Upper extremity venous thrombosis associated with primary antiphospholipid syndrome and immunoglobulin M nephropathy in diabetes mellitus type II
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Abstract
Antiphospholipid syndrome (APS) is a disorder characterized by antiphospholipid antibody positivity, arterial or venous thrombosis, and fetal loss. In APS, renal as well as vascular and glomerular involvement is observed. Systemic lupus erythematosus and other connective tissue diseases should be excluded to diagnose primary APS. Immunoglobulin M (IgM) nephropathy is characterized by single or dominant IgM deposition in glomerular mesangium. It often presents with hematuria and proteinuria. In a 45-year-old female patient admitted to our clinic with diabetes mellitus and proteinuria, fundus examination did not reveal diabetic retinopathy but a high anticardiolipin IgM and venous thrombosis in the upper extremity were observed. Renal biopsy revealed IgM nephropathy. The patient was diagnosed with primary APS and IgM nephropathy. Cyclophosphamide and steroid treatment was started. Her proteinuria decreased as a result of the treatment. Although, it is reported in the literature that primary APS coexists with other glomerulonephritis, we did not detect coexistence of primary APS and IgM nephropathy.

Keywords: Anti-phospholipid syndrome, IgM nephropathy, diabetes mellitus

Introduction
Antiphospholipid syndrome (APS) is a clinical entity characterized with thrombotic events (arterial and venous) associated with the presence of anti-phospholipid antibodies (anticardiolipin antibodies, antibeta 2 glycoprotein 1, and lupus anticoagulant), and/or fetal loss. Although APS was initially defined in patients with systemic lupus erythematosus, there are no clinical or laboratory findings showing any other autoimmune diseases in 50% of patients with APS, which is defined as primary APS. Renal involvement is observed in 2.7% of the patients with APS (1). However, due to its high risk, renal biopsy cannot be performed in patients on coagulants. Thus, its real frequency is considered to be higher. Other conditions, such as hypertension and lupus nephritis, frequently contribute to renal involvement in APS. IgM nephropathy is described as isolated or dominant IgM deposition which is defined by immunopathological properties similar to IgA nephropathy and displays generalized diffuse distribution in glomerular mesangium. Idiopathic nephrotic syndrome predominantly develops in both children and adults. Cases with hematuria are also observed less frequently. The disease is more frequently seen in children than in adults.

Case Presentation
A 45-year-old female patient was admitted to our clinic with a complaint of lower extremity edema. Her physical examination revealed a blood pressure of 140/80 mmHg and pretibial edema. She had a history of diabetes mellitus for 6 years and a miscarriage (12 weeks). Laboratory examination showed a serum creatinine of 0.72 mg/dL, total protein of 3.5 g/dL, serum albumin of 1.9 g/dL, low density lipoproteins (LDL) of 190 mg/dL, triglycerides of 187 mg/dL, high density lipoproteins (HDL) of 67 mg/dL, total cholesterol of 282 mg/dL, hemoglobin of 10.7 g/dL, hematocrit of 33%, platelet count of 337,000/mm³, anti-thrombin 3 activity of 102% (80-120), protein C of 200% (70-130), and protein S of 104% (65-140). Amount of proteinuria was 6.9 g in 24-hour urine. Serological viral markers and antinuclear antibodies, anti-double stranded DNA, glomerular basement membrane antibody, cytoplasmic antineutrophil cytoplasm antibodies, and perinuclear antineutrophil cytoplasm antibodies were negative while complements were within normal limits. Fundus examination did not reveal retinopathy. Glomeruli were observed by renal biopsy. Glomerular global sclerosis was observed in one glomerulus and increased mesangial cells and matrix, and glomerular hypertrophy in other glomerulus. Vascular involvement was not detected in renal biopsy.
Direct immunofluorescence examination, mesangial granular IgM was (+ +) and other stains were negative. The patient was diagnosed with IgM nephropathy. Upper extremity doppler ultrasound performed upon detecting a swelling on the left arm revealed a thrombosis in vena baslica in the 5th segment extending to the point where the axillary vein is drained. Thrombosis of the axillary vein was also observed. Magnetic resonance imaging performed for headache showed tonsillar herniation. During her follow-up, anti-cardiolipin IgM level was found to be high. The patient was diagnosed with IgM nephropathy and primary APS. Cyclophosphamide (100 mg/day), valsartan (160 mg/day), atorvastatin (20 mg/day), steroids (0.5 mg/kg/day), and warfarin were started. During her follow-up, the amount of proteinuria (0.5 mg/kg/day), atorvastatin (20 mg/day), steroids (0.5 mg/kg/day), and warfarin were started. During her follow-up, the amount of proteinuria in 24-hour urine decreased to 1.2 g.

**Discussion**

Antiphospholipid syndrome, characterized by recurrent arterial and venous thrombosis, morbidity in pregnancy, thrombocytopenia, and the presence of anti-phospholipid antibodies was defined by Graham Hughes in 1983. Other features of this syndrome have been identified over time. Our case, after exclusion of other connective tissue diseases, was diagnosed as primary APS based on upper extremity vein thrombosis, high anti-cardiolipin IgM, and a history of miscarriage (12 weeks). Warfarin was started at the time of diagnosis.

In this disease, any organ of the body connected to vascular thrombosis may be involved. Renal involvement is one of the most important features of this syndrome. Renal manifestations reflect the extension of the thrombotic process in the renal vascular bed. The main renal artery, intrarenal arteries and arterioles, and glomerular capillaries, and renal vein can be involved; thrombotic lesions and glomerulonephritis (GN) have also been identified in primary APS (2). These lesions are represented by thrombotic microangiopathy, arteriosclerosis, fibrous intimal hyperplasia of arterioles and interlobular arteries, organized thrombi in arteries and arterioles with or without recanalization, fibrous arterial and arteriolar occlusions, and focal cortical atrophy. Clinical manifestations of APS nephropathy are arterial hypertension, acute and chronic renal failure, proteinuria, and hematuria. Our case had proteinuria and hypertension. Renal Doppler did not reveal renal artery stenosis or thrombosis. Thrombosis may occur at any level of the renal vascular tree (intra renal arteries, glomerular capillaries, and renal vein). Renal biopsy of our case did not show glomerular capillary or thrombosis.

In the literature, the frequency of IgM nephropathy has been reported to range between 2%–45% in renal biopsies of adults (3). Membranous GN is the most commonly identified GN in APS (2). Crescentic GN has been reported in primary APS cases (4). Recently, renal diseases associated with APS have been identified in a wide spectrum. Fakhouri et al. (2) identified 29 biopsies performed in patients with APS and reported that 9 of the said cases had pathological features distinct from vascular nephropathy. Namely, membranous nephropathy in three cases, minimal change disease/focal segmental glomerulosclerosis in three cases, mesangial C3 nephropathy in two cases, and pauci-immune crescentic GN in one case.

Significantly higher frequency of anti-phospholipid antibodies [IgG or IgM anticardiolipin antibodies (ACA) or lupus anti-coagulant] has been reported in patients with types 1 and 2 diabetes with macroangiopathy than in patients with uncomplicated diabetes or controls (5). On the other hand, Tarkun et al. (6) could not find any association between retinopathy and nephropathy. In a study conducted by Calvo-Romero on 56 patients with type 2 diabetes mellitus, only one patient had a titer of IgM ACA higher than 15 MPL units, six patients had low IgM ACA titers (4-15 MPL units), no patient had a titer of IgG ACA higher than 15 GPl units, and 18 patients had low IgG ACA titers (4-15 GPl units) (7). In a series of 205 patients with type 1 or type 2 diabetes mellitus, only one patient had moderate to high IgM ACA titers (>20 GPl units) (8).

In a study conducted by Zwi et al. (9) on 93 patients with type 2 diabetes mellitus, 32% of the patients had isolated diabetic nephropathy (DN), 49% had coexistence of DN and non-diabetic renal disease (NDRD), and 18% had isolated NDRD. In the said study, the most common NDRD was found to be focal segmental glomerulosclerosis (9) Byun et al. (10) studied 110 patients having type 2 diabetes mellitus and found that 37.3% had ND, 53.6% had NDRD, and 91% had NDRD superimposed on DN. Immunglobulin A nephropathy (43.5%) was found to be the most common NDRD while membranous GN accounted for 14.5% of all NDRD, followed by crescentic GN (7.2%), tubulointerstitial nephritis (4.3%), minimal change disease (2.9%), membranous GN (1.4%), focal segmental glomerulosclerosis (1.4%), lupus nephritis (1.4%), and others (20.3%).

Glomerulonephritis associated with APS is treated using steroids, immunosuppressant drugs, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, aspirin, and anticoagulants (2). We treated the present case with oral cyclophosphamide, prednisone, angiotensin receptor blockers, and Coumadin. After a three months follow-up, 24 hours urine protein was reduced to 1.2 g, lipid profile was normal and serum albumin level was 2.8 g/dL.

As a result, it should be considered that both the primary APS and IgM mesangial GN may have a role in the etiology of venous thrombosis. We believe that the combination of antiphospholipid antibody syndrome and nephrotic syndrome would further increase the risk of thrombosis. Thus, we recommend investigating APS in cases of nephrotic syndrome causing thrombosis.

**Informed Consent**: N/A.

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**References**