

# Aortic thrombus and pulmonary embolism in a patient with hyperhomocysteinemia

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## SUMMARY

**Background** A 32-year-old man presented at hospital with persistent pain, hypothermia and paraesthesia in his right leg, caused by embolic occlusion of all three large arteries as a result of massive thrombi in the abdominal aorta. Previously, the patient had been diagnosed with pulmonary embolism and admitted at least a 6-month history of alcohol abuse. Laboratory assessment of the patient's lipid levels, platelet function and coagulation factors yielded normal results. Duplex ultrasound revealed substantial media thickening of the carotid and femoral arteries, without evidence of calcification. Further laboratory tests revealed elevated plasma levels of homocysteine, asymmetric dimethylarginine, symmetric dimethylarginine and 8-isoprostaglandin  $F_{2\alpha}$ .

**Investigations** Physical examination, laboratory analyses, bronchoscopy, duplex ultrasonography, CT scan and CT angiography

**Diagnosis** Severe hyperhomocysteinemia associated with acute aortic thrombi and peripheral emboli

**Management** Diet supplementation with folic acid, vitamin  $B_6$  and vitamin  $B_{12}$ , low-molecular-weight heparin and L-arginine.

**KEYWORDS** arginine, asymmetric dimethylarginine, embolism, homocysteine, thrombus

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## THE CASE

A 32-year-old man presented at the emergency department complaining of persistent pain, hypothermia and paraesthesia in the calf of his right leg for about 1 week. His heart rate was 85 beats/min and his systemic blood pressure was 110/80 mmHg. Physical examination revealed small areas of necrosis developing in the toes of his right foot (Figure 1). Posterior tibial, dorsalis pedis and popliteal arteries were not palpable in his right leg. Apart from abnormally low skin temperature on his lower right leg and a slightly enlarged liver, no other physical abnormalities were noted. The patient did not have a history of cardiovascular disease and this was the first time he had been admitted to hospital. He disclosed a period of alcohol abuse lasting at least 6 months before hospital admission. As the patient had no contact with his parents or relatives, his family history could not be assessed.

A CT scan revealed partial thrombosis of the patient's abdominal aorta, below the origin of the renal arteries (Figure 2), partial thrombosis of the right common iliac artery, an occluded right internal iliac artery and embolic occlusion of all three arteries of the right lower extremity, almost leading to absence of perfusion in the toes of his right foot (Figure 3). Furthermore, CT and CT angiography scans of the patient's thorax showed evidence of intrapulmonary lesions from previous venous emboli or thrombi, as well as minor pleural effusion. Bronchoscopy and microbiological cultures did not reveal any infectious diseases or neoplasm. Duplex ultrasound examination of the carotid and femoral arteries revealed significant thickening of the medial arterial wall, without evidence of calcification. Transthoracic echocardiography showed normal left and right ventricular dimensions and function. There were no signs of ventricular hypertrophy, valvular dysfunction or shunting. The diameter of his left atrium (2.8 cm) and a 12-lead surface electrocardiogram were normal.

Analysis of the patient's lipid profile showed that his HDL-cholesterol levels had decreased to 0.82 mmol/l (normal range >0.9 mmol/l). His LDL-cholesterol level was 0.72 mmol/l (normal

range  $<4.0$  mmol/l), triglycerides were within normal range (0.7–2.1 mmol/l). Liver function tests revealed substantially elevated levels of  $\gamma$ -glutamyl transpeptidase at 6.68  $\mu\text{mol/l}$  (normal range  $<1.10$   $\mu\text{mol/l}$ ). Alanine transaminase and aspartate aminotransferase were within normal range, but bilirubin was bordering on high at 17.8  $\mu\text{mol/l}$  (normal range  $<17$   $\mu\text{mol/l}$ ).

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, thrombin time, activated recalcification, fibrinogen and levels of clotting factors II and XII. His level of clotting factor VIII was slightly elevated at 165% (normal range 70–130%). Resistance to activated protein C (2.39; normal range  $>2.3$ ) and protein S were within normal range (105%; normal range  $>70\%$ ) and antiphospholipid antibodies were absent. Screens for vasculitis syndromes, connective tissue diseases and paroxysmal nocturnal hemoglobinuria yielded negative results. Although the patient's levels of vitamin B<sub>12</sub> (226 pg/ml; normal range 150–675 pg/ml) and folate (1.6  $\mu\text{g/l}$ ; normal range 1.4–11.8  $\mu\text{g/l}$ ) were low, they were within normal range. Levels of anti-intrinsic factor antibodies and methylmalonic acid were not measured.

Further laboratory assays showed that the patient's blood concentration of homocysteine was at least 12 times higher than normal (173  $\mu\text{mol/l}$ ; normal range  $<15$   $\mu\text{mol/l}$ ), prompting us to carry out further analyses of cofactors and enzymes involved in homocysteine metabolism. The patient's serum levels of 8-isoprostaglandin F<sub>2 $\alpha$</sub>  had elevated to 2.32 nmol/l (normal range 0.194–0.222 nmol/l) and asymmetric dimethylarginine (ADMA) peaked at 0.774  $\mu\text{mol/l}$  (normal range 0.225–0.485  $\mu\text{mol/l}$ ). Plasma concentrations of arginine peaked at 107  $\mu\text{mol/l}$  (normal range 50–100  $\mu\text{mol/l}$ ) and symmetric dimethylarginine (SDMA) at 0.696  $\mu\text{mol/l}$  (normal range 0.280–0.640  $\mu\text{mol/l}$ ). His serum level of creatinine was 45  $\mu\text{mol/l}$  (normal range 79–118  $\mu\text{mol/l}$ ) and urine analysis revealed an increased excretion of 8-isoprostaglandin F<sub>2 $\alpha$</sub>  normalized to creatinine excretion (315 nmol/mol creatinine; normal range 72.5–83.0 nmol/mol creatinine).

A mutation screen of the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene revealed that the patient was heterozygous for the 677C•T sequence variant.

The patient was diagnosed with severe hyperhomocysteinemia and prescribed 5 mg oral folic



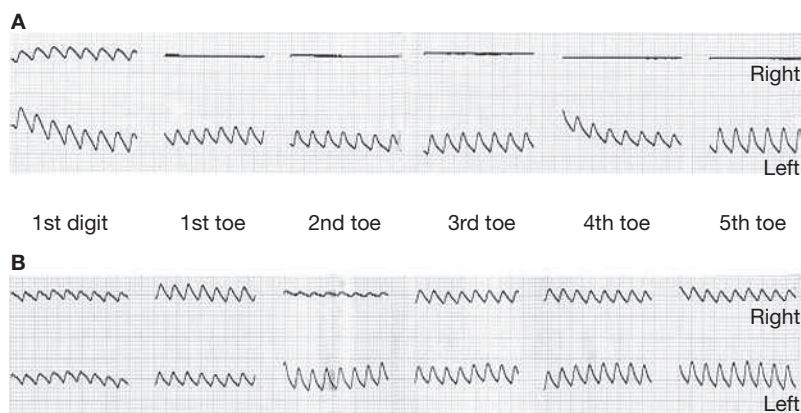
**Figure 1** Necrotic lesions in the patient's feet at presentation. Small necrotic lesions are indicated by an arrow at the tip of the toes on the patient's right foot.



**Figure 2** Computer tomography of the patient's abdomen. An arrow indicates thrombotic material in the aortic wall, narrowing the lumen of the aorta.

acid and 20 mg oral vitamin B<sub>6</sub> daily. He also received 1000  $\mu\text{g}$  vitamin B<sub>12</sub> intravenously every 3 days and weight-adapted low molecular weight heparin (LMWH; subcutaneous injection of 60 IU enoxaparin sodium twice daily). After 7 days, daily vitamin supplements were changed to 5.6 mg folic acid, 24 mg vitamin B<sub>6</sub> and after three doses, the prescription for vitamin B<sub>12</sub> was changed to an oral dose of 0.03 mg daily. In addition, the patient was prescribed 12 g oral L-arginine daily for 6 weeks.

Clinical follow-up after 2 weeks demonstrated that the patient's level of homocysteine had decreased to 57.6  $\mu\text{mol/l}$ . Three weeks later his homocysteine level was 18.1  $\mu\text{mol/l}$ , and after 3 months it was 5.5  $\mu\text{mol/l}$ . After completing his



**Figure 3** Light reflex rheography and oscillography demonstrating absence of perfusion in the toes of the patient's right foot. Results obtained from the patient's left foot are shown for comparison (A). After therapy, perfusion in the first, third, fourth and fifth toes returned to normal. At follow-up, perfusion in the patient's second toe remained moderately lower than normal (B).

therapy regimen 9 weeks later, plasma levels of the following metabolites had decreased: ADMA, to 0.363  $\mu\text{mol/l}$ ; SDMA, to 0.32  $\mu\text{mol/l}$ ; arginine, to 62.8  $\mu\text{mol/l}$  (Table 1). Normal perfusion of the patient's toes was demonstrated using light reflex rheography and oscillography (Figure 3). Furthermore, the patient experienced less pain and paraesthesia in his right leg and his pain-free walking distance increased.

**DISCUSSION OF DIAGNOSIS**

Hyperhomocysteinemia is a causal risk factor for atherosclerosis, and for venous and arterial thrombosis.<sup>1,2</sup> Increasing evidence suggests that the adverse vascular effects of elevated homocysteine are mediated through endothelial dysfunction, which is usually an early manifestation of atherosclerosis.<sup>1,2</sup> Elevated concentrations of homocysteine are found in up to a third of patients with atherosclerosis, and levels greater than 15  $\mu\text{mol/l}$  are associated with a 3-fold increase in the risk of acute myocardial infarction.

In the present case, significant coagulation disorders, vasculitis syndromes and antiphospho-

lipid antibodies were excluded in the laboratory work-up. A hyperhomocysteinemia screen—a routine assessment for patients with arterial thrombi at our institution—revealed substantially elevated levels of homocysteine, leading to a diagnosis of hyperhomocysteinemia. Alcohol abuse reportedly increases the blood concentration of homocysteine, particularly if MTHFR enzyme activity and folate intake are low, which is usually the case in people who consume high quantities of alcohol. Although the patient was heterozygous for the 677C>T sequence variant in the MTHFR gene, the level of MTHFR enzyme activity was not assessed. This genetic polymorphism is relatively common and might not necessarily affect homocysteine levels; it could however, become relevant if levels of folate and Vitamin B<sub>12</sub> are low, as in the present case.<sup>7</sup>

As well as extreme hyperhomocysteinemia, the patient had increased levels of 8-isoprostaglandin F<sub>2a</sub>, which is an experimental marker of oxidative stress formed *in vivo* by a mechanism involving free radical-initiated peroxidation of arachidonic acid. ADMA is an endogenous inhibitor of endothelial nitric oxide synthase (eNOS) and, in this patient, was substantially higher than normal.<sup>3–5</sup> Stühlinger *et al.* showed that homocysteine can inhibit activity of the enzyme dimethylarginine dimethylaminohydrolase (DDAH)—the enzyme that degrades ADMA to dimethylamine and citrulline. Inhibition of DDAH might lead to accumulation of ADMA with suppression of eNOS, decreased levels of nitric oxide and increased oxidative stress.<sup>2</sup>

Recent evidence also suggests that elevated levels of homocysteine can reduce bioavailability of nitric oxide, which can decrease nitric-oxide-dependent flow-mediated vasodilation. *In vitro* data have shown that free homocysteine inactivates nitric oxide, promoting generation of oxygen-derived free radicals. Furthermore, animal studies have demonstrated that homocysteine infusions can lead to patchy necrosis of the endothelium.<sup>6</sup>

Although the patient had substantially elevated levels of ADMA, his levels of SDMA were only

**Table 1** Comparison of the patient's levels of homocysteine and factors involved in its metabolism before and after therapy.

Marker	Normal values ( $\mu\text{mol/l}$ )	Before therapy ( $\mu\text{mol/l}$ )	After therapy ( $\mu\text{mol/l}$ )
Homocysteine	<15	173.3	5.5
Arginine	50–100	68.9	62.8
Asymmetric dimethylarginine	0.225–0.485	0.60	0.363
Symmetric dimethylarginine	0.280–0.640	0.529	0.321

slightly elevated, which indicated that his renal function was normal as SDMA is only eliminated by the kidneys. As the patient was relatively young and also had normal renal function, his hyperhomocysteinemia might have been caused by nutritional depletion of folate and vitamin B<sub>12</sub> and further aggravated by alcohol abuse.<sup>7</sup>

Typical causes for thrombosis, such as coagulation disorders and vasculitis syndromes, were excluded in this patient. It is, therefore, possible that hyperhomocysteinemia led to aortic and venous thrombosis, with secondary embolism in the patient's right leg and pulmonary circulation. Vascular endothelial necrosis caused by extremely high homocysteine levels might have caused localized thrombus formation in the vascular tree. Nevertheless, duplex ultrasonography and a CT scan did not detect deep vein thrombosis in the patient's legs, abdomen or pelvis.

### TREATMENT AND MANAGEMENT

Patients with arterial and venous thromboembolic complications are generally treated with an anti-coagulant such as heparin or warfarin. In this case, treatment with LMWH was initiated immediately and is likely to have helped to restore perfusion in the patient's right leg. LMWH is a symptomatic treatment, however, and does not influence the underlying cause of thromboembolic events.

Genetic and nutritional factors can impact on blood concentrations of homocysteine.<sup>1,2,7</sup> Vitamin B<sub>12</sub> and folic acid are essential cofactors in the remethylation pathway that degrades homocysteine to methionine. Diet supplementation with these factors can reduce homocysteine levels by up to 30%.<sup>8</sup> In this case, the patient's level of ADMA decreased after therapy and homocysteine levels declined to 5.5 µmol/l.

Although several studies have shown that homocysteine levels can be reduced by vitamin supplementation, it has yet to be proven that reduction leads to a reduced risk of cardiovascular morbidity and mortality.<sup>9,10</sup> There is some evidence to suggest that L-arginine therapy can antagonize the inhibitory effects of ADMA on eNOS. Sydow *et al.* showed that L-arginine improved endothelium-dependent vasodilation in a patient with peripheral arterial occlusion disease, hyperhomocysteinemia, and increased level of ADMA. Reduced levels of urinary 8-isoprostaglandin F<sub>2α</sub> in the patient's urine indicated a reduction in oxidative stress levels, whereas diet supplementation with B vitamins alone had no effect.<sup>4</sup> Therapeutic

benefits of L-arginine have also been described by other groups.<sup>11,12</sup> In the present case, however, we do not know which part of the combined therapy regimen improved the patient's acute vascular complication.

### CONCLUSION

In rare cases, severe hyperhomocysteinemia can be identified as the underlying cause of thromboembolic complications. After common causes of venous and arterial emboli have been excluded, screening for hyperhomocysteinemia in association with endothelial dysfunction markers might be appropriate for some patients. In this case, combined therapy with LMWH, vitamin B<sub>12</sub>, vitamin B<sub>6</sub>, folic acid and L-arginine substantially improved symptoms of paraesthesia in the patient's right leg, his painless walking distance, oxidative stress, endothelial dysfunction and vascular perfusion.

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### Competing interests

The authors declared they have no competing interests.