

Persistent Aseptic Pyelonephritis After Acute Bacterial Pyelonephritis: Possible Role of Corticosteroids



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Received 11 April 2022; revised 16 May 2022; accepted 23 May 2022; published online 6 June 2022

Kidney Int Rep (2022) 7, 1897–1900; <https://doi.org/10.1016/j.ekir.2022.05.025>

KEYWORDS: acute kidney injury; infection; interstitial nephritis; post-infectious; pyelonephritis

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INTRODUCTION

Acute pyelonephritis (APN) is a common cause of acute kidney injury (AKI) in kidney graft recipients but only few cases of severe AKI after uncomplicated non-obstructive native kidney APN have been reported.¹ In some of these latter, renal dysfunction persists despite appropriate anti-infectious treatment and urine sterilization.^{2–4} Some authors suggest the use of corticosteroids to treat inflammatory tubulointerstitial nephritis (TIN) triggered by the infection.^{2–4} Nevertheless, this approach is not validated by any evidence-based study and therefore not mentioned in any guideline.

We aim at describing the clinicopathologic presentation, management, and outcome of such persistent TIN in patients of the Tenon Hospital nephrology and pathology departments between January 1, 2010 and December 31, 2020.

RESULTS

Patients and Initial Presentation

Fifteen patients were studied following the case definition (see [Supplementary Methods](#) in the [Supplementary Material](#)). The initial characteristics of the patients and the initial APN are summarized in [Table 1](#).

All the infections were complicated by AKI as follows: KDIGO stage 2 in 2 of 15 patients (13%) or stage 3 in 13 of 15 patients (87%), mean estimated glomerular filtration rate (eGFR) after stabilization was 12.9 ± 8.4 ml/min per 1.73 m^2 , and mean eGFR loss was -57.5 ± 33 ml/min per 1.73 m^2 . All radiologically documented

infections were bilateral except in 1 case. The documentation exclusively included ascending infections because of Enterobacteriales, mostly with *Escherichia coli*. All patients were treated accordingly as per the current French Infectious Diseases Society (Société de Pathologie Infectieuse de Langue Française) guidelines.

Persistent Aseptic Pyelonephritis

Antibiotic treatment allowed resolution of the infectious symptoms and urine sterilization in all 15 cases (100%). A total of 58 (interquartile range: 28–102) days after antibiotic initiation, all patients presented persistent kidney impairment (mean eGFR of 19.6 ± 11.2 ml/min per 1.73 m^2 , $P = 0.08$). Urinary analysis was indicative of active TIN: aseptic leukocyturia $>10,000$ cells/ μl in 14 of 15 cases (93%), and $>100,000$ cells/ μl in 9 of 15 cases (60%). Low molecular weight proteinuria was constant ([Table 1](#)).

As expected, given our case definition, kidney biopsy systematically revealed tubulo-interstitial inflammation. The infiltrate was predominantly lymphoplasmacytic in all patients. Neutrophils (sometimes clustering into microabscesses, [Supplementary Figure S1B](#)) and eosinophils were observed in 13 of 15 (86.7%) and 1 of 15 cases (6.7%) respectively among this infiltrate. Extensive inflammatory fibrosis with edema was constant ([Supplementary Figure S1A](#)). Lymphoid nodules were identified in 7 of 15 cases (46.7%) ([Supplementary Figure S1D](#)), some of them forming germinal center-like patterns.

Table 1. Clinical and biological presentation

Characteristics	Cases (N = 15) n (%), mean ± SD, or median [IQR]		
	At APN	At biopsy	At LFU ^a
General information		58 [52–64]	
Age, yrs			
Sex (female)		8 (53.3)	
		74.6 ± 29.1	
Baseline eGFR (ml/min/1.73 m ²)			
Immunosuppression		5/15 (33)	
Diabetes		8/15 (53)	
≥1 severe infection predisposing factor		13/15(86.7)	
≥1 severe infection predisposing factor		8/15 (53)	
Urinary tract anomalies		6/15 (40)	
Severity and complications			
Hemodynamic severity ^b	4 (26.7)	NA	NA
eGFR, ml/min/1.73 m ²	12.9 ± 8.4	15 ± 9.2	38.3 ± 27.5
KDIGO stage of AKI ^c			
- 1	0 (0)	0 (0)	—
- 2	2 (13.3)	2 (13.3)	
- 3	13 (86.7)	13 (86.7)	
Kidney(s) involved			
- both	13 (86.7)		
- left	1 (6.7)		
- unknown	1 (6.7)		
C-reactive protein, mg/l	228.6 ± 100.0	9.0 ± 3.0	—
Leukocyte count, cells/μl	17430 ± 5425	6800 ± 2750	—
Leucocyturia, cells/μl	1 × 10 ⁶ [654 × 10 ³ –1 × 10 ⁶]	1.5 × 10 ⁴ [2.6 × 10 ³ –1 × 10 ⁶]	5000 ± 2200
Proteinuria, g/mmol	NA	0.09 [0.06–0.16]	—
Albuminuria, mg/mmol	NA	15.07 [10.98–30.25]	—
Urinary RBP, ^d mg/mmol	NA	3.67 [1.24–10.16]	—
Urin cultures		Durably sterile	Durably sterile
<i>Escherichia coli</i> of which	10 (66.7)		
- WT	5 (33.3)		
- low level penicillinase producers	3 (20)		
- high level penicillinase producers	2 (13.3)		
<i>Morganella morganii</i> WT	2 (13.3)		
<i>Klebsiella pneumoniae</i> WT	3 (20)		
Treatment			
Antibiotics choice adapted to the guidelines	15 (100)		
- Duration, wks	4 ± 2		
Steroid therapy	—		11/15 (73)
- Duration, wks	—		4.8 ± 4.0
Complementary antibiotic therapy			12/15 (80)
- Duration, wks			5.4 ± 2.7

AKI, acute kidney injury; APN, acute pyelonephritis; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; LFU, last follow-up; NA, not applicable; RBP, retinol-binding protein; WT, wild type.

^aLast follow-up.

^bDefined as the presence of one of the following criteria: arterial blood pressure <65 mm Hg, lactataemia ≥2 mmol/l, fluid resuscitation needs ≥3000 ml in the first 24 hours of sepsis, multisystemic dysfunction.

^cAKI according to the KDIGO classification.

^dRBP, normal value <0.08 mg/mmol of creatinine.

Neutrophilic intratubular casts were constant although rarely abundant (Supplementary Figure S1B). Tubulitis (Supplementary Figure S1F) was present in all biopsies except 1, mediated by neutrophils in half of the cases (Supplementary Figure S1E). Features of acute tubular necrosis (usually mild) were revealed in 13 of 15 biopsies (86.7%). There was no argument for malakoplakia, xanthogranulomatous pyelonephritis or signs of glomerulonephritis, or acute vascular involvement.

Seven days Brain Heart Infusion Broth cultures of the frozen biopsy specimens did not reveal any relevant documentation.

Treatment and Outcome

Eight patients were treated with corticosteroids (0.5 or 1 mg/kg tapered over a mean duration of 1.2 ± 1.0 months) and antibiotics (mean duration 5.4 ± 2.7 weeks), 4 patients treated with antibiotics only, and 3

treated with corticosteroids only. There were no reported side effects of corticosteroids.

After a mean follow-up period of 8.7 ± 3.8 months, kidney function stabilized or improved in all patients (mean eGFR variation to biopsy was $+18.7 \pm 21.6$ ml/min per 1.73 m^2 , $P = 0.02$). However, renal function often remained severely hampered (mean eGFR was 38.3 ± 27.5 ml/min per 1.73 m^2 , mean eGFR loss to baseline was -27.3 ± 10.8 ml/min per 1.73 m^2). By the end of the study follow-up, 9 of 15 patients (60%) presented stage IV or V chronic kidney disease compared with none before APN onset.

Urinary signs of active TIN regressed in all treated patients (leukocyturia at last follow-up of 5000 interquartile range [5000–113,250] cells/ μl , median variation of $-35,000$ interquartile range [0–156,000] cells/ μl). One patient died after 2 months of follow-up; and a second patient died after 12 months of follow-up. The second patient was treated with steroid therapy from the third to the fifth month of follow-up.

Better renal outcome (i.e., last follow-up eGFR >30 ml/min per 1.73 m^2) was associated with early steroid treatment initiation (≤ 65 days), higher baseline eGFR, and per-AKI eGFR in a univariate analysis (Supplementary Table S1). The presence of lymphoid nodules tended to be associated with a worse outcome.

We further compared the patients' renal function according to corticosteroid exposure (Supplementary Figure S1). Baseline, APN, and kidney biopsy eGFR were not significantly different but last follow-up eGFR was significantly higher in the corticosteroid group (45.8 ± 28.1 vs. 17.5 ± 10.1 ml/min per 1.73 m^2 , $P = 0.01$).

Associated Comorbidities and Factors

All patients presented conditions known to be associated with severe infections (Table 1). One-third of the patients matched our definition of immunosuppression (5 of 15, 33.3%), 13 of 15 patients (86.7%) presented ≥ 1 severe infection predisposing factors, and 8 of 15 (53%) presented ≥ 2 severe infection predisposing factors. Nonsteroidal anti-inflammatory drugs consumption at initial APN was found in 4 of 15 patients (26.7%). A total of 6 of 15 (40%) patients presented urinary tract anomalies, including 5 (33.3%) with urinary catheters at APN onset.

DISCUSSION

We herein present a report on 15 patients who were treated at our institution for severe AKI because of bilateral pyelonephritis, and presenting persistent kidney impairment several weeks or even months after appropriate antibiotic therapy and urine sterilization. Urinary analysis and kidney biopsy revealed

lymphoplasmacytic and neutrophilic TIN. A second prolonged antibiotic challenge and/or corticosteroid treatment allowed partial kidney function improvement in some cases. Overall prognosis was poor because 60% of the patients recovered $<50\%$ of their initial eGFR and developed stage IV to V chronic kidney disease within 1 year after AKI.

Some rare cases were reported in the literature.^{1–3} but this is the first case series describing the biological, histologic, and clinical presentation and evolution since Richet and Mayaud's⁵ description in 1978. In this study, most cases were attributed to drug allergy or toxicities but may have been misclassified because of the absence of preexisting data. There is no mention of steroid use, and only 1 patient recovered their baseline kidney function (Supplementary Table S2). Subsequent reports show a positive outcome with steroid use but publication bias is very likely (Supplementary Table S2).

Given the small sample size and the retrospective nature of this study, it is not possible to draw definitive conclusions.

The long delay between AKI and renal biopsy, and the recovery kinetics are not indicative of acute tubular necrosis (Supplementary Figure S1). Histologic and clinical presentations are not indicative of immunoallergic nephritis. There were no extrarenal features that suggest corticosteroid sensitive systemic disease associated interstitial nephritis.

Although it is coherent with high range leukocyturia and low molecular weight proteinuria, APN histologic natural course is not known. Therefore, we cannot affirm that the interstitial inflammation we describe is specific.

As suggested by Richet and Mayaud⁵ in 1978, we believe this entity could correspond to persisting autonomous tubulo-interstitial inflammation, resembling pyelonephritis but aseptic, which is persistent aseptic pyelonephritis.

A mechanistic lead could be that in some patients with pathogen clearance altering factors, tubulo-interstitial inflammation does not regress despite effective antibiotic therapy. The lymphoid nodules found in half of the patients could be a hallmark of this inflammatory autonomous process. Concomitant evolution of leukocyturia, eGFR, and possible corticosteroid efficiency support this hypothesis. Prevalence is not known but it is likely underestimated. Initial presentation can easily be mistaken for ATN. Persistent aseptic pyelonephritis occurring after unilateral APN, without AKI in most of the cases, most likely goes unnoticed. Larger prospective studies are required. Prompt delay to treatment seems important to prevent definitive kidney

scarring. If corticosteroid efficiency were confirmed, biomarker development allowing early ATN or persistent aseptic pyelonephritis discrimination would be highly relevant. Even though we believe this entity is postinfectious, further studies are needed to determine if complementary antibiotic therapy can be avoided.

We suggest systematic monitoring of leukocyturia and urinary low molecular weight protein in all patients who are treated for APN-related AKI. Patients who present persistent aseptic leukocyturia, proteinuria and kidney failure should be referred to a nephrologist to discuss kidney biopsy and potential subsequent corticosteroid and/or antibiotic treatment.

DISCLOSURE

All the authors declare no conflict of interest. No specific funding was needed for this study.

ACKNOWLEDGMENTS

The authors would like to thank the Professor J. Turret for his valuable help.

SUPPLEMENTARY MATERIAL

[Supplementary File \(Word\)](#)

Supplementary Methods.

Figure S1. Histological presentation. Interstitial fibrosis with chronic inflammatory infiltrate (HESx50) (A). Intratubular casts of altered neutrophils (HESx400) (B).

Interstitial clustering of neutrophils forming a microabscess (HESx400) (C). Interstitial nodular organization of lymphocytes (HESx200) (D). Neutrophilic tubulitis (HESx400) (E). Severe tubulitis with tubulorrhexis (tubular membrane rupture) (HESx400) (F). Inflammation in the adipose tissue outside the renal capsule (perinephritis) (HESx50) (G).

Table S1. Factors associated with renal outcome.

Table S2. Literature reporting potential persisting aseptic pyelonephritis.

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