on morphology, the Ig gene rearrangement assay can provide more accurate information regarding BM involvement in malignant lymphomas.

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The imbalance of procoagulant and anticoagulant factors in patients with chronic liver diseases in North India

TO THE EDITOR: Patients with chronic liver diseases (CLD) tend to experience severe hemostatic anomalies because of reduced levels of most of the coagulant proteins and anticoagulant factors such as protein C, protein S, and antithrombin. In contrast, it has been observed that levels of certain procoagulant factors such as factor VIII and von Willebrand factor (vWF) levels may be increased [1]. Various mechanisms such as increased levels of vWF antigen and reduced synthesis of ADAMTS 13 cleavage protease have been described to explain elevated factor VIII levels in these patients [2]. Additionally, the fact that factor VIII is an acute-phase reactant could elucidate partly these findings [3]. Not only increased procoagulant factor levels but a reduction in these factors may also lead to prothrombotic tendency in these patients. Concurrent reduction in protein C and factor VIII may also result in the procoagulant imbalance. It is important to distinguish the mechanism for increased factor VIII level in CLD patients since its sustained elevations may provoke the thrombosis. This study was aimed to compare the levels of factor VIII and protein C in CLD patients with a superimposed acute insult [acute-on-chronic liver failure (ACLF)] and in patients with compensated cirrhosis (CC), and to detect the correlations between the these factors and the disease activity using Model for End-Stage Liver Disease (MELD) scores in these respective groups. Furthermore, the ratio of factor VIII and protein C levels was evaluated as an indicator of the severity of liver disease in both groups.

This prospective study comprising 2 groups of patients with underlying CLD in a tertiary care center in North India was approved by the institutional Review board, with written informed consent obtained from all participants. Group 1 included 58 patients with ACLF (Asian Pacific Association for the Study of the Liver criteria [4]), and group 2 included 58 patients with biopsy-proven CC. The blood samples for coagulation study were collected from

both groups using vacutainers containing buffered sodium citrate (0.109 M, 3.2%). The samples were processed within 30 minutes of collection. The citrated tubes were centrifuged at 3,000 g for 10 minutes to obtain plasma and analyzed for factor VIII and protein C on a fully automated coagulometer. The factor VIII and protein C values between the 2 groups were compared using the Mann-Whitney test and those of each group were analyzed the correlation with their MELD scores using Pearson's correlation. *P*-values of <0.05 were considered as statistically significant.

Patient characteristics are summarized in Table 1. The mean age in group 1 was 44.46±11.3 years with 89.7% being men, while in group 2, the mean age was 50.32±10.45 years with 94.8% being men. The median [interquartile range (IQR)] factor VIII and protein C levels in group 1 were 232.55% (150.0–331.5%) and 10.5% (10.25–22.10%), respectively, with a mean MELD score of 26.06±8.19. In group 2, the median (IQR) factor VIII and protein C levels were 178.20% (105.60–261.45%) and 36.8% (25.3–45.07%), respectively, with a mean MELD score of 16.19±3.91. The differences in factor VIII ($P=0.04$) and protein C ($P<0.001$) levels between the 2 groups were statistically significant.

The factor VIII levels in group 2 showed significantly positive correlation with MELD score, while those in group 1 did not show the significant correlation with their MELD score. A weak and negative correlation of protein C with MELD scores was seen in both groups, but it did not reach statistical significance. In addition to the above parameters, the ratio of factor VIII to protein C levels was calculated as an index of the procoagulant tendency in both groups. A statistically significant difference in the ratios between the 2 groups ($P<0.001$) was observed. The factor VIII to protein C ratio in group 1 showed a weak positive correlation with the MELD scores that was statistically insignificant, while the ratio in group 2 showed a weak positive but significant ($P<0.001$) correlation with MELD scores (Table 2).

Patients with CLD do not experience only bleeding complications but also thrombotic events. The main procoagulant drivers in CLD include elevated factor VIII and vWF and reduced protein C levels. Factor VIII elevations can arise from increased vWF levels, decreased expression of low-density lipoprotein receptor, and an acute-phase response to inflammation [2]. Of the 2 study groups included in our study, the ACLF group had patients with increased levels of C-reactive protein (44.0±29.3 mg/L) and procalcitonin (mean >2.10 ng/mL). However, the CC group had patients with no elevations of C-reactive protein (3±0.5 mg/L) and procalcitonin (mean <0.05 ng/mL). The factor VIII levels in both groups were elevated, but the elevation was significantly higher in the ACLF group, which can be attributed to additional acute insults. High factor VIII levels are a major risk factor in venous thrombosis [5] and may lead to thrombosis in CLD, especially in ACLF. Treatment of the acute-phase response in these patients might reduce the thrombotic tendencies.

Protein C levels are known to decrease in CLD as the liver is the major site of protein C synthesis. Our study has shown a significantly decrease in protein C levels in patients with ACLF (compared with the patients with CC), which may lead to an exacerbation of thrombotic tendencies in these patients. A negative correlation of protein C with the MELD score was observed in both groups, although the values were not statistically significant (Table 2).

Based on the fact that factor VIII is one of the most important components of thrombin generation and protein C is one of its most important inhibitors [6], the ratio of

Table 1. Demographic and clinical characteristics of patients.

	Group 1 (N=58)	Group 2 (N=58)	*P*
Age (mean±SD)	44.46±11.3	50.32±10.45	
Gender, male (%)	89.7	94.8	
MELD score (mean±SD)	26.06±8.19	16.19±3.91	
F8, % (median with IQR)	232.55 (150–331.3)	178.2 (105.6–281.4)	0.04
PrC, % (median with IQR)	10.5 (10.2–22.1)	36.8 (25.3–45.07)	<0.001
F8:PrC ratio	22.1	4.8	<0.001

Abbreviations: F8, factor VIII; IQR, interquartile range; PrC, protein C; MELD, model for end-stage liver disease.

Table 2. Correlations coefficients with MELD score for each parameters.

	Group 1 (N=58)	*P*	Group 2 (N=58)	*P*
Factor VIII	0.15	0.9	0.37	0.004
Protein C	-0.3	0.09	-0.2	0.13
Factor VIII : Protein C ratio	0.12	0.51	0.5	<0.001

Abbreviation: MELD, model for end-stage liver disease.

the 2 components was considered as an indicator of prothrombotic tendency. We found values in patients with CC similar to those of Tripodi *et al.* [7], but patients with ACLF had significantly higher ratios (Table 2). The ratio in the patients with CC had a direct and significant correlation with the MELD score compared to the ACLF group in which the coagulopathic defects were more serious. In patients with ACLF, other causes of hemostatic defects except for CLD, making more complex and heterogeneous coagulopathies, might interrupt correlation with MELD scores compared to those with CC [4, 8].

To conclude, the patients with ACLF have higher factor VIII and lower protein C than those with CC. The factor VIII levels and the ratio of factor VIII to protein C may be used as a predictable marker for the severity of liver disease in patients with CC.

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The first case of paroxysmal nocturnal hemoglobinuria and Budd-Chiari syndrome treated with complement inhibitor eculizumab in Korea

TO THE EDITOR: Budd-Chiari syndrome (BCS) is a rare and potentially life-threatening disorder characterized by hepatic venous outflow obstruction [1]. BCS is associated with thrombogenic conditions such as myeloproliferative neoplasms or inherited deficiencies in protein C, protein S, and antithrombin in at least 75% of patients [2]. However, paroxysmal nocturnal hemoglobinuria (PNH) is another well-recognized cause of BCS [3]. PNH is an acquired disorder of hematopoietic stem cells, characterized by chronic intravascular hemolysis, thromboembolic episodes, and varying degrees of bone marrow failure caused by uncontrolled complement activation [4]. Patients with BCS, in whom no other etiological factor has been identified after a thorough clinical and laboratory investigation, are required to be tested by routine flow cytometry screening for PNH in Western countries [5].

Eculizumab, a humanized monoclonal antibody that blocks the activation of terminal complement C5 components, is currently used in the treatment of PNH. Treatment with eculizumab reduces transfusion requirements, ameliorates anemia, decreases the risk of thrombosis, and improves quality of life by resolving the constitutional symptoms associated with chronic intravascular hemolysis [6, 7]. Long-term treatment with eculizumab in patients with concomitant BCS and PNH has shown a favorable safety profile [8-10]. To the best of our knowledge, this is the first report of eculizumab treatment in a patient with BCS and PNH in Korea.

CASE

A 39-year-old man was admitted to our hospital with newly developed abdominal pain, fatigue, pancytopenia, abdominal distension, and jaundice. He had a history of liver cirrhosis secondary to BCS and undergone splenectomy and inferior vena cava (IVC) stent insertion 15 years ago. The laboratory results on admission were as follows: white blood cell count, 3.2×10^9/L; hemoglobin, 5.3 g/dL; platelets, 41×10^9/L; reticulocyte count, 10.3%; haptoglobin, <100 mg/L (lower limit of reference range, 300 mg/L); lactate dehydrogenase (LDH), 5,005 IU/L (upper limit of reference