

Case Report

Nephrotic Syndrome and Acute Tubular Necrosis and Interstitial Nephritis Associated with Diclofenac

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Keywords

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- Acute renal failure
- Minimal change disease
- Acute tubular necrosis
- Acute interstitial nephritis

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are a kind of drugs used worldwide. Renal damages induced by NSAIDs are frequently reported in China. But its reported case of the coexistence of nephrotic syndrome (NS), acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) is limited.

Case diagnosis/treatment: A case of a 59-year-old man, in July 28, 2016, presented with increasing fatigue, edema of legs, anuria and deterioration in renal function after the oral diclofenac. A renal biopsy revealed minimal change disease (MCD) with ATN and mild AIN. The history of use of diclofenac and the renal biopsy led to a diagnosis of MCD with ATN and AIN caused by NSAIDs. The patient's urine volume and the renal function improved slowly after taking oral corticosteroids for 6 weeks. The serum creatinine level recovered completely 10 weeks later. However the 24-hour urine protein excretion increased to 11g with the improvement of renal function. We gave oral administration of cyclophosphamide 50mg/d, thereafter 24-hour urine protein excretion decreased to 0.2g/d. This is a rare case of MCD with AIN and ATN associated with the use of NSAIDs.

Conclusions: This case makes us understand the kidney damages caused by NSAIDs drugs more deeply. We should give considerable concern with side effect of NSAIDs.

ABBREVIATIONS

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; ARF: Acute Renal Failure; MCD: Minimal Change Disease; ATN: Acute Tubular Necrosis; AIN: Acute Interstitial Nephritis

INTRODUCTION

NSAIDs are a kind of drugs different from glucocorticoids, which is widely used to treat a variety of fever and acute and chronic pains worldwide. It is one of the most commonly prescribed drugs [1,2]. In addition, most Chinese follows the principle of self-treatment with these analgesics due to the convenience of over-the-counter availability of these drugs. In the United States, about 1 million people suffer different side effects of the NSAIDs drug toxicity each year. The incidence of adverse reactions is about 1~5% in the population of using these drugs [3]. The most seriously life-threatening complications are the upper gastrointestinal bleeding and the acute renal failure. Renal damages induced by NSAIDs are frequently reported in China. We are highlighting here a case of biopsy-proven minimal change disease (MCD) with ATN and AIN for a patient who was aware of a similar 'harmless and necessary' painkiller. This is a

rare case report associated with the use of NSAIDs. Moreover, the recovery of AKI in this case is very slowly. The coexistence of ATN and AIN could delay the recovery of renal function. This case makes us understand the kidney damages caused by NSAIDs drugs more deeply.

CASE PRESENTATION

This is a 59-year-old man, who was previously in good health and had no significant past medicinal history. History-taking disclosed that he took diclofenac 30mg/d for 3 days because of a headache 35 days ago. 18 days ago, he began to have anorexia, fatigue, eyelids and double legs pitting edema, although his urine volume was not significantly reduced. 10 days ago, there was a significant decrease in urine volume, 400~600ml/d, and his anorexia and edema were more severe accompanied with nausea and vomiting. He had no fever, skin rash and joints pain, etc. He went to see doctors in a local hospital. A urinalysis indicated a gravity of 1.021 and 600mg/dl proteinuria, sugar ±, leukocyte 20~25/HP, red blood cell 3~7/HP. Blood analysis revealed the white blood cell count and classification, the platelet count were

normal, hemoglobin 127g/L. Serum creatinine was 307.3umol/L, Albumin 35g/l, blood urea 15.24mmol/L. The blood glucose, the blood lipid and the liver function were all normal. Meanwhile, the ultrasound showed that the sizes of the two kidneys were normal, and there was no renal pelvis dilatation. 7 days ago the urine volume was further reduced, and serum creatinine concentration was increased to 363umol/l with a blood urea 21.9mmol/L. The patient was treated with hemodialysis in local hospital. Later, he was transferred to our hospital for further diagnosis and treatment. There was no other medicinal history except for smoking for more than 20 years.

Physical examination

T: 36.8, P: 82/min, R: 16/min, BP: 140/90mmHg. The general condition was good. There was mild eyelids edema, no conjunctiva pale and jugular venous engorgement, no abnormal findings in heart, lungs and abdomen. But severe symmetric pitting edema of both legs was found.

Investigations

Urinalysis: sugar +, protein: 4+, leukocytes 2989/ μ l, red blood cells 157/ μ l. Urinary white cell classification: lymphocytes 57%, monocytes 29% Neutrophils 13% eosinophils1%. NAG 19.3U/L \uparrow . Microscopy for urinary sediment: a large number of thin and long coarse granular casts and waxy casts were presented, most of which were waxy casts. We could find significant number of renal tubular epithelial cell casts and occasionally red blood cell casts. Blood routine test: white blood cell 8.91×10^9 /L (percentage of neutrophils, lymphocytes and eosinophils 68.1%, 19.9%, 2.19%, respectively; eosinophil count 0.19×10^9 /L), hemoglobin 102g/L \downarrow , platelet 190×10^9 /L. Serum biochemical test: albumin 28.9g/L \downarrow , blood urea 19.81mmol/L \uparrow , creatinine 1261umol/L \uparrow , eGFR 3.3ml/min/1.73m² \downarrow , potassium 3.3mmol/L \downarrow sodium 140mmol/L, calcium 2.47mmol/L, phosphorus 0.48mmol/L \downarrow , Cholesterol 3.46mmol/L, Triglyceride 1.23mmol/L, Fasting glucose 4.70mmol/L, serum IgE 263IU/ml \uparrow . Abdominal ultrasonography: The left kidney sizes 10.9 \times 6.4 \times 5.5cm the right one is 11.6 \times 5.5 \times 5.7cm. The thickness of the renal parenchyma is 22mm (left) and 20mm (right) respectively. Echo enhancement of double renal parenchyma was found.

Case analysis

With a sudden onset, the state of this patient rapidly progressed to oliguria and anuria. The normal size of double kidneys and the mild lower hemoglobin suggested the possibility of acute renal failure (ARF). According to the history of taking NSAIDs (diclofenac) drugs, and numerous coarse granular casts and waxy casts and renal tubular epithelial cell casts in the urine, we considered the high possibility of ATN. However the duration between taking diclofenac and the onset of AKI was very long. The large number of white blood cells in the urine, mainly lymphocytes, could not support a simple ATN. The glucose level in blood was normal but positive in urine, which indicated the possibility of AIN. But the patient had no fever, no skin rash, no joints pain and any allergic manifestations, and blood eosinophil are not high. Meanwhile the patient revealed a heavy proteinuria, which was not the characteristics of the ATN and AIN, but was a clue of glomerular disease. Later, we tested the ANCA and the

anti GBM antibodies, both negative. Also, the blood and urine immunoglobulin light chain protein were negative. The level of serum immunoglobulins (IgA, IgG, IgM) and complements were all normal. Although the level of serum IgE was significantly increased. For further diagnosis and treatment, the renal biopsy was performed.

Renal histopathology

Light microscopy: There were 19 glomeruli in the specimen. Except a sclerosed glomerulus and slight glomerular basement membrane vacuolar degeneration, no obvious pathological changes were observed (Figure 1). The renal tubular epithelial cells were vacuolar degeneration, and multiple focal brush hair loss. Tubular cell debris in the lumen could be seen. The renal interstitial was edema. There were focal interstitial inflammatory cells infiltrates, predominantly lymphocytes and mononuclear cells, and a small amount of eosinophil (Figure 2a, 2b). The thickness of the small arteries showed slight increment.

Immunofluorescence microscopy: C3+~++, IgA-, IgG-, IgM-, FRA-C1q-.Weak C3 mainly deposited in glomerular mesangial region, there was no C3 deposition in the tubular region.

Electron microscopy: Diffused effacement of the glomerular foot processes was showed. There were no immune complex deposits or basement membrane abnormalities (Figure 3).

Diagnosis: Based on the clinical and the pathologic manifestations, the final diagnosis was MCD with ATN and AIN, likely caused by NSAIDs.

Treatments: We gave the patient hemodialysis, glucocorticoids (60mg/d, body weight 75kg) and some supportive therapy. After 6 weeks of treatments, the patient's urine volume began to increase, and the laboratory data demonstrated a decreased serum creatinine. At the 8th week, the hemodialysis therapy was discontinued and at the 10th week, the serum creatinine level returned to normal and his urine volume arrived at 1200-1700ml/d, without a typical polyuria stage. At the same time, 24h urinary protein excretion was increased gradually with

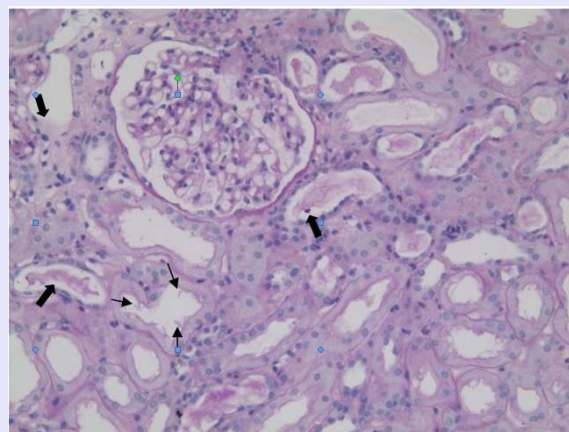


Figure 1 Light micrograph showing slight glomerular basement membrane vacuolar degeneration, no obvious pathological change was observed in glomeruli. The renal tubular epithelial cells multiple focal brush hair loss (black arrow) and the cell debris in the lumen could be seen (solid arrow). (periodic acid-Schiff, original magnification $\times 200$).

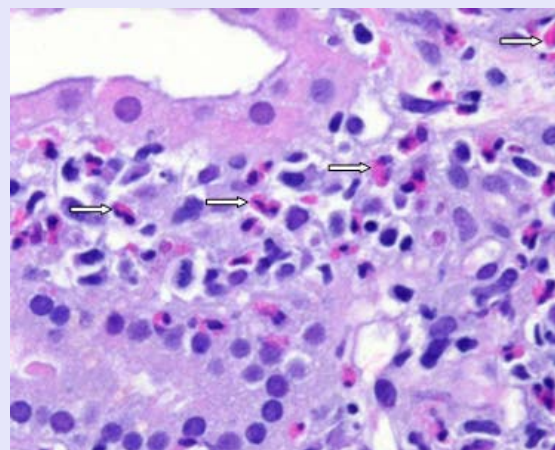
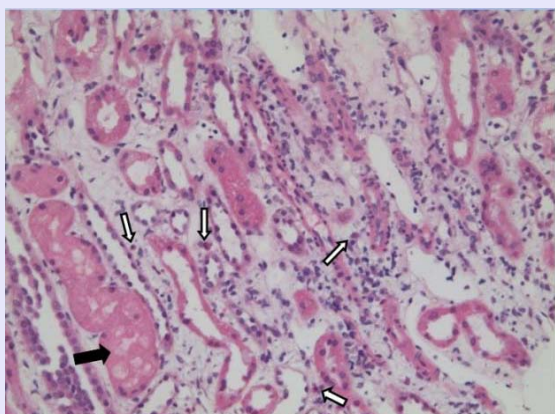


Figure 2 Light micrograph shows the renal tubular epithelial cells vacuolar degeneration (solid arrow). The renal interstitial was edema. There were focal interstitial inflammatory cells infiltrates, predominantly lymphocytes and mononuclear cells, and a small amount of eosinophils (black arrow). Periodic acid-Schiff, original magnification.

an increase of urine volume, up to 11g/d (most of them albumin). The serum albumin level was reduced from 28.9g/L to 19.8g/L. So we combined cyclophosphamide 50mg/d with glucocorticoid. At the 11th week (1 week after the use of cyclophosphamide), 24h urinary protein excretion was reduced from 11g/d to 2.4-3.5g/d. At 14th week, the serum albumin concentration was elevated to 35g/L. The 24h urinary protein excretion was reduced to 1.0g/d. We called this patient at the 18th week. The 24h urinary protein excretion was reduced to 0.2g/d.

DISCUSSION

The renal damages induced by NSAIDs can often be reported, including ATN, AIN and nephrotic syndrome (mainly MCD and membranous nephropathy). But two kinds of damages occur in the same patient simultaneously is very rarely. In 2002, Alper AB Jr and his colleagues reported a case of MCD with AIN induced by celecoxib [4]. In 2008, Galešić K et al., reported a case of MCD with ATN induced by diclofenac [5]. In 2014, Hiroaki K found a case of MCD with AIN induced by topical application of loxoprofen patch [6].

This case is rarely reported for glomerular MCD with ATN and AIN caused by NSAIDs.

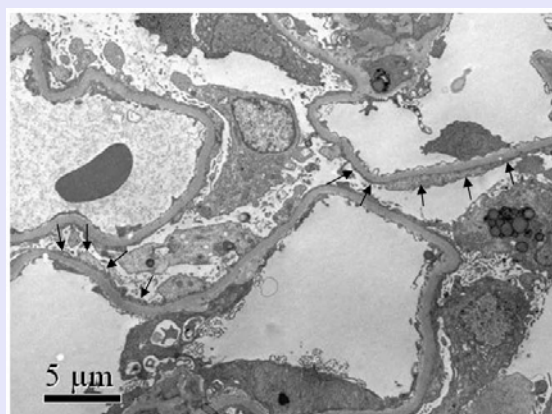


Figure 3 Electron micrograph shows the focal effacement of glomerular foot processes (black arrows) without deposits or basement abnormalities (original magnification $\times 5,000$).

What is the mechanism behind the kidney damage caused by NSAIDs drugs? Normally, the arachidonic acid (AA) is catalyzed by cyclooxygenase (COXs) to form prostaglandins (PGs), and by lipoxygenase (LOs) to form leukotrienes (LTs). PGs mediate the biological effect of dilating blood vessels. However, LTs has a strong effect on the contraction of blood vessels. Diclofenac inhibits the activity of COXs to interfere the synthesis metabolism of PGs and LTs from AA.

On one hand, NSAIDs mediate AKI by hemodynamic mechanism. There is a variety of tissue COXs in kidney glomerular, tubular and interstitial cells, mainly producing 5 kinds of PGs products (PGD₂, PGE₂, PGF₂, PGI₂ and TXA₂). These native PGs of kidney mainly induce the dilating of blood vessels, maintain the renal perfusion, reduce the ischemic injury [7], especially under stress conditions. When the COXs are blocked by NSAIDs drugs, the reduction of PGs level in the local tissue of the kidney attenuates the ability of adjusting blood flow, resulting in renal ischemia ultimately. Patients often show a rapid increase in serum creatinine generally 3~7 days after taking the drug. Because a high and stable drug concentration in blood needs a period of accumulation firstly, and then largely affects the inhibition of COXs. In case of ATN induced by hemodynamic disorder, there are no significantly red blood cells in urine under microscopy. In addition, the urine protein level is low (mostly lower than 500mg/d). Also the renal tubular epithelial cell casts may be found. The key point to distinguish ATN from AIN is no white blood cells for the former one and the white blood cells casts in the urine for the latter.

On the other hand, NSAIDs may mediate AIN and nephrotic syndrome by immunological mechanism. The common pathological types of glomerular disease were MCD and membranous nephropathy. It is considered as non-dose-dependent. As a kind of inflammatory factors, LTs have chemotaxis to inflammatory cells, which causes the infiltration of inflammatory cells in the kidney interstitial tissue. The increased concentration of LTs and various inflammatory cytokines released by inflammatory cells both increase the permeability of glomerular basement membrane, thereby, result in the proteinuria even nephrotic syndrome. Typical AIN often appears

obvious hematuria, leukocyturia/pyuria and rapid elevation in serum creatinine. In our case the systemic allergic reactions are atypical. There are parts of the performance including the urine white blood cells, mainly lymphocytes and monocytes, and positive urine glucose (normal blood glucose), significantly increased the serum IgE. These supported a diagnosis of AIN. Thereafter, the renal biopsy confirmed the existence of interstitial nephritis.

It is reported that simple AIN or ATN induced by NSAIDs drug remit within 6 weeks after the withdrawal of NSAIDs and the treatment with glucocorticoid [5-7]. But the recovery of AKI in this case is very slowly. After 9 weeks, the volume of urine of the patient began to increase. But, there is no polyuria stage after that. Following a long treatment of 13 weeks, the renal function eventually returned to normal. The coexistence of ATN, AIN and NS delay the recovery of renal function. Besides, the atherosclerosis in the renal small arteries can also delay the recovery of the renal failure. The factors above make the renal tubular epithelial cells regenerate slowly, and the renal tubular reconstruction is prolonged. Therefore, the urine volume could not increase rapidly.

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