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The Association of Upper Extremity Deep Vein Thrombosis and Homozygosity for the MTHFR 1298A-C Mutation in a Young Women with Membranoproliferative Glomerulonephritis

Membranoproliferatif Glomerülonefrit Tanılı Genç Kadın Hastada Üst Ekstremite Derin Ven Trombozu ve Homozigot MTHFR 1298A-C Mutasyonu Birlikteliği

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ABSTRACT

Nephrotic syndrome increases the tendency to thromboembolic complications in both adults and children. Changes in the plasma concentrations of many proteins concerned with regulation of clotting and fibrinolytic systems, hyperviscosity, dehydration, corticosteroid and diuretic therapy may also contribute to thromboembolism. In addition, some of the genetic disorders also increase tendency to thromboembolic events. One of these disorders is methylene tetrahydrofolate reductase (MTHFR) A1298C mutation, which may cause hyperhomocysteinemia and thrombotic events when the folate level is low. A 26-year-old female was admitted to hospital with upper extremity deep vein thrombosis and nephrotic range proteinuria. On her renal biopsy, membranoproliferative glomerulonephritis (MPGN) was found. The other causes of thrombosis were excluded and homozygosity for the MTHFR A1298C mutation was determined. The levels of homocysteine and folic acid were normal. We report a first case of MPGN together with homozygosity for MTHFR 1298C mutation in adult nephrotic syndrome, complicated with unusual upper extremity venous thrombosis.

KEY WORDS: Membranoproliferative glomerulonephritis, Nephrotic syndrome, Thrombosis, MTHFR A1298C homozygote mutation

ÖZ

Nefrotik sendrom erişkinlerde ve çocuklarda tromboembolik komplikasyonların artışına neden olmaktadır. Plazmadaki pıhtılaşma ve fibrinolitik sistemde görevli birçok protein konsantrasyonundaki değişikliklerin yanı sıra hiperviskozite, dehidratasyon, kortikosteroid ve diüretik tedavi gibi faktörler tromboembolik olaylara yol açmaktadır. Bunlara ek olarak bazı genetik bozukluklarda tromboembolik olaylara neden olabilmektedir. Bunlardan birisi de oldukça nadir görülen metilen tetrahidrofolat redüktaz (MTHFR) A1298C mutasyonudur. Bu mutasyonun varlığı folat düzeyi düşük olan bireylerde hiperhomosisteinemi ve trombotik olaylara neden olabilmektedir. 26 yaşında bayan hasta üst ekstremite derin ven trombozu ve nefrotik proteinüri ile hastanemize başvurmuştur. Yapılan renal biyopside membranoproliferatif glomerülonefrit (MPGN) saptanmıştır. Hastada tromboza neden olabilecek diğer faktörler dışlanmış ve MTHFR A1298C mutasyonunun eşlik ettiği tespit edilmiştir. Serum homosistein ve folik asit düzeyleri normal bulunmuştur. Üst ekstremite derin ven trombozu ile başvuran ve beraberinde MPGN ile homozigot MTHFR A1298C mutasyonu saptanan hastamız literatürde birlikteliği bildirilmemiş nadir bir olgu olması nedeniyle sunulmuştur.

ANAHTAR SÖZCÜKLER: Membranoproliferatif glomerülonefrit, Nefrotik sendrom, Tromboz, MTHFR A1298C homozigot mutasyon

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INTRODUCTION

Primary and secondary nephrotic syndrome are associated with an increased risk for thrombosis or embolism compared with the general population (1,2). Both venous and arterial thrombosis have been noted in nephrotic syndrome (1,3). Deep vein thrombosis (DVT) develops in approximately 15% of patients with the nephrotic syndrome (4). The risk for DVT seems to be higher when the serum albumin concentration is < 2.5 g/dl. The underlying factors of the thrombosis are multiple but seem to related to an imbalance of prothrombotic factors (*e.g.*, increased fibrinogen levels, increased factor VIII levels, increased platelet adhesiveness) and antithrombotic factors (*e.g.*, reduced antithrombin III levels, reduced protein C and S levels or activity) and impaired thrombolytic activity (decreased plasminogen levels, elevated plasminogen activator inhibitor-1 levels or albumin deficiency related impairment of the interaction of plasminogen-fibrin) (1,5). Volume depletion, diuretic agents with or without steroid therapy, venous stasis, immobilization, or immune complex activation of the clotting cascade may also affect thrombosis in nephrotic syndrome. In addition some of the genetic disorders also increase tendency of thromboembolic events. The coexistence of hereditary resistance to the activation of protein C (Leiden trait), methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C mutation and prothrombin 20210 mutation may be another factor in the generation of thrombotic events (6).

We report a first case of MPGN together with homozygosity for MTHFR A1298C mutation in adult nephrotic syndrome, complicated with unusual upper extremity venous thrombosis.

CASE REPORT

A 26-year-old female was referred to the invasive radiology department for the treatment of left upper extremity deep vein thrombosis (Figure 1). She had admitted to a doctor for sudden onset of pain on her left arm one week ago. She had no history of any systemic disease. Her physical examination revealed blood pressure of 120/70 mmHg, ascites, lower extremity pitting edema and marked pleural effusion.

Evaluation on admission serum testing showed hemoglobin 10.5 g/dL, platelet count $447\times10^3/\mu$L, blood urea nitrogen 10 mg/dL, serum creatinine 0.8 mg/dL, sodium 138 mEq/L, potassium 4.7 mEq/L albumin 1.5 g/dL, total cholesterol 313 mg/dL, and triglyceride 426 mg/dL. The liver function tests, prothrombin time, and activated partial thromboplastin time were normal. The fibrinogen concentration and antithrombin III level were normal. The concentration of free protein S and protein C were 81.0% (normal 60-140 %) and 110.0 % (70-130 %) respectively. Thyroid function tests were normal. Plasminogen and platelet aggregation test were not performed. Examination of urine sediment showed 6-8 erythrocyte and 6-8 leucocytes in each area. Repeated urine cultures were sterile. Twenty-four hour urine collection revealed proteinuria of 6 g/day, and creatinine clearance rate was estimated at 117 ml/min. Serological tests for anti-nuclear antibodies, double stranded DNA antibodies were normal and viral serology including HIV, hepatitis B surface antigen and core antigen and hepatitis C antibody were negative. Serum complement levels (C3, C4), homocycteine and folic acid were normal. Anticardiolipin IgM was < 2 MPL unit/mL (normal <12 MPL unit/mL). Anticardiolipin IgG was 3.03 GPL unit/mL (normal <12 GPL unit/mL). The thrombus in the subclavian vein, brachiocephalic vein and superior vena cava was removed with an aspiration thrombectomy procedure. Control venography showed that the procedure was succesful and thrombus clearance was nearly complete (Figure 2). Supportive care for the deep vein thrombosis was initiated and she received anticoagulation therapy with low molecular weight heparin.

A renal biopsy was performed in January 2011 to determine the cause of the patient's nephrotic syndrome. The renal biopsy specimen contained 16 glomeruli. Microscopic evaluation revealed that six of the 16 glomeruli were sclerotic and other glomeruli showed a lobular pattern, mesangial hypercellularity, and diffuse glomerular capillary wall thickening, Immunofluorescence staining demonstrated granular glomerular basement membrane and variable mesangial staining only with C3. The biopsy and immunofluorescence staining findings were consistent with membranoproliferative glomerulonephritis (Figure 3).

While screening for the causes of thrombosis gene mutations, homozygosity for the MTHFR A1298C mutation was found.

Based on the renal biopsy findings, the patient was started on 0.5 mg/kg/day oral prednisolone in two divided doses,

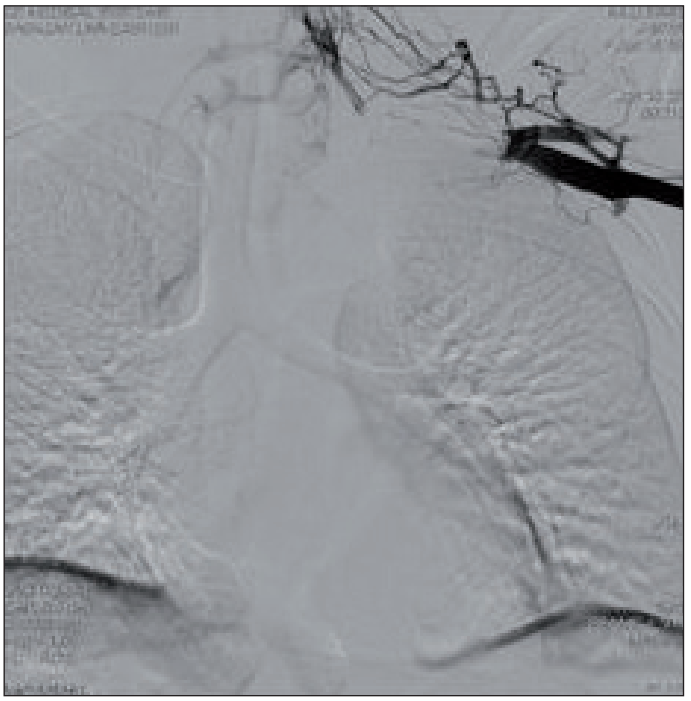

Figure 1: *Occlusion in the subclavian vein.*

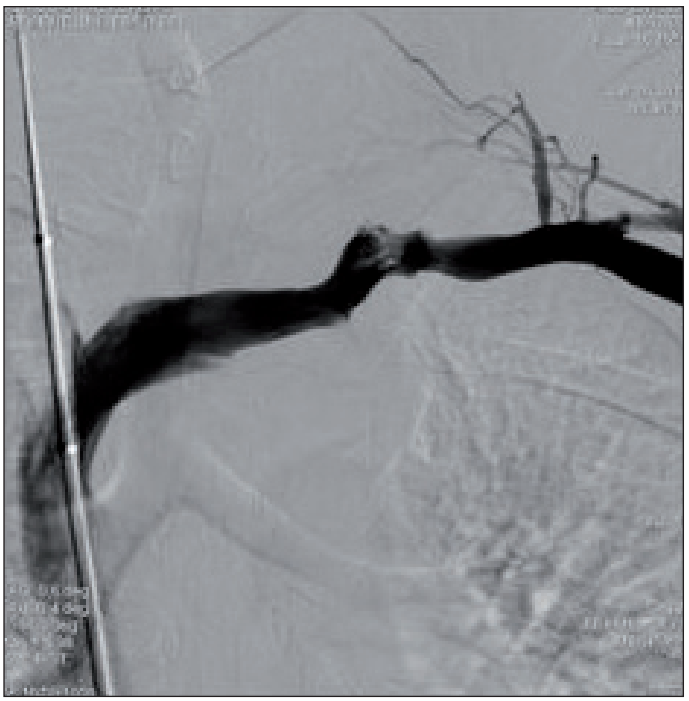

Figure 2: *That the occlusion has been removed after the procedure.*

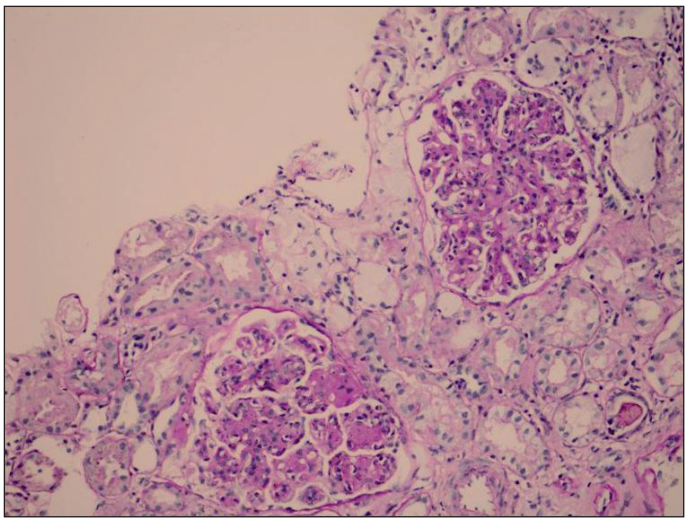

Figure 3: *Glomeruli show global increased cellularity and lobular pattern. x200 H.E, Right, Periodic-acid-Schiff x200.*

Angiotensin II receptor blocking agent Valsartan 80 mg/day and Atorvastatin 10 mg/day. After the thrombosis was removed with endovascular treatment she received Coumadin 5 mg/day. The Hematology Department added folic acid 5 mg/day.

DISCUSSION

Thromboembolic complications are well known as clinically important sequelae and the incidences of both venous and arterial thrombosis are much higher in patients with nephrotic syndrome compared to estimates in the general population (7). In a retrospective study of 298 (predominantly adult) patients who presented with the nephrotic syndrome, the absolute risk of venous thrombosis was 1.02 percent per year, which is eight times higher than that observed in a general population (8).

The reported risk for thromboembolism in these disorders varies widely, depending on the causes of nephrotic syndrome or severity of the nephrotic state. The risk is highest with membranous nephropathy followed by membranoproliferative glomerulonephritis (MPGN) and minimal change disease (9,10). The risk for thromboembolism seems to be higher when serum albumin concentration is < 2.0 to 2.5 g/dL.

Membranoproliferative glomerulonephritis is an uncommon kidney disorder characterized by mesangial cell proliferation and structural changes in glomerular capillary walls. This lesion can occur in an idiopathic form, or much more commonly, secondary to a wide variety of disorders, including monoclonal immunoglobulin deposition diseases, autoimmune diseases (such as systemic lupus erythematosus), chronic thrombotic microangiopathies, disorders of complement metabolism, hereditary disorders, and chronic infections (mainly hepatitis C) (11).

Idiopathic MPGN is one of the least common types of glomerulonephritis, accounting for approximately 4 and 7% of primary renal causes of nephrotic syndrome in children and adults, respectively (2). In our patient secondary cause of MPGN was excluded because the serological tests for anti-nuclear antibodies and double stranded DNA antibodies were normal and viral serology including HIV, hepatitis B surface antigen and core antigen and hepatitis C antibody were negative.

Both acute and chronic renal vein thrombosis and deep venous thrombosis of the lower extremities are well known as clinically important complications in patients with nephrotic syndrome. However, upper limb venous thrombosis is an infrequent complication in nephrotic syndrome. Dickey W et al. reported an upper limb venous thrombosis case associated with nephrotic syndrome secondary to amyloidosis (12). As far as we know, our patient is the first reported case of MPGN complicated with upper limb venous thrombosis.

The risk of thrombosis has been attributed to a variety of intrinsic factors, including coagulation protein abnormalities, impaired fibrinolysis, and increased platelet aggregation as well as dehydration, trauma, diuretic and corticosteroid use. A mutation in the factor V and methylenetetrahydrofolate reductase (MTHFR) gene, the commonest inhered risk factor for venous thrombosis, may contribute to the risk of both arterial and deep vein thrombosis in patients with nephrotic syndrome.

Methylenetetrahydrofolate reductase catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for homocysteine remethylation to methionine (13).

Two frequent thermolabile MTHFR polymorphisms (MTHFR 677C-T, and MTHFR, 1298A-C) were investigated in several diseases. Homozygote state for the MTHFR 677C-T allele has been associated with elevated plasma homocysteine levels and an important genetic risk factor thromboembolism. There are many articles connecting MTHFR mutations, mostly MTHFR 677C-T, with plasma homocysteine levels (14,15). Several meta-analyses showed a positive association of MTHFR mutations with vascular diseases (16-18) although several did not (19,20). The association of arterial thrombosis and homozygosity for the MTHFR-677T gene mutation has been reported in a child with MPGN and membranous glomerulonephritis (21). Hyperhomocysteinemia and folic acid abnormality were not found in our patients and she had homozygous MTHFR 1298C mutation. A second polymorphism, MTHFR 1298C-A, is not as well characterized compared to MTHFR- 677C-T mutation.

We report a case of upper extremity deep vein thrombosis and homozygote state for the MTHFR-1298C mutation in a young woman. Serological tests for anti-nuclear antibodies and double-stranded DNA antibodies were normal and viral serology including HIV, hepatitis B surface antigen and core antigen and hepatitis C antibody were negative.

We did not find any reported case associated with MTHFR 1298C mutation and venous thromboembolism in adult patient with nephrotic syndrome. This is therefore the first reported case of MPGN together with homozygosity for MTHFR 1298C mutation in adult nephrotic syndrome, complicated with an unusual upper extremity venous thrombosis. In conclusion, screening for genetic disorders such as MTHFR gene mutation, may be beneficial in patients with nephrotic syndrome with unusual localized thromboembolic events.

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