

Multicentric study on the thrombotic events of patients with Hepatocarcinoma.

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Abstract

In recent years there has been an important change regarding the thrombotic risk estimation of patients with liver cirrhosis, underestimated in the past in favor of the hemorrhagic risk. The appearance of the hepatocarcinoma in the chronic liver diseases evolution increases the thrombotic risk of the patients. We have created a retrospective, multicentric clinical study, including 215 consecutive patients hospitalized in 3 university sites from Transylvania. We have analyzed the complete blood panel parameters, coagulation tests, the thrombotic risk score and the thrombotic and hemorrhagic events of the patients. Over a third of the patients presented thrombosis. The mean platelet volume and the other platelet parameters do not correlate with thrombotic events. The number of platelets correlates directly with the thrombotic risk score. The results are analyzed in the light of the physiopathologic disturbances induced to these patients.

Keywords: Hepatocarcinoma, liver cirrhosis, mean platelet volume, platelets, thrombosis

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Introduction

The medical world assisted recently to a reevaluation of the coagulation status of the patients with liver cirrhosis. Until recently it was considered that they have a main hemorrhagic risk. The body of proof accumulated last time argue justified that they are also predisposed to thrombosis. The development of hepatocarcinoma, which occurs more frequently in liver cirrhosis evolution, contributes to the increased thrombotic risk of these patients. The incidence of hepatocarcinoma in liver cirrhosis is 3-5% per year [1]. Because the prevalence of hepatocarcinoma in our geographic area is much smaller than that from East and South-East Asia, in order to study the thrombotic complications we endorsed the creation of a multicentric study. The increased mean platelet volume (MPV) is an independent risk factor for stroke in patients with chronic atrial fibrillation. We proposed to study also the significance of the MPV and other platelet parameters at patients with hepatocarcinoma.

Material and Method

We carried out a retrospective, multicenter study including all the patients with hepatocarcinoma admitted between January 2010 and December 2012 in the Internal Medicine and Gastroenterology Department of Emergency County Clinical Hospitals of Braşov, Oradea and Sibiu. From the electronic evidence systems of medical data we have selected the following parameters of the patients: age, gender, liver disease coexistent with hepatocarcinoma, the presence of obesity, leukocyte amount, value of hemoglobin and haematocrit, mean platelet volume (MPV), platelet distribution width (PDW), platelet large cell ratio (P-LCR), plateletcrit (PCT), international normalized ratio (INR), prothrombin activity, Quick's test (QT), activated partial thromboplastin time (APTT), eventual portal vein thrombosis, thrombotic antecedents (myocardial infarction, ischemic stroke, thrombophlebitis, carotid artery occlusion, inferior vena cava thrombosis, suprahepatic vein thrombosis, partially thrombosed aortic

aneurysm, superior mesenteric vein thrombosis), recent thromboses (in the past 2 months), ongoing thromboses, the total number of thrombotic events, thrombotic risk score, recent hemorrhages (in the past 2 months). The thrombotic risk score was calculated as: 1 point for each of the following factors that were present: platelets number before chemotherapy $\geq 350 \times 10^9/l$, hemoglobin level below 100 g/l or use of erythropoietin, the number of leukocytes before chemotherapy over $11 \times 10^9/l$, body mass index $\geq 35 \text{ kg/m}^2$ [2].

The data obtained was statistically analyzed: arithmetic mean, standard deviation, t Student test and Pearson test.

Results

The group included 215 patients. The mean age was 65.96 ± 10.83 years. Gender repartition: 140 men (65.1%) and 75 women (34.9%). The type of hepatopathy of the patients with hepatocarcinoma is found in table I. The analyzed parameters of the complete blood panel are

found in table II. The coagulation tests had the following mean values: prothrombin time 16.68 ± 4.28 s, prothrombin activity $60.68 \pm 16.97\%$, INR 1.37 ± 0.41 and APTT 34.18 ± 12.61 s. The mean thrombotic risk score was 0.57 ± 0.78 . The thrombotic events are represented in table III. Recent hemorrhagic accidents: 31 (14.42%). The coagulation tests were not correlated with the thrombotic events. The platelet count, MPV and the other platelet indices were not correlated with the thrombotic risk score, the thrombotic antecedents, and current thrombotic events and with the total thrombotic events of the patient even after the exclusion from the group of the patients with recent hemorrhagic episodes. Neither after the exclusion of the patients with current thrombosis the above mentioned parameters were not correlated with the thrombotic antecedents or the MPV with the platelet count of these patients ($r=0.173$). The thrombotic risk score was not correlated with MPV ($r=-0.07$) or with the past ($r=0.023$), current ($r=-0.078$) or with the total number of thrombotic events ($r=-0.043$), but was directly correlated with the platelet count ($r=0.447$).

Table I: The type of liver diseases coexisting with hepatocarcinoma

Hepatopathy	Number of cases	%
Cirrhosis with hepatitis B virus	24	11.16
Cirrhosis with hepatitis C virus	63	29.30
Cirrhosis with hepatitis B + C virus	3	1.40
Alcoholic cirrhosis	40	18.60
Cirrhosis with hepatitis B virus + ethanol	3	1.39
Cirrhosis with hepatitis C virus + ethanol	5	2.33
Cirrhosis with hepatitis B + D virus	1	0.47
Nonalcoholic steatohepatitis	1	0.47
Cryptogenic cirrhosis	2	0.93
Cirrhosis with unspecified etiology	53	24.65
Hepatitis	20	9.30

Table II: Blood panel parameters

Parameter	Arithmetic mean	Standard deviation
Leucocytes (/mm ³)	8690	5070
Hemoglobin (g/dl)	11.90	2.47
Haematocrit (%)	35.50	7.01
Platelets (/mm ³)	200650	120660
MPV (fl)	10.04	1.53
PDW (%)	17.20	1.98
p-LCR (%)	32.78	8.04
PCT (%)	0.20	0.13

Table III: Thrombotic events

Type of thrombotic event	Number of thrombotic events	%
Thrombotic antecedents	27	1.26
Recent thrombosis	5	2.33
Ongoing thrombosis (including portal vein thrombosis)	48	22.33
Portal vein thrombosis	38	17.67
Total of thrombotic events	80	37.21

Discussion

An increased MPV, indicator of platelet activation [3], is considered a thrombotic risk factor in different circum

stances, including to the patient with atrial fibrillation, to whom the increased risk of ischemic stroke is associated [4]. Also the patients with fatty liver disease have MPV increased. MPV inverse correlates with the platelet number at these patients [3], as at healthy subjects. Any situation that involves increased platelet consumption (thrombosis with various locations) is followed by the release into the blood stream of sequestered platelets until then in the spleen, where are young and with increased MPV - hyper-functional platelets. Also the patients with primary immune thrombocytopenia, with platelet destruction through immune mechanisms, have increased MPV. Also in patients with chronic hepatitis B a significantly higher MPV compared to the healthy control population has been found. The MPV was not increased for those with advanced liver fibrosis compared with those with minor fibrosis [5]. The MPV does not have the same value in any liver disease. Thus, in another study, the number of platelets and the MPV of the patients with hepatopathies were significantly smaller than control group. Additionally, in cirrhosis the platelet number and the MPV do not correlate inversely as in healthy subjects [6]. We have not found any correlation between the MPV and platelet number, the thrombotic risk score or the thromboses of patients with hepatocarcinoma, most of them occurred in the development of some liver cirrhoses.

Besides the MPV, we have also studied the other platelet parameters because in liver cirrhosis the PDW and the megathrombocyte index are better indicators of an altered platelet homeostasis compared with MPV [7]. Neither these have a correlation with the thrombotic events.

Why are there no correlations between the platelet indices and the thrombotic events at patients with hepatocarcinoma? There are multiple explanations: MPV and the other platelet parameters can be influenced by the thrombotic or hemorrhagic events but it was observed that the MPV does not increase when the platelet number decreases at cirrhotic patients. Because the majority of the patients with hepatocarcinoma have liver cirrhosis, this finding was confirmed for our study group, too. The thrombocytopenia of patients with liver cirrhosis +/- hepatocarcinoma (explainable by spleen sequestering and increased destruction by hypersplenism, with procoagulation status and low thrombopoietin levels) doesn't lead to an increased number of medullary megakaryocytes as it happens in other peripheral thrombocytopenia cases. In case of thromboses, the platelet number is lower than in their absence [8] because the hematopoietic bone marrow doesn't compensate for the platelets loss (through young platelets with high MPV). It results that the thrombotic

risk of patients with liver cirrhosis + hepatocarcinoma is not influenced by the MPV but by the disturbance of the coagulation, fibrinolysis and homeostasis processes.

The patients with decompensated liver cirrhosis have an impaired hepatic synthesis, affecting also the synthesis of some coagulation factors (I, II, V, VII, IX, X, XI, XIII). Additionally the platelets function is deficient. It was thought for a long time that the liver cirrhosis is a model of acquired hemorrhagic coagulopathy. In this nosologic entity not only the procoagulation factors are decreased but also some of the anticoagulation factors, thus the global coagulation tests are usually normal for patients with chronic liver diseases. The thrombotic events are promoted by the increased level of coagulation factor VIII, von Willebrand factor and by the decrease of the antithrombin, plasminogen, protein C and S levels. There is a weak correlation between the hemorrhagic risk and the usual hemostasis tests [9]. Cirrhotic patients can have an increased risk of thrombotic events [10, 11] due to a systemic and portal prothrombotic state [11]. It is believed that the portal vein thrombosis increases the morbidity and mortality associated with the liver transplant at patients with liver cirrhosis. When the thrombus extends to the superior mesenteric vein this procedure becomes contraindicated [12]

The presence of the hepatocarcinoma grafted on the cirrhosis significantly increases the patient's thrombotic risk. In our study 37.21% of the patients had thromboses in antecedents or during the admission. In the scientific literature there was one case published, that, starting from the diagnosis had disseminate tumor thrombosis, including mobile thrombus in the right atrium and pulmonary embolism [13]. The portal vein thrombosis at patients with hepatocarcinoma constitutes an independent prognostic factor for them [14]. At 17.67% of the patients studied by us the thrombosis of the portal vein was present. The thrombi can be present even in the biliary tract at these patients leading to difficulties in differentiating from biliary calculus or cholangiocarcinoma [15].

The presence of the portal vein thrombosis can create imagistic diagnostic difficulties of the hepatocarcinoma because the characteristic hypervascularization can be absent, supplied by the hepatic parenchyma background [16]. TGFβ1 had higher values at patients with hepatocarcinoma with portal vein thrombosis and can be involved in the neoplasia progression [17].

What is the explanation of this prothrombotic status? The patients with hepatocarcinoma have significant changes regarding the coagulation and the fibrinolysis: a decreased number of platelets, antithrombin level, plasminogen, protein C, coagulation factors XI, X, VII, V was discovered whereas the APTT, thrombin time, fibrin degradation products, von Willebrand factor, tissue plasminogen acti-

vator and prothrombin fragments 1 + 2 had higher values than in the control group (without hepatocarcinoma) [18].

After splenectomy or simultaneously hepatectomy and splenectomy for hepatocarcinoma made on a group of 38 consecutive patients with liver cirrhosis, the postoperative incidence of the portal or splenic veins thrombosis was 34.2% [19]. After hepatocarcinoma resection the presence of the portal vein thrombosis was significantly correlated with shorter survival without progression [20]. Venous thromboses (of portal or hepatic veins) were cited after hepatocarcinoma ablation by radiofrequency but their incidence was only of 1.08% in a group of 1046 patients, with 1379 ablations [21]. Besides hepatocarcinoma, the risk factors for portal vein thrombosis are: liver cirrhosis, abdominal infections, umbilical catheterization, abdominal surgery, including hepatectomy, and very rarely thrombophilia [22]. The deficit of proteins C and S was involved in the chronic thrombosis of the portal vein [23]. The portal vein thrombosis can be influenced by the gene IL-28B polymorphism: an increased thrombotic event risk was observed at Chinese Han population with genotype GA + GG at rs4803223 polymorphism [24]. Hypoxic hepatitis does not appear only after digestive hemorrhage at cirrhotic patients but also at those with portal vein thrombosis, that was proved to be an independent risk factor for hypoxic hepatitis [25].

Could the thrombotic complications of these patients be prevented? In a recent Italian study, enoxaparin administered to patients with Child-Pugh B7-C10 liver cirrhosis, at dosage of 4000UI/day, for 48 weeks, has significantly reduced the incidence of the portal vein thrombosis and has delayed the liver decompensation, contributing to the patient's life expectancy prolongation, in safety conditions [26]. Additionally, the anticoagulant treatment can lead to splenic-portal ax re-permeabilization and can prevent the thrombosis progression [12]. However, the guide of the American Association for the Study of Liver Diseases makes no recommendation on anticoagulant treatment for cirrhotic patients with venous thrombosis [9]. A case of recanalization of the portal vein in a patient with advanced hepatocellular carcinoma after treatment with sunitinib was reported [27].

Conclusions

Over a third of the patients with hepatocarcinoma had in the past or at the study moment venous thrombosis. The most frequent thrombosis was of the portal vein (17.67%). The thrombotic risk was not correlated with MPV or with other platelet indices, but was directly correlated with platelet number. The thrombotic events were not correlated with the thrombotic risk score or with the platelet indices. The low number of megakaryocytes and the low level of thrombopoietin explain this lack of corre-

lation. The coagulation, fibrinolysis and hemostasis processes dysfunctions and the direct tumoral effects are involved in the thrombotic events of these patients and can aggravate the disease evolution and, sometimes, establish the prognosis. Therefore, their prophylaxis must be taken into account in each case and the opportunity of it must be analyzed dependent on individual particularities and risks.

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