CASE STUDY

CONTENTS

Three cases of fatal postoperative thromboembolic complications in patients with liver cirrhosis and bleeding from esophageal varicose veins after COVID-19

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ABSTRACT

Coronavirus disease (COVID-19), which broke out in China and caused a devastating pandemic worldwide, is associated with a significantly increased risk of thrombotic complications, especially pulmonary embolism. During the COVID-19 pandemic, investigations have reported a high incidence of venous thromboembolic (VTE) events in hospitalized patients with COVID-19, often despite thromboprophylaxis. Current recommendations for thromboprophylaxis are based on randomized clinical trials, which usually exclude patients at a potentially high risk of hemorrhagic complications. This category includes patients with liver cirrhosis complicated by variceal bleeding, thrombocytopenia, and coagulopathy. We present three patients who suffered severe covid pneumonia and were hospitalized with acute variceal bleeding, who developed fatal thromboembolic complications in the postoperative period.

KEY WORDS: thrombosis, pulmonary embolism, thromboembolic complications, COVID associated thromboembolic complications

Wiad Lek. 2024;77(8):1627-1632. doi: 10.36740/WLek202408114 DOI

INTRODUCTION

Coronavirus disease (COVID-19), which broke out in China and caused a devastating pandemic worldwide, is associated with a significantly increased risk of thrombotic complications, especially pulmonary embolism [1]. During the COVID-19 pandemic, investigations have reported a high incidence of venous thromboembolic (VTE) events in hospitalized patients with COVID-19, often despite thromboprophylaxis [1-4].

Emerging evidence suggests that the coagulation function is significantly deranged during SARS-CoV-2 (COVID-19) infection and may predispose to arterial and venous thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction and stasis [5].

However, as many researchers point out, the risk of hospital-associated VTE extends from the moment of admission and over the first 90 days after discharge from the hospital also in COVID-19 patients [6-9].

In this article, we would like to present the cases of 3 patients with cirrhosis and variceal bleeding who recently underwent Covid 19 and whose postoperative period was complicated by thrombosis or thromboembolic complications.

CASE REPORT

CASE REPORT 1

A 56-year-old women with autoimmune liver cirrhosis (Child-Pugh class A) and first massive bleeding from esophageal veins was referred by ambulance to the emergency department of Kyiv City Emergency Hospital. Her vital signs on admission were as follows: blood pressure, 80/40 mmHg; heart rate, 120 beats/min. The endoscopy revealed a dilated and tortuous veins in the low part of the esophagus with oozing blood, with "red sign", evidence of acute bleeding (Fig. 1).

It was known that three monts ago the patient was hospitalized with severe bilateral COVID-19 pneumonia and received LMWH at a therapeutic regimen. Severe COVID-19 disease was also identified when computed tomography of the chest reveals lung infiltrates >90%.

The patient's medical history of thromboembolic complications has not been reported in the past, but for the past twelve years she has been controlled for diabetes mellitus on insulin therapy, overweight and hypertention. Laboratory tests showed decreased hemoglobin (57 g/L), hematocrit (27.1%); leukocyte (4.6×10^9/L) and platelet (78×10^9/L) counts, total

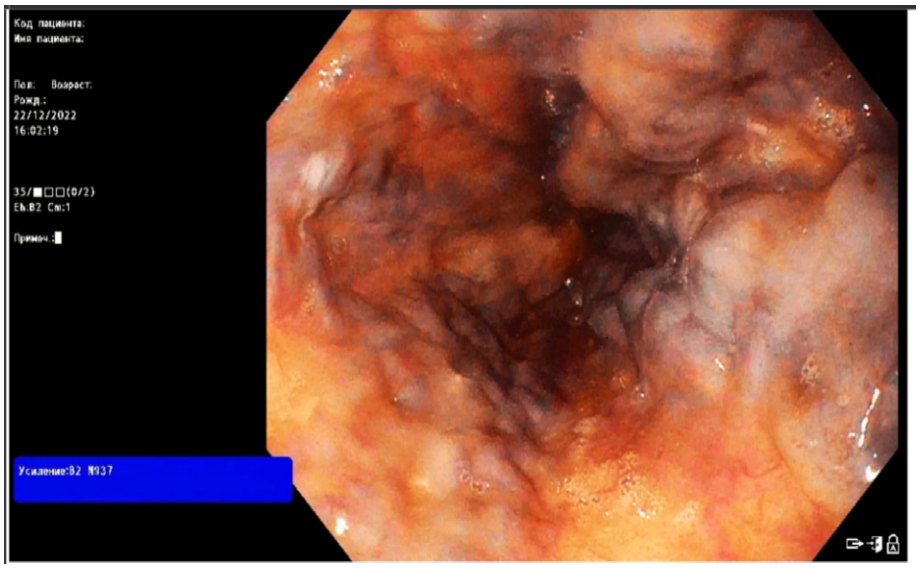

Fig. 1. Endoscopic examination of the upper gastrointestinal tract of a 56-year-old woman showed dilated and tortuous varices of the esophagus with red marks and blood leakage.

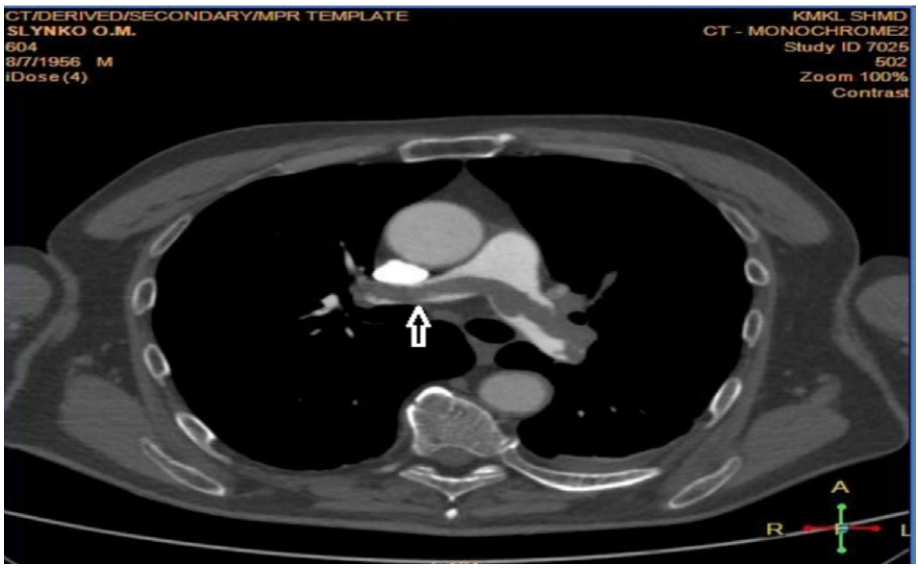

Fig. 2. A 56-year-old woman with autoimmune cirrhosis of the liver shows a massive pulmonary embolism on a contrast-enhanced computed tomography scan. The thrombus, which almost completely closes the pulmonary artery, is indicated by an arrow.

bilirubin (28.9mmol/L), and alanine aminotransaminase (67U/L); aspartate aminotransferase (39U/L), urea 11,6 mmol/L; creatinine (0.7 mkmol/L); glucose (9,1mkmol/L); sodium (144 mmol/L); potassium (4.8 mmol/L); total protein (62 g/L); serum albumin (29 g/L). Blood coagulation tests showed: increased prothrombin time (24.0seconds); activated partial thromboplastin time (30 sec); International Normalized Ratio (1.4). Serological markers for previous or current hepatitis B and C infection were negative. There was no previous history of alcohol abuse.

The patient was admitted to intensive care unit for preoperative preparation. The active bleeding was stopped by endoscopic ligation and administration of hemostatic agents. After stabilization of hemodynamic parameters, surgical intervention was performed, which consisted of devascularization of the upper part of the stomach, distal part of esophagus, followed by transection with a circular stapler. During the operation, the patient was transfused four units of packed erythrocytes and fresh-frozen-plasma. The patient was discharged on the tenth postoperative day in satisfactory condition. The next day after discharge, her condition suddenly deteriorated. The patient had difficulty breathing, chest pain, and an ambulance was immediately called. A contrast-enhanced computed tomography (CT) scan performed in the hospital confirmed the suspicion and revealed a massive pulmonary embolism (Fig. 2).

In the intensive care unit, the patient received cardiopulmonary support, anticoagulant therapy and unsuccessful thrombolysis, and unfortunately, the patient died.

Despite the patient's hypersplenism and the absence of hypercoagulability according to coagulation tests, we did not expect such a complication, which nevertheless led to a shift in the balance of our patient's haemostasis towards hypercoagulation and led to death.

CASE REPORT 2

A 40-year-old female patient with liver cirrhosis (Child-Pugh class B) was admitted to the emergency department with severe gastrointestinal bleeding, manifested by vomiting blood, loss of consciousness and melena. This was the fifth esophageal variceal bleeding in the past two years. Serological markers for previous or current hepatitis B and C infection were negative. There was no previous history of alcohol abuse also.

Fore months ago, the patient was treated for 3 weeks for severe bilateral COVID-19-associated pneumonia. Severe disease is also identified when computed tomography of the chest reveals lung infiltrates >45%. She did not receive anticoagulant therapy due to the high risk of rebleeding from esophageal varices.

Endoscopic evaluation with esophagogastroduodenoscopy revealed massively bleeding, grade III, lower esophageal varices. The active source of bleeding was stoped by the introduction of a Sengstaken-Blakemore tube and hemostatic therapy.

Physical examination revealed blood pressure 90/40 mmHg; pulse rate, 122 beats/min; pallor; melena. The liver function parameters were appropriate to patient with cirrosis and blood examination showed severe anemia. Hepatic enchephalopaty corresponded to grade I.

Laboratory tests showed decreased hemoglobin (60g/L), hematocrit (25.1%), leukocyte (15.6×10^9/L) and platelet (51×10^9/L) counts, alanine aminotransaminase (77 U/L); aspartate aminotransferase (69U/L), urea (4,3 mmol/L), creatinine (77 mkmol/L), glucose (6,9 mkmol/L), sodium (141 mmol/L), potassium (4.3 mmol/L), total protein (59 g/L), serum albumin (29 g/L), total bilirubin (68.9mmol/L). Blood coagulation tests showed: increased prothrombin time (25.0seconds), activated partial thromboplastin time (50 sec), International Normalized Ratio (1.56). Serological markers for previous or current hepatitis B and C infection were negative. After stabilization of vital signs, an operation was performed aimed at porto-azigal separation, which consisted in devascularization of the proximal part of stomach, distal part of esophagus, followed by transection of the esophagus with a circular stapler. During the operation, the patient was transfused several units of fresh-frozen-plasma.

The patient suddenly developed serious respiratory failure developed on the 7th day after operation, which manifested as a feeling of lack of air, shortness of breath and coughing. Patient was started on oxygen therapy, continued with antibiotic, intravenous hydration, anticoagulant therapy (Heparin), and supportive care. Despite the therapy, the clinical and laboratory picture deteriorated rapidly. Due to progressive respiratory failure and critical drop in oxygen saturation, the patient was intubated and mechanical ventilation was initiated. The patient died the next day with progressive multiorgan failure. An autopsy showed the presence of thrombotic mass in the branches of the pulmonary arteries with pulmonary infarctions associated with bilateral pneumonia and pleural effusion.

This case also demonstrates the need for further research and rethinking of the mechanisms of blood coagulation system imbalance in the post-COVID period, despite the presence of hypersplenism and the absence of obvious signs of hypercoagulation according to the patient's coagulogram and, probably, the need for thromboprophylaxis in the postoperative period.

CASE REPORT 3

A 72-year-old woman with a history of liver cirrhosis (Child-Pugh class B) presented to the emergency room with the first episode of massive bleeding from esophageal veins. Four weeks prior to admission she was treated with bilateral COVID associated pneumonia with lung damage exceeding 50% and was receiving anticoagulant therapy. The active bleeding was stopped by endoscopic ligation (Fig. 3) of varicose veins and hemostatic therapy, after which a porto-azigal disconnection operation was performed with devascularization of the proximal stomach and distal esophagus with reduction of splenic perfusion by ligation of the a.lienalis in the proximal part. On the eleven postoperative day she was discharged in satisfactory condition. Three weeks after discharge, the patient suddenly developed nausea, vomiting, distention and diffuse abdominal pain that had started without a clear trigger. The vital parameters at entry were as follows: temperature 38.5 ° C, blood pressure 110/60 mm HG, heart rate 89 beats per minute and oxygen saturation of 98% on room air. Blood analysis showed: hemoglobin (88 g/L), Hct (24.9%), leukocyte (34.6×10^9/L, 83.5% neutrophils) and platelet (95×10^9/L), total bilirubin (18.9mmol/L), ALT (8I U/L), AST (9IU/L), total protein (68 g/L), serum albumin (32.8g/L), urea (9,9 mmol/L), creatinine (119 mkmol/L), glucose (6.0 mmol/L), sodium (141 mmol/L), potassium (4.6 mmol/L). Blood coagulation tests showed: increased prothrombin time (35 sec), PTI 45%, activated partial thromboplastin time (31 sec).

Physical examination revealed diffuse abdominal pain, which worsened with deep palpation, and peritoneal symptom appeared. Ultrasonographic examination revealed thrombosis of the portal vein with spread to the branches and signs of intestinal obstruction (Fig. 4.,

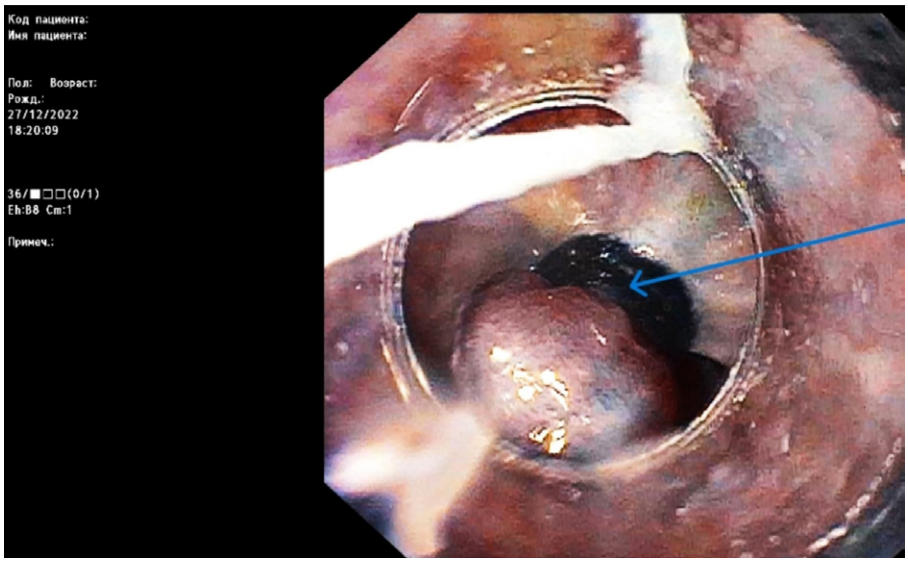

Fig. 3. Active bleeding was stopped by endoscopic ligation.

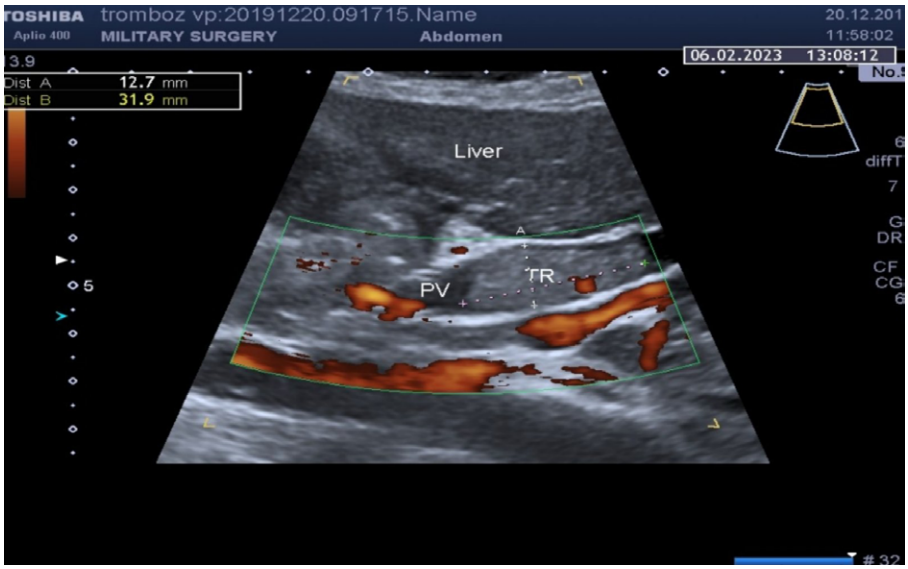

Fig. 4. Ultrasound Doppler examination of a 72-year-old woman with toxic cirrhosis reveals a thrombus in the portal vein that completely blocks the lumen of the vessel.

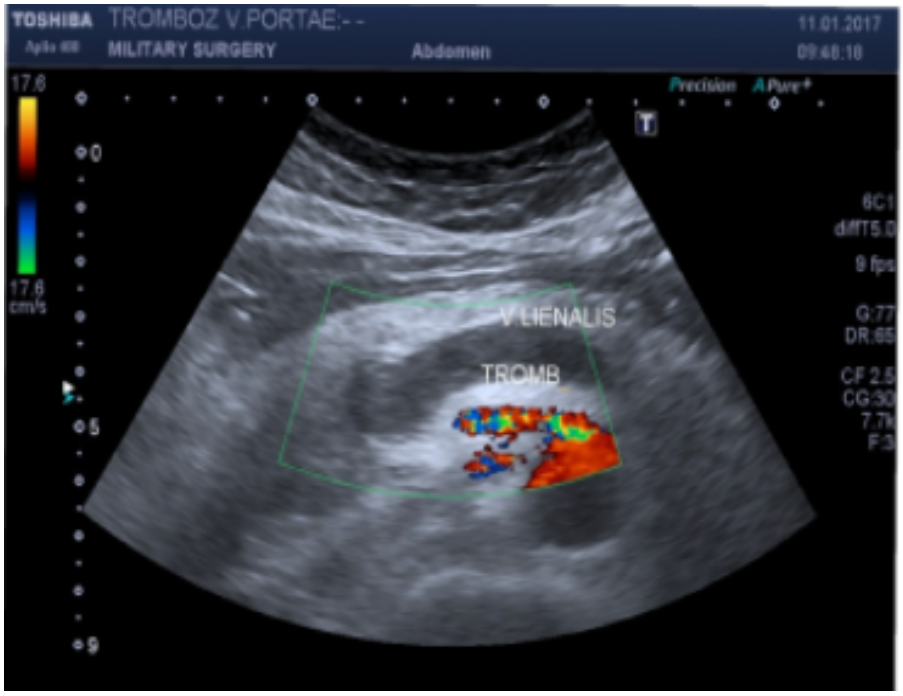

Fig. 5. Ultrasound examination of a 72-year-old woman with toxic cirrhosis reveals a thrombus in the portal vein, which spreads to the branches (splenic and superior mesenteric veins), which caused mesenteric thrombosis and intestinal necrosis.

Fig. 5.). The next step was laparoscopic revision, which revealed a necrotized ileal loop located 50 cm proximal to the ileocecal valve. An intestinal resection with entero-enteral anastomosis was performed. Recurrent retrombosis on the 9th day of the postoperative period and progression of liver failure led to the patient's death.

When analysing the three deaths in patients with cirrhosis, we noted that thrombotic complications occurred in all of these patients who had a recent history of severe covid pneumonia, despite the fact that 2 of these patients were receiving adequate anticoagulant therapy, which requires further investigation and special attention in patients with covid history.

The liver plays a central role in the regulation of homeostasis. By producing the majority of plasma proteins involved in hemostasis including pro– and anticoagulant factors, pro– and antifibrinolytic factors, and thrombopoietin [11]. It follows that liver diseases are commonly responsible for hemostasis abnormalities including decreased production of clotting factors, thrombocytopenia, platelet dysfunction, and increased circulating fibrinolytic activity. Such alterations in the hemostatic system were historically interpreted as indicators of bleeding risk in liver disease and patients were considered to be anticoagulated.

There are many lines of evidence which contradict this point of view. Not only are procoagulant pathways reduced in liver disease but also anticoagulant and fibrinolytic mechanisms are impaired. Moreover, low platelet count can be counterbalanced by increased platelet activity. Several clinical studies on the risk of bleeding and thrombosis suggest that liver disease is not simply a bleeding disorder, but also confirms that the hemostatic system in liver disease is rebalanced [11,14].

Bleeding from esophageal varices is a common complication in patients with liver cirrhosis. However, it has now been well established that this complication is unrelated to a defective hemostatic system [13]. Routine tests of hemostasis such as the prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count are frequently abnormal in these patients and these test results all indicate a hypocoagulable status [11]. However, standard coagulation tests do not fully reflect hemostatic disorders and do not accurately predict the risk of bleeding or thrombosis.

For a long time, thrombotic complications were traditionally considered rare events in patients with cirrhosis, but our observations have shown that thrombotic complications can paradoxically occur in the posthemorrhagic/postoperative period, especially in patients after covid pneumonia. Therefore, it is likely difficult to predict using laboratory tests or clinical scores which patient is more likely to tip towards a bleeding and which one is more likely to develop thrombosis. The clinical reality is that patients may present with bleeding and thrombosis simultaneously, and obviously management of such patients is a particularly difficult clinical challenge.

CONCLUSIONS

Rebalanced hemostasis in patients with liver disease is unreliable and may shift toward hemorrhage or thrombosis, depending on coexisting circumstantial risk factors.

Patients with liver cirrhosis and variceal bleeding with previous COVID-19 infection require special attention to prevent thromboembolic complications. However, in this category of patients, the use of anticoagulants requires caution and should be selected individually, taking into account the risks of thrombosis and rebleeding.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 13.11.2023
ACCEPTED: 17.07.2024