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Bacteroides fragilis bacteremia associated with portal vein and superior mesentery vein thrombosis secondary to antithrombin III and protein C deficiency: a case report

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Hypercoagulability is one of the causes of portal vein and superior mesentery vein thrombosis. We report a case of *Bacteroides fragilis* bacteremia associated with portal vein and superior mesentery vein thrombosis secondary to antithrombin III and protein C deficiency. The patient presented with high fever for more than 3 weeks. Abdominal sonography revealed a liver cyst of 1.7 cm in diameter over segment 4 and a renal stone of 0.7 cm in size over the lower portion of the right kidney but no evidence of hydronephrosis. Elevation of liver enzymes was also noted. Intermittent fever was noted despite treatment with ceftriaxone and doxycycline. On Day 15 of hospitalization, blood culture revealed *B. fragilis*, which prompted further investigation of the source of intraabdominal and pelvic infection. Abdominal computed tomography revealed portal vein and superior mesentery vein thrombosis. Endoscopic studies of the gastrointestinal tract showed no tumor or diverticulum. Study of coagulation factors disclosed deficiency of antithrombin III and protein C. Clinicians should remain aware of the need to promptly search for a portal or mesentery vein thrombosis in cases of *Bacteroides* bacteremia of unknown origin.

Key words: Antithrombin III, protein C deficiency, bacteremia, *Bacteroides fragilis*, portal vein thrombosis

Septic portal vein thrombosis, also called septic pylephlebitis, is a well-known but uncommon entity with various manifestations. It has many causes including appendicitis, diverticulitis, cholecystitis, pancreatitis, inflammatory bowel disease, abdominal and pelvic infections, and tumors [1]. In addition, hypercoagulable state associated with malignancy or clotting factor deficiency may also be the inciting cause [2-4]. Here we report a case of *Bacteroides fragilis* bacteremia associated with portal vein and superior mesentery vein thrombosis secondary to deficiency of antithrombin III and protein C.

Case Report

A 43-year-old man had low-grade fever and loose stool starting 8 days prior to admission. On the morning after the onset of symptoms, chills, fever, general weakness, and shortness of breath developed. He visited the emergency room of a hospital at Kinmen island where a body temperature of 39°C was noted. He received symptomatic treatment and was sent back home. However, attacks of fever and chills continued every day afterwards, and poor appetite was also noted. He was admitted to the local hospital 3 days after the onset of fever and treated with doxycycline and amoxicillin. Ceftriaxone was substituted for amoxicillin 3 days after his symptoms worsened. He was then transferred to Tri-Service General Hospital. The patient had been admitted due to jaundice 6 years before. He had a habit of consuming 200 mL of liquor per week for the past 10 years. Family history and other personal history were unremarkable. After admission, physical examination revealed an ill-looking patient with mildly icteric sclera. Laboratory studies showed the following values: hemoglobin 14.5 g/dL; leukocyte count 10 130 /mm^3 with a differential count of 68% neutrophils and 19% lymphocytes; platelet count 129 000 /mm^3; aspartate transaminase 36 U/L (normal range, 10-34 U/L); alanine transaminase 63 U/L (normal range, 7-33 U/L); total bilirubin 1.5 mg/dL (normal range, 0.2-1.3 mg/dL); urea nitrogen 8 mg/dL; and creatinine 1.1 mg/dL. Anti-HBs and Anti-HBc antibodies were positive.

On admission, doxycycline was given after performing blood cultures and serologic studies. Fever subsided gradually, but relapsed 4 days after admission. Abdominal distension persisted and ceftriaxone was added. Weil-Felix reaction was negative. Abdominal

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sonography revealed a liver cyst 1.7 cm in diameter over segment 4 and a renal stone 0.7 cm in size over the lower portion of the right kidney but no evidence of hydronephrosis. Fever improved after the administration of ceftriaxone but relapsed (up to 40°C) again on the 6th day of ceftriaxone administration. On the 15th hospital day, blood culture yielded *B. fragilis*. The clinical course improved dramatically after the administration of metronidazole. Computed tomography of the abdomen and pelvis revealed right portal vein thrombosis with downward extension into the superior mesentery vein, a liver cyst around 2 cm in diameter over segment 4, prominence of the spleen, superior mesentery vein thrombosis with increased fat density over the uncinate process of the pancreas, mild ascites in the pelvis, normal appearance of small bowel and colon, and no evidence of appendicitis or diverticulitis (Figs. 1 and 2). Endoscopic study of the gastrointestinal tract showed no tumor or diverticulum.

Studies of coagulation factors showed that antithrombin III was 64% (normal range, 80%-120%), protein C was 40% (normal range, 60%-120%), and protein S was 81% (normal range, 60%-120%). *B. fragilis* bacteremia in association with portal vein and superior mesentery vein thrombosis secondary to antithrombin III and protein C deficiency was diagnosed. Anticoagulation therapy was administrated. The patient was discharged after 18 days of treatment with metronidazole (500 mg intravenously every 6 h). He was well at 3 months after discharge.

Discussion

This patient presented with fever of unknown origin. Blood culture yielded *B. fragilis* 2 weeks later. Further studies identified portal vein thrombosis and superior mesentery vein thrombosis, and deficiency of antithrombin III and protein C.

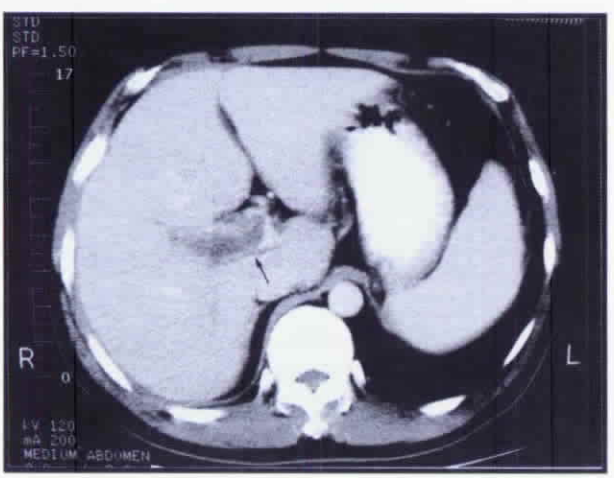

Fig. 1. Contrast-enhanced computed tomography scan of the abdomen showing right lobe portal vein thrombosis (arrow).

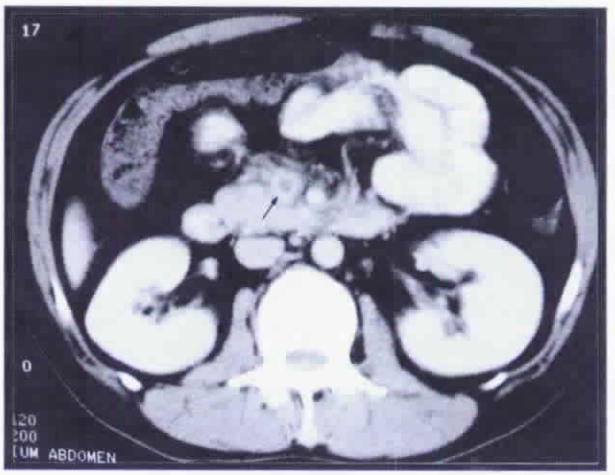

Fig. 2. Contrast-enhanced computed tomography scan of the abdomen showing superior mesentery vein thrombosis (arrow).

The clinical features of pylephlebitis are generally nonspecific. Patients usually present with fever, chills, malaise, diarrhea, and right upper quadrant tenderness [1]. In the late stages of disease, hepatomegaly is present in one half of cases and splenomegaly in 10% to 25% of cases [1]. Jaundice may be present and abnormal liver function is present in only 25% of cases [1]. Leukocytosis is frequently present, although it may be absent in neutropenic patients with hematologic malignancies [1,5]. Plain abdominal radiographs are generally nondiagnostic unless air is seen in the portal veins [6]. Ultrasound with color flow Doppler is a sensitive test for the diagnosis of portal vein thrombosis [6]. Sonographic features of portal vein thrombosis include echogenic material within the lumen of the vein and enlargement of the thrombosed segment of the vein [6]. However, in this patient, the abdominal sonogram at admission did not reveal evidence of thrombosis of the portal vein or the mesentery vein. Mathieu *et al* [7] found that computed tomography with contrast enhancement can demonstrate portal vein thrombus and reveal concomitant intraabdominal process such as abscesses and tumors. They also reported that patients with neoplasms constituted up to 30% of those with mesenteric venous thrombosis.

Bacteroides spp., particularly *B. fragilis*, are the organisms most frequently recovered from intra-abdominal abscesses (intraperitoneal and visceral), as well as from peritonitis occurring after a breach of the integrity of the intestinal mucosa [8]. Plemmons *et al*

[9] reported that bacteremia (often polymicrobial) was present in 88% of the patients with pylephlebitis. The most common blood isolate was *B. fragilis* [9]. Other frequently identified organisms include *Escherichia coli*, *Proteus vulgaris*, *Aerobacter aerogenes*, and *Enterococcus faecalis*. Staphylococci are recovered in nearly half the cases in which organisms are found [1,10]. Plemmons *et al* [9] found that the overall mortality was 32%, but most of the patients who died had severe sepsis prior to the initiation of antibiotic therapy. *Bacteroides* bacteremia of unknown origin should prompt the search for a pylephlebitis, that is, portal or mesenteric vein thrombosis [11].

The presence of portal and mesentery vein occlusion in primary hypercoagulable states, that is, clotting factor deficiencies or abnormalities, is well described and can occur in the absence of a septic focus [2]. Thrombotic complications due to antithrombin III abnormalities were first reported in 1965 [12]. Antithrombin III is a predominant and naturally occurring inhibitor of serine protease-generated blood coagulation, and hereditary antithrombin III deficiency is a rare autosomal-dominant disorder characterized by recurrent deep thrombosis and pulmonary embolism, as well as venous thrombosis such as that of the inferior mesentery vein. In Japan, antithrombin III deficiency induced portal vein thrombosis was first reported in 1995 [13]. Protein C is a vitamin K-dependent zymogen synthesized in the liver. Hereditary protein C deficiency is usually transmitted as an autosomal dominant trait with varying penetrance [14,15]. Both homozygous and heterozygous protein C deficiency have been associated with thrombotic phenomena [15,16]. Homozygous protein C deficiency is fatal in early life, although patients with milder symptoms or late onset have been reported [14]. Acquired deficiency of protein C may be encountered in patients with disseminated intravascular coagu-lation or liver diseases. We did not study coagulation factors in the family members of this patient although they appeared to be healthy.

Luzzato *et al* [17] reported 15% of patients with cancer have clinical thromboses and about 50% have thromboses on autopsy. Myeloproliferative disorders are described as a major source of portal vein thrombosis in many series. Decreased levels of protein coagulation factors, circulating anticoagulants, and platelet numbers and function changes have all been described. Factors I, V, VII:C, IX, and XI have all been reported as being elevated and implicated in hypercoagulability in patients with neoplasms [2].

Early diagnosis and treatment of pylephlebitis is critical. If left untreated, it may progress to involve the mesenteric and splenic vein, leading to bowel ischemic infarction, hepatic abscess, and death [18]. Strategies for the treatment of pylephlebitis should include awareness of the need for early recognition and management of intraabdominal infections and the use of appropriate antibiotic therapy. The newer penicillins and cephalosporins combined with an aminoglycoside are preferred [1]. Addition of metronidazole may be necessary if anaerobes are suspected [1].

The role of anticoagulation in the treatment of pylephlebitis is controversial [19]. Anticoagulation is considered to be indicated for patients with a documented coagulation disorder or with hypercoagulable states associated with neoplasm or hematological disease. Superior or inferior mesentery vein involvement in patients with normal clotting function may also be an indication for anticoagulation therapy. Anticoagulation in patients with thrombus isolated to the portal vein and normal clotting function may be unnecessary [19].

B. fragilis bacteremia of unknown source should alert the clinician to search for an intraabdominal focus, such as portal vein and mesentery vein thrombosis. Etiology of the underlying hypercoagulable disorder should be further studied.

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