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Original Article

Pancreatic pseudocyst or a cystic tumor of the pancreas?

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Abstract

Pancreatic pseudocysts are the most common cystic lesions of the pancreas and may complicate acute pancreatitis, chronic pancreatitis, or pancreatic trauma. While the majority of acute pseudocysts resolve spontaneously, few may require drainage. On the other hand, pancreatic cystic tumors, which usually require extirpation, may disguise as pseudocysts. Hence, the distinction between the two entities is crucial for a successful outcome. We conducted this study to highlight the fundamental differences between pancreatic pseudocysts and cystic tumors so that relevant management plans can be devised. We reviewed the data of patients with pancreatic cystic lesions that underwent intervention between June 2007 and December 2010 in our hospital. We identified 9 patients (5 males and 4 females) with a median age of 40 years (range, 30–70 years). Five patients had pseudocysts, 2 had cystic tumors, and 2 had diseases of undetermined pathology. Pancreatic pseudocysts were treated by pseudocystogastrostomy in 2 cases and percutaneous drainage in 3 cases. One case recurred after percutaneous drainage and required pseudocystogastrostomy. The true pancreatic cysts were serous cystadenoma, which was treated by distal pancreatectomy, and mucinous cystadenocarcinoma, which was initially treated by drainage, like a pseudocyst, and then by distal pancreatectomy when its true nature was revealed. We conclude that every effort should be exerted to distinguish between pancreatic pseudocysts and cystic tumors of the pancreas to avoid the serious misjudgement of draining rather than extirpating a pancreatic cystic tumor. Additionally, percutaneous drainage of a pancreatic pseudocyst is a useful adjunct that may substitute for surgical drainage.

Key words Pancreas, pseudocysts, cystic tumors, algorithm

Pancreatic pseudocysts are enzyme-rich, encysted, peripancreatic fluid collections that follow an attack of acute pancreatitis, chronic pancreatitis, or pancreatic trauma[1]. In up to 50% of cases of acute pancreatitis, exudative fluids collect in the peripancreatic region, which resolve spontaneously in the majority of cases. However, in about 10% of patients, spontaneous resolution does not occur and the fluid becomes encysted within a wall of fibrous and granulation tissue, forming a pseudocyst. The absence of an epithelial lining in the cyst wall distinguishes it from a true pancreatic cyst, making it a *pseudocyst*[2].

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On the other hand, certain pancreatic tumors present in a cystic form, with the majority being malignant or having a malignant potential[3]. The most common of these are serous cystadenoma, mucinous cystic neoplasms, intraductal papillary mucinous tumors, and solid pseudopapillary tumors[4].

The inadvertent drainage of a pancreatic cystic tumor, misdiagnosed as a pseudocyst, has obvious deleterious consequences, as tumor dissemination is inevitable if it was a malignant one. It is therefore mandatory to ascertain the nature of the cyst in question before embarking on treatment. The aim of the current work was to highlight the possibility of this mishap and to provide an accurate diagnostic algorithm which can avert it.

Patients and Methods

The radiology and operation theater registries from Armed Forces Hospital-Southern region in Saudi Arabia were reviewed to identify patients with pancreatic cystic lesions who underwent

an intervention between June 2007 and December 2010. Patient medical records were retrieved and the following data were collected: the patient's demography, the intervention performed, the indication for intervention, and the final pathologic diagnosis. All patients who presented with a cyst related to the pancreas and underwent an intervention were included in this study; there were no exclusion criteria.

The study was approved by the institutional review board. Because the data were collected from medical records and presented anonymously, the board waiver for the patient's informed consent was granted.

Pseudocysts were drained either surgically into the gut (internal drainage) or percutaneously under computerized tomography (CT) guidance (external drainage). A cyst wall biopsy was concomitantly taken during internal drainage for histologic confirmation, whereas a sample of the aspirate collected during external drainage was sent for analysis (mainly cytologic analysis and occasionally mucin and tumor markers). For cystic tumors, pancreatic resection was performed.

Results

Patient demographics and final diagnosis

We identified 9 patients, 5 males and 4 females, with a median age of 40 years (range, 30–70 years). The final diagnosis was pseudocyst in 5 cases, pancreatic cystic tumor in 2 cases (a mucinous cystadenocarcinoma and a serous cystadenoma), whereas the nature of the cyst was undetermined in the remaining 2 cases. In 1 case, which occurred in a known tuberculous patient, there was an incidental 4-cm cyst in the head of the pancreas, lying on the superior mesenteric artery. Percutaneous aspiration revealed yellowish pus-like material, and the pancreatic lesion was assumed to be an extension of the tuberculous process. The patient underwent antituberculous treatment and was under follow-up when this paper was submitted. The second patient, who presented with acute cholecystitis, also had two incidentally discovered, small cysts in the head of the pancreas, the larger being 1.8 cm in diameter. She was referred to a specialized center, where fine needle aspiration of the cysts failed. She was also under follow-up when this paper was submitted, and her latest CT scan showed no change in the size of the cysts.

Description of the observed cysts

The median pseudocyst diameter was 11.2 cm (range, 7.4–17.4 cm), whereas the diameter of the two cystic tumors was 6.5 cm and 9.2 cm. All pseudocysts and cystic tumors occurred in the body and tail of the pancreas. All pseudocysts in this series followed an attack of acute biliary pancreatitis. On the other hand, history of acute pancreatitis was also present in the case of mucinous cystadenocarcinoma.

Indications for intervention

For pseudocysts, the indication for intervention was the persistence of the cyst in association with upper abdominal pain. The median time between the onset of pancreatitis and the intervention was 43 days. Pancreatectomy was performed once a cystic tumor was diagnosed.

Two pseudocysts were drained into the stomach by pseudocystogastrostomy, whereas 3 pseudocysts were drained percutaneously under CT guidance. Of the 3 patients, 2 were successfully treated by percutaneous drainage, whereas 1 had pseudocyst recurrence and therefore underwent pseudocystogastrostomy. On the other hand, mucinous cystadenocarcinoma was mistakenly managed as a pseudocyst by Roux-en-Y cystojejunostomy, but when cyst wall biopsy revealed its neoplastic nature, distal pancreatectomy was performed. The other patient with serous cystadenoma underwent distal pancreatectomy from the outset.

Out of the 3 patients with pseudocysts who underwent percutaneous drainage, 2 underwent endoscopic retrograde cholangiopancreatography before drainage to investigate the presence of a communication with the pancreatic duct, and in no case was this communication present.

In all cases with open drainage, cyst wall biopsy was an integral part of surgery, whereas with percutaneous drainage, cyst fluid was analyzed for cytology and yielded uninformative results of cellular debris in 3 cases. However, in the case of mucinous cystadenocarcinoma, the aspirate was tested for cytology as well as tumor markers, where a very high level of carbohydrate antigen 19-9 (CA19-9) was observed (5.6×10^9 U/L, normal value 0–3.09×10^4 U/L), indicative of a malignant tumor.

Two representative cases

First case

A 43-year-old female, a known diabetic on oral hypoglycemics, presented with epigastric pain with nausea and vomiting. Her past surgical history included laparoscopic cholecystectomy and acute pancreatitis 3 years and 3 months before presentation, respectively.

On examination, she was generally well. Her pulse was 86 beats/min, blood pressure was 110/65 mmHg, and temperature was 36.8°C. Abdominal examination showed mild tenderness and upper abdominal fullness.

Her blood picture, electrolytes, hepatic and renal functions, serum amylase, and blood glucose were all normal. Ultrasound examination and CT scanning showed a 9.2 cm × 6.7 cm cystic swelling in the upper abdomen, suggestive of a pancreatic pseudocyst (**Figure 1**). CT-guided percutaneous drainage was performed and the aspirate was sent for cytologic analysis in addition to carcinoembryonic antigen (CEA), CA19-9, and mucin. As our hospital lacks the facility of estimating these parameters, the sample was sent to another facility and, unfortunately, the results were much

delayed. After 2 weeks, the cyst disappeared and the catheter was timely removed. Four weeks later, she presented with recurrent cyst. Endoscopic retrograde cholangiopancreatography (ERCP) was done to explore the possibility of internal drainage, but there was no communication with the main pancreatic duct. The leukocyte count dropped progressively to reach 1.6 × 10^9/L and was attributed to sepsis within the cyst. A semi-urgent operation was performed in the late afternoon when no frozen section facilities were available. During the operation, an 8 cm × 8 cm globular swelling was found behind the stomach on the left side of the midline. A cyst wall biopsy was taken, and Roux-en-Y cystojejunostomy was performed. The patient tolerated surgery well and her postoperative recovery was uneventful. Surprisingly, cyst wall biopsy showed borderline mucinous cystadenoma, for which distal pancreatectomy was performed (**Figure 2**).

The postoperative course was complicated by adhesive bowel obstruction, which responded to conservative therapy. Eventually the patient recovered and was referred to the medical oncologist, who started her on chemotherapy.

Cyst fluid analysis, obtained several days after the second operation, showed a very high value of CA19-9. The histopathology indicated mucinous cystic neoplasm with few microscopic foci of mucinous cystadenocarcinoma (**Figures 3–4**). Interestingly, the neoplasm exhibited extensive epithelial loss over large areas, resembling a pseudocyst at these sites.

Second case

A 50-year-old female presented with epigastric pain and bilious vomiting for 1 week. She had a left loin pain for 2 years and underwent cholecystectomy 10 years earlier. Abdominal examination was unremarkable except for mild epigastric tenderness.

Laboratory investigations showed normal blood picture, renal functions, and serum amylase. Liver functions were also normal apart from raised gamma glutamyl transpeptidase (252 U/L; reference

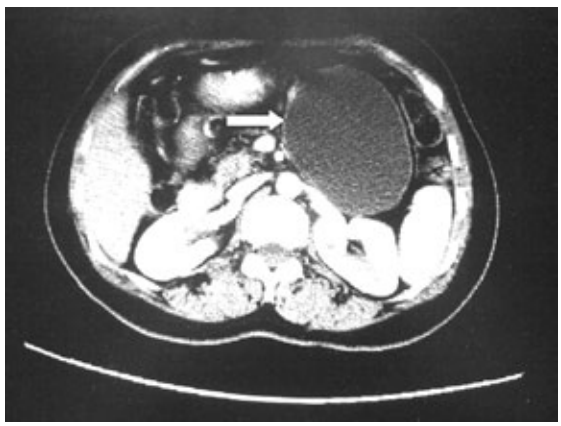

Figure 1. **Computed tomography (CT) findings of a mucinous cystadenocarcinoma.** CT scan of the abdomen of the first patient shows a cystic swelling in the upper abdomen (white arrow), with no apparent evidence of neoplasia.

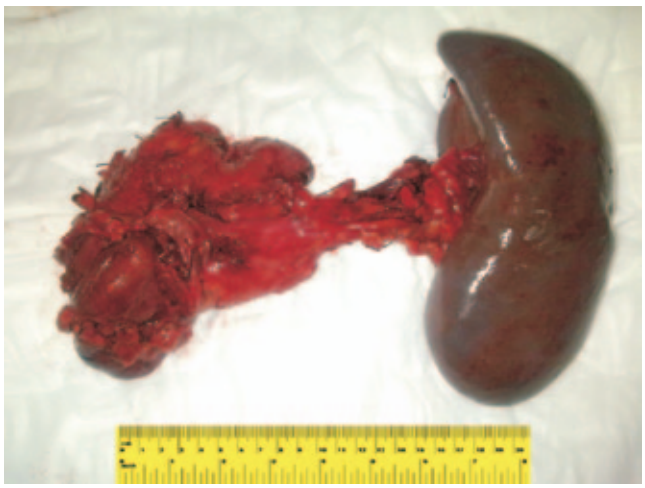

Figure 2. **Resected cystadenocarcinoma with distal pancreatectomy. This specimen resected from the first patient with mucinous cystadenocarcinoma is composed of the spleen, as well as the body and tail of the pancreas, containing the cystic neoplasm (specimen measurement: spleen, 13 cm × 6 cm × 4 cm; pancreas, 16 cm × 6 cm × 3 cm).**

range, 5–64 U/L).

Abdominal ultrasonography (US) showed dilated common bile duct (12 mm) with prominent central intrahepatic biliary radicles. Abdominal CT showed a multilocular cystic lesion measuring 6.5 cm × 4.7 cm in the body and tail of the pancreas with gross calcification (**Figure 5**), a picture highly suggestive of a pancreatic cystic tumor. Pneumococcal vaccination was given and distal pancreatectomy was performed.

The postoperative convalescence was smooth apart from basal atelectasis, which responded well to physiotherapy, and a small fluid collection in the region of the resected pancreas that disappeared gradually with no intervention. Histopathologic examination of the resected specimen showed serous cystadenoma (**Figure 6**).

She was discharged in good condition and remained well in the

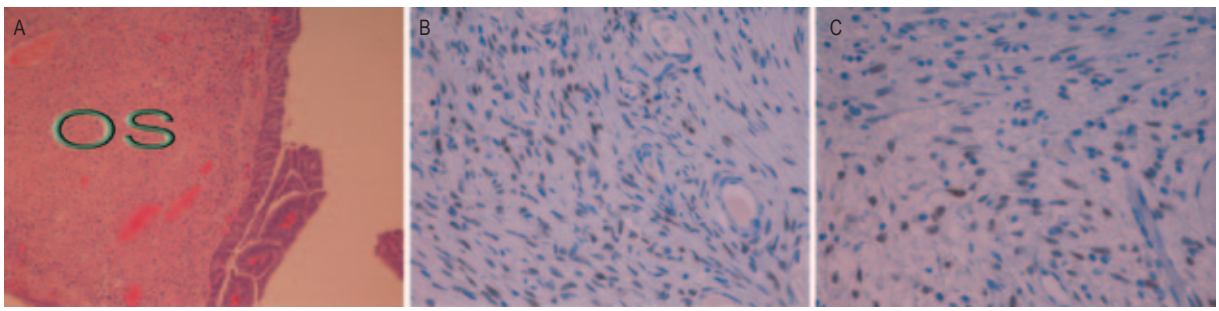

Figure 3. **Mucinous cystadenocarcinoma with ovarian-like stroma. A, photomicrograph of the resected mucinous cystadenocarcinoma from the first patient shows ovarian-like stroma (OS) in the cyst wall, a characteristic of mucinous cystic neoplasms (HE, 40×). B and C, photomicrographs show ovarian-like stroma with brown-stained nuclei (B, immunohistochemistry, estrogen receptor antibody, 40×; C, immunohistochemistry, progestrone receptor antibody, 40×).**

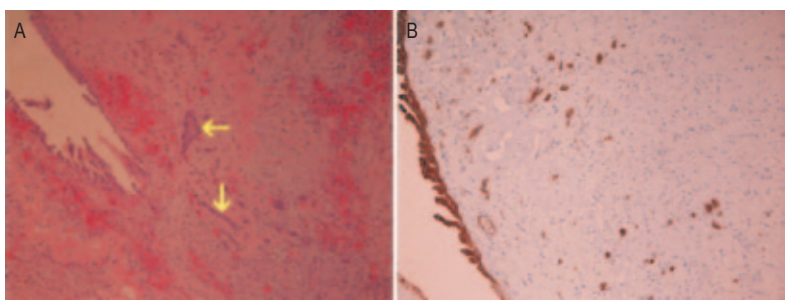

Figure 4. **Microscopic featuies of malignancy of mucinuous cystic neoplasms. A, the wall of the mucinous cystadenocarcinoma from the first patient shows microscopic foci of invasion by malignant epithelial cells (yellow arrows). This separates it from other types of mucinous neoplasms: the benign, the borderline, and the *in situ* cancer variants (HE, 10×); B, invasion of stroma is stained brown in malignant epithelial cell groups (immunohistochemistry, cytokeratin MNF116 antibody, 10×)**

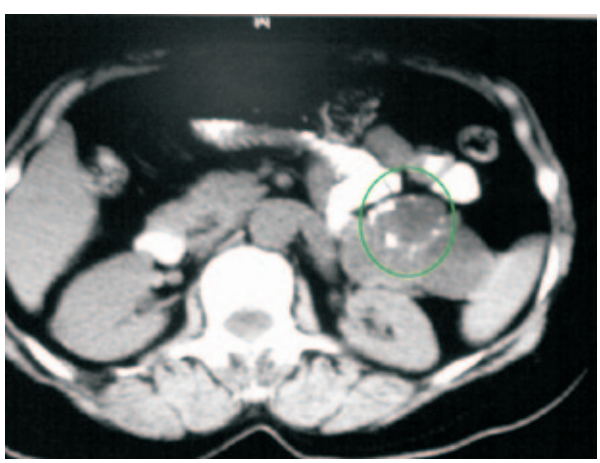

Figure 5. **Evidence of neoplasia in the second patient. CT scan of the abdomen of the second patient shows a cystic lesion in the body and tail of the pancreas, with internal septa and calcification (green circle), features suggestive of cystic neoplasia. Other features include thick wall, internal septa, mural nodules, papillary projections, solid components, lobulated margins, and cyst complexity with solid components (not shown here).**

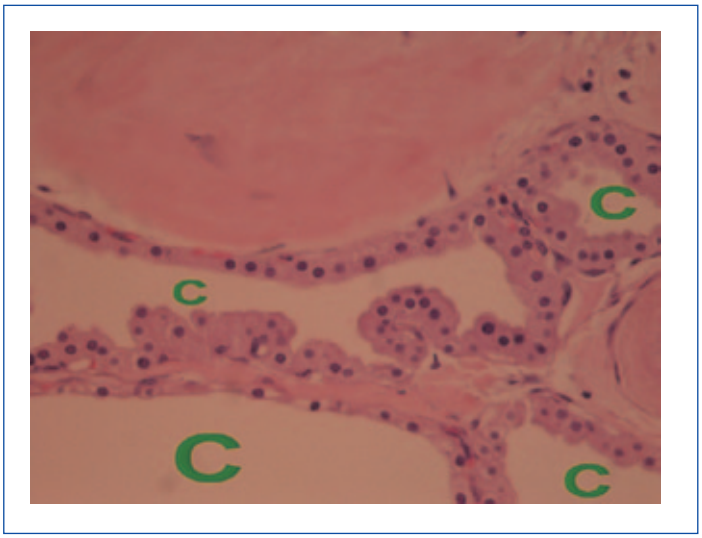

Figure 6. **Microscopic features of serous cystadenoma. Photomicrograph of the reseceted specimen from the second patient shows multiple microcysts (c) lined by a single layer of cuboidal/ low columnar epithelium, a feature of serous cystadenoma. This contrasts to the tall columnar lining of the mucinuous cystic neoplasms (HE, 40×).**

subsequent outpatient follow up.

Discussion

This work demonstrates the ease with which a pancreatic cystic tumor may disguise as a pancreatic pseudocyst, leading to a faulty intervention, with potentially grave consequences. It also highlights how a clear distinction could be made between these two different entities, before embarking on treatment.

Cystic lesions of the pancreas are either pseudocysts or, less commonly, true cysts. The latter are usually neoplastic lesions with malignant potential or frank malignancy[2]. The most common of these rare tumors are serous cystadenoma, mucinous cystic neoplasms, intraductal papillary mucinous tumors, and solid pseudopapillary tumors, with other still rarer types reported in the literature. These tumors have other synonyms, which might confuse the unwary, and as with other rare pathologies, their diagnosis requires a high index of suspicion. They might be asymptomatic and discovered incidentally or cause a variety of symptoms, mostly nonspecific. In this regard, recurrent episodes of unexplained pancreatitis should direct the attention to the possibility of their existence[4].

On the other hand, pancreatic pseudocysts, which might complicate 5%–10% of cases of acute pancreatitis and up to 50% of cases of chronic pancreatitis, form more than 75% of cystic lesions of the pancreas[5]. Again, they may remain asymptomatic or cause a variety of symptoms, including upper abdominal pain, early satiety, gastric outlet obstruction, and obstructive jaundice. In addition, rupture, infection, or bleeding inside the cyst may complicate their course[2].

Surgeons tend to consider any cyst which is discovered after an attack of pancreatitis to be a pseudocyst and to treat it accordingly. Although this is true in the majority of cases, there are occasions where the discovered cyst is, in fact, a cystic tumour, as happened in the first case presented here. This mistake ought not to happen if the necessary precautions, outlined later, were strictly followed.

Treatment of pancreatic pseudocysts has been long influenced by the work of Bradley *et al*.[6], who suggested that pseudocysts more than 5–6 cm in diameter, which persist beyond 6 weeks, should be drained to avoid complications. Relatively recently, this has been challenged with the observation that larger cysts may resolve spontaneously beyond this period. An accepted policy is to manage asymptomatic cysts conservatively with radiologic monitoring. Enlargement of the cyst, development of symptoms, or onset of complications should be heeded as a call for intervention[1, 5].

Once thought to be rare, pancreatic cystic neoplasms are on the rise, which could be partially attributed to improved diagnostic techniques[7,8]. History of acute pancreatitis usually leads to the assumption that a newly discovered pancreatic cyst is, in effect, a pseudocyst. Although this is true in the majority of cases, the possibility of a cystic neoplasm should never be ignored. In this regard, a previous attack of acute pancreatitis is very common in certain cases of pancreatic cystic tumors, namely intraductal papillary mucinous neoplasia[4]. In the first patient presented here, history of acute pancreatitis and absence of radiologic evidence of neoplasia led to misdiagnosis of a mucinous cystadenocarcinoma as a pseudocyst. Critical analysis of all available information is therefore mandatory before embarking on treating a pancreatic cystic lesion[7].

Mucinous cystic tumors are the most common pancreatic cystic tumors, comprising 30% of this category but only 2% of all pancreatic neoplasms. They mainly occur in women in their 40s and 50s, and typically affect the body and tail of the pancreas. These tumors share common characteristics with similar lesions in the liver and ovary, as they occur predominantly in females, their malignant potential increases with advanced age, and their thick wall shows ovarian-like stroma (**Figure 3**). As previously mentioned, they may be asymptomatic and discovered incidentally or may cause symptoms.

In this regard, an episode of acute pancreatitis is common.

Histologically, the same cyst wall may contain benign adenomatous areas, areas of *in situ* cancer, and areas of frank malignancy. This observation suggests that mucinous cystadenocarcinoma progresses from benign adenoma to atypical hyperplasia and finally to frank malignancy, a situation akin to the progression of colonic adenocarcinoma from adenoma. For this reason, the pathologic search for areas of invasiveness should be meticulous[4]. This was seen in our first case, where the diagnosis was changed from borderline mucinous cystic tumor to invasive mucinous cystadenocarcinoma when the whole cyst wall was examined after excision. This change in the pathologic diagnosis has both prognostic and therapeutic implications.

Radiologic features of pancreatic cystic tumors have been recognized. A thick wall, internal septa, mural nodules, papillary projections, and solid components may be demonstrated. Additionally, lobulated margins, cyst complexity, and wall calcification are other features of neoplasia[2,4,9,10]. In our second patient with serous cystadenoma, there was no history of pancreatitis, and the radiologic features were highly suggestive of neoplasia. For these reasons, distal pancreatectomy was performed from the outset. This tumor has a predilection for females in their seventh decade, can affect the head or the body and tail of the pancreas, and, again, may be asymptomatic or cause a variety of symptoms. Although its malignant potential is slight, surgical resection is recommended[4].

Although not encountered here, there are two other cystic pancreatic tumors: intraductal papillary mucinous neoplasm (IPMN) and solid pseudopapillary tumor (Hamoudi tumor). Since its discovery in the 1980s, IPMN has generated much discussion, and the frequency with which it is diagnosed has risen in recent years. The tumor is more common in men in their sixth and seventh decades and has two variants: main duct and side branch. A characteristic feature of the main duct variant is the presence of mucin-rich fluid passing from the patulous papillary orifice on ERCP, a feature that enables a confident diagnosis to be made. The last of these tumors to be discussed here is the solid pseudopapillary tumor, which is rarer than the aforementioned tumors. It primarily affects young females, with a mean age at presentation of 25 years. Although it has a malignant potential and can metastasize, the lethality of solid pseudopapillary tumor appears to be extremely low[4].

Different minimally invasive options are available for draining pancreatic pseudocysts. Endoscopic transpapillary or transmural drainage[11,12], percutaneous US–guided drainage and endoscopic US–guided drainage[13,14], CT-guided drainage[15], and laparoscopic drainage[16] have all been reported with varying success. However, except for laparoscopic drainage, these approaches do not allow for an appropriate cyst wall biopsy to be obtained at the time of drainage and may therefore lead to misdiagnosis of a true cyst, if one is present. Although the majority of pseudocysts present with no significant reason to suspect a neoplasm, cyst wall biopsy is imperative with drainage[1]. Alternatively, cyst fluid analysis for mucin and tumor markers should be employed when a minimally invasive technique is chosen. In this series, CT-guided drainage was successful in 2 patients with pancreatic pseudocysts but failed in the third and, expectedly, in the patient with mucinous cystadenocarcinoma. This led to an open drainage procedure and cyst wall biopsy that unveiled the cyst's true nature. However, cyst fluid analysis could have provided the correct diagnosis before open drainage, if the result was timely obtained. In this regard, cyst fluid aspiration could be done under transcutaneous US endoscopic US, or CT guidance and analyzed, as is common, for cellular atypia, mucin and tumor markers, CEA, and CA19-9. The most important of these is mucin (usually present in mucinous cystic tumors and intraductal papillary mucinous neoplasia), followed by elevated levels of CA19-9, with cytologic analysis being the least important[4]. High amylase content of the fluid aspirate discloses the presence of communication between the cyst and pancreatic duct[17], a feature of the majority of pseudocysts, but also of intraductal papillary mucinous neoplasms[4]. In our previous work, we stressed the importance of cyst wall biopsy at the time of surgery[18], which should be generous or multiple, to avoid biopsying areas with denuded epithelium, and we questioned the value of minimally invasive techniques that ignore this step. As was observed in our first case, the epithelium was lacking over wide areas of the cyst, resembling a pseudocyst at these sites. This has been observed with some frequency and is attributed to atrophy of the epithelium with the increased pressure inside the cyst.

Although not used in this series, endoscopic US has been used with success, both for diagnosis and for treatment of pancreatic pseudocysts. Potential benefits include identification and avoidance of major vessels, finding the closest access to the cavity and the creation of an internal, rather than an external, fistula between the cyst cavity and the bowel[19]. Both radiology-guided and endoscopic US-guided drainage have been proved effective in expert hands, with comparable results[20].

Based on our experience as well as the experience of others, the following algorithms for managing pancreatic cystic lesions are suggested. The first (**Figure 7**) is an ERCP and interventional radiology–based algorithm, whereas the second (**Figure 8**) is an endoscopic US-based algorithm, when such expertise is available. In both, cyst fluid analysis is crucial before undertaking the drainage procedure.

Conclusions

Every effort should be exerted to distinguish between pancreatic pseudocysts and cystic tumors of the pancreas, to avoid the serious mistake of draining instead of extirpating a pancreatic cystic tumor. When employed properly, percutaneous drainage of pancreatic pseudocyst is a useful adjunct that may substitute for more invasive surgical drainage.

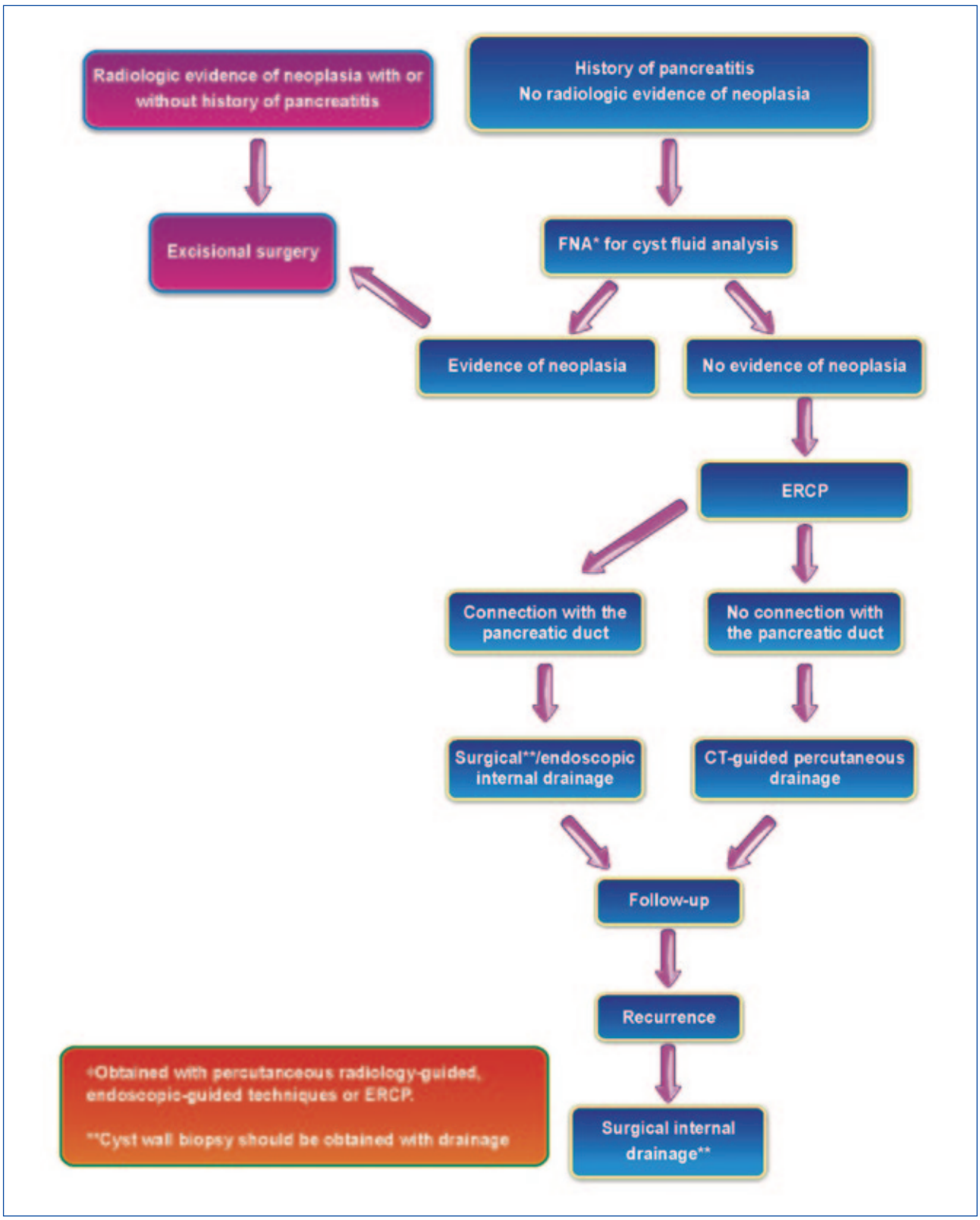

Figure 7. **ERCP-based algorithm for managing a pancreatic pseudocyst. FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography.**

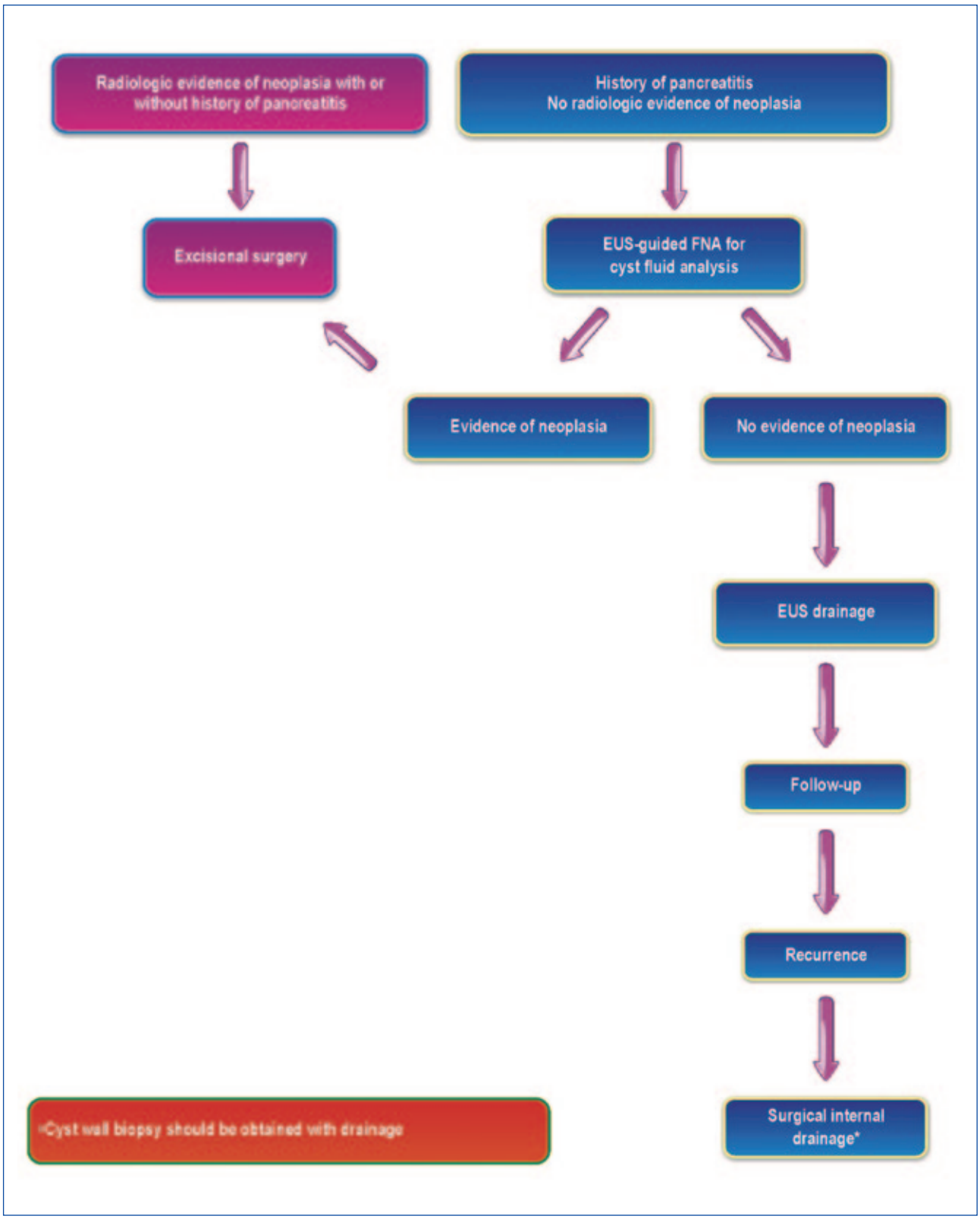

Figure 8. **EUS-based algorithm for managing a pancreatic pseudocyst.** EUS, endoscopic ultrasound; FNA, fine needle aspiration.

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