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Hepatopulmonary syndrome and liver transplantation: the review and a case report

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Hepatopulmonary syndrome is a liver disease complication characterized by the clinical triad of an advanced chronic liver disease, a pulmonary vascular dilatation, and a reduced arterial oxygenation (hypoxemia: PaO_2 less than 70 mm Hg at rest) in the absence of intrinsic cardiopulmonary disease. Precapillary vasodilatation, intrapulmonary angiogenesis and hyperdynamic circulation lead to arteriovenous shunting and reduced gas diffusion. In case of detecting macroscopic shunts, the pulmonary artery branch embolization could be performed. However, the hepatopulmonary syndrome can be cured nowadays by means of liver transplantation only. A 5-year survival in these patients is about 70%. The observed mortality is the highest during the surgery or early after, especially in patients with PaO_2 lower than 50 mm Hg. It ranges from 8.5 to 29%. A prolonged oxygenation support is often required after liver transplantation

using invasive or non-invasive ventilation, or even extracorporeal membrane oxygenation. In this review, we have focused on the recent advances in this field as described in available literature and have presented a case report of successful liver transplantation in a patient with a severe hepatopulmonary syndrome.

Keywords: hepatopulmonary syndrome, liver transplantation, liver cirrhosis

Introduction

Hepatopulmonary syndrome (HPS) is a severe complication of liver disease and/or portal hypertension that is characterized by an impaired venous blood oxygenation resulted from a pulmonary vascular dilatation [1, 2]. Usually, HPS occurs in liver cirrhosis, but there are case reports of this complication occurring in patients with prehepatic portal hypertension without chronic liver disease, or with the Budd-Chiari syndrome and even with an acute or chronic inflammatory liver disease without liver cirrhosis and portal hypertension [3- 7].

Diagnosis of HPS is documented in the presence of the following evidence: liver disease, pulmonary vascular dilatation, arterial hypoxemia (partial pressure of arterial oxygen [PaO_2] under 70 mmHg at rest in a sitting position), the alveolar-arterial oxygen gradient increased by over 15 mm Hg, or by over 20 mm Hg in patients of 64 years and older [8, 9].

HPS has been classified into 2 types, depending on the degree of pulmonary vascular abnormalities: the first type is characterized by a diffuse precapillary dilatation of the pulmonary vascular bed; in this case the blood oxygen saturation may increase in response to the oxygen therapy. The second type is characterized by an arteriolar dilatation and the formation of

arteriovenous shunts, wherein the oxygen breathing does not improve the patient's condition [8].

HPS of different stages can be found in patients with liver cirrhosis as frequent as from 10 to 30% [10-12].

The HPS risk factors include living at a low altitude (above sea level), and a native genetic predisposition. M.A.Valley et al. examined the data of 65,264 candidates for liver transplantation (LT) and showed that living at a low altitude was associated with higher risks of HPS development than living at a high altitude (the HPS risk reduced by 46% with each 1000 m increment of altitude) [13].

Recent studies have found the relationship between HPS and the telomere syndrome. This syndrome is caused by abnormal telomere shortening and usually manifests itself as idiopathic pulmonary fibrosis and emphysema that may be concomitant with HPS [14]. Also, the genetic analysis has shown that a single nucleotide polymorphism in eight genes involved in the angiogenesis regulation (namely, caveolin, endoglin, NADPH-oxidase 4 receptor, type II estrogen receptor, von Willebrand factor, Runt-related transcription factor 1, collagen type XVIIIa-1, tyrosine kinase) is a HPS risk factor [15].

Pathogenesis

The HPS pathogenesis has not been well studied yet, but the precapillary pulmonary vasodilation is known to play a key role in the disease development, as it causes a ventilation-perfusion mismatch and an increase in the alveolar-arterial oxygen gradient [1, 16, 17]. Precapillary vasodilation impedes the oxygen molecules from reaching the red blood cells at the center of a dilated capillary [18] (Fig. 1 [19]). The hyperdynamic

circulation exacerbates this condition because it increases the blood flow rate in the lung capillaries, which reduces the time for gas exchange [20, 21]. The circulating angiogenic growth factors stimulate angiogenesis in the lungs leading to the formation of shunts de novo. Retained hypoxemia after transplantation and a positive effect of endothelial growth factor (VEGF) blockers confirm the presence of additional shunts [22, 23].

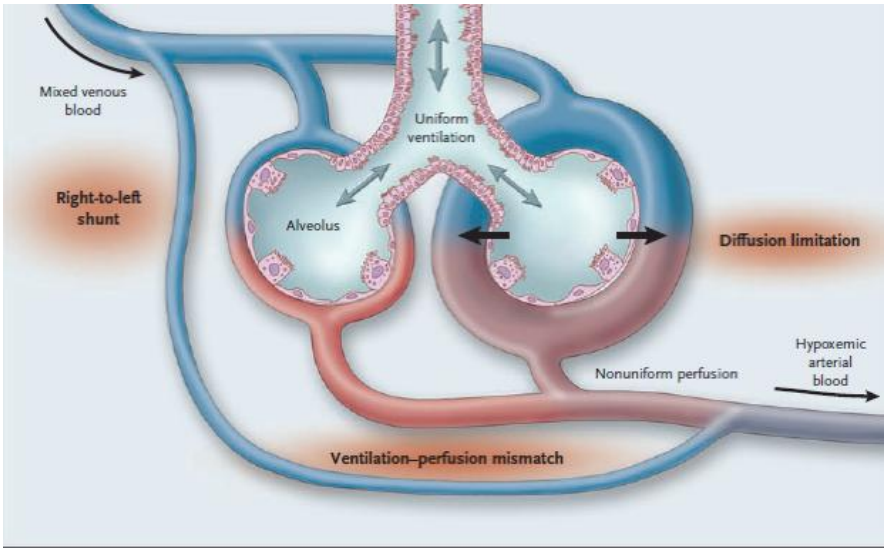

Fig. 1. Mechanisms of an impaired oxygenation in hepatopulmonary syndrome

There are several mechanisms of pulmonary vasodilation. An increased pressure in the portal vein system leads to the development of portal gastro- and enteropathy, which contributes to the bacterial translocation across the gut wall, while the liver dysfunction causes the prolonged circulation of endotoxins [3]. In this case, the lungs take over the function of inactivating endotoxins: blood monocytes actively migrate to the pulmonary interstitium, where they differentiate into lung macrophages. The latter, in turn, phagocytose foreign substances from the blood, become activated, and synthesize a variety of vasoactive mediators such as the

tumour necrosis factor-alpha (TNF), heme oxygenase (HO), carbon monoxide (CO), endothelin-1 (ET-1), and nitric oxide (NO) [24].

Experimental and clinical data suggest that an increased NO production in the lungs is a central element in the HPS pathogenesis. An increased NO-sintase activity induced by TNF and ET-1 leads to an increased NO concentration that causes a vasodilation. The increased NO concentration in the exhaled air of HPS patients correlates with the increase in the alveolar-arterial oxygen gradient [16, 25]. CO, similarly to NO, is a vasodilator, and it also stimulates angiogenesis [26].

Clinical presentation

Dyspnea is common in all patients with HPS; however, it may occur due to ascites and hydrothorax developed in decompensated liver cirrhosis. A more specific symptom is the platypnea-orthodeoxia [27]. This symptom is manifested as growing dyspnea and decreased blood oxygen saturation parameters (SpO_2) and PaO_2 (by over 5%, or by 4 mm Hg) at changing the body position from horizontal to vertical [28]. Other symptoms typical for HPS are less specific and can occur in the patients with liver cirrhosis without HPS; they include a stellate angioma and dilated venous portocaval collaterals [29]. Peripheral cyanosis and "*drumstick fingers"* (or clubbed fingers) are the markers of chronic hypoxia that can develop in any lung diseases unrelated to liver disease [30].

In the majority of patients with HPS it is asymptomatic or accompanied by mild dyspnea. Interestingly, the HPS severity does not correlate with the MELD score (Model for End-Stage Liver Disease), and Child-Pugh class, i.e. the HPS may develop regardless of the liver disease progression [31].

Making diagnosis

The first step recommended while making the diagnosis of HPS is a noninvasive measurement of SpO_2 using a pulse oximetry, and then the analysis of arterial blood gases (PaO_2). The diagnosis is confirmed by the contrast-enhanced transthoracic echocardiography (EchoCG) and lung perfusion scintigraphy (PS) using ^{99m}Tc-labeled macroagregated albumin [1]. A reduced saturation less than 97% in the vertical position of the patient while breathing ambient air indicates the presence of hypoxemia. Also, the SpO_2 measured values shall be comparatively assessed before and after changing the body position from horizontal to vertical: if the change in SpO_2 is equal to or greater than 4%, it indicates the presence of orthodeoxia [32, 33].

Contrast-enhanced EchoCG

A prepared saline solution stirred preliminary to form small air bubbles is used as a contrast agent for echocardiography. The finished solution is administered intravenously. Bubbles are well traced by the ultrasonic probe. Normally, the bubbles shall be found only in the right chamber of the heart. In case of HPS, the contrast passes through dilated pulmonary capillaries (the normal pulmonary capillary diameter is equal to 8 microns). So, the presence of bubbles in the left chambers of the heart is indicative of arteriovenous shunts. Meanwhile, a differential diagnosis should be made to differentiate between intracardiac and intrapulmonary blood shunting: in patients with intracardiac shunting, the contrast agent enters the left chambers after 1-2 cardiac cycles (early shunting; while in

patients with HPS, the bubbles appear in the left atrium only after 4-8 cycles (late shunting) [34, 35].

Transesophageal echocardiography is a more sensitive method, but the presence of esophageal varices is a contraindication to using this technique [17, 36].

Perfusion scintigraphy

PS is a less sensitive method compared to the contrast-enhanced EchoCG. It is based on registering the radioisotope radiation from ^{99m}Tc-labeled macroaggregated albumin (> 20 microns in diameter). Normally, the entire agent is retained in the lungs, since the microspheres are not capable to pass through the pulmonary capillaries of the normal diameter. In case of HPS, some portion of the macroaggregate penetrates through the dilated lung capillaries and enters the capillaries of the brain, kidneys, and the spleen, and all that is recorded by the device [37, 38]. An acceptable extrapulmonary drug accumulation (shunt fraction) is no more than 6% [39].

A contrast-enhanced angiography of pulmonary vessels allows visualization of large macroscopic arteriovenous shunts that can immediately be embolized. However, this is an invasive technique, and less sensitive than the contrast-enhanced echocardiography and PS [40].

The external respiratory function assessment, radiography, and computed tomography do not detect pulmonary abnormalities typical for HPS, and are used to exclude a concomitant pulmonary pathology [1].

Treatment

Pharmacological therapy

Despite numerous studies, efficient conservative therapies for HPS have not yet been found. The formulations of somatostatin, almitrine, indomethacin, norfloxacin, L-NAME (N-nitro-L-arginine methyl ester) and aspirin showed no proper effect [41, 42]. The pentoxifylline formulation proved effective in relation to oxygen saturation values, but the sample size was too small to make definite conclusions [43, 55]. Some attempts were made to use the methylene blue after LT to reduce hypoxia; that was described in a single clinical case report [44].

The effect of rosuvastatin and anti-TNF antibodies on the angiogenesis and vasodilation is currently under study. The experimental animal studies have demonstrated a decrease in the alveolar-arterial oxygen gradient, the decreased plasma concentrations of TNF, NO, and endotoxins [45-47].

Transjugular intrahepatic portosystemic shunt (TIPS)

The TIPS procedure is used to control portal hypertension and prevent its complications. The impact of the procedure on HPS course is ambiguous: there are case reports demonstrating either the symptom improvement, or no change [48, 49]. TIPS is recommended for use to treat the portal hypertension. The procedure may have a positive effect on patients with HPS, as it eliminates the portal hypertension and prevents its complications that worsen the prognosis regardless the HPS course [50].

Embolization of pulmonary arteries

The embolization of pulmonary arteries is one of the promising methods of the HPS palliative treatment. Reducing the number of arteriovenous shunts improves the oxygen saturation and a patient's condition [18]. Many authors consider the embolization to be the best treatment for type I HPS, both before and after transplantation [40]. Previously, the procedure was considered helpful for type II HPS only, i.e. for cases of local dilation of the pulmonary artery branches. In recent years, there have been scarce reports on the successful use of this technique in patients with type I HPS (the diffuse dilation of arterioles). Clinical case reports of using the embolization of pulmonary arteries for HPS are too few to recommend this technique as a routine treatment for HPS of both type I, and type II [40, 51, 52].

Liver transplantation

Patients with HPS having severe hypoxemia (PaO_2 <60 mm Hg) should be considered as candidates for LT, and they should be given the priority on the waiting list [41]. In initially severe hypoxemia (PaO_2 <45-50 mm Hg), symptom worsening is possible in the early postoperative period, and the incidence of adverse outcomes becomes higher [53, 54]. A 5-year survival of patients with HPS after LT is 76%, compared to 26% in the natural course of the disease; so HPS is an independent indication for transplantation even in compensated cirrhosis and low MELD score [41, 55].

Extra points to MELD score

According to the study by Pascasio et al., the presence of HPS is associated with an increased mortality on the waiting list [56]. Given the

poor prognosis of patients with HPS, many centers practice assigning extra points to such cases on the waiting list (22 points) [41]. This system can shorten the time of awaiting for a donor organ and reduce mortality in patients with this severe complication [41]. The stage of the disease does not affect the postoperative prognosis, but severe hypoxia is a risk factor of a high mortality after transplantation [54, 57]. Giving the priority enables to prevent the disease progression and thus to reduce the early postoperative mortality. Obviously, the careful regular monitoring of hypoxemia severity is required for those on the waiting list of [54].

Specific features of surgery

The most important task of anesthesia for the patients with HPS during LT is to maintain a satisfactory arterial oxygen saturation. Even in severe hypoxemia, PaO_2 increases substantially in most patients when breathing 100% oxygen [19].

The effect of chosen anesthesia (inhalation or intravenous) in HPS has been studied. No differences in the oxygenation level at 30 minutes after induction of anesthesia were seen [58].

Given orthodeoxia phenomenon, a strictly horizontal position during surgery may be preferable for the patients with HPS [41].

Postoperative management

Hypoxia may exacerbate in the first hours after transplantation due to adverse effects of narcotic analgesics, sedation, the negative impacts of surgical traumatizing the anterior abdominal wall, volume overload, atelectasis, etc. The start of the graft function, a swift relief of portal hypertension, and the interruption of pathophysiological process that causes

pulmonary vasodilation, all those can lead to the spasm of pulmonary arteries and the ventilation-perfusion mismatch [59].

Early extubation after LT with switching to breathing 100% oxygen via a nasal cannula or mask are recommended to reduce the incidence of ventilator-associated pneumonia [41]. A mechanical lung ventilation, specifically an airway pressure release ventilation (APRV), a non-invasive ventilation, an endotracheal oxygen therapy aimed at maintaining $SpO_2 \geq$ 85% can be successfully used in patients with hypoxemia [22]. The benefits of the latter, in authors' opinion, include a significant decrease in oxygen demand and an early postoperative mobilization of patients [60]. There have been described the cases of inhaled NO, epoprostenol, methylene blue, the embolization of pulmonary artery branches bringing a positive effect [61]. A prolonged (up to 14 days) NO inhalation may increase the blood oxygen level postoperatively by improving the perfusion of the ventilated lung areas without increasing the blood flow through intrapulmonary shunts [62, 63]. Methylene blue may also increase PaO_2 by inducing the vasoconstriction in the poorly ventilated lung areas [44]. The Trendelenburg position and an early patient activation in bed have been recommended [41].

In postoperative severe refractory hypoxemia in the patients with HPS, the veno-venous extracorporeal membrane oxygenation (VV ECMO) has been proposed for use. This may contribute to their early weaning from oxygen support and, as a result, avoid using long-term sedation, as well as reduce the risk of related complications. On the other hand, the use of VV ECMO per se carries a risk of complications [61, 64].

Results

Despite the changed priority policy, the advances in anesthesia and surgical techniques, the level of perioperative mortality in transplantation for HPS remains high: from 8.5% to 29% [65-67].

A hypoxemia severity is the most common factor raising the perioperative mortality. An intraoperative PaO_2 of 50 mm Hg in combination with a macroaggregated albumin shunting fraction of over 20% constitute the risk factors for early postoperative death [53, 67]. The results of studied UNOS database demonstrate the PaO_2 reduction lower than 44 mm Hg as being critical. Below we present the summarized LT outcomes of HPS patients graded with respect to PaO_2 median in various centres (Table). Goldberg et al. analyzed more than 700 transplants in HPS patients, and calculated their survival with regard to the severity of hypoxemia [54]. When PaO_2 exceeded 50 mm Hg, the prognoses were quite optimistic: after transplantation, the symptoms completely disappeared in most patients [56].

Table. A 1-year survival after liver transplantation in patients with hepatopulmonary syndrome.

Study author	Number of patients	PaO_2 median at the moment of LT, mmHg	A 1-year survival rate, %	Reference
V.N. Iyer et al.	49	50	83	[57]
C. Taille et al.	23	52	91.3	[66]
M.R. Arguedas et al.	24	54	71	[67]
M.J Krowka et al.	32	55	84.4	[68]

K.L. Swanson et al.	24	57	79	[69]
M. Deberaldini et al.	25	74.9	68	[70]
J.M. Pascasio et al.	49	77	77.6	[56]
S. Gupta et al.	14	50.7	93%	[71]
D.S. Goldberg et al.	739	41.0	84.4	[54]
		50.3	91.8	
		57.0	92.5	
		66.3	84.8	

The early postoperative clinical course may vary, but at 6 months after transplantation the SpO_2 values increase in majority of patients. Oxygen therapy may be discontinued after the oxygen saturation has exceeded 88% (at rest, on exertion, and during sleep) [41]. In the study by Gupta et al., the median period till the oxygen support discontinuation was 130 days (from 9 to 700 days), and by the 6^{th} month of follow-up 75% of patients needed no oxygen therapy.

A clinical example

A patient of 14 years old with the diagnosis of HPS and liver cirrhosis of unknown etiology was known to have the first symptom of the disease as telangiectasias on the face appeared at the age of 3 years old. However, the liver disease was detected only 4 years later. The diagnosis made was "liver cirrhosis as a result of Rendu-Osler disease, with a portal hypertension syndrome (Grade II esophageal varices, hepatosplenomegaly), hepatocellular insufficiency (hypoprothrombinemia), ascites".

The Rendu-Osler disease is characterized by the transformation of small blood vessels in multiple telangiectasias on the skin, mucosal, and serous membranes, in arteriovenous shunts in visceral organs, and aneurysms. The disease is inherited in an autosomal dominant fashion and is manifested with bleeding resulted from the damaged vascular wall malformations. The diagnosis in the patient was made on the basis of clinical symptom combination: telangiectasia and liver disease. However, neither cases of the disease in the patient's family history, nor computed tomography (CT) signs of lung vascular neoplasms were identified.

The first signs of hypoxia were seen at the age of 11 years old when the child began to complain of the shortness of breath on exertion. Shortness of breath gradually increased; and a year later, the oxygen therapy in an intermittent mode was required during the day and during sleep. Soon a hepatocellular failure was detected and the patient was sent to the Academician V.I. Shumakov Federal Research Center of Transplantation and Artificial Organs (FNCTIO) where the presence of hypoxemia was confirmed (by SpO_2 of 65% when breathing ambient air). On physical examination, the multiple bright stellate telangiectasias, acrocyanosis of the limbs and nasolabial triangle, the drumstick fingers, and nail clubbing were evident. Scintigraphy using ^{99m}Tc-labeled macroaggregated albumin detected right to left shunt. Congenital heart defects were excluded by EcoCG. Thoracic and abdominal CT revealed no lung pathology, but identified the dilated portal and splenic veins. Despite additional examinations performed, the causes of liver cirrhosis were not identified and the diagnosis read as follows: Class A Child-Pugh liver cirrhosis of unknown etiology, MELD 10; hepatopulmonary syndrome. The patient was on intermittent oxygen therapy at home, satisfactorily tolerating the SpO_2

reduction to 70% when breathing ambient air for several hours. The measurements of arterial blood gases showed the PaO_2 drop below 50 mm Hg.

The PaO_2 reduction below 50 mm Hg in patients with HPS is known to be a risk factor for mortality after transplantation. On the other hand, these patients have a poor prognosis in the natural course of the disease. Therefore, the council of experts took a decision to include the patient in the waiting list for LT. At follow-up, no episodes of decompensated cirrhosis were observed, but hypoxia progressed (with minimum SpO_2 of 59%). Karnofsky Performance Scale Index was 50%. Despite a low MELD score, the patient received a priority order for transplantation.

On May 15, 2014, a whole liver transplantation from a standard-criteria cadaveric donor was performed using piggyback technique (The operating surgeon was Professor Moysyuk Ya.G.). The morphology study of the removed liver tissue revealed the signs of cirrhosis as a result of autoimmune hepatitis.

Despite the reasoned concerns, no critical complications were observed during surgery. The minimum PaO_2 at mechanical ventilation during anesthesia was 66 mm Hg, the lowest SpO_2 was 91%. The patient was transferred to ICU and extubated within the first day, SpO_2 being 87% with a continuous breathing oxygen of 10-12 liters per minute. The patient subjectively noted a deteriorated condition compared to that in the preoperative period. Karnofsky Performance Scale Index was 30%. A continuous oxygen therapy was performed for a rapid development of dyspnea, even at rest. Walking, long periods of breathing without oxygen support that had been possible before surgery became unattainable for the patient. However, hypoxemia began regressing over time without any

medical or surgical treatment, and after 12 months returned to preoperative levels (Fig. 2). So, the hypoxia level and the patient's condition improved. Although intolerant of physical exercising, the patient became capable of self-care, of moving within the room while breathing ambient air.

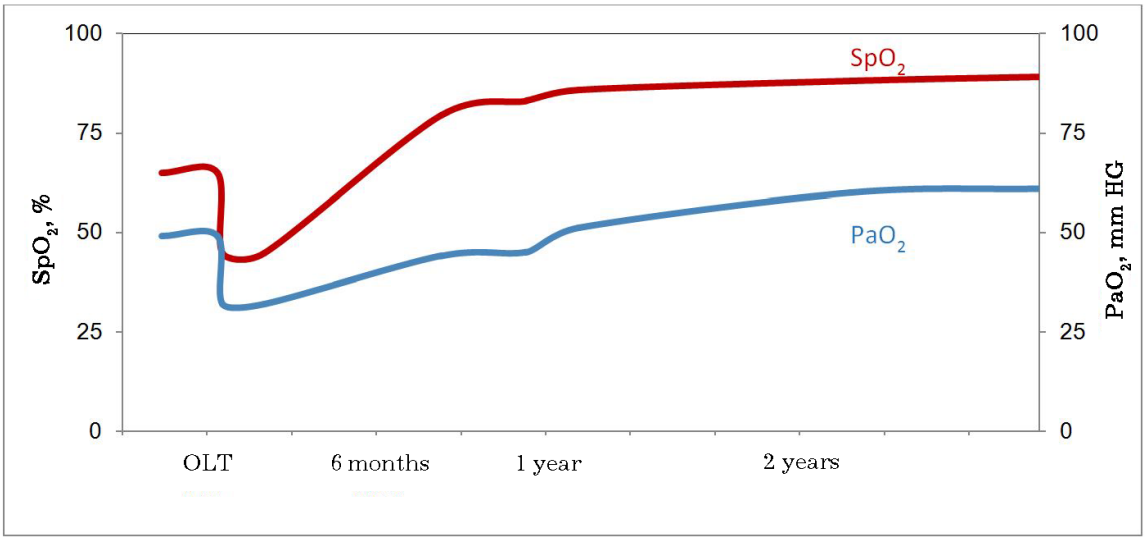

Fig. 2. Changes in the oxygen saturation of hemoglobin (SpO_2) and the partial pressure of arterial oxygen (PaO_2)

Note: OLT: orthotopic liver transplantation

A year after transplantation, the scintigraphy with labeled albumin was repeated. That revealed a 4-fold decrease in shunting, but there was no complete disappearance of shunts (Fig. 3).

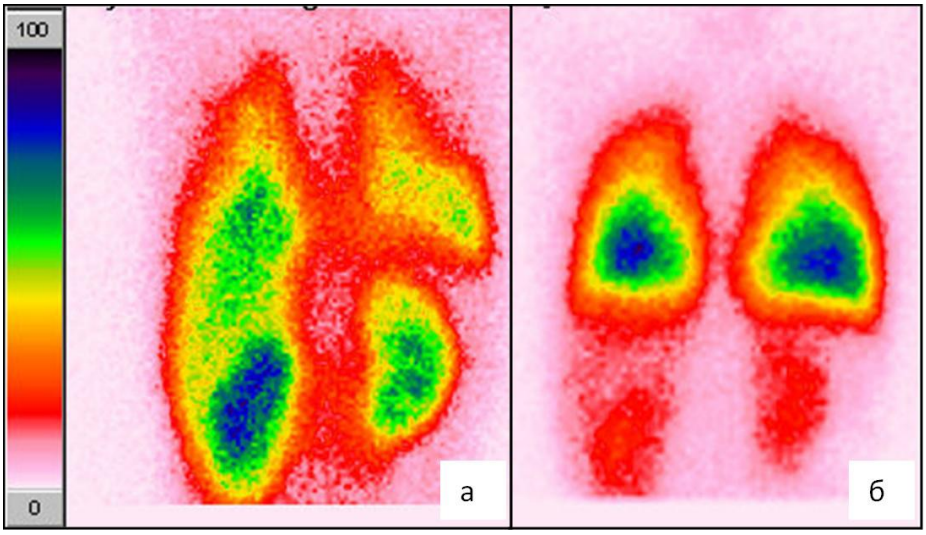

Fig. 3. Scintigraphy using ^{99m}Tc-labeled albumin microspheres: before liver transplantation (a) demonstrates a relatively large extrapulmonary accumulation of the radiopharmaceutical; after liver transplantation (b) shows a significantly decreased shunting

At 1.5 years after transplantation, the patient was capable of breathing without oxygen support for several hours, including while walking; he returned to his studies at school. His graft function kept satisfactory. At 2.5 years after transplantation, the patient's quality of life was 80% as assessed by Karnofsky Performance Status Scale.

At further follow-up the patient's condition and the graft function remained satisfactory.

Conclusion

HPS is a serious complication of liver disease and no efficient conservative therapies has been found for it yet. Various formulations posing a potential effect on HPS pathogenesis are being investigated in clinical practice and in experiments, but their results do not enable us to recommend any of the drugs.

LT still remains the only effective treatment. A 5-year survival after transplantation being of 76% has been comparable to the long-term outcomes of transplants for other nosologies. However, HPS patients have a higher risk of death in the perioperative period.

HPS symptoms regress after transplantation in many cases, but severe and very severe forms of pre-existing HPS hypoxemia can worsen. Severe hypoxia requires using auxiliary support techniques: from non-invasive ventilation to ECMO.

Further research is needed, aimed at finding a conservative therapy for HPS and preventing perioperative complications.

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