Serous Cystadenoma of the Pancreas With Papillary Features

A Diagnostic Pitfall on Fine-Needle Aspiration Biopsy

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Serous cystadenoma (SC), also known as microcystic adenoma or glycogen-rich cystadenoma, is a rare, usually benign pancreatic neoplasm that occurs most often in women and is typically diagnosed during the sixth to ninth decades of life. The characteristic histologic features of this tumor include multiple microcysts separated by fine connective tissue septa, lined by flattened or cuboidal epithelium, and most often filled with proteinaceous fluid. Less common presentations of SC include the oligocystic variant with fewer but larger cysts and a predominantly solid form. The cytomorphicologic structure of pancreatic SC has been described only rarely.\(^1\)\(^-\)\(^7\) Whereas intracystic papillary growth of neoplastic epithelium has been histologically described for SC,\(^8\) to the best of our knowledge, no such morphologic structure has been previously reported in the cytology literature.

**REPORT OF A CASE**

A 77-year-old woman presented to the University of Texas Medical Branch at Galveston with mild abdominal pain. Admission history and physical examination depicted a normally active individual with no remarkable weight loss, nausea, emesis, or changes in bowel habits. Medical history, as related by the patient, was significant for the occurrence of a mild stroke several years earlier and a similar episode recently that was associated with resultant aphasia. Evaluative procedures administered with regard to this more recent event included ultrasonography and computed tomographic (CT) exploration of the head and carotid arteries and a CT survey of the chest and abdomen. Available medical records do not address the results of the head and neck studies; abdominal CT, however, revealed a 5.2 × 4.5 × 4-cm mass within the midbody of the pancreas without evidence of biliary dilatation or metastases. A follow-up esophagogastroduodenoscopy with endoscopic ultrasound (EUS) was performed and demonstrated the lesion to be a well-defined, solid/cystic pancreatic mass that displaced the celiac axis without invasion and was thought to be suggestive of solid pseudopapillary tumor. Fine-needle aspiration (FNA) cytologic examination was performed with endoscopic image guidance. An exploratory laparotomy with distal pancreatectomy was subsequently performed.

**EUS Findings**

A 4.0 × 3.8-cm mass in the region of the pancreatic body was noted, displacing but not invading, the celiac trunk. The lesion was round and had well-defined margins. The ultrasonic image displayed solid and cystic components (Figure 1). Atrophy was noted throughout the pancreas, and the gallbladder was normal. No lymph nodes were visualized. The FNA was performed under ultrasonographic guidance. The ultrasonographic findings were consistent with a pancreatic cystic neoplasm, and the differential diagnosis included solid pseudopapillary neoplasm and non-functioning islet cell tumor.

**Cytologic Findings**

The aspirates were expressed onto glass slides and smears were prepared. A total of 3 smears (1 from each needle pass) were air-dried and immediately stained with Quik-Dip (Mercedes Medical Inc, Sarasota, Fla) for rapid assessment of specimen adequacy and preliminary evaluation at the endoscopy suite. Additionally, 13 smears were immersed in 95% ethanol for fixation and further Papanicolaou staining. The needles were rinsed in

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saline solution for centrifugation and further cell recovery by the Cytospin (Shandon, Pittsburgh, Pa) technique. Two Cytospin slide preparations were made.

The aspirates were hypocellular and contained a few neoplastic cells in a bloody background on only 2 slides obtained from the first pass. The epithelial tumor cells were arranged in well-formed papillary fronds (Figure 2). Additionally, there were rare sheets of cuboidal, monotonous neoplastic cells with no distinct cytoplasmic borders. The cytoplasm was clear and moderately abundant. The nuclei exhibited minimal nuclear crowding, minute nucleoli, and rare grooves. No nuclear atypia or mitosis was identified. The cytologic examination was reported as scant monotonous epithelial proliferation with papillary and microacinar arrangements consistent with solid pseudopapillary tumor. However, the specimen was limited by hypocellularity that precluded further investigation of the tumor.

**Gross Findings**

On excision, a solitary, well-circumscribed, bosselated, ovoid tumor mass of the distal pancreas was identified and measured $4.5 \times 4 \times 4$ cm. Sectioning of the specimen revealed the tumor to consist almost exclusively of innumerable microcysts, with a honeycomb-like configuration. The cysts measured from less than 0.1 to an approximate maximal diameter of 1.2 cm, were filled with slightly viscous amber fluid, and exhibited multiple foci of hemorrhage probably due to the previous aspiration (Figure 3).
Histologic Findings

Microscopic examination revealed that the cysts were lined by low-cuboidal epithelial cells with occasional foci of papillary proliferation (Figure 4, A). The lining cells exhibited pale, vacuolated cytoplasm with hematoxylin-eosin staining. Mitoses were not identified and there was no pleomorphism. Nuclear morphologic structure and chromatin pattern were as previously described for cysticologic examination (Figure 4, B). Histopathologic staining with periodic acid-Schiff (PAS) and mucicarmine, respectively, demonstrated the epithelial cells as glycogen rich and without evidence of mucin. Immunohistochemical stains further characterized these cells as diffusely positive for cytokeratin (AE1/3), neuron-specific enolase, α1-antitrypsin, and α1-antichymotrypsin, but nonreactive for carcinoembryonic antigen, vimentin, and desmin stains.

COMMENT

Most pancreatic neoplasms are adenocarcinomas. Whereas this tumor most often is manifested in a solid, infiltrating pattern, cystic and solid/cystic variants are not uncommon. Even when confined to the pancreas, adenocarcinoma usually carries an unfavorable prognosis, since a diagnosis is usually not established until an advanced tumor stage. In these instances, palliative surgery, often associated with significant morbidity, and/or chemotherapy is usually required. Because of the deep retroperitoneal location of the pancreas, a less invasive alternative method for establishing a diagnosis of pancreatic carcinoma is CT-guided core biopsy or FNA. Percutaneous image-guided FNA is regarded as the most suitable method for tissue diagnosis of pancreatic carcinoma before surgery.9

Serous cystadenomas are almost always benign, although a rare malignant variant has been documented.10,11 Except for their metastasizing behavior, serous cystadenocarcinomas are histologically, and presumably also cytologically, indistinguishable from typical SC. The radiologic appearance of cystic pancreatic tumors is excellent but imperfect,12 and hence may not be diagnostic of SC. It usually correlates well with the gross appearance of excised neoplasms. Postoperatively, the diagnosis of SC is ultimately established on the basis of routine histologic examination and histochemical stains.

During the past 2 decades, FNA cytologic examination guided by imaging modalities has been increasingly used for sampling of pancreatic and other deep-seated mass lesions, because of its diagnostic reliability, good patient tolerance, low morbidity, and cost-effectiveness. Core biopsy specimens can also be obtained under CT or ultrasonographic guidance. Ancillary studies, such as histochemical and immunocytochemical special stains, can be performed on these aspirates or core biopsy specimens, as required.

The patient's presenting symptom, consisting of vague abdominal pain, was nonspecific. Preoperative CT demonstrated a midbody pancreatic mass lesion. Whereas subsequent surgical resection of the mass was an option, it was determined that performing FNA under EUS guidance was an appropriate next step in the diagnostic approach for this lesion. With the addition of FNA, EUS of pancreatic lesions may establish or exclude malignancy, assess resectability,9 and help to direct planning for definitive therapy.13,14 The sensitivity and specificity of EUS-FNA for identification of pancreatic malignancy have been reported as 94% and 100%, respectively.13 The current lesion was characterized by endoscopurographic imaging as likely a solid pseudopapillary neoplasm or a nonfunctioning islet cell tumor.

The aspirates were hypocellular and contained aggregates of monotonous, nonatypical, cuboidal neoplastic epithelial cells, which were arranged in occasional well-formed papillary arrays. The cytologic pattern, although limited by paucity of the tumor cells, was interpreted as suggestive of solid pseudopapillary tumor, with recognition to the fact that this patient's age falls outside the young age range usually associated with this neoplasm. This inconclusive cytologic interpretation was made with consideration of the ultrasonographic impression in a triple testlike15 approach. Histologic examination of the excised pancreatic neoplasm established the diagnosis of SC with papillary proliferation, which was further supported by consistent histochemical and immunohistochemical profile. Clinical follow-up for 1 year revealed no tumor recurrence or evidence of metastatic disease.

The finding of true papillary arrangements in aspirates from low-grade solid/cystic neoplasms of the pancreas indicates the need to consider several entities in the differential diagnosis. Papillary differentiation has not been previously reported for FNA cytologic examination of pancreatic SC. However, as illustrated by the current case and in previous histologic descriptions,8 a papillary pattern can be a prominent component in aspirates from SC of the pancreas. The cytomorphicologic structure of SC has been described as usually consisting of monolayered sheets of cuboidal epithelium with moderate amounts of nonmucinous cytoplasm and bland nuclear features in a hypocellular pattern.1-7 In addition, SC characteristically shows cytoplasmic PAS positivity because of its glycogen content and lack of mucicarmine staining. Mucinous cystic neoplasm of the pancreas often exhibits variable atypia, occasional papillary groups, and mucin pools, along with strong intracytoplasmic and extracellular positivity for mucicarmine stain. Islet cell tumors of the pancreas present in aspirates as sheets of monotonous cells with monomorphic nuclei and “salt and pepper” chromatin, which are usually positive for neuroendocrine markers. Papillae, however, are not typically found in pancreatic islet cell neoplasms.

As its name implies, solid pseudopapillary neoplasm of the pancreas is a low-grade, malignant epithelial tumor8 with papillary groups of small cells with scant cytoplasm and bland nuclei centered around fibrovascular cores,4 along with solid areas. On aspirates, this neoplasm often presents in a hypercellular pattern. The tumor cells typically exhibit eosinophilic or clear, vacuolar cytoplasm, and neither mucin nor glycogen is usually demonstrated in their cytoplasm. However, intracellular and extracellular PAS-positive globules can be occasionally observed in solid pseudopapillary tumors of the pancreas. These tumors are diffusely positive for vimentin, neuron-specific enolase, α1-antitrypsin, and α1-antichymotrypsin, and their cystic spaces usually lack single epithelial lining.8 The current case had a spongy gross appearance owing to its microcystic architecture, which occasionally exhibited microscopic papillary structures. Despite immunoreactivity for α1-antitrypsin, α1-antichymotrypsin, and neuron-specific enolase stains (also seen in solid pseudopapillary tumor of the pancreas), the gross and histologic patterns of this case are most consistent with SC. Additional distinguishing features shown in our index case were diffuse cyto-

Arch Pathol Lab Med—Vol 125, December 2001

Serous Cystadenoma of the Pancreas—Rampy et al 1593
plasmic positivity for PAS and lack of vimentin expression.

As indicated by a recent study and with the current case as an illustrative example, cytopathologists involved in the evaluation of cytologic specimens obtained by EUS-FNA are likely to encounter a variety of lesions not previously described solely on FNA.14 Whereas the finding of a papillary component to SC in histologic material is widely recognized, the current case illustrates that well-formed papillary structures can be the presenting feature of pancreatic SC in FNA cytologic examination, posing significant diagnostic challenges to the pathologist. Hence, SC should also be considered in the differential diagnosis of solid/cystic lesions of the pancreas that exhibit papillary proliferation on aspirates. Ancillary studies, along with correlation with the clinical and radiologic findings, are indicated to help differentiate this neoplasm from other diagnostic entities.

References