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Review Article

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LITERATURE REVIEW OF THE PROBLEM OF SPONTANEOUS BACTERIAL PERITONITIS IN LIVER CIRRHOSIS AND VIRAL ETIOLOGY

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SUMMARY

This review is devoted to the study of spontaneous bacterial peritonitis in liver cirrhosis of viral etiology. The results of the conducted studies serve as scientific confirmation of the infectious nature of SBP, its polyetiological nature, and also allow us to consider various variants of SBP as clinical and laboratory manifestations of a single pathogenetic process. There is a need for further research in the direction of studying the subtle mechanisms of pathogenesis, solving problems for the prevention and treatment of SBP. In the future, the use of genetically engineered cytokines (preparations of recombinant alpha- and gamma-interferons, recombinant colony-stimulating factors, some recombinant interleukins) may be pathogenetically justified and promising in the prevention and treatment of SBP in cirrhosis. This is due to the fact that in the processes of generalization of inflammation as a trigger for the formation of early multiple organ failure in sluggish purulent-inflammatory diseases, as in SBP, the failure of the immune system plays a leading role.

KEYWORDS: liver cirrhosis, spontaneous bacterial peritonitis, cytokines, interleukins, viral hepatitis.

Topicality. Spontaneous bacterial peritonitis is a prognostically severe polyetiological complication of decompensated liver cirrhosis that develops as a result of translocation of the intestinal flora, against the background of portal hypertension and excessive bacterial growth, characterized by inflammation of the peritoneum and contamination of ascitic fluid, systemic inflammatory response syndrome (SIRS), followed by the development of sepsis and multiple organ failure. The main distinguishing characteristic of SBP is inflammation of the visceral and parietal peritoneum without violating the integrity of internal organs and severe inflammatory processes in the abdominal cavity and small pelvis, which does not require surgical intervention.[1,5,12,14,26,29] Data on the frequency of this complication of cirrhosis are contradictory: according to various observations, SBP ranges from 8 to 31% of the total number of patients with cirrhosis observed in a hospital.[2,3,7,11,17,19] In the 1960s, when SBP was first described by Harold Conn[1,8], the mortality rate for this complication was about 90%. The lack of correct diagnosis, timely and adequate therapy led to unreasonably high mortality. In subsequent years, the mortality rate from SBP in hospital conditions decreased, according to different authors, to 20-38%.[6,8,10,13,18,21,22]

As is known, the pathogenetic mechanisms of SBP are based on the theory of bacterial translocation. The essence of this phenomenon is the penetration of viable bacteria (representatives of the resident flora) through the epithelial barrier of the gastrointestinal tract into the extraintestinal, usually sterile, tissues of the macroorganism, for example, mesenteric lymph nodes, the spleen, where some of them undergo lysis by macrophages, and some enter through the portal vein. into the hepatic sinuses and is lysed by liver macrophages.[8,9,14,16,24,28] Along with bacteria, endotoxins and particles of microbial cells penetrate into the internal environment. In the pathogenesis of SBP, like any other infectious process, the leading role is played by the interaction of three factors: the pathogenic qualities of the microbe, the number of microbes, and the body's defense mechanisms. Of particular importance in the development of the disease are the factors of pathogenicity and virulence of aerobic and anaerobic microorganisms. The resident flora is classified as low pathogenic. The processes caused by normal microflora are characterized by either deviations from the typical clinical picture of the disease, or difficulties in determining the nosological form to which it can be attributed. This provision is particularly applicable to the SBP. There are descriptions in the literature of SBP caused by almost all known bacteria. According to numerous clinical microbiological studies, the following microorganisms are most often detected in SBP in AF: Escherichia coli (according to some authors, up to 70% of cases), somewhat less often - Streptococci, Staphylococci, less often - Klebsiella oxytoca, Salmonella enteritidis, Enterococcus faecium, Acinectobacter anitratus. Isolated cases of tuberculosis

and fungal (Cryptococcus neoformans) etiology have been described.[4,7,19,23,28,30] The number of microorganisms necessary for the development of the disease is called the "critical number". In medical practice, there are no data on the “critical number” for both clinically expressed manifestations and unexpressed infections. A direct dependence of the level of bacterial translocation on the level of their population in the intestine has been proven. From this point of view, the role of the bacterial overgrowth syndrome in cirrhosis is especially great.[7,18,19,24,26] It has been established that in decompensated cirrhosis of class B and C according to Child-Pugh, a number of interrelated mechanisms arise that disrupt the normal functions of the body and contribute to bacterial intestinal translocation and the development of SBP. These are portal hypertension, ascites, increased intra-abdominal pressure, slowing down the passage of contents through the intestines, bacterial overgrowth syndrome, decreased protein-synthetic function of the liver, protein starvation, decreased overall immunoreactivity, enteral insufficiency, endotoxemia, as well as local changes in the intestinal mucosa in the form of microcirculation disorders and permeability.[2,7,14,26] An important role in the development of SBP is played by intra-abdominal hypertension (IAH), which increases with cirrhosis decompensation due to portal hypertension and ascites, on the one hand, and the development of bacterial overgrowth syndrome, on the other. An increase in IAH slows down blood flow through the inferior vena cava and reduces venous return, helps to reduce lymphatic drainage through the thoracic lymphatic duct, and slows down the reabsorption of AF. As is known, the presence of LC, class B and C with impaired liver function, is accompanied by both a decrease in protein-synthetic function and a dysfunction of the reticuloendothelial system, which leads to a decrease in the ability to form antibodies and the formation of secondary immunodeficiency. It has been proven that microorganism-activated neutrophils, monocytes, macrophages and endothelial cells produce pro-inflammatory mediators - cytokines (CK), kinins, arachidonic acid metabolites, platelet activating factor and nitric oxide, which initiate and maintain an inflammatory response, cause secondary release of similar mediators with endothelial damage and decreased organ perfusion and oxygen delivery. Under these conditions, instead of the synthesis of albumin, which is already sharply reduced in decompensated cirrhosis, the liver begins to produce acute phase proteins, such as glycoproteins, a1-antitrypsin, C-reactive protein, ceruloplasmin, coagulation factors, complement components, ferritin - substances that, having a different effect, they contribute to the enhancement of coagulation, inflammation, and metabolic disorders.[5,8,12,15,25] In addition, with SBP, as a result, there is a decrease in the function of neutrophils, a violation of the synthesis of leukotriene, superoxide anion, and platelet-activating factor. Control over the implementation of immune and inflammatory reactivity is carried out by a system of cytokines: pro-inflammatory interleukins - IL-1 betta, IL-6, IL-8, tumor necrosis factor, as well as their endogenous antagonists, such as IL-4, IL-10, IL-13 , soluble receptors for TNF-alpha, etc. (anti-inflammatory mediators). When the balance of the cytokine system is disturbed, the destructive effects of inflammatory mediators prevail. The concentration of individual pro-inflammatory cytokines in the blood, which usually does not exceed 5–20 pg/ml in normal conditions, can increase by 5–10 or more times[8,13,16,21,27], all this leads to impaired endothelial permeability and function. capillaries, the triggering of the DIC syndrome, the formation of systemic inflammation, the development of organ dysfunction. Phenomena such as fever, release of neutrophils into circulation from the vascular and bone marrow depots, increased leukocytopoiesis in the bone marrow, overproduction of acute phase proteins in the liver, and the development of generalized forms of the immune response are attributed to systemic adaptive changes during inflammation[27,29,31,31], the fundamental differences between systemic and "classical" inflammation are expressed in the development of a response to systemic alteration, when pro-inflammatory mechanisms lose their protective basis for curbing damage factors and themselves become the main driving force of the pathological process. Obviously, for patients with decompensated cirrhosis, this process develops much faster than for patients with preserved liver function and the immune system. According to many studies, SBP is a difficult diagnostic problem for the clinician and is one of the most severe and difficult to recognize complications of decompensated cirrhosis. The clinical picture of SBP, as a rule, is mild and consists of diffuse abdominal pain of varying intensity, fever, vomiting, diarrhea, signs of intestinal paresis, in some cases, rapidly increasing hepatic encephalopathy (HE) and hepatorenal syndrome (HRS) are noted. Many patients with SBP present predominantly with systemic inflammatory response syndrome (SIRS). Diagnosis of SIVR is based on the registration of at least two of the four clinical and laboratory parameters: 1) temperature > 38°C or < 36°C; 2) heart rate > 90 beats/min; 3) RR > 20 breaths/min or PaCO2 < 32 mm Hg. Art.; 4) peripheral blood leukocytes> 12 x 109/l or <4 x 109/l or the number of stab forms is more than 10.[14,15] According to our studies, among the clinical and laboratory signs, the most common are: leukocytosis with a stab shift (62.1%), fever (51.7%), abdominal pain syndrome (41.0%), tachycardia (41.4%), dyspeptic phenomena - nausea, vomiting (34.5%), diarrhea (20.7%), HRS (10.3%), unmotivated increase in PE (20.7%).[7,9,14,18] Renal failure is one of the most formidable complications that largely determine the prognosis. In this regard, any clinical deterioration in a patient with cirrhosis, complicated by edematous-ascitic syndrome, may be a consequence of SBP.[17,22,28,31] It is obligatory in the diagnosis of SBP to carry out diagnostic paracentesis with the study of ascitic fluid (AF), counting the number of polymorphonuclear leukocytes (PMN), determining

the protein content, albumin concentration, inoculation of AF on culture media. Before diagnostic paracentesis, as a rule, an ultrasound examination is performed, in which fibrin threads, suspension can be visualized in the AF. In bacterial peritonitis, regardless of etiology, the number and caliber of suspended particles increase, multiple fibrin filaments are detected, freely oscillating in the AF in time with respiratory movements, located mainly in the small pelvis, in the subhepatic and suprahepatic spaces, in hernial protrusions. The results of our studies have shown that ultrasound in patients with cirrhosis, both with spontaneous and secondary bacterial peritonitis, most often reveals acoustic inhomogeneity of AF in the form of suspension, fibrin filaments and moorings (specificity 79.8%, sensitivity 86%). This allows us to propose the use of acoustic inhomogeneity of the AF as one of the additional criteria for peritonitis.[5,18,22,29,30] In accordance with the Recommendations of the International Club for the Study of Ascites, the treatment regimen for a patient with SBP in cirrhosis can be presented as follows: • antibiotic therapy; • paracentesis with replacement of plasma volume with albumin; • treatment with pro- and prebiotics.

Classic SBP criteria

1. Detection of microorganisms by the classical microbiological method;
2. Ascitic fluid (AF), counting the number polymorphonuclear leukocytes (PMN), > 250/mm^3;

Criteria for a systemic inflammatory response

1. Temperature > 37-38 °C or < 36 °C;
2. Peripheral blood leukocytes> 12 x 109/l or < 4 x 109/l and / or the number of stab forms is more than 10;
3. Tachycardia - heart rate > 90 bpm;
4. Shortness of breath - respiratory rate> 20 respiratory movements / min;
5. CRP AF > 5.0 g/l;
6. Increasing the level of CK in the SC and AF;

Local SBP criteria

1. Abdominal pain (with palpation or independent);
2. Dyspeptic phenomena (nausea, vomiting);
3. Diarrhea;

General criteria

1. "Unexplained" increase in encephalopathy;
2. Hepatorenal syndrome;
3. Class B and C cirrhosis according to Child-Pugh, hepatocellular insufficiency;

Additional criteria

1. Acoustic heterogeneity of AF (suspension, fibrin threads);
2. Determination of specific chemical markers, according to GC-MS, short-chain fatty acids by gas chromatography;
3. DNA detection by PCR diagnostics.

CONCLUSION

The results of the conducted studies serve as scientific confirmation of the infectious nature of SBP, its polyetiological nature, and also allow us to consider various variants of SBP as clinical and laboratory manifestations of a single pathogenetic process. Analyzing the data obtained, it is possible to trace the relationship between SBP and SIRS (systemic inflammatory response syndrome or SIRS), which opens up opportunities for understanding the role of SIS as one of the stages in the development of multiple organ failure syndrome and sepsis in patients with cirrhosis in the natural course of the disease. Patients with cirrhosis of the liver, complicated by SBP, often die from esophageal-gastric bleeding and do not survive to MODS and sepsis. However, the development of hepatorenal, hepatopulmonary syndromes in combination with hepatocellular insufficiency brings SBP as close as possible to this condition. The development of MODS can be considered as the final and irreversible moment in the course of the SBP. The presence of clinical manifestations of peritonitis and / or heterogeneity of AF dictate the need for paracentesis, followed by biochemical analysis of AF, determination of the content of PNL, CRP and CK, as well as inoculation of AF on media.

There is a need for further research in the direction of studying the subtle mechanisms of pathogenesis, solving problems for the prevention and treatment of SBP. One of the most real and promising directions is the preventive correction of the syndrome of excessive bacterial growth, the use of rifaximin, pre- and probiotics in the early stages of the development of liver cirrhosis. Improving the methods of molecular diagnostics opens up new possibilities in the diagnosis and determination of the etiology of microbial infections. The use of PCR diagnostics of microorganisms allows not only to reveal the etiology of bacteremia in SBP. Recently, the first reports of the clinical use of commercial tests to identify the etiology of bacteremia have appeared.

In the future, the use of genetically engineered cytokines (preparations of recombinant alpha- and gamma-interferons, recombinant colony-stimulating factors, some recombinant interleukins - rIL-2, rIL-12) may be pathogenetically justified and promising in the prevention and treatment of SBP in cirrhosis. This is due to the fact that in the processes of generalization of inflammation as a trigger for the formation of early multiple organ failure in sluggish purulent-inflammatory diseases, as in SBP, the leading role is played by the failure of the immune system.[9,17] Improvement of algorithms for clinical and laboratory assessment of the effects of cytokine preparations and determination of indications for the appointment of cytokine therapy are those directions in the development of clinical immunology, the movement along which will allow solving many problems of complex treatment of patients with cirrhosis.

Consistent and purposeful work in this direction, the practical implementation of the treatment and prevention algorithm for SBP in cirrhosis, its further development and improvement, as well as the use of new drugs and treatment options will create a coherent system for providing specialized care to this extremely difficult category of patients.

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