Deep Vein Thrombosis Associated with Marked Hyperhomocysteinemia and Active Pulmonary Tuberculosis

Chiung-Zuan Chiu¹,² and Kou-Gi Shyu¹,²,³

We report a 32-year-old male patient presented with acute deep vein thrombosis of his right leg after recent onset of active pulmonary tuberculosis. Marked hyperhomocysteinemia (> 50 \text{nmol/L}), folic acid deficiency, and abnormal coagulation profiles (elevations of fibrinogen and fibrinogen degradation product) were noted after a series of work-ups. After treatment with low-molecular-weight heparin, deep vein thrombosis improved. Serum homocysteine level returned to normal after folic acid and vitamin B12 supplementation for 2 months. After therapy with four-combined anti-tuberculosis drugs for 9 months, the pulmonary tuberculosis subsided. In the present case report, the cause of hyperhomocysteinemia may be related to folic acid deficiency and chronic renal insufficiency.

Key Words: Deep vein thrombosis • Hyperhomocysteinemia • Pulmonary tuberculosis • Folic acid deficiency • Hypercoagulable state

INTRODUCTION

Deep vein thrombosis is a disease resulted from different congenital or acquired prothrombotic disorders and is not uncommon to be associated with other chronic illness in clinical settings. In advanced cases of deep vein thrombosis, pulmonary embolism may develop and become life-threatening Hyperhomocysteinemia, a prothrombotic condition, is a well-known risk factor of venous thrombosis and pulmonary thromboembolism. Severe pulmonary tuberculosis can induce a hypercoagulable state and therefore may result in deep vein thrombosis. Pulmonary tuberculosis is endemic in Taiwan. The association of hyperhomocysteinemia and pulmonary tuberculosis in deep vein thrombosis has not previously been reported. Here, we report a case of deep vein thrombosis associated with marked hyperhomocysteinemia and active pulmonary tuberculosis.

CASE REPORT

A 32-year-old man presented with a history of increasing swelling and tenderness of his right leg for 1 week. He was a smoker (one pack of cigarettes per day for 5 years) and had clinical history of chronic glomerulonephritis with impaired renal function noted since age 10. Body weight loss up to 10 kg within 6 months with productive cough was noted 2 weeks before his leg swelling, and active pulmonary tuberculosis was diagnosed by chest radiography and positive acid-fast stain in his sputum. Impaired renal function (BUN, 30 mg/dl; creatinine, 2.9 mg/dl; creatinine clearance rate, 20.54 mL/min/1.73 m²) with proteinuria (24-hour urine protein, 2940 mg) and hematuria were noted at the same time. He started to receive four-combined anti-tuberculosis therapy (isoniazid 300 mg, rifampicin 600 mg,
pyrazinamide 1000 mg, and ethambutol 800 mg per day) with pyridoxine (10 mg per day). His daily activity was normal, without any history of bed-ridden state or surgery. No trauma history was noted. He did not take antacid. He visited our emergency department due to progressive swelling and tenderness of his right leg. On examination, he was ill-looking and distressed. He had a blood pressure of 120/70 mmHg with a rapid heart rate (88 beats per minute) and a respiratory rate of 16 breaths per minute. The heart sound was normal, and bilateral breathing sounds were clear. The electrocardiogram revealed normal sinus rhythm without ST-T change, and chest X-ray showed active pulmonary tuberculosis (Figure 1). Leg duplex revealed venous thrombus and venography of the lower extremities showed deep vein thrombosis involving the right lower limb (Figure 2). Under the impression of deep vein thrombosis and active pulmonary tuberculosis, administration of low-molecular-weight heparin (1 mg/kg twice daily) was begun. Initial laboratory tests in the emergency department revealed leucocytosis (white counts, $11.59 \times 10^3/\mu l$; normal, $3.8-10.0 \times 10^3/\mu l$), normochromic anemia (hemoglobin, 10.6 gm/dl; normal, 13-18 gm/dl), and normal platelet counts. A series of work-ups revealed marked hyperhomocysteinemia (> 50 $\mu$mol/L; normal, 4.45-12.42 $\mu$mol/L), low folic acid level (2.4 ng/mL; normal, 4.2-19.9 ng/mL), normal vitamin B12 level, low serum albumin level (2.5 gm/dl; normal, 3.4-4.8 gm/dl), high C reactive protein level (8.64 mg/dl; normal, < 0.5 mg/dl) and erythrocyte sediment rate (59 mm/hr; normal, < 15 mm/hr), and elevated fibrinogen (635 mg/dl; normal, 200-500 mg/dl) and fibrinogen degrade product (10-20 $\mu$g/mL; normal, < 10 $\mu$g/mL) levels. Work-up for other coagulation factors (protein C, protein S, and antithrombin III), malignancy, infection, and autoimmune state did not reveal abnormality. Folic acid (10 mg per day) and vitamin B12 (20 mg per day) supplementation were given under the impression of folic-acid deficiency-related hyperhomocysteinemia. Low-molecular-weight heparin was replaced by oral warfarin after improvement of deep vein thrombosis one week later. The patient was discharged under stable condition and followed up in our outpatient clinic. Serum homocysteine level returned to normal (11.62 $\mu$mol/L) after folic acid and vitamin B12 supplementation for 2 months. Follow-up chest X-ray revealed resolution of pulmonary tuberculosis 3 months later. Anti-

Figure 1. Chest radiograph revealed active pulmonary tuberculosis involving bilateral lung fields (thin arrows).

Figure 2. Venography revealed swelling of right thigh (thin arrow) and deep vein thrombosis involving right lower limb (thick arrow).
and kept following up in the outpatient clinic.

**DISCUSSION**

Hyperhomocysteinemia, a prothrombotic condition, is well known as a risk factor for coronary artery disease, myocardial infarction, venous thrombosis, cerebral infarct, and pulmonary thromboembolism in previous reports. Marked hyperhomocysteinemia (> 50 μmol/L) was noted in the present case and may be the major cause of subsequent deep vein thrombosis in this patient.

Homocysteine is the transmethylation product of the essential sulfur-containing amino acid methionine. S-adenosylmethionine and -adenosylhomocysteine are intermediates in this pathway. Homocysteine can be either remethylated to methionine or degraded through the transsulfuration pathway. There are two different remethylation pathways. The first requires 5-methyltetrahydrofolate as methyl donor and reduced cobalamin as a cofactor. 5-methyltetrahydrofolate is generated by a reaction catalyzed by 5,10-methyltetrahydrofolate reductase, for which a common, thermolabile variant resulting from a cytidine to thymidine point mutation at position 677 has been described.1 The second remethylation reaction uses betaine as methyl donor. In the transsulfuration pathway, homocysteine condenses with serine to form cystathionine, which is subsequently cleaved into cysteine and alpha-ketobutyrate. Both reactions are irreversible and require the active form of vitamin B6, pyridoxal 5'-phosphate, as cofactor.

Common causes of hyperhomocysteinemia include genetic disorder, dietary deficiency of folic acid, vitamin B12, or vitamin B6, chronic renal insufficiency, lifestyle factors (chronic alcohol intake, smoking, or high coffee intake), end-stage diabetes, systemic lupus erythematosus, hyperproliferative disorders, and medications (methotrexate, sulfonamides, or antacid).2 Elevations of homocysteine of 16 to 30 μmol/L, 31 to 100 μmol/L, and >100 μmol/L are classified as mild, moderate, and severe hyperhomocysteinemia, respectively. So the causes of hyperhomocysteinemia in our patient may be related to low folate level, chronic renal insufficiency, and smoking.

Severe hyperhomocysteinemia (> 100 μmol/L) is the homozygous deficiency of cystathionine-β-synthase with clinical syndrome of homocysteine, characterized by ectopic lens, skeletal abnormalities, premature vascular disease, thromboembolism, and mental retardation. Our patient did not have the above manifestations.

Folic acid deficiency is a common cause of hyperhomocysteinemia in previous reports.3 In 1985, Brattsrom et al. reported a substantial homocysteine reduction in 15 volunteers who received 5 mg folic acid per day for 4 weeks. Franken et al.4 and van den Berg et al.5 reported significant reductions in postmethionine-loading homocysteine concentrations with vitamin B6, folic acid, or a combination of both in patients with vascular disease. Naurath et al.6 reported high-dose multivitamin, including folate, vitamin B6, and vitamin B12, resulted in 49.5% reduction of mean homocysteine level. Heijer et al.7 reported that combined supplementation with folate, cobalamin, and pyridoxine reduced homocysteine levels by 30% within 8 weeks in patients with recurrent venous thrombosis. However, whether the reduction in homocysteine levels by vitamin supplementation will lead to prevention of arterial vascular disease and venous thrombosis is still unknown.

Chronic renal insufficiency, even mild, is well-known as another cause of hyperhomocysteinemia in many reports.7-9 Wicken and Gupta10 reported a threefold increase of homocysteine levels in patients with renal impairment when comparing with normal subjects. Chauveau et al.11 reported an inverse relationship between plasma homocysteine level and glomerular filtration rate presented in the range from normal renal function to dialysis dependency. Nerbass et al.8 reported that the determinants of total homocysteine in nondialyzed chronic kidney disease patients were plasma folate, plasma vitamin B12, and creatinine clearance. The possible mechanisms for hyperhomocysteinemia in chronic renal insufficiency include (1) genetic-related loss of normal influence of homocysteine; (2) deficiency of folic acid due to reduced folate absorption, inhibition of intracellular folate, or enhanced folate excretion in hemodialysis patients; (3) impaired nonrenal clearance and metabolism of plasma homocysteine in renal failure; and (4) impaired renal clearance and metabolism of urine homocysteine in renal failure.9 Austen et al.12 indicated that both patients with chronic renal insufficiency and normal renal function had effects of reduced homocysteine after folic acid and vitamin B12 supplementation. Folate restores endothelial function in chronic renal insufficiency, which is associ-
ated with hyperlipidemia, diabetes, and hyperhomocysteinemia. The beneficial effect appears to be independent of its homocysteine-lowering capacity and is possibly related to an improved bioavailability of nitric oxide. In patients with nephrotic syndrome (proteinuria > 3.5 gm per day), the incidences of renal vein thrombosis are higher. The location of deep vein thrombosis in our case was lower extremity, and the severity of proteinuria did not reach criteria of nephrotic syndrome. So nephrotic syndrome-associated deep vein thrombosis is not favored in our patient.

Smoking is another cause of hyperhomocysteinemia, but our patient only smoked a small amount for only 5 years. So smoking may be not the major cause of hyperhomocysteinemia in our case.

Another possible cause of deep vein thrombosis in our patient is active pulmonary tuberculosis. After two weeks of diagnosis and treatment for pulmonary tuberculosis, the patient developed deep vein thrombosis. Severe pulmonary tuberculosis is often complicated by deep vein thrombosis in previous reports.13 The incidence of deep vein thrombosis in patients with pulmonary tuberculosis is about 3-8% confirmed by venography, and the real incidence may be closer to 10%. Because of the association between inflammation and hemostatic changes that can result in hypercoagulable state in patients with pulmonary tuberculosis. Robson et al.1 reported an 8.8% incidence of deep vein thrombosis in patients with active pulmonary tuberculosis proven by venography. These patients had higher fibrinogen, fibrinogen degradation product, tissue plasminogen activator and inhibitor, which may result in hypercoagulable state. Our patient also had higher level of fibrinogen and fibrinogen degradation product, which may have resulted in deep vein thrombosis due to hypercoagulability.

White et al.14 reported rifampicin may increase 4.74-fold the risk of deep vein thrombosis in patients with pulmonary tuberculosis comparing with other regimens, and the deep vein thrombosis usually occurred within 2 weeks of treatment being started. The probable association between rifampicin and deep vein thrombosis does not contraindicate the use of this drug, but measures to prevent deep vein thrombosis, like heparin, should be taken by patients receiving rifampicin. The administration of rifampicin is associated with proliferation of smooth endoplasmic reticulum of the hepatocyte and with induction of cytochrome P450. This is the mechanism of the increased rate of metabolism of warfarin taken concurrently with rifampicin. Through enzyme induction, rifampicin could also alter the balance of anticoagulant and coagulant proteins produced by the liver. Decreased production or increased clearance of anticoagulant proteins favors hypercoagulability. Our patient developed deep vein thrombosis 2 weeks after starting to take rifampicin, so we could not exclude the possibility of deep vein thrombosis resulted from rifampicin-related hypercoagulability besides active pulmonary tuberculosis. In addition, rifampicin is metabolized by the liver, and we don’t need to adjust its dosage in patients with chronic renal insufficiency. Another possibility to cause hyperhomocysteinemia is isoniazide-related vitamin B6 deficiency. In our case, we used both isoniazide and pyridoxine for pulmonary tuberculosis, and isoniazide-related vitamin B6 deficiency and hyperhomocysteinemia is not likely.

CONCLUSION

The cause of hyperhomocysteinemia in this case report may be related to folic acid deficiency and chronic renal insufficiency. Hyperhomocysteinemia may be the major cause of deep vein thrombosis in this patient. Folic acid and vitamin B12 supplementation in reducing homocysteine is good and has effects in both patients with chronic renal insufficiency and normal renal function. However, whether normalization of homocysteine level after folate and vitamin B12 supplementation can prevent deep vein thrombosis is still unknown. Both active pulmonary tuberculosis and the use of rifampicin can result in hypercoagulability and may be additional precipitating factors of deep vein thrombosis in our patient. So measures to prevent deep vein thrombosis, like heparin, in patients with pulmonary tuberculosis or pulmonary tuberculosis patients taking rifampicin should be considered in the clinical setting.

REFERENCES

Cardiol 2006;48:914-23.
我們報告一位 32 歲之慢性腎功能不全 (chronic renal insufficiency) 病患同時發生急性肺結核及深層靜脈栓塞合併嚴重高半胱胺酸血症，葉酸缺乏 (folic acid deficiency)，及凝血功能異常。深層靜脈栓塞經 heparin 治療後改善。半胱胺酸指數經葉酸及維他命 B12 補充後回復正常。肺結核亦於藥物治療後痊癒。此篇報告中，高半胱胺酸血症是由於葉酸缺乏及慢性腎功能不全造成的。

關鍵詞：深層靜脈栓塞、高半胱胺酸血症、肺結核、葉酸缺乏、高度凝血狀態。