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【 CASE REPORT 】

Acute Interstitial Nephritis and Acute Tubular Injury Due to a Transdermal Loxoprofen Patch

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Abstract:
A transdermal patch formulation of a non-steroidal anti-inflammatory drug (NSAID) used by a 44-year-old man resulted in acute interstitial nephritis and acute tubular injury. This patient also had a history of mild kidney dysfunction and osteoporosis. The NSAID patch had been prescribed after a traffic accident. He was also receiving a vitamin D analog and taking over-the-counter calcium supplements. Two months later, renal dysfunction and hypercalcemia were discovered. A renal biopsy showed acute interstitial nephritis and acute tubular injury. Once these agents were withdrawn, the renal function recovered. This is the first reported occurrence of biopsy-proven acute interstitial nephritis attributable to NSAID patch usage.

Key words: acute interstitial nephritis, non-steroidal anti-inflammatory drugs, hypercalcemia

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Introduction

A low percentage of patients (1.5%) exposed to non-steroidal anti-inflammatory drugs (NSAIDs) experience adverse renal events (1, 2). There are two chief mechanisms of acute kidney injury in this setting. Decreases in prostaglandin E2 and prostacyclin, which regulate glomerular and arteriolar vasodilation through cyclooxygenase inhibition (3-6), may reduce the renal blood flow and thereby induce renal dysfunction in patients with chronic kidney disease (7, 8) or volume depletion (9). An immunologic reaction after NSAID treatment may likewise impair the renal function, producing acute interstitial nephritis (6). The prevalence of biopsy-proven acute interstitial nephritis in all renal biopsies ranges between 0.5 and 2.6% (10).

Although a few published reports of acute kidney injury or nephrotic syndrome have implicated topical NSAID use (11-13), none has yet linked a patch formulation with histologic evidence of acute interstitial nephritis. We herein describe the first known case of biopsy-proven acute interstitial nephritis involving a transdermal NSAID patch.

Case Report

The patient was a 44-year-old man with mild kidney dysfunction and a serum creatinine (Cr) level of ~1 mg/dL [estimated glomerular filtration rate (eGFR) =65 mL/min/1.73 m^2]. Blood and urine tests and diagnostic imaging had failed to reveal the cause, and renal biopsy had not been done. No proteinuria or occult hematuria was detected, only a slight decline in his renal function. While bicycling in 2017, he suffered a trochanteric fracture of left femur that was fixed by intramedullary nail. Quantitative bone mineral testing at that time indicated the onset of osteoporosis. However, there was no indication of a predisposing endocrine (i.e., diabetes mellitus) or hereditary disorder, nor was there a history of steroid use. He was diagnosed with primary (idiopathic) osteoporosis.

The intramedullary nail was removed on August 2018. Treatment with eldecalcitol, an active vitamin D analog, began end of September and was undertaken in conjunction

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Table. **Laboratory Data on Admission.**

Complete blood count		Serology	
Red blood cell	340 $\times 10^4/\mu L$	Immunoglobulin G	750 mg/dL
Hemoglobin	10.7 g/dL	Immunoglobulin A	163 mg/dL
Hematocrit	31.9 %	Immunoglobulin M	50 mg/dL
White blood cells	75 $\times 10^2/\mu L$	C3	95 mg/dL
Neutrophils	72.5 %	C4	28 mg/dL
Eosinophils	1.9 %	CH50	56 CH50/mL
Basophils	0.5 %	Myeloperoxidase-ANCA	<0.5 IU/mL
Lymphocytes	16.1 %	Proteinase 3-ANCA	<1 IU/mL
Monocytes	9.0 %	Anti-GBM antibody	<1 IU/mL
Platelets	18.0 $\times 10^4/\mu L$	Antinuclear antibody	negative
Blood chemistry tests		Urinalysis	
Total bilirubin	0.8 mg/dL	pH	7.5
Alanine aminotransaminase	19 IU/L	Protein	(±)
Aspartate aminotransferase	25 IU/L	Blood	(-)
Alkaline phosphatase	193 IU/L	Glucose	(-)
Gamma-glutamyl transferase	6 IU/L	Ketones	(-)
Lactate dehydrogenase	162 IU/L	Bilirubin	(-)
Total protein	5.7 g/dL	Sediment	
Albumin	3.1 g/dL	Red blood cells	0-1 /HPF
Urea nitrogen	49.6 mg/dL	White blood cells	1-2 /HPF
Creatinine	6.52 mg/dL	Urine protein to creatine ratio	0.16 g/g creatinine
Sodium	132 mEq/L	N-acetyl-β-D-glucosaminidase	22.2 IU/L
Chloride	84 mEq/L	β2-microglobulin	21,075 IU/L
Potassium	4.2 mEq/L		
Phosphate	6.7 mg/dL		
Calcium	11.0 mg/dL		
Glucose	86 mg/dL		
C-reactive protein	0.16 mg/dL		

ANCA: antineutrophil cytoplasmic antibodies, GBM: glomerular basement membrane

with an over-the-counter calcium supplement. In middle of October, the patient was struck by another vehicle while driving, causing a cervical sprain. He used oral loxoprofen on three occasions for pain relief, eventually switching to a twice-daily patch. Serum Cr, calcium, and albumin levels on end of October (1.09, 8.9 and 3.5 mg/dL, respectively) rose sharply by end of November (5.16, 12.0, and 4.0 mg/dL, respectively), thus prompting immediate hospitalization. No allergic symptoms (i.e., rash or mild fever) or abnormal physical findings were evident. The laboratory test findings at the time of admission are shown in Table.

Following intravenous hydration and the withdrawal of the culprit medications (eldecalcitol, loxoprofen patch, and calcium supplement), serum calcium and albumin levels fell to 8.5 and 2.7 mg/dL, respectively; whereas serum Cr continued to climb, reaching 8.01 mg/dL in the absence of proteinuria or hematuria. The urinary levels of β2-microglobulin and N-acetyl-β-D-glucosaminidase were 21,075 μg/dL and 22.2 U/L, respectively.

A renal biopsy performed in early December, two days after transfer to our hospital, showed lymphocytic interstitial infiltrates with some plasma cells amidst a scattering of normal and sclerotic glomeruli. Tubular epithelial cells appeared to be swollen and they were also detached from the basement membranes or demonstrated atypical cytoplasmic blebs. The tubular lumens were obstructed by Tamm-Horsfall protein and necrotic debris (Fig. 1). There were no specific clues regarding the basis of mild kidney dysfunction. Our diagnosis was acute interstitial nephritis and acute tubular injury. Physical examination and laboratory diagnostics excluded any conditions predisposing to interstitial nephritis, such as sarcoidosis, Sjogren's syndrome, or infectious disease (e.g., tuberculosis). The presumptive cause of renal decompensation was thus the loxoprofen patch. The patient's kidney function spontaneously improved after its withdrawal.

The patient was discharged in middle of December with a serum Cr level of 2.74 mg/dL, which fell to 1.27 mg/dL by January 2019 and later stabilized at 1.1-1.3 mg/dL (Fig. 2).

Discussion

This particular account is a cautionary one, offering the following caveats: 1) the use of a transdermal NSAID patch may induce acute interstitial nephritis and acute tubular injury; and 2) young patients with hypercalcemia or mild kid-

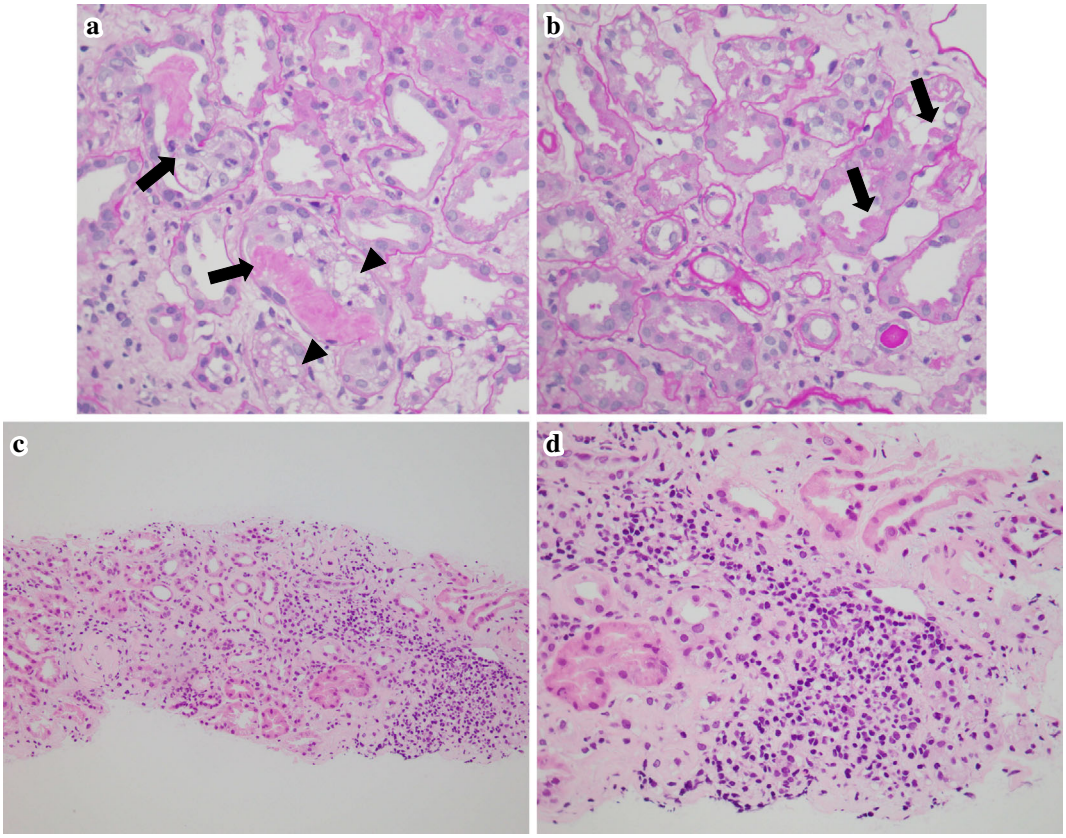

Figure 1. **Microscopic features of a renal biopsy: (a) Swelling of the tubular epithelial cells (arrowheads), with luminal retention of Tamm-Horsfall protein and necrotic debris (arrows), periodic acid-Schiff (PAS) stain, 400×; (b) atypical cytoplasmic blebs (arrows), PAS stain, 400×; (c) focal interstitial inflammatory cell infiltrates, Hematoxylin and Eosin (H&E) staining, 200×; (d) interstitial nephritis consisting of mononuclear cells with a few plasma cells, H&E staining, 400×.**

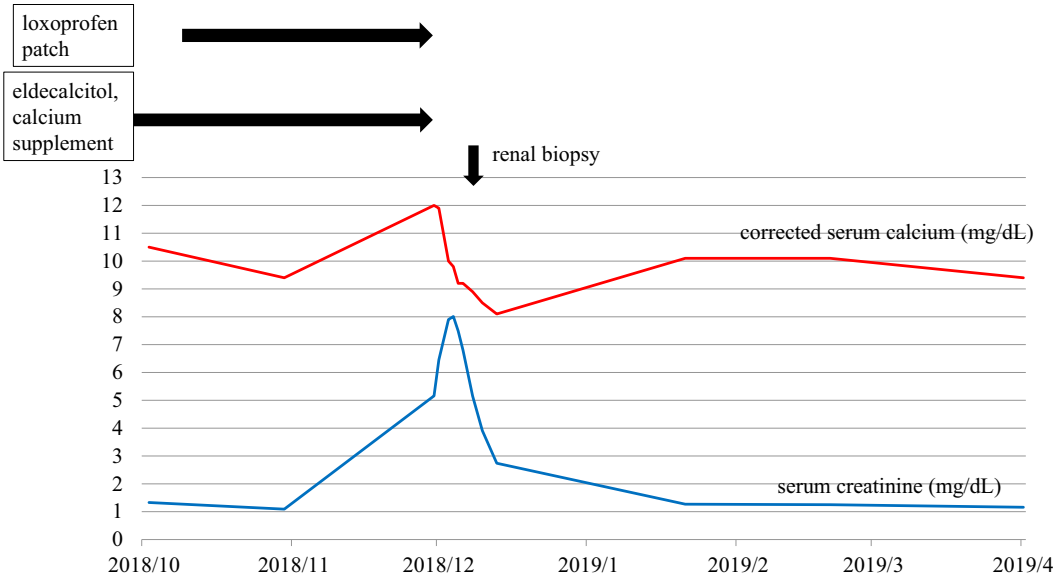

Figure 2. **Clinical course of the patient.**

ney dysfunction may risk renal impairment when electing such treatment.

It is not uncommon for NSAIDs to cause acute interstitial nephritis or acute kidney injury, although topical formulations are rarely implicated. Past reports include a 74-year-old woman with interstitial nephritis and nephrotic syndrome (due to piroxicam gel), a 57-year-old woman with acute kidney injury (after benzydamine hydrochloride cream application) (11), and a 74-year-old man with focal segmental glomerulosclerosis and nephrotic syndrome (caused by

ibuprofen and felbinac gel) (12). Similarly, a 76-year-old woman showing improvement of interstitial nephritis and nephrotic syndrome after cessation of oral NSAIDs developed worsening renal function and proteinuria when using a loxoprofen patch (13). The patient developed biopsy-proven acute interstitial nephritis and nephrotic syndrome after oral NSAID use. The withdrawal of the offending agent did improve the renal function while reducing the degree of proteinuria, but both worsened after a transdermal NSAID patch was applied. This is the first instance of biopsy-proven interstitial nephritis involving a NSAID patch, adding to existing reports (above) of renal impairment linked to topical NSAIDs. Although pre-existing interstitial nephritis cannot be entirely ruled out, acute inflammatory cells were present; and aside from NSAID use, other potential causes of interstitial nephritis were lacking.

Under the given circumstances, we suspect that hypercalcemia and mild kidney dysfunction enhanced the acute kidney injury triggered by topical loxoprofen. The observed histologic changes of acute interstitial nephritis were focal in nature and thus were not considered to be the chief cause of renal dysfunction. More likely, glomerular and arteriolar vasoconstriction imposed by reduced prostaglandin synthesis (NSAID effect) was primarily responsible. Acute tubular injury was noted as well, suggesting an element of hemodynamic compromise. A dysfunction of this sort, provoked by a topical NSAID, rarely occurs in healthy individuals.

A plasma steady concentration of loxoprofen with multiple topical dosing is much lower than a maximal concentration of loxoplofen in the plasma associated with oral dosing (54.9 ng/mL vs 5.04 μg/mL) (13). However, the glomerular/arteriolar vasoconstrictive impact of NSAIDs may be enhanced by hypercalcemia (14), leading to severe renal impairment; and mild kidney dysfunction (as in this patient) may have exacerbated these adverse hemodynamic consequences (7, 8). Even less robust topical NSAID applications may then precipitate renal dysfunction. Although earlier reports have been confined to older patients, this particular narrative indicates that young patients with hypercalcemia or mild kidney dysfunction are also vulnerable.

Oral loxoprofen, which was used by our patient on three occasions, is an unlikely basis for the acute kidney injury diagnosed 2 months later. The plasma creatinine levels usually rise within the first 3-7 days after initiating oral therapy (15). The fact that renal dysfunction peaked 1 week after topical loxoprofen discontinuation further implicates the patch formulation as a direct cause.

In conclusion, a transdermal NSAID patch may cause acute interstitial nephritis and acute tubular injury, as shown by this first biopsy-proven occurrence. Young patients with hypercalcemia or mild kidney dysfunction are therefore not exempt from such events.

The authors state that they have no Conflict of Interest (COI).

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