

NEPHROTIC SYNDROME COMPLICATED BY LIFE-THREATENING PULMONARY EMBOLISM IN AN ADULT PATIENT

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We report a 23-year-old male presenting with edema. He was originally admitted for an elective renal biopsy for diagnosis of renal pathology. Unfortunately, because of acute abdominal pain an exploratory laparotomy was done. Progressive azotemia and oliguria then developed, and he required temporary hemodialysis. However, he suffered from sudden-onset severe respiratory distress, and blood gas analysis showed profound hypoxemia with a marked arterial-alveolar oxygen difference. Assessment of a pulmonary embolism by radioisotope imaging was not possible because of his dependence on mechanical ventilation. Subcutaneous low molecular weight heparin and intravenous methylprednisolone were given to treat the presumed pulmonary embolism and the underlying nephrotic syndrome. His partial oxygen level gradually increased after continuous heparin and steroid administration. Complete obliteration of one major pulmonary artery and partial obliteration of other smaller arteries were revealed by magnetic resonance angiography. He was discharged and followed-up as an outpatient, and was given oral warfarin and prednisolone. Follow-up magnetic resonance angiography 5 months later showed a normal pulmonary tree with no residual lesions.

Key Words: low molecular weight heparin, nephrotic syndrome, pulmonary arterial thromboembolism

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Nephrotic syndrome (NS) is a consequence of the reduced ability of the glomerulus barrier to exclude proteins of intermediate size (40–200 kDa) and other macromolecules from urine. Substances lost in urine include albumin, immunoglobulins, hormones, and proteins that modulate the coagulation cascade [1,2]. The well-known clinical features of NS include

hypoalbuminemia, abnormal lipid profiles, edema, and hypercoagulability. These systemic complications of NS are responsible for much of the morbidity and mortality seen with this condition. Thromboembolism is one of the most serious, but frequently overlooked, extrarenal complications [3]. The exact incidence of thromboembolism in NS is not known, but varies from 6% to 44% in the literature [4,5]. One of the reasons for the increased coagulation is the loss of small proteins (antithrombin-III, proteins C, and protein S) and the increased concentrations of procoagulants because of their high molecular weight [6]. Although the majority of embolic episodes in nephrotic patients involve the venous system, significant arterial



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thromboses can occasionally occur [7]. Pulmonary embolism (PE) is a rare, but clinically significant situation and more sensitive methods have revealed evidence of PE in more than 15% of NS patients [4,7]. Here, we report a patient with NS who developed severe PE and consequently life-threatening respiratory distress. Treatment with steroids and heparin was successful, and the embolic lesions were clearly demonstrated by magnetic resonance angiography (MRA).

CASE PRESENTATION

A 23-year-old male was admitted to our hospital with decreased urine volume, lower-limb edema and body weight gain during the preceding week. He was a healthy college student, and did not have any history of systemic illness. Two weeks before admission, he reported pain in the epigastric area. A gastroendoscopic examination was performed, but only mild gastric mucosal erosion was found. Routine urinalysis showed microscopic hematuria with 5–10 red blood cells per high power field and presence of proteinuria (+++) semi-quantitatively using dipsticks (Hema-Combistix, Bayer Diagnostics). Under the impression of nephrotic syndrome, he was admitted for further evaluation and elective renal biopsy.

Physical examination revealed a body weight of 70 kg, a regular pulse of 80 beats/min, and high blood pressure of 140/94 mmHg at that time. His conjunctiva was not pale or injected. There was no jugular venous engorgement, and his heart sound was normal. His breathing sounds, rate and pattern were also normal. He felt no tenderness upon palpation on the abdomen and his bowel sound was not hyperactive. However, moderate degree of bilateral lower limb edema was noted. Laboratory examinations showed a normal hemogram (white blood cells, $6.28 \times 10^3/\mu\text{L}$; hemoglobin, 14.7 g/dL; and platelets, $322 \times 10^3/\mu\text{L}$). Biochemical analysis showed albumin, 2.03 g/dL; cholesterol, 365.4 mg/dL; triglycerides, 951.3 mg/dL; blood urea nitrogen, 34.5 mg/dL; creatinine, 1.6 mg/dL; and uric acid, 9 mg/dL. The prothrombin time and activated partial thromboplastin time were within normal ranges. Plasma electrolyte levels were also normal, but urinary sodium was only 7 mmol/L (normal range, 15–250 mmol/L). Routine urinalysis showed severe proteinuria and microscopic hematuria with

dysmorphic changes. His creatinine clearance was only 9.8 mL/min and he lost 10.1 g of creatinine into urine per day. The antinuclear antibody test was negative and the immunoglobulin (Ig) G, IgA, and IgM levels were 107.0, 136.0, and 87.3 mg/dL, respectively. Ultrasonography revealed enlarged bilateral kidneys with increased echogenicity.

Sudden onset of abdominal pain over the right lower abdominal area with a positive peritoneal response and fever (38.8°C) developed 4 hours after admission. Exploratory laparotomy was done on the same day under the impression of peritonitis. During the operation, more than 1.5 L of chyle-like ascites was obtained (cell count, $52 \times 11^9/\text{L}$; polymorphic neutrophils/monocytes, 5/47; lactate dehydrogenase, 219 U/L; total protein, 0.034 g/L; triglyceride, 830.8 mg/dL) and bacterial peritonitis with *Escherichia coli* was diagnosed.

His postoperative recovery was satisfactory. However, progressive azotemia, oliguria, and marked pulmonary congestion were then developed, despite the use of diuretics. Thus, temporary hemodialysis was carried out to correct the elevated serum blood urea nitrogen and creatinine levels of 114.9 mg/dL and 9.1 mg/dL, respectively. Shortly after two sessions of hemodialysis, severe dyspnea developed. A chest X-ray revealed bilateral pleural effusions. Cardiopulmonary resuscitation rapidly restored his cardiac rhythm, and he was placed on assisted mechanical ventilation supported with 100% oxygen (O₂). After resuscitation, his arterial blood gas analysis showed pH, 7.325; partial pressure (Pa) of carbon dioxide, 28.2 mmHg; PaO₂, 42.9 mmHg; HCO₃⁻, 14.3 mM; and O₂ saturation, 76%. PE was highly suspected because of the marked arterial–alveolar difference in O₂ content (634.8 mmHg; normal < 15 mmHg).

Another complication, upper gastrointestinal hemorrhage, as demonstrated by the outflow of finely ground substances from the nasogastric tube, also prevented the use of heparin for PE. His serum fibrinogen was found to be at a very high level (13.1 g/L; normal, 1.51–3.75 g/L) and D-dimer was not detectable. The hemorrhage was not aggravated after observation for 12 hours. Heparinization, using low molecular weight heparin (4,100 U/0.4 mL, Fraxiparin®; Sanofi Winthrop, New York, NY, USA), was given subcutaneously three times per day. He was also treated with 500 mg methylprednisolone twice daily for 3 days followed by 1 mg/kg/day of oral prednisolone. His renal

function deteriorated because of the unstable cardiopulmonary condition, and we had to treat his renal failure with continuous arterio-venous hemodialysis. Unfortunately, tension pneumothorax developed and caused a cardiac arrest event. The immediate insertion of a 28-French chest tube rapidly relieved the severe situation.

After the use of low molecular weight heparin for 7 days, extubation of the endotracheal tube and weaning from the ventilator became feasible because the follow-up blood gas analysis showed a gradual improvement in PaO₂, and the O₂ concentration used in the ventilator could be tapered. A ^{99m}Tc-diethylenetriaminopentaacetic acid lung ventilation and ^{99m}Tc-macroaggregated albumin perfusion (^{99m}Tc-MAA/DTPA) scans were performed immediately after extubation and revealed significant segmental perfusion defects in the posterior basal segment of the right lung (Figure 1). MRA was performed to reveal the localization of the vascular lesions. It revealed a space-occupying lesion in the right superior pulmonary artery (a remnant embolus) and decreased vascularity over the right lower lung (Figure 2A). His respiratory condition remained stable and the renal biopsy was obtained smoothly. He was discharged and followed up as an outpatient, and treated with 1 mg/kg/day prednisolone and 2.5 mg/day warfarin. Histological analysis of his kidney tissue showed a grossly normal glomerulus. There was no electro-dense deposition and electronic microscope examination showed

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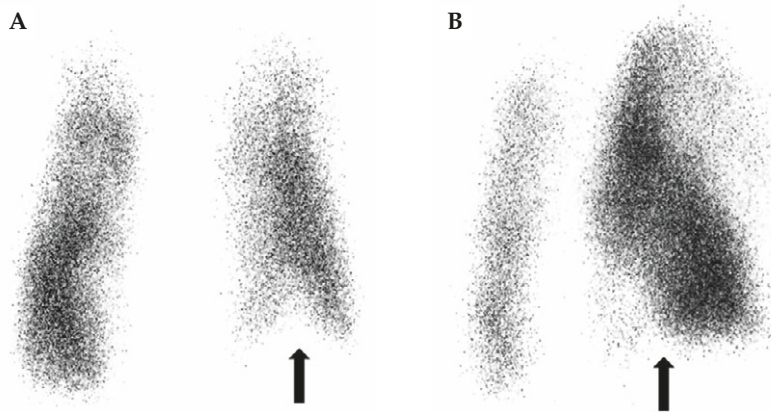


Figure 1. ^{99m}Tc MAA/DTPA aerosol lung perfusion/ventilation scan performed after extubation of the endotracheal tube and with the patient breathing unassisted. The scan showed significant segmental perfusion defects (arrows) in the posterior basal segment of (A) right lung in the posterior and (B) in the right posterior oblique view.

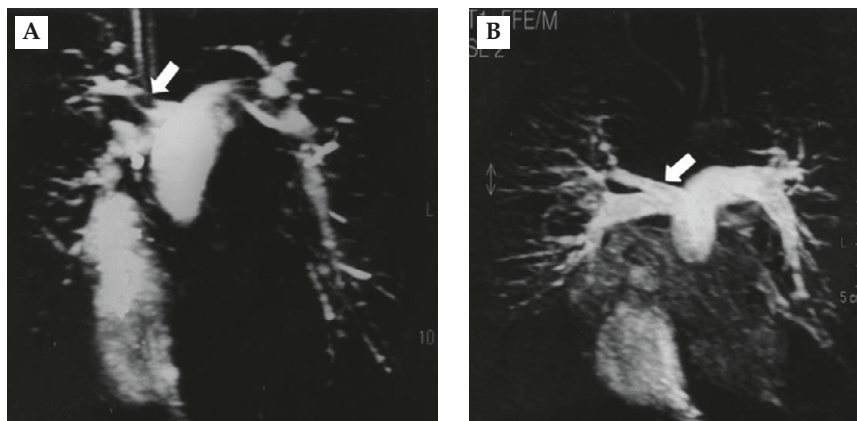


Figure 2. Pulmonary arterial embolism shown by the magnetic resonance angiography performed after the respiratory distress was resolved. (A) Filling defect (remnant thrombus) in the right superior pulmonary artery (arrow) and abrupt interruption of right inferior pulmonary artery with decreased vascularity over the right lower lung, versus the vascularity over the left side. (B) Magnetic resonance angiography was repeated 5 months later, and no filling defect was found.

effaced foot processes. The above findings were compatible with the diagnosis of minimal change disease.

MRA was performed 5 months later and showed no filling defect in the previously obliterated vessels (Figure 2B). Urine protein became negative after steroid treatment for 6 weeks and serum albumin increased to 4.4 mg/dL. The steroid dose was gradually tapered and he is now receiving 5 mg prednisolone every 2 days, and his serum creatinine level has improved to 1.2 mg/dL.

DISCUSSION

Hypercoagulability and thromboembolism are well-known features of NS and thromboembolic complications have emerged as a major complication of NS [8]. As early as 1948, Addis et al drew attention to the high incidence of these complications in NS patients [9]. More recent studies have shown that thromboembolic complications occur in approximately 40% of adults with NS and in 1.8–5.0% of children [10]. Thromboembolic complications are more frequent when the NS is due to membranous glomerulonephritis [11]. Although thromboembolic complications develop in both the venous and arterial sides of the systemic circulation, arterial thrombosis is less common than venous thrombosis in adults with NS [12,13]. PE is one of the most serious complications, causing severe morbidity, and is mainly reported in children with NS, rarely in adults [14–16]. The incidence of PE is not exactly known, but lung scintigraphy revealed that it was possibly present in one-third of adults with clinically silent NS [17]. However, it is usually life-threatening once it is clinically manifested. Our patient with minimal change disease experienced an unusually dangerous course of NS, chiefly intervened by the development of clinically manifested PE. The possibility of genetic defects might be due to the fact that the development of PE is rarely associated with nephritic syndrome in minimal change disease.

The hypercoagulable state has been related to abnormalities in coagulation factors. Small proteins (antithrombin-III, protein C, and protein S) that inhibit clotting are lost into the urine because of their small size [18,19]. Increased coagulation factors (V, VIII and fibrinogen) also contribute to clot formation [20]. Other factors that may enhance the hypercoagulable state in NS include increased fibrinogen level,

intensive diuretic and steroid treatment, and reduced vascular volume [21,22]. Our patient had a very low serum albumin level (2.03 g/dL) and the resulting vascular contraction (revealed by very low urinary sodium levels) was so severe that it caused acute renal failure. More than 10 g of protein was lost into urine and large amounts of antithrombin-III (and protein C and protein S) may also have been lost, although the amounts were not examined. His fibrinogen level was very high. He underwent abdominal surgery and his hydration status might have been aggravated by inadequate postoperative fluid supply. These factors—hypoalbuminemia, hyperfibrinogenemia, contracted volume status, abnormal coagulation factors, inadequate fluid supply and the need for dialysis (and the inevitable decline in vascular volume during the procedures)—all contributed to the development of severe PE and the life-threatening clinical course for this patient.

Little published data are available on the incidence of PE in adult patients with NS and, hence, the exact incidence is unknown. Mehls et al retrospectively reviewed and analyzed the clinical course of 116 adult patients (average age of 34 years) with NS. They found that 8.6% (10/116 patients) of NS cases were noted as having PE during admission [23]. However, the methods used for the diagnosis of PE were not described, and this might mean the incidence (8.6%) is not substantial. By using ventilation/perfusion (V/Q) lung scintigraphy (^{133}Xe for ventilation and $^{99\text{m}}\text{Tc}$ MAA for perfusion imaging), Cherng et al studied the incidence of PE in 89 adult patients with NS with severe hypoalbuminemia (<2.0 g/dL) [17]. They reported that 21% of the patients had a high probability of PE, 49% had intermediate probability, 21% had low probability, and 9% had no or very low probability. They had also performed pulmonary angiography correlation analysis, but only on 40% of the patients with intermediate or low probabilities, and they found evidence of PE in 10 of those patients. Moreover, angiography was not done for cases with high or very low probabilities. Consequently, the false-positive and false-negative prediction rates of the lung scans are unknown. Therefore, the exact role of lung scans on the identification of PE remains unclear. Our patient represented a severe situation because he experienced not only marked dyspnea, but also profound hypoxemia, and this directly prompted the suspicion of PE, which was later confirmed by a lung

scan and MRA. Conventional angiography has a leading role in the diagnosis of vascular defects, but this may be challenged by more recent techniques such as MRA, particularly when the patient's condition means that conventional angiography cannot be performed. The role of MRA in the diagnosis of PE has been reported and shows high sensitivity and specificity [24,25]. In our opinion, MRA is a reliable alternative to conventional angiography for the diagnosis of PE because of its noninvasiveness, its wide applicability to most patients, the lower exposure to X-rays, and the reduced burden of iodinated contrast medium.

PE is a potentially fatal disorder, particularly when it occurs with certain illnesses. The mortality rate is relatively low (2.5%) if appropriate treatment is applied [26]. Anticoagulant therapy with heparin is essential once thromboembolic events have been documented. However, successful treatment with urokinase, anti-thrombin III concentrate, and tissue plasminogen activator were also reported [27,28]. The potential benefit of prophylactic anticoagulation for patients with membranous nephropathy has been examined with decision analysis, and it was shown to be safer than *ad hoc* anticoagulation [29]. Nevertheless, prophylactic anticoagulation should be considered only if the risk is high, such as in the presence of severe hypoalbuminemia (<2.0 g/dL) or marked volume contraction, after considering the inevitable risk of bleeding. We treated this patient with subcutaneous low molecular weight heparin instead of conventional non-fractionated heparin, because he experienced upper gastrointestinal tract hemorrhage. This treatment was successful and satisfactory. Low molecular weight heparin was reported as a preventative measure for thrombotic complications in NS; one case report has described the use of subcutaneous low molecular weight heparin for the treatment of PE in patients with NS [30,31]. Further studies are needed to document its effectiveness.

In conclusion, PE is a relatively rare complication in adult patients with NS. Once it is clinically manifested, it usually contributes to morbidity and, occasionally, mortality. Immediate identification and prompt anticoagulation are necessary for rescue. Lung scintigraphy followed by angiography is the most commonly used diagnostic method, but MRA may be an effective alternative in some situations when the patient's condition is not suitable for conventional angiography. For anticoagulation therapy,

low molecular weight heparin can be an alternative to non-fractionated heparin, although the effectiveness of this approach needs further confirmation.

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腎病症候群合併致命性肺動脈栓塞 — 病例報告

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本文報告一例 23 歲男性，因為下肢水腫而住院實施腎臟切片。住院後因為急性腹痛而實施剖腹手術。而後因為寡尿及氮血症而短暫的施行血液透析。不幸的突然發生嚴重的呼吸衰竭，動脈氣體分析顯示低血氧及明顯的動脈－肺泡氧氣飽和度差，懷疑是發生肺動脈栓塞，但因為插了氣管內管而無法實施核子醫學造影。為治療肺動脈栓塞及本身腎病症候群，給予皮下低分子量肝素及靜脈注射類固醇。在經過肝素及類固醇治療後，病人血中氧濃度逐漸上升，成功拔管。核磁共振血管攝影顯示一條主肺動脈完全阻塞及其他小動脈部份阻塞。病人出院後於門診規則服用口服可邁丁錠（**warfarin**）及類固醇。五個月後追蹤其核磁共振血管攝影：呈現正常肺動脈血管攝影，無阻塞情形。

關鍵詞：低分子量肝素，腎病症候群，肺動脈栓塞
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