Course of pancreatic duct lesions following acute pancreatitis associated with pseudocyst

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SUMMARY

Aims — After an episode of acute pancreatitis, there is usually no sequelae; nevertheless cases of ductal stenosis have been reported. The aim of our study was to evaluate the frequency of pancreatic duct lesions after acute pancreatitis complicated by pseudocyst.

Patients and methods — Between 1983 and 2004, 67 patients were admitted for severe acute pancreatitis. Out of these 67 patients, 36 patients were excluded because of chronic pancreatitis or pancreatic morphological anomalies, apparently related to dysfunction, poor quality-of-life, as well as pancreatic and extra-pancreatic neoplasia. These results show that complete resolution of pancreatic abnormalities after acute pancreatitis is not achieved systematically.

RÉSUMÉ

Evolution des lésions du canal pancréatique principal après pancréatite aiguë compliquée de pseudo-kyste

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(Gastroenterol Clin Biol 2006;30:949-953)

Objectifs — Après une pancréatite aiguë, il est admis qu’aucune séquelle anatomique ne persiste; néanmoins des cas de sténose du canal pancréatique ont déjà été rapportés. Notre travail avait pour but d’évaluer la fréquence des anomalies du canal de Wirsung dans les suites d’une pancréatite aiguë compliquée d’un pseudo-kyste.

Malades et méthodes — Soixante-sept malades ont été hospitalisés pour une pancréatite aiguë sévère entre 1983 et 2004. Parmi ces malades, ont été exclus 36 malades ayant une pancréatite chronique (N = 12), une TIPMP (N = 3), un cancer (N = 2), un cystadénome (N = 3), une consommation d'alcool supérieure à 40 g/j (N = 6), une pancréatite aiguë post-traumatique (N = 3), et un suivi inférieur à 12 mois (N = 7).

Résultats — Une sténose du canal pancréatique principal a été observée chez 16/31 (52 %) des malades. Cette sténose était unique dans 100 % des cas, complète pour 69 % d’entre eux (11/16) et associée à une dilatation des canaux en amont dans 69 % des cas (11/16). Bien que le pseudo-kyste fût au niveau du corps du pancréas dans 7/31 cas (48 %), la sténose était au niveau de la tête dans 9/16 cas (56 %). Le critère prédictif de lésion canalaire séquellaire était une complication du pseudo-kyste : la compression extrinsèque (P = 0,01), et la thrombose vasculaire (P = 0,02).

Conclusion — Après une pancréatite aiguë compliquée de pseudo-kyste, une sténose du canal observée dans 52 % des cas. Cela prouve que la restitution complète du pancréas après une pancréatite aiguë n’est pas systématique.

Introduction

Restitutio ad integrum was the central idea of the symposium on acute pancreatitis held in Marseille France in 1963. Since that time a substantial body of evidence has accumulated demonstrating on the contrary that sequelar lesions of the pancreatic ducts are not uncommon after acute pancreatitis [1-4].

The different types of lesions observed after acute pancreatitis were summarized during the 2001 consensus conference [5]. Observations include altered exocrine and endocrine pancreatic function, poor quality-of-life, as well as pancreatic and extra-pancreatic morphological anomalies, apparently related to disease severity. For example the risk of developing diabetes and steatorrhea appears to be related to the extent of necrosis. The purpose of the present study was to analyze anomalies of the main pancreatic duct observed after acute pancreatitis. For this study cases of acute pancreatitis associated with pseudocysts were included as this generally correlates well with a more severe form of the disease. We compared disease severity, patient characteristics, and morphology of the pseudocyst between patients presenting morphological anomalies and those free of pancreatic lesions.

Patients and methods

Sixty-seven patients treated for acute pancreatitis associated with pseudocyst between 1983 and April 2004 were reviewed retrospectively. Patients excluded from the study population had associated chronic calcifying pancreatitis (N = 12), intraductal papillary mucinous tumor (N = 3), neoplasia (N = 2), cystadenoma (N = 3), mucinous 2 and serous 1, alcohol...
intake ≥40 g/d with suspected early-phase chronic calcifying pancreatitis (N=6), and post-traumatic pancreatitis (N=3). Seven other patients were excluded from the analysis because of insufficient follow-up (<1 year). The study population thus included 31 patients.

Patient-related data noted were: medical history, age, gender, body mass index (BMI), and daily alcohol intake. The characteristic features of the pseudocysts (number, localization, size), presence of complications (bleeding, fistulization, extrinsic compression (digestive tract, bile ducts, vessels), infection, endoscopic or surgical management (for puncture or drainage)) and any recurrence were noted. Signs of intestinal occlusion were considered to signify digestive compression; cholestasis with Caroli-Sarles type IV stenosis was taken as a sign of common bile duct compression; and portal hypertension with splenomegaly and a vicarious network (esophageal and/or perigastric varices) were considered signs of vascular compression.

Follow-up was the time from diagnosis of acute pancreatitis to the last imaging procedure. Endoscopic retrograde cholangiopancreatography (ERCP) (N=21) or magnetic resonance cholangiopancreatography (MRCP) (N=10) were performed by two independent experienced operators at 23 months average follow-up to search for ductal anomalies. The length, diameter, and localization of any stenotic area were noted as well as any upstream dilatation and the treatment applied. Other types of morphological anomalies of the main pancreatic duct or secondary ducts were also noted.

Statistical analysis

Mean ± standard deviation or median with range were used for quantitative variables; contingency tables with proportions for qualitative variables. Fisher's exact test was used to search for independence of dichotomic variables among patients with and without sequelar stenosis in comparison with the full data set. This yielded a 2×2 contingency table. The chi-square test was used for discrete or nominal variables and the Wilcoxon test for continuous variables. The Kaplan Meier method was used to draw survival curves which were compared with the logrank test. P<0.05 was considered significant. Data were processed with SAS 8.2.

Results

Mean age of the 31 patients (20 men and 11 women) presenting with acute pancreatitis with pseudocyst was 55 years (range: 20—78 years). Eight patients experienced two or three episodes of acute pancreatitis before treatment of their pseudocyst.

The etiology of the acute pancreatitis was biliary in 55% (N=17, patients including four who underwent cholecystectomy), hyperlipidemia in 6% (N=2), pancreas divisum in 13% (N=4), postoperative in 6% (N=2), and idiopathic in 20% (N=6). Mean daily alcohol intake was 22 g (range: 8 – 40 g). Daily intake was not noted for 19 patients. Mean BMI was 24. The mean duration of the pseudocyst was 40 days (range: 0–630). The pseudocyst was located in the pancreatic body in 15 patients (48%), and extended over the length of the entire organ in seven (22%). Several pseudocysts (≥3) were noted in six patients (19%). Average size of the pseudocyst was 7 cm (range: 1–18).

There pseudocyst was complicated in 23/31 patients (74%) including: extrinsic compression in 18/23 (78%), infection in 14/23 (61%), bleeding in 5/23 (22%) and fistulization to a neighboring organ in 6/23 (26%) (table I). ERCP demonstrated a cyst communicating with the main pancreatic duct in 9/31 patients (29%). Treatment options are summarized in Table II. Ten patients developed a new pseudocyst within a mean of 4.5 months.

After a median follow-up of 23 months, stenosis of the main pancreatic duct was diagnosed in the 16 of the 31 patients (52%) (figure 1). The area of stenosis was located in the head of the pancreas in 9/16 cases (56%), in the body in 6/16 (38%), and in tail in 1/16 (6%). Complete obstruction was noted in 69% of patients. For 11/16 patients (69%) MRCP demonstrated proximally dilated pancreatic ducts (figure 2). Stenosis of the main pancreatic duct was noted at a mean of nine months after the episode of acute pancreatitis. Three of the 16 patients (18%) complained of paroxysmal pain compatible with a pancreatic disorder. Therapeutic management is summarized in table III.

We searched for a link between the development of stenosis of the main pancreatic duct and the characteristic features of the pseudocyst observed following acute pancreatitis. There was no

| Table I | Complications of pseudocysts (23/31, 74%).

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Number</th>
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<tbody>
<tr>
<td>Extrinsic compression</td>
<td>18/31 (58%)</td>
</tr>
<tr>
<td>- Digestive</td>
<td>14/18 (78%)</td>
</tr>
<tr>
<td>- Biliary</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>- Vascular</td>
<td>11/18 (61%)</td>
</tr>
<tr>
<td>Infection</td>
<td>14/31 (45%)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5/31 (16%)</td>
</tr>
<tr>
<td>Fistulization</td>
<td>6/31 (19%)</td>
</tr>
</tbody>
</table>

| Table II | Treatment of pseudocysts.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonography</td>
<td>Drainage 4</td>
</tr>
<tr>
<td></td>
<td>Simple aspiration 9</td>
</tr>
<tr>
<td>Surgery</td>
<td>Cystogastrostomy 2</td>
</tr>
<tr>
<td>EUS</td>
<td>Cystogastrostomy 1</td>
</tr>
<tr>
<td>ERCP</td>
<td>Cystogastrostomy 5</td>
</tr>
<tr>
<td></td>
<td>Cystoduodenostomy 2</td>
</tr>
<tr>
<td></td>
<td>Transpapillary drainage 3</td>
</tr>
<tr>
<td></td>
<td>Transpapillary drainage + Cystogastrostomy 3</td>
</tr>
<tr>
<td></td>
<td>Transpapillary drainage + Cystoduodenostomy 2</td>
</tr>
<tr>
<td></td>
<td>Failure 2</td>
</tr>
</tbody>
</table>

| Table III | Treatment of ductal stenosis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP</td>
<td>Transpapillary drainage 7</td>
</tr>
<tr>
<td></td>
<td>Failure 3</td>
</tr>
<tr>
<td>Surgery</td>
<td>Cystogastrostomy 1</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
</tr>
</tbody>
</table>

ERCP: Endoscopic retrograde cholangiopancreatography
significant relationship with pseudocyst number, localization or size. Among the 16 patients with a ductal lesion, 15 developed a pseudocyst (94%, P<0.015). Extrinsic compression by the pseudocyst was more frequent in patients with stenosis of the main pancreatic duct: 13/16 (81%) versus 5/15 (33%) (P=0.01). Vascular compression was strongly correlated with portal hypertension: 9/16 (56%) versus 2/15 (13%) (P=0.02).

Communication of the pseudocyst with the main pancreatic duct was not a supplementary risk factor for ductal sequelae. The type of therapeutic management (ultrasound-guided drainage, endoscopic or surgical procedure) did not appear to affect the risk of ductal lesions. Sequelar stricture did not necessarily develop at the site of the pseudocyst. It was located in the head in 56% of patients. Ductal lesions were more frequent in patients with a recurrent pseudocyst. Fifteen months after an episode of acute pancreatitis complicated by a pseudocyst the risk of recurrent pseudocyst was 43% for patients with a stenosis of the main pancreatic duct (95% confidence interval [35.3-91.8]) (figure 3). The difference was not significant.

**Discussion**

Debate continues concerning the natural history of acute pancreatitis. The distinction between acute and chronic pancreatitis, as defined in the Marseille symposium in 1963, is not applicable in all patients. In series of 30 and 53 patients [7, 8] exocrine pancreatic insufficiency has been reported in 66% to 85% of patients at 6 to 18 months following an episode of acute pancreatitis. The risk appears to be greater for necrotizing pancreatitis because of the extensive destruction of parenchymal tissue [9].

Data on sequelar lesions of the main pancreatic duct after acute pancreatitis are scarce [9-12]. Most reports concern clinical cases of acute pancreatitis of variable severity. The proportion of patients with strictures of the main pancreatic duct...
secondary to pancreatitis ranged from 29% to 76%, irrespective of the etiology. Angelini et al. [10] followed 27 patients over four years with exocrine pancreatic insufficiency which progressively normalized and found that at four years 50% had persistent ductal lesions. In another more recent study, the same authors found a normal duct in 75/118 patients (64%) [9]. Büchler et al. [12] found lesions of the main pancreatic duct after acute pancreatitis in 16/21 patients (76%). Seidnsticker et al. [11] demonstrated ductal lesions in 50% of their 38 patients and exocrine insufficiency in 25%.

The main problem with these reports is that the presence of ductal lesions might be explained by an underlying chronic calcifying pancreatitis. In two reports [9, 11] chronic pancreatitis was later diagnosed in 10 and 18% of patients. These patients were not excluded so that the statistical analysis considered situations highly suggestive of chronic pancreatitis. It was also noted that the percentage of what was termed “sequelar” ductal lesions was greater (41% and 79%) when alcohol consumption was the cause of the acute pancreatitis. The risk of acute biliary pancreatitis has been estimated to range from 13% to 30% [13].

Our retrospective analysis started with a cohort of 67 patients hospitalized for acute pancreatitis with pseudocysts. We excluded 36 of these patients. Our first selection criteria was to exclude patients recognized as having chronic pancreatitis (N=12). It is well known that certain patients treated for a first episode of acute pancreatitis are later found to have had chronic pancreatitis, which has a very different prognosis. We also excluded all cases of post-alcoholic pancreatitis (N=6) and post-traumatic acute pancreatitis (N=3) since the latter present specific types of ductal lesions which may even develop late after trauma.

The length of the follow-up also appears to be an important factor when searching for ductal lesions [14]. In certain studies the follow-up was either not mentioned or too short to retain the diagnosis of sequelar stenosis [13, 15]. Repeated opacification procedures enable confirmation of the lesion in the main duct and its persistence late after the acute event [10, 16]. In our series, 22/31 patients (70%) underwent two or three ERCPs performed for therapeutic purposes within a mean of nine months from the acute event to the development of stenosis. In 8/22 patients (36%) for whom this information was available, stenosis of the main duct was identified early. The first exploration was however normal (regular duct without narrowing) in others who later developed sequelar stenosis.

Ductal lesions appear to be more frequent in patients with acute necrotizing pancreatitis (ANP): 35—100% with ductal lesions versus 5—30% in patients with edematous pancreatitis [9-12]. Ductal necrosis, which would be more frequent in ANP, and the subsequent healing processes within the ducts or the neighboring parenchyma, could explain the frequency of sequelar lesions. Our selection criteria eliminated all cases of acute edematous pancreatitis from our series. Uomo et al. [15] reported lesions in 60% of patients with acute biliary pancreatitis, and in 100% of those with necrosis. Unfortunately, the authors did not mention the type of ductal anomaly observed (stenosis, irregularity or rupture) or the degree of pancreatic necrosis.

The characteristic features of the pseudocysts observed in our patients were similar to those reported in the literature. Half (48%) were located in the pancreatic body and complications most frequently included extrinsic compression (78%). Infection was observed in 61% of patients, comparable with reports of 40—70% in the literature [17, 18]. The rate of fistulization (26%) was similar to the series reported by Van Sonnenberg [15] [19]. Bleeding was more frequent in our patients (22%) than in other series (7%) [20]. We found that the risk of stenosis was significantly related to pseudocyst complications, and more precisely to vascular complications subsequent to compression (56% versus 13%, P=0.02). Conversely, the type of treatment given for the pseudocyst had little effect on the subsequent course, even after endoscopic intubation of the main pancreatic duct (8 cases in our series, one associated with transmural drainage).

Complete obstruction of the duct was noted in 77% of patients, associated or not with upstream dilatation. Most of the strictures were located in the head (56%) and all were isolated. The localization of pancreatic duct strictures did not necessarily correspond to the position of the pseudocyst so that the sequelar lesion was probably not directly related to pseudocyst healing. In addition, no relationship could be identified between the communicating or non-communicating nature of the pseudocyst at the first ERCP and the subsequent development of ductal stricture.

The clinical consequences of these morphological anomalies were variable. Despite the presence of ductal anomalies, few patients (only three) complained of paroxysmal pain suggestive of pancreatic involvement. When cancer is ruled out (exclusion criterion in the present series), ductal stricture does not appear to lead to new attacks of acute pancreatitis [9, 11]. Obstruction of the main pancreatic duct induces upstream dilatation and appears to be associated with fibrosis and secondary parenchymal atrophy. Such histological lesions have been well described following surgical biopsies [1]. Pancreatic atrophy might explain the absence of symptoms - as symptomatic patients may observe...
regression in intensity and frequency over the years following the acute episode. Feller et al. [3, 4] followed two series of patients and advocated opacification of the pancreatic ducts only in the event of clinical manifestations, although routine opacification might have identified missed lesions. According to these authors this attitude is warranted because the main pancreatic duct can communicate with the Santorini duct, facilitating secretions and decreasing excessive pressure upstream from a cephalic obstruction. Andrew et al. [21] reported that certain cases diagnosed as pancreas divisum are probably erroneous, more likely corresponding to the result of the healing process after acute pancreatitis. Local inflammation would lead to the formation of fibrous scar tissue and subsequent ductal obstruction.

Control ERCP was performed when the stent was removed after cyst drainage. Although the stenosis was rarely symptomatic (3/16 patients), an attempt was made to treat the obstruction since in our experience it is a risk factor for recurrent pseudocyst formation after stent withdrawal.

MRCP was performed in 10/31 patients (32%) without follow-up ERCP. The diagnostic value of MRCP has been perversely compared with that of ERCP in our center [22]: visualization of the main pancreatic duct was better with MRCP than with ERCP (77% versus 50%); analysis of the stenosis was similar with the two methods; and visualization of the secondary ducts was better with ERCP (36% versus 18%). MRCP is a reliable exploration for diagnosis and surveillance of stenosis of the main pancreatic duct and appears to be better than ERCP in the event of complete obstruction. We find it useful to propose this non-invasive examination for surveillance purposes, particularly in symptom-free patients.

In conclusion, ductal lesions after an episode of acute pancreatitis associated with pseudocyst are frequent (16/31), particularly in the event of vascular compression. The high rate of sequelar lesions suggests that restitutio ad integrum is rarely achieved after acute pancreatitis and may add confusion with other pathological conditions (cancer, chronic calcifying pancreatitis). Ductal lesions are generally asymptomatic (13/16 patients) and routine endoscopic treatment does not appear to be warranted.

REFERENCES