

## Idiopathic Interstitial Nephritis: An Autoimmune Disease with a Chameleon Presentation and High-Potential for Kidney Loss

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### ABSTRACT

Data on the clinical picture, prognosis and management of 12 cases of idiopathic interstitial nephritis (IIN) are presented. Clinically; 5 patients had acute renal failure (ARF) with sudden fluid overload and azotemia, 2 had ARF on top of chronic renal disease (CRD) and 6 with unexplained CRD. The outcome of the 5 patients with ARF and short duration of illness was better. One had infrequent relapses, 1 had frequent relapses and 3 were steroid-dependent. The latter 4 patients had required maintenance immunosuppression (IS) initially with Prednisone, Mycophenolate and finally with Rituximab. The 2 patients with ARF on top of CRD were stabilized after IS. The remaining 5 patients with CRD became stable and/or improved while 1 patient progressed to end-stage kidney disease since her IS was late and inadequate prior to inclusion with us. In conclusion: IIN can mimic any kidney disease and can only be diagnosed with kidney biopsy. Aggressive IS can control the disease at its early stages otherwise, the prognosis is poor.

**Keywords:** Acute Renal Failure, Interstitial Nephritis, Kidney, Autoimmune, Idiopathic.

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### INTRODUCTION

Interstitial nephritis (IN) is a disease of the renal interstitium and its tubular cells. It accounts for 2% of native renal biopsies<sup>1</sup> and up to 27% of cases of unexplained kidney disease in adult patients.<sup>2</sup> Clinically and histopathologically, IN has been classified into acute and chronic ones. The etiology of each is diverse and with varied prognosis. Acute IN is usually induced by drugs, autoimmune diseases and infections while the chronic one includes drugs/toxins, hereditary diseases, hematological and metabolic disorders, obstruction, radiation nephritis and renal allograft rejection.<sup>3</sup> Retrospective studies had revealed that 8% of biopsy-proven IN-cases were idiopathic i.e. not associated with a precipitating factor.<sup>4</sup> Moreover, data on the clinical picture, prognosis and management of such idiopathic IN (IIN) are rare. In the current article, we report on our experience with management of 12 cases of IIN that was diagnosed and followed prospectively, in an attempt to expand knowledge on this type of kidney injury.

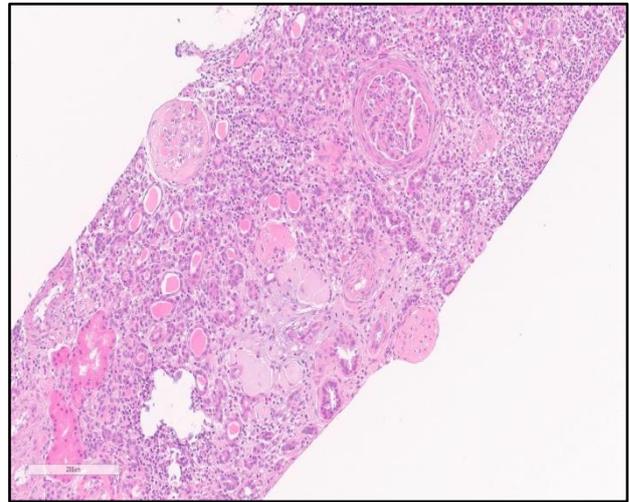
### PATIENTS AND METHODS

The study was conducted by the renal unit of Al-Amiri hospital. The unit is a referral center for patients with renal disease in 2 major hospitals and is a tertiary care unit for the other hospitals in Kuwait. A total of 415 kidney biopsy was done in the past 5 years.

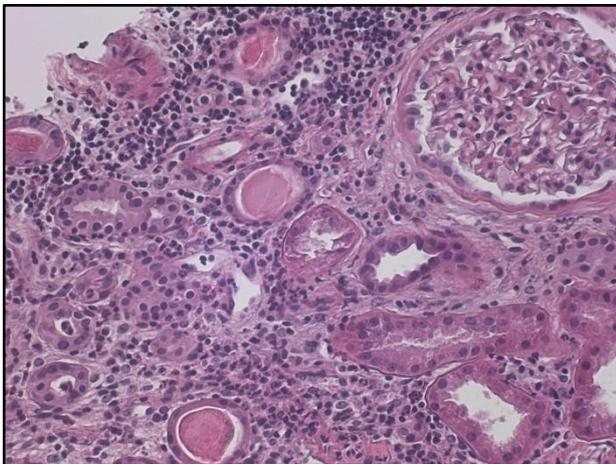
**Criteria of Inclusion for Patients with IIN:** Patients were included in analysis if they had all the following criteria: (a) an acute or progressive renal disease, (b) biopsy-proven diffuse IN, (c) lack of evidence of obstruction to the urinary tract, pre-renal insult, cardiovascular derangement and drug-effect, (d) lack of clinical, laboratory and serological evidence of infections and autoimmune disorders. The latter was established by: (a) negative Schirmer's test and ophthalmological examination for uveitis, (b) negative chest and high-resolution CT scan of the chest for sarcoidosis and tuberculosis as well as normal level of angiotensin-converting enzyme and Quanteferon test, (c) negative

serological tests for brucellosis, histoplasmosis, coccidioidomycosis, toxoplasmosis, polyoma virus, HIV and Epstein-Barr virus as well as urinary antigen test for legionella infection and urine culture for leptospirosis, (d) normal serum protein electrophoresis, IgA level and complement 3 & 4, (e) negative anti-CCP, ANA, anti-dsDNA, anti-GBM antibodies, ANCA, anti-Ro/SSA, anti-LA/SSb antibodies, hepatitis B & C serology and cryoglobulins, (f) Normal serum complements and lack of histological its deposition with/without immunoglobulin in the glomeruli and/or tubular basement membrane. (h) Lack of deposition of crystals and materials in the interstitium.

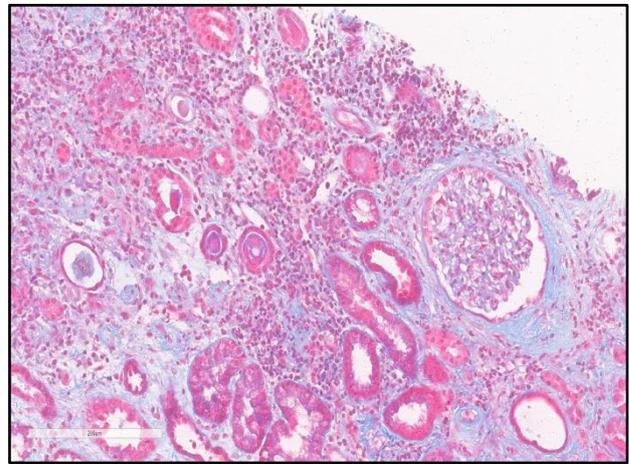
**Diagnosis and Staging of IIN:** Diagnosis of acute IN was established by documenting the presence of diffuse interstitial oedema, lymphocytic infiltration and tubular cell-damage. Eosinophils, macrophages, plasma cells and neutrophils may exist in the interstitium. The glomeruli and vascular structures are usually spared with evidence of periglomerular fibrosis. Chronic disease is characterized by tubulointerstitial fibrosis as evident by deposition of fibrous tissue and thyroidization of tubular ducts. Occasional glomerular sclerosis whether segmental or global without immune-deposition as well as crescents and vascular changes of hypertension are accepted secondary phenomena.



**Figure 2:** Photomicrograph of a kidney biopsy of patient (n: 6) showing evidence of chronic interstitial disease with diffuse interstitial infiltrate and periglomerular fibrosis. Note that some glomeruli show global sclerosis and fibrous crescents, the tubules show extensive thyroidization and the vessels show medial hypertrophy (H&E X 100).



**Figure 1:** Photomicrograph of kidney biopsy of patient (n: 1) showing normal glomerulus with acute interstitial nephritis. Note the oedema of the interstitium which is infiltrated by mononuclear, neutrophilic and plasma cell infiltrate (H&E X200).



**Figure 3:** Photomicrograph of kidney biopsy of patient (n: 8) showing an intact glomerulus with periglomerular fibrosis. The interstitium show oedema with mononuclear, neutrophilic and plasma cell infiltrate as well as fibrosis (Trichrome 200).

**Table 1: Clinicopathological presentation of the patients presenting with idiopathic interstitial nephritis**

S. No.	Sex	Age	Incubation period	Kidney	Course	Stage of disease		Drug-therapy	Follow up (months)
		(years)	(months)	ultrasound		initial	final		
1	M	46	1	11	Infrequent acute relapses	5	1	P	60
2	F	21	1	11	Frequent acute relapses	5	1	P,M,R	42
3	M	76	1	11	Acute steroid-dependent	5	3	P & M	10
4	M	34	1	10	Acute steroid-dependent	3	1	P & M	6
5	F	40	1	10	Acute steroid-dependent	4	2	P & M	5
6	M	15	24	8	Chronic with relapses	4	3	P,M,R	23
7	F	66	> 4	9	Rapid progression	5	3	P & M	11
8	F	19	UK	8	Chronic progressive	4	3	P & M	24
9	M	62	UK	8	Chronic progressive	3	3	P & M	13
10	M	66	18	8	Chronic progressive	4	3	P & M	4
11	M	28	3	9	Chronic progressive	4	3	P & M	4
12	M	37	5	9	Chronic progressive	5	5	P & M	25

## RESULTS

A total of 12 patients were diagnosed with IIN during the past 5 years. As seen in table 1; the demographical data was not an age- or sex-specific.

### Clinicopathological Correlation

Patients (n: 1-5) presented with progressive shortness of breath, generalized oedema and high serum creatinine over a period of 1 month. They improved with immunosuppression (IS) with Prednisone, Mycophenolate and Rituximab. Two patients (n: 3 and 4) had required supportive hemodialysis and had improved. Patient (n: 6) had hypertension for 2 years and serum creatinine at 180  $\mu\text{mol/L}$ . The latter had increased from 230 to 370  $\mu\text{mol/L}$  over a period of 2 months and hence had sought our advice. Patient (n: 7) presented with severe malaise due to uremia and severe anemia while her serum creatinine was 170  $\mu\text{mol/L}$  4 months ago. Both patients (n: 6 and 8) became stable with IS. Patients (n: 8-11) were diagnosed with unexplained chronic renal disease on routine checkup. They improved with IS. Patient (n: 12) had high serum creatinine at 200  $\mu\text{mol/L}$  that was neglected till reaching 600  $\mu\text{mol/L}$  4 months later. At that point; a kidney biopsy was done and it has shown an acute on top of chronic IIN (Fig.). He was started on Prednisone 1 mg/kg/day yet due to proximal muscle weakness; his dose was decreased rapidly and was discontinued 1 month later. Three months after that incident, he presented to us with uremic symptoms, serum creatinine at 900  $\mu\text{mol/L}$  and 9-cm kidneys with thin and echogenic cortex. Aggressive trial with IS for 6-weeks was futile and he remained hemodialysis-dependent since then.

## DISCUSSION

Glomerulonephritis is the most common renal presentation of systemic autoimmune diseases.<sup>5</sup> Immune-mediated interstitial pathology can be seen in systemic lupus erythematosus, sarcoidosis, Sjogren's syndrome, hypocomplementemia, IgG4-associated disease, tubulointerstitial nephritis with uveitis and mixed cryoglobulinemia.<sup>3</sup> Our patients, with IN, did not have clinical, laboratory, serological and radiological evidence of those systemic diseases, recent drug-exposure and infection. Hence, they fulfilled the criteria of IIN. The rarity of the disease and the retrospective nature of its biopsy reports did not permit adequate knowledge regarding its clinical presentation, treatment and prognosis.<sup>1</sup> In our series; 12 patients had evidence of IIN over the past 5 years. Contrary to glomerular syndromes which present with hypertension, oedema and abnormal urine sediment<sup>6</sup>; IIN is a silent yet relentless disease. It can present as (a) a frequently or infrequently relapsing acute oliguric renal failure with fluid overload, (b) steroid-dependent chronic illness that does not remit after 6 weeks contrary to usual drug-induced IN, and (c) chronic progressive disease without significant proteinuria, hematuria and hypertension and with bilateral equal sized kidneys. The latter finding is essential and excludes chronic reflux nephropathy and polyarteritis nodosa in patients presenting with renal failure and bland urine routine.<sup>7,8</sup> Moreover, in the chronic disease; secondary vascular and glomerular changes such as focal and global sclerosis as well as occasional crescent formation were evident. The latter can mislead diagnosis to nephroangiosclerosis or a primary glomerular disease viz. idiopathic crescentic glomerulopathy or focal segmental glomerulosclerosis in epidemiological studies and its management. The diffuse nature of

interstitial disease and lack of immunoglobulin deposition by immunofluorescent stains or immunoperoxidase should swing the pendulum towards diagnosis of IIN.<sup>6</sup> Aggressive diagnostic intervention, including biopsy of relatively small kidneys, may delay renal replacement therapy and prove to be cost effective.<sup>9</sup> The small number of patients in our study and hence their definite immunosuppressive management may open the door for future use of more aggressive protocols to save those kidneys.

## CONCLUSION

IIN is an underdiagnosed and serious kidney disease. It is a chameleon that can mimic any kidney disease and can be diagnosed only with a kidney biopsy. Aggressive corticosteroid and immunosuppressive therapy can control the disease at its early stages otherwise, kidney loss is inevitable.

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