A New Entity of Walled off Extra Pancreatic Necrosis is Associated with Better Outcomes Following Endoscopic Transmural Drainage

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ABSTRACT

Background & Aims: Previous studies have shown that patients with extra-pancreatic necrosis (EPN) alone are associated with better outcomes than patients with pancreatic necrosis (PN) in acute pancreatitis (AP). The natural history and drainage outcome of pancreatic collections resulting from PN vs. EPN has not been studied. Methods: Clinical records of a prospectively maintained cohort of AP patients who underwent endoscopic drainage of walled of necrosis (WON) were reviewed. Computed tomography (CT) done on day 4 to 7 of illness was reviewed to identify EPN alone (Group 1) or PN with or without EPN (Group 2). Group 1 and 2 were compared for WON characteristics, as well as outcome and adverse effects of endoscopic drainage. Results: Seventy-one patients in Group 2 (57 males; mean age 38.6±11.5 years) were compared with sixteen patients in Group 1 (12 males; mean age 34.5±10.8 years). WON developing in Group 2 were significantly larger (11.7±2.8 cm vs. 9.5±2.03 cm) with higher solid necrotic debris (30.4±9.8% vs. 13.7±7.2%). Endoscopic transmural drainage of WON associated with PN required a greater number of direct endoscopic necrosectomy (DEN) sessions along with a longer time for resolution. The time taken for resolution correlated with size (r=0.629, p < 0.01) and solid debris content (r=0.647, p<0.01), which were significantly higher in the PN group. Conclusions: This new entity of walled of extra pancreatic necrosis alone has lesser solid necrotic debris and its endoscopic drainage is associated with better outcomes as compared to patients with walled off pancreatic necrosis.

Key words: pancreatic necrosis – extra pancreatic necrosis – walled off necrosis – endoscopic drainage – acute pancreatitis.

Abbreviations: AP: acute pancreatitis; CECT: contrast enhanced computed tomography; DEN: direct endoscopic necrosectomy; EPN: extra-pancreatic necrosis; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography; PN: pancreatic necrosis; PNC: pancreatic necrosis; WOEPN: walled off extra-pancreatic necrosis; WOPN: walled off pancreatic necrosis; WON: walled off necrosis.

INTRODUCTION

The pathophysiological hallmark of acute pancreatitis (AP) is an acute inflammatory insult to pancreatic and extrapancreatic tissues triggered by the overactivation and premature release of pancreatic enzymes [1]. The resultant inflammatory cytokine storm and hypoperfusion causes tissue necrosis in and around the pancreas. The revised Atlanta classification has defined necrotizing and interstitial pancreatic morphologies as two distinct entities with varying clinical outcomes with necrotizing pancreatitis being associated with a poor prognosis [2, 3].

In AP, the process of tissue necrosis can extend beyond the boundaries of pancreatic parenchyma to involve the peripancreatic and other intra-abdominal spaces. This extent of tissue injury is predominantly determined by the individual susceptibility and severity of the initial insult [4]. Pancreatic necrosis (PN) has been defined as a non-enhancing area within the pancreatic tissue on contrast enhanced computed tomography (CECT) imaging and has been found to be often associated with variable degrees of extra pancreatic necrosis (EPN) [5], and therefore isolated PN or EPN are relatively less commonly encountered entities [6]. The clinical significance of EPN alone has been a research topic of great interest in the last decade. It was first described as necrosis of the peripancreatic tissue with a normally enhancing pancreas on CECT imaging [7]. Since then, different studies have defined EPN with minor variations and it has been further classified into limited or extensive subtypes [6, 8, 9]. Moreover, studies have reported that the clinical outcome of EPN alone is slightly worse than interstitial pancreatitis but better than combined PN and EPN as well as PN alone [8-10].

Pancreatic necrosis is best recognized on CECT evaluation done on day 3 to 5 following the onset of the disease [11, 12]. Eventual fate of necrotizing AP is either spontaneous resolution or transformation into acute necrotic collections that on subsequent maturation form encapsulated collections called walled off necrosis (WON) [13, 14]. The natural history and drainage outcome of WON developing from PN and EPN is likely to be different considering the difference in site and nature of tissues that are affected. However, the morphological features of WON developing following EPN alone has not been previously studied. Moreover, there is paucity of data on the outcome following endoscopic drainage of these walled off collections. Therefore, we conducted this study to compare the morphological features as well as outcomes of endoscopic drainage of walled off necrotic collections developing after EPN alone with those developing after PN with or without EPN.

METHODS

A retrospective analysis of data base of patients with pancreatic necrotic collections (PNC) treated with endoscopic transmural drainage at a tertiary care centre in North India over last 10 years was done. Patients diagnosed with AP who underwent endoscopic transmural drainage of WON with plastic or metallic stents with evidence of necrotizing pancreatitis on initial CECT performed between days 4 to day 7 of disease onset were included. Patients with interstitial AP or underlying chronic pancreatitis and malignancy and those who underwent CECT prior to day 4 or beyond day 7 after disease onset and those in whom CECT was contraindicated were excluded. Patients in whom the CT done at day 4-7 of illness were not available for review by a radiologist were also excluded. Informed consent was obtained from all patients prior to endoscopic drainage and the study protocol for retrospective analysis was approved by the Institute Ethics Committee (IEC) (INT/IEC/2021/SPL-1705). Patients underwent endoscopic drainage of PNC's if they had persistent sepsis (persistent, worsening or new onset organ failure, fever, leukocytosis), persistent abdominal pain or symptoms due to biliary or gastric outlet obstruction.

Diagnosis of AP was based on the presence of two out of the following three criteria: abdominal pain consistent with AP, greater than three times elevation of amylase/ lipase levels and radiological evidence of AP. Interstitial and necrotizing morphology and local complications were defined as per the revised Atlanta classification 2.

Pancreatic necrosis was defined as focal or diffuse non enhancement of pancreas on CECT done between day 4 and 7 of the onset of illness whereas EPN was defined as extrapancreatic changes that were more than simple fat stranding [8]. Extrapancreatic necrosis alone was diagnosed when there were extra-pancreatic changes defined above with complete enhancement of the pancreatic parenchyma on contrast enhanced CT [6].

Walled off necrosis was defined as an encapsulated collection with a well-defined inflammatory wall after a minimum of 4 weeks of onset of AP. Walled off necrosis that developed in subjects with combined necrosis as well as isolated PN were termed as walled off pancreatic necrosis (WOPN) and the walled off collection resulting in patients with EPN alone was defined as walled off extra-pancreatic necrosis (WOEPN).

Apart from the demographic and clinical variables, the initial CECT of the included patients that was performed between day 4 and day 7 of disease was retrospectively evaluated to look for PN and EPN. The later CECT that was done prior to the endoscopic transmural drainage was evaluated for morphological characteristics of WON including the size and location. The CECT films were reviewed by an experienced radiologist who was blinded to the clinical data and patient outcome. All patients had also undergone a detailed endoscopic ultrasound (EUS) examination using a linear scanning echoendoscope (EG-3870 UTK linear echoendoscope, Pentax Inc, Tokyo, Japan or UCT180 linear echoendoscope, Olympus Optical Co. Ltd., Tokyo, Japan) prior to the endoscopic drainage. During EUS, detailed morphological evaluation of the WON including the calculation of amount of solid necrotic debris was performed. The echogenic material present in WON was suggestive of necrotic debris and using an approximate visual judgment of the experienced endosonologist (S.S.R.), amount of solid necrotic debris was judged as a percentage of the total size of the necrotic collection. The choice of stent (metal or plastic stent) was based upon the treating endoscopist discretion, percentage of solid necrotic debris, size of collection and patient's preference depending upon affordability due to economic considerations and availability of health insurance. Collections >10 cm or having >30% solid debris were preferentially drained with metal stent. The endoscopic drainage parameters including type of stent (metallic vs. plastic), number of direct endoscopic necrosectomy (DEN) sessions, need for simultaneous percutaneous drainage, complications and time to resolution of WON were retrieved from the data base. Subjects with combined necrosis (i.e. concomitant PN and EPN) were designated as Group 1 and those with EPN alone were designated as group 2. The pancreatic duct disruption was diagnosed on either endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) that was done after the resolution of PNC.

The primary outcome of the study was to compare the time to resolution of PNC as documented on cross sectional imaging (CECT or magnetic resonance imaging) following drainage between the two groups. Other parameters that were compared between the two groups included the size of WON, the percentage of solid debris, and the need for metallic vs. plastic transmural stents or DEN as well as adverse events associated with endoscopic drainage.

All statistical analyses were performed using SPSS software (version 22). Continuous variables were expressed as mean \pm standard deviation and categorical variables were expressed as

total frequency with percentages. As the numbers of subjects in the two groups were skewed, a Welsh independent-t test was done to compare continuous variables and Chi-square tests or Fisher's exact t test were used to compare categorical data. Whenever considered feasible, one-way analysis of variance (ANOVA) was used to compare categorical data with unequal frequencies in the two groups. Bivariate Pearson correlation coefficient was used to find linear relationships between continuous variables. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Eighty-seven patients fulfilled the inclusion criteria, of which 71 were included in Group 1 and 16 in Group 2 respectively. There was a preponderance of males in both groups. Alcohol and gallstones were the most commonly encountered etiologies across the two groups. Pain was present in all patients in both groups and fever was significantly higher amongst patients in group 1 (49.3% vs. 6.3%, p<0.01) (Table I).

Table I. Walled off Pancreatic Necrosis. Demographic and clinical profile
as well as outcomes following endoscopic drainage

Parameter	Group 1, WOPN (n=71)	Group 2, WOEPN (n=16)	р
Age, years, mean	38.6±11.5	34.5±10.8	0.182
Male gender, n (%)	57 (80.3):	12 (75)	0.734
Etiology, n (%)			0.016
Alcohol	48 (67.6)	5 (31.3)	
Gallstone	15 (21.1)	5 (31.3)	
Idiopathic	8 (11.3)	4 (25.1)	
Post ERCP	0 (0)	1 (6.3)	
Trauma	0 (0)	1 (6.3)	
Pain, n (%)	71 (100)	16 (100)	-
Fever, n (%)	35 (49.3)	1 (6.3)	< 0.01
Size (cm), n (%)	11.7±2.8	9.5±2.03	0.014
Solid debris (%)	30.4±9.8	13.7±7.2	< 0.01
Location			0.899
Head	9 (12.7)	2 (12.5)	
Body	56 (78.9)	13 (81.3)	
Body tail	1(1.4) 2(2.8)	1(0.3) 0(0)	
Head body	2 (2.8)	0 (0)	
Head body tail	1 (1.4)	0 (0)	
Pancreatic duct disruption	56 (78.9)	0 (0)	< 0.01
Time to drainage (days)	54.58±12.8	58.56±13.2	0.285
Metallic stent	21 (29.6)	1 (6.3)	0.061
Number of sessions	3.9±1.17	1.3 ± 0.48	< 0.01
Plastic stent	49 (69)	15 (93.8)	0.059
DEN	13(18.3)	0(0)	0.114
PCD	6(8.5)	0(0)	0.228
Time to resolution (days)	28.6±5.2	19.3±4.17	< 0.01
Complications	4 (5.6)	0 (0)	0.331

WOPN: Walled off pancreatic necrosis; WOEPN: Walled off extra-pancreatic necrosis; DEN: direct endoscopic necrosectomy; PCD: pancreatic necrotic collections.

Patients with WOPN (Group 1) had significantly larger size (11.7 \pm 2.8 vs. 9.5 \pm 2.03 cm, p=0.014) with higher mean proportion of solid debris (30.4 \pm 9.8 vs. 13.7 \pm 7.2 %, p<0.01) in comparison to WOEPN (Group 2). There was no significant difference in the location of necrosis between the two groups. Main pancreatic duct disruption was found to be present in patients with WOPN only. Fifty-six patients (78.9%) with WOPN had pancreatic duct disruption.

The mean time of intervention since the onset of disease was comparable between the two groups. Technical as well as clinical success was achieved in all the patients in both the groups. Metallic transmural stent placement and DEN was performed in a higher proportion of WOPN patients, while plastic stents were used more amongst WOEPN patients (Figs. 1-3). Four patients developed bleed during drainage, all of which occurred during the drainage of WOPN. One patient had peri-procedural bleeding and three patients had postprocedural bleeding. The patient with peri-procedural bleed had self-limiting bleed and no pseudoaneurysm was identified on CECT angiography. The post-procedural bleeding was selflimiting in one patient and due to bleeding pseudoaneurysm in other two patients. The pseudoaneurysm bleeding could be successfully controlled with angioembolization. The time to resolution was significantly longer amongst WOPN patients (28.6±5.2 vs. 19.3±4.17 days, p<0.01; Fig. 4) and these patients required an additional number of endoscopy sessions for resolution as compared to patients with WOEPN (Table I). Time to resolution showed significant and positive correlation with size of WON (r=0.629, p<0.01) and solid debris content (r=0.647, p<0.01), both of which were significantly higher among patients with WOPN (Fig. 5).

DISCUSSION

In this study, we observed that endoscopic transmural drainage of WOEPN was associated with quicker resolution as well as lesser need for aggressive endoscopic drainage techniques such as DEN. Also, WOPN were of larger size with higher solid debris content and were more frequently associated with ductal disruption in comparison to WOEPN. Acute pancreatitis is a disease of a varying spectrum of severity ranging from mild to moderate and severe disease [2]. Correspondingly, the radiological morphology has been found to be different in concordance to this severity spectrum. The necrotizing type of pancreatitis has been found to be associated with increased severity in terms of organ failure, hospitalizations and mortality in comparison to the interstitial variant [5]. Recently, necrotizing pancreatitis has also been reported to be of two subtypes: peri-pancreatic or extra-pancreatic necrosis alone and pancreatic necrosis with or without EPN. This new entity of EPN alone has been reported to be having a prognosis which is better than pancreatic parenchymal necrosis but worse than acute interstitial pancreatitis [6, 8-10].

As the disease progresses, the ill-defined pancreatic or peripancreatic necrosis matures and gets eventually replaced by well-defined necrotic fluid collections [15]. Extrapolating the existing evidence of favorable prognosis among patients with predominantly EPN, we hypothesized that the morphology as well as the outcome of drainage of necrotic collections



Fig. 1. WOEPN treated with transmural metal stent insertion: A) CT abdomen done at day 4 of illness shows predominantly extra pancreatic necrosis with enhancing pancreatic parenchyma; B) CT abdomen at 7th week of illness: well circumscribed WOEPN; C) EUS guided drainage of WOEPN with metal stent. The collection is having predominantly liquid content; D) CT: Resolved WOEPN with metal stent in situ.

resulting from PN and EPN are likely to be different. The difference in outcomes to the drainage between the two entities is probably fundamental to the biochemical nature of the tissues involved in necrosis and that probably determines what subsequently constitutes these collections. Necrosis of the pancreatic parenchyma predominantly involves necrosis of protein proteomers constituting the gland; while, on the other hand extra pancreatic necrosis is largely fat necrosis [16, 17].



Fig. 2. WOEPN treated with multiple plastic stent insertion: A) CT abdomen done at day 5 of illness shows predominantly extra pancreatic necrosis with enhancing pancreatic parenchyma; B) CT abdomen at 4th week of illness: well circumscribed WOEPN; C) EUS guided drainage of WOEPN with multiple plastic stents. The collection is having predominantly liquid content; D: CT after first session of endoscopic drainage: reduced size of WOEPN with multiple plastic stents in situ.



Fig. 3. WOPN treated with multiple plastic stent insertion: A) CT abdomen done at day 5 of illness shows extensive pancreatic as well as extra pancreatic necrosis; B) CT abdomen at 8th week of illness: well circumscribed large WOPN; C) EUS guided drainage of WOPN with multiple plastic stents. The collection is having ~50% solid necrotic content; D) CT after two sessions of endoscopic drainage: significant residual WOPN with multiple air specs and multiple plastic stents in situ.



Fig. 4. Longer time to resolution WOPN (blue) compared to WOEPN (green).

Protein digestion in AP is predominantly a nonliquefactive coagulative form of necrosis whereas fat necrosis is predominantly liquefactive which is easier to evacuate by drainage techniques compared to protein necrosis that tends to be more solid [18]. Therefore, protein is comparatively harder to degrade and is therefore more durable with less likelihood of undergoing liquefaction compared to digested fat. This hypothesis was confirmed by our observation of patients with WOPN having a higher proportion of solid necrotic content as compared to patients with WOEPN. This also probably explains the better drainage outcomes as well as the less frequent need of aggressive endoscopic drainage techniques such as the use

Fig. 5. 3-D Scatter plot depicting positive correlation between time to resolution, size and sold debris of WON.

of metal stents and DEN in WOEPN compared to WOPN in our study. Previously, we have reported that morphology of the pancreatic fluid collections determine the outcomes of endoscopic transmural drainage with collections having large size and more solid debris requiring more aggressive endoscopic therapeutic strategy for a successful outcome [19]. Newly developed cautery enhanced lumen-apposing metal stents (EC-LAMSs) such as Hot Axios stent, Boston Scientific, Natick, MA, USA and Hot-Spaxus (Taewoong Medical Co, Gimpo, Korea) have improved the results of endoscopic drainage of pancreatic fluid collections with high technical and clinical success [20]. A recent meta-analysis assessing the prognosis of EPN alone compared to combined necrosis found significantly lower risk of organ failure and infected necrosis along with a much lesser need for intervention and open necrosectomy amongst patients with EPN alone [21].

Pancreatic duct disruption is an important consequence of acute necrotizing pancreatitis and has been reported variably in 16-84% patients with acute necrotizing pancreatitis or WON [22, 23]. The duct disruption leading on to disconnected pancreatic duct syndrome has a significant negative impact on the outcomes of endoscopic transmural drainage of WON. Bang et al. [22] have demonstrated that disconnected pancreatic duct syndrome has a significant effect on endoscopic management of WON as patients having duct disruption required more frequently hybrid drainage techniques (combination of endoscopic transmural drainage with multiple transluminal gateway drainage technique, DEN and percutaneous drainage), reinterventions, and rescue surgery for successful outcomes as compared to patients without duct disruption. Since the pancreatic parenchyma is viable in patients with EPN alone, these patients do not have pancreatic duct disruption. This was confirmed in our study where none of the patients with WOEPN had duct disruption whereas 78.9% patients with WOPN had duct disruption. The absence of duct disruption in WOEPN could also explain better outcomes following endoscopic drainage.

Based on our findings it is therefore important to determine the extent of necrosis in the CECT of the abdomen done in the first week of illness and determine the extent of necrosis as predominantly pancreatic, extra-pancreatic or both. This could help in predicting the expected course as well as the management of subsequent developing collections. Pancreatic parenchymal necrosis does not readily liquefy posing challenges in performing effective drainage and minimally invasive necrosectomy. Therefore, collections resulting from PN i.e WOPN are expected to require wide diameter transmural stents with greater need for necrosectomy and increasing use of hybrid drainage modalities. Also, as the time to resolution of WOPN is longer, the expected length of hospitalization; costs of procedure; associated complications of drainage and disease morbidity are obviously expected to be higher in comparison to WOEPN.

To the best of our literature search, ours is the first study that has evaluated the difference in the outcome following endoscopic drainage of collections developing from pancreatic and extrapancreatic necrotizing pancreatitis. There are, however many limitations to the study. First and foremost, it is a retrospective study from a tertiary hospital and thus suffers from the inherent drawbacks of a retrospective study, including the selection bias. Also, there is unequal distribution of subjects in the comparison of the groups. This is expected, considering isolated EPN is a rare clinical entity compared to combined necrosis and moreover, only a fraction of patients with EPN will develop symptomatic fluid collections requiring drainage. The study was conducted in the unit with extensive experience in interventional EUS and pancreatic endotherapy and therefore the results may not be generalizable.

CONCLUSIONS

We have a described new entity of WOEPN that has a lesser proportion of solid necrotic content with better clinical

outcomes following endoscopic transmural drainage in comparison to WOPN. Prospective comparative studies with larger sample size are required to confirm these results as well as to determine the exact pathophysiology and clinical consequences of WOEPN.

Conflicts of interest: None to declare.

Authors' contributions: S.S.R. conceived and designed the study. S.S.R., N.B., M.K., R.G: collected the data. S.S.R. and N.B. interpreted the data and drafted the paper. S.S.R. critically evaluated the manuscript for intellectual content. All the authors approved the final version of the manuscript.

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