A CASE OF FOCAL GLOMERULOSCLEROSIS ASSOCIATED WITH CYSTINURIA

MASAO KANAUCHI*, HIDEO SHIIKI*, YOSHIHIRO FUJII*, KAZUHIRO DOHI*, TAKASHI FUTAMI**, YOSHIHIKO HIRAO** and EIGORO OKAJIMA**
*First Department of Internal Medicine, **Department of Urology, Nara Medical University
Received February 23, 1996

Abstract: We report a case of cystinuria in which the nephrotic syndrome developed during treatment with tiopronin (alpha-mercaptopropionylglycine). Light microscopy of renal biopsy specimen showed focal glomerulosclerosis. Proteinuria resolved after withdrawal of the drug and without corticosteroid administration. The pathogenesis of tiopronin-induced nephropathy and this unusual presentation of symptoms are discussed with respect to the literature.

Index Terms

cystinuria, focal glomerulosclerosis, nephrotic syndrome, tiopronin

INTRODUCTION

Cystinuria is an inherited disorder characterized by excessive renal excretion of cystine. In recent years, tiopronin (alpha-mercaptopropionylglycine; Thiora) has been used to treat urolithiasis in patients with cystinuria[1-3]. There have been a few cases of nephrotic syndrome due to tiopronin[4-7]; histological examination has revealed either minimal-change nephrotic syndrome (MCNS) or membranous nephropathy (MN). We present an unusual case of focal glomerulosclerosis (FGS) that occurred during tiopronin therapy for cystinuria.

CASE REPORT

An 18-year-old student was admitted to the Nara Medical University Hospital on March 23, 1993 for the treatment of nephrotic syndrome. None of his relatives had renal disease or urolithiasis. His medical history was unremarkable until September 26, 1991, when he complained of back pain. In mid-August 1992, he was hospitalized at our clinic because of recurrent renal colic. An abdominal x-ray showed significant right-sided nephrolithiasis with hydronephrosis. Urinary chromatography revealed abnormal cystine excretion, confirming a diagnosis of cystinuria. Tiopronin 600 mg daily was introduced on September 21 and increased to a maximum of 1,200 mg daily on October 11. Extracorporeal shock wave lithotripsy was performed on November 5 and December 10, and percutaneous nephrolithotomy was subsequently performed on December 22. Right-sided calculi were successfully crushed and removed. In February 1993, after 5 months of tiopronin therapy, his face became puffy and he experienced pretibial edema; during the following days, anasarca developed. No fever or skin rashes were present.

Physical examination on admission revealed the following: body height 170 cm, body weight 73 kg (14 kg weight gain in the previous 2 weeks), blood pressure 122/62 mmHg, and pulse rate

72/min. Physical examination demonstrated no abnormalities in the chest, but marked edema in the lower extremities and ascites.

Urinalysis revealed severe proteinuria, microscopic hematuria, and sediment containing numerous red cells with hyaline casts on high power. Urinary protein excretion was 24.3 g/day and creatinine clearance was 121 ml/min. Peripheral blood cell count was within the normal range. Biochemical data were as follows: total serum protein 3.6 g/dl, serum albumin 2.0 g/dl, total cholesterol 535 mg/dl, and serum creatinine 0.7 mg/dl.

Renal biopsy was performed on April 9, 1993. The biopsy specimen contained 21 glomeruli, showing minimal expansion of the mesangial areas. Two glomeruli exhibited a small segmental sclerosis adherent to Bowman's capsule at the urinary pole (Fig. 1). There were small foci of tubular atrophy and lymphocytes. However, no cystine deposits were observed within tubular lumina and in the interstitium. Immuno fluorescence study revealed no deposition of immunoglobulins and complement. Electron microscopy demonstrated focal effacement of foot processes, but there were neither electron dense deposits nor cystine crystalline deposits in the glomeruli (Fig. 2). Based on these findings, a histological diagnosis of focal glomerulosclerosis was made.

The proteinuria decreased 7 days after the withdrawal of tiopronin, and the nephrotic syndrome eventually improved without corticosteroid administration.

DISCUSSION

The crystallization of cystine is believed to depend mainly on urinary supersaturation with cystine. Therefore, treatment has been directed at lowering the urinary concentration of cystine to below its solubility limit[1-3]. Tiopronin may be useful in the management of

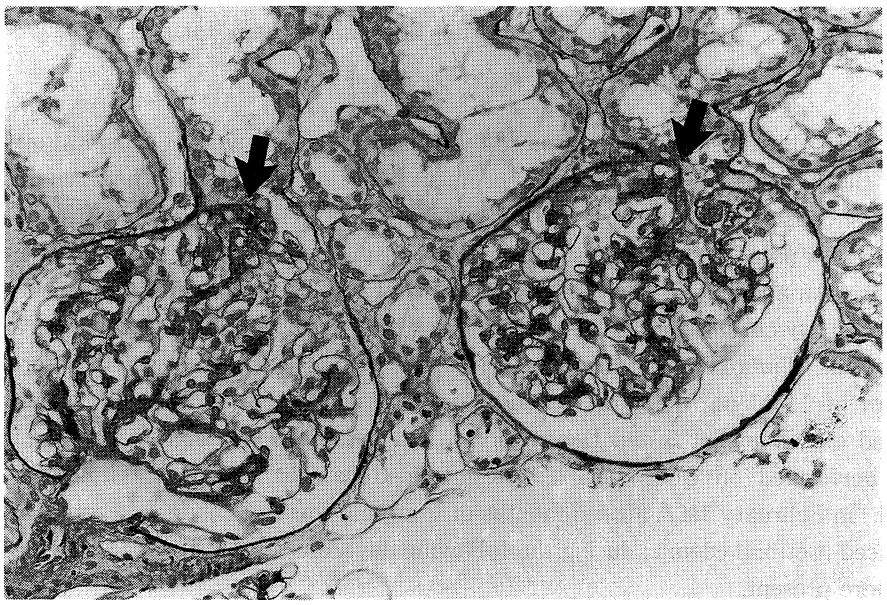

Fig. 1. Two glomeruri showing small sclerotic lesions in the vicinity of the urinary pole (arrows) (Periodic acid-Schiff staining, ×180).

cystinuria[1-3]. It shares similar chemical properties with D-penicillamine, which frequently induces proteinuria[8], but side effects of tiopronin are apparently less common that those associated with D-penicillamine[3]. Side effects of tiopronin such as urticaria, fever and lymphadenopathy have been mentioned[9]. Since tiopronin is also used as a remission-inducing drug in rheumatoid arthritis (RA), a few cases of tiopronin-related nephropathy have been described in patients with RA[10-12]. Patients with cystinuria treated by tiopronin may develop glomerular disease[4-7]; two histopathologic types of glomerulonephritis have been described. Lupo et al.[5] reported two nephrotic patients with cystinuria; one had MCNS and another

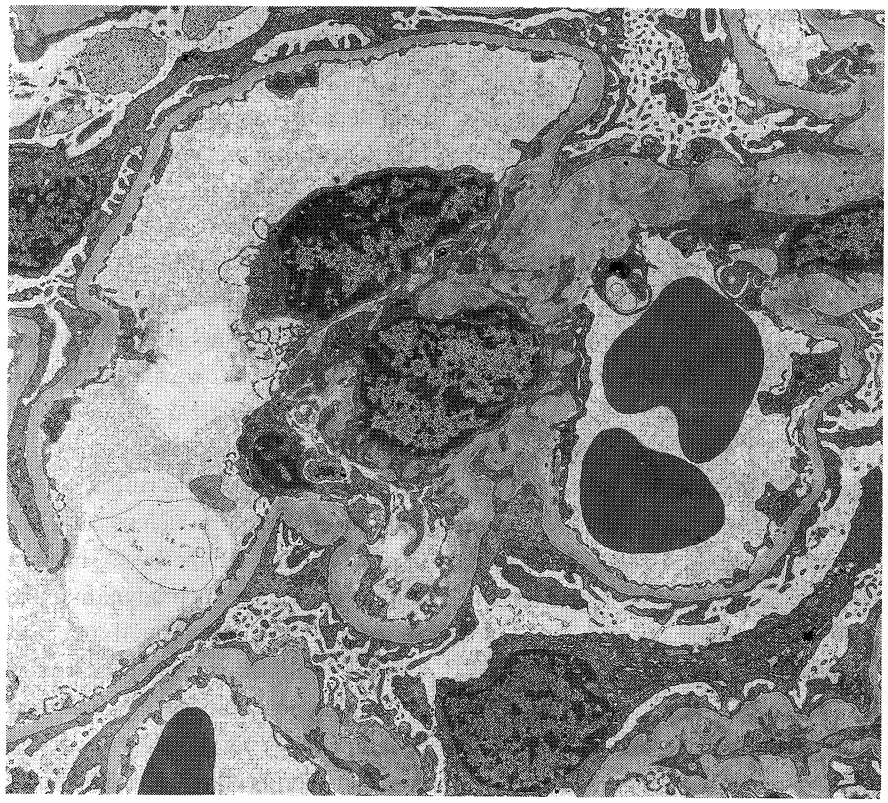

Fig. 2. Electron micrograph. Focal loss of foot process is observed (×5,000).

Table 1. Cases of tiopronin-induced nephropathy associated with cystinuria

Author	Age/sex	Tiopronin administration		Urinary protein (g/day)	Renal biopsy
		Dose (mg/day)	Duration (mo)		
Lupo (1981)	23/F	1,500	8	13.0	MCNS
	47/F	2,000	6	4.0	MN
Lindell (1990)	34/F	1,500	14	6.1	MN
Shibasaki (1991)	26/M	400	5	4.8	MN
Present case	18/M	1,200	5	24.0	FGS

MCNS : minimal change nephrotic syndrome
MN : membranous nephropathy
FGS : focal glomerulosclerosis

displayed MN. MN associated with cystinuria was reported by Lindell et al.[6] and Shibasaki et al.[7] However, we are unaware of any previous reports of FGS associated with cystinuria. The above-mentioned cases are summarized in Table 1.

Whether the mechanism by which tiopronin induces the nephrotic syndrome involves toxicity or immunological factors is unknown. However, the nephrotic syndrome due to tiopronin seemed to be dose-related, since it appeared 40 to 60 days after the tiopronin dosage was increased to more than 50 mg/kg/day[4-7]. The similar chemical structure of tiopronin and D-penicillamine suggests that they act in the same way. Some reports have suggested that immunological mechanisms play a role in side effects of D-penicillamine[8,13-16]. Membranous nephropathy is the most common lesion found in these cases; IgG and complement deposition were observed in the glomerular basement membranes in immunofluorescent studies[15], suggesting an immune complex glomerulonephritis. A minimal change lesion in association with D-penicillamine[16], which is evidence of changes in glomerular basement membrane charge and permeability, has also been descrided; this may result from the activity of various cytokines. The production of such cytokines may be induced by D-penicillamine, perhaps via effects on lymphocytes. Since a prominent role of tiopronin was supported by a reduction in proteinuria after withdrawal of the drug in a previous report[12], a close causal relationship between tiopronin administration and the nephrotic syndrome can be assumed in our case.

It is difficult to determine the exact cause of FGS in our patient. An immunological insult induced by tiopronin, as renal involvement could be considered. However, the pathogenesis of the FGS was uncertain; there is little else to indicate an immunological pathogenesis. Another possibility is that hemodynamic changes played a role in the pathogenesis of FGS. Although the association of nephrotic syndrome with either hydronephrosis or reflux nephropathy is extremely rare, a relationship with some types of glomerulonephritis such as MCNS[17], MN[17,18] or FGS[19], has been reported. Based on studies in a rat model, a hypothesis that may explain the development of FGS was constructed[20]. It maintains that the hemodynamic changes that occur in surviving glomeruli that have adapted to a reduction in renal mass may cause proteinuria and eventual glomerulosclerosis. A third possibility, direct cytotoxicity of tiopronin, should also be taken into account. It is known that tiopronin inhibits collagen synthesis and especially induces glomerular epithelial cell damage. Several investigators have noted vacuolization, degeneration, necrosis and detachment of glomerular visceral epithelial cells in models of FGS[21]. Glomerular injury in the visceral epithelial cells initiates a sequence of events that culminates in the production of segmental scars leading to FGS. We therefore believe that our patient probably developed FGS as a consequence of tiopronin admisistration.

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