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Case Report

Profound Urinary Protein Loss and Acute Renal Failure Caused by Cyclooxygenase-2 Inhibitor

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Abstract

Cumulative evidence has shown that nonsteroidal anti-inflammatory drugs (NSAIDs) can induce acute renal failure and nephrotic-range proteinuria. Cyclooxygenase-2 (COX-2) inhibitors have less nephrotoxicity; however, recent data indicate that they may cause the same renal problems as NSAIDs do. Herein, we present a case of celecoxib-associated minimal change disease (MCD) with profound urinary protein loss and acute renal failure. Renal function and nephrotic syndrome in this patient resolved completely after discontinuation of celecoxib and treatment with methylprednisolone. Clinicians should keep high index of suspicions in patients developing nephrotic syndrome and acute renal failure after taking COX-2 inhibitors since secondary MCD responds well to timely cessation of COX-2 inhibitors and administration of steroid therapy.

Key Words: acute renal failure, cyclooxygenase-2 (COX-2) inhibitors, minimal change disease

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to adverse renal effects including the decline in glomerular filtration rate (GFR), electrolyte abnormality, nephrotic syndrome, interstitial nephritis and renal papillary necrosis (14). Although nephrotoxicity of cyclooxygenase-2 (COX-2) inhibitors has not well been investigated, some reports have shown that COX-2 inhibitors potentially induce acute renal failure, allergic interstitial nephritis (AIN) and nephrotic syndrome (2, 3, 10, 15). To date, only 2 cases of celecoxib-induced minimal change disease (MCD) have been reported (2, 3). One case presented with MCD and AIN; and the other developed MCD and acute tubular necrosis (ATN). We here report a case developing profound urinary protein loss and acute renal failure after usage of celecoxib. The present case is unique since MCD developed without being accompanied by AIN or ATN.

Case Report

A 75-year-old Chinese male presented to our hospital with a history of 2-week progressive edema of both lower legs and increase of body weight of 12 Kg. Upon admission, the patient had blood pressure of 181/89 mmHg, both lower legs pitting edema and shortness of breath. He was intermittently treated with celecoxib (Pfizer, Illertissen, Germany), 100 mg orally twice a day, to relieve the knee joint pain 5 years ago. No Chinese herbs or other over-the-counter drugs were used. He had no history of hypertension or diabetes mellitus.

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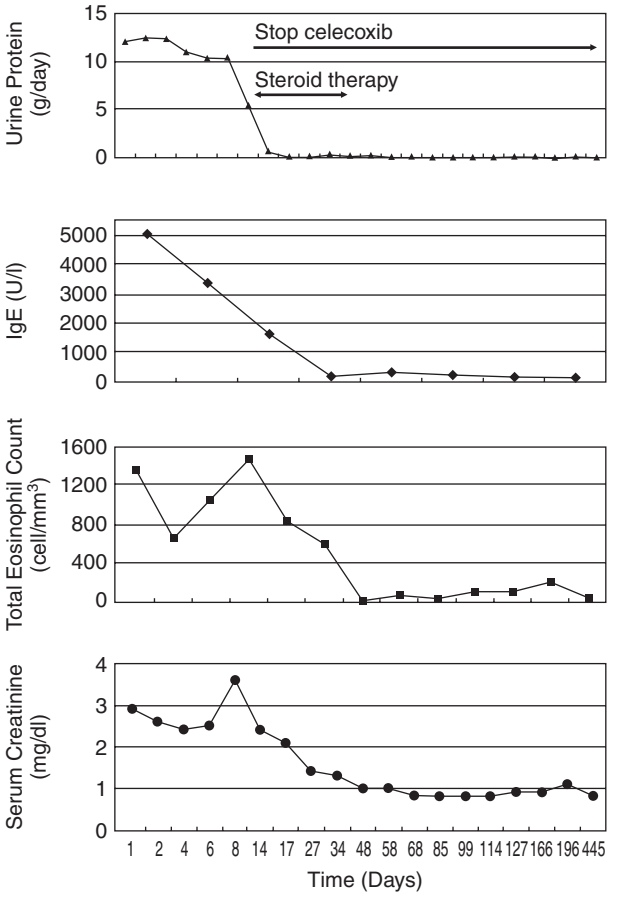

Fig. 1. The changes of daily urinary protein excretion, IgE, total eosinophil count, and serum creatinine during the follow-up period.

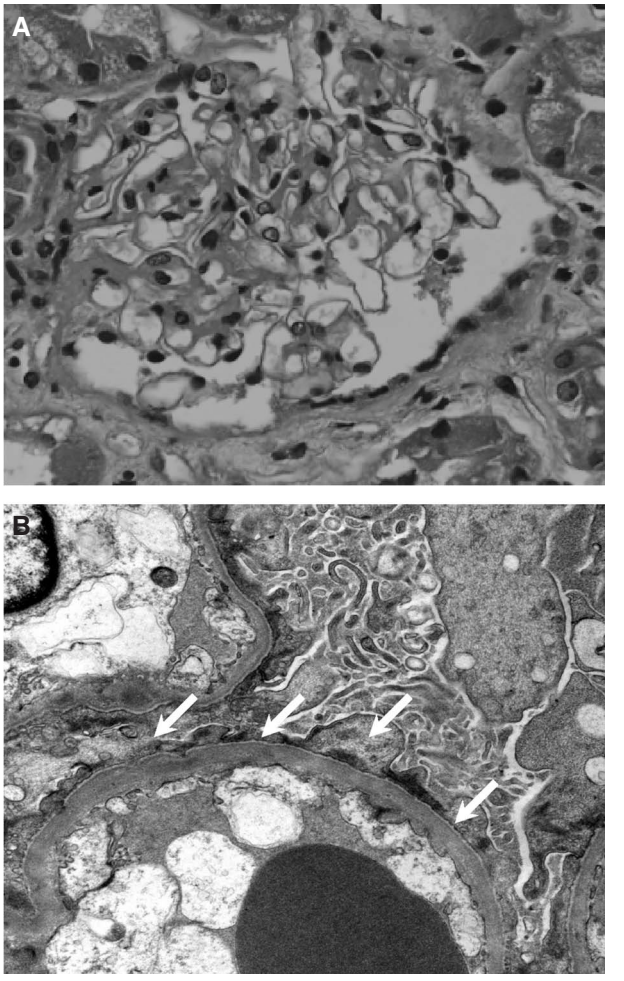

Fig. 2. A. Light microscope disclosed only interstitial edema with unremarkable change in glomerular and vascular tissue. H & E stain, magnification 400×. B. Electron microscopy showed extensive diffuse global complete effacement of visceral epithelial foot processes (white arrows), mild segmental widening of subendothelial space, and mild segmental expansion of mesangial matrix.

Physical examination disclosed decreased breathing sound over right lower lung and crackles over left lung. No retinopathy or neuropathy was noted. The laboratory tests showed hemoglobin 13.8 g/dl and leukocyte counts 9,000 cells/mm^3 with 15.3% eosinophilia. Blood urea nitrogen and creatinine had risen to 64 mg/dl and 2.9 mg/dl, whereas serum albumin was 2.4 g/dl. Urinalysis revealed mild granular casts 3-5 /high power field under microscopy; daily urinary protein excretion was 12.1 g; and calculated CCr 25.8 ml/min. Series of serology studies including hepatitis B and C, human immunodeficiency virus, anti-nuclear antibody (ANA), venereal disease research laboratory test (VDRL) for syphilis and anti-streptolysin O were negative. Immunoglobulin G (IgG) level 744 mg/dl was mildly decreased and no monoclonal spike was disclosed on serum protein electrophoresis. Ultrasound disclosed normal kidney size with right kidney 10.6 cm and left kidney 10.7 cm in length. In addition, total IgE was abnormally elevated to > 5,000 U/l and paralleled by the changes in renal function and total eosinophil counts (Fig. 1). The patient was treated with albumin infusion followed by furosemide during hospitalization. The patient's body weight decreased after diuretic therapy, and the symptoms of edema improved. Thoracocentesis of right lung was performed and transudated pleural effusion secondary to nephrotic syndrome was noted. A percutaneous renal biopsy was performed under sonography guidance. Light microscopy revealed mild interstitial edema with unremarkable glomerular and vascular tissue (Fig. 2A) and fluorescent immunohistochemistry showed diffuse global linear capillary wall pattern with IgG (+). Electron microscopy showed extensive diffuse global effacement of visceral epithelial foot processes, mild segmental expansion of mesangial matrix with no significant dilatation of glomerular capillary lumens, no attenuation of glomerular basement membrane, and no

deposition of electron-dense material in glomeruli (Fig. 2B).

Since this patient didn't take any other drugs at that time and no clinical evidence suggested he had infection or tumor, MCD was probably due to celecoxib with allergic reaction was diagnosed based on clinic-pathological findings. In addition to stopping celecoxib, methylprednisolone 12 mg daily was started for persistently heavy proteinuria (daily protein loss of 5.3 g) 3 weeks after pathological diagnosis. Unfortunately, hyperglycemia occurred after 21-day steroid therapy. Insulin therapy was then prescribed for blood sugar control. The dose of methylprednisolone was tapered to 8 mg daily at the same time. The patient's proteinuria was completely remitted after 27-day steroid therapy and his daily urinary protein was reduced to 0.11 g. The dose of methylprednisolone was further tapered to 4 mg daily on the 41st day of therapy and 4 mg every other day 2 weeks later. Since nephrotic syndrome was not relapsed during the 3-month steroid therapy, we stopped the steroid therapy. His serum creatinine was 0.9 mg/dl and urine protein excretion was 0.02 g per day. The patient was regularly followed up at our outpatient clinic service. No disease recurrence was found till now.

Discussion

NSAIDs inhibit COX non-selectively. Two isoforms of COX have been identified: COX-1 and COX-2. Both COX isoforms convert arachidonic acid to prostaglandins and thromboxanes. COX-1, constitutively expressed in most tissues, regulates cellular housekeeping functions, such as gastric cytoprotection, vascular homeostasis, and kidney function. COX-2 is thought to be inducible with low or undetectable levels in most tissues, which can be increased markedly by a number of inflammatory, mitogenic, and physical stimuli (9).

Nephrotoxicity of NSAIDs is primarily mediated by blocking normal renal regulatory mechanisms through inhibiting synthesis of vasodilator prostaglandins, prostaglandin E2 and prostacyclin (5, 8). Inhibition of prostaglandin E2 and prostacyclin can reduce renal perfusion and then decrease GFR especially in patients with underlying renal dysfunction, volume depletion, or edema-forming status, which mainly depend upon prostaglandin E2 and prostacyclin to maintain renal perfusion status (2). COX-2 inhibitors may also affect the production of renal prostaglandins and decline GFR, although it is not constitutively expressed (15). Previous study showed that when the luminal chloride concentrations is low, macula densa cells in the thick ascending part of the loop of Henle enhance COX-2 expression by activation of p38 MAP kinase pathway (6). COX-2 might be up-regulated as sequels to diuretics-induced subtle volume and salt depletion, cyclosporine-induced renal vasoconstriction, and angiotensin converting enzyme inhibitors-induced GFR decrease. Acute renal failure had developed in patients taking diuretics and rofecoxib (a COX-2 inhibitor) at the same time (15). In contrast, renal dysfunction was also reported in patients taking rofecoxib or celecoxib without salt depletion (12). It indicates that COX-2 inhibitors may induce acute renal failure even in euvolemic status.

The cause of nephrotic syndrome, most frequently MCD, by nonselective NSAIDs seems to be idiosyncratic in nature. The pathophysiology is obscure, but it is suggested that COX blockade by NSAIDs leads to shunting of the arachidonic acid pathway into the alternative lipoxygenase pathway, and subsequent production of proinflammatory and vasoactive leukotrienes (2, 4, 12). Leukotriene-mediated increased vascular permeability could result in nephrotic-range proteinuria and interstitial nephritis (4, 12). Nephrotic-range proteinuria happens after several days or months of NSAIDs use with a mean exposure time of 5.4 months (range from 2 weeks to 18 months) (1). However, the exposure time of COX-2 inhibitors were longer with range of 7 months to 2 years in the previous reports (2, 3, 10). Since COX-2 inhibitors cause renal toxicity by inhibiting the production of prostaglandin E2 and prostacyclin, the inhibitory effect is higher in "non-selective" cyclooxygenase inhibitors, *i.e.* NSAIDs, than in "selective" ones. It may explain why COX-2 inhibitors lead to the noticeable insults after longer exposure time than NSAIDs do. Our patient had been "intermittently" treated with celecoxib for 5 years. Compared with two reported cases developing celecoxib-induced MCD 1 and 2 years after (2, 3), one had type 2 diabetes mellitus which could damage kidney further and the other took larger dosage of celecoxib (200 mg twice daily) than our case (100 mg twice daily). Low dosage of celecoxib, intermittent exposure and no prior kidney disease in our patient may lead to the clinical nephrotic syndrome 5 years after. Furthermore, celecoxib could make some incipient insults before the development of nephrotic-ranged proteinuria during the 5 years and no routinely laboratory checks were performed before the onset of clinical symptoms. It highlights that nephrotic syndrome could develop even COX-2 inhibitors have been used for a long time.

After discontinuation of the offending agents, most patients with nephrotic syndrome have a spontaneous remission within 1 month, but some cases can take up to 1 year. Empirical use of corticosteroid has been tried often but shown no definitive benefits. A trial of corticosteroids is recommended if significant proteinuria persists for more than 1 month (7) or

Table 1. Minimal change disease in association with selective COX-2 inhibitors

	Alper *et al*. (2002)	Almansori *et al*. (2005)	Our case (2010)
Age (years)	59	62	75
Gender	Male	Male	Male
Race	African-American	East-Indian	Chinese
COX-2 inhibitor	celecoxib	celecoxib	celecoxib
Dosage	100 mg QD-BID	200 mg BID	100 mg BID
Duration of COX-2 inhibitors exposure to onset of nephrotic syndrome	About 1 year	At least 2 years	5 years
Underlying disease	Type 2 diabetes mellitus	Peptic ulcer disease and osteoarthritis	Osteoarthritis
Serum creatinine (mg/dl)	2.1	3.12	2.9
Serum albumin (g/dl)	1.1	2	2.4
24 h urine protein (g)	10.6	16.6	12.1
Pathology of renal biopsy	MCD and AIN	MCD and ATN	MCD
Treatment	Stop celecoxib; Prednisolone 60 mg daily	Stop celecoxib; Lisinopril 5 mg daily	Stop celecoxib; Methylprednisolone 12 mg daily
Outcome: renal function	Full recovery	No full recovery	Full recovery
Outcome: proteinuria	Full recovery	Full recovery	Full recovery

Abbreviations: AIN, acute interstitial nephritis; ATN, acute tubular necrosis; BID, twice daily; MCD, minimal change disease; and QD, once daily.

renal failure persists more than one to two weeks after discontinuation of NSAIDs (11). In our patient, methylprednisolone was administered due to persistent proteinuria and impaired renal function 3 weeks after celecoxib has been discontinued.

MCD is associated with allergy and elevated IgE. Takei *et al*. (13) proposed that MCD patients with high IgE levels have higher relapse rate. Eosinophilia may be present in AIN and seldom be linked to MCD. Our case had elevated IgE and eosinophilia at the time when MCD was diagnosed. IgE level and eosinohil counts returned to normal during recovery of MCD (Fig. 1). It implies that the elevated IgE and eosinophilia in our patient are mainly due to allergic reaction to celecoxib. Skin rash or pruritus was not distinct when taking celecoxib, which is similar to NSAIDs. The interrelation between MCD and allergy is not clear. In the present case, celecoxib might induce MCD and allergy, respectively.

Up to now, COX-2 inhibitor-caused nephrotic syndrome has been reported in only 3 cases (2, 3, 10). One case had membranous glomerulopathy (10) and the other two cases had MCD (2, 3). Two cases of MCD had AIN or ATN in their pathology. Our patient, however, had MCD only. We summarize the two cases with COX-2 inhibitor-induced MCD and our patient in Table 1. COX-2 inhibitor-induced MCD seems benign with complete recovery and no recurrence of nephrotic syndrome. But the prognosis gets worse if ATN is present. Taken collectively, our case and the previously reported cases (2, 3, 10, 15) point out the message that selective COX-2 inhibitors might potentially be nephrotoxic and lead to MCD, AIN and ATN. Although the incidence is still unknown, renal function and urine protein should be closely monitored in patients taking the COX-2 inhibitors.

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