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LUPUS NEPHRITIS: A COMPREHENSIVE REVIEW OF PATHOGENESIS, DIAGNOSTIC INNOVATIONS AND THERAPEUTIC MANAGEMENT

Venkat Sainavaneeth Gurrala
Assistant lecturer, Department of Internal Medicine No.1, Samarkand State Medical University,Samarkand,Uzbekistan.
Mail: sainavaneeth1996@gmail.com

Akhmedov Ibrat Amrelevich
Assistant, PhD. Department of Internal Medicine No. 1, Samarkand State Medical University, Samarkand, Uzbekistan. Mail: ibrat.jamshed.axmedov@mail.ru
Orcid: - 0000-0003-0732-0798

Annotation. Lupus nephritis (LN), a common manifestation of systemic lupus erythematosus (SLE) that usually affects the kidneys, is a leading cause of morbidity and mortality in affected individuals. This article explores the pathophysiology of LN, emphasising the intricate interactions that lead to kidney injury between hereditary, environmental, and immunological variables. New insights into the molecular mechanisms of LN have made it possible to develop more effective diagnostic techniques. Biomarkers, like serum and urine indicators, are becoming more and more important for tracking the progression of diseases and for early identification. The article also addresses the current challenges in LN management, highlighting the limitations of conventional medicines, which frequently have considerable side effects and unpredictable efficacy. It emphasises the relevance of personalised medicine approaches, which are tailored to each patient's unique genetic and molecular profiles, in improving therapeutic outcomes. Emerging treatments, such as biologics and targeted immunosuppressive drugs, are explored because they have the potential to provide more effective and safer options. In conclusion, this comprehensive review provides a detailed overview of the latest advancements in the pathogenesis, diagnosis, and management of LN.

Keywords: Lupus Nephritis, Systemic Lupus Erythematosus, Kidney Involvement, Autoimmune Disease, Immune Complexes ,T-Cell Dysregulation, B-Cell Activation, Complement System, Autoantibodies, Renal Biopsy, Anti-dsDNA Antibodies, Complement System, Immunosuppressive Therapy, Corticosteroids, Cyclophosphamide, Mycophenolate Mofetil, Biologic Agents, Belimumab, Rituximab

Introduction

SLE is a chronic autoimmune illness that affects multiple organs, including the kidneys. LN, has a considerable impact on morbidity and mortality in SLE patients. This review summarizes our current understanding of the pathophysiology, diagnostic methods, and therapeutic strategies for kidney involvement in SLE. Pathogenesis is a complicated interaction of immunological dysregulation, genetic susceptibility, environmental stimuli, and renal microvascular injury [1]. For conclusive diagnosis and categorization, diagnostic evaluation includes clinical assessment, laboratory tests such as urine analysis, serological markers, and a kidney biopsy [2]. Various categorization methods, like the International

Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, help to stratify LN severity and guide treatment options [3]. A multidisciplinary strategy including rheumatologists, nephrologists, and other experts is needed for the management of LN. Depending on the severity of the disease, the histology results, and the patient's features, several treatment modalities are used, such as corticosteroids, immunosuppressive drugs, and biologic therapy [2]. Despite breakthroughs, problems remain in getting optimal outcomes, necessitating continued research into novel therapeutic targets and personalized treatment strategies. This study emphasizes the need of early identification, quick intervention, and comprehensive management to reduce renal damage and enhance long-term outcomes in SLE patients with kidney involvement.

Pathogenesis of Kidney Involvement in SLE

SLE kidney involvement is caused by a multifaceted pathophysiology that involves intricate interactions between immunological, genetic, and environmental variables.

Immune Dysregulation and Autoantibody Production:The abnormal activation of both innate and adaptive immune responses contributes to immunological dysregulation in SLE. Dysregulated T lymphocytes, particularly Th1, Th2, and Th17 subsets, are implicated in the persistence of renal inflammation and injury [4]. These T cell subsets generate chemokines and pro-inflammatory cytokines that stimulate leukocyte recruitment and activation in the renal parenchyma, which eventually results in tissue damage [5]. B lymphocytes also contribute significantly to LN development by producing autoantibodies against nuclear antigens such as anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), and anti-ribonucleoprotein (anti-RNP) antibodies. These autoantibodies generate immune complexes with self-antigens, which deposit in glomeruli and activate complement pathways, causing tissue inflammation and injury [6].

Genetic Predisposition: It has a substantial impact on the etiology of kidney involvement in SLE, influencing both disease susceptibility and lupus nephritis severity. Several genetic loci and polymorphisms have been found to contribute to these processes.

The Major Histocompatibility Complex (MHC) Region is one of the most important genetic regions related with SLE and LN, specifically the human leukocyte antigen (HLA) genes. Certain HLA alleles, including HLA-DR2 and HLA-DR3, have been associated to an increased risk of developing SLE and LN. These alleles are critical for antigen presentation and immunological control, and alterations can cause immune dysregulation and increased autoimmunity [7]. In addition to the MHC region, some non-MHC genes play an important role. Polymorphisms in genes that encode complement components, such as C1q, C2, and C4, can have a major impact on immune complex clearance. Deficiencies or mutations in these genes can hamper clearance, leading in the formation of immunological complexes in the kidneys and consequent tissue injury [8]. Variants in genes related to the type I interferon (IFN) pathway, including IRF5, IRF7, and STAT4, have been linked to SLE and LN. These genes regulate immunological responses, and their polymorphisms can result in increased production of type I IFNs, which promotes autoimmune activity and renal involvement [9]. SLE etiology and LN severity are substantially influenced by polymorphisms in genes controlling B cell activation and differentiation, such as BLK, BANK1, and PTPN22 [10]. Genetic variations causing dysregulated B cell responses lead to increased generation of autoantibodies and immune complex deposition in the kidneys, which in turn drives renal inflammation. Genetic polymorphisms in genes associated in the NF-κB signaling pathway, specifically TNFAIP3 and TNIP1, have been linked to LN susceptibility [11]. Genetic variations alter NF-κB activity, leading to inflammation and immune-mediated injury in renal tissues.

Environmental Triggers: They have a substantial impact on the development of SLE and its renal manifestation, LN. Various environmental stimuli can interact with genetic predispositions to activate autoimmune processes that eventually harm the kidneys.

UV exposure is one of the most well-documented environmental causes of SLE. UV light can cause skin

damage, causing cells to liberate nuclear material, which can result in the development of autoantibodies and immunological complex formation in genetically sensitive individuals. These immune complexes can accumulate in the kidney's glomeruli, causing LN-like inflammation and damage [4]. Certain infections are known to worsen or precipitate the onset of SLE. Epstein-Barr virus (EBV) infections have been linked specifically to this. EBV can cause molecular mimicry, in which viral antigens resemble self-antigens, resulting in an autoimmune reaction. Chronic immune activation caused by such infections might result in immune complex deposition in the kidneys, which contributes to lupus nephritis [12, 13]. It has been demonstrated that hormones, especially estrogen, have an impact on how SLE develops. In addition to promoting the survival of autoreactive B cells, which generate autoantibodies, estrogen can also influence immunological responses. The kidneys may become inflamed and damaged as a result of these autoantibodies forming complexes that deposit there and result in lupus nephritis. Hormonal effects play a role in the greater occurrence of SLE in women, especially during the reproductive years [14]. SLE risk has been associated with exposure to environmental contaminants, including silica, cigarette smoke, and certain chemicals. These toxins have the potential to cause oxidative stress and inflammatory reactions, which could boost the synthesis of autoantibodies and the development of immune complexes, ultimately resulting in renal involvement in SLE [15].

Immune Complexes: The accumulation of immune complexes in the renal glomeruli causes an inflammatory response. This response activates the complement system, which recruits inflammatory cells and releases cytokines and chemokines. The resulting inflammatory cascade causes glomerular damage, which is characterized by proteinuria, hematuria, and eventually renal damage [4]. Research has indicated a positive correlation between the degree of renal injury in LN and the existence of these immune complexes. Immune complex accumulation in the kidney's glomerulus triggers a number of pathological processes, such as mesangial proliferation, endothelial injury, crescent formation, and fibrosis [16].

DIAGNOSTIC APPROACHES

Clinical, laboratory, and histological assessments are used in the diagnosis of LN, a severe symptom of SLE. Verifying the diagnosis, assessing the severity of the illness, and directing treatment are the main objectives.

Clinical Evaluation: Patients with LN may exhibit symptoms such as edema, hypertension, and clinical signs of nephrotic syndrome (e.g., severe proteinuria, hypoalbuminemia, and hyperlipidemia) or nephritic syndrome (e.g., hematuria and impaired kidney function) [17].

Laboratory Tests: Urinalysis is an important technique in the early diagnosis of LN because it detects proteinuria, hematuria, and cellular casts, all of which indicate glomerular inflammation [18]. Proteinuria can be assessed with a 24-hour urine collection or a spot urine protein-to-creatinine ratio. Proteinuria above 500 mg/day is indicative of active LN [4]. Elevated blood creatinine levels or a decreased eGFR suggest compromised renal function and are important markers in the evaluation of LN [19]. It is critical to assess anti-dsDNA antibodies and complement levels (C3 and C4) in LN because high anti-dsDNA levels and low complement levels are frequently associated with disease activity and renal involvement [2].

Histopathological Assessment: Biopsy is used in lupus nephritis (LN) to confirm the diagnosis, characterise the type and severity of renal involvement, and guide treatment decisions. Key indications for doing a kidney biopsy in suspected LN are

Persistent Proteinuria: A biopsy is necessary to identify the underlying renal pathology when there is significant proteinuria (more than 0.5 g/day), particularly if it is ongoing or accompanied by hematuria [20].

Renal insufficiency: A biopsy is warranted to determine the degree and activity of renal involvement when there is an elevated blood creatinine level or a declining estimated glomerular filtration rate (eGFR)

that indicates deteriorating renal function [20].

Active Sediment: To assess the degree of glomerular inflammation, a biopsy is indicated when there is active urinary sediment, such as hematuria, white blood cell casts, or red blood cell casts [21].

Failure to Respond to medication: A second biopsy might reveal whether a patient's LN is chronically damaged or still active when standard immunosuppressive medication fails [22].

Uncertain Diagnosis: A biopsy is helpful in firmly diagnosing LN and ruling out other renal diseases when the clinical presentation is unusual, or the diagnosis is unclear [23].

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system divides lupus nephritis (LN) into six separate classes based on histological findings from kidney biopsies, with a focus on glomerular lesions. This classification aids treatment planning and outcome prediction.

Class I (Minimal Mesangial LN): Characterized by minimal mesangial deposits visible only under immunofluorescence, with normal findings under light microscopy. It usually manifests with mild clinical symptoms [24].

Class II (Mesangial Proliferative LN): Involves mesangial hypercellularity and mesangial matrix expansion visible on light microscopy, with immune deposits in the mesangium. This class typically has a good prognosis and minor clinical symptoms [24].

Class III (Focal LN): Defined by involvement of less than 50% of glomeruli with segmental or global endocapillary or extra capillary proliferation and necrosis. This class is frequently associated with hematuria, proteinuria, and, in certain cases, decreased renal function [24].

Class IV (Diffuse LN): Involvement of more than 50% of the glomeruli, with segmental or global endocapillary or extra capillary growth and necrosis. This class is frequently linked with significant clinical symptoms and a poor prognosis, requiring vigorous therapy [24].

Class V (Membranous LN): Subepithelial immune deposits cause glomerular basement membrane thickening. This class can be associated with nephrotic syndrome and is frequently handled according to the severity of proteinuria [24].

Class VI (Advanced Sclerosing LN): Marked by global sclerosis of more than 90% of glomeruli, indicative of advanced chronic damage. This class is commonly associated with poor renal function and is frequently regarded as indicative of end-stage renal disease [24].

MANAGEMENT STRATEGIES: A multidisciplinary strategy is required for effective lupus nephritis (LN) management, which includes collaboration among nephrologists, rheumatologists, primary care physicians, and other healthcare providers. Nephrologists are essential in the diagnosis, monitoring, and interpretation of kidney biopsies as well as in the management of associated conditions such proteinuria and hypertension [25]. Rheumatologists focus on the systemic components of lupus and work with immunosuppressive medication to limit disease activity [3]. Primary care physicians have an important role in ongoing patient treatment, including monitoring for pharmaceutical adverse effects and managing comorbid illnesses such as cardiovascular disease and infections [2]. Nurses and nurse practitioners educate patients, encourage adherence to treatment protocols, and help manage adverse effects. Pharmacists monitor medication safety, manage drug interactions, and educate patients on medication adherence [25]. Psychologists and social workers assist patients in managing the psychological effects of long-term sickness, assisting them in overcoming the social and emotional obstacles associated with living with lung disease (25). This coordinated treatment paradigm improves patient outcomes by ensuring that both renal and systemic lupus symptoms are managed comprehensively and consistently.

Treatment Modalities:

Induction Therapy: Cyclophosphamide or mycophenolate mofetil (MMF) are frequently used in conjunction with high-dose corticosteroids. Because MMF has a superior safety profile than cyclophosphamide, studies have shown that it is an effective substitute [26].

Maintenance Therapy: To avoid relapses, lower dosages of corticosteroids are used with MMF or

azathioprine. Maintenance therapy is essential for long-term illness control [26].

Biologic Agents: Belimumab, a monoclonal antibody that targets the B-cell activating factor (BAFF), has been licensed for use in LN therapy after demonstrating efficacy in lowering disease activity. Rituximab, which targets CD20 on B cells, is used in refractory patients, but its efficacy varies [26].

Voclosporin: A novel calcineurin inhibitor, voclosporin, has demonstrated encouraging outcomes in clinical studies, offering patients with LN that is challenging to treat an extra choice [26].

Challenges:

Heterogeneity of Disease: Lupus nephritis (LN) is highly varied in clinical presentation and course, making it difficult to create a single therapy approach. This diversity needs personalised treatment approaches, complicating standardization and widespread adoption of therapy regimens [27].

Treatment Side Effects: Immunosuppressive medications (e.g., cyclophosphamide, mycophenolate mofetil) and high-dose corticosteroids, which are the cornerstones of LN therapy, are linked to serious side effects. These can include a higher chance of infections, infertility, and chronic issues like cancer, all of which have a negative effect on treatment compliance and quality of life [28][29].

Therapeutic Resistance and Relapse: A significant fraction of patients with LN progresses to end-stage renal disease (ESRD) and develops resistance to standard therapy or relapses often. The high relapse rate and resistance are significant obstacles to the efficient long-term management of the illness [30].

Future Directions:

Advances in genetics and biomarkers are enabling personalised medicine in LN. Identifying unique biomarkers that indicate response to therapy might assist personalise therapies to individual patients, thereby boosting efficacy and lowering side effects [28]. Developing medicines that target specific pathways in LN is a potential field of research. Belimumab and rituximab have shown promise in clinical trials. These medicines provide the advantage of treating the underlying immunological dysregulation with potentially fewer side effects than standard immunosuppressants [31]. Another interesting method is to use lower doses of numerous medicines to reduce toxicity while increasing therapeutic efficacy. This strategy seeks to alleviate the burden of adverse effects associated with high-dose monotherapies. Early research indicates that combo therapy may be more effective and more tolerated [28].

CONCLUSION

LN remains a significant clinical problem due to its heterogeneity and serious consequences. Key concerns include the heterogeneity in clinical presentation, which needs personalised treatment methods, as well as the significant side effects of existing standard medicines such as high-dose corticosteroids and immunosuppressive drugs. These treatments, while successful, frequently raise the risk of infections, infertility, and long-term consequences, affecting patient quality of life and adherence. Future LN management strategies will focus on the development of targeted medicines and the identification of reliable biomarkers to guide treatment and monitor disease activity. Advances in personalised medicine, which incorporate genetic and molecular data, are positioned to improve therapeutic success while minimising side effects. Continued research into novel therapeutic targets and the long-term safety of developing biologics is critical to improving patient outcomes. In conclusion, although current LN therapies are successful, the difficulties they present highlight the necessity for more sophisticated, customised treatment plans. Future studies concentrating on biomarkers and specific treatments could result in safer and more efficient LN management.

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