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Paradox: Does liver insufficiency protect the patient? A hypothesis

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Despite the fact that the key role of the liver in the formation of the immune response to injury is not in doubt, the mechanisms of weakening the immune response to infectious and noninfectious lesions in patients with hepatic failure remain unclear. We propose an original hypothesis of forming the ways to limit the amplitude of the systemic inflammatory response in patients with the end-stage liver disease. The basis of the hypothesis is the idea that as a result of reducing the intensity of the natural stimulation of membrane mCD14 receptors by the ligands of infectious nature, the basic mechanism of the systemic immune response induction by liver macrophages (Kupffer cells) is interrupted. According to the proposed hypothesis, in condition of liver failure, the synthesis of lipopolysaccharide-binding protein by hepatocytes is reduced. This leads to a decreased amplitude and intensity of the protective immune responses. This fact explains a number of clinical

phenomena observed in patients with liver failure/dysfunction that consist in a reduced reactivity of the organism to the damage inflicted by infectious and noninfectious agents. The authors consider it possible to use this hypothesis in the search for new trends to prevent the immune system hyper-reactivity in sepsis, and to improve the therapeutic strategies for the management of patients at high risk of infectious complications after liver transplantation.

Keywords: sepsis, systemic inflammatory response, Kupffer cells, hepatic failure, lipopolysaccharide, lipopolysaccharide-binding protein

"Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

Sir William Osler (1904)

Introduction

As in intensive therapy practice, infectious complications generally take a leading place among the complications of orthotopic liver transplantation (OLT) in perioperative period and constitute one of the main challenges in clinical transplantation [1-4].

Despite rigorous efforts made by specialists, and undeniable advances in understanding the mechanisms running the development of infection-associated critical conditions, in the recent decade no new effective strategies have been proposed to combat these conditions in practice.

Currently, our Centre has the experience of 420 liver transplantations (LT); moreover, the Center admits for treatment the patients with liver disease in their end-stage, and also patients with a fulminant hepatic failure. A many-year experience of rendering an anesthetic and critical care to that patient population enabled us to identify a number of common patterns in the development of severe infectious complications and their course in patients with a hepatic dysfunction/failure.

In general, the essence of those patterns implied an "unexplainable" body's tolerance to a highly-traumatic surgery, such as OLT, in the patients with a severe liver dysfunction or liver failure and also the absence of a marked systemic response when infectious complications occurred. Based on a systematic analysis of their own data and considering the current concepts about the mechanisms of systemic inflammatory response (SIR) reactions and the liver role in them, the authors have formulated the hypothesis that would help to explain some clinical phenomena observed in this patient population, and the regularities in the development of severe infectious complications and their course.

Phenomena that need explaining

1. *The impact of liver failure on the stress response to surgery*. In 2002, H.Kehlet and D. Wilmore postulated that the stress response to surgery should be considered an essential factor inducing dysfunctions of various organs and systems. That postulate was the basis for developing the strategy of a multimodal anesthetic protection from the effects of highly-traumatic surgical stress, and currently that strategy is generally accepted [5].

However, a number of this strategy requirements can not be followed in transplant surgery, due to a high risk of breaking the extremely tense homeostasis-keeping mechanisms in patients with the end-stage liver disease. This actually implies contraindications to using the thoracic epidural anesthesia, non-steroidal anti-inflammatory agents, paracetamol, etc. Despite the surgical risk and extreme severity of a patient's condition, LT is characterized by a high efficacy and tolerance with an in-hospital mortality being 5-10% in most centers. One should note that at least 2/3 of the

recipients belong to Class IV by American Society of Anesthesiologists (ASA) Physical Status Classification System.

Clinical Example 1

Patient A., 56 years old, Medical record No. 8139/171. On 12-03-2012, he underwent LT for hepatitis C virus-related liver cirrhosis (LC) with hepatocellular carcinoma. Hepatic lesion of Child-Pugh Class C, the Model for End Stage Liver Disease (MELD) score 28. The patient was diagnosed hepatorenal syndrome (HRS) type 2, ascites, hydrothorax, hyperbilirubinemia, hypersplenism, Class IV by ASA Physical Status Classification System. The hepatectomy stage was characterized by significant bleeding, the organ exposure phase was associated with violent bleeding from hepatic veins that was controlled by means of the total vascular isolation of the liver. From the moment of the skin incision, the Cell Saver intraoperative cell salvage device was used for replacement of the blood lost during surgery, so the blood loss was accurately recorded; its volume reached 16 liters. The violent and massive intraoperative hemorrhage required using the second "Cell Saver" device, the blood loss was replaced using a rapid infusion system at a rate of 1.2 liters per minute, and jet bolus infusions of blood products with 50 ml syringes. The systolic blood pressure was maintained at 60 mm Hg by using ultra-high doses of vasopressors: norepinephrine, phenylephrine, epinephrine, 5-10 times higher than the maximum concentrations used in cardioanesthesiology, for hemodynamics control in traumatic or hemorrhagic shock. During the surgery, the patient received more than 30 liters of infused and transfused fluids, including 1.2 liters of a 4% sodium bicarbonate solution, a hyperfibrinolysis prevention therapy.

After the organ replacement, the coagulation balance was restored under the control of thromboelastometry, by administering the prothrombin complex concentrate, cryoprecipitate, packed platelets, and the antithrombin III (AT III) concentrate; hyperlactatemia was controlled (the maximum blood lactate level reached 16 mmol/L), other homeostasis parameters were returned to normal, the need in extreme doses of vasopressors was reduced. The patient was extubated on the next day having stable homeostasis, hemodynamics and gas exchange parameters, adequate diuresis. During further postoperative follow-up, the patient was stable and discharged home on the 14^{th} day after surgery.

The described clinical case report demonstrates the resistance of the patient with the end-stage liver disease (or with a temporary absent liver function during the anhepatic phase of OLT) to common reactions of a classical stress response to injury (in the described case, to severe surgical trauma with an extremely high blood loss). Meanwhile, in this clinical situation, the described unresponsiveness was related to the endocrine-metabolic link of the stress response. Despite the massive blood loss and large amounts of transfused fluids, the patient did not develop a hemorrhagic shock with pathophysiological reactions, such as the centralization of blood circulation and multiple organ dysfunction syndrome (MODS).

2. The next clinical phenomenon in OLT patients that deserves attention includes the common patterns of the postoperative course complicated by a graft dysfunction and bacterial infection in the patients undergoing OLT. These patterns are expressed as the absence of SIR and MODS in response to infection during the first 5 days in case of the allografted liver dysfunction; and conversely, as the presence of a very swift

response, with MODS and a fatal outcome in case the septic complication occurs after 3-5 days post OLT.

Clinical example 2

Patient G., 59 years old. The diagnosis read: "hepatitis C virus-related LC, hepatocellular carcinoma; hepatic lesion of Child-Pugh Class C, MELD score 28; HRS type 2, ascites, hydrothorax, hyperbilirubinemia (up to 600 mcmol/L), hypersplenism, hepatic encephalopathy Grade 2, Class IV by ASA Physical Status Classification System". Prior to surgery, the patient stayed in hospital for a month for LC decompensation. Before surgery, a Klebsiella pneumoniae strain was isolated in repeated cultures of pharynx smears without any clinical signs of infection. During 5 postoperative days the patient received cefepime 2 g daily (the only one from the drugs of his preoperative antibiotic therapy. OLT was performed on 24.02.2014. During surgery: there was a marked blood loss of over 3 liters, hyperfibrinolysis; the anhepatic period lasted about 2 hours. After the surgery, there were laboratory signs of a severe ischemia-reperfusion injury (IRI), with a maximum elevation in alanine and aspartate aminotransferase activities over 8000 U/ml, lactate dehydrogenase over 15 000 U/ml. Clinically, for 5 days after surgery, multiple organ dysfunction retained necessitating a mechanical lung ventilation (MLV), renal replacement therapy (RRT), the titration of vasopressors, and correction of hemostasis disorders. Meanwhile, the clinical and laboratory signs indicated the present metabolic functions of the "new" liver and a delayed recovery of its synthetic functions. The values of acute phase proteins, coagulation parameters and natural anticoagulants (AT III) remained low. Meanwhile, the presepsin and procalcitonin (PCT) levels were high. Antibacterial therapy was supplemented with ciprofloxacin (400

mg/day). On postoperative day 5, a multidrug-resistant strain of Klebsiella pneumoniae sensitive to polymyxin was cultured from bronchial secretions of the wound.

Later on, while on intensive therapy, the patient's condition improved within a week, the multiorgan dysfunction resolved, the ventilation support and RRT were discontinued, the hemostasis balance restored, and the synthetic graft function recovered. The elevated laboratory parameters of inflammation, namely leukocytes with band neutrophils, blood C-reactive protein (CRP), and fibrinogen were recorded starting from postoperative day 6. The presepsin levels remained high. On the 7^{th} postoperative day, the patient was transferred from the intensive care unit to a hospital ward in a stable condition; further the patient received treatment for the complication of postoperative wound suppuration.

Clinical Example 3

Patient A., 47 years old. Diagnosis read " hepatitis C virus-related LC, hepatocellular carcinoma; hepatic lesion of Child-Pugh Class C, MELD score 32; HRS type 2, ascites, bilateral hydrothorax, hyperbilirubinemia (up to 700 mcmol/L), hypersplenism; hepatic encephalopathy Grade 3, Class IV by ASA Physical Status Classification System". For 2 months before surgery the patient received in-hospital treatment for LC decompensation and persistent encephalopathy, hyperbilirubinemia up to 600-700 mcmol/L, ascites-peritonitis, HRS, periodically the efferent therapy methods (plasmapheresis) were used. Before the surgery, Enterococcus faecium (10^5 CFU/ml) resistant to vancomycin, sensitive to linezolid was isolated from urine cultures. Preoperatively the patient received ciprofloxacin 400 mg/day, tienam 1.5 g/day, voriconazole 200 mg/day. On 17.06.2014, the patient

underwent LT. The surgery was uneventful, the operative blood loss was 1.5 liters. When transferred from the Operating Room, the patient had stable homeostasis parameters, achieved the hemostatic balance, received a minimal dose of vasopressors (norepinephrine); she was extubated at 8 hours after surgery. Postoperative hepatic transaminase activities and a rapid recovery of hemostasis parameters and renal function indicated the absence of a significant graft IRI, its function being satisfactory. During 3 postoperative days, the clinical improvement was progressing, and the laboratory test results confirmed the recovery of metabolic and synthetic graft functions. The laboratory parameters indicating the inflammatory reaction (moderate leucocytosis with stab cell shift), and the biochemical markers of inflammation: CRP (150 ng/ml), PCT, presepsin (over 5000 pg/ml) were recorded. At the same time, the patient had normal body temperature; the hemodynamics, gas exchange, and other homeostasis parameters were stable, the glomerular filtration rate (GFR) increased. Postoperatively, the ongoing antibacterial and antifungal therapy was supplemented with the linezolid 1.2 g/day. On the 4-th postoperative day, the patient suddenly developed the clinical signs of septic shock, MODS with anuria, and the refractory to intensive care hypotension and adult respiratory distress syndrome. An additional administration of intravenous polymyxin E with an increased maximum daily dose to 9,000,000 IU/day (Colistat manufactured by *TriplePharm*, Republic of Belarus) appeared ineffective. The patient died at 36 hours after the onset of complications. Post mortem cultures of bronchial secretion and pharynx smears isolated a hospital multidrug-resistant strain of Klebsiella pneumoniae.

The given clinical examples illustrate the relationship between the development of severe SIR reactions and the recovery rate of the allografted

liver function in an infected recipient with end-stage LC. It is indicative that a delayed functional recovery of IRI-compromised graft in Patient G. limited the amplitude of SIR reactions and "protected" the body from self-damage. In contrast, an active recovery of liver functions in Patient A. resulted in uncontrollable SIR reactions with irreversible damage to organs and systems.

3. *Ascites-peritonitis phenomenon.* Spontaneous bacterial peritonitis (SBP), a widely known in clinical practice LC complication, is a phenomenon that needs reconsidering from the standpoint of the concept on the SIR attenuation in response to the infection onset in patients with hepatic dysfunction/failure. In contrast to the tactics of the "classical" surgical peritonitis treatment, currently there is a common point of view on the conservative treatment of SBP as the only correct tactics avoiding the progression of LC decompensation. Ascites-peritonitis can quite successfully be controlled by administration of cephalosporin antibiotics. In the conservative treatment, according to some authors, the mortality from SBP makes 10-30%; and only in 4% of cases SBP is accompanied by the septic shock development [6-7].

However, in peritonitis caused by Escherichia coli (that, along with Klebsiella spp., causes ascites-peritonitis in 70% of cases [6-7]), the patients without LC develop abdominal sepsis with extended SIRS manifestations, which in most cases requires an immediate surgical intervention for disinfecting the nidus of infection. Obviously, the presence of hepatic failure in patients with ascites-peritonitis is the main determinant restraining the development of SIRS and its irreversible consequences.

What is known?

It is known that in most patients, the inflammatory response might restrain and neutralize the infection. The mechanism of switching the earliest anti-infectious protective barrier includes the recognition of evolutionary conservative pathogen-associated molecular patterns (PAMPs) typical for large groups of various microorganisms by genetically encoded receptors present on myeloid cells [8]. According to current views, the excess inflammatory response develops in relation to the host and pathogen nature and is caused by two fundamentally different stimuli: PAMPs and DAMPs (damage-associated molecular patterns). PAMPs are alien molecules and the natural ligands for the signal pattern recognition receptors (PRRs) (TLR1-9, NOD-12, Ig-FcR) [9]. DAMPs are the native tissue degradation products having antigen-nonspecific properties [10]. The latter ones play a major role in the induction of the so-called sterile immune response at an early stage of organ (acute liver) failure before the onset of infection [11].

The membrane receptor molecule mCD14 in the cell receptor complex TLR-4 is known to be expressed on the surface of macrophages and binds to various ligands of infectious origin: PAMPs (the major one being the lipopolysaccharide (hereinafter referred to as LPS) of gram-negative bacteria cell wall, and also components of gram-positive bacteria and fungi) [12].

It has been found that the major mechanism inducing the systemic inflammatory responses is the activation of PAMPs binding to macrophage receptor mCD14 by the involvement of lipopolysaccharide-binding protein (hereinafter referred to as LBP) in this process, which enhances the effect of bacterial ligand binding to the receptor by 100-1000 times. However, there are the data suggesting an isolated binding of LPS mCD14 and a subsequent transmission of the signal on bacterial infection into macrophages [13].

Despite its name, LBP was found capable to bind, besides LPS, to the components of gram-positive bacterial cell walls, and fungi, i.e. it can be a universal means that by binding to PAMPs "amplifies" the signal to activate inflammation [14].

LBP is an acute phase protein; it is synthesized primarily in the liver and released into the blood after glycosylation with a molecular weight of 58-60 kDa [15]. Furthermore, it has been found that TLR4 receptors are expressed not only on Kupffer cells but also on the membranes of hepatocytes, monocytes, dendrocytes, neutrophils, mast cells, T-lymphocytes, stellate cells, endothelial cells and the bile duct epithelial cells; while both PAMPs, and DAMPs may act as the ligands for TLR4 receptors [16-17].

The receptor activation leads to the translocation of the kappa-beta nuclear factor on the inner surface of the cell nucleus membrane, and to the transcription of the genes controlling the proinflammatory cytokine production. The release of interleukin-6 initiates the acute phase response of the liver [18]. The increase of positive acute phase response is provided by the decreased production of inhibiting acute phase reactants (prealbumin, transferrin, ceruloplasmin, etc.) and is accompanied by decreased synthesis of AT III, protein C, S, glutathione, which is clinically manifested in microcirculation impairments [19]. A subsequent development of the insulin resistance due to an impaired regulation of genes encoding for glucose transporter activity leads to a mitochondrial dysfunction and MODS development in sepsis. Therefore, the resolution of mitochondrial dysfunction is considered a key factor in the recovery from organ disorders in sepsis [20, 21].

It has been established that the main causes of liver dysfunction induced by severe infection include hypoxic hepatitis (HH) and sepsis-associated cholestasis [22]. The HH development is associated with universal mechanisms of cell damage in critical condition, namely an inadequate oxygen delivery to tissues under conditions of their increased requirements in oxygen. Sepsis-associated cholestasis clinically manifests itself as jaundice and growing hyperbilirubinemia. Recent studies have shown that sepsis-associated cholestasis occurs due to an impaired biotransformation and adenosine triphosphate (ATP)-dependent transport of bile acids in hepatocytes. Bile acids that accumulate in hepatocytes and, while possessing surface active properties, cause further damage to the cells and contribute to the excretory function impairment [23]. An impaired bile acid transport is believed to be induced by proinflammatory cytokines [24].

The hypothesis formulation

We conceive the mechanism of SIR induction in patients with a severe liver failure/dysfunction as follows.

In conditions of an impaired synthetic liver function, the production of acute phase proteins, namely CRP, fibrinogen, and others, is reduced. It is logical to assume that this decreases the LBP production, leading to a reduced natural stimulation of mCD14 receptors on the macrophage surface, and to a slowed-down or disrupted transmission of the signal on bacterial infection inside phagocyte by the active ligand-complex mCD14-LBP-PAMP (LPS) through the active trans-membrane co-receptors TLR4. In this way, the induction of the inflammatory cascade reactions with the secretion of pro and anti-inflammatory cytokines is broken (weakened). Hence, we may suggest that the disrupted synthesis of acute phase proteins

(specifically, LBP) in patients with hepatic failure or graft dysfunction in the immediate postoperative period has an inhibitory effect on the course of SIR immune reactions, limiting their amplitude.

Theoretical background

In our view, the integration and interrelation of the immune and synthetic functions of the liver help to explain the phenomenon of reducing the SIR reaction amplitude in patients with a hepatic dysfunction/failure. In infectious complications, the liver becomes both the subject, and the object of developing events: on the one hand, the liver in sepsis induces and modulates the protective systemic inflammatory reactions, on the other hand, it is subjected to the damage by the mediators of these reactions. In liver failure, the stimulation of macrophage membrane receptors is reduced in its intensity that leads to disrupted intracellular signaling and a subsequent expression of genes that control the production and release of cytokines. It results in a reduced secretion of proinflammatory cytokines (e.g., interleukin-6 and others) triggering the synthesis reactions of proinflammatory acute phase proteins, including LBP. Consequently, according to the feedback principle, the reactant synthesis stimulation is reduced, which, in fact, plays a key role in the recognition, binding, and presentation of LPS and other PAMPs to macrophage cell receptors to trigger the first-line anti-infectious barrier reactions [25].

In our opinion, the course of the immediate post-transplant period is determined by several important processes: the IRI that damages both the synthetic function (a clinically relevant ability to LBP and CRP synthesis), and the function of bacterial clearance by Kupffer cells (an inability to eliminate the products of bacterial translocation and other PAMPs).

Furthermore, the postoperative course is affected by: a prolonged delivery of bacterial antigens (due to severe portal hypertension in a patient, a probably high MELD, and infection); the liver function regeneration (the liver parenchymal and nonparenchymal pools are known to regenerate asymmetrically: hepatocytes earlier, macrophages later) and its timing (the liver from a young donor regenerates faster in the body of a young recipient); and also by the genetically determined severity of IRI, SIR reactions, and rejection (with TLR4, 3 gene polymorphisms playing the leading role) [26-34].

We should note that the liver (graft) dysfunction in the early postoperative period is manifested primarily in rising bilirubin. Meanwhile, the differential diagnosis of cholestasis nature often becomes a cardinal issue. It is often difficult to determine which factors cause and support cholestasis: infection (sepsis-induced cholestasis), an IRI-associated early graft dysfunction, a rejection, postoperative mechanical causes, or a so-called small-for-size syndrome after a major liver resection? The relevance of this problem is associated with the need to take decisions that determine the further treatment strategy. And here, the treatment options and even management strategies may require making a specific, diametrically opposed decision for each individual patient. Unfortunately, the results of fast-track biopsy do not always reliably clarify the dysfunction cause, due to polymorphism and non-specific morphological signs.

However, P. Matzinger's key point on the immune system priority concern with recognizing and responding to alarm signals from damaged cells (tissues) rather than with differentiating between "self" and "non-self", in relation to the problem, leads to an important conclusion that in hepatic dysfunction, the simultaneous occurrence of the systemic reactions to

combat the damage (PAMPs and DAMPs), and rejection reactions is unlikely [35]. This gives grounds to call into question the appropriateness of the immunosuppressive therapy after OLT in the case of severe infectious complications. The pulse therapy for a probable rejection frequently applied in such cases would be rather for making a differential diagnosis (ex juvantibus).

In the end-stage LC when hepatocytes are surrounded by fibrous tissue, the absolute count of Kupffer cells is reduced in the cirrhotic liver, and the portal hypertension creates a high resistance to the intrahepatic blood flow, results in the formation of collaterals and portacaval shunt flowing from the intestine, through these shunts, bypassing the liver. We suppose that it reduces the stimulation of the hepatic macrophage receptors: PAMPs and DAMPs. However, the presence of infection, the impaired physiological protective barriers in patients with the end-stage liver disease suggest a permanent blood supply to tissue macrophages, the blood containing the substrate to induce antigen specific immune response. Thus, in terms of liver failure and a decreased blood supply to the cirrhotic liver with a reduced macrophage count (normally macrophages make 10% of the liver tissue [36]), the inflammatory reactions are limited. Perhaps, in patients with liver failure in a kind of Kupffer cell blockade, there is an imbalance in the pool of the cell-secreted proinflammatory and anti-inflammatory cytokines. This can also explain the lack of pronounced clinical manifestations of SIR in patients with the end-stage liver disease in the form of a severe SIR syndrome and septic shock, severe SIR manifestations in the OLT perioperative period. In the latter case, nonspecific clinical and laboratory abnormalities (hypotension, decreased urine output, high levels of lactate in the blood) are associated with pathophysiological changes that arise due to

the main cause (hepatic failure) and the unique pathophysiology of LT surgery (uncoupling the systemic circulation when using a classical LT technique, the presence of anhepatic period, reperfusion syndrome, etc.).

Our observations have demonstrated such unresponsiveness also in the early postoperative period during the first 3-4 days until the recovery of the liver graft immune and synthetic functions.

We should note that the recovery of liver synthetic function usually "lags behind" its metabolic function recovery and depends on the IRI severity. We explain this by a different sensitivity of circulatory acinar zones to reperfusion injury. According to current concepts, even under normal conditions, the centrilobular zone hepatocytes receive the least oxygenated blood, and so, they are more susceptible to hypoxemic injury during the organ ischemia/reperfusion [37]. Since there are still not clear in which of the 3 acinar zones the coagulation factors are synthesized, it is logical to assume that a later resume of their activity documented after the OLT followed by a graft dysfunction may indicate the centrilobular zone, the place most sensitive to hypoxia and susceptible to IRI, as being the site where these substrates are produced. On the other hand, in infectious complications, and the development of sepsis-induced cholestasis after transplantation, at a later date the synthetic function recovery is usually observed in the presence of a persistently impaired excretory function, which is usually associated with a poor prognosis. Recent studies have shown that these impairments are the result of reprogrammed metabolic functions due to the impact of pro-inflammatory cytokines on the regulation of the functioning ATP-dependent membrane transporters of bile acids that, while accumulating, cause the hepatocyte damage and cholestasis aggravation [38].

The definition of blood LBP concentrations as a marker of an emerging or latent infectious complication in surgical patients did not become widely used because of a scanty evidence base [39]. Probably, an active movements of LBP in conjunction with LPS from blood, the fixation of that complex on mCD14 receptors followed by the expression of TLR-4 co-receptors, the transformation into a sCD14 soluble complex and its entering the free circulation after fulfilling the signaling function make the definition of "unbound" LBP fraction insufficiently informative. Meanwhile, the activity of the processes where the LBP is in a bound state is not taken into account. This version can indirectly be favoured by "difficult to explain" changes in a concentration of presepsin, a new inflammation marker, that is per se a truncated form of sCD14 after the cleavage of the so called C-terminal site responsible for LPS binding [40]. Since it is believed that the presepsin level increase is possible only after the phagocytosis activation, it is logical to assume that in terms of normal synthetic liver function, a high presepsin level may indicate an active LBP synthesis, without which sCD14, and its truncated form: the sCD14-ST subtype (presepsin) can not be formed [40-41]. Presepsin is formed during the further transformation of the sCD14-PAMP-LBP complex by proteases under conditions of bacterial infection, and represents a truncated sCD14 fragment of 64 amino acid residues with a molecular mass of 13 kDa [40-42].

There is an evidence that, besides the signal function, the sCD14-PAMP-LBP complex in its free form (the protein is detached from the membrane, becoming plasma-soluble) induces inflammatory reactions in the cells lacking mCD14 receptors on membranes, the so-called CD14-negative cells (specifically, endothelium and epithelium cells [43, 44]. Probably, this mechanism plays a role in the MODS progression in patients with liver

failure, despite a reduced stimulation of LBP synthesis acting as a "catalyst" of anti-infection immunity reactions.

This is indirectly indicated by high presepsin levels in deceased patients with severe hepatic insufficiency and slowly progressing MODS without any signs of severe systemic reactions that would have followed as a result of phagocytosis activation. Furthermore, the presence of the mechanism inducing the inflammatory responses through a direct stimulation of LPS hepatocyte membrane receptors TLR-4 without LBP involvement can explain a torpid MODS course in patients with liver failure without hyperergic uncontrolled SIR reactions such as the septic shock.

It remains unclear, whether the quantitative LBP reduction alone could explain the decreased immune reactions of SIR in patients with hepatic dysfunction/failure. As it is known, the qualitative alterations of proteins (e.g., albumin) are possible in conditions of impaired liver synthetic function and can also affect their functional properties [45]. Meanwhile, focusing on one of the mechanisms inhibiting the launch of the systemic response in patients with the hepatic failure that is global by nature as the liver plays a key role in the immune system function; however, we do not exclude the presence of other defects in the process of launching a cascade of SIR reactions.

Evidence

In addition to above described clinical phenomena, a logical argument in favor of this hypothesis may be a well-known fact about the key role of the liver in a systemic immune response, including that to infection. The liver macrophages (Kupffer cells) have also been proved to make up 80% of total plasma cells in the body and therefore carry most of the load of

maintaining the reactions of nonspecific anti-infective immunity [46]. It is logical to assume that liver function impairments would lead to weakened immune responses. This conclusion may be confirmed by the above mentioned clinical phenomena that are well known in the daily practice of the intensive care for patients with severe liver diseases.

The analysis of clinical and laboratory parallels in patients with hepatic failure undergoing LT also revealed certain patterns that support the above hypothesis. Interesting is the fact that the values of new laboratory markers of infectious inflammation, namely PCT, presepsin, quantitative values of CRP in patients with liver failure/dysfunction significantly differ in their reference values from those of "common" infectious patients (with preserved liver function). Thus, all recipients who developed postoperative infectious complications, preoperatively had shown normal or moderately elevated PCT concentrations with low concentrations of CRP and presepsin.

Due to non-specific PCT values in patients undergoing a highly traumatic intervention accompanied by a massive destruction of tissues and cells with the DAMP formation, the interpretation of the growth in this parameter is problematic for the differential diagnosis of infectious complications, and consequences of severe surgical trauma [47]. In this case, the PCT level and its changes over time may appear false positive in the diagnosis of sepsis. It should be noted that the intensity of PCT production in sepsis, or tissue damage is not directly associated with the liver function; according to current concepts, PCT is produced in various organs and by various cell types [48].

In patients with severe infectious complications, a 50-100-time growth in PCT was observed at day 0-1 after OLT that was difficult to explain by the inflammatory process developed due to bacterial or fungal infection.

Previously, it was found that the blood PCT was increasing for 6-12 hours after the inflammatory process activation [47, 49]. We suppose that the pre-existing portal hypertension, portal vein cross-clamping in an anhepatic period, and the lack of bacterial clearance by Kupffer cells in the early neohepatic period promote the bacterial translocation and antigenemia, which, in our opinion, lead to increased PCT levels.

It is logical to assume that the absence of phagocytosis function, as such, with broken systemic inflammatory reactions during the anhepatic OLT stage or with a limited amplitude of these reactions in the perioperative period creates the conditions for the escalation of bacterial infection.

The PCT growth reflects these processes, especially in infected recipients; however, due to a non-specific increase of this parameter with respect to infection, it is difficult to interpret correctly the absolute values of the PCT concentration as a marker of sepsis in postoperative patients.

At the same time, in patients with a severe hepatic failure and impaired synthetic liver function, the variables indicating acute inflammation phase reactions (e.g., CRP, LBP) demonstrate low concentrations that do not correlate with the levels of bacterial contamination markers.

At day 1-4 of postoperative period, as the functions of "new" liver were recovering, the patients with infectious complications showed the growing levels of acute phase proteins and presepsin. Among all patients who died in this group, the clinical manifestations of infectious complications in severe SIRS, sepsis, and septic shock were preceded by the growth of the parameters reflecting the active recovery of the graft synthetic function (the recovery of the synthesis of V, VII, IX and AT III coagulation

factors, acute phase proteins: CRP, fibrinogen, etc.). Meanwhile, a rapid growth of the presepsin level was recorded.

Significant was the fact that the absence of severe IRI in the transplanted graft and a rapid recovery of its function had a paradoxical effect: in that case, the inflammation was rapidly generalized with the development of septic shock and MODS (see Clinical Example 3). Such pattern was observed in 6 patients.

On the contrary, in recipients with the graft dysfunction, a torpid infection course was observed without clinical and laboratory manifestations of severe SIRS and septic shock. In case of progressing infectious complications secondary to the liver failure, the fatal outcome occurred after a long period (up to 3 months) of persistent sepsis with MODS development.

According to the proposed hypothesis, the concept of a possible controlled pharmacological blockade of the Kupffer cell immune function could be attractive to prevent the development of SIRS uncontrollable reactions. In the experiments aimed to assess the phagocytosis effect on the development and course of acute lung injury, and to explore a possible reduction of inflammatory reactions caused by the ischemia-reperfusion after liver resections in rats, the gadolinium chloride, the blocker of hepatic macrophage function, demonstrated the attenuation of inflammatory reactions in a series of studies both in vitro, and in vivo; and meanwhile, we observed an increased anti-inflammatory cytokine secretion by Kupffer cells [50]. Other experimental studies demonstrated a decline in the activation of Kupffer cells by using gadolinium, calcium channel blockers [51-53], pentoxifylline [54] in order to improve the transplanted graft survival. Donor organ washing with solutions containing calcium channel blockers, glycine, antioxidants, adenosine, and energy substrates after the organ preservation

also reduced the Kupffer cell activation, and endothelial cell damage, and improved the graft survival [55]. In rat experiments, X. Wu et al. found that the addition of LBP-inhibiting P12 peptide, reduced the endotoxin-induced macrophage activation and mortality in septic shock [56].

Our hypothesis was supported by the study of G.L.Ackland et al. (2010) who demonstrated a reduced severity of systemic inflammation reactions by using polyethylene glycol in the experiment on the animal model of the septic shock induced by the LPS administration [57]. It has been emphasized that the polyethylene glycol is an inert non-immunogenic molecule which accumulates in hepatic macrophages. We believe that it is possible to reconsider from this point a many-year experience of using synthetic colloids (polyvinyl-pyrrolidone, hemodesis) in clinical practice aiming at "detoxification", as they are known to retain in macrophages for long. Wasn't that related to a known anti-inflammatory clinical effects of hemodesis, which at that time were explained by binding "toxins", the stimulation of diuresis, etc.? The same can be referred to the effects of using perfluorane that is also completely absorbed by macrophages through blocking their activity for a while.

Moreover, our hypothesis could indirectly be confirmed by the data on the prevention of the inflammatory response generalization by means of portocaval bypass evading the liver in experimental animal models of pancreatonecrosis [58, 59]. In that case, unlike the control group, no injury of the target organ (the lung) developed. This aspect can be applied to consider a good tolerance to a transjugular intrahepatic portosystemic shunt (TIPS) procedure by the patients with the end-stage liver disease (portal hypertension, resistant ascites). As a rule, it was not accompanied by a systemic inflammatory response.

As the liver is retrieved from a brain-dead donor, we assume that the organ can be damaged as early as in a donor's body as a result of SIR induced by the donor's critical condition [60]. The investigated counts of activated(invalid) hepatocytes (the expression of amphoterine or high-mobility group protein B1 [HMGB1]) and Kupffer cells (the expression of CD68 receptors) in the donor liver biopsy and the studied correlation between the degree of expression for these cells and the levels of proinflammatory and anti-inflammatory cytokines in the blood flowing from the liver immediately after the reperfusion and at 1 hour later showed that:

a) The activation of Kupffer cells (a marked expression of CD68 receptors) occurs as early as in the donor's body;

b) There were no correlation found between the levels of IL-6, 8, 17, 23, TNF-α, macrophage inflammatory protein (MIP)-1α, P-selectin, on the one hand, and the degree of expression of HMGB1 and CD68 receptors, on the other hand;

c) The use of tacrolimus immunosuppressant solution possessing anti-inflammatory properties for donor organ washing before transplantation showed a statistically significant reduction in the growth of the blood level of the IL-17 pro-inflammatory cytokine compared to the control group in a series of studies; moreover, there was a tendency towards a decreased expression of Kupffer cells [61 62].

With regard to our proposed hypothesis, this means that, despite an excessive DAMP production (the DAMPs being, in fact, the activated Kupffer cells, and damaged hepatocytes or HMGB1) secondary to the temporary perioperative dysfunction of the transplanted liver, no generalized non-infectious SIR reactions with remote lesions of other parenchymal organs occur. Probably, this can explain the above-mentioned phenomenon

of tolerance to a highly traumatic LT surgery in the patients with a high functional ASA class. Furthermore, one can assume that the present liver dysfunction can smooth over the genetic differences (or their manifestations) in the recipient's body SIR reactions induced by the products damaging its own cells (DAMPs). Also this study has confirmed that not only SIR reactions, but also some other mechanisms are involved in inducing the graft damage during IRI.

The application site

1. In our opinion, the most interesting is the prospect of using the above hypothesis of the hepatic dysfunction/failure impact on the induction of SIR reactions as a model for the search of new trends in the prevention of the immune system hyperactivity in sepsis. It seems logical to search the possible ways to influence the SIR modulation (an experimental use of phagocytosis short-range inhibitors; a controlled inhibition of the acute phase protein synthesis). It is important to establish whether the hepatic dysfunction/failure uncoupling the basic liver functions that normally are interconnected, can be used as a model to develop the methods to control SIR reactions?

2. Understanding of these complications may optimize management strategies for the patients with high risk of infectious complications after OLT.

In reference with the proposed hypothesis, new opportunities emerge in clinical practice to predict the risk of infectious complications, to make their early diagnosis (differential diagnosis), prevention, and a comprehensive treatment in the patients with liver failure in the OLT perioperative period. In our opinion, the sepsis-induced cholestasis

developed in the period of restoring the liver immune and synthetic functions leads to a further body's damage due to a formed closed pathologic circle: the stimulation of Kupffer cells by LPS – the induction of SIR – hepatocyte damage – the bile acid transport derangement, cholestasis – additional damage of hepatocytes and their destruction. In our opinion, theoretically reasonable could be the preemptive measures aimed at preventing the development of the above-mentioned "circulus vitiosus". The first is the prevention of the LPS excessive accumulation by a timely cleansing and elimination of possible biological fluid collections that serve the environment for the infection progressing in infected patients. Such environment may be formed by unavoidable blood collections, clots, and ascites in the abdominal cavity of the infected patients after OLT, especially of those with the complications of surgery, and unstable hemostasis, and those after major resections. The practice shows that the traditional surgical drains are ineffective in such situations.

In our opinion, a revision is needed for the traditional indications to relaparotomy adopted in the practice of general abdominal surgery and based on the clinical and laboratory findings suggesting the progression of inflammation in the abdominal cavity in patients with hepatic dysfunction/failure (read: in infectious complications of the liver transplantation and resection surgery). Relaparotomies and abdominal cavity debridement performed when MODS is already progressing or after the septic shock development are usually the delayed measures and ineffective de facto.

In addition, based on P. Matzinger's postulate on the immune system priority in response to injury over rejection reactions, we can make an important practical conclusion on the appropriateness and necessity of the

maximal reduction or withdrawal of immunosuppressive therapy in the case of severe infectious complications in patients after OLT.

Thus, the key determinant of the management strategy for the patients at high risk of serious infectious complications after abdominal surgery includes the measures to prevent the occurrence of reservoirs with infected biological secretions (usually highly virulent nosocomial Gram-negative flora) that may be the source of LPS high concentrations. Excessive numbers of LPS entering the bloodstream during the recovery of the deranged liver synthetic and immune functions generate and maintain SIR reactions causing a secondary damage to the liver and other organs, and contributing to the MODS progression.

On the hospital flora virulence

The analysis of more than 350 OLTs undertaken without infectious complications suggests that the postoperative natural delivery of LPS as a product of commensal intestinal flora, even in an inevitably increased permeability of entero-hematic barrier after surgery does not lead to the induction of uncontrolled SIR reactions and MODS development. The hospital Gram (-) multidrug-resistant flora was isolated in all the cases of severe infectious complications developed after OLT.

The obtained clinical experience also suggests that the SIR reactions induced by the PAMPs that are formed by the hospital strains of Gram (-) microorganisms occur more actively and destructively, unlike the PAMPs that are the products of the commensal gut microflora. Since it is postulated that any molecular patterns of infectious nature (PAMPs) trigger the similar reactions, it is logical to assume that their amplitude and intensity may be associated with higher concentrations of PAMPs (LPS in our case) entering

the bloodstream from the infection source(s) and a longer duration of this entering, rather than only with genetically determined characteristics of these reactions in the body of an individual patient. If there are undrained infection foci in the form of infected body fluid collections, the antibiotic therapy aimed at inhibiting the growth of abnormal microflora appears ineffective (even if administered as a result of antibiogram) and, in our experience, does not prevent the progression of complications and MODS.

The application of new extracorporeal detoxification techniques (LPS-sorption, plasma exchange)

Currently, options to prevent SIR reactions are actively investigated, including the prevention by using extracorporeal techniques of a selective LPS elimination (biospecific LPS sorption); by making attempts to eliminate inflammatory mediators (via plasma exchange, a high-volume hemofiltration, a CytoSorb hemoperfusion, the plasma filtration with adsorption i.e. a Coupled plasma filtration-adsorption [CPFA]) [63-65]. There are also reports on using the combination of LPS-sorption and CPFA [66]. Despite the fact that the above method, when used alone or in combination, showed a positive effect on the number of surrogate clinical and laboratory parameters, we should state that this trend in intensive therapy did not bring a breakthrough in the global strategy to combat sepsis. Also, of note is a high cost of the mentioned techniques, difficulties in their standardizing, and, as a consequence, the lack of an evidence base. With regard to the proposed hypothesis, the logical questions of "what?", "who?", "when?" and "how much?" arise in relation to the classical "weak" points of using the methods of extracorporeal detoxification for sepsis in intensive therapy. In this regard, the method of eliminating the molecules that induce

and support an avalanche-like, poorly controlled process of the systemic self-damage usually lags behind the time. Besides, the endotoxin entrance to circulation a priori is considered to cease or be reduced in response to the applied hardware techniques for its elimination, however, it is not always possible to achieve in practice. Moreover, the individual genetic determinacy of SIRS reaction amplitudes is not taken into account either. Obviously, in this case, the blocking effect on the modulation of the initial SIRS induction stages must be more preemptive.

With continuous entrance of LPS large quantities in circulation from the undrained lesions, the specific and non-specific methods (LPS-sorption, plasma exchange) aimed at eliminating these substances from the bloodstream, from our experience, have a limited effect due to empirical approaches to their application and difficulties in assessing their benefits. With regard to using these methods in the complex treatment, it would be logical to reconsider the starting time for these procedures and their duration. Also, an available laboratory marker to assess the efficacy of these technologies is strongly needed.

The way in which the above theoretical calculations can be used in practice is illustrated by the following case report.

Clinical Example 4

A female patient S., 59 years old, Medical Record No. 23281, was transferred in critical condition from one of the regional hospitals to the Intensive Care Unit of the Organ and Tissue Transplantation Center. Medical history, the clinical presentation, and additional lab tests revealed an associated injury of the bile ducts and the hepatic artery, ischemic cholangiopathy with necrosis of intrahepatic biliary tree after surgical

treatment of acute calculous cholecystitis (cholecystectomy) with the development of sclerosing cholangitis, multiple bilobar liver abscesses, the subhepatic abscess and external incomplete infected gallbladder fistula (*Pseudomonas aeruginosa*). The underlying disease was complicated by sepsis, cholestatic hepatitis, and sepsis-associated cholestasis, MODS with Stage II hepatic encephalopathy. There was also bilateral hydrothorax and ascites.

The surgical history included: the first surgery performed in one of the central district hospitals at 2.5 months prior to admission in our Center, and then she underwent 2 interventions for draining the liver abscesses and subhepatic space. Despite the intensive therapy measures with addition of extracorporeal techniques (3 Fractionated Plasma Separation and Adsorption [FPSA] procedures, Prometeus technology), the patient's condition progressively deteriorated. The patient was admitted in our Center in critical condition with hyperthermia up to 38.6 °C, fatigue, weakness, severe jaundice, and encephalopathy. The patient was unable to cooperate due to severity of her condition. There was an external fistula with scanty pyo-serous bile-containing discharge in the right subcostal area. Diuresis was 800 ml/day.

Hematology laboratory values read as follows: erythrocytes $2.9x10^{12}$/L, hemoglobin 98 g/L, WBC count $16.4x10^{9}$/L, stab neutrophils 18%, platelets $500x10^{9}$/L, hematocrit 0.25; total bilirubin 604 pmol/L, direct bilirubin 481 mmol/L, urea 9 mmol/L, creatinine 62 pmol/L, GFR estimated by cystatin C 28 ml/min, total protein 55 g/L, albumin 24 g/L, alanine 95 U/L, aspartate aminotransferase 30 U/L, alkaline phosphatase 586 U/L, amylase 37 U/L, international normalized ratio (INR) 1.3, fibrinogen 2.3

g/L, activated partial thromboplastin time 40 s, prothrombin index 69%, AT III 70%, CRP 206 mg/L, PCT 3.4 ng/ml.

After ex consilio additional examination, due to hopeless prognosis for conservative treatment and for any possible surgical resections, the patient was placed on a waiting list for LT. The present sepsis and MODS were relative contraindications for liver transplantation that was considered a single possible option of definite treatment and saving the patient's life.

Prior to surgery, the patient received the intensive therapy in the form of a "bridge" to LT. Intensive therapy was aimed at improving the homeostasis disorders and its maintenance, and involved antibiotic therapy administered according to the bacteriology test results and detected sensitivity; the patient received 3 sessions of exchange plasmapheresis (1-1.5 of circulating plasma volume) for increasing hyperbilirubinemia.

At 14 days after admission in the Center (and 3 months after the first surgery), the patient underwent OLT. The surgery was uneventful with blood loss of 1 liter; the clinical, laboratory data and instrumental test results confirmed the immediate function of the transplanted organ. The patient was extubated at 5 hours after the operation having stable hemodynamics, respiratory function, and homeostasis parameters. Normothermia, and adequate urine output were documented.

On the next day after surgery, the urine output decreased, the encephalopathy deterioration at normal body temperature; there were complaints of an abdominal pain and increased distention. Hemodynamics and gas exchange parameters remained stable; there was neither increase in lactate levels, nor deficit of buffer bases in blood plasma. The increase in inflammation variables was documented as follows: in white blood cells from 24 to 31 x 10^9/L, PCT from 8 to 22.5 ng/ml, presepsin up to 3268

pg/ml, CRP from 69 to 83 mg/L. There was a marked growth of pancreatic amylase up to 2400 U that was suspicious of postoperative pancreatitis. A series of abdominal ultrasonography examinations revealed the fluid collection in the abdominal cavity and excessive intestinal gas. Abdominal and thoracic computed tomography (CT) scanning was performed yielding the following pathological findings: an increased right hydrothorax with compression atelectasis without the signs of pulmonary tissue infiltration, a minor volume of free fluid in the pelvic cavity. At 29 hours after surgery, the relaparotomy for surgical revision was performed to the patient. It revealed the signs of peritonitis: a moderate amount of cloudy effusion collections with a touch of fibrin, thick pancreas. The abdominal cavity was cleansed. After the surgery, the patient received a plasma exchange session (the exfusion of 3.6 liters), and LPS-sorption using anti-lipopolysaccharide sorbent on a polymyxin matrix, the perfusion volume was 3.6 liters.

Subsequently, the regular planned surgical cleansing of abdominal cavity and surgical wound was performed at an interval of 2-3 days. During the 2nd relaparotomy, the wound therapy vacuum system ("WaterLily^{TM} Wound Therapy", Italy) was applied, that was replaced at subsequent surgical procedures. A total of 6 reoperations were performed. Indications for a reoperation included the lack of improvements in clinical and laboratory parameters for 1-2 days of the postoperative period. At 5-12 hours after each relaparotomy, LPS-sorption was performed using anti-lipopolysaccharide sorbent.

The patient's condition stabilized and progressively improved in response to the conducted complex treatment that, besides the options listed above, also included all the standard measures of a post-operative intensive therapy intended for post-transplant patients. The multiple organ dysfunction

was resolving, the encephalopathy manifestations regressed, the gastrointestinal tract and kidneys recovered their functions, cholestasis resolved; at the time of patient's transfer from the ICU to a hospital ward, the blood total bilirubin was 28 pmol/L, the GFR activity increased from 28 to 118 ml/min/1.73 m^2 (estimated by cystatin C), blood levels of glucose, total protein, fibrinogen normalized as did the INR and transaminase activities. The activity of coagulation factors II, V, and VII reached 60%. The AT III activity at the time of transfer from ICU was 67% and postoperatively decreased to 28% before the 2nd repeated surgery and after the 3rd relaparotomy; on the 1st day after the OLT, the AT III activity was 36%. The postoperative WBC count ranged from 40.1 x 10^9/L to 12 x 10^9/L, the band neutrophil making from 20 to 8% (at the time of the transfer to the hospital ward), CRP was 60 mg/L at postoperative day 0 with a maximum rise to 172 mg/L before the 2nd relaparotomy, and it decreased to 36 mg/L on the day of the transfer. The PCT level at day 0 was 8.9 ng/ml, it increased maximum to 22 ng/ml (before the 1st laparotomy), and declined to 0.68 ng/ml after the 3rd surgery. The PCT level before discharge from the ICU was 0.86 ng/ml. The presepsin level reached its maximum of 3268 pg/ml before the first surgical revision; during the postoperative treatment, it ranged from 792 to 1112 pg/ml (before the transfer from the ICU).

The cultures of contents from the abdominal cavity, and wound drains (the material for culture was taken during every surgery) revealed the following flora: *Enterococcus faecium* (abdominal cavity) sensitive to linezolid, vancomycin, teicoplanin, tigecycline; *Pseudomonas aeruginosa* (wound drains) sensitive to colistin only. The post-OLT antibacterial therapy administered to the patient included colistin, tigecycline, co-trimoxazole;

caspofungin was given to prevent infection; later on, at day 12 after OLT, tigecycline in the above scheme was replaced by linezolid, and meronem.

At day 12 after transplantation, the urine cultures revealed Pseudomonas aeruginosa resistant to colistin (with an identified sensitivity to piperacillin/tazobactam). As an immunosuppressive therapy while being in the ICU, the patient received only corticosteroids (per standard protocol established in the center). On the 17th day after the OLT, the patient was transferred to the specialized hospital department where the treatment for wound suppuration was continued; and at day 28, she was discharged for an outpatient treatment.

Conclusion

The provocative title of the article was chosen deliberately; actually the hepatic dysfunction/failure does not protect the patient. We declare that under the condition of delayed SIR reactions, the clinicians has an extended "opportunity window" to make the decision on the search for and/or correction of the management tactics for patients with sepsis.

In our view, the presence of liver failure limits a systemic inflammation response, reduces the amplitude of SIR reactions, and restrains the development of uncontrolled self-damage in the form of fulminant "burst out" (septic shock, severe SIR). In clinical practice, the infectious complications in patients with hepatic failure vary in their clinical course, in laboratory signs of inflammation and their changes over time; they are persistent by nature, since the formation of MOD components is stretched in time. In general, the systemic inflammation reactions in these patients become protracted, while in clinical practice, some difficulties arise with the differential diagnosis of patients, and with making timely changes of their

treatment. We believe that one of the mechanisms of the immune system reactivity disorders in these patients may be a reduced synthesis of lipopolysaccharide-binding protein (LBP) that plays a fundamental role in modulating the induction of SIR defense reactions.

It should be noted that in the current scientific literature on the liver role in the development of severe infectious complications in patients with hepatic dysfunction/failure, nobody raised the issue on the impact of low LBP levels on limiting the immune response reactions. Experimental studies are required to test the hypothesis.

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