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Effect of SLE on kidneys

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Abstract

Background :Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology, characterized by multi-organ inflammation and positive serum autoantibodies.

Methods :Human tissues , urine samples have been used and circulating T cells and were assessed by flow cytometry in peripheral blood samples

Results :Tissue damage associated with high levels of circulating T cells and elevate protein level in the urine

Conclusion : Pathogenesis of LN such as generation of autoantibodies, secretion of proinflammatory and anti-inflammatory cytokines and abnormality of T lymphocytes, particularly the T-helper subsets, is also highly pertinent in the development of LN. Lupus nephritis (LN) is the foremost common and serious complication of SLE

Introduction

Systemic lupus erythematosus (SLE) is an immune system disorder that comes about in incessant aggravation and harm of more than one organ. It is analyzed clinically and serologically with the nearness of autoantibodies.[1]

"Lupus" is a Latin term meaning "wolf," since one of the trademark facial SLE rashes is comparative to the bitemark of a wolf [1]

In this disorder , autoantibodies are directed against DNA, histones, nucleolar proteins, and other components of the cell core. Antibodies against double-stranded DNA are the hallmark of systemic lupus erythematosus. The disease influences basically females between the ages of 20 and 60 years. People with HLA-DR2 or-DR3 qualities are inclined to systemic lupus erythematosus [2]

The agent that actuates these autoantibodies in most patients is not clear . On the other hand , two drugs, procainamide and hydralazine, are known to cause systemic lupus erythematosus . Most of the clinical discoveries are caused by immune complexes that actuate complement and, as a result, harm tissue. For instance , the characteristic rash on the cheeks is the result of a vasculitis caused by immune complex deposition . The joint pain and glomerulonephritis commonly seen in systemic lupus erythematosus are too caused by immune complexes. The complexes found on the glomerulus contain antibodies (IgG, IgM, or IgA) and the C3 component of complement [2]

Lupus nephritis (LN) is one of the foremost severe signs of systemic lupus erythematosus (SLE), resulting in increased morbidity and mortality [3]

LN is fundamentally caused by type-III hypersensitivity reaction , which results within the arrangement of immune complexes. Anti-double-stranded DNA (anti-dsDNA) binds to DNA and forms an anti-dsDNA immune complex. These immune complexes store within the mesangium and subendothelial and/or subepithelial space close the glomerular basement membrane of the kidney, driving to an inflammatory reaction with the onset of LN, in which the complement pathway is actuated with a resultant convergence of neutrophils and other inflammatory cells . During this process, innate immune cells (granulocytes, common killer cells, macrophages, and dendritic cells), adaptive immune cells (T cells, B cells), inflammatory factors

(interleukin, sort I interferons, tumor corruption calculate α), and complement proteins (C1q, C3b) are included in tissue damage [4]

Aim of this study is to review the pathophysiology of SLE and it's effect on kidneys and complications of lupus nephritis

Methods and Materials

Studies reviewed in this report used human tissue ,urine and blood samples

In the first study

Urinalysis ,microscopic hematuria, red blood cells, or red blood cell casts, biopsy has been done . A kidney biopsy is indicated when the patient develops nephrotic range proteinuria [1]

The second study used in this report included 67 SLE patients

A total of 67 SLE patients and 30 age- and sex-matched HCs [Healthy control] were included in the study. A total of 32 SLE patients were categorized with LN based on the results of renal biopsy and immunohistochemistry., [7]

Low cytometry analysis

The percentages of circulating T cells and EPCs [endothelial progenitor cells] were measured by flow cytometry. Briefly, according to the manufacturer's instructions, T cells were stained with peridinin chlorophyll protein (Percp)-conjugated CD3, phycoerythrin (PE)-conjugated CD31, and allophycocyanin (APC)-conjugated CXCR4 (BD Biosciences, San Diego, CA, USA). The EPCs were stained with fluorescein isothiocyanate (FITC)-conjugated CD34 (BD Bioscience), PE-conjugated VEGFR2 (BD Bioscience), and APC-conjugated CD133 (Miltenyi Biotech, Bergisch Gladbach, Germany). The appropriately conjugated IgG antibodies were used as isotype controls. The labeled cells were acquired on a FACS Calibur flow cytometer (BD Biosciences) and data were analyzed using Cell Quest software (BD Bioscience) and FlowJo 7.6.1 software [7]

Quantification of cytokine plasma levels

The plasma samples were collected and preserved at −80°C until the evaluation of cytokines. The plasma levels of interleukin (IL)-17, IL-8, and vascular endothelial growth factor (VEGF) were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, San Diego, CA, USA), according to the manufacturer's instructions [7]

Statistical analysis

The comparison between the groups was evaluated by Mann–Whitney U test. The correlations were analyzed using Spearman's rank correlation analysis. All analyses were performed using SPSS 17.0 software (SPSS, Chicago, IL, USA). A P value <0.05 was considered as statistically significant [7]

Results

The results showed specifically the complexity of immune populations in LN kidneys and it supported the high level of T cells and other immune cells, identifying multiple disease-specific subsets and giving rise to several observations.

Laboratory

Urinalysis shows a high level of proteinuria which indicates glomerular damage.

Proteinuria that exceeds more than 3.5 g per day is in the nephrotic rang.

If significant proteinuria exists, complete metabolic panel (CMP) will show low albumin count ,with active SLE, complement levels (C3 and C4) are usually low with the presence of anti-dsDNA autoantibody. Creatinine (Cr) may be elevated or normal with the presence of proteinuria [1]

Results of tissue biopsy

Evidence for within-tissue differentiation of inflammatory CD16+ macrophages into M2-like cells, which may orchestrate the renal infiltration and retention of other .leukocyte subsets

- An abundance of dividing CTLs [cytotoxic T cells] and NK cells, indicated to be a major source of IFNγ and cytolytic molecules, and lack of expression of exhaustion markers in CD8+ T cells, suggesting a role for cytotoxic activity in LN;

- Two additional populations of CD8+ T cells, which could not be easily identified by cell surface markers.

- A range of B-cell activation states from naive cells to ABCs in the kidney

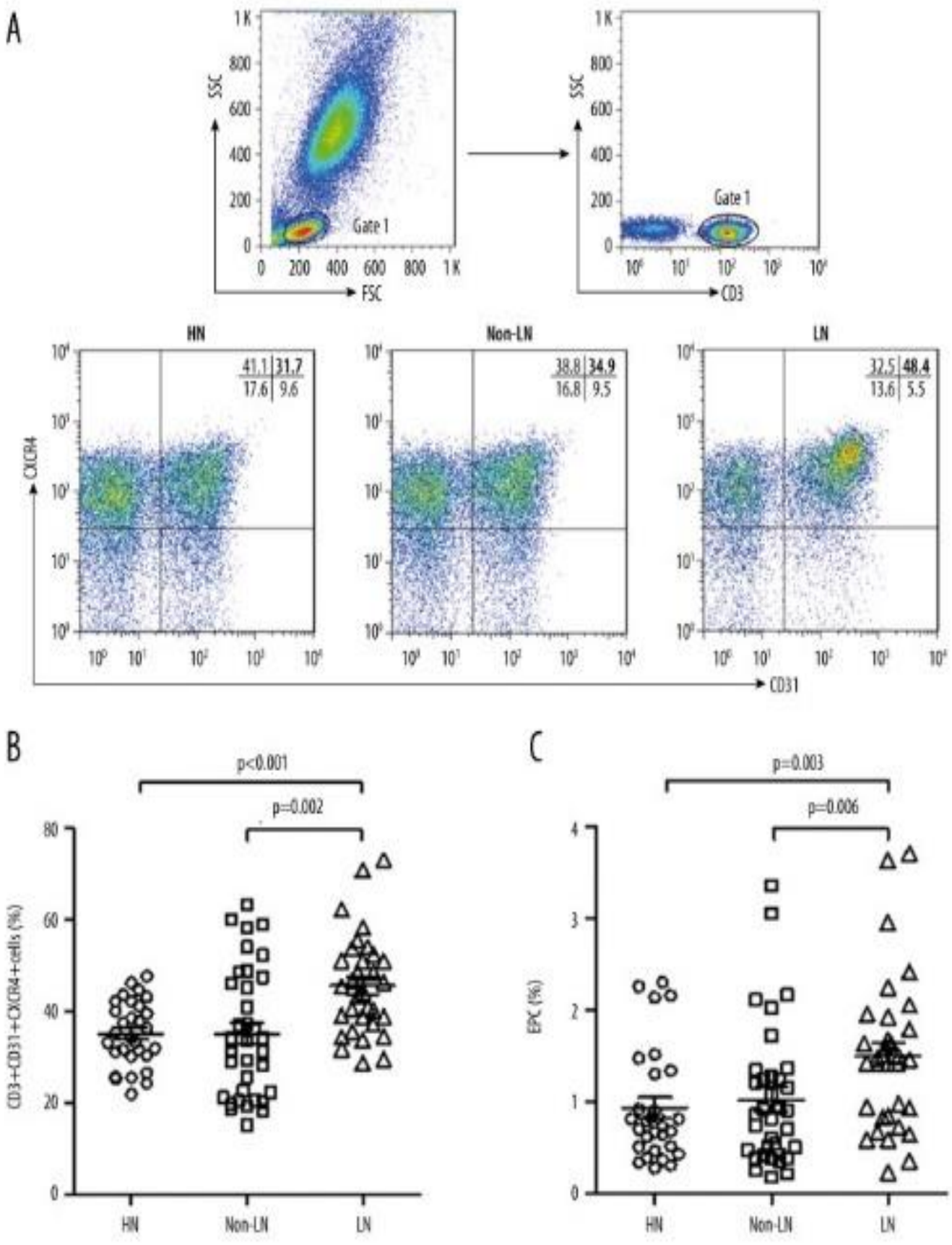
- An interferon response signature in infiltrating leukocytes, correlated with the same signature in blood

- Frequent expression by kidney immune cells of the chemokine receptors CXCR4 and CX3CR1 suggesting they may serve as potential therapeutic targets[6].

The result of the second study supported the first and also showed the level of circulating CD31+CXCR4+ cells in total CD3+ T cells in LN patients were significantly increased as compared to the non-LN patients [7]

Presence of circulating T cells in SLE patients and HCs. (A) Flow cytometric dot-plots of circulating Tang cells (CD31+CXCR4+ cells in CD3+ T cells) obtained from 1 representative healthy control (HC), and SLE patients with lupus nephritis (LN) and without lupus nephritis (non-LN). Percentages of circulating T cells (B) and EPCs (CD34+CD133+VEGFR2+ cells) (C) in HC, LN, and non-LN patients (figure 1)[7]

Although the LN and non-LN patients exhibited higher levels of IL-8 as compared to HCs, the differences were not significant between the LN and non-LN patients . Moreover, significantly higher levels were observed in LN patients as compared to the non-LN patients Additionally, the levels of VEGF, but not IL-17 and IL-8, were positively correlated with circulating T cells in LN patients [7]


A
SSC
FSC
Gate 1
CD3
HN
Non-LN
LN
41.1
31.7
17.6
9.6
38.8
34.9
16.8
9.5
32.5
48.4
13.6
5.5
CXCR4
CD31
B
p<0.001
p=0.002
CD3+CD31+CXCR4+cells (%)
HN
Non-LN
LN
C
p=0.003
p=0.006
EPC (%)
HN
Non-LN
LN

Discussion

All studies reviewed in this report agreed about the presence and the accumulation of immune complexes and autoantibodies in the kidneys and the other organs involved in SLE

Autoantibodies and abnormalities in lymphocyte subsets have putative parts within the pathogenesis of SLE and LN, and might reflect disease action and are agreeable to immunosuppressive medications. Anti-DNA is one of the well-studied autoantibodies, which connects with disease movement and has direct nephritogenic impacts on resident renal cells and different glomerular components. Other critical autoantibodies within the pathogenesis of LN include anti-C1q, anti-α-actinin and anti-nucleosome antibodies. Changes in naive and memory B cells and plasma cells have been seen in SLE and LN patients [5]

These immune complexes deposit on the mesangium, subendothelial, and/or subepithelial space close the glomerular basement membrane of the kidney. This leads to an inflammatory reaction with the onset of lupus nephritis, in which the complement pathway is actuated with a resultant deluge of neutrophils and other inflammatory cells. Whereas an immune system phenomenon causes lupus nephritis, there are moreover hereditary components which may predispose an SLE quiet to develop lupus nephritis [1]

For occurrence, polymorphisms within the allele coding for the immunoglobulin receptors on macrophages and APOL1 gene varieties found exclusively in African American populaces with SLE were found to be related with predisposition to lupus nephritis[1]

Lupus nephritis may affect different compartments of the kidney, which are the glomeruli, interstitium, tubules and capillary loops. Aside from anti-dsDNA immune complex deposits, immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM) and complement (C1, C3, and properdin) are commonly found as mesangial, subendothelial and subepithelial deposits Leukocytes may also be present. [7]

Also one of the important finding is the present of peripheral monocytes in the injured tissues entering it and differentiate into inflammatory and reparative/resolving macrophages. If the cells are hronically exposed to damage-associated molecular pattern molecules (DAMPs) and endosomal TLR ligands, resolution may fail, and macrophages with mixed functions may emerge. Here, the three subpopulations of CD16+ macrophages are suggested to transition through an inflammatory to a resolution phase. Of note, there is no clusters of infiltrating cells with high similarity to CD14+ monocytes. It is still unclear why some types of tissue injury recruit CD14+ macrophages while others recruit CD16+ macrophages; influences may include the types of expressed DAMPS and/or other microenvironmental cues such as cytokines and chemokines [6]

If the degree of proteinuria meets the nephrotic syndrome criteria of more than 3.5 grams per day of protein excretion, then peripheral edema develops due to hypoalbuminemia . There may also be microscopic hematuria that is not grossly visible.

The current standardized classification system for lupus nephritis is derived from the World Health Organization (WHO) and International Society of Nephrology/Renal Pathology Society's recommendations.

The classification system is based on glomerular morphologic changes seen on microscopy, immune deposits seen on immunofluorescence, and also electronic microscopy

Class I is minimal mesangial lupus nephritis, in which glomeruli appear normal on light microscopy. Immunofluorescence shows immune complex deposits in the mesangial space

Class II is proliferative mesangial LN since mesangial proliferation is seen on light microscopy unlike Class I. Similar to class I, immunofluorescence also shows immune complex deposits in the mesangial space

Class III is focal lupus nephritis. Immune complex deposits may be visualized in the mesangial, subendothelial and/or subepithelial space on immunofluorescence imaging

Class IV is diffuse LN in which immune complex deposits may occur in the mesangial, subendothelial and/or the subepithelial space.

Lesions may be segmental, involving less than 50% of the glomeruli, or global, which instead involves more than 50%

Class V is membranous LN, in which immune complex deposits are in the mesangial and subepithelial space. Capillary loops are thickened due to subepithelial immune complex deposits. At this class, nephrotic range proteinuria occurs

Class V may also include Class III and IV pathology

Class VI is advanced sclerosing LN in which most of the glomeruli are sclerosed. However, immune complex deposits are not visualized on immunofluorescence since more than 90% of the glomeruli are scarred [1]

Conclusion

The circulating T cells appeared a positive relationship with the degree of proteinuria in LN patients ,this phenomenon may be somewhat clarified by immunological variations from the norm and the hoisted serum creatinine and proteinuria in LN patients

Hence, the present information support that LN patients are related with endothelial damage and increase cardiovascular risk , and the expanded levels of circulating T cells may be related to expanded cardiovascular chance and renal involvement

These patients need very close monitoring because not only does lupus have high morbidity, but the drugs used to manage and control the progression of the disease also have a number of adverse effects

The overall prognosis for patients with lupus nephritis is guarded.

When the disease advances, end-stage renal failure is inevitable , patients should be educated about renal transplant and its benefits before the disease has progressed .

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