Clinical Case Report

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# Chronic thromboembolic pulmonary hypertension as the first manifestation of nephrotic syndrome in a 12-year-old child

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**Abstract**

**Rationale:** Chronic thromboembolic pulmonary hypertension (CTEPH) is rare in children and determining the underlying etiologies is essential for treatment. Venous thromboembolism, a well-known complication in nephrotic syndrome (NS), always occurrs during the treatment in course of the disease. However, CTEPH as the first manifestation of NS has not been reported till now.

**Patient concerns:** A 12-year-old boy initially complained of hemoptysis, cough and shortness of breath with exertion, any symptoms regarding NS such as edema were not presented. Due to the identification of P2 enhancement, liver enlargement (2 cm below the rib) and jugular vein distension, pulmonary hypertension (PH) was firstly suspected and ultimately confirmed by detection of enlargement of right atrium (RA) and right ventricle (RV) enlargement (RA = 45mm, RV = 30mm), mild tricuspid valve regurgitation (TR) and elevation of pulmonary arterial pressure (63 mmHg) on echocardiogram. In order to search the underlying causes of PH, series of targeted laboratory evaluation and imaging were conducted, and pulmonary arterial embolism (PE) in inferior lobes of double lungs was found on chest contrast-enhanced computed tomography.

**Diagnosis:** NS was unexpectedly discovered by detection of lower serum albumin level (24.4 g/L), severe proteinuria (+++, 4.62 g/24 h) when we were searching for the predisposing factors causing thromboembolism.

**Interventions and outcomes:** After treatment of NS, the symptom regarding shortness of breath with exertion gradually became less apparent and was relieved one month later. Proteinuria and microscopic hematuria also disappeared. Encouragingly, RA and RV dilation, and the pulmonary arterial pressure almost returned to a normal range half a year later, with alleviation of MR.

**Lessons:** CTEPH can occur rarely in children and NS is an important predisposing factor. PE could be the first manifestation of NS. When pediatricians encounter children with PE or CTEPH, NS as the underlying etiology should be considered. Except for renal venous thrombosis, the possibility of PE needs to be paid more attention in children with NS.

**Abbreviations:** AAO = ascending aorta, ANCA = antineutrophil cytoplasmic antibodies, BPD = bronchopulmonary dysplasia, CRP = C reaction protein, CT = computed tomography, CTEPH = chronic thromboembolic pulmonary hypertension, DAO = descending aorta, DDI = D-dimer, ESR = erythrocyte sedimentation rate, FDP = fibrin degradation products, GBM = glomerular basement membrane, HBV = hepatic B virus, HIV = human immunodeficiency virus, LA = left atrium, LPA = left pulmonary artery, LV = left ventricle, NS = nephrotic syndrome, PA = pulmonary artery, PE = pulmonary embolism, PH = pulmonary hypertension, PNS = primary nephrotic syndrome, RA = right atrium, RPA = right pulmonary artery, RV = right ventricle, SLE = systemic lupus erythematous, SVC = superior vena cava, TOPP = tracking outcomes and practice in pediatric pulmonary hypertension, TR = tricuspid valve regurgitation.

**Keywords:** children, nephrotic syndrome, pulmonary embolism, pulmonary hypertension

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*The authors have no conflicts of interest to disclose.*

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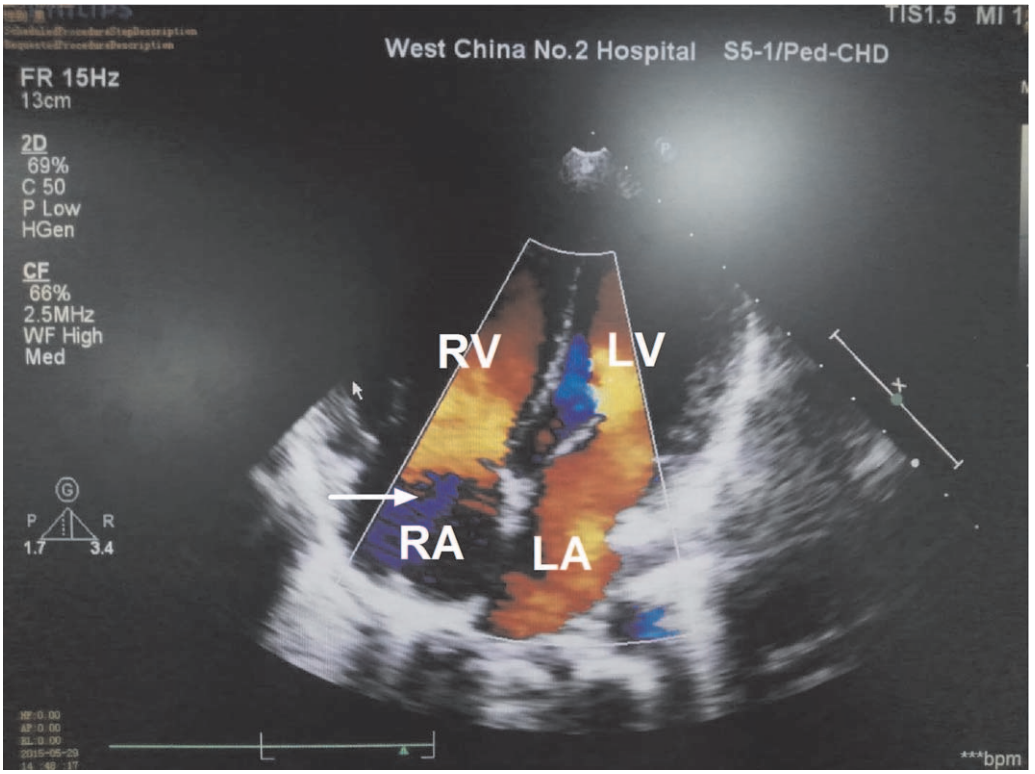


**Figure 1.** Chest contrast-enhanced computed tomography reveals filling defect (white arrows) of bilateral pulmonary arteries (A) and its branches in inferior lobes of double lungs (B) suggesting pulmonary embolism. AAO = ascending aorta, DAO = descending aorta, LPA = left pulmonary artery, PA = pulmonary artery, RPA = right pulmonary artery, SVC = superior vena cava.

## 1. Introduction

Pulmonary hypertension (PH) is a progressive and incurable disease, which is characterized by extensive remodeling of the pulmonary circulation.[1] Overall, compared with adult, PH caused by chronic pulmonary thromboembolism in children is relatively rare as the incidence of pulmonary embolism (PE) in children only ranges from 0.5% to 3.8% in unselected autopsy studies.[2] Nephrotic syndrome (NS), characterized by edema, heavy proteinuria, hyperlipidemia and hypoalbuminemia, has long been recognized to be associated with hypercoaguable states and with a subsequent high risk of venous thromboembolism, including PE.[3–5] Accumulating studies have reported that NS is always complicated with venous thrombosis during treatment in course of the disease, and PE is the second most frequent thromboembolic complication of NS in children.[6] However, PH resulting from PE as the first manifestation is very rare in NS and, to our knowledge, has not been reported so far. Here we reported on the case of an adolescent boy who presented with chronic thromboembolic pulmonary hypertension (CTEPH) initially and was subsequently found to have an otherwise asymptomatic NS.

## 2. Ethics statements

Informed written consent was obtained from the patient's parents for publication of this case report and accompanying images. The study was approved by the University Ethics Committee on Human Subjects at Sichuan University.

## 3. Case report

A 12-year-old boy was firstly admitted to a local hospital with a main complaint of fever, cough, hemoptysis, and shortness of breath with exertion. Chest x-rays revealed inflammatory changes in double lungs. The patient was initially diagnosed as pneumonia and treated with anti-infection drugs for several days. Thereafter, the temperature recovered to normal and the symptom of cough obviously relieved. However, shortness of breath progressively became more aggravated. He was transferred to our hospital later and hospitalized in pediatric cardiology department.

On arrival, we found that he was conscious, afebrile, had no tachypnea, no hypotension, no hypoxia, and no edema. Physical examinations were only remarkable for P2 enhancement, liver enlargement (2 cm below the rib) and jugular vein distension. The diagnosis of moderate PH was made by identification of right atrium (RA) and right ventricle RV enlargement (RA = 45 mm, RV = 30 mm), mild tricuspid valve regurgitation (TR) and elevation of pulmonary arterial pressure (63 mm Hg) on echocardiogram (Fig. 1). Then, series of targeted laboratory evaluation and imaging were carried out to help searching the underlying etiologies causing PH. Any histories of residence in plateau area, special drugs consumptions, recurrent respiratory tract infections prior to illness onset, and familial history of PH were denied. Blood routine test, C reaction protein (CRP), erythrocyte sedimentation rate (ESR), human immunodeficiency virus (HIV) antibody, thyroid function, autoimmune antibody, antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin antibody and antiglomerular basement membrane (GBM) antibody were unremarkable. Echocardiogram did not show any congenital heart defects. Notably, the pulmonary arterial embolism in inferior lobes of double lungs was discovered on chest contrast-enhanced computed tomography (CT) (Fig. 2). Meanwhile, lower serum albumin level (24.4 g/L), severe proteinuria (+++, 4.62 g/24 h), elevation of D-dimer (DDI,

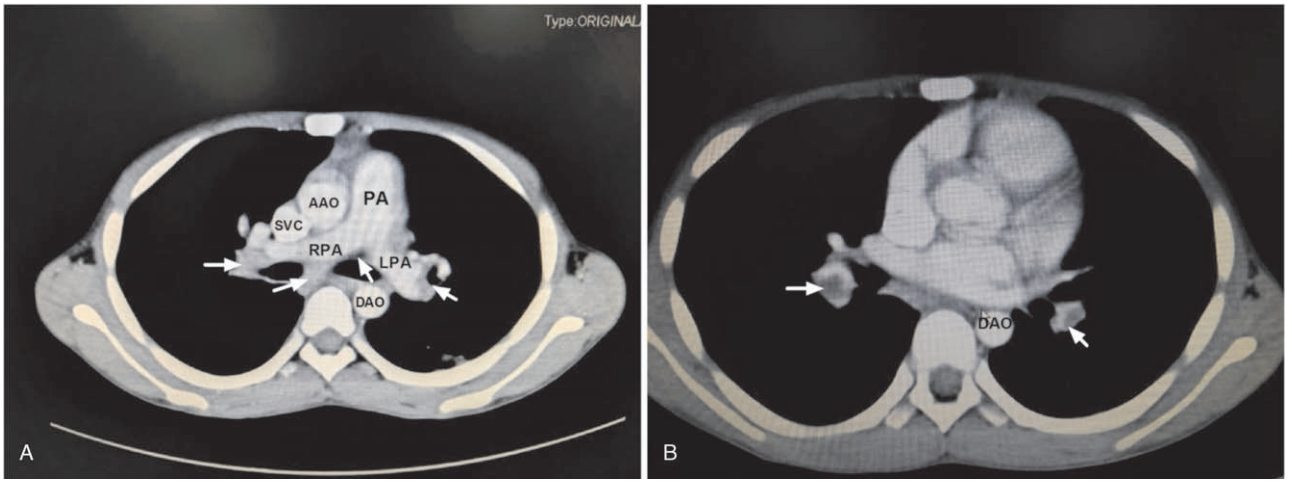


**Figure 2.** Echocardiography shows dilated RA and RV and mild tricuspid valve regurgitation (white arrow) before treatment. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle.

2.36 mg/L) and fibrin degradation products (FDP, 7.30 μg/ml) level, were detected. Other predisposing factors causing thromboembolism such as lupus anticoagulant, anticardiolipin antibody and protein C/S deficiency, were excluded. According to those findings, the diagnosis of CTEPH resulting from NS was established.

The history of Henoch–Schonlein purpura was denied. Negative Hepatic B virus (HBV) examination and autoimmune antibody excluded the possibility of HBV infection and systemic lupus erythematous (SLE). Urinary system ultrasound and CT scan did not detect any tumor. After eliminating those above secondary factors, primary NS (PNS) was considered. Although the blood pressure, complement level, and renal function were normal, PNS (nephritic type) was diagnosed because microscopic hematuria was detected. To further clarify the type of renal pathology, percutaneous renal biopsy under ultrasound guidance was conducted. The results demonstrated mild increase in mesangial matrix and formation of spikes, swollen epithelial cell in renal tubule, without evidence of focal-segmental glomerulosclerosis or tubular atrophy. On immunofluorescence examination, there were bright staining for IgG (+++) and a lesser extent for IgA (+), C1q (++), and complements 3 (+), and 4 (+), but no staining for IgM. Pathological diagnosis of the patient was membranous nephropathy (I–II stage).

Thereafter, the patient received treatment with oral prednisone (2 mg/kg/d bid), captopril (1 mg/kg/d bid), dipyridamole (3 mg/kg/d tid), and subcutaneous injection of low molecular weight heparin calcium (150 U/kg/d bid). The symptom regarding shortness of breath with exertion gradually became less apparent and was relieved one month later. Proteinuria and microscopic hematuria also disappeared. Encouragingly, RA and RV dilation, and the pulmonary arterial pressure almost returned to a normal range half a year later, with alleviation of MR.

## 4. Discussion

PH is defined by an increased mean pulmonary arterial pressure > 25 mm Hg at rest or > 30 mm Hg during exercise.[7] The Venice classification divided PH into 5 categories on the basis of pathophysiological mechanisms, clinical courses, and therapeutic options. In children, idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease are the majority of causes, while PH caused by connective tissue diseases and thromboembolic disorders are rare etiologies.[7,8] The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry enrolled 362 patients with confirmed PH. In this registry, (88%) had PAH, which was characterized as idiopathic PAH or familial PAH in 182 (57%) or associated with CHD in 115 (36%). Forty-two of the 362 patients (12%) had PH associated with respiratory disease or hypoxemia, with bronchopulmonary dysplasia (BPD) the most frequent. Only 3 patients had either CTEPH or miscellaneous causes of PH.[9]

Till now, Madani et al[2] have reported the largest case series of pediatric CTEPH patients, which only included 17 children. Fifteen (88%) of them had one or more risk factors for thromboembolism. The most common thrombophilic states were lupus anticoagulant (n = 5), anticardiolipin antibody (n = 4), and protein C deficiency (n = 3), with 2 patients testing for both the lupus anticoagulant and anticardiolipin antibody. One patient exhibited testing suggestive of both protein C and S deficiency. A third of patients had a positive family history of thromboembolism and/or hypercoagulable state. Other disorders seen in this cohort that are associated with increased risk of thromboembolism include thoracic inlet obstruction (n = 1), NS (n = 1), and Klippel–Trenaunay–Weber syndrome (n = 1). Despite the young age of this cohort, 3 of 9 female patients were either on a regimen of contraceptive pills or were postpartum at the time of diagnosis. To our knowledge, this is the first case of pediatric CTEPH caused by NS reported in Chinese population.

Hypercoaguable states of blood is a well-known complication associated with NS. Venous thromboembolism, including deep venous thrombosis, renal vein thrombosis, pulmonary thrombosis and even internal jugular vein thrombosis,[4,10,11] can appear in course of the disease with the incidence as high as 25% to 40%.[12] Several mechanisms have been suggested for the development of thrombosis in NS, including imbalance between prothrombotic and antithrombotic factors, hyperviscosity and increased platelet aggregation. PE occurs in approximately 40% of adults with NS, but only in about 1.8% to 5% of children, in whom the state can be more severe.[6] Although most cases are secondary to renal vein thrombosis, pulmonary embolism has also been described as the primary site of thrombosis in this

setting. The classical risk factors for thromboembolism during NS are severe hypoalbuminemia (<20 g/L), proteinuria above 3 g/24 h, a low plasma antithrombin-III level and a fibrinogen level above 6 g/l. Additionally, several cohort studies have suggested that plasma DDI level was closely associated with the risk of thromboembolism in NS.[5,6] The risk of thromboembolism increased rapidly in a linear association when plasma DDI was more than 0.5 mg/L. When plasma DDI was reaching 8.9 mg/L, the cumulative probability of pulmonary embolism was about 90%. Furthermore, membranous nephropathy is also inherently thrombogenic,[13] for poorly understood reasons, and thromboembolic complications are more frequent when NS is due to membranous nephropathy rather than other causes. The presence of above risk factors may have exacerbated the emergence of pulmonary embolism in our patient.

Venous thromboembolism always happened within the first few months of disease and during relapses.[14] However, PE as the first manifestation in NS is very rare and, to our knowledge, has not been reported so far. In our case, the first complaint of the patient was hemoptysis, cough and shortness of breath with exertion, no symptoms with respect to NS such as edema were presented at the initial course. Due to the identification of P2 enhancement, liver enlargement (2 cm below the rib) and jugular vein distension, PH was firstly suspected and ultimately confirmed by detection of enlargement of RA and RV, mild TR and elevation of pulmonary arterial pressure (63 mm Hg) on echocardiogram. In order to verify the underlying etiologies for PH, series of targeted laboratory evaluation and imaging were performed, and pulmonary artery embolism was found by chest contrast-enhanced CT. NS was unexpectedly discovered when we were searching for the predisposing factors causing thromboembolism and/or hypercoagulable state.

## 5. Conclusions

We reported on the case of an adolescent boy who presented with CTEPH initially and was subsequently found to have an otherwise asymptomatic NS. This is the first case of pediatric CTEPH caused by NS reported in Chinese population. It raises the pediatricians' attention that CTEPH can occur rarely in children and NS is an important predisposing factor. Additionally, although venous thrombosis always occurs during the treatment in course of NS, PE could be the first manifestation of NS. When pediatricians encounter children with PE or CTEPH, NS as the underlying etiology should be considered. Similarly, except for renal venous thrombosis, the possibility of PE needs to be paid more attention in children with NS. The anticoagulant therapy in time might improve the clinical outcome of patient with CTEPH secondary to NS. However, Due to the limited number of patients and short-term follow-up results in our case, more patients with long-term follow-up outcomes need to be accumulated in the future, and thereby to improve the recognition of chronic thromboembolic pulmonary hypertension (CTEPH) and atypical onset symptoms of nephrotic syndrome (NS) in children.

## Author contributions

**Data curation:** Fan Ma, Kaiyu Zhou.
**Formal analysis:** Kaiyu Zhou, Yimin Hua, Hongyu Duan, Yifei Li, Chuan Wang.
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**Methodology:** Kaiyu Zhou, Yimin Hua, Hongyu Duan, Chuan Wang.
**Resources:** Kaiyu Zhou, Yimin Hua, Xiaoliang Liu, Chuan Wang.
**Software:** Fan Ma, Xiaoliang Liu, Yifei Li, Chuan Wang.
**Writing – original draft:** Fan Ma.
**Writing – review & editing:** Chuan Wang.

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