Abnormal hematological indices in cirrhosis

Amir A Qamar MD, Norman D Grace MD

AA Qamar, ND Grace. Abnormal hematological indices in cirrhosis. Can J Gastroenterol 2009;23(6):441-445.

Abnormalities in hematological indices are frequently encountered in cirrhosis. Multiple causes contribute to the occurrence of hematological abnormalities. Recent studies suggest that the presence of hematological cytopenias is associated with a poor prognosis in cirrhosis. The present article reviews the pathogenesis, incidence, prevalence, clinical significance and treatment of abnormal hematological indices in cirrhosis.

Key Words: *Anemia; Cirrhosis; Hypersplenism; Leukopenia; Thrombocytopenia*

Indices hématologiques anormaux dans la cirrhose

On observe souvent des anomalies des indices hématologiques dans la cirrhose. Plusieurs causes contribuent à ces anomalies hématologiques. De récentes études donnent à penser que la présence de cytopénies hématologiques soit associée à un pronostic sombre dans la cirrhose. Le présent article passe en revue la pathogenèse, l'incidence, la prévalence, la portée clinique et le traitement des indices hématologiques anormaux dans la cirrhose.

Abnormalities in hematological parameters are common in patients with cirrhosis. The pathogenesis of abnormal hematological indices (HIs) in cirrhosis is multifactorial and includes portal hypertension-induced sequestration, alterations in bone marrow stimulating factors, viral- and toxin-induced bone marrow suppression and consumption or loss (Tables 1-4). Abnormalities in HIs are associated with an increased risk of complications including bleeding and infection. The present article reviews the pathogenesis, occurrence, incidence and clinical significance of abnormal HIs in cirrhosis.

PATHOGENESIS

Portal hypertension

Splenic sequestration and destruction of platelets, white blood cells (WBCs) and red blood cells (RBCs) in the portal hypertension-induced enlarged spleen is defined as hypersplenism (1). In patients with cirrhosis, there is a redistribution of platelets, with up to 90% of the circulating platelet mass located in the enlarged spleen (2-4). Similarly, splenic sequestration of RBCs contributes to the anemia of liver disease. Using ^{51}Cr-labelled RBCs, Subiyah and Al-Hindawi (5) demonstrated a correlation between a decrease in RBC survival and splenomegaly related to portal hypertension. They also showed that splenectomy resulted in improved RBC survival. Blackman et al (6) investigated the disappearance rates of autologous granulocytes in the blood of 20 patients with alcoholic cirrhosis. Granulocytes were labelled with ^{32}P-labelled diisopropyl fluorophosphate (^{32}DFP), and disappearance curves were obtained and correlated with splenic pulp pressure and size. Portal pressures were estimated by splenic pulp pressure. A biphasic curve was obtained in which 59% of ^{32}DFP-labelled granulocytes were recovered in an initial rapid phase. This initial phase correlated with splenic pulp pressure but not splenic size. In the second phase, the remaining granulocytes disappeared at a slower rate. Overall, there was no relationship between granulocyte recovery and spleen size or splenic pulp pressure, suggesting that sequestration occurs outside of the spleen, possibly in the splanchnic circulation.

In patients with compensated cirrhosis, we have shown (7,8) a significant correlation between the hepatic venous pressure gradient (HVPG [a marker of portal hypertension]), and HI. However, there was only a mild to moderate correlation between platelet counts, WBC counts and hemoglobin. This suggests that other factors, in addition to splenic sequestration, contribute to the occurrence of abnormal HIs in cirrhosis. For both leukopenia and anemia, portal hypertension appears to have a limited contribution.

HEMATOPOIETIC GROWTH HORMONES

Thrombopoietin

Thrombopoietin is produced by liver, kidney, muscle and bone marrow, and its synthesis is mainly dependent on hepatic function. Thrombopoietin stimulates the production and differentiation of megakaryocytes into mature platelets. Studies have shown it to be effective in increasing the platelet count in noncirrhotic conditions. Numerous studies have evaluated thrombopoietin in cirrhosis. Peck-Radosavljevic et al (9) evaluated peripheral thrombopoietin levels in 28 patients with cirrhosis, none of whom had detectable thrombopoietin. However, seven of these patients underwent liver transplantation, with an increase in the thrombopoietin level two days after surgery. On the other hand, five of these patients, who underwent decompression for portal hypertension, showed no improvement in thrombopoietin levels. In a similar study, Martin et al (10) were unable to detect plasma thrombopoietin in 39 of 44 patients with cirrhosis. They also noted that among 16 of 17 patients who underwent liver transplantation, thrombopoietin became detectable. Subsequent studies have confirmed these findings (11-15).

Because the liver is one of the major organs that produces thrombopoietin, alterations in hepatic perfusion may alter either the synthesis or release of the hormone. Giannini et al (16) used a monoethylglycinexylidide test, which is partially dependant on hepatic perfusion, to assess thrombopoietin levels. They demonstrated a modest correlation between monoethylglycinexylidide test times and thrombopoietin levels in

Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
Correspondence: Dr Amir A Qamar, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115, USA.
Telephone 617-732-5849, fax 617-566-0338, e-mail aqamar@partners.org
Received for publication November 29, 2008. Accepted January 29, 2009

TABLE 1
Causes of thrombocytopenia in cirrhosis

Portal hypertension-induced splenic sequestration
Alterations in thrombopoietin
Bone marrow suppression mediated by toxins (eg, alcohol, hepatitis B and C)
Consumptive coaguloapathy (eg, low-grade disseminated intravascular coagulation, acquired intravascular coagulation and fibrinolysis)
Increased blood loss (eg, hemorrhage)

TABLE 2
Causes of leukopenia in cirrhosis

Portal hypertension-induced splenic and splanchnic sequestration
Alterations in granulocyte-colony stimulating factor and granulocyte macrophage-colony stimulating factor
Bone marrow suppression mediated by toxins (eg, alcohol, hepatitis B and C)

TABLE 3
Causes of abnormal hematological indices in cirrhosis

Portal hypertension-induced splenic sequestration
Alterations in erythropoietin
Bone marrow suppression mediated by toxins (eg, alcohol, hepatitis B and C)
Increased blood loss (eg, hemorrhage, hemolysis)

TABLE 4
Association between hematopoietic stimulating factors and thrombocytopenia, anemia and leukopenia in cirrhosis

Hematopoietic stimulating factor	Association with cirrhosis
Thrombopoietin	Significant association with the presence of thrombocytopenia
Erythropoietin	Possible association, data limited
Granulocyte colony-stimulating factor	No data

patients with cirrhosis. This suggests that hepatic perfusion may play a role in regulating thrombopoietin levels. Rios et al (17) found that thrombopoietin levels correlated with spleen size but not platelet count. After these patients underwent partial splenic embolization, the physiological relationship between thrombopoietin levels and platelet counts was restored. The report concluded that increased thrombopoietin degradation in the portal hypertension-congested spleen may contribute to the thrombocytopenia of cirrhosis.

In 19 patients with cirrhosis, Sezai et al (18) showed that hepatofugal circulation, which is generally associated with lower portal venous pressures and less severe portal hypertension, had a lower hepatic vein to portal vein ratio of thrombopoietin. This suggests that a certain perfusion pressure may be needed for the release of thrombopoietin. However, a larger study is needed to confirm these findings. Furthermore, the authors used the portovenous pressure to assess portal hypertension, which does not account for intrahepatic sinusoidal hypertension. A more accurate determinant of portal hypertension is HVPG; this measurement should be used in future studies.

Anemia

Erythropoietin is produced predominantly by the kidney but also by the liver. It protects RBCs from apoptosis and enhances the development of precursor RBCs. Yang et al (19) investigated the significance of erythropoietin in 67 patients with varying severity of cirrhosis, and reported that plasma erythropoietin levels were significantly higher in cirrhotic patients than in controls. They also found levels to be higher in patients with anemia. Interestingly, they demonstrated a positive correlation between the HVPG and erythropoietin, and a negative correlation between hepatic blood flow and erythropoietin. Bruno et al (20) found an increase in erythropoietin in cirrhotic patients with anemia only when the hemoglobin level was less than 120 g/L. The authors believed that the erythropoietin response was blunted in comparison with other causes of anemia such as iron deficiency.

WBC stimulating factors

Very little is known about the role of granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) in leukopenia associated with cirrhosis. These factors are produced by the immune cells to stimulate the bone marrow to produce and release granulocytes and stem cells into the circulation. They also have a role in the differentiation and function of mature neutrophils. Gurakar et al (21) have shown that GM-CSF treatment for seven days in patients with cirrhosis and leukopenia resulted in an increase in the WBC count. Moreover, they showed no increase in the fraction of trapped leukocytes in the spleen.

Bone marrow suppression

Viral hepatitis B or C, excess alcohol consumption and medications are commonly associated with cirrhosis and an increased risk of pancytopenia due to bone marrow suppression as a result of bone marrow hypoplasia. Interferon, azathioprine and mycophenolate mofetil are examples of medications that may cause pancytopenia in patients with cirrhosis.

Other factors

Many other factors contribute to the development of abnormal HIs in cirrhosis. Patients with portal hypertension may experience occult or chronic bleeding from portal hypertensive gastropathy and/or enteropathy, leading to anemia and thrombocytopenia. Patients with ongoing alcohol consumption may have hemolysis, which exacerbates anemia. Low-grade disseminated intravascular coagulation may contribute to thrombocytopenia in patients with decompensated cirrhosis.

ABNORMAL HIs IN CIRRHOSIS

Prevalence

Heterogenous studies of patients with varying stages of cirrhosis have shown a prevalence of abnomal HIs ranging from 6% to 77% (22-29). Many of these studies, however, consist of patients with differing severities of cirrhosis with or without decompensation. In a recent analysis of homogenous patients with compensated Child-Pugh class A/B cirrhosis, 84% were found to have abnormalities in the HI, defined as a platelet count of less than or equal to 150×10^9/L, WBC count of less than or equal to 400×10^9/L or hemoglobin level less than or equal to 135 g/L for men and 115 g/L for women. Thirty-two per cent of these patients had a combination of cytopenias (8). Thrombocytopenia was the most common single abnormality, and thrombocytopenia and leukopenia was the most common combined abnormality.

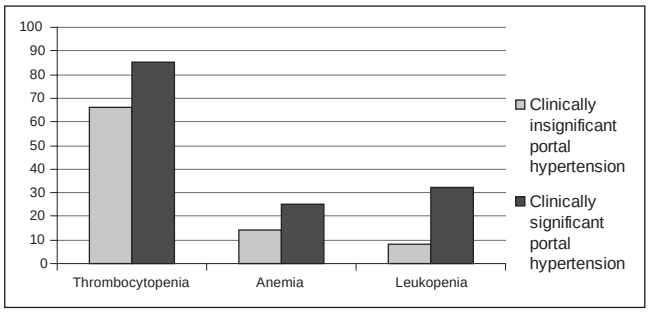
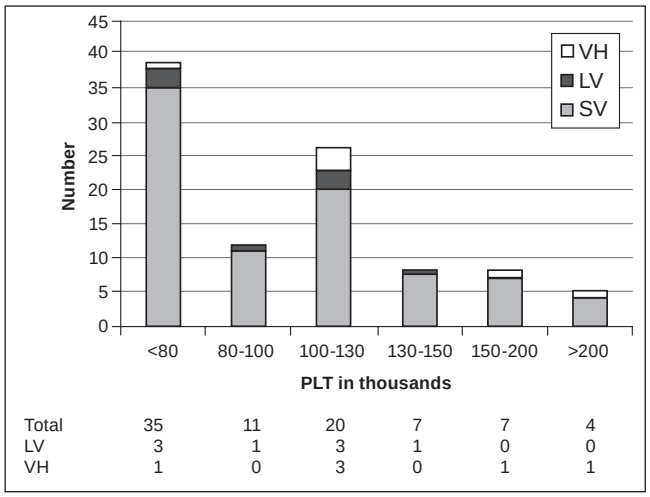


Figure 1) *The prevalence of abnormal hematological indices in cirrhosis patients with clinically significant (hepatic venous pressure gradient ≥10 mmHg) compared with clinically insignificant (hepatic venous prssure gradient <10 mmHg) portal hypertension (n=213). Anemia defined as a hemoglobin level of less than 135 g/L for men and less than 115 g/L for women. Leukopenia defined as a white blood cell count of less than 400×10^9/L. Thrombocytopenia defined as a platelet count of less than 150×10^9/L*



Total	35	11	20	7	7	4
LV	3	1	3	1	0	0
VH	1	0	3	0	1	1

Figure 2) *Relationship between the presence of small varices (SV), large varices (LV), variceal hemorrhage (VH) and platelet count (PLT) ranges at the time of occurrence of varices or VH. Adapted from reference 7*

Incidence

Assessment of the true occurrence of abnormal HIs in cirrhosis is limited by the cross-sectional design of most studies reporting these findings. Recently, a cohort of 34 patients with compensated Child-Pugh class A/B cirrhosis with a normal baseline HI were followed longitudinally for approximately five years to determine the sequence of abnormal HIs in cirrhosis (8). Thrombocytopenia was the most common and earliest HI abnormality to develop, followed sequentially by anemia and thrombocytopenia.

Clinical significance

The occurrence of thrombocytopenia, leukopenia or anemia in patients with cirrhosis may have significant clinical implications. They may be a limiting factor when considering invasive procedures such as liver biopsy, paracentesis, or dental, endoscopic or surgical procedures. Leukopenia may also increase the risk for infection. Chronic anemia may contribute to a poorer outcome after any hemorrhagic episode.

There is now evidence to support the increased morbidity and mortality associated with hypersplenism. Liangpunsakul et al (30) reported that the presence of severe hypersplenism independently predicted the development of variceal bleeding and death.

A study (8) evaluating the risk of death or transplant among 213 patients with compensated Child-Pugh class A/B cirrhosis reported that both thrombocytopenia and leukopenia were significantly associated with an increased risk of morbidity and mortality, even when controlling for factors such as Child-Pugh score, portal hypertension as determined by the HVPG or alcohol use. The greatest risk occurred in patients who had both thrombocytopenia and leukopenia. The prevalence of abnormal HIs differed in patients with clinically significant portal hypertension (HVPG 10 mmHg or higher) compared with clinically insignificant portal hypertension (HVPG less than 10 mmHg) (Figure 1).

Thrombocytopenia has been suggested to be a noninvasive marker for the presence of esophageal varices. Many studies (31-35) have reported a wide range of platelet count thresholds that would prompt examinations using upper endoscopy to screen for esophageal varices. The interpretation of these studies was limited by their cross-sectional nature and the differing severity of cirrhosis among included subjects. Our group recently addressed this issue by analyzing patients included in a prospective, randomized controlled study (7) in which subjects were followed for a median of 54.9 months. Cross-sectional evaluation found no platelet count threshold that was clinically useful for indicating the presence of gastroesophageal varices. Surprisingly, 14% of patients with large varices or variceal hemorrhage had normal platelet counts (Figure 2). Longitudinal evaluation of platelet counts fared no better and was found to be inadequate for predicting the occurrence of gastroesophageal varices in compensated cirrhosis. Thus, it can be concluded that the use of platelet counts is inadequate for detecting the presence or occurrence of gastroesophageal varices in cirrhosis.

TREATMENT

Treatment of abnormal HIs in cirrhosis involves a multifaceted approach. Prevention of bleeding with gastrointestinal prophylaxis using proton pump inhibitors, and transfusion of platelets before procedures may reduce the risk of exacerbating underlying HI abnormalities. Advising patients to reduce alcohol intake can prevent further exacerbation of HI abnormalities. However, presently, reduction of portal pressure and the use of hematopoietic growth factors are the most often used treatments.

Reduction of portal hypertension

Portosystemic shunts: Many studies have shown an improvement in the HI when portal pressures are reduced using surgical or transjugular intrahepatic portosystemic shunts (TIPS). Felix et al (36) compared leukopenia and thrombocytopenia among patients treated with either a portocaval shunt or conventional medical therapy. Patients in the medical group did not receive beta-blockers or nitrates. Leukopenia improved in 50% of the subjects in the surgical group compared with only 14% in the medical group. Similarly, thrombocytopenia improved in 43%

of subjects in the surgical group compared with 0% in the medical group. The greatest benefit occurred when the preshunt portal pressure was greater than 30 mmHg and reduced by at least 10 mmHg after surgery. A postshunt portal pressure above 15 mmHg was most likely to be associated with an improvement in both thrombocytopenia and leukopenia. In the study, 100% of subjects with postshunt portal pressures greater than 15 mmHg had an improved HI, compared with only 50% in the group with postshunt portal pressures of less than 15 mmHg. They also found that when the postshunt portal pressures were reduced by more than 10 mmHg, the HI improved in 100% of subjects compared with only 44% among those with less than a 10 mmHg reduction. These findings have been confirmed (26,37-41). In contrast, Mutchnick et al (42) and other groups (43,44) have demonstrated the disappearance of thrombocytopenia with equal frequency among patients who underwent surgical portosystemic shunting compared with controls.

Similar to the results demonstrated with surgical shunts, many studies have shown that TIPS improved HIs (45-48). Gschwantler et al (45) showed an average increase of 19% in platelet count after the placement of TIPS compared with a 17% decrease in controls. Similar to the findings of Felix et al (36) with surgically created shunts, subjects with higher post-TIPS portal pressures had a greater improvement in thrombocytopenia. A post-TIPS gradient of 12 mmHg or higher had a twofold greater increase in thrombocytopenia compared with individuals who had a gradient of less than 12 mmHg. However, a number of groups have shown no difference in platelet and WBC counts after TIPS placement (49-51). Sanyal et al (49) reported a subgroup of patients that had TIPS placed for ascites in whom the platelet count increased by more than 25%. The mean post-TIPS gradient in this group was 12 mmHg.

Nonselective beta-blockers: If abnormalities in the HI are at least partially related to portal hypertension, then a reduction in portal pressure related to treatment with nonselective beta-blockers might be expected to show an improvement in the abnormal HI. Preneta et al (52) reported that patients with cirrhosis and esophageal varices treated with propranolol had a 37% increase in platelet count compared with a 3.8% decrease in controls. This was associated with a greater reduction in HVPG after propranolol therapy (propranolol 10.7% versus placebo 6.7%). However, patients achieving a significant reduction in HVPG (ie, more than 20%) had a paradoxical reduction rather than the expected increase in platelet count. Sekai et al (53) treated 19 patients with propranolol or placebo for one week. Using Doppler ultrasonography to measure splenic artery hemodynamics, they found that propranolol improved splenic artery pulsatility and increased platelet count by 16×10^9/L, compared with no effect using placebo.

These data suggest that the effect of beta-blockers in producing an improvement in platelet count is variable and may be related to factors other than decompression of portal hypertension.

HEMATOPOIETIC GROWTH FACTORS

Thrombopoietin

An important study using the thrombopoietin receptor agonist eltrombopag was recently published (54). In 74 patients with cirrhosis who had platelet counts between 20×10^9/L and 70×10^9/L, treatment with eltrombopag or placebo was administered for four weeks. Platelet count increased to greater than 100×10^9/L in 75% to 95% of the patients treated with eltrombopag compared with no increase in patients treated with placebo. Certain concerns, however, remain. First, the effect of eltrombopag on the coagulable state or malignancy risk is unknown. Second, because portal hypertension appears to influence thrombopoietin, it may also influence eltrombopag's effect on platelet counts. Finally, the hemostatic effect of the increased platelet count as a result of eltrombopag treatment in cirrhosis is unknown.

Erythropoietin

Patients with hepatitis C virus cirrhosis who receive antiviral therapy with interferon and ribavirin are at higher risk of developing anemia. These patients have been treated successfully with erythropoietin agents, with noted improvement in hemoglobin levels (55,56). Whether treatment benefits patients with cirrhosis in settings other than antiviral therapy is not known. Studies investigating the effect of preventing anemia in cirrhosis are lacking.

G-CSF and GM-CSF

GM-CSF has been safely used in patients with cirrhosis and leukopenia, with an improvement in WBC counts. However, it is unknown whether this increase in WBC count is associated with a reduced risk of infection (21).

SUMMARY

There has been great progress in our understanding of the occurrence, clinical significance and treatment of abnormal HIs in cirrhosis. A number of different factors contribute to abnormal HIs in cirrhosis, but portal hypertension and alterations in bone marrow hormones appear to be the strongest contributors. The occurrence of abnormal HIs is associated with a poor clinical outcome. This may be related to clinical consequences of hematological abnormalities including the risk of bleeding and infection. Reduction of portal pressure using pharmacological agents and shunt procedures have a variable effect on the improvement of abnormal HIs. The potential benefit of recombinant growth factors and analogues needs to be assessed in well-designed, prospective clinical trials.

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