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ORIGINAL ARTICLE

Impact of the site of necrosis on outcome of acute pancreatitis

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Abstract

Objecives: To compare the clinical outcome of patients with extrapancreatic necrosis (EXPN) alone with that of acute interstitial pancreatitis (AIP), pancreatic parenchymal necrosis (PPN) alone, and combined PPN and EXPN.

Background: There are only a few studies in the literature in which EXPN has been recently recognized as a subtype of acute necrotizing pancreatitis (ANP), with a better prognosis.

Methods: We analyzed clinical data and outcome variables of 411 consecutive acute pancreatitis (AP) patients between January 2012 and December 2014. Contrast-enhanced computed tomography (CECT) images of each patient were reviewed and characterized as AIP or ANP. Patients with ANP were divided into EXPN alone, PPN alone, and combined PPN and EXPN. Outcome variables were then compared between these groups.

Results: Of the 411 patients, 74 (18%) had AIP, and 337 (82%) had ANP. Patients with EXPN alone (n = 40; 11.8%) had similar outcomes as patients with PPN alone (n = 12; 3.5%); however, their outcome was worse than that of patients with AIP, with a higher frequency of persistent organ failure (POF), need for percutaneous catheter drainage (PCD), and longer length of hospitalization (LOH). Patients with combined PPN and EXPN (n = 285; 84.7%) had the worst clinical course, with higher frequency of POF, infected necrosis, intervention requirement, and longer LOH.

Conclusion: Patients with combined PPN and EXPN have a severe disease course with the worst clinical outcomes; patients with AIP patients have the most benign course, while patients with EXPN alone stand between the two extremes of disease course with an intermediate grade of severity.

Introduction

The revised Atlanta classification (RAC) divided acute pancreatitis (AP) into two morphological types on the basis of the presence or absence of pancreatic parenchymal necrosis (PPN): acute interstitial pancreatitis (AIP) and acute necrotizing pancreatitis (ANP).[1] This distinction is essential as patients with ANP have worse outcomes compared to those with AIP. However, in spite of these clear definitions provided by the RAC[1], there is yet another group of patients who have necrosis of peripancreatic tissue alone without parenchymal necrosis. After its first description by Howard and Wagner in 1989,[2] a few small series had reported on this disease among patients undergoing surgical necrosectomy.[3–5] This group of patients was later categorized into a distinctive group termed extrapancreatic necrosis (EXPN) alone, the diagnosis of which was based on contrast-enhanced computed tomography (CECT) findings and was later confirmed intraoperatively (showing absence of PPN).[5] Currently, EXPN is the term used to characterize this group of patients, although Koutroumpakis *et al.*[6] had used isolated peripancreatic necrosis to describe the same patients.

EXPN is defined variably on the basis of CECT showing peripancreatic tissue appearing as more than mere fat stranding[7] or a heterogeneous collection of both liquid and nonliquid densities on at least two consecutive CECTs,[8] or as ill-defined, nonliquefied nodular areas of increased fat attenuation with higher visual density than fat stranding or simple fluid.[6] One study also defined EXPN on EUS as peripancreatic areas of heterogeneous echotexture.[9] The pathophysiological mechanism suggested to be responsible for EXPN is necrosis of peripancreatic fatty tissue caused by pancreatic enzymes,[10,11] resulting in the release of adipocytokines in blood. Various studies have shown a good correlation between the serum level of adipokines and peripancreatic necrosis.[12–14] Although the accuracy of CECT for diagnosing EXPN had been questioned in previous studies,[15,16] there are now reports showing a good correlation

between CECT and surgical or autopsy findings of the presence of fat necrosis.[17,18]

The first prospective study on EXPN was published by Singh *et al*.[8] who reported that patients with EXPN had a more severe disease course compared to patients with AIP. However, the first large study was by the Dutch Pancreatitis Study Group, which reported that patients with EXPN alone had better prognosis compared to patients with PPN and proposed that it should be considered a separate entity.[7] Since then, EXPN alone has become an area of clinical interest, and three more studies have been published.[6,19,20] There are several drawbacks in the data found in these studies—(i) the prevalence of EXPN is variable and different outcome parameters have been studied in different studies, (ii) the diagnostic criteria used have been different in different studies, and (iii) patients with EXPN have been clubbed with PPN into one group in most of the studies.[6,7,19,20] To overcome these deficiencies in previous studies, we conducted the present study to compare the clinical course and outcome parameters of patients with EXPN alone with patients of AIP, PPN alone, and patients with combined PPN and EXPN.

Materials and methods

This study was carried out at a large tertiary care center in India between January 2012 and December 2014, and prospectively collected data were analyzed retrospectively. Ethical approval was obtained from the institutional ethics committee and informed consent for the use of data for research purpose was obtained at admission. Diagnosis of AP was based on RAC,[1] which incorporates two or more of the following criteria: abdominal pain typical of AP, serum enzyme levels more than three times the upper normal limit, and imaging features of AP. The demographic profile, severity parameters including systemic inflammatory response syndrome[21], modified Marshall[22], acute physiological and chronic health examination scores[23], along with laboratory and radiological data including the CT severity index (CTSI)[24] were recorded. The management was according to the standard guidelines and protocol followed in the institution. It included intensive resuscitation, fluid and electrolyte monitoring, analgesics, and oxygen and nutritional support. Antibiotics were given for any documented focus of infection (either infected pancreatic necrosis or extrapancreatic infection). Patients with persistent organ failure (POF) or infected fluid collections were subjected to radiologically guided percutaneous catheter drainage (PCD) placement. Surgery in the form of necrosectomy and closed lesser sac drainage was considered in the event of worsening clinical condition despite maximal supportive management. Patients were followed up from hospitalization until final outcome (either discharged or death).

Study population. After obtaining all data, only patients who underwent initial CECT imaging within 5–7 days after disease onset were included in our study protocol and were followed up. Patients for whom CECT was not performed due to contraindications or when CECT was performed beyond the above specified period were excluded.

Radiological evaluation and definitions. CECT images were reported by a single trained abdominal radiologist who was blinded to the clinical outcome of the patient, and RAC[1] definitions were used for morphological classification and fluid collections. AIP was defined as the relatively homogeneous enhancement of pancreas on a CECT without any evidence of pancreatic or peripancreatic necrosis. PPN was defined as a lack of enhancement of pancreatic parenchyma without any evidence of peripancreatic necrosis[1]. Finally, evidence of liquid or heterogeneous peripancreatic collection or ill-defined, nonliquefied nodular areas of increased fat attenuation with higher visual density than mere fat stranding or simple fluid with completely preserved enhancement of pancreatic parenchyma was defined as EXPN.[6]

Based on the above-mentioned definitions, patients with necrotizing pancreatitis were divided in three groups: EXPN alone group, PPN alone group, and the group with combined PPN and EXPN.

Outcome variables measured were frequency of POF; multiorgan failure (MOF); infected necrosis; need for ventilator, dialysis, and intensive care (ICU); length of hospital stay (LOH); need for PCD; and need for surgery and mortality. These outcome variables were then compared between groups of patients with AIP, PPN alone, EXPN alone, and combined PPN and EXPN.

Statistical analysis. Quantitative data were expressed as mean $\pm$ SD or the medians and the interquartile range (IQR) as appropriate. For categorical data, results were expressed as numbers and percentages. Differences between two groups with continuous data were assessed through the student *t*-test, and the Chi square test was used for the analysis of categorical variables. Statistical significance was set at <0.05 ($P < 0.05$). All statistical calculations were performed using the statistical package for social sciences (SPSS) II software for Windows version 20.0.

Results

A total of 450 patients with AP were managed by us during the study period. Of these, 39 patients were excluded due to various reasons (25 patients had not undergone CECT abdomen, and 14 patients did not have CECT images available in the database); thus, 411 patients were included in the study. Of these 411 patients, 74 (18%) had AIP, and 337 (82%) were categorized as ANP. ANP patients were further subdivided into three groups according to the site of necrosis as mentioned above. The EXPN alone group consisted of 40 (12%) patients, PPN alone group had 12 (3.5%) patients, and the combined PPN and EXPN group comprised 285 (84.5%) patients (Fig. 1).

Baseline demographic characteristics of each study group are given in Table 1. The most common cause of pancreatitis was alcohol (n = 193; 46.95%). About 11% of patients had recurrent attacks of AP. Baseline characteristics were comparable between the study groups, including body mass index (BMI).

Outcome variables of study population. During hospitalization, organ failure developed in 215 (52%) patients, of whom 137 (33%) had POF and 87 (21%) had multiorgan failure (MOF); 153 (37.2%) patients required ICU care, whereas need for ventilator support and dialysis was seen in 64 (15.5%) and 29 (7%) patients, respectively. A total of 95 (23.1%) patients developed infected necrosis during the disease course. Image-

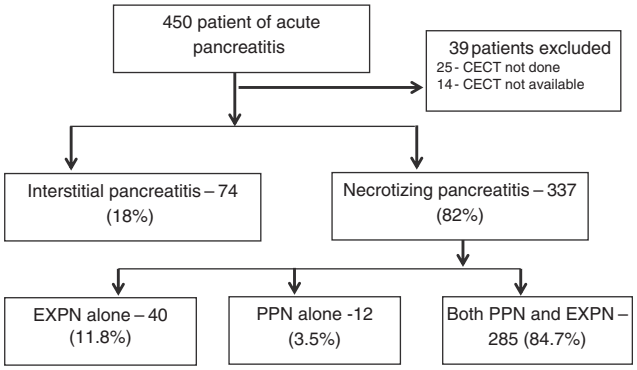

Figure 1 Study population.

guided PCD as a part of a step-up approach was carried out in 158 (38.4%) patients, and 41 (9.9%) underwent surgical necrosectomy; 59 (14.3%) patients died during the disease course.

A comparison of outcome variables between patients with EXPN alone (n = 40) and AIP (n = 74) showed that the EXPN alone group had a significantly higher frequency of POF (15% *vs* 2.7%, P = 0.014), requirement of ICU care (27.5% *vs* 5.4%, P < 0.001), ventilator support (10% *vs* 0%, P = 0.014), and PCD (20% *vs* 1.4%, P < 0.001). This group also had prolonged hospitalization (15.2 ± 7.9 *vs* 9.6 ± 6.1 days, P < 0.001) compared to AIP patients. However, the difference in other parameters, such as CTSI score, number of patients requiring dialysis, frequency of MOF, infected necrosis, surgery, and mortality, did not reach statistical significance (Table 2).

Comparative analysis of patients with EXPN alone (n = 40) and PPN alone (n = 12) showed that outcome variables were comparable in terms of POF, MOF, proportion of patients needing ICU care, dialysis, and ventilator support. Similarly, LOH, the proportion of patients having infected necrosis, need for interventions (PCD and surgery), and mortality rates were also not statistically different between these two groups. However, a significantly higher CTSI score was observed in the PPN alone group (5.7 ± 1.1 *vs* 3.9 ± 0.8, P < 0.001) (Table 2).

Finally, when outcome variables were compared between the EXPN alone group (n = 40) and the combined PPN and EXPN group (n = 285), the analysis showed that the latter group had a significantly higher CTSI score (8.41 ± 1.8 *vs* 3.95 ± 0.8%,

Table 1 Baseline characteristics of study population

Characteristic	AIP (n = 74)	EXPN alone (n = 40)	PPN alone (n = 12)	Combined PPN and EXPN (n = 285)	P value
Age (years)	41 ± 14.8 (18–85)	42.7 ± 13.4 (21–70)	41.5 ± 12.7 (26–67)	38.5 ± 13.3 (18–90)	0.155
Gender					
Male/female	44(59%) / 30(41%)	24 (60%) / 16 (40%)	9 (75%) / 3 (25%)	204 (72%) / 81 (28%)	0.636
Etiology					
Alcohol	26 (35%)	19 (48%)	6 (50%)	142 (50%)	0.019
Gallstone	30 (40%)	10 (25%)	1 (8%)	97 (34%)	
Post-ERCP	1 (1%)	0 (0%)	1 (8%)	2 (1%)	
Idiopathic	17 (24%)	11 (27%)	4 (34%)	44 (15%)	
Episode of acute pancreatitis					
First	61 (82%)	35 (88%)	10 (84%)	259 (91%)	0.196
Recurrent episode	13 (18%)	5 (12%)	2 (16%)	26 (9%)	
Body mass index	24 ± 3.6	24.3 ± 4.2	23.1 ± 2.7	24 ± 3.8	0.849

AIP, acute interstitial pancreatitis; ERCP, endoscopic retrograde cholangiopancreaticography; EXPN, extrapancreatic necrosis; PPN, pancreatic parenchymal necrosis.

Table 2 Comparison of outcome parameters between patients with EXPN alone *and* AIP, PPN alone, and combined PPN and EXPN

Parameter	EXPN alone (n = 40)	AIP (n = 74)	PPN alone (n = 12)	Combined PPN and EXPN (n = 285)	P1	P2	P3
CT severity index (mean ± SD)	3.95 ± 0.876	3.43 ± 1.68	5.17 ± 1.19	8.41 ± 1.808	0.736	0.000	0.000
Persistent organ failure	6 (15%)	3 (4.1%)	2 (16.7%)	124 (43.5%)	0.0641	1.000	0.000
Multiorgan failure	3 (7.5%)	4 (5.4%)	2 (16.7%)	78 (27.4%)	0.694	0.324	0.005
ICU need	11 (27.5%)	4 (5.4%)	2 (16.7%)	136 (47.7%)	0.002	0.706	0.017
Need for ventilator	0 (0%)	0 (0%)	2 (16.7%)	62 (21.8%)	1.000	0.049	0.000
Need for dialysis	0 (0%)	2 (2.7%)	1 (8.3%)	26 (9.1%)	0.540	0.230	0.056
Hospital stay (days/mean)	13.42 ± 1.68	8.37 ± 1.67	8.08 ± 1.72	19.26 ± 2.14	0.004	0.014	0.000
Infected necrosis	1 (2.5%)	1 (1.4%)	2 (16.7%)	91 (31.9%)	1.000	0.129	0.001
Percutaneous catheter drainage placement	8 (20%)	5 (6.8%)	3 (25%)	142 (49.8%)	0.059	0.701	0.000
Surgery	0 (0%)	0 (0%)	0 (0%)	40 (14%)	1.000	1.000	0.007
Mortality	0 (0%)	0 (0%)	2 (16.7%)	57 (20%)	1.000	0.049	0.000

P1, P value that resulted from comparison of EXPN alone with AIP; P2, P value that resulted from comparison of EXPN alone with PPN alone; P3, P value that resulted from comparison of EXPN alone with combined PPN and EXPN; AIP, acute interstitial pancreatitis; EXPN, extrapancreatic necrosis; PPN, pancreatic parenchymal necrosis.

$P < 0.001$) and a higher frequency of POF (43.5% *vs* 15%, $P = 0.001$) and MOF (27.4% *vs* 7.5%, $P = 0.001$). Similarly, patients in the combined group had longer LOH (25.2 ± 20.4 *vs* 15.2 ± 7.9 days, $P = 0.005$), a higher need for ICU care (47.7% *vs* 27.5%, $P = 0.016$), and a higher frequency of infected necrosis (31.9% *vs* 2.5%, $P < 0.001$). Intervention requirements in the form of PCD (49.8% *vs* 20%, $P < 0.001$) and surgery (14% *vs* 2.5%, $P = 0.04$) were also statistically higher in the combined group compared to the EXPN alone group. There was a trend toward higher mortality rate (20% *vs* 7.5%, $P = 0.056$) and a greater need for ventilator (21.8% *vs*10%, $P = 0.084$) and dialysis support (9.1% *vs* 5%, $P = 0.55$) in the combined PPN and EXPN group compared to EXPN alone group, but the differences did not reach statistical significance (Table 2).

Discussion

The present study is a retrospective analysis of prospectively collected data comparing the outcome of patients with EXPN alone with other morphological types. We found that patients with combined PPN and EXPN had the most severe disease course, with worse clinical outcomes than those with AIP, and required aggressive management strategies. Patients with EXPN alone lie between the two extremes of disease course, with intermediate grade of severity, but with similar severity and clinical outcome as patients with PPN alone.

The frequency of EXPN alone in our study population was 12%, which is similar to a recent prospective US study[6] in which isolated peripancreatic necrosis was seen in 11% of patients and a study from China[20] in which the frequency of isolated EXPN was 14.7%.The prevalence of EXPN alone varies in different reports from 6.3 to 22%,[6,19,20,30] except in one study by Bakker *et al.*[7] who reported that 315 (49%) of 639 patients with ANP had EXPN. The discrepancy among different studies can be explained by selection and referral bias or because of the different criteria used in defining isolated EXPN by the radiologists. The variable timing of performing a CT scan (based on which the diagnosis was made) may also be a factor for differences in the prevalence of EXPN.

The RAC[1] has used CECT to categorize AP into ANP and AIP. Further subclassification of ANP into PPN and EXPN is also based on CECT. Recent reports have also shown a good correlation between CECT findings and operative/autopsy findings of extrapancreatic fat necrosis.[17,18] CECT can also be used for the quantification of fat necrosis, and Meyrignac *et al.*[25] have recently shown that a threshold of 100 mL of EXPN had a sensitivity of 95% and specificity of 83% for the prediction of severe AP. Isolated EXPN is a relatively new term for radiologists, and a recent study reported only fair interobserver agreement (range 0.326–0.408) for the diagnosis of EXPN, with central experts diagnosing it more frequently than the local radiologists (59% *vs* 33%, $P < 0.0001$).[26] Although the diagnostic criteria for EXPN have been a matter of debate, the CECT-based criteria used by Koutroumpakis *et al.*[6] have gained wide acceptance, and we have used the same criteria in the present study.

Recognition of EXPN alone as a distinct and separate entity from AIP has been suggested by several studies. Singh *et al.*[8] compared severity and the need for interventions between patients with AIP and EXPN alone and concluded that the latter had a significantly higher frequency of POF, longer LOH, and increased need for ICU care and ventilator support. However, the mortality rate was similar to patients with AIP. Other researchers have also reported that patients with EXPN alone have a higher rate of POF[19] and higher CTSI and APACHE II scores[20]. Our results are in consonance with these reports, with higher CTSI, longer LOH, higher rate of POF, and increased need for ICU care and ventilator support in patients with EXPN alone. The need for surgery and the mortality rate of patients with EXPN alone were also comparable to patients with AIP as reported in some of the previous studies.[8,19]

The need for interventions in patients with EXPN has varied in different studies. We noted that patients with EXPN alone had a higher requirement for PCD (20%) compared to patients with AIP (1.4%) despite a similar frequency of infected necrosis. Bruennler *et al.*[27] reported that 2% of edematous pancreatitis patients who required CT-guided drainage actually had EXPN. Wang *et al.*[20] reported that a very high proportion (59.2%) of patients with EXPN alone needed PCD, whereas none of the patients in AIP group required it. In contrast to these reports, Rana *et al.*[19] reported that patients with AIP had a higher intervention rate than those with EXPN. Their PCD rate was otherwise also higher than reported in other long-term follow-up studies of AIP.[8,28,29] Our results suggests that patients with EXPN alone have a more severe clinical course and require more aggressive management compared to those with AIP. It is easy to explain this as the chances of development of complications in patients with necrotic tissue are understandably higher than when there is only edematous pancreatitis without any necrosis. Indeed, most patients with AP have only AIP, and a minority have ANP. However, it is the patients with severe AP, be it AIP or ANP, who require longer hospitalization and care in a referral center.

Among patients with necrotizing pancreatitis, the largest group was combined PPN and EXPN. On comparing the outcome of patients with EXPN alone with patients of combined PPN and EXPN, we noted that the former group had a significantly lower CTSI and a lower risk of developing organ failure and infected necrosis. LOH, the need for ICU care, and the need for interventions (PCD and surgical necrosectomy) were also significantly lower in the EXPN alone group. A surgical series by Sakorafas *et al.*[5] noted that the EXPN alone group required fewer reoperative surgeries, and none of them developed pancreatic or gastrointestinal fistulas or hemorrhage and had a significantly shorter length of hospital stay. Other studies have also reported lower frequency of infected necrosis[6,7,20] and interventions[6,7,20] in patients with EXPN alone. There are contradicting results regarding organ failure in patients with EXPN alone, with some studies reporting a lower frequency of OF,[7,20] with others showing no difference.[6,19] Data on mortality in patients with EXPN alone is also variable, with two studies[6,19] showing no difference in mortality, while other studies[7,20] report significant difference in mortality. We observed no mortality in EXPN alone, while it was 20% in patients with combined EXPN and PPN. This discrepancy can be because of differences in study design, CECT criteria of diagnosing EXPN, and patient selection bias.

We also compared the outcome of patients with EXPN alone with those with PPN alone. Although the patients with PPN alone constitute the smallest subset of the patients with necrotizing pancreatitis, we had 12 such patients. Most previous

studies had clubbed such patients in the combined PPN and EXPN group. We found that both groups were comparable in terms of organ failure and the need for organ support. Similarly, LOH, proportion of patients with infected necrosis, requirement of interventions, and mortality were also not statistically different between these two groups. However, a significantly higher CTSI score was observed in the PPN alone group, which is self-evident as pancreatic parenchyma is preserved in patients with EXPN alone.

The strengths of our study include the prospective nature of data collection and the large number of patients studied. We also had an adequate number of patients of all categories, including AIP, EXPN alone, PPN alone, and combination of EXPN and PPN. The diagnosis of EXPN was established as per standard definitions,[6] and radiological findings were interpreted by a blinded radiologist. In keeping with the recommendations of RAC,[1] we have included patients who had CECT within 5–7 days of onset of pain. However, we did not subdivide EXPN into limited and extensive, which may have a bearing on complications and disease course as has been suggested by some researchers.[6,19] Another limitation of our study is the possibility of referral bias. Our institute is a tertiary referral center for three states, and more patients with severe disease are referred to us; thus, only a small proportion of our study population had AIP.

To conclude, our study highlights the need for the subclassification of necrotizing pancreatitis into different groups as EXPN alone and PPN alone have a better clinical course and outcomes compared to combined PPN and EXPN.

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