

## Massive Pulmonary Embolism in a Patient with Undiagnosed Homocystinuria

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### Abstract

**Background:** Homocystinuria is an autosomal recessively inherited defect of methionine catabolism. This rare condition causes abnormal accumulation of homocysteine in the blood and urine that is not typically found in significant quantities. While elevated homocysteine levels can cause damage to multiple organ systems, they most often affect the cardiovascular, musculoskeletal, ocular, and central nervous systems. Nearly 20% of affected individuals who are untreated die from thrombotic complications before the age of 30.

**Case report:** The authors present the case of a 54-year-old man with massive pulmonary emboli and severe pulmonary hypertension secondary to undiagnosed homocystinuria.

**Conclusion:** When dealing with unexplained thrombophilia, it is important to include homocystinuria in the differential diagnosis in order to avoid delayed diagnosis which can be life threatening.

**Keywords:** Homocystinuria; Pulmonary hypertension; Pulmonary embolism; Pulmonary endarterectomy

### Introduction

Homocystinuria affects an estimated 1 out of 50,000 to 200,000 people worldwide [1]. The most common form of homocystinuria is caused by a deficiency of cystathionine  $\beta$ -synthase (CBS), an enzyme that uses pyridoxine (vitamin B6) as a cofactor to catalyze the intracellular conversion of homocysteine to cystathionine and cysteine [1]. A deficiency of CBS diminishes the rate of this conversion, resulting in the abnormal accumulation of homocysteine in the blood and urine.

Homocystinuria secondary to CBS deficiency is clinically characterized by the presence of a combination of inferior lens subluxation, myopia, moderate intellectual disability, Marfanoid habitus, and hypercoagulability. Untreated individuals most commonly present with vision problems in the first two decades of life [2].

As seen in the case presented herein, failure to include homocystinuria in differential diagnosis resulted in life-threatening complications that could have been avoided.

### Case Report

A 54-year-old Caucasian man with hypertension presented to his primary care physician with shortness of breath, palpitations, epigastric discomfort, and chest "heaviness" that had been fluctuating for past two weeks. He further characterized the feeling of "heaviness" as constant, unaffected by rest, and occurring across his entire thoracic cavity. The patient reporting having no diaphoresis, dizziness, or radiation of the heaviness to his neck or arms. He offered no insight as to what may have precipitated the event, and could not identify any alleviating or aggravating factors for his dyspnea. The patient also reported having no cough or sputum production, no fevers or chills, no recent contact with sick individuals, no exposure to animals, no changes to his medications, and no recent over-the-counter supplement use.

Six months prior to this visit, the patient was evaluated for suspected pneumonia. At that time, a chest x-ray showed a left upper hilar nodular density. Two weeks later, a follow-up chest CT with IV contrast revealed clear lungs and no left hilar mass or pulmonary nodule. The report made no mention of filling defects in the pulmonary artery. The patient had a history of bilateral leg pain and swelling since adolescence, hypertension that was well controlled with Losartan-HCTZ 100-12.5 mg daily, myopia, unilateral cataract extraction, chronic lower extremity venous

insufficiency and thrombosis, and recurrent lower extremity infections. His lower extremity venous insufficiency had been treated with a greater saphenous vein ablation. No other surgeries were reported.

At the time of his visit, the patient was working in the glass industry. He never smoked, abused alcohol, or used drugs, and played basketball several times a week. The patient's brother had aortic valve surgery as a child, as well as deep vein thrombosis, and cornea surgery. His father had open heart surgery at age 55 and died of congestive heart failure at age 75. His paternal grandfather died of heart disease at age 55 while his paternal grandmother had blood clots and heart problems. His maternal grandmother also died of heart problems at an early age. His paternal ancestry is Norwegian and maternal ancestry is Polish.

Physical examination was remarkable for tachycardia, pulse oxygenation of 93% on room air, respirations 20 per minute, pectus excavatum, and indurated, hemosiderin-stained varicose veins in the lower extremities. The patient had no murmurs, rubs, or gallops and he was afebrile with lungs clear to auscultation bilaterally. An ECG performed in clinic revealed sinus tachycardia at 130 bpm and evidence of an old right-bundle branch block.

The patient was sent to the emergency department, where serial cardiac enzymes were negative. On chest x-ray, pulmonary vascularity and heart size were normal and lungs were clear. There were no ischemic ST segment changes noted during the exercise stress test or during recovery. A myocardial perfusion study revealed uniform radiotracer uptake within the myocardium at stress and rest, without any evidence of ischemia. The patient was discharged home the following day.

One week later, the patient's symptoms recurred and the patient was admitted to the ICU. Ventilation-perfusion scan indicated multiple

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pulmonary embolisms (PE) in both lungs. An echocardiogram revealed severe pulmonary hypertension (estimated right ventricular (RV) systolic pressure of 85 mmHg). Lower extremity venous Doppler ultrasound showed extensive bilateral deep vein thrombosis, including bilateral common femoral vein thrombosis. A chest CT scan showed a large central PE extending bilaterally into the main pulmonary arteries. The patient was immediately started on enoxaparin. A follow-up echocardiogram was conducted a few days after adequate anticoagulation had been achieved, and revealed worsening pulmonary hypertension (95 mmHg estimated RV pressure). As a result, a decision was made to place an inferior vena cava filter and start apixaban.

Six weeks following the inferior vena cava filter placement and continuous anticoagulation, a third echocardiogram demonstrated persistent severe pulmonary hypertension. A surgical consultation was ordered.

Six months after his initial diagnosis of severe pulmonary hypertension secondary to PE, the patient underwent bilateral pulmonary endarterectomy under profound hypothermic circulatory arrest (Figure 1 shows the thrombi removed during complete bilateral pulmonary endarterectomy). The patient suffered life-threatening postoperative complications, including acute hypoxemic respiratory failure secondary to reperfusion lung injury, septic shock from MRSA pneumonia, and atrial fibrillation with rapid ventricular response. The patient required several re-intubations during this difficult and unstable recovery period. He was finally extubated on postoperative day 20, remained hemodynamically stable, and was discharged on amiodarone and warfarin. Amiodarone was discontinued after 3 months.

On routine visit with his primary care physician 4 months following surgery, the patient reported significant improvement in symptoms and a progressively increasing tolerance to physical activity. During this time, the physician discussed this complex case with a medical student rotating on her third year Family Medicine clerkship. Observing the constellation of symptoms and striking physical exam findings, the student suggested testing the patient for homocystinuria. Testing revealed a serum homocysteine level of 191 ( $<15$ ). As a result, the patient was referred for genetic testing, which confirmed the diagnosis of homocystinuria due to CBS deficiency. The homozygous mutation in the CBS gene on chromosome 21 was identified as c.919G>A. Because this pathogenic variant is associated with a more severe, non-B6-responsive phenotype, it was recommended that all of his family members undergo genetic testing as well. The patient was started on trimethylglycine, folate, pyridoxine, and B12.

Eighteen months after surgery, the patient continues this therapeutic regimen, reports no bleeding complications after switching from warfarin to apixaban, and wears compression stockings daily. His homocysteine levels have remained well controlled, and right ventricle pressures have decreased (estimated peak RV pressure of 35 mmHg on most recent echo). The patient is presently asymptomatic, working full-time, and playing several games of basketball each week (Figure 1).

## Discussion

Each year, PE affects between 300,000 and 600,000 patients in the United States [3]. Mortality ranges from 15% to 30% [4]. Most cases of PE result from thromboemboli originating from the proximal veins of the lower extremities. The pathogenesis involves endothelial injury, hypercoagulability, and blood stasis or turbulence. Important risk factors include malignancy, smoking, immobilization, hyperestrogenemia, obesity, and genetic conditions. Homocystinuria is a genetic condition that causes hypercoagulability and subsequent thrombosis. Since

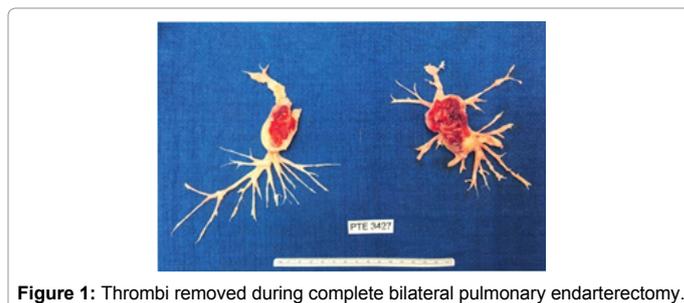


Figure 1: Thrombi removed during complete bilateral pulmonary endarterectomy.

routine screening of patients with venous thromboembolism or PE, to rule out this condition, is not recommended, it can be easily overlooked as a cause of unexplained thrombosis.

In discussing the medical management of homocystinuria, it is first important to understand the biochemical underpinnings of this condition. Homocystinuria stems from a disruption of the methionine catabolism pathway. Methionine is an essential amino acid, which means that it cannot be synthesized *de novo* and must be obtained from the diet. Methionine derives its name from the fact that it is required for all methylation reactions in the body. Encoded by the start codon AUG, methionine is the first amino acid in every polypeptide chain. It is also one of only two sulfur-containing amino acids, the other being cysteine [5].

Ordinarily, methionine catabolism begins with its demethylation to form homocysteine. CBS (with pyridoxine as a cofactor) then converts homocysteine to cystathionine, which is then converted to L-cysteine. In homocystinuria, due to CBS deficiency, homocysteine cannot be efficiently transformed to cystathionine. Consequently, homocysteine accumulates intracellularly, eventually spilling into the extracellular space. Excess serum homocysteine causes endothelial damage, chiefly via a reactive intermediate called homocysteine-thiolactone. This species of homocysteine promotes protein N-homocysteinylation through the formation of amide bonds with  $\epsilon$ -amino groups of lysine residues on endothelial cell membrane proteins. This modification then alters the net charge and conformation of the affected proteins, thereby increasing their susceptibility to aggregation and proteolysis [6].

This chronic cycle of endovascular damage manifests clinically as venous thrombosis. It is also believed to account for the disease's pattern of mild intellectual impairment. While it is less clear, how precisely elevated homocysteine levels can affect collagen synthesis (causing inferior lens subluxation and skeletal abnormalities), a similar mechanism involving N-homocysteinylation of collagen is plausible.

Treatment of homocystinuria varies, depending on whether the mutation is B6-responsive or B6-non-responsive. B6-responders are simply treated with vitamin B6 supplementation, with doses titrated to achieve maximal reduction of plasma homocysteine and methionine level. Increased pyridoxine levels enhance binding of the scarce CBS enzyme to its homocysteine substrate, augmenting the conversion of homocysteine to cystathionine and cysteine [2]. There are two main approaches for lowering homocysteine levels in B6-non-responders and they are dietary methionine restriction and facilitating remethylation of homocysteine to methionine.

The first approach is particularly important and, like phenylalanine restriction in phenylketonuria, is most effective when initiated at a young age. Because methionine is the only known source of homocysteine in the human body, methionine restriction equates to homocysteine restriction. The authors advocate consultation with a dietician for all homocystinuria patients.

The second approach is accomplished using B12, folate, and betaine supplementation. The Food and Drug Administration has approved anhydrous trimethylglycine (a betaine compound) for the treatment of homocystinuria. The remethylation process that converts homocysteine back to methionine can occur via two pathways. The major pathway involves the enzyme methionine synthase, which requires B12 and folate cofactors. The minor pathway is regulated by betaine-homocysteine methyltransferase, which requires trimethylglycine (TMG) as a cofactor [7]. The side effects of TMG supplementation can include nausea, dyspepsia, diarrhea, and elevation of serum LDL cholesterol [8]. Rarely, taking TMG in combination with foods high in methionine can result in hypermethioninemia-induced cerebral edema [9]. It is therefore vitally important for B6 non-responders who are on betaine therapy to restrict methionine consumption.

## Conclusion

Homocystinuria patients who are B6-responsive can usually be managed with pyridoxine supplementation alone, but can also benefit from folate, B12, and betaine treatment. Non-B6-responsive patients must be treated with methionine restriction coupled with TMG, folate, and B12 repletion. When homocystinuria is diagnosed early, the treatments discussed can drastically improve quality and duration of life. Adhering to a methionine-restricted diet from a young age has been shown to mitigate intellectual disability [5]. Betaine and pyridoxine supplementation reduces thrombosis and other morbidities associated with untreated homocystinuria. Most untreated individuals present with eye problems and nearly 20% die of thromboembolic events by the age of thirty [2].

In the case report presented herein, the patient was not diagnosed until age 55 and represents a particularly unusual case. Despite being evaluated by numerous physicians and undergoing a complicated pulmonary endarterectomy, specialists overlooked the possibility

of a homocystinuria diagnosis. In light of this, the authors highly recommend screening for homocystinuria and other genetic conditions in thrombophilic patients who are lacking common risk factors (malignancy, tobacco use, immobilization, obesity, and hyperestrogenemia). In fact, including homocystinuria in the differential for unexplained thrombophilia, even though it is a rare occurrence after the age of 40, has the potential to save many lives.

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