Acute occlusion of iliac artery and pulmonary thromboembolism due to hyperhomocysteinemia

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Abstract

A 48-year-old woman, without any risk factors for the peripheral arterial disease, was admitted with a history of persistent pain and paresthesia in her left leg and cyanosis in her left first toe for the duration of 1 month. She was complaining of intermittent claudication in 200 meters during the last 4 months. Investigations revealed occlusion of the abdominal aorta and left common iliac artery. During the hospitalization, she had acute deep vein thrombosis and pulmonary emboli. Laboratory tests and further investigations revealed the elevated homocysteine levels as the unique risk factor in this patient. She was discharged after successful medical therapy without any symptoms.

Introduction

The association of hyperhomocysteinemia and development of the thrombovascular disease have been known for a long time. Hyperhomocysteinemia has been identified as an independent risk factor for atherosclerosis, coronary artery disease, carotid occlusive disease, peripheral arterial occlusive disease (PAOD), and veno-occlusive disease [1]. Homocysteine is an amino acid that contains sulfur, produced by demethylation of methionine. Increases in homocysteine levels of up to 30 mmol/L (called a moderate increase) may be the result of a combination of genetic and dietary factors [2].

Numerous previous studies have provided consistent evidence that hyperhomocysteinemia is a risk factor for PAOD in men. A raised level of homocysteine has been estimated to be a greater risk factor for cardiovascular disease (20-40 fold) than an increased level of cholesterol (1-3 fold), high blood pressure (8-18 fold), or use of tobacco (3-5 fold) [2]. Here, we report a case with hyperhomocysteinemia related iliac artery thrombosis concomitant with pulmonary thromboembolism.

Case Report

A 48-year-old woman was admitted to the hospital with a history of persistent pain and paresthesia in her feet and cyanosis in her left first toe for the duration of about one month. She was complaining of intermittent claudication in 200 meters during the last 4 months. There was no history of any trauma or infection. She was not a smoker, nor was she using any drugs. Her family history was insignificant relative to premature vascular disease or any clotting diathesis. She did not have hypertension, elevated low-density lipoprotein (LDL) cholesterol levels, or diabetes.

The physical examination revealed cyanosis and reduced sensation in her left leg and paresthesia in her left first toe, which was painful with palpation. Femoral, popliteal, posterior tibial, and dorsalis pedis arteries were not palpable in her left leg. There was no evidence of an abnormal skin temperature, discoloration, or increased diameter of her legs. The cardiac examination was normal. The ankle-brachial index (ABI) was determined for both extremities; on the right side, the ABI was 1.1; and on the left side, it was 0.56. Electrocardiography was normal.

Her serum electrolytes were within normal ranges. Her serum chemistry revealed a serum creatinine concentration of 0.8 mg/dL (reference range 0.4-1.0 mg/dL), an urea level of 33 mg/dL (reference range 17-43 mg/dL), and LDL-cholesterol and triglycerides were within normal ranges. A thyroid study showed free T4 1.49 ng/dL (reference range 0.8-1.5 ng/dL).
range 0.93–1.7 ng/dL) and TSH 1.38 μIU/mL (reference range 0.27–4.2 μIU/mL).

A screen for typical clotting abnormalities was carried out. This showed that the patient had a normal platelet count, activated partial thromboplastin time, international normalized ratio (INR), thrombin time, fibrinogen, and levels of clotting Factors II, VIII, and IX. Protein C, protein S, and antithrombin III were within normal ranges. Screening tests for vasculitis syndromes and connective tissue diseases yielded negative results. Further, work-up revealed an elevated fasting homocysteine level of 23.7 μmol/L (reference range 5.5–14 μmol/L). A mutation screen of the 5,10-methylenetetrahydrofolate reductase gene revealed that the patient was heterozygous for the 677C•T sequence variant. Furthermore, a factor V Leiden mutation and G20210A mutation analysis showed negative results.

The magnetic resonance imaging angiography scan revealed partial thrombosis of the patient’s abdominal aorta, below the origin of the renal arteries, partial thrombosis of the right common iliac artery, and an occluded left common iliac artery (Figure 1). On the second day of hospitalization, she complained of chest pain with a high level of troponin (5.82 ng/ml; reference range 0-1 ng/ml). An acute coronary syndrome has thought as the cause, so an emergency coronary angiography was performed. There were no occlusions in the coronaries, and the troponin levels decreased during the following hours.

Transthoracic echocardiography showed normal left and right ventricular dimensions and function. There were no signs of ventricular hypertrophy, shunting. Transthoracic echocardiography revealed 2° tricuspid insufficiency and pulmonary artery pressure measured 40 mmHg.

A computed tomography (CT) and CT angiography of her chest showed evidence of acute thromboembolism inside the pulmonary arteries (Figure 2). A duplex ultrasound examination of the right popliteal vein revealed intraluminal thrombus.

The patient was diagnosed with moderate hyperhomocysteinemia and prescribed 5 mg of oral folic acid, 250 mg of oral Vitamin B6, and 1 mg of Vitamin B12 daily. In addition, oral warfarin was prescribed for the patient to keep levels of her INR between 2 and 3. Clinical follow-up after 3 months demonstrated that the patient’s level of homocysteine had decreased to 6 μmol/L. Impaired perfusion caused the patient’s left first toe to deteriorate significantly by the 8th week of her therapy regimen. Unfortunately, the necrotic toe had to be amputated. Furthermore, the patient experienced less pain and paresthesia in her feet and could walk a longer distance without experiencing pain.

**Discussion**

The association of hyperhomocysteinemia and the development of thrombovascular disease have been well-known for a long time. Multiple studies have identified hyperhomocysteinemia as an independent risk factor for atherosclerosis, myocardial infarction, carotid occlusive disease, cerebrovascular disease, coronary artery disease, PAOD, and veno-occlusive disease [3].

It has been shown that the adverse effects of elevated levels of homocysteine to the vascular tree are mediated through endothelial dysfunction, which is usually an early manifestation of atherosclerosis. On the other hand, animal studies have demonstrated that homocysteine infusions can lead to
patchy necrosis of the endothelium. Recent evidence also suggests that elevated levels of homocysteine can reduce the bioavailability of nitric oxide which can decrease nitric oxide that is dependent on flow-mediated vasodilatation. In vitro data have shown that free homocysteine inactivates nitric oxide, promoting the generation of oxygen-derived free radicals [4].

Venous thrombosis is an important cause of morbidity and mortality. Most cases of venous thrombosis arise due to prolonged immobilization, major surgery, trauma, or cancer. It has been also suggested that elevated total plasma homocysteine levels are associated with the risk of venous thrombosis [5]. A meta-analysis of prospective and retrospective epidemiological studies showed that there is a 27% higher risk of venous thrombosis with a 5 µmol/L increase in homocysteine. This observation in prospective studies was only half as extreme as that in retrospective studies [6]. In the case presented, the patient had acute thrombosis of the popliteal vein and pulmonary emboli during the hospitalization. This may be attributed to immobilization of the patient due to peripheral arterial disease and also due to hyperhomocysteinemia.

The lack of risk factors for atherosclerosis as well as the absence of evidence of hypercoagulability directed our attention toward a newly emerging and easily reversible risk factor for occlusive vascular disease, hyperhomocysteinemia. In the present case, significant coagulation disorders and vasculitis syndromes were excluded in the laboratory work-up. Our patient had a homocysteine level of 23.7 µmol/L. A moderately elevated level of total homocysteine (between 15 and 100 µmol/L) can be due to genetic defects of enzymes participating in the metabolism of homocysteine [3]. Other conditions that may be associated with high levels are advanced age, hypothyroidism, impaired renal function, systemic lupus erythematosus, and certain drugs such as theophylline, methotrexate, and L-dopa [7]. In the absence of acquired causes such as deficiencies of folate, Vitamin B6, or Vitamin B12; use of certain drugs that interfere with the metabolism of these vitamins; a history of chronic renal insufficiency or a history of other systemic disorders, hyperhomocysteinemia may be caused by some hereditary enzymatic defect in homocysteine metabolism. In our patient, genetic analysis to identify enzymatic defects in homocysteine metabolism was conducted. It revealed that the patient was heterozygous for the 677C>T sequence variant.

In young patients, without well-known risk factors for cardiovascular events, hyperhomocysteinemia can be identified as the underlying cause of thromboembolic complications. In such patients, screening for hyperhomocysteinemia might be appropriate after excluding the common causes of venous and arterial thromboembolism. Patients without known risks, but who have occlusions in both venous and arterial systems, should be evaluated for genetic and hematological systems that may cause hyperhomocysteinemia and thrombosis. This will improve a patient’s prognosis and will be extremely important for their therapy, as well.

References