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Case Report

Splanchnic vein thrombosis in a young patient with congenital antithrombin III deficiency treated with segmental resection of small bowel and thrombectomy of portal vein thrombus

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A 42-year-old man, who was previously healthy, presented with progressive abdominal pain for five days. Portal vein, main portal vein, splenic vein and proximal superior mesenteric vein thromboses were observed on computed tomography scan. Antithrombin III deficiency was found following an extensive workup for hypercoagulable state. Anticoagulation therapy was immediately administered with low-molecular weight heparin and coumadin. Repeated computed tomography scan showed small intestinal wall thickening, ascites and progressive portal vein thrombosis. Emergency laparotomy was performed with small bowel segmental resection and thrombectomy of portal vein thrombosis.

Key words: Splanchnic vein thrombosis; Antithrombin deficiency; Intestine infarction

Introduction

Congenital antithrombin III deficiency is an autosomal dominant disorder. Prevalence rates for antithrombin III deficiency in the general population are between 1 in 500 and 1 in 5000. (2) Major clinical manifestation is venous thromboembolism, although some cases of arterial thrombosis have been reported. Venous thromboembolism typically occurs as lower extremity deep vein thrombosis and pulmonary embolism but can involve unusual sites, such as the inferior vena cava, or cerebral, mesenteric, hepatic or renal veins. (2)(3) Patients with antithrombin III deficiency may have resistance to therapy with unfractionated heparin or low-molecular-weight heparin and require higher dose. We describe a case of portal vein, splenic vein, superior mesenteric vein thromboses, with ischemic enterocolitis, attributable to anti-thrombin III deficiency.

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Case report

A 42-year-old Taiwanese man was admitted due to progressive abdominal pain for five days. The pain had no relationship to eating, position or stool passage and was not associated with nausea or vomiting. He had previously smoked over 6 cigarettes per day but had quit for some years. His younger brothers and younger sister all had past history of deep venous thrombosis over the lower extremities. On examination, the patient's height was 167 cm and weight was 84

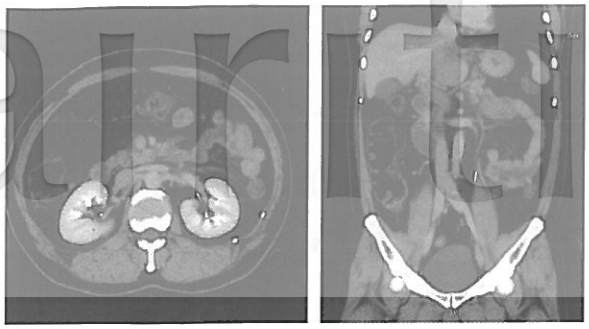


Figure.1. Day1 Computed tomography (CT) of the abdomen, with administration of contrast materials, showed thromboses of portal veins, main portal vein, splenic vein and proximal superior mesenteric vein.

Kg. His blood pressure was 126/86 mmHg, pulse 88 beats per minutes, respiratory rate 18 breaths per minutes and oxygen saturation 98% while breathing ambient air. His body temperature was 37C. The abdomen was obese and soft, with normal bowel sound and tenderness over the epigastric region without rebound or guarding. The remainder of the examination was normal. Initial investigations revealed white blood cell count of 13090 per cubic millimeter, with 65.6% granulocytes, 23.8% lymphocytes, and 9.7% monocytes. Platelet count was 169000UL. CRP was 6.04 mg/dl, fibrinogen 423.3 mg/dl and D-D dimer 7313.46 ng/ml. Liver function tests disclosed ALT of 47 IU/L (normal range 3-37) and total bilirubin of 2.23 mg/dl (normal range 0.2-1.2). The other liver function tests, i.e., amylase and lipase, were normal. The results of renal function tests and the levels of electrolytes and glucose were also all normal. Computed tomography (CT) of the abdomen, with the administration of contrast materials, showed thromboses of portal veins, main portal vein, splenic vein and proximal superior mesenteric vein. (Fig. 1). He was treated with intravenous fluids and analgesia and the pain and tenderness lessened. Warfarin and low molecular heparin were administered. On the second day, serology for hepatitis B and C was negative. Tumor markers, including APF, CEA, CA125 and CA199, were all within normal limits. C3, C4, antinuclear antibody and antinuclear cardiolipin antibody were negative. On the third day, abdominal MRI was performed and intra-arterial thrombolysis via superior mesenteric artery with diluted thrombolytic agent (urokinase) by continuous drip was planned. However, on the fourth day, abdominal pain dramatically worsened and abdominal ultrasonography revealed small intestinal distension, ascites and positive peritoneal sign. Mild fever and tachycardia were recorded. Metabolic acidosis was not observed based on the results of laboratory studies. However, the white blood cell count was elevated to 18790 per cubic millimeter, with 83% granulocytes, 7% lymphocytes, and 8% monocytes. The platelet count was 227000UL. CRP was 16.1 mg/dl. Other laboratory data including liver function and renal function tests were normal. Broad-spectrum antibiotics were administered. An emergency CT of the abdomen was performed on the fifth day, which showed extensive thrombosis with highly suspicious segmental ischemic small bowel and new onset ascites (Fig.2). On the basis of clinical presentation and radiologic findings, laparotomy was performed. Intraoperatively, mesenteric venous thrombosis with small intestinal infarction was found. Resection of small intestine was performed. The pathology report confirmed hemorrhagic necrosis of mucosa and submucosa of small intestine. The results of thrombophilia tests before the laparotomy were as follows: antithrombin-III 47.8 % (78-125%), protein S 80.8% (60-130%) and protein C 76.4% (70-140%). Congenital antithrombin III deficiency was diagnosed after exclusion of the acquired etiology and confirmed

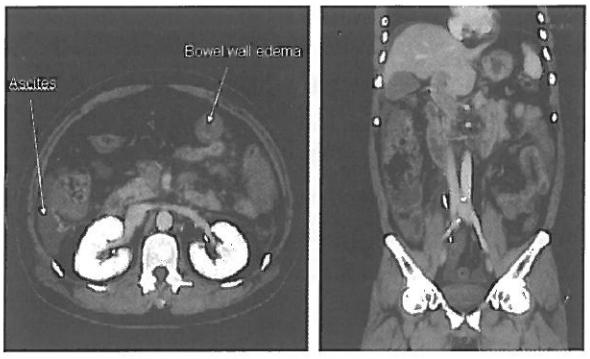
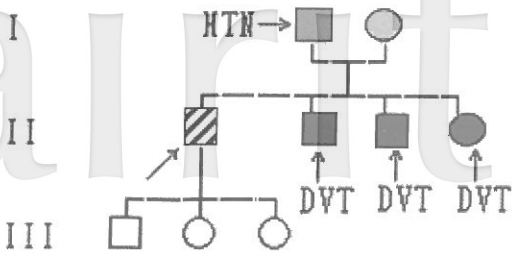


Figure.2. Day5 Computed tomography (CT) of the abdomen, with administration of contrast materials, showed extensive thrombosis with small intestinal wall edema and new onset ascites.



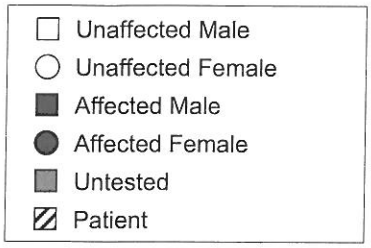


Figure.3. Family pedigree of the patient

by family history of venous thromboembolism. (Fig. 3). The patient's postoperative course was smooth and anti-coagulation with low molecular weight heparin was continued throughout his admission to the intensive care unit. Long term oral factor Xa inhibitor was prescribed after discharge. Repeat antithrombin III values one, two, and six months after surgery were 38.9%, 46.6% and 55%, respectively, and the patient remained clinically well at the time of this case report.

Discussion

Clinical presentation in this case included acute portal vein, superior mesenteric vein and splenic vein thromboses. This patient had no prior history of thrombotic events. Antithrombin activity levels and family history confirmed the diagnosis of primary antithrombin III deficiency. Antithrombin III is a potent inactivator of thrombin and Factor Xa and, thereby, regulates thrombin formation. Antithrombin III deficiency accounts for 2% of patients with venous thrombotic episodes. (1). Association with arterial thrombosis is rare. Thrombotic manifestations of congenital antithrombin III deficiency usually develop between the ages of 15 and 40. (2) The diagnosis of congenital antithrombin III deficiency is only established after acquired causes have been excluded and repeat antithrombin III testing after the acute episode has resolved. Most patients with inherited heterozygous antithrombin III deficiency have antithrombin III activity levels in the range of 35-70%. (2)(3). Whether the risk for developing a venous thromboembolism event correlates with the decrease in antithrombin activity has not been investigated.(3) The deficiency usually includes lower extremity deep venous thrombosis, pulmonary embolism, or thromboses of unusual sites, such as the interior vena cava or mesenteric, renal, or cerebral veins. (2)(3)

The initial management of venous thromboembolism in patients with antithrombin III deficiency is similar to that in patients without antithrombin III deficiency. Patients with very low antithrombin level may have resistance to therapy with heparin and require higher heparin doses to achieve therapeutic activated partial thromboplastin time. Patients receiving antithrombin replacement therapy should be monitored using antithrombin functional assays to ensure adequate antithrombin concentration. (3) No guidelines exist regarding when to use antithrombin concentrates. Intravenous anticoagulation therapy should be started immediately. Replacement with alternative anticoagulant has been reported including with direct thrombin inhibitor (argatroban, lepirudin, bivalirudin) and fondaparinux. Direct thrombin inhibitors work independently of antithrombin. In a previous case report, successful anticoagulation was achieved with argatroban. (4) Argatroban administration may delay antithrombin consumption and increase antithrombin activity, leading to rapid improvement of thrombosis. (4)

Thrombolytic therapy with streptokinase, urokinase and tissue plasminogen activator has been used in hemodynamically stable patients with splanchnic vein thrombosis. Various routes for infusion of thrombolytic agents have been described, including indirect trans-arterial infusion and direct to the portal vein via percutaneous transhepatic or transjugular-intrahepatic approaches. The decision to operate is dependent on the presence of peritoneal signs and/or systemic

toxicity, indicating the strong possibility of bowel infarction. Survival rates are 30% to 50% for patients undergoing surgery and resection. (5)

In our patient, we used low molecular weight heparin, as well as planned for thrombolytic therapy. However, the disease progressed four days after anticoagulation therapy. A repeat abdominal CT scan revealed extensive portal vein thrombosis, bowel wall edema and new onset ascites. CRP was elevated to 16.1 mg/dl. Emergent surgery to remove and repair the necrotic bowel was undertaken. Low-molecular weight heparin may not provide effective anticoagulation in patients with antithrombin III deficiency, since it needs antithrombin for activity. Timely initiation of alternative anticoagulant therapy should be considered to minimize the damage in patients who do not respond to unfractionated or low-molecular-weight heparin therapy. Direct thrombin inhibitor may be a suitable choice. Another explanation for the extensive thrombosis in this patient may be that arterial vasospasm persists after temporary venous obstruction relief, which causes increased intestinal wall tension, secondary arterial thrombosis and intestinal infarction (6)

Four members of this patient's family were diagnosed with antithrombin III deficiency. Among them, three had a history of deep venous thrombosis. Only our patient developed splachnic venous thrombosis with infarction. The pathophysiologic mechanisms of deep venous thrombosis and spanchnic vein thrombosis differ. In contrast to the lower extremities vasculature, the splanchnic vessels do not have venous valves which are involved in the pathogenesis of deep vein thrombosis. (7) Endothelium structure, gastrointestinal bacterial components and arterial vasospasm may be related to the development of rare splanchnic venous thrombosis. (6)(7) Some local factors such as recent splenectomy or pancreatitis may postulate for acute thrombus formation. (6) In addition, venous thromboembolism is a multifactorial disease that is rarely caused by a single risk factor.(7) A predisposing feature or a temporary risk factor; such as local intra-abdominal problems, which we did not find in this patient, may trigger the development of splanchnic venous thrombosis.

Ideally, a patient should undergo repeat antithrombin functional assay at least 3 months after the event to determine potential antithrombin deficiency. (2). Acute thrombosis and anticoagulant therapy can transiently influence antithrombin levels. No patient should be diagnosed based on a single abnormal test result, no matter how profound the antithrombin deficiency. (2)(3) It is important to perform repeat testing if a low activity level is found. Testing of first-degree relatives may be helpful for diagnosis of congenital antithrombin III deficiency. There is no indication that patients with antithrombin deficiency have a higher recurrence rate while taking standard intensity oral anticoagulants. Thus, an International Normalized Ratio target of 2.0-3.0 is appropriate. (2,3). It is noteworthy that, despite long-term anticoagulation, a substantial risk of recurrence of 2.7% per year exists. (3)

Acute splanchnic vein thrombosis is a life-threatening condition requiring rapid diagnosis and aggressive treatment. The finding of hereditary thrombophilia may influence the choice of treatment and long-term management. Patients with thrombosis events due to congenital antithrombin III deficiency should receive lifelong oral anticoagulant therapy.

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