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Review Article

Understanding tubulointerstitial injury and repair mechanisms paves the way for renal outcome improvement in lupus nephritis

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ABSTRACT

Despite improvements in patient survival and quality of life, long-term renal survival has not changed significantly in the recent decades and nephritis relapses affect over 50% of patients with lupus nephritis. Renal fibrosis affecting the tubulointerstitial compartment is a central determinant of the prognosis of any kidney disease. Notwithstanding this evidence, the current 2003 ISN/RPS classification still focuses on glomerular pathology and does not include a mandatory score with clear subcategories of the tubulointerstitial injury in the biopsy. The pathogenesis, and the morphological and molecular characteristics of this process in patients with lupus nephritis will be considered, together with a discussion about the concepts the clinician needs to efficiently address in this injury during daily practice and in future clinical trials.

Both tubulointerstitial inflammation and fibrosis are strongly correlated with poor renal outcomes in lupus nephritis, regardless of the extent of glomerular damage. Therefore, it is essential to develop reliable and noninvasive approaches to predict which patients are most likely to develop CKD so that appropriate interventions can be adopted before ESRD is established. Currently, no ideal method for monitoring kidney fibrosis exists, since repeated renal biopsies are invasive. Promising methods for assessing and monitoring fibrosis non-invasively include imaging techniques, such as magnetic resonance imaging or ex vivo confocal microscopy, integrated in computational and digital pathology techniques.

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Finally, beyond specific immunosuppressive treatment in Lupus Nephritis, identifying and treating cardiovascular risk factors should be a cornerstone of treatment in these patients.

Entender la lesión tubulointersticial y los mecanismos de reparación será la vía para mejorar los desenlaces renales en nefritis lúpica

Palabras clave:
Nefritis lúpica
Inflamación intersticial
Atrofia tubular
Fibrosis intersticial
Biopsia renal

RESUMEN

A pesar de las mejoras en la sobrevida de los pacientes y su calidad de vida, la sobrevida renal en el largo plazo no ha cambiado significativamente durante las últimas décadas, y las recidivas nefríticas afectan a más del 50% de los pacientes con nefritis lúpica. La fibrosis renal, que afecta el compartimiento tubulointersticial, es un factor determinante central en el pronóstico de todas las patologías renales. A pesar de la evidencia, la actual clasificación ISN/RPS del 2003 todavía se concentra en la patología glomerular y no incluye un score obligatorio con claras subcategorías de la lesión tubulointersticial en la biopsia. Se hablará de la patogenia y las características morfológicas y moleculares de este proceso en pacientes con nefritis lúpica, así como de los conceptos que el clínico necesita para abordar esta lesión de manera eficiente en su práctica cotidiana y en los estudios clínicos a futuro.

Tanto la inflamación tubulointersticial como la fibrosis se relacionan fuertemente con desenlaces renales pobres en la nefritis lúpica, con independencia de la extensión del daño glomerular. Resulta por lo tanto esencial desarrollar sistemas confiables y no invasivos para predecir cuáles pacientes tendrán mayor probabilidad de desarrollar enfermedad renal crónica, a fin de realizar las intervenciones apropiadas antes de que se establezca la enfermedad renal terminal (ERT). En la actualidad, no existe un método ideal para monitorear la fibrosis renal, dado que las biopsias repetidas son procedimientos invasivos. Algunos de los métodos promisorios para evaluar y monitorear la fibrosis de manera no invasiva son las técnicas de imágenes, tales como la resonancia magnética o la microscopía confocal ex vivo, integradas en técnicas de patología computarizadas y digitales. Finalmente, más allá del tratamiento inmunosupresor específico para la nefritis lúpica, identificar y tratar los factores de riesgo cardiovascular deberá ser uno de los pilares de tratamiento en estos pacientes.

Background

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that affects mainly young women, and can result in progressive organ failure, leading to a four-fold relative risk of death compared to the general population. This risk is further increased in patients who develop chronic kidney disease (CKD) or end stage renal disease (ESRD).[1–3] Despite improvements in patient survival and quality of life, long-term renal survival has not changed significantly in the recent decades and nephritis relapses affect over 50% of patients with lupus nephritis (LN).[4]

The clinical manifestations of the disease were classified by the American College of Rheumatology (ACR) in 1982, revised in 1997[5,6] and these classification criteria were updated by the Systemic Lupus International Collaborating Clinics (SLICC) group in 2012[7] and subsequently by a EULAR/ACR working group in 2019.[8] Given that LN leads to ESRD in 17–25% of patients[9–10] and portends increased mortality,[11] the 2012 SLICC classification established biopsy-proven nephritis (compatible with SLE) as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Significant efforts have been made in the development of diagnostic tests but reliable lupus non-invasive biomarkers remain elusive.[12] Therefore, despite limitations of the histological classifications, the role of renal biopsy in SLE patients remains critical when there is suspicion of renal involvement.[13,14] Histology permits the assessment of disease activity and fibrosis, especially affecting the tubulointerstitium.[1] Tubulointerstitial (TI) injury is thought to begin as an inflammatory process, but unresolved inflammation may promote interstitial fibrosis and atrophy damage, two structural changes that are currently irreversible. Moreover, TI injury results in worse clinical outcomes with the development of progressive impairment of renal function.[15,16] Renal fibrosis affecting the TI compartment is a central determinant of the prognosis of any kidney disease.[17]

Notwithstanding this evidence, the current 2003 ISN/RPS classification focuses on glomerular pathology and does not include a mandatory score with clear subcategories of the TI injury in the biopsy. Since only a subset of patients develop chronic damage and kidney fibrosis is yet irreversible, it is essential to develop reliable and on-invasive approaches to predict which patients are most likely to develop CKD so that appropriate interventions can be adopted before ESRD is established.[15,18]

Following is a review the pathogenesis, the morphological and molecular characteristics of this process in patients with LN, including a discussion about the concepts the clinician needs to efficiently address in TI injury during daily practice. Brief consideration is also given to the design of future clinical trials intended to achieve earlier and longer sustained renal remission in SLE patients.

Pathogenesis of inflammation and tubulointerstitial damage

Among other factors, LN flares are initiated as a result of the deposition of nucleic acid-containing material and immune complexes in the glomeruli, which triggers the complement activation pathways and the recruitment of circulating pro-inflammatory cells. Disease progression is associated with TI ischemia and capillary disturbance, metabolic dysregulation of the tubular cell, accumulation of inflammatory infiltrates and finally fibrosis.[19] Thus, glomerular disease initiates TI disease (Fig. 1). Renal fibrosis is a pathological process characterized by an excessive accumulation of extracellular matrix proteins that result in the loss of the architecture and function of the organ. TI damage has been reported as an independent poor prognostic factor for long-term renal survival. However, the exact pathogenetic mechanisms that lead to TI inflammation and damage in LN remain unclear.[20] The following paragraphs discuss some of the pathways suggested in the pathogenesis of this condition.

Inflammation

Based on the known roles of both inflammation and fibrosis, as part of the normal processes for organ repair following injury, there is increasing evidence that inflammation leads to fibrosis.[21] In addition to glomerular infiltration of inflammatory cells in proliferative LN, TI infiltration is also common. It is not just limited to diffuse or patchy cellular infiltration, but it can also be observed as organized aggregates of T and B cells that differentiate into plasmablasts. Moreover, these are often organized into structures reminiscent of those observed in secondary lymphoid organs, such as germinal centers, also containing follicular dendritic cells.[22] Furthermore, these structures appear to be functional, as they are associated with in situ lymphocyte expansion and antigen-driven selection.[23] This cellular infiltration induces cytokine expression and is followed by tubular atrophy and interstitial fibrosis (IFTA).

Many cell-mediated injury pathways have been described, ranging from local reaction of activated T cells to interaction with antigen presenting cells (APC) (dendritic cells, recruited macrophages, B lymphocytes among others), to delayed-type hypersensitivity reaction of CD4+ T cells. Direct cytotoxic lymphocyte T CD8+ reaction has also been observed, but its role seems to be secondary. The presence of B cells in addition to high numbers of NK cells in aggressive proliferative LN, associated with TI immune deposits could indicate that antibody dependent cell-mediated cytotoxicity is also present in LN.[24] Local production of autoantibodies directed at renal antigens, such as vimentin, have been described which may themselves be pathogenic and imply a secondary intra-renal immune dysregulation in LN. Finally, macrophages may also play an additional role apart from APC: together with monocytes – found in lower numbers compared to lymphocytes –, they may contribute to tissue destruction through the release of proteolytic enzymes or via phagocytosis, finally leading to renal failure. Furthermore, the extent of macrophage infiltration correlates with the extent of fibrosis.[21]

Immunologic pathway

LN is initiated by an immunological disorder. In the vast majority of cases there is glomerular damage, although exceptionally cases of exclusively TI damage have been reported.[25] As previously mentioned, glomerular damage has on many occasions overshadowed the importance of interstitial damage, which is common in patients with LN. There is an immunological link between glomerulonephritis and TI inflammation in LN. Data from experimental models have provided mechanisms whereby breaking of tolerance in glomeruli leads to TI inflammation, through amplified TI immune responses, including production of intrarenal cytokines and infiltration by monocyte-derived dendritic cells and macrophages.[26] In this sense, glomeruli and the tubulointerstitium are not two totally independent compartments, since they interact with each other. In fact, the glomeruli of the juxtamedullary nephrons are surrounded and wrapped by a large amount of interstitial tissue. Thus, recruitment of circulating pro-inflammatory cells into the glomeruli in lupus glomerulonephritis may lead to TI inflammation.

In addition, proximal tubular epithelial cells (PTEC), which constitute the predominant cells within the tubulointerstitium and play not only a physiologic role in transport of fluid and electrolytes, but also a pivotal role in the initiation of the renal inflammatory response, act as a directional regulator/effector of immune-mediated inflammation and fibrosis.[20] It has been shown that PTEC may express HLA-DR antigens in response to immunological stimuli. The proportion of HLA-DR expressing tubular cells was greater in LN in comparison to other forms of glomerular diseases, thus indicating the high degree of tubular cell activation in LN. PTEC can process and present foreign antigen and synthesize proinflammatory cytokines, such as IL-6, thus contributing to tubular inflammation[20] and inducing a T helper cell response.[24]

Apart from the inflammatory response of PTEC generated by their function as APC, it has also been shown that they may contribute to recruitment of proinflammatory cells and the progression of TI inflammation through other mechanisms, such as stimulating the local synthesis of IL-6, IL-1β, and TNF-α, in response to the binding of anti-dsDNA antibodies to PTEC.[20] The mechanisms of PTEC-mediated renal damage

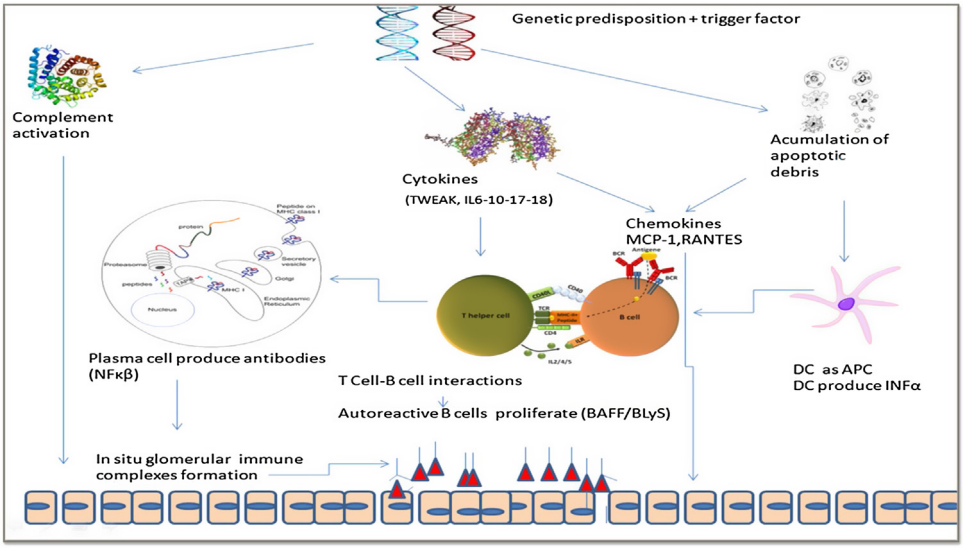

Fig. 1 – Pathogenesis of lupus nephritis. Genomics has identified risk genes in several pathways but with each having only a moderate impact on SLE risk. Environmental, hormonal, and epigenetic factors, add complexity to this pathogenic model and result in immune system deregulation. In situ formation of immune complexes between circulating antichromatin antibodies and extracellular glomerular chromatin seems the most plausible initiating event in LN. Such autoreactive specificities are generated by immune responses related to the defective uptake of apoptotic cell debris by neutrophils and macrophages and an increase in inflammatory cell turnover. Tubulointerstitial lymphoid tissue formation and intrarenal antibody production and complement activation contribute to renal inflammation. Activation of dendritic cells (DC) increases production of MHC class II for antigen presentation and augments release of IFN-**α**, leading to T-cell activation and differentiation of B cells into antibody-producing plasma cells. IFN-**α** serum levels and leukocyte mRNA are high in patients with SLE. Leukocytes and intrinsic kidney cells produce proinflammatory cytokines and chemokines in response to immune complexes and complement fragments 20, amplifying the vicious circle of renal inflammation and promoting new nephritis flares. Several intermediaries of inflammation such as tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), promotes glomerular epithelial cell proliferation, inflammation, and apoptosis. Conversely, others such as transforming growth factor beta (TGF-**β**) promotes scarring in injured glomeruli and the tubulointerstitium through accelerated matrix deposition.
Adapted from Quintana LF, Jayne D. Sustained remission in lupus nephritis: still a hard road ahead. Nephrol Dial Transplant [Internet]. 2016;31(12):2011–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26590267.

are extremely complex, and are not only due to a systemic inflammatory response of the disease but also to intrinsic renal damage pathways.

Extra-glomerular immune complex deposits

Over one half of the biopsy samples of patients with SLE have shown extra-glomerular immune deposits[25] containing immunoglobulins, complement and, less frequently, DNA products, presumably as antigen–antibody complexes. These were found in the peritubular capillaries of the interstitium and in the tubular basement membrane (TBM) using electron and sometimes light microscopes.[16]

Circulating immune complexes may be trapped in the renal vasculature and deposit in all segments of the nephron, including the TI compartment. There may also be in situ immune complex formation where an antibody binds to antigens that are constituents of the normal nephron structures or to antigens that become localized or 'planted' there. Native DNA or DNA-binding proteins may be found among these antigens, already deposited in the tubules or attached to endogenous tubular epithelial proteins. The predominance of one of these mechanisms of immune complex deposition in the TI compartment is not known. Furthermore, it is not yet clear whether TI immune complexes are of the same type as those observed in the glomeruli, and therefore have the same pathogenic mechanism.[27]

The functional relevance of interstitial immune deposits in the pathogenesis of the associated tubular and interstitial lesions, including inflammation and IFTA in LN remains to be evaluated. Some studies suggest that interstitial inflammation in LN may occur in response to immunoglobulin and/or complement deposition in the TBM and interstitium, although this point is controversial, since some authors report that they only play a minor role in the development of tubular epithelial lesions.[16,22,24,28]

Proteinuria

Loss of integrity of the glomerular filtration barrier allows proteins, mainly albumin, to pass through the renal tubule, and to come into close contact with PTEC. Proteinuria leads to up-regulation of the renal tubular cells, particularly proximal tubules, of a large quantity of different chemokines, particularly macrophage chemoattractants, major histocompatibility complex antigens and vasoactive substances, such

as endothelin-1. These proteins can then be released into the interstitium triggering the formation of T cells and macrophages, with up-regulation of transforming growth factor-β (TGF-β), monocyte chemoattractant protein 1 (MCP-1), platelet-derived growth factor and other inflammatory and fibrogenic chemokines, thus amplifying the inflammatory response. These, in turn, lead to fibroblast proliferation, myofibroblastic transformation and subsequent IFTA.[21,28]

Ischemia

Finally, another mechanism whereby TI injury could be initiated is through ischemia induced by glomerular inflammation. The glomerular efferent arteriole supplies the peritubular vascular bed. Severe GN may result in TI ischemia and damage, with subsequent inflammation. Progression to TI fibrosis activates additional mechanisms that accelerate progression to renal failure. There is an exuberant matrix deposition, which creates barriers to the diffusion of oxygen.[21] Hypoxic PTEC produce less VEGF, leading to attenuation of peritubular vessels and capillary loss,[19] thus accentuating this hypoxic vicious cycle.

Renal prognosis in patients with tubulointerstitial damage

Initially, the data obtained in earlier studies revealed that predictors of poor response to therapy and progression to ESRD were mainly associated with glomerular findings such as acute proliferative glomerulonephritis.[21] However, in these studies, other features such as TI inflammation were not systematically assessed. Moreover, many of them were performed in the early stages of cytotoxic and biologic treatments, which dramatically changed the prognosis of these patients, especially in the proliferative LN group. According to these studies, other predictors poor response involved clinical factors such as, anti-dsDNA antibodies and low complement levels despite treatment, hypertension, elevated serum creatinine, proteinuria and medication non-adherence.[29] Currently no validated tools are available to predict outcomes in lupus nephritis that include TI features.

Over the years, the distinction between acute and chronic renal damage, has been based not only on the evaluation of the glomerular compartment, but also TI damage to predict renal prognosis. Austin et al. developed a semi quantitative biopsy scoring system at the NIH which allows for the definition of an activity and chronicity index from the findings in renal histology evaluating both TI and glomerular compartments.[18,30] However, though these scores are still used, they are insufficient for an accurate evaluation of the TI compartment. The NIH activity index evaluates 6 pathologic features and only 1 of them refers to TI, assigning a maximum of 3 out of 24 points to this compartment. The Austin chronicity index has a total of 12 points, six correspond to IFTA, and 6 to chronic glomerular pathology (glomerulosclerosis and fibrous crescents). Interstitial inflammation is basically measured by the activity index, and the distinction between acute and chronic inflammation can be confusing. Moreover, TI inflammation is thought to precede IFTA. Thus, the NIH chronicity index is a composite score that equally reflects scarring in both the glomeruli and the tubulointerstitium.[21]

Several other studies have evaluated the prognostic factors in patients with LN based on the 2003 ISN/RPS classification.[31] However, the main objective of this classification is to establish the different classes of kidney injury in LN, excluding some potentially important histopathological features which might have a marked impact on LN treatment and prognosis. Among these are the extra glomerular lesions indicative of CKD, such as IFTA, interstitial inflammation and chronic vascular injury.

Over the past few years, the evaluation of TI injury, particularly the chronic forms, has become increasingly important in the design of studies, allowing for a multivariate analysis of the different factors that result in worse renal outcomes. These studies revealed that both TI inflammation and IFTA strongly correlate with poor renal outcomes in LN, regardless of the extent of glomerular damage.[32] On one hand, TI inflammation, which has been shown to be more prevalent in the proliferative classes of LN,[23,33] has been identified as one of the strongest histological correlates of baseline serum creatinine.[23,34] On the other hand, IFTA seems to be an independent risk factor for both ESRD and death.[29,35] In addition to these results, a greater risk of ESRD and death among patients with chronic vascular injury has been observed.[29] Notably, complement components and anti-dsDNA correlate poorly with TI lesions or chronicity.[36] This suggests that the prognostic value of Austin's chronicity index is primarily associated with those components that capture interstitial scarring,[21,23] as observed in many studies which address this question,[37,38] rather than glomerulosclerosis and fibrous crescents.

Assessment of renal fibrosis: renal biopsy, digital pathology, ex vivo confocal microscopy

Renal biopsy: conventional microscopy, immunofluorescence and electron microscopy

The gold-standard for the evaluation of TI inflammation and IFTA is the study of renal biopsy using different techniques, such as hematoxylin and eosin (H&E), periodic acid–Schiff (PAS) and Masson's trichrome stains under light microscopy. This is a laborious process involving slow processing times, adequate for identifying severe cases of interstitial inflammation, but apparently less effective for the identification of patients at intermediate risk for progression to ESRD. For mild or moderate interstitial inflammation, immunohistochemistry may provide additional information in these patients.[23]

Interstitial inflammation may be determined with semi-quantitative methods using monoclonal antibodies against CD45, a pan-leukocyte marker; CD20, a pan-B cell marker; and anti-CD3, a pan-T cell marker, all of them on paraffin tissue sections. Identification of immunoglobulins and complement components can be performed with standard immunofluorescence microscopy using fluorescein isothiocyanate-conjugated antibodies for the antigens IgG, IgA, IgM, C3, C1q, fibrinogen, κ and λ light chains, and albumin. Finally, histology samples can be processed with electron microscopy procedures that are also useful in LN to asses minimal changes of the disease, podocytopathies, delimitation of

immunocomplexes, inter alia, and for additional diagnostic information using light microscopy and immunofluorescence to visualize the renal ultra-structure.

Digital pathology in nephropathology

The pathological study of the renal biopsy is fundamental to establish the diagnosis and prognosis of renal diseases. However, routine histopathological evaluation is a time-consuming and irreversible process in a small tissue sample. These characteristics limit the type and the extent of the analysis to be conducted in fresh tissue and restrict the performance of post-processing molecular studies.[39] To solve these problems and obtain more information from kidney samples, computational pathology and digital pathology have emerged over the last decade. These tools and systems are used to digitize pathology slides and associated meta-data, facilitate their storage, review and analysis.[40,41] Digital image analysis software is built on artificial intelligence and uses deep learning algorithms that enable a computer to automatically discover relevant image features that contribute to gain high-level understanding from digital Images,[42] through an automated structures detection, such as cellular nuclei or fibrosis quantification. It includes methods for acquiring, processing, analysing and understanding digital images (for instance, H&E-like digital staining obtained from kidney biopsies), and extraction of real world high-dimensional data to produce numerical or symbolic information. These image analysis algorithms have been used in the past for the assessment of IFTA and inflammation in the field of renal transplantation.[43]

Ex vivo confocal microscopy

A digital pathology technique that is becoming increasingly relevant in nephrology is confocal microscopy (CM), a real-time technique which provides high-resolution images of fresh, non-fixed tissues, both in vivo and ex vivo.[44] CM is largely used in many clinical settings to enhance diagnostic and treatment capabilities, recently confirming its utility in nephropathology.[39] The ease and speed of acquisition of a two dimensional computer-built grayscale and fluorescence image of kidney samples,[45] combined with the quality of the images obtained with this fusion mode of ex vivo CM, suggests a promising future for this technique in renal practice. Confocal microscopy optimizes the information previously collected through conventional techniques, allowing nephropathologists to recognize the whole spectrum of renal lesion patterns in optical sections through thick, fresh tissues.[39]

Targeting tubulointerstitial injury – treatment considerations

Treatment of TI disease should be considered a lifelong treatment in all patients with LN, regardless of whether acute inflammatory activity is present or not. This includes a conscientious effort to prevent cardiovascular risk factors using lifestyle changes, including regular exercise, dietary recommendations, smoking cessation, and avoiding overweight, inter alia. In case of hypertension, angiotensin-converting enzyme inhibitors are generally the drugs of choice, since they specifically lower intraglomerular pressure, thus reducing the risk of proteinuria. Controlling cardiovascular risk factors has proven to be effective in slowing the progression of kidney injury and reducing mortality. Furthermore, patients with SLE not only have a higher risk of cardiovascular disease, but also CKD per se is an additional cause of endothelial dysfunction and increased cardiovascular risk.[19]

The treatment of renal fibrosis requires an improved understanding of the mechanisms of renal scar generation. Multiple lines of research have been developed focusing on various therapeutic targets and signaling pathways in renal fibrosis. These studies have focused on the drivers of fibrosis, such as myofibroblasts, extracellular matrix, matrix metalloproteinases and TGF-β1, among others.[46] The role of the M2 macrophage subpopulation, responsible for promoting a regenerative response in kidney damage, has also been extensively researched.[47] Unfortunately, beyond the immunosuppressive therapy[48] aimed at treating the inflammatory activity of TI lesions, there are no approved and effective therapies available (besides the above-mentioned) that halt or even reverse renal fibrosis in LN. However, there is growing interest in this field, as has been exemplified by the sodium-glucose transporter 2 (SGLT2) inhibitors in patients with diabetic CKD,[49] or tolvaptan in autosomal dominant polycystic disease.[50]

Conclusions

Persistent inflammation of the renal parenchyma in LN leads to IFTA, the key contributor to the progression of CKD. This pathological process is characterized by an excessive accumulation of extracellular matrix proteins that result in the loss of architecture and organ function. Both TI inflammation and IFTA strongly correlate with poor renal outcomes in LN, regardless of the extent of glomerular damage. Moreover, IFTA has shown to be an independent risk factor for both ESRD and death. Therefore, it is essential to develop reliable and noninvasive approaches to predict which patients are most likely to develop CKD so that appropriate interventions can be adopted before ESRD is established. No ideal method for monitoring kidney fibrosis is yet available, since repeated renal biopsies are invasive.[46] Promising methods for assessing and monitoring fibrosis non-invasively include imaging techniques, such as magnetic resonance imaging or CM, integrated in computational and digital pathology techniques. Finally, in addition to specific immunosuppressive treatment in LN, identifying and treating cardiovascular risk factors should be a cornerstone of treatment in these patients.

Key points

- Lupus nephritis is a major cause comorbidity and mortality in patients with systemic lupus erythematosus. Renal biopsy remains critical when renal involvement is suspected, despite histological subgrouping limitations,

because prompt recognition and treatment of renal involvement is correlated with better outcome.

- The 2003 ISN/RPS classification was based exclusively on glomerular lesions; nevertheless, increasing evidence shows that tubulointerstitial lesions are independent risk factors for the progression of some glomerular diseases, including LN.
- A mandatory biopsy scoring system of the tubulointerstitial injury is an urgent need in lupus nephritis. There is no ideal method currently available for monitoring kidney fibrosis, since repeated renal biopsies are invasive. Promising non-invasive methods for assessing and monitoring fibrosis include imaging techniques, such as magnetic resonance imaging or ex vivo confocal microscopy, integrated in computational and digital pathology techniques.
- Beyond specific immunosuppressive treatment in lupus nephritis, identifying and treating cardiovascular risk factors should be a cornerstone of treatment in these patients.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2021.05.003.

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