

Atypical presentation of allergic interstitial nephritis likely induced by ciprofloxacin

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Accepted 10 June 2021

SUMMARY

Though the prevalence of drug induced allergic interstitial nephritis (AIN) appears to be increasing, the diagnostic and treatment strategies still remain vague. We present a 56-year-old man with a history of hypertension, chronic kidney disease stage IIIa, recent exposure to ciprofloxacin who presented with acute kidney injury. Though the suspicion of AIN was high, his urinary sediment was bland, that is, no leucocytes or leucocyte casts. A renal biopsy subsequently showed features of AIN correlating with a resolving phase of inflammation. Given the resolving nature of the pathology, we chose not to complete a course of corticosteroids despite his need for temporary haemodialysis. He was able to fully recover his renal function. In this report, we emphasise the unreliable nature of the urinary sediment in the diagnosis of AIN, the utility of a renal biopsy in helping to guide treatment, and the controversial data in corticosteroid treatment.

BACKGROUND

Acute interstitial nephritis (AIN) is a renal lesion that typically causes a decline in kidney function and is characterised by an inflammatory infiltrate in the kidney tubulointerstitium. It is most often induced by medications (eg, penicillins/cephalosporins, fluoroquinolones, non-steroidal anti-inflammatory drugs, proton pump inhibitors).^{1,2} AIN is also caused by autoimmune disorders or other systemic disease (eg, systemic lupus erythematosus, Sjögren's syndrome, the tubulointerstitial nephritis with uveitis syndrome, sarcoidosis) or a variety of infections (eg, legionella, leptospirosis and streptococcal organisms).³ Clinical manifestations of drug-induced AIN are highly variable, that is, the traditional triad of fever, rash and eosinophilia occur in less than 5%–10% of patients.^{4,5} The most consistent finding is an increase in serum creatinine within days or weeks to exposure of the culprit agent. Urinary findings may demonstrate subnephrotic range proteinuria, red and white blood cells, as well as white blood cell casts. A bland urine sediment, however, can occur in up to 20% of patients.⁶

Case presentation

We present a 56-year-old Hispanic man from Mexico with a medical history of hypertension, chronic kidney disease stage IIIa (eGFR 52 mL/min/1.73 m² and baseline creatinine of 1.4 mg/dL) who was recently admitted to the hospital with a diagnosis of liver abscess of unclear aetiology. The liver abscess was surgically drained, but was

complicated by the formation of portal vein thrombosis that was treated with apixaban. To treat the culture-negative abscess, the patient was initially administered intravenous piperacillin–tazobactam 2.25 g every 8 hours for 14 days and then discharged on oral ciprofloxacin 750 mg two times per day and metronidazole 500 mg three times daily, the duration of which was to be determined by further assessment by the infectious disease specialist at outpatient follow-up 3 days later. At this follow-up, it was discovered that the patient's serum creatinine had increased from 1.4 mg/dL (3 days prior) at discharge to 4.0 mg/dL (table 1). In addition, the patient had nausea and decreased urine output though denied vomiting, shortness of breath or additional uraemic symptoms. His medications on admission were: apixaban 5 mg two times per day, hydrochlorothiazide 25 mg daily, losartan 100 mg daily, nifedipine 60 mg daily, ciprofloxacin 750 mg two times per day, metronidazole 500 mg three times daily, ergocalciferol 50 000 units once weekly, ferrous sulfate 325 mg once daily. His physical examination showed vital signs of BP 154/88 mm Hg, pulse 90/min, temperature 98.1°F, while he appeared to be in no acute distress, harbouring clear lungs bilaterally with normal heart sounds, a soft abdomen with a Jackson-Pratt drain stemming from the right upper quadrant, and lower extremities without signs of oedema. His laboratory data are shown in table 1. His renal ultrasound showed bilateral normal-sized kidneys (9.9 cm on the right and 11.1 cm with a 6 mm cyst on the left).

INVESTIGATIONS

On admission, culprit and potentially nephrotoxic agents were held, that is, ciprofloxacin, metronidazole, hydrochlorothiazide and losartan. A renal biopsy was performed on day 8 of hospital readmission due to deteriorating renal function despite these manoeuvres.

RENAL PATHOLOGY

The predominant findings by light microscopy are of mild to moderate interstitial inflammation, mild interstitial oedema and mild tubular degenerative changes, which in light of history of down-trending creatinine are most consistent with resolving acute interstitial nephritis and mild tubular degenerative changes (figure 1A,B). Approximately 10%–20% of the renal cortex shows tubular atrophy and interstitial fibrosis and mild tubular degenerative changes. By immunofluorescence microscopy, there are isolated mesangial deposits that stain ± for C3 only, and electron microscopy shows trace mesangial



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To cite: Valdez Imbert R, Sekulic M, Saad P, et al. *BMJ Case Rep* 2021;**14**:e243079. doi:10.1136/bcr-2021-243079

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Table 1 Laboratory values during readmission and after hospitalisation

Laboratory values (normal range)	Day 1 of readmission	Day 2	Day 3	Day 5	Day 10	Discharge	6 months after
Haemoglobin (13.5–17.5 g/dL)	75	77	8.9	8.2	8.1		12.3
white cell count (3.9–10.6/nL)	11.9	11.37	9.13	8.07	7.0	7.2	6.22
Platelet count (150–440/nL)	514	505	516	492	228		197
Blood urea nitrogen (5–26 mg/dL)	34	35	41	48	32	25	29
Creatinine (0.1–1.5 mg/dL)	4.1	5.1	6.0	8.0	6.6	1.8	1.4
Sodium (135–145 mg/dL)	134	131	127	126	134	137	142
Potassium (3.5–5.0 mg/dL)	5.0	5.1	5.0	4.0	3.7	4.6	3.6
Carbon dioxide (24–26 mg/dL)	21	15.5	16	17	22.8	21	30.3
Phosphorus (2.5–4.5)	5.4	5.4	7.7	8.8	7.1	17	
Hepatitis B surface Ag (non reactive)				Non-reactive			
Hepatitis C surface Ab (non reactive)				Non-reactive			
Complement 3 (90–180 mg/dL)				78.9			
Complement 4 (10–40 mg/dL)				15.7			
Cryoglobulin (negative)				Negative			
Antinuclear antibody titre (<1:80)			Negative				
Cytoplasmic antineutrophil cytoplasmic antibody (negative)	Negative		Negative				
Perinuclear antineutrophil cytoplasmic antibody (negative)	Negative		Negative				
Antiglomerular basement antibodies (<1.0 AI)			<1.0				
Urinalysis		pH 7.5, yellow, clear, negative for blood and leucocyte esterase, 30 mg/dL of protein					
Random urine protein to creatinine ratio (≤84 mg/g)		2094		612			131
Urine sediment		No cells or casts					

electron dense deposits. The findings of trace C3-dominant deposits are not of clinical significance and likely represent sequelae of an infection-related process

When the pathology report returned and the patient's serum creatinine was still elevated at 3.8 mg/dL, the patient was administered one dose of prednisone at 50 mg. However, on further review of the pathological findings with the renal pathologist, it was decided that the patient appears to be in the resolving phase of his disease given the relatively mild intensity of interstitial inflammation and the paucity of neutrophils and eosinophils, further treatment with prednisone was abandoned. He required a total of three dialysis sessions before renal recovery was apparent.

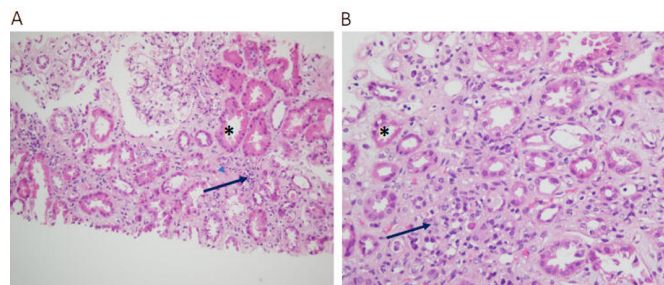


Figure 1 The kidney biopsy revealed by light microscopy mild to moderate interstitial inflammation (arrow) composed of predominately mononuclear inflammatory cells and rare plasma cells, mild interstitial oedema and mild tubular degenerative changes (*) (A and B, both stained with h&E). Original magnifications for A at ×200, and B at ×400.

OUTCOME AND FOLLOW-UP

In the following week, the patient slowly improved his renal function and was discharged with a serum creatinine of 1.8 mg/dL. A clinic follow-up 6 months later showed a serum creatinine of 1.4 mg/dL, a return to his baseline level.

DISCUSSION

The prevalence of AIN has been increasing in recent years, especially in the elderly population age >65 years, presumably driven by the greater use of antibiotics and other common drugs such as non-steroidal anti-inflammatory drugs and proton pump inhibitors.⁶ Though the most common clinical manifestations are acute kidney injury, haematuria, non-nephrotic proteinuria, leucocyturia, a Spanish registry study showed that up to 20% of patients had a bland urine sediment.⁶ AIN due to antibiotics of the penicillin and cephalosporin classes present typically with the hypersensitivity syndrome of fever, rash and eosinophilia in more than 75% of the cases.⁵ In contrast, fluoroquinolone antibiotics, in particular ciprofloxacin, appear to manifest as these reactions in less than 50% of the cases (table 2). Reports of AIN induced by ciprofloxacin significantly increased after its FDA approval for use in 1987. Many case reports were presumed diagnoses given the clinical manifestations and time course of exposure and removal of the culprit agent without a renal biopsy. We have summarised the clinical manifestations of only renal biopsy-proven cases of ciprofloxacin-induced AIN (table 2). Though it is conceivable the causative agent in our patient was piperacillin–tazobactam, the lack of hypersensitivity syndrome in this patient and the fact that he was already discontinued on it when he developed acute kidney injury render it less

Table 2 Clinical characteristics of Patients with cipro-induced allergic interstitial nephritis

Patient age/ gender	Coexisting disease	Durat-ion of drug therapy before acute kidney injury	Other clinical features	Peak serum creatinine (mg/dL)	Oliguric (Y/N)	Concomitant nephrotoxins	Kidney biopsy	Therapy	Final serum creatinine	Reference
31/F	None	3	Fever, Urine eosinophils	7.9	N	None	Diffuse Interstitial Nephritis	Prednisone, discontinue CIPRO,	1.4	Allon <i>et al</i> ¹¹
64/F	Pneumonia	11	Fever, Urine eosinophils	8.2	N	Gentamicin	Diffuse allergic interstitial nephritis	Discontinue cipro, prednisone	2.1	Rippelmeyer <i>et al</i> ¹²
68/F	Pyelonephritis	7	5–8 rbc, 20–30 wbcs, few leucocyte casts/10 fields	7.7	N	Omeprazole	Diffuse allergic interstitial nephritis and tubulitis	Discontinue norfloxacin	1.1	Hadimeri <i>et al</i> ¹³
70/F	Small cell anaplastic pulmonary carcinoma	8	No eosinophilia	4.8	N	Carboplatin	Diffuse allergic interstitial nephritis and tubulitis	Discontinue cipro	1.2	Hadimeri <i>et al</i> ¹³
73/F	Non-small cell lung cancer	8	Urine: no cells or protein	9.8	N	None	Moderate severe interstitial infiltrates, interstitial oedema and focal tubular atrophy	Discontinue cipro, complete 10 day course of tapered steroids	1.1	Bailey <i>et al</i> ¹⁴
45/F	Urinary tract infections	10	Erythematous rash, no eosinophilia	2.2	N	None	Diffuse lymphocytic interstitial infiltrate with occasional eosinophils, mild tubular epithelial damage	Discontinue cipro, Prednisone 40 mg/d for 1 month	1.2	Ortiz <i>et al</i> ¹⁵
56/M	Liver abscess	3	None	8.0	N	metronidazole	Mild to moderate interstitial inflammation	Discontinue cipro, RRT for three sessions, one dose of prednisone	1.2	Present case

CIPRO, ciprofloxacin; F, female; M, male; Rbcs, red blood cells; RRT, renal replacement therapy; wbcs, white blood cells.

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Table 3 Retrospective studies of corticosteroid use in allergic interstitial nephritis

Type of study, First author (reference)	Sample size		Histology		Follow-up, Months	Benefit (Y/N)
	Steroid	No Steroid	Steroid	No Steroid		
Retrospective, Galpin ¹⁶	8	6	No mention	No mention	53 (average)	Y
Retrospective, Laberke ¹⁷	7	20	Absence of severe tubular damage	Absence of severe tubular damage	9	Y
Retrospective, Bhaumik ¹⁸	6	13	No difference in tubular atrophy/interstitial oedema/interstitial infiltration/interstitial fibrosis	No difference in tubular atrophy/interstitial oedema/interstitial infiltration/interstitial fibrosis	3–12	N
Retrospective, Clarkson ⁴	26	16	40% interstitial fibrosis	40% interstitial fibrosis	12	N
Retrospective, González ¹⁹	52	9	61.5% mild interstitial fibrosis, 27% moderate interstitial fibrosis, 11.5% severe interstitial fibrosis	44% mild interstitial fibrosis, 22.2% moderate interstitial fibrosis, 33% severe interstitial fibrosis	19 in steroid group, 18 in no steroid group	Y
Retrospective, Raza ²⁰	37	12	No mention	No mention	14.8 in steroid group, 34.9 in no steroid group	Y
Retrospective, Muriithi ¹	83	12	13% globally sclerotic glomeruli	2.5% globally sclerotic glomeruli	6	N
Retrospective, Valluri ²¹	73	51	10% interstitial fibrosis/tubular atrophy	33% interstitial fibrosis/tubular atrophy	12	N
Retrospective, Predecki ²²	158	29	30% tubular atrophy	30% tubular atrophy	24	Y

likely. On the other hand, his clinical presentation and timing of medication exposure are more consistent with AIN due to ciprofloxacin.

The main pathological findings in renal pathology of AIN are interstitial inflammation and tubulitis. The predominant cell types that make up the interstitial infiltrates are lymphocytes (50%–70%) and monocytes (10%), with fewer numbers of eosinophils, plasma cells, neutrophils and histiocytes.⁷ The presence of interstitial oedema indicates an earlier course of AIN, which if left unresolved, can transform into interstitial fibrosis and tubular atrophy. This destructive process is triggered by profibrotic cytokines and growth factors that are synthesised by inflammatory cells which result in the accumulation of fibroblasts and extracellular matrix proteins. Given that T cells are the predominate cell types seen, a type IV (delayed-type)

hypersensitivity response is believed to be the most likely pathogenetic mechanism of injury. It is theorised that there is either molecular mimicry or direct binding of the drug to the tubular basement membrane. Most drugs are relatively small molecules and cannot induce an immunological response unless it is bound to a macromolecule such as a protein to become immunogenic. Once bound, the drug becomes antigenic and is processed by T helper cells to result in an immune response. The absence of significant immunoglobulin or complement staining on immunofluorescence renders a humoral response less likely. There is literature supporting the incorporation of pathology findings to help direct therapy,⁸ however, this is not a part of the currently recommended guidelines. The reason for this may be due to the inter-rater variability of biopsy results⁹ and the impracticality of performing biopsies on all suspected cases of AIN.

Treatment for AIN with corticosteroids remains controversial, as all studies are retrospective in nature and hence are inherently biased with selection of patients, unevenly matched severity of renal disease, treatment protocols and duration of follow-up (table 3). All studies were small as most comprised less than 100 patients per study. The assumption that patients with more interstitial fibrosis would respond less well to corticosteroids was not found to be consistently true (table 3). A systematic review of eight retrospective trials found that four studies showed benefit while four did not, the analysis was however plagued by significant heterogeneity between the studies.¹⁰

In our patient, a safe and timely renal biopsy was helpful in guiding our treatment strategy as the histology showed a ‘resolving’ picture of AIN, negating the necessity of continuing corticosteroids. In addition to the extent of interstitial fibrosis, the degree of inflammatory activity was an important element in our decision making. In summary, we conclude that it is important to keep AIN in the differential in a patient with no urinary sediment findings while using the renal biopsy to guide treatment whenever possible given the unclear data on the use of corticosteroids.

Contributors RIV collected clinical data, analysed the data and prepared the manuscript. MS interpreted the pathology findings and aided in preparation of manuscript. PS helped to research and prepare the manuscript. BJ helped to analyse the data and prepared the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Patient's perspective

I still do not fully understand what happened to my kidneys but now know to avoid ciprofloxacin in the future. I am glad that my kidneys are better.

Learning points

- ▶ Allergic interstitial nephritis (AIN) is not an infrequent diagnosis attributed to commonly prescribed medications such as antibiotics (penicillins and ciprofloxacin), non-steroidal anti-inflammatory drugs and proton pump inhibitors.
- ▶ AIN from fluoroquinolones may appear less as a hypersensitivity reaction with fever, rash, eosinophilia or eosinophiluria as compared with penicillins, cephalosporins, rifampicin or sulfonamide.
- ▶ The urinary findings usually range in severity of proteinuria, haematuria and leucocyturia, however, up to 20% may not have any urinary findings.
- ▶ Discontinuing possible offending agents is the most important step.
- ▶ The severity of inflammation, as well as the presence of interstitial fibrosis, on renal biopsy may help to guide therapy given the controversial role of steroids.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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