A Cirrhotic Patient With Spontaneous Intramuscular Hematoma Due to Primary Hyperfibrinolysis

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Introduction

Severe coagulopathy in advanced hepatic disease is characterized by coagulation factor deficiencies as well as accelerated fibrinolysis.[1] Hyperfibrinolysis in cirrhotic patients is the result of excess fibrin breakdown leading to defective hemostasis. We present a case of a cirrhotic patient with extensive spontaneous ecchymosis and an acute drop in hemoglobin level, which were due to primary hyperfibrinolysis.

Case Report

A 65-year-old man with alcoholic cirrhosis presented with extensive bruises on his back. He had not experienced any physical trauma and was not receiving antiplatelet agents or anticoagulants. The physical examination showed severe pallor, conjunctival icterus, and splenomegaly. There was a large, tender hematoma involving the neck and the back with extension into the flanks. His Child-Pugh classification was category B, with a score of 8.

Laboratory testing showed that hemoglobin was 6.5 g/dL, platelet count was 110,000/mm^3, prothrombin time was 16.3 seconds, international normalized ratio was 1.6, and partial thromboplastin time was 40 seconds. All liver-dependent coagulation factors were low (Table 1). Factor VIII level was normal. The serum fibrinogen level was low, at 104 mg/dL (normal range, 175–400 mg/dL), and antithrombin III was low at 24% (normal range, 80–120%). Alpha-2 antiplasmin was low at 20% (normal range, 80–120%). A schistocyte review was negative. The euglobulin lysis time was 60 seconds (normal, >180 seconds). Euglobulin lysis time is a modified plasma clot lysis time and measures increased plasminogen activation. A computed tomography scan of the neck showed a large intramuscular, subcutaneous hematoma.

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An acute drop in hemoglobin caused by intramuscular bleeding due to hyperfibrinolysis was diagnosed, based on the decreased alpha-2 antiplasmin and euglobulin lysis time and normal measures of factor VIII and activated partial thromboplastin time.[2] The patient received 4 units of packed red blood cells and 4 units of fresh frozen plasma in a 6-hour period. The bleeding did not stop. A repeat test of hemoglobin showed that the level was 7 g/dL. The patient was treated with epsilon-aminocaproic acid (EACA). An oral loading dose of 150 mg/kg was followed by a dose of 1 g given during 4 hours in 2 separate doses, in addition to 2 more units of packed red blood cells. This treatment resulted in resolution of bleeding. The patient's hemoglobin level remained stable at 9.2 mg/dL.

Discussion

In patients with cirrhosis, the fibrinolytic pathway is activated by an increased endothelial release of tissue plasminogen activator (t-PA), decreased hepatic clearance of t-PA, decreased thrombin activatable fibrinolysis inhibitor, and decreased synthesis of alpha-2 antiplasmin and plasminogen activator inhibitor.[1,3] Hyperfibrinolysis in cirrhotic patients usually causes mucocutaneous bleeding, but it can also cause gastrointestinal bleeding.[4]

Table 1. Assessment of Liver-Dependent Coagulation Factors

Coagulation Factor Activity	Results	Normal Range
II	35%	50–150%
V	12%	50–150%
VII	40%	50–150%
IX	37%	50–150%
X	20%	50–150%
VIII	110%	45–150%

Treatment of hyperfibrinolysis is supportive and includes transfusion of packed red blood cells and therapies that inhibit plasminogen activation and fibrin breakdown. EACA is a synthetic derivative of the amino acid lysine that binds reversibly to the lysine-binding site of plasminogen and blocks the binding of fibrin. EACA is effective and safe in treating patients with accelerated fibrinolysis who develop bleeding.[5] Aprotinin is another drug commonly used in hyperfibrinolysis after liver transplantation. It works as a serine-protease inhibiting plasmin and kallikrein. Hyperfibrinolysis in cirrhotic patients correlates with the Child-Pugh classification, but it is often difficult to identify.[2]

Conclusion

Specific tests, as discussed above, assessing plasminogen activation and clot-lysis are required to correctly diagnose hyperfibrinolysis and differentiate it from other causes of bleeding, including disseminated intravascular coagulation. Prompt diagnosis of hyperfibrinolysis in cirrhotic patients and early administration of EACA may provide an effective management for life-threatening bleeding.

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Review

Primary Hyperfibrinolysis in Liver Disease: A Critical Review

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Nair and colleagues[1] described a rare case of spontaneous intramuscular hematoma in a patient with cirrhosis. Only few cases with a similar clinical picture have been described in the literature. Nair and colleagues deduced that the intramuscular hematoma was a consequence of primary hyperfibrinolysis, based on shortened euglobulin lysis time and few other tests that helped to rule out disseminated intravascular coagulation (DIC). In the present review, we will discuss primary hyperfibrinolysis in liver disease, its pathophysiology, the pitfalls of the tests currently used, and therapeutic interventions. Although hyperfibrinolysis in liver disease is an accepted fact, the topic still has debatable aspects.

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Hemostasis is a finely tuned, complex system that depends on the intricate balance among procoagulant, anticoagulant, and fibrinolytic proteins. The liver plays a major role in this process. It is the site of synthesis of all the vitamin K–dependent coagulation proteins (factors II, VII, IX, and X, and proteins C and S), factor V, and factor XIII.[2] The liver also synthesizes fibrinogen, antithrombin, alpha-2 antiplasmin, and plasminogen.

Fibrinolysis (ie, the degradation of fibrin) is regulated by different factors that either activate the process (eg, tissue plasminogen activator [tPA] and the urokinase plasminogen activator) or act as "antiactivators" (eg, plasminogen activator inhibitor 1 [PAI-1] and alpha-1 plasmin inhibitor).[3] Thrombin activatable fibrinolysis inhibitor (TAFI), a more recently identified inhibitor, is produced by the liver. As suggested by its name, it is activated by thrombin or plasmin and consequently converted to an enzyme (TAFIa) that inhibits fibrinolysis through the removal of C-terminal lysines from partially degraded fibrin.[4] Any imbalance in the fibrinolysis pathways may lead to hypofibrinolysis or hyperfibrinolysis.

Primary hyperfibrinolysis in chronic liver insufficiency has been described since the early 1900s.[5] Its incidence may be as high as 31%, and it may correlate with liver disease severity.[6]

Pathogenesis

Primary hyperfibrinolysis pathogenesis is still not clear. Studies have suggested that it may be related to decreased tPA hepatic clearance.[7] Other studies have shown a decreased or impaired synthesis of PAI-1, alpha-2 antiplasmin, and histidine-rich glycoprotein.[8] The role of TAFI in hyperfibrinolysis has raised some controversy. In one study, a decreased TAFI level did not correlate with increased fibrinolysis in patients with cirrhosis. It was concluded that a reduction in antifibrinolytic factors was compensated by concurrent reduction in profibrinolytics.[9] A similar study, however, suggested the opposite: that an impaired antifibrinolytic TAFI pathway contributes to hyperfibrinolysis.[10] These differences likely reflect the use of nonstandardized assays for global fibrinolysis.

Assays Pitfalls

The extent of hyperfibrinolysis in liver cirrhosis and its role in the bleeding diathesis is still debatable, mostly because studies are based on individual fibrinolysis tests, and there is no standardized global test that measures both profibrinolytic and antifibrinolytic activators.[11,12] A shortened euglobulin lysis time—a modified plasma clot lysis time—is often used to diagnose excess fibrinolysis. It detects increased plasminogen activation and subsequent fibrinolysis. However, it misses the complex interactions between activators and antiactivators that regulate plasminogen to plasmin conversion.[13]

Thromboelastography, an old test used to assess primary and secondary hemostasis, is back in favor since advances in technology and computerized automated calculations and graphing have made it more user friendly and added to its reliability.[14] Currently, this test is mainly used in surgical settings, especially liver transplants. Thromboelastography allows detection of abnormalities from clot formation to lysis. During a liver transplant, where bleeding is a frequent complication, it helps to pinpoint the etiology of the bleeding: whether it is a consequence of platelet dysfunction, coagulation factor deficiency, presence of inhibitors, or hyperfibrinolysis. As a result, thromboelastography not only reduces the amount of blood transfused during liver transplants but also helps to direct therapy to specific blood components.[14,15] Thromboelastography could be proposed as a more global test to assess hyperfibrinolysis, although prospective studies are needed.

DIC and Hyperfibrinolysis

DIC may mimic hyperfibrinolysis findings in patients with cirrhosis. However, characteristics specific to hyperfibrinolysis include elevated factor VIII, a relatively stable platelet count, and absence of the multiorgan failure frequently associated with DIC. Not uncommonly in patients with decompensated liver disease, this distinction cannot be made based on laboratory data. Accelerated intravascular coagulation and fibrinolysis (AICF) is a newly recognized entity that combines the characteristics of both disorders.[12] Seen in 30% of patients with moderate to severe liver failure, AICF is possibly the result of an imbalance between profibrinolytic and antifibrinolytic processes. Infection may tilt this already precarious balance toward AICF.[12,15,16]

Some studies suggest that hyperfibrinolysis may be a good predictor for the risk of gastrointestinal bleeding.[17] Several explanations are possible: hyperfibrinolysis may affect formation of the platelet plug through an increase in von Willebrand factor and glycoprotein Ib and IIb/IIIa degradation; it may reduce platelet adhesion; or it may cause early disruption of the hemostatic plug that consequently increases the risk of additional bleeding.[15]

Treatment

Both epsilon-aminocaproic acid and tranexamic acid have been used, especially to prevent bleeding during liver transplant. These agents prevent plasminogen from binding to fibrin and reduce the conversion of plasminogen to plasmin. Studies have suggested that these agents effectively stop blood loss, although current evidence is limited.[15,18] Prospective randomized studies are needed.

Aprotinin, another antifibrinolytic agent, acts by inhibiting plasmin and kallikrein. In a randomized, double-blind, placebo-controlled, multicenter trial, aprotinin reduced the need for blood transfusion by approximately 30% in patients who had received a liver transplant.[19] Aprotinin is associated with well-known risks, including thromboembolic events and renal toxicity. In 2007, a large, multicenter, randomized study in patients undergoing coronary artery bypass grafting showed a significantly higher 5-year mortality rate in the group that received aprotinin compared to controls (approximately 21% vs 13%).[20] Consequently, aprotinin was withdrawn from the market by the US Food and Drug Administration.

Conclusion

Primary hyperfibrinolysis should be included in the differential diagnosis of coagulopathy in liver disease. Appropriate work-up and treatment should be initiated based on a thorough evaluation. More studies are needed for both diagnosis and therapy.

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