CORRELATION BETWEEN SERUM SCF LEVEL AND DISEASE ACTIVITY, PATHOLOGICAL TYPE AND REFRACTORY DEGREE OF LUPUS NEPHRITIS

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ABSTRACT

Objective*: To explore the correlation between serum stem cell factor (SCF) level and disease activity, pathological type, and refractory degree of lupus nephritis.*

Methods: *Eighty-five patients with lupus nephritis were randomly selected from patients treated in the Ya'an Polytechnic College Affiliated Hospital from May 2018 to January 2020. They were divided into a disease activity group (43 cases) and a stable disease group (42 cases) based on whether their systemic lupus erythematosus disease activity scores (SLEDAI) were over 10 points. According to the new standard for pathological classification of lupus nephritis, they were classified as type I (0 cases), type II (10 cases), type III (14 cases), type IV (18 cases), type V (21 cases), type VI (0 cases), and mixed type (type III + V, 12 cases; type IV + V, 10 cases). The patients were divided into a refractory lupus group (29 cases) and a treatment-sensitive group (56 cases) based on their response to therapy. A total of 43 normal healthy subjects who underwent physical examination in our hospital during the same period were selected as the control group. Changes in erythrocyte sedimentation rate (ESR), complement C3 level, complement C4 level, serum SCF level, clinical index, activity index (AI), and pathological index were measured. The Pearson correlation test was used to analyze the correlations between the serum SCF level and ESR, complement C3, complement C4, UTP, antinuclear antibody (ANA) titer, anti-dsDNA quantification, SLEDAI score, AI, CI, and renal tubulointerstitial disease (TIL) score.*

Results: *Serum SCF and ESR levels of patients in the disease activity group and the stable disease group were significantly higher than those of patients in the control group, and levels in the disease activity group were significantly higher than those in the stable disease group (P<0.05). The levels of complement C3 and complement C4 were markedly lower in the disease activity group and stable disease group than in the control group, and those in the disease activity group were clearly lower than those in the stable disease group (P<0.05). The serum SCF levels of type III and IV patients were significantly higher than those of type II and V patients (P<0.05). Compared with those in the treatment-sensitive group, serum SCF levels in the refractory lupus group were significantly greater (P<0.05). UTP, SLEDAI score, ANA titer, anti-dsDNA level, AI index, TIL score, and CI index were significantly greater in the disease activity group (P<0.05) than in the stable disease group. Pearson correlation analysis showed that SCF was positively correlated with ESR, ANA titer, anti-dsDNA quantification, SLEDAI score, AI index, and TIL score, and negatively correlated with complement C3 and complement C4 (P<0.05). There was no significant correlation between SCF level and CI index (P>0.05).*

Conclusion: *The serum SCF level of lupus nephritis patients was obviously higher than that of the normal control group, and SCF level was significantly correlated with the disease activity, pathological type, and refractory degree of lupus nephritis, indicating that it can play an important role in determining the prognosis of patients.*

Keywords: *SCF, lupus nephritis, disease activity, pathological type, refractory degree, correlation.*

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease produced by a variety of autoantibodies. It is often accompanied by the deposition of immune complexes in multiple organs, complement activation, infiltration of inflammatory cells, etc., which can occur in multiple organs. Lupus nephritis is one of the main clinical manifestations of SLE, and a chief factor affecting the prognosis of patients with SLE[1]. According to statistics, about 70% of patients with systemic lupus erythematosus have been clinically shown to have renal involvement[2]. The pathogenesis of SLE is complex and unclear at present but is believed to be closely related to environment, heredity, hormone

levels, and other factors[3]. With the development of medical technology and continuous progress in developing various immunosuppressive drugs, the therapeutic effects of treatments for lupus nephritis and patient prognoses have continuously improved, but they remain unsatisfactory.

After a slow progression, about 25% of patients with lupus nephritis progress to end-stage renal failure or even death. Therefore, early detection, timely intervention, and active treatment play an important role in reducing sustained injury to the kidney (target organ) and delaying renal failure. Stem cell factor (SCF) is a pluripotent cytokine produced mainly by stromal cells in the bone marrow microenvironment. Studies have found that serum SCF and a variety of immune cells play an important role in kidney injury, but the relationship between SCF level and disease activity in patients with lupus nephritis has rarely been reported[4]. In this study, the correlations between serum SCF level and disease activity, pathological type, and refractory degree of lupus nephritis were discussed and analyzed.

Data and methods

Basic information

This study was approved by the hospital ethics committee. Eighty-five patients with lupus nephritis who were treated in the Ya'an Polytechnic College Affiliated Hospital from May 2018 to January 2020 were randomly selected. These included 37 males and 48 females, with an average age of 33.59±6.73 years and a mean course of disease of 3.85±2.96 months. They were divided according to their systemic lupus erythematosus disease activity scores (SLEDAI) into the disease activity group (43 cases, SLEDAI ≥10 points) and the stable disease group (42 cases, SLEDAI <10 points).

According to the new standard for pathological classification of lupus nephritis[5], they were classified as type I (0 cases, mild mesangial lupus nephritis), type II (10 cases, mesangial proliferative lupus nephritis), type III (14 cases, focal lupus nephritis), type IV (18 cases, diffuse lupus nephritis), type V (21 cases, membranous lupus nephritis), type VI (0 cases, severe sclerosing lupus nephritis), and mixed type (type III + V, 12 cases; type IV + V, 10 cases). The patients were divided into the refractory lupus group (29 cases) and the treatment-sensitive group (56 cases) based on their responses to treatment.

Inclusion criteria were as follows:

• All patients met the diagnostic and treatment criteria for lupus nephritis proposed by the Nephrology Group of the Pediatrics Society of the Chinese Medical Association[6];

• All patients were confirmed to have lupus nephritis by renal biopsy pathological examination.

All studies conformed to the principles of medical ethics. The patients and their families were informed and signed informed consent forms. No parathyroid surgery has been performed on any patients.

Exclusion criteria were as follows:

• Patients who had complications due to infectious diseases, who received glucocorticoid or cytotoxic drug therapy 2 months before the study, who had incomplete pathological data, or who had serious cardiovascular disease were excluded from the study.

A total of 43 normal healthy subjects who underwent physical examination in the Ya'an Polytechnic College Affiliated Hospital during the same period were selected as the control group. This group consisted of 15 males and 28 females, with an average age of 32.21±5.96 years. There were no statistically significant differences in age, gender, and other indexes among the groups (P>0.05).

Observation indexes

5 mL of fasting elbow median venous blood were collected from all subjects in the morning before and after admission, and allowed to rest.

The blood was centrifuged at 3000 r/min using a low-temperature high-speed centrifuge. The supernatant was collected and stored in a –80°C ultra-low temperature refrigerator for subsequent research and testing.

Clinical indexes

The erythrocyte sedimentation rate (ESR) level was measured using an automatic erythrocyte sedimentation rate analyzer. The levels of complement C3 and complement C4 in each group were determined by automatic biochemical analyzer.

Determination of serum SCF level

Enzyme-linked immunosorbent assay (ELISA) was used to determine serum SCF levels in each group.

Disease activity

The levels of 24-hour urine protein quantification (UTP) were determined by automatic biochemical analyzer. Antinuclear antibody (ANA) titer levels

were detected using indirect immunofluorescence assay. Quantitative levels of anti-dsDNA antibody (anti-dsDNA) of each group were measured by ELISA. SLEDAI scores were observed in each group.

Pathological indicators

The renal pathological activity index (AI), chronic index (CI), and renal tubulointerstitial disease score (TIL) in each group were measured by Austin score.

Correlation

The Pearson correlation test was used to analyze the correlations between serum SCF level and ESR, complement C3, complement C4, UTP, ANA titer, anti-dsDNA quantification, SLEDAI score, AI, CI, and TIL.

Statistical methods

In this study, an independent sample t-test was used to compare the measured data between two groups, and single-factor multiple comparisons of means were used for comparison among multiple groups, all of which were expressed as ($\bar{x}\pm s$).

The Pearson correlation test was used for correlation analysis. All experimental data were statistically analyzed using the SPSS19.0 software package. Results were considered statistically significant when $P<0.05$.

Results

Comparison of serum SCF levels in patients with different disease activity

Serum SCF levels of patients in the disease activity group and the stable disease group were significantly higher than those of patients in the control group, and those of patients in the disease activity group were obviously higher than those of patients in the stable disease group ($P<0.05$), as shown in Table 1.

Group	Cases	SCF (ng/L)
Control group	43	155.07±21.48
Disease activity group	43	358.31±61.86
Stable disease group	42	307.04±33.18
F		266.28
P		<0.001

Table 1: Comparison of serum SCF levels in patients with different disease activity ($\bar{x}\pm s$).

Comparison of serum SCF levels in patients with different pathological types

The serum SCF levels of type III and IV patients were significantly higher than those of type II and V patients ($P<0.05$), as shown in Table 2.

Group	Cases	SCF (ng/L)
Type II	10	265.33±15.68
Type III	14	368.02±36.69
Type IV	18	404.74±43.55
Type V	21	288.59±10.27
Type III+V	12	323.22±36.45
Type IV+V	10	319.88±10.79
F		45.28
P		<0.001

Table 2: Comparison of serum SCF levels in patients with different pathological types ($\bar{x}\pm s$).

Comparison of serum SCF levels among patients with different responses to treatment

Serum SCF levels of patients in the refractory lupus group were significantly higher than those of patients in the treatment-sensitive group ($P<0.05$), as shown in Table 3.

Group	Cases	SCF (ng/L)
Refractory lupus group	29	357.79±61.23
Treatment-sensitive group	56	311.17±42.32
t		4.116
P		<0.001

Table 3: Comparison of serum SCF levels among patients with different responses to treatment ($\bar{x}\pm s$).

Comparison of clinical indicators in each group

Serum ESR levels of patients in the disease activity group and the stable disease group were significantly higher than those of the control group, and those in the disease activity group were obviously higher than those in the stable disease group ($P<0.05$).

The levels of complement C3 and complement C4 were markedly lower in the disease activity group and stable disease group than in the control group, and levels in the disease activity group were obviously lower than those in the stable disease group ($P<0.05$), as shown in Table 4.

Group	Cases	ESR (mm/b)	Complement C3 (g/L)	Complement C4 (g/L)
Control group	43	8.87±3.88	1.26±0.31	0.26±0.06
Disease activity group	43	43.98±8.57	0.59±0.24	0.08±0.04
Stable disease group	42	32.78±7.58	0.86±0.22	0.14±0.04
F		284.52	72.35	158.89
P		<0.001	<0.001	<0.001

Table 4: Comparison of clinical indicators in each group ($\bar{x}\pm s$).

Comparison of clinical activity indexes in each group

UTP, SLEDAI score, ANA titer, and anti-dsDNA level were significantly higher in the disease activity group than in the stable disease group (P<0.05), as shown in Table 5.

Group	Cases	UTP (g)	SLEDAI score (points)	ANA titer (dilution ratio)	anti-dsDNA (U/mL)
Disease activity group	43	2.89±1.18	12.98±1.85	158.25±88.02	1246.77±814.87
Stable disease group	42	2.25±0.97	4.72±2.29	83.27±41.68	446.32±285.81
t		2.728	18.316	5.000	6.014
P		0.008	<0.001	<0.001	<0.001

Table 5: Comparison of clinical activity indexes in each group ($\bar{x}\pm s$).

Comparison of pathological indexes of patients in each group

AI index, TIL score, and CI index were significantly higher in the disease activity group compared with the stable disease group (P<0.05), as shown in Table 6.

Group	Cases	AI index	TIL score	CI index
Disease activity group	43	8.77±2.44	4.63±1.10	3.91±1.64
Stable disease group	42	5.44±2.47	3.28±1.79	2.91±1.18
t		6.253	4.200	3.220
P		<0.001	<0.001	0.002

Table 6: Comparison of pathological indexes of patients in each group ($\bar{x}\pm s$).

Correlations between serum SCF level and ESR, complement C3, complement C4, UTP, ANA titer, anti-dsDNA quantification, SLEDAI score, AI index, CI index, and TIL score

Pearson correlation analysis showed that SCF was positively correlated with ESR, ANA titer, anti-dsDNA quantification, SLEDAI score, AI index, and TIL score, and negatively correlated with complement C3 and complement C4 (P<0.05). There was no significant correlation between SCF level and CI index (P>0.05). The results are shown in Table 7.

Index	SCF	
	r	*P*
ESR	0.313	<0.05
Complement C3	–0.323	<0.05
Complement C4	–0.362	<0.05
UTP	0.298	<0.05
SLEDAI score	0.470	<0.05
Anti-dsDNA quantification	0.356	<0.05
ANA titer	0.286	<0.05
AI index	0.391	<0.05
CI index	0.182	>0.05
TIL score	0.318	<0.05

Table 7: Correlation analysis.

Discussion

SLE is a chronic autoimmune disease characterized by systemic multi-system involvement and the presence of multiple autoantibodies in the serum. Pathogenic autoantibodies and immune complexes can cause damage to multiple target tissues, and the course of SLE is mainly characterized by alternation of remissions and acute attacks[7]. The kidney is the most frequently-involved visceral organ in systemic lupus erythematosus. Kidney involvement often presents as lupus nephritis; clinical manifestations of kidney damage occur in about 50% to 85% of lupus patients. Kidney failure is the main cause of death for SLE patients and is one of the important determinants of patient prognosis[8].

Therefore, the treatment of lupus nephritis is of great significance. The pathogenesis of lupus nephritis is complex. It is believed that many different genes affect different aspects of immune cell function, leading to abnormal activation of immune functions and immune disorders. In addition, a variety of cytokines and their receptors

are involved, and the cell network is complex[9]. SCF is an important regulator produced by stromal cells in the bone marrow microenvironment. Studies have confirmed that binding of SCF and its receptor can directly stimulate lymphocyte proliferation and indirectly lead to dendritic cell proliferation, playing an important role in the occurrence and development of lupus nephritis[10]. This study mainly investigated the correlation between serum SCF level and disease activity, pathological type, and refractory degree of lupus nephritis.

The SLEDAI score is a commonly-used method to evaluate disease activity established by the University of Toronto School of Medicine. The SLEDAI score includes multiple items including organic encephalopathy syndrome, proteinuria, and positive anti-dsDNA antibody; the more clinical manifestations, the higher the score, indicating higher disease activity[11]. Additionally, proteinuria, the complement system, ANA titer, and anti-dsDNA can all be used as indicators to evaluate disease activity to a certain extent[12]. The results of this study showed that serum SCF level was significantly correlated with lupus nephritis disease activity.

Pathological diagnosis of the kidney can directly reflect kidney damage, which can be used as the "gold standard" for the diagnosis of lupus nephritis. At present, the AI index is a general indicator to evaluate the pathological activity of lupus nephritis. The CI index indicates the level of renal fibrosis, renal tubular atrophy, and renal interstitial fibrosis, and is an important indicator of irreversible renal lesions[13]. Studies have found that the degree of renal interstitial damage is also significantly related to the degree of glomerular damage, and renal tubulointerstitial lesions are also an important factor in the activity and prognosis of lupus nephritis[14]. The TIL score is an important method to evaluate renal tubulointerstitial lesions in patients with lupus nephritis. The results of this study showed that higher degrees of disease activity were associated with higher SCF, AI index, TIL score, and CI index, and that SCF was significantly correlated with the above indexes. This may be because SCF and other factors form a microenvironment in the renal interstitial fibrosis through the interaction of autocrine and paracrine pathways, inducing the activity of lupus nephritis disease and thus leading to the occurrence and development of the disease[15].

At present, glucocorticoid or immunosuppressor therapy is commonly used clinically to treat lupus nephritis. After 6 months of treatment, a UTP level exceeding 3.5 g/24 h is considered to indicate refractory lupus nephritis, while a significantly reduced UTP level of less than 3.5 g/24 h is considered to indicate treatment-sensitive lupus nephritis. Refractory lupus nephritis is more common in patients with type III, type IV, type III+V, and type IV+V lupus nephritis. At the same time, the incidences of hypertension, renal failure, proteinuria, and hematuria are relatively high in patients with lupus nephritis, and a large amount of immune complex deposition and crescent formation can be seen in renal interstitial biopsy, which is now recognized as a therapeutic problem. It was found in this study that serum SCF level may be closely related to the refractory degree and pathological type of lupus nephritis.

In conclusion, the serum SCF level of lupus nephritis patients was obviously higher than that of the normal control group, and its level was significantly correlated with the disease activity, pathological type, and refractory degree of lupus nephritis, indicating that serum SCF levels can play an important role in determining the prognosis of patients.

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