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Case Report

Portal Vein Thrombosis Repeatedly Observed in a Cirrhotic Patient with Antiphospholipid Antibody Syndrome

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Abstract

Background : Although portal vein thrombosis in cirrhotic patients is frequently observed, the detailed process remains to be clarified, and the role of anticardiolipin antibody in the development of portal vein thrombosis has been controversial.

Case Report : A 52-year-old man, who had been diagnosed with alcoholic cirrhosis of the liver, was admitted to our hospital suffering from dyspnea and ascites. Just after being diagnosed as having antiphospholipid antibody syndrome with lung thrombosis and delivering a positive result for the β2-glycoprotein I-dependent anticardiolipin antibody, he sustained rupture of the esophageal varices with rapid development of portal vein thrombosis, which resolved under anticoagulant therapy. Two years later, he was admitted again on suspicion of thrombosis because of an elevation in the serum D-dimer level, and computed tomography showed portal and upper mesenteric vein thrombosis. Although immediate anticoagulant therapy resulted in complete recanalization, he suffered the same episode 2 months later, which occurred with re-elevation of the serum D-dimer level.

Conclusion : A positive finding of an anticardiolipin antibody in cirrhotic patients has been considered to be nonspecific and not related to the development of thrombus in the portal vein. This case, however, seems to indicate that cirrhotic patients with the β2-glycoprotein I-dependent anticardiolipin antibody should be regarded as being at high risk for portal vein thrombosis. Monitoring with the serum D-dimer was useful in detecting portal vein thrombosis in its early stage.

Key words : venous thrombosis, portal vein, liver cirrhosis, antiphospholipid syndrome, fibrin fibrinogen degradation products

Introduction

Portal vein thrombosis (PVT) in cirrhotic patients is frequently observed, especially in those with advanced fibrosis. Earlier reports showed the prevalence of PVT in cirrhotic patients had a range of 5～20%[1)]. Although it has been accepted that the decreased portal flow and the imbalance between fibrinolytic and coagulant systems contribute to the development of PVT, the full and detailed process remains to be clarified[2)3)].

The role of anticardiolipin antibody in the development of PVT has been controversial. In 2003, Öksüzoglu et al. showed that anticardiolipin antibody levels were significantly higher in cirrhotic patients with PVT[4)]. However, subsequent authors have reported contrary results[5)6)].

In diagnosing antiphospholipid syndrome (APS),

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a positive result for the β2-glycoprotein I (β2-GPI) -dependent anticardiolipin antibody or lupus anticoagulant antibody is indispensable. Conversely, portal vein thrombus among patients with APS is relatively rare, while Budd-Chiari syndrome is one of its major manifestations[7]. In this report, we describe the case of a cirrhotic patient complicated by APS who experienced repeated PVT. Cirrhotic patients with a β2-GPI-dependent, and not a β2-GPI-independent, anticardiolipin antibody might be considered a population at high risk for PVT.

Case Report

A-52-year-old man was admitted to our hospital suffering from abdominal fullness and dyspnea in December 2010. He had been a heavy consumer of alcohol for more than 20 years, and ultrasonographic examination showed coarse liver parenchyma, splenomegaly, dilated collateral gastric veins, and massive ascites, indicating alcoholic cirrhosis of the liver. The serum albumin was decreased to 2.6 g/dL while the serum bilirubin, platelet count, and prothrombin time were within normal ranges. His hepatic functional reserve was classified as Child-Pugh A. A computed tomography (CT) scan on admission showed esophageal varices but no portal vein thrombosis. His dyspnea persisted even after the level of ascites was lowered with diuretics. Lung blood flow scintigraphy demonstrated lung thrombosis, which implied possible abnormality in the coagulation system. On obtaining a positive result from a serum β2-GPI-dependent anticardiolipin antibody, he was diagnosed with APS coexisting with alcoholic cirrhosis. Before anticoagulant treatment could be introduced, he sustained rupture of esophageal varices with rapid development of PVT, which was successfully treated with ligation of the esophageal varices (Fig. 1). Danaparoid sodium and prednisolone (1 mg/kg) was not only effective in resolving the lung thrombus and improving dyspnea, but also recanalized the PVT (Fig. 2).

To suppress reactivation of the APS, the patient continued on low-dose prednisolone (2.5 mg/body) and underwent a test for the serum D-dimer every 2 months. He ceased to drink alcohol and was doing well until August 2012 when the serum D-dimer increased to 5.3 μg/mL, which previously had not been beyond 2.0 μg/mL. Contrast-enhanced CT revealed a thrombus in the portal vein that extended to the superior mesenteric vein. Treatment with danaparoid sodium completely resolved the thrombus, and the serum D-dimer decreased to 0.4 μg/mL within 2 weeks. Only 2 months after this episode, portal and superior mesenteric vein thrombosis appeared again, leading to re-elevation of serum D-dimer by 3.3 μg/mL. After treatment for the recurrence of PVT with danaparoid sodium, the patient underwent warfarinization, and no recurrence of any thrombosis has since been observed for more than 14 months.

Discussion

PVT occurs in a variety of clinical settings such as myeloproliferative disease, cancer, infection, and cirrhosis of the liver, which is the most frequent cause of PVT[3)8)]. It was previously reported that 5～20% of patients with liver cirrhosis experienced PVT[1)]. Viewed from a different perspective, only a minority of patients with cirrhosis thus encounters PVT, implying that factors other than portal hypertension might play a part in the development of PVT.

Although the contribution of the anticardiolipin antibody to PVT in cirrhotic patients has been controversial, a recent study of a large cohort of patients showed that anticardiolipin antibody had no relation to the development of PVT[9)]. Amitrano et al. showed that the β2-GPI-independent anticardiolipin antibody played no role in PVT associated with cirrhosis of the liver, and found no cirrhotic patients with a positive β2-GPI-dependent anticardiolipin antibody in their survey, which indicated that cases of cirrhosis complicated by APS are likely to be very rare[6)].

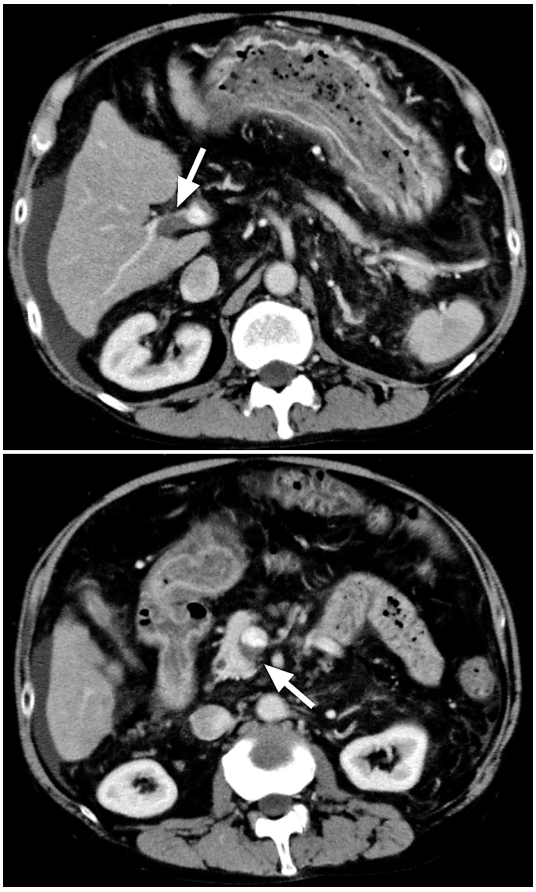

Fig. 1 Computed tomography on the day the patient sustained rupture of esophageal varices. The thrombus in the portal vein (upper panel) extended to the upper mesenteric vein (lower panel). The irregular surface of the atrophic liver was compatible with liver cirrhosis.

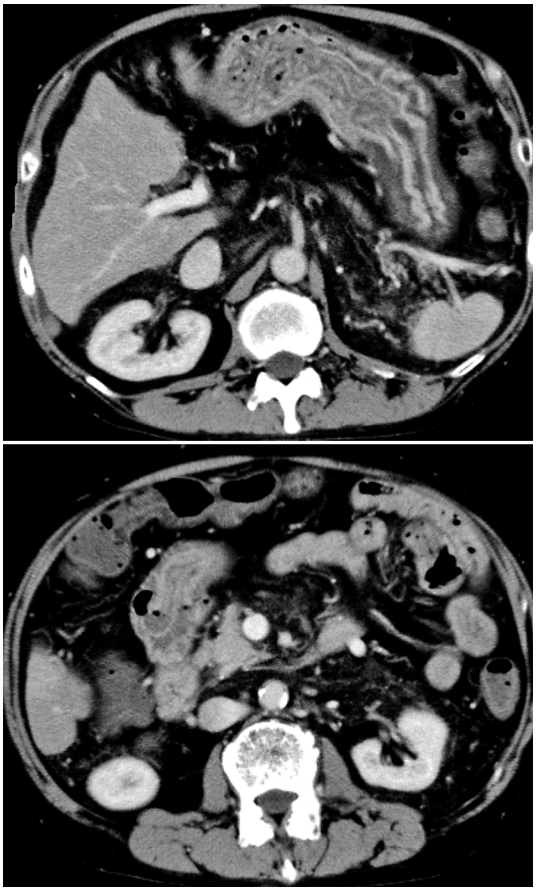

Fig. 2 After anticoagulant treatment with danaparoid sodium for a week, the thrombus in the portal vein extending to the upper mesenteric vein completely disappeared.

Conversely, patients with APS seldom develop PVT, whereas they evince various forms of arterial and/or venous thrombosis. This finding contrasts with the fact that among the abdominal manifestations of APS, Budd-Chiari syndrome is considered an important complication[7]. The differing prevalence between PVT and Budd-Chiari syndrome, however, has not been adequately discussed.

The patient described in this report was considered to have both APS and cirrhosis before the onset of portal and supra-mesenteric vein thrombosis. Certainly, PVT is rarely seen in patients with APS, and cirrhosis could be solely responsible for the development of PVT. It is possible, however, that the coexistence of APS and liver cirrhosis with such portal hypertension able to cause esophageal varices could increase the risk of contracting PVT. Our case indicates that those patients with cirrhosis of the liver complicated by firmly diagnosed APS should be treated as a subpopulation at high risk for PVT.

We found several reports contending the usefulness of the serum D-dimer for monitoring patients with PVT, which may be divided into two streams : use of the serum D-dimer as a negative marker to exclude the existence of PVT[10)11)], and its use as a positive marker to predict the development of PVT after surgery related to the splenic vein[12)13)]. The former studies revealed that normal values of the D-dimer in cirrhotic patients excluded the presence of PVT, and the

latter showed that the increase of the D-dimer through dynamic monitoring after surgery helped in the early diagnosis of PVT. Deng et al. described that the possibility of PVT was very high when D-dimer levels exceeded 16 $\mu g/mL$[12]. In our case, the increase in the value of the D-dimer, even though it was at a relatively low level, sharply reflected the development of PVT, indicating that the continuous observation of the D-dimer is important in predicting PVT in its early stage ; in addition, dynamic changes in the value might harbor further meaning. Although anticoagulant treatment is more effective for the early stage of thrombosis, it is certainly impractical to monitor the value of the D-dimer for all patients with cirrhosis to survey PVT. Nonetheless, it would be worthwhile to limit the targets to a high-risk subset and monitor the D-dimer levels, which might make the treatment of PVT easier and improve the prognosis. According to past reports, those patients who are in an advanced stage of cirrhosis after treatment for rupture of varices and who have previously experienced PVT can be considered as a population at high risk for PVT, as would those for whom the diagnosis of APS is confirmed.

Conclusion

A positive finding of an anticardiolipin antibody in cirrhotic patients has been considered to be nonspecific and not related to the development of PVT. This case, however, seems to indicate that cirrhotic patients with the β2-GPI-dependent anticardiolipin antibody should be regarded as being at high risk for PVT. Monitoring with the serum D-dimer was useful in detecting PVT in its early stage.

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（和文抄録）

門脈血栓症を繰り返した，抗リン脂質抗体症候群を合併した肝硬変の一例

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肝硬変患者では門脈血栓の発症をしばしば認めるが，その成立機序は十分解明されておらず，抗カルジオリピン抗体の関与も定見がない．今回我々は，繰り返し門脈血栓症を来した抗カルジオリピン抗体陽性の肝硬変患者を経験したので報告する．

症例はアルコール性肝硬変と診断されていた52歳の男性．呼吸困難を主訴に当院に初回入院した際，肺動脈血栓症を伴った抗リン脂質症候群と診断され，β2-glycoprotein I 依存性抗カルジオリピン抗体陽性であることが確認された．入院後に門脈血栓が急速に発症し，食道静脈瘤破裂を来したが，止血後の抗凝固療法で血栓は溶解した．経過観察中の2年後にD-dimerの上昇から血栓形成を疑われ，CTにて門脈から上腸間膜静脈に至る血栓を認めた．抗凝固療法にて血栓は消失したが，その2ヶ月後には，再度D-dimerの上昇を伴う門脈血栓形成を認めた．

肝硬変患者においては抗カルジオリピン抗体は非特異的に陽性化し，門脈血栓症との関係はないとする意見もある．しかし，β2-glycoprotein I 依存性抗カルジオリピン抗体陽性の場合には門脈血栓症の発生と関係がある可能性を，本症例は示唆している．D-dimerの定期観察は，門脈血栓の早期発見に有用である．

キーワード：静脈血栓症，門脈，肝硬変，抗リン脂質抗体症候群，フィブリン・フィブリノゲン分解産物