B-cell-attracting chemokine CXCL13 as a marker of disease activity and renal involvement in systemic lupus erythematosus

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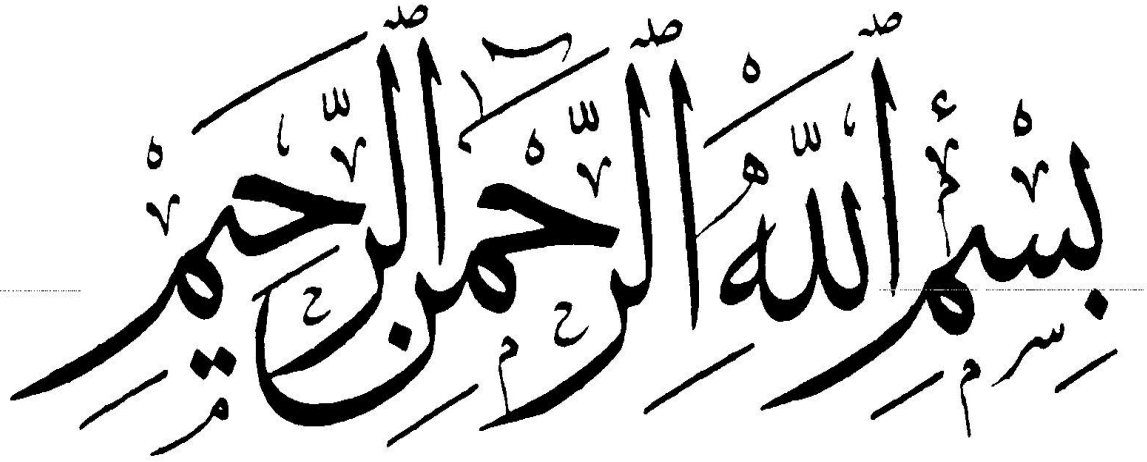
بسم الله الرحمن الرحيم

"و قل اعملوا فسيري الله
عملكم و رسوله
و المؤمنون"

صدق الله العظيم

التوبة/١٠٥

ABSTRACT

This work aimed to study whether serum CXCL13 levels (1) are elevated in patients with SLE, (2) correlate with disease activity and (3) indicate renal involvement in SLE patients.

64 patients with SLE fulfilling the 1997 revised criteria for the classification of SLE and 20 age/ sex- matched healthy controls included in this study were subjected to full history taking, clinical examination, routine laboratory investigations as well as measurement of serum CXCL13 level.

Serum CXCL13 levels were found to be elevated in SLE patients and levels correlated with disease activity. In addition, CXCL13 levels were significantly higher in patients with active LN compared to those without renal involvement.

Keywords: Systemic lupus erythematosus - Lupus nephritis - CXCL13

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LIST OF ABBREVIATIONS

aa	Amino acid
ACE	Angiotensin converting enzyme
ACR	American College of Rheumatology
ANA	Antinuclear antibody
ANCA	Antineutrophil cytoplasmic antibody
Anti-DNA	Anti- deoxyriboneuclic acid
Anti-Sm	Anti-Smith antibody
APC	Antigen-presenting cell
aPL	Antiphospholipid antibody
APRIL	A proliferation-inducing ligand
APS	Antiphospholipid syndrome
ARB	Angiotensin receptor blocker
BAFF	B-cell activating factor
BAFFR	B-cell activating factor receptor
BCA-1	B-cell-a rac ng chemokine 1
BCMA	B-cell maturation protein
BILAG	The British Isles Lupus Assessment Group
BL	Burkitt lymphoma
BLC	B-lymphocyte chemoattractant
Blys	B-lymphocyte stimulator
BM	Basement membrane
BUN	Blood urea nitrogen
C	Complement
CAT	Catalase
CBC	Complete blood count
CD	Cluster of differentiation
CHD	Coronary heart disease
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease

CPG	Cytosine-phosphateguanine
CRP	C- reactive protein
CSF	Cerebrospinal fluid
CTLA-4	Cytotoxic T-lymphocyte an gen 4
CVA	Cerebrovascular accident
CXCL13	CXC ligand 13
DAMPs	Damage associated molecular patterns
DC	Dendritic cell
DHEA	Dehydroepiandrosterone
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusing capacity for carbon monoxide
DLE	Discoid lupus erythematosus
dsDNA	Double stranded deoxyriboneuclic acid
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECLAM	European Consensus Lupus Activity Measurement
ELISA	Enzyme-Linked Immunsorbant Assay
EM	Electron microscopy
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
Fab	The antigen binding fragment of antibody
Fc	The constant fragment of antibody
g	Gram
GAS	IFN-γ activation site
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
glu-leu-arg	glutamine – leucine - arginine
GM-CSF	Granulocyte macrophage-colony stimulating factor
GN	Glomerulonephritis
GP	Glycoprotein
Gpx	Glutathione peroxidase
GSH	Glutathione

H2O2	Hydrogen peroxide
Hb	Hemoglobin
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficieny virus
HLA	Human leucocyte antigen
HUS	Hemolytic Uremic Syndrome
IC	Immune complex
IF	Immunofluorescence
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IP-10	Interferon-γ-inducible protein 10
IRF	Interferon regulatory factor
ISN	International Society of Nephrology
ISRE	Interferon stimulated responsive element
ITP	Immune thrombocytopenic purpura
JAK 1	Janus kinase-1
LAI	Lupus Activity Index
LC	Langerhans cells
LM	Light microscopy
LN	Lupus nephritis
LNB	Lyme neuroborreliosis
LPO	Lipid peroxidation
LPS	Lipopolysaccharide
MALT	Mucosa-associated lymphoid tissue
MCAF	Monoyte chemotactic factor
MCP-1	Monocyte chemotactic protein-1
MDA	Malondialdehyde
MDSC	Myeloid-derived tumor suppressor cells
mg	Milligram
MHC	Major histocompatibility complex
MIG	Monokine induced by IFN-γ

mm	Millimeter
MMF	Mycophenlate mofetil
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NET	Neutrophil extracellular trap
NHL	Non-Hodgkin lymphoma
NOD	Nucleotide-binding oligomerization domain
NSAIDs	Non-steroidal anti-inflammatory drugs
OPG	Osteoprotegerin
PAMPs	Pathogen-associated molecular patterns
PBMC	Peripheral blood mononuclear cells
PDC	Plasmacytoid dendritic cells
PDGF	Platelet derived growth factor
PLT	Platelets
PR3	Proteinase 3
PRR	Pattern recognition receptor
R	Receptor
RA	Rheumatoid arthritis
RANTES	Regulated upon Activation, Normal T cell Expressed, and Secreted
RIG-1	Retinoic acid inducible gene I
RNA	Ribonucleic acid
RNP	Riponucleoprotein
ROC	Receiver Operating Characteristic
ROS	Reactive oxygen species
RPGN	Rapidly progressive glomerulonephritis
RPS	Renal Pathology Society
rSLEDAI	renal Systemic Lupus Erythematosus Disease Activity Index
SD	Standard deviation
SDF-1	Stromal cell derived factor-1
SF	Synovial fibroblast

SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLO	Secondary lymphoid organ
SOD	Superoxide dismutase
TACI	Transmembrane activator and calcium modulating cyclophilin ligand interactor
T-ALL	T-cell acute lymphoblastic leukemia
TCR	T cell receptor
TFH	Follicular helper T cells
TGF-β	Transforming growth factor-beta
Th	T-helper
TLR	Toll-like receptors
TMA	Thrombotic microangiopathy
TNF-α	Tumor necrosis factor-α
tSLEDAI	total Systemic Lupus Erythematosus Disease Activity Index
TTP	Thrombotic Thrombocytopenic Purpura
VCAM- 1	Vascular cell adhesion molecule-1
WBC	White blood cells
WHO	World health organization

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INTRODUCTION

Systemic lupus erythematosus is a chronic autoimmune disease affecting different organ systems **(Rahman and Isenberg, 2008)**. Chemokines have been shown to orchestrate migration to and preferential sequestration of B and T cells in inflammatory lesions. The significance of chemokines in the pathogenesis of SLE and lupus nephritis is widely accepted **(Kulkarni and Anders, 2008)** and recent interventional studies could demonstrate the therapeutic benefit of pharmacologic chemokine and chemokine receptor blockade in experimental SLE **(Anders et al., 2004)**.

The chemokine CXC ligand 13 protein (CXCL13), also known as B-cell-attracting chemokine-1 (BCA-1) or B-lymphocyte chemoattractant (BLC), is a CXC subtype member of the chemokine superfamily **(Gunn et al., 1998)**.

CXCL13 is one of the most potent B-cell chemoattractants and is constitutively expressed in the B-cell follicles of secondary lymphoid organs, pleural and peritoneal cavities, and in ectopic lymphoid follicles within the synovial membrane of patients with rheumatoid arthritis. Via its receptor CXCR5, expressed on follicular dendritic cells, CXCL13 is crucial for germinal centre formation **(Vissers et al., 2001)**.

The role of CXCL13 is particularly interesting in the course of LN, since aberrant CXCL13 expression is sufficient to induce the formation of ectopic lymphoid tissues in non-lymphoid organs and thus could be responsible for the accumulation of inflammatory cells in the kidneys in SLE **(Ishikawa et al., 2001)**.

Furthermore, it is believed that the presence of ectopic lymphoid tissues promotes the local activation of T and B cells leading to exacerbation of disease **(Segerer and Schlondorff, 2008)**.

Recently, the expression profiles of 61 inflammatory molecules were characterized in the kidneys of NZB/W-F1 mice at different stages of LN. It was found that CXCL13 was one of only a few inflammatory markers that were expressed in the kidney at an early point of disease,

suggesting a possible pathogenic role for disease manifestation **(Schiffer et al., 2008**)..

Since kidney biopsy is still the gold standard for diagnosis of LN but bear potential complications, non-invasive tests to investigate kidney involvement are of great interest.

AIM OF THE WORK

The aim is to find whether serum levels of CXCL13

(1) are elevated in patients with SLE,

(2) correlate with disease activity,

(3) indicate renal involvement in SLE patients.