Mesenteric and portal vein thrombosis associated with hyperhomocysteinemia and heterozygosity for factor V Leiden mutation

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A 79-year-old man was hospitalized because of worsening upper abdominal pain which started two days before admission and was continuously present. His personal and family history was uneventful, he did not smoke and denied toxic habits or using any medications, including over-the-counter medications, herbal remedies or any vitamin supplements.

At admission, the patient was fully alert and oriented, afebrile, but distressed due to severe abdominal pain; his vital parameters were normal. On physical examination, there was abdominal guarding and rebound with hypoactive bowel sounds, rectal examination revealed no masses, liver and spleen were normal, and a stool sample was guaiac negative. The remaining physical examination was unrevealing.

Laboratory tests showed a leukocyte count of 12×10^9 cells/L, 90% of which were neutrophils; electrolytes, amylase, lipase, and liver and renal function tests were normal. An electrocardiogram and a chest X-ray were also normal. A color Doppler ultrasonography and an emergency contrast-enhanced computed tomography disclosed thrombosis with complete occlusion of both intra- and extra-hepatic branches of the portal vein and partial obstruction of the superior mesenteric vein; abundant intraperitoneal fluid was observed with no collateral venous vessels or any direct or indirect evidence of transmural intestinal infarction. Endoscopy of both the upper and lower gastrointestinal tract was negative.

A thrombophilic screening showed extremely elevated blood levels of homocysteine (91 and 88 µmol/L on the 1st and 5th d of hospital stay; normal values < 15); search for antiphospholipid antibody and lupus anticoagulant was negative and blood levels of antithrombin and protein C and S were normal. Circulating vitamin B12, folate, and homocysteine concentrations were also normal.

The patient was treated with bowel rest, intravenous fluids, antibiotics, and enoxaparin (100 IU/kg twice daily) and he reported complete recovery from abdominal pain on the 2nd d after admission. We added folate and vitamin B12 to his regimen and the patient was discharged free of symptoms on the 15th d; at this time blood homocysteine was 75 µmol/L. At a follow-up visit 2 mo later, while still on enoxaparin and folate, he was doing well with no clinical or laboratory evidence of active thrombosis. We received the results of molecular studies performed on blood samples taken at admission, which showed heterozygosity for factor V Leiden mutation; search for prothrombin G20210A and MTHFR C677T mutations was negative. Blood homocysteine concentration was <15 µmol/L and imaging studies showed normal flow in the superior mesenteric vein along with a complete occlusion of the portal vein, which was unchanged; there were venous collaterals in the hilar area of the liver. Anticoagulant therapy was shifted to warfarin with a targeted international normalized ratio (INR) 2-3 and, when last seen six months after discharge, the patient was asymptomatic with INR 2.6, normal blood homocysteine and no active thrombosis.

Combined thrombosis involving one mesenteric vein and the portal vein is rare, difficult to diagnose and can be fatal, with diffuse abdominal pain, distension and tenderness being the most common symptoms and physical findings [1,2]. Stricture and bowel necrosis with peritonitis due to transmural intestinal infarction may complicate the course and are important causes of mortality among those patients [1,3]. The early initiation of anticoagulation using unfractionated heparin or low-dose warfarin is crucial. The finding of hyperhomocysteinemia and factor V Leiden heterozygosity predicted a poor outcome in this patient; however, comparison with a control group of similar patients is needed to confirm our findings.

Key words: Portal; Mesenteric; Thrombosis hyperhomocysteinemia; Factor V Leiden heterozygosity

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molecular weight heparin heparin has been shown to minimize the risk of serious complications, nonetheless spontaneous resolution of extensive superior mesenteric and portal vein thrombosis has been also reported. Common causes include liver disease, pancreatitis, inflammatory bowel disease, cancer, sepsis, an underlying myeloproliferative disorder, surgery or trauma, and systemic thrombophilia. The association of hyperhomocysteinemia with extremely elevated blood levels of homocysteine and heterozygosity for factor V Leiden mutation was the cause of such a severe abdominal venous thrombosis in the case we report on. No precipitating events of venous thromboembolism were recognized and the patient had none of the abdominal disorders that may trigger thrombosis of the mesenteric veins or the portal vein or any other inherited or acquired prothrombotic condition. Available data consistently suggest a moderate, positive, and dose-related relationship between blood levels of homocysteine and the risk of portal or mesenteric venous thrombosis. However, almost all the patients so far described in whom portal or mesenteric venous thrombosis was linked with hyperhomocysteinemia also had at least one additional prothrombotic disorder. Our Medline search yielded no case of combined mesenteric-portal vein thrombosis associated only with hyperhomocysteinemia and no other risk factors for venous thromboembolism. It is not surprising in our opinion that, despite being heterozygous for factor V Leiden mutation, our patient did not experience any thrombotic disorders until severe hyperhomocysteinemia developed. This adds weight to the relevance of hyperhomocysteinemia in the pathophysiological mechanisms as a trigger of venous thrombosis in this case.

The mechanisms of hyperhomocysteinemia in our patient remain unclear. The patient was not exposed before presentation to any folate or vitamin B6 antagonists, i.e. methotrexate, phenytoin, estrogens, or theophylline, and we ruled out upon history and clinical examination atherosclerosis, smoking or elevated blood pressure, which are also associated with raised circulating concentrations of homocysteine. An acquired nutritional deficiency of folate also sounds a non reliable cause. Even though blood levels of folate, vitamin B6 and vitamin B12 were normal, homocysteine concentrations returned to the normal range after eight weeks of treatment with folate and vitamin supplements. This apparent discrepancy is difficult to explain, however we could reasonably speculate that the exogenous supplementation of folate and vitamins did ultimately correct a subtle age-dependent impairment of folate metabolism.

We claim that patients with apparently unexplained combined thrombosis involving both one mesenteric vein and the portal vein should be screened for hyperhomocysteinemia. Outcome could be favorable, even in those carrying other prothrombotic conditions such as factor V Leiden mutation, with a complete recovery if appropriate treatment with anticoagulants, folate and vitamin supplements is timely started.

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