SCIENCE BOX

Ushbu maqolaga onlayn kiring

Quick Response Code:

Website: https://sciencebox.uz

ISSN: 2181-3464

Jild: 02 Nashr:12 2023 yil

The Prognostic Importance of Clinical Aspects of Lyupus Nephritis

Nazarova Nigina Otabek qizi[1]

Jabbarov Azim Ataxanovich[2]

[1]PHD., assistent, TASHKENT MEDICAL ACADEMY, DEPARTMENT OF FACULTY AND HOSPITAL THERAPY №2, NEPHROLOGY AND HEMODIALYSIS

[2]DcS., professor, TASHKENT MEDICAL ACADEMY, DEPARTMENT OF FACULTY AND HOSPITAL THERAPY №2, NEPHROLOGY AND HEMODIALYSIS

Annotatsiya: Lupus nephritis (LN) affects 30–60% of adults and up to 70% of children with systemic lupus erythematosus (SLE) and is characterized by the glomerular deposition of immune complexes followed by recruitment of an inflammatory response. Glomerular disease is classified by light microscopy into five histologic subtypes of which classes III–V have the potential for long term damage. Further histologic classification uses composite scores for active inflammation and chronic scarring. Although classification drives therapeutic decision-making, the current scheme does not adequately predict which patients will respond to therapy, indicating that additional phenotyping based on mechanisms of tissue injury is required. In addition, patients in clinical remission may exhibit progressive inflammation and fibrosis in repeat biopsies suggesting that improved disease monitoring could prevent undertreatment of subclinical disease.

Kalit so'zlar: SLE, lupus nephritis, factor, mechanism.

Despite marked improvements in the survival of patients with severe lupus nephritis over the last 50 years the rate of complete clinical remission following immune suppression is less than 50% and renal impairment still occurs in 40% of affected patients. An appreciation of factors leading to the development of chronic kidney disease (CKD) following acute or subacute renal injury in lupus patients is beginning to emerge. Processes that contribute to endstage renal injury include continuing inflammation, activation of intrinsic renal cells, cell stress and hypoxia, metabolic abnormalities, aberrant tissue repair and tissue fibrosis. This understanding is leading to the development of novel or adjunctive therapies that may protect from the secondary non-immune consequences of acute injury. Approaches based on a molecular/proteomic/lipidomic classification of disease should yield new information about the functional basis of disease heterogeneity so that the most effective and least toxic treatment regimens can be formulated for individual patients.

While advances in immunosuppressive regimens and general medical care have erased most of the differences in long-term outcomes between proliferative and membranous LN (7, 10–11), the rate of complete remission for proliferative disease remains below 50% (12–14), and up to 40% of LN patients still develop some degree of renal impairment (11, 14). This failure of immunosuppressive agents to adequately treat LN, even in the setting of well-monitored clinical trials, reflects an incomplete understanding of disease pathogenesis. Either immune cell proliferation is not the only relevant cause of renal injury, or there is a therapeutic time window after which this type of intervention is no longer effective.

In the first section of this review I will discuss current knowledge of LN pathogenesis including disease initiation by immune complexes, immune activation in the kidney, and the responses of renal parenchymal cells to this insult. In the second part I will discuss approaches to identifying new pathogenic mechanisms, and review alternate ways to classify and monitor disease that include molecular and proteomic analyses. Finally I will address how these concepts may lead to improved therapies.

LN is initiated in most cases by the glomerular deposition of IgG and complement. Rarely, LN occurs in the absence of immune complexes, presumably due to direct damage by soluble inflammatory mediators (15). Sources of immune complexes include circulating anti-nuclear, anti-C1q, and crossreactive anti-glomerular autoantibodies (16), opsonized apoptotic particles, microparticles, and neutrophil NETs (11). Particulate DNA such as that within neutrophil NETs can be resistant to digestion by DNAse (20), and downregulation of renal DNAse I can be a late feature of disease (23). Although antibodies eluted from LN kidneys are enriched for anti-DNA activity, not all anti-DNA antibodies are pathogenic. Furthermore, non-DNA binding antibodies, some arising *in situ*, also contribute to renal disease (6). This heterogeneity of renal depositing antibodies limits the ability of serum antibody profiles to predict LN flares (16).

Immune complexes initiate renal damage by several mechanisms. Complexes that deposit in the subendothelium injure endothelial cells and are the hallmark of Class III and IV proliferative disease. These deposits have access to the vascular space and may activate circulating myeloid cells that express Fc receptors, allowing them to infiltrate the renal tissue (17). By contrast, subepithelial deposits, found in Class V disease, injure podocytes but elicit a less severe inflammatory response as they contact only the urinary space. If the glomerular basement membrane ruptures however, these immune complexes can access the whole glomerulus. Immune deposits may initiate the complement cascade, or they may directly activate intrinsic glomerular cells (20), inducing the release of inflammatory chemokines and cytokines. Complexes containing nucleic acids additionally activate intracellular TLRs, thereby enhancing the inflammatory response.

Following immune complex deposition, a large variety of inflammatory mediators is produced in LN kidneys with spreading of the response as disease progresses. Several locally produced cytokines and chemokines that contribute to inflammatory damage and whose absence or inhibition greatly attenuates disease activity have been identified. Examples include CCL2, a chemokine expressed early in the glomerulonephritis process, and TNF that is expressed at proteinuria onset. A Type I IFN signature is also a feature of LN kidneys. IFN has multiple detrimental effects on the kidneys including vascular rarefaction and injury to glomerular parietal cells and podocytes. Once tissue injury occurs, soluble products released from injured cells amplify the inflammatory response by stimulating extracellular and intracellular innate immune receptors. Podocytes, for example, are sensitive to TLR-mediated signals and other inflammatory mediators such as NO, which induce foot process effacement and podocyte loss. Nevertheless, not all renal inflammatory mediators are necessary for the inflammatory process. For example, IL-17 deficiency alters the course of LN only in some models in which TH17 cells infiltrate the kidneys. Thus, targeting of single inflammatory mediators may not be sufficient to reverse the established renal inflammatory

Inflammatory cells may infiltrate the kidney through glomerular or interstitial blood vessels. The anatomic organization of these infiltrates is quite variable. They may consist of scattered cells, disorganized aggregates, or rarely, organized structures containing germinal centers. There is also evidence for *in situ* activation of pathogenic adaptive immune responses to degraded or modified renal antigens. Both B cells and T cells from LN kidneys are clonally expanded, and the same T cell expansions have been detected in the peripheral blood. Multiple T cell cytokines such as IFNγ, IL-21 and IL-17 have also been detected in LN kidneys, and T cells appear in the urine of LN patients. In a small exploratory study, clonal CD8 T cell infiltrates were found adjacent to epithelial cells in LN biopsies and were associated with more severe disease, suggesting an effector function elicited by local antigens.

Strikingly, a measurable proportion of B cells derived from human LN biopsies recognize vimentin, an intracellular structural protein that is cleaved and extruded from apoptotic cells. Serum anti-vimentin antibodies are associated with decreasing GFR and increasing tubulointerstitial damage in other forms of CKD, and are similarly associated with severe interstitial disease in LN. Autoantibodies to annexin1 and αenolase have also been detected in LN kidneys. These local adaptive immune responses may amplify inflammation independently of systemic autoimmunity.

Macrophages play a central role in both injury and repair; renal infiltration of LN kidneys with macrophages, particularly at the second biopsy, is associated with poor prognosis (52–54). Both infiltrating inflammatory macrophages and resident interstitial macrophages may be present in diseased kidneys. Macrophages recruited from the peripheral blood are pro-inflammatory during acute inflammation but can then switch to a reparative phenotype. Resident interstitial macrophages may have self-renewal properties, and in mouse models of chronic LN, they increase in number, become activated, and acquire MMP and cathepsin activity, suggesting that they contribute to aberrant tissue remodeling (15).

It is increasingly recognized that several types of dendritic cells also infiltrate the kidneys during LN potentially propagating local adaptive immune responses. Importantly, an increase in both $CD141^{hi}$ and myeloid DCs is observed in human glomerulonephritis biopsies and correlates with fibrosis.

Non-immune mechanisms of tissue injury in LN

Several lines of evidence suggest that non-immune mechanisms of renal damage need to be therapeutically addressed in LN. First, many patients do not adequately respond to immunologic interventions. Second, remission can take months, during which time damage may continue to accrue. Third, progression may occur even if systemic autoimmunity is controlled. Although the role of each intrinsic renal cell during the stages of injury and repair is still not fully understood, some general mechanisms of CKD should also be applicable to LN.

Maintenance of the complex structure of the nephron requires cell-cell interactions (2) (Figure 1). In the glomerulus, endothelial cells directly contact mesangial cells (3). Mesangial cells sequester latent TGFβ, preventing TGFβ-mediated damage to endothelial cells (4). Endothelial cells produce PDGF-B whose interaction with PDGF-Rβ on mesangial cells is required for glomerular development. Expression of PDGF isoforms is upregulated in many forms of renal injury, causing mesangial hyperproliferation, matrix production, cytokine and chemokine release, and renal fibrosis (5).

Podocytes and endothelial cells also interact by bidirectional diffusion of cytokines/growth factors through the glomerular basement membrane (3). Podocytes secrete angiopoietin 1 and VEGF-A that support endothelial cell survival; loss of renal VEGF-A characterizes LN both in humans and mouse models and distinguishes LN from other forms of CKD (4). In diseased tissue, both activated glomerular endothelial cells and damaged podocytes release endothelin 1 that amplifies glomerular injury by causing mitochondrial stress (6). Since podocyte regenerative capacity is limited in adults, loss of podocytes eventually leads to glomerulosclerosis. As nephrons are lost, compensatory mechanisms cause a rise in intraglomerular pressure and glomerular stress in the remaining nephrons (7).

A cell that has received much recent attention is the pericyte which contacts and shares a basement membrane with capillary endothelial cells. Pericytes secrete VEGF-A, chemokines and other inflammatory mediators, they help maintain endothelial cell quiescence, they contribute to the basement membrane and they regulate both medullary blood flow and cell traffic through the endothelial barrier during inflammation (5). Mesangial cells are the pericytes of the glomerulus and the interstitium has its own pericyte network attached to tubular capillaries. During inflammation, these pericytes rapidly dissociate from tubular capillaries and migrate into the interstitial space where they differentiate into myofibrobasts (11).

Glomerular endothelial cells are coated with a glycocalyx layer that forms a crucial barrier to protein loss (2); this barrier can be degraded by the enzyme heparanase that is induced by endothelial hypoxic stress (13). As pericytes dissociate from capillaries and VEGF-A production diminishes, the capacity for angiogenesis and capillary repair is lost, leading to capillary rarefaction in both the glomerulus and the interstitium (18). Other disturbances of angiogenesis reported in LN include a decrease in the ratio of pro-angiogenic Ang1/anti-angiogenic Ang2, downregulation of the angiogenic factor FGF-2, an increase in the VEGF inhibitor ADAMTS-1, and alterations in endothelial nitric oxide synthase (16). In a mouse model of LN, downregulation of VEGF-A and FGF-2 persists even after induction of complete remission, suggesting that vascular injury is not completely reversible (10).

Some areas of the kidney, especially the medulla, maintain a low pO2 even under normal physiologic conditions and are sensitive to hypoxia. The interstitial blood supply derives from post-glomerular blood vessels, so glomerular hypertension and sclerosis can cause interstitial ischemia. Loss of VEGF-A, oxidative stress due to inflammation, increased energy demands, endothelial cell injury by cytokines, enhanced endothelin release, hypertension and anemia may all contribute to hypoxia (13); the relative contribution of each of these mechanisms is not well understood.

Ischemia, hypertension or failed regeneration contribute to atrophy of tubular epithelial cells; such injury promotes both interstitial immune cell infiltrates and fibrosis. Recent studies have shown that injured renal tubular cells have a defect in fatty acid oxidation which causes mitochondrial dysfunction, reprograms them to a pro-fibrotic phenotype, and contributes to their death (20). The defect can be reversed by tubule-specific expression of the mitochondrial biogenesis regulator PGC-1α. Importantly, human fibrotic kidneys have a similar alteration in tubular fatty acid metabolism, suggesting a potential new therapeutic approach.

Renal fibrosis is a poor prognostic feature in LN as in CKD generally. The extent of fibrosis is determined by the balance of matrix production with enzyme-mediated matrix breakdown and turnover. Mesangial cells are the classical myofibroblasts in the glomerulus, but parietal epithelial cells and podocytes may also contribute. In the interstitium, pericytes and resident fibroblasts are the major sources of myofibroblasts that produce extracellular matrix, MMP inhibitors and collagen. Both tissue macrophages and tubular epithelial cells produce growth factors that support myofibroblast differentiation, including TGFβ, PDGF and CTGF. These factors are balanced by local anti-fibrotic factors such as the TGFβ antagonists BMP-7 and hepatocyte growth factor. In addition, cytokines, chemokines, matrix proteins, procoagulants and remodeling enzymes produced by inflammatory cells, tubular cells and macrophages provide a pro-fibrotic microenvironment.

Although it has not been shown unequivocally that an area of fibrosis will damage adjacent healthy nephrons, several lines of evidence indicate that fibrosis can amplify renal damage. Fibroblasts may contribute to tissue injury by producing pro-inflammatory mediators. Fibrotic tissue may disrupt normal anatomic structures and interfere with oxygen diffusion, thus exacerbating hypoxia. In addition, epigenetic changes can reprogram fibroblasts to maintain their profibrotic state even after inflammation has resolved. One epigenetic change that has received considerable attention is the upregulation of miR-21 that protects against acute renal inflammation and damage but may also exacerbate fibrosis.

Literature

1. Тареева И.Е., Краснова Т.Н. Поражение почек при системной красной волчанке. Нефрология. Руководство для врачей. Под ред. И.Е.Тареевой. М.: Медицина, 2000.
2. Vu T.V., Escalante A. A comparison jf quality of life of patients with systemic lupus erythematosus. J Revmatol 1999; 26: 2595–601.
3. Trager J., Ward M.M. Mortality and causes of death in systemic lupus erythematosus. Current Opinion in Rheumatology 2001; 13: 345–51.

4. Cervera R., Khamashta M.A., Font J. Morbidity and mortality in systemic lupus erythematosus during a 10-year period. Medicine 2003; 82(5): 299–308.
5. Камерон Дж.С. Волчаночный нефрит и его ведение в 2001 г. В кн.: Успехи нефрологии. Под ред. Н.А. Мухина. М.: Русский врач, 2001; 145–64.
6. Тареева И.Е., Шилов Е.М, Краснова Т.Н. и др. Волчаночный нефрит в середине XX и начале XXI века. Тер арх 2001; 6: 5–10.
7. Метелева Н.А., Козловская Н.Л. Поражение почек при антифосфолипидном синдроме. Тер арх 2004; 9: 91–6. 8. Мухин Н.А., Козловская Л.В., Козловская Н.Л. и др. Первичный антифосфолипидный синдром – «венозный» и «артериальный» варианты течения. В кн.: Клинические разборы. Внутренние болезни. Под ред. Н.А. Мухина. М.: Литтерра, 2005; 261–77.
8. Стенина О.А., Сорокин Е.В., Фомичева О.А. и др. Распространенность и факторы риска атеросклероза у больных системной красной волчанкой. Кардиология 2005; 11: 105–8.
9. Kao A.H., Sabatine J.M., Manzi S. Update on vascular disease in systemic lupus erythematosus. Current Opinion in Rheumatology 2003; 15: 519–27.
10. Kohler H.P., Futers T.S., Grant P.J. Prevalence of three common polymorphisms in the A-subunit gene of factor XIII in patients with coronary artery disease. Thromb Haemost 1999; 81(4): 511–5.
11. Ward M.M. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. Arthritis and rheumatism 1999; 42(2): 338–46.
12. Шилов Е.М. Волчаночный нефрит: стратегия и лечение. Тер арх 2006; 5: 76–85.
13. D'Crus. Mycophenolate mofetil of systemic vasculitis. Lupus 2005; 14: 55–7.
14. Chan T., Tse K., Tang C. et al. Long-term study of micophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. Am J Soc Dis 2005; 16: 1076–84.
15. Nazarova, N., & Jabbarov, A. (2020). STUDY OF KIDNEY DAMAGE SIGNIFICANCE OF APOL1 G1/G2 and HAS2 GENE POLYMORPHISM IN SYSTEMIC LUPUS ERYTHEMATOSUS IN THE UZBEK NATION. Матеріали конференцій МЦНД, 54-55.
16. Назарова, Н. О., Жаббаров, А. А., & Мадазимова, Д. Х. (2020). ГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ ПОРАЖЕНИЯ ПОЧЕК У БОЛЬНЫХ СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКОЙ. In Современная патология: опыт, проблемы, перспективы (pp. 432-437).
17. Nazarova, N., & Jabbarov, A. (2020). STUDY OF KIDNEY DAMAGE SIGNIFICANCE OF APOL1 G1/G2 and HAS2 GENE POLYMORPHISM IN SYSTEMIC LUPUS ERYTHEMATOSUS IN THE UZBEK NATION. Матеріали конференцій МЦНД, 54-55.
18. Назарова, Н., & Жаббаров, О. (2022). ЛЮПУС НЕФРИТ РИВОЖЛАНИШИДА CD14 ГЕНИНИНГ АҲАМИЯТИ.
19. Назарова, Н., & Жаббаров, О. (2022). ЛЮПУС НЕФРИТ РИВОЖЛАНИШИДА TGFB1 ГЕНИНИНГ АҲАМИЯТИ.