Serous Cystadenoma of the Pancreas

Limitations and Pitfalls of Endoscopic Ultrasound-Guided
Fine-Needle Aspiration Biopsy

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BACKGROUND. Expectant management of serous cystadenoma (SCA) of the pancreas requires an accurate preoperative diagnosis. Previously published cytologic diagnostic sensitivities have ranged widely, from 10% to 100%. In the current study, the authors evaluated the diagnostic sensitivity of endoscopic ultrasound (EUS)-guided fine-needle aspiration biopsy (FNAB) and cross-sectional imaging for SCA.

METHODS. Group I consisted of 21 histologically confirmed SCAs. Group II (n=7 lesions) lacked histologic confirmation and was defined by EUS findings that were consistent with SCA and a cyst fluid carcinoembryonic antigen (CEA) level <5 ng/mL. Group III was comprised of 2 nonserous and potentially malignant cysts of the pancreas for which a preoperative diagnosis of SCA was considered. Cross-sectional imaging data were recorded. The smears were evaluated for the presence of serous lining epithelium, gastrointestinal-contaminating epithelium, and inflammatory cells including hemosiderin-laden macrophages. The authors also evaluated the presence of hemosiderin-laden macrophages in a series of 110 FNA specimens from histologically confirmed neoplastic mucinous cysts of the pancreas and 45 pseudocysts of the pancreas.

RESULTS. Prospectively among Group I lesions, the appearance on computed tomography (CT) was considered definitive for SCA in 3 of 12 cases (25%). The histologically confirmed SCA cases had CEA levels of <5 ng/mL, except for 1 case for which the CEA level was 176.5 ng/mL. A cytologic diagnosis of SCA was made prospectively in only 1 CT-guided case. Retrospectively, 3 intraoperative FNAs and 1 additional CT-guided aspirate contained rare epithelial cells of a SCA. None of the EUS-guided aspirates demonstrated serous epithelium. Among Group II aspiration specimens, only 1 contained serous epithelial cells. Approximately 52% of the EUS-guided aspirates demonstrated gastrointestinal contamination. This glandular epithelium was categorized as atypical in 2 cases. Hemosiderin-laden macrophages were identified in 43% of the SCAs. Conversely, only 2% of neoplastic mucinous cysts and 9% of pseudocysts produced hemosiderin-laden macrophages in aspirate fluid.

CONCLUSIONS. In the current study, serous epithelial cells were identified in <20% of cases. Gastrointestinal-contaminating epithelium, often observed in EUS-guided aspirates, further contributes to difficulties in interpretation. The presence of hemosiderin-laden macrophages as a surrogate marker for SCA requires further study. A preoperative diagnosis of SCA remains a challenge, and an EUS-guided FNAB is unlikely to provide the high level of diagnostic accuracy necessary to permit a nonoperative approach.


KEYWORDS: serous cystadenoma, pancreatic cyst, fine-needle aspiration biopsy, endoscopic ultrasound, cytology.
advances in imaging techniques. Among the cystic neoplasms, serous cystadenoma (SCA) (incidence of 32–39%), mucinous cystic neoplasms (MCN) (incidence of 10–49%), and intraductal papillary mucinous neoplasms (IPMN) (incidence of 21–33%) represent the majority of the neoplasms encountered in clinical practice.

SCA is a benign neoplastic cyst of the pancreas. Nearly half of all SCAs are asymptomatic at the time of presentation. Although it is generally agreed that symptomatic SCAs require surgery, to our knowledge no definitive treatment recommendations regarding asymptomatic neoplasms currently exist. It has been suggested that large SCAs (measuring >4 cm) be excised, whereas expectant management for smaller tumors is considered reasonable. However, these recommendations are for the most part dependent on an unequivocal preoperative diagnosis of SCA, and a high degree of diagnostic reliability is critical. The primary goal of all diagnostic procedures is to distinguish low-risk pancreatic cysts (ie, SCA and pseudocyst) from high-risk neoplastic mucinous cysts, including MCN and IPMN.

Despite the availability of high-quality imaging techniques, a definitive preoperative diagnosis of SCA frequently remains elusive. In 1 series, an accurate preoperative diagnosis of tumor type based on imaging features and cytologic and chemical analysis of cyst fluid was proposed in only 20% of SCAs. In the current study, we report a comprehensive analysis of the cross-sectional imaging and cytomorphologic features of 28 SCAs of the pancreas.

MATERIALS AND METHODS

The case files of the Massachusetts General Hospital were searched for fine-needle aspirations (FNAs) of pancreatic cysts performed between 1993 and 2005. Demographic data, imaging evaluations, and findings of cyst fluid analysis (carcinoembryonic antigen and amylase) were recorded when available. The cytomorphic, histologic slides, and endoscopic ultrasound (EUS) images were reviewed retrospectively.

The study group was comprised of 21 histologically proven SCAs (Group I) and 13 presumptive SCAs without histologic follow-up (Group II). The latter group was defined based on EUS findings that were consistent with an SCA and a cyst fluid CEA level <5 ng/mL. In addition, the study group also included 2 cysts for which the cytologic or radiologic findings were initially considered to be consistent with SCA but that, after surgical resection, proved to be potentially malignant nonserous cysts of the pancreas (Group III).

Eighteen patients were evaluated with an EUS and EUS-guided FNA biopsy (FNAB), performed using a linear echoendoscope. Four patients underwent a computed tomography (CT)-guided biopsy. The remaining 8 samples were collected intraoperatively. The EUS-guided aspirates were performed using a 19-gauge or 22-gauge needle occluded with a stylet (Wilson Cook Inc., Winston-Salem, NC; or Mediglobe, Tempe, Ariz) using a transgastric approach for those lesions located in the body and tail of the pancreas and a transduodenal approach for those lesions located in the head of the organ. Concurrent CT-guided core needle biopsies were performed in 2 patients. The CT-guided biopsies were performed using 18-gauge to 20-gauge needles.

Papanicolaou (Pap)-stained slides, including conventional smears, and Cytospin and ThinPrep preparations (Table 1) were evaluated for the presence of sheets and small groups of monomorphic cuboidal epithelial cells with round nuclei and clear, nonmucinous cytoplasm. The characteristic lining epithelium of an SCA is demonstrated in Figure 1a. This direct smear of a surgically resected SCA was used as the morphologic standard. Gastrointestinal contamination and background mucin were noted. Inflammatory cells were recorded, including histiocytes, lymphocytes, neutrophils, and eosinophils. Pigment within histiocytes, when present, was categorized as hemosiderin and nonhemosiderin. Hemosiderin was defined as chunky, brown, refractile pigment. The presence of iron was assessed on a Pap stain. In an attempt to investigate the specificity of these findings, if any, we compared this cohort of SCAs with FNABs from 91 IPMN cases and 19 MCN cases. These included 46 adenomas, 32 borderline tumors, 18 in situ adenocarcinomas, and 14 invasive adenocarcinomas arising within a neoplastic mucinous lesion. All neoplastic mucinous cysts were confirmed by exhaustive histologic evaluation of the
corresponding pancreatectomy specimen. The SCAs were also compared with 45 histologically confirmed pseudocysts of the pancreas.

RESULTS

Demographic Details

Of the 13 unresected neoplasms, 7 were determined to be clinically consistent with an SCA based on corroborative imaging studies and a cyst fluid CEA level <5 ng/mL (Group II). The other 6 cases were excluded from Group II because of cyst fluid CEA levels of >5 ng/mL. The mean age of the patients with SCA (Groups I and II) was 59 years and included 25 women and 3 men. The tumors were predominantly located in the body and/or tail of the pancreas (20 tumors; 71%). The median tumor size

FIGURE 1. (a) Direct smear of a resected serous cystadenoma. Cuboidal cells with small round nuclei and clear cytoplasm are observed (H & E). (b) Fine-needle aspiration. Cytospin preparation with less than ideal preservation is shown. A cluster of bland cuboidal to columnar epithelial cells with amphophilic cytoplasm and round nuclei, consistent with serous epithelial lining cells, is observed (Papanicolaou stain). (c) Fine-needle aspiration. A cluster of bland cuboidal to columnar epithelial cells with clear cytoplasm and round nuclei, consistent with serous epithelial lining cells, is observed (Papanicolaou stain). (d) Fine-needle aspiration. A sheet of bland epithelial cells with round to oval nuclei and apical cytoplasm, oriented in a streaming fashion and consistent with gastrointestinal epithelial contamination, is shown (Papanicolaou stain). These cells bear a close resemblance to those shown in Panel c. (e) Hemosiderin-laden macrophages within the lumina of a serous cystadenoma (H & E). (f) Macroscopic photograph of a pancreatic resection specimen revealing a multiloculated cystic lesion with central fibrous tissue (Magnification not available.)
was 4.4 cm. One patient in Group II had a previous diagnosis of von Hippel-Lindau syndrome. The 2 patients in Group III were women aged 70 years and 78 years, respectively (mean age, 74 years).

**Imaging Data**

On EUS imaging, the histologically proven cases of SCA were either multicystic and septated or unilocular (Table 2) (Fig. 2). However, EUS did not provide a definitive prospective diagnosis of SCA for any of these cases. On a retrospective review of the available images, 1 macrocystic and 7 microcystic lesions were found to be suggestive of SCA and 1 case, which was microcystic, was considered diagnostic for SCA. Based predominantly on the appearance on CT, an unqualified diagnosis of SCA was proposed prospectively in 3 of the 12 cases imaged with this modality (2 microcystic lesions and 1 macrocystic lesion). Magnetic resonance imaging was used in only 1 case, revealing a microcystic lesion considered to be diagnostic for SCA.

Two of the 7 lesions in Group II were unilocular cysts (Table 3). The remainder were multicystic and thinly septated. Group III included a branch duct intraductal papillary mucinous neoplasm (IPMN) and a cystic pancreatic endocrine neoplasm. All cases included in these categories were, on imaging, deemed to be consistent with a diagnosis of SCA.

**Cyst Fluid Analysis**

Cyst fluid analysis was performed in 8 of the histologically proven cases (Group I). All but 1 case demonstrated a CEA level of <5 ng/mL. The CEA level in 1 case was 176.5 ng/mL. By definition, the lesions considered to be clinically consistent with SCA (Group II) had a CEA level <5 ng/mL (range, 0–1.3 ng/mL). Among Group III lesions, the CEA level of the branch duct IPMN was 37.7 ng/mL, which on repeat aspiration increased to >500 ng/mL. For the pancreatic endocrine tumor, the CEA level was <0.2 ng/mL. By comparison, all but 4 of the 45 mucinous neoplasms demonstrated CEA levels of >5 ng/mL, with a median level of 296 ng/mL.

Amylase levels ranged from 11 U/L to 90 U/L for the histologically proven cases (Group I) and from 49 U/L to 299 U/L for the unresected cysts (Group II), and were 88 U/L and 72 U/L, respectively, for the branch duct IPMN and endocrine tumor (Group III).

**Cytomorphologic Features (Groups I and II)**

The mean fluid volume aspirated in Group I was 4.9 mL, whereas that of Group II was 2.3 mL.

All 28 aspirates demonstrated a clear background devoid of tenacious mucin. A cytologic diagnosis of SCA was made prospectively in only 1 of the histologically proven aspirates, a CT-guided aspirate (Group I). Retrospectively, 4 additional aspirates (3 intraoperative and 1 CT-guided aspirate) demonstrated a few monolayers and single cells with clear cytoplasm and well-defined cytoplasmic outlines (Table 4) (Fig. 1b). None of the 13 EUS-guided aspirates from Group I demonstrated similar glycogenated epithelial cells. Among the cysts that were considered to be clinically consistent with SCA (Group II), only 1 EUS-guided aspirate revealed epithelial cells that were consistent with cyst-lining cells (Fig. 1c).

Benign-appearing glandular epithelium, some with visible cytoplasmic mucin (Fig. 1d) was identified in 52% of the EUS-guided aspirates (11 of 21 aspirates), whereas the CT-guided aspirates were found to be devoid of such epithelium. However, although scant and delicate mucin was present, thick tenacious or abundant mucin was not identified.

Histiocytes were identified in 68% of Group I and Group II SCAs (19 of 28 SCAs) and 63% of these cases (12 of 19 cases) contained noticeable hemosiderin (Fig. 3). This hemosiderin pigment was visible as chunky, brown, and refractile intracellular material.

There were no significant cytomorphicologic differences noted between the oligocystic/macrocytic and microcystic variants of SCA.

**Macroscopic and Histologic Pathology**

**Characteristics of Group I**

Within Group I, using macroscopic and histologic evaluation, there was only 1 unilocular cyst and 20 multilocular cysts. Sixteen of the multilocular cysts (80%) were classified as microcystic (Fig. 1f) and 4 (20%) were classified as macrocystic. All cysts were lined by a single layer of cuboidal epithelium with clear cytoplasm. The lining epithelium was closely associated with a dense and delicate capillary network. Hemosiderin-laden macrophages were occasionally identified within cystic spaces (Fig. 1e), and more frequently entrapped in the hyalinized intratumoral stroma.

**Characteristics of Group III**

The FNA specimen of the branch duct IPMN revealed a few benign-appearing cells that were originally interpreted as possibly representing cyst-lining cells of an SCA (Table 5). These cells were reinterpreted as likely representing gastrointestinal contamination.

Similarly, the FNA specimen of the endocrine tumor did not contain any cyst-lining epithelial cells or mucin and only proteinaceous fluid was present. Although this was considered nondiagnostic, it was
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Site</th>
<th>Size, mm</th>
<th>Type of SCA</th>
<th>EUS</th>
<th>CT</th>
<th>Method of biopsy</th>
<th>CEA, ng/mL</th>
<th>Cytologic diagnosis</th>
<th>Preoperative diagnosis</th>
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<tbody>
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<td>1</td>
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<td>Macrocystic</td>
<td>Septated cyst</td>
<td>NA</td>
<td>EUS</td>
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<td>Negative</td>
<td>Cystic neoplasm</td>
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<td>2</td>
<td>Body</td>
<td>40</td>
<td>Macrocystic</td>
<td>NA</td>
<td>NA</td>
<td>Intraoperative</td>
<td>NA</td>
<td>Atypical</td>
<td>Cystic neoplasm</td>
</tr>
<tr>
<td>3</td>
<td>Body</td>
<td>40</td>
<td>Microcystic</td>
<td>Multilocular</td>
<td>NA</td>
<td>CT</td>
<td>NA</td>
<td>Unsatisfactory</td>
<td>Not applicable</td>
</tr>
<tr>
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<td>Body</td>
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<td>Cyst</td>
<td>CT</td>
<td>EUS</td>
<td>NA</td>
<td>Negative; consistent with SCA</td>
<td>Pancreatic mass</td>
</tr>
<tr>
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<td>Head</td>
<td>50</td>
<td>Macrocystic</td>
<td>Cystic mass, consistent with SCA</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst</td>
</tr>
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<td>NA</td>
<td>NA</td>
<td>EUS</td>
<td>3.4</td>
<td>Atypical; mucinous epithelium</td>
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<td>NA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst</td>
<td>SCA</td>
</tr>
<tr>
<td>9</td>
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<td>Septated cyst, honeycombed</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst</td>
</tr>
<tr>
<td>10</td>
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<td>160</td>
<td>Macrocystic</td>
<td>Multi-loculated lesion</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
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<td>Negative; cyst contents, mucinous neoplasm</td>
</tr>
<tr>
<td>11</td>
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<td>25</td>
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<td>Complex cystic lesion</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst contents, mucinous neoplasm</td>
</tr>
<tr>
<td>12</td>
<td>Body</td>
<td>32</td>
<td>Microcystic</td>
<td>NA</td>
<td>CT</td>
<td>Intraoperative</td>
<td>2.4</td>
<td>Negative</td>
<td>SCA</td>
</tr>
<tr>
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<td>Head</td>
<td>50</td>
<td>Microcystic</td>
<td>NA</td>
<td>NA</td>
<td>Intraoperative</td>
<td>NA</td>
<td>Negative; cyst</td>
<td>SCA</td>
</tr>
<tr>
<td>14</td>
<td>Body</td>
<td>25</td>
<td>Microcystic</td>
<td>Complex cystic lesion</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst</td>
</tr>
<tr>
<td>15</td>
<td>Head</td>
<td>25</td>
<td>Microcystic</td>
<td>Multi-loculated lesion</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>NA</td>
<td>Negative; cyst</td>
</tr>
<tr>
<td>16</td>
<td>Head</td>
<td>80</td>
<td>Microcystic</td>
<td>Cystic mass s/o IPMN</td>
<td>CT</td>
<td>EUS</td>
<td>NA</td>
<td>Negative; cyst</td>
<td>Pancreatic cystic neoplasm</td>
</tr>
<tr>
<td>17</td>
<td>Body</td>
<td>40</td>
<td>Microcystic</td>
<td>Thinly septated cyst</td>
<td>EUS</td>
<td>MRI multicystic mass, SCA</td>
<td>EUS</td>
<td>NA</td>
<td>Positive; cyst contents, mucinous neoplasm</td>
</tr>
<tr>
<td>18</td>
<td>Body/tail</td>
<td>20</td>
<td>Microcystic</td>
<td>Thinly septated cyst</td>
<td>EUS</td>
<td>MRI multicystic mass, SCA</td>
<td>EUS</td>
<td>0.2</td>
<td>Negative; cyst contents, mucinous neoplasm</td>
</tr>
<tr>
<td>19</td>
<td>Tail</td>
<td>47</td>
<td>Microcystic</td>
<td>Septated cyst with solid component, favor IPMN</td>
<td>EUS</td>
<td>MRI multicystic mass, SCA</td>
<td>EUS</td>
<td>0.5</td>
<td>Unsatisfactory</td>
</tr>
<tr>
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<td>Body</td>
<td>23</td>
<td>Microcystic</td>
<td>Heterogenous solid and cystic mass</td>
<td>CT</td>
<td>MRI multicystic mass, SCA</td>
<td>CT</td>
<td>0.9</td>
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<td>21</td>
<td>Body</td>
<td>35</td>
<td>Microcystic</td>
<td>NA</td>
<td>Intraoperative</td>
<td>NA</td>
<td>NA</td>
<td>Negative; cyst</td>
<td>Cystic neoplasm</td>
</tr>
</tbody>
</table>

SCA indicates serous cystadenoma; EUS, endoscopic ultrasound; CT, computed tomography; CEA, carcinoembryonic antigen; NA, not available; MRI, magnetic resonance imaging; IPMN, intraductal papillary mucinous neoplasm; s/o, suggestive of; SPT, solid pseudopapillary tumor.
noted that the cytologic findings (or absence of findings), in conjunction with a negative cyst fluid analysis and EUS findings, supported the clinical impression of SCA. Consequently, the tumor was not immediately resected. However, 2 years after this initial FNA, a 1-cm enlargement of the cyst prompted a repeat FNA that revealed features characteristic of a pancreatic endocrine tumor.

**Neoplastic Mucinous Cysts and Pseudocysts**

Of the 110 surgically confirmed neoplastic mucinous cysts, 55 (50%) were negative for neoplastic mucinous epithelium and 55 (50%) were found to lack extracellular mucin on a Pap stain. Forty-seven cases (43%) lacked both background mucin and neoplastic mucinous epithelium. Two neoplastic mucinous cysts (2%) and 4 pseudocysts (9%) demonstrated hemosiderin-laden macrophages.

**DISCUSSION**

An unequivocal pathologic diagnosis of SCA requires the presence of cuboidal epithelium with abundant clear cytoplasm. Lal et al. identified serous epithelial cells in all 11 CT-guided biopsies from SCAs. This series included a single EUS-guided FNAB, whereas the other 10 aspirates were performed under CT guidance. In a recently published series, the diagnostic accuracy of EUS-guided biopsies was reported to be 17%. Of our histologically proven cases, we were able to identify lesional cells in only 5 cases (21%), 4 of which were identified retrospectively. Two of the 4 CT-guided aspirates (50%) and 3 of 8 intraoperative fluid analyses (37.5%) demonstrated typical glycogenated serous epithelium. None of the EUS-guided

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**TABLE 3**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Site</th>
<th>Size, mm</th>
<th>EUS</th>
<th>Cytologic preparation</th>
<th>CEA, ng/mL</th>
<th>Cytopathologic diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Head</td>
<td>50</td>
<td>Multiloculated, consistent with SCA</td>
<td>Cytospin</td>
<td>0.3</td>
<td>Benign epithelial cells, suggestive of serous-lined cyst, consistent with SCA</td>
</tr>
<tr>
<td>2</td>
<td>Head</td>
<td>15</td>
<td>Multiloculated, suspicious for SCA</td>
<td>Smears</td>
<td>NA</td>
<td>Atypical bland epithelial cells, cannot exclude SCA</td>
</tr>
<tr>
<td>3</td>
<td>Body</td>
<td>48</td>
<td>Multiloculated, consistent with SCA</td>
<td>ThinPrep</td>
<td>NA</td>
<td>Consistent with SCA</td>
</tr>
<tr>
<td>4</td>
<td>Body</td>
<td>40</td>
<td>Multiloculated, suspicious for SCA</td>
<td>ThinPrep</td>
<td>&lt;0.2</td>
<td>Poorly preserved nonmucinous epithelial cells, consistent with SCA</td>
</tr>
<tr>
<td>5</td>
<td>Uncinate</td>
<td>35</td>
<td>Multiloculated, suspicious for SCA</td>
<td>ThinPrep</td>
<td>0.5</td>
<td>Rare bland epithelial cells, may represent SCA, but too scant for definite diagnosis</td>
</tr>
<tr>
<td>6</td>
<td>Head</td>
<td>20</td>
<td>Multiloculated, consistent with SCA</td>
<td>Cytospin</td>
<td>NA</td>
<td>Benign epithelial cells, suggestive of serous-lined cyst, consistent with SCA</td>
</tr>
<tr>
<td>7</td>
<td>Neck</td>
<td>23</td>
<td>Multiloculated, consistent with SCA</td>
<td>Cytospin</td>
<td>1.3</td>
<td>Benign epithelial cells, suggestive of serous-lined cyst, consistent with SCA</td>
</tr>
</tbody>
</table>

EUS indicates endoscopic ultrasound; CEA, carcinoembryonic antigen; SCA, serous cystadenoma; (-), negative; AB, alcian blue; NA, not available; IPMN, intraductal papillary mucinous neoplasm; VHL, von Hippel-Lindau syndrome.
aspirates demonstrated definitive evidence of an SCA. It should be noted that the CT-guided aspirates were performed using needles varying in size from 18-gauge to 20-gauge. By comparison, the size of the EUS-guided aspiration needles varied from 19-gauge to 22-gauge.

On cross-sectional imaging, the finding of multiple small (<3 mm) compartments within a cystic lesion is suggestive of an SCA, with an accuracy of 92% to 96%.7 When associated with a central stellate scar, these cysts are considered virtually diagnostic of an SCA. Mucinous cystadenomas typically lack both these features.7 However, in the majority of cases, the macrocystic variant of SCA cannot be distinguished from mucinous neoplasms by imaging studies. Although EUS provides superior images, this modality likewise cannot distinguish oligocystic SCA from a mucinous neoplasm.8

The results of these previous reports are confirmed in the current study. On the basis of cross-sectional imaging, a confirmatory diagnosis of SCA was made in only 19% of the histologically proven cases (4 of 21 cases). Neither EUS imaging nor cytology provided an unequivocal diagnosis of SCA.
However, on a retrospective review, the EUS images were suggestive of SCA in 87.5% of cases (7 of 8 cases) and were diagnostic of SCA in 1 case. Recent medical literature has reported the incidence of an accurate diagnosis of SCA based on imaging studies to vary from 27.2% to 77.7%. Of greater concern is the potential misdiagnosis of a malignant neoplastic mucinous cyst as an SCA, an event that was reported to occur in 7 of 28 patients in 1 study and in 2 of 49 patients in another. The high proportion of macrocystic SCA (24%), which is notoriously more difficult to diagnose, may explain the relatively low accuracy of cross-sectional imaging noted in the current study. It should also be noted that the current study, with a high percentage of surgically resected SCAs, was biased toward SCAs with an atypical imaging appearance.

An analysis of pancreatic cyst fluid can provide powerful diagnostic ancillary evidence. SCAs typically demonstrate CEA levels of $<5$ ng/mL, as do pseudocysts. Indeed 8 of the 9 cases in the current study demonstrated CEA levels $<5$ ng/mL. However, occasionally cases of SCA demonstrate significantly elevated levels of CEA, as observed in 1 case from the current series (in this case, the level was $\leq 200$ ng/mL). Conversely, although the majority of mucinous lesions of the pancreas demonstrate markedly elevated CEA levels ($>200$ ng/mL), a minority are found to have relatively low levels of CEA, including some cases with a CEA level $<5$ ng/mL. As demonstrated in Group III, endocrine tumors also demonstrate low CEA levels.

EUS samples have the additional drawback of contaminating gastrointestinal epithelium, as was evident in 11 of the 21 EUS-guided aspirates reported herein. Indeed, 2 aspirates were interpreted as atypical, in which gastrointestinal-contaminating epithelium could not be distinguished from sampling of a mucinous neoplasm. However, these 2 aspirates lacked the characteristic (although not always present) abundant and dense extracellular mucin, observed in neoplastic mucinous cysts. In addition, the glandular atypia was in the form of slightly disorganized fragments of glandular epithelium without nuclear atypia. Nevertheless, neoplastic low-grade glandular epithelium is sometimes virtually indistinguishable from gastrointestinal contamination. Conversely, 48.5% of neoplastic mucinous lesions lacked both mucin and mucinous epithelium. Thus, the absence of mucin and mucinous epithelial cells on aspiration cytology does not exclude MCN or IPMN.

Conversely, it is the authors’ opinion that gastrointestinal-contaminating epithelium is frequently misread as serous lining epithelium. On a retrospective review of Group II cases, we were able to identify definitive serous lining epithelium in only 1 of the 8 cases, although such cells were either identified or alluded to in all the cases. In addition, gastrointestinal-contaminating epithelium from the branch duct IPMN was considered to represent serous epithelium. The strong clinical suspicion based on imaging studies and chemical analysis of these cases may bias the pathologist. Adherence to strict morphologic criteria should help to prevent contaminating epithelium being misinterpreted as serous lining epithelium. In addition, negative features (ie, a lack of background mucin, a lack of epithelial cells, and low cyst fluid markers) should not suffice as evidence of a specific lesion, even if consistent with the clinical picture. Although periodic acid–Schiff (PAS) and PAS/diastase stains could help identify the abundant glycogen typical of SCA cells, these aspirates are invariably hypocellular and therefore inadequate for additional studies.

Hemosiderin-laden macrophages were identified in 11 of the 21 cases of SCA (52%) in Group I, but in only 2% of IPMNs/MCNs and in 9% of pseudocysts. SCAs are characterized by a rich subepithelial capillary network and frequently demonstrate aggregates of hemosiderin-laden macrophages. However, at the current time, the presence of hemosiderin-laden macrophages is not a diagnostic feature and can only serve as a surrogate marker to suggest a diagnosis of SCA.

Although the overall data are conflicting, the current study raises questions regarding the need to routinely perform EUS-guided FNAB in cases with imaging features that are typical of SCA. Although to our knowledge the complications of EUS-guided FNAB are few, the risks include pancreatitis (incidence of 2–3%), hemorrhage within the cyst (incidence of <1%), and infections (incidence of <1%). The rich subepithelial vascular plexus makes SCAs prone to intracystic hemorrhage during FNAB.

Early data with EUS-guided Trucut biopsies of cystic pancreatic neoplasms have shown promising results. In the study by Levy et al., 5 of 6 SCAs were correctly identified on a Trucut biopsy. Both biopsies performed in this study were diagnostic, without any procedural complications reported. This finding, if confirmed by a larger series, may supersede FNAB, particularly when a diagnosis of SCA is being considered.

In conclusion, FNAB specimens from SCAs lack the extracellular mucin and neoplastic mucinous epithelium that are characteristic of neoplastic mucinous cysts, and the dirty background typical of a pseudocyst. Glycogenated serous epithelial cells,
typical of a serous cystadenoma, rarely are present on FNAB by either CT or EUS guidance. The recognition of hemosiderin-laden macrophages in a clean, nonmucinous background may serve as a clue to the diagnosis of SCA in the appropriate clinical setting. However, the preoperative diagnosis of SCA remains a challenge, and an EUS-guided FNAB alone is unlikely to provide the high level of diagnostic accuracy necessary to permit a nonoperative approach.

REFERENCES