Nonmucinous Cystadenomas of the Pancreas With Pancreatobiliary Phenotype and Ovarian-Like Stroma

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Abstract

Among 31 benign cystic neoplasms of the pancreas diagnosed as mucinous cystadenomas, we identified 9 (29%) cases of nonmucinous cystadenomas with a pancreatobiliary phenotype and an ovarian-like stroma. Although both cystic tumors belong to the same family, they should be separated because their epithelial lining and cyst fluid are different. The lining cells of the nonmucinous cystadenomas consisted of a single layer of cuboidal cells, similar to the epithelial cells of the normal pancreatic ducts, and were not dysplastic (90%-100% of the lining cells). The cyst fluid was described as serous or clear. The remaining 22 classical mucinous cystadenomas, lined predominantly by mucinous and foveolar epithelium, revealed focal pancreatobiliary epithelium in 86% of the cases, and 6 pancreatic invasive mucinotic cystadenocarcinomas failed to show pancreatobiliary differentiation. We believe that these nonmucinous cystadenomas of the pancreas represent a distinctive subset of cystic neoplasms of the pancreas that probably have no malignant potential.

Although mucinous cystic neoplasms of the pancreas were initially described more than 100 years ago,1 it was not until 1978 that Compagno and Oretel2 defined the morphologic features that allowed separation of mucinous from serous cystic tumors of the pancreas. Their observations were subsequently confirmed by many other studies.3-8 In addition to the tall columnar mucinous epithelium, the presence of an ovarian-like stroma was emphasized in these tumors.2,4,6,8-10 The Armed Forces Institute of Pathology (AFIP) fascicle on tumors of the pancreas11 described the microscopic features of mucinous cystic tumors as lined by “tall mucin producing epithelium with gastric foveolar differentiation and in some cases goblet cells scattered among columnar cells. The septa of the cysts at least focally contain a distinctive ovarian like stroma.” The World Health Organization’s classification of tumors of the digestive system12 basically uses the same histologic criteria for these pancreatic cystic neoplasms. Foci of low- or high-grade dysplasia have subsequently been recognized and incorporated into the classification of these tumors.8,11,13,14 However, there is no reference to pancreatobiliary epithelium lining the cysts in any publication on mucinous cystic pancreatic neoplasms.

The purpose of this report is to describe 9 cystic neoplasms of the pancreas that belong to the family of mucinous cystic neoplasms but should be distinguished from them because they display a predominant or exclusive nondysplastic cuboidal epithelial lining similar to the normal ductal epithelium of the pancreas or to the epithelium of biliary-type tubular adenomas of the gallbladder. For this reason, we will refer to this as pancreatobiliary-type epithelium.
Materials and Methods

During a review of 31 tumors that had been interpreted as mucinous cystadenomas of the pancreas filed in the Departments of Pathology from 3 academic hospitals (University Hospital of the University of Minnesota, Minneapolis; Medica Sur Hospital, Mexico City, Mexico; and Instituto Nacional de Ciencias Médicas y Nutrición “Salvador Zubirán,” Mexico City, Mexico), we identified and selected 9 cases (29%) of cystic neoplasms with a predominant or exclusive pancreatobiliary epithelium for this study. Clinical and follow-up information was obtained from the patients’ charts. Gross findings, including tumor size, location, and type of cyst fluid, were obtained from the pathology reports. In addition, a specific search for pancreatobiliary-type epithelium was made among the remaining 22 mucinous cystic tumors lined predominantly by mucinous and foveolar epithelium, as well as 6 invasive mucinous cystadenocarcinomas of the pancreas.

In 7 cases, the entire cystic neoplasms were submitted for microscopic examination. Multiple H&E-stained sections were available for review in all 9 cases. Paraffin blocks were available in 8 cases, and additional slides were prepared for immunohistochemical analysis. Immunostains were performed using the standard avidin-biotin-peroxidase method. The following antibodies were studied (Table 1) with appropriate controls.

Results

Clinical Features

All patients were female with a mean age of 45 years (range, 24-64 years). Seven tumors were symptomatic and 2 were incidental findings. A distal pancreatectomy was performed in all patients.

Table 1

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Dilution</th>
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<tbody>
<tr>
<td>CK7a</td>
<td>1:100</td>
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<tr>
<td>CK20b</td>
<td>1:250</td>
</tr>
<tr>
<td>MUC1c</td>
<td>1:50</td>
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<tr>
<td>MUC2c</td>
<td>1:100</td>
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<tr>
<td>MUC5ACa</td>
<td>1:100</td>
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<tr>
<td>MUC6b</td>
<td>1:100</td>
</tr>
<tr>
<td>CDX2a</td>
<td>1:50</td>
</tr>
<tr>
<td>CAM5.2a</td>
<td>1:10</td>
</tr>
<tr>
<td>Inhibina</td>
<td>1:100</td>
</tr>
</tbody>
</table>

* Biocare (Concord, CA).
  b BioSB (Santa Barbara, CA).
  a Abcam (Cambridge, MA).

Immunohistochemistry

The cuboidal epithelial lining of 8 cystadenomas showed strong and diffuse immunoreactivity for CK7 and CAM5.2, as well as focal reactivity for MUC1. Focal expression of MUC5AC was noted in 8 tumors. CDX2 and MUC2 were focally positive in 2 cystadenomas that contained goblet cells, whereas CK20 and MUC6 were negative in all cystadenomas. The ovarian-like stroma showed immunoreactivity for estrogen and progesterone receptors in 7 of the 8 tumors, whereas the cuboidal pancreatobiliary epithelium was unreactive. Focal expression of inhibin was noted in the ovarian-like stroma of 5 cystadenomas.
Discussion

Our findings indicate that nonmucinous and mucinous cystadenomas of the pancreas share a number of clinico-pathologic features. Similarities include middle-age female predominance, location in the tail of the pancreas, multiloculation, and ovarian-like stroma. Among the most important differences are the lack of mucinous or foveolar epithelium, the nonmucinous quality of the fluid, and the lack of dysplastic changes in the cuboidal pancreatobiliary epithelium. Surprisingly, nonmucinous cystadenomas are not uncommon. In our material, they represented 29% of classical mucinous cystadenomas with ovarian-like stroma, and more than 86% of these latter neoplasms showed the focal (5%-50%) pancreatobiliary phenotype. We believe pancreatic cystadenomas that show more than 50% of lining cells with the pancreatobiliary phenotype should be included in the nonmucinous cystadenoma category. Surprisingly, in the chapter on mucinous cystic neoplasms in the AFIP fascicle on tumors of the pancreas, Figures 5-23 and 5-24 illustrate pancreatobiliary differentiation, not mucinous epithelium, as indicated by the figure legends.11 The pancreatobiliary differentiation, as reported in biliary-type tubular gallbladder adenomas, is supported by
In addition, these IPMNs arise in the main pancreatic duct or its branches. Cystic neoplasms of the extrahepatic biliary system may also show pancreatobiliary differentiation, and some may lack a mucinous epithelial component and contain serous fluid. Among 6 cystadenomas of the extrahepatic bile ducts we examined, 4 had a predominant or exclusive pancreatobiliary phenotype and contained serous or clear fluid (J. Albores-Saavedra, unpublished observations).

Our findings also indicate that mucinous cystadenomas of the pancreas display a broader morphologic spectrum than previously reported. The identification of nondysplastic...
Nonmucinous pancreatic cystic tumors with the pancreatobiliary phenotype and ovarian-like stroma should be distinguished from all other cystic lesions of the pancreas, especially those lined by pancreatic ductal cuboidal epithelium. Although retention cysts are lined by cuboidal pancreatic ductal epithelium, they result from ductal obstruction commonly caused by chronic pancreatitis or a neoplasm located in the head of the pancreas or ampulla of Vater. They are usually single and unilocular, and they lack the ovarian-like stroma. Serous cystadenomas, which are usually microcystic and less frequently macrocystic, are lined by cuboidal glyco-gren-rich clear cells. The ovarian-like stroma is not present in these tumors. Congenital cysts usually occur in children and are lined by cuboidal nondysplastic epithelium but lack the ovarian-like stroma. Although pseudocysts lack an epithelial lining clinically, they can be confused with the nonmucinous pancreatic cystic tumors that are the subject of this report. Pseudocysts, however, are often seen in patients with a history of acute pancreatitis. They are unilocular, and their fibrotic wall contains inflammatory cells.

On the basis of the presence of an ovarian-like stroma, some authors may contend that cystic pancreatic tumors should be classified as mucinous cystic neoplasms, an opinion we do not share for the following reasons: the 9 cystic pancreatic tumors we have described were not lined by mucinous or foveolar epithelium, they did not produce a mucinous fluid, and their nondysplastic epithelial lining was similar to the epithelium of normal pancreatic ducts. Moreover, their cuboidal epithelium did not show dysplastic changes, a sine qua non for the diagnosis of mucinous pancreatic cystadenomas. Furthermore, these pancreatic cystic neoplasms with a pancreatic biliary phenotype probably did not have malignant potential. The ovarian-like stroma was similar to that of mucinous cystic pancreatic neoplasms, and it has been recognized in other cystic neoplasms such as cystic nephromas and, of course, ovarian cystic neoplasms, which are classified according to their epithelial lining. Finally, we emphasize that cystic pancreatic tumors are epithelial in origin, not mesenchymal neoplasms.

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References


