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A Different Etiology of Pre and Post Transplant Period Proteinuria in a Liver Transplant Patient with Wilson's Disease

Karaciğer Nakilli Wilson Hastasında Nakil Öncesi ve Sonrası Dönemde Proteinürinin Farklı Bir Nedeni

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ABSTRACT

Wilson disease (WD) is an autosomal recessive inherited disease caused by abnormalities of the copper-transporting protein encoding gene ATP7B. Wilson's disease can cause various types of renal involvement. We present the case of a 56-year-old male liver transplant receiver patient who had proteinuria and cellulitis.

KEY WORDS: Wilson disease, Proteinuria, Renal failure

ÖZ

Wilson hastalığı, bakır taşıyan protein kodlayan ATP7B genindeki mutasyon sonucu oluşan otozomal resesif geçiş gösteren genetik bir hastalıktır. Wilson hastalığı seyrinde farklı renal tutulumlar görülebilmektedir. Burada proteinüri ve selülit yakınması ile başvuran, karaciğer transplant öyküsü olan 56 yaşındaki erkek hastayı sunduk.

ANAHTAR SÖZCÜKLER: Wilson hastalığı, Proteinüri, Böbrek yetersizliği

INTRODUCTION

Wilson's disease (WD) is a rare autosomal-recessive disorder characterized by a mutation in the ATP7B gene, located on chromosome 13, which encodes a protein involved in the metabolism of copper (1). Copper deposition occurs in the liver, brain and renal proximal cells. In WD, renal involvement such as Fanconi syndrome, hypercalciuria, nephrocalcinosis, and glomerulonephritis may occur. The serum ceruloplasmin level and the Kayser-Fleischer ring in the eye are helpful to diagnose WD. The best treatment choice is liver transplantation

Herein we report a liver transplant receiver with severe proteinuria and cellulitis. He had been using prednisolone, tacrolimus and sirolimus for 2 years. His primary liver disease was WD. In his medical history, there was a diagnosis of primary MPGN which was steroid responsive and unrelated to the use of D-penicillamine or any treatment 16 years ago, and liver transplantation 2 years ago.

CASE

On November 2011, a 56-year-old male applied to our out-patient clinic due to bilateral lower extremity edema and hyperemia on the right pretibial region. In his medical history, he had been treated with prednisolone for membranoproliferative glomerulonephritis 16 years ago (1995). Renal biopsy was performed for proteinuria and acute renal failure that regressed with prednisolone. At that time, there was no liver disease findings or symptoms except splenomegaly. He was lost after the almost 1 year (1996) follow-up period with regression of renal findings until the last visit (2011) for edema, proteinuria and cellulitis. He underwent liver transplantation for hepatic failure secondary to WD on July 2009 at another center. For the current bilateral lower extremity edema and hyperemia on the right tibial region for 4 weeks, he had been treated with parenteral antibiotics at another hospital but his symptoms did not get any better. His blood pressure, temperature and pulse rate

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were within normal limits. Only edema of lower extremities and hyperemia of the right tibial region and an incisional scar related to the liver transplantation surgery were found on physical examination. Tacrolimus, sirolimus, prednisolone, daily 4 doses of insulin and amlodipine were the current medication of the patient. Laboratory measurements are presented on Table I. On ultrasonographic examination, the left lobe of the liver was not observed but the transplant liver's echogenicity was increased slightly; the kidneys were normal. On Doppler ultrasonography, the renal arteries and veins and arteries of the lower extremities were normal.

Renal biopsy was not performed but Rapamune was stopped. The edema and cellulitis dramatically regressed in two weeks and proteinuria decreased to 1100 mg/day from 7812 mg/day in 4 months. On the last visit, he was symptom free and AST/ALT, serum total protein/albumin levels were within normal limits.

DISCUSSION

The first acute renal failure and proteinuria attack MPGN in our case was detected on renal biopsy and recovered with only steroid therapy. At that time, MPGN could be secondary to WD or D-penicillamine treatment. He was not treated with any drug including D-penicillamine. There could be a correlation between MPGN and WD as he also had splenomegaly but the Wilsons disease was not diagnosed at that time. The patient recovered with steroid therapy during that period. He was then lost to follow-up. Liver transplantation was performed later on 07.07.2009 for Wilson's disease. The immunosupressive drugs were tacrolimus, rapamine, and prednisolone. While under treatment with these drugs, edema at the lower extremities was detected, but there was no venous thrombosis and no recovery occurred in the patient despite intensive antibiotic treatment. Severe proteinuria was found on simultaneous laboratory tests of the patient. There was no systemic disease that could cause nephrotic syndrome. His chest X-ray was normal. C3 and C4 levels were within normal limits. Renal biopsy was not performed. Both the cellulitis on the foot and proteinuria were observed to dramatically recover after stopping the rapamine without changing any other treatment.

Renal failure development is common during long-term follow-up of liver transplant patients. The nephrotoxicity of the immunosuppressives used is an important problem. While renal tubular fibrosis develops due to calcineurin inhibitors, mTOR inhibitors cause podocyte damage and proteinuria. Wilson's disease commonly causes renal tubular injury and Fanconi syndrome. However, the renal biopsy of patients with WD also shows cellular proliferation and IgA deposition on the mesangium. Of the 25 patients without penicillamine treatment, 12 had proteinuria, 14 had hematuria, and 5 had both proteinuria and hematuria (2). Low molecular weight proteinuria was detected in a series of 41 cases (3). In patients with WD undergoing D-penicillamine treatment, the proteinuria was more severe. Nephrotic syndrome also developed in another WD case treated with D-penicillamine treatment (4).

On the renal biopsy of a 10-year-old girl with the liver lesion, Ig A and C3 deposition were detected in the mesangium and subendothelial region. D-penicillamine had not been used in this patient's treatment (5). In our case, proteinuria was detected and MPGN was diagnosed in the renal biopsy before the diagnosis of WD and the D-penicillamine treatment.

Table I: Laboratory parameters during primary membranoproliferative glomerulonephritis[1] and posttransplant[2] and after stopping Rapamune[3].

	13.02.96 (1)	**11.03.96 (1)**	**18.11.11 (2)**	**03.01.12 (2)**	**03.05.12 (3)**	**20.06.12 (3)**	**19.09.12 (3)**	**5.12.13 (3)**
BUN (8-20 mg/dL)	61	27	21	12	22	21	19	28
Creatinine (0.8-1.2 mg/dL)	1.6	2.3	1.74	1.82	1.36	1.49	1.6	1.54
Total protein (6-8 g/dL)	8.1	8.1	6.1	5.3	5.3	6	6.3	6.4
Albumin (4-6 g/dL)	3.8	3.8	3.4	3.3	3.6	3.6	4	4.1
AST/ALT (<30 IU/L)	20/25	27/27	32/42	27/27	21/19	16/32	21/31	18/24
Urinary protein (mg/day)	**Not available**		6450	7812	1414	1100	657	143
C3/ C4 (90-180/10-40)	**Not available**	**Not available**		145.6/35.1		63.2/13.1		
CRP (0-8)	**Not available**	**Not available**	**1.2**	0.8	0.1	1.15	0.63	0.58

Of the 9 patients with WD diagnosis who underwent renal biopsy, 5 had severe proteinuria and 4 had moderate proteinuria. Three of these patients had not received treatment with D-penicillamine prior to the detection of proteinuria (6). On renal biopsy, membranous glomerulonephritis characterised by epimembranous IgG and C3 deposition was found. The regression of renal biopsy findings was reported during the follow-up period of 1 year. In fact, depending on treatment with D-penicillamine, diffuse granular deposition of IgG and C3 was defined in the glomerular basement membrane. At the time of diagnosis our patient did not use any medication. Our patient also did not have a diagnosis of WD when renal biopsy was performed. The diagnosis of WD was made and liver transplantation was performed at another center. While he was being treated with tacrolimus, rapamune, and prednisolone cellulitis (lymphedema?) and severe proteinuria developed. At the other hospital, he was treated with intensive antibiotic therapy for the cellulitis. The edema, hyperemia and proteinuria did not get better. There are few possibilities for the cause of the severe proteinuria. He could have had postinfectious glomerulonephritis secondary to cellulitis or reactivation of previous MPGN due to the infection. The patient did not consent and renal biopsy could not performed. However, C3 and C4 levels were normal. The patient was also receiving triple immunosuppressive therapy. Another reason for the proteinuria was Rapamune. The proteinuria and hyperemia of the lower extremity improved after stopping only the mTOR inhibitor. Severe proteinuria may be associated with WD but he had a functional transplanted liver. Improvement of renal pathology was reported after treatment of WD. Another reason could be other immunosuppressive drugs that cause proteinuria. Severe proteinuria can be observed due to mTOR inhibitors but heavy proteinuria and nephrotic syndrome has never been defined due to calcineurin inhibitors. However, metabolic problems such as hypertension, diabetes, and hyperlipidemia have been observed due to calcineurin inhibitors. Regression of symptoms after stopping mTOR suggests mTOR toxicity.

In summary, MPGN or some glomerular pathologies can develop in WD unrelated with D-penicillamine treatment. In liver transplanted patients, severe proteinuria can also develop secondary to Rapamune in addition to renal dysfunction related with nephrotoxicities of drugs and especially calcineurin inhibitors. It should be remembered that any complication can be related with the drugs used, especially immunosupressives, in the follow-up period. Nephrological evaluation should be undertaken in such cases.

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