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【 CASE REPORT 】

Pyuria without Casts and Bilateral Kidney Enlargement Are Probable Hallmarks of Severe Acute Kidney Injury Induced by Acute Pyelonephritis: A Case Report and Literature Review

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Abstract:

The patient was a 38-year-old man who had experienced nausea and fever for a few days and presented with back pain, oliguria, and pyuria, suggesting acute pyelonephritis (APN). He showed acute kidney injury (AKI) with bilateral kidney enlargement and was using nonsteroidal anti-inflammatory drugs (NSAIDs). AKI-induced by APN was confirmed by kidney biopsy. The AKI was successfully treated with antibiotic therapy. A search of the relevant literature for reports on histopathologically-proven APN-induced severe AKI revealed that the key characteristics were bilateral kidney enlargement with pyuria without casts. Oligoanuria was frequently associated with APN-induced severe AKI, and NSAID use may be a possible risk factor. Prompt antibiotic treatment based on the clinical characteristics of APN-induced AKI can improve the renal outcome.

Key words: acute kidney injury, kidney enlargement, nonsteroidal anti-inflammatory drug, pyelonephritis, pyuria

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Introduction

Acute pyelonephritis (APN) is the most common community-based bacterial infection of the kidney (1). APN has the potential to cause death due to sepsis or septic shock, which may lead to acute kidney injury (AKI) due to acute tubular necrosis. Severe AKI [defined as Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3 (2)] caused by APN itself is rare. The typical histopathology of APN is a tubulointerstitial lesion showing patchy infiltration of the renal interstitium and tubules by inflammatory cells, with tubular necrosis and pus cast formation. The focal accumulation of leukocytes may result in abscess formation at the site of the destroyed renal tissue (3). Early treatment of APN may avoid death and improve the renal prognosis.

APN shows signs and symptoms of both systemic inflammation and bladder inflammation. However, up to 20% of patients do not have bladder symptoms (4). The clinical presentations and disease severity vary widely, ranging from mild flank pain with or without fever to septic shock (4, 5). It is unlikely that both kidneys will be infected at the same time. Thus, APN-induced severe AKI is quite rare in the absence of coexisting urinary tract obstruction (5), and it may be difficult to clinically confirm APN-induced AKI.

We herein report a rare case of APN-induced severe AKI that was confirmed by kidney biopsy. We reviewed the relevant English literature for patients with APN-induced severe AKI, who were treated within the last 50 years, and analyzed the clinical characteristics.

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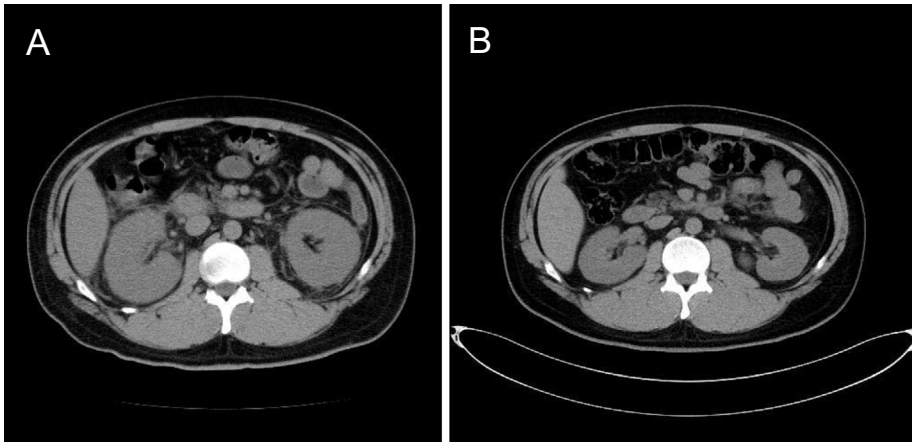

Figure 1. Plain CT of the abdomen. A: Bilateral kidney enlargement. B: The bilateral kidneys were normal in size.

Case Report

A 38-year-old man presented to our department with nausea and appetite loss, which had persisted for 4 days prior to his admission and a fever of 39℃ and sore throat, which had persisted for 3 days prior to his admission. He was taking tramadol hydrochloride, acetaminophen, and loxoprofen sodium hydrate as needed. One day before the patient's admission, he appeared at the emergency unit in our hospital, complaining of the abovementioned symptoms. After returning home, he began to experience dull abdominal pain and left low back pain and was transferred to our hospital. His previous history included Kawasaki disease and cerebral infarction with left hemiplegia of unknown cause at 11 years of age. His Kawasaki disease had been inactive since that time. He was taking carbamazepine, trihexyphenidyl hydrochloride, and tizanidine hydrochloride for the management of symptoms after cerebral infarction. He had also taken 200 mg/day of celecoxib for general pain in his left extremities for 10 days prior to admission. Although he had cerebral infarction, the patient was not diagnosed with neurogenic bladder and he had no urinary disturbance before his admission. He did not drink alcohol and denied intravenous drug use. A serum creatinine level of 0.66 mg/dL had been recorded 6 years previously. A physical examination on admission revealed the following: alert consciousness; height, 165.0 cm; body weight, 75.0 kg; body temperature, 38.5℃; blood pressure, 127/87 mmHg; heart rate, 107 beats/min; oxygen saturation, 99%. Palpation of the middle to left lower abdominal areas was painful, and tenderness existed in the left costovertebral angle. Spastic left hemiplegia was found. A urinalysis revealed the following results: pH 5.0; negative occult blood; 3+ protein; 1+ leukocyte esterase; positive nitrites; 1-4 red blood cells (RBCs)/high-power field; 30-49 white blood cells (WBCs)/high-power field; the presence of bacteria; and the absence of pathologic casts. Urinary chemistry revealed the following findings: protein, 0.91 g/g creatinine; N-acetyl-β-D-glucosaminidase, 37.1 U/L; β2-microglobulin, 1.4210 μg/L; and alpha 1-microglobulin, 51.0 mg/L. A blood analysis revealed the following findings: hemoglobin, 14.7 g/dL; WBC count, 24,400/μL; platelet count, 155,000/μL; albumin, 2.5 g/dL; blood urea nitrogen, 49.3 mg/dL; creatinine, 2.67 mg/dL; hemoglobin A1c, 5.6%; Na, 128 mEq/L; and K, 3.5 mEq/L. The immunological findings were as follows: C-reactive protein, 31.66 mg/dL; normal complement 3 and 4 levels; hepatitis B and C serology, negative; anti-streptolysin O titer, normal; anti-nuclear antibody, negative; and anti-DNA antibody, negative. A chest X-ray showed a normal lung field. Computed tomography showed bilateral kidney enlargement without hydronephrosis or signs of papillary necrosis (Fig. 1a).

Our patient had a high fever, low back pain, oliguria, pyuria, bacteriuria, nitrites in his urine, leukocytosis and a high C-reactive protein level, which suggested that APN was an appropriate presumptive diagnosis upon admission; thus, ceftriaxone sodium (2 g every 24 hours) was intravenously administered. Although he showed AKI with oliguria without hypotension and his fractional excretion of Na was 0.01%, sufficient hydration did not increase his urine volume and his serum creatine did not decrease, ruling out prerenal AKI alone. Rather, his serum creatinine increased from 2.67 mg/dL to 5.22 mg/dL on the 2nd day of admission. Although his serum creatinine level peaked, a kidney biopsy was performed on the 4th day of admission to clarify the cause of AKI.

The kidney biopsy revealed global sclerosis in 1 of 23 glomeruli. Some glomeruli showed small numbers of inflammatory cell infiltration, including polymorphonuclear leukocytes (Fig. 2a). There was a mild-to-moderate degree of mixed inflammatory cell infiltration, composed of polymorphonuclear leukocytes, lymphocytes, and rare eosinophils, in zonal areas of the tubulointerstitium with patchy tubular epithelial cell flattening and atrophy (Fig. 2b). Pus casts were sporadically found in the tubules (Fig. 2b, c). A mild degree of arteriolar hyalinosis was seen. No vasculitis was found in any level of the arteries. An immunofluores-

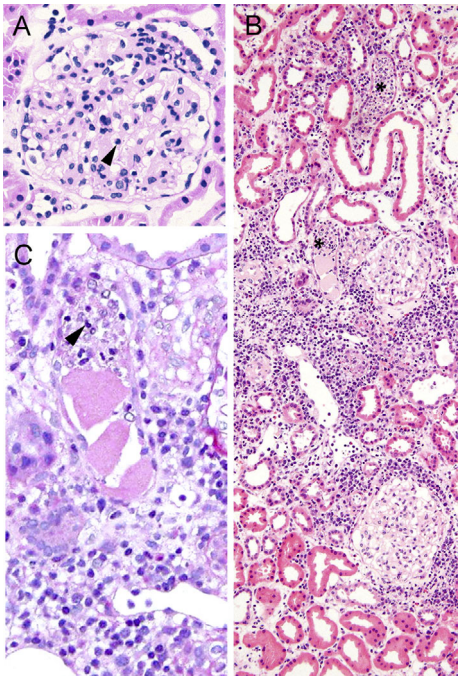

Figure 2. Light microscopy of the kidney biopsy specimen. A: A glomerulus with infiltration of some polymorphic leukocytes (arrowhead; periodic acid-Schiff staining; original magnification ×400). B: Patchy inflammatory cell infiltration, tubular atrophy and tubular dilatation are observed in zonal areas. Some tubules with flattened epithelial cells include pus casts (asterisks; Hematoxylin and Eosin staining; original magnification ×200). C: A tubule with flattened epithelial cells is obstructed with pus cast formation with polymorphic leukocytes (arrowhead; Periodic acid-Schiff staining; original magnification ×200).

cence study was negative for IgG, IgA, IgM, C3 and C1q. These findings confirmed that AKI was mainly caused by acute interstitial nephritis (AIN) due to APN.

The serum free kappa and lambda light chain levels, myeloperoxidase- and proteinase 3-anti-neutrophil cytoplasmic antibody levels and anti-glomerular basement membrane (GBM) antibody level were reported to be within the normal ranges. Although no bacteria were grown in urine and blood cultures, probably due to previous antibiotic use, antibiotic therapy with ceftriaxone sodium was continued for 14 days in addition to daptomycin (700 mg every 48 hours intravenously). The patient's serum creatinine level improved to 1.60 mg/dL on the day of the kidney biopsy and gradually decreased to 0.70 mg/dL on the 15th day of admission. Follow-up ultrasound showed no residual urine in the bladder just after urination. Computed tomography showed that the bilateral kidneys were of normal size with no signs of papillary necrosis at 2 months after discharge (Fig. 1b).

Discussion

We experienced a rare case with APN-induced severe AKI that was confirmed by kidney biopsy. Mild AKI from inflammation-related hemodynamics is common in APN and resolves quickly with treatment. However, severe AKI in the absence of coexisting urinary tract obstruction is rare (5). Our case involved a middle-aged man who presented with constitutional symptoms and who was using NSAIDs; his renal function worsened 24 hours after antibiotic therapy with sufficient hydration. Thus, we thought that other causes of AKI (besides APN-induced AKI) should be considered, since it has been reported that APN patients without urinary tract obstruction tend to improve within 24 to 48 hours after antibiotic therapy (5).

The characteristics of adult cases with severe AKI caused by APN without urinary tract obstruction, single kidney, or chronic kidney disease (CKD), that were reported in the relevant English literature from 1969 to 2019 are shown in Table (6-24). Severe AKI was defined as KDIGO stage 2 or 3. However, the AKI stage could not be clearly confirmed due to the limited data that were available in some cases. APN-induced AKI was proven by histopathology or by clinical course with antibiotic therapy. A total of twenty-six cases (T-group) were reported over the approximately 50-year period. Among them, 19 cases were histopathology-proven (H-group). The incidence of AKI stage 3 (serum creatinine ≥4.0 mg/dL or renal replacement therapy) (2) were 84.6% in the T-group and 89.4% in H-group. Female patients accounted for 61.5% of the patients in the T-group and 63.1% of the patients in the H-group. The mean ages were 53.8 years in the T-group and 55.1 years in the H-group. The analysis of available data showed that the incidence of oligoanuria was 46.1% in the T-group and 52.5% in the H-group. The rates of pyuria, which was defined as a urine WBC count of >5/high-power field or dipstick positivity for leukocyte esterase (25), and the absence of pathologic casts were 73.0%/78.9% in the T-group and 57.6%/68.4% in the H-group, respectively. The incidence of bilateral kidney enlargement on imaging was 61.5% in the T-group and 68.4% in the H-group. Urine and/or blood were positive for E. coli in 73.0% of the patients in both groups. Both blood and urine were positive for Klebsiella in 15.3% of the patients in the T-group and 21.0% of the patients in the H-group. Pregnancy, indwelling catheter, immunocompromised status, and nonsteroidal anti-inflammatory drug (NSAID)/analgesic use were reported as predisposing factors. NSAIDs were used in 30.7% of cases in the T-group and 26.3% of the cases in the H-group. A total of 38.4% of the cases in the T-group and 36.8% of the cases in the H-group recovered from AKI; 38.4% of the cases in the T-group and 31.5% of the cases in the H-group showed improvement of AKI but developed CKD; 11.5% of the cases in both groups became dialysis-dependent; and 11.5% cases in both groups died. Accordingly, the key characteristics of APN-induced AKI were pyuria without casts and bilateral kidney enlargement. Bilateral kidney enlargement may be caused by interstitial infiltration, edema, and pus casts in the tubules of both infected kidneys. Oligoanuria was frequently associated. NSAID use is a possible risk factor for APN-

Table. **The Characteristics of Adult Cases with Severe AKI Caused by APN That was Proven by Histopathology or by the Clinical Course with Antibiotic Therapy in Reports in the Relevant English Literature.**

Case No.	References	Age (years/sex)	Predisposing factors	Oligoanuria	Pyuria	Proteinuria	Hematuria	Casts	Peak Cr/RRT	Causative organism	Positive cultures U/B	Bilateral kidney enlargement	Kidney biopsy (autopsy)	Outcome
1	**6**	**41/F**	**catheter**	**-**	**+**	**-**	**+**	**-**	**NR**	***Klebsiella***	**+/+**	**+**	**+**	**recovered**
2	**7**	**49/M**	**none**	**+**	**+**	**+**	**+**	**-**	**13.5 mg/dL/PD**	***E. coli***	**+/+**	**+**	**+**	**CKD**
3	**8**	**53/M**	**alcoholism**	**+**	**-**	**+**	**+**	**-**	**9.2 mg/dL/HD**	***E. coli***	**+/+**	-	**autopsy**	**died**
4	9	48/F	analgesics	-	+	-	-	NR	466 µmol/L	*E. coli*	+/-	+	-	CKD
5	**9**	**61/F**	**analgesics**	**+**	**+**	**-**	**-**	**-**	**NR/HD**	***E. coli***	**+/+**	**+**	**autopsy**	**died**
6	9	73/F	analgesics	-	+	-	+	no	59 mmol/L*	Coliform Bacteria	+/NR	-	-	CKD
7	10	55/M	none	+	+	+	+	no	16.1 mg/dL/PD	*E. coli*	+/+	+	-	recovered
8	**11**	**74/M**	**chronic bronchitis**	**NR**	**+**	**+**	**-**	**-**	**1,000 µmol/L<**	***E. coli***	**+/+**	**+**	**+**	**recovered**
9	**12**	**30/F**	**ectopic pregnancy**	**+**	**+**	**-**	**+**	**-**	**13 mg/dL/HD**	***E. coli***	**+/NR**	**+**	**+**	**CKD**
10	13	27/F	NSAID	NR	NR	NR	NR	NR	199 µmol/L	No growth	-/-	right+ left-	-	recovered
11	13	61/F	NSAID	NR	NR	NR	NR	NR	9.3 mg/dL/PD	*E. coli*	+/NR	NR	-	CKD
12	**14**	**56/M**	**alcoholism**	**+**	**+**	**+**	**+**	**-**	**6.6 mg/dL**	***E. coli***	**+/+**	**+**	**+**	**recovered**
13	**15**	**66/F**	**none**	**+**	**+**	**+**	**+**	**-**	**627.6 µmol/L**	***Klebsiella***	**+/+**	**+**	**+**	**recovered**
14	**16**	**68/F**	**catheter, NSAID, DM**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR/HD**	***E. coli***	**+/+**	-	**+**	**HD**
15	16	55/M	catheter	NR	NR	NR	NR	NR	NR/HD	*E. coli*	+/+	-	-	recovered
16	**17**	**69/M**	**none**	**NR**	**+**	**+**	**+**	**-**	**665 µmol/L**	**No growth**	**+/NR**	**-**	**+**	**recovered**
17	**17**	**79/F**	**NSAID**	**NR**	**NE**	**+**	**+**	**NR**	**820 µmol/L/HD**	***E. coli***	**+/+**	**-**	**+**	**HD**
18	**18**	**74/F**	**alcoholism**	**NR**	**-**	**-**	**-**	**NR**	**NR**	***Klebsiella***	**+/+**	**right- left+**	**autopsy**	**died**
19	**19**	**74/F**	**none**	**+**	**+**	**+**	**+**	**-**	**709 µmol/L/HD**	***E. coli***	**+/+**	**+**	**+**	**CKD**
20	**19**	**30/F**	**bladder infection**	**+**	**+**	**+**	**+**	**-**	**1,137 µmol/L/HD**	***E. coli***	**+/+**	**+**	**+**	**recovered**
21	**20**	**34/M**	**NSAID**	**+**	**+**	**-**	**+**	**-**	**877 µmol/L/HD**	***Klebsiella***	**+/+**	**+**	**+**	**CKD**
22	**21**	**48/F**	**HIV, NSAID, DM**	**NR**	**+**	**-**	**+**	**-**	**7.3 mg/dL**	***E. coli***	**+/+**	**+**	**+**	**recovered**
23	21	33/M	HIV, NSAID, drug abuse	+	+	+	+	WBC+	7.6 mg/dL/HD	*E. coli*	+/+	+	-	CKD
24	**22**	**24/F**	**cystitis, NSAID, sepsis**	**+**	**+**	**NR**	**NR**	**NR**	**864 µmol/L/HF nephrectomy**	***E. coli* (O4:H51) VF**	**+/+**	**-**	**nephrectomy**	**HD-transplantation**
25	**23**	**63/M**	**none**	**NR**	**+**	**+**	**+**	**NR**	**15.9 mg/dL/HD**	***E. coli***	**+/+**	**+**	**+**	**CKD**
26	**24**	**54/F**	**DM, drug abuse**	**NR**	**+**	**+**	**-**	**NR**	**9.3 mg/dL/HD**	***E. coli***	**+/NR**	**+**	**+**	**CKD**
Our case		**38/M**	**NSAIDs**	**+**	**+**	**+**	**-**	**-**	**5.22 mg/dL**		**-/-**	**+**	**+**	**recovered**

Bold, histopathologically-proven cases. *level of blood urea nitrogen. F: female, M: male, -: absent or negative, +: present or positive, NR: not reported, Cr: creatinine, RRT: renal replacement therapy, PD: peritoneal dialysis, HD: hemodialysis, NSAID: non-steroidal anti-inflammatory drug, HIV: human immunodeficiency virus, DM: diabetes mellitus, U: urine, B: blood, CKD: chronic kidney disease

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induced severe AKI. However, the causal relationship between NSAID use and APN-induced severe AKI is not known. NSAIDs can delay the presentation of APN patients due to the temporary alleviation of pain and fever, and thus delay appropriate management. In addition, NSAIDs can reduce the glomerular filtration rate, contributing to the development of APN-induced severe AKI. Our case featured characteristics of APN-induced severe AKI, including NSAID use, oliguria, pyuria without casts and bilateral kidney enlargement. We did not perform screening for human immunodeficiency virus (HIV) infection, because he did not show any history, symptoms, or laboratory abnormalities suggesting HIV infection. With the exception of NSAID use, he did not have any other reported predisposing factors for bilateral APN. Interestingly, he was taking tizanidine hydrochloride, a muscle relaxant, which affects the bladder skeletal muscle function, and which can be used to treat bladder dysfunction in patients with multiple sclerosis spasticity (26). There have been no reports of tizanidine-associated APN; however, the present patient should be carefully followed up for symptoms, including overactive bladder.

Some of the abovementioned features of APN-induced severe AKI seem to resemble other causes of AKI, including AIN, acute tubular necrosis (ATN) and rapidly progressive glomerulonephritis (RPGN). All of these conditions can cause AKI with bilateral kidney enlargement (27, 28). The common clinical manifestations of AIN are nonspecific, including asthenia, anorexia, nausea and vomiting. Laboratory data show AKI with or without oliguria, microscopic hematuria, non-nephrotic proteinuria, and pyuria (29, 30). Unlike APN, AIN can be associated with WBC casts and nonpigmented granular casts in urine (29). Patients with ATN also present with nonspecific clinical symptoms. Unlike APN, pigmented "muddy brown" granular casts or tubular epithelial cell casts, usually with microscopic hematuria and mild proteinuria, are found. However, casts can be absent (29). Patients with RPGN due to crescentic glomerulonephritis show loin pain, which is not uncommon (31). Leukocytosis, anemia, and elevated inflammatory marker levels are usually found. A urinalysis reveals modest proteinuria, microscopic hematuria, and RBC and WBC casts, unlike APN. Pyuria is also a common urine finding (32). Rarely, urine findings may be minimal, and the absence of active urine sediment does not exclude a diagnosis of RPGN. The rate of progression to renal failure is variable, ranging from hours to months.

When the characteristics of AIN, ATN and RPGN are compared, pyuria without pathological casts may be a hallmark of APN-induced severe AKI. Isolated pyuria is unusual since inflammatory reactions in the kidney or collecting system are also associated with hematuria. The presence of WBCs with bacteria is indicative of pyelonephritis. However, if patients have used medicines, such as NSAIDs, which can induce AIN or ATN (33, 34), it is difficult to discriminate drug-induced AKI from APN-induced AKI, as in our case. Moreover, in AKI patients with constitutional symptoms and nonspecific urinalysis results, the possibility of RPGN cannot be excluded. A definite diagnosis of APN-induced AKI requires kidney biopsy. However, in certain patients, kidney biopsy cannot always be smoothly and quickly performed due to illness. If AKI patients have infectious signs, pyuria without casts, and bilateral kidney enlargement, after starting antibiotic therapy and withdrawing suspected medicines, kidney biopsy can be postponed until other information, including the results of PRGN-related laboratory data and the efficacy of antibiotic therapy over another several days, can be obtained.

In summary, the key characteristics of APN-induced severe AKI include bilateral kidney enlargement with pyuria without casts. Oligoanuria was frequently associated with APN-induced severe AKI, and NSAIDs may be a possible risk factor. Prompt antibiotic treatment based on the clinical characteristics of APN-induced AKI is essential to improve the renal outcome.

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

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