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Observational Study

Clinical Features and Outcome of Acute Interstitial Nephritis Diagnosed using Urinary Biomarkers - An Observational Study

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Introduction

Acute Interstitial Nephritis (AIN) is a reversible cause of acute kidney injury. Histopathologically diagnosed AIN accounts for 15% - 27% of cases of acute renal failure [1]. Despite the growing recognition of AIN, there remains a paucity of prospective studies detailing its etiology, clinical course, management, and outcomes. AIN is not frequently reported due to diagnostic hurdles as a kidney biopsy is required to establish the diagnosis [2]. The use of non-invasive urinary biomarkers like MCP-1 and TNF-alpha may be helpful in this regard [3]. They have been found to be useful in differentiating ATN from AIN and can differentiate between glomerular and tubular sites of inflammation [4]. We have demonstrated the utility of urine MCP-1/ TNF-alpha in the diagnosis of AIN in our setting [5]. This study describes the clinical features and outcome of acute interstitial nephritis. Here we have utilized urine MCP-1 in the diagnosis of acute interstitial nephritis.

Methodology

The study was a prospective cross-sectional descriptive study conducted at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, from November 2021 to June 2023. The study protocol was reviewed and approved by the Institute Ethics Committee (Human studies), JIPMER, Puducherry (No. JIP/IEC/2021/280).

The study participants were hospitalized patients with acute kidney injury under the department of Medicine. Patients with previously diagnosed chronic kidney disease, diabetes mellitus with retinopathy, presence of RBC casts in urine or nephrotic range proteinuria, acute diarrhea and/or severe vomiting preceding the renal failure, hypotension preceding the renal failure, urinary tract infection, obstructive uropathy, active hemolysis/rhabdomyolysis/tumor lysis, multiple myeloma, hepatorenal syndrome, patients who had received cyclosporine, aminoglycosides were excluded from the study. As controls, we enrolled 25 healthy adults, who were the relatives of the patients.

All patients were included in the study after obtaining informed consent. A complete clinical history along with history of fever, rash, oliguria and autoimmune illness and recent drug history were recorded. After obtaining history, a physical examination was done. Complete hemogram, renal function tests and serum electrolytes were performed. Leptospira serology was done when indicated. Urine investigations - urine R/E, urine culture, 24 hour urinary protein, and urine eosinophils were done. Midstream urine samples were collected from all patients. The obtained urine samples were centrifuged at 2500 rpm for 10 minutes within 2 hours of collection. Five milliliters of urinary supernatant were stored at −80 °C for MCP-1 and TNF-alpha analysis. All investigations which were required for the patients including kidney biopsy were decided by the treating units. Patients were monitored for trends in serum creatinine, withdrawal of any drugs, treatment given in the form of steroids and dialysis. In case if an alternative diagnosis was established, they were excluded from the study. Urinary MCP-1 and TNF-α were estimated in them. Urine for inflammatory markers was processed at the end of the study. The urinary

MCP-1 and TNF-α levels were measured by specific ELISA methods according to the manufacturers' protocols (R and D systems for MCP-1 and Abbkine for TNF-α). The lower limits of detection were 15 pg/ml for MCP-1 and 3 pg/ml for TNF alpha. Urinary levels below these limits were considered undetectable and expressed as zero. The 90th percentile values among control samples were 24.58 ng/mmol Cr for normalized urine MCP-1 and 4.72 ng/mmol Cr for normalized TNF alpha.

A diagnosis of definitive acute interstitial nephritis was made on the basis of a kidney biopsy report. Probable AIN was diagnosed if the following were present. AKI or serum creatinine > 1.5 mg/dL and Urinary MCP-1 > 242 ng/mmol Cr with glomerulonephritis/ pyelonephritis being reasonably ruled out (absence of RBC casts in the urine, proteinuria less than 1 gm per dl and sterile urine culture). Urinary MCP-1 > 242 ng/mmol Cr has been found to provide a sensitivity of 92.9% and a specificity of 90.8% the detection of interstitial inflammatory cell infiltration [6].

Patients with a clinical diagnosis of AIN were followed up for 6 months or till serum creatinine normalized (whichever was earlier). Recovery of kidney function was based on the serum creatinine at 6 months. Complete recovery was defined as an improvement in serum creatinine level to within 25% of its baseline (or to < 1.4 mg/dL if baseline was not available). Partial recovery as a 50% decrease in serum creatinine level from its peak value, but not reaching within 25% of its baseline value and no recovery as a failure to meet the criteria for complete or partial recovery or continuing to require renal replacement therapy.

Statistical analysis

Data from the collection proforma were entered using Microsoft Excel. All the data mentioned in the study procedure was entered at the time of admission and after the evaluation, compiled and coded using a Microsoft Excel spreadsheet, and analyzed using IBM SPSS version 19. Descriptive and inferential statistics were used to analyze the data. Categorical variables were reported as the frequency with percentage. Continuous data were first tested for the normalcy of distribution by the Wilcoxon rank-sum test, and then summarized with mean (SD) or median (IQR) based on their distribution.

Results

The study was conducted between November 2021 and June 2023. 800 patients with acute kidney injury were screened and 65 patients (8%) were initially included. Of the 65 patients, 27 patients underwent kidney biopsy. Of them, 17 patients were found to have an alternative diagnosis and hence were excluded from this study. The biopsy diagnosis was AIN in 10 patients (37% among the patients who were biopsied) and they were included in the study. Among 38 patients managed without kidney biopsy, AKI resolved within 10 days in 13 patients (NSAID use in 7 patients) and hence was considered improbable for an inflammatory condition and were excluded. A total of 35 patients (10 biopsy proven AIN and 25 with AKI without kidney biopsy) were further studied. This is summarized in Figure 1.

Urinary TNF alpha and urinary MCP-1 were measured in all patients who underwent kidney biopsy, 25 probable AIN and 25 control samples. Based on the results, we have published a report on the performance of urinary biomarkers in the diagnosis of AIN. 30 patients had TNF alpha and MCP-1 levels more than the 90th percentile of normal values and Urinary MCP-1 > 242 ng/mmol Cr and they were diagnosed to have acute interstitial nephritis (3.7% of the initial 800 patients). Clinical features and outcome of these 30 patients have been described.

Baseline clinical and demographic data

The clinical and demographic information of all 30 patients with acute interstitial nephritis have been described below (Table 1). Patients were middle-aged (mean age 45 years) and 86% were males. 21 patients (66%) did not have any comorbidities. Two patients were diabetic and seven patients had hypertension. 14 patients (47%) of the patients had oliguria at presentation. Loin pain was a prominent clinical feature in three patients. The classic triad of fever, rash and eosinophilia was not seen in any of the patients. Eight patients (26%) had fever and 16 (53%) had leukocytosis. Eosinophilia was present in 9 (30%) of the patients. Anemia was seen in 19 (63%) patients, out of which 3 patients had severe anemia. The median serum creatinine at presentation was 5 mg/dl with a corresponding median eGFR of 16 ml/min. The peak creatinine levels rose to a median value of 7 mg/dl. No urinary abnormalities were seen in 20% of patients. 12 patients had WBC's in the urine (40%) and eosinophiluria was not seen in any patients. Urinary casts were seen in 10% of patients. Proteinuria was

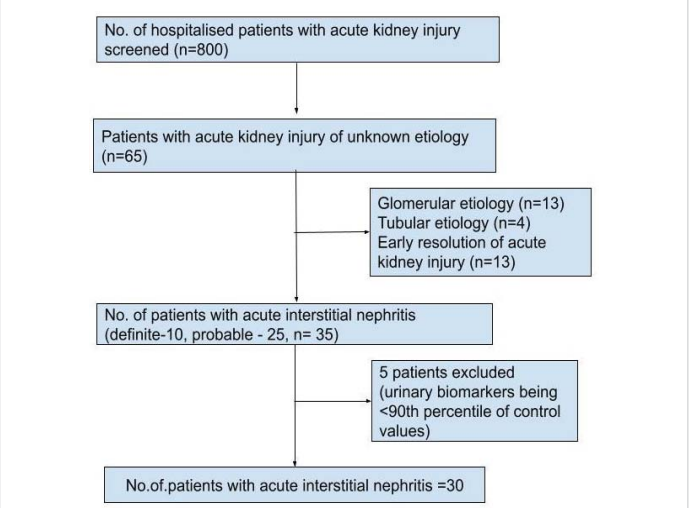

Figure 1: STROBE flow chart.

Table 1: Clinical features of patients with AIN.

	n = 30	*n* = 10 (Biopsy proven)
Systemic manifestations		
Rash	1(3%)	0
Fever	8(26%)	3(30%)
Leukocytosis (>11000 cells/μL)	16(53%)	7(70%)
Eosinophilia (500 cells /μL)	9(30%)	2(20%)
Neutrophilia	7(23%)	5(50%)
Anemia(g/dl)	19(63%)	5(50%)
Rash + fever + eosinophilia	0	0
Renal manifestations		
Oliguria	14(47%)	7(70%)
eGFR at presentation(ml/min)	16 (8.7 - 16)	18.3(3 - 45)
Stages of AKI		
Stage 1	2(6.7%)	0
Stage 2	4(13%)	0
Stage 3	24(80%)	10(100%)
Serum creatinine at presentation (mg/dl)	5(3.0 - 7.3)	6.4(2.1 - 18)
Peak serum creatinine (mg/dl)	7.0 (4.4 - 10.2)	9.7(2.9 -18.2)
Urine diagnostics		
Urine eosinophils	0	0
Urine WBCs	12(40%)	6(60%)
Urinary casts	3(10%)	3(30%)
Proteinuria		
Nil	10(33%)	6(60%)
Trace	4(13%)	-
1+	11(36%)	-
2+	1(3%)	-
3+	3(10%)	3(30%)
4+	1(3%)	1(10%)

present in 20 (66%) patients. Four patients (13%) had higher degree of proteinuria (more than 3+) of which three patients had biopsy proven AIN and one had wasp sting related interstitial nephritis. We compared the clinical features of all patients and of those in whom there was a pathological confirmation. Renal failure was more severe in the latter group. Leukocytosis and urinary WBC's were seen in a lesser proportion of patients of the former group.

Etiology of AIN

The causes of AIN are listed in Table 2. Most of the cases were due to drugs (22 patients, 73%). Envenomation accounted for 5 patients (17%) and leptospirosis in 3 patients (10%). In the absence of another etiology, exposure to a drug in the antecedent phase to the development of AKI was considered to be the cause of AIN. Also if a particular drug had been stopped and AKI had resolved then that drug was considered to be the culprit drug. Most cases of drug induced AIN were due to PPIs followed by NSAIDs and antibiotics. Omeprazole and pantoprazole were the common PPIs used in these patients. Cephalosporin and vancomycin caused AIN among the antibiotics.

Clinical course and outcomes

24 (80%) patients had complete renal recovery at the end of 6 months and 4 (13%) patients progressed to CKD requiring maintenance dialysis and 2 patients (7%) died.

Table 2: Etiology of AIN.

Etiology	*n* = 30
Drugs	73%
PPIs (Omeprazole, Pantoprazole)	6(27%)
NSAIDs (Diclofenac, Aceclofenac)	5(22%)
Antibiotics (Cephalosporin and Vancomycin)	3(13.6%)
Other drugs (Rifampicin. Herbs. Allopurinol, Acyclovir)	8(36%)
Envenomation	17%
Snake bite	4
Wasp sting	1
Infections	10%
Leptospira	3

Table 3: Clinical outcome.

Outcome	Definite AIN (with histopathological diagnosis) N = 10	Probable AIN N = 20
Complete recovery	70%	85%
No recovery	20%	10%
Death	10%	5%

The breakup of the outcome in the definitive AIN group and the probable AIN group has been shown in Table 3. Of the 22 drug induced AIN patients, in 11 patients (50%) the putative drug was withdrawn and this was followed by resolution of AKI. Corticosteroids were given in 2 patients (both with histopathological diagnosis) and in the rest of the patients the drug had already been stopped and the patients responded spontaneously. Renal replacement therapy was required in 40% of patients (etiology was hemotoxic envenomation in one third of these patients). The mean duration of renal recovery from AKI onset was 21 days.

Discussion

This study was undertaken to describe AIN among hospitalized patients with AKI. The diagnosis of AIN was based on a urinary biomarker alone in 60% of the patients and on histopathology in the rest of the patients.

The proportion of patients with AKI with a lack of common etiologies was 8%. AIN was diagnosed in 46% of them (3.7% of all included patients). AIN accounted for 37% of cases among patients who underwent a kidney biopsy for the evaluation of AKI with unknown etiology. In a retrospective study from South India, AIN was diagnosed in 156 biopsy specimens (2.5%) among 6234 biopsies analyzed [7]. The higher proportion seen here in biopsied cases may be due to stringent selection criteria for performing a kidney biopsy.

We have described the clinical characteristics of all the patients. The degree of systemic manifestations were higher and the severity of illness was more in the histopathologically diagnosed subgroup than the overall group of patients in our study. This is more likely to be due to selection bias as the decision on kidney biopsy is likely to have been taken based on severity of the illness. We have compared the clinical features with other Indian studies, though these studies included patients with Drug Induced Acute Interstitial Nephritis (DIAIN) only and the diagnosis had been made

by renal histopathology. Peripheral eosinophilia was more prevalent (30%) compared to 9% in the study by Surendra M, et al. [8]. More patients were oliguric (47% *vs.* 13% (Surendra M, et al.)) but the requirement of renal replacement therapy (RRT) was similar (26%) in the DIAIN subgroup. However, in a separate study by Ramachandran, et al. 54% of patients required RRT [9].

In our study, the classic triad of fever, rash and eosinophilia were not seen in any of the patients. 70% of the patients had no peripheral eosinophilia. 20% of patients had no urinary abnormalities and urine eosinophils were not seen in any patient. This mirrors findings by Nussbaum, et al. and highlights the clinical diagnostic challenges [2]. A viable solution is the use of urinary biomarkers to aid diagnosis. [10].

DIAIN accounted for 73% of the cases of AIN. PPI's, antibiotics and NSAIDs were the culprit drugs as seen in the previous studies. In a trial by Ramachandran, et al. herbal medicines accounted for 27.5% of DIAIN which was not seen in our setting. PPIs were the commonest (27%) cause here. PPIs have now become a leading global cause of AIN [11]. Despite AKI being reversible, indiscriminate PPI use should be avoided.

80% of patients had complete recovery. Outcome data in Indian patients is available for a subgroup of patients who were treated with corticosteroids. Generally, 50% of these patients achieved complete remission at three-month follow-up [12]. Most patients, including those requiring hemodialysis, improved after withdrawal of the offending drug. Therefore, a stepwise strategy as proposed by Surendra M, et al. —initial withdrawal of the offending agent followed by corticosteroids for the subgroup of patients who do not improve following the same appears to be a prudent strategy [8].

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