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Peripheral blood cell variations in cirrhotic portal hypertension patients with hypersplenism

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ABSTRACT

Objective: To explore peripheral blood cell variations in hepatic cirrhosis portal hypertension patients with hypersplenism. **Methods:** Clinical data of 322 hypersplenism patients with decreased peripheral blood cells, admitted with cirrhotic portal hypertension, was retrospectively studied over the last 17 years. **Results:** In 64% (206/322) of patients, more than 2 kinds of blood cell were decreased, including 89 cases of pancytopenia (43.2%), 52 cases of WBC + PLT decrease (25.2%), 29 cases of RBC + PLT decrease (14.1%), and 36 cases of WBC + RBC decrease (17.5%); in 36% (116/322) of patients, single type blood cell decrease occurred, including 31 cases of PLT decrease (26.7%), 29 cases of WBC decrease (25%) and 56 cases of RBC decrease (48.3%). Of 227 routine bone marrow examinations, bone marrow hyperplasia was observed in 118 cases (52.0%), the remainder showed no hyperplasia. For the distinct scope and extent of peripheralblood cell decreases, preoperative blood component transfusions were carried out, then treated by surgery, after whole group splenectomy, the peripheral blood cell count was significantly higher ($P<0.05$). **Conclusions:** Of portal hypertensive patients with splenomegaly and hypersplenism, 64% have simultaneous decrease in various blood cells, 36% have decrease in single type blood cells, 52% of patients have bone marrow hyperplasia. A splenectomy can significantly increase the reduction of peripheral blood cells.

1. Introduction

In cirrhotic portal hypertension splenomegaly patients with hypersplenism, peripheral blood cell counts demonstrats different levels of decrease in the overwhelming majority of patients because of strengthened splenic pathological function, but how to quantify the degree and range of the blood cell decrease is still a challenge[1]. Between January, 1991 and June, 2010, 322 cirrhotic portal hypertension patients with decreased peripheral blood cell count were studied. The summary report is as follows:

2. Materials and methods

2.1. Clinical data and methods

Among selected 322 patients, 199 were male and 123 female, and the ratio of male to female was 1.6:1. They were aged from 5-66 years old, and the average was 43 years old. Among them were 312 cases (96.9%) of posthepatitic cirrhosis, 6 cases of biliary cirrhosis, 2 cases of schistosomial cirrhosis, and 2 other types of cirrhosis.

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All the patients suffered universal splenomegaly, upper gastrointestinal radiography or endoscopy examinations showed moderate and severe varicous veins in the lower esophagus and fundus gastricus (stomach fundus), 65 patients (20.2%) were hospitalized due to gastrointestinal hemorrhaging, 219 patients (68.0%) had a history of hemorrhaging. The average size of the spleen as measured by B ultrasound examination or CT scan was 224 mm×159 mm×95 mm.

2.2. Statistical analysis

The Blood cell decrease scope was analyzed by analysis of variance (ANOVA), SPSS software package processing, data with F value indicated, the uneven use of variance Kruskal-Wallis test, $P<0.05$ was considered as statistically significant difference.

3. Results

Peripheral blood white blood cell (WBC) count was $<4.0\times10^9$/L, red blood cell (RBC) count $<4.0\times10^{12}$/L and platelet (PLT) count $<110\times10^9$/L, indicating peripheral blood cell decrease. In this paper, simultaneous decreases in WBC, RBC and PLT occurred in 89 cases (27.6), WBC + PLT decreases in 52 cases (16.1%), RBC + PLT decreases in 29 cases (9.0%), and WBC + RBC decreases in 36 cases (11.2%); single type PLT decreases occurred in 31 cases (9.6%), single type WBC decreases in 29 cases (9.0%), and single type RBC decreases in 56 cases (17.4%) (Table 1).

Table 1
Peripheral blood cell decrease in 322 case (mean±SEM).

Group	*n*	WBC($\times10^9$/L)	RBC($\times10^{12}$/L)	PLT($\times10^9$/L)
Pancytopenia	89	2.35±0.76	2.99±0.24	58.6±19.8
WBC+PLT	52	2.76±0.71*	–	56.9±21.2
RBC+PLT	29	–	2.83±0.20*	67.2±21.3
WBC+RBC	36	2.85±0.76*	3.11±0.30	–
PLT	31	–	–	66.2±23.3
WBC	29	2.98±0.65*	–	–
RBC	56	–	2.71±0.50*	–

*$P<0.05$ *vs.* Pancytopenia group. The difference in PLT was insignificant ($P>0.05$, $F=1.61$).

Of 227 bone marrow aspiration examinations, 118 cases had bone marrow hyperplasia (52.0%). After complete blood transfusions to replenish the shortage of tangible blood components, all the patients underwent splenectomy, and simultaneously 252 cases had cardiac peripheral vascular surgery, 56 cases had splenorenal shunt, 9 cases had mesocaval shunt, and 5 cases had portacaval shunt. Measurement via the right gastroepiploic vein showed the free portal venous pressure was 26 cm H_2O-54 cm H_2O, and the average was 34 cm H_2O. The average spleen size was 236 mm×169 mm×96 mm. In postoperative pathological examinations, splenic blood stasis, lots of phagocyte and severe fibroplasia was observed. Postoperative follow-up was conducted in 226 patients, for 3-96 months, and 63 months on average.

The comparison of pre-operative and post-operative peripheral blood cell count is shown in Table 2.

Table 2
Pre-operative and post-operative hemocyte in 226 case (mean±SEM).

Item	Pre-operation	Post-operation	*t* value	*P* value
WBC($\times10^9$/L)	2.57±0.71	7.43±3.03	8.59	<0.01
RBC($\times10^{12}$/L)	2.98±0.54	3.88±0.63	5.33	<0.01
PLT($\times10^9$/L)	51.75±21.68	243.6±128.49	5.67	<0.01

4. Discussion

In China, most portal hypertension splenomegaly is caused by posthepatitic cirrhosis. Splenomegaly and decreases in single or multiple type blood cells in peripheral blood are the main clinical manifestation of hypersplenism and an important foundation of hypersplenism diagnosis. Hypersplenism was proposed by Cretsel as early as 1866, described in detail by Banti in 1883 and consequently named as Banti syndrome, and definitively named by Chauffard in 1907[2]. In 1955, Doan[3] conducted further research and the prerequisites for hypersplenism: splenomegaly; decrease in single or multiple type blood cell components; normal bone marrow or bone marrow hyperplasia; the pathological changes in blood constituent disappears after splenectomy. The above 4 prerequisites are for general hypersplenism diagnosis, but to assess whether cirrhotic patients with portal hypertension have hypersplenism due to splenomegaly itself even as a condition of portal hypertension, is mainly diagnosed based on the changes in peripheral blood cell. In this group, 64% manifested decreases in multiple type blood cells and 36% manifested decreases in single type blood cells.

There are currently 5 main theories for the pathogenesis of multiple type blood cell decreases: (1) Intrasplenic stasis theory[4] Following splenomegaly, splenic blood volume is

increased, large quantities of WBC, RBC and PLT clog the spleen, the ratio of clogged blood cells in the spleen is 5.5-20 times larger than that of a normal spleen, which leads to decrease in peripheral blood cells; (2) Phagocytic theory says the spleen contains a large amount of monocyte and macrophage, in pathological conditions, the abilities of monocyte and macrophage to swallow and destroy blood cells are significantly strengthened, especially the destruction of red blood cells[5]. In recent years, related researches were conducted by RBC life-sensitive marker EC, and found EC level in patients with splenomegaly and postnecrotic cirrhosis is significantly higher than those in patients with normal spleen and hepatic cirrhosis and in patients of normal control group ($P < 0.05$), and the difference between the later two groups was insignificant[4], which illustrates that splenomegaly accelerates RBC destruction; (3) Bone marrow suppression theory says alcohol and hepatitis viruses have direct inhibitory effect on bone marrow precursor cells, and can affect blood cell generation[6,7]. Furthermore, the spleen may produce redundant "splenic hormones" inhibiting the blood-producing function of bone marrow and accelerating destruction of generated blood cells and obstructing their entrance into blood circulation[8]; (4) Autoimmune theory says the spleen is a large lymphatic organ, where antibodies are produced. Antigens untreated by the liver enter the periphery of splenic lymphoid follicles (splenic nodule), and after antigen stimulation, causes prolymphocyte and plasmocyte reactions, producing antibodies[4], which results in the destruction of its own blood cells and consequently decreasing peripheral blood cells; (5) Blood loss theory shows acute blood loss can decrease complete blood cell count. Usually, these theories coexist, and rarely do only one theory comes into play.

The pathogenesis of decreases in single type blood cells is currently not clear. The further studies on haematopoietic physiology in recent years, especially the discovery of blood cell growth factor, have opened another door to the pathophysiological disorder of blood cells in hepatic diseases.

There are various factors to red blood cell decreases, but all are closely related to erythropoietin (EPO), which is produced by kidney and liver. Renal failure and EPO level maladjustments are important factors, the EPO value in cirrhosis patients is insufficient and insensitive to the anemia degree[9], and in renal failure patients, various factors can cause EPO resistance[10].

Similarly, there are more than one single factor at play in the decrease of white blood cells. It has been proven by in vitro culture and testing that the apoptosis of neutrophil and polymorphonuclear leukocyte in cirrhosis patients is more rapid than that in normal control patients, which can lead to a decrease in the white blood cell count[11].

Research in recent years has demonstrated that thrombocytopenia is related to thrombopoietin (TPO), while in cirrhosis patients, TPO reduces[12], the production and destruction of TPO is unbalanced[13]. TPO is seemingly only produced by hepatocyte, and in hepatic cirrhosis patients, functional hepatocyte that secretes TPO is decreased, which leads to decreases in TPO secretion[14-16], even if the spleen does not destroy PLT, in circulating blood PLT may be decreased still. Some scholars who think[17] in cirrhosis patients, the immune system is dysfunctional and various hemocyte autoantibodies are produced, among which, PAIgG is the most close to hypersplenism. PAIgG is a kind of platelet autoantibody combined with the glycoprotein on the surface of the platelet membrane, mainly produced by the spleen, and significantly increased in patients with thrombocytopenic purpura and hepatic cirrhosis. PAIgG combined platelets are easily captured and phagocytized by antibody mediated macrophage when flowing through the spleen. Furthermore, PAIgG can also combine with megakaryocytes and their precursors to destroy the megakaryocytes, the precursors and to inhibit their differentiation and platelet formation.

Clinically, genuine single type WBC, RBC and PLT decreases only account for 9.4%, 16.9% and 10% respectively, and in most cases, 2 or more kinds of blood cell decrease[18]. Regardless of multiple or single type blood cell decreases, the decreased blood cells significantly increased after splenectomy ($P<0.01$), among which, PLT were most susceptible to increase, even starting half an hour after the surgery, peaking in 2 weeks[19], and then gradually decreasing and stabilizing at a normal level[20]; next was WBC and RBC. Mastuura *et al*[21]suggested that the excessive postoperative PLT count was also a life-threatening factor, so the condition of the patient should be closely monitored[22,23]. It has been proven in recent years that autologous stem cell transplantation has good therapeutic effects on peripheral blood cell decrease in cirrhotic portal hypertension[24].

Conflict of interest statement

We declare that we have no conflict of interest.

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