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A Case of Focal Segmental Glomerulosclerosis Accompanied By Truncus Arteriosus: Effectiveness of Angiotensin Receptor Antagonist and Cyclosporine A

Truncus Arteriosus ile Birlikte Görülen Fokal Segmental Glomerülosklerоz Olgusu: Anjiyotensin Reseptör Antagonisti ve Siklosporin A'nın Etkinliği

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ABSTRACT

Although glomerular injury has been recognized as a prominent complication of cyanotic congenital heart disease (CCHD), the nephrotic syndrome is rarely observed. A 23-year-old male with CCHD presented with edema in the eyelids and ankles since three months. He was cyanotic at birth and was diagnosed as having persistent truncus arteriosus and atrial septal defect. On admission, blood pressure was 130/90 mmHg and heart rate 76/minute. Laboratory findings revealed 5 g/day proteinuria, hemoglobin 17.1 g/dL, hematocrit 55.5%, serum creatinine 1.8 mg/dL, total protein 4.1 g/dL, serum albumin 2.2 g/dL and hypoxemia. Renal biopsy was performed and showed global sclerosis and focal segmental glomerulosclerosis (FSGS). Phlebotomy was performed and prednisolone 1 mg/kg/day and losartan 100 mg/day were started. After three months, cyclosporine A (CsA) (5 mg/kg/day) was added to the treatment with a proteinuria level of 5.9 g/day. On the eight month of treatment proteinuria was reduced to 1.9 g/day with a serum creatinine level of 1.5 mg/dL, and albumin 3 g/dL. In this rare case, partial remission which was achieved by CsA and angiotensin receptor antagonist showed the important role of glomerular hyperfiltration in the development of CCHD-associated FSGS. When the secondary FSGS causes were ruled out, CCHD should be kept in mind and echocardiographic assessment should be performed.

KEYWORDS: Glomerulonephritis, Focal segmental glomerulosclerosis, Truncus arteriosus, Cyanotic congenital heart disease, Nephrotic syndrome, Cyclosporine

ÖZ

Glomerül hasarı, siyanotik konjenital kalp hastalığının (SKKH) önde gelen komplikasyonlarından olmasına rağmen, bu hastalarda nefrotik sendrom nadir olarak gözlenmektedir. SKKH olan 23 yaşında erkek hasta 3 aydır devam eden göz kapaklarında ve ayak bileklerinde ödem yakınması ile başvurdu. Doğumunda siyanotik olan hastaya, o dönemde yapılan incelemeler sonucunda persistan trunkus arteriosus ve atrial septal defekt tanıları konulmuş. Başvuru sırsında, kan basıncı 130/90 mmHg ve kalp hızı 76/dakika idi. Laboratuvar incelemelerinde; 5 gr/gün proteinüri, hemoglobin 17,1 g/dL, hematokrit %55,5, serum kreatinin 1,8 mg/dL, total protein 4,1 g/dL, albumin 2,2 g/dL ve hipoksemi saptandı. Böbrek biyopsisi yapıldı ve sonucunda glomerüllerde global skleroz ve fokal segmental glomerülosklerоz (FSGS) görüldü. Tedavi olarak flebotomi, prednizolon 1 mg/kg/gün, losartan 100 mg/gün başlandı. Tedavinin 3. ayında proteinüri değeri 5,9 g/gün saptanınca siklosporin A (CsA) (5 mg/kg/gün) tedaviye eklendi. Tedavinin 8. ayında proteinüri 1,9 g/gün, serum kreatinin 1,5 mg/dL ve serum albumin 3 g/dL bulundu. Nadir görülen bu olguda, CsA ve anjiyotensin reseptör antagonisti ile elde edilen kısmi remisyon, SKKH ile ilişkili FSGS gelişiminde glomerüler hiperfiltrasyonun önemli bir rol oynadığını göstermektedir. Ayrıca FSGS'li olgularda sekonder FSGS nedenleri gözden geçirilirken, hastalar SKKH açısından sorgulanmalı ve ekokardiyografik değerlendirme yapılmalıdır.

ANAHTAR SÖZCÜKLER: Glomerülonefrit, Fokal segmental glomerülosklerоz, Trunkus arteriosus, Siyanotik konjenital kalp hastalığı, Nefrotik sendrom, Siklosporin

INTRODUCTION

Persistent truncus arteriosus is a rare but serious anomaly in which a single vessel forms the outlet of both ventricles and gives rise to the systemic, pulmonary, and coronary arteries (1). Glomerular injury has been recognized as an important complication of cyanotic congenital heart disease (CCHD). The structural characteristics of glomerular injury in patients with CCHD have been described as glomerulomegaly, capillary dilatation, thickening of the capillary walls, focal or diffuse proliferation of mesangial cells and segmental or global glomerulosclerosis (2). Glomerular enlargement accompanied by the development of focal segmental glomerulosclerosis (FSGS) also occurs in the setting of hypoxemia in patients with CCHD. Although proteinuria is the major urinary abnormality in patients with CCHD, the nephrotic syndrome is an uncommon complication and renal biopsy has been seldom performed. The treatment of nephrotic syndrome in secondary FSGS is still a matter of controversy. There have been few clinical reports examined the drug treatment of nephropathy in CCHD (3, 4). Here, we report on a patient with CCHD complicated by nephrotic syndrome that was responded to treatment with an angiotensin-II type 1 receptor blocker (ARB) and cyclosporine A (CsA).

CASE

A 23-year-old male with CCHD presented with edema in the eyelids and ankles since three months. He was cyanotic at birth and was diagnosed as having persistent truncus arteriosus and atrial septal defect. The patient had no history of kidney disease, diabetes mellitus or liver disease. There was no history of kidney disease in his family. His medication consisted of 25 mg of metoprolol and 100 mg of acetylsalicylic acid. On admission, he had pretibial edema, the body mass index was 22.7 kg/m2, blood pressure was 130/90 mmHg and heart rate 76/minute. A grade 3/6-flow murmur was audible at the upper left sternal border with splitting of the second heart sound throughout respiration on cardiac auscultation. A high-pitched diastolic murmur over the mid-sternum was also heard. Laboratory findings revealed 5 g/day proteinuria, hemoglobin 17.1 g/dL, hematocrit 55.5%, serum creatinine 1.8 mg/dL, total protein 4.1 g/dL, serum albumin 2.2 g/dL and hypoxemia (sO2 91%, PaO2 62 mmHg, and PaCO2 46 mmHg). Examination of the urine sediment revealed no red blood cells, white blood cells or casts. Echocardiography revealed persistent truncus arteriosus, atrial septal defect and left ventricular hypertrophy in combination with right ventricular hypertrophy and truncal valve regurgitation (Figure 1). After consultations with cardiology and cardiovascular surgery consultants, no cardiovascular surgery was recommended and the patient was considered inoperable because of his age and concomitant renal failure. Renal biopsy was performed because of the nephrotic syndrome and the glomeruli were found to be markedly increased in size; of eleven glomeruli, two showed global sclerosis and three had FSGS (Figure 2). There was also mild interstitial fibrosis. The patient was screened for other causes of FSGS. He had no history of heroin abuse, his BMI was normal and anti-HIV serology was negative. Phlebotomy was performed and prednisolone 1 mg/kg/day and losartan 100 mg/day were started. On the first month of treatment, serum uric acid was found to be 13.4

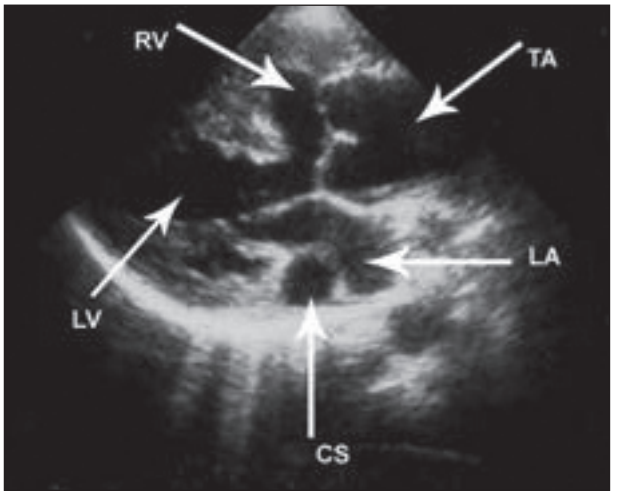

Figure 1: *Echocardiographic image of the patient revealed persistent truncus arteriosus (TA), atrial septal defect (ASD) and left ventricular (LV) hypertrophy in combination with right ventricular (RV) hypertrophy and truncal valve regurgitation (LA: left atrium, CS: coronary sinus).*

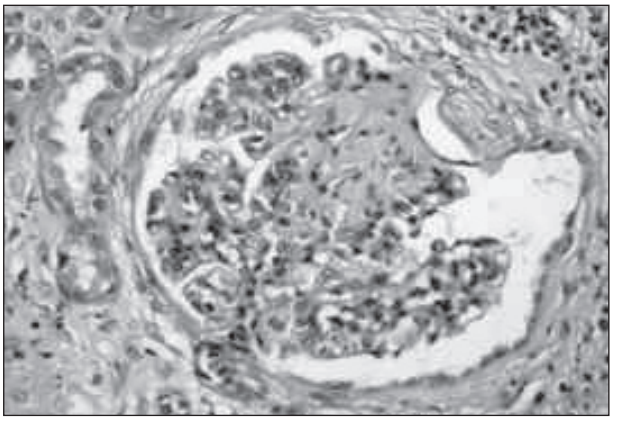

Figure 2: *Light micrograph of renal biopsy specimen from the patient with CCHD. The size of the glomeruli is increased and FSGS of glomeruli was also observed. PAS, periodic acid-Schiff, original magnification x200.*

mg/dL and allopurinol 150 mg/day was initiated. After three months on prednisolone (1 mg/kg/day) and losartan (100 mg/day) treatment, he had no response and he was classified as steroid-resistant nephrotic syndrome with a proteinuria level of 5.9 g/day. Cyclosporine A (CsA) (5 mg/kg/day starting dose, followed by tapering to reach the minimum dose required for maintaining CsA serum trough levels between 50 and 150 ng/mL) was added to the treatment, losartan 100 mg/day was continued and the daily dose of prednisolone was reduced gradually. On the fifth month of CsA treatment proteinuria was reduced to 1.9 g/day with serum creatinine level of 1.5 mg/dL, hemoglobin 15.2 g/dL, hematocrit 46.4%, serum total cholesterol 186 mg/dL, serum albumin 3 g/dL and uric acid level of 8.5 mg/dL.

DISCUSSION

The pathogenesis of glomerulopathy and FSGS associated with CCHD is still unclear. Several contributing factors, including elevated hematocrit, hyperviscosity, chronic hypoxia, increased venous pressure, and glomerular hyperfiltration, seem to be involved in the glomerulopathy associated with CCHD (5). In previous reports, blood hyperviscosity was frequently seen in patients with CCHD and caused an overall increase in renal vascular resistance with an increment of intraglomerular blood pressure (6,7). Despite a slow flow of blood in the glomerular capillary bed, the effective filtration pressure was adjusted to conserve the glomerular filtration rate. Diminished glomerular filtration rate, proteinuria, and glomerulomegaly with segmental sclerosis are found in late survivors with CCHD (6,7). On the other hand, hyperfiltration has been considered to be one of the most plausible pathological entities associated with FSGS and glomerulomegaly (6, 7). Other contributing factors to secondary FSGS such as obesity, drug abuse (heroin) and anti-HIV seropositivity were also not found in this patient.

Hypoxia, elevated hematocrit, polycythaemia, and hyperdynamic circulation could play pathogenic roles in the CCHD-associated glomerulopathy in the present case. In this regard, the partial effectiveness of ARB and especially losartan in the present case may be due to a reduction in intraglomerular pressure.

Hyperuricemia is also common in patients with CCHD. The role of the kidney in causing basic biochemical disturbances, and the relative importance of impaired urate excretion versus urate overproduction have not been established. High plasma uric acid levels in late survivors with CCHD are suggested to be secondary to an inappropriately low fractional uric acid excretion (8). The ARB losartan has been shown to provoke uricosuria, a phenomenon not observed with other angiotensin-1 receptor antagonists (9). Losartan may also have had beneficial effects on uric acid levels in the present case.

As mentioned previously, hypoxia, elevated hematocrit, and polycythaemia may be contributory factors for glomerulopathy in CCHD, but they may not be prerequisites. An association between glomerular damage and duration of cyanosis was reported in CCHD patients (10, 11). However, the glomerular lesions were not always correlated with the degree of oxygen desaturation or polycythaemia in CCHD. Phlebotomy is an important treatment option in a CCHD patient, as it reduces the hematocrit and also decreases proteinuria (10, 11). Reduced blood viscosity seems to exert beneficial effects on hypoxia and glomerular permeability with arterial oxygen transport higher at normal hematocrit levels (12,13).

In the presented CCHD case, which had no chance of cardiovascular operation, the same treatment options as in primary FSGS were considered. Cyclosporine A (CsA) has been employed in the treatment of FSGS (14). The influences of CsA on permselectivity, charge selectivity, and impairment of glomerular filtration rate have been discussed as mechanisms of action (15-17). Because CsA is known to cause preglomerular vasoconstriction (16,17), a reduction in filtration through a decrease in glomerular plasma flow or ultrafiltration pressure could reduce proteinuria on a purely hemodynamic basis.

In conclusion, we considered that the patient's nephrotic syndrome could originate from CCHD after exclusion of other causes of FSGS. CCHD should be kept in mind and echocardiographic assessment should be performed when the secondary FSGS causes are ruled out. Additionally, the partial remission which was achieved by CsA and ARB in our case primarily showed the important role of glomerular hyperfiltration in the development of CCHD-associated FSGS.

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