

ORIGINAL ARTICLE

Characterization of Malignant Pancreatic Cystic Lesions in the Background of Chronic Pancreatitis

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ABSTRACT

Context Cystic lesions of the pancreas in association with chronic pancreatitis are a diagnostic and therapeutic challenge.

Objective The aim of the study was to study clinical and radiological features that may differentiate between benign and malignant cystic lesions of the pancreas and examine the indications for surgery in these patients.

Design Retrospective case note study.

Patients Patients with concomitant cystic lesions of the pancreas and chronic pancreatitis stated in radiology reports between 1995 and 2005.

Results Thirty-one patients were identified with alcohol-related chronic pancreatitis with a median age of 53 years (range: 27-82 years). Eight patients (26%) had deranged liver function tests and four (13%) presented a raised CA 19.9. Radiological features of cystic lesions of the pancreas included median cyst size of 3 cm (range: 0.8-10 cm), solitary cyst in 28 patients (90%) and multi-loculated in 3 patients (10%). Dilatation of the main pancreatic duct was seen in seven cases (23%). Overall, 12 patients (39%) underwent surgery, 13 patients (42%) were managed with radiological follow-up, five patients

(16%) were managed conservatively and one patient (3%) was treated with chemotherapy for advanced malignancy. Overall, three cases (10%) of this series had malignant cystic lesions of the pancreas. Malignant cystic lesions of the pancreas are associated with deranged liver function tests, elevated CA 19.9, and are larger solitary cysts on imaging.

Conclusion The differentiation between benign and malignant cystic lesions of the pancreas remains a diagnostic challenge, although malignant cysts tend to be solitary and larger. The high prevalence of malignancy merits an aggressive approach to follow-up and early surgical intervention.

INTRODUCTION

Over the past two decades, there has been a significant increase in awareness of cystic lesions of the pancreas (CLP) [1, 2, 3]. Kosmahl *et al.* has recently proposed an extensive histopathological classification of pancreatic cystic neoplasms and tumour-like lesions with cystic features [4]. This classification includes neoplastic and non-neoplastic lesions of epithelial and non-epithelial origin [4]. The main differential diagnoses are benign lesions such as pancreatitis-associated pseudocysts and inflammatory cysts, neoplasms with

malignant potential such as mucinous neoplasms and solid pseudopapillary neoplasms, and malignancy such as intraductal papillary-mucinous carcinoma and invasive ductal adenocarcinoma.

In the clinical setting, it is crucial to differentiation between a benign and malignant CLP as the management of these conditions is entirely different. It is not uncommon for CLP to be identified in association with chronic pancreatitis (CP). However, determining their neoplastic potential is a diagnostic challenge for clinicians due to the background of extensive pancreatic fibrosis and the increased prevalence of inflammatory cysts or pseudocysts in these patients. The aim of the current study was to study clinical and radiological features that may help differentiate between benign and malignant CLP associated with CP and examine the indications for surgical intervention in these patients.

METHODS

Patients diagnosed with concomitant CLP and CP at the Leeds Teaching Hospitals NHS Trust during the 11-year period (January 1995 to December 2005) were identified using the hospital's radiology computer coding system (Radiology Management System). Radiological reports studied include computer tomography (CT), magnetic resonance imaging of the pancreas (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound scan (EUS). The diagnostic criteria for CP applied in this study were based on the Cambridge classification [5].

Case notes were retrospectively reviewed for demography, clinical presentation, laboratory studies, radiological investigations, treatment and clinical outcome. In particular, CLP characteristics on radiological imaging were analyzed, including size, loculation (single versus multiple), evidence of calcification (cyst wall, cyst content and surrounding pancreatic parenchyma), anatomical distribution (head, uncinate process, neck,

body, tail and multiple locations) and identification of associated dilatation of the main pancreatic duct. In the absence of confirmed histology, patient's diagnosis was based on long-term clinical and radiological follow-up.

ETHICS

This is a retrospective study based on the usual clinical practice. Informed consent was obtained for all procedures performed in patients in this study.

STATISTICS

Medians, ranges, and frequencies were used as descriptive statistics. The Mann-Whitney U, the Fisher's exact, and the Pearson's chi-squared test were used to assess for differences between the benign and malignant CLP. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows™ version 12.0 (SPSS Inc, Chicago, IL, USA), and statistical significance was taken at the two-tailed 0.05 P level.

RESULTS

During the study period, 121 patients with CLP were identified, of which 31 patients (25.6%) had concomitant CP. All patients had alcoholic-related CP with a median age at presentation of 53 years (range: 27-82 years) and a male to female ratio of 17:14 (54.8%:45.2%).

All patients presented with recurrent abdominal pain as their main symptom. Others reported one or more symptoms that included weight loss (n=10; 32.3%), recurrent diarrhoea (n=3; 9.7%), steatorrhoea (n=3; 9.7%), worsening diabetic control (n=2; 6.5%), new onset diabetes (n=1; 3.2%) and jaundice (n=1; 3.2%).

Primary radiological investigation performed were CT (n=29; 93.5%) (Figure 1) and MRI (n=2; 6.5%). Further investigations were performed in 18 cases (58.1%) which had indeterminate radiological diagnosis, which



Figure 1. Abdominal computer tomography demonstrating a 7x4.9 cm multi-locular cystic lesion in the head of the pancreas; the largest loculation being 4.1x3.8 cm. Histopathological analysis revealed a pancreatic cyst associated with chronic pancreatitis.

included MRI (n=10; 32.3%), ERCP (n=9; 29.0%) and EUS (n=8; 25.9%). One patient also underwent an EUS-guided biopsy. As far as the demographic data, biochemical analysis and radiological characteristics of CLP are concerned, the median cyst size was 3 cm (range: 0.8-10 cm), while cystic lesions were solitary in 28 cases and were multi-loculated in three cases. Calcification of the cyst wall was present in one case while nine cases demonstrated pancreatic parenchyma calcification surrounding the cyst. CLP were located in the head and uncinata process of the pancreas in 16 cases, followed by pancreatic body (n=7), tail of pancreas (n=4), and two in the pancreatic neck. Synchronous cystic lesions in more than one location of the pancreas were reported in two cases.

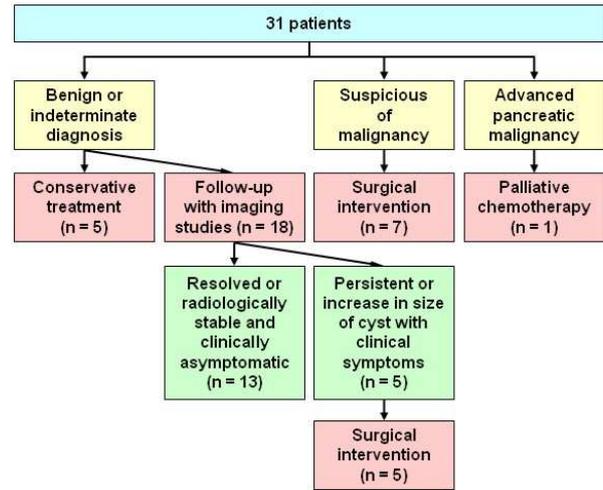


Figure 2. Management of cystic lesions of the pancreas in the present study following initial radiological investigations.

Dilatation of the main pancreatic duct was reported in seven cases. CLP were associated with an abnormality in one or more liver function tests (LFTs: alkaline phosphatase, alanine aminotransferase and bilirubin) in eight patients. Cancer antigen CA 19.9 was raised in four patients (range: 41-268 U/mL). Seven patients underwent surgery due to features suggestive of malignancy on radiological imaging and 18 patients were managed with radiological follow-up (Figure 2). Five patients were managed conservatively due to significant co-morbidity (ASA equal to, or greater than, 3) and one patient was treated with palliative chemotherapy for advanced pancreatic malignancy. Five patients from the radiological follow-up group subsequently

Table 1. Types of surgery performed with corresponding histology of cystic lesions of the pancreas in this study.

Surgery	Histology
Pancreaticoduodenectomy (n=5)	Intraductal papillary-mucinous carcinoma (n=2) Groove pancreatitis (n=2) Chronic obstructive pancreatitis (n=1)
Frey's procedure (n=3)	Simple cyst (n=2) Pseudocyst (n=1)
Distal pancreatectomy and splenectomy (n=2)	Simple cyst (n=1) Pseudocyst (n=1)
Spleen-preserving total pancreatectomy (n=1)	Congenital diffuse cystic ectasia of main pancreatic duct (n=1)
Cystogastrostomy ^a (n=1)	Simple cyst (n=1)

^a Cystogastrostomy was performed following exploratory laparotomy in one case, which revealed a simple pancreatic cyst.

underwent surgery following a median follow-up period of 3 months (range: 2-6 months). Indications for surgical intervention were the persistent presence of the cystic lesion coupled with worsening chronic pain and gastric-outlet obstruction (n=3) or an increase in size of the CLP (n=2). The type of surgical intervention is summarized in Table 1. Histology was obtained in 14 patients (surgery: 12; biopsy: 2). Eleven patients were

diagnosed with benign CLP, which included simple pancreatic cyst (n=5), pseudocyst (n=2), groove pancreatitis (n=2), congenital diffuse cystic ectasia of the pancreatic duct (n=1), and chronic obstructive pancreatitis secondary to a nodule of ectopic pancreatic tissue (n=1). Three patients had histological diagnosis of malignant tumours, which included intraductal papillary-mucinous carcinoma (n=2) and invasive ductal

Table 2. Clinical, biochemical and radiological characteristics of cystic lesions of the pancreas (CLP) in a background of chronic pancreatitis in this study.

	Clinical and radiologically determined benign CLP (n=17)	Histologically confirmed benign CLP (n=11)	Histologically confirmed malignant CLP (n=3)	P value ^a
Demographics				
Male:female ratio	12:5 (70.6%:29.4%)	4:7 (34.6%:63.6%)	1:2 (33.3%:66.7%)	0.576 ^b
Age at diagnosis (years) ^c	50 (27-82)	51 (35-68)	67 (61-76)	P=0.082 ^c
Biochemical analysis				
Elevated liver function tests: ^f	4 (23.5%)	1 (9.1%)	3 (100%)	0.012 ^b
- Alanine aminotransferase (U/L) ^e	191 (102-304); n=4	54; n=1	138; n=1	
- Alkaline phosphatase (U/L) ^e	364 (332-386) ; n=4	3,233; n=1	408 (358-437); n=3	
- Bilirubin (µmol/L) ^d	28; n=1	125; n=1	25; n=1	
Elevated CA 19.9 (U/mL) ^{eg}	41; n=1	186; n=1	153, 268; n=2	0.037 ^b
Radiological features				
Cyst size (cm) ^e	3 (1-7)	2.6 (0.8-7.3)	7.5 (4-10)	0.035 ^c
Calcification:	7 (41.2%)	2 (18.2%)	1 (33.3%)	1.000 ^b
- Cyst wall	1	0	0	
- Pancreatic parenchyma	6	2	1	
Cyst loculation:				1.000 ^b
- Solitary	15 (88.2%)	10 (90.9%)	3 (100%)	
- Multiple	2 (11.8%)	1 (9.1%)	0	
Surrounding inflammatory changes	6 (35.3%)	2 (18.2%)	0	0.550 ^b
Dilatation of the main pancreatic duct	4 (23.5%)	2 (18.2%)	1 (33.3%)	0.550 ^b
Cyst distribution:				0.779 ^d
- Head and uncinate	7 (41.2%)	7 (63.6%)	2 (66.7%)	
- Neck	2 (11.8%)	0	0	
- Body	5 (29.4%)	1 (9.1%)	1 (33.3%)	
- Tail	2 (11.8%)	2 (18.2%)	0	
- Multi-site	1 (5.9%)	1 (9.1%)	0	

^a Comparison between malignant (n=28) and benign (n=3) CLP

^b Fisher's exact test

^c Mann-Whitney U-test

^d Pearson's chi-squared test

^e Median (range) were reported when applicable; the single value(s) was(were) reported for n equal to 1 or 2

^f Reference ranges: alanine aminotransferase, 0-40 U/L; alkaline phosphatase, 70-300 U/L; bilirubin: 5-21 µmol/L

^g Reference range: serum CA 19.9, 0-5 U/mL

adenocarcinoma (n=1). The histological findings of the background of pancreatic parenchyma in these cases were loss of exocrine parenchyma and irregular, patchy distribution of fibrosis in interlobular spaces. In addition, protein plugs and dilatation of the pancreatic ducts were identified in several cases. In the histologically confirmed benign CLP, there was no evidence of dysplasia or malignancy. The remaining 17 patients were presumed to have a diagnosis of a simple pancreatic cyst based on radiological imaging and long-term follow-up (median follow-up period of 12 months; range: 4-84 months). From this group, eight patients have been discharged from follow-up, eight patients are still under review and one patient died at four months from causes unrelated to the CLP. All five patients who underwent surgery following a period of interval imaging had benign histology. Overall, 10% of cases in the present series had diagnosis of malignancy.

Demographic data, biochemical analysis and radiological characteristics of the three groups of patients based on histological diagnosis are summarized in Table 2. Malignant CLP showed significantly higher frequencies of elevated biochemical findings: elevated LFTs were recorded in all cases of malignant CLP (P=0.012), as well as, raised CA 19.9 levels were also noted in two of the three cases of malignant CLP (P=0.037). The median size of the malignant cysts (7.5 cm; range: 4-10 cm) was significantly larger than benign cysts (3 cm; range: 0.8-7.3 cm; P=0.035). The majority of benign cystic lesions had solitary loculation and all cases of malignant CLP were solitary in nature (P=1.000). Dilatation of the main pancreatic duct occurred in six cases of the benign cystic lesions group and one case of malignant CLP. Although the median age at diagnosis was older in the malignant cysts (67 years; range: 61-76 years) compared to the benign cysts (51 years; range: 27-82 years), there was no significant difference (P=0.082).

There was no post-operative mortality. There was one in-hospital death from hepato-renal syndrome following embolization of a pseudo-aneurysm associated with the CLP.

Six patients developed pancreatic exocrine insufficiency post-surgery and were placed on replacement therapy with pancreatin (Creon[®], Solvay Pharmaceuticals, Southampton, United Kingdom) (Table 3). The overall median follow-up period was 27 months (range: 8-84 months).

DISCUSSION

CLP are often misdiagnosed as pseudocysts, occurring in one-third of cases [1]. Mucinous and serous cystic tumours have been reported to account for between 75% and 90% of pancreatic cystic tumours [6, 7]. However, in patients with a background of CP, it is often more difficult to differentiate a pancreatic cystic tumour from a pseudocyst despite advances in radiological imaging.

Previous studies have described clinical syndromes associated with cystic neoplasms which consist of abdominal pain and symptoms associated with pancreatic insufficiency such as recurrent diarrhoea, steatorrhoea, weight loss and diabetes mellitus [1, 8, 9]. However, patients with a background of CP often have clinical features of pancreatic exocrine and endocrine insufficiency, and this is in keeping with the present series, irrespective of the underlying pathology of the CLP.

Cystic tumours of the pancreas are typically found in middle-aged women [1, 8, 9]. Although only three patients in the present series had malignant CLP, there was a tendency for these lesions to be associated with female gender and advancing age.

Sperti *et al.* demonstrated that serum CA 19.9 levels were significantly higher in intraductal

Table 3. Morbidity data of surgical treatment of cystic lesions of the pancreas in this study. Morbidity occurred in 7 of 12 patients (58.3%).

Early complications	
- Abdominal collection	2 (16.7%)
Pancreatic exocrine insufficiency	
- Steatorrhoea	6 (50.0%)
- Recurrent diarrhoea	3 (25.0%)
Pancreatic endocrine insufficiency	
- Diabetes mellitus	5 (41.7%)

papillary-mucinous neoplasms and mucinous cystic neoplasms compared to pseudocysts and benign serous cystadenomas [10]. In the present study, two of the three malignant CLP cases had a raised serum CA 19.9 level. In addition, all three cases of malignant CLP had deranged LFTs.

Differentiating pancreatic pseudocysts from cystic tumours is crucial as the clinical management and natural history of these conditions differ [1, 6, 8]. The initial evaluation of a pancreatic cyst should be directed towards confirming its intra-pancreatic origin, followed by exclusion of a pseudocyst [6]. An abdominal CT is the preferred first-line investigation to identify the origin and characteristics of the CLP and also assess the presence of intra-abdominal involvement [6, 8]. The appearance of a pancreatic pseudocyst on CT and MRI can vary depending on the contents of the cyst such as protein material, necrotic debris and blood [11], which can lead to misdiagnosis of a cystic tumour. Chronic pseudocysts also tend to have calcified cyst wall on imaging studies. Cases of intraductal papillary-mucinous neoplasms often demonstrate dilatation of the pancreatic duct, and these cases are usually diagnosed as CP [12, 13] until duct dilatation become cystic in appearance. In the majority of cases, intraductal papillary-mucinous neoplasms are multi-loculated [14]. ERCP can demonstrate filling defects in the dilated ducts and mucinous secretions issuing from papilla of Vater are pathognomonic [13]. In this study, radiological features such as calcification of the cyst wall or surrounding pancreatic parenchyma, dilatation of the main pancreatic duct and cyst distribution did not appear to differentiate between benign and malignant cystic lesions. However, all malignant CLP had solitary loculation on radiological imaging, including both cases of intraductal papillary-mucinous carcinomas. Hence, it is important to carefully note these observations as not all intraductal papillary-mucinous carcinomas are multi-loculated. In one of the intraductal papillary-mucinous carcinoma cases, ERCP findings were pathognomonic.

The inability to distinguish between benign and malignant cystic lesions may be due to the damaged and distorted pancreatic parenchyma and ductal system from recurrent episodes of pancreatitis. Although there are various radiological characteristics of pancreatic cystic tumours, imaging studies may still be inadequate to elucidate the underlying diagnosis in patients with a background of CP. In the present series, 10% of cases were malignant CLP. Hence, the conventional teaching of a pancreatic pseudocyst usually preceding a history of pancreatitis can certainly be challenged.

Some authors suggest that the size of the CLP is an indicator of its malignant potential [13]. CLP larger than 2 cm in size merit aggressive management due to the higher risk of malignant potential [1, 15, 16, 17, 18]. In the current study, although the majority of CLP were greater than 2 cm in size (25 patients; 81%), only three cases (12%) were malignant. This discrepancy may be attributable to the background of CP in this cohort; in previous publications CLP have formed in apparently "normal" pancreatic parenchyma or data relating to pancreatic fibrosis was not reported. Hence, the accepted malignant risk categorization for CLP may not be applied to patients with a background of CP. Nevertheless, although limited by a relatively small sample size, our data suggest that malignant cysts are significantly larger compared to benign cysts, in patients with CP. In cases where pre-operative radiological diagnosis is indeterminate, interval imaging is recommended. Development of clinical symptoms, cyst complications and/or increase in cyst size on follow-up imaging may merit surgical intervention. Nevertheless, it is well established that surgical resection of the pancreas can have a significant impact on the quality of life in patients with CP [19], and hence it is crucial that CLP in these patients are evaluated in more detailed and accurately pre-operatively.

Recently, EUS has emerged as a diagnostic modality with the additional advantage of obtaining tissue sampling [7, 20] and a recent study reported similar tissue sampling

sensitivity when compared to CT or US-guided sampling [20]. EUS-guided biopsy has a reported sensitivity and specificity of 69% and 90% respectively for diagnosing malignancy in CLP [15]. In this study, EUS did not contribute further information already acquired from other imaging studies. However, its potential in the management of this clinical condition should not be discounted.

CONCLUSION

Current literature recommends the resection of cystic tumours of the pancreas. However, the presence of a pancreatic cystic lesion in patients with a background of CP continues to be a diagnostic challenge for clinicians. Deranged LFTs and a raised serum CA 19.9 level, together with radiological features of a large, solitary loculated CLP, merits aggressive surgical intervention due to high prevalence of malignancy.

Received June 24th, 2006 - Accepted July 24th, 2006

Keywords Neoplasms, Cystic, Mucinous, and Serous; Pancreas; Pancreatic Pseudocyst; Pancreatitis

Abbreviations CLP: cystic lesions of the pancreas; CP: chronic pancreatitis; LFT: liver function test

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