Nephrotic Syndrome Due to Metformin

Metformine Bağlı Nefrotik Sendrom

ABSTRACT

Heavy proteinuria and nephrotic syndrome may occur in association with a wide variety of primary and systemic diseases and also with drugs. Major drugs that can induce nephrotic syndrome and glomerular damage are gold, penicillamine, bucillamine and non-steroidal anti-inflammatory drugs. In nephrotic syndrome due to these drugs, the major type of renal disease is membranous glomerulonephritis and the nephropathy resolves completely when the drug is withdrawn. Here we report a patient who developed nephrotic syndrome after the initiation of metformin. Laboratory parameters improved rapidly after the discontinuation of the drug. Our case is important as it is the first case with nephrotic syndrome due to metformin in the literature.

KEY WORDS: Proteinuria, Nephrotic syndrome, Metformin, Drug nephropathy

ÖZ

Ağır proteinüri ve nefrotik sendrom primer, sekonder hastalıklar ya da ilaçların değişik oranlarda katkıları ile birlikte oluşabilir. Altın, penisilamin, busilamin ve steroid olmayan yangı giderici ilaçlar nefrotik sendrom ve glomerüler hasarı oluşturan önemli ilaçlardır. Bu ilaçlardan dolayı oluşan nefrotik sendromda renal hastalığın önemli tipi membranöz glomerülonefrittir ve ilaç kesildiği zaman nefropati tamamı ile gerileyebilir. Biz metformin başlandıktan sonra nefrotik sendrom gelişen olguyu rapor ediyoruz. Laboratuvar parametreleri ilaç kesildikten sonra hızlı birşekilde iyileşmişti. Bizim olgumuz literatürde metformine bağlı nefrotik sendrom olan ilk olgu olmasından dolayı öneme sahiptir.

ANAHTAR SÖZCÜKLER: Proteinüri, Nefrotik sendrom, Metformin, İlaç nefropatisi

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INTRODUCTION

Heavy proteinuria and the nephrotic syndrome may occur in association with a wide variety of primary and systemic diseases. In adults, approximately 30 percent have a systemic disease such as diabetes mellitus, amyloidosis, or systemic lupus erythematosus; the remaining cases are usually due to primary renal disorders such as minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy (1, 2)

Nephrotic syndrome can be induced by drugs. Major drugs that induce drug-related nephrotoxicity are antibiotics, NSAID, radiocontrast media, anticancer drug and antirheumatic drugs. Drug-induced nephropathy can cause various forms of renal diseases. The nephropathy consists of acute tubular necrosis, acute tubulointerstitial nephritis, pre-renal type renal failure, obstructive renal failure, chronic tubulointerstitial nephritis and glomerular damage (3, 4).

Major drugs that induce nephrotic syndrome and glomerular damage are gold, penicillamine, bucillamine and NSAID. In the nephrotic syndrome due to these drugs, the major type of renal disease is membranous glomerulonephritis and the nephropathy resolves completely when the drug is withdrawn; renal function does not deteriorate, and corticosteroids are unnecessary (3-5).

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Our case is important as it is the first case with serious proteinuria due to metformin in the literature.

Here, we report a case with nephrotic range proteinuria that developed during treatment with metformin.

CASE REPORT

A 49 year-old woman patient presented with a 2-3 week history of fatigue and progressive-diffuse peripheral oedema and was hospitalized in 11 November 2012. Her previous history was unremarkable; however, she had used metformin 2*500 mgr in the last month.

On physical examination, blood pressure was 130/80 mmHg and pulse72 per min. Symmetrical 3+ pretibial oedema was found. Her eye examination did not show hypertensive or diabetic retinopathy.

Before the use of metformin, blood count, clotting, serum electrolytes ,renal functions, lipid profile and liver function values were all normal. The microscopic examination of urine was normal.

One month after starting metformin, blood chemistry revealed hypoproteinemia with total protein of 4.5 g/dl (normal 6.0-8.5) and albumin of 2.0 g/dl (normal 3.5-5), and hyperlipidemia with total cholesterol of 454 mg/dl (normal 112-200). LDL cholesterol was 207 mg/dl (normal 0-100), triglyceride level was 1320 mg/dl. A 24-h urine collection identified 7.45 g of protein. Other hematological and biochemical parameters were within normal limits. The microscopic examination of urine was normal. Hepatitis markers and anti nuclear antibody were negative Complement levels were also normal. Serum immunoglobulin and serum protein electrophoresis were normal. Renal ultrasonographic evaluation was normal.

A total of 18 glomeruli were seen in the renal biopsy specimen. Two of them were globally sclerotic. One of two glomeruli showed mild increase in mesangial matrix and mesangial hypercellularity. Other glomeruli, tubular, vascular, interstitium were normal. Immunofluorescence study did not show immune deposits (Figure 1).

The diagnosis was nephrotic syndrome due to metformin usage with these findings.

A month after metformin was discontinued, her renal function improved with 80% reduction of proteinuria to 1.59 g/day. The albumin, which had decreased to a maximum of 1.8- 2 g/dl increased to 3.4 mg/dl at this time and lipids were normal.

At 2 months after diagnosis, proteinuria of 7.45 g/day had reduced to 1.1 g/day Serum albumin increased to 3.6 mg/dl and the LDL cholesterol level decreased to 74 mg/dl.

Monthly controls were continued during this period. The serum albumin levels were normal and proteinuria level was about < 300 mg/day.

DISCUSSION

Drug-induced kidney disease is an important cause of acute renal failure and chronic kidney disease. Drug-induced nephropathy can show various forms of renal diseases by various mechanisms. Some mechanisms are decreased renal perfusion, vascular or direct tubular injury, allergic interstitial inflammation, and glomerular basement membrane injury (3). In this paper we report a case with nephrotic range proteinuria that developed during treatment with metformin. The major type of renal disease in the nephrotic syndrome due to these drugs is membranous glomerulonephritis (4). Drugs that induce nephrotic syndrome and glomerular damage are gold, penicillamine, bucillamine and, NSAIDS, certain COX-2 inhibitors, mercury, captopril, lithium formaldehyde, trimethadione, probenecid 2-Mercaptopropionyl glycine, procainamide, hydralazine, isoniazid, methyldopa, chlorpromazine, quinidine, propylthiouracil, anti-TNF drugs and anti cancer drugs (5). In these cases, the nephropathy may resolve completely after withdrawal of the drug and immunosuppressant drugs, glucocorticoids, hemodialysis are required for the treatment of renal failure in most of the cases.

We presented a case of nephrotic syndrome that developed during using metformin for type 2 diabetes mellitus. Metformin is an oral biguanide used in the management of non insulin dependent diabetes mellitus. It is one of the most widely prescribed oral antidiabetic drugs in type 2 diabetes. It reduces blood glucose levels by improving peripheral sensitivity to insulin, and reducing gastrointestinal glucose absorption and hepatic glucose production (6). Metformin has potentially beneficial effects on serum lipid levels and fibrinolytic activity. Metformin reduces cardiovascular morbidity and mortality (7). Metformin also has intracellular antioxidant properties, prevents glucose-induced oxidative stress in podocytes and prevents the development of glomerular injury as a complication of diabetes mellitus (8). Metformin also provides protection against gentamycin-induced renal injury by preventing mitochondrial permeability disorders and decreasing the production of highly reactive oxygen species (9). Metformin is considered a safe and effective drug and is used widely but has some side effects in addition to the abovementioned beneficial effects. The most serious complication associated with metformin is lactic acidosis. Other side effects are gastrointestinal disturbances and vitamin B12 deficiency (10). In our literature review, we could not find any other cases of nephrotic syndrome that developed after metformin usage. To the best of our knowledge, this is the first case that developed nephrotic syndrome after using metformin. In our case, the proteinuria started after initiation of metformin and the patient's renal function improved without specific treatment after metformin was discontinued. No other etiological factors were found and these strongly suggest that the nephrotic syndrome occurred due to metformin usage.

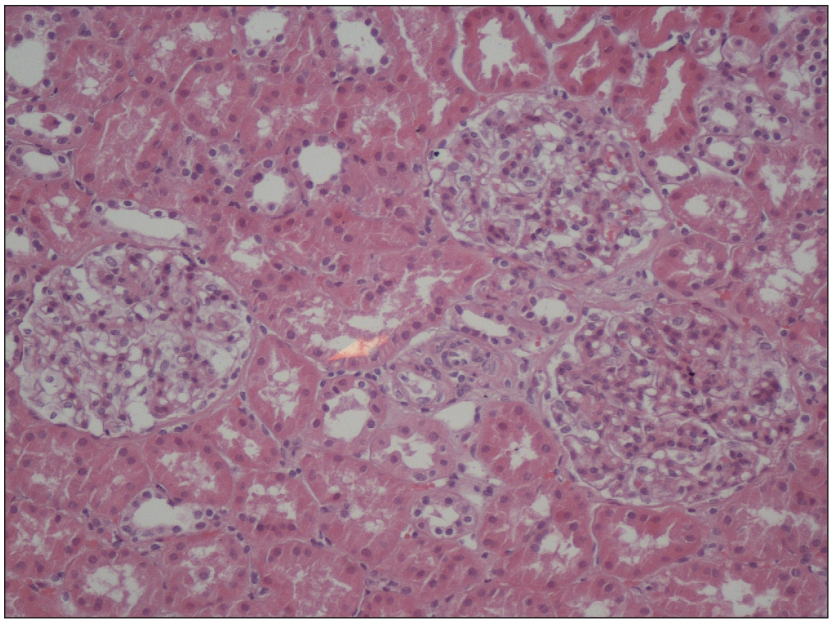

Figure 1: *The glomerulus at the lower right shows a mild increase in mesangial matrix and cellularity. Other glomeruli, tubules and interstitium are unremarkable (H&E x100).*

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