
Original Article
Signficance of Tubulointerstitial Lesions in Kidney Biopsy Specimen of Nephrotic Patients in Iraq

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Abstract and Introduction

Abstract

Background: Tubulointerstitial lesions (TIL) adversely affect the prognosis of various glomerulonep
The aim of this study is to evaluate the significance of TIL in the cortical area of renal biopsy specim
Methods: A clinicopathologic prospective study was performed on patients with idiopathic nephrotic
syndrome (NS). The presence of TIL was assessed qualitatively by light microscopic observation and
correlated with several histopathologic and clinical parameters at biopsy time, as well as with status a
follow-up.
Results: The total number of patients was 136 with a mean duration of follow-up of 23.8 ± 11.9 mon
all patients with idiopathic NS, the presence of TIL in the cortical area was correlated significantly w
hypertension at presentation, response to treatment, and outcome. Histopathologically, TIL correlated
glomerular lesions.
Conclusion: It was concluded that qualitative evaluation of TIL in the cortex could reflect glomerula
and could contribute to the assessment of prognosis in patients with idiopathic NS.

Introduction

It is well known that tubulointerstitial lesions (TIL), such as interstitial cell infiltration, interstitial fib
(IF), and tubular atrophy (TA), can be observed in renal biopsy specimens of primary glomeruloneph
(GN), especially when specimens contain sclerosed glomeruli.[1-4]

According to many investigators, IF and TA usually reflect glomerular obsolescence.[1,3,4] If this we
an evaluation of such lesions would provide helpful information in estimating the severity and progn
primary GN on biopsy specimen, even when the biopsy material includes only a small number of glo
However, the body of literature that focuses on the importance of TIL in examining renal biopsy spec
small, and such lesions may have been overlooked and regarded as minimally significant, in contrast
glomerular and vascular lesions.[1-10]

Therefore, we carried out a prospective study to evaluate the significance of TIL in assessing the seve
the prognosis of the most common type of adult primary GN presented as nephrotic syndrome (NS).

Readers are encouraged to respond to George Lundberg, MD, Editor of *MedGenMed*, for the editor's only or for possible publication via email: glundberg@medscape.net

Methods

This study included 136 patients with idiopathic NS. Those patients were referred to Al-Rasheed Mil Hospital, Baghdad, Iraq -- renal unit -- from November 1991 to June 1994 for diagnosis, evaluation, treatment, and follow-up.

Definitions

NS was diagnosed on clinical ground with proteinuria > 3.5 g/day, serum total protein concentrations g/dL, and serum albumin < 3 g/dL.

Hypertension was defined as blood pressure ≥ 140/90 mm Hg on 2 occasions.

Heavy proteinuria was considered when proteinuria was > 10 g/day during any time in the course of t disease.

Renal impairment was considered when the serum creatinine concentration was > 1.5 mg/dL.

Complete remission was defined as proteinuria < 200 mg/day.

Partial remission was defined as proteinuria < 2 g/day but > 200 mg/day, as defined by others.[4]

Unremitting disease was defined as persistent nephrotic range proteinuria.

Chronic renal failure was defined as a persistent and irreversibly low glomerular filtration rate below mL/minute, regardless of the need for dialysis with a serum creatinine concentration always > 2.5 mg

Steroid responsiveness was defined as complete remission following a course of prednisolone 40-60 initially, according to body weight.

Steroid dependency was defined as 2 or more relapses within a year, when corticosteroid treatment w reduced or discontinued.

Steroid resistance was defined as persistent nephrotic range proteinuria despite 4-6 months of treatme

Only cases of idiopathic NS were included. Patients with clinical, laboratory, or histologic evidence c underlying disease were excluded.

Exclusion Criteria

The exclusion criteria include patients who have been known to be nephrotic, patients who have beer to be hypertensive, patients with diabetes mellitus, patients who are taking drugs that are known to ca patients with positive antinuclear antibodies, hepatitis B surface antigen-positive patients, VDRL-pos patients, patients with clinical features that are suggestive of vasculitis, and patients with sickle cell a

For all patients, percutaneous kidney biopsy was done with a modified Menghini (Sure cut) needle af stabilizing the patient's general condition. Two pieces of kidney tissue were sent to 2 histopathologist

specimen slides were stained with hematoxylin and eosin, periodic acid-Schiff and silver, whereas Co staining was used only if there was a suspicion of amyloidosis. Only light microscopy was used. Immunofluorescence and electron microscopy were not available.

In evaluating the significance of TIL, interstitial inflammation (II), IF, TA, and blood vessel wall thic (BT) in the interstitium were assessed qualitatively; II was defined as any degree of mononuclear cell infiltration, whether focal or diffuse and scored as present or not; IF whether focal or diffuse was also as present or not; TA was reported as positive when seen; and, again, BT in the interstitium was repo positive when seen. Specimens in which no TIL were seen were reported as an intact interstitium.

Glomerular lesions that were taken in comparison with TIL included mesangial expansion of any deg mesangial cell proliferation, whether diffuse or focal; polymorphonuclear leukocytes in the glomerul capillary lumen; epithelial crescents of any number; and global glomerulosclerosis, regardless of the of glomeruli examined and the number of glomeruli sclerosed.

Biopsy specimens, which showed amyloidosis, inadequate tissues, or inconsistent results between the histopathologists, were excluded. The time of biopsy was taken as the date of diagnosis and used as a objective point in the calculation of progress.

For statistical analysis, the chi-square test was used when indicated, and a P value of $< .05$ was consi be significant.

Results

Characteristics of patients at presentation, outcome, and response to treatment as well as TIL and glo lesions are indicated in Tables 1 and 2.

Table 3 shows that patients presenting with hypertension had more II, IF, TA, and BT, and each of th lesions was statistically significant ($P < .05$). Only 2% of hypertensive patients had an intact interstiti patients presenting with heavy proteinuria, the only statistically significant association was with IF a Regarding renal impairment at presentation, there was no statistically significant association with TII of those patients who achieved complete remission had an intact interstitium, whereas only 14.2% ha 4.7% had TA ($P < .05$). Of those with unremitting diseases, only 10.9% had an intact interstitium, wh 78% had II; 61.6% had IF; and 24.6% had TA ($P < .05$). Only 5% of those who progressed to chronic failure had an intact interstitium, whereas 85% had II; 45% had TA; and 35% had BT ($P < .05$). Conc steroid responsiveness or dependence, 37.8% of patients had an intact interstitum; 48.6% had II; 29.7 IF; and 8.1% had TA ($P < .05$). For steroid-resistant patients, 11.8% had an intact interstitium, where 88.1% had II and 71.1% had IF ($P < .05$).

Table 4 shows the correlation between TIL and glomerular lesions. Mesangial expansion was associa II in 80%, IF in 59%, TA in 22.7%, and BT in 14.5% in decreasing frequency. Mesangial cell prolife correlated significantly with II (77.3%), and only 12% had an intact interstitium. None of those with Bowman's capsule and periglomerular fibrosis had an intact interstitum, and the association with TIL significant in both of these glomerular lesions. The association between polymorphonuclear leukocyt glomerular capillary lumen and TIL was not statistically significant except for II in 85.7% of patients of those with epithelial crescents had an intact interstitium, and there was a significant association wi and TA. Global glomerulosclerosis, regardless of the number, was significantly associated with TIL, for BT, and only 5.3% had an intact interstitium.

Table 5 shows the prevalence of hypertension, response to treatment, progression to chronic renal fai the absence of TIL among different types of primary GN in 136 patients presenting with NS.

Discussion

TIL adversely affect the prognosis of various types of GN-like focal segmental glomerulosclerosis, membranoproliferative GN, membranous nephropathy, minimal change nephropathy, and immunogl (Ig)A nephropathy.[1-4, 9-17] These lesions are often observed in various types of chronic progressive The cause of such lesions has not yet been clarified.

It is impossible to conclude which lesions, glomerular or tubulointerstitial, initially occur and lead to decline of renal function. Additional studies are needed to clarify this point.[1,18]

Glomerular lesions rather than interstitial damage may be affected by sample errors because the glom lesions occur individually in which the interstitial damage is zonal in nature.[1]

From our study, a statistically significant correlation existed between TIL and hypertension, response treatment, and outcome in patients with primary GN. Moreover, TIL were clearly associated with glo lesions. These findings seem to suggest that the lesions may be secondary to ischemia, which occurs glomerular damage, and TIL reflect the degree of glomerular obsolescence. In any case, TIL are very important in estimating nephron injuries, especially when a sample of renal tissue obtained by needle contains a limited number of glomeruli.

Although it is known that TIL accompany GN, the body of literature that stresses their importance in evaluating biopsy specimens is rather small. This may be due to the difficulty of assessing the lesion quantitatively. This problem may be partly solved by a computer-assisted image-analysis device that come into use in the field of laboratory medicine.[1]

In conclusion, to assess the prognosis of GN from renal biopsy specimens, TIL are one of the most in indexes. And attention should be focused not only on the glomerular and vascular changes, but also o TIL in examining renal biopsy specimens of patients with primary GN. TIL at the time of biopsy pro only decisive morphologic parameter that can be used to predict whether the disease will follow a fav course, even in the same type of GN. In addition, pathologists, when examining renal biopsy materia give relevant information concerning the prognosis of GN.

Table 1. Characteristics of 136 Patients With Primary Glomerulonephritis

Characteristic	Number (%)
Total	136 (100)
Men	126
Women	10
Age (years) (24.7 ± 6.4)(mean +SD)	(24.7 ± 6.4)
Duration of follow-up (23.8 ± 11.9)(months) (mean ±SD)	(23.8 ± 11.9)
Hypertension	50 (36)
Heavy proteinuria	45 (33)
Renal impairment at presentation	26 (19)

Complete remission	42 (30.8)
Partial remission	21 (15.4)
Unremitting	73 (53.6)
Chronic renal failure	20 (14)
*Death	7 (5)

*(Cause of death: 2 sepsis, 2 pulmonary embolism, 2 end-stage renal disease, and 1 hypokalemia)

Table 2. Tubulointerstitial Lesions and Glomerular Lesions in Biopsy Specimens of 1 Patients With Primary Glomerulonephritis

Characteristic	Number (%)
Interstitial inflammation	94 (69.1)
Interstitial fibrosis	70 (51.4)
Tubular atrophy	26 (l 9.1)
Blood vessel wall thickening	16 (11.7)
Intact interstitium	25 (18.3)
Mesangial expansion	110 (80.8)
Mesangial cell proliferation	75 (55.1)
Fusion to Bowman's capsule	23 (18.9)
Periglomerular fibrosis	33 (24.2)
Polymorphonuclear leukocytes in the glomerular capillary lumen	42 (30.8)
Epithelial crescent	13 (9.5)
Glomerulosclerosis	56 (41.1)

Table 3. Correlation Between Clinical Presentation, Outcome, and Tubulointerstitia Lesions in 136 Patients

Clinical Presentation and Outcome Number	Interstitial Inflammation Number (%)	Interstitial Fibrosis Number (%)	Tubular Atrophy Number (%)	Blood Vessel Wall Thickening Number (%)	Intact Interstitia Number (%)
Hypertension 50	43 (86)*	31 (62)*	15 (30)*	10 (20)*	1 (2)*
Heavy	36 (80)*	29 (64.4)*	11 (24.4)	5 (11.1)**	7 (15.5)**

proteinuria 45			**		
Renal impairment 26	15 (57.6)**	13 (50)**	6 (23)*	3 (11.8)**	0*
Complete remission 42	21 (50)**	6 (14.2)*	2 (4.76)*	5 (11.8)**	14 (33.3)*
Unremitting disease 73	57 (78)*	45 (61.6)*	18 (24.6)*	8 (10.9)**	8 (10.9)*
Chronic renal failure 20	17 (85)*	13 (65)**	9 (45)*	7 (35)*	1 (5)*
Steroid-responsive or -dependent 37	18 (48.6)*	11 (29.7)*	3 (8.1)*	4 (10.8)**	14 (37.8)*
Steroid-resistant 59	52(88.1)*	42(71.1%)*	14 (23.7%) **	5 (8.4%)**	7 (11.8%)*

**Statistically significant (*P *< .05)*
***Statistically not significant (*P *> .05)*

Table 4. Correlation Between Glomerular Lesions and Tubulointerstitial Lesions in Patients With Primary Glomerulonephritis

Glomerular Lesion Number	Interstitial Inflammation Number (%)	Interstitial Fibrosis Number (%)	Tubular Atrophy Number (%)	Blood Vessel Wall Thickening Number (%)	Intact Interstitia Number (%)
Mesangial expansion 110	88 (80)*	65 (59)*	25 (22.7) *	16 (14.5)*	14 (12.7)*
Mesangial cells proliferation 75	58 (77.3)*	41 (54.6)**	16 (21.3) **	9 (12)**	9 (12)*
Fusion to Bowman's capsule 23	21 (91.3)*	18 (78.2)*	8 (34.7)*	6 (27.2)*	0*
Periglomerular fibrosis 33	30 (90.9)*	29 (87.8)*	12 (36.3) *	9 (27.2)*	0*
Polymorphonuclear leukocytes in the glomerular capillary lumen 42	36 (85.7)*	19 (45.2)**	7 (16.6) **	3 (7.1)**	5 (11.9)**
Epithelial crescents 13	13 (100)*	11 (84.6)*	5 (38.4) **	3 (23)**	0*
Glomerulosclerosis 56	46 (82.1)*	33 (58.9)*	15 (26.7) **	12 (21.4)**	3 (5.3)*

***P *< .05*

***P > .05*

Table 5. Prevlance of Hypertension, Response to Treatment, Progression to Chronic Failure, and Intact Interstitium in Different Types of Glomerulonephritis

Type of Glomerulonephritis Number	Hypertension Number (%)	Received Corticosteroid Number (%)	Steroid-Responsive or -Dependant Number (%)	Progression to Chronic Renal Failure Number (%)	Intact Interstitiu number (%)
MCN 27	2 (7)	27 (100)	16 (59.2)	1 (3.7)	19 (70)
FSGS 24	8 (33)	18 (75)	6 (25)	4 (16.6)	1 (4.1)
MSPGN 23	11 (47)	12 (52)	5 (21.7)	3 (13)	1 (4.3)
MN 21	6 (28)	15 (71)	6 (28.5)	0	2 (9.5)
MPGN 19	15 (78)	13 (68)	1 (5.2)	3 (15.7)	1 (5)
FSPGN 12	0	8 (66)	3 (25)	0	1 (8)
GS 5	4 (80)	2 (40)	0	4 (80)	0
RPGN 3	2 (66)	0	0	3 (100)	0
DPGN 2	2 (100)	1 (50)	0	2 (100)	0

MCN = minimal change nephropathy; FSGS = focal segmental glomerulosclerosis; MSPGN = mesangial proliferative glomerulonephritis; MN = membranous nephropathy; MPGN = membranoproliferative glomerulonephritis; FSPGN = focal segmental proliferative glomerulonephritis; GS = glomerulosclerosis; RPGN = rapidly progressive glomerulonephritis; DPGN = diffuse proliferative glomerulonephritis

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