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Apoptosis in lupus nephritis patients: a study of Bcl-2 to assess glomerular and tubular damage

Hossam Salaheldin Labib¹ , Manal Ibrahim Salman² , Mariam Ibrahim Halim³ and Shereen Ismail Fawaz^{1*}

Abstract

Background Systemic lupus erythematosus (SLE) is an immune-mediated disease, due to exposure of self-antigens, through impairment of apoptosis and failure of lymphocytic tolerance. Impaired regulation of the pro- and anti-apoptotic gene products which coordinate programmed cell death may result in autoreactive B and T cells and autoimmunity. Genetically engineered mice that over-express the anti-apoptotic molecule Bcl-2, B cell lymphoma 2 (Bcl2) in B-lymphocytes advance a lupus-like illness. Lupus nephritis (LN) is one of the most serious manifestations of this autoimmune disorder. Glomerulonephritis (GN) is caused by either impaired regulation of apoptosis and/or clearance of apoptotic cells leading to a T cell-mediated autoimmune reaction with initiation of pathological immune complex deposits.

Objective To evaluate the correlation between Bcl2 glomerular and tubular expression and pathological findings and laboratory data in different types of SLE GN.

Results Compared to the control group, patients with lupus nephritis have significantly higher glomerular, interstitial and tubular expression level (P value < 0.001). BCL2 expression was positively correlated with serum anti-ds-DNA, urine 24-h protein and with the chronicity index. All LN patients had significant glomerular, interstitial and tubular deposits of BCL2, P value < 0.001 , P value 0.004, and P value 0.03, respectively.

Conclusion The intrinsic pathway of apoptosis interferes not only with the pathogenesis of lupus glomerulonephritis but also interferes with the pathogenesis of tubulointerstitial lupus nephritis. tubulointerstitial lesions may not only be a result of glomerular injury but also a significant factor in lupus nephritis.

Keywords Lupus nephritis, Apoptosis, Serum Bcl-2, Glomerulonephritis, Tubulo-interstitial inflammation

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Background

Systemic lupus erythematosus (SLE) is a prototype of immune-mediated disorders. The suggested pathological mechanism is due to exposure of self-antigens secondary to failure of apoptosis and lymphocytic tolerance, with resultant pathogenic autoreactive cell populations [1]. Impaired regulation of the pro- and anti-apoptotic gene products which coordinate programmed cell death could lead to autoreactive B and T cells and autoimmunity [2]. Genetically engineered mice that over-express the anti-apoptotic molecule Bcl-2 (B cell lymphoma 2) in B-lymphocytes advance a lupus like illness [3, 4].

Lupus nephritis (LN) is considered one of the main manifestations of this autoimmune disorder. Lupus nephritis is linked to intraglomerular cell apoptosis, which results in the exposure of nucleosomal contents, which serves as an activator for autoantibodies formation. Glomerulonephritis is caused by either impaired apoptosis or defective clearance of apoptotic bodies which causes nucleosome exposure, activation of antigen-presenting cells, and T cell-mediated reaction with the initiation of pathological immune complexes with subsequent complement fixation, activation, perpetuated inflammation and cellular activation [5].

Secondary SLE tubulo-interstitial nephritis (TIN) may be masked by GN, however it has major pathogenetic impact on renal outcome. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) does not include SLE TIN in its schema of renal lupus classification and management. The pathogenesis of secondary SLE TIN was considered as a sequela of GN, or non-immunologic, i.e., a nonspecific injury in the tubular and interstitial tissue following advanced glomerular injuries, disregarding the main etiology [6]. Despite the frequency of TIN, its possible clinical value, and imperative pathogenesis, research on this subject is quite scarce, in contrast to the extensive studies on lupus GN. Hence, we proposed that tubulointerstitial pathology may not only be a consequence of glomerular injury, but also an important influencer in lupus nephritis. The present study aims to evaluate the correlation between Bcl 2 glomerular and tubular expression, pathological findings and laboratory data in different types of SLE GN.

Patients and methods

This study included 30 patients with SLE renal involvement fulfilling the criteria of The Systemic Lupus International Collaborating Clinics (SLICC) group [7]. A thorough clinical assessment was done with lab assessment of anti-ds-DNA titre and was measured by enzyme linked immune sorbent assay (ELISA). Other lab investigations; CRP, CBC, serum creatinine, BUN, serum C3,

and C4, urine examination, and 24-h urinary protein. Renal biopsy specimens were obtained from all patients. A control group of 30 normal renal biopsies was attained from normal renal tissue in proximity to neoplasms from nephrectomy samples. We excluded patients who have age of less than 18 years and patients with antiphospholipid syndrome. All patients with infections and/or malignancies. The Histopathology classification of lupus nephritis, including activity and chronicity indices according to ISN/RPS 2003 Classification of lupus nephritis [8]. All included patients signed informed consent for their participation in this study. The study was approved by the local ethics committee, numbered (FMASU R 74a \ 2022) and a written informed consent was taken from each participant.

Tissue specimens

Immunohistochemical staining was performed to all the patients by mice monoclonal antibodies for BCL2 (clone 124, Bcl-2; Dako Corporation, CA, USA) using avidin-biotin immune peroxidase technique. Peroxidase blocking solutions were applied for 15 min on tissue specimens from formalin-fixed paraffin-embedded specimens for blocking endogenous peroxidases. The specimens were then embedded in citrate buffer and put for 9 min in a microwave at 80 °C, for antigen collection. After cooling, incubation of the slides overnight with the diluted primary antibodies (1:25) was done. Then, diaminobenzidine (DAB) chromogen solution was added and counter-staining was done with Mayer's hematoxylin. Positive and negative control was included in each run.

The immunohistochemical evaluation for each case was done by examination of the section to localize and detect the distribution of staining. The scoring system was applied as follows: 1+ mild intensity/ focal or diffuse distribution. 2+ moderate intensity/focal or diffuse distribution. 3+ marked intensity/ focal or diffuse distribution.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data were tested for normality using the Shapiro-Wilk test, then described as mean \pm SD (standard deviation) as well as minimum and maximum of the range, and then compared using an independent *t* test. Qualitative data are described as numbers and percentages and compared using Fisher's exact test. Correlations of the studied markers' grades were done using Spearman's test. The level of significance was taken at *p* value ≤ 0.05 was significant, otherwise was non-significant.

Table 1 A summary of the Laboratory results of all patients

Variables	Mean ± SD	Range
Urine 24-h protein (mg/day)	2112.0 ± 1429.9	204.0–5600.0
Serum creatinine (mg/dL)	4.1 ± 3.2	0.8–10.7
Serum C3 (mg/dL)	66.1 ± 34.8	20.0–155.0
Serum C4 (mg/dL)	16.5 ± 8.7	8.0–36.0
Serum anti-dsDNA (IU/L)	91.3 ± 44.8	20.0–210.0

Table 2 A summary of the activity and chronicity indices and the number of the different classes of LN

Activity index	7.6 ± 4.8	3.0–14.0
Chronicity index	5.5 ± 3.5	2.0–11.0
	<i>n</i>	%
LN class		
II	4	13.3
III	7	23.3
IV	14	46.7
V	3	10.0
VI	2	6.7

Results

Regarding the demographic data of all our cases, the patient's group had a mean age of 26.4 ± 8.8 years with 28 females and 2 males. F:M ratio was 14:1. While the control group had a mean age of 28.1 ± 6.1 years. There was no significant difference between the patients and the control group as regards age and sex. A summary of the Laboratory results of our patients showed: Table 1.

The pathology samples of our patients showed: according to (ISN/RPS) 2003 Classification of Lupus Nephritis, there were 4 patients (13.3%) with stage II (mesangial proliferative LN), 7 patients (23.3%) with class III (Focal LN), 14 patients (46.7%) with class IV (diffuse LN), 3 patients (10.0%) with class V (membranous LN), and 2 patients (6.7%) with class VI (advanced sclerosing LN). the mean ± SD of the activity index was (7.6 ± 4.8) while the chronicity index was (5.5 ± 3.5) (Table 2).

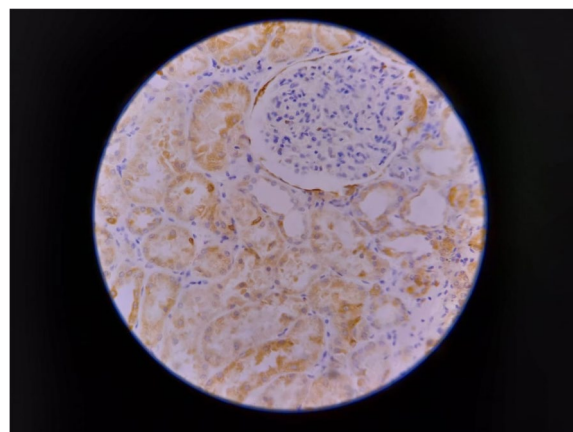
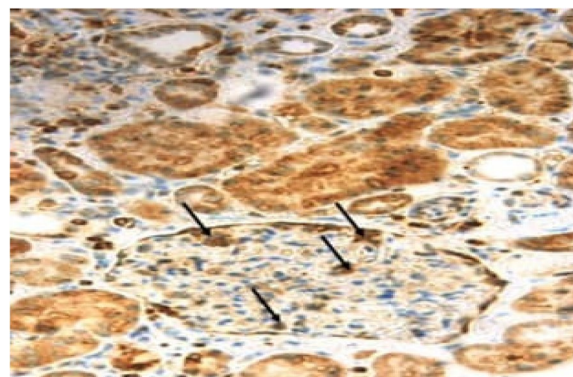
Bcl2 immuno-histochemical staining results

Control group

Bcl2 staining was found in the renal tubular epithelial cells of three of the 30 control cases (faint + 1 deposits) (Fig. 1).

LN cases

Bcl2 staining was observed in the glomerular tuft's mesangial cells, within the cellular crescents,

**Fig. 1** Control slide showing positive staining of tubules epithelial cells but negative mesangial cells**Fig. 2** Case of lupus nephritis showing strong + 3 positive staining of mesangial cells (black arrow). Graph 1. Deposit distribution of BCL among LN patients

inflammatory cells were found in the interstitium, and the tubules, in addition to other sites where it is normally found (Fig. 2). Compared to the control group, patients with lupus nephritis have significantly higher glomerular, interstitial and tubular expression level than the control group (P value < 0.001).

This study also correlated laboratory findings with Bcl-2 renal deposition and found significant positive correlation between BCL-2 histologic expression (tubular, interstitial, and glomerular) and serum anti-dsDNA titre and urine 24-h protein. However, BCL-2 had no significant correlations with serum creatinine levels. The study also compared BCL2 expression in relation to activity and chronicity indices and found a significantly positive correlation between glomerular, interstitial, and tubular BCL-2 ($p < 0.001$, $P = 0.009$, and $p < 0.001$) and the Chronicity Index. While there were no significant correlations with activity index (Table 3).

Table 3 Correlations between BCL-2 and laboratory findings, activity, and chronicity index in the LN group

Variables	Measures	BCL2-glomerular	BCL2-interstitial	BCL2-tubular
Urine 24-h protein	<i>R</i>	0.510	0.482	0.461
	<i>p</i> value	0.004*	0.007*	0.010*
Serum creatinine	<i>R</i>	0.148	0.048	0.314
	<i>p</i> value	0.436	0.801	0.091
Serum C3	<i>R</i>	- 0.655	- 0.464	- 0.721
	<i>p</i> value	< 0.001*	0.010*	< 0.001*
Serum C4	<i>R</i>	- 0.628	- 0.457	- 0.719
	<i>p</i> value	< 0.001*	0.011*	< 0.001*
Serum anti-dsDNA	<i>R</i>	0.549	0.296	0.664
	<i>p</i> value	0.002*	0.112	< 0.001*
Activity index	<i>R</i>	- 0.023	0.168	0.107
	<i>p</i> value	0.902	0.374	0.574
Chronicity index	<i>R</i>	0.682	0.466	0.710
	<i>p</i> value	< 0.001*	0.009*	< 0.001*

Total = 30. Spearman's correlation

* Significant

All the patients of LN had significant glomerular, interstitial and tubular deposits of BCL2, (*P* value < 0.001), (*P* value 0.004), and (*P* value 0.03), respectively (Graph 1).

Comparing BCL2 deposition in the different classes of LN: the most prominent findings were in class IV cases, the biggest number of our patients belonged to this group, 14 cases; seven of which had +1 glomerular deposits, while the other seven had + 2 deposits in the glomerulus. Regarding interstitial deposits 9 of the cases had + 1 (64.29%), and only one case had + 2 (7.14%). On the other hand, tubular deposits were evident in 12 of the 14 cases (85.71%), 5 of which had + 1 deposits and 7 of them had +2 deposits (Fig. 3).

Discussion

SLE is an immune-mediated disease characterized by a cellular and humoral immune reaction to self-proteins with consequent deposition of immune complexes in the different organs with resultant impairment of function [1, 2]. LN is one of the most serious complications affecting lupus patients and a major mortality and morbidity cause. It mainly affects young adults especially females as was found in this study, where the mean age of patients was 26.4 ± 8.8 years, female to male ratio (14: 1 ratio) [9].

According to ISN/RPS, 2003 classification of LN, Class IV was the predominant class (46.7%) which is similar to many other studies on LN in which class IV was also the predominant class [5–7].

In this study, we investigated one of the intrinsic pathways of apoptosis; bcl2; and its glomerular, tubular, and interstitial expression in LN. Bcl2 deposits were absent from the glomeruli and interstitial tissue of the normal

kidney tissue (control group), and its presence was evident only in a few number of cases within the epithelial cells of their renal tubules which was documented in previous studies [5, 8, 10].

In this study, the expression of the anti-apoptotic Bcl-2 (glomerular, tubular, and interstitial) was statistically significantly in lupus patients compared to the controls. This confirms a previous study by Soto et al. [11], who discovered a decrease in apoptosis in LN upon comparing it to the control group. They proposed that LN could be secondary to excessive proliferation without an equivalent increase in apoptosis. Accordingly, they concluded that apoptosis was reduced in LN. Additionally, Hosny et al. noticed that bcl2 intraglomerular immune expression in LN was increased and was significantly associated with class IV LN comparing it to other classes. The presence of intraglomerular bcl2 was also linked to higher levels of endocapillary proliferation and mesangial cells in proliferative glomerulonephritis [5]. These findings are consistent with those of Uguz et al. [12], who found Bcl-2 in mesangial cells and occasionally in infiltrating leucocytes in LN. Because Bcl-2 inhibits apoptosis and promotes cell survival, its expression has been linked to glomerular proliferation, implying that Bcl-2 plays a role in the persistent proliferation of glomerular cells in various types of GN. Bcl-2 is an anti-apoptotic protein that has been found to be elevated in the glomeruli and serum of LN patients [13]. Bcl-2 overexpression may play a part in glomerular hypercellularity and the survival of infiltrating leukocytes in the LN [11]. Furthermore, LN renal cell patients showed excessive proliferation in absence of an equivalent increase in apoptosis [11, 13]. The results of

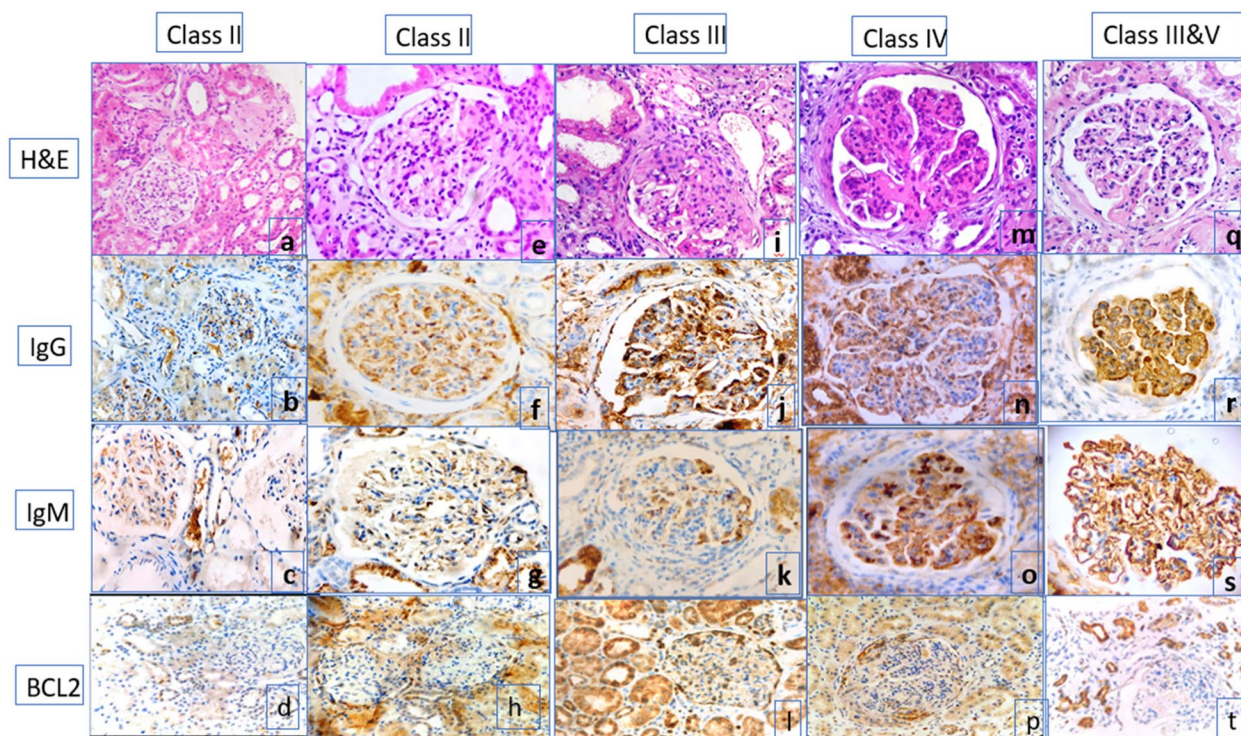


Fig. 3 The sites and distribution of the staining of BCL2 in LN classes: ISN/RPS Class II mesangial proliferative LN (**a**) with granular mesangial deposits for IgG1+ (**b**), and IgM1+ (**c**). BCL2 showed negative staining of glomeruli and focal faint staining of renal tubules (**d**). ISN/RPS Class II mesangial proliferative LN (**e**) with granular mesangial deposits for IgG2+ (**f**), and IgM1+ (**g**). BCL2 showed negative staining of glomeruli and strong staining of renal tubules (**h**). ISN/RPS Class III Focal proliferative LN with segmental endocapillary hypercellularity and segmental capillary wall thickening (**i**) showing granular capillary wall and mesangial deposits for IgG3+ (**j**), and IgM1+ (**k**). BCL2 showed segmental strong staining of glomeruli and strong staining of renal tubules (**l**). ISN/RPS Class IV Diffuse proliferative LN with global endocapillary hypercellularity and wire capillary wall thickening (**m**) showing granular capillary wall and mesangial deposits for IgG 3+ (**n**), and IgM3+ (**o**). BCL2 showed segmental strong staining of glomeruli and strong staining of renal tubules (**p**). ISN/RPS Class III/V combined Focal proliferative and membranous LN with moderate hypercellularity and global capillary wall thickening (**q**) showing granular capillary wall and mesangial deposits for IgG3+ (**r**), and IgM3+ (**s**). BCL2 showed negative staining of glomeruli and focal strong staining of renal tubules (**t**). (**a, b, c, d, h, l, p, t** × 200), (**e, f, g, i, j, k, m, n, o, q, r, s** × 400)

this study support the role of the bcl2 protein in the survival of glomerular cells in human LN renal tissue, which contributes to persistent glomerular hypercellularity [14].

Tubulointerstitial inflammation (TII) is common in lupus nephritis, and the presence and severity of TII are a stronger predictor of renal failure than glomerular inflammation [15]. In situ antigen-driven clonal expansion of B cells is a hallmark of TII in lupus nephritis, indicating that propagation of adaptive autoimmune responses occurs locally [16]. In our study, the expression of Bcl-2 (tubular and interstitial) was significantly higher in lupus patients compared to the controls. This is in accordance with the findings of a previous study by Ko et al. [4], who discovered that Bcl-2 expression was significantly more common in renal tissues with severe interstitial inflammation. Bcl-2 was expressed by both B cells and T cells, these Bcl-2-expressing lymphocytes were primarily found in the tubulointerstitial space and at a lower frequency in the glomerulus. These findings were

later confirmed at the mRNA level by laser capture. This study also compared the expression of BCL2 in the different classes of LN and showed that the most prominent expression of both the glomerular and interstitial deposits were in class IV cases. The other classes also showed prominent deposits in the tubules and the interstitium, in addition to the glomerular deposits. These findings support the known concept from previous studies that class IV LN is considered the worst class histopathologically [17]. It also shows the intense immune complex deposition disease in the histopathology of class IV LN, with its implications on disease severity.

Renal biopsies are frequently used in LN to evaluate the degree of renal involvement, provide a prognosis, and support therapeutic decisions. A higher risk of developing renal failure was linked to higher levels of tubulointerstitial nephritis. In contrast, the glomerular-based NIH activity index offered no prognostic information, and the ISN/RPS lupus nephritis classification was

a poor predictor of prognosis [18]. Scores of CI were reported to be more significant prognostic factors for renal failure than those of AI [19]. In patients receiving conventional treatment, the AI scores might be less significant [4]. In our study, we found significant positive correlations between glomerular, interstitial, and tubular BCL-2 expression and chronicity index while there were no significant correlations with activity index. The results of Ko and colleagues [4], who discovered a significant correlation between CI and interstitial inflammation, were in agreement with ours. They proposed that in-situ adaptive immune responses are associated with severe interstitial inflammation. Thus, in lupus nephritis, increased interstitial inflammation was associated with the dysregulation of apoptotic proteins, which led to the survival of autoreactive immune cells and maintained the disease's persistent activity. In lupus nephritis, interstitial Bcl-2 expression functions as both a regulator of immune cell survival and a regulator of in situ immunity [4, 16]. Our study's findings are comparable to those of Lee et al., who discovered that interstitial inflammation was significantly correlated with CI scores and that Bcl-2 positivity was significantly correlated with CI but not AI, concluding that in order to predict renal prognosis in lupus nephritis patients, it is crucial to assess the degree of tubulointerstitial inflammation, increasing tubulointerstitial nephritis severity was linked to a higher risk of developing renal failure [20]. On the other hand, according to Fathi et al., the levels of serum Fas and Bcl-2 protein expression and the chronicity index are directly correlated. Due to circulating T and B lymphocytes with abnormally high Bcl-2 and Fas expression, lupus nephritis patients' serum Bcl-2 and Fas protein levels increased. The direct correlation between the chronicity index, Bcl-2 protein levels, and Fas protein levels raises the possibility of a shared mechanism regulating the expression of these molecules and the emergence of pathological changes in lupus nephritis [10].

Another finding in our study was that serum anti-dsDNA which reflects the overall lupus activity. Urinary 24-h proteins, that reflects kidney function, had significant positive correlations with BCL-2 expressions (tubular, interstitial, and glomerular). While serum C3 and C4 had significant negative correlations with BCL2. On the other hand, BCL-2 had no significant correlations with serum creatinine levels [21, 22]. This implies that BCL2 expression detects early kidney damage especially the tubulointerstitial expression that is not included in ISN/RPS classification.

Our results are in accordance with those of Take-mura et al., who found that the degree of proteinuria was correlated with the number of Bcl-2-positive cells [10]. Our findings support those of Uguz et al. and

Rodriguez-Lopez et al., who found no correlation between Bcl-2 and plasma Cr or BUN levels [12, 23]. In accordance with the study of Wakasugi et al. and Zabaleta et al., significant numbers of SLE cases with renal impairment and/or overt proteinuria have glomerular lesions linked to histopathological IC deposition in the mesangium. Both studies also noted during their extended follow-up periods, that these patients' kidney function did not significantly deteriorate. These studies suggest that the tubulointerstitial compartment should be examined in the pathogenesis of this disease since seldom involvement of glomerular IC depositions is insufficient for the development of clinically relevant LN [24, 25]. Jeruc et al. found that TII correlated with proteinuria [26]. Although there was no direct relationship between the GN and the quantification of proteinuria, yet proteinuria is considered the marker of glomerular ultrafiltration and tubulopathy [27]. Protein overload activates the proximal tubular epithelial cells and up-regulates the gene of endothelin-driven factor and cytokines, leading to macrophage activation and tubular epithelial cells experiencing epithelial-to-mesenchymal transition (EMT), and eventually, fibrosis takes place. Complement activation is an essential mediator during this progression and TII may be caused directly by the activation of the complement in circulation or may be triggered by the local production of complement in the tubular lumen [26]. In human LN, inflammatory cells have been shown to infiltrate the tubulointerstitium with germinal center-like structures formation containing in situ immunoglobulins (Ig) repertoire with B cell clonal expansion [23]. Plasma cells secreting anti-dsDNA antibodies were mainly found in the kidney tubulointerstitium [28]. These findings identify the tubulointerstitial compartment as an essential site of autoreactive B cell immunity in LN. IC deposits nearby the tubular basement membrane (TBM) causes activation of the complement system, more severe tubulointerstitial pathology, more active disease, and poor prognosis. tubular ICs are formed independently of ICs from the circulation and glomeruli [29–31].

Limitations to this study

Other pro- and anti-apoptotic markers should be studied and correlated with the clinical activity.

Conclusion

According to our hypothesis, the intrinsic pathway of apoptosis interferes not only with the pathogenesis of lupus glomerulonephritis but also interferes with the pathogenesis of tubulointerstitial lupus nephritis. Tubulointerstitial lesions may not only be secondary to glomerular injury but also a primary cause of lupus nephritis.

Abbreviations

AI	Activity index
Bcl2	B cell lymphoma 2
CI	Chronicity index
DAB	Diaminobenzidine
ELISA	Enzyme linked immune sorbent assay
EMT	Epithelial-to-mesenchymal transition
GN	Glomerulonephritis
ICs	Immune complexes
Ig	Immunoglobulins
ISN/RPS	International Society of Nephrology/Renal Pathology Society
LN	Lupus nephritis
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
TII	Tubulointerstitial inflammation
TIN	Tubulo-interstitial nephritis

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Authors' contributions

The author(s) read and approved the final manuscript.

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Availability of data and materials

We approve the availability of our data upon request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee of the Faculty of Medicine, Ain Shams University (FMASU R 74a\2022). An informed and written consent was taken from each participant.

Consent for publication

We confirm and approve to publish this article in the Egyptian Rheumatology and Rehabilitation journal.

Competing interests

The authors declare that they have no competing interests.

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