Grand Rounds

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Anticoagulation in chronic liver disease

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Summary

In this Grand Round presentation, the case of a man with decompensated liver disease is described. He subsequently developed a fatal pulmonary embolism, which may not have occurred if he had been prescribed prophylactic anticoagulation to prevent venous thromboembolic disease. The burden of thrombotic disease in those with chronic liver disease is discussed, before a more detailed analysis of the current evidence, safety data, and clinical dilemmas regarding the use of anticoagulation in patients with chronic liver disease. Finally, the future directions within this field are explored.

Keywords: Anticoagulation; Thrombosis; Cirrhosis; Heparin; Direct oral anticoagulants; Thromboembolism; Liver diseases; Teaching rounds.

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Clinical case

A 59-year-old man, with a history of cirrhosis related to chronic hepatitis C virus (HCV) infection, was admitted to hospital through the emergency department, complaining of a painful and swollen left leg. He had experienced several hospital admissions over the previous few months because of recurrent diuretic-resistant ascites, and worsening hepatic encephalopathy. His problems with ascites and encephalopathy had resulted in reduced mobility, worsening nutrition and sarcopenia. Despite achieving a sustained virological response following antiviral treatment, his Model for End-stage Liver Disease (MELD) score had continued to increase and he had been listed for orthotopic liver transplantation.

Following admission, Doppler ultrasonography confirmed a large thrombus within the left common femoral vein. Laboratory tests at this time demonstrated haemoglobin of 12.8 g/dl, a platelet count of 114×10^9/L, and an international normalised ratio (INR) of 1.3; a thrombophilia screen was negative. A CT scan of his chest, abdomen and pelvis revealed cirrhosis, splenomegaly and ascites, but no evidence of malignancy. Gastroscopy three months earlier had shown grade 2 oesophageal varices but no red signs, and he had been started on carvedilol at this point. He underwent a repeat endoscopy following this admission, which demonstrated grade 2 varices with red signs, and it was decided that his varices should be eradicated by band ligation prior to commencing anticoagulation. During his previous hospital admissions, the physicians had decided not to administer pharmacological prophylaxis against venous thromboembolism, owing to concerns regarding bleeding risk related to his cirrhosis and the need for repeated large volume paracentesis.

Following endoscopy, the patient complained of chest pain and dyspnoea. He suffered a cardiac arrest from which he could not be resuscitated. A post-mortem examination revealed a large pulmonary embolus as the cause of death.

There are many clinical questions that are prompted by this case, including:

(1) What is the burden of thrombotic disease (venous thromboembolism and splanchnic vein thrombosis) in patients with chronic liver disease?
(2) Which patients with cirrhosis should be given prophylaxis against venous thromboembolic disease?
(3) What are the treatment options for thrombotic disease in patients with chronic liver disease?
(4) How safe is it to use anticoagulation therapy in patients with chronic liver disease?
(5) What emerging therapies are there in the field, and what are the likely future directions for the treatment of thromboembolic disease in patients with chronic liver disease?
(6) Are there potential benefits for the use of anticoagulant drugs beyond the prophylaxis and treatment of thrombosis in patients with chronic liver disease?

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What is the burden of thrombotic disease (venous thromboembolism and splanchnic vein thrombosis) in patients with chronic liver disease?

The interaction between liver injury and the coagulation cascade is multi-faceted and complex [8]. Coagulopathy is a well-documented sequel of chronic liver failure. However, there is also increasing evidence to suggest that profibrotic states are prothrombotic, and that activation of the coagulation cascade has a role in the generation of chronic liver injury.

Advanced fibrosis is associated with impaired synthesis of all clotting factors, except factor VIII and von Willebrand factor [60,58]. This defect is demonstrated by prolongation of the prothrombin time (PT) and the activated partial thromboplastin time (APTT) tests, which both represent the status of procoagulant proteins synthesised by the liver. However, the results of these haemostasis tests on peripheral blood predicts poorly with the risk of bleeding in chronic liver disease [59], reflecting the inability of these tests to account for an imbalance in endogenous anticoagulants and procoagulants. Patients with advanced fibrosis have significantly lower levels of protein C and antithrombin [60]. Furthermore, this partial deficiency of anticoagulant proteins in patients with advanced chronic liver disease is accompanied by enhanced thrombin generation [24], resulting in a procoagulant state. This could explain the current disproval of the historical assumption that patients with cirrhosis are 'auto-anticoagulated', and therefore, protected against developing peripheral thromboembolic disease, has now been disproved.

Key point

Alterations in the balance between thrombotic proteins and antithrombotic proteins in people with cirrhosis may result in procoagulant tendencies.

Studies have demonstrated a 0.5–6.3% incidence of newly-diagnosed pulmonary thromboembolism (PE) or deep vein thrombosis (DVT) amongst hospitalised patients with cirrhosis; these patients do not demonstrate a reduced risk of PE/DVT when compared to patients without cirrhosis [37,25]. Furthermore, a prolonged INR does not negate a risk of venous thromboembolism (VTE) in this setting [15]. Validated risk stratification scores that predict VTE within a general population of hospitalised patients, also appear to accurately predict VTE amongst hospitalised patients specifically with chronic liver disease i.e., Padua Predictor Score [7]. More surprisingly, an increased relative risk of VTE has been observed amongst patients with chronic liver disease in a case-control population-based study [54]. In this Danish study of 99,444 patients with thromboembolic disease, patients with cirrhosis had a 1.7-fold increased relative risk of venous thrombosis compared to the general population. This increased relative risk of VTE was similarly found in cirrhotic patients under the age of 45 years in a large US-based population study of hospitalised patients [64]. Interestingly, in patients over 45 years of age, there was no significant increase in VTE risk observed in patients with cirrhosis, compared to matched non-cirrhotic control participants. However, this may have solely reflected age-related risk factors for VTE outweighing that of cirrhosis itself [64]. As well as cirrhosis possibly increasing the risk of VTE, recent data suggest that patients with cirrhosis and VTE may have increased mortality over 30 days, compared to those with VTE but without cirrhosis [55].

Key point

Cirrhosis is associated with an increased risk of thromboembolic events.

Aside from VTE, one other major category of thrombotic disorders found in people with chronic liver disease is splanchnic vein thrombosis, a category that includes mesenteric, portal and hepatic vein thromboses. Portal vein thrombosis (PVT) may occur in those with or without chronic liver disease, but it is the most common thrombotic complication in patients with cirrhosis. It is more commonly found in those with decompensated cirrhosis with a prevalence ranging from 8–25% [22], compared to ~1% in compensated cirrhosis [38]. The incidence of PVT occurring over a 12-month period in patients with cirrhosis awaiting orthotopic liver transplantation (OLT) has been reported as 7% [22]. Mechanistic factors involved in the development of PVT in cirrhotic patients are likely to be multifactorial. Thrombophilic genetic defects within these patients have also been extensively investigated; the *G20210A* prothrombin gene mutation is the most consistently identified genetic variant associated with PVT in cirrhotic patients [1,21], although the factor V Leiden (FVL) *G1691A* mutation [21] may also be a risk factor. There is no current evidence to suggest the *JAK2 V617F* mutation is associated with PVT within cirrhotic patients [50]. Whereas non-selective beta-blockers could theoretically precipitate PVT by decreasing portal venous blood flow, a large longitudinal study found no evidence that their use was an independent risk factor for occurrence of PVT [35]. Whereas local factors (including intra-abdominal surgery, infections and/or inflammatory conditions of the abdomen) are well-established as risk factors for PVT in general [20], the specific risk they present for the development of PVT in those with chronic liver disease is undefined.

Which patients with cirrhosis should be given prophylaxis against venous thromboembolic disease?

Studies have looked at the role of anticoagulation in both preventing and treating thromboembolic disease in people with chronic liver disease. Current guidelines do not recognise the thromboembolic risk associated with chronic liver disease, and do not make specific recommendations for the prophylaxis or treatment of thromboembolic disease [36].

The reported use of prophylactic anticoagulation for VTE in patients with chronic liver disease (21–25%) remains significantly lower than in other inpatient groups (30–70%) [13]. Studies investigating the