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Splenectomy Combined with Anticoagulation Therapy for Antithrombin Deficiency with Portal Vein Thrombosis and Refractory Thrombocytopenia in Children

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Antithrombin deficiency with portal vein thrombosis is an unusual disease in clinic. A 16-year-old adolescent with a history of frequent spontaneous epistaxis and hypersplenism in his childhood presented with abdominal pain and distension. Chronic portal vein thrombosis, portal hypertension, and hypersplenism were caused by antithrombin deficiency based on laboratory data and image findings. He underwent splenectomy and subsequent anticoagulation therapy with warfarin. Postoperative course was uneventfully. During 1 year follow-up, he had no epistaxis and epigastric pain and platelet count showed normal value (366,000/μL)

Key words: thrombocytopenia, warfarin, thrombin, thrombosis, portal vein thrombosis, splenectomy

INTRODUCTION

In children and adolescents, portal vein thrombosis is a major cause of portal hypertension. Less than 5% of all children and adolescents with portal vein thrombosis present with a deficiency in one or more coagulation inhibitor proteins such as protein C, protein S, and antithrombin.[1,2] We present a case of antithrombin deficiency, a hypercoagulation disease, inducing portal vein thrombosis, portal hypertension, and hypersplenism. It is interesting that the patient showed coagulopathy. The patient was treated by splenectomy and subsequent anticoagulation therapy.

CASE REPORT

A 16-year-old male was referred to us from a local hospital with portal vein anomaly related to portal hypertension and splenomegaly with hypersplenism. According to the records of the referring hospital, he had experienced a sudden-onset attack of epigastric pain when he was 6 years old. Computed tomography revealed splenomegaly and portal vein anomaly. Thrombocytopenia was also noted. When he was 12 years old, esophageal varices were noted on upper gastrointestinal panendoscopy and prophylactic esophageal variceal ligation was performed. He then received regular endoscopic examination, which showed no recurrent esophageal varices. He also developed off-and-on spontaneous epistaxis and required platelet transfusion. Because of the worsening thrombocytopenia, splenectomy was suggested by the referring doctor. He came to our hospital for a second opinion.

The boy was slim on physical examination, his spleen was found to be palpable 8 cm below the left costal margin, and clubbing fingers were observed. Abdominal computed tomography (figure 1) revealed a grossly enlarged spleen, measuring 20 cm across the longitudinal axis, with an engorged splenic vein and portal vein thrombosis. No thrombosis was identified in the splenic vein. The laboratory results revealed leukocytopenia (3,000 cells/μL) and thrombocytopenia (40,000 cells/μL). Aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, sodium, and potassium levels were within normal limits. The preliminary investigation led to the diagnosis of portal vein thrombosis complicated by

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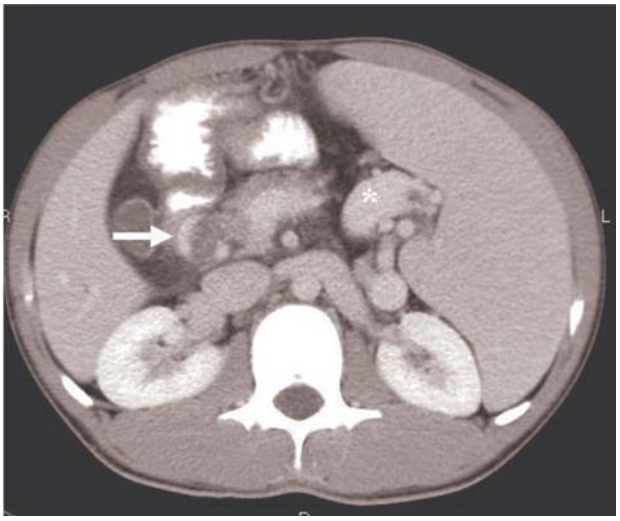

Fig. 1 Computed tomography image indicating an enlarged spleen, with an engorged splenic vein (asterisk) and portal vein thrombosis (arrow).

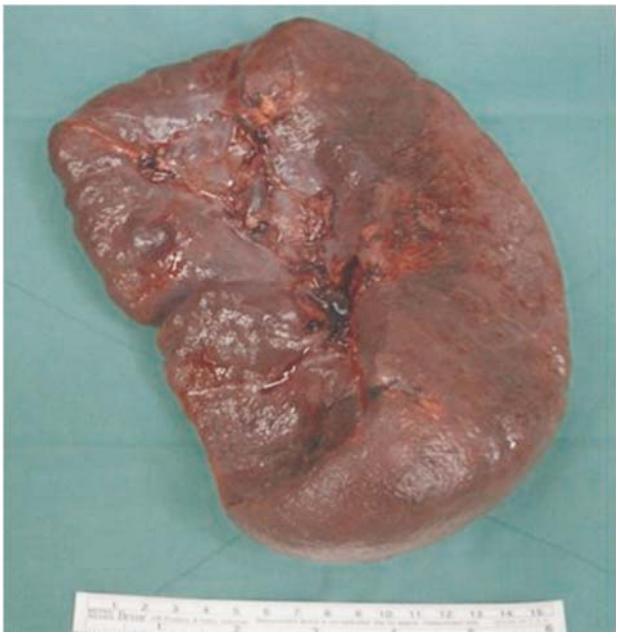

Fig. 2 The grossly enlarged spleen, measuring 19×12×6 cm and weighing 858 g.

portal hypertension, splenomegaly, and hypersplenism.

Because of his thrombotic disease, the patient underwent a series of coagulation studies. The coagulation panel (prothrombin time/partial thromboplastin time: 12/23.9 s), protein C (79.2%; reference range: 70–140%), and protein S (67.6%; reference range: 60–145%) were normal. Antithrombin was low (41.7% reference range: 70–120%). Gene examination revealed an antithrombin Nagasaki mutation (Ser116Pro), which produces a heterozygous antithrombin variant with defective heparin binding.

To prevent peri-operative thromboembolic events, we prescribed oral warfarin after the operation. During the open splenectomy procedure, the spleen was found to be grossly enlarged, measuring 19×12×6 cm and weighing 858 g (figure 2). A spontaneous spleno-renal shunt was noted and we preserved the spleno-renal collateral vessels around the huge spleen. The blood loss was approximately 2000 mL, and the operation time was 3h and 8min. Pathological analysis indicated congestion with decreased white pulps in the spleen tissue.

Following the operation, the platelet count improved from 40,000/μL to 366,000/μL, and white blood cell count improved from 3,000 cells/μL to 7,400 cells/μL after 12 months. The patient received sustained anticoagulant treatment with warfarin (target international normalized ratio, 2.0–3.0). At 12 months' follow-up, the symptoms of epistaxis and epigastric pain had subsided.

DISCUSSION

In the field of pediatrics, the main clinical manifestation of portal vein thrombosis is esophageal varices, and the second most common clinical manifestation is hypersplenism. Approximately 84.9% of children with portal vein thrombosis show esophageal varices on upper gastrointestinal panendoscopy, and 70.9% will have at least 1 episode of upper gastrointestinal bleeding in their lifetime.[3] In patients with hypersplenism, leukocytopenia and thrombocytopenia usually can be detected.[4]

Antithrombin is a plasma protease inhibitor that inactivates thrombin and factors Xa, IXa, and XIa by forming irreversible complexes. Thus, antithrombin deficiency leads to a decrease in the inhibition of the coagulation pathways, causing a hypercoagulable state. Normal plasma levels of antithrombin range from 112 to 140 μg/mL, and most laboratories express antithrombin activity levels in percentages, with a normal range of approximately 80–120%. Most patients with inherited heterozygous antithrombin deficiency exhibit antithrombin activity in the range of 40–60%.[5]

The most common clinical manifestations of antithrombin deficiency are venous thromboembolism, which typically occurs as deep vein thrombosis of the legs and arms, and pulmonary embolism. However, embolism can also occur at unusual sites, such as the cerebral, sinus,

mesenteric, portal, hepatic, renal, and retinal veins. Portal vein thrombosis develops at the early phase of splenectomy in patients with portal hypertension. Warfarin is useful for the prevention of portal vein thrombosis after splenectomy.[6]

In the absence of antithrombin, warfarin is recommended. To prevent recurrent venous thromboembolism, conventional-intensity (target international normalized ratio, 2.0–3.0) is more effective than low-intensity (target international normalized ratio, 1.5–1.9) therapy.[7] Thrombophilic defects are not associated with a higher risk of recurrent venous thromboembolism during warfarin therapy.[8] However, the venous thromboembolism observed in our patient affected the portal vein. The portal hypertension induced by hypersplenism in this patient was associated with a low platelet count (40,000/μL) and frequent spontaneous nasal bleeding. During splenectomy in patients with thrombophilc disorder, anticoagulation therapy was found for preventing extension of portal vein thrombosis. Therefore, we elected to perform a splenectomy to treat his thrombocytopenia first and then prescribed sustained treatment with anticoagulants.

A consensus has promoted the conservative treatment of patients with portal vein thrombosis related to portal hypertension. However, the following aspects should be taken into consideration when selecting the appropriate treatment strategy: the risk of death or post-transfusion hepatitis, children's and parent's anxiety about possible new episodes of upper gastrointestinal bleeding, cost of hospitalization, and school absenteeism. Sclerotherapy and esophageal variceal ligation, although efficient in the prophylaxis against upper gastrointestinal bleeding, do not eliminate portal hypertension and are associated with complications. The major indications for surgery include (i) persistent bleeding following endoscopic treatment, (ii) prominent splenomegaly with symptomatic hypersplenism, (iii) growth retardation, and (iv) symptomatic portal biliopathy.[4]

In patients with hypersplenism and spontaneous bleeding, splenectomy is indicated. However, most experts suggest that concomitant splenorenal shunt should be performed to decompress the portal system. Our patient had chronic portal vein thrombosis for 10 years, but did not experience ascites or recurrent esophageal varices under prophylactic esophageal variceal ligation. A spontaneous spleno-renal shunt was observed and we preserved the spleno-renal collateral vessels around the huge spleen. Thus, collateral vessels have already formed in our patient. Further, due to the grossly enlarged spleen and engorged splenic vein, it would have been difficult to construct a splenorenal shunt in our patient. Therefore, we therefore elected to perform only splenectomy, followed by anticoagulation therapy.

CONCLUSION

Antithrombin deficiency is a possible cause of portal vein thrombosis in children and adolescents, and hypersplenism with spontaneous epistaxis is one of the major clinical manifestations of portal vein thrombosis. As in the present case, splenectomy and subsequent warfarin therapy can be considered a possible treatment option in such patients. Moreover, in patients with thrombophilc disorder treated by splenectomy, subsequent anticoagulation therapy is useful for preventing extension of portal vein thrombosis and its complication.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DISCLOSURE

The author declares that this study has no conflict of interest.

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