Presence, extent and location of pancreatic necrosis are independent of aetiology in acute pancreatitis

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Objective The most common aetiologies of acute pancreatitis (AP) are gallstones, alcohol and idiopathic. The impact of the aetiology of AP on the extent and morphology of pancreatic and extrapancreatic necrosis (EXPN) has not been clearly established. The aim of the present study was to assess the influence of aetiology on the presence and location of pancreatic necrosis in patients with AP.

Patients and methods We carried out a post-hoc analysis of a previously established multicentre cohort of patients with AP in whom a computed tomography was available for review. Clinical data were obtained from the medical records. All computed tomographies were revised by the same expert radiologist. The impact of aetiology on pancreatic and EXPN was calculated.

Results In total, 159 patients with necrotizing pancreatitis were identified from a cohort of 285 patients. The most frequent aetiologies were biliary (105 patients, 37%), followed by alcohol (102 patients, 36%) and other aetiologies including idiopathic (78 patients, 27%). No relationship was found between the aetiology and the presence of pancreatic necrosis, EXPN, location of pancreatic necrosis or presence of collections.

Conclusion We found no association between the aetiology of AP and the presence, extent and anatomical location of pancreatic necrosis. Eur J Gastroenterol Hepatol 30:342–345

Background

Acute pancreatitis (AP) is morphologically classified as either interstitial oedematous or necrotizing pancreatitis according to the revised Atlanta classification [1]. Interstitial oedematous pancreatitis is the most frequent type, whereas necrotizing pancreatitis represents the severe form of the disease. Necrotizing pancreatitis can be complicated by organ failure or secondary infection, both with a negative impact on patient outcome. Necrosis may occur in the peripancreatic tissues [extrapancreatic necrosis (EXPN)], the pancreatic gland (pancreatic parenchymal necrosis or, in short, pancreatic necrosis) or both. Previously, it has been shown that patients with pancreatic necrosis have a worse prognosis than those with EXPN alone [2]. Pancreatic necrosis can be further categorized into extent (i.e. less than or more than 30% of pancreatic volume) and anatomical location (head, neck, body and tail of the pancreas). The location of necrosis is of importance as this could affect the development of specific complications such as vascular thrombosis [3] and fluid collections. Also, it can impact therapeutic options and approach.

Gallstones and alcohol abuse are the main causes of AP, representing 65–80% of the patients [4,5]. The rest is caused by a wide spectrum of other aetiologies including hypertriglyceridaemia, drug-induced and idiopathic causes [6]. Early cellular mechanisms in AP, such as dysregulation of calcium levels, energy depletion, activation of trypsinogen and initiation of inflammatory mediators, seem to be independent of the initiating cause. Nevertheless, the extent and localization of affected cells might differ with aetiology. In biliary pancreatitis, the inflammatory process is allegedly driven by pancreatic duct obstruction and direct cell toxicity of bile acids. In alcohol-induced pancreatitis, the pathogenetic mechanisms are direct toxicity of alcohol on pancreatic tissue, formation of protein plugs and oxidative stress [6]. The disparities in aetiology could thus lead to different morphological patterns of disease in the pancreas. The association between aetiology of AP and the extent of inflammation, presence of necrosis and patient outcome is still contentious [7–14].

The aim of the present study was to assess the impact of aetiology on the presence and location of pancreatic necrosis in patients with AP.

Patients and methods

This was a post-hoc analysis of a previously established multicentre cohort [15]. In six European centres, 50

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consecutive patients with AP were enroled in whom one or more contrast-enhanced computed tomography (CECT) had been performed. Only adult patients with a first episode of AP were included. Exclusion criteria were insufficient quality of the CECT, signs of chronic pancreatitis (i.e. pancreatic calcifications and/or irregular pancreatic duct) or previous pancreas-related invasive intervention, except for endoscopic retrograde cholangiography. In patients with multiple CECTs, the first available CECT (index CECT) showing pancreatic necrosis was used. This choice was based on the fact that later on in the course of the disease, a cascade of progressive inflammation could obscure the role of the initiating event. All CECTs were reviewed in a blinded manner by the same expert abdominal radiologist (T.L.B.).

Definitions for organ failure, grade of severity and CECT morphology of AP were assessed according to the revised Atlanta classification [1]. Pancreatic necrosis was established as focal or diffuse nonenhancement of the pancreatic gland as determined on CECT. EXPN alone (without pancreatic necrosis) was defined as extrapancreatic morphological changes exceeding fat stranding (i.e. heterogeneous peripancreatic collections) with complete enhancement of the pancreatic parenchyma as established on the index computed tomography (CT).

Statistical analysis was carried out using descriptive statistics where appropriate. For comparison between groups, the χ^2-test was used for nominal variables and analysis of variance was used for continuous variables. A Kruskal–Wallis test was used for ordinal analysis of severity category and percentage of parenchymal necrosis. A *P*-value of less than 0.05 was considered statistically significant. Data analysis was carried out using IBM SPSS, version 22 (IBM Corp., Armonk, New York, USA). Formal approval of the local medical ethical committee was requested and obtained at each study centre.

Results

A total of 301 patients were included at the six study sites. Sixteen cases were excluded because of insufficient quality of the CT, leaving 285 patients for analysis in the present study. Of these, 159 patients were men (56%). The median age at the time of inclusion was 58 years (range: 18–92 years). Overall mortality for the entire cohort was 4.9% (14 patients). The most frequent aetiology of pancreatitis was biliary (105 patients, 37%), followed by alcohol (102 patients, 36%) and other aetiologies including idiopathic (78 patients, 27%). At baseline, patients with alcoholic pancreatitis were significantly younger, more often male and less often known with a previous medical history of renal failure, diabetes and coronary artery disease (Table 1). Review of all CTs indicated that 159 (56%) patients had necrotizing pancreatitis.

The mean time between the onset of symptoms and CT was 15 days (range: 1–90 days), with no significant difference between aetiology groups. The presence of pancreatic necrosis, EXPN, location of pancreatic necrosis or presence of collections was the same in the three different aetiologies (Table 2). Also, analysis of C-reactive protein, systemic inflammatory response syndrome and organ failure showed no intergroup differences. When looking at parenchymal necrosis, there appears to be a trend towards more necrosis in the alcoholic group. Also, the alcoholic groups appeared to have more necrosis located in the tail of the pancreas. These trends, however, failed to reach statistical significance. In terms of the Atlanta severity classification, the difference was borderline significant, with a *P*-value of 0.05. This difference, *albeit* not below the predefined statistical threshold, was mostly because of a relatively large proportion of patients with moderate and severe pancreatitis in the alcohol group compared with the biliary and other group, which included more mild pancreatitis patients. To strengthen our conclusions, analyses were carried out again with the parameters both as ordinal and categorical measures, yielding similar nonsignificant results using both methods. Also, the Computed Tomography Severity Index (CTSI) was calculated for all patients with pancreatic necrosis. The mean CTSI for alcoholic, biliary and other groups was 5.18 (range: 3–10),

Table 1. Patient characteristics by aetiology

Parameters	Biliary	Alcohol	Other	*P*-value
Number of patients	105	102	78	NA
Age [median (range)] (years)	68 (18–92)	46 (22–86)	62 (18–92)	0.000
Male/female [*n* (%)]	34 (32)/71 (68)	83 (81)/19 (19)	42 (54)/36 (46)	0.000
BMI [median (range)]	28 (21–45)	28 (19–43)	27 (18–50)	0.251
Comorbidity [*n* (%)]				
Chronic renal failure	4 (4)	1 (1)	2 (3)	0.014
Diabetes mellitus	14 (14)	6 (6)	14 (18)	0.040
Chronic lung disease	4 (4)	7 (7)	6 (8)	0.171
Coronary artery disease	24 (23)	7 (7)	21 (27)	0.001

NA, not available.

Table 2. Outcome of pancreatitis by aetiology

Parameters	Biliary (*N* = 105) [*n* (%)]	Alcohol (*N* = 102) [*n* (%)]	Other (*N* = 78) [*n* (%)]	*P*-value
Necrotizing pancreatitis	53 (50)	60 (59)	46 (59)	0.664
Extrapancreatic necrosis[a]	53 (51)	59 (59)	44 (56)	0.752
Pancreatic necrosis[b]	20 (19)	30 (29)	15 (19)	0.140
Necrosis of pancreatic parenchyma (%)				0.149
None	85 (81)	72 (71)	63 (81)	
<30	10 (9)	23 (22)	8 (10)	
30–50	4 (4)	4 (4)	4 (5)	
>50	6 (6)	3 (3)	3 (4)	
Necrosis-location[c]				
Head	11 (11)	11 (11)	8 (10)	0.993
Neck	15 (14)	9 (9)	10 (13)	0.461
Body	13 (12)	11 (11)	10 (13)	0.902
Tail	11 (11)	21 (21)	8 (10)	0.059
Presence of collections	67 (64)	79 (78)	58 (74)	0.097
SIRS at the time of admission	22 (21)	26 (26)	21 (27)	0.850
CRP at admission [median (range)]	9 (0–416)	31 (0–455)	15 (0–477)	0.178
Highest CRP [median (range)]	283 (3–553)	284 (0–520)	277 (0–519)	0.588
Atlanta classification				
Mild/moderate/severe (%)	45/47/8	29/61/10	38/45/17	0.050
Systemic complications	76 (73)	84 (82)	74 (77)	0.427
Organ failure (%)				
Non/transient/persistent	84/9/7	80/9/11	72/13/15	0.304

CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.
[a]With or without parenchymal necrosis.
[b]With or without extrapancreatic necrosis.
[c]One or more locations could be necrotic at the same time.

5.26 (range: 3–10) and 5.04 (range: 4–10), respectively. This difference was not statistically significant.

Discussion

We found no association between aetiology of AP and the presence, extent and anatomical distribution of pancreatic necrosis. To the best of our knowledge, this is the first large study to specifically explore this relationship. In baseline characteristics, differences were found in age and comorbidities between biliary and alcoholic groups. Hypothetically, factors such as age, pre-existing vascular disease and diabetes affect pancreatic perfusion, and thus the development of pancreatic necrosis. This is the reason why several of the factors are included in for example the Apache-II score. Also, animal models using different triggers of AP suggest that different aetiologies could lead to a distinct pattern of pancreatic damage [16]. However, our results indicate that, once the inflammatory process of AP starts, the triggering factor is irrelevant to the presence, extent and location of necrosis. Our findings are supported by two previous studies in patients with necrotizing pancreatitis that found no relationship between the aetiology and the development of pancreatic and EXPN, or between aetiology and the need for invasive interventions [2,17]. Previous studies have described an association between the aetiology of pancreatitis and haemoconcentration, cytokine levels and fluid sequestration [8,9]. The impact of such phenomena on the development of pancreatic necrosis, however, was not observed in our study. The fact that no significant differences were observed across the spectrum of morphological abnormalities supports the robustness of our data. Furthermore, the validity of our findings is supported by the fact that aetiology is not part of any of the currently used scoring systems for predicting the severity of pancreatitis. Also, when calculating the previously validated CTSI score for all patients with necrosis, no intergroup differences were found. Next, there are several explanations for the differing findings between our study and other studies that did find a correlation between aetiology and the presence or absence of pancreatic necrosis and pancreatic fluid collections [9,11–13]. First, our series consists of patients who all had a CT scan during their initial admission, therefore excluding a large group of patients without any imaging or only ultrasonography performed. Second, we used a large multicentre cohort including the entire spectrum from mild to very severe cases of pancreatitis. In the study by Kim and colleagues – for example, only patients with peripancreatic collections were investigated. Third, all CTs were scored prospectively by one expert abdominal radiologist, uniform terminology was used according to the revised Atlanta classification and cases of chronic pancreatitis were excluded. This differs from the study by Weitz and colleagues who had a 42% prevalence of chronic pancreatitis in their cohort of patients with acute alcoholic pancreatitis. Chronic pancreatitis has a different pathogenesis. Also, the use of alcohol and tobacco has been shown to impact morphological changes such as pseudocysts and calcifications in chronic pancreatitis; thus, it is important to thoroughly exclude these patients when reporting on AP. Use of an expert radiologist for review has previously been shown to be important. Sternby *et al.* [15] have shown, using interobserver agreement analyses, that especially EXPN is frequently missed by nonexpert radiologists.

Kim *et al.* [11] carried out a specific analysis looking at different anatomical compartments that was not applied in our study. Considering the limited use of this scoring system in the international literature and lack of apparent clinical relevance, we refrained from such a detailed analysis. Nevertheless, our study has several limitations. First, the group with aetiology other than alcohol or biliary is most likely a very heterogeneous group including idiopathic, toxic and post-endoscopic retrograde cholangiopancreatography pancreatitis. Second, despite the large study cohort, for some parameters, the numbers were too small for a reliable (multivariate) analysis (e.g. the occurrence of pancreatic necrosis at specific anatomical locations). The nonsignificant trend towards more necrosis located in the tail region could prove to be real in larger cohorts. A such, future prospective studies should be sufficiently powered to carry out a multivariate analysis for the accurate evaluation of potential risk factors (including extensive demographic and biochemical data) for the development of pancreatic parenchymal and EXPN. Another potential valuable aspect of future studies could be the use and analysis of sequential imaging of necrosis to provide insights into the dynamics of necrotizing pancreatitis.

Conclusion

We found no statistically significant association between the aetiology of AP and the presence, extent and anatomical location of pancreatic necrosis.

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Conflicts of interest

There are no conflicts of interest.

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