

Non-Hypersplenism Causes of Peripheral Cytopenias in Patients with Cirrhotic Portal Hypertension: A Review

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Abstract

Hypersplenism and non-hypersplenism factors, either alone or in combination, can cause peripheral cytopenias in patients with cirrhotic portal hypertension. Although non-hypersplenism factors account for only a small proportion of patients, they do exist. When peripheral cytopenias do not improve, or fail to improve adequately, or even become worse after splenectomy in these patients, non-hypersplenism factors should be considered. This review aims to provide an overview of non-hypersplenism factors.

Keywords: Cirrhotic portal hypertension; Peripheral cytopenias; Etiology; Non-Hypersplenism factor

Introduction

Peripheral cytopenias refer to the lower-than-normal counts of circulating leukocytes, erythrocytes, and platelets. Leukopenia can lead to decreased immunity with consequent susceptibility to infection. The main function of erythrocytes is to transport oxygen (O₂) and participate in carbon dioxide (CO₂) exhalation [1], and transportation of O₂ by erythrocytes is achieved via hemoglobin (Hb) within cells. The gas transportation function may be lost in extreme erythropenia or erythrocytic rupture resulting in escape of Hb, tissue ischemia and hypoxia. Thrombocytopenia can lead to bleeding diathesis [2]. Theoretically and clinically, severe cytopenias affect prognosis [3], and can even lead to death [4]. Peripheral cytopenias can be caused by both hypersplenism and non-hypersplenism factors. These factors, either alone or in combination, can cause peripheral cytopenias in patients with cirrhotic portal hypertension. Peripheral cytopenias were previously thought to be caused by hypersplenism alone in patients with cirrhotic portal hypertension [5-7], and decreased blood cells levels would return to normal after splenectomy. However, in some patients, peripheral cytopenias do not improve, or fail adequately to improve, or become even worse after splenectomy. In such cases, non-hypersplenism factors should be considered. Unfortunately, little attention has been paid to non-hypersplenism factors as they are uncommon, and sometimes they coexist with hyperplenism factors. There have only been a few studies conducted on peripheral cytopenias caused by non-hyperplenism factors. This review aims to provide an overview on these non-hypersplenism factors (Table 1). Although this is not a systematic review, the authors tried to include as many articles published on this field as possible to avoid introducing personal biases into this review.

Hypersplenism Causes
Non-hypersplenism Causes
Toxic effects of viruses on bone marrow
Hepatitis B
Hepatitis C
Human parvovirus B19
Human cytomegalovirus
Hepatic dysfunction
Immunodeficiency
Dystrophy - ? poor nutrition
Drugs toxicity
Circulating platelet destruction
Blood loss

Table 1: Hypersplenism and non-hypersplenism causes of peripheral cytopenias in patients with portal hypertension.

Non-hypersplenism Factors

Toxic effects of viruses on bone marrow

The bone marrow is a hematopoietic organ. Viral infection can lead to impaired cellular and humoral immunity, impaired ability to clear the virus, and consequent viral persistence, thus resulting in bone marrow hematopoietic dysfunction [8,9]. Hepatitis B and C viruses can cause bone marrow suppression and affect the development of all nucleated bone marrow cells, leading to hypoplastic anemia and cytopenias. In these cases, survival is possible only with bone marrow

transplant [10]. Djordjevic et al. [11] pointed out that thrombocytopenia in patients with splenomegaly due to portal hypertension had a variety of causes, and that one important cause was bone marrow suppression by hepatitis virus. Even with liver transplant, cytopenias can also be caused by continuous toxic effects of hepatitis virus on bone marrow [12]. Human parvovirus B19 and human cytomegalovirus (HCMV) also can produce inhibition of bone marrow. Espanol [13] believed that direct infection or abnormal immune mechanisms may explain thrombocytopenia in patients with chronic liver disease.

Forbes et al. [14] suggested that hepatic exogenous myofibroblasts played an important role in hepatic fibrosis in liver diseases of different etiologies. In hepatic fibrosis, bone marrow stem cells differentiate into hepatic endothelial parenchymal cells but not into myofibroblasts. This indicates that the change in hemopoietic function and inner environment of the bone marrow might be somehow related to, or interactive with, the occurrence and development of hepatic fibrosis or even hepatic cirrhosis. These findings suggest that bone marrow changes in patients with liver cirrhosis do not result from one single factor, but a combination of multiple factors, with a complicated regulatory mechanism. Their relationship and the detailed pathogenesis remain to be further investigated. Solving this puzzle will be of great importance to clinical treatment.

Hepatic dysfunction

The liver has many important physiological functions, such as detoxification, metabolism, bile secretion, and immune defense. Hepatic dysfunction can lead to dysfunction in detoxification, which results in accumulation of toxic substances in the body, thus affecting the bone marrow hematopoietic function. Sezai [15] found decreased serum albumin accompanied by significant thrombocytopenia in patients with cirrhotic portal hypertension. Liver disease complicated by thrombocytopenia occurs at an incidence of 15-70%, and is usually mild to moderate in severity, which is considered to be a prognostic indicator.

Thrombopoietin (TPO) is almost exclusively produced by hepatocytes, and the number and functions of hepatocytes determine the production of TPO. In cirrhosis, there is a decrease in functional hepatocytes. A correlation between decreases in serum levels of TPO with platelet counts has been found by Wolber et al. [16] during transition from compensated to decompensated cirrhosis.

Many studies have pointed out that a deficiency of thrombopoietin (TPO) in liver disease was an important factor in the etiology of thrombocytopenia [17-19]. However, studies have also shown that there was no significant difference in TPO levels between thrombocytopenia and non-thrombocytopenia patients, suggesting that thrombocytopenia was unrelated to the TPO level [20], and may have been directly related to the splenic volume and platelet-associated immunoglobulin G (PAIgG) [21-23]. In addition, PAIgG can also bind to and destroy megakaryocytes and their precursors, thus inhibiting their differentiation and platelet formation [24], resulting in decreased production of blood cells.

Cirrhotic patients with a low hepatic functional reserve have low blood viscosity, low hematocrit, low platelet count, and prolonged clotting time. Patients with low blood viscosity are at a high risk of bleeding [25]. During cirrhosis, there is a reduction in reverse T3 5'-deiodinase activity, serum total and free T3, and even in T4 in severe cases. These factors affect the hematopoietic system, thus resulting in

decreased production of blood cells. Hypoxemia is likely to occur in severe cirrhosis, which can also cause peripheral cytopenias.

Metabolism disorders and abnormal membrane lipid synthesis of erythrocytes can result in increased erythrocyte morphology fragility, leading to shortened life and increased destruction of erythrocytes [25].

Immunodeficiency

Immunodeficiency is a low resistance to infection caused by developmental defects in the immune system or immune response dysfunction, with clinical manifestations of recurrent infections or serious infectious diseases.

Due to immune dysfunction or disorders, a variety of blood cell autoantibodies are produced in cirrhotic patients and blood cells are easily ingested by phagocytes, leading to cytopenias [26-28]. Liver disease complicated by thrombocytopenia is most closely related with cirrhosis [14], and is also significantly related with antiplatelet autoantibodies. Olariu [19] believed that bone marrow suppression, immune deficiency, and liver fibrosis were determinants of thrombocytopenia.

Thrombocytopenia due to immunodeficiency can be autoimmune or acquired immune thrombocytopenia. The former is more common [26] and includes cytopenias caused by post-autoimmune hepatitis cirrhosis and autoimmune lymphoproliferative syndrome [29,30]. The latter, also known as basic immune thrombocytopenia, is an acquired immune disease common in chronic lymphocytic leukemia [31,32], variable immunodeficiency disease [33,34], and hemophagocytic syndrome [35], presenting with abnormal bleeding due to decreased platelet counts. Thrombocytopenia due to immunodeficiency occurs in cases of increased antibody-mediated platelet destruction coupled with decompensation due to bone marrow defect [36]. It was previously reported that the average life of platelets in immune thrombocytopenia was 12 hours, which was shorter than that in hypersplenism (56 hours) and bone marrow hypoplasia (102 hours) [37]. These suggest severe destruction of platelets by immunodeficiency.

Dystrophy

It has long been considered that poor nutrition leads to liver cirrhosis, but there is still a lack of evidence to support this view. In animal experiments, food deficient in protein, choline and vitamin results in changes in the liver. Unfortunately, these changes do not have the secondary changes in blood vessels typical of a cirrhotic liver in man, and the changes are usually reversible if a diet rich in protein is given to the animal. Furthermore, mild fibrous hyperplasia happens in only a small number of these animals. Patients with liver disease often have malabsorption of nutrients, which leads to malnutrition. Lavigne et al. [38] found vitamin deficiency was a common factor of pancytopenia. Patients with vitamin deficiency present with severe iron deficiency anemia and thrombocytopenia [39], and have a mean corpuscular volume higher than patients with erythropenia caused by other factors.

Drugs toxicity

Allergic reactions and drugs toxicity also affect liver function, leading to cytopenias related to iron storage proteins. Improvement in liver function with an immediate increase in serum ferritin have been observed after discontinuation of treatment [40]. Thus, serum ferritin

levels may be a reliable indicator in the diagnosis of liver dysfunction and cytopenias. 5-Fluorouracil is an anticancer drug, whose toxicity can lead to cytopenias and diarrhea [41,42]. Most other anti-cancer drugs, such as cyclophosphamide and oxaliplatin, also have such side effects [43,44]. Some antibiotics, such as β -lactam-containing antibiotics, can induce cytopenias in patients with hepatic decompensation, which may be due to the abnormal liver metabolism caused by excessive β -lactam-containing antibiotics, leading to suppression of leukocyte precursor cells in the bone marrow [45].

Circulating platelet destruction

Platelets are commonly found in human blood. Binding of human anti-platelet autoantibodies to receptors (glycoproteins) on the platelet membrane in any part of the body leads to increased platelet destruction [46,47]. Destruction of platelets may occur in the spleen or in the circulating blood. The destruction of circulating platelets remains even after splenectomy, leading to a low level of platelets. If platelets account for a large proportion of cells in the spleen, peripheral platelet count rises soon after splenectomy; otherwise, peripheral platelet count does not change much after splenectomy, and may even be lower than before surgery. Cho et al. [48] found that destructed peripheral platelets became immature platelet fragments (IPF). IPF% is used as a reference value in trials, and increased IPF% has become an important indicator for laboratory diagnosis of thrombocytopenia. Any causes in hematopoietic dysfunction can lead to liver damage and liver functional abnormalities, aggravating liver fibrosis and cirrhosis.

Blood loss

Srichaikul [49] suggested that gastrointestinal bleeding can cause pancytopenia. The volume of blood loss is related to peripheral cytopenias. A small volume of blood loss does not lead to peripheral cytopenias, whereas a large volume of blood loss may result in peripheral cytopenias, in addition to severe anemia [50]. Patients with portal hypertension are often complicated by gastrointestinal bleeding, thus leading to cytopenias [51]. Patients with renal transplantation are susceptible to gastrointestinal tract cytomegalovirus infection, presenting with gastrointestinal bleeding, and significant cytopenia can occur soon after bleeding [52].

Peripheral cytopenias due to non-hypersplenism factors are complicated, since a variety of non-hypersplenism factors are often combined, and they often coexist with hypersplenism factors.

Treatment

Different treatments should be administered for peripheral cytopenias due to non-hypersplenism factors according to the specific cause.

Etiological treatment

Antiviral treatment should be administered for cytopenias caused by viral infection, and combination of pegylated interferon and ribavirin has been shown to be a feasible treatment [53]. Vitamin supplements should be given for pancytopenia caused by vitamin deficiency [54]. Medication should be discontinued immediately for cytopenias caused by excessive use of anti-cancer drugs or certain antibiotics.

Symptomatic treatment

Supplements should be given for what is deficient, for example, transfusion of erythrocytes for erythropenia, platelets for thrombocytopenia, whole blood for leukopenia, and coagulation factors for coagulation factor deficiency. For autoimmune cytopenia, special treatment should be given with high-dose corticosteroids and intravenous immune globulin. Eltrombopag is a new, orally active thrombopoietin receptor agonist that can stimulate platelet production and increase platelet counts in thrombocytopenia due to HCV-related cirrhosis [38]. Continuous BKT140 monotherapy has been shown to significantly increase the levels of megakaryocytes and hematopoietic progenitor cells in bone marrow, thus reducing the severity of thrombocytopenia before and after chemotherapy, and shortening the duration of thrombocytopenia [41]. BKT140 is a chemokine receptor (CXCR4) antagonist.

Liver transplantation

Liver transplantation can be considered for patients with severe liver cirrhosis and severe cytopenias. Liver transplantation not only greatly improves long-term survival in patients with decompensated cirrhosis, but also is an effective treatment for peripheral cytopenias [55,56] Li [57] and Chu [58] demonstrated that liver transplantation combined with concurrent splenectomy did not increase the risk in the treatment of cirrhosis and hypersplenism, and suggested it may provide better effects.

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