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The role of extra-pancreatic infections in the prediction of severity and local complications in acute pancreatitis☆

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ABSTRACT

Background: The aim of our study was to determine the risk factors for extrapancreatic infection (EPI) occurrence and its predictive power for assessing severity and local complications in acute pancreatitis including infected pancreatic necrosis (IPN).

Methods: Clinical data of 176 AP patients prospectively enrolled were analysed. EPI analysed were bacteraemia, lung infection, urinary tract infection and catheter line infection. Risk factors analysed were: Leukocyte count, C-reactive protein, liver function test, serum calcium, serum glucose, Blood urea nitrogen, mean arterial pressure at admission, total parenteral nutrition (TPN), enteral nutrition, hypotension, respiratory, cardiovascular and renal failure at admission, persistent systemic inflammatory response (SIRS) and intrapancreatic necrosis. Severity outcomes assessed were defined according to the Atlanta Criteria definition for acute pancreatitis. The predictive accuracy of EPI for morbidity and mortality was measured using area-under-the-curve (AUC) receiver-operating characteristics.

Results: Forty-four cases of EPI were found (25%). TPN (OR:9.2 CI95%: 3.3–25.7), APACHE-II>8 (OR:6.2 CI95%:2.48–15.54) and persistent SIRS (OR:2.9 CI95%: 1.1–7.8), were risk factors related with EPI. Bacteraemia, when compared with others EPI, showed the best accuracy in predicting significantly persistent organ failure (AUC:0.76, IC95%:0.64–0.88), ICU admission (AUC:0.80 IC95%:0.65–0.94), and death (AUC:0.73 CI95%:0.54–0.91); and for local complications including IPN (AUC:0.72 CI95%:0.53–0.92) as well. Besides, it was also needed for an interventional procedure against necrosis (AUC:0.74 IC95%: 0.57–0.91). When bacteraemia and IPN occurs, bacteraemia preceded infected necrosis in all cases. On multivariate analysis, risk factor for IPN were lung infection (OR:6.25 CI95%1.1-35.7 $p = 0.039$) and TPN (OR:22.0CI95%:2.4–205.8, $p = 0.007$), and for mortality were persistent SIRS at first week (OR: 22.9 CI95%: 2.6–203.7, $p = 0.005$) and Lung infection (OR: 9.7 CI95%: 1.7–53.8).

Conclusion: In our study, EPI, played a role in predicting the severity and local complications in acute pancreatitis.

1. Introduction

Severe acute pancreatitis is a complex disease, which involves a complex systemic inflammatory response in the acute phase of the disease as a consequence of the injury to the acinar cells, realising inflammatory mediators and products of the cell death, producing secondary damage to distant organs [1,2]. When necrotizing pancreatitis occurs, the rate of several complications is higher than 50%, including a 20%–40% chance of infections of the necrosis and a 50% chance of mortality [3–5]. In this scenario, extrapancreatic infections (EPI) are a frequent complication, bacteraemia, lung infection, urinary infection and catheter line related infections being the most frequent. We assumed that the co-existence of extrapancreatic infections will worsen the prognosis of the disease, regarding the impairment of a previous organ failure, increasing the risk of sepsis or even, developing a secondary infection of the necrosis. Previous reports confirm this hypothesis while others showed contradictory results [6,7].

The bacterial translocation from the gut is the most recognized

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way for infection of the pancreatic necrosis, and it's related with the disruption of the intestinal barrier in acute pancreatitis (AP) patients [8,9]. Haematogenous way is considered another source of secondary infection of the necrosis, but there are not extended reports regarding the clinical evidence; on the contrary, it has been reproduced successfully in the animal model [9]. Other less explored ways for secondary infections seem to be peripancreatic infections and interventional procedures against the necrosis or duodenum or bile duct system. Previous authors reported a higher incidence of lung infection and bacteraemia in patients with infected pancreatic necrosis, and it usually appeared before the diagnosis of infected pancreatic necrosis. It was also related with higher mortality and persisting organ failure in severe AP patients [6].

The aim of this study was to analyse the risk factors for developing extrapancreatic infections and its accuracy to predict the severity of AP and infection of pancreatic necrosis.

2. Methods

Clinical data of 176 AP patients prospectively enrolled for study at our institution, which is a third-level referral centre in our region, were analysed.

We included patients with AP according to the 2012 Atlanta definitions [10]; 1) typical abdominal irradiated pain, 2) serum amylase or lipase more than 3 times normal values and 3) Computed tomography (CT) contrast scan with radiological findings related with pancreatitis; when CT was not performed, Magnetic pancreatic resonance imaging (MRI) and abdominal ultrasound (US) with signs of pancreatitis were admitted. Definition for severity was based on Atlanta definitions, which are: mild disease, moderate-severe disease and severe disease, based on the presence of organ and multi-organ failure and local complications. We included transferred patients from other institutions.

Exclusion criteria were patients with chronic pancreatitis with more than 4 previous episodes, because these patients are more likely to have pancreatic changes in parenchyma related with chronicity, that could affect the course of the disease. (calcification and/or pancreatic duct abnormalities, or previous collections, pseudochyst, etc [11].

A CT scan was performed in 100 cases, a Cholangio-pancreatic MRI in 117, 41 patients performed both CT and MRI.

Definition for pancreatic necrosis was: non-enhancement in pancreatic tissue after CT-contrast or MRI cholangiography and also the presence of extrapancreatic fat necrosis. The CT-protocol for pancreatic evaluation consists in a retarded venous phase after 35 s of venous contrast administration. A CT scan was performed at least 24 h after the onset of abdominal pain, and preferably between 72-96 h. Local complications were defined according to the Atlanta classifications.

According to our institutional management protocol for AP; initially fluid-therapy was installed according to the patient characteristics with a goal of urinary output of more than 0.5 ml/kg/h, based on crystalloids and sodium physiologic solutions. Infected pancreatic (IPN) necrosis was defined by a positive culture after necrosectomy, either from surgical, radiological or endoscopic approach. No antibiotic prophylactic for pancreatic necrosis was used. In case of IPN, a minimally invasive step-up-approach was performed.

Acute Pancreatitis Severity and Clinical Parameters were established by the revised Atlanta Classification of Acute Pancreatitis in 2012: mild acute pancreatitis requires no organ failure or local or systemic complication, moderately severe acute pancreatitis requires an organ failure to be resolved within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure (POF). Finally, severe acute pancreatitis refers to persistent single or multiple organ failure (PMOF) (>48 h). Organ failure was defined as a score of 2 or more for one of three organ (renal, cardiovascular or respiratory) systems using the modified Marshall scoring system14. Local complications include peripancreatic fluid collections and acute necrotic collections, while systemic complications can be related to exacerbations of underlying co-morbidities.

Other severity parameters were collected during the patients' course of hospitalisation including length of hospital stay, in-hospital mortality, need for intensive care unit (ICU), presence and duration of organ failure (transient or persistent), infected (positive necrotic culture) or suspected infection of pancreatic necrosis (See definitions below) and invasive procedure needed (endoscopic, radiological or surgical). APACHE II (*American Society of Anesthesiologists classification)* and C-reactive protein (CRP) at admission were also measured. Sensitivity and specificity as well the Youden index were analysed for APACHE-II>8, CRP>15 and haemoconcentration regarding IPN, mortality and EPI.

Risk factors analysed were: APACHE-II>8 points, Leukocyte value at admission, haemaconcentration at admission adjusted by sex (Female>39.6 %and Male >43.0%) [12], CRP-protein >15 mg/dl at admission, liver function test at admission (total bilirubin, alanine aminotransferase, alanine aspartate transferase), serum calcium registered on first 72 h at admission, Glucose value at admission, Blood urea nitrogen (BUN) at admission, mean arterial pressure at admission, use of total parenteral nutrition (TPN), time between onset of abdominal pain and patient admission, use of enteral nutrition (EN), hypotension at admission, respiratory, cardiovascular, and renal failure at admission, persistent SIRS (more than 48 h) presented on first week of disease, grade of pancreatic necrosis according to Balthasar index (grade 0: 0% of necrosis, grade 1: less than 30%, grade 2: between 30% and 50%, grade 3; more than 50%). We also considered the presence of extrapancreatic necrosis for the analysis of infected cases, due to in some cases patients presented only extrapancreatic necrosis and also experienced infection.

Extrapancreatic infections analysed were: bacteriemia, lung infection, urinary tract infection and catheter line infection. Definitions for extrapancreatic infections were made when a positive culture for bacteria or yeast was detected; in the case of lung infection, a positive culture of tracheal aspirate was needed. In cases of bacteraemia with positive culture for coagulase negative staphylococci, it was considered positive only if the second culture was positive as well. Antibiotic therapy, starting day and the reason were registered in all cases.

Triggers to look for extra-pancreatic infections were fever, a rise in CRP or leukocytes, new OF or MOF, or worsening previous OF or MOF, clinical deterioration, pathological bronchial secretions or abnormal findings on chest thorax, erythema or signs of infections at catheter insertion site.

For suspected IPN; after 4 weeks we usually suspect the presence of IPN. The criteria for suspected infected necrosis are persistent sepsis without extrapancreatic origin despite negative FNP; patients with pancreatic necrosis with gas who presented clinical decompensation due to multiorgan failure (MOF) that did not respond to intensive medical support at ICU, irrespective of the FNP result. This usually happens after the first 2 weeks since the [Better: onset] debut of “acute pancreatitis,” according to the natural history of the disease. For the [better: diagnosis] diagnostic of IPN, it is necessary to obtain a definitive positive culture, otherwise this is called a “sterile” necrosis.

When suspected necrosis was done at early stages of the disease (less than 4 weeks), we follow the principles of “*delay and debride*” by giving a broad spectrum of antibiotics and performing

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