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EDİTÖRE MEKTUP / LETTER TO EDITOR

A case of thromboembolic events as first manifestation of membranous nephropathy

İlk prezentasyonu tromboembolik olaylar ile olan membranöz nefropati olgusu

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To the Editor,

Nephrotic syndrome (NS) is a glomerular disease typically characterized by massive proteinuria (≥3.5 g/24 hours), hypoalbuminemia (<3 g/dL), peripheral edema and hyperlipidemia[1,2]. Patients with NS are at risk of developing thromboembolic complications and may rarely present with thromboembolism as the first presentation of NS. Thromboembolism is one of the life threatening complications of NS and certain incidence and prevalence of thromboembolism in NS is unknown[3]. Increased glomerular permeability is the main mechanism involved in the pathophysiology of NS[4]. Albumin binds to arachidonic acid and prevents its conversion to thromboxane a2 and impairs platelet activation and clot formation. TxA2 levels are elevated in patients with NS due to hypoalbuminemia, thus promoting clot formation and platelet hyperactivity[1]. The net effect resulting from increased urinary excretion of coagulation inhibitors such as antithrombin 3, plasminogen, protein C, protein S and increased hepatic synthesis of coagulation factors such as fibrinogen, factor 5, factor 8, von willebrand factor, decrease in the activity of the fibrinolytic system and activation of the coagulation cascade[5]. Increased hemoconcentration as a result of excessive diuretic therapy may facilitate thrombus formation in these patients who are already prone to clotting[6]. Hyperlipidemia, a common finding in patients with NS, may also cause increased platelet aggregation[1].

We report a case who presented with thromboembolism and was found to have NS as a result of the examinations. Thromboembolism as first presentation of NS is a rare issue.

A 59-year-old male patient presented with a one month history of flank pain, difficulty urinating and progressive swelling of the legs. He applied a clinic with these complaints. Blood, urıne tests revealed hematuria, proteinuria, hyperlipidemia, a computed tomography (CT) scan of the abdomen demonstrated vena cava inferior thrombosis. They started treatment with acetylsalicylic acid and the patient was referred to our nephrology division for further examination and treatment.

He had no prior significant medical history. 35 pack-year active smoking, history of hematuria-1 month ago, use of nonsteroidal antiinflammatory drugs were detected in his anamnesis. On clinical examination he was conscious and alert. His blood pressure was 140/80 mm/Hg, pulse rate was regular at 72 beats/min, body temperature was 36,5 °C. There was bilateral pitting pretibial edema of +2. Other internal system examinations were considered normal.

Laboratory data disclosed the following values: serum creatinine:0.79 mg/dL, GFR:99 mL/min, BUN:25 mg/dL, serum albumin:1.8 g/dL, total protein:5.9 g/dL, serum electrolytes and complete blood count was normal. He had dyslipidemia with elevated total cholesterol 355 mg/dL, low density lipoprotein 246

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mg/dL and triglyceride 203 mg/dL. Anti- HCV and HBsAg serology were both negative. Urinalysis revealed proteinuria (+3), hematuria (+3) by dipstick and a 24-h urinary protein excretion measurement was 12 g/day.

A CT scan of the abdomen demonstrated thrombosis of femoral vein, renal vein and inferior vena cava (Figure 1,2). Warfarin sodium was started in the patient with severe thrombosis, renal biopsy for diagnosis could not be performed because the interruption of treatment for thrombosis was found risky by cardiovascular surgery.

Immunologic markers and tumor markers were normal and phospholipase A2 receptor antibody (antiPLA2R) was positive. The patient was diagnosed as idiopathic membranous glomerulonephritis and treatment was started. Initial treatment with pulse 500 mg/day iv methylprednisolon for 3 days followed by maintenance oral therapy with 64 mg/day methylprednisolon for 7 days was given but he had no response to the treatment. Cyclosporine was added to oral steroid treatment. 24 hours urinary protein excretion measurement was decreased by fifty percent and regressed to 6 g/day on the twenty-first day of adding cyclosporine to the treatment. Other laboratory data revealed as serum creatinine:0.78 mg/dL, GFR:99 mL/min, serum albumin:4.2 g/dL. He was discharged with warfarin sodium, oral steroid and cyclosporin. After discharge he applied to cardiovascular surgery for dose adjustment of warfarin sodium. However, warfarin sodium was changed to rivaroxaban by the cardiovascular surgery because the use of warfarin sodium was irregular and the patient could not comply with the drug use. The patient came to one of the control examinations with complaints of cough and sputum. His physical examination was normal and renal function was stabil but c-reactive protein was high (5.3 mg/dl). He was hospitalized due to infectious processes. Antibiotherapy was given. At his thorax ct there was a suspection of pulmonary embolism. Ventilation perfusion scintigraphy was reported as consistent with moderate-probability pulmonary embolism. And ct scan of throax demonstrated pulmonary embolism at upper lobe of left lung and segmental pulmonary artery branches (Figure 3). Acute kidney injury (AKI) and pulmonary embolism have developed while he was on rivaroxaban. Laboratory data showed serum creatinine:3.2 mg/dL, GFR:20 mL/min, BUN:38 mg/dL, D-dimer:593 ng/mL. On the recommendation of cardiovascular surgery, rivaroxaban was discontinued and enoxaparin sodium was started. 24-hours urine protein decreased to 4 g/day, serum creatinine decreased to 1.5 mg/dL and GFR increased to 50mL/min. And serum albumin value was measured as 4.1 g/dL. AKI regressed without need for hemodialysis and the patient was discharged with low molecular weight heparin.

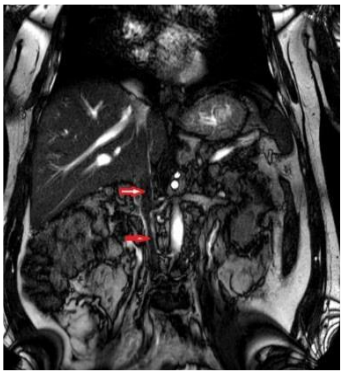

Figure 1. Inferior vena cava thrombosis.

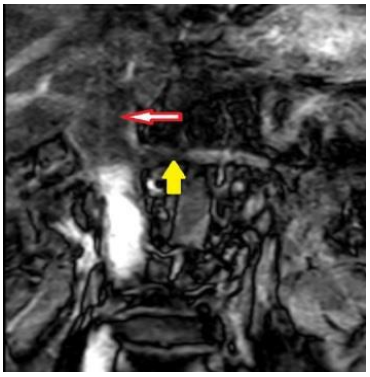

Figure 2. inferior vena cava, renal vein thrombosis.

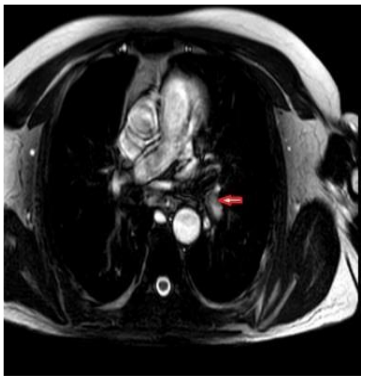

Figure 3. Pulmonary embolism.

In 80% of patients with membranous glomerulonephritis, there is no underlying cause and this is called idiopathic/primary menbranous glomerulonephritis[7]. Renal biopsy is not required to confirm the diagnosis of membranous glomerulonephritis in patients with nephrotic syndrome who test positive for antiPLA2R antibody[8]. As in our case, this test helps the diagnosis,

especially in patients with high bleeding risk who receive anticoagulant therapy. Studies have shown that venous thromboembolism is seen in a wide range of 7-40% in patients with nephrotic syndrome[9]. Although deep vein thrombosis and renal vein thrombosis are more common, pulmonary embolism is also relatively common and can occur asymptomatically[8]. Thromboembolism is the most important life-threatening complication of NS after infections[10]. Like in our case, the risk of thrombosis is greater in patients with nephrotic syndrome who have a 24-hour urine protein more than 10 g/day and serum albumin less than 2 g/dL at baseline[11]. It should be kept in mind that every patient with NS is at risk for thrombosis and even the first presentation of NS may be thromboembolic events. Appropriate anticoagulant prophylaxis should be initiated when necessary. Although cases with nephrotic syndrome in which new oral anticoagulant agents (NOAC) are used in prophylaxis of venous thromboembolism have been reported in the literature, studies investigating the safety of drug use in these patients are needed[8]. Cases with nephrotic syndrome have been reported with recurrent thromboembolism under NOAC prophylaxis. Insufficient plasma levels of highly protein-bound NOAC in the hypoalbuminemic state have been thought to be the reason for its failure to prevent or treat thromboembolism in NS[12].

In conclusion, although thromboembolism is a condition that can be seen in NS, it can rarely be encountered as the first presentation of NS. This situation should not be overlooked and appropriate treatments should be provided without delay. In this case there was a very high risk of morbidity and mortality and with appropriate therapy stabilization of clinic status and renal function was maintained.

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