Cystic Pancreatic Endocrine Neoplasms: A Distinct Tumor Type?

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BACKGROUND: Cystic pancreatic endocrine neoplasms (CPENs) are considered rare, and their behavior is thought to be similar to that of solid pancreatic endocrine neoplasms (PENs). This study aims to describe the characteristics of CPENs in a large patient cohort.

STUDY DESIGN: We performed a retrospective review of 170 patients who underwent resections for PENs at Massachusetts General Hospital from 1977 to 2006. Twenty-nine patients (51% men, mean age 53) with CPENs were compared with 141 patients with solid PENs. Differences in clinical presentation, pathologic and radiographic features, and survival were described.

RESULTS: CPENs comprised 17% of all PENs (29 of 170) and 5.4% of all resected cystic pancreatic neoplasms(29 of 535). Ten (34%) were purely cystic and 19 (66%) were partially cystic. Compared with solid PENs, CPENs were larger (49 mm versus 23.5 mm, $p < 0.05$), more likely symptomatic (73% versus 45%, $p < 0.05$), and more likely nonfunctional (80% versus 50%, $p < 0.05$). They expressed synaptophysin (100%), chromogranin (82%), and cytokeratin (CK)-19 (24%). Multiple endocrine neoplasia type 1 (MEN-1) was 3.5 times more common in CPENs than in solid tumors (21% versus 6%, $p < 0.05$). No significant difference was found in location, propensity for metastasis, invasion, or 5-year survival (87% versus 77%, $p = 0.38$).

CONCLUSIONS: This series, the largest report of CPENs in the literature, shows that CPENs are more common than previously thought, so they should be included in the differential of the cystic lesions of the pancreas. CPENs are larger and more likely to be symptomatic then solid PENs. They are also more likely to be associated with MEN-1 and to be nonfunctional, suggesting they may be a distinct tumor type. (J Am Coll Surg 2008;206:1154–1158. © 2008 by the American College of Surgeons)

Although most pancreatic endocrine neoplasms (PENs) are solid, cystic pancreatic endocrine neoplasms (CPENs) have been described, mostly in case reports.[1-11] Our review of the literature suggested that fewer than 30 cumulative cases of CPEN have been described in detail, and the largest case series contained 10 patients.[2-12] Otherwise, CPENs are usually reported in passing as part of larger series of cystic tumors of the pancreas.[2,13] Most of these studies describe CPENs as unusual. For example, the Cooperative Pancreatic Cyst Study identified only 5 CPENs among 341 cystic neoplasms of the pancreas.[13] A similar multicenter French study identified 10 CPENs among 527 cases of cystic tumors of the pancreas.[14]

Competing Interests Declared: None.

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It has been assumed that CPENs are similar to solid PENs as far as behavior and malignant potential.[2,12,13,15] This assumption derives from the hypothesis that CPENs arise as a result of tumor necrosis within solid PENs.[3,9] But only 1 study supports this hypothesis by directly comparing 6 patients with CPENs with 16 patients with solid PENs. Within this small cohort, no statistical differences between the two groups could be observed.[12]

This article reviews our data in 29 patients treated for CPENs at our institution (5 of these patients were previously reported, as part of a study on the cytomorphologic features of these lesions on fine needle aspiration biopsy).[16] We believe that this is the largest series of CPENs in the literature. Our goal was to retrospectively analyze this large cohort and assess whether the clinical presentation and radiologic and pathologic features of CPENs are truly similar to those of their solid PEN counterparts.

METHODS

The Institutional Review Board of the Massachusetts General Hospital (MGH) determined that this study was exempt from review.

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Abbreviations and Acronyms

CK = cytokeratin
CPEN = cystic pancreatic endocrine neoplasm
MEN-1 = multiple endocrine neoplasia type 1
PEN = pancreatic endocrine neoplasm

We collected retrospective data on a group of 170 patients who underwent pancreatic resections for pancreatic endocrine neoplasms (PENs) at Massachusetts General Hospital from 1984 to 2005. Pathology reports were reviewed to identify tumors with a cystic component (CPENs). Using gross pathology as the gold standard for a cystic neoplasm, we identified 29 patients with CPENs, and their characteristics were compared with those of 141 patients with solid PENs.

Our comparison was accomplished by a retrospective review of the medical and electronic records. Information was gathered regarding preoperative symptoms, clinical functionality of the tumor, presence of multiple endocrine neoplasia type 1 (MEN-1) syndrome (suspected because of a history of another neuroendocrine neoplasm before subsequent diagnosis with a PEN and confirmed with gene sequencing), and whether a PEN was found incidentally or because there were symptoms. Neoplasm size and location, type of operation performed, evidence of lymph node or microvascular invasion, presence of positive surgical margins, and presence of metastatic disease were also recorded. We noted duration of postoperative followup, evidence of recurrence, evidence of later metastases, and tumor-related deaths.

In the patients in whom CPENs were identified, preoperative CT scans were reviewed by an experienced radiologist (DS), and the radiologic characteristics were recorded. Finally, gross pathology and immunohistochemistry was reviewed on each patient by an experienced pathologist (VD). Each specimen was inspected for staining with chromogranin, synaptophysin, somatostatin, vasoactive intestinal polypeptide, glucagons, pancreatic polypeptide, insulin, serotonin, and cytokeratin (CK)-19. Pathologic specimens that were not stained for CK-19 during their original pathologic evaluation were stained for it for the purposes of this study.

Results were reported as mean and standard deviations (SD) or medians and range, as appropriate. Comparisons between the patients with CPENs and those with PENs were done using the Fisher's exact or chi-square tests, as appropriate, based on individual cell sizes. Continuous variables were compared with an independent *t*-test. The tests were 2-sided, and a p value less than 0.05 was considered statistically significant.

Table 1. Demographic Comparison of Patients with Solid Versus Cystic Pancreatic Endocrine Neoplasms

Demographic feature	PEN (n = 141)	CPEN (n = 29)	p Value
Male gender, %	51.1	50.0	NS
Mean age (SD), y	56 (14.7)	53 (16.6)	NS
MEN-1, %	21	6	0.021

CPEN, cystic pancreatic endocrine neoplasm; PEN, pancreatic endocrine neoplasm.

RESULTS

In a group of 170 patients operated on for a PEN, we identified 29 patients (17%) with CPENs. These cystic neoplasms constituted 5.4% of all resections for a cystic pancreatic neoplasm (29 of 535). Demographically, these 29 patients were similar to the group of 141 patients with solid PENs, but the CPEN group was 3.5 times more likely to have MEN-1, and this difference was statistically significant (Table 1).

Clinically, CPENs were more likely to be symptomatic on diagnosis (73% versus 45%, p = 0.012). Twelve patients (57%) reported abdominal or back pain, and the remaining had other nonspecific symptoms, such as weakness, anemia, and weight loss. One patient presented with pancreatitis and another with a palpable abdominal mass. Compared with solid PENs, CPENs were more likely nonfunctional (80% versus 50%, p = 0.007). In the group of 6 patients with functional CPENs, 4 (67%) were insulinomas. One patient presented with a glucagonoma and another had an ACTH-producing lesion.

We were able to retrospectively review preoperative CT scans of 13 (45%) patients with CPENs. Overall, a correct preoperative radiologic diagnosis was made in only 3 patients (23%), even though 12 patients (92%) had a cystic component present on their imaging studies. One patient did not have a visible mass, but his CT scan was suspicious for a pancreatic neoplasm because of obstruction of the pancreatic duct. All of the other CT scans (12 of 13) revealed that these neoplasms appeared partially cystic, with or without a solid component. Their radiologic appearance was heterogeneous. In most patients, the lesion enhanced on the arterial phase and appeared septated. Calcifications were rarely present (Fig. 1). In fact, one patient was diagnosed as having a benign pseudocyst.

Review of CPEN pathology revealed that 7 CPENs (24%) were located in the head or neck of the pancreas, and 22 (76%) were in the body or tail of the pancreas. Ten neoplasms (34%) were purely cystic and 19 (66%) were partially cystic. These cysts were lined with a purple glistening capsule, with multiple septae (Fig. 2). Necrosis was rarely encountered. The tumors that contained microcystic changes were generally nestled in a gray-white fibrous cap-