

Hematological Disorders in Patients with Liver Viral Cirrhosis

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ABSTRACT

Liver cirrhosis and hepatocellular carcinoma are the most frequent and severe complication of chronic C hepatitis. Results of recent researches indicated that HCV persists and replicates not only in hepatic tissue, but in the other organs, too. In patients with chronic C hepatitis and cirrhosis extrahepatocellular areas of virus persistence and replication and the extrahepatocytal manifestation of the disease complicates the hepatitis and worsens the outcome. The goal of our investigation was to determine hematological disorders during chronic HCV and HCV+HBC hepatitis, to find correlation between activity of chronic hepatitis, stage of cirrhosis and degree of hematological disorders. We have studied patients with chronic C and B+C hepatitis (36 persons) and 77 HCV-infected persons on the stage of cirrhosis. Out of all investigated persons 14 patients had low activity hepatitis, 22 persons suffered from high activity of infectious process. From cirrhotic patients 22 had A stage of pathological process, 25 persons had B stage and 30 persons - C stage. The erythrocytes morphology was investigated through light microscope. The osmotic resistance of erythrocytes was investigated using the method of lanovski (modification of Ribiera); the thrombocytes' ability to adhe and aggregate was studied through the method of Rite. The absolute number of thrombocytes was counted by means of phase-contras microscope. RESULT: During chronic HCV hepatitis in line with development of cirrhosis hematological disorders became more serious. This was particularly evident at the C stage of cirrhosis. CONCLUSION: With the development of viral liver cirrhosis the patients display severe hematological disorders, which are directly correlated with the liver damage degree.

KEYWORDS: *viral hepatitis, cirrhosis, hepatocellular carcinoma, hypersplenism, extrahepatocytal manifestation, peripheral blood, atypical erythrocytes, thrombocytes, megakaryocytopoiesis, hemopoiesis, bone marrow*

Liver cirrhosis and hepatocellular carcinoma are the most frequent and severe complication of chronic C hepatitis. Approximately 20%-30% of infected persons tend to appear cirrhosis after 20-30 years and 5% of them are liable to progression in hepatocellular carcinoma every year [1,2]. For 90% of compensate cirrhotic patients the length of their lives is approximately 5 years, for 80% - 10 years. At the same time the length of the life for decompensate cirrhotic patients is not more than 5 years.

Results of recent researches indicated that HCV persists and replicates not only in hepatic tissue, but in the other organs, too. The fact of replication of HCV in peripheral blood mononuclear cells, lymph nodules and pancreas is presently verified. The intensity of virus replication is less in bone marrow, spleen, and thyroid and adrenaline nodule [3]. By other sources, in 47.5% of patients, who received bone marrow transplantation because of hematological disorders, the cause of chronic liver disease is HCV, in 6.5% of such patients the cause of chronic liver disease is HBV [4]. According to the opinion of other researchers the intensity of intrahepatocellular replication is less than extrahepatocellular replication. In patients with chronic C hepatitis and cirrhosis extrahepatocellular areas of virus persistence and replication and the extrahepatocytal manifestation of the disease complicates the hepatitis and worsens the outcome.

MATERIAL AND METHODS

The goal of our investigation was to determine hematological disorders during chronic HCV and HCV+HBC hepatitis, to find correlation between activity of chronic hepatitis, stage of cirrhosis and degree of hematological disorders. We have studied the following groups: patients with chronic C and B+C hepatitis (36 persons) and 77 HCV-infected persons on the stage of cirrhosis. The age of investigated persons was from 15 to 75 years. 98 (78%) of them were men, 24 (22%) - women. In 62 (69.6%) cases men had chronic hepatitis on

the stage of cirrhosis. In women this complication was found in 15 (62.5%) cases. HBV+HCV mix infectious serological markers were found in 21.6% of patients with chronic hepatitis, and in 27% of patients with viral cirrhosis. Etiological verification was made using third age immunoferment assessment (ELISA-3) through detection of HBsAg, antiHBe, antiHBc(tot) and anti-C antibodies in blood serum. In 55 cases viral load was determined by means of PCR method. We discussed activity of chronic hepatitis using the level of cytolitic ferments (ALT, AST). Rising of their concentration in blood 1.5-3 times was considered as a low activity hepatitis, 3-10 times - middle activity, and if cytolitic ferments level rose more than 10 times, it suggested high activity infection process. We judged the stages of cirrhosis according to Chaidls' classification. Out of all investigated persons 14 patients had low activity hepatitis, 22 persons suffered from high activity of infectious process. From cirrhotic patients 22 had A stage of pathological process, 25 persons had B stage and 30 persons - C stage. In line of biochemical and serological research specific hematological tests were made. The studies involved morphology and osmotic resistance of erythrocytes, the absolute number and ability of adhesion and aggregation of the thrombocytes. The erythrocytes morphology was investigated through light microscope. The osmotic resistance of erythrocytes was investigated using the method of lanovski (modification of Ribiera), the thrombocytes' ability to adhe and aggregate was studied through the method of Rite. The absolute number of thrombocytes was counted by means of phase-contras microscope.

RESULTS AND DISCUSSION

As a result of our investigations we found correlation between hematological disorders and liver damage degree. Viral cirrhosis, especially its C stage, was characterized with important hematological changes. The absolute number of thrombocytes was significantly low and their ability to adhere and aggregate was greatly reduced as well. The morphology of erythrocytes had also

significantly changed. In morphological smear of peripheral blood the anisocytosis become constant and mainly it has macrocytal nature. Atypical erythrocytes (acanthocytes, tear-shaped erythrocytes, and ovalocytes) are often seen too. Together with changes of erythrocytes morphology their osmotic resistance becomes significantly lower. During chronic HCV hepatitis in line with development of cirrhosis haematological disorders become more serious. This is particularly evident at the C stage of cirrhosis. At this moment substantially lowers the most important proteins synthesis function of the liver. Presumably, deep thrombocytopenia is directly connected this. Thrombopoietin - humoral regulator of megakaryocytopoiesis is synthesized in liver [5]. Moreover, parts of the scientists consider chronic hepatitis as direct megakaryocytal infection [5]. Suppression of thrombopoiesis on the one hand can be conditioned by immune mechanisms and on the other hand the reason for it may be the virus tropism to hemopoietic cells. There is data on the combination of inquired aplastic anemia and chronic C hepatitis, when the hemopoietic tissue of the bone marrow is replaced by lipocytes [6]. It is known that the viral infections facilitate development of aplastic anemia and in approximately 15% of cases it develops with the background of hepatitis-like diseases [6]. The mentioned haematological pathology occurs with 28% of the patients having liver transplantation due to HCV hepatitis [7]. Therefore, aplastic anemia developed against the background of chronic hepatitis and cirrhosis may be one of the possible causes for the results

obtained during our investigation. Moreover, portal hypertension characteristic for cirrhosis and accordingly hypersplenism (intensified deposition and destruction of blood cells in the spleen) in itself dramatically reduces the number of thrombocytes [5]. Indeed, according to the number of investigations, among the cirrhosis patients the level of thrombopoietin is insignificantly decreased compared to healthy controls and chronic C hepatitis patients, therefore the primary reason of thrombocytopenia is considered hypersplenism.

As far as the erythrocytes are concerned circulation of atypical erythrocytes (ovalocytes, acanthocytes, tear-shaped erythrocytes) in the peripheral blood of the patients with cirrhosis again can be explained by ineffective hemopoiesis of infected bone marrow and disorder of the function of damaged liver. According to the opinion of the one group of researchers 'maturation arrest' of the erythroid lineage seen in the bone marrow is the result of an immune mechanism, induced by the HCV, and that the elimination of this mechanism, rather than the elimination of the HCV, provided the opportunity for regeneration of erythropoiesis [8]. And the osmotic resistance of atypical erythrocytes in itself is significantly lower compared to healthy controls.

Thus, with the viral cirrhosis of the liver the patients display a severe hematological disorder, which is directly correlated with the degree of damage of the liver.

MORPHOLOGY OF ERYTHROCYTES		Precise anisocytosis	20%±7
		Macrocytosis	24%±8
		Atypical erythrocytes	56%±9%
RESISTANCE OF ERYTHROCYTES	Minimal 0,48% NaCl	0.40% NaCl	47%±9
		0.38% NaCl	43%±9
		0.36% NaCl	10%±6
	Maximal 0,32% NaCl	0.30% NaCl	33%±9
		0.28% NaCl	40%±9
		0.26% NaCl	27%±8
THROMBOCYTES	Absolute number 180 000-320 000	140 000-120 000	57%±14
		120 000-50 000	43%±12
	Ability of adhesion 20%-50%	17%-15%	51%±16
		14%-12%	49%±12
	Ability of aggregation 15-20mA	10mA-8mA	53%±15
7mA-5mA		47%±7	

Tab.1 Hematological disorders in patients with viral C cirrhosis on the C stage according to Chailds' classification (n=113).

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Гематологические нарушения при вирусном циррозе печени

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Р Е З Ю М Е

Цирроз печени и гепатоцеллюлярная карцинома - самые частые и тяжелые осложнения хронического вирусного гепатита С. Исследования последних лет показали, что вирус персистирует и реплицирует не только в печени, но и в других органах. Внепеченочные участки персистенции и размножение вируса обуславливают экстрагепатоцеллюлярную манифестацию болезни и осложняют ее исход. Исследование ставило целью изучить гематологические нарушения в периферической крови у больных с хроническими гепатитами и с хроническим С гепатитом на стадии цирроза. Обследовали 36 больных хроническим гепатитом С и В+С и 77 HCV-инфицированных на стадии цирроза. У 14 исследуемых больных был хронический гепатит низкой активности, у 22 - высокой активности. У 22 больных обнаружился цирроз на стадии А, у 25 больных стадия В патологического процесса, а у 30 - стадия С. Морфологию эритроцитов изучали с помощью светового микроскопа; осмотическую резистентность – методом Яновского (модификация Рибиеры); абсолютное количество тромбоцитов определяли фазоконтрастным микроскопом; адгезивную и агрегативную активность тромбоцитов изучали методом Райта. При хроническом гепатите С, по мере появления клинико-морфологических симптомов цирроза, гематологические нарушения становятся более серьезными. Это наиболее выражено у больных циррозом на стадии С. Считаем возможным заключить, что у больных с тяжелым вирусным циррозом развиваются глубокие гематологические нарушения, которые непосредственно связаны со степенью поражения печени.

Ключевые слова: вирусный гепатит, цирроз печени, гепатоцеллюлярная карцинома, гиперспленизм, экстрагепатоцитарные проявления, периферическая кровь, нетипичные эритроциты, тромбоциты, мегакариоцитопоз, гемопоэз, костный мозг