Bilateral Pulmonary Embolism in a 12-Year-Old Girl with Steroid-Resistant Nephrotic Syndrome

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Received: 13 May 2020; Accepted: 11 June 2020; Published: 15 June 2020

Abstract: Nephrotic syndrome is the most common glomerular disease among children. Although most cases respond to steroid therapy, approximately 10–20% of patients exhibit resistance to conventional steroid therapy and are labeled as steroid-resistant. Such patients are at risk of complications, including infection, thrombosis, and chronic kidney disease. Nephrotic syndrome is considered a thrombogenic condition. Pulmonary embolism is associated with high mortality, and early treatment is essential for the survival of patients. Here, we report the case of a 12-year-old girl with late steroid resistance who developed bilateral pulmonary embolism.

Keywords: nephrotic syndrome; pulmonary embolism; steroid resistance

1. Introduction

Pulmonary embolism is a respiratory condition that is potentially fatal in patients with nephrotic syndrome. Early diagnosis and treatment are essential to improve the prognosis. Steroid-resistant nephrotic syndrome is considered a risk factor for hypercoagulable status owing to non-selective proteinuria and a significant decrease in the expression of anticoagulant proteins, such as protein C and protein S. Thus, patients with steroid-resistant nephrotic syndrome are at a high risk of developing venous thrombosis. There have been a few reported cases of bilateral pulmonary embolism related to nephrotic syndrome in pediatric patients. Here, we report the case of a 12-year-old girl with steroid-resistant nephrotic syndrome who developed bilateral pulmonary embolism. Computed tomography (CT) confirmed the diagnosis, and low-molecular-weight heparin (LMWH) was initiated immediately. The patient survived, demonstrating the importance of early diagnosis and initiation of treatment for this fatal condition.

2. Case Presentation

A 12-year-old Indonesian girl was diagnosed with nephrotic syndrome at the age of 4 years. From that age, she responded well to oral steroids with occasional relapses. At 12 years of age, she experienced a relapse and did not respond to 4 weeks of oral steroids. Because of the late development of steroid resistance, we performed renal biopsy, which revealed focal segmental glomerulosclerosis. Cyclosporine (50 mg twice per day) was administered, and the patient showed a partial response with a decrease in proteinuria by more than 50%. Three months before the time of writing, she experienced a serious relapse and was started on intravenous methylprednisolone (600 mg/m²/day).
She presented to the emergency room of our hospital complaining of shortness of breath, requiring oxygen, and with a decreased level of consciousness. Pulse oximetry at the time of admission revealed tachycardia; however, the patient reported no chest pain. Her medical history was otherwise insignificant with no past history of surgery, blood transfusions, or known allergies. Examination at the time of admission revealed cushioned features (moon face and abdominal striae). The patient weighed 49 kg, and her height was 129 cm. Her vital signs were as follows: temperature, 37.1 °C (axillary); pulse, 120 beats/min (brachial); blood pressure, 124/88 mmHg; and respiratory rate, 24 breaths/min (tachypneic). Cardiovascular examination showed normal heart sounds with no abnormal sounds or murmurs on auscultation, intact pulsation, and good perfusion on palpation. Respiratory examination showed equal bilateral air entry with no abnormal sounds, wheezing, or crepitation. Systemic examination showed no significant factors. The results of laboratory investigations at the time of admission are detailed in Table 1.

**Table 1. Laboratory results at the time of admission.**

| Test Name                        | Result | Unit   | Reference Range |
|----------------------------------|--------|--------|-----------------|
| White blood cell count           | 13.86  | K/UL   | 4.5–13.5        |
| Red blood cell count             | 4.50   | M/UL   | 4.0–5.40        |
| Hemoglobin                       | 12.6   | g/dL   | 12–15           |
| Hematocrit                       | 37     | %      | 35–49           |
| Mean cell volume                 | 84.0   | FL     | 80–96           |
| Mean cell hemoglobin             | 28.0   | Pg     | 32–36           |
| Platelet count                   | 328    | K/UL   | 150–450         |
| C-reactive protein               | 3.13   | mg/L   | 0–3             |
| Prothrombin time                 | 10.8   | s      | 10–13           |
| Activated partial thrombin time  | 45.4   | s      | 25.1–36.5       |
| D-Dimer                          | 43.793 | mg/L   | 0–0.5           |
| International Normalized Ratio   | 0.96   | Ratio  | 0.85–1.3        |
| Sodium                           | 137    | mmol/L | 136–145         |
| Potassium                        | 3.9    | mmol/L | 3.5–5.1         |
| Chloride                         | 106    | mmol/L | 98–107          |
| Urea                             | 4.7    | mmol/L | 2.5–6.4         |
| Creatinine                       | 22     | µmol/L | 53–115          |
| Total protein                    | 46     | g/L    | 64–82           |
| Albumin                          | 5      | g/L    | 40.2–47.6       |
| Alkaline phosphatase             | 146    | U/L    | 141–460         |
| Aspartate amino transferase      | 16     | U/L    | 15–37           |
| Alanine amino transferase        | 18     | U/L    | 12–78           |
| Gamma glutamyl transferase       | 155    | U/L    | 5–85            |
| Total bilirubin                  | 2      | U/L    | 0–17            |
| Antinuclear antibody titer       | 1:640  |       | Negative        |

CT brain venography obtained 2 days after admission revealed that the cerebral venous system, including both internal jugular veins, both sigmoid and transverse sinuses, the straight sinus, and the inferior and superior sagittal sinuses were well opacified with contrast and no filling defects, ruling out venous sinus thrombosis. Electrocardiography revealed sinus rhythm, and cardiac echocardiography showed very small thread-like structures at the entry of the superior vena cava, which did not cause the obstruction. This may have indicated a normal variant or a very small thrombus for clinical correlation. The CT pulmonary angiogram showed filling defects of the right-middle, lower-lobar, and segmental pulmonary artery and those of the left-upper, lower-lobar, and segmental pulmonary artery. The pulmonary trunk was normal in size, measuring 2.4 cm in diameter. A peripheral truncated consolidation with cystic spaces was noted in the superior segment of the right lower lobe. A thrombus was detected within the inferior vena cava, and there was a right-ventricle-filling defect representing a thrombus. There were no intra- or extra-thoracic lymph nodes of significant size, and no pericardial or pleural effusion was detected (Figure 1). A diagnosis of bilateral pulmonary embolism was made based on these findings.
These factors include medications, inflammation, and the presence of a central venous catheter. Finally, protein loss in the urine, the production of hemostatic proteins in the liver increases, resulting in the polymorphisms associated with the prothrombotic state, or other unknown genetic predispositions. Other than the genetic factors, environmental factors play a major role in thromboembolic events. These factors include medications, inflammation, and the presence of a central venous catheter. Finally, the thrombogenic nature of the disease plays an important part and is mainly due to the leakage of high-molecular-weight proteins, such as albumin, through the primary defect in the glomeruli, which is caused by massive proteinuria [1]. As well as the loss of high-molecular-weight proteins, proteins that regulate coagulation (such as protein S, antithrombin III, plasminogen, and plasmin) are lost, resulting in a state of thrombogenesis [1]. To counteract the changes that occur in the plasma due to protein loss in the urine, the production of hemostatic proteins in the liver increases, resulting in the development of a prothrombotic state. Fibrinogen, which enhances platelet activity and aggregation of red blood cells, increased in patients with nephrotic syndrome. These patients also had higher levels of factor V, factor VII, and alpha-2 macroglobulin, which promote thrombus formation [1].

The patient in the present case report had low serum albumin (5 g/L) levels at the time of admission. Hypoalbuminemia increases thromboxane A2 synthesis, which stimulates platelet adhesiveness [2]. Furthermore, platelet hyperactivity is enhanced by hypercholesterolemia and increased levels of Von Willebrand factor, which also promote platelet adhesion. Hypovolemia increases the viscosity of the blood, resulting in increased aggregation of red blood cells and formation of blood clots [1,3]. Fibrinolysis is also compromised by urinary loss of plasmin, which also contributes to the hypercoagulable state [1]. A combination of these factors is considered to result in the increased incidence of thromboembolic events in patients with nephrotic syndrome [4]. One of the most serious forms of venous thromboembolism is acute pulmonary embolism; however, there are few reports or studies of pulmonary embolism in young adults or children [5].

The patient was started on 0.5 L oxygen until vital and clinical signs were stable, after which enoxaparin (1 mg/kg/dose) was administered subcutaneously, every 12 h. Plasma heparin was monitored by plasma anti-Xa assay, and bilateral lower-limb Doppler ultrasound was used to locate the source of the thrombus. Ultrasound findings were normal.

3. Discussion

The pathophysiology of thrombogenesis in nephrotic syndrome is not clearly understood; however, it is known to involve three major aspects. Firstly, it involves genetic background, such as a history of congenital antithrombin deficiency or factor V Leiden (which are known mutations), single-nucleotide polymorphisms associated with the prothrombotic state, or other unknown genetic predispositions. Other than the genetic factors, environmental factors play a major role in thromboembolic events. The pathophysiology of thrombogenesis in nephrotic syndrome is not clearly understood; however, it is known to involve three major aspects. Firstly, it involves genetic background, such as a history of congenital antithrombin deficiency or factor V Leiden (which are known mutations), single-nucleotide polymorphisms associated with the prothrombotic state, or other unknown genetic predispositions. Other than the genetic factors, environmental factors play a major role in thromboembolic events. These factors include medications, inflammation, and the presence of a central venous catheter. Finally, the thrombogenic nature of the disease plays an important part and is mainly due to the leakage of high-molecular-weight proteins, such as albumin, through the primary defect in the glomeruli, which is caused by massive proteinuria [1]. As well as the loss of high-molecular-weight proteins, proteins that regulate coagulation (such as protein S, antithrombin III, plasminogen, and plasmin) are lost, resulting in a state of thrombogenesis [1]. To counteract the changes that occur in the plasma due to protein loss in the urine, the production of hemostatic proteins in the liver increases, resulting in the development of a prothrombotic state. Fibrinogen, which enhances platelet activity and aggregation of red blood cells, increased in patients with nephrotic syndrome. These patients also had higher levels of factor V, factor VII, and alpha-2 macroglobulin, which promote thrombus formation [1].

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![Computed tomography pulmonary angiogram showing filling defects of the right-middle, lower-lobar, and segmental pulmonary artery and of the left-upper, lower-lobar, and segmental pulmonary artery. White arrows indicate the defects.](image_url)
A cohort study involving 512 patients with nephrotic syndrome (72 of whom were below 18 years old) found that the prevalence of thrombosis is lower among children than among adults with nephrotic syndrome (17% vs. 37%) [6]. The prevalence of thrombosis was also found to be higher among patients with membranous nephropathy [6]. Another study found the prevalence of the condition to be higher among patients with diabetic nephropathy or an unspecified nephrotic syndrome than among patients with other nephrotic syndrome types. This may be due to the different combinations of risk factors for thromboembolism in patients with different types of nephropathies [7]. The patients in this previous study were older with a higher prevalence of hypertension, diabetes, and previous incidence of thromboembolism [7]. Another retrospective study carried out over 22 years involving 447 children with nephrotic syndrome found that 2% experienced thromboembolism; 1.5% had steroid-sensitive nephrotic syndrome, and 3.8% had steroid-resistant nephrotic syndrome, which indicates that steroid-resistant nephrotic syndrome is a risk factor for thromboembolism [8].

Pulmonary embolism is a serious condition in children with nephrotic syndrome. According to the results of previous case reports (Table 2), symptoms can range from asymptomatic to death; therefore, timely treatment and diagnosis are critical for survival. The patient in the present report developed unspecific symptoms of respiratory distress with normal findings on chest radiographs. We administered LMWH to manage pulmonary embolism, which is considered standard pharmacological management for pulmonary embolism.

A meta-analysis of 12 randomized trials (with a total of 1951 patients) compared the administration of fixed-dose subcutaneous LMWH with dose-adjusted intravenous unfractionated heparin as introductory treatments for pulmonary embolism and found the two treatments to be equivalent in terms of safety and efficacy for non-massive pulmonary embolism. The simple administration and lack of obligatory follow-up blood tests make LMWH a very good option for patients with pulmonary embolism. Previous meta-analysis reported that massive bleeding occurred in 1.4% of patients who received LMWH compared with 2.3% who received unfractionated heparin, which represents an insignificant difference.
Table 2. Summary of previous case reports involving patients who experienced pulmonary embolism.

| Age (Years) | Underlining Disease                        | Presenting Symptoms                                                                 | Prompt Diagnosis of PE | Method of Diagnosis | Prompt Treatment of PE | Outcome                                                                 | Reference |
|------------|--------------------------------------------|-------------------------------------------------------------------------------------|------------------------|---------------------|------------------------|--------------------------------------------------------------------------|-----------|
| 17         | Factor V Leiden nephrotic syndrome         | Respiratory tract infection with cough and back pain                                | Presumptive            | Echocardiography    | Yes                    | Improvement and disappearance of pain and cough (lived)                  | [9]       |
| 10         | Focal segmental glomerulosclerosis nephrotic syndrome | Shortness of breath                                                                 | NO                     | Autopsy             | NO                     | Died                                                                     | [10]      |
| 10         | Nephrotic syndrome                         | Pyrexia, vomiting, poor fluid intake, and poorly localized chest/abdominal pain     | YES                    | Pulmonary angiography| YES                    | Resolved and lived                                                       | [11]      |
| 12         | Nephrotic syndrome                         | Increasing weight, abdominal pain, and reduced urine output                          | YES                    | CTPA with contrast   | YES                    | Resolved and lived                                                       | [12]      |
| 2.6        | Nephrotic syndrome                         | Abdominal pain, edema, and diarrhea                                                | YES                    | CTPA                | YES                    | Resolved and lived                                                       | [13]      |
| 14         | Nephrotic syndrome                         | Vomiting, watery diarrhea, abdominal pain, and chest pain.                          | YES                    | Contrast enhanced CT| YES                    | Resolved and lived                                                       | [14]      |
| 6          | Nephrotic syndrome                         | Non-productive cough and dyspnea on exertion                                        | NO                     | Autopsy             | NO                     | Died                                                                     | [15]      |
| 5          | Nephrotic syndrome                         | Difficulty in breathing and decreased urine output                                  | YES                    | CTPA                | YES                    | Resolved and lived                                                       | [16]      |
| 10         | Nephrotic syndrome                         | Sharp chest pain, dyspnea, and periordial cyanosis                                  | NO                     | Autopsy             | NO                     | Died                                                                     | [17]      |
| 15         | Nephrotic syndrome                         | Signs of complications                                                              | NO                     | Autopsy             | NO                     | Died                                                                     | [18]      |
| 2          | Asthmatic bronchitis and nephrotic syndrome | Tachypnea Edema of eyelids and legs Hypertension                                     | YES                    | Ventilation–perfusion lung scanning | YES               | Resolved and lived                                                       | [19]      |
| 2          | Nephrotic syndrome                         | Relapse and spontaneous bacterial peritonitis features                              | YES                    | Lung perfusion scan  | YES                    | Resolution and lived                                                     | [20]      |
| 4.5        | Nephrotic syndrome                         | Submandibular swelling, cough, abdominal distention                                 | YES                    | Lung perfusion scan  | YES                    | PE resolved but she died                                                 | [21]      |
| 10.5       | Nephrotic syndrome                         | Mild right-sided pleuritic pain                                                    | YES                    | Radionuclide ventilation and perfusion scans | YES | Resolved and lived                                                      | [22]      |
| 3          | Nephrotic Syndrome                         | Malaise, breathlessness, and tachycardia                                            | YES                    | Pulmonary angiography| YES                    | Resolved and lived                                                       | [23]      |
| 12         | Nephrotic Syndrome                         | Hemoptysis, cough, and shortness of breath                                         | YES                    | Contrast enhanced CT| YES                    | Resolved and lived                                                       | [24]      |
| 3          | Nephrotic Syndrome                         | Mild respiratory distress                                                          | YES                    | Ventilation–perfusion lung scanning | YES | Resolved and lived                                                      | [25]      |
| 10         | Nephrotic syndrome                         | Chest pain and shortness of breath                                                 | YES                    | CTPA                | YES                    | Resolved and lived                                                       | [26]      |
| 16         | Nephrotic syndrome                         | Severe left-sided chest pain and hemoptysis                                         | YES                    | CTPA                | YES                    | Resolved and lived                                                       | [27]      |
| 20         | Nephrotic syndrome                         | Abdominal discomfort and fatigue                                                   | YES                    | CTPA                | YES                    | Resolved and lived                                                       | [28]      |

Abbreviations: CT, computed tomography; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.
In many pediatric cases, LMWHs are the anticoagulants, which are selected for initial prophylaxis and the treatment of thromboembolism due to their many advantages. These include an expected pharmacokinetic profile, which decreases the need for monitoring, the possibility of outpatient use due to the long half-life of the drug, the lack of drug–drug or drug–diet interactions, and a decreased risk of complications, such as heparin-induced thrombocytopenia and osteoporosis. The LMWHs that are most frequently used in pediatric patients are enoxaparin, dalteparin, reviparin, and tinzaparin. However, most clinical data on LMWH use in pediatric patients arises from research involving enoxaparin [21]. Enoxaparin has predictable pharmacokinetics and appropriate subcutaneous administration, which is associated with greater bioavailability. It also needs less demanding monitoring than other anticoagulants [29].

In conclusion, bilateral pulmonary embolism is a rare condition which can be fatal when it occurs in children with nephrotic syndrome. Early diagnosis and management are critical to patient survival, and LMWHs are the standard treatment for this potentially fatal condition.

Author Contributions: R.H.R. and G.A.T. wrote the case history; R.G.A., N.A.A. and A.A.A. wrote the discussion; A.K.H.: designed the table and organized the references; O.Y.S.: reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: All authors declare no conflict of interest.

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