Clinical Kidney Journal, 2021, vol. 14, no. 1, 197–204

doi: 10.1093/ckj/sfaa018
Advance Access Publication Date: 11 March 2020
Original Article

ORIGINAL ARTICLE

Recurrent acute interstitial nephritis: what lies beneath

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ABSTRACT

Background. Acute interstitial nephritis (AIN) is an emerging cause of acute kidney disease. While this disease usually follows an acute course, it may occasionally recur, representing a major challenge for the clinician.

Methods. We performed a retrospective, observational cohort study in 13 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases. Patients with biopsy-proven AIN between 1996 and 2018 were included.

Results. The study group consisted of 205 patients with AIN, 22 of which developed recurrent AIN (RAIN) after a median of 111 days from diagnosis. RAIN was due to a surreptitious reintroduction of a previously known implicated drug or toxic in six patients (27%), sarcoidosis in two (9%), Sjögren's syndrome in three (14%), light-chain-mediated AIN in two (9%) and tubulointerstitial nephritis and uveitis syndrome in two (9%), while in the rest of cases (32%), no precise cause could be identified. Microscopic haematuria was more frequent in patients with underlying systemic diseases. The first RAIN episode was treated with a repeated course of corticosteroids in 21 patients (95%). In six cases (27%), azathioprine and mycophenolate mofetil were added as corticosteroid-sparing agents. During a median follow-up of 30 months, 50 patients (27%) with no recurrences and 12 patients (55%) with RAIN reached Stages 4 and 5 chronic kidney disease (CKD). By multivariable logistic regression analysis, RAIN was independently associated with the risk of reaching Stages 4 and 5 CKD, even after adjusting for potential covariables.

Conclusions. RAIN is infrequent but is associated with poor kidney survival. RAIN should prompt clinicians to search for an underlying aetiology other than drug induced. However, in a large percentage of cases, no precise cause can be identified.

Received: 14.9.2019; Editorial decision: 24.1.2020

Keywords: acute interstitial nephritis, chronic kidney disease, recurrent acute interstitial nephritis

INTRODUCTION

Acute interstitial nephritis (AIN) is an emerging cause of acute kidney disease (AKD) [1]. An increased incidence of AIN has been reported in several studies, especially among older patients [2].

Drug-induced AIN is the most common aetiology, representing almost two-thirds of total cases [3–5]. The typical overt clinical presentations (e.g. fever, rash and eosinophilia), commonly related with the exposure to several antibiotics, have largely been replaced by other less symptomatic forms characterized by longer intervals between drug exposure and the onset of symptoms [1, 6, 7], making it more difficult to identify the causative agent. For instance, in a large case series recently published, the culprit drug could not be precisely identified in almost 30% of cases [8]. This lack of crucial information hampers the main therapeutic option, as it is the withdrawal of the causative drug, and may also increase the probability of developing recurrences and incomplete recovery of kidney function. AIN may also be an earlier clinical manifestation of an underlying systemic or infectious disease with fewer extrarenal symptoms [1, 9, 10], thereby hindering the correct diagnosis and therapy [7].

Recurrent AIN (RAIN) represents a major challenge for clinicians that requires more thorough investigations and therapeutic approachs.

A few case series of RAIN have already been published; however, certain important questions still need to be answered, including the underlying diseases, treatment response and main outcomes of this pathological condition [10, 11].

Therefore we performed this multicentre retrospective study, in which we tried to characterize the main clinical features, treatment regimens and their responses, as well as kidney outcomes of RAIN in a cohort of patients diagnosed with AIN.

MATERIALS AND METHODS

Patients

Thirteen nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases participated in the present study. All patients with biopsy-proven AIN diagnosed between 1996 and 2018 were included. Patients with chronic interstitial nephritis, urinary tract obstruction and patients with missing data were excluded.

In all participating centres, baseline and follow-up data were collected from medical records using a research protocol that included demographics, corbidities, clinical presentation and a complete diagnostic workup with serum complement levels; angiotensin-converting enzyme, serum immunoglobulin G4 (IgG4), serum protein electrophoresis and immunofixation, hepatitis B and C and human immunodeficiency virus serology, complete autoimmunity panel [antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-Sjögren's syndrome-related antigen A (anti-Ro/SSA) and B (anti-La/SSB)] , 24-h proteinuria and urine sediment. Urine cultures and Ziehl–Neelsen staining were done in selected cases. Information about specific treatment regimens for AIN or RAIN was also recorded.

Patients were regularly followed until death, initiation of maintenance dialysis, loss to follow-up or the end of data collection period (31 December 2018): 71 patients of 205 were discharged from nephrology follow-up after a complete recovery of kidney function and 32 cases were lost to follow-up. The study was approved by the Ethical Committee at the study coordinating centre, Hospital Universitario Fundación Alcorcón.

Kidney biopsies

Kidney biopsy specimens were examined in the pathology departments of participating hospitals using standard processing that included light microscopy and immunofluorescence. Most kidney biopsies (70%) were also assessed by electron microscopy, while IgG4 immunohistochemical staining was only performed in selected cases.

The histologic diagnosis of AIN was made based on the presence of diffuse infiltrates of inflammatory cells (lymphocytes, monocytes, plasma cells and/or eosinophils) within the interstitial compartment, tubulitis and diverse degrees of interstitial oedema and fibrosis. We used semi-quantitative scores for interstitial inflammation, fibrosis and tubular atrophy according to the Banff working group criteria [12].

Definitions and outcomes

Kidney function was evaluated with serum creatinine (SCr) concentrations. According to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [13], acute kidney injury (AKI) was defined as an abrupt decrease in kidney function occurring within 7 days, AKD was defined as an acute or subacute loss of kidney function for between 7 and 90 days after an AKI insult and chronic kidney disease (CKD) was defined as kidney function impairment persisting >90 days. The estimated glomerular filtration rate was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [14] and expressed as millilitres per minute per 1.73 m^2.

Recurrence was defined as an AKI or AKD occurring after a previous AIN episode, with clinical and biochemical findings compatible with the disease, and after excluding other potential secondary causes of kidney impairment, including low blood pressure, dehydration, heart failure or urinary tract obstruction. A second kidney biopsy was performed at the clinicians' discretion and when the potential cause of kidney impairment was not clear.

The main outcome analysed was the progression to Stages 4 and 5 CKD, as defined by KDIGO guidelines, at 6 months from diagnosis and at the last follow-up.

Statistical analyses

We performed a retrospective, multicentre observational cohort study. Descriptive statistics are presented as mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables and absolute values and percentages for categorical variables.

For comparisons of continuous variables, Student's *t*-test, analysis of variance or Mann–Whitney test were used according to the distribution characteristics of the variable. For comparisons of categorical variables, the chi-square test was used.

Logistic regression models were used to analyse the main determinants of the outcome. Covariates in multivariable models were selected on the basis of prior knowledge and using

Table 1. Demographic, clinical and histologic characteristics of all patients during the first episode and according to recurrence of the disease

Variable	All patients (N = 205)	Recurrent AIN (n = 22)	Non-recurrent AIN (n = 183)	P-value
Demographics				
Age (years), mean ± SD	67 ± 14	68 ± 17	67 ± 14	0.704
Sex (male), n (%)	101 (49)	10 (46)	91 (50)	0.705
Previous CKD, n (%)	20 (10)	2 (9)	18 (10)	0.911
Clinical presentation				
Outpatient diagnosis, n (%)	170 (83)	19 (86)	151 (83)	0.650
Skin rash, n (%)	17 (8)	3 (14)	14 (8)	0.336
Fever, n (%)	39 (19)	5 (23)	34 (19)	0.640
Uveitis, n (%)	4 (2)	1 (5)	3 (2)	0.563
Serum creatinine (mg/dL), median (IQR)	4.8 (3.4–7)	4.8 (3.1–6.4)	4.8 (3.5–7)	0.539
Eosinophilia (>500 eosinophils/mm^3)	54 (26)	8 (36)	46 (25)	0.259
Proteinuria (g/24 h), median (IQR)	0.7 (0.3–0.8)	0.6 (0.3–1.2)	0.7 (0.3–0.8)	0.670
Microscopic haematuria, n (%)	108 (53)	9 (41)	99 (54)	0.242
Leucocyturia, n (%)	154 (75)	19 (86)	135 (74)	0.197
Histopathology				
Glomerulosclerosis (%), median (IQR)	14 (0–25)	13 (0–29)	14 (0–24)	0.517
Granuloma, n (%)	10 (5)	2 (9)	8 (5)	0.351
Interstitial fibrosis and tubular atrophy, n (%)				0.368
None (<25)	93 (45)	12 (55)	81 (44)	
Mild (25–50)	62 (30)	4 (18)	58 (32)	
Moderate (50–75)	42 (21)	6 (27)	36 (20)	
Severe (>75)	8 (4)	0 (0)	8 (4)	
Presumptive aetiology				
Unknown, n (%)	63 (31)	9 (41)	54 (30)	0.273
Drug-induced, n (%)				0.248
Antibiotics	42 (21)	1 (5)	41 (22)	
NSAIDs	56 (27)	7 (32)	49 (27)	
Other drugs	35 (17)	4 (18)	31 (17)	
PPI	9 (4)	1 (5)	8 (4)	
Outcomes at 6 months after first episode				
Serum creatinine (mg/dL), median (IQR)	1.5 (1.2–2.1)	1.6 (1.2–3)	1.5 (1.2–2.1)	0.400
CKD stages, n (%)				0.700
Stage 3	90 (46)	8 (44)	82 (46)	
Stage 4	36 (18)	3 (17)	33 (17)	
Stage 5	28 (13)	4 (13)	24 (22)	
Outcomes at the end of follow-up, median (IQR)				
Follow-up (months)	30 (11–57)	51 (19–66)	27 (10–55)	0.058
Serum creatinine (mg/dL)	1.5 (1.2–2.1)	1.8 (1.4–2.5)	1.4 (1.1–2.1)	0.012
CKD stages, n (%)				0.014
Stage 3	84 (41)	7 (32)	77 (42)	
Stage 4	35 (17)	9 (41)	26 (14)	
Stage 5	27 (13)	3 (14)	24 (13)	
Incidence rate of the main outcome[a] per 100 patient-years (95% CI)	10 (8–12)	13 (8–23)	9 (7–12)	

[a]Main outcome: progression to Stages 4 and 5 CKD.

CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; PPI: proton-pump inhibitors.

the backward progressive conditional elimination process. Continuous variables were not categorized for regression analysis.

P-values <0.05 were considered to be significant. Analyses were performed using SPSS Statistics 24.0 (IBM, Armonk, NY, USA).

RESULTS

Patients

The study group consisted of 205 patients diagnosed with AIN, 22 of which developed RAIN later in the course of follow-up [median 30 months (IQR 11–57)]. Demographic, clinical and biochemical characteristics of patients according to recurrence are displayed in Table 1. Presumptive drug-induced AIN was initially diagnosed in 142 of 205 patients (70%).

At baseline, no significant differences were observed in clinical presentation or histologic characteristics between patients who later recurred and those who did not. Neither kidney recovery after the first episode of AIN nor duration of corticosteroid therapy differed between subgroups (Table 1).

The median time to the first recurrence was 111 days (IQR 67–248). Recurrences were significantly less frequent in antibiotic-induced AIN [n = 1 (2.4%)] as compared with AIN caused by other drugs (P = 0.05). Table 2 displays the main clinical characteristics of patients with RAIN. In five patients (23%), RAIN occurred after the use of previously suspected offending

Table 2. Clinical presentation, treatment and outcomes of 22 patients with recurrent AIN

Patient	Sex	Age	Serum creatinine at diagnosis (mg/dL)	Initially suspected aetiology	Initial treatment	Serum creatinine at 6 months	Time to recurrence (days)	Extrarenal manifestations	Serum creatinine at recurrence	Final aetiology	Initial t reatment after RAIN	Alternative regimens	Number of recurrences	Serum creatinine at last follow-up
1	F	74	3	Unknown	CS	1.2	85	None	2.9	Unknown	CS	MMF and RTX	5	3.2
2	F	77	4.9	NSAIDs	CS + AZA	4.5	123	None	4.5	Sarcoidosis	CS	MMF	4	2.9
3	M	82	6	NSAIDs	CS	1.5	46	Malaise and fever	9.8	DI	CS	–	1	9
4	F	84	5	Allopurinol	CS	2.5	134	Malaise	3.3	DI	CS	–	1	2.4
5	M	73	4.3	Gabapentin	CS + AZA	1.4	53	None	1.9	DI	CS	MMF	1	1.5
6	F	85	3.1	Allopurinol	CS + MMF	1.8	395	Malaise, xerosis and xerophthalmia	2.7	Sjögren	CS	AZA	1	1.9
7	M	81	4.7	NSAIDs	CS	1.7	87	Malaise and dyspnoea	2.4	Unknown	CS	MMF	3	1.3
8	M	75	3.5	Unknown	CS	1.8	420	None	2.4	Unknown	CS	–	1	2.2
9	F	80	5.6	Unknown	CS	2.9	71	None	2.6	MGRS	CS-BTZ		1	1.8
10	F	60	5.2	Unknown	CS	–	137	None	2.1	Sarcoidosis	CS	–	1	1
11	M	81	6.1	Unknown	CS	1.1	119	Xerosis	3.4	Sjögren	CS	–	2	2.4
12	F	70	4	Unknown	CS	1.1	101	None	3.5	Unknown	CS	–	1	1.2
13	M	15	1.9	Unknown	CS	0.8	110	Uveitis	4.2	TINU	CS	–	3	1.8
14	M	55	1.7	Unknown	CS	1.7	438	None	2.6	Sjögren	CS	–	1	2
15	F	79	3.1	Lenalidomide	–	1.8	23	Fever	10.5	MGRS	CS-BTZ		1	1.2
16	F	79	7.1	Fosfomycin	CS	4.9	215	Malaise and fever	4.5	DI	CS	–	1	1.6
17	M	46	3.4	NSAIDs	CS	0.9	985	Oedema	1.8	Unknown	CS	–	1	1.4
18	F	64	8.8	Unknown	CS	1.5	2113	Erythroderma	5.8	Unknown	CS	–	4	2.4
19	F	44	7.5	NSAIDs	CS	3.3	119	Uveitis and fever	3.4	TINU	CS	CsA, MMF	1	1
20	F	85	2.1	PPI	CS	1.3	537	Arthralgia	1.9	Unknown	CS	AZA	1	1.8
21	M	62	7.6	PPI	CS	1.6	273	None	9.3	DI	MMF	–	1	9.3
22	M	51	17	Mushroom	CS	5.1	94	Malaise, fever and abdominal pain	7	Mushroom	CS	–	1	3.3

BTZ, bortezomib; CR, complete recovery; CS, corticosteroids; CsA, cyclosporine A; DI, drug-induced AIN; F, female; M, male; MM, multiple myeloma; NR, no recovery; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton-pump inhibitors; PR, partial recovery; RTX, rituximab.

Table 3. Demographic and clinical characteristics and outcomes of the 22 patients who recurred during the follow-up period according to aetiological groups

Variable	RAIN of unknown aetiology (*n*=7)	Drug-related RAIN (*n*=6)	RAIN due to systemic diseases (*n*=9)	P-value
Clinical characteristics at recurrence				
Age (years), median (IQR)	74 (64–81)	76 (59–82)	77 (49–80)	0.650
Sex (male), *n* (%)	3 (42)	4 (67)	3 (33)	0.440
Outpatient diagnosis, *n* (%)	4 (57)	6 (100)	9 (100)	0.024
Fever, *n* (%)	2 (29)	1 (17)	2 (22)	0.900
Rash, *n* (%)	1 (14)	1 (17)	1 (11)	0.900
Eosinophilia (>500 eosinophils/mm^3), *n* (%)	2 (29)	2 (33)	4 (44)	0.800
Serum creatinine (mg/dL), median (IQR)	2.4 (1.9–2.5)	5.7 (2.9–9.4)	3.4 (2.6–4.3)	0.100
Proteinuria (g/24 h), median (IQR)	0.6 (0.3–1.2)	0.6 (0.3–1.2)	0.6 (0.2–1.2)	0.800
Leucocyturia, *n* (%)	7 (100)	5 (83)	7 (78)	0.400
Microscopic haematuria, *n* (%)	3 (43)	0 (0)	6 (67)	0.036
Outcomes				
Last SCr (mg/dL), median (IQR)	1.8 (1.3–2.6)	2.8 (1.6–9)	1.8 (1–2.3)	0.050
CKD stages, *n* (%)				0.765
Stage 3	2 (28)	2 (28)	3 (43)	
Stage 4	3 (43)	2 (33)	4 (44)	
Stage 5	1 (14)	2 (40)	0 (0)	
Death, *n* (%)	1 (14)	3 (50)	1 (11)	0.200

drugs, surreptitiously reintroduced by the patient or erroneously prescribed by another physician. These drugs were non-steroidal anti-inflammatory drugs, proton-pump inhibitors, metamizole or allopurinol (drug-related RAIN). In addition, one case of RAIN was due to repeated mushroom-related poisoning.

In addition, RAIN led to a comprehensive diagnostic workup to rule out other potential causes of AIN, yielding the diagnosis of systemic diseases in nine cases (41%): primary Sjögren's syndrome in three (14%), sarcoidosis in two (9%), light-chain-mediated AIN [monoclonal gammopathy of renal significance (MGRS)] in two (9%) and tubulointerstitial nephritis and uveitis syndrome (TINU) in two (9%; RAIN due to a systemic disease). The underlying aetiology of RAIN could not be accurately identified in seven cases (32%; RAIN of unknown aetiology).

Characteristics of patients according to the aetiology of RAIN

Kidney impairment was present in all cases with a median SCr of 4.8 mg/dL (IQR 3.1–6.3) and a median proteinuria of 0.64 g/day (IQR 0.3–1.2). Microscopic haematuria was present in 8 cases (36%) and sterile leucocyturia in 15 (68%). Microscopic haematuria was most frequently observed in patients with underlying systemic diseases as compared with other subgroups (Table 3). No significant differences were observed in the incidence of other hypersensitivity reactions between subgroups.

Initial symptoms were non-specific, including fatigue and malaise in 12 patients (54%), isolated fever in 4 (18%) and generalized erythroderma in 1 (5%).

Patients diagnosed with TINU exhibited concurrent anterior uveitis with kidney impairment at the time of RAIN diagnosis, and two of three cases with Sjögren's syndrome complained of sicca symptoms, with a positive Schirmer's test (<10 mm). Salivary gland biopsy confirmed the diagnosis. The third patient with Sjögren's syndrome did not present signs or symptoms compatible with the disease, but a high index of suspicion led to a gland biopsy and established the final diagnosis. All three patients had negative SSA/Ro and SSB/La antibodies.

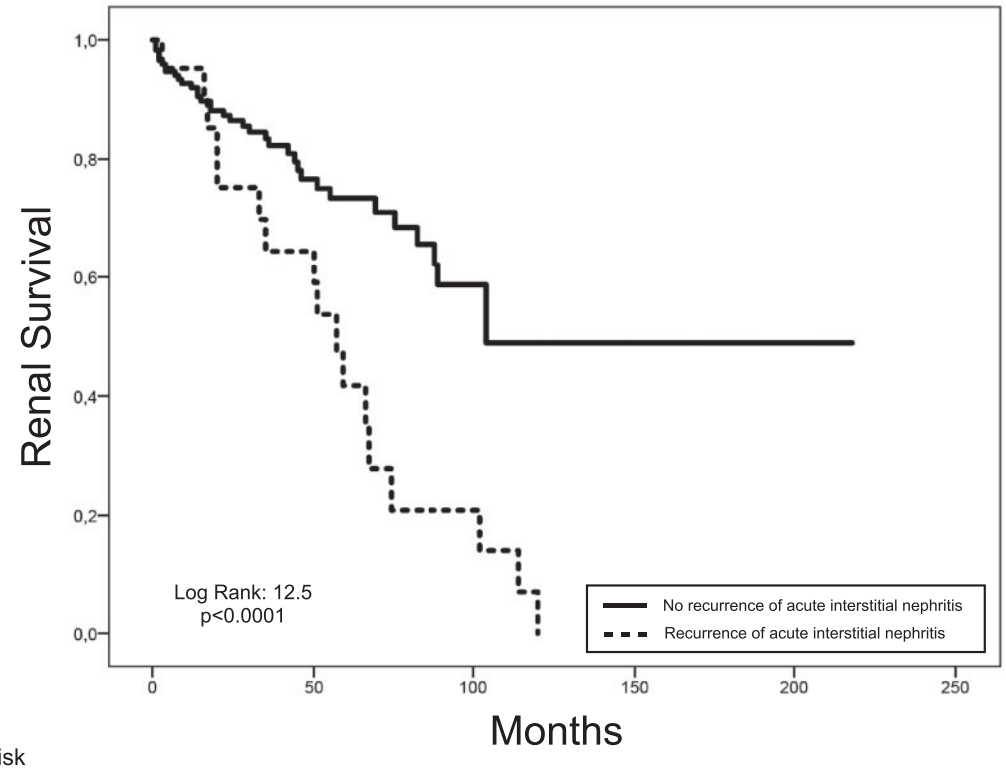
Neither patients with MGRS nor those with sarcoidosis presented systemic symptoms consistent with the underlying disease. The diagnosis of light-chain-mediated AIN in Patient 9 (Table 2) was established by the presence of a monoclonal kappa light chain in urinary immunofixation, together with a re-evaluation of the immunofluorescence of the kidney biopsy that revealed a linear tubular basement membrane positivity for kappa. In Patient 15 (Table 2), an IgA kappa monoclonal gammopathy of unknown significance was initially detected, fulfilling diagnostic criteria for high-risk smouldering multiple myeloma. Treatment with dexamethasone and lenalidomide was instituted early after the haematological diagnosis. However, over the following weeks, SCr rose from 1 to 3 mg/dL and a kidney biopsy was performed showing acute tubulointerstitial damage. A presumptive diagnosis of lenalidomide-induced AIN was made and therefore this treatment was discontinued, with mild improvement of kidney function. Three weeks later the patient developed severe AKD in the setting of a febrile syndrome. A subsequent kidney biopsy demonstrated glomerular mesangial expansion with glomerular basement membrane thickening and a tubular basement membrane positivity for kappa. Thus RAIN led to the final diagnosis wrongly attributed to the medication.

Two patients with sarcoidosis had initial normal serum levels of angiotensin-converting enzyme that became elevated during recurrence. High-resolution computed tomography yielded the final diagnosis in both cases.

A second kidney biopsy was performed in two additional patients (9%) to confirm the diagnosis of RAIN, with histopathologic findings compatible with AIN with no other particular characteristics.

Treatment

The first episode of AIN was treated with corticosteroid therapy (mean initial dose of 0.8 ± 0.2 mg/kg/day) in 199 patients for a median of 9 weeks (IQR 7–13).



Patients at risk

No recurrence of acute interstitial nephritis	183	48	8	3	1
Recurrence of acute interstitial nephritis	22	12	3		

FIGURE 1: Kaplan–Meier renal survival curves according to recurrence of AIN.

Table 4. Multivariable logistic regression analysis for association between covariables and progression to Stages 4 and 5 CKD[a]

	Univariable		Multivariable	
Variable	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1.045 (1.011–1.079)	0.009	1.040 (1.008–1.072)	0.012
Sex	0.571 (0.286–1.143)	0.114		
Serum creatinine at presentation	1.176 (1.066–1.298)	0.001	1.175 (1.068–1.293)	0.001
Proteinuria at presentation	1.136 (0.774–1.667)	0.516		
Glomerulosclerosis	1.029 (1.002–1.055)	0.032	1.035 (1.013–1.058)	0.002
Tubular atrophy	1.199 (0.707–2.031)	0.501		
Interstitial fibrosis	1.217 (0.720–2.057)	0.463		
Acute interstitial infiltrate	1.662 (0.233–1.871)	0.612		
Recurrence of AIN	3.532 (1.251–9.976)	0.017	3.431 (1.274–9.238)	0.010

[a]Number of events: 62.
CI: confidence interval.

Of the 22 patients who presented with RAIN, 21 (95%) received a repeated course of corticosteroids after diagnosis (mean dose of 0.8 ± 0.3 mg/kg/day). This treatment was tapered over a median period of 8 months (IQR 3–28). Prolonged corticosteroid therapy was prescribed in those patients with underlying autoimmune disease [median 19 months (IQR 5–48)] and in those with unknown aetiology [median 15 months (IQR 4–35)] as compared with patients with drug-induced RAIN [median 3 months (IQR 1–20)]. However, these differences did not reach statistical significance (P = 0.173).

In three patients (14%), azathioprine (AZA) and mycophenolate mofetil (MMF) were added to avoid potential adverse effects or limit the cumulative dose of corticosteroid therapy. Mean doses of AZA ranged from 50 to 100 mg/day, whereas doses of MMF ranged from 500 to 1500 mg/day.

Subsequent recurrences were treated with MMF in three patients (14%), AZA in three (14%), cyclosporine in one (5%) and rituximab in one (5%; Table 2). No significant adverse events were found with these corticosteroid-sparing agents.

Patients with MGRS were treated with the combination of dexamethasone and bortezomib.

Outcomes

Six patients developed more than one RAIN. The total number of recurrences was greater in patients with RAIN of unknown aetiology [median recurrences 1 (IQR 1–4)], followed by those of autoimmune aetiology [median recurrences 1 (IQR 1–3)]. No further recurrences were observed in patients with drug-induced RAIN.

The median period until the development of RAIN was significantly longer in patients with RAIN of unknown aetiology [median 13 months (IQR 3–39)] as compared with patients with drug-induced RAIN [median 3 months (IQR 1–6)] and RAIN of autoimmune aetiology [median 4 months (IQR 2–4); $P = 0.04$]. However, median SCr levels at the last follow-up were significantly higher in patients with drug-induced RAIN [SCr 2.8 mg/dL (IQR 1.6–9)] compared with those of patients with underlying autoimmune disease [SCr 1.8 mg/dL (IQR 1–2.3)] or unknown aetiology [SCr 1.8 mg/dL (IQR 1.3–2.6)] ($P = 0.05$).

Ten patients (5%) reached end-stage kidney disease requiring maintenance dialysis after the first episode of drug-induced AIN.

At the last follow-up, 50 patients (27%) without recurrences and 12 patients (55%) with RAIN reached Stages 4 and 5 CKD. Over a medianof 30 months (IQR 12–58), the likelihood of reaching Stages 4 and 5 CKD was two times greater in RAIN patients as compared with non-RAIN patients (absolute risk 0.55 versus 0.27). Figure 1 shows renal outcomes according to recurrence of AIN.

By multivariable logistic regression analysis, the main determinants of progression to Stages 4 and 5 CKD at last follow-up in the whole cohort are presented in Table 4. RAIN was significant and independently associated with this outcome after adjusting for other potential covariables [odds ratio 3.43 (95% confidence interval 1.27–9.23); $P = 0.01$].

DISCUSSION

The results of this study show that recurrences of AIN are infrequent (only 11% of the studied patients) but are associated with worse kidney prognosis.

An important number of cases were wrongly attributed to drug exposure in the first episode of AIN, and recurrence led to the diagnosis of an underlying systemic condition in 41% of cases. Thus the development of RAIN should prompt clinicians to conduct an exhaustive investigation for secondary causes of AIN. Unfortunately, despite a detailed investigation of patients with RAIN, the underlying aetiology remains elusive in a significant number of cases.

Oligo-symptomatic presentations of certain drug-induced AIN often result in delayed diagnosis and can also make it difficult to correctly identify the culprit drug [1, 15, 16]. Therefore the question arises as to whether a correct assignment of the aetiology was performed in the initial episode of AIN.

In this case series, only the presence of microscopic haematuria in the urinary sediment at the time of RAIN helped to identify the underlying immunologic aetiology as compared with other causes. However, no other clinical characteristic helped to foresee the development of a recurrence during the follow-up or an incorrect diagnosis at presentation. Therefore close follow-up is always warranted in patients diagnosed with AIN, even if an initial favourable response is achieved, to detect a possible early recurrence.

Drug-induced AIN represents a dose-independent type IV hypersensitivity reaction that occurs in kidney parenchyma after the exposure to different agents [17]. This hypothesis is supported by the fact that the interstitial infiltrate in AIN is predominantly composed of T-lymphocytes, without a significant deposition of complement or immunoglobulins [18]. In our study, six patients presented with a recurrence after a re-exposure to certain medications, thus confirming its pathogenic contribution to the disease. Although these recurrences could have been avoided, it is possible that the recommendations made to these patients were not sufficiently clear to avoid the culprit drugs. In fact, unlike patients with underlying systemic diseases, no second or third recurrence occurred among patients with drug-induced RAIN. One might speculate that the uncertainties in the underlying aetiology of the first episode of AIN could have resulted in a milder recommendation to avoid the potential culprit drug. On the other hand, the kidney prognosis of drug-induced AIN was worse than that of other aetiologies, and these findings are in agreement with those from other studies [19].

Finally, a third subset of patients was those in which the underlying aetiology of RAIN remained elusive at the end of the follow-up period. In this scenario, one may question if the potential causative drug was not correctly identified, and therefore not discontinued, or whether the underlying aetiology was a different systemic disease with fewer extrarenal manifestations, making its diagnosis difficult.

From a clinical perspective, the therapeutic strategy to be used in cases of RAIN due to a systemic disease or in cases of re-exposure to a culprit drug is well defined. However, this situation may become more challenging in patients with RAIN of unknown aetiology. Considering the higher risk of recurrences in these patients, as observed in this study, a longer duration of immunosuppressive therapy and/or the combination of corticosteroid-sparing agents such as MMF could be a good alternative in selected cases [20].

In a recent study that included 157 patients diagnosed with AIN, the causes of AIN were redefined in 32 patients (20%) in the course of follow-up [10]. While the majority of patients had been initially labelled as having a drug-induced AIN, an increased number of patients were finally diagnosed with autoimmune-mediated AIN with late-onset systemic manifestations, such as TINU syndrome. However, unlike our case series, recurrences occurred in 26% of their patients.

Interstitial inflammation in the setting of AIN leads to fibrosis if not treated early after diagnosis [8, 21]. Thus recurrent episodes of interstitial inflammation result in increased fibrosis and chronic damage to the kidney parenchyma. Indeed, in our study, recurrences were associated with worse kidney survival and a higher percentage of patients with Stages 4 and 5 CKD. Furthermore, recurrences of AIN were independently associated with worse kidney prognosis in multivariable analysis.

This study is subject to limitations. First, due to the observational and retrospective nature of the study, no causal relationships could be established. In addition, a second biopsy was performed in isolated cases and therefore the underlying cause of RAIN could have been misdiagnosed in some cases. Despite these limitations, this study collects one of the largest case series of AIN regularly followed up after diagnosis.

In conclusion, our data indicate that RAIN is an infrequent condition associated with worse kidney outcomes than in those of non-recurrent AIN. However, no clinical feature at the initial episode can predict the development of a recurrence. Apart from avoiding re-exposure to the causative agent, close follow-up after the first episode is warranted and a complete diagnostic approach is necessary to diagnose the underlying aetiology

of the disease. Better clinical tools or new biomarkers are needed to improve risk prediction and diagnosis.

FUNDING

This study was funded by Red de Investigación Renal (grant RD016/0021 to M.P.), Instituto de Salud Carlos III, Spain.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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