Recurrent Nephrotic Syndrome Induced by Nonsteroidal Anti-inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known potential nephrotoxic agents with a wide range of different effects on the kidney. One less commonly seen effect is nephrotic syndrome. The following case demonstrates the easily overlooked possibility of NSAIDs being a cause of nephrotic syndrome. [Hong Kong J Nephrology 2003;5(2):98–100]

Key words: nephrotic syndrome, nonsteroidal anti-inflammatory drugs, NSAIDs

非類固醇抗發炎藥物（NSAIDs）公認具有潛在的腎臟毒性，可對腎臟造成多種不同的影響，包括較為少見的腎病症候群（nephrotic syndrome）。以下的個案，說明了在腎病症候群的各種致病因素中，NSAIDs是一個容易被忽略的成因。

CASE REPORT

A 78-year-old male with a history of hypertension for 7 years, on regular treatment, with paroxysmal atrial fibrillation and hyperlipidemia was admitted into the urologic ward in June 2000 because of acute urine retention secondary to benign prostate hyperplasia (BPH). His usual medication included metoprolol, simvastatin and perindopril, which was changed to candesartan after admission. His serum creatinine level was about 130 μmol/L in 1998 but had risen to around 180 μmol/L on admission. Serum albumin was noted to be 25 g/L only. Terazosin, and subsequently doxazosin, was prescribed for the urine retention, but without much improvement. Transurethral resection of the prostate (TURP) was performed on 19 July 2000. Twenty-four hour urine collection 5 days after surgery documented proteinuria of 7.1 g/day. However, he was discharged without further investigations.

Two months later, he was admitted again because of urinary tract infection with significant proteinuria. His serum creatinine level was about 130 μmol/L in 1998 but had risen to around 180 μmol/L on admission. Serum albumin was noted to be 25 g/L only. Terazosin, and subsequently doxazosin, was prescribed for the urine retention, but without much improvement. Transurethral resection of the prostate (TURP) was performed on 19 July 2000. Twenty-four hour urine collection 5 days after surgery documented proteinuria of 7.1 g/day. However, he was discharged without further investigations.

Two months later, he was admitted again because of urinary tract infection with significant proteinuria. His serum creatinine was around 160 μmol/L, and ultrasound of the kidneys showed normal-sized kidneys (left, 11.1 cm; right, 9.8 cm). Immune markers revealed negative results for anti-nuclear factor, anti-glomerular basement membrane antibody, and anti-neutrophil cytoplasmic antibodies. He had normal serum C3 and C4 levels, but elevated IgG and IgA levels (32.83 and 5.74 g/L, respectively). Serology for hepatitis B, C and syphilis were negative. The infection responded to cefuroxime. He was referred to our clinic upon discharge. One month later, his creatinine level was static at around 180 μmol/L, but the proteinuria had spontaneously improved to 1.5 g/day. Renal biopsy was suggested but refused by the patient. Serum albumin subsequently rose to 35 g/L. Serum creatinine remained around the same range on subsequent follow-up. A provisional diagnosis of hypertensive nephropathy with an episode of nephrotic syndrome of unknown etiology was made.

In January 2002, he presented again with generalized edema and frothy urine for 1 month. Creatinine was found to be 432 μmol/L, with proteinuria of 12.5 g/day. Serum albumin had dropped to 17 g/L. Ultrasound of the kidneys was similar to the previous scan. The findings of the immunologic tests were also similar to the previous test results, except for the normalization of immunoglobulin levels. A more detailed drug history revealed that he had taken analgesics prescribed by other doctors for several months prior to and during the episode of acute urine retention in 2000, and one month before this admission in 2002 for his low back pain. However, he denied taking any analgesics in between. After checking the
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computerized drug record of the Hospital Authority, Hong Kong, the analgesic was subsequently identified as diclofenac acid. Diclofenac acid was not prescribed after the TURP in 2000.

Soon after the administration of diclofenac acid was stopped, serum creatinine spontaneously fell back to between 180 and 200 µmol/L within a month. Retrospective analysis of the blood picture revealed mild eosinophilia on 10 July 2000 (0.8 × 10³/L) and at admission on 1 January 2002 (0.6 × 10³/L). In both instances, it was normalized several days afterwards. There was no increase in white cell count during this episode and eosinophilia was not particularly looked for. The only urinary abnormality while not having urinary tract infection was the presence of hyaline cast. Urinary N-acetyl-glucosaminidase and α₁-microglobulin was not checked due to the unavailability of the tests in our service laboratory.

After discharge, proteinuria decreased to only 2 g/day within 2 months and serum albumin increased to above 35 g/L within 1 month. Based on the clinical picture, detailed drug history, and the temporal relationship with the use and cessation of the drug, nephrotic syndrome induced by nonsteroidal anti-inflammatory drugs (NSAIDs) was diagnosed. The patient was therefore advised to avoid all forms of NSAIDs in future. On subsequent follow-ups, his renal function and proteinuria were stable. The Figure shows the temporal relationship between serum creatinine, degree of proteinuria, and use of diclofenac acid.

**DISCUSSION**

Although there was a lack of renal biopsy proof, the temporal relationship between the onset of nephrotic syndrome and the administration of diclofenac acid indicated their causal relationship. The withdrawal of diclofenac acid after TURP in 2000 and after admission in 2002 was followed by a reduction in the extent of proteinuria, normalization of serum albumin and improvement in the serum creatinine level. The mild eosinophilia associated with the two episodes and the subsequent normalization after cessation of diclofenac acid added further to the supportive evidence. The likely pathology was minimal change nephropathy induced by NSAIDs and NSAID-induced acute interstitial nephritis (AIN), which was more apparent in the second episode, with acute deterioration of renal function and eosinophilia. The polyclonal increase in IgG and IgA in 2000 was likely to be related to the urinary tract infection. However, as he had persistent mild proteinuria and slightly raised baseline serum creatinine in between the two episodes, it is highly likely that he also has background hypertensive nephropathy, which explains the slow but progressive rise in serum creatinine on follow-up. This case demonstrates that without a high index of suspicion and detailed drug history, NSAID-induced nephrotic syndrome can be easily overlooked.

NSAIDs may cause a variety of renal problems, which include acute renal failure, abnormalities in sodium, water and potassium homeostasis, AIN, chronic renal injury and nephrotic syndrome. The two main mechanisms for its renal toxicity are hemodynamically and immunologically mediated. Most renal effects of NSAIDs are hemodynamically mediated. Interstitial nephritis and nephrotic syndrome are closely associated and their pathogeneses are thought to be immunologically mediated.

The incidence of NSAID-related AIN has been reviewed. It was only diagnosed in 1% of 460 renal biopsies reviewed by Abraham and Keane [1] and 0.4% of 1,500 renal biopsies and 200 autopsy specimens.

![Figure](image.png)

**Figure.** Relationship between (A) serum creatinine and diclofenac acid prescription, and (B) proteinuria and diclofenac acid prescription. The horizontal arrows indicate the period of regular diclofenac acid administration. The dotted arrows indicate the period of occasional consumption of diclofenac acid prescribed by orthopedic surgeons. TURP = transurethral resection of the prostate.
in a 10-year survey [2]. Nevertheless, AIN was present in 18.6% of renal lesions associated with the use of NSAIDs [3]. Various NSAIDs have been reported as causing AIN [4]. Nephrotic proteinuria occurs in 80% of NSAID-related AIN cases [4]. The clinical features of AIN with heavy proteinuria induced by NSAIDs are non-specific. Patients are usually elderly and may have taken the drug for months. Symptoms and signs of hypersensitivity are usually absent [5]. Urine microscopy may show red blood cells and leukocytes with a low fractional excretion of sodium. However, the proteinuria may improve within days or weeks after discontinuation of the responsible drug. Complete remissions are often seen [2,6]. However, some patients may have permanent damage resulting in chronic renal insufficiency or even progression to end-stage renal disease. The classical renal biopsy findings are interstitial nephritis with only mild mesangial proliferation. Electron microscopy typically shows diffuse fusion of epithelial deposits similar to minimal change nephropathy with occasional mesangial electron-dense deposition [4]. Immunofluorescence studies are typically normal.

NSAID-induced nephrotic syndrome may also occur without any interstitial nephritis. About 10% to 12% of patients developing renal lesions while receiving NSAIDs have nephrotic syndrome in which renal biopsy shows only minimal change disease [1,3]. They usually have complete remission within a few weeks but may have a relapse of proteinuria even if they are not re-exposed to the drug [7]. A few cases of membranous nephropathy have also been reported, but the proteinuria may persist for a period of 3 months to 3 years after the responsible drug has been withdrawn [4].

Treatment is supportive and the occult drug is stopped. Usually, renal function will gradually improve unless the patient has already suffered permanent damage. Use of steroid therapy is controversial, although there have been reports showing some improvement in patients with drug-induced AIN with epithelioid cell granulomas [4]. A detailed drug history is important for making the correct diagnosis, such as in this patient presenting with nephrotic syndrome without significant renal impairment. The patient should avoid any further exposure to NSAIDs, as even cutaneous application of NSAIDs has been reported to induce nephrotic syndrome [8].

REFERENCES