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Pulmonary Thrombosis, Homocysteinemia, and Reperfusion Edema in an Adolescent

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Deep vein thrombosis, pulmonary embolism, and pulmonary thrombosis in situ are rare in childhood and adolescence [1,2]. Unfortunately, these diagnoses may be unsuspected in a pediatric patient with dyspnea and chest pain. This article illustrates the diagnostic and therapeutic challenges that arose from unrecognized chronic thrombotic disease in an adolescent. ***Cathet. Cardiovasc. Intervent. 50:59–62, 2000.***

Key words: homocysteine; pulmonary embolism; adolescent; thrombosis; reperfusion

CASE REPORT

A 14-year-old, obese, black female with a history of mild asthma and nocturnal snoring presented with a 2-year history of worsening exercise intolerance and dyspnea and a 1-week history of pedal edema. At presentation, she denied any chest pain, syncope, rashes, arthritis, oral contraceptive or dietary pill use, renal or liver disease, or any other chronic systemic illness. She denied use of any medications, herbal remedies, or vitamin supplements.

On physical examination, she weighed 266 pounds, her pulse was 80 bpm, and her blood pressure was 130/80 mm Hg. She was mildly tachypneic with a resting oxygen saturation of 85%. Her lungs were clear to auscultation. Cardiovascular examination revealed an increased right ventricular impulse, a loud second heart sound, and a II/VI holosystolic regurgitant murmur at the left lower sternal border. The liver edge was palpable 3 cm below the right costal margin with a span of 15 cm and she had evidence of bilateral pitting pedal edema.

Her electrocardiogram revealed marked right ventricular hypertrophy with a qR pattern in V1 and deep S-waves in V6 (Fig. 1). Chest x-ray demonstrated significant right heart enlargement with a relative paucity of pulmonary markings. On echocardiographic evaluation, there was right ventricular hypertrophy with dilatation (Fig. 2) and evidence of pulmonary hypertension with an estimated right ventricular systolic pressure of 60–65 mm Hg. She had a normal bicarbonate level of 20 mEq/L and a sleep study demonstrated no evidence of significant obstructive sleep apnea.

A cardiac catheterization demonstrated low cardiac index (1.4 L/min/m^2), descending aortic saturation of 84%, and elevated pressures in the pulmonary arteries (75/35 mm Hg; mean, 50 mm Hg). The wedge pressures had a mean of 10 mm Hg, indicating that there was no pulmonary venous or left heart obstruction. Angiography demonstrated complete occlusion of the right upper and lower pulmonary arteries (Fig. 3, left) and significant narrowing of the left lower pulmonary artery (Fig. 3, right), probably secondary to thrombus formation. Hypercoagulable screening demonstrated normal fibrinogen levels, negative rheumatologic screen, including lupus anticoagulant, normal protein C, protein S, antithrombin III levels, and no factor V Leiden mutation. An ultrasound demonstrated no evidence of lower limb deep venous thrombosis. A homocysteine level was also sent.

Following the catheterization, the patient was placed on intravenous heparin. The consulting hematologists were pessimistic regarding anticoagulant efficacy because the patient's 2-year history of dyspnea on exertion, insidious onset of edema, and degree of right ventricular hypertrophy suggested a chronic thrombotic process. Cardiothoracic and vascular surgical consults were obtained regarding possibility of thrombectomy. Unfortunately, the patient's obesity, disease extent, and severe right heart dysfunction were judged to place her at unacceptable surgical risk. Transplant evaluation was initiated but the patient's obesity made her a poor transplant candidate as well. The patient was enrolled in a weight reduction program to lower her metabolic demands.

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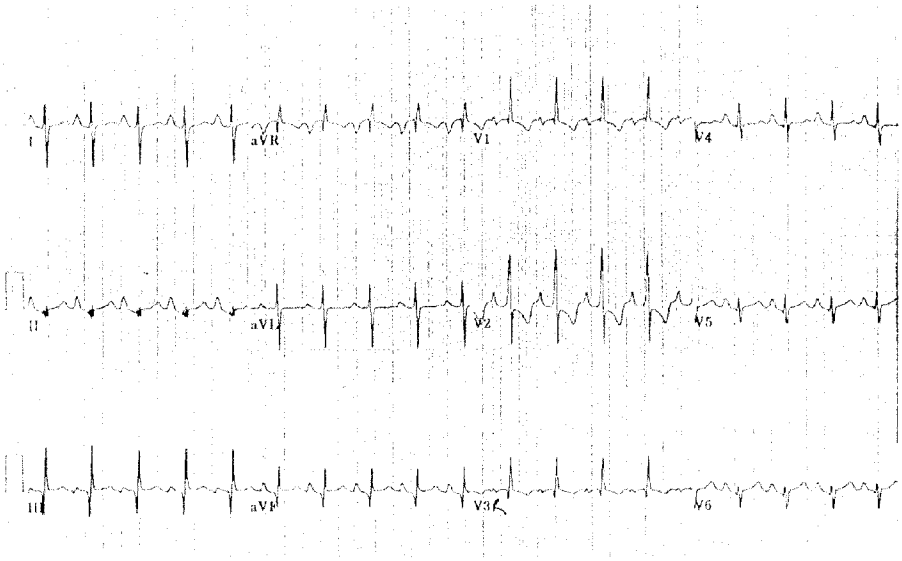

Fig. 1. Electrocardiogram depicting severe right ventricular hypertrophy with strain.

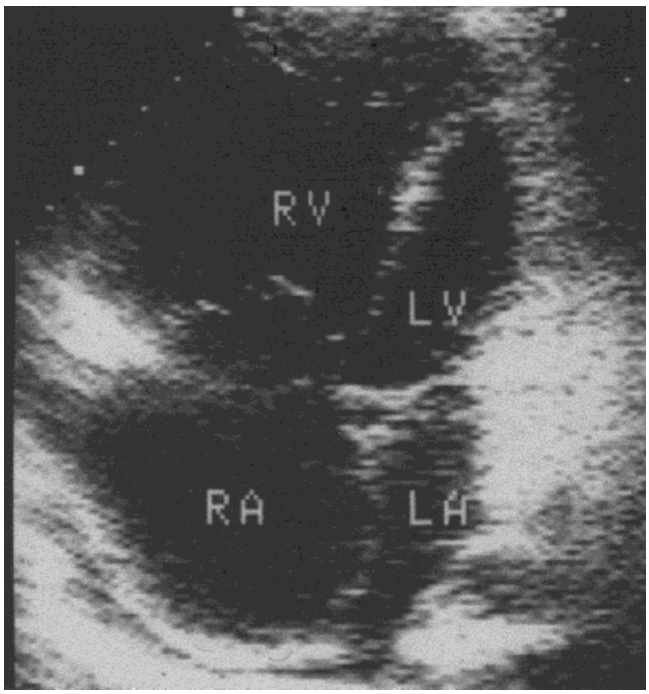

Fig. 2. Four-chamber view from two-dimensional echocardiogram reveals marked right ventricular hypertrophy and right atrial enlargement.

Since no other therapeutic options were judged to be viable, balloon angioplasty of the left lower lobe stenosis was performed in an attempt to improve cardiac output and pulmonary blood flow. Although experimental, successful balloon angioplasty has been described in patients with pulmonary embolism [3]. In addition, balloon angioplasty is routinely used to improve segmental pulmonary blood flow in peripheral pulmonary artery stenoses [4,5]. While angioplasty significantly improved flow to the left lower lobe, the patient developed significant reperfusion pulmonary edema and died 12 hr after the angioplasty despite maximal inotropic and ventilatory support. An autopsy was refused by the family.

Her homocysteine level returned on the day of her angioplasty and was markedly elevated at 55 nmol/ml (normal, < 12). Blood was sent for further tests, the results of which were available only after her death. These revealed a normal vitamin B12 and folate level. Her methionine level was normal but her mixed disulfide cysteine-homocysteine level was elevated. DNA analysis revealed a C-to-T substitution at bp 667 in the methylene tetrahydrofolate reductase (MTHFR) enzyme.

DISCUSSION

Chronic pulmonary embolism and thrombosis in situ may both present with silent pulmonary hypertension [6]. In situ pulmonary thrombosis may be seen following pulmonary endothelial damage from high-pressure, high-shear forces, immune-mediated or direct toxic damage, as well with primary or secondary clotting factor imbalances (e.g., nephrotic syndrome) [6,7]. Prior pulmonary emboli may predispose to thrombosis in situ, both by direct extension and by increasing pressure and flow to the rest of the lung, causing endothelial damage in the previously normal lung [8].

Pulmonary thrombosis may easily be misdiagnosed in children and adolescents [9]. Although the patient initially denied chest pain, she retrospectively described an episode of dyspnea, chest pain and syncope beginning abruptly following an 18-hr bus trip 2 years previously. Upon presentation to the local emergency room that

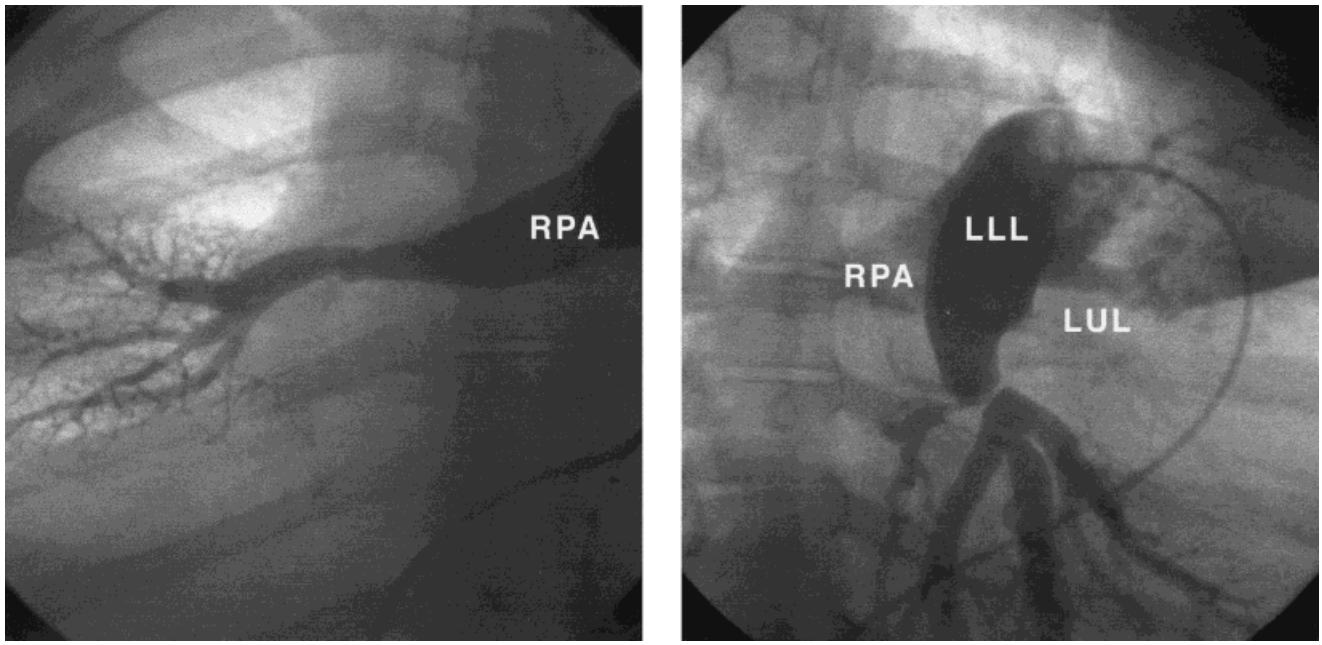

Fig. 3. Left: Frontal projection of right pulmonary artery angiogram demonstrating obliteration of right upper and right lower pulmonary artery. Right: Frontal projection of left pulmonary artery. Left upper lobe vessels are diffusely distorted with sluggish flow, suggesting pulmonary vascular disease. A discrete narrowing is observed in the left lower pulmonary artery with relatively normal appearing distal pulmonary vessels.

evening, she was diagnosed with asthma and discharged home. She denied any other episodes, but she remained physically limited thereafter. Unfortunately, her exercise intolerance was thought to be secondary to her morbid obesity. Only when the patient developed peripheral edema did she seek further medical attention.

Thrombosis in children or adolescents must provoke a search for genetic thrombophillic risk factors [10]. Increased homocysteine levels should be added to the differential diagnosis of thrombosis and thromboembolism in young adults [11–15]. Elevated homocysteine is an independent risk factor for thrombosis as well as increasing thrombotic risk synergistically with factor V Leiden [13–15]. In the Physician Health Study [15], patients having homocysteine levels greater than the 95th percentile had three times the risk of idiopathic venous thrombosis. In adults, the relative risk appears to be dose-dependent, increasing sharply above fasting levels of 22 μmol per liter [13]. Modestly elevated homocysteine levels are common in patients with homozygous thermolabile tetrahydrofolate reductase enzyme, caused by a cysteine for thiamine substitution at base pair 667 (C667T) [16,17]. This patient's level was extremely high, even for a patient with known homozygous C667T mutation, approaching those observed in homozygous homocystinuria [18]. While dietary deficiencies can increase blood homocysteine, her B12 and folate were normal. Although folate and B12 supplementation lowers homocysteine levels, it is unknown whether it decreases the incidence of vascular thrombosis.

While anticoagulation remains the mainstay of acute pulmonary embolism, it is ineffective in chronic thromboembolic disease [6,8,19]. Surgical thrombectomy is the treatment of choice for proximal pulmonary artery obstruction [8,20]. Midline sternotomy approach and cardiopulmonary bypass have greatly lowered surgical mortality to 10%–20% in experienced centers [8,20]. Although probably this patient's best chance for significant functional recovery, her severely compromised cardiac and respiratory mechanics made her a very-high-risk surgical candidate. Nevertheless, transfer to a center specializing in chronic thromboembolism might have been considered. Her morbid obesity effectively precluded lung or heart-lung transplantation, which might otherwise have been a viable therapy [20].

Balloon angioplasty has been used to improve cardiac output and ventilation perfusion matching in patients with thromboembolic disease [3]. Successful relief of peripheral pulmonic stenosis, mimicking thromboembolic disease in young adult patients, has also been reported with improved functional class at a mean follow-up of 52 months following balloon angioplasty [4]. Although unproven, balloon angioplasty of the left pulmonary artery was felt to have the best risk-benefit ratio for this patient, given her high surgical risk and poor medical prognosis.

Unfortunately, reperfusion pulmonary edema is common following either balloon angioplasty or surgical embolectomy when high pressures and flows are delivered to previously underperfused areas [4,6,8]. This was a known risk as most of the cardiac output was directed to her angioplastied pulmonary artery. In retrospect, partial occlusion of the angioplastied pulmonary artery using a balloon catheter or covered stent could have been attempted once significant progressive reperfusion edema developed. Alternatively, cardiopulmonary support with extracorporeal membrane oxygenation may have been lifesaving but the patient expired before this could be instituted.

In conclusion, thrombotic disease should not be forgotten as a cause of chest pain, dyspnea, or pulmonary hypertension in pediatric patients. Once documented, pediatric thrombosis mandates a thorough thrombophillic investigation, including homocysteine levels. In patients where thrombectomy is not possible, balloon angioplasty may be effective in increasing pulmonary flow. However, angioplasty also carries a risk of reperfusion edema and mortality in cases of significant and diffuse thrombosis.

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