CASE REPORT

Rare cause of isolated severe coagulation failure in cirrhosis: traditional healing with fenugreek

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SUMMARY

Patients with cirrhosis develop decompensation events during the natural history of the disease that encompass ascites, variceal bleeding, hepatic encephalopathy and jaundice. Coagulation failure, defined using the international normalised ratio, even though not a decompensation event, is important in patients with stratifying cirrhosis into those who require liver transplantation for long-term survival. Isolated coagulation failure in cirrhosis is rare and usually occurs with use of anticoagulants in the setting of vascular diseases. We reported the case of a patient with compensated cirrhosis in whom, isolated severe coagulation failure was found to be due to excessive use of fenugreek milk porridge as part of traditional healing. The coagulation failure was promptly reversed with avoidance of fenugreek and supplementation with vitamin K.

BACKGROUND

The model for end-stage liver disease (MELD) was initially created to predict survival following elective placement of a transjugular intrahepatic portosystemic shunt. Subsequently validation as a predictor of survival in several cohorts of patients with varying levels of liver disease severity was demonstrated. MELD incorporates three widely available laboratory variables including the international normalised ratio (INR), serum creatinine and serum bilirubin into a logarithmic mathematical formula. Application of MELD to organ allocation led to streamlined categorisation and immediate reduction in liver transplant waiting list registrations, leading to better and earlier selection of deserving patients, even though there are exceptions within MELD allocation.¹ In the MELD score, $(3.8(\log_e \text{ serum bilirubin (mg/dL)}) + 11.2(\log_e \text{ INR}) + 9.6(\log_e \text{ serum creatinine (mg/dL)}) + 6.4)$, highest weightage is given to INR. The liver plays a central role in haemostasis, as it is the site of synthesis of clotting factors, coagulation inhibitors and fibrinolytic proteins, and coagulation failure is an important aspect in assessment of the failing liver. According to the Baveno classification, cirrhosis is divided into five stages: compensated cirrhosis without varices (stage 1), compensated cirrhosis with varices (stage 2), bleeding without other disease complications (stage 3), first non-bleeding decompensating event (stage 4) and any second decompensating event (stage 5).² Even though coagulation failure is not a major component in the natural history

of cirrhosis, its value in the transplant scenario cannot be disregarded. Patients with cirrhosis who have severe coagulation failure usually have other advanced decompensating events such as jaundice, hepatic encephalopathy, ascites and intercurrent infections and bleeds.³ We present the interesting case of a cirrhotic with severe isolated coagulation failure without other decompensating events, listed for liver transplantation, in whom, identifying and correcting the cause of severe coagulopathy resulted in delisting from transplant and continuation of medical management thereafter.

CASE PRESENTATION

A 55-year-old man diagnosed as a case of non-alcoholic steatohepatitis-related cirrhosis for 28 months was referred to our Liver Unit for counselling and work-up for liver transplantation in view of persistently high MELD score of 29 over a period of 3 months. His index presentation at diagnosis of cirrhosis was facial skin hyperpigmentation and bilateral lower limb oedema. He did not suffer from jaundice, development of ascites or gastrointestinal bleeding and had no episodes of overt hepatic encephalopathy after the diagnosis of cirrhosis. Clinical examination revealed an overweight male oriented to time, place and person without icterus, pallor, clubbing or peripheral adenopathy. Mild bilateral pedal pitting oedema, few scattered spider angiomas over upper chest, firm palpable left lobe of the liver and splenomegaly were noted. Imaging of the abdomen revealed features of cirrhosis and portal hypertension with dilated portal vein (15 mm), splenomegaly, few splenic hilar collaterals and minimal ascites. Oesophagogastroduodenoscopy revealed small low-risk oesophageal varices. The medication history included ursodeoxycholic acid, multivitamin B complex, zinc supplements, disaccharides, propranolol and metformin for diabetes mellitus. He denied the use of over-the-counter medications or complementary and alternative drugs except for a short course of levocetirizine for allergic rhinosinusitis a month back. The patient denied consumption of anticoagulants and was not on any injectables.

INVESTIGATIONS

Blood investigations revealed haemoglobin 11.3 g/dL (normal 12–15 g/dL), total leucocyte count $6.4 \times 10^9/\text{L}$ ($4.00\text{--}10.0 \times 10^9/\text{L}$), platelet count $138 \times 10^9/\text{L}$ ($150\text{--}450 \times 10^9/\text{L}$), total bilirubin 2.8 mg/dL (normal 0.3–1.0 mg/dL), direct bilirubin

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1.4 mg/dL (0.0–0.2 mg/dL), aspartate aminotransferase 78 U/L (<37 U/L), alanine aminotransferase 56 U/L (<41 U/L), γ -glutamyl transferase 186 U/L (5–61 U/L), alkaline phosphatase 74 U/L (35–129 U/L), albumin 3.2 g/dL (3.5–5.0 g/dL), prothrombin time 38.4 s (control 13.3 s), INR 4.52 (0.9–1.2), activated partial thromboplastin time (aPTT) 68 s (normal 30–40 s), blood urea 28 mg/dL (7–20 mg/dL) and serum creatinine 1.2 mg/dL (0.8–1.4 mg/dL). Work for infections including blood and urine cultures were unremarkable. D-dimer and fibrinogen levels were within normal limits and factor VII assay was suggestive of mild deficiency as was expected in liver disease. A thromboelastography showed mild delay in clot formation. Lupus anticoagulant and associated antibody tests (including anticardiolipin, antiphospholipid antibodies and anti-beta-2-glycoprotein) were unremarkable. Renal function tests were normal. In view of isolated INR elevation and aPTT prolongation, the drug history was re-examined, this time in the presence of all family members. The patient's mother admitted to serving him large portions of 'Uluva Paal Kanji' (initially two to three times a day, increasing in the last 2 months to three to four times a day)—a traditional medical practice in the state of Kerala in South India, in which fenugreek (*Trigonella foenum-graecum*)-based rice milk porridge is served to cure multiple ailments—cirrhosis included.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of isolated elevated INR includes liver dysfunction, vitamin K deficiency, long-term use of antibiotics leading to modulation of intestinal bacterial communities, inherited and acquired factor VII deficiency and the lupus anticoagulant. In our patient, we systematically ruled out the above mentioned factors as the only cause of high INR. The family of vitamin K antagonists, known as coumarins are known to cause primary elevation in INR, but also affect aPTT to some degree in higher doses. In our patient, we found that mild factor VII deficiency was possibly due to underlying cirrhosis and that a markedly elevated INR was associated with high aPTT also—raising the possibility of coumarin use or disseminated intravascular coagulation, the latter which was ruled out.

OUTCOME AND FOLLOW-UP

The patient was advised to stop the traditional medicine treatment and was given 20 mg of intravenous vitamin K, followed by 10 mg of oral vitamin K once daily for a week, allowed to consume diet rich in vitamin K and advised to repeat coagulation tests. On follow-up, after 2 weeks, his total bilirubin was 1.9 mg/dL, serum creatinine 1 mg/dL and the INR had improved to 1.8 with aPTT 42 s and his MELD score improved to 15 points. Since the local transplant listing cut-off for MELD was 16, he was delisted from the liver transplant work-up and advised to follow-up and undergo treatment as per Baveno staging of cirrhosis including surveillance for hepatocellular carcinoma.

DISCUSSION

Fenugreek is one of the oldest traditional medicinal plants, mostly cultivated and used for the same in the Indian subcontinent, parts of West Asia, Middle East and North Africa. It belongs to the family of Fabaceae and is used in the production of steroid and other hormones for the pharmaceutical, nutraceutical and functional food industries.⁴ Fenugreek is traditionally recommended for increasing milk production, as appetite enhancer, antidiabetic, hypolipidaemic, antioxidant, hepatoprotective, anti-inflammatory, antimicrobial, anticarcinogenic and neuroprotective agent in both experimental animals as well as

Table 1 Biologically active compounds present in *Trigonella foenum-graecum* (fenugreek)

Component	Constituents
Alkaloids	Trigonelline, choline and carpaine
Coumarins	Methyl coumarin, trigocoumarin, trimethyl coumarin, esculetin and scopoletin
Flavonoids	Naringenin, lilyin, kaempferol, vicenin, tricin, glucopyranoside, saporetin, isovitexin, orientin, vitexin, luteolin, quercetin, geraniol and terpenol
Saponins	Fenugrins, foenugrins, glycoside, yamogenin, trigonoesides, milagenin, gitogenin, sarsapogenin, yuccagenin, hederagenin, diosgenin, tigonin and neotigonin
Others	Protocatechuic acid, quinic acid, gallic acid, apigenin, trypsin, chymotrypsin, beta-pinene, beta-caryophyllene and dimethylpyrazine

clinical trials in humans.⁵ Benefits of fenugreek use have been reported by a large number of research groups. However, studies of its toxicological effects increased considerably. Toxicity studies emerged largely due to associated antifertility and abortifacient effects as well as locomotor disorders reported after ingestion of fenugreek during the 1960s. Ouzir *et al* elegantly reviewed the acute, subacute and subchronic toxicity of the fenugreek seeds and leaves suggesting that consumption of fenugreek induced some serious toxicological side effects.⁶

Table 1 shows the biologically active components of fenugreek.

Fenugreek contains alkaloids, saponins, flavonoids, amino acids and are also rich in coumarins—methyl, trimethyl coumarin and trigocoumarin.⁵ It also contains esculetin, a naturally occurring lactone and a dihydroxy coumarin derivative that can potentiate anticoagulant effect. Esculetin was found to be transformed into scopoletin (7-hydroxy-6-methoxycoumarin) and isoscapoletin (6-hydroxy-7-methoxycoumarin) when incubated with rat liver catechol-O-methyltransferase.⁷ These naturally occurring coumarins and systemically transformed derivatives can have high anticoagulant properties in the presence of dose modification and drug interactions in a susceptible individual. It is recommended that fenugreek be avoided in patients with cardiovascular diseases on warfarin because of its potential to increase bleeding risk.⁸ We believe that long-term and high-volume

Learning points

- ▶ Fenugreek, a frequently used traditional plant medicine and natural additive to foods is associated with multiple adverse effects ranging from diarrhoea and flatulence to being a potent teratogen in a dose-dependent manner.
- ▶ Fenugreek can alter haematology, blood biochemistry and histology in vital organ systems as shown in animal and human studies.
- ▶ Fenugreek is rich in naturally occurring coumarins and associated derivatives that can potentiate coagulation failure in susceptible patients.
- ▶ Patients with cirrhosis and severe isolated coagulation failure should be assessed for complementary and alternative medication use and must be questioned for traditional healing practices which they might consider safe and not reportable.
- ▶ Coagulation failure secondary to fenugreek overdose is promptly reversible with avoidance of further intake and supplementation of vitamin K.

consumption of fenugreek led to a state of coagulation failure in our patient with cirrhosis, from the exogenous coumarins and potent derivatives, leading to state of vitamin K antagonism that was promptly reversed by avoidance of the herb and supplementation with vitamin K. Patients with chronic liver disease with unexplained complications that deviate from the natural history of disease should be reassessed for potential reversible causes including a meticulous and methodical drug history. Traditional medical practices are considered 'extremely safe' among many communities and knowledge regarding such local practices by clinicians could benefit patient outcomes by modifying treatment decisions.

Contributors CAP: study concept and design, acquisition of data. PA: critical revision of the manuscript for important intellectual content. Both authors finalised the manuscript content.

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