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Portal and mesenteric vein thrombosis after portal vein embolization in a patient with protein S deficiency

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Abstract
Portal vein embolization can be performed safely, and so far no major complications have been reported. We report an extremely rare complication of portal vein embolization, a case of portal and mesenteric thrombosis in a 65-year-old patient with protein S deficiency. Right portal vein embolization was carried out prior to extended right hepatectomy for advanced gallbladder carcinoma involving the hepatic hilus. Computed tomography 14 days after embolization revealed massive thrombosis of the portal and the superior mesenteric veins. A protein S deficiency was found by means of an extensive workup for hypercoagulable state. Portal vein embolization may have triggered a cascade of events that was expressed as portal and mesenteric vein thrombosis resulting from deficiency of protein S. It may be better to determine the concentrations of such coagulation regulators prior to portal vein embolization.

Key words Portal vein embolization · Portal vein thrombosis · Protein S deficiency

Introduction

Portal vein embolization (PVE) has become an important component of the preoperative management of patients scheduled for extensive hepatectomy.[1,2] Experience has demonstrated that PVE can increase the safety of resection and enlarge the pool of potential candidates for hepatectomy.[3,4] PVE can be performed safely, and so far no major complications have been reported, while minor complications include the need for re-embolization, transient hemobilia, and small-bowel obstruction. This report describes an extremely rare complication of PVE, a case of portal and mesenteric vein thrombosis in a patient with protein S deficiency.

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Case report

A 65-year-old woman was admitted to a local hospital for obstructive jaundice, with a total serum bilirubin concentration of 20.4 mg/dl. She had no personal or family history of any thrombotic event. The patient underwent percutaneous transhepatic biliary drainage, and a diagnosis of advanced gallbladder carcinoma involving the hepatic hilus was made. Subsequently, she was referred to our hospital for possible surgery. Diagnostic imaging studies indicated that right hepatectomy with en-bloc resection of the caudate lobe and extrahepatic bile duct was required for curative resection. A volumetric study using computed tomography (CT) revealed that the anticipated remnant liver, i.e., the left liver, was 356 cm^3 (29% of the whole liver), so we decided to perform right PVE preoperatively.

Right PVE was carried out, using absolute ethanol and steel coils without difficulty or complication. Doppler ultrasonography demonstrated that the flow velocity at the umbilical portion of the left portal vein increased to 17.5 cm/s 1 day after PVE. It also confirmed that the right portal vein was completely obstructed and that there was no thrombosis in the left portal vein or the main portal trunk. These findings were again confirmed using Doppler ultrasonography on day 3 after PVE. Although the patient was asymptomatic, her platelet count had decreased from 209 000/μl before PVE to 62 000/μl on day 11 after PVE, and the fibrinogen concentration had also decreased, from 580 mg/dl before PVE to 148 mg/dl on day 15 (Fig. 1). CT performed 14 days after PVE showed massive thrombosis, extending from the left portal vein to the superior mesenteric and splenic veins (Fig. 2). The small bowel was not dilated or thickened, and no ascites was present. Heparin (10 000 U/day for 7 days) and urokinase (480 000 U/day for 1 day and 240 000 U/day for the following 3 days) were administered intravenously. The patient's platelet count gradually increased after reach-

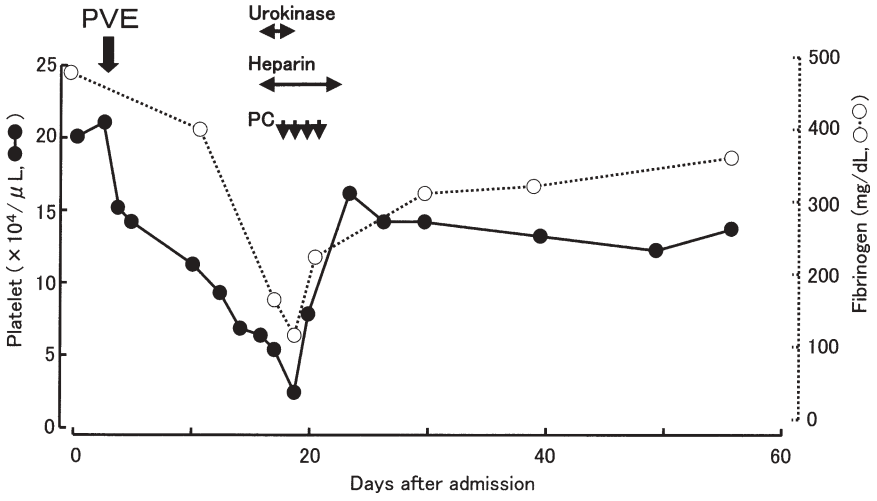

Fig. 1. Sequential changes in the platelet counts and fibrinogen concentrations before and after portal vein embolization (*PVE*). *PC*, platelet concentration

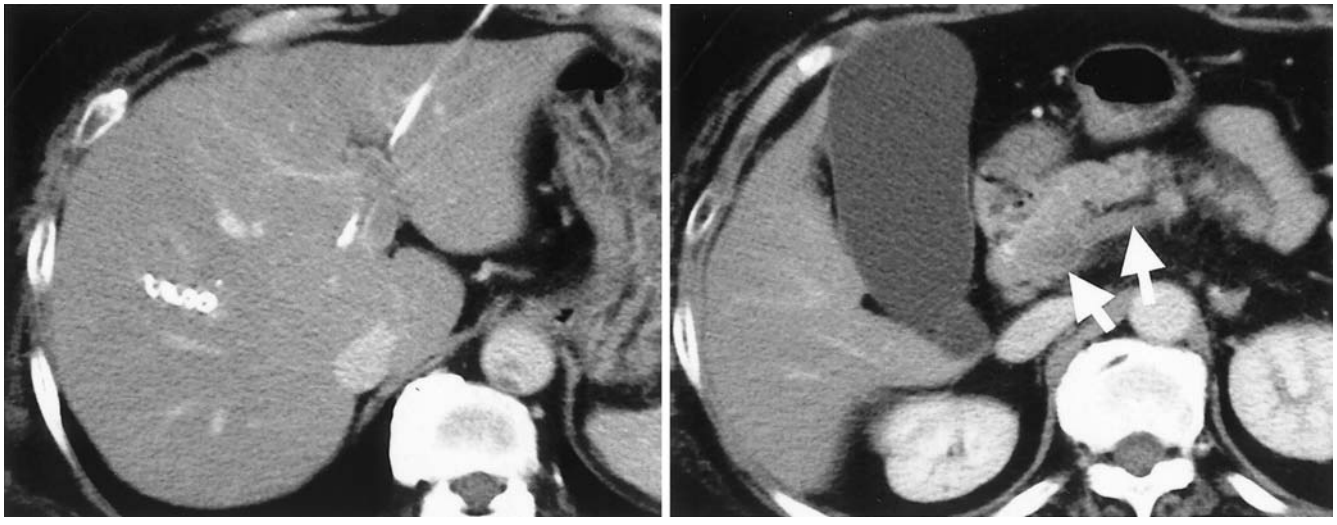

Fig. 2. Computed tomography 14 days after portal vein embolization. *Arrows* indicate massive portal and mesenteric vein thrombosis. **Left**, umbilical portion of the left portal vein; **right**, superior mesenteric vein below the pancreas

ing a nadir of 29 000/μl on day 16 after PVE (Fig. 1). After discontinuing heparin, warfarin was initiated and continued for 14 days. CT performed 17 days after the thrombolytic therapy showed normal flow in the left portal vein, with the development of collateral vessels in the pancreatic head and hepatoduodenal ligament (Fig. 3).

Extensive laboratory testing to look for a hypercoagulable state was performed, including measurement of antithrombin III, protein C, protein S, and plasminogen levels. All tests were normal, with the exception of a low protein S concentration, which was only 25% to 50% of normal, measured at four discrete time points.

Fifty-three days after PVE, we performed laparotomy to attempt curative resection. However, the tumor involved the head of the pancreas as well as the hepatic hilus, and many collaterals were found in the hepatoduodenal ligament. The tumor was considered unresectable. The patient received radiation therapy and was discharged from the hospital. At the time of this writing (10 months after the surgery), she is relatively asymptomatic and has had no further thrombotic episodes.

Discussion

We have performed preoperative PVE in 206 patients scheduled for extensive hepatectomy. Fibrin glue was used as the embolic material in the first 161 patients,

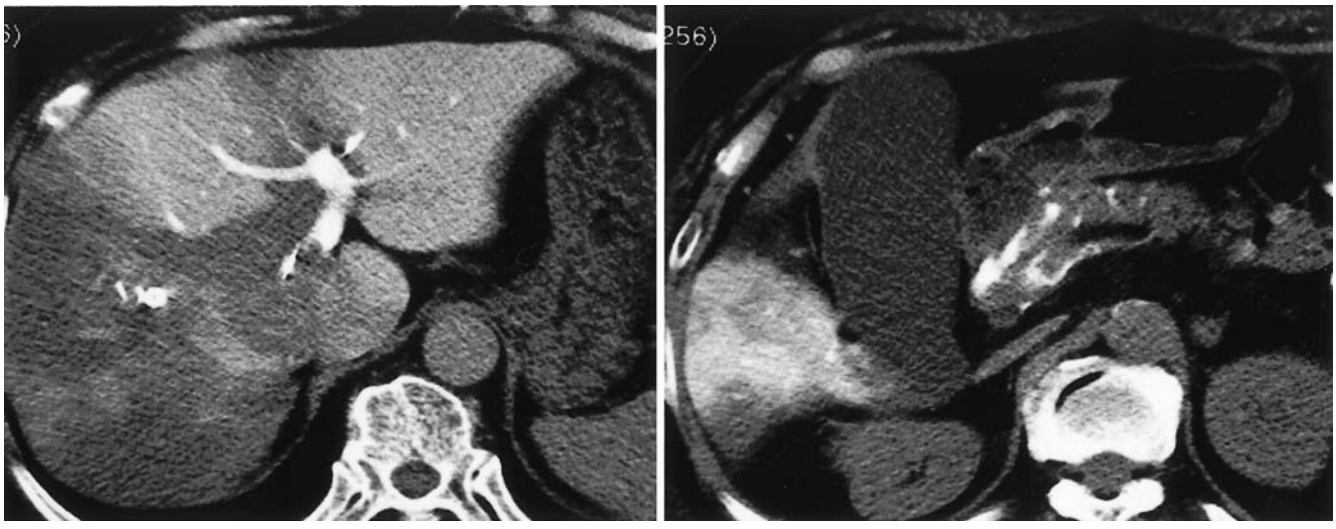

Fig. 3. Computed tomography during arterial portography, performed 17 days after thrombolytic therapy. Portal flow has partly recovered through collateral vessels in the pancreatic head and hepatoduodenal ligament

and absolute ethanol with steel coils in the subsequent 45 patients. We experienced minor complications, including mild hemobilia, transient fever, and abdominal pain in a limited number of patients. The present case was our first experience of serious complications related to PVE, and, to our knowledge, the first case report of portal vein thrombosis after PVE. In this particular patient, the right anterior and posterior portal branches were embolized separately, but the right portal trunk itself was not embolized. Furthermore, Doppler ultrasonography revealed adequate blood flow in the left portal vein 3 days after PVE. These data suggest that a technical problem, such as backflow of embolic material or endothelial injury of the main portal trunk, was unlikely to have occurred. Most likely, thrombi in the portal and mesenteric vein formed slowly, beginning 3 days after the PVE.

Mesenteric and portal vein thrombosis is a rare, but life-threatening, condition. An immediate laparotomy is mandatory when bowel infarction is suspected. Fortunately, our patient was asymptomatic and had no peritoneal signs, so we were able to manage her conservatively with only anticoagulation. Several authors have reported successful treatment with thrombolytic therapy.[5] However, the optimal dosage, route of administration, and duration of treatment remain controversial. A number of etiologies of mesenteric and portal vein thrombosis have been reported, including systemic inflammation, malignancy, pregnancy, oral contraceptive use, and absence of a spleen. Deficiencies of proteins S and C, and antithrombin III, have been reported increasingly frequently.[6]

Protein S, a vitamin K-dependent glycoprotein, is a protein C cofactor that is necessary for the full anticoagulant effect of activated protein C. In plasma, protein S is partly free and partly bound to C4b-binding protein, but only the free form functions as a cofactor. The present patient had only 25% to 50% of the normal level of free antigen, justifying the diagnosis of protein S deficiency. The true incidence of inherited protein S deficiency is unknown, because not all the individuals with this disorder necessarily develop thrombotic events. Reportedly, 2% to 5% of patients with deep venous thrombosis or pulmonary embolism have protein S deficiency; this is less common than protein C deficiency (5% to 8%) or antithrombin III deficiency (12% to 15%).[7] Patients with protein S deficiency have a 50% chance of developing recurrent thrombosis before age 45.[8] These thrombotic events are frequently associated with some precipitating factors, such as oral contraceptive use or pregnancy. Our patient had been delivered of two children uneventfully. Surgery and trauma are also precipitants of deep venous thrombosis and pulmonary embolism. In the present patient, PVE, which should be considered as a kind of iatrogenic trauma, was thought to have been the triggering factor.

In conclusion, we should consider the delayed occurrence of portal and mesenteric vein thrombosis after PVE as being suggestive of a coagulopathy, possibly protein S or C or antithrombin III deficiency. It may be better to determine the concentrations of these coagulation regulators prior to PVE as these disorders are not rare. However, whether routine measurement is practical is debatable, requiring further studies.

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