Association of Renal CD68+ Cell Infiltration with Oxford Classification in IgA Nephropathy

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Introduction. IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. The Oxford classification (MEST-C) a standardized histopathological scoring system evaluating mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), interstitial fibrosis/tubular atrophy (T), and cellular or fibrocellular crescents (C), provides a histopathological framework to predict disease progression. However, the role of immune cell infiltration—particularly CD68+ macrophages—in these pathological features remains underexplored.
Objective. To investigate the association between renal CD68+ macrophage infiltration and the Oxford classification parameters in patients with IgA nephropathy.
Methods. This study included 146 patients with biopsy-proven IgAN at Hasheminejad Kidney Center between 2013 and 2020. Immunohistochemical staining for CD68 was performed on paraffin-embedded kidney biopsy sections. CD68+ macrophages were quantified separately in the glomerular and interstitial compartments. Finally, the associations between macrophage counts and Oxford classification components (M, E, S, T, C) were analyzed.
Results. Glomerular CD68+ cell counts were significantly higher in samples with M1, E1, T1, and C1 lesions ($P < .05$). Interstitial CD68+ cells were significantly elevated in T1 lesions (mean: 10.6 vs. 4.7 in T0; $P < .001$). Receiver operating characteristic (ROC) analysis demonstrated high diagnostic accuracy for interstitial CD68+ cells in predicting T1 (AUC = 0.98) and for glomerular $CD68^+$ macrophage in predicting E1 (AUC = 0.88).
Conclusion. CD68+ macrophage infiltration is closely associated with active and chronic lesions in IgAN, particularly endocapillary hypercellularity and tubular atrophy. Quantification of CD68+ macrophage may serve as a valuable histological marker for assessing disease activity and guiding prognosis in IgAN.

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INTRODUCTION

IgA nephropathy (IgAN) is the most common type of glomerulonephritis worldwide, characterized by the deposition of IgA-dominant immune complexes in the glomeruli. The Oxford classification provides a standardized, evidence-based histopathological scoring system (MEST-C) to predict prognosis and guide treatment decisions in IgAN.[1-3] This classification is based on the MEST-C scoring system, which includes mesangial hypercellularity

(M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and cellular/fibrocellular crescents (C).[4,5]

Since its introduction in 2009, the Oxford classification has undergone multiple validation studies. Overall, these studies have demonstrated that the presence of M, E, S, and T lesions independently predicts decreased glomerular filtration rate (GFR) and poorer renal survival.[6-9] Moreover, patients with S1, T1, or T2 lesions tend to respond less favorably to immunosuppressive therapy.[10]

Among immune cells, macrophages, particularly those expressing the CD68 marker, play a key role in initiating and amplifying renal inflammatory responses. Increased infiltration of renal CD68+ macrophages has been associated with poor prognosis and rapid disease progression in patients with IgAN.[11] Silva *et al.* reported that higher intrarenal macrophage density is a negative prognostic marker in these patients.[12]

Patients with IgAN exhibit elevated oxidative stress and increased interstitial infiltration of CD68+ macrophages, which correlate with progressive renal fibrosis and declining renal function.[13] Several studies have highlighted the role of macrophages in the pathogenesis of IgAN. Infiltration of CD68+ macrophages in both glomeruli and interstitial compartments is associated with more severe inflammation and tissue damage. These macrophages contribute to glomerular injury and fibrogenesis by releasing proinflammatory cytokines.[14]

Furthermore, macrophage infiltration has been correlated with specific pathological features in IgAN. For instance, glomerular CD68+ macrophages are associated with mesangial hypercellularity (M) and crescent formation (C), while interstitial CD68+ macrophages correlate with tubular atrophy and interstitial fibrosis, both of which are independent predictors of long-term decline in GFR.[14]

Despite advances in the diagnosis of IgAN, identifying accurate prognostic markers remains a clinical challenge.[15] This study aims to evaluate the association between renal CD68+ Macrophage infiltration and Oxford classification scores in patients with IgAN to improve risk stratification, inform targeted therapeutic strategies, prevent rapid disease progression, and reduce the risk of renal failure

MATERIALS AND METHODS

The study population consisted of patients who underwent kidney biopsy and diagnosed with IgAN at Hasheminejad Kidney Center between 2013 and 2020.

The inclusion criteria consisted of a biopsy-confirmed diagnosis of IgA nephropathy, availability of histopathological slides along with complete pathological data, and kidney biopsy samples containing a minimum of eight glomeruli. Exclusion criteria were cases with a T2 score in the Oxford classification (indicating tubular atrophy affecting more than 50% of the cortical area) and the presence of extensive subcortical sclerosis. Patients with T2 lesions were excluded because extensive tubular atrophy and interstitial fibrosis represent advanced, irreversible chronic damage, which may obscure the relationship between inflammatory cell infiltration and histopathological activity.

Formalin-fixed paraffin-embedded (FFPE) kidney biopsy blocks from patients with biopsy-proven IgAN, meeting the study's inclusion and exclusion criteria, were selected. Sections were prepared using a microtome, and immunohistochemical (IHC) staining was performed to detect the CD68 marker.

CD68+ cells were defined as cells with distinct cytoplasmic brown granules, with or without visible nuclei, and clearly outlined borders. CD68+ cells were counted separately in both the glomerular and interstitial compartments. For interstitial macrophages, the average number of CD68+ cells was calculated across 10 high-power fields (HPFs). Glomerular CD68+ cell density was calculated by dividing the total number of CD68+ cells in all glomeruli of each sample by the total number of non-sclerotic glomeruli. Sclerotic glomeruli were excluded from the analysis.

Two pathologists independently performed all cell counts in a double-masked manner. In cases of discrepant interpretation, the slides were jointly reviewed and a consensus diagnosis was reached. The correlation between CD68+ cell counts in glomerular and interstitial areas and the Oxford MEST-C scores was statistically analyzed. Oxford classification parameters were recorded for each biopsy specimen based on the updated MEST-C criteria.[4,5]

Analysis

Continuous variables were assessed for normality

using the Shapiro–Wilk test. Depending on data distribution, comparisons were performed using the independent-samples t-test or one-way ANOVA for normally distributed variables, and the Mann–Whitney U test or Kruskal–Wallis test for non-normally distributed variables.

For categorical comparisons, the chi-square test was utilized when the assumptions of the test were satisfied; otherwise, Fisher's exact test was employed. Additionally, a log-link function was used to evaluate the risk associated with increasing CD68+ cell counts with higher pathological scores in the Oxford classification.

To assess diagnostic accuracy and determine the discriminatory power of CD68+ cell counts, receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC) was calculated. All analyses were conducted using SPSS version 26.0, with a *P*-value of less than .05 considered statistically significant.

RESULTS

A total of 168 patients with biopsy-confirmed IgA nephropathy, diagnosed between 2013 and 2020 at Hasheminejad Kidney Center, were initially identified based on pathological criteria. Among these, eight cases were excluded due to incomplete pathology data or the unavailability of paraffin blocks, seven cases because of an insufficient glomerular count (fewer than eight glomeruli), and two cases due to extensive tubular atrophy affecting more than 50% of the cortical area (Oxford score T2). Additionally, five samples were excluded following sectioning and immunohistochemical staining due to having fewer than eight glomeruli remaining on the final slides.

Ultimately, 146 kidney biopsy samples met the inclusion criteria and were included in the final analysis. Among the 146 patients with IgA nephropathy included in the study, 46 (32%) were male and 100 (68%) were female. The mean age of the participants was 38 ± 11 years.

A total of 42 biopsies (29%) exhibited M1, 56 biopsies (38%) presented E1, 102 biopsies (70%) demonstrated S1, and 39 biopsies (27%) indicated T1. Cellular or fibrocellular crescents were identified in 82 biopsies (56%); among these, 70 cases (48%) showed crescents in less than 25% of the glomeruli (C1), while 12 cases (8%) had crescents in 25% or more of the glomeruli (C2).

The mean number of interstitial CD68+ cells was 6.3 ± 3.1 cells per high-power field (HPF), and the mean number of glomerular CD68+ cells was 4.3 ± 2.1 per glomerulus.

Association Between Interstitial CD68+ Macrophages and Oxford Classification

The distribution of interstitial and glomerular CD68+ cell counts across the presence or absence of each Oxford classification parameter is presented in Table 1. A statistically significant difference was observed in the mean interstitial CD68+ cell

Table 1. Interstitial and Glomerular CD68$^+$ Cell Counts Across Oxford variables

Oxford	Interstitial CD68+ cell count		*P*	Glomerular CD68+ cell count		*P*
	Mean ± SD	Median (IQR)		Mean ± SD	Median (IQR)	
Mesangial hypercellularity (M)						
M0	6.3 ± 3.3	5 (4, 7)	.797	3.9 ± 2.0	3 (2, 6)	< .001
M1	6.3 ± 2.8	5 (5, 7)		5.3 ± 2.0	5 (4, 7)	
Endocapillary hypercellularity (E)						
E0	6.3 ± 3.4	5 (4, 7)	.690	3.2 ± 1.5	3 (2, 4)	< .001
E1	6.3 ± 2.7	5 (4, 7)		6.0 ± 1.7	6 (5, 7)	
Segmental glomerulosclerosis (S)						
S0	7.1 ± 4.2	6 (4, 12)	.223	4.0 ± 2.4	4 (2, 6)	.128
S1	5.9 ± 2.5	5 (4, 6)		4.5 ± 1.9	4 (3, 6)	
Tubular atrophy/interstitial fibrosis (T)						
T0	4.7 ± 1.3	5 (4, 5)	< .001	4.0 ± 2.0	4 (2, 6)	.003
T1	10.6 ± 2.6	11 (9, 13)		5.2 ± 2.0	5 (3, 7)	
Cellular/ fibrocellular crescents (C)						
C0	6.0 ± 2.8	5 (4, 7)	.427	3.4 ± 1.6	3 (2, 4)	< .001
C1	6.7 ± 3.4	5 (4, 8)		5.2 ± 2.0	5 (4, 7)	
C2	5.4 ± 3.2	5 (3, 7)		4.0 ± 3.0	3 (1, 7)	

count between the T0 and T1 groups. Patients with T1 exhibited a markedly higher mean interstitial CD68+ cell count (10.6) compared to those with T0 (4.7) ($P < .05$). No significant association was found between interstitial CD68+ cell infiltration and the M (mesangial hypercellularity), E (endocapillary hypercellularity), S (segmental sclerosis), or C (crescents) components of the Oxford classification.

A statistically significant difference in the mean glomerular CD68+ cell count was observed across the subgroups of the Oxford classification components M, E, T, and C ($P < .05$). The glomerular CD68+ cell count was higher in samples with M1, E1, T1, and C1 compared to their corresponding M0, E0, T0, and C0 groups. No difference in glomerular CD68+ cell counts was observed between S0 and S1 subgroups.

Diagnostic Performance of Interstitial and Glomerular CD68+ Cell Counts Based on ROC Analysis

Table 2 presents the diagnostic accuracy of interstitial and glomerular CD68+ cell counts for predicting Oxford classification lesions using cut-off values derived from ROC curve analysis. For each lesion type, the optimal threshold, sensitivity, specificity, and area under the curve (AUC) were reported (Table 2).

The ROC curve for interstitial CD68+ cell count identified a cut-off value of > 5 cells/high power field for distinguishing T1 lesions from T0, with a sensitivity of 97%, specificity of 77%, and an AUC of 0.98. Additionally, with a cut-off value of more than 6 cells per high power field, the sensitivity and specificity were 92% and 94%, respectively (Figure 1).

For glomerular CD68+ Macrophages, a threshold of > 4 cells per glomerulus was optimal for predicting E1 lesions (vs. E0), with a sensitivity of 86%, specificity of 80%, and an AUC of 0.88 (Figure 2).

Lesions M (M1 vs. M0) and C (C1 + C2 vs. C0) showed moderate diagnostic performance, where glomerular CD68+ cell counts had slightly higher accuracy than interstitial counts. As a lower interstitial CD68+ cell count was observed in S1 lesions compared to S0, fewer interstitial CD68+ Macrophages were considered a potential predictor for the presence of S1 lesions. Finally, both interstitial and glomerular CD68+ counts showed poor diagnostic value for S lesions.

Table 2. Diagnostic Accuracy of Interstitial and Glomerular CD68+ Cell Counts for Oxford Classification Lesions

Oxford	Interstitial CD68+ cell count					Glomerular CD68+ cell count				
	cut-off	sensitivity	Specificity	area under the curve	95% Confidence Interval	cut-off	sensitivity	specificity	area under the curve	95% Confidence Interval
Mesangial hypercellularity (M)	4.5	76	34	0.51	0.42 – 0.61	4.5	64	64	0.69	0.60 – 0.78
Endocapillary hypercellularity (E)	4.5	73	33	0.52	0.43 – 0.61	4.5	86	81	0.88	0.82 – 0.94
Segmental glomerulosclerosis (S)	4.5	68	30	0.56	0.44 – 0.68	3.5	60	48	0.58	0.47 – 0.68
Tubular atrophy/interstitial fibrosis (T)	5.5	97	77	0.98	0.95 – 1.0	3.5	69	47	0.66	0.56 – 0.75
Cellular/ fibrocellular crescents (C)	4.5	72	34	0.52	0.43 – 0.62	3.5	72	61	0.72	0.64 – 0.80

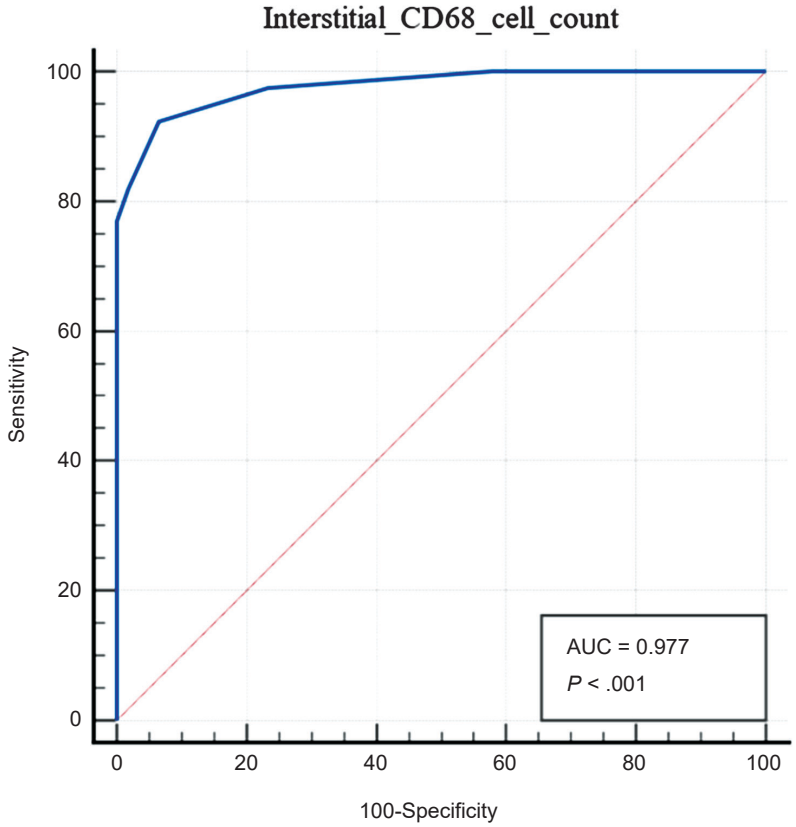

Figure 1. ROC Curve for Interstitial CD68⁺ Cell Count in Predicting Tubular Atrophy (T1).

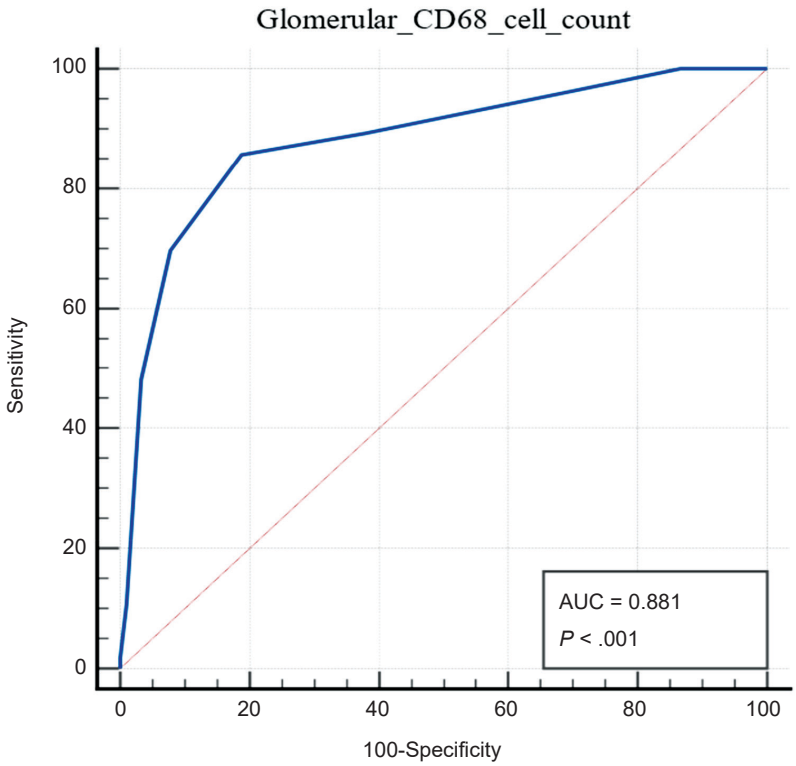

Figure 2. ROC Curve for Glomerular CD68⁺ Cell Count in Predicting Endocapillary Hypercellularity (E1).

DISCUSSION

This study investigated the relationship between CD68+ macrophage infiltration in renal tissue and the Oxford classification parameters in patients with IgA nephropathy (IgAN). Our results demonstrated a significant association between increased CD68+ cell infiltration—both glomerular and interstitial—and specific histopathological lesions.

Notably, glomerular CD68+ cell counts were significantly elevated in cases with mesangial hypercellularity (M), endocapillary hypercellularity (E), tubular atrophy/interstitial fibrosis (T), and crescent formation (C). In contrast, interstitial CD68+ cells were significantly associated with T lesions, with an extreme difference observed between T0 and T1 lesions.

We observed a significant association between glomerular CD68+ macrophages and endocapillary hypercellularity (E) (P = .00), as well as a strong correlation between interstitial CD68+ macrophages and tubular atrophy (T) (P = .001).

Interestingly, our study found no significant association between CD68+ cell counts and segmental glomerulosclerosis (S). This may reflect the chronic, sclerotic nature of S lesions, which develop after the resolution of active inflammation and may no longer contain high levels of infiltrating immune cells.[16] This interpretation aligns with the understanding that segmental sclerosis reflects a scarring process rather than an ongoing immune response.[14] The absence of a significant association between CD68+ cell counts and S lesions may be explained by the fact that segmental sclerosis represents a late, largely irreversible stage of glomerular injury characterized by fibrotic replacement rather than active inflammation.[1,16] In contrast, other chronic lesions such as tubular atrophy/interstitial fibrosis (T) reflect ongoing tissue remodeling and progressive damage, which may still be influenced by inflammatory cell infiltration. The stronger association observed between CD68+ macrophages and T and C lesions supports the concept that macrophage accumulation is more closely related to active or progressive injury than to established glomerular scarring.[12,18]

These findings are consistent with prior research. Agrawal *et al.* found significantly higher glomerular CD68+ cell counts in patients with E1 lesions, supporting our observation of a strong correlation between glomerular macrophage infiltration and endocapillary hypercellularity.[17] Similarly, Soares *et al.* reported a strong correlation between glomerular CD68+ cells and E lesions and a moderate association with crescents but no significant correlation with M or S lesions—paralleling some aspects of our results.[18]

Caliskan *et al.* also reported a relationship between glomerular CD68$^+$ Macrophages and M and C lesions and linked interstitial CD68+ infiltration to tubular atrophy, interstitial fibrosis, and proteinuria. This aligns with our observation of a strong association between interstitial macrophages and T lesions, suggesting that macrophage accumulation in the interstitial space may drive fibrosis and irreversible tubular damage.[13]

From a pathophysiological perspective, macrophages play a key role in promoting and amplifying inflammation in glomeruli. CD68+ macrophages contribute to glomerular injury by secreting proinflammatory cytokines such as TNF-α and IL-6, which stimulate mesangial proliferation and contribute to M lesions.[12,17] In the interstitium, these cells promote fibrosis via TGF-β signaling, which is known to drive tubular atrophy and interstitial fibrosis—a key mechanism observed in chronic kidney disease progression.[14,19]

The current study concentrated on patients with IgA nephropathy, but examining data from other glomerulopathies may enhance our understanding of the role of CD68+ macrophages. For example, Bos *et al.* identified glomerular CD68+ macrophages as reliable markers of endocapillary hypercellularity in lupus nephritis, with a cut-off of seven cells per glomerulus providing high sensitivity and specificity for E1 lesions.[20] Our ROC analysis similarly identified a cut-off of > 4 glomerular CD68+ cells as optimal for predicting E1 in IgAN, highlighting the potential generalizability of CD68+ cell quantification as a pathological tool.

Importantly, this study also highlights the potential prognostic value of CD68+ macrophage infiltration. Given its association with key histological lesions that are linked to disease progression, CD68+ cell quantification could enhance early risk stratification and may even help predict responses to immunosuppressive therapy. Furthermore, the strong diagnostic performance observed in ROC analysis—particularly for T and E lesions—suggests that, by supporting future validation studies, macrophage counts may be

integrated into pathological evaluations.

Future research should explore the longitudinal prognostic implications of CD68+ cell infiltration, assess its responsiveness to therapy, and evaluate whether targeting macrophage-mediated pathways (e.g., IL-6, TGF-β) could offer novel therapeutic strategies in IgAN.

Limitations

This study has several limitations that should be considered when interpreting the results. First, the retrospective, single-center design may limit the generalizability of our findings to other populations or clinical settings. Second, we excluded patients with advanced tubular atrophy (T2 lesions) and those with extensive subcortical sclerosis, which may have reduced the spectrum of disease severity analyzed and potentially underestimated the association between CD68+ infiltration and end-stage histopathological changes. Exclusion of cases with T2 lesions may have resulted in selection bias toward less advanced disease and may limit the generalizability of the findings to patients with severe chronic kidney damage. Third, although two independent pathologists performed immunohistochemical evaluation and cell counting in a blinded manner with consensus review in discrepant cases, formal statistical assessment of inter-observer agreement (e.g., Intraclass Correlation Coefficient (ICC) or Cohen's kappa) was not conducted, which may limit evaluation of reproducibility. Fourth, the cross-sectional nature of our study precludes assessment of the temporal relationship between macrophage infiltration and disease progression. Future prospective, multi-center studies with longitudinal follow-up are warranted to validate the prognostic utility of CD68+ macrophage quantification and to explore its dynamic changes in response to therapy.

CONCLUSION

This study highlights a significant association between CD68+ macrophage infiltration in renal tissue and key histopathological features of the Oxford classification in IgA nephropathy. Elevated glomerular CD68+ cell counts were associated with active glomerular lesions, including mesangial and endocapillary hypercellularity, while interstitial CD68+ infiltration was linked to tubular atrophy and fibrosis. These findings suggest that CD68+ macrophage counts reflect both inflammatory activity and chronic injury and may represent a potential biomarker for assessing disease severity, though validation in longitudinal and multi-center cohorts is warranted.

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