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Original Research Article

Increased expression of the intercellular adhesion molecule-1 (ICAM-1) on peripheral blood neutrophils in acute pancreatitis

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ABSTRACT

Purpose: Considering the important role of neutrophils' activation in the pathogenesis of acute pancreatitis (AP), the aim of our study was to evaluate the expression of leukocytes' adhesion molecules in patients with AP.

Patients/methods: Thirty-five patients (16 women and 19 men; age 32–77 years, median 56 years) with AP were prospectively included into our study. The absolute number of leukocytes was estimated by haematologic analyser. Surface neutrophils antigens (CD) were assayed by the direct fluorescence method for whole blood, using a flow cytometer.

Results: At the day 1, significant increase of ICAM-1 expression was found in patients with severe AP (S-AP) (7280 mm^{-3} vs 2850 mm^{-3} in healthy control; $p < 0.05$). In the days 2, 3 and 5 it sharply decreased and peaked again to 4860 mm^{-3} at the day 10. In patients with mild AP (M-AP), not significant elevation of ICAM-1 quickly returned to normal level. In both forms of AP, neutrophil CD62L (L-selectin) expression reached the highest level at the day 1 (8800 mm^{-3} and 9020 mm^{-3}, respectively in M-AP and S-AP, in comparison to 3400 mm^{-3} in control; $p < 0.05$). Expression of CD69 (neutrophils' marker of early activation) significantly increased in both M-AP and S-AP.

Conclusions: We have found an early and significant increase of peripheral blood neutrophil CD54/ICAM-1 expression, specific for S-AP but not for M-AP. It may provide a good marker predicting severe course of pancreatitis.

1. Introduction

Excessive leukocyte activation with cytokinemia represents one of the most important mechanisms leading to increased mortality in early acute pancreatitis (AP). It has been hypothesized that fatal pancreatitis is a consequence of excessive leukocytic phagocytes stimulation provoked by severe trauma or persistent injury due to an agent noxious to the pancreas [1]. Leukocyte accumulation from circulating blood to the site of inflammation includes multiple steps involving different kind of adhesion molecules. The molecules involved in this reaction come from the selectin (E-, P- and L-selectins) and superimmunoglobulin family, such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Both E-selectin and ICAM-1 are known to be necessary for transendothelial migration of neutrophils [2].

It has been suggested that leukocytes play an important role in the pathogenesis of complicated pancreatitis. Indeed, increased plasma concentrations of neutrophil elastase as a marker of neutrophil activation could be detected in patients with a severe course of the disease [3–5]. There are many reports indicating that activation of not only leukocytes but also endothelial cells takes place early in the course of AP, leading to massive release of cytokines, reactive oxygen species (ROS) generation and adhesive molecules activation. These mediators are being considered as major elements responsible for transformation of local inflammatory response within the pancreas into systemic inflammatory response syndrome (SIRS) which overwhelms compensatory anti-inflammatory response syndrome (CARS) and eventually leads to multiorgan failure (MOF) [6–8].

Previous studies have suggested that AP is frequently associated with sequestration of inflammatory cells, particularly neutrophils, within pancreas, and it is generally believed to be an early and important event in the evolution of pancreatitis [9].

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Table 1
Clinical characterization of studied patients with mild and severe pancreatitis.

	M-AP $n=20$	S-AP $n=15$	p value M-AP vs S-AP (Mann–Whitney U test)
Predisposing etiology factors			
Biliary	9 (45.0%)	9 (60.0%)	
Alcohol	10 (50.0%)	6 (40.0%)	
Idiopathic	1 (5.0%)	0 (0%)	
Ranson's score, median (range)	1 (0–2)	4 (2–8)	$p<0.01$
Balthazar's score			
A	6 (30.0%)	0	
B	14 (70.0%)	0	
C	0	2 (13.3%)	
D	0	5 (33.3%)	
E	0	8 (53.3%)	
CRP (mg/L), median (range)			
Day 1	22.9 (5.0–139.0)	216.0 (5.0–466.1)	$p<0.01$
Day 2	50.5 (5.2–135.4)	186.2 (43.1–342.0)	$p<0.01$
Day 3	34.6 (3.0–223.9)	195.0 (126.5–370.2)	$p<0.01$
APACHE II score, median (range)			
Day 1	4 (1–8)	5 (1–14)	n.s.
Day 2	3.5 (0–8)	5 (0–13)	n.s.
Day 3	3 (0–6)	4 (0–12)	n.s.
MOD score, median (range)			
Day 1	1.5 (0–3)	3 (0–7)	$p<0.01$
Day 2	1 (0–3)	2 (0–5)	n.s.
Day 3	1 (0–4)	2 (0–4)	n.s.

The aim of our study was to evaluate parameters of peripheral neutrophils activation, focused on the expression of adhesion molecules, in patients with AP.

2. Patients and methods

2.1. Clinical evaluation

Thirty-five patients (16 women and 19 men; age 32–77 years, median 56 years) with AP were prospectively included into our study. In all patients, the time between the abdominal pain onset and admission to the hospital was not longer than 48 h. The control group comprised of 15 healthy volunteers (7 women and 8 men; age 19–77 years, median 41 years) without the history of recent inflammatory disease. The diagnosis was made on the basis of a history consistent with AP and serum amylase activity >3 times the upper limit of normal (20–90 U/L). In all patients, additional biochemical and imaging (ultrasound and computed tomography) tests were carried out to confirm the diagnosis as well as to determine the predisposing etiological factors (18 patients presented with biliary pancreatitis, 16 with alcoholic pancreatitis and 1 with idiopathic pancreatitis) (Table 1). AP severity was defined according to Ranson's criteria [10], Balthazar's criteria [11] and serum C-reactive protein (CRP) concentration measurements.

Twelve patients met the Atlanta criteria [12] of severe AP (S-AP), with grade C, D, or E in dynamic intravenous contrast-enhanced computed tomography of the abdomen [11], serum CRP concentrations ≥150 mg/L within the first 3 days, 3 or more of the Ranson's criteria and local or/and systemic complications. One patient, who had low levels of serum CRP on days 1 and 2 (8.3 mg/L and 43.1 mg/L, respectively), however, was finally classified as S-AP because of high serum CRP concentration at the day 3 (195.0 mg/L), pulmonary complications, grade E in Balthazar's criteria and 3 positive Ranson's criteria. Another patient in S-AP group had low serum CRP at the day 1 (5.0 mg/L), but showed high CRP levels at days 2 and 3 (186.2 mg/L and 193.6 mg/L, respectively), and additionally – pancreatic necrosis (more than 30%), pulmonary complications, grade E in Balthazar's criteria and 4 positive Ranson's criteria. The third patient with only two positive Ranson's criteria was qualified to the S-AP group because of high CRP concentration, specifically 294.0 ml/L at the admission and grade C according to Balthazar's criteria, with intrapancreatic necrosis. On the contrary, in the mild AP (M-AP) group we included one patient with high serum CRP level at the day 3 (223.9 mg/L), but with the grade B according to Balthazar's criteria and only one positive Ranson's criterion.

APACHE II (*Acute Physiology And Chronic Health Evaluation*) [13] score was calculated in order to assess the severity of illness. Physiologic dysfunction in organ systems was defined by multiple organ dysfunction score (MODs) [8]. Local and systemic complications are shown in Table 2. Pulmonary complications which were diagnosed in 12 patients, included 8 patients with pulmonary insufficiency ($PaO2 \leq 60$ mm Hg), 10 patients with pleural effusions, 9 patients with interstitial pneumonia, and 5 patients with atelectasis (Table 3).

Two patients with S-AP have died during the course of hospitalization.

Table 2
Complications among patients with severe pancreatitis.

Complications of S-AP	S-AP, $n=15$ n (%)
Local complications	
Acute fluid collections	4 (26.7%)
Pancreatic necrosis	14 (93.3%)
Pancreatic abscess	2 (13.3%)
Systemic complications	
Pulmonary	12 (80.0%)
Shock	2 (13.3%)
Renal failure	5 (33.3%)
Coagulation disorders	4 (26.7%)
Encephalopathy	2 (13.3%)
Multiple organ failure	2 (13.3%)