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Original Article

Gelsolin deposits in renal tissues of the patients with lupus nephritis

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Abstract: Plasma gelsolin (pGSN) is a putative biomarker of inflammation. Recently the declining pGSN levels were found correlated with renal fibrosis. In this study, we used renal biopsies from Lupus nephritis (LN) patients to investigate the value of renal pGSN deposits for LN disease inflammatory states evaluation. 210 samples of renal biopsy were collected with pathology data from LN patients. pGSN deposits were tested with immunofluorescent assay and classified into six grades (-, ±, +, 2+, 3+, 4+). The interrelationships between pGSN deposits, morphological appearances and immune complexes (ICs) deposits were assessed with statistic analysis. We have documented 67.1% and 71.3% pGSN deposits rates in glomerular (gGSN) and tubular (tGSN). The gGSN deposits rates showed significant correlation with LN morphologic classifications (R^2=0.8108, P=0.0371), and gGSN strong deposits (3+, 4+) groups showed higher IgA, IgM and C3 deposits rates than gGSN weak deposits (-, ±, +, 2+) groups (P<0.05). Interestingly, lower IgG deposits rates were found in gGSN strong deposits groups (P<0.05). Our study has documented pGSN deposits in renal tissues in patients with LN, the higher pGSN deposits rates indicate more serious incidence of progressive inflammation with LN morphology progressions, the lower IgG deposits rates indicate IgG deposits play less important role in releasing larger magnitude of inflammatory mediators which are proposed to induce local accumulation of pGSN.

Keywords: Gelsolin deposits, lupus nephritis, morphological classification, immune complexes deposits

Introduction

Glomerulonephritis leading to severe persistent proteinuria, chronic renal failure and end-stage renal disease remains one of the most severe complications of SLE and is the major predictor of poor prognosis [1]. Sociodemographic factors such as sex, race, and ethnicity play an important role in the incidence of the disease, frequency of its manifestations, and therapeutic response [2, 3]. LN has been typically regarded with immune complexes-induced microvascular injury which results from circulating double-stranded DNA polynucleotide antigens/anti-DNA antibody complexes and other mechanisms including in situ reactivity for free antibodies with fixed antigens and the presence of sensitized T cells which are an important part of the picture [4]. Beside the immune globulins, some sub endothelial deposits contain a wide variety of plasma proteins, such as fibrinogen, albumin, and transferrin [5].

Gelsolin (GSN) contains an extracellular form circulates in the blood and plays important roles in the extracellular actin-scavenging system during tissue damage [6]. The decreased plasma GSN (pGSN) levels have been observed in many inflammatory diseases and proposed to be used as a biomarker of inflammation [7-9]. pGSN accumulation at injury sites as a result of interaction with insoluble F-actin that associates with cell membranes is the mainly proposed molecular mechanism for pGSN levels declining [9-13]. In the previous study, We have documented the decreased pGSN levels in

Table 1. Clinical characteristics in patients with LN[#]

Clinical characteristic	LN
Gender, female/male	192/18 (n=210, F/M=10.67/1)
Age, years	31.94±11.3 (n=207)
Age, 0-20 years	31
Age, 21-45 years	148
Age, 46-90 years	28
Class I[#]	17 (n=210)
Class II[#]	95
Class III[#]	27
Class IV[#]	49
Class V[#]	22
$HBsAg^-/HBsAg^{+\#}$	53/14 (n=67)
$IgA^-/IgA^{+\#}$	39/162 (n=201)
$IgM^-/IgM^{+\#}$	50/151
$C3^-/C3^{+\#}$	28/173
$IgG^-/IgG^{+\#}$	64/137

[#]LN, Lupus nephritis; Class I-V, World Health Organization (WHO) morphologic classification of lupus nephritis (revised in 1995) [26]; HBsAg: renal HBsAg deposits from IHC; IgA, IgM, C3 and IgG: Renal proteins deposits from immunofluorescence.

patients with SLE, and statistical analysis revealed increased incidence of kidney disorders [14]. Meanwhile, we have documented pGSN deposits in renal tissues in patients with IgA nephritis, the declining pGSN levels were found correlated with renal fibrosis [15].

In this study, we preformed research to analyse pGSN deposits and the interrelationships between pGSN deposits, morphological appearances and immune complexes deposits, attempted to clarify the value of renal pGSN deposits for LN disease inflammatory states evaluation.

Materials and methods

Patients and clinical data

210 LN renal biopsy tissue freezing sections were collected from patients taking pathologic examination in Pathology Department of Harbin Medical University. All the patients satisfied the classification standards for SLE set by American College of Rheumatology (ACR) in 1987, and the pathology examination and diagnosis were carried out by the same doctor. All the patients were provided informed consent. The average age of the patients was 31.94±11.3, including 18 males and 192 females.

Clinical pathologic examination

Renal biopsies were collected from LN patients with percutaneous puncture in clinical pathology. The collected biopsies were divided into 2 parts. One part was stored in 10% formalin solution for 1.5 h, after dehydration and paraffin embedding, tissues were cut to 3 μm thick sections for HE, PAS, PASM, Masson and Fibrin staining, this section was also used for IHC test for HBsAg. One part was stored in Tip tube with wet gauze and immediately transported to the lab, after OCT embedded and frezen, tissues were cut to 3 μm thick section with cryostat microtome. Frozen sections were used for IgG, IgM, IgA and C3 deposits detection with immunofluorescence assay. Some frozen sections were stored at -80°C.

pGSN deposits measurement

Frozen sections were used for pGSN deposits detection. pGSN deposits were detected with mouse monoclonal anti-GSN antibody 2C4 (Abcam, Hongkong) (1:50, 2 hours, 37°C) as first antibody. Secondary antibody used here was fluorescence labelled horse anti-mouse IgG (Vector, USA) (1:50, 1 hour, 37°C). The fluorescence was detected with fluorescence microscopy.

Statistical analysis

SPSS 13.0 was used for statistical analysis. A Chi-square test was used for percentage comparison between GSN deposits, morphological appearances and immune complexes deposits. Liner correlation was used for correlation analysis between GSN deposits and morphological classifications, immune complexes deposits and GSN deposits classifications. *P* values <0.05 indicated a significant difference.

Results

Clinical characteristics of LN patients

Gender, age, morphological classification, immune complexes deposits, et al. were collected as clinical characteristics of LN patients (**Table 1**). Female to male ratio was 10.67:1 which was close to China epidemiologic sex ratio in SLE

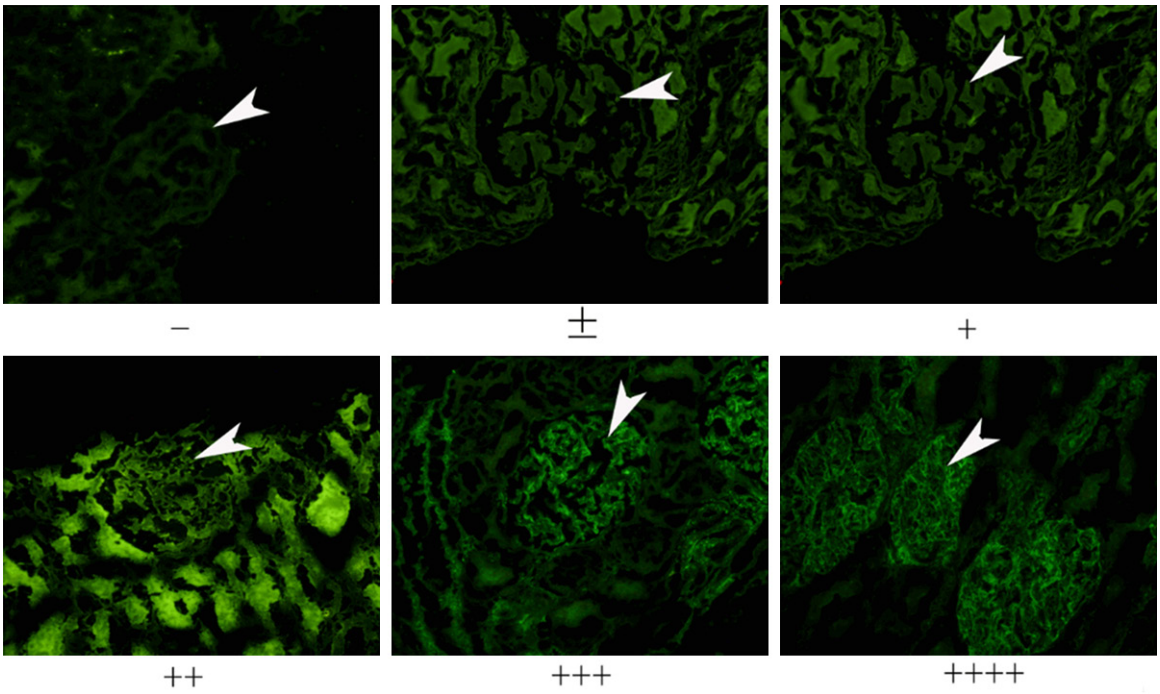

Figure 1. gGSN deposits classification in LN patients (×20). The green fluorescence indicates pGSN deposits, and the arrows point to glomerular site. pGSN deposits states were classified into six grades (-, ±, +, 2+, 3+, 4+).

Table 2. pGSN deposits and classification criteria

Classification	Glomeruli (n=210)	Tubule (n=209)	Criteria
$GSN^-/GSN^{+\#}$	69/141	60/149	GSN ± included into GSN^+
GSN -[#]	69	60	No fluorescence in low (×10) and high (×20, ×40) power field[#]
GSN ±	38	37	No fluorescence in low power field, small or punctiform fluorescence in high power field
GSN +	55	72	Small or punctiform fluorescence in low power field, significant fluorescence in high power field
GSN 2+	25	36	Significant fluorescence in low power field
GSN 3+	10	3	Strong fluorescence in low power field with wide range
GSN 4+	13	1	Super strong fluorescence in low power field with entire field of vision

[#] GSN, Gelsolin; pGSN deposits classification criteria referred to "Atlas of renal biopsy pathology" [12].

disease (female/male =9:1). Patients were divided into three groups according to the childbearing age, the population in childbearing age 20-45 years accounts for 71.5% of the LN patients. The population in Class II accounts for up to 45.2% of the LN patients. Only 67 patients with clear HBsAg deposits state were included in all the patients.

pGSN deposits and classification in renal tissues

pGSN deposits were detected in renal tubules and glomeruli from biopsy freezing sections with immunofluorescent assay, the deposits intensity varied in the samples, so pGSN deposits states were classified into six grades (-, ±, +, 2+, 3+, 4+) based on their observations under immunofluorescent microscopy (**Figure 1**; **Table 2**). The classification criteria referred to "Atlas of renal biopsy pathology" edited in 1999 [16].

Comparison between different pathological indexes in LN patients

The pathological indexes of LN patients were divided into groups based on their specific characteristics; chi-test was used for the comparison of indexes' abnormal rate between the groups. In gender groups, only $HBsAg^+$ rate was

Table 3. Comparison between different pathological indexes

	HBV^{+} (%)	*P*	IgA^{+} (%)	*P*	IgM^{+} (%)	*P*	C3^{+} (%)	*P*	IgG^{+} (%)	*P*	gGSN^{+} (%)	*P*	tGSN^{+} (%)	*P*
Male vs$^{\#}$ Female$^{\#}$	83.3 vs 14.8	0.001*	82.4 vs 80.4	0.848	70.6 vs 75.5	0.651	76.5 vs 87	0.232	58.5 vs 69	0.388	66.7 vs 67.2	0.964	66.7 vs 71.7	0.65
Age, 0-20 vs 21-45	0 vs 22.4	0.114	82.8 vs 81.6	0.879	93.1 vs 75.2	0.033*	96.6 vs 85.1	0.094	82.8 vs 67.4	0.1	54.8 vs 69.6	0.112	61.3 vs 71.6	0.254
Age, 0-20 vs 46-90	0 vs 25	0.110	82.8 vs 71.4	0.308	93.1 vs 57.1	0.002*	96.6 vs 78.6	0.039*	82.8 vs 57.1	0.035*	54.8 vs 67.9	0.306	61.3 vs 77.8	0.176
Age, 21-46 vs 46-90	22.4 vs 25	0.873	81.6 vs 71.4	0.222	75.2 vs 57.1	0.049*	85.1 vs 78.6	0.389	67.4 vs 57.1	0.298	69.6 vs 67.6	0.855	71.6 vs 77.8	0.510
HBV^{-} vs HBV$^{+\#}$	-	-	73.1 vs 100	0.029*	69.2 vs 64.2	0.724	82.7 vs 64.2	0.135	76.9 vs 50	0.048*	56.6 vs 57.1	0.971	62.3 vs 78.6	0.253
IgA^{-} vs IgA$^{+\#}$	0 vs 26.9	0.029*	-	-	48.7 vs 81.5	0.000*	69.2 vs 90.1	0.001*	53.8 vs 71.6	0.033*	71.8 vs 65.4	0.449	69.2 vs 70.8	0.846
IgM^{-} vs IgM$^{+\#}$	23.8 vs 20	0.724	60 vs 87.4	0.000*	-	-	64 vs 93.4	0.000*	46 vs 75.5	0.000*	68 vs 66.2	0.818	70 vs 70.9	0.908
C3^{-} vs C3$^{+\#}$	35.7 vs 17.3	0.135	57.1 vs 84.4	0.001*	35.7 vs 81.5	0.000*	-	-	25 vs 75.1	0.000*	75 vs 65.3	0.313	71.4 vs 70.3	0.908
IgG^{-} vs IgG$^{+\#}$	36.8 vs 14.9	0.048*	71.9 vs 84.7	0.033*	57.8 vs 83.2	0.000*	67.2 vs 94.9	0.000*	-	-	70.3 vs 65	0.454	73.4 vs 69.1	0.532
gGSN^{-} vs gGSN$^{+\#}$	20.7 vs 21.1	0.971	83.6 vs 79.1	0.449	76.1 vs 74.6	0.818	89.6 vs 84.3	0.313	71.6 vs 66.4	0.454	-	-	30.9 vs 90.8	0.000*
tGSN^{-} vs tGSN$^{+\#}$	13 vs 25	0.253	79.7 vs 80.9	0.846	74.6 vs 75.2	0.919	86.4 vs 85.8	0.908	71.2 vs 66.7	0.532	21.7 vs 85.9	0.000*	-	-

P values by Chi-test, $^{*}P<0.05$ stands for significant difference. $^{\#}$VS, Chi-test analysis in the index; GSN, Gelsolin; gGSN, glomerular gelsolin; tGSN, tubular gelsolin; HBV, IgA, IgM, C3, IgG and GSN, Renal proteins deposits from immunofluorescence.

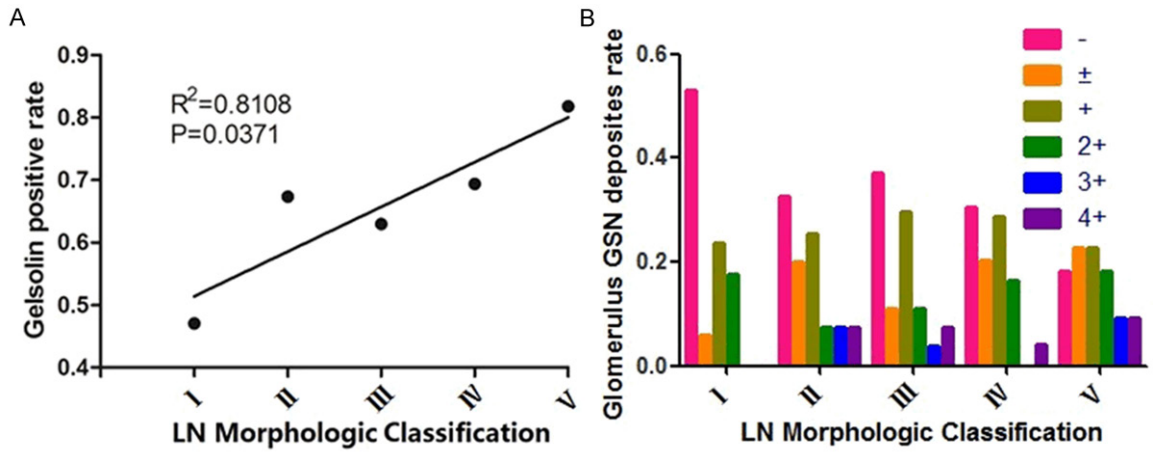

Figure 2. The correlation between gGSN deposits and LN morphologic classifications. A. Liner correlation between gGSN deposits positive rates and LN morphologic classifications. B. Detail distribution of gGSN deposits classifications in LN morphologic classifications.

significant higher in male than female population (P=0.001). IgA$^+$ rate was significant higher in HBV$^+$ than HBV$^-$ population (100% vs 73.1%, P=0.029), but IgG$^+$ rate was significant lower in HBV$^+$ than HBV$^-$ population (50% vs 76.9%, P=0.048). IgM deposits rates decreased significantly with growing age, 93.1%, 75.2% and 57.1% in 0-20, 21-45 and 46-90 years group, C3 and IgG deposits rates were significant higher in 0-20 than 46-90 years group. In the ICs deposits groups, IgA, IgM, C3 and IgG deposits related closely to each other, other ICs deposits rates were significant higher in one immune protein deposits positive than negative population. tGSN$^+$ rate was significant higher in gGSN$^+$ than gGSN$^-$ population (90.8% vs 30.9%, P=0.000) (**Table 3**).

Interrelationships between pGSN deposits, morphological appearances and immune complexes deposits in LN patients

Liner correlation was documented between gGSN$^+$ rates and LN morphologic classifications (R^2=0.8108, P=0.0371) (**Figure 2**), but no correlation was documented between tGSN$^+$ rate and LN morphologic classification (R^2= 0.594, P=0.12). No incidence of GSN strong deposits (3+, 4+) in LN class I population (**Figure 2**). IgM$^+$, C3$^+$ and IgA$^+$ rates were higher in the gGSN strong deposits (3+, 4+) than gGSN weak deposits (-, ±, +, 2+) groups. Interestingly, IgG$^+$ rate showed significant differences in gGSN deposits groups, gGSN deposits 2+ group showed highest IgG$^+$ rate, and gGSN strong deposits (3+, 4+) groups showed lower IgG$^+$ rate (**Figure 3**). No significant differences in immune complexes deposits were documented between tGSN deposits classifications.

Discussion

SLE is one typical chronic inflammatory autoimmune diseases in which diverse immunological events can lead to a similar clinical picture, characterized by a wide range of clinical manifestations and target organs with unpredictable flares and remissions that eventually lead to permanent injury [2]. Poor prognosis will happen with LN when lupus involves the kidneys, the varied and unpredictable nature of lupus nephritis and the risks associated with its treatment have challenged investigators to refine the estimates of prognosis and to develop rational approaches to therapy [17]. In this study, we introduce an inflammation related plasma protein which accumulated at renal tissues in patients with LN, and the interrelationships between pGSN deposits, morphological appearances and immune complexes deposits have been analysed.

pGSN has been reported accumulated at renal tissues in diseases with different mechanisms and roles. In GSN amyloid disease, GSN accumulates at renal tissues as primary and pathogenic factor with the mechanism of mutation in GSN coding gene [18]. In IgA nephropathy, which is an immune complex glomerulonephri-

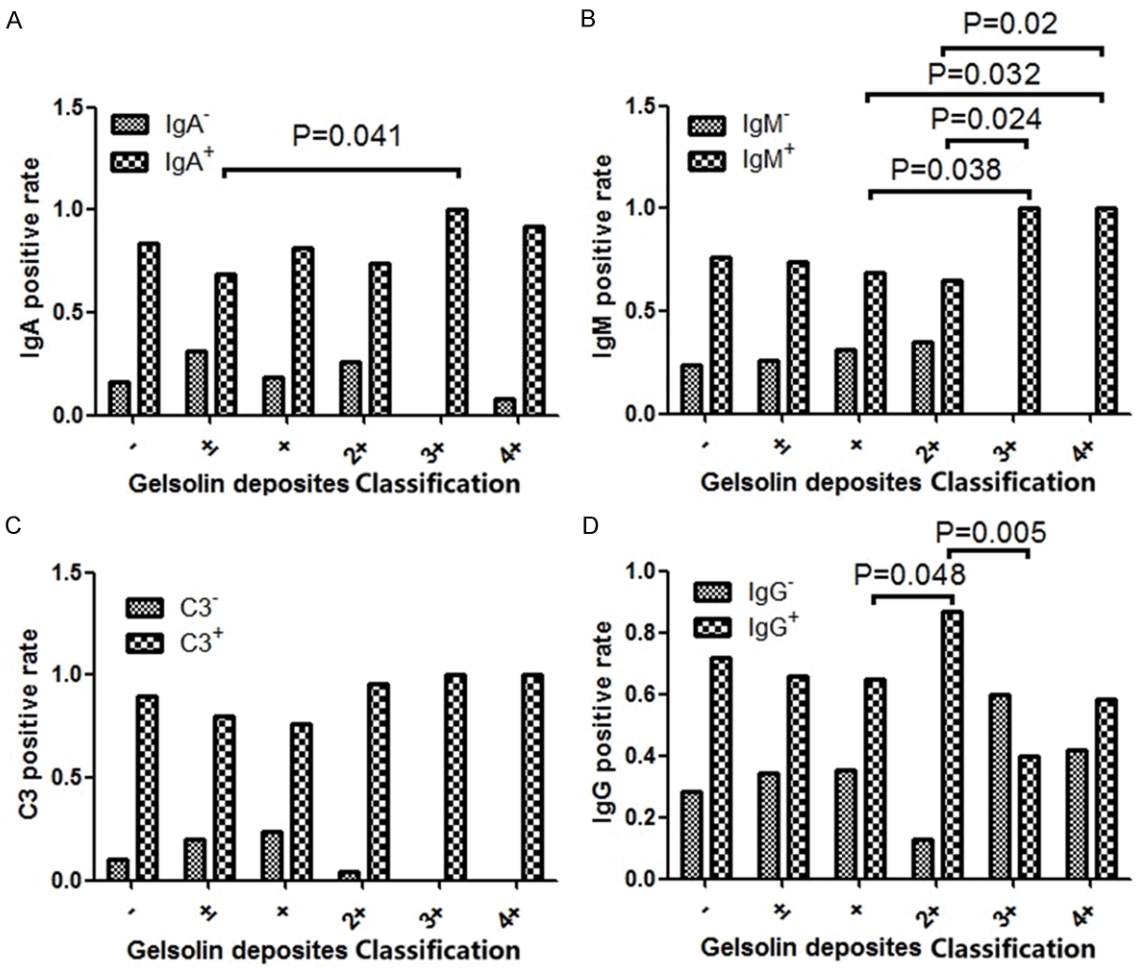

Figure 3. The correlation between gGSN deposits and ICs deposits. A. Interrelationship between gGSN deposits and IgA deposits; B. Interrelationship between gGSN deposits and IgM deposits; C. Interrelationship between gGSN deposits and C3 deposits; D. Interrelationship between gGSN deposits and IgG deposits.

tis and shows similar autoimmunity pathogenesis with lupus nephritis, pGSN level decreases and correlates with GSN deposits in glomeruli, and pGSN deposits seems more like to play a protective role in IgAN pathogenic process [15]. Our results were consistent with the findings in IgA nephropathy mouse model. Decreased pGSN levels were detected in SLE patients [19]. pGSN deposits were detected and varied in samples, significant liner correlation between gGSN deposits and LN morphologic classifications indicated the potential biological marker value of gGSN deposits in LN severity and glomerular injury, and this finding also added evidence for more serious incidence of progressive inflammation with LN morphology progressions [20]. We didn't included patients with more than one classification into analysis because of too small numbers that couldn't meet the requirements of statistical quantity. The general existence of pGSN deposits in patients with LN morphologic classification I to V indicated pGSN deposits should be better used as a biomarker for LN disease activity rather than specific diagnosis index [21].

Extended data analysis has been made in pGSN deposits and pathology data, and interesting findings were revealed. Higher incidence of HBsAg related LN in male was similar to the finding of predominantly male in HBV related membranous nephropathy and higher HBV infection rate in males in SLE patients [22, 23]. Compared to $HBsAg^-$ group, $HBsAg^+$ group showed higher incidence of IgA deposits but lower incidence of IgG deposits, and no differ-

ence in IgM and C3 deposits. The totally different characteristics of Ig subclass deposits in HBV^+ group indicate that LN patients with HBV infection require different evaluation and treatment [24]. In the age groups, IgM deposits rate decreased significantly with growing age, 93.1%, 75.2% and 57.1% in 0-20, 21-45 and 46-90 years group, other significant differences were in C3 and IgG deposits rates which were significant higher in 0-20 than 46-90 years group. These findings were consistent with more serious disease expression of SLE in youngers than elders, especially bad manifestation in children [25]. In the immune complexes groups, one immune protein deposits state was consistent with the states of other immune proteins deposits. For example, compared to IgA deposits negative group, the rates of IgM, C3 and IgG deposits were significant higher in IgA deposits positive group. These findings indicate close relation in the immune complexes deposits, but their roles in pathologic process and values for LN diagnosis and disease activity evaluation need more research [26, 27]. In the pGSN deposits groups, gGSN deposits were consistent with tGSN deposits, such as higher gGSN deposits rate in tGSN deposits positive than negative group. pGSN deposits rates were higher in elders (>20 years) than youngers (≤20 years), but with no significance.

Further analysis has been made based on pGSN and immune complexes deposits classification, different characteristics of interrelationship between pGSN and immune proteins deposits have been revealed. gGSN strong deposits (3+, 4+) groups showed higher IgA, IgM and C3 deposits rates than gGSN weak deposits (-, ±, +, 2+) groups. However, IgG deposits rates showed parabolic curve property in gGSN deposits classifications, highest rate in gGSN 2+ deposits group and lower rates in gGSN strong deposits (3+, 4+) groups. These findings indicated immune proteins deposits, with different characteristics in correlation with pGSN deposits which was a potential local inflammation marker, may play different roles in LN pathologic process. In the previous studies, IgG deposits are regarded as primary factors in initiating glomerulonephritis especially the anti-double-stranded DNA (dsDNA) antibody (IgG subclass) which is the best serological correlate for lupus nephritis, but the frequent lack of correlation between serum anti-dsDNA and glomerulonephritis is a long recognized conundrum in the clinical evaluation of individual SLE patients [28]. Our data documented high rates absence of IgG deposits but low rates absence of IgA, IgM and C3 deposits in gGSN strong deposits (3+, 4+) groups which suggested IgA, IgM and C3 deposits may play more important roles in releasing larger magnitude of inflammatory mediators than IgG deposits, and pGSN may be better used as severity biomarker for the evaluation of glomerulonephritis than anti-dsDNA [21].

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Disclosure of conflict of interest

None.

Authors' contribution

Yunlong Hu, Hongxue Meng, Lei Zhang and Di Sun did the immunofluorescence experiments and imagine preparations, Tingting Chen, Song Liu and Bin Liu did the data analysis, Xiaoming Jin and Fengmin Zhang directed the experiments, Yong Dai, Deyin Guo and Guangyi Jin directed the editing and guiding the data preparations. Yunlong Hu managed the article submission.

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