DOI: https://doi.org/10.2298/SARH160926080P
UDC: 616.24-005.7; 616.61-06

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Pulmonary embolism as the first sign of the nephrotic syndrome

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SUMMARY

Introduction Pulmonary embolism (PE) is a serious complication of deep venous thrombosis, with a significant morbidity and mortality. More often, PE complicates the course of the nephrotic syndrome (NS), in particular when the disease is active, but it may occur as the first sign of illness when the diagnosis of the NS is being delayed as a result. Membranous nephropathy is, generally speaking, the most commonly reported glomerulonephritis associated with the increased risk of thrombosis.

Case outline This report summarizes our experience with three young male patients (a 26-year-old, a 22-year-old, and a 45-year-old), in which PE was the first presenting feature of the NS. All of them were admitted to the hospital experiencing chest pains, dry cough, and shortness of breath. One of them had high temperature and the other two swelling of the lower parts of legs. Computed tomography of the thorax showed pulmonary artery thrombosis in all three patients. Diagnosis of the NS was confirmed by laboratory analysis, while renal biopsy showed membranous nephropathy. The treatment was based on the pulse of methylprednisolone (1.5 g over a period of three days), with alternating therapy of oral corticosteroids and cyclophosphamide on a monthly basis during six months. After six months, two patients reached incomplete remission, while the third one still has the NS and normal renal function.

Conclusion Not so rare occurrence of thromboembolic events in the NS suggests that one should always suspect the NS in all patients with deep venous thrombosis or PE.

Keywords: nephrotic syndrome; membranous nephropathy; pulmonary embolism

INTRODUCTION

Pulmonary embolism (PE) is a serious complication of deep venous thrombosis (DVT), with a significant morbidity and mortality [1, 2]. PE most commonly occurs from DVT of legs or renal venous thrombosis, although in many cases the location of thrombosis hasn't been found in other areas. Thromboembolism is among the most serious complications of the nephrotic syndrome (NS) [3, 4]. PE may complicate the course of the NS, especially when the disease is already active, or, less commonly, it may appear as the first sign of illness and fail to be identified, in which case usually delays the diagnosing of NS.

We shall present three cases of NS, where PE was the first sign of membranous nephropathy (MN).

Case report 1

A 26-year-old man was admitted to the Clinic for Lung Diseases complaining of chest pains, dry cough, high temperature, and shortness of breath. The initial chest radiography was normal. Bronchopneumonia was suspected and treatment with antibiotics was initiated. Two days upon admission, additional deterioration of breathing occurred. Electrocardiogram showed sinus tachycardia. In laboratory analysis, an elevation in D-dimer (36 mg/l) was observed, as well as a decrease in antithrombin III activity (76%). Computed tomography of the thorax showed thrombosis of the pulmonary arteries and also in the branches of the lower lobes. Anticoagulant therapy was introduced (low-molecular-weight heparin, then oral anticoagulation). Other sites of thrombosis were excluded after performing the Doppler sonography of the lower limbs and renal veins. On cardiac echography, there were no signs of pulmonary hypertension. Ultrasound examination revealed enlarged kidneys (13 cm in diameter) with normal parenchymal thickness and echogenicity. Immunology tests were normal. Blood analysis: hemoglobin 156 g/l, urea nitrogen 3.4 mmol/l, creatinine 57 umol/l, total protein 36 g/l, albumin 14 g/l, total cholesterol 8.2 mmol/l, and triglyceride 3.3 mmol/l. Urine sediment analysis revealed 10–15 red blood cells. Urinary protein excretion was 12 g / 24 hours, clearance of creatinine was 181 ml/min. A nephrologist was consulted and the diagnosis of nephrotic syndrome was confirmed. Percutaneous renal biopsy was done and the specimen showed glomeruli with mild thickening of the glomerular basement membrane with granular deposition of IgG, compatible to MN (Figures 1 and 2). A detailed examination

Примљено • Received: September 26, 2016
Ревизија • Revised: January 10, 2017
Прихваћено • Accepted: January 17, 2017
Online first: March 17, 2017

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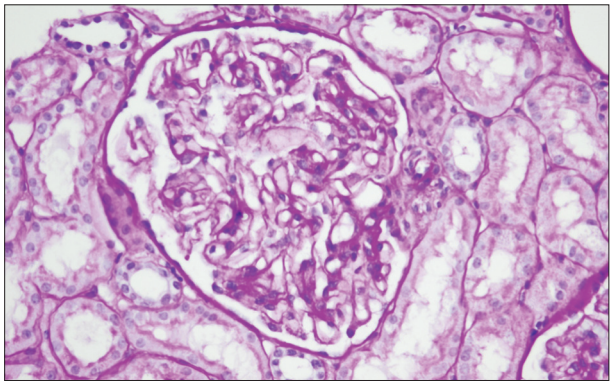

Figure 1. Light microscopy – mild thickening of the glomerular basement membrane (periodic acid – Schiff reaction, × 400)

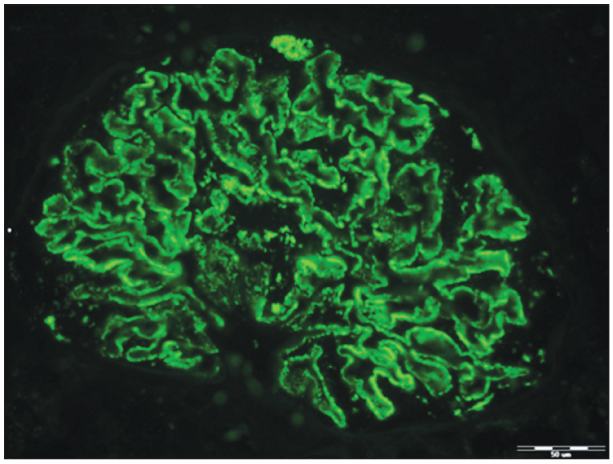

Figure 2. Immunofluorescence microscopy – granular deposition of immunoglobulin alongside glomerular basement membrane (× 400)

excluded secondary causes of MN. The treatment was based on the pulse of methylprednisolone (1.5 g over a period of three days), with alternating therapy of oral corticosteroids and cyclophosphamide on a monthly basis during six months. The symptomatic therapy included ACE inhibitors, a diuretic, and statin. After six months of treatment, we registered partial remission of NS, and after 12 months, complete remission with proteinuria 0.3 g / 24 hours.

Case report 2

A 22-year-old man was admitted to the Coronary Intensive Care Unit with chest pain and shortness of breath. Several days before the admission to the hospital, the patient noticed a swelling of his legs, which disappeared quickly. In initial laboratory tests, D-dimer was high, while cardiac enzymes were normal. Electrocardiogram showed sinus tachycardia. Blood gases in arterial blood were normal. Computed tomography of the thorax showed thrombosis of the pulmonary artery. The patient was treated with anticoagulant therapy (low-molecular-weight heparin, then oral anticoagulation). On cardiac echography there were no signs of the pulmonary hypertension. Other sites of thrombosis were excluded after performing the Doppler sonography of the lower limbs and renal veins. Thrombophilia screening tests (antiphospholipid antibodies, protein C and S, antithrombin III, factor V mutation) were normal.

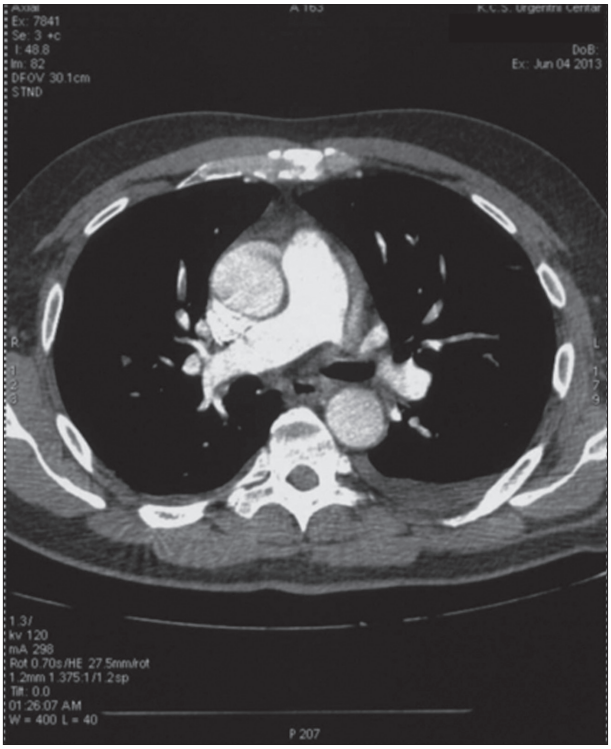

Figure 3. Computed tomography of the thorax – thrombosis in lobar branches of the right pulmonary artery

The laboratory analysis showed that the renal function was normal, while total cholesterol was high. Analyses of urine were not done. Upon full recovery, he was discharged from the hospital with oral anticoagulation. After four months, the patient got respiratory infection with secretions from the nose, followed by cough and high temperature. He suddenly began to swell (swelling of the eyelids and legs, stomach distension) and became oliguric, when he went to the Emergency Room. A nephrologist was consulted and he was admitted to the Clinic for Nephrology. Laboratory analysis showed hemoglobin 136 g/l, urea nitrogen 6.2 mmol/l, creatinine 78 umol/l, total protein 34 g/l, albumin 17 g/l, total cholesterol 9.2 mmol/l, and triglyceride 2 mmol/l. Urine sediment analysis revealed 5–7 red blood cells. Urinary protein excretion was 10 g / 24 hours, clearance of creatinine was 171 ml/min. Ultrasound examination revealed enlarged kidneys (12 cm in diameter) with normal parenchymal thickness and echogenicity. The diagnosis of the NS was confirmed. The patient's treatment was changed to low-molecular-weight heparin, and percutaneous renal biopsy was done. The specimen showed glomeruli with diffuse thickening of the glomerular basement membrane with granular deposition of IgG, compatible with MN. A detailed examination excluded secondary causes of MN. The treatment was based on the pulse of methylprednisolone (1.5 g over a period of three days), with alternating therapy of oral corticosteroids and cyclophosphamide on a monthly basis during six months. Symptomatic therapy included ACE inhibitors, a diuretic, and statin. After six months of treatment, we registered partial remission of NS, proteinuria decreased to 3 g / 24 hours. After 12 months, the proteinuria continues to maintain the same level.

Case report 3

A 45-year-old man was admitted to the Clinic for Lung diseases complaining about the stabbing pain in the left half of the thorax (that intensifies during the intake of air), shortness of breath, and swelling of lower legs. The symptoms began two days before the admission. Auscultation of the lungs revealed impaired breathing on both lower sides. Electrocardiogram showed sinus tachycardia. The arterial blood gases were normal, with a PH of 7.47, partial pressure of oxygen of 8.3 kPa, partial pressure of carbon dioxide of 5.5 kPa, oxygen saturation of 93%. Laboratory analysis showed that the D-dimer was elevated (16.5 mg/l). Computed tomography of the thorax showed partial thrombotic mass in both lobar and segmental branches of the medial segment of the right middle lobe and smaller pleural effusions in laterobasal segment of the lower lobe (Figure 3). PE was diagnosed. He was treated with low-molecular-weight heparin (80 mg of enoxaparin twice per day), oxygen, and antibiotics. Other sites of thrombosis were excluded by Doppler sonography of the lower limbs and renal veins. On cardiac echography there were no signs of pulmonary hypertension. Immunology tests were normal. Laboratory analysis showed elevated white blood cell count and C-reactive protein (12.7×10^9/l and 117 mg/l), creatinine 69 umol/l, total protein 51 g/l, albumin 19 g/l, total cholesterol 14.6 mmol/l, and triglyceride 2.9 mmol/l. Urine protein was quantified at 7.4 g / 24 hours, clearance creatinine 128 ml/min. A nephrologist was consulted and the diagnosis of NS was confirmed. Renal biopsy was performed and specimen showed glomeruli with mild thickening of glomerular basement membrane with granular deposition of IgG, compatible with MN. A detailed examination excluded secondary causes of. The treatment was based on the pulse of methylprednisolone (1.5 g over a period of three days), with alternating therapy of oral corticosteroids and cyclophosphamide on a monthly basis during six months. ACE inhibitors, a diuretic, and statin were prescribed. After six months of treatment, proteinuria continues to maintain the high value of 9.6 g / 24 hours. After 12 months, cyclosporin was introduced and we have registered clinical improvement (without leg edema) and incomplete remission of NS with proteinuria of 4.5 g / 24 hours.

DISCUSSION

Membranous nephropathy is the most common cause of the NS in adults [5]. The etiology of approximately 75% of MN cases is idiopathic [6]. The peak incidence occurs in the fourth to fifth decade of life, with predominance in men [7, 8]. Proteinuria is the typical presentation of MN and the NS occurs in 70–80% of patients [9]. Thromboembolism is the most significant life-threatening complication of NS [3, 4]. It can be found in any major blood vessel and incidence varies from 8% to 36% in literature [10, 11]. Most of venous thromboses occur within the first six months after the NS diagnosis [12].

Kayali et al. [13] found that patients with NS had greater risk for both DVT and PE, with a relative risk of 1.72 and 1.39, respectively. In contrast to them, Suri et al. [14] showed that PE was more common than DVT (25.7 versus 16.6%, respectively); however, this study included only 34 pediatric patients with the NS. Kumar et al. [15] confirmed in their examination that idiopathic MN is a prothrombotic state, particularly in the first six months of the diagnosis, and that PE was the most common thromboembolic event in their patients.

According to Annual Report of Kidney Biopsies in Serbia, incidence of the MN in Serbia (observed period 2010–2014) was 9.4–11.7% [16, 17, 18]. In our cases, PE was the first presenting feature of the NS. No other site of thrombosis was detected in our patients. Only one patient experienced, in addition to respiratory symptomatology, swollen legs on admission to the hospital, and the second one reported the known history of swelling. Two of the patients were very young men, and the third one was a middle-aged man. In one patient, urine analysis wasn't done during the first hospitalization, thus delaying confirming the diagnosis of the NS.

Several specific clinical markers are being used for stratifying patients with the risk of thrombotic events, such as a biopsy-proven diagnosis of MN and albumin level < 28g/l in patients with MN.

Barbour et al. [19] analyzed patients with the idiopathic NS and showed that the diagnosis of MN was associated with an increased risk of thromboembolism compared to FSGS and IgAN. Lionaki et al. [20] showed that an albumin level < 28 g/l was independently associated with a higher thrombotic risk. Kumar et al. [15] found that the 24-hour proteinuria > 10 g/day could be regarded as an independent risk factor for thromboembolic events in patients with idiopathic MN, irrespective of the serum albumin. In all of our cases, all the patients had serum albumin < 20 g/l. Two of them had proteinuria > 10 g/day. All the patients had a biopsy-confirmed diagnosis of MN. Considering that they were all treated with anticoagulation therapy, the kidney biopsy was done with great caution, and we didn't detect any relevant complications. By detailed examination, secondary causes of MN were excluded (diabetes mellitus, infection, autoimmune disease, malignancies, effect of drugs). In addition to anticoagulation therapy by heparin or warfarin, they were treated with immunosuppressive protocol for MN. We didn't detect a repeated thromboembolic event. Full remission of the NS was achieved in one patient, while partial remission occurred with other two patients.

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Емболија плућа као први знак нефротског синдрома

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САЖЕТАК

Увод Емболија плућа (ЕП) представља компликацију дубоке венске тромбозе коју карактерише значајан морбидитет и морталитет. Често се јавља код болесника са већ дијагностикованим нефротским синдромом (НС), посебно када је болест у активној фази, али може се јавити и као први знак болести и тада се лако превиди. Мембранозна нефропатија (МН) најчешћи је тип гломерулонефритиса који се повезује са повишеним ризиком за тромбозу.

Приказ болесника Код три мушкараца ЕП је дијагностикована као први знак НС. Сви болесници су на пријему у болницу имали бол у грудима, сув кашаљ и осећај недостатка ваздуха. Један болесник је имао повишену температуру, а друга два су дали податак о отицању потколеница. Компјутеризованом томографијом грудног коша постављена је дијагноза тромбозе плућне артерије. Додатним анализама откривен је НС, а биопсијом бубрега код сва три болесника утврђена је МН. Болесници су лечени пулсевима метилпреднизолона (1,5 *g* током три дана) и наизменичном месечном применом кортикостероида и циклофосфамида *per os* током шест месеци. После завршене шестомесечне терапије, код два болесника је постигнута инкомплетна ремисија НС, а код трећег болесника одржао се НС са нормалном функцијом бубрега.

Закључак Имајући у виду честу појаву тромбоемболијских компликација код НС, код свих болесника са дубоком венском тромбозом и ЕП треба мислити на НС.

Кључне речи: нефротски синдром; мембранозна нефропатија; емболија плућа