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Two-Level Immunocorrection Therapy of Acute Destructive Pancreatitis in a Multidisciplinary Surgical Hospital

ABSTRACT

This work is based on the analysis of complex treatment of patients with pancreatic necrosis treated at the surgical department of the Republican Hospital №2 - Emergency Center of the Sakha (Yakutia) Republic in the period from 2010 to 2015. The study allowed adapting and improving a duplex immunocorrection in pancreatic necrosis in a multidisciplinary surgical hospital that along with the other constituents of intensive therapy has allowed in a whole to reduce the amount of intra- and extra abdominal complications and lethal outcomes in a sterile pancreatic necrosis phase and in the phase of infectious complications.

Keywords: pancreatic necrosis, immunocorrection therapy.

INTRODUCTION

The last decade is marked with a qualitatively new stage of comprehensive research in the area of abdominal surgery such as urgent pancreatology, in the structure of which, acute destructive pancreatitis ranks first [1, 10, 11]. The range of the main directions of scientific and practical research includes not only the study of various aspects of pathogenesis and tanatogenesis disease and its complications, and improved methods of diagnosis, intensive care choices and tactics of surgical procedures [2-4, 13].

A significant part of the researchers involved in the problem of the treatment of acute destructive pancreatitis found that the risk of complications, including purulent destructive processes directly related to developing this category of patients with secondary immunodeficiency [1-6, 12 - 14]. It is for this reason that one of the main problems facing the surgeon is timely, reasonable and adequate immunotherapy. Consequently, the question of choice of tactics of treatment of patients with different clinical and pathologic forms of complications sterile and infected pancreatic necrosis and the inclusion of a comprehensive treatment program immunotherapy require further research and development, which was the basis for the implementation of this work.

RESEARCH MATERIALS

This work is based on a comprehensive analysis of the results of conservative and surgical treatment of 497 patients with pancreatic necrosis treated at the surgical department of the Republican Hospital №2 - Center for Emergency Medical Aid of the Republic of Sakha (Yakutia) in the period from 2010 to 2015.

All patients included in the study cohort were separated into two groups and three subgroups in each group, depending on the fact of infection and embodiments of pancreatic necrosis pathomorphogenesis. The first group of observations - the group «A», consisted of patients with sterile clinical and pathologic forms of pancreatic necrosis. The second group of observations - the group «B», consisted of patients infected with clinical and pathologic forms of pancreatic necrosis. Group «A» is divided into three subgroups: the subgroup «a» - those with enzymatic ascites-peritonitis; subgroup «b» - patients with the formation parapancreatic infiltration, morphological basis which was "aseptic" abscess of various departments of the retroperitoneal fat; subgroup «c» - patients with pseudocyst formation postnecrotic alternatively the evolution of necrosis occurring in abacterial conditions (time of formation of a false cyst usually accounted for more than 4 weeks from the onset of the disease, provided these posts with large formations of pancreatic duct). In turn, the group «B» is divided into three groups depending on the different options for transforming the sterile clinical and pathological forms in infected necrotizing pancreatitis: a subgroup «d» - patients with abscess formation pancreatogenic; subgroup «e» - patients with infected pancreatic necrosis formation; subgroup «f» - patients with infected pancreatic necrosis formation in conjunction with pancreatogenic abscess.

The diagnosis of pancreatic necrosis and the development of its complications was verified based on a comprehensive survey include: clinical findings, laboratory tests (including an assessment of the level of endogenous intoxication (EI) on the content of low and medium molecular weight (SL & AMW) by the method M.Y. Malakhova [7] and oligopeptide (ARS) by Lowry [9] in plasma, erythrocytes and urine with the release of five phases of EI, as well as control and accounting of important biochemical markers of pancreatic tissue necrosis and retroperitoneal tissue, systemic inflammatory response (SVR), and infection of pancreatic necrosis (LDH , C-reactive protein, procalcitonin). Instrumental methods of diagnosis include ultrasound and radiopaque computer scan of the abdominal cavity, retroperitoneal fat, videolaparoscopy, transdermal therapeutic and diagnostic puncture liquid formations of the pancreas, abdominal and retroperitoneal tissue under ultrasound followed by microbiological and cytological analysis of the resulting material. Assessment of the severity of the general condition and the severity of multiple organ failure in patients with pancreatic necrosis was performed using integrated systems scales, APACHE II [12] and TFS [10].

Immune status was evaluated by the number of lymphocytes and their subpopulations (T lymphocytes and B lymphocytes).

To study the T-system of immunity were determined by plaque subpopulation of T cells: T helper (Th), T-suppressor (TS), and calculates the immunoregulatory index (IRI), equal to the ratio Tx to Tc (Th / Ts) [8].

Analysis of B-immune system included its quantitative characteristics - determination of B-lymphocytes in the blood (the percentage and absolute content) [8] and functional characteristics - determination of serum immunoglobulin classes A, M, G by radial immunodiffusion on C. Manchini [8].

Statistical analysis of clinical material produced using the software package Stat Plus 2007 for Windows XP. In assessing the totality of the average value (μ) and standard deviation (σ); confidence factor differences (p) was determined by the Mann-Whitney test.

RESULTS AND DISCUSSION

According to several authors [1, 3, 4, 6, 10], in 24-68% of patients with necrotizing pancreatitis immune system disorders and functional impairment of the liver develop, which greatly exacerbates the severity of the disease due to the development of secondary immunodeficiency and eventually worsens its prognosis.

The causes of immunodeficiency in necrotizing pancreatitis are: significant loss of proteins with exudate, pus; insufficient intake of complete proteins from food (forced starvation, malnutrition); toxic inhibition of liver function, including protein-synthesizing; immunosuppression drug due to prolonged administration of antibiotics and etc [4,5, 14].

The object of our study was to evaluate the immune status of 188 (37.8%) patients with a sterile and in 57 (82.6%) patients with positive clinical and pathologic forms of pancreatic necrosis. Cellular (T-lymphocytes and their subpopulations immunoregulatory index (IRI)), and humoral immunity (B-lymphocytes, immunoglobulins A, M and G) were evaluated during the first day after admission and then every 3-5 days.

Studies on the first day, showed a violation of the immune status in all representations of groups and subgroups of patients (Table 1).

Table 1

Immune status of patients -sterile (group A) pancreatic necrosis in the first days of intensive care

Indicator	Control	Subgroup «a» (n=75)	Subgroup «b» (n=102)	Subgroup«c» (n=11)
Leukocytes(·10^9/л)	6,7±1,3	12,6±1,4**	15,1±1,8***	8,2±1,3*
Lymphocytes (%)	20,1±2,1	15,3±2,3**	12,1±3,5**	17,4±1,5*
(·10^9/л)	1,4±0,1	0,7±0,4*	0,6±0,3*	1,1±0,6*
T-lymphocytes (%)	44,9±2,3	22,3±1,5**	19,3±1,2**	36,6±2,4*
(·10^9/л)	1,1±0,9	0,7±0,4*	0,5±0,2*	0,9±0,7*
T-helpercells (%)	39,6±3,3	28,1±3,3**	26,1±3,4**	31,4±2,3*
(·10^9/л)	0,8±0,8	0,4±0,3*	0,3±0,4*	0,6±0,8*
T-suppressors (%)	25,5±2,8	19,5±2,7**	18,1±3,1**	22,3±4,1*
(·10^9/л)	0,7±0,4	0,4±0,2*	0,3±0,4*	0,5±0,5*
IRI (y.e.)	1,6±0,1	1,4±0,3*	1,4±1,6*	1,4±0,4*
B-lymphocytes (%)	27,3±2,6	17,4±7,1**	15,3±4,1***	24,6±1,6*
(·10^9/л)	0,7±0,3	0,4±0,9*	0,3±0,5*	0,6±0,1*
IgA (г/л)	2,4±0,1	3,7±1,1**	4,1±0,3***	3,2±1,5**
IgM (г/л)	1,48±0,7	1,0±0,1*	0,9±0,2**	1,1±0,4*
IgG (г/л)	14,2±2,6	17,6±4,1**	19,8±1,5***	16,5±2,4**

* - index significantly different from control (p<0,05),

** - index significantly different from control (p<0,01),

*** - index significantly different from control (p<0,001)

Presented in Table 1 data show that major shifts in sterile pancreatic necrosis characteristic of cellular immunity and appear absolute and relative decline in the number of lymphocytes, predominantly T-lymphocytes and their subpopulations. Absolute content of T lymphocyte Th and Tc, in patients, especially in the subgroups «a» and «b» is reduced as compared with the control value of 1.5; 1.6 and 1.4; 1.3 times, respectively. It may be noted that among the subpopulations of T-lymphocytes, Tx quantity change, compared with T is somewhat more pronounced. Presented changes have led to a decrease in IRI, which has made in these subgroups values 1.4±0.4 and 1.4±0.3 c.u. respectively, which could indicate a moderate immunodeficiency. In the subgroup «c» change of cellular immunity were much less pronounced in comparison with the subgroups «a» and «b» and generally approached the check digit.

Changes in the immune system in the presented study groups were less pronounced and expressed decrease in absolute and relative content of B-lymphocytes. The indicator of its functional characteristics - blood levels of immunoglobulins, usually remained within normal limits, except for IgA and IgG, the absolute values exceeded in 1.6-2.5 times or more check digits. This fact, in spite of dissimmunoglobulinemia, according to the literature, is characterized as increased activity of humoral immunity [5]. It should be noted, since the voltage of the immune system of the human body is realized in the North, mainly due to the activation of B-cell level [8], therefore, we can expect its early failure.

More significant changes were observed in the immune status of subgroups «e» and «f» patients in the phase of infected pancreatic necrosis. Against the backdrop of severe general condition of patients and the manifestation of clinical signs of systemic inflammatory response of the body, these changes correspond to a pronounced degree of secondary immunodeficiency (SID). Thus, in patients subgroups «e», and «f» content absolute and relative amount of T-lymphocyte populations and Tx and Tg significantly below as reference numbers and indexes of patients subgroup «d». The most pronounced decrease in Tj and Tc, the absolute content in the blood was 0.3±0.5 (10^9/l), 0.4±2.4 (•10^9/l) and 0.2±1.2 (•10^9/l), 0.3±0.9 (10^9/L), respectively, which is lower almost in 1.5 times than the values of the subgroup of patients with «d» and check digits in 2 times. Analyzing changes in IRI, it may be noted that its value amounted to 1.4±0.5 and 1.5±1.1 c.u. respectively, which is also lower than in the subgroup of patients with «d» and the reference values in the presented study groups.

The total number of B-lymphocytes in infected pancreatic necrosis forms (Table. 2), especially in the subgroups «e», and «f» were significantly lower than those in the subgroup «d», and compared with values in a group of patients with clinical sterile pathomorphological forms an average of 2.5-3 times. Quantitative values of immunoglobulins, especially IgA and IgG, quite clearly correlated with the severity of sepsis and pancreatogenic above the reference value and the subgroup «d» in 3-4 times. However, Table 2 shows that in patients with sepsis pancreatogenic greater variation of the standard deviation of the mean is noted, which can be explained by the different severity of sepsis.

Table 2

Immune status of patients infected (group B) pancreatic necrosis in the first days of intensive care

Indicator	Control	Subgroup «d» (n=9)	Subgroup «e» (n=28)	Subgroup «f» (n=20)
Leukocytes(·10^9/л)	6,7±1,3	7,6±1,1*	19,3±2,8***	16,1±1,1**
Lymphocytes (%)	20,1±2,1	15,5±1,8*	11,1±3,3**	11,9±3,3**
(·10^9/л)	1,4±0,1	1,0±1,6*	0,4±2,4*	0,5±1,6*
T-lymphocytes (%)	44,9±2,3	34,1±2,2*	19,2±3,5**	18,1±2,2**
(·10^9/л)	1,1±0,9	0,8±0,3*	0,5±0,3*	0,6±1,7*
T-helpercells (%)	39,6±3,3	29,4±1,3*	24,2±1,3**	25,4±1,4**
(·10^9/л)	0,8±0,8	0,5±3,1*	0,3±0,5*	0,4±2,4*
T-suppressors (%)	25,5±2,8	20,1±2,1*	16,8±2,1**	17,5±3,3**
(·10^9/л)	0,7±0,4	0,4±1,5*	0,2±1,2*	0,3±0,9*
IRI (y.e.)	1,6±0,1	1,4±0,6*	1,4±0,5*	1,5±1,1*
B-lymphocytes (%)	27,3±2,6	22,5±1,3*	15,7±3,5**	16,1±2,1**
(·10^9/л)	0,7±0,3	0,5±3,1*	0,3±0,1*	0,4±0,2*
IgA (г/л)	2,4±0,1	4,6±3,5**	6,3±4,1***	5,5±1,6**
IgM (г/л)	1,48±0,7	1,0±0,2*	0,8±0,9*	0,9±1,2*
IgG (г/л)	14,2±2,6	18,1±1,4**	21,8±1,1***	20,3±2,5**

* - index significantly different from control (p<0,05),

** - index significantly different from control (p<0,01),

*** - index significantly different from control (p<0,001)

For patients with severe sepsis pancreatogenic except pronounced decrease of T-cell immunity, there is significant, compared with the control and with the patients with uncomplicated, reduction in the absolute and relative number of B-lymphocytes. Thus, the content of B lymphocytes in the blood of an average amounts at 0.2±0.1 (·10^9 / L), significantly lower than control values and the «d» subgroup. Reduction of IgM and in some cases, especially in severe pancreatogenic sepsis, IgA and IgG require uniform application of immunomodulation tactics.

Thus, the analysis of the immune status of patients with necrotizing pancreatitis shows the development of VID, due mainly to deficient T cell immunity. At the same time we observed that immune deficiency is more pronounced in the transformation of sterile clinical and

pathological forms in infected pancreatic necrosis, the development of pancreatogenic sepsis, and in general, it depends on the nature of the clinical course of the disease. The ongoing evaluation of the immune status in the course of the treatment process and revealed SID character allowed drawing up a program for immunotherapy of patients with necrotizing pancreatitis.

Immunotherapy of patients with sterile pancreatic necrosis, often had a preventive focus and included therapeutic doses of thymus peptides (Taktivin) during the period of the patients in the ICU and was recommended after their transfer to relevant department (for 7-10 days). On the contrary, an immunomodulating treatment in patients with infected pancreatic necrosis and generalization of infection is a more complicated task, requiring individual approach and includes two levels (Table. 3).

Table 3

Immunotherapy of patients with pancreatic necrosis

Methods of immunotherapy	**The number of patients**	
	absolute	%
Immunotherapy first level		
Passive replacement therapy		
Freshfrozenplasma	57	100
Immunoglobulins	44	77,2
Immunostimulatory therapy		
Taktivin	15	26,3
Immunotherapy second level		
Immunocorrectors complex action		
Polyoxidonium	54	94,7

At the initial stage (1-3 days), expressed in terms of the inflammatory syndrome, SID correction was conducted with a focus on passive, replacement therapy. Correction of deep disorders of immunity in patients was carried out by introducing to subgroups «e» and «f» of fresh frozen plasma, intravenous immunoglobulin.

It should be noted that only after the improvement of the general condition, normalization of central and peripheral hemodynamics, reduce signs of inflammatory syndrome and a stabilization of the immunity indices we prescribed immunotherapy second level. As a rule, it happened not earlier than 7-10 days after the operation and the beginning of immune therapy. So, against first- level immunotherapy, further, to activate cellular immune defense mechanisms 54 (94.7%) patients received Polioksidony. Thus, the usefulness of the presented immunotherapy scheme was confirmed by the stabilization of the immune status at all stages of treatment (Table. 1, 2).

Summarizing the results of the study it can be **concluded** that the main changes of the immune status in necrotizing pancreatitis are characteristic T-cell immunity and mainly are most pronounced in patients with common clinical and pathologic forms of pancreatic necrosis as sterile, and the phase of infection in which there is a decrease in more than twice of the absolute and relative number of T lymphocytes and T helper cells in 1.5 - immunoregulatory index. These violations demonstrate the need for immunotherapy, the choice of which is determined individually and depends on the nature and extent of the identified changes.

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