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RESEARCH

Clinico-Pathological Particularities of the Shock-Related Pancreatitis

Judit Kovacs · Simona Gurzu · Janos Jung · Janos Szederjesi · Sanda-Maria Copotoiu · Ruxandra Copotoiu · Leonard Azamfirei

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Abstract Acute pancreatitis can develop in patients with shock due to the underlying diseases, surgical interventions or because of severe hypoperfusion. The aim of our work was to study the histological alterations of the pancreas in patients dying after cardiogenic, hypovolemic or septic shock, to demonstrate the presence and severity of pancreatic injury. We performed a retrospective study which included patients who died and who were autopsied after different types of shock, hospitalized between 2007–2009 in general and cardiac intensive care units. We excluded the patients with known pancreatic diseases. From 223 patients included in our study 39 presented necrotising hemorrhagic alteration of the pancreatic tissue. There were no differences in histological and immunohistochemical findings between the different etiopathogenetic types of shock. None of the patients had characteristic clinical signs for acute pancreatitis. The digestive symptoms, they presented, could be related to the underlying disease or to postoperative state. The common findings in these patients were prolonged and severe hypotension, associated renal dysfunction, leucocytosis, hyperglycemia and hypocalcemia. Pancreatitis can occur in patients with shock, due to prolonged hypoperfusion of the pancreas. It is difficult to diagnose it because clinical signs are altered due to severity of underlying disease or analgo-sedation commonly used in intensive care. We therefore recommend in patients with shock to consider the possible development of ischemic pancreatitis for prompt and efficient treatment.

Keywords Acute pancreatitis · Analgo-sedation · Hyperglycemia · Hypocalcemia · Severe hypotension

J. Kovacs · J. Szederjesi · S.-M. Copotoiu · R. Copotoiu · L. Azamfirei
Department of Anesthesia and Intensive Care, University of Medicine and Pharmacy Tg-Mureş, Targu-Mureş, Romania

S. Gurzu · J. Jung
Department of Pathology, University of Medicine and Pharmacy Tg-Mureş, Targu-Mureş, Romania

J. Szederjesi · S.-M. Copotoiu · R. Copotoiu · L. Azamfirei
Anesthesia and Intensive Care Unit, University Emergency County Hospital Tg-Mures, Targu-Mureş, Romania

S. Gurzu (✉)
540193 Gheorghe Marinescu 38, Targu-Mureş, Romania
e-mail: simonagurzu@yahoo.com

Introduction

The commonest causes of acute pancreatitis are mechanical obstruction and alcohol misuse, but in shock severe hypoperfusion may also lead to ischemia-related pancreatitis. Several authors demonstrated the existence of severe pancreatic injuries in patients who had experienced prolonged hypotension [1–3].

The acute pancreatitis is an inflammatory condition of the pancreas, with characteristic clinical and laboratory signs (epigastric and back pain, nausea, vomiting, elevated pancreatic enzymes in the serum), but these symptoms are often hidden in the intensive care patients due to analgo-sedation or mechanical ventilation, therefore the diagnosis could be difficult.

The aim of our work was to study the histological particularities of the pancreas in patients who died after cardiogenic, septic or hypovolemic shock, to demonstrate the type and severity of pancreatic injury. We analysed the clinical

and laboratory findings in these patients and the main risk factors, in order to elaborate a protocol for early diagnosis of acute pancreatitis in shock states.

Material and Methods

We performed a retrospective study which included 223 patients (140 men, 83 women, median age 45,2±27,3 years) who died after cardiogenic, hypovolemic or septic shock, hospitalized in general and cardiac intensive care units between 2007–2009. The patients with known pancreatic diseases were excluded.

To avoid confusion with postmortem autolysis of pancreas, in all studied cases, the time between dead and autopsy was about 12–15 h. In necroptic tissues, we studied the morphological changes of pancreas, and in those with pancreatic injury we performed histological and immunohistochemical examinations to determine the severity of injuries. The collected specimens were stained with hematoxylin-eosin and for immunohistochemical examination we used the following antibodies: VEGF-A (Vascular Endothelial Growth Factor-A), clone VG1 (LabVision) and HSP-70 (Heat Shock Protein-70), clone 8B11 (Novocastra). For immunohistochemical stains EnVision system from LabVision was used in formalin-fixed, paraffin-embedded tissues. Sections were deparaffinated and were incubated at 100°C in EDTA, pH 9. The primary antibodies were applied for 60 min and Streptavidine Peroxidase solution for other 5 min. The development was performed with substrate-chromogen solution (DAB). Te nuclei were coloured with Mayer's Hematoxylin.

In patients with pancreas injury we reviewed the hospital records in order to assess the clinical data and biochemistry.

Results

From 223 patients included in our study, 105 (47.1 %) died in severe sepsis or septic shock, 91 (40.8 %) after cardiogenic shock and 27 (12.1 %) after hemorrhagic shock. In 39 cases on macroscopical and examination we observed steatonecrosis and acute hemorrhagic pancreatic necrosis (Fig. 1).

The mean age of patients with acute pancreatitis was 57.2± 15.7 years (ranging from 1.7 to 78 years). Most of them were men (26–66.7 %), only 13 being women (33.3 %). 19 patients (48.7 %) had severe sepsis or septic shock, 11 patients (28.2 %) cardiogenic and in 9 patients shock was caused by severe blood loss.

Histological Data

From 223 patients, 39 (17.5 %) presented morphological signs of pancreatic injury. We should mentioned that in all cases, the diagnosis of acute pancreatitis was made postmortem. No clinical symptoms or characteristic laboratory data were observed during lifetime.

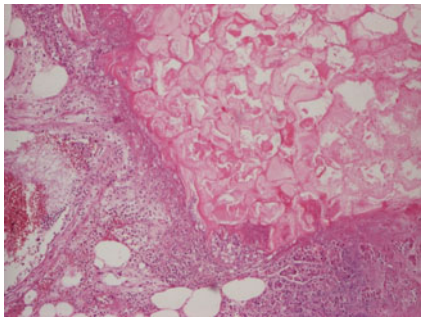

Fig. 1 Acute pancreatitis with steatonecrosis after hemorrhagic shock in a 54 year old man (H&E, ob. x4)

On histological examinations in the pancreatic tissue cell necrosis surrounded by inflammatory cells, steatonecrosis and hemorrhage was almost always found in all 39 cases, independently of the ethiopathogenetic type of shock (Figs. 1 and 2).

The immunohistochemical examinations revealed a strong intracytoplasmatic expression of both VEGF-A and HSP-70 in the perinecrotic areas (Figs. 3 and 4). No differences were observed between the antibody intensity and the ethiopathogenetic type of shock, the grade of histological severity or other clinico-pathological data.

Clinical and Paraclinical Data

None of the patients was diagnosed with acute pancreatitis during life, due to lack of the characteristic clinical signs: epigastrial pain, nausea, vomiting. Some of the patients had nonspecific gastro-intestinal symptoms, but these could be related to the underlying disease or to usual postoperative complaints (Table 1). 17 patients had fever above 38°C.

Laboratory results wich usually can be altered in acute pancreatitis, found in patients records are presented in Table 2. Because acute pancreatitis wasn't suspected in most of the cases, the specific biochemical parameters were not

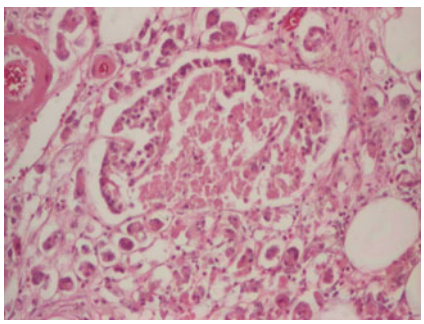

Fig. 2 Necrosis and acute pancreatitis with disruption of vessel wall in a 61 year old male patient with hemorrhagic shock (H&E, ob. x4)

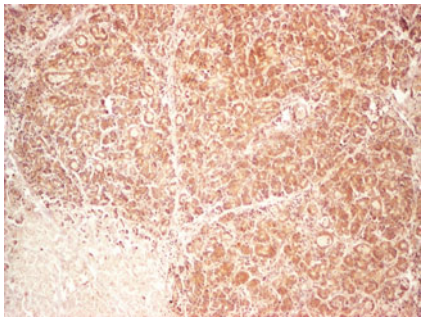

Fig. 3 Strong expression of VEGF-A in pancreas, around the steato-necrotic area, in a 1,7 year old femele with cardiogenic shock (ob.x 4)

analysed. Serum amylase was determined in only 17 patients, and showed only mild elevation.

In one patient we found undiagnosed acute calculous cholecystitis and in hospital records in two patients chronic alcohol abuse was mentioned. In 21 patients with acute pancreatitis major surgical interventions were performed: open heart surgery (n=6), reconstruction of thoracic (n=4) or abdominal aortic aneurysm (n=1), abdominal surgery (esophagectomy:3, splenectomy:3, gastrectomy:4).

Multiple organ and system dysfunction was present in all cases with acute pancreatitis, the most implicated organs being the kidney and the lung. In 19 patients inotropic and vasoactive drugs (epinephrine and norepinephrine) were given for hemodynamic stabilisation.

The mean time of hospitalisation in intensive care unit was 9.5±7.7 days (2–30 days). No relationsheep between the time of hospitalisation and risk of pancreatitis was observed.

Discussion

Inflammation and necrosis of pancreas parenchyma, focal necrosis of pancreatic fat and vessel wall necrosis with thrombosis and hemorrhage are characteristic morphological signs of acute hemorrhagic pancreatic necrosis. These histological changes were present in 39 patients who died

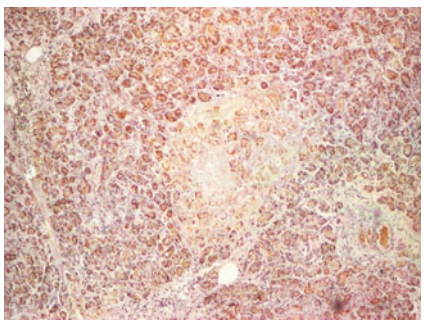

Fig. 4 Strong HSP-70 expression in pancreas, in the perinecrotic area, in a 65 year old femele in septic shock (ob.x 10)

Table 1 Gastrointestinal symptoms in patients with acute pancreatitis

Digestive symptoms	Nr. of patients
Nausea, vomiting	12
Ileus	12
Upper abdominal bleeding (erosive gastritis on gastroscopy)	10
Diffuse abdominal pain	9
Diarrhea	3

after a state of shock, even in the absence of characteristic clinical and laboratory signs of acute pancreatitis. In some cases we also found extensive fat necrosis, suggesting an increased activation of lipolytic enzymes: lipase and phospholipase A_2.

Some authors suggested that vascular changes might be responsible for pancreatic necrosis [4], but there are other studies which either proved that thrombosing vasculitis could be a secondary phenomenon in acute pancreatitis [5], or no differences exists between cases with more or less than 50 % of parenchymal necrosis and vascular injury [6]. Intrapancreatic vascular injury, together with systemic hypoperfusion in shock could be important cofactors in the extension of pancreatic necrosis, because the pancreas is vulnerable to hypoxia [7]. At the same time, the vascular damage seems to be correlated with the postoperative clinical course in patients with acute pancreatitis, so it could be a sign of severity of the disease [6]. Whatever, it seems that there are no correlation between histology and ethiopathogenetic types of shock.

VEGF-A acts on the endothelial cells and has various effects: increases vascular permeability, stimulates angiogenesis, vasculogenesis and endothelial cell growth, promots cell migration, and inhibits apoptosis. In patients with shock-related pancreatitis there are strong expression of VEGF-A in pancreas, around the necrotic areas. This could suggest the initiation of angiogenesis and pancreatic regeneration [8, 9]. At the same time, in this lesions VEGF-A function not as a vascular permeability factor, but as a protective factor through its anti-apoptotic effect against organ injuries [10].

Table 2 Laboratory findings in patients with acute pancreatitis

Laboratory findings	Nr. of patients	Mean values	Range
Serum amylase (U/L)	17	160±39	89–258
Glicemia (mg/dL)	39	243.3±61.3	151–438
Nr. leucocytes (/mm^3)	38	18,842±6,988	1,800–48,200
Ionized calcium (mg/dL)	36	0.99±0.12	0.8–1.2

HSP-70 is a stress-induced protein. High levels can be produced by cells in response to hyperthermia, oxidative stress, and changes in pH [11]. Recent studies reveal that HSP70 induction protects against pancreatitis by preventing intrapancreatic activation of trypsinogen and confering a protective effect for the remaining acini [12, 13].

The typical symptoms, which characterize acute pancreatitis seem to be unusual in pancreatic injury developed after shock or major surgical interventions. In these cases acute pancreatitis tends to have only subtle findings and a bland clinical course, until severe complications such as infection or necrosis develops [14]. In our study, diffuse abdominal pain was registered in 9 patients, but this pain wasn't typical for pancreatic injury, and the band-like radiation to the back was also missing.

Fifteen patients received continuous analgo-sedation with midazolam and morphine and 3 with midazolam and fentanyl. The daily interruption of sedation was never long enough to allow the reccurence of the pain. Moreover, the morphine administred, could potentially worsen the pancreatic injury because it can cause spasm of the sphincter of Oddi [15].

Serum amylase showed no or only a mild elevation in our study. Serum amylase can be higher in many other conditions, like intestinal diseases, trauma, major surgery, renal failure. In lactic acidosis (present in all patients with shock) or after mild injury of the salivary glands, especially after transesophageal echocardiography (used in all 11 patients with cardiac surgery and thoracic aortic reconstruction), hyperamylasemia can be due to elevation of salivary isoamylase [16]. On the other hand, its measurement has some limits: in acute pancreatitis serum amylase rises within 6–12 h after the onset and is rapidly cleared from the blood, therefore if it is not verified in the first day after the onset of pancreatic injury, the serum amylase level could be normal, even in the presence of acute pancreatitis. The specificity and sensitivity of lipase measurements are better than those of amylase measurement, but are not rutinely used in our settings [17].

Serum Ca concentration falls early because of Ca "soaps" formation, secondary to excess generation of free fatty acids, especially by pancreatic lipase [18]. Pancreatic B-cell injury may lead to hyperglycemia. These laboratory findings were present in all patients who developed necrotizing pancreatitis.

A CT-scan or MRI examination could be useful to demonstrate the presence of pancreatic injury but because our patients were in severe condition, and the suspicion of acute pancreatitis wasn't confirmed by clinical and laboratory data, we didn't performed them.

In all patients severe hypotension and low cardiac output syndrome were common. In these patients vasoconstrictor drugs were given to maintain blood pressure. Severe hypotension can cause splanchnic hypoperfusion, but in combinaton with the use of vasoconstrictors, can have a detrimental effect [19].

Acute pancreatitis can develop after major surgery. After cardiac surgery it appears with a 0.4 % frequency [20], and it is attributed to splanchnic hypoperfusion due to low perfusion pressure during prolonged cardiopulmonary bypass, low cardiac output, use of vasoconstrictor agents [19, 21]. The inflammatory mediators, released during extracorporeal circulation induce pancreas hypoperfusion, altering the vasomotor tone in the mesenteric circulation [14]. Alteration of mesenteric circulation can be the cause of pancreas injury in acute thoracic or abdominal aortic dissections. Acute pancreatitic can develop after major abdominal surgery with an incidence of 0.5-9.5 %, the suggested etiological factors could be: peroperative manipulation of pancreas, release of inflammatory mediators caused by extensive tissue injury or subsequent bacterial injury [22, 23].

Conclusions

Acute necrotizing pancreatitis can occur in patients with shock, and seems to be a major factor which alter the prognosis. Because clinical signs are altered due to severity of underlying disease, clinical diagnosis is very difficult. On the other hand analgo-sedation commonly used in intensive care may alleviate the symptoms.

Independently of the etiopathogenetic type of shock, VEGF-A and HSP-70 may act as protective factors against acini damage. Further studies are necessary to prove if serum level of the VEGF-A should be a predictive factor in these cases and may indicate the severity of cases.

Acute pancreatitis may range from a mild to a life-threatening condition. Establishing a rapid diagnosis through laboratory testing and radiologic studies is very important. Even with aggressive and appropriate care, acute necrotizing pancreatitis has a high mortality rate. We therefore recommend in patients with shock with associated leucocytosis, hyperglycemia and hypocalcemia (which were the most common findings in our patients) to consider the possible development of pancreatitis for prompt diagnosis and efficient treatment.

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