—Review—

The Role of the Spleen in Portal Hypertension

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As liver disease progresses, intrahepatic vascular resistance increases (backward flow theory of portal hypertension) and collateral veins develop. Adequate portal hypertension is required to maintain portal flow into the liver through an increase in blood flow into the portal venous system (forward flow theory of portal hypertension). The splenic artery resistance index is significantly and selectively elevated in cirrhotic patients. In portal hypertension, a local hyperdynamic state occurs around the spleen. Splenomegaly is associated with a poor prognosis in cirrhosis and is caused by spleen congestion and by enlargement and hyperactivation of splenic lymphoid tissue. Hypersplenism can lead to thrombocytopenia caused by increased sequestering and breakdown of platelets in the spleen. The close relationship between the spleen and liver is reflected in the concept of the hepatosplenic axis. The spleen is a regulatory organ that maintains portal flow into the liver and is the key organ in the forward flow theory of portal hypertension. This review summarizes the literature on the role of the spleen in portal hypertension. (J Nippon Med Sch 2023; 90: 20–25)

Key words: spleen, hemodynamics, portal hypertension

Introduction

The spleen is the largest lymphatic organ in the body. The fundamental phagocytic function of splenic macrophages is removing bacteria from the blood. The spleen is functionally and morphologically divided into red pulp and white pulp, which are divided by a perifollicular zone[1]. Red pulp filters blood and removes opsonized, damaged, and dying cells from circulation. White pulp is divided into T- and B-zones, similar to lymph nodes of the immune system. The perifollicular zone monitors the circulation for antigens and pathogens. A normal spleen is about 11 cm in craniocaudal length and weighs 100 to 150 grams. Normal portal pressure and blood flow are 5 to 7 mm Hg (7-10 cm H_2O) and about 1,000 to 1,200 mL/min, respectively. The spleen receives 5% of the total cardiac output-a blood flow of about 200-300 mL/min.

As liver disease progresses, intrahepatic vascular resistance increases (backward flow theory of portal hypertension) and collateral veins develop. Adequate portal hypertension is required to maintain portal flow into the liver through an increase in blood flow into the portal venous system (forward flow theory of portal hypertension)[2–8]. Splenomegaly may develop and some patients with portal hypertension develop hypersplenism.

This review summarizes previous studies of the role of the spleen in portal hypertension.

Portal Hypertension

Portal hypertension is associated with a variety of symptoms, including esophagogastric varices[9]. According to General Rules for Recording Endoscopic Findings of Esophagogastric Varices[10], established in Japan, red color signs are a risk factor for bleeding from esophagogastric varices[11], and massive esophagogastric variceal hemorrhage is a catastrophic complication of portal hypertension. Although esophagogastric varices reduce portal pressure as drainage veins for the portal venous system, appropriate treatment based on portal hemodynamics is required.

In chronic liver disease, increased intrahepatic vascular

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resistance causes portal hypertension[12]. Hepatic sinusoids are small blood vessels responsible for liver microcirculation, and multiple pathological events occur in sinusoidal circulation in chronic liver disease. Blockage of hepatic sinusoids, and the resulting increase in hepatic vascular resistance to portal venous flow, is the initial cause of portal hypertension (backward flow theory)[2–6]. Therefore, adequate portal hypertension is required to maintain portal flow into the liver through an increase of the blood flow into the portal venous system (forward flow theory)[2–8]. Portal hypertension is necessary to maintain portal flow into the liver.

Hyperdynamic State

Portal flow velocity is significantly diminished in patients with cirrhosis[13]. However, it is unclear whether portal flow volume is decreased in these patients. An intrahepatic portal venous shunt maintains portal flow, even in cirrhotic patients, but effective portal flow volume is decreased. Because of anatomical features and disease progression, the direction of portal venous blood flow changes in the portal venous system. Bidirectional or hepatofugal portal flow is occasionally detected in cirrhotic patients[14].

In cirrhosis, arteriolar vasodilatation is brought about by the combination of increased concentrations of circulating vasodilators and reduced sensitivity to vasoconstrictors. Impairment of the sympathetic nervous system has also been implicated in hypocontractility of mesenteric arteries and development of hyperdynamic circulatory syndrome in portal hypertensive rats[15–17].

Despite increased portal vascular resistance, splanchnic circulation, and splenic circulation in particular, is hyperdynamic[6–8,18–20], which is consistent with the forward flow theory of portal hypertension. The splenic artery resistance index is significantly and selectively elevated in cirrhotic patients. Increased splenic blood flow increases portal pressure and maintains portal flow into the liver[21].

The percentage of splenic venous flow in portal venous flow is approximately 20% to 40% in normal liver, 50% in chronic hepatitis and cirrhosis, and 75% in idiopathic portal hypertension[22,23]. Mesenteric flow is also elevated in cirrhosis[24] but not to the same extent as splenic flow[25].

The spleen is a regulatory organ that maintains portal flow into the liver. Portal hypertension causes a local hyperdynamic state, especially around the spleen. The spleen is the key organ in the forward flow theory of portal hypertension.

Splenomegaly

Splenomegaly is present in 50% to 75% of cirrhotic patients[26–28]. Clinically, splenomegaly is associated with a poor prognosis in cirrhosis and hepatocellular carcinoma[29,30]. Pancytopenia caused by splenomegaly is an unfavorable immunological finding[31–34]. Splenic stiffness may increase as splenomegaly advances[35,36].

Splenic blood flow increases in splenomegaly[37,38]. Spleen size is related to portal vein diameter[36], splenic blood flow[39], and portal blood flow[36,40]. Portal congestion is widely considered to be the initial cause of splenomegaly, but splenomegaly in cirrhosis cannot be simply classified as congestive. If splenomegaly is caused only by congestion due to portal hypertension, a relationship between splenomegaly and portal pressure would be expected. Although spleen size is weakly correlated with portal vascular resistance, portal hypertension is not the main causative factor of splenomegaly.

Histologically, chronic portal hypertension-induced splenomegaly is characterized by expanded white pulp and marginal-zone areas and is distinct from congestive splenomegaly, which is characterized by more-prominent red pulp and less distinct white pulp regions[34]. The increase in reticular fibers evolves into diffuse fibrosis extending throughout the parenchyma[41]. Increases in the white pulp arterial bed and periarterial lymphatic sheaths lead to an increase in white pulp volume[42]. In cirrhotic patients, spleen size may also vary in relation to the cause of the disease. Splenomegaly was reported more frequently in patients with post-hepatitic cirrhosis than in patients with alcoholic cirrhosis[27,43].

Splenomegaly in portal hypertensive rats arises from an interplay of several factors, including spleen congestion and enlargement and hyperactivation of splenic lymphoid tissue, as well as increased angiogenesis and fibrogenesis. More importantly, mTOR inhibition by rapamycin markedly improved splenomegaly, causing a 44% decrease in spleen size[34]. Rapamycin reduces portal pressure and mitigates hyperdynamic splanchnic circulation[34,44]. In contrast, after transplantation, a dramatic decrease in outflow resistance of the splenic vein is followed by a slight decrease in spleen size. Splenic hyperplasia might be irreversible, because complete resolution of splenomegaly has never been reported[45,46].

Splenomegaly is caused by spleen congestion, and by enlargement and hyperactivation of splenic lymphoid tissue, as well as by increased angiogenesis and fibrogenesis.

Hypersplenism

Hypersplenism adversely affects the hematologic profile, as it leads to anemia, thrombocytopenia, and leukopenia[47]. The incidence of hypersplenism was reported to range from 11% to 55% in patients with cirrhosis and portal hypertension[48]. A large amount of blood reaches the splenic red pulp, a filter that removes particulate matter and aged and damaged red blood cells. They are continually being removed from circulation and are stored or destroyed by lymphocytes in the spleen. The percentage of splenic blood flow entering open circulation may increase in pathologic conditions, with longer transit time of blood cells in the spleen and slowing of splenic circulation[40,49]. The spleen is important in maintaining normal physiological levels of platelets. It acts as a platelet reservoir and contains about one-third of the body's platelets at any one time. Hypersplenism can lead to thrombocytopenia, due to increased sequestering and breakdown of platelets in the spleen[17].

Relationship with the Liver

The close relationship between the spleen and liver is reflected in the concept of the hepatosplenic axis[50,51]. The spleen and liver are anatomically connected via portal circulation and have shared responsibilities. The apparent participation of the spleen in regulating hepatic repair can be further redefined as the role of immunity in regeneration[52]. In liver exposed to continuous damage, splenic venous blood promotes liver fibrosis in the right lobe and eventually flows more into the left lobe in milder fibrosis[53,54].

In the context of cirrhosis and hypersplenism, splenic TGF-β1 production is critical in the development of hepatic fibrogenesis, and splenic red pulp macrophages are a major source of TGF-β1[55]. Increased TGF-β1 expression in resected spleens from patients with cirrhosis was significantly correlated with cirrhosis progression[56]. Splenectomy significantly decreases serum TGF-β1 levels while improving variables associated with liver fibrosis and regeneration[55].

Partial hepatectomy promotes increased expression of IL-10 in the liver and spleen; thus, splenectomy blocks inflow of IL-10 via the portal vein[57]. The correlation was similar in liver transplantation models. Benefits include a decrease in portal hypertension and alleviation of endothelial damage, apoptosis, and proinflammatory cytokine synthesis[58].

Treatment

Various non-shunting procedures such as the Hassab operation, esophageal transection, splenectomy, and terminal esophago-proximal gastrectomy have been developed to treat esophagogastric varices[59–61]. All non-shunting procedures include splenectomy. Recently, laparoscopic surgery was developed as a minimally invasive treatment[62–64], and laparoscopic splenectomy is performed to treat various disease[65].

Even after splenectomy, the fine reticuloendothelial system, such as in the liver, lymph nodes, and bone marrow, compensates for function; therefore, no significant functional decline occurs, and activities of daily living are maintained.

Despite the apparent simplicity of total resection of the spleen, 2 to 10 years after the procedure, some patients develop complications-collectively referred to as post-splenectomy syndrome-which usually manifest as recurrent infections of varying severity[66]. Post-splenectomy infection (OPSI) can progress quickly from flu-like illness to fulminant sepsis and is associated with high mortality[67]. Some studies have reported an increased risk of tumorigenesis after splenectomy[68,69].

After splenectomy, functionally active fragments of splenic lymphoid tissue may occasionally settle in the abdominal cavity, a phenomenon known as splenosis[70,71]. To avoid delayed immunological complications, autotransplantation of the spleen is performed after splenectomy[72].

Partial splenic embolization has been used to treat hypersplenism, esophagogastric varices, portal hypertensive gastropathy, pancreatic carcinoma, splenic aneurysm, and portal-systemic encephalopathy[6,47,73–86]. Partial splenic embolization can preserve part of the spleen.

In conclusion, splenic artery resistance index is significantly and selectively elevated in cirrhotic patients. A local hyperdynamic state occurs around the spleen in portal hypertension. Splenomegaly is associated with a poor prognosis in cirrhotic patients and is caused by spleen congestion and enlargement and hyperactivation of splenic lymphoid tissue, as well as by increased angiogenesis and fibrogenesis. Hypersplenism can lead to thrombocytopenia caused by increased platelet sequestering and breakdown in the spleen. The close relationship between the spleen and liver is reflected in the concept of hepatosplenic axis. The spleen is a regulatory organ that maintains portal flow into the liver and is the key organ in the forward flow theory of portal hypertension.

Conflict of Interest: None.

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