LETTER TO THE EDITOR

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Thrombophilia after total gastrectomy for morbid obesity

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To the Editor,

Thrombophilia is a group of hereditary and acquired conditions which results in a propensity for repeated thrombi formation in the veins or arteries. Several conditions are involved in thrombophilia. Among them, high plasma homocysteine levels are associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism. Elevated homocysteine levels can be genetic or acquired. The most common genetic disorder associated with hyperhomocysteinemia is C677T substitution on the methylenetetrahydrofolate reductase (MTHFR) gene. Acquired hyperhomocysteinemia can be caused by renal failure, hypothyroidism, and vitamin B_{12}, vitamin B_6, or folate deficiency. Serum levels of homocysteine are elevated in patients with vitamin B12 deficiency because of the role of vitamin B_{12} in homocysteine metabolism. Vitamin B_{12} deficiency is a common long term sequelae of total gastrectomy because it can only be absorbed when intrinsic factor is released from the gastric parietal cells of the gastric body and fundus. This report describes a case of acquired thrombophilia with recurrent venous thromboembolism which developed after total gastrectomy for morbid obesity.

A 32-year-old Arab male was referred for evaluation of recurrent venous thromboembolism. In 2011, he had total gastrectomy for morbid obesity. Following the surgery, he was admitted repeatedly for recurrent venous thromboembolism. He was admitted on April 5, 2012, for extensive DVT, pulmonary thromboembolism (PTE) and thrombosis of the inferior vena cava. He was started on anticoagulation with enoxaparin and warfarin. He was then readmitted on April 29, 2012 with chest pain and dyspnea. A computed tomography scan of the chest showed right sided PTE. An inferior vena cava (IVC) filter was inserted on April 30, 2012. In May 2012 he was noted to have an international normalization ratio (INR) of 4.3 and his warfarin prescription was stopped for 2 days. He had several episodes of chest pain on May 27, 2012 and the low molecular weight heparin and warfarin was restarted.

On arrival to the reporting hospital, his physical examination was unremarkable. His height and body weight was 175.1 cm and 99.6 kg, respectively (body mass index, 32.5 kg/m^2). He was a current smoker. His mother had a history of thrombosis during pregnancy. All routine laboratory tests were within the reference ranges, except for a serum vitamin B12 of 65 pg/mL (reference range, 180 to 914) and a homocysteine level of 21.9 μmol/L (reference range, 3.0 to 15.0). Screening for inherited

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thrombophilia was negative. No deficiencies in protein C, protein S, and protein V activity were detected. Factor V Leiden and prothrombin gene mutation testing were negative. MTHFR C667T was wild-type and a MTHFR A1298C heterozygous mutation, a common polymorphism, was detected. Negative results for intrinsic factor and gastric parietal cell antibodies were noted. Screening for paroxysmal nocturnal hemoglobinuria and Coombs' test was negative. A coagulation factor assay and testing of plasminogen activator inhibitor-1 were normal. Screening for autoimmune disease including anti-cardiolipin antibody, anti-nuclear antibody, and anti-ds antibody were also negative. As he did not know the specific type of surgery he underwent in his country, an upper gastrointestinal series was done to check the anatomy of the stomach. The upper gastrointestinal series showed that the patient had a total gastrectomy. Our patient had no apparent risk factors for venous thrombosis other than the hyperhomocysteinemia associated with vitamin B12 deficiency. Recurrent thrombosis caused by hyperhomocysteinemia was highly suspected. Vitamin B12 replacement with anticoagulation was initiated intramuscularly at a dose of 1,000 μg every other day. Serum homocysteine levels fell to 13.7 μmol/L from an initial level of 21.9 μmol/mL in 2 weeks after the initiation of vitamin replacement. However, after an initial decrease in the homocysteine level, there was no further response. This could be expla ined by the role of folic acid as a cofactor in the conversion of homocysteine to methionine. Folic acid and vitamin B6 oral supplementation was added to his regimen, with a subsequent decrease in the homocysteine level to around 10 mmol/L with some fluctuation. There has been no further thrombosis in this patient up to the time of this writing.

Multiple risk factors are associated with thrombosis. There is a large body of evidence implicating hyperhomocysteinemia as a risk factor for vascular disease. Hyperhomocysteinemia promotes thrombosis by damaging the vascular endothelium. It stimulates thromboxane-A_2 synthesis and inhibits prostacyclin effects which activates platelet aggregation. It also promotes local thrombin formation and impairs fibrinolysis [1]. The plasma level of total homocysteine is affected by many factors such as age, smoking, drugs, and folate, vitamin B12 levels [2]. Vitamin B12 deficiency in particular is a common cause of hyperhomocysteinemia. The results of multivariate analysis demonstrate that serum vitamin B12 is related to thromboembolism (relative risk, 0.998; confidence interval, 0.997 to 0.999) [3].

In this case, the patient suffered from recurrent thrombosis due to hyperhomocysteinemia after total gastrectomy. The hyperhomocysteinemia likely resulted from vitamin B12 deficiency after total gastrectomy, which is a known complication of the surgery. The risk of developing vitamin B12 deficiency increases as the extent of resection increases [4]. Because a total gastrectomy depletes intrinsic factor, which is required for absorption of vitamin B12 at the distal ileum, intramuscular injection has been suggested as the treatment of choice for preventing vitamin B12 deficiency after total gastrectomy. The patient was given antithrombotic therapy which consisted of heparin followed by oral anticoagulants to prevent recurrent thrombosis. However, it was very difficult to maintain a therapeutic INR in this patient, which may be related to the impaired absorption of anticoagulants caused by the total gastrectomy. Thus, the patient was administered both heparin subcutaneously as well as oral warfarin. Homocysteine rises with either folate or vitamin B12 deficiency because there are two pathways in homocysteine metabolism. The first pathway involves remethylation to methionine, which requires folate and vitamin B12. The second pathway involves transsulfuration to cystathionine, which requires pyridoxal-5'-phosphate, the coenzyme form of vitamin B6 [5]. Therefore, low vitamin B6 and folate levels are also associated with an increased risk of venous thrombosis. The primary physician should consider the role of both folate and vitamin B6 as cofactors in homocysteine metabolism. Elevated homocysteine can be lowered with supplementation of vitamin B12, folic acid, vitamin B6. However, results from randomized clinical trials have failed to translate convincingly lowering homocysteine into improved clinical outcomes for the secondary prevention of cardiovascular disease. However, because most of the randomized intervention trials published to date have included patients with only mildly elevated homocysteine levels, the role of combined vitamin supplementation should be clarified in patients with moderately or severely elevated homocysteine levels in future studies.

In conclusion, for patients with acquired thrombophilia, serum homocysteine levels should be measured to avoid missing this curable but potentially life-threat-

ening disease. In addition, parenteral vitamin B12 should be administered for the treatment of hyperhomocysteinemia resulting from vitamin B12 deficiency, and additional supplementation of folate and vitamin B6 should also be considered to improve impaired homocysteine metabolism.

Keywords: Hyperhomocysteinemia; Vitamin B12 deficiency; Thrombophilia

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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