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Case Report / Приказ случаја

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Pulmonary Embolism as First Sign of Nephrotic Syndrome

Емболија плућа као први знак нефротског синдрома

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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 diagnosis of NS is being delayed as a result. Membranous nephropathy (MN) is, generally speaking, the most commonly reported glomerulonephritis associated with increased risk of thrombosis.

Case outline This report summarizes our experience with three young male patients (26–year-old, 22-year-old and 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 NS syndrome was confirmed with laboratory analysis, while renal biopsy showed MN. Treatment was based on the pulse of methylprednisolone (1.5g during 3 days), with alternating therapy of oral corticosteroids and cyclophosphamide on monthly basis during six months. After 6 months, two patients reached incomplete remission, while the third one still has NS and normal renal function.

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

Keywords: nephrotic syndrome; membranous nephropathy; pulmonary embolism

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 олако превиди. Мембранозна нефропатија (МН) је најчешћи 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 се 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 г током 3 дана) и наизменичном месечном применом кортикостероида и циклофосфамида *per os* током шест месеци. Након завршене шестомесечне терапије, код два болесника је постигнута инкомплетна ремисија НС, а код трећег болесника је перзисто 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

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 nephrotic syndrome (NS) [3,4]. PE may complicate the course of the NS; in particular, when the disease is already active, or less commonly, it may appear as the first sign of illness and fails to be identified, and then usually delays the diagnosing of NS.

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

REPORT OF CASES

Case 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, elevation in d-dimer (36mg/l) was observed, as well as decrease in antithrombin III activity (76%). Computed tomography of the thorax was done and 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/24h, clearance of creatinine was 181 ml/min. Nephrologist was consulted and 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 (Figure 1 and 2). Detailed examination excluded

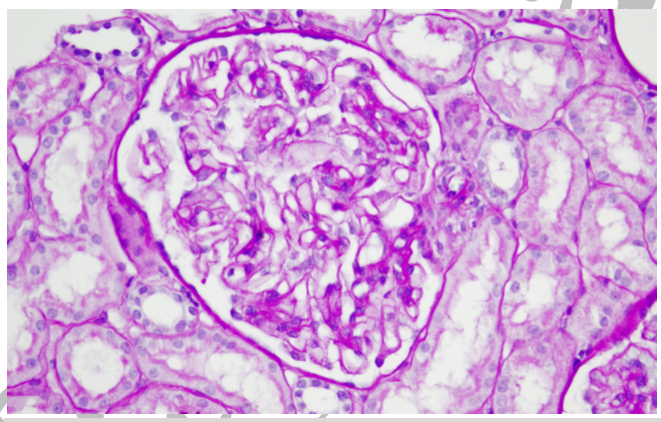

Figure 1. Light microscopy - mild thickening of the glomerular basement membrane, (periodic acid- Schiff reaction, x 400).

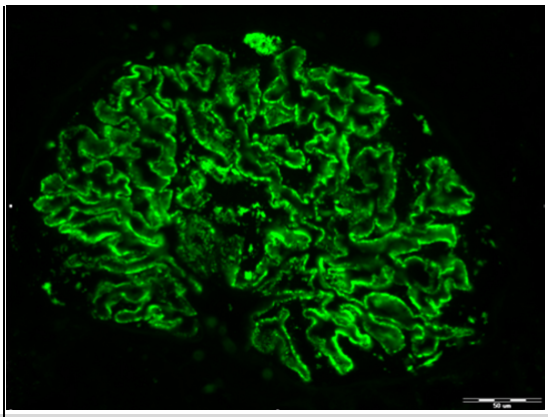

Figure 2. Immunofluorescence microscopy: granular deposition of IgG alongside glomerular basement membrane (x 400).

secondary causes of MN. Treatment was based on the pulse of methylprednisolone (1.5g during 3 days), with alternating therapy of oral corticosteroids and cyclophosphamide on monthly basis during six months. . Symptomatic therapy included ACE inhibitors, diuretic and statin. After 6 months of treatment we registered partial remission of NS and after 12 months complete remission with proteinuria 0.3 g/24h.

Case 2

A 22-year old man was admitted to the Coronary Intensive Care Unit with chest pain and shortness of breath. Few days before the admission to hospital, patient noticed swelling of his legs which disappeared quickly. In initial laboratory, d-dimer was high, while the cardiac enzymes were normal. Electrocardiogram showed sinus tachycardia. The blood gases in arterial blood were normal. Computed tomography of the thorax was performed and it showed thrombosis of the pulmonary artery. He 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. The laboratory analysis showed that the renal function was normal, while total cholesterol was high. Analyses of the urine weren't done. Upon full recovery, he was discharged from the hospital with oral anticoagulation. After 4 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. Nephrologist was consulted and he was admitted to Clinic of 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 2.0 mmol/l. Urine sediment analysis revealed 5-7 red blood cells. Urinary protein excretion was 10 g/24h, clearance of creatinine was 171ml/min. Ultrasound examination revealed enlarged kidneys (12 cm in diameter) with normal parenchymal thickness and echogenicity. Diagnosis of NS was confirmed. His treatment was changed to low molecular weight heparin and percutaneous renal biopsy was done. Specimen showed glomeruli with diffuse thickening of the glomerular basement membrane with granular deposition of IgG, compatible to MN. Detailed examination excluded secondary causes of MN. Treatment was based on the pulse of methylprednisolone (1.5g during 3 days), with alternating therapy of oral corticosteroids and cyclophosphamide on monthly basis during six months. Symptomatic therapy included ACE inhibitors, diuretic and statin. After 6 months of treatment, we registered partial remission of NS, proteinuria decreased at 3 g/24h. After 12 months, the proteinuria continues to maintain the same level.

Case 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 the lower legs. 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 (enoxaparin 80 mg 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 the pulmonary hypertension. Immunology tests were normal. Laboratory analysis showed elevated white blood cell count and C reactive protein ($12.7x10^9$/l and 117mg/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/24h, clearance creatinine 128 ml/min. Nephrologist was consulted and 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 to MN. Detailed examination excluded secondary causes of. Treatment was based on the pulse of methylprednisolone (1.5g during 3 days), with alternating therapy of oral corticosteroids and cyclophosphamide on monthly basis during six months. . ACE inhibitors, diuretic and statin were prescribed. After 6 months of treatment, proteinuria continues to maintain the high value of 9.6 g/24h. After 12 months, cyclosporin was introduced and we have registered clinical improvement (without leg edema) and incomplete remission of NS with proteinuria 4.5 g/24h.

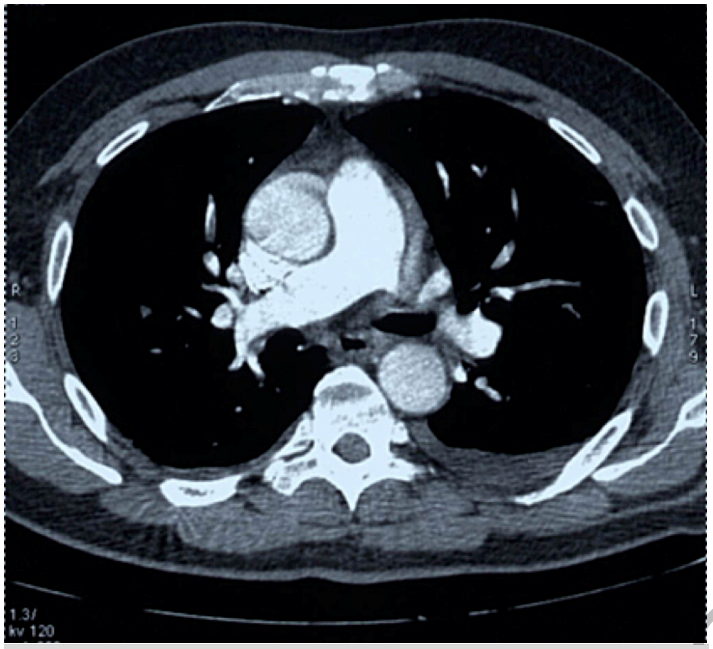

Figure 3. CT of the thorax: thrombosis in lobar branches of the right pulmonary artery.

DISCUSSION

Membranous nephropathy is the most common cause of NS in adults [5]. The etiology of approximately 75% of MN cases is idiopatic [6]. The peak incidence occurs in the fourth to fifth decade of life [7], with predominance of men [8]. Proteinuria is the typical presentation of MN and 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 [10] and incidence varied from 8% to 36% in literature [11]. Most of venous thrombosis occur within the first 6 months after 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%, resp.) but this study included only 34 pediatric patients with NS. Kumar et al. [15] confirmed in their examination that Idiopathic MN is protrombotic state, particularly in the first six months of diagnosis, and that PE was the most common thromboembolic event in their patients

According to Annual Report of kidney biopsies in Serbia, incidence of MN in Serbia (observed period 2010-2014) was 11.7-9.4% [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, besides respiratory simptomatology, swollen legs on admission to the hospital and second one reported known history of swollowing. Two of them were very young men and third patient was a middle-aged man. In one patient, urine analysis wasn't done during the first hospitalization, thus delaying confirming the diagnosis of NS.

Several specific clinical markers are being used for stratifying patients with 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 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-h proteinuria greater than 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 patients had serum albumin <20 g/l. Two of them had proteinuria greater than 10 g/day. All patients had biopsy-confirmed diagnosis of MN. Considering that they were all treated with anticoagulation therapy, 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). Besides anticoagulation therapy by heparin or warfarin, they were treated with immunosuppressive protocol for MN. We didn't detect repeated thromboembolic event. Full remission of NS was achieved in one patient, while partial remission occurred with other two patients.

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