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The effect of variceal bleeding on T-cell subsets in patients with cirrhosis

Maria Lagadinou*, Dimitris Velissaris, Marina Karakantza and Charalambos Gogos

*Correspondence: m_lagad2004@yahoo.gr

University Hospital of Patras, Rio, Patra Greece.

Abstract

Aim: Variceal bleeding may lead to infectious complications in patients with liver failure. The aim of the present study was to investigate the effect of variceal bleeding on T-cell subsets of patients with cirrhosis.

Patients and Methods: The study included 21 patients with biopsy proven liver cirrhosis, that were admitted to the hospital. Six of them were admitted to the Hospital due to variceal bleeding (group 2) while the rest 15 were free of bleeding (group 1) and were admitted due to another cause. T-cell subsets (Total T-cells [CD3], helper T-cells [CD4], suppressor T-cells [CD8] and Natural Killer cells [CD56]) were measured upon admission and day 3, by using flow cytometry.

Results: The absolute number of T-cell subsets in group 1 vs group 2 were the following (mean ± SEM): Admission=CD3: 565±88 vs 507±197, CD56: 160±37 vs 95±14 ($P<0.05$) CD4: 379±60 vs 311±143, CD8: 192±35 vs 172±56, Day 3 = CD3: 565±88 vs 259±62: ($P<0.05$) CD56: 160±37 Vs 60±13, CD4: 379±60 vs 178±36 ($P<0.05$), CD8: 192±35 vs 111±62.

Conclusions: It seems that variceal bleeding may cause immunosuppression through a significant decrease of Natural Killer cells, as well as a decrease in total and helper T-cells. This may compromise immune response and may be associated with the observed increased in the frequency of infectious complications in cirrhotic patients, complicated with variceal bleeding.

Keywords: Cirrhosis, Bacterial infections, Variceal bleeding, T cells

Introduction

Acute variceal bleeding is one of the major causes of death in cirrhotic patients. It is also the major cause of upper gastrointestinal (GI) bleeding in cirrhotic patients, accounting for 70% of cases. Mortality during the first episode is estimated to 15–20%, but is higher in severe patients (Child Pugh C), at around 30%, whereas it is very low in patients with compensated cirrhosis [1].

Variceal bleeding may lead to infectious complications in patients with liver failure. Bacterial infections and/or endotoxaemia have been associated with failure to control variceal bleeding,more early variceal rebleeding, abnormalities in coagulation, vasodilatation of the systemic vasculature, and worsening liver function. There has also been increased recognition that bacterial infections are involved in several pathophysiological abnormalities in cirrhosis [2].

Many immune abnormalities have been associated with liver-cirrhosis, and several immunologic mechanisms may influence the course of the disease, by increasing patient susceptibility to bacterial infections and leading tohemodynamic derangement and sepsis. An alteration of the number and function of lymphocytes, including T lymphocytes and natural killer (NK) cells, has beenreported in liver disease [3].

The aim of this study was to investigate the differences in lymphocyte subsets between cirrhotic patients with gastrointestinal bleeding compared to cirrhotic patients without hemorrhage, and to evaluate the possible prognostic significance of these lymphocyte subsets as well aswell as the possible correlation with the occurrence of predisposition for developing infections.

Patients and methods

The study was conducted at the University Hospital of Patras, inSouth Western Greece. It was approved by the Ethics Committeeof the University Hospital of Patras, and written informed

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consent was obtained from all patients who participated in the study. The diagnosisof cirrhosis was confirmed in all study subjects by liver biopsy.

Twenty one patients were included in the study and were divided in two subgroups as follows:group 1 (n=15)included cirrhotic patients admitted to hospital for reasons other than bleeding These included weakness, worsening of ascites, anemia, neurologic problems, dyspnea and coughing, chest or abdominal pain, elevated liver enzymes and jaundice. Group 2 (n=6): included cirrhotic patients admitted to hospital due to variceal bleeding. The sample of cirrhotic patients with hemorrhage is small due to the rarity of such cases. Also, the total period of the study was short (3 months).

Flow cytometry

Blood samples were collected from each patient in EDTA anticoagulant tubes for measurement of absolute number of Tlymphocyte subpopulations. Samples were analyzed by flow cytometry using the Coulter EPICS-XL-MCL cytometer, and data were processed using the XL-2 software (Coulter, Miami, FL, USA). The percentage and absolute numbers of the peripheral blood lymphocyte subpopulations were determined by a dual-color direct immunofluorescence technique in whole blood method, using the following mouse–anti-human monoclonal antibodies: CD3-PE, CD56-FITC, CD4-PE,CD8-FITC.

All samples were collected within 24 h of admission (day 1) and on hospital day 3, so that we had a measurement at the beginning and a value during hospitalization. Day 3 was arbitrary selected. T-cell subsets (Total T-cells [CD3], helper T-cells [CD4], suppressor T-cells [CD8] and Natural Killer cells were measured with that method.

Statistical analysis was performed using the SPSS statistical software package version 16 (SPSS, Chicago, IL, USA).

Results

To determine whether patients with cirrhosis, and cirrhosis with variceal bleeding had alterations in T-cell subsets, we measured the absolute numbers of peripheral blood lymphocyte sub populations using a dual-color direct immunofluorescence technique in whole blood. All measurements per group are shown in **Tables 1** and **2**.

In our study, lymphocytes from patients with cirrhosis were abnormal in both groups. We found a significant decrease in total CD3+, CD4+, CD8+, and CD56+ T cells between cirrhotic patients with variceal bleeding compared to cirrhotic patients with other reasons, on admission day as well as on day 3. The results are shown in **Figures 1** and **2** respectivelly.

We also investigated a significant decrease in all T cells subpopulations (CD3,CD56,CD4,CD8) on Day 3 in group of cirrhotic patients with variceal bleeding compared to those on admission day. Those results are shown in **Figure 3**.

Comparing the results between group 1 and 2, we founda statistical significant decrease in total CD56+ T cells in cirrhotic patients who were admitted due to gastrointestinal hemorrhage on admission. We also found a statistical significant lower measurement of CD4 T cells in patients from group 2,

Table 1. Measurements of T cells subpopulations among group 1 and group 2 on admission.

T cells	Group 1 Admission	Group 2 Admission
CD3	565±88	507±197
CD56	160±37	95±14 (p<0.05)
CD4	379±60	311±143
CD8	192±35	172±56

Group 1: cirrhotic patients admitted to hospital for reasons other than bleeding, group 2: cirrhotic patients admitted to hospital due to variceal bleeding.

Table 2. Measurements of T cells subpopulations among group 1 and group 2 on day 3.

T cells	Group 1 Day 3	Group 2 Day 3
CD3	565±88	259±62
CD56	160±37	60±13
CD4	379±60	178±36(p<0.05)
CD8	192±35	111±62

Group 1: cirrhotic patients admitted to hospital for reasons other than bleeding, group 2: cirrhotic patients admitted to hospital due to variceal bleeding.

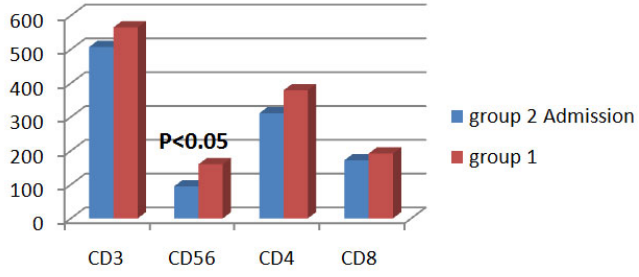

Figure 1. Decreased number of T cell subsets in group of patients with variceal bleeding (group 2) compared to cirrhotic patients admitted due to other reasons (group1), on admission.

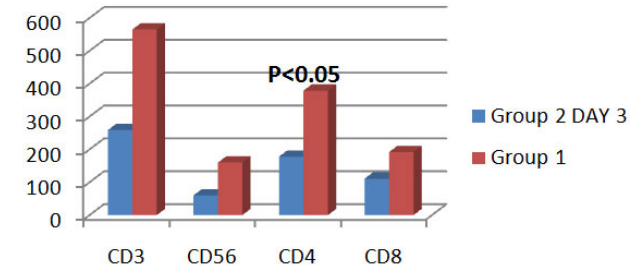

Figure 2. Decreased number of T cell subsets in group of patients with variceal bleeding (group 2) compared to cirrhotic patients admitted due to other reasons (group1), on day 3.

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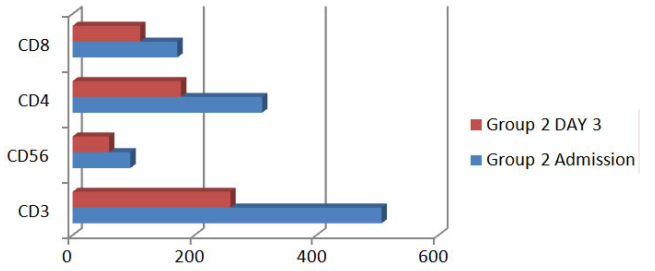

Figure 3. Here is shown the decrease in T subpopulations in the group of cirrhotic patients with variceal bleeding (group 2) on Day 3 compared to Admission.

on Day 3 of hospitalization.

Discussion

In the present study we investigated that cirrhotic patients with variceal bleeding show an immune suppression due to decrease in the number of Natural killer cells and T helper cells. Approximately 20% of patients with cirrhosis who develop acute variceal bleeding are affected by subsequent bacterial infections within 48 h after the onset of bleeding. Bacterial infections occur more frequently in cirrhotic patients admitted with gastrointestinal bleeding than for other causes [4,5]. During acute variceal hemorrhage, prophylactic antibiotics are mainstay of treatment [6]. That statement has been approved by our study, since we found significant reduction in T helper and NK cells during the episode of bleeding.

The guidelines of major gastrointestinal societies recommend the administration of short-term prophylactic antibiotics as standard treatment for all patients with cirrhosis who develop variceal bleeding, irrespective of the presence or absence of actual infection.A meta-analysis of 12 RCTs shows clear survival benefit for theearly use of prophylactic antibiotics during an acute variceal bleed (RR ¼ 0.79, 95%CI 0.63–0.98). These trials also showed that antibiotics reduced the risk of bacterial infections and early re-bleeding [7]. However, whether this treatment strategy should be applied to all patients with variceal bleeding remains unclear [8].

The main predictors of bleeding in clinical practice are: large versus small varices, red wale marks, Child Pugh C versus Child Pugh A.

It is already known that patients with liver cirrhosis have an impaired immune response. Adaptive immune dysfunction is also common in cirrhotic patients. Nourieta et al. demonstrated a broad defect of T cells and hyperactivity of B cells in patients with alcoholic liver disease. Specifically, these patients have circulating IgG and T lymphocytes that recognize epitopes against lipid peroxidation derived antigens and are associated with an increase in hepatic production of proinflammatory cytokines and chemokines.Doi et al. reported that memory CD27+ B cells were reduced in the peripheral blood of patients with cirrhosis, independent of etiology, and that this reduction led to impaired TNF-b and IgG production, vaccine hyporesponsiveness and susceptibility to bacterial infection [9].

We investigated that more specifically, variceal bleeding may cause immunosuppression through a significant decrease of Natural Killer cells, as well as a decrease in total and helper T-cells. This may compromise immune response and may be associated with the observed increased in the frequency of infectious complications in cirrhotic patients, complicated with variceal bleeding.

Impaired monocyte function is a contributor to cirrhosis associated immune dysfunction, leading to defects in chemotaxis, phagocytosis, superoxide degeneration and production of lysosomal enzymes. Neutrophils, which are the first-line of defense against bacterial infection, are also impaired in cirrhotics. On the one hand, this creates an impaired ability to deliver neutrophils to the infective focus, while, on other hand, this generates a reduced phagocytic activity of the neutrophils as compared to those in the healthy population. Also, the various defects in B and T cell functions in alcoholic liver disease have been known for a long time.These factors should be taken into account in interpreting the results of our study.

Our study was the first to investigate the decrease in absolute number of natural killer cells and T helper cells in cirrhotic patients with variceal bleeding and demonstrates the particular immunosuppression in patients with variceal bleeding. Possibly, measuring the T cell subpopulations can direct us to the administration or not of antibiotics.

There are a few limitations to the present study. First, this was a retrospective study carried out in a single hospital. University hospital of Patras is the only one which manages such cirrhotic patients. Further cooperation with hospitals in other cities is needed to increase the number of patients for even more valid results. Second, because of the rarity of GFV bleeding, the study had a relatively small sample size. Even more multicentre studies must be done for better results.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	ML	DV	MK	CG
Research concept and design	✓	--	--	✓
Collection and/or assembly of data	✓	✓	✓	--
Data analysis and interpretation	✓	--	✓	--
Writing the article	✓	✓	--	✓
Critical revision of the article	--	--	✓	✓
Final approval of article	--	--	--	✓
Statistical analysis	✓	✓	--	--

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