Clinical Case Report

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Nephrotic syndrome with acute pulmonary embolism in young adults

Two case reports

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Abstract

Introduction: Pulmonary embolism (PE) is often misdiagnosed, or the diagnosis is delayed because of its diverse clinical manifestations, it may even remain asymptomatic until sudden death. Most risk factors are not associated with young people, and there is a paucity of literature regarding PE in children and young adults.

Case presentation: Patient 1 who died was diagnosed with nephrotic syndrome more than 10 years before. He presented to a clinic with gradually worsening dyspnea, which was initially misdiagnosed as myocarditis. Patient 2 presented with sudden shortness of breath after treatment for nephrotic syndrome. His PE was quickly diagnosed, allowing prompt initiation of anticoagulant therapy. At follow-up 30 days after hospital discharge, his symptoms had disappeared, and his abnormal laboratory results had returned to almost normal.

Conclusion: The diagnosis and treatment of the above 2 patients suggest that the possible occurrence of PE in a young person with nephrotic syndrome should not be ignored. The early diagnosis and delayed diagnosis will have different clinical outcomes.

Abbreviations: CBC = complete blood cell count, CTPA = computed tomography pulmonary angiography, DVT = deep vein thrombosis, LDL = low-density lipoprotein, NT-proBNP = N-terminal pro-brain natriuretic peptide, $PaCO_2$ = arterial carbon dioxide partial pressure, PaO_2 = arterial oxygen partial pressure, PE = pulmonary embolism, sPESI = simplified PE severity index, TC = total cholesterol, VTE = venous thromboembolism.

Keywords: coagulation factor, hypoalbuminemia, nephrotic syndrome, pulmonary embolism

1. Introduction

Pulmonary embolism (PE) is now the third most common cardiovascular disease.[1] The epidemiology of PE is difficult to characterize because PE may be asymptomatic, detected only as an incidental finding; diagnosed only after many visits to medical professionals; or remain undiagnosed during a person's life.[2,3] Similarly, the prevalence of PE among young persons is poorly documented. Current guidelines provide little information regarding the diagnostic workup for PE in children and young adults. Among the many risk factors for PE, hypoalbuminemia caused by nephrotic syndrome is one of the most important in younger patients because of their higher incidence of this syndrome.

Hypoalbuminemia leads to increased production of coagulation factors in the liver; this produces a hypercoagulable state and an increased risk of thrombotic events, including PE. Herein we describe 2 young men with nephrotic syndrome complicated by PE, who had different outcomes. In the first case, the correct diagnosis was delayed for a month, and the man died. The other man received timely diagnosis and treatment and had a good outcome.

1.1. Case 1

This 28-year-old male was admitted to the hospital because of gradually worsening dyspnea over the past 1 month. He initially presented to a clinic, where his electrocardiogram showed V1-V5 ST depression, and his cardiac troponin-T level was 2 times above normal. Accordingly, he was diagnosed with myocarditis, for which treatment was begun. One day before presenting to our hospital, the man had a 30-second syncopal episode while walking up stairs. His parents indicated that he had nephrotic syndrome with minimal change disease on renal biopsy at 10 years of age, for which he received a several-month course of prednisone. He subsequently stopped the prednisone and did not undergo routine follow-up. During the years, he had no specific discomfort but often experienced lower extremity edema.

Upon arrival in the hospital, the man had a heart rate of 96 beats/min, blood pressure of 110/76 mm Hg, respiratory rate of 26 breaths/min, and pulse oxygen saturation of 95% on room air. He had no heart murmur, but edema was obvious in both lower extremities. Complete blood cell count (CBC), liver function tests, and renal function tests were unremarkable. Cardiac troponin-T and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels

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Table 1

Physical examination and laboratory results of the 2 cases.

Result	Case 1	Case 2	Reference range
Blood pressure	110/76	121/83	–
Heart rate	96	112	–
Respiration rate	26	24	–
D-dimer, pg/mL	16.95	9.88	<0.50
NT-proBNP, pg/mL	5689.00	82.75	<125.00
Troponin-T, ng/mL	0.032	0.006	<0.014
PaO_2, mm Hg	74.1	51.1	80.0–100.0
$PaCO_2$, mm Hg	32.2	41.2	35.0–45.0
SaO_2, %	95.0	92.3	95.0–98.0

NT-proBNP = N-terminal pro-brain natriuretic peptide, $PaCO_2$ = arterial carbon dioxide partial pressure, PaO_2 = arterial oxygen partial pressure, SaO_2 = oxygen saturation.

were also normal. However, urinalysis showed 3+ proteinuria, plasma total protein and albumin were significantly lower than normal, low-density lipoprotein (LDL) was high, D-dimer level was very elevated, and arterial blood gas analysis revealed hypoxemia (Table 1). Echocardiography and lower extremity venous compression ultrasound results were normal.

Because of the man's history of nephrotic syndrome, clinical presentation, hypoalbuminemia, hypoxemia, and high D-dimer level, PE was highly suspected. To confirm the diagnosis, computed tomography pulmonary angiography (CTPA) was performed, which showed intraluminal filling defects representing thromboses in the bilateral pulmonary artery trunk and branches (Fig. 1). To select the appropriate treatment strategy, we conducted PE risk stratification and determined the simplified PE severity index (sPESI). His initial stratification was "not high-risk" and his sPESI score was 0; therefore, he was immediately prescribed anticoagulant therapy with low molecular weight heparin. Nine hours later, the man had sudden loss of consciousness with pulse less electrical activity of the heart. Unfortunately, cardiopulmonary resuscitation attempts were unsuccessful.

1.2. Case 2

This 24-year-old male was hospitalized with an approximately 4-month history of whole body edema. In hospitalization, nephrotic syndrome due to minimal change disease was diagnosed by renal biopsy. Five days after prednisone and intravenous albumin therapy, the patient's facial and lower limb edema were significantly reduced, plasma total protein and albumin were definitely improved, and 24-hour urine protein was reduced. Seventh day of admission, he developed sudden onset of worsening dyspnea, with a heart rate of 112 beats/min, blood pressure of 121/83 mm Hg and respiratory rate 24 breaths/min. Heart examination was unremarkable. Breath sounds in both lower lung fields were diminished. D-dimer and NT-proBNP were increased. Hypoxemia was demonstrated by blood gas analysis. Although global coagulation tests (prothrombin time, activated partial thromboplastin time, international normalized ratio) were normal, the activity of various coagulation factors (V, VIII, and IX) was increased (Table 2). Electrocardiogram showed sinus tachycardia. Thoracic ultrasound revealed bilateral pleural effusions. The result of transthoracic echocardiography was normal, and lower limb venous compression ultrasonography revealed lymphedema, but no deep vein thrombosis (DVT). At the same time, CTPA was performed immediately and showed emboli in the right proximal pulmonary artery and the right inferior pulmonary artery branch (Fig. 2).

Risk stratification of acute PE for this patient was "not high-risk," but the sPESI score was 1, so anticoagulation therapy with rivaroxaban was initiated. The man was discharged from the hospital 12 days after admission; at discharge, he continued to receive prednisone and rivaroxaban. At follow-up 30 days after discharge, his symptoms had disappeared, and laboratory results, including plasma total protein and albumin, 24-hour urine protein quantification, total cholesterol (TC) and LDL, D-dimer and arterial blood gases had returned to almost normal. The activity of coagulation factors V, VIII, and IX was also significantly improved (Table 2). Our case report was waived from the First Hospital of Jilin University Ethical Board, based

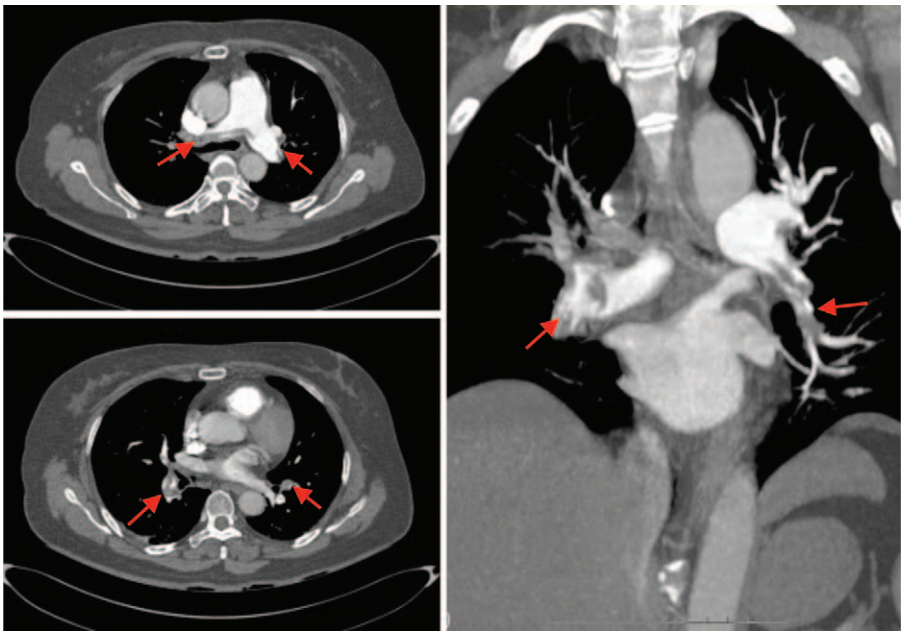

Figure 1. Intraluminal filling defects representing thromboses in the bilateral pulmonary artery trunk and branches.

Table 2

Laboratory results in case 2 around the time of the pulmonary embolus and at follow-up.

Result	On admission	Follow-up	Reference range
Coagulation factor II, %	81	87	70–120
Coagulation factor V, %	159	114	70–120
Coagulation factor VII, %	108	83	70–120
Coagulation factor VIII, %	600	239	60–150
Coagulation factor IX, %	200	150	60–150
Coagulation factor X, %	67	89	70–120
Total protein, g/L	45.1	63.2	65.0–85.0
Albumin, g/L	21	38.1	40.0–55.0
Urine protein/24 h, mg	10260.00	80.62	0–200.00
Proteinuria	3+	Negative	Negative
TC, mmol/L	7.20	5.75	2.60–6.00
LDL-C, mmol/L	5.77	3.20	2.07–3.10
D-dimer, pg/mL	9.88	1.14	<0.50
PaO_2, mm Hg	51.1	91.0	80.0–100.0
$PaCO_2$, mm Hg	41.2	43.5	35.0–45.0
SaO_2, %	92.3	98.0	95.0–98.0

LDL-C = low-density lipoprotein-cholesterol, $PaCO_2$ = arterial carbon dioxide partial pressure, PaO_2 = arterial oxygen partial pressure, SaO_2 = oxygen saturation, TC = total cholesterol.

upon their policy to review all intervention and observational study except for a case report. The patient provided informed consent for the publication of his clinical data. The presented data are anonymized and risk of identification is minimal.

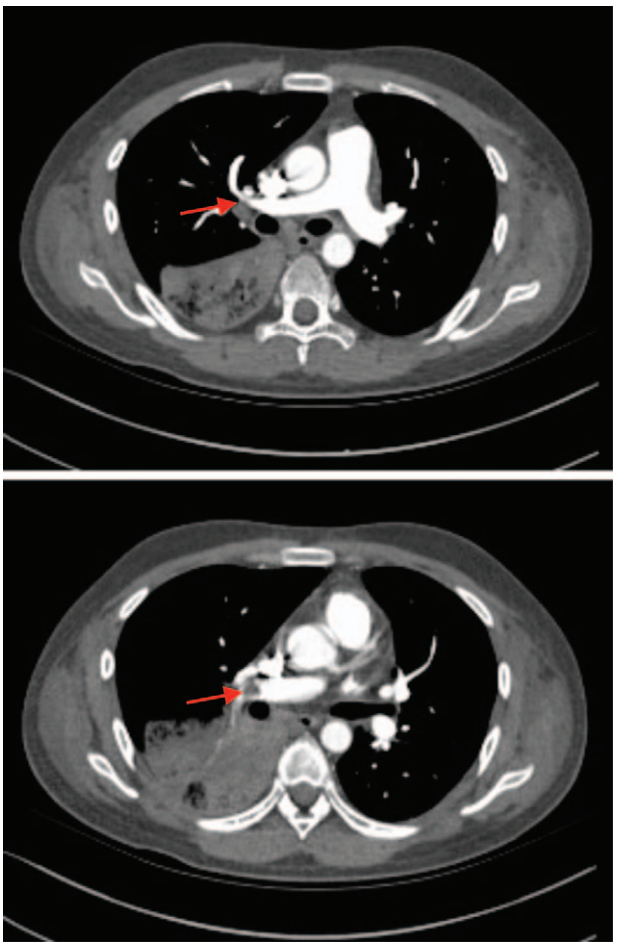

Figure 2. Intraluminal filling defects representing emboli in the right proximal pulmonary artery and the right inferior pulmonary artery branch.

2. Discussion

Venous thromboembolism (VTE) encompasses PE and DVT. Acute PE is the most serious clinical presentation of VTE and may be lethal in the acute phase.[4,5] So far, there have been few reports and no large-scale studies of children and young adults with PE.

It is well established that the occurrence of venous thrombotic events generally requires 3 basic conditions: vascular endothelial injury, slow blood flow or stasis, and a hypercoagulable state. The pathological process of nephrotic syndrome involves increased glomerular permeability to large molecules—particularly albumin-resulting in leakage of albumin through the glomerulus into the urine. As hypoalbuminemia occurs, the plasma colloid osmotic pressure decreases, producing movement of water from the blood to the tissues. This, in turn, decreases the circulating blood volume and leads to increased concentrations of blood coagulation factors. Concurrently, the liver increases production of many substances, including albumin, coagulation factors, TC, and LDL, and the kidney reduces excretion of these substances (except albumin); this results in an imbalance between procoagulant and anticoagulant factors and thereby triggers thrombosis.[6,7]

Nephrotic syndrome is classified as primary or secondary, depending on whether it is a primary kidney disorder or secondary to a systemic disease.[8] Minimal change disease is a renal disorder that causes primary nephrotic syndrome. Like other types of nephrotic syndrome, it is characterized by substantial albuminuria, hypoalbuminemia, and systemic edema.[9] It may occur at any age but is most common in children, adolescents, and young adults and is often accompanied by PE.[10–12] One study reported that 35% of 512 patients with nephrotic syndrome had PE and/or renal vein thrombosis and that 19% of children and youth with nephrotic syndrome had PE.[13] Despite this relatively high association rate, few reports of PE in patients with nephrotic syndrome have been published. More importantly, the association has received insufficient attention from doctors and patients, leading to delayed diagnosis, and even misdiagnosis, in patients with nephrotic syndrome plus PE.

Our first patient had nephrotic syndrome more than 10 years previously and was treated for several months at that time. Because of a paucity of symptoms, he did not undergo medical follow-up. He also did not receive the correct diagnosis when he presented to the clinic. If the possibility of PE had been considered at the clinic, given his edema, dyspnea, and history of nephrotic syndrome, appropriate tests may have been performed to confirm the presence of PE and begin anticoagulation. His death may have therefore been avoided. Although his risk stratification was "not high-risk" for PE, his sPESI was only 0,[1,14] and no thrombi were found in the lower limb veins, his hypercoagulability persisted, resulting in pulmonary artery blockage by a large thrombus and sudden death.

The second patient had systemic edema for several months before hospitalization, as well as severe proteinuria, hypoalbuminemia, high TC and LDL, and increased activity of multiple coagulation factors. Although symptoms and laboratory tests improved with initial treatment, a PE occurred. Fortunately, subsequent anticoagulant therapy resolved the symptoms, returned laboratory results to almost normal, and produced no adverse events during 30-day follow-up.

These 2 cases illustrate important points. They suggest that a hypercoagulable state may persist through the course of nephrotic syndrome. The possible occurrence of PE in a young person with nephrotic syndrome should not be ignored.

Healthcare professionals should not only focus on symptoms, D-dimer levels, and arterial blood gas results, but they should also evaluate changes in blood coagulation factor levels as powerful tools for diagnosing PE. Hypercoagulation in patients with nephrotic syndrome is a major risk factor for thromboembolic events especially at an increased risk of VTE. Early diagnosis and treatment of nephrotic syndrome may prevent the occurrence of VTE. Though there is no guidelines or consensus on the prevention with anticoagulants in patients with nephrotic syndrome, but the study suggested the patients with nephrotic syndrome and combined with hypercoagulation should receive anticoagulants therapy to prevent thrombotic events.[15] We look forward to the well-powered clinical trials to be achieved.

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