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Causes of Peripheral Blood Cytopenias in Patients with Liver Cirrhosis Portal Hypertension and Clinical Significances

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Abstract

Liver cirrhosis portal hypertension patients to reduce the number of blood cells are common in clinical, and often affect the prognosis. This paper discusses cirrhotic portal hypertension patients complicated by the reason of the decrease in the number of peripheral blood cells and what is the clinical significance of these reasons so as to provide theoretical support for the choice of treatment. Splenomegaly and hypersplenism caused should be the main reason for reducing the number of blood cells, but not all, other reasons are alcohol and virus inhibition of bone marrow, liver function impairment, autoimmune damage and loss of blood, etc. If it is a function of the spleen hyperfunction caused by blood cells decreases, blood should rise to normal after splenectomy, or consider other reason or there are other reasons at the same time.

Keywords

Liver Cirrhosis Portal Hypertension, Peripheral Blood Cytopenias, Causes, Cilinical Significances

1. Introduction

There are approximately 350 million carriers of hepatitis B virus (HBV) worldwide, and more than half of them are in the Asia-Pacific region. China has a high carrier rate of HBV, with 9.8% of the population being HBV positive; the rate is as high as 16.4% in Hainan Province. Overall, 20% of HBV infections develop into chronic hepatitis. The incidence of the resulting nonalcoholic cirrhotic portal hypertension is thus very high and most patients are complicated by monolineage or multilineage cytopenias [1]. Cytopenias indicate that a leukocyte (WBC) counts of $<4.0 \times 10^9$/L, a erythrocyte (RBC) counts of $<4.0 \times 10^{12}$/L and/or a platelet (PLT) counts of $<100 \times 10^9$/L. People usually put the cirrhotic portal hypertension patients to reduce the number of blood cells

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are attributed to the splenic function, actually otherwise, the splenic function must have blood cells decreases, but are not necessarily blood cells caused by the splenic function. There are numerous causes for cytopenias in patients with hepatocirrhotic portal hypertension, including the toxic effects of hepatic viruses and alcohol on the bone marrow, hypofunctioning of the liver [2], splenomegaly, hypersplenism, gastrointestinal bleeding, and hematopoietic dysfunction caused by malnutrition. In most cases, cytopenias are caused by multiple factors.

2. Causes

2.1. Toxic Effects of Hepatic Virus

1) Hepatic viruses can directly suppress the differentiation and proliferation of hemopoietic stem cells and progenitor cells [3]. 2) Hepatic virus can cause disorders of cellular immunity and humoral immunity *in vivo*, to compromise the body's capacity to eliminate the viruses. The constant presence of viruses damages the hemopoietic functioning of the bone marrow [4]. 3) Viruses can impair the activity of bone marrow stromal cells to reduce the secretion of cytokines and to affect the proliferation of hemopoietic cells. 4) During pathogenesis caused by cytokines, the increase in the γ-interferon level and decrease in the interleukin-6 and erythropoietin levels, can affect the proliferation of hemopoietic cells [5]. The hepatitis B virus (HBV) and hepatitis C virus (HCV) can suppress the bone marrow, and affect the growth of all karyocytes in the bone marrow. This may lead to hypoplastic anemia, and patients must undergo a bone marrow transplant to survive.

The liver and bone marrow are target tissues of HBV. This virus can kill or injure hemopoietic cells directly, causing myelosuppression, and leading to leukopenia and reduction in the detoxification ability of the liver. This renders the body more sensitive to certain medicines, toxins and environmental pollutants, and cause hypofunctioning of bone marrow hematopoiesis. Leukopenia further damages immunity to cause the active replication of HBV, forming a vicious cycle. Currently, antiviral therapy is the first choice for chronic hepatitis B patients; however, antiviral medications also lead to myelosuppression. Therefore, monitoring leukocytes in the peripheral blood is conducive to the regulation of antiviral therapy. If the leukocyte count is lower than 2×10^9/L, antiviral therapy should be discontinued. Both HBV and HCV can induce suppression of the precursor cells of the bone marrow, and affect the lymph cells, causing lymphopenia and hypofunctioning of the bone marrow.

2.2. Toxic Effects of Alcohol

In the 1980s, studies of patients with alcoholic liver disease reported that neutrophil granulocytes demonstrated retarded growth and delayed release in the bone marrow. Later studies showed increased apoptosis of neutrophil granulocytes. Patients with end-stage cirrhosis complicated with neutropenia underwent Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) therapy for 7 days, and the leukocyte count increased more than 100%. However, the increased leukocytes could not be destroyed in the spleen, for no leukocyte fragments were found in the spleen. Ethanol can suppress or stimulate cellular proliferation, but in most cases, it suppresses cellular growth and increases cytotoxic effects. Its mechanism includes retarded cellular proliferation and induced apoptosis and necrosis [6]-[8]. A foreign study reported [9] that long-term alcoholism could cause abnormalities in the bone marrow and peripheral blood. In that study, 91% patients manifested changes in the peripheral blood including granulopenia, thrombopenia, etc., and changes in bone marrow included highly-differentiated hemopoietic tissue and myelofibrosis. Long-term alcohol consumption can reduce the absorption of folic acid and vitamin B_{12}, which impairs the synthesis of erythrocytes. Djordjevic *et al.* [10] believed both that hepatic viruses and alcoholism were able to cause cytopenias.

2.3. Hypofunctioning of Liver

Hypofunctioning of the liver reduces degradation of toxic metabolites by liver cells; in this case, the liver cannot detoxify the toxins that suppress the bone marrow, thus affecting hemopoietic function. The incidence of liver disease combined with thrombopenia is 15% - 70%. It is usually at mild or moderate level, and its severity is a prognostic indicator. In liver diseases, thrombopenia is closely related to hepatocirrhosis, anti-platelet autoantibodies [11], bone marrow suppression caused by HBV and HCV, and toxic effects from excessive alcohol consumption [12]. The discovery of thrombopoietin (TPO) in 1994 ushered in a new era in the study of cirrhotic thrombopenia. TPO is almost exclusively produced in liver cells; a small proportion of TPO is produced in the kidneys, bone marrow stromal cells and muscle. The production of TPO depends on the function and amount of

liver cells. In cirrhosis, functional liver cells become less able to decrease the secretion of TPO. A study by Wolber *et al*. [13], of cirrhotic patients developing from the compensation to decompensation stage, demonstrated that the expression or serum level of TPO changed from an increase to a decrease, and that the platelet count decreased gradually. The decrease in liver function, to some extent, was related to hemocytopenia and bone marrow dysfunction. Forbes *et al*. [14] suggested that hepatic exogenous myofibroblasts played an important role in hepatic fibrosis. 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 observations suggest that changes in the bone marrow of cirrhotic patients do not result from one single factor but a combination of multiple factors, with a complicated regulation mechanism. The changes in bone marrow might be directly or indirectly related to the severity of hepatic cirrhosis and changes in liver or spleen function. Their relationship and the detailed mechanism remain to be further explored. Solving this puzzle will be of significant importance to clinical practice.

2.4. Splenomegaly and Hypersplenism

Hypersplenism is secondary to splenomegaly. Two mechanisms for splenomegaly caused by liver diseases exist. The first mechanism is expansionary splenomegaly, including congestive splenomegaly caused by increased venous pressure and hyperemic splenomegaly caused by increased splenic arterial flow; the former is the main cause. The second mechanism is hypertrophic splenomegaly, including: 1) Hepatic virus antigen and exogenous antigens unprocessed by the liver due to a shunting procedure, can stimulate the spleen and lead to hypertrophy of the immune tissue in the spleen (splenic corpuscle, periarterial lymphatic sheath, marginal zone). 2) In hepatic cirrhosis, increased necrotic cells and hypofunctioning of the hepatic reticuloendothelial system promote compensatory hypertrophy and lead to hyperfunctioning of the splenic reticuloendothelial system. 3) Increased intrasplenic pressure, stasis of blood circulation, change in the metabolic environment and other factors can cause fibroplastic proliferation. Generally speaking, intrasplenic immune tissues show obvious hypertrophy during hepatitis, and middle or end stage cirrhotic patients mainly manifest splenic sinus dilation, hypertrophy of reticuloendothelial system and fibrous tissues.

Currently, there are several hypotheses concerning the mechanism of cytopenia: 1) The hypothesis of intrasplenic trapping [15]. After the formation of splenomegaly, blood volume in the spleen increases, and a great number of leukocytes, erythrocytes and platelets are trapped in the spleen. The ratio of trapped hemocytes compared with that in the normal spleen is 5.5- to 20-fold, resulting in hemocytopenia in the peripheral blood. 2) The hypothesis of cytophagy: There are a large number of mononuclear-macrophages in the spleen. Under pathological circumstances, mononuclear-macrophages demonstrate hyperfunctioning in cytophagy and destruction of hemocytes, especially erythrocytes [16]. Recently, a study using erythrocyte creatine (EC), the life-span sensitive marker of erythrocytes, revealed that the EC level was significantly increased in patients with splenomegaly due to post-necrotic cirrhosis compared with patients with hepatic cirrhosis with normal spleens ($P < 0.05$). In addition, the same was observed compared with the normal control group but without a significant difference [17]. This suggested that splenomegaly accelerated the destruction of erythrocytes and the determination of the EC value could be used to evaluate the severity of cirrhotic splenomegaly [18]. 3) The spleen can produce excessive "splenic hormones" to suppress the hemopoietic function of the bone marrow, and accelerate the destruction of trap produced hemocytes to prevent them from entering into blood circulation [19]. 4) The hypothesis of autoimmunity: The spleen is a large lymph organ that produces antibodies. Antigens unprocessed by the liver enter the marginal zones of splenic lymph follicles (splenic nodule) and activate the pro-lymphocytes and plasma cells to generate antibodies. These antibodies can destroy hemocytes causing hemocytopenia in the peripheral blood.

2.5. Gastrointestinal Bleeding

Gastroesophageal fundus varices bleeding is a common complication for patients with cirrhotic portal hypertension. Gastrointestinal bleeding of any cause can directly lead to a decreased amount of hemocytes in the effective circulatory blood volume. Usually, these theories coexist, and rarely only one theory comes into play [20].

Chronic gastrointestinal bleeding can result in iron, folic acid and vitamin B12 deficiencies, and insufficient material for the synthesis of erythrocytes. Massive loss of erythrocytes can lead to anemia in patients. A Cr^{51} la-

beled-erythrocyte test demonstrated that only 20% of patients with cirrhosis complicated with anemia had increased erythrocytes in their spleens.

2.6. Malnutrition

Portal hypertensive gastropathy can cause malabsorption of hematopoietic growth factors and non-visible loss of nutrients necessary for hematopoiesis. Additionally, the lack of iron, folic acid and vitamin B_{12} results in insufficient materials for the synthesis of erythrocytes, leading to decreased hematopoiesis.

3. Clinical Significances

The significance of exploring the causes of hemocytopenia in the peripheral blood in the patients with cirrhotic portal hypertension lies in its guidance for treatment and evaluation for therapeutic effects [21]. If hemocytopenia is caused by splenomegaly or hypersplenism, whether monolineage or multi-lineage, the decreased hemocytes will rise significantly after a splenectomy ($P < 0.01$) [22]. The most sensitive hemocyte is the platelet, which will increase half an hour after the operation, and reach the highest level in 2 weeks; afterwards it will decrease gradually and remain at a normal level. Leukocytes and erythrocytes would increase following the platelets. Hemocytopenia in the peripheral blood caused by non-splenic factors does not lead to a definite increase in hemocytes after splenectomy.

References

[1] Lv, Y.-F., Li, X.-Q. Huang, W.-W., *et al*. (2007) Peripheral Blood Cytopenia in Patients with Hypersplenism Due to Portal Hypertension. *Chinese Journal of General Surgery*, **22**, 702.

[2] Bashour, F.N., Teran, J.C. and Mullen, K.D. (2000) Prevalence of Peripheral Blood Cytopenias (Hypersplenism) in Patients with Nonalcoholic Chronic Liver Disease[J]. *Gastroenterology*, **95**, 2936-2939.

[3] Van, E., Niele, A.M. and Kroes, A.C. (1999) Human Parvovirus B19: Relevance in Internal Medicine[J]. *The New England Journal of Medicine*, **54**, 221-230. http://dx.doi.org/10.1016/S0300-2977(99)00011-X

[4] Kevin, E., Brown, J.T., Barrett, A.J., *et al*. (1997) Hepatitis-Associated Aplastic Anemia[J]. *The New England Journal of Medicine*, 1059-1064.

[5] Dilloo, D., Vohringer, R., Josting, A., *et al*. (1995) Bone Marrow Fibroblasts from Children with Aplastic Anemia Exhibit Reduced Interlukin-6 Production in Response to Cytokines and Viral Challenge[J]. *Pediatric Research*, **38**, 716-721. http://dx.doi.org/10.1203/00006450-199511000-00014

[6] Young, N.S. and Maciejewski, J. (1997) The Pathophysiology of Acquired Aplastic Anemia[J]. *The New England Journal of Medicine*, **336**, 1365-1372. http://dx.doi.org/10.1056/NEJM199705083361906

[7] Jacobs, J.S. and Miller, M.W. (2001) Proliferation and Death of Cultured Fetal Neocortical Neurons: Effects of Ethanol on the Dynamics of Cell Growth[J]. *Journal of Neurocytology*, **30**, 391-401. http://dx.doi.org/10.1023/A:1015013609424

[8] Hao, L.P., Hu, X.F., Pang, H., *et al*. (2006, The Study on Apoptosis and Its Molecular Mechanism in Mouse Insulinama Cells Induced by Ethanol[J]. *Journal of Toxicology*, **20**, 138-140.

[9] Neuman, M.G., Haber, J.A., Malkiewicz, I.M., *et al*. (2002) Ethanol Signals for Apoptosis in Cultured Skin Cells[J]. *Alcohol*, **26**, 179-190. http://dx.doi.org/10.1016/S0741-8329(02)00198-2

[10] Djordjević, J., Svorcan, P., Vrinić, D. and Dapcević, B. (2010) Splenomegaly and Thrombocytopenia in Patients with Liver Cirrhosis. *Vojnosanit Pregl*, **67**, 166-169.

[11] Sezai, S., Kamisaka, K., Ikegami, F., *et al*. (1998) Regulation of Hepatic Thrombopoietin Production by Portal Hemodynamics in Liver Cirrhosis[J]. *The American Journal of Gastroenterology*, **93**, 80-82. http://dx.doi.org/10.1111/j.1572-0241.1998.080_c.x

[12] Lu, Y.F., Yue, J., Gong, X.G., *et al*. (2009) Anaemia of Cirrhotic Portal Hypertension with Hypersplenism. *Journal of Surgery: Concepts & Practice*, **14**, 669-670.

[13] Wolber, E.M., Ganschow, R., Burdelski, M., *et al*. (1999) Hepatic Thrombopoietin mRNA Levels in Acute and Chronic Liver Failure of Childhood[J]. *Hepatology*, **29**, 1739-1742. http://dx.doi.org/10.1002/hep.510290627

[14] Forbes, S.J., Russo, F.P., Rey, V., *et al*. (2004) A Significant Proportion of Myofibroblasts Are of Bone Marrow Origin in Human Liver Fibrosis[J]. *Gastroenterology*, **126**, 955-963. http://dx.doi.org/10.1053/j.gastro.2004.02.025

[15] Shah, S.H., Hayes, P.C., Allan, P.L., *et al*. (1996) Measurement of Spleen Size and Its Relation to Hypersplenism and Portal Hemodynamics in Portal Hypertension Due to Hepatic Cirrhosis[J]. *The American Journal of Gastroenterology*,

91, 2580-2583.

[16] Jiao, Y.F., Okumiya, T., Saibara, T., Kudo, Y. and Sugiura, T. (2001) Erythrocyte Creatine as a Marker of Excessive Erythrocyte Destruction Due to Hypersplenism in Patients with Liver Cirrhosis. *Clinical Biochemistry*, **34**, 395-398. http://dx.doi.org/10.1016/S0009-9120(01)00242-9

[17] Friedman, L.S. (1999) The Risk of Surgery in Patients with Liver Disease. *Hepatology*, **29**, 1617-1623. http://dx.doi.org/10.1002/hep.510290639

[18] Zhou, Y.X. (2002) Modern Diagnostics & Therapeutics of Liver Cirrhosis. 1st Edition, People's Military Medical Press, Beijing, 247-249.

[19] Faeh, M., Hauser, S.P. and Nydegger, U.E. (2001) Transient Thrombopoietin Peak after Liver Transplantation for End-Stage Liver Disease. *British Journal of Haematology*, **112**, 493-498. http://dx.doi.org/10.1046/j.1365-2141.2001.02567.x

[20] Lv, Y.F., Li, X.Q., Han, X.Y., Gong, X.G. and Chang, S.W. (2013) Peripheral Blood Cell Variations in Cirrhotic Portal Hypertension Patients with Hypersplenism. *Asian Pacific Journal of Tropical Medicine*, **6**, 663-666. http://dx.doi.org/10.1016/S1995-7645(13)60115-7

[21] Lv, Y.F. (2009) Characteristics and Clilical Significance of Hypersplenism Secondary to Splenomegaly Caused by Cirrhotic Portal Hypertension. *World Chinese Journal of Digestology*, **17**, 2969-2971.

[22] Lv, Y.F., Li, X.Q., Gong, X.G., Xie, X.H., Han, X.Y. and Wang, B.C. (2013) Effect of Surgery Treatment on Hypersplenism Caused by Cirrhotic Portal Hypertension. *Minerva Chirurgica*, **68**, 409-413.