lead to distension of these spaces. Once tension occurs, the principle of management is similar to that for pneumothorax. Emergent decompression is thus indicated. There have been several case reports of percutaneous decompression of tension pneumatocele (TP) by needle aspiration, catheter drainage, or chest tube drainage under CT or fluoroscopic guidance. Surgical pneumonostomy with subsequent pulmonary resection has also been reported.

In the present case report, surgery was initially considered in managing the complicated pulmonary conditions during the early course of treatment. However, it was not recommended, since extensive debridement might compromise residual lung function. On the other hand, initial unstable conditions prohibited the transportation to facilities for further radiologic-guided procedures.

Persistent air leak during mechanical ventilation is a serious complication of ventilator therapy. In critically ill patients, the loss of a substantial portion of inspired tidal volume through BPF may significantly alter the intrapulmonary distribution of ventilation, ventilation-perfusion matching, and arterial blood gases. Several techniques have been used to decrease air loss through BPF, promote closure, and maintain good gas exchange. High-frequency ventilation is one of these procedures. The rationales for its use are to decrease airway pressure, reduce risk of barotrauma, and improve ventilation/perfusion matching and gas exchange. As noted in this case, we switched ventilator mode from CMV to HFOV. Not only did TP not enlarge, it further decreased in size with the reduction of MAP and amplitude. This observation supported the proposed mechanism of HFOV in patients with TP.

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**Unilateral Chronic Thromboembolic Pulmonary Disease Associated With Combined Inherited Thrombophilia**

Klaus Laczika, MD; Irene Martha Lang, MD; Peter Quehenberger, MD; Christine Mannhalter, MD; Manfred Muhm, MD; Walter Klepetko, MD; and Paul Alexander Kyrle, MD

Chronic thromboembolic pulmonary hypertension (CTEPH) is considered to be an extreme variant of pulmonary thromboembolism. The underlying mecha-
nisms for the failure of thrombus resolution are still unclear. In looking for inherited thrombophilia, an association with a lupus anticoagulant has been described repeatedly, and single cases of anticoagulant deficiencies (ie, antithrombin [AT], protein C, and protein S) have been reported. We describe a young patient with type I AT deficiency, the heterozygous prothrombin G20210A mutation, and unilateral chronic thromboembolic pulmonary disease presenting after a single thrombotic event. Pulmonary vascular patency was restored successfully by surgical pulmonary thromboendarterectomy. This case is unique because unilateral CTEPH is extremely uncommon, and it illustrates the severe clinical sequelae of the cosegregation of inherited thrombophilic defects.

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Key words: compound inherited thrombophilia; unilateral thromboembolic pulmonary hypertension

Abbreviations: AT = antithrombin; CTEPH = chronic thromboembolic pulmonary hypertension; FII G20210A = prothrombin G20210A mutation; FVL = factor V Leiden; PE = pulmonary embolism; PTE = pulmonary thromboendarterectomy; VTE = venous thromboembolism

Chronic thromboembolic pulmonary hypertension (CTEPH) is an aberrant outcome of pulmonary embolism (PE) that is due to inadequate thrombus dissolution. CTEPH has been found to be present in about 1 to 3% of autopsy series. The clinical incidence is estimated to range between 0.01% and 0.5% of embolic events. The particular causes for the failure of emboli resolution have not been identified. Although abnormalities in the fibrinolytic system have been implicated as the reason for the failure of thrombus resolution, the pathogenesis of CTEPH remains obscure. Prothrombotic coagulation disorders initially have been found in a small proportion of CTEPH patients, and not until recently has thrombophilia been investigated. The presence of the lupus anticoagulant has been diagnosed in up to 30% of CTEPH patients. Deficiencies of antithrombin (AT), protein S, or protein C have been identified in about 1% of cases. Knowledge of inherited thrombophilia has significantly increased during the last decade, and prothrombotic abnormalities can be detected in more than half of the patients with venous thromboembolism (VTE). Based on these data, the thromboembolic nature of CTEPH has been questioned. We report on a young patient with the joint occurrence of type I AT deficiency and a heterozygous prothrombin G20210A mutation (FII G20210A), who developed CTEPH with total occlusion of the right pulmonary artery.

Case Report

A 19-year-old white woman first presented to a hospital outside of our institution in November 1998 with the sudden onset of acute dyspnea and chest pain. A diagnosis of acute PE was confirmed by spiral CT scan, demonstrating a total occlusion of the right pulmonary artery with a saddle thrombus in the presence of a small right-sided pleural effusion. A lung scan revealed a complete right-sided ventilation-perfusion mismatch. The results of color-coded duplex sonography of both legs were normal. The patient was obese, had a history of smoking 30 cigarettes per day, and had used a third-generation oral contraceptive. During her initial hospitalization, treatment consisted of high-dose IV unfractionated heparin (Heparin; Immuno AG; Vienna, Austria), 5,000-U bolus followed by a continuous infusion of 1,000 U/h, followed by oral anticoagulation therapy with phenprocoumon (Marcumar; Hoffmann-La Roche; Basel, Switzerland) [international normalized ratio target range, 2 to 3]. The patient was referred to our institution for further monitoring of oral anticoagulation therapy and a thorough diagnostic workup of thrombophilia 3 months after the incident.

The laboratory evaluation (Table 1) revealed a type I AT deficiency (ie, AT activity, 50% [as determined by chromogenic substrate analysis; Stago; Assignieries, France]; AT antigen level, 48% [as determined by Laurell immunoelectrophoresis; Dakopatts; Alvsjö, Sweden]). On a molecular level, a nonsense mutation in codon 197 arginine to stop (exon 3B), and a C-to-T transition at nucleotide position 6490 (CGA to TGA) was identified. The second instance of thrombophilia that was found was a heterozygosity for the prothrombin gene G20210A variant, as detected by polymerase chain reaction. The results of additional

Table 1—Parameters of Thrombophilia Screening

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Values</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets, g/L</td>
<td>360</td>
<td>150–350</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>56</td>
<td>80–140</td>
</tr>
<tr>
<td>APTT (actin FS), s</td>
<td>35.2</td>
<td>28–44</td>
</tr>
<tr>
<td>Thrombin time, s</td>
<td>14.4</td>
<td>16–30</td>
</tr>
<tr>
<td>Fibrinogen (Clauss), ng/dL</td>
<td>409</td>
<td>180–390</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>AT III activity, %</td>
<td>50</td>
<td>80–120</td>
</tr>
<tr>
<td>AT III antigen, %</td>
<td>48</td>
<td>70–120</td>
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<tr>
<td>Protein C antigen</td>
<td>82</td>
<td>70–140</td>
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<tr>
<td>Free protein S, %</td>
<td>69</td>
<td>50–160</td>
</tr>
<tr>
<td>Factor VIII activity, %</td>
<td>162</td>
<td>60–230</td>
</tr>
<tr>
<td>Factor IX activity, %</td>
<td>85</td>
<td>60–140</td>
</tr>
<tr>
<td>APC-resistance ratio</td>
<td>2.37</td>
<td>&gt; 1.9</td>
</tr>
<tr>
<td>FV B506Q</td>
<td>Wild type</td>
<td></td>
</tr>
<tr>
<td>FII G20210A</td>
<td>Heterozygous</td>
<td></td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>5.3</td>
<td>4–10</td>
</tr>
<tr>
<td>MTHFR C677T</td>
<td>Wild type</td>
<td></td>
</tr>
<tr>
<td>PAI-I, ng/mL</td>
<td>45.8</td>
<td>4–49</td>
</tr>
<tr>
<td>t-PA, ng/mL</td>
<td>11.4</td>
<td>1–12</td>
</tr>
<tr>
<td>PAP, ng/mL</td>
<td>265</td>
<td>95–410</td>
</tr>
</tbody>
</table>

*APTT = activated partial thromboplastin time; APC = activated protein C; FV = factor V; MTHFR C677T = methylene tetrahydrofolate reductase; PAI-I = plasminogen activator inhibitor; t-PA = tissue plasminogen activator; PAP = plasmin-antiplasmin complex.

From the Intensive Care Unit (Dr. Laczika) and the Division of Hematology (Dr. Kyre), the Department of Internal Medicine I, the Department of Internal Medicine II (Dr. Lang), Division of Cardiology, the Clinical Institute of Laboratory Medicine (Drs. Quiehenberger and Mannhalter), Departments of Hematology and Molecular Biology, the Department of Cardiothoracic/Vascular Anesthesia (Dr. Mühl), and the Department of Cardiothoracic Surgery (Dr. Klepetko), Vienna University Hospital, Vienna, Austria.

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CHEST / 121 / 1 / JANUARY, 2002  287
screening investigations, including that for the factor V Leiden (FVL) mutation, and coagulation assays, which were carried out by standard protocols, were normal. Fibrinolytic parameters for tissue plasminogen activator, plasminogen activator inhibitor, and plasmin-antiplasmin complex were within the normal range.

A family study showed a maternal inheritance of the FII G20210A mutant. No data from the patient’s father and his kindred were available. A family history of the maternal kindred was unremarkable for VTE, but the patient’s mother had experienced a myocardial infarction at 23 years of age.

Despite temporary clinical improvement and initial signs of thrombus regression on follow-up CT scans, the patient’s clinical status deteriorated to a New York Heart Association functional class III status. Cardiovascular reevaluation after her referral revealed CTEPH with invasively measured borderline pulmonary artery pressures at rest (systolic BP, 43 mm Hg; diastolic BP, 12 mm Hg; mean, 28 mm Hg) and a calculated pulmonary vascular resistance at rest of 390 dyne · s · cm⁻². Digital subtraction angiography showed a total occlusion of the right pulmonary artery at the level of the mainstem. A lung scan disclosed a lack of perfusion to the occluded side. Pulmonary vascular patency was successfully restored by pulmonary thromboendarterectomy (PTE). Intraoperatively, total unilateral thrombotic occlusion of perfusion to the occluded side. Pulmonary vascular patency was successfully restored by pulmonary thromboendarterectomy (PTE). Intraoperatively, total unilateral thrombotic occlusion of the right main pulmonary artery was found. The surgical specimen was a white, organized thromboembolus, as shown in Figure 1. In order to minimize the risk for further VTE, AT concentrates (target range, 120% activity) were substituted throughout the perioperative period, and oral anticoagulation was restarted on day 10 after PTE. PTE resulted in normal reperfusion and in an immediate and persistent hemodynamic and functional improvement toward a New York Heart Association functional class I status. At the 16-month postdischarge follow-up, the patient had normal results for a lung perfusion scan performed while receiving oral anticoagulation therapy, which will be maintained lifelong.

**Discussion**

We present a rare case of unilateral chronic thromboembolic pulmonary arterial occlusion associated with a rare combined thrombophilic defect. The natural history of PE is either a total resolution of the condition or resolution leaving only minimal residua with restoration of normal pulmonary hemodynamics within weeks to several months. In a small subgroup of patients, this resolution does not occur. Clinically, CTEPH developed in this case after a single clinical thromboembolic event with serial CT scans demonstrating the regression of a saddle thrombus after 12 weeks of oral anticoagulation therapy. The surgical specimen that was obtained 24 weeks after the initial clinical presentation was a white organized tissue mass occluding the right pulmonary mainstem (Fig 1). Thus, complete organization of the thrombus must have proceeded within several weeks. Because AT exerts an anti-inflammatory effect, one may speculate that the underlying AT deficiency may have contributed to this unusual pattern of thrombus organization on a cellular level. Given the fact that the pathophysiology of CTEPH is a vast area of speculation, the contribution of multifunctional molecules such as AT to abnormal thrombus organization deserves consideration. Hemodynamic evaluation showed almost normal pulmonary vascular resistance at rest, according to the typical presentation of unilateral disease. Furthermore, the patient displayed the typical features of unilateral disease, as she was young and a woman. In the only reported cohort of patients with unilateral disease undergoing PTE, recurrent postoperative thrombosis occurred in 4 of 11 patients, and inadequate perfusion occurred in 6 of 11 patients. Few data exist on the long-term results of PTE in patients with thrombophilia. Our patient had normal perfusion of the right lung 16 months post PTE.

VTE is now regarded as a multicausal process and occurs only when two or more risk factors are present. Inherited deficiencies of natural coagulation inhibitors such as AT, protein C, and protein S are rare with a prevalence in VTE patients of approximately 5%. AT-deficient patients carry a risk of VTE of about 7 to 10%, and about half of them experience their first thrombotic event before 25 years of age. The coincidence of natural anticoagulant deficiencies with CTEPH was found to be only approximately 1%. Small series have reported higher prevalences but almost all investigations date from a period prior to the discovery of thrombophilic genetic point mutations such as FII G20210A. This transition, located in the 3′-untranslated region of the prothrombin gene (ie, prothrombin 20210 G’A), increases the thrombotic risk, probably through enhanced plasma prothrombin levels. The incidence of this mutation in the white population varies between 0.7% and 3.8% and confers a

**Figure 1.** Thromboendarterectomy specimen showing an organized thromboembolus that is totally occluding the right pulmonary artery mainstem.
relative risk of VTE of about 2.0. In contrast to the most common cause of congenital thrombophilia, a point mutation at position 1691 in the factor V gene (ie, FVL), G20210A has been proposed as an independent risk factor for PE. Whereas FVL is not associated with CTEPH, the occurrence of FII G20210A in CTEPH patients has not yet been reported. The calculated prevalence for the combination of congenital type 1 AT deficiency and the FII G20210A mutation is estimated to be approximately 1 in 500,000 cases. So far, only four cases of such a combination of AT deficiency and the heterogeneous FII G20210A mutation have been reported. It seems that the concomitant presence of FII G20210A renders patients with inherited thrombophilia more susceptible to thrombotic episodes, but more reliable information about the interaction of FII G20210A with other prothrombotic effects is required.

The greatest progress in the management of CTEPH is the clinical awareness of the disease and the diagnostic workup of surgical thrombus accessibility. The present case is unique in that it demonstrates a rare combined thrombophilic defect underlying severe unilateral CTEPH. To this date, no knowledge exists on the precise mechanism causing CTEPH. Although a combined coagulation defect found in only 1 of 500,000 patients is unlikely to have a great bearing even on a rare disease such as CTEPH, this case illustrates a potential pathophysiologic contribution of plasmatic coagulation and thromboembolism in patients with CTEPH.

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REFERENCES


Bilateral Thumb Burns Leading to the Diagnosis of Crack Lung*

David Gatof, MD, Richard K. Albert, MD, FCCP

Bilateral thumb burns on a young woman admitted to the hospital with the diagnosis of community-acquired pneumonia led us to consider the diagnosis of crack lung despite the fact that the woman denied cocaine use. Cocaine was found on a urine toxicology study, and its use was subsequently confirmed by history. The patient was treated for crack lung with complete resolution of her symptoms and radiographic findings. Inspection of the hands for burns consistent with handling cocaine pipes should prompt a consideration of crack lung in patients with pulmonary infiltrates.

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