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The type of interstitial inflammatory cell infiltrate and the severity of glomerular injury; an underestimated morphologic correlation

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ABSTRACT

Introduction: The interrelation between the type of interstitial inflammatory cells and the severity of glomerulonephritis was not considered in most of the relevant medical literature.

Objectives: To investigate the relationship between the type of interstitial cell infiltrate and the morphological severity of glomerular injury in different types of proliferative glomerulonephritides.

Patients and Methods: We retrospectively reviewed 138 native kidney biopsies and assessed the relationship between the type of interstitial inflammatory cell infiltrate and the severity of glomerular injury in the form of cellular crescents and fibrinoid necrosis.

Results: The predominant type of interstitial inflammatory cell infiltrate was lymphocytic, noted in more than half of the cases. Lymphoplasmacytic inflammatory cell infiltrate was the second most common type which observed. Fifty-five of patients had inflammation in areas of fibrosis. Cellular/fibrocellular crescents were observed in 44% of cases, and fibrinoid necrosis in 30% of cases. As compared to the 'lymphocytic' group, patients in the 'lymphoplasmacytic' group had ~3 times higher probability of presenting with crescents and fibrinoid necrosis.

Conclusion: Our study highlights the significance of morphological correlations that may predict the severity of glomerular injury. Such findings would be helpful in limited or inadequate renal biopsy samples where the pathologist can alert the clinician, in the appropriate clinical context, to the possibility of having crescents and/or necrotizing lesions in the unsampled glomeruli.

Implication for health policy/practice/research/medical education:

The interrelation between the type of interstitial inflammatory cells and the severity of glomerulonephritis was not considered in most of the relevant medical literature. Our study highlights the significance of morphological correlations that may predict the severity of glomerular injury. Such findings would be helpful in limited or inadequate renal biopsy samples, where the pathologist can alert the clinician, in the appropriate clinical context, for the possibility of unsampled glomeruli with crescents or necrotizing lesions.

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Introduction

The renal interstitium consists of the extravascular intertubular spaces of the parenchyma, with cellular and extracellular elements. The cells in this compartment are comprised of few migrating immune system cells like lymphocytes, macrophages, dendritic cells and resident fibroblasts which render structural support to the kidney, assist in matrix production and turnover, and take part in immune functions. Lymphocytes are rare in the normal kidney; neutrophils and plasma cells are virtually absent (1).

Tubulointerstitial abnormalities such as tubular atrophy, interstitial inflammatory cell infiltrates and interstitial fibrosis are frequently detected in renal biopsies in various forms of progressive glomerulonephritis including infection-related, lupus nephritis, and immunoglobulin A nephropathy (IgAN) (2).

The literature that focuses on the importance of tubulointerstitial abnormalities in renal biopsies is minimal, because these lesions are sometimes not given much consideration in comparison to glomerular and vascular findings (2).

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Objectives

The present study aims to assess the relationship between the predominant type of interstitial inflammatory infiltrate and the morphological severity of glomerular injury in various proliferative glomerulonephritides. This association, if exists, would be of particular importance in cases of inadequate sampling of the renal cortex with a limited number of glomeruli. As renal biopsy is an invasive procedure and a repeat biopsy is not always feasible, such morphologic findings may help to alert the clinician about the possibility of the presence of unsampled active glomerular injury and hence a closer monitoring of the patient's clinical and laboratory parameters.

Patients and Methods

Study design

This is a retrospective study carried out at the department of histopathology, Mubarak Al-Kabeer hospital, Jabriya, Kuwait. A total of 138 native kidney biopsies, with a diagnosis of proliferative glomerulonephritis (including Immune-complex mediated glomerulonephritis, lupus nephritis, IgA nephropathy, pauci-immune glomerulonephritis, and infection-related glomerulonephritis), were randomly collected from our laboratory information system. Cases with minimal change disease, membranous nephropathy, focal segmental glomerulonephritis, and diabetic nephropathy were excluded from the study.

All biopsies were optimally fixed in 10% neutral buffered formalin. Routine paraffin embedding was done; sections of 4 µm thickness were cut, stained with hematoxylin & eosin and periodic acid-Schiff, Jones silver and Masson trichrome stain. An immunohistochemical antibody panel of immunoglobulins and complement (IgG, IgM, IgA, C3c and C1q) and, if needed, κ and λ light chains were performed. Blinded histopathological review of the cases was done independently by two pathologists with experience in nephropathology.

The following histological features were assessed;

- The predominant type of inflammatory cell infiltrate (e.g. lymphocytic, lymphoplasmacytic, or mixed inflammation)
- Severity of tubulointerstitial inflammation (mild < 25%, moderate 26-50%, severe > 50% of the core biopsy)
- Inflammation in areas of fibrosis (Yes/No)
- Presence of cellular or fibro-cellular crescents (Yes/No)
- Percentage of crescents (< 50% or > 50%)
- Fibrinoid necrosis in the glomeruli (Yes/No)
- Presence or absence of tubulitis in non-atrophic/partially atrophic tubules (Yes/No)

The relationship between the type of interstitial inflammatory infiltrate and the morphological severity of

glomerulonephritis was assessed. An attempt was made to correlate the severity of glomerulonephritis with the presence of a particular inflammatory cell type within the interstitium.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study was conducted according to the general guidelines for studies using human material. The use of archival biopsy material was approved by the local ethics committee. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all the patients.

Data analysis

Data were encoded by the researcher in MS Excel. Stata MP version 14 software was used for data processing and analysis. Continuous data (i.e. age) was presented as median and interquartile range. Categorical data were presented as frequencies and percentages, and were analyzed using Fisher's exact test. Logistic regression analysis was performed to determine the association between the predominant cell type of inflammatory infiltrate and presence of crescents. Screening for potential confounders was performed using simple logistic regression analysis and variables with $P < 0.20$ were entered into the model. Model building was then performed using multiple logistic regression analysis, and the researcher applied the change-in-estimate criterion (10%). P values ≤ 0.05 were considered statistically significant.

Results

Study population

A total of 138 patients were included in the study. The patients' ages ranged from 9 to 81 years (median age; 34 years). Among these cases, 75 were female while 63 were male with a male-to-female ratio of 1:1.2. Final diagnosis of majority of the patients was IgA nephropathy (38%) followed by lupus nephritis (36%).

Histomorphological findings

All biopsies included adequate renal cortical tissue. On microscopy, sections examined revealed interstitial mononuclear inflammatory cell infiltrates in 116 biopsies (84%). Twenty-two cases did not show any significant inflammation. Mild tubulointerstitial inflammation was observed in about half of patients, while only 6% had severe inflammation. The predominant type of inflammatory cell in the interstitium was lymphocytic interstitial inflammatory infiltrate, noted in more than half of cases. Lymphoplasmacytic inflammatory infiltrate was the second most common type observed. Moreover, 55% of patients had inflammation in areas of fibrosis (Table 1).

Morphological features of severity of glomerulonephritis included cellular/fibrocellular crescents and fibrinoid necrosis. Out of the 61 patients with cellular/fibrocellular crescents, 10 (16%) patients had more than 50% crescents. Furthermore, the prevalence of cellular/fibrocellular crescents was 44% (95% CI: 36-53%), while that of fibrinoid necrosis was 30% (95% CI: 23-38%).

An attempt was also made to study the relationship between the predominant cell type of inflammatory infiltrate separately with both presence of crescents and fibrinoid necrosis. Out of the initial 138 patients, 22 cases with no inflammation and 5 cases with plasmacytic, mixed, or eosinophilic cell infiltrate were dropped out from the analyses due to low sample size. A significant association was observed between predominant cell type and presence of crescents. As compared to the 'lymphocytic' group, the 'lymphoplasmacytic' group had about 3 times higher odds of presenting with crescents (Table 2). A similar significant association was also noted

in the relationship between the predominant cell type of inflammatory infiltrate and fibrinoid necrosis (Table 3). However, there was no association between the type of inflammatory infiltrate and the percentage of cellular/fibrocellular crescents (Table 4).

A significant association was observed between presence of inflammation in fibrotic areas and tubulitis. As compared to those with no fibrosis, patients with inflammation in fibrotic areas had about seven times higher odds of tubulitis. Additionally, patients with inflammation in both fibrotic and non-fibrotic areas had about 5 times higher odds of tubulitis (Table 5).

A significant association with P value of 0.006 was found between the final diagnosis and severity of tubulointerstitial inflammation using Fisher's exact test (Table 6). Mild tubulointerstitial inflammation was observed in most of patients with IgA nephropathy and lupus nephritis whereas moderate inflammation was noted in most of ANCA-associated glomerulonephritis.

For further analysis, 22 patients without significant inflammation were excluded. The association between final diagnosis with type of inflammatory cell infiltrate in the interstitium was also conducted using Fisher's exact test. A significant association was observed between final

Table 1. Summary of diagnoses and histomorphological findings in all cases (n=138)

Characteristics	No. (%)
Final diagnosis	
IgA nephropathy	52 (38)
Immune complex-mediated GN (NOS)*	14 (10)
Lupus nephritis	50 (36)
ANCA-associated GN	16 (12)
Infection-related GN	4 (3)
Anti-GBM disease	2 (1)
Interstitial inflammatory infiltrate	
Lymphocytic	76 (55)
Lymphoplasmacytic	35 (25)
Plasmacytic	2 (1)
Mixed (ie. neutrophilic/lymphocytic)	2 (1)
Eosinophilic	1 (1)
Not applicable(no significant inflammation)	22 (16)
Severity of tubulointerstitial inflammation	
No inflammation	22 (16)
Mild	65 (47)
Moderate	43 (31)
Severe	8 (6)
Inflammation in area of fibrosis	
No fibrosis	48 (35)
Yes, in fibrotic area	76 (55)
Yes, both in fibrotic and non-fibrotic areas	14 (10)

Abbreviations: ANCA, Antineutrophil cytoplasmic autoantibody; GN, glomerulonephritis; GBM, glomerular basement membrane; NOS, not otherwise specified.

* A specific diagnosis was not reached in this group, even after clinicopathological correlation.

Table 2. Relationship between type of interstitial inflammatory infiltrate and presence of cellular/fibrocellular crescents (n=111)

Predominant cell type	Crude OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Lymphocytic	Ref	Ref	Ref	Ref
Lymphoplasmacytic	2.59 (1.14-5.92)	0.024	3.15 (1.29-7.72)	0.012

*Adjusted for the confound effects of inflammation in areas of fibrosis. The plasmacytic, eosinophilic and mixed inflammatory cell type groups were not included due to their small sample size.

Table 3. Association between the predominant type of cell and fibrinoid necrosis (n=111)

Variables	Crude OR (95% CI)	P value
Lymphocytic	Ref	Ref
Lymphoplasmacytic	2.92 (1.24-6.88)	0.014

Table 4. Association between predominant type of cell and percentage of cellular crescents (n=52)

Variables	Crude OR (95% CI)	P value
Lymphocytic	Ref	Ref
Lymphoplasmacytic	1.1 (0.26-4.73)	0.887

Table 5. Association between presence of inflammation in fibrotic areas and tubulitis (n=138)

Variables	Crude OR (95% CI)	P value
Inflammation in area of fibrosis		
No fibrosis	Ref	Ref
Yes, in fibrotic area	6.64 (2.53-17.46)	<0.0001*
Yes, both in fibrotic and non-fibrotic areas	5.25 (1.35-20.47)	0.017*

diagnosis and type of inflammatory cell with lymphocytic cell type being noted in majority of the diagnoses (Table 7).

Discussion

Despite the remarkable advances in clinical medicine diagnostic modalities, renal biopsy remains the gold standard for the management and prognosis of patients with glomerulonephritides. Interstitial inflammation, whether in non-scarred or scarred areas, is frequently manifested in most types of active glomerulonephritis. The inflammatory cell population can be predominantly single cell type or mixed type. Herein, we demonstrate that the predominant cell type of inflammatory infiltrate is significantly associated with the presence of severe glomerular injury in various types of proliferative glomerulonephritis. We defined the severely injured glomeruli as those having cellular/fibrocellular crescents and/or necrotizing lesions. Our renal biopsy analysis

revealed that, as compared to the 'lymphocytic' group, the 'lymphoplasmacytic' group has about three times higher probability of presenting with crescents. Likewise, a significant association was observed between predominant cell type and fibrinoid necrosis. We found that as compared to the 'lymphocytic' group, the 'lymphoplasmacytic' group has about three times higher probability of having fibrinoid necrosis.

We also studied the association between the interstitial inflammatory cell type and the extent of cellular/fibrocellular crescent formation. However, we could not demonstrate any sufficient evidence to say that an association exists between the predominant cell type and extent or percentage of crescents formation.

Other relevant morphologic correlations

Inflammation within the scarred interstitium is classically considered as 'non-specific'. Nevertheless interestingly, in our cohort, we could demonstrate that as compared to those with no fibrosis, cases with inflammation in fibrotic areas have about 7 times higher odds of tubulitis in non-atrophic or partially atrophic tubules. A finding considered as a feature of ongoing, active tubulointerstitial inflammatory damage.

Comparison with results from other studies

In our study, we investigated the morphologic association between the predominant interstitial inflammatory cell infiltrate and the severity of glomerular injury. Other similar studies correlated the morphologic findings and

Table 6. Association between final diagnosis and severity of tubulointerstitial inflammation (n=138)

Diagnoses	No inflammation No. (%)	Mild No. (%)	Moderate No. (%)	Severe No. (%)	P value
IgA nephropathy	5 (10)	25 (48)	18 (35)	4 (8)	0.006
Immunecomplex-mediated GN (NOS)	4 (29)	4 (29)	6 (43)	0 (0)	0.006
Lupus nephritis, class III or IV (ISN/RPS)	13 (26)	25 (50)	11 (22)	1 (2)	0.006
ANCA-associated GN	0 (0)	5 (31)	8 (50)	3 (19)	0.006
Others	1 (14)	6 (86)	0 (0)	0 (0)	

Abbreviations: ANCA, Antineutrophil cytoplasmic autoantibody; GN, glomerulonephritis; ISN/RPS, International Society of Nephrology/Renal Pathology Society;

Table 7. Association between final diagnosis and type of inflammatory cell (n=116)

	Lymphocytic No. (%)	Lymphoplasmacytic No. (%)	Others No. (%)	P value
IgA nephropathy	33 (70)	14 (30)	0 (0)	0.004
Immunecomplex-mediated GN	7 (70)	3 (30)	0 (0)	0.004
Lupus nephritis	27 (73)	10 (27)	0 (0)	0.004
ANCA-associated GN	8 (50)	5 (31)	3 (19)	0.004
Others	1 (17)	3 (50)	2 (33)	

Abbreviations: ANCA, Antineutrophil cytoplasmic autoantibody; GN, glomerulonephritis.

the progression of the renal disease. These studies primarily focused on IgA nephropathy and lupus nephritis.

Myllymäki et al studied 204 IgAN cases and investigated the severity of tubulointerstitial inflammation and prognosis in IgA nephropathy. They concluded that in addition to the known histologic factors, inflammation predicts a poor course of renal disease in IgAN (3). Rankin et al found a significant association between active tubulointerstitial nephritis and renal outcome in patients with IgAN, independently of established histological features and baseline clinical characteristics (4). Furthermore, Hsieh et al found that lupus nephritis patients are at a higher risk for progression to renal failure when associated with tubulointerstitial inflammation (5). A similar study conducted by Alexopoulos et al found that the degree of renal impairment at the time of biopsy was strongly correlated with the density of interstitial infiltration by T cells, monocytes/macrophages and HLA-DR expressing interstitial cells. T cells and monocytes/macrophages may play an important role in the pathogenesis of chronic tubulointerstitial lesions in lupus nephritis (6). Moreover, a study by Freese et al found that cellular infiltrates in the interstitium signified shorter progression (7).

Conclusion

Our study is a single-center study and therefore it is possible that some specific genetic or local environmental factors contributed to our observations. Furthermore, our cohort showed a scarcity of other inflammatory cell types in particular eosinophils. This could be attributed to the limited role of these cells in the pathogenesis of proliferative glomerulonephritis or other unknown local factors within our cohort. Of note, prominent interstitial eosinophils are most often associated with allergic-type acute interstitial nephritis. Other conditions with prominent interstitial eosinophils including diabetic nephropathy, tubulointerstitial nephritis with uveitis, eosinophilic polyangiitis (Churg-Strauss syndrome) and parasitic infections (10). Most of the aforementioned are already eliminated from our study.

In addition, the retrospective nature of our study, could pose other limitations. Therefore, a multicenter study will be needed. Nevertheless, our study highlights the significance of morphological correlations that may predict the severity of glomerular injury. Such findings would be helpful in limited or inadequate renal biopsy samples, where the pathologist can alert the clinician, in the appropriate clinical context, for the possibility of unsampled glomeruli with crescents or necrotizing lesions.

Limitations of the study

The main limitation of our study is that, it is a single

center study. In addition, our cohort showed a scarcity of some inflammatory cell types in particular eosinophils. This could be attributed to the limited role of these cells in the pathogenesis of proliferative glomerulonephritis or other unknown local factors within our cohort. We therefore suggest to further investigate the relationship between this type of interstitial cell infiltrate and the morphological severity of glomerular injury in larger multi-centric studies.

Authors' contribution

AT and SR were the principal investigators of the study. AT and SR were included in preparing the concept and design. AT and SR revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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