Case Report

A Case of Acute Interstitial Nephritis Induced by Flurbiprofen

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Recently, acute interstitial nephritis (AIN) presenting nephrotic syndrome and renal failure induced by nonsteroidal anti-inflammatory drug (NSAID) has been recognized with increasing frequency. We described here a 43-year-old woman who developed this type of nephropathy after taking NSAID for rheumatoid arthritis. Flurbiprofen (Froben) was assumed to be a causal drug based on a clinical course and a positive result of lymphocyte transformation test. Withdrawal of flurbiprofen therapy led no sufficient improvement, and high-dose steroid therapy done 15 months after the onset resulted in only a minor improvement. So far as we know, this was the second case of AIN associated with flurbiprofen and the youngest in NSAID-induced AIN with irreversible chronic renal insufficiency.

Key Words: Acute renal failure, Nephrotic syndrome, NSAID, Flurbiprofen.

The renal disease induced by nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported by several authors1-12. In these cases, acute interstitial lesions in the kidney are demonstrated by histological examinations, and clinically, frequent associations with the nephrotic syndrome and renal failure are also pointed out. Fenoprofen3-7, ibuprofen3-7, naproxan3,4,8, or some other NSAIDs have been reported as causative drugs. But, only one case associated with flurbiprofen has been reported9 up to the present. The pathogenesis of acute interstitial nephritis (AIN) and the effectiveness of steroids on this disease remain uncertain. We describe herein a case of flurbiprofen-induced AIN who remitted incompletely even after high-dose steroid therapy and discuss about a cause of irreversibility.

REPORT OF A CASE

A 43-year-old Japanese woman was admitted to our clinic on September 22, 1982, for further evaluations of proteinuria, azotemia and liver injury. Arthralgia and swelling of bilateral hands and fingers had developed 2 years prior to the admission. Although serological tests gave negative results, the diagnosis of rheumatoid arthritis was made on the basis of criteria of the American Rheumatism Association. Immediately she had been medicated flurbiprofen (160-320 mg/day) and then received the first trial of gold sodium thiomalate (total 35 mg) and benoxaprofen (400 mg/day) and the second trial of gold salt (total 800 mg). At that time, she had had normal urinalysis and renal functions (Figure 1). About one month after flurbiprofen and gold salt therapy, general skin rash and eosinophilia (18%) had developed. After suspension of gold salt, facial rash and eosinophilia had disappeared gradually, but eruption on the chest, abdomen and extremities had remained unchanged. About 11 months prior to the admission, she had received gold salt therapy again, and the same side-effects developed as in the first medication of gold. One month before the admission elevated alkaline phosphatase (ALP), leucine aminopeptidase (LAP) and γ-glutamyl-
transpeptidase (γ-GTP) were noticed by her physician. One week before the admission she visited her local hospital with the complaints of nausea, vomiting and eyelid edema, and was pointed out again of proteinuria (14.0–17.5 g/day), azotemia [blood urea nitrogen (BUN) 31.3 mg/dl, serum creatinine 2.4 mg/dl] and abnormal ALP, LAP and γ-GTP.

On admission to our hospital, physical examinations showed a blood pressure of 130/80 mmHg, facial and peripheral edema and ascites.

Urinalysis revealed 2 plus protein, 1 plus glucose and sediments contained some white blood cells and red blood cells, and occasionally granular casts and hyaline casts. A 24-hour urine collection showed a oliguria (450 ml/day) and 28.0 g of proteinuria. White blood cell wa 6200/cumm with 4% eosinophils and erythrocyte sedimentation rate was 156/hr, 173 mm/2 hr. The serum creatinine was 2.5 mg/dl, BUN 38 mg/dl, uric acid 6.7 mg/dl, total protein 4.9 g/dl and serum albumin 1.9 g/dl. Glutamate oxaloacetic transaminase was 18 U/l, glutamate pyruvate transaminase 8 u/l, ALP 144 U/l (normal 42–115), LAP 72 U/l (normal 27–48) and γ-GTP 125 U/l (normal 4–23). Endogenous creatinine clearance was 20.0 ml/min. Test results for antistreptolysin O, complements, antinuclear antibody, anti-DNA, anti-ENA, anti-tubular basement membrane antibody, and anti-mitochondrial antibody were normal or negative. Bilateral enlarged kidney without urinary tract obstruction was observed ultrasonographycally and pyelographically.

Renal biopsy done on October 5, 1982, revealed only minor glomelular alterations by light microscopy as shown in Fig. 2, the most striking changes were found in the renal tubules and interstitium. There was tubular dilatation together with tubular epithelial flattening, necrosis and degenerations. The interstitium was edematous and contained inflammatory infiltrations of numerous lymphocytes, plasma cells and a small number of eosinophils. Findings by direct immunofluorescence staining were negative for immunoglobulins,
C₃ and fibrinogen. Electron microscopy revealed diffuse fusion of epithelial cell foot process. From these results, the diagnosis of interstitial nephritis was made.

Immediately after the admission, flurbiprofen was stopped, and on September 24, she began to take furosemide for edema, and 15 days later prednisolone, 40 mg/day, for the interstitial nephritis.

However, prednisolone was tapered and stopped on November 26, 1982, because of steroid psychosis. Remarkable effect with prednisolone was not seen on heavy proteinuria, hypoproteinemia and renal insufficiency. Namely, her serum creatinine was 2.7 mg/dl, BUN 19 mg/dl, total protein 4.2 g/dl, serum albumin 2.0 g/dl, proteinuria 26.6 g/day and endogenous creatinine clearance 21.0 ml/min, but her liver function was apparently improved (ALP 100 u/l, LAP 55 u/l and y-GTP 56 u/l). Lymphocyte transformation test showed the results of flurbiprofen 189%, benoxaprofen 94% and gold sodium thiomalate 104%.

About four weeks after the withdrawal of prednisolone, she was discharged from our hospital and admitted to a local hospital at her request. During the year of 1983, she was treated in the local hospital, and her serum creatinine was 2.2 mg/dl, BUN 20.0 mg/dl, total protein 5.4 g/dl, serum albumin 2.0 g/dl, proteinuria 22.3 g/day and endogenous creatinine clearance was 25.0 ml/min. Liver function was normal.

On December 8, 1983, she received prednisolone again 40 mg daily for 14 days and tailed down to 20 mg daily, under attentions to side-effects particular to psychosis. Fortunately, she became symptom-free and discharged after 4 months. At that time, laboratory data were as follows: serum creatinine 1.7 mg/dl, BUN 18.8 mg/dl, total protein 6.6 g/dl, serum albumin 3.2 g/dl, proteinuria 3.2 g/day and endogenous creatinine clearance was 31.8 ml/min. Total amounts of prednisolone used during this period was 3,420 mg.

DISCUSSION

It has been known that acute interstitial nephritis is often induced by various drugs. Penicillin and its derivative is known as the most common causative agents. Recently, NSAID-induced AIN accompanying by nephrotic syndrome and acute renal failure has been also reported. For the pathogenesis, a delayed hypersensitivity responsible for NSAID is suggested rather than a humoral mechanism as in other forms of acute allergic interstitial nephritis due to penicillins and others. In our case, lymphocyte transformation test for flurbiprofen was positive indicating that her nephropathy was due to delayed hypersensitivity for flurbiprofen. Though propionic acid derivatives are often responsible for this nephropathy, so far as we know, only one case associated with flurbiprofen has been reported. Thus, flurbiprofen should be added to the list of NSAID induced AIN accompanying by nephrotic syndrome and acute renal failure.

Our case had also taken gold sodium thiomalate. However, in cases of gold nephropathy, membranous nephropathy was the most common feature. Renal histology of our patient was not a membranous nephropathy by light, immunofluorescence and electron microscopy. Participation of an acute allergic interstitial nephritis implicated with gold salt was not ruled out completely because worsening of skin rash and eosinophilia had appeared immediately after the use of gold salt, but a delayed hypersensitivity for gold salt was seemed to be unresponsible from the negative lymphocyte transformation test.

Drug induced renal disease usually recovered after stopping the causal drug. However, available literatures dealing with the beneficial effect of steroids on this disease was controversial. Most patients have regained renal function satisfactory with steroids therapy. In our case, the withdrawal of flurbiprofen and the first trial of prednisolone was not effective followed by persistent heavy proteinuria, hypoproteinemia and renal insufficiency during the subsequent 13 months, and the second trial of prednisolone resulted in only minor improvement. As a cause of ineffectiveness of the withdrawal of flurbiprofen and the first trial of prednisolone, the following three reasons were suspected. Firstly, our patient had liver injury, probably drug induced, one month prior to the onset of nephropathy and to the withdrawal of flurbiprofen. Consequently, the half-life of flurbiprofen might be prolonged because the drug me-
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tabulated in the liver. Flurbiprofen might have accumulated for a long time in her body. Finkelstein et al\(^6\), Mitnich et al\(^9\) and Abt et al\(^11\) reported a case complicating liver injury similar to our case, and mentioned that no renal improvement was observed after the withdrawal of drugs and high-dose of steroids was required. Secondary, Favre et al\(^12\) described that NSAID-induced renal dysfunction occurred more often in patients treated with diuretics. Since our patient had received relatively high-dose diuretics for her edema, this drug might have interacted with flurbiprofen. Thirdly, because of steroid psychosis, the amount of prednisolone used was not sufficient.

Our patient remained unchanged despite a long-term discontinuation of the drug and the second trial of prednisolone produced only an incomplete remission. In regard to the long-term outcome in NSAID-induced AIN, only few papers have dealt with this problem. Some cases with NSAID-induced AIN\(^3,6,8,9\) developed irreversible chronic renal insufficiency. However, these cases were older than 60 years and so far as we know, our case of 43 years old was the youngest. Side effects of flurbiprofen has been reported generally in aged patients, and most of them were associated with gastrointestinal, psyconeurologic and dermatologic symptoms. However, the frequency of AIN with nephrotic syndrome induced by flurbiprofen is very rare. This report stress the necessity to encounter the history of NSAID in a case of nephrotic syndrome and acute renal failure from unknown origin.

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REFERENCES