Hemostasis in Advanced Liver Disease

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Hemostasis is a dynamic host defense mechanism that prevents the escape of blood from a damaged vessel. It involves a large number of complex interactions between the blood and the vessel wall, which must occur in a concerted fashion. With trauma to a vessel wall of any size, the subendothelial matrix and extravascular tissue initiate a series of adhesive and platelet aggregatory reactions that lead to the formation of the primary hemostatic plug. The platelet plug is stabilized by the activation of the coagulation mechanism, which generates thrombin, leading to the deposition of fibrin that strengthens the friable first hemostatic plug. Degradation of fibrin that is deposited between and attached to the platelets must proceed in an orderly manner to confine the hemostatic process to the site of vascular injury.

Because the liver is the primary site of synthesis of most coagulation factors and inhibitors of the coagulation cascade and also plays a role in the clearance of activated and degraded clotting products from the circulation, complex and often variable derangements of hemostasis may develop in patients with liver disease. Impaired hemostatic function results from reduced synthesis of clotting factors and normally occurring inhibitors of coagulation, synthesis of abnormal clotting proteins, vitamin K deficiency, disseminated intravascular coagulation (DIC), enhanced fibrinolytic activity, and quantitative as well as qualitative platelet defects.[1–3]

DEFICIENT OR ABNORMAL SYNTHESIS OF CLOTTING FACTORS

In liver cirrhosis, vitamin K-dependent factors (II, VII, IX, and X) may either be depressed because of deficient hepatic synthesis or be inactive secondary to lack of gamma-carboxylation. The deficiency is more marked for Factor VII and then for Factors IX, X, and II. Prothrombin time is the most sensitive test for detecting a deficiency of these factors. If it is prolonged and unresponsive to vitamin K administration, one can assume that the synthesis of clotting factors by the liver is impaired. Because vitamin K is a fat-soluble vitamin synthesized by intestinal bacteria, a deficiency may also develop during therapy with oral antibiotics, in the presence of intrahepatic or extrahepatic biliary obstruction, or during therapy with bile acid binders.

Decreased levels of prekallikrein, high molecular weight kininogen, Factor XI, and Factor XII may contribute to prolongation of the partial thromboplastin time. In contrast, in mild liver disorders characterized by considerable inflammation, the plasma levels of Factor VII increase as an acute-phase reaction.[2,3]

Synthesis of abnormal factors also may occur. Dysfibrinogenemia is commonly present in patients with cirrhosis, usually as a manifestation of severe disease. It appears that the defect is limited to abnormal polymerization of fibrin monomers. Initial observations revealed that these patients had fibrinogen containing excessive numbers of sialic acid residues.[4,5] We found abnormalities accounting for dysfibrinogenemia in 9 of 30 patients with liver cirrhosis that were characterized by an increase of sialic acid residues and normalization of the thrombin time of purified fibrinogen after enzymatic removal of these residues.[6]

DEFICIENT SYNTHESIS OF INHIBITORS OF THE CLOTTING CASCADE

A series of proteins synthesized in the liver counterbalance the procoagulant activity physiologically, limiting the extent of fibrin formation when the clotting cascade is activated. These proteins include antithrombin III (ATIII), protein C, and protein S. Antithrombin III is

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severely depressed in cirrhosis. In addition, α_2-macroglobulin, which also bears antithrombin activity, is normal or increased in cirrhosis and may help to compensate for the ATIII deficiency. In general, ATIII levels in cirrhosis are lower than expected from the severity of the liver failure, suggesting that increased consumption contributes to the deficiency.

Proteins C and S are vitamin-K dependent anticoagulants synthesized by the liver. They are consistently reduced in cirrhosis, although their deficiency is not associated with an increase in thrombotic events, probably because of the coexistence of alterations in the clotting system.[7]

ENHANCED FIBRINOLYSIS

Pathological fibrinolysis in patients with liver disease has been recognized since 1914, when Goodpasture described the accelerated lysis of incubated clotted blood taken from patients with cirrhosis.[8] This phenomenon has been confirmed by other investigators, who demonstrated that the blood and plasma clot lysis times are abnormally short in patients with liver cirrhosis. These findings are relevant, as hyperfibrinolysis in patients with an already compromised clotting cascade may contribute to clinical bleeding.[9,10] Two pieces of evidence indicate enhanced fibrinolysis in these patients: (1) poor clearance of plasminogen activators, demonstrated by an exaggerated response to nicotinic acid as well as by the finding of high levels of tissue plasminogen activator (t-PA) in patients undergoing portocaval shunts and hepatectomy; and (2) underproduction of inhibitors, mainly α_2-antiplasmin and type-1 plasminogen activator inhibitor (PAI-1).[11–13]

We performed a study of patients with chronic liver disease. The patients were divided into two categories according to biopsy evidence of cirrhosis or chronic hepatitis. The role of fibrinolysis was assessed by measuring plasma levels of t-PA, PAI-1, plasminogen, and α_2-antiplasmin.[14] We found a marked increase in t-PA and PAI-1 antigen and a significant decrease in plasminogen and α_2-antiplasmin in patients with cirrhosis and hepatitis compared with controls. This suggests that extensive alterations in the fibrinolytic system are common in chronic liver disease. The ability of the plasma inhibitors PAI-1 and α_2-antiplasmin to inhibit t-PA and plasmin, respectively, undoubtedly plays a critical role in the hyperfibrinolytic state.[15] Reduced levels of histidine-rich glycoprotein also seem to be implicated in enhanced fibrinolysis.[16] A positive correlation between t-PA antigen (Ag) and serum bilirubin concentration was observed, indicating that the activator can be a marker of severe liver failure.[14] Therefore, in patients with advanced liver disease, a marked elevation of t-PA and a reduction of α_2-antiplasmin clearly contribute to excessive fibrinolysis.

DISSEMINATED INTRAVASCULAR COAGULATION

It has long been debated whether patients with cirrhosis, chronic active hepatitis, and severe acute hepatitis have concurrent DIC or a coagulopathy induced by the diseased liver that closely mimics DIC. Most of the laboratory abnormalities of hemostasis in these patients involve those that are critical for the diagnosis of DIC, such as prolongation of prothrombin times, partial thromboplastin times, and thrombin times; decreased fibrinogen survival times; and elevated amounts of fibrinogen/fibrin degradation products (FDP: FgDP/FbDP).[17,18]

In advanced hepatic disease, the loss of function of the reticuloendothelial system can predispose to the perpetuation of DIC. Activated proteases of the clotting cascade are removed less efficiently by the diseased liver than in normal subjects, and their continued presence in the circulation represents a continuous stimulus for coagulation that may lead to DIC. In addition to decreased clearance of activated factors, liver disease leads to deficiencies of the plasma inhibitors that may also contribute to DIC. Possible initiating factors include the release of procoagulants by necrotic hepatocytes and activation of the intrinsic and extrinsic pathways of blood coagulation by bacterial endotoxins that gain access to the systemic circulation from the bowel but fail to be cleared by the diseased liver.[19] Other authors suggest, however, that evidence implicating DIC is indirect, as intravascular microthrombi are infrequently found at autopsy, levels of fibrinopeptide A are not always increased; hypofibrinogenemia might be attributable to extravascular loss, and increased FDP could originate from extravascular fibrin deposits.[20,21]

In an attempt to document the presence of DIC in liver disease and fibrinolysis activation, we measured thrombin–antithrombin (TAT) complexes, t-PA, fibrinogen, and FDP in 66 patients with chronic liver disease, which was caused by cirrhosis in 34 patients and chronic hepatitis in 32.[22] As shown in Table I, there was a significant increase in TAT complexes and t-PA Ag in the two groups of patients. A significant elevation in FgDP and FbDP also was observed in these patients. These data suggest both thrombin and plasmin activity in vivo in chronic liver disease. Because the generation of thrombin represents a central event in the coagulation cascade, determination of TAT complexes may be relevant to the diagnosis of clotting activation in these patients. On the other hand, a significant increase in fibrinolysis parame-

TABLE 1. Amounts of Hemostatic Substances (Mean ± SD) in Patients with Liver Disease and Controls

	Cirrhosis (n = 34)	*Hepatitis (n = 32)*	*Control (n = 30)*	*p value vs. controls*
TAT (μg/l)	6.0 ± 4.1	6.4 ± 4.8	3.6 ± 1.7	< 0.004
t-PA Ag (ng/ml)	12.8 ± 7.8	9.2 ± 7.1	4.8 ± 2.8	< 0.002
FgDP (μg/ml)	12.3 ± 15.2	11.6 ± 12.9	1.1 ± 1.0	< 0.01
FbDP (μg/ml)	24.1 ± 19.1*	12.8 ± 18.6	1.4 ± 1.2	< 0.03

*p <0.01 compared with hepatitis group.

ters indicates plasmin generation. The fact that the levels of FbDP were higher in patients with cirrhosis than in those with chronic hepatitis indicates that fibrinolysis plays a more important role than fibrinogenolysis in those patients with more advanced disease. Impaired removal by the liver of these substances and the excessive generation of FDP in cirrhosis may contribue to the hemorrhagic complications in these patients, as FDP inhibit fibrin polymerization, impair platelet aggregation, and have antithrombin activity.[23]

We found a correlation between TAT, t-PA, and fibrinogen degradation products with some liver function tests, indicating that these parameters may be good markers of severe liver disease. According to our own data from patients with advanced disease, increased thrombin activity followed by plasmin activity suggests that low-grade intravascular coagulation may occur.[22]

THROMBOCYTOPENIA AND ABNORMAL PLATELET FUNCTION

Thrombocytopenia in cirrhosis is essentially secondary to hypersplenism that may be severe in advanced disease, and platelet counts may fall below 50×10^9/L. Thrombocytopenia in cirrhosis may also be the result of folic acid deficiency, bone marrow alcohol toxicity, and peripheral consumption by subclinical DIC.

The contribution of alterations in platelet function to the hemostatic disorders of cirrhosis remains controversial. Nevertheless, there are alterations reported in cirrhotic patients that impair platelet function, such as deficient platelet production of thromboxane A_2 and increased systemic synthesis of prostacyclin. As previously pointed out, in patients with DIC or hyperfibrinolysis, the accumulation of FDP may impair platelet aggregation. It has been postulated that other unidentified factors, dialyzable from cirrhotic plasma, play a role in these alterations.[24] Clinically, bleeding in excess of what is expected from deficiencies in platelet count and clotting tests should raise concerns about platelet function.

ROLE OF CYTOKINES IN LIVER DISEASE

The role of cytokines in some of the underlying phenomena is far from being established. Tumor necrosis factor (TNF) and interleukin-6 (Il-6) belong to a group of endogenous mediators of the complex reactions of the host to injury or infection. In addition to their pathophysiological role as mediators of the immune and inflammatory responses, they are involved in the pathogenesis of a variety of chronic disease states when overexpressed in vivo.[25–28] The prevailing hypothesis is that whereas low-level local cytokine accumulation is important for physiological homeostasis, at high local concentrations or when released into the systemic circulation, cytokines have the potential to exert harmful effects.

Although a regulated cytokine response to pathogens or toxins is essential to host defense and tissue repair, cytokine excess can lead to tissue damage and fibrosis. This has increased interest in the role of cytokines in normal liver function and in liver disease.[29] However, studies correlating cytokine homeostasis with abnormalities in coagulation and fibrinolysis are lacking. We therefore sought to correlate circulating concentrations of TNF and IL-6 with clinical and hemostatic parameters in patients with liver disease. We carried out a study of 44 patients with chronic liver disease, all of whom were in Child's stages B and C according to well-established clinical and analytical criteria: ascites or encephalopathy, high bilirubin and low albumin levels, and prolonged prothrombin times. Final diagnoses of alcoholic cirrhosis were made in 15 patients, postnecrotic cirrhosis secondary to viral hepatitis in 22, and cirrhosis secondary to different liver diseases in 7 patients. The study included analysis of in vivo clotting activity, as assessed by the measurement of TAT complexes and prothrombin fragment F1+2, and fibrinolysis activity as determined by the plasma levels of plasminogen, α_2-antiplasmin, PAI-1, and t-PA antigen. Finally, the plasma concentrations of TNF and IL-6 were determined.

As shown in Figure 1, there was a dramatic increase in both cytokines in the patients, with highly statistically

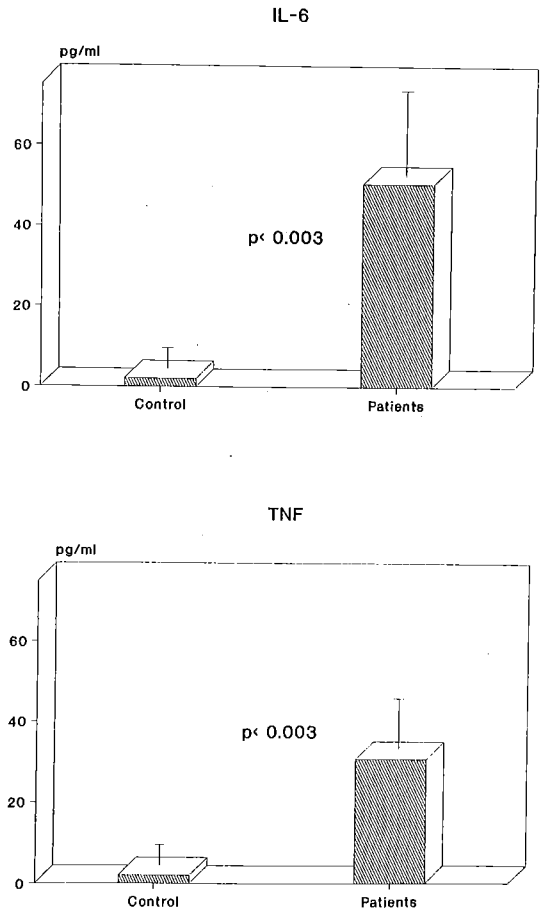

FIG 1. Mean Plasma Concentrations of IL-6 and TNF in Patients with Advanced Liver Disease and Controls.

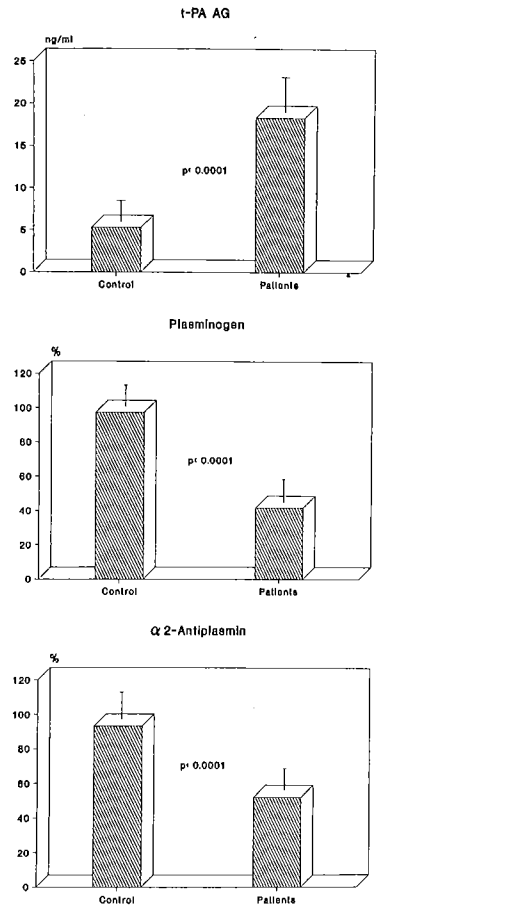

FIG. 2. Mean Concentrations of t-PA, Plasminogen, and α_2-Antiplasmin in Patients with Advanced Liver Disease and Controls.

significant differences compared with control subjects ($p < 0.003$), and a good correlation between the two parameters could be demonstrated ($r = 0.92$). Fibrinolysis parameters showed the pattern typical of severe liver insufficiency with a significant increase in t-PA and decreases in plasminogen and α_2-antiplasmin in patients compared with controls (Fig. 2). We also found a significant increase in TAT complexes and prothrombin fragment F1+2 in the patients (Fig. 3), again indicating that a certain degree of intravascular coagulation might be present in patients with advanced liver disease.[30] No correlations could be demonstrated between cytokine concentrations, indicators of liver injury or hepatic insufficiency, or hemostatic abnormalities.

The liver appears to be an important source of cytokine production as well as the main clearance organ for circulating cytokines.[29] Two recent reports have clearly shown that Il-6 and TNF-α are produced by infiltrating cells in focal areas of the liver, thereby modulating the inflammatory and immune reactions in chronic liver disease.[31,32] In addition, Lotz and associates[33] showed that human hepatoma cells and primary hepatocytes produce Il-6.

Some authors have also found a significant increase in TNF, IL-6, and other cytokines in chronic hepatitis, liver cirrhosis, and fulminant hepatic failure.[34–42] Other investigators have demonstrated increased TNF and IL-6 secretion by lipopolysaccharide-stimulated monocytes isolated from patients with both alcoholic and nonalcoholic liver disease, suggesting these cells as the source of circulating cytokines.[43,44] Whether the changes indicating an abnormal expression of these cytokines are a primary event in the disease process or a secondary consequence is not yet known. The increase in plasma levels probably reflects higher production, although decreased clearance might also be involved. Although endotoxin and possibly other abnormal components in the serum of patients with liver cirrhosis could induce cytokine expression, Khoruts et al could not demonstrate a relation between cytokine concentrations and peripheral endotoxemia.[45]

Although the lack of correlation between TNF and IL-6 and hemostatic parameters suggests that the ob-

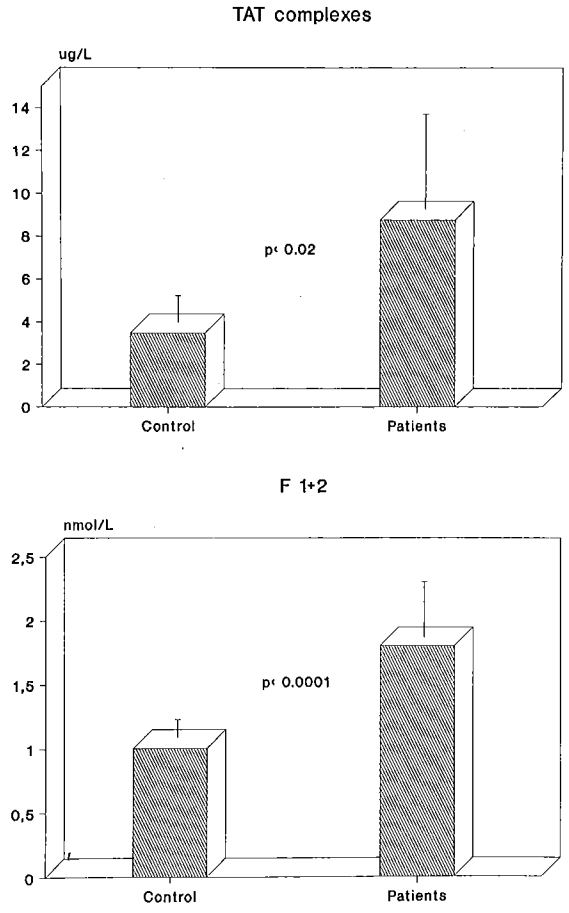

FIG. 3. Mean Plasma Concentrations of TAT and F1+2 in Patients with Advanced Liver Disease and Controls.

served changes in hemostasis are related mainly to liver damage, a possible role for an indirect pathway involving these monokines cannot be ruled out. It is interesting that the infusion of either endotoxin or TNF in normal subjects induces tissue factor generation and clotting activation in a pattern similar to DIC.[46,47] It is also known that TNF induces procoagulant activity in cultures of vascular endothelium.[48] Moreover, a significant increase in t-PA, plasmin–antiplasmin complexes, and FgDP and FbDP has been reported after TNF infusion in humans. This indicates that fibrinolysis is indeed active, although the initial fibrinolytic response is counteracted by the subsequent release of PAI-1.[49,50]

Taking all these data together, we tentatively formulated the following hypothesis to explain some of the changes observed in patients with advanced liver disease (Fig. 4). Increased endogenous production of cytokines (TNF, IL-6, etc), mainly by macrophages and endothelial cells, in response to different stimuli may mediate the pathophysiological events leading to tissue damage and fibrosis as well as to the multiple organ failure seen in liver cirrhosis. Furthermore, the cytokine-induced release of tissue factor by these cells and the release of procoagulants by necrotic hepatocytes could explain some of the hemostatic changes contributing to DIC. Finally, increased cytokine production in combination with impaired clearance by reticuloendothelial cells could contribute to pathological fibrinolysis in these patients.

Further studies of cytokine actions may lead to a better understanding of the pathogenesis of liver disease and to the development of new therapeutic options. Already, prostaglandin E1, a known inhibitor of TNF-α secretion, has been shown to reduce mortality in animal models of liver disease, and encouraging results have been obtained in preliminary studies using this prostaglandin in patients with fulminant hepatic failure.[51,52]

CONCLUSION

The liver plays a pivotal role in coagulation. In addition to its synthesis of clotting factors and inhibitors of coagulation, the reticuloendothelial system is a major organ for the clearance and catabolism of coagulation proteins. The pathogenesis of altered hemostasis in pa-

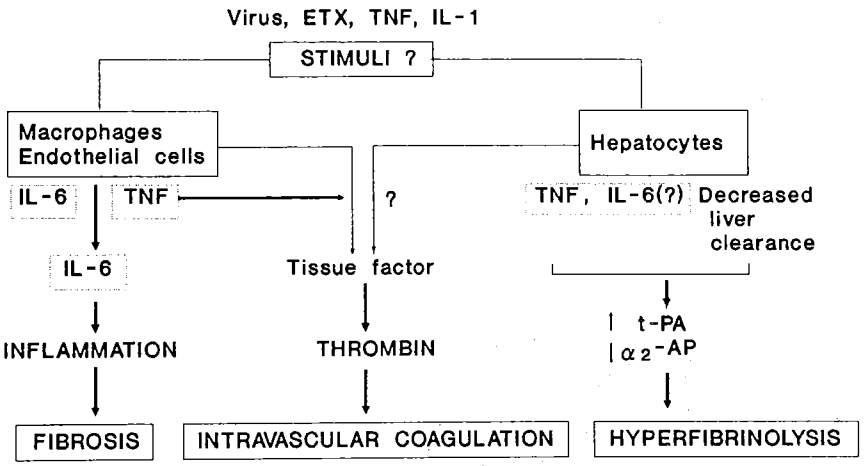

FIG. 4. Possible Role of Cytokines in Liver Disease. Increased endogenous production of cytokines may play a role in fibrotic transformation of liver and contribute to intravascular coagulation and fibrinolysis. For further explanation, see text.

tients with advanced liver disease is complex and multifactorial. Although there is no specific characteristic abnormality, different observations indicate that enhanced fibrinolysis and a certain degree of intravascular coagulation are commonly present, contributing to the clinical manifestations. Recent data indicate the involvement of cytokines in these events. Increased endogenous production of IL-6 and TNF could play an important role in the fibrotic transformation of the liver and explain some of the hemostatic abnormalities observed in chronic liver disease.

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