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Early Detection of Subclinical Nephritis in Systemic Lupus Erythematosus Patients

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting many systems in the body. Because of the disease's tremendous variety, some researchers believe that it is a syndrome rather than a single disease. One of the most prevalent manifestations of SLE is lupus nephritis (LN). Nearly 40% to 70% of patients with SLE have LN.

The manifestations of LN range from asymptomatic urinary findings to nephrotic syndrome and progressive renal impairment. The International Society of Nephrology and the Renal Pathology Society (ISN/ RPS) have indicated that the various LN classes exhibit different natural history and clinical patterns. Subclinical lupus nephritis (SLN) is nephritis diagnosed via renal biopsy despite normal urinalysis. Renal biopsy is the most important procedure to detect renal damage and SLN.

Keywords: Lupus nephritis, Subclinical nephritis, Systemic lupus erythematosus.

Introduction

SLE is an autoimmune disorder affecting many systems in the body. Because of the disease's tremendous variety, some researchers believe that it is a syndrome rather than a single disease. One of the most prevalent manifestations of SLE is lupus nephritis (LN) with 40%-70% of patients having it. During a flare-up of SLE, inflammatory injury to the nephrons is known aslupus nephritis.[1-3] Not only can varied clinical images be seen in the same patient, but also may be changing from normal to severe damage to the kidney. Patients having LN differ in clinical manifestations and duration of illness. Severe damage of the kidney occurs quickly through intense inflammation. It may be reversible with the right medications that suppress the immunity, however, end stages of LN do not respond to these medications.[4] Subclinical lupus nephritis (SLN) is diagnosed when renal biopsy reveals pathological evidence of nephritis in patients having no or little proteinuria and normal laboratory markers. [5] As a result, it's assumed that the true prevalence of LN is larger thanwhat's been reported; about 60%-70 % of cases are Class I / II LN — suggesting mild nephritis, while 15%-20% of cases are a class III / IV LN —with bad prognosis. [6 and 7] The most approved pr-ocedure to detect nephritis in SLE pat-ients is renal biopsy. However, no obvi-ous criteria for renal biopsy have yet been established.

β2 microglobulin (B2M) is generally

detected in serum, urine, and other bodily fluids, and is virtually entirely broken down within the kidney; glomerular filtration eliminates 95 percent to 100 percent of circulating β2M. The cause that the β2M level is high in LN is vague, it may be due to the higher lymphocyte transformation seen in SLE patients. [8]

Epidemiology

Lupus prevalence rates in the United States range from 100 per 100,000 white women to 400 per 100,000 black women. Two and 8 per 100,000 per year is the estimated rate in North America, South America, and Europe. [9]

Etiology

SLE female patients having both hereditary and environmental factors which influence the pathogenesis. Immunological toleranceis irreversibly broken and endogenous nuclear antigen causes immune responses to them.

Pathogenesis

In SLE, increased autoantigen production during apoptosis (UV induced or spontaneous), reduced disposal, and presentation are all involved in the autoimmune response beginning.

Apoptotic blebs include nucleosomes that contain endogenous danger ligands that can bind to pathogen-associated molecular pattern receptors, promoting DC, [10] IFN alpha, and autoantibodies produced by B cell activation.

Classification criteria

In 1971, criteria for SLE were established and in 1982 it was reviewed and in 1997 reviewed again. the most recent one is the 2019 EULAR/ACR classification criteria (Table-1).

SLE Disease Activity Index (SLEDAI)

The change in disease activity and the predictors of damage and mortality had been observed by studies and consequently, the SLEDAI score has been developed. [12]

Subclinical lupus nephritis (SLN) includes patients in whom renal biopsy was abnormal in presence of little or no proteinuria and normal lab markers. [5]

Lupus nephritis (LN)

is one of the most prevalent and debilitating manifestations of (SLE), affecting more than 40%-60% of SLE patients. During SLE flare, inflammatory damage to the nephrons causes lupus nephritis. Not only unique Clinical images, as well as varying from normal kidney, to damage kidney. [13]

Criteria for diagnosing lupus nephritis

Proteinuria more than 0.5 g/day, or more than 3+ urinary dipstick protein, P/C ratio>0.5 mg/mg or more than five cells per high-power field of urinary cellular casts without infection of the urinary systemare all considered LN by criteria of the ACR lupus classification criteria.[14] The World Health Organization (WHO) classified LN in 1974 based onlyon glomerular lesions, and it went through several revisions until the Inte-rnational Society of Nephrology (ISN) and the Renal Pathology Society (RPS) came up with the most widely accepted classification (Table-2).

Table-1. 2019 EULAR/ACR classification criteria for systemic lupus erythematosus (SLE) (11)

Entry criterion	
Antinuclear antibodies (ANA) at a titer of≥1:80 other-2cells or an equivalent positive test (ever)	
↓	
If absent, do not classify as SLE If present, apply additive criteria	
↓	
Additive criteria Do not count a criterion if there is a more likely explanation than SLE The occurrence of a criterion on at least one occasion is sufficient.SLE classification requires at least one clinical criterion and ≥ 10 points Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total scores	
Clinical domains **Weight**	**Immunology domains** **Weight**
Constitutional Fever 2	**Antiphospholipid antibodies** Anti-cardiolipin antibodies OR Anti-B2GP1 antibodies OR lupus anticoagulant 2
Hematologic Leukopenia 3 Thrombocytopenia 4 Autoimmune hemolysis 4	**Complement proteins** Low C3 OR low C4 3 LowC3 AND low C4 4
Neuropsychiatric Delirium 3 Psychosis 3 Seizure 5	**SLE-specific antibodies** Anti-dsDNA antibody OR Anti-smith antibody 6
Mucocutaneous Non-scarring alopecia 2 Oral ulcers 2 Subacute cutaneous OR discoid lupus 4 Acute cutaneous lupus 6 Acute cutaneous lupus 6	
Serosal Pleural or pericardial effusion 5 Acute pericarditis 6	
Musculoskeletal Joint involvement 6	
Renal Proteinuria>0.5 g/24h 4 Renal biopsy Class II or V lupus nephritis 8 Renal biopsy Class III or IV lupus nephritis 8	
Total score:	
↓	
Classify as SLE with a score of 10 or more if entry criterion fulfilled	

Table-2: Classification of lupus nephritis (15).

ISN/RPS class	Description
I	Minimal Mesangial Lupus Nephritis
II	Mesangial proliferative Lupus Nephritis
III	Focal Lupus Nephritis
IV	Diffuse Lupus Nephritis
V	Membranous Lupus Nephritis
VI	Advanced Sclerosing Lupus Nephritis

Pathogenesis

Multiple variables, including genetic, epigenetic, and environmentalvariables are involved in the pathogenesis of SLE and LN. It's marked by a loss ofself- tolerance that leads to polyclonal antibody activation, which shows up in the form of a positive ANA and a full-house pattern on immunofluorescence in renal biopsy specimens.

T-cells and activators of B-cells are activated by the innate immune system in the early stages of illness, which leads to adaptive immune responseactivation of T- cells, such as type 1 T-helper (TH1) cells and TH17, are responsible forB-cell activation both systemically and intrarenal. After being activated by T cells or the innate immune system, B cells produce a variety of autoantibodies and cytokines. (16)

Renal Biopsy

The most important procedure to detect renal disease is a renal biopsy that was first time used in 1951.(17)

Role of renal biopsy in (LN)

LN is a histological diagnosis despite the existence of clinicalcriteria. The LN diagnosis is unmistakable thanks to the kidney biopsy. It gives proof for disease prediction, activity, chronicity, andtherapeutic planning. Because LN therapy includes potentially harsh medicines, startingtreatment without a clear diagnosis could be dangerous. Extraglomerular symptoms of SLE, such as TMA, non-lupus renal illness, or drug-induced interstitial nephritis, may be present in SLE patients who have signs suggestive of renal involvement, all of which have different therapy and results. As a result, kidney biopsy is considered a must-have in the treatment of LN. Proteinuria >0.5 g/day, 5 red blood cells or white blood cells detected by high-power field, typically dysmorphic withoutsigns of infection or rising serum creatinine are the most common reasons for a first kidney biopsy. (18)

Beta-2 Microglobulin (B2M)

In 1964, B2M was detected in the urine of peoplesuffering from Wilson's disease or cadmium poisoning. The structure of B2M consists of 100 amino acids with a low molecular weight (11,800 Da, size 11) that's encoded by a human gene on chromosome 15. (19)

Using β2M to Assess Glome-rular Function

Renal function can be measured in a variety of methods, the most common method used is glomerular filtration rate. This is accomplished by determining filtration marker clearance in plasma or in urine. B2M is a perfect en-dogenous marker that appears at a constant rate in plasma, the glomeruli filter B2M freely, not removed from extrarenal sites, tubules do not secrete B2M and are not absorbed into the circulation. (20)

Urinary markers can be predictors of renal damage

such as IgG (150 kD) which is a protein of high molecular weight excreted in large quantities when permselectivity of the glomerular capillary wall is severely disrupted.(21)

Therefore, these proteins could be markers of the severity of glomerular damage.

Monocyte chemoattractant protein-1 (MCP-1) is a leukocyte chemotactic factor that is involved in mediating inflammation and injury in lupus nephritis (22).

In lupus nephritis, increased expression of MCP-1 on endothelial cells, renal epithelial cells, and infiltrating mononuclear cells in the tubulointerstitial regions can be demonstrated by immunohistochemical staining. (23)

Urinary Tumor necrosis factor receptor (TNFR) is part of the superfamily of T-NF receptors which regulate the signaling of survival, proliferati6on, differentiation, and action of the immune and non-immune system cells (24). TNFR-1 is expressed in the glomerulus and di-stal and collecting tubules. High urina-ry levels correlate significantly in patients with active LN. (25)

Urinary Interleukin-6 (IL-6) is a pleiotropic cytokine produced by monocytes, T and B lymphocytes, fibroblasts, endothelial cells, and mesangial cells. (26)

The IL-6 production in mesangial cells, tubule epithelial cells, endothelial cells, and podocytes, have linked this cytokine to CKD, acute kidney disease (AK-D) and LN. (27)

N-acetyl-b-D-glucosaminidase (NAG) is a hydrolase-class enzyme, found abundantly in the lysosomes of cells located in the proximal tubules (28). Elevated urinary levels of NAG have been found in patients with LN compared with healthy individuals. Additionally, high levels of this enzyme correlate with proteinuria. (29)

Urinary epidermal growth factor: Hefny et al raised the attention to test the sensitivity of urinary EGF in detecting the early and the subsequent changes in renal pathology of SLE patients as an easy, non-invasive, accurate, cheap marker that could help in following up the nephritis progression and adjusting the plan of treatment; also, it can be used to guide the time of biopsy or as an alternative in cases when the renal biopsy is contraindicated. (30)

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