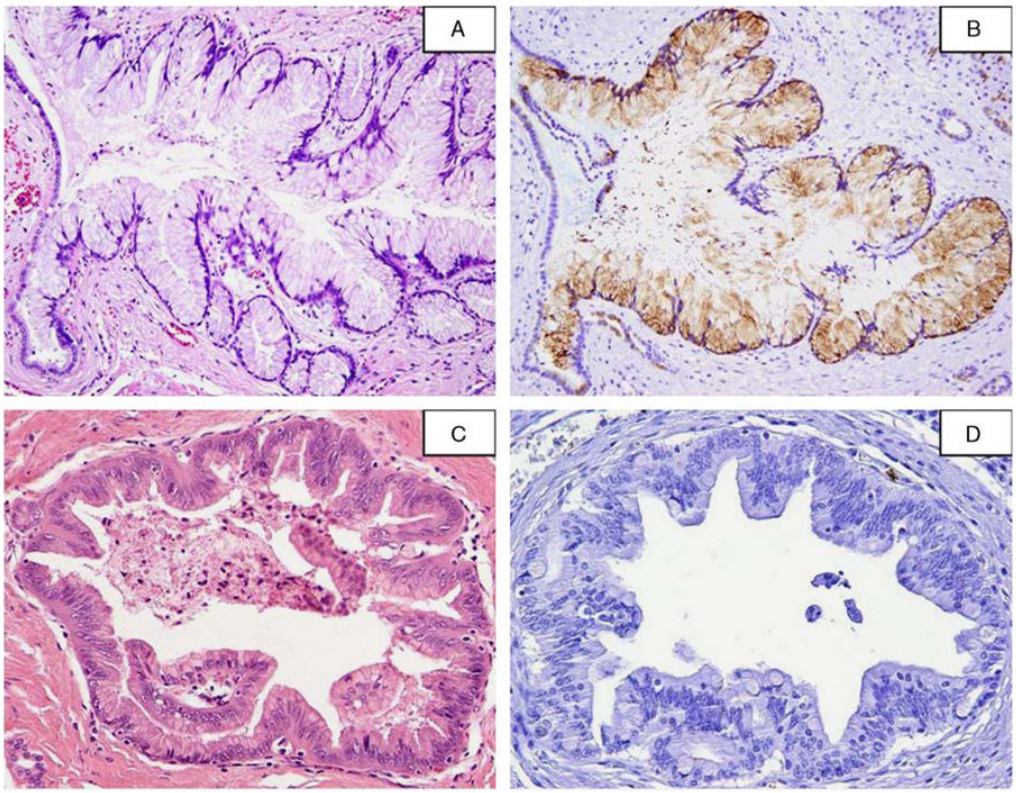

FIGURE 2.
MUC6 was expressed in only a minority of PanINs, mostly in areas with pyloric gland type features (A&B). It was not detected in higher-grade PanINs (C&D).

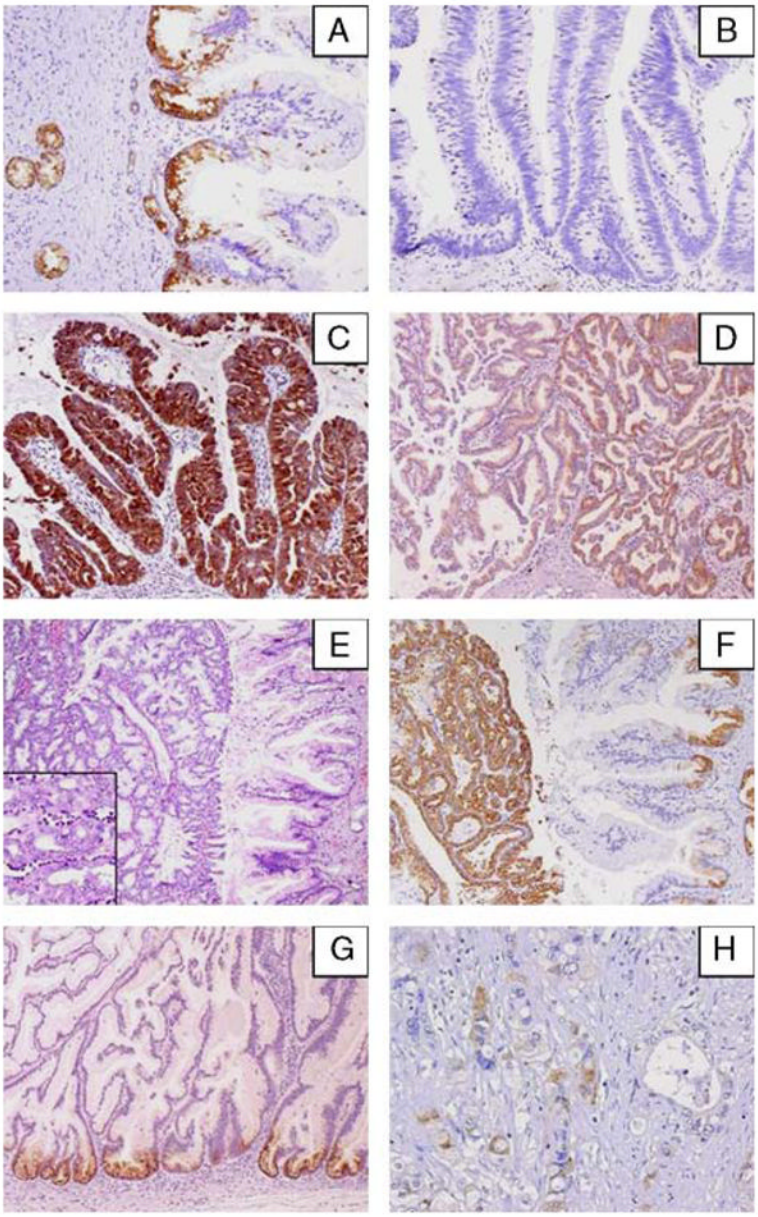

FIGURE 3.

In intraductal papillary mucinous neoplasms (IPMNs), MUC6 was commonly expressed in the cystic (nonpapillary) areas with pyloric gland-like appearance. It was also detected at the base of the papilla forming regions (A), but the expression in the papillae themselves (transformed areas) seemed to be lineage dependent, was negative in most gastric/foveolar (A) and villous/intestinal-types papillae (B) but was positive in oncocytic (C) and, to a lesser degree of intensity, in pancreatobiliary-types (D). The only gastric/foveolar-type IPMN that was positive for MUC6 displayed labeling only in the areas with high-grade dysplastic changes (E&F), which acquired pancreatobiliary type features but not in lesser grade areas. In the majority of mucinous cystic neoplasm (MCNs), MUC6 was negative in the papillary component. Even if it was positive, the positivity was confined to the base of the papillae (G). Only 1/3 of ductal adenocarcinomas (DAs) studied (35%) labeled with MUC6, mostly focal and weak. There was a trend with higher MUC6 expression and higher grade (H).

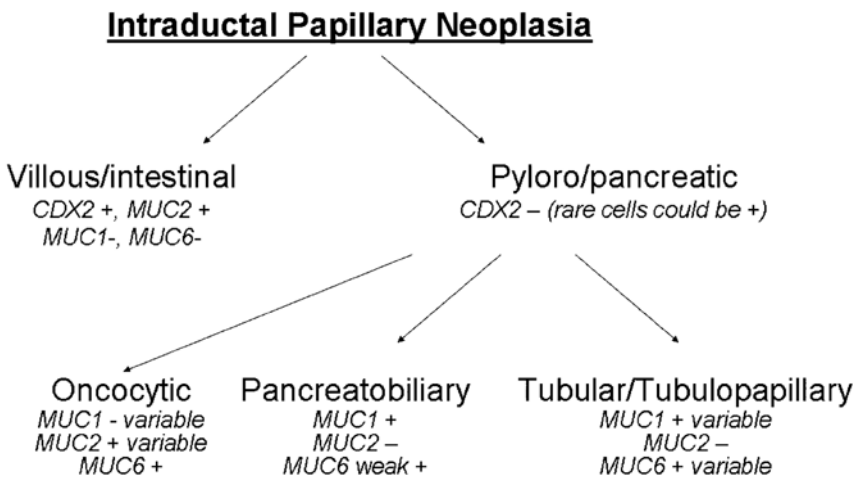

FIGURE 4.

It is difficult to classify mucinous cystic neoplasm (MCN) papillae either as villous/intestinal (columnar-cell) or pancreatobiliary (cuboidal-cell) owing to their chimeric morphology.

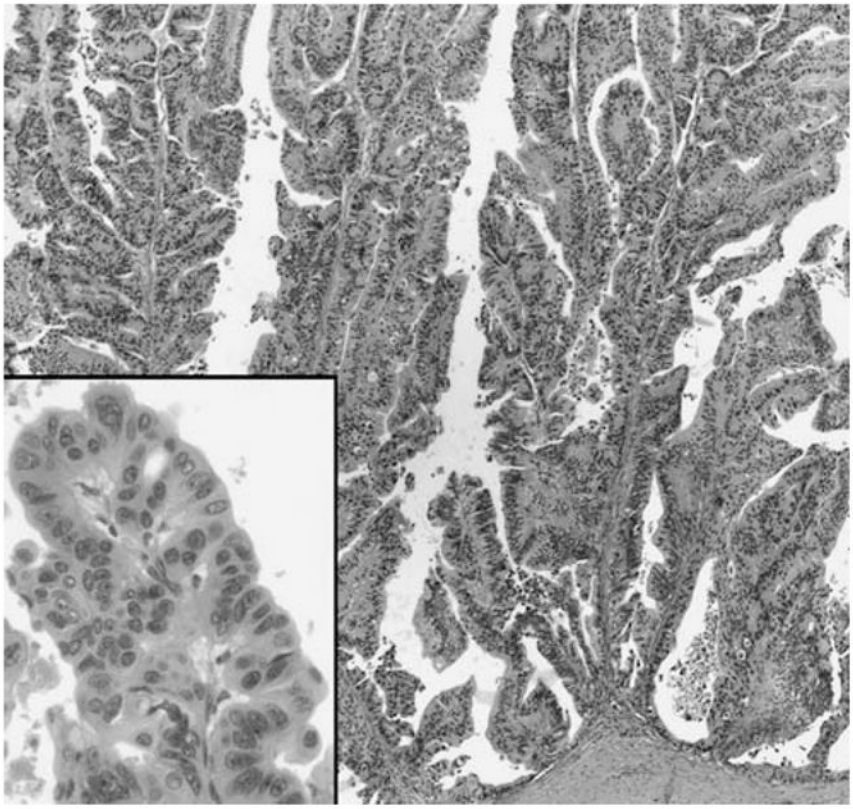

FIGURE 5.
It is difficult to classify mucinous cystic neoplasm (MCN) papillae either as villous/intestinal (columnar-cell) or pancreatobiliary (cuboidal-cell) owing to their chimeric morphology.

TABLE 1

MUC6 Expression in the Papillary Neoplasms of the Pancreas