The Interesting Case

Multiple venous thrombosis and massive pulmonary artery thrombus as the presenting features of steroid-responsive nephrotic syndrome

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Introduction

We report the unusual case of a patient who was admitted with multiple venous thromboses (bilateral popliteal and iliofemoral, inferior vena cava and right subclavian) and a large left pulmonary artery thrombus as the presenting features of nephrotic syndrome. Prompt and complete remission of the nephrotic syndrome with steroid therapy, concurrent with the resolution of the hypercoagulable state, strongly suggested the diagnosis of minimal change nephropathy.

Case

A 42-year-old man presented with chest pain and swelling of his right lower extremity. A week later, the patient was admitted to the hospital because of swelling of both legs, anterior chest pain, cough and dyspnoea. Deep venous thrombosis and pulmonary thromboembolism were highly suspected. Doppler ultrasonography revealed a right femoropopliteal thrombosis and he was treated with intravenous heparin. Eight days later, he presented with sudden onset of chest pain and cough. Dyspnoea and haemoptysis developed later, and the patient was referred to our hospital. He had smoked 40 cigarettes every day for 15 years, but did not drink alcohol. He had no history of illicit drug abuse.

Physical examination on admission revealed an obese man 111 kg in weight (BMI = 36) with tachypnoea and moderate distress. His body temperature was 37.2°C, pulse rate was regular at 100 beats per minute and blood pressure was 150/98 mmHg. Cardiovascular examination was normal, with no heaves, thrills or gallops. His breathing sounds were reduced bilaterally at the lower lung fields with a few crackles. The abdomen was soft, and no ascites or hepatosplenomegaly was detected. Oedema was noted in both legs and in the scrotum.

His haemoglobin was 16 g/dl and haematocrit 48%. Arterial blood gases revealed pH 7.43, PO₂ 71 mmHg, PCO₂ 37 mmHg and HCO₃ 25 mmol/l. Biochemistry results were as follows: total serum protein 5.3 g/dl, serum albumin 1.3 g/dl, serum creatinine 1 mg/dl, serum urea 42 mg/dl, total cholesterol 449 mg/dl, and lactic dehydrogenase 734 U/l. Serum fibrinogen was 653 mg/dl, platelet count 166 000/ml, serum IgG 1200 mg/dl, IgA 632 mg/dl, IgM 373 mg/dl, C3 217 mg/dl, and C4 54 mg/dl. VIH, VCH, VBH, ASLO, ANA, anti-DNA antibody, rheumatoid factor, cryoglobulins, anticardiolipin and ANCA antibodies were normal or negative. Screenings for malignancies were all negative. The serum d-dimer was positive (>3 μg/ml). The urinary sediment was normal. The 24 h urinary protein excretion was 25 g and creatinine clearance was 118 ml/min.

A venography revealed right iliofemoral and left femoropopliteal thromboses. The renal veins and inferior vena cava were normal. A permanent inferior vena cava filter was inserted via the left femoral vein. The patient presented hypotension and hypoxaemia, and he needed pressor drugs and ventilatory support for 7 days. The patient’s chest X-ray films revealed left lower lung infiltration and pleural effusion. The pleural fluid was bloody in appearance and transudate in nature. The electrocardiogram showed sinus tachycardia. The echocardiogram showed no evidence of intracardiac thrombosis. On day 20, a lung perfusion scan revealed a left basal perfusion defect (Figure 1) with high probability of pulmonary thromboembolism. A conventional computed tomography (CT) of the chest with contrast showed an image of infarct of the lower lobe with cavitation in the left lung. A spiral CT angiogram was then performed which showed a large thrombus in the left pulmonary artery, and an infarct of the lower lobe with cavitation (Figure 2). There
were also thromboses of the right subclavian vein and of the inferior vena cava below the filter. Because of the clinical presentation suggestive of pure nephrotic syndrome, steroid therapy was started at a dose of 1 mg/kg/day methylprednisolone. Intravenous heparin was continued. One week after the start of steroid therapy, proteinuria decreased, and 1 week later urinary protein was not detected. Two weeks later, complete remission of the nephrotic syndrome was maintained, strongly suggesting the diagnosis of minimal change disease, which could not be confirmed histologically because of the necessity of continuing anticoagulant treatment. Spiral CT angiography follow-up showed progressive decrease of the occlusive thrombus of the left pulmonary artery. The patient’s condition steadily improved and he was discharged after 6 weeks with a prescription of oral methylprednisolone and subcutaneous heparin. Six weeks after discharge, serum fibrinogen levels had returned to normal. The serum albumin was 4.3 g/dl and serum creatinine was 1.0 mg/dl. The methylprednisolone dose was maintained for 8 weeks and tapered off in a further 8 weeks. Four weeks after withdrawal of methylprednisolone, the proteinuria remained negative. His recovery was complicated by a left pleural empyema, which required tube drainage and prolonged antibiotic therapy.

**Discussion**

The association between nephrotic syndrome and thromboembolic phenomena is well known. In adults with nephrotic syndrome, common sites of thrombosis are the deep veins of the lower limbs and the renal vein [1]. However, thrombosis has been described in the esplomomesenteric portal axis and the inferior vena cava [2,3]. There are reports of arterial thrombosis affecting the renal, femoral, subclavian, brachial, ophthalmic, mesenteric, aortic, cerebral and coronary arteries [4]. Intracardiac thrombosis has also been noted in some patients with the nephrotic syndrome [5]. Pulmonary artery thrombosis has been reported mainly in nephrotic children; most of these cases occur at the time of massive generalized oedema or during the phase of steroid treatment and intensive diuretic therapy [6–8]. This condition is very rare in adults and only two cases have been reported. Ahmed and Saeed [9] reported a case of primary right lower lobe pulmonary artery thrombosis followed by thrombosis of the middle cerebral artery, and Kao et al. [10] reported another case with bilateral involvement of the pulmonary artery. Our patient, who developed a left pulmonary artery thrombus soon after the onset of nephrotic syndrome, presented a massive pulmonary infarct, which is a rare complication of thromboembolism. Judging from the clinical presentation, the size and location of the thrombus suggest that the pulmonary artery was the primary site of thrombosis.

The nephrotic syndrome is associated with many haematological changes and is characterized by a hypocoagulable state resulting, to a varying extent, from: alterations in zymogens and cofactors (increased plasma levels of factors II, V, VIII, XIII, fibronectin and fibrinogen); alterations in the fibrinolytic system;
fibrinogenaemia. It was probably associated with profound changes in the regulatory systems. Although there were other common predisposing factors for thrombosis, such as long-term heavy smoking and obesity, the thrombosis in this case was believed to be a complication of the nephrotic syndrome.

In adult patients with the nephrotic syndrome, pulmonary artery thrombosis or thromboembolism is often associated with deep vein thrombosis and less frequently with other venous thromboses. Because it is frequently asymptomatic, this complication is diagnosed clinically much less frequently than it is detected by routine ventilation/perfusion scanning. An alternative to lung scanning or conventional pulmonary angiography is spiral CT of the chest. This approach is best suited for identifying pulmonary thromboembolism in the proximal pulmonary vascular tree [15,16]. The present case illustrates the effective use of spiral CT in diagnosing pulmonary artery thrombosis after conventional CT had failed to confirm the diagnosis.

Pulmonary artery thrombosis or thromboembolism complicating nephrotic syndrome has been treated successfully by thrombolytic therapy with intravenous urokinase or intrapulmonary artery streptokinase infusion in severely ill nephrotic children [17] or in patients with only minor pulmonary symptoms [18,19]. The poor prognosis of major pulmonary artery thrombosis or thromboembolism and the possibility of its relatively silent occurrence make early therapy essential. It is rational to initiate anticoagulant therapy for nephrotic patients with documented pulmonary artery thromboembolism that is either clinically silent or symptomatic. Steroid treatment should be instituted if a steroid-sensitive form of nephrotic syndrome is suspected. A 6 month duration of anticoagulant therapy is recommended [20,21] and it should be continued as long as the risk of thromboembolism persists, is indicated by hypoalbuminaemia <2.0 g/dl and hypovolaemia.

Our patient, who was anticoagulated immediately with heparin, achieved complete remission of the nephrotic syndrome 4 weeks after the onset of steroid therapy. Whether he had recurrent embolization from the deep venous thrombosis or indeed had local propagation from an initial pulmonary artery thrombus remains unclear. The fact that he was put on heparin and yet developed further pulmonary arterial blockade reinforces the doubt of the usefulness of heparin in nephrotic patients. In addition, the insertion of an inferior vena caval filter did not halt the thrombotic process and caval thrombosis developed. The net effect of heparin in the presence of a low concentration of antithrombin III in the nephrotic state may therefore be insufficient or even adverse in terms of thrombin antagonism [21]. Therefore, in this patient, the partial resolution of the pulmonary thrombus observed after 2 months was perhaps the effect of natural fibrinolysis.

In summary, this report documents the rare presentation of steroid-sensitive nephrotic syndrome which was probably due to minimal change disease, with multiple venous thromboses and pulmonary

Fig. 2. Spiral CT angiography showing a thrombus in the inferior branch of the left pulmonary artery (A and B). Note the infarcted zone of the inferior left lobe with cavitation.

alterations in the coagulation inhibitors (deficiency of ATIII, often, but not always, reduced functional levels of protein C and S despite increased total levels); and platelet dysfunction [11,12]. It has been shown that all these disturbances have a general tendency to correlate with the degree of hypoalbuminaemia. A significant correlation between the degree of ATIII deficiency and the likelihood of a thromboembolic event has been shown [13]. Hyperfibrinogenaemia is also a major risk factor for thrombosis [14]. Our patient was predisposed to hypercoagulability because of severe hypoalbuminaemia, hypercholesterolaemia and hyper-
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artery thrombosis. Spiral CT angiography was effective in documenting pulmonary artery thrombosis non-invasively.

References