ORIGINAL ARTICLE

CONTENTS

Pathomorphological features of systemic manifestations of severe acute pancreatitis complicated by abdominal compartment syndrome

Olexii I. Dronov[1], Inna O. Kovalska[1], Ivanna A. Shchyhel[1], Tetiana P. Shevchyk[2], Vitaliy R. Balyak [1], Vadym O. Kostiukevich[1]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

[2]KYIV CITY CLINICAL HOSPITAL №10, KYIV, UKRAINE

ABSTRACT

Aim: To classify systemic pathomorphologic changes in severe acute pancreatitis (SAP) and to identify histologic features associated with abdominal compartment syndrome (ACS).

Materials and Methods: The retrospective cohort examination of 53 patients with SAP, who died due to progressive organ failure. Microscopic specimens of the heart, lungs, liver, kidneys and intestines have been reviewed, divided by the proposed four levels of pathological changes and comparable between the two groups, depending on the presence of ACS (25 and 28 patients).

Results: When comparing in two groups the levels of lesions of each studied organ, according to given levels of change, a statistically significant difference between groups in the level of kidney and intestine lesions ($P < 0.05$, Mann-Whitney U-Test) was obtained. The changes in moderate and severe levels were significantly dominating in the microscopic specimens of the kidneys and intestines of group A compared to group B ($p < 0.001$).

Conclusions: Histopathological changes in the examined organs of patients who died from severe acute pancreatitis complicated by abdominal compartment syndrome were characterized by more pronounced ischemic and inflammatory damage in the kidneys and intestines. The variability of extrapancreatic pathological changes in SAP patients depended on intra-abdominal pressure levels. Monitoring and timely correction of intra-abdominal hypertension aimed at preventing ACS in SAP patients may influence disease progression and treatment outcomes.

KEY WORDS: Severe acute pancreatitis, Abdominal Compartment-Syndrome, Pathology

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INTRODUCTION

Acute pancreatitis (AP) is one of the most common emergency diseases of the gastrointestinal tract [1-3]. Approximately 10-30% of patients develop severe acute pancreatitis (SAP) characterized by persistent organ failure and pancreatic necrosis [4-5]. The mortality rate in SAP reaches 50%, which is almost ten times higher than the mortality rate from other forms of AP [5].

Intra-abdominal hypertension (IAH) complicates the course of AP in 50-60% and in 15-30% progresses to abdominal compartment syndrome (ACS), which is characterized by an increase in intra-abdominal pressure (IAP) above 20 mm Hg and a decrease in abdominal perfusion pressure of less than 60 mm Hg [6,7]. The consequence of a critical increase in IAP is intra- and extra-abdominal organ perfusion disorders, which, in turn, lead to a new "wave" of organ failure (OF) and increase mortality by up to 83% [7]. Consequently, ACS is considered a marker of adverse treatment outcomes in patients with AP, which requires constant monitoring of IAP, timely recognition and correction of IAH [7-9].

Multiorgan failure inherent in SAP is characterized by clinical variability and pathomorphologic polymorphism, and in patients with SAP complicated by ACS may have characteristic manifestations.

AIM

To classify systemic pathomorphologic changes in severe acute pancreatitis and to identify histologic features associated with abdominal compartment syndrome.

MATERIALS AND METHODS

A retrospective single-center cohort study was conducted at the Bogomolets National Medical University

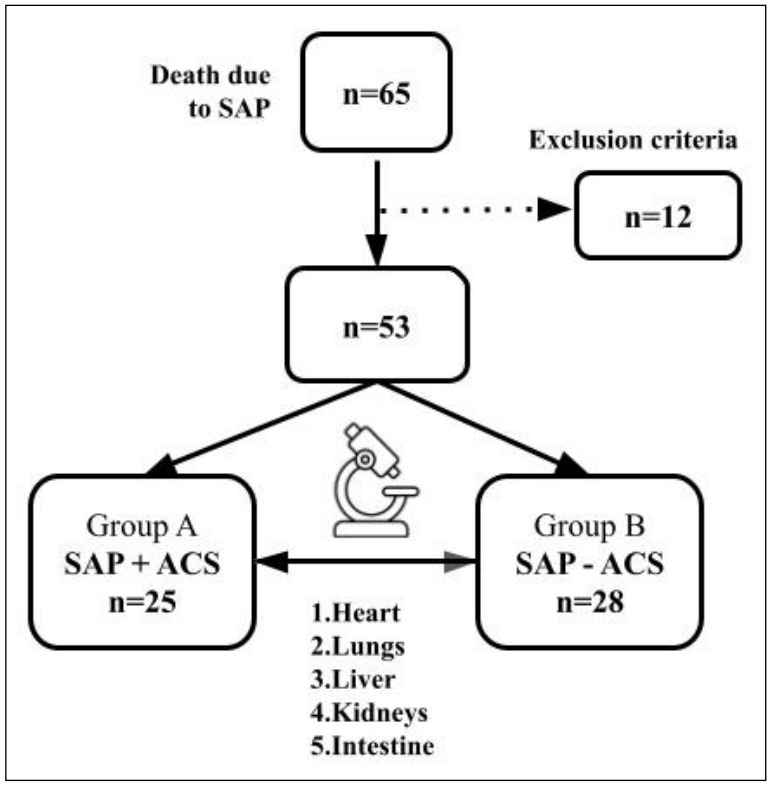

Fig. 1. Flowchart of the study design.

Department of General Surgery No. 1 in the Kyiv City Clinical Hospital No. 10. In the course of the given study 65 cases of patients with the main diagnosis of severe acute pancreatitis (K-85) were selected, who died in the early phase of the disease (up to 14 days from the onset of complaints) due to progressive multiorgan failure in the period 2017-2023. The diagnosis and severity of acute pancreatitis (AP) in patients were determined according to the criteria of the 2012 revised Atlanta classification [10].

All patients underwent autopsy in the pathology department, followed by pathologists' description of the microscopic changes in the selected sectional material. The obtained descriptions of the organs were stratified into four levels of pathological changes.

Out of 65 case histories, 12 patients were excluded, resulting in 53 patients included in the study groups. Criteria for exclusion from the study were the following:

- patients without an autopsy due to the recorded refusal of relatives/legal representatives to perform an autopsy (N=5);
- patients with significant chronic pathology that distorted the morphologic assessment (liver cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, significant cardiosclerosis, etc.) (N=7).

The study included 33 (62%) men and 20 (38%) women, with a mean age of 55 ± 14.5 years. The median (QI - QIII) Charlson comorbidity index was 3 (2-5) points. The median (QI - QIII) time from onset to hospitalization was 8 (7-12) hours. The median (QI - QIII) length of stay in hospital was 10 (8-12) bed days, i.e. the period from the moment of hospitalization to the moment of death. Of 53 patients included, 19 were diagnosed with AP of alcoholic origin (36%), 14 (26%) with biliary pancreatitis, 10 (19%) with hypertriglyceridemic pancreatitis, 3 (6%) with postoperative pancreatitis, and 7 (13%) with idiopathic acute pancreatitis.

The average BMI was 31.8±4.2 kg/m^2. Comorbidities were mainly represented by cardiovascular disease and chronic liver disease, whereas arterial hypertension was observed in 41 (77%), steatohepatosis in 39 patients (73.5%). Obesity was also common in the cohort - 34 (64.2%) cases. Diabetes mellitus was observed in 8 (15%) patients. The median (QI - QIII) length of hospital stay (duration of CAP from hospitalization to patient death) was 10 (8-12) days.

The selected patients included to the study were divided into two groups:

Group A: severe acute pancreatitis complicated by abdominal compartment syndrome (n = 25); Group B: severe acute pancreatitis not complicated by abdominal compartment syndrome (n = 28).

The study design, represented in the form of a flowchart, is shown in Fig. 1.

The level of IAP in patients was recorded in each group in the medical records every 8-12 hours of ob-

Table 1. Comparative characteristics of clinical and epidemiologic data of patients in group A (SAP+ACS) and group B (SAP - ACS)

Parameters		Group indicators		P
		ACS "+" (A)	ACS "-" (B)	
Age, years,X ± SD		53,7 ± 12,8	56,5 ±15,9	0,47[a]
Gender, n (%)	Men	18 (72)	15 (54)	0,25[b]
	Women	7 (28)	13 (46)	
BMI, kg/m2,X ± SD		32,2 ± 4,3	31,4 ± 4,1	0,51[a]
Comorbidity index, points, Me (Q_I - $Q_{(III)}$))		3 (3 - 5)	4 (3 - 5)	0,6[c]
Etiology, n (%)	Alcoholic	8	11	0,89[b]
	Biliary	8	6	
	GTG-associated	5	5	
	Postoperative	1	2	
	Idiopathic	3	4	
Time to hospitalization, hours, Me (Q_I - $Q_{(III)}$))		8 (7 - 12)	8 (6 - 12)	0,67[c]
Length of inpatient stay, bed days, Me (Q_I - $Q_{(III)}$))		9 (8 - 11)	11 (8,75 - 12.25)	0,015[c]

a - Student's t-test
b - Fisher's exact test
c - Mann-Whitney U test.

Table 2. Comparison of the levels of organ damage between groups 1 and 2 (Mann-Whitney U-test)

Body	Level of change	Group A, n (%)	Group B, n (%)	p-value
Heart	Absent	4 (16%)	6 (22%)	0,48
	Mild	16 (64%)	18 (64%)	
	Moderate	4 (16%)	4 (14%)	
	Expressed	1 (4%)	0	
Lungs	Absent	0	0	0.14
	Mild	10 (40%)	6 (22%)	
	Moderate	13 (52%)	18 (64%)	
	Expressed	2 (8%)	4 (14%)	
Liver	Absent	0	2 (7%)	0,09
	Mild	7 (28%)	12 (43%)	
	Moderate	17 (68%)	13 (46%)	
	Expressed	1 (4%)	1 (4%)	
Kidneys	Absent	0	1 (4%)	<0,001
	Mild	0	8 (28%)	
	Moderate	11 (44%)	18 (64%)	
	Expressed	14 (56%)	1 (4%)	
Intestines	Absent	0	9 (32%)	<0,001
	Mild	3 (12%)	17 (61%)	
	Moderate	16 (64%)	2 (7%)	
	Expressed	6 (24%)	0	

Note: All results were considered statistically significant at $p < 0.05$

servation. The classical indirect method was used to measure intra-abdominal pressure [11]. Group A (SAP, complicated by ACS) included patients with a recorded IAP level above 20 mmHg.

The study used archival data on the results of sectional examinations of the given patients, and the autopsy was performed at the Pathological and Anatomical Department of the Kyiv City Clinical Hospital No. 10. Sectional material was collected no later than 6 hours after the death of the patients. Pathological changes were assessed under a light microscope after hematoxylin-eosin staining.

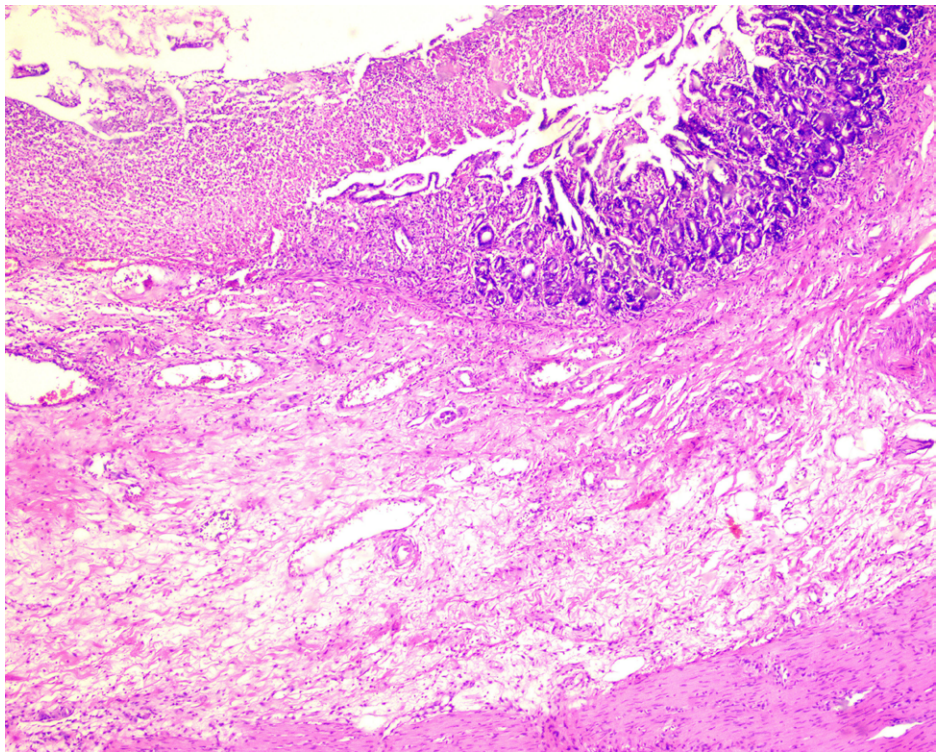

Fig. 2. Small intestine microscopic specimen with moderate changes. Small intestine wall with focal necrosis of the mucosa and leukocyte infiltration. Explicit submucosal edema with venous fullness. Magnification: 4x10, hematoxylin-eosin stain.

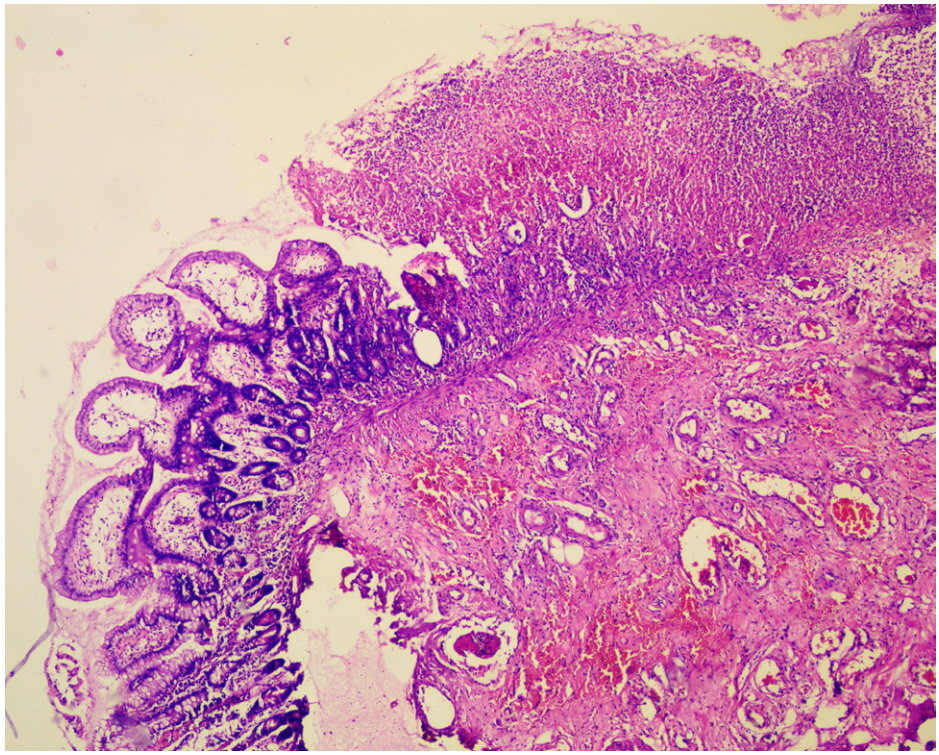

Fig. 3. Small intestine microscopic specimen with moderate changes. The wall of the small intestine with severe edema and mild leukocyte infiltration of the villi stroma, venous hemorrhage of the submucosal layer, and an acute ulcer with inflammatory infiltration of necrotic masses. Magnification: 10x10, hematoxylin-eosin stain.

In case with the morphological study, tissue pieces were fixed in a 10% solution of neutral formalin, subjected to standard paraffin wiring through alcohols of increasing concentration (70%, 80%, 96% (1), 96% (2) alcohol), xylene 1, xylene 2, "porridge" (xylene + paraffin 50/50) 1, "porridge" 2 (xylene + paraffin 50/50), paraffin 1, paraffin 2, and then embedded in paraffin. Serial sections of 4-5 mm thickness were made from the blocks prepared in that particular way.

The endpoints of the study were pathomorphologic microscopic changes in the heart, lungs, kidneys, liver, and intestines. Records of the examination of named organs were selected for the study from the documented autopsy data and microscopic evaluation, where the severity of edema, inflammation, ischemia, and necrosis was assessed. To assess objectively and compare morphologic changes in organs in patients of the two

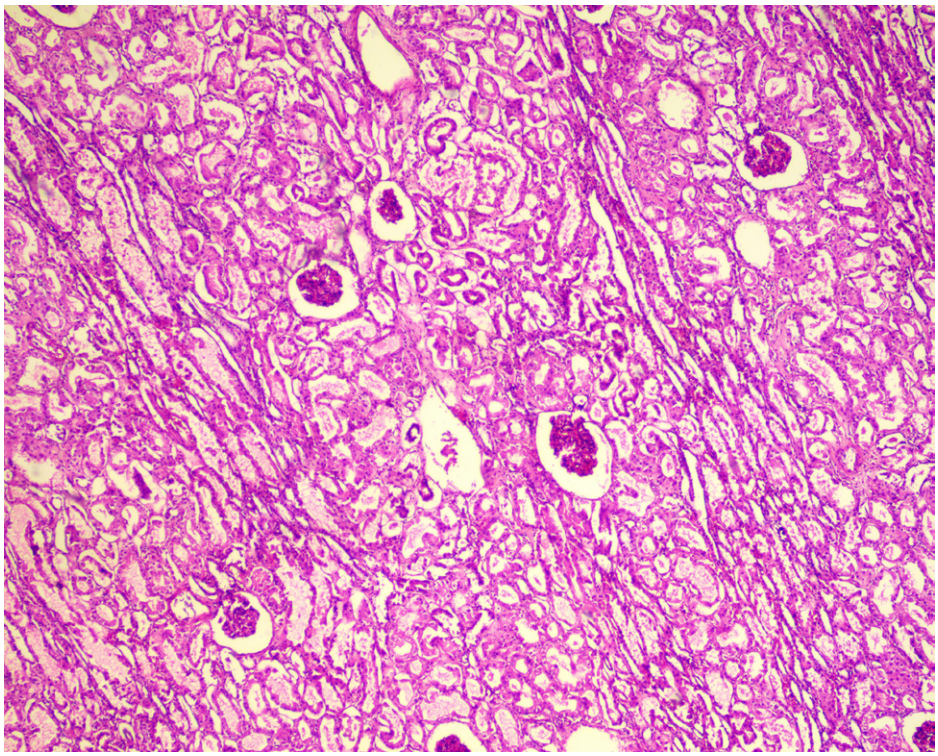

Fig. 4. Microsection of the kidney with a mild level of changes. Interstitial edema of the kidney with granular dystrophy of the convoluted tubule epithelium and glomerular hemorrhage: 4x10, hematoxylin-eosin stain.

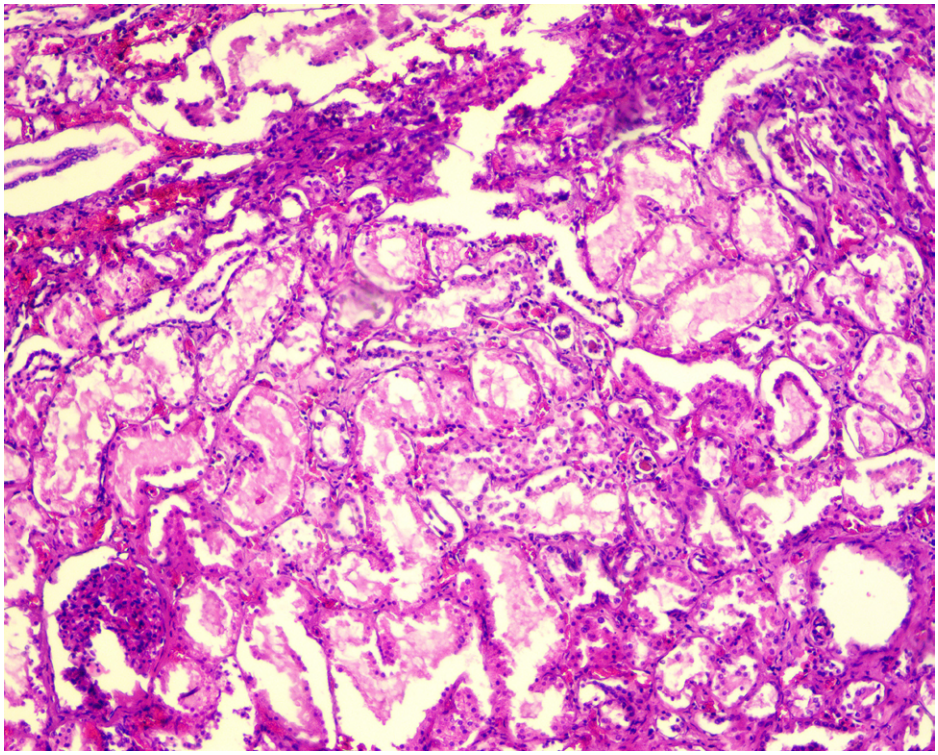

Fig. 5. Microscopic specimen of a kidney with moderate changes. Granular dystrophy of convoluted tubules and foci of vacuolar dystrophy. Magnification 10x10, hematoxylin-eosin stain.

groups, changes in organs were reviewed according to the proposed levels of damage.

1. Heart: assessment of cardiomyocyte necrosis, inflammatory infiltration and fibrosis, depending on the severity of the changes, in accordance with the four levels (0 - no changes, 1 - mild changes, 2 - moderate changes, 3 - severe changes).
2. Lungs: assessment of the severity of interstitial edema, alveolar collapse, necrosis and inflammatory infiltration, depending on the severity of the changes, in accordance with the four levels.
3. Liver: assessment of venous congestion and edema, necrosis in different zones of acinus, depending on the severity of the changes, in accordance with the four levels.
4. Kidneys: assessment of venous stasis, dystrophy, tubular necrosis in accordance with the four levels.

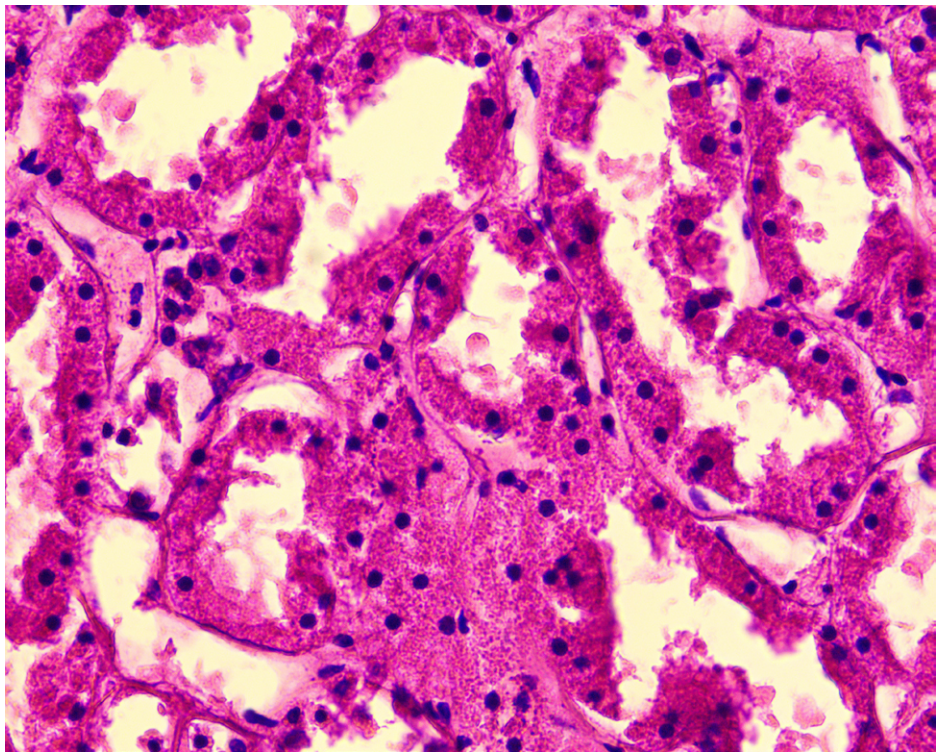

Fig. 6. Microscopic specimen of the kidney with a severe level of changes. Irreversible processes in the form of hyaline droplet dystrophy. Magnification 20x10, color: hematoxylin-eosin.

5. Intestines: assessment of the severity of ischemic changes in the intestinal mucosa, venous congestion and inflammation, in accordance with the four levels.

STATISTICAL PROCESSING

The mean value ± standard deviation was used to present quantitative data in a normal distribution. The median and interquartile range (IQR) were given in a distribution other than normal. As for qualitative data, they were absolute numbers and percentage. Given the type and distribution of data and the limited number of observations, nonparametric methods of analysis were chosen to compare pathomorphologic changes in the study between the two groups of patients. The Mann-Whitney U-test was used to test the hypothesis on the differences between the two independent groups in the level of damage between the selected organs (heart, lungs, liver, kidneys, intestines). All results were considered statistically significant at a p value < 0.05. The standard Microsoft Excel 365 package was used to record the data from the medical records of the selected patients. The EZR (R-statistics) package was used to calculate and analyze the data [12].

RESULTS

When comparing the clinical and epidemiological data shown in Table 1, we found no statistically significant difference between patients in the two groups, except for the period from hospitalization to death: on average, patients in group A - acute severe pancreatitis complicated by abdominal compartment syndrome lived less ($p<0.05$).

The microscopic evaluation of the organs examined in the two groups of patients revealed different patterns described by pathologists according to the proposed scale. Table 2 shows the comparative characteristics of the degree of pathomorphologic changes in the organs for the two groups: those who died of SAP with ACS (group A) and those who died of SAP with no ACS (group B).

In the assessment of cardiac injury, mild changes were observed in group A in 64% of patients, and similarly in 64% of patients in group B. In the assessment of lung damage, moderate changes were the most common in both groups (52% and 64%, respectively). When assessing microscopic changes in the liver, moderate changes also prevailed in the groups (68% and 46%, respectively). The microscopic description of kidney damage in group A showed 56% of severe changes and 44% of moderate changes, with no patients without any changes, while in group B, the kidneys were moderately affected in 64% of patients. When describing changes in the intestinal wall, moderate changes (64%) prevailed in group A and mild changes (61%) in group B.

A statistically significant difference between the groups in the level of damage to the kidneys and intestines was obtained ($p<0.05$, Mann-Whitney U-test) when comparing the levels of damage to each organ in the two groups, according to the specified levels of change.

Thus, in the microscopic specimens of the kidneys and intestines of group A, compared to the changes in group B, significantly moderate and severe changes prevailed (Table 2). Below are microphotographs of the examined microscopic speciments of the intestine (Fig. 2, Fig. 3) and kidneys (Fig. 4, Fig. 5) of patients of both groups with moderate and severe changes.

DISCUSSION

The patterns of significant damage to selective organ systems in SAP complicated by ACS revealed in our study are consistent with previously published data, including modeling of prolonged significant IAH in animals. This underscores the importance of preventing the progression of MOF by rapidly correcting elevated IAP.

The kidneys are considered a target organ in case of critical increase in IAP due to early clinical manifestations of morphological changes [13]. Abdominal compartment syndrome and SAP are etiologic factors of pre-renal acute kidney injury (AKI) resistant to fluid resuscitation, and prolonged IAH with hypoperfusion leads to damage to the tubular epithelial cells, which leads to the adhesion of internal (structural) AKI [14]. The mortality rate from AKI in SAP has decreased by about three times as of 2018 [15]. AKI in SAP occurs as a result of a decrease in the volume of circulating fluid from the vascular space caused by fluid extravasation, accompanied by a complex interaction of inflammatory, vascular and humoral factors [16].

The intestine is extremely sensitive to ischemia caused by increased IAP due to its anatomical and physiological features: a decrease in mesenteric blood flow is caused by arterial vascular compression and venous stasis. Intra-abdominal hypertension significantly reduces microcirculatory blood flow in the intestinal mucosa, increases intestinal permeability, leads to endotoxemia and irreversible mitochondrial damage and necrosis of the intestinal mucosa. [17] Severe abdominal microcirculatory disturbances may remain masked during successful stabilization of systemic blood pressure and cardiac output. [18] Artificially induced intra-abdominal hypertension in pigs with a decrease in abdominal perfusion pressure by 12-18 mmHg, reduced intestinal mucosal blood flow by 45-63% and diuresis by 50-80%. [19] In the experiment on female rats, induced intra-abdominal hypertension significantly worsened the histological picture of the colon mucosa, mucosal permeability and the balance of pro- and antioxidants, and an increase in IAP even below threshold values also demonstrated negative effects [20].

CONCLUSIONS

1. Pathologic changes in the studied organs of the group of patients, who died due to acute severe pancreatitis complicated by abdominal compartment syndrome, were characterized by more pronounced ischemic and inflammatory damage in the kidneys and intestines ($p<0.001$).
2. Pathologic changes in the heart, lungs and liver of patients, who died of acute severe pancreatitis, did not differ significantly, depending on the presence of abdominal compartment syndrome. ($p > 0.05$)
3. According to the results of the study, the variability of extra-pancreatic pathomorphologic changes in patients with severe acute pancreatitis depended on the level of intra-abdominal pressure. Complicated by abdominal compartment syndrome, severe acute pancreatitis led to the most pronounced irreversible changes in organs that are extremely sensitive to intra-abdominal pressure. Monitoring and timely correction of intra-abdominal hypertension aimed at preventing abdominal compartment syndrome in patients with acute severe pancreatitis may affect the course of the disease and the outcome of treatment.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ivanna A. Shchyhel
Bogomolets National Medical University
13 T. Shevchenko Blvd., 01601 Kyiv, Ukraine
e-mail: ringoo3110@gmail.com

ORCID AND CONTRIBUTIONSHIP

Olexii I. Dronov: 0000-0003-4033-3195 E F
Inna O. Kovalska: 0000-0002-6264-2928 E F
Ivanna A. Shchyhel: 0000-0002-1672-8149 A B C D
Tetyana P. Shevchyk: 0009-0006-0026-0330 A B
Vitaliy R. Balyak: 0009-0009-5415-2361 A B
Vadym O. Kostiukevich: 0009-0005-9263-9032 A B

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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