CASE REPORT

Tubulointerstitial Nephritis Associated with Enteritis and Sacroiliitis

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Abstract:

The association between sacroiliitis and tubulointerstitial nephritis has not been reported. A 28-year-old man with a history of clinically diagnosed ulcerative colitis (4 years earlier) and sacroiliitis (6 months earlier) developed renal dysfunction 9 months ago, which progressed thereafter. We diagnosed him with tubulointerstitial nephritis by a renal biopsy, for which we started steroid therapy. Subsequently, his renal dysfunction, sacroiliitis, and enteritis partially improved. A pathological analysis of the kidney and intestine revealed lymphocyte infiltration and non-caseating granuloma in both organs. The similarities in the pathological findings and treatment response suggested a pathogenetic association between tubulointerstitial nephritis, enteritis, and sacroiliitis.

Key words: tubulointerstitial nephritis, sacroiliitis, enteritis, granuloma

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Introduction

Tubulointerstitial nephritis is a disease characterized by renal dysfunction and inflammatory infiltration in the kidney interstitium. The causes of tubulointerstitial nephritis vary; however, many cases have undetermined etiologies. It is important to identify cases of tubulointerstitial nephritis with the potential for renal recovery as some patients with tubulointerstitial nephritis show at least partial improvement with early medical treatment (1, 2). We encountered a case of tubulointerstitial nephritis associated with the systemic chronic inflammatory diseases of ulcerative colitis and sacroiliitis. Although there have been reports of cases of tubulointerstitial nephritis associated with enteritis (3), tubulointerstitial nephritis associated with sacroiliitis has yet to be reported.

We herein report a rare case of steroid-responsive tubulointerstitial nephritis with a possible association with enteritis and sacroiliitis.

Case Report

A 28-year-old man with a history of enteritis (clinically diagnosed as ulcerative colitis) and sacroiliitis was referred to our nephrology clinic with progressive kidney dysfunction. Four years ago, he had had an episode of loose stool that progressed to watery diarrhea; this led to the diagnosis of mild ulcerative colitis by colonoscopy, which improved without medication. He had also reported having mild lumbar pain. At that time, his serum creatinine level was normal (0.89 mg/dL). Nine months earlier, during a routine medical checkup, he was found to have a serum creatinine level of 2.1 mg/dL, for which he did not consult a physician. Six months earlier, he had experienced right buttock pain, which was diagnosed as sacroiliitis and was resolved symptomatically with non-steroidal anti-inflammatory drug (NSAID) administration. Three months earlier, he visited a hospital repeatedly for numbness of the right femoral flexor, and his serum creatinine level had increased to 2.75 mg/dL, for which he was referred to our clinic.

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Table. Laboratory Data at the Time of Admission.

| Blood Count       | Urinalysis findings |
|-------------------|---------------------|
| White blood cells | Gravity 1.013       |
| Segment           | pH 5.5              |
| Neutrophil        | Protein 221.5 mg/day|
| Lymphocyte        | Albumin 33 mg/day   |
| Monocyte          | Glucose (-)         |
| Eosinophil        | Occult blood (+)    |
| Basophil          | Red blood cells 5-9 /HPF |
| Red blood cells   | Epithelial cast (+) |
| Hemoglobin        | Leukocyte cast (+)  |
| Hematocrit        | α1-microglobulin 44.5 mg/L |
| Platelet          | β2-microglobulin 2,426 µg/L |
| Blood chemistry   | NAG 10.8 U/L        |
| Total protein     | Immunologic findings|
| Albumin           | 4.5 g/dL            |
| Total bilirubin   | Immunglobulin A 522 mg/dL |
| AST               | Immunglobulin G 2,828 mg/dL |
| ALT               | Immunglobulin M 256 mg/dL |
| ALP               | ASO 719 IU/mL       |
| LDH               | M protein (-)       |
| Creatinine        | Anti-nuclear antibody(-) |
| Urea nitrogen     | c-ANCA (-)          |
| Sodium            | p-ANCA (-)          |
| Potassium         | Cryoglobulin (-)    |
| Chloride          | Anti-cardiolipin antibody(-) |
| Calcium           | Anti-SS-A antibody (-) |
| Phosphorus        | Anti-SS-B antibody (-) |
| C-reactive protein| Complement 3 126 mg/dL |
|                   | Complement 4 32 mg/dL |
|                   | ACE 17.8 U/L        |
|                   | KL-6 555 U/mL       |

NAG: N-acetyl-β-D-glucosaminidase, ASO: antistreptolysin O, c-ANCA: cytoplasmic-anti-neutrophil cytoplasmic antibody, p-ANCA: perinuclear-anti-neutrophil cytoplasmic antibody, ACE: angiotensin-converting enzyme. KL-6: Krebs von den Lungen-6.

His medical history included systemic chronic inflammatory diseases (enteritis and sarcoiditis) with chronic leukocytosis [white blood cell (WBC) count 10,000-13,000/µL; neutrophil count 64%, eosinophil count 9%]. His family medical history included rheumatoid arthritis (paternal grandmother) and Crohn’s disease (younger brother) but no renal failure or urinary abnormalities. His current medications were clarithromycin (dose unknown) and NSAID, administered as required. He was a non-smoker and non-drinker and had no allergies.

A physical examination showed a single painless canker sore and mildly enlarged intestinal peristalsis without pain and distension; in addition, the patient reported an uncomfortable feeling (no pain or tenderness) in the sacroiliac joint and spine; otherwise, findings of the muscles, bones, joints, and skin were unremarkable. Table presents the laboratory data obtained from the patient on admission. Urinalyses revealed hematuria, with 5-9 red blood cells/high-power field (HPF), 20-29 WBCs/HPF (no eosinophils in the urine), an epithelial cast, a leukocyte cast, and poikilocytosis, although no abnormality on urinalysis had been reported previously.

The urine protein excretion was 0.2 g/day (albuminuria 0.03 g/day), and the urinary N-acetyl-β-D-glucosaminidase (NAG), urinary alpha-1 microglobulin (α1-MG), and urinary beta-2 microglobulin (β2-MG) levels were elevated to 10.8 U/L (reference range, 0.8-11.0 U/L), 44.5 mg/L (reference range, 0-8.3 mg/L), and 2,426 µg/L (reference range, 0-200 µg/L), respectively. On a complete blood cell count analysis, the WBC and eosinophil counts were found to be elevated to 10,800/µL and 9% eosinophilia, respectively. An ultrasonogram of both kidneys showed that they measured about 10.0 cm, without hydronephrosis, and had an irregular shape and echogenic renal parenchyma. Plain chest-abdominal computed tomography showed that both kidneys were mildly atrophic, without hydronephrosis.

Suspecting that the patient had systemic chronic inflammatory diseases, we performed more tests to assess his kidney dysfunction. A blood test showed an elevated sedimentation rate, polyclonal gammapathy (IgA level 522 mg/dL, IgG level 2,828 mg/dL, and IgM level 256 mg/dL) with no M protein detected on immunoelectrophoresis, and an elevated antistreptolysin O (ASO) level (719 IU/mL). The pa-
cause of the concomitant course of the three pathologies. En
teritis were associated with each other be-
NAG), and sterile pyuria. We suspected that renal failure,
urinary tubular biomarker levels (α1-MG, β2-MG, and
were normal as well. A fat biopsy was negative for amy-
lyoids. Thus, the aforementioned blood and imaging test re-
results indicated that although the patient had chronic inflam-
mation, paraproteinemia and ANA- or ANCA-associated
vasculitis or collagen diseases were unlikely to be the cause.
The patient had enteritis, clinically diagnosed as ulcerative
colitis, with the disappearance of the visible vascular pattern
of the intestine macroscopically and lymphocyte infiltration
and granuloma pathologically. However, our gastrointestinal
specialist could not diagnose this lesion as inflammatory
bowel disease (IBD), although there were potential signs of
remnant IBD. As a result, we suspected that he had autoim-
une enteritis of an unknown etiology.

To make a definitive diagnosis, we performed a percuta-
ous renal biopsy on day 34 from the initial presentation.
Light microscopy showed diffuse interstitial cell infiltration
and mild-to-moderate fibrosis (Fig. 3A). Of the 24 glomeruli
obtained, 2 showed global sclerosis, and the others were al-
most intact. The HPF showed tubulitis and interstitial cellular
invasion, with the infiltrating cells including many lympho-
cytes and plasma cells as well as few eosinophils but no
neutrophils. The granuloma consisted of the interstitium of
the renal tissue (cortex) (Fig. 3B). The results of an immu-
nohistochemical analysis for IgA, IgG, IgM, C1q, C3c, k, and
were all negative. Electron microscopy showed inter-
stitial cellular invasion, although the glomeruli were intact.
We confirmed a diagnosis of tubulointerstitial nephritis.

We expected his renal disorder to improve with treatment
because his renal tissue had an acute lesion and the
glomerular formation was intact. We started intravenous ster-
oid pulse therapy for 3 days, followed by oral prednisolone,
starting at a dose of 30 mg/day with tapering. We reduced
the prednisolone dose by 5 mg every month until it was 10
mg/day and then reduced the dose by 2.5 mg every month
until it was 5 mg/day and then by 1 mg every month there-
after. The serum creatinine level decreased from 3.15 mg/dL
to 2.32 mg/dL, but no further improvement was observed.
The C-reactive protein (CRP) level decreased from 2.22 mg/
dL to <0.03 mg/dL. The urinary tubular biomarker levels
decreased as well [NAG from 10.8 U/L to 0.9 U/L (refer-
ence range, 0.8-11.0 U/L), α1-MG from 44.5 mg/L to 5.7
mg/L (reference range, 0-8.3 mg/L), β2-MG from 2,426 μg/
L to 647 μg/L (reference range, 0-200 μg/L)]. The symp-
toms of saccroilitis (buttock pain) and enteritis (diarrhea)
also improved simultaneously; indeed, 4 months after start-
ing steroid therapy (prednisolone 10 mg), his buttock pain
and diarrhea had almost disappeared. Magnetic resonance
imaging (fat-suppressed T1-weighted imaging) showed the
disappearance of the unilateral high-intensity area after ste-
roid therapy (Fig. 1B).
Figure 2. Patient’s clinical course. Renal failure had been progressing for several years. The symptoms of both arthritis and enteritis had been maintained for four years. We considered that the renal failure, arthritis, and enteritis were associated with each other. The serum creatinine level, CRP level, and urinary tubular biomarker level were improved by steroid therapy. The symptoms of arthritis and enteritis were also improved simultaneously. Cr: creatinine, CRP: C-reactive protein, mPSL: methylprednisolone, PSL: prednisolone, NAG: N-acetyl-β-D-glucosaminidase, α1-MG: alpha-1 microglobulin, β2-MG: beta-2 microglobulin

Figure 3. Histological findings of the kidney. (A) This field shows the overall infiltration of lymphocytes, plasma cells, and eosinophils in the interstitium, along with moderate tubular atrophy and interstitial fibrosis (Masson trichrome staining, ×20). (B) Granuloma in the interstitium of the cortex (arrow) (periodic acid-Schiff staining, ×200).
earlier, the ASO titer had been 693 IU/mL. The rapid test present case, the ASO titer was 719 IU/mL, but 2 months year (8). In some cases, an association between the ASO sizes within several months; however, some patients experi- pharyngitis. It has been reported that the ASO titer normal- with the peak ASO titer reached at three to five weeks after progress, tubulointerstitial nephritis. Regarding infections, drugs were unlikely to be the cause of his drug-induced manifestations, the patient had taken clarithro- sarcoidosis, infection (specifically tuberculosis), vasculitis (particularly granulomatosis with polyangiitis), tubulointer- stitial nephritis, uveitis syndrome, and IBD have been re- (particularly granulomatosis with polyangiitis), tubulointer- stitial nephritis associated with enteritis and sacroiliitis. We differentiated the causes of granulomatous tubulointer- stitial nephritis in the present case. Regarding potential drug-induced manifestations, the patient had taken clarithromycin and NSAIDs but had only had a few episodes of tubu- lointerstitial nephritis during the past four years, suggesting that these drugs were unlikely to be the cause of his progressive tubulointerstitial nephritis. Regarding infections, there was a report of streptococcal infection aggravating tu- bulointerstitial nephritis (6), and the ASO titer varied (7), with the peak ASO titer reached at three to five weeks after pharyngitis. It has been reported that the ASO titer normal- izes within several months; however, some patients experi- enced continued elevation of the ASO titer for more than a year (8). In some cases, an association between the ASO titer and sacroiliac joint disorder was reported (9). In the present case, the ASO titer was 719 IU/mL, but 2 months earlier, the ASO titer had been 693 IU/mL. The rapid test result for group A Streptococcus was negative. We consid- ered the possibility of the involvement of chronic streptococ- cal infection, but the patient had no clinical manifestations of infection, so this was considered unlikely. However, the possibility of tubulointerstitial nephritis induced by ulcerative colitis was considered. The association between tubu- lointerstitial nephritis and IBD was first reported by Larchet et al. in 1988 (10). Their report of 83 renal biopsy cases of IBD included 16 cases of tubulointerstitial nephritis. Nine of these cases had current aminosalicylate exposure or expo- sure to aminosalicylates in the recent past, including all cases of granulomatous interstitial nephritis (11), although one case of tubulointerstitial nephritis with IBD without aminosalicylate use was also reported (12, 13). Marcus et al. reported a case in which tubulointerstitial nephritis appeared regardless of IBD activity (14). In some cases, kidney dys- function has been observed in an early stage of Crohn’s dis- ease (15). We believe that tubulointerstitial nephritis became associated with enteritis in the long term in our patient. To our knowledge, a case in which sacroiliitis or spondylitis caused tubulointerstitial nephritis has never been reported, although the association of IBD with sacroiliitis is well known (16-18).

We speculated that tubulointerstitial nephritis was associ- ated with enteritis because of the homology of the granulo- matous lesion in the kidney and intestinal tissues. We per- formed a colonoscopy, including a biopsy, to evaluate the activity of enteritis four days after the renal biopsy. A granulomatous lesion existed in the kidney and intestine si- multaneously (Fig. 3B, 4). The infiltrating cells mainly in- cluded lymphocytes and plasma cells and a few eosinophils but no neutrophils. The cell constitution in the interstitium of the kidney was nearly the same as that in the intestine. The predominant infiltration by lymphocytes and plasma cells along with the granuloma further supported the diagno- sis of tubulointerstitial nephritis secondary to IBD-like enteritis rather than a drug-induced manifestation (19). In the present case, both the intestines and kidneys had a granu- loma or the accumulation of histiocytes preceding granu- loma formation. The existence of a granuloma between indi- vidual organs highlights a common etiology (20).

The association between tubulointerstitial nephritis and sacroiliitis has not been previously reported. However, some cases have reported associations between ankylosing spondylitis and abnormal findings on a urinalysis (hematuria, proteinuria, or urinary cast) (21). Cases of HLA-B27-positive ankylosing spondylitis have also been reported in Japan (22). The association between ankylosing spondylitis and sacroiliitis is well known (23). Kang reported that MRI findings of iliac-dominant bone marrow edema, absent caps- sulitis, absent extracapsular fluid collection, and absent peri- articular muscle edema indicate spondyloarthritis rather than infectious sacroiliitis (24). In the present case, MRI showed localized unilateral high density in the bone marrow before steroid therapy (Fig. 1A); however, the high density disappeared after treatment (Fig. 1B). Simultaneously, the serum creatinine level also improved. We made a diagnosis of sacroiliitis based on his MRI findings and considered the tubulointerstitial nephritis and sacroiliitis to be associated with each other.

Furthermore, during the patient’s clinical course, steroid treatment improved the kidney function and the symptoms of diarrhea due to enteritis and back pain due to sacroiliitis.

Discussion

To our knowledge, this is the first report of tubulointerstitial nephritis associated with enteritis and sacroiliitis. We considered tubulointerstitial nephritis to be associated with enteritis on the basis of the homology of the granulomatous lesion. Granulomatous interstitial nephritis is considered to have various etiologies, of which drug hypersensitivities and sarcoidosis, infection (specifically tuberculosis), vasculitis (particularly granulomatosis with polyangiitis), tubulointer- stitial nephritis, uveitis syndrome, and IBD have been re- ported (4, 5).

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Furthermore, during the patient’s clinical course, steroid treatment improved the kidney function and the symptoms of diarrhea due to enteritis and back pain due to sacroiliitis.
A reduction in steroid treatment caused the symptoms to recur and depressed the kidney function. Indeed, when his prednisolone dose was tapered to 5 mg, his back pain recurred after 3 weeks, and when the dose was tapered to 3 mg, the serum creatinine level increased from an average value of 2.35 mg/dL to 2.60 mg/dL, and the urinary NAG increased from a normal level to 12.9 U/L. For this reason, we started tacrolimus and re-increased the prednisolone dose to 5 mg. Given these findings, we considered the patient’s tubulointerstitial nephritis, enteritis, and sacroiliitis to be associated with each other.

We herein report a case of tubulointerstitial nephritis associated with enteritis or sacroiliitis, possibly from the same etiology. To our knowledge, this is the first reported case of sarcoidosis with sacroiliitis and/or enteritis.

A combination of enterocolitis and sacroiliitis exhibits acute interstitial nephritis may be complicated if a patient with a combination of enterocolitis and/or enteritis.

We start tacrolimus and re-increased the prednisolone dose to 5 mg. Given these findings, we considered the patient’s tubulointerstitial nephritis, enteritis, and sacroiliitis to be associated with each other.

The findings from the present case suggest that tubulointerstitial nephritis may be complicated if a patient with a combination of enterocolitis and sacroiliitis exhibits acute kidney injury. If tubulointerstitial nephritis is found on a renal biopsy, treatment with steroids will improve the acute renal injury; it may therefore be best to perform a renal biopsy proactively.

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

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