Lupus Nephritis

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease defined, as suggested by J.S. Cameron, by "its clinical picture" typically dominated by proteiform signs and symptoms, together with autoantibodies directed against one or more nuclear components, in particular, double-stranded DNA Ab (dsDNA). Lupus nephritis (LN) consists in kidney involvement in SLE. Glomerular inflammation dominates the histological picture, but any renal structure may be involved to different degrees.

8.1 Epidemiology of Kidney Involvement

After more than 40 years of investigation, and despite the huge amount of available data on the epidemiology of SLE (and LN), no firm conclusions have been reached, and results from different studies are heterogeneous, thus leading to a certain degree of confusion. Several variables should be considered when predicting the individual and collective risk of developing LN and SLE, in particular age, sex, geographic location, income, ethnicity, comorbidities, and genetics.

The incidence of SLE is now at least threefold higher as compared to estimates made in the 1950s [1]; the reasons underlying this phenomenon are still not fully understood. Similarly, the incidence of LN in the United States has progressively

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increased to 6.9 per 100,000 adults with a prevalence of 30.9 per 100,000 [2]. When subclinical LN is excluded, LN is clinically detectable in 3.1–76.1 % of individuals with a diagnosis of SLE [3, 4].

Until the 1970s, the overall survival rates of SLE with LN were comparable to those of patients with some solid tumors and ranged from 10 to 50 % 5 years after diagnosis. Overall survival in SLE has now progressively improved and has been reported to be as high as 91.4 % in recent studies [5, 6]. These data are probably influenced by the progressive inclusion of subjects with benign disease (previously not recognized or not identified by applied diagnostic tests). However, despite the recent decrease in overall mortality rate (estimated at 1.4 % and 1.6 % at 5 and 10 years, respectively), the annual incidence of patients that progress to end-stage renal disease (ESRD) because of LN is still high, i.e., 4.9 patients per million/year [7]. Indeed, even an early therapeutic approach is often not sufficient to prevent the decline of renal function in some patients with SLE.

8.1.1 Risk factors and development of LN

Increasing use of oral contraception and estrogen replacement therapy and exposure to ultraviolet radiation, pollution, and smoke are some of the potential factors underlying the increased prevalence of LN. Female gender is an independent risk factor for SLE, since women are six times more likely to be affected than men [2]; women are also more prone to show renal involvement. However, males are likely to develop more aggressive disease, leading to increased rates of ESRD [2]. Ethnicity is an important factor that weighs on incidence rates and prognosis and thus on the response of LN treatment. The LUMINA study, a multiethnic cohort of American individuals affected with SLE, showed that Hispanic and African-American individuals were more likely to develop LN (60.6 and 68.9 %, respectively) [8] compared to other ethnicities. In 2004, the GLADEL cohort confirmed these observations, showing that the cumulative incidence of renal involvement in SLE patients was 43.6 % in Caucasians, 58.3 % in Mestizos, and 55.3 % in African-Latin Americans 32 months after diagnosis [9]. Socioeconomic factors have been found to impact on the onset of LN [10]. The LUMINA analysis showed that the risk of developing LN in individuals having the same ethnic roots but with relevant sociopolitical differences, such as Puerto Rican Hispanics (US citizens) and Texan Hispanics (recent immigrants), was higher for those in low income groups [10]. Notably, alcohol intake, smoking, and recreational drug use do not appear to affect the onset of LN [8].

8.2 Clinical Features of LN

8.2.1 Clinical Renal Syndrome at Presentation

LN is the first manifestation in 20–25 % of patients with SLE. In general, LN develops within 5 years of SLE diagnosis. Clinical manifestations may be identified by six patterns: (1) urinary abnormalities, (2) nephritic syndrome, (3) nephrotic

syndrome, (4) acute renal failure, (5) chronic renal failure, and (6) rapidly progressive renal failure.

These six patterns may be concurrent, and together they define four main clinical presentations:

(a) Mild urinary abnormalities (microscopic hematuria, inflammatory casts, sterile leukocyturia) with or without mild to moderate proteinuria. These patients may have normal urine sediment most of the time; therefore, to avoid missing this subtle presentation of LN, urine analysis should be performed every 6–12 months in all SLE patients.
(b) Nephrotic (proteinuria >3.5 g/day, serum albumin <2.5 g/dl) or nephritic syndrome (sometimes together) and reduced renal function. They are often concomitant with systemic flares and suggest proliferative ± class V LN.
(c) Acute renal failure may be the first manifestation of the disease. Although infrequent, diffuse glomerular thrombosis induced by antiphospholipid antibodies may be observed. Acute interstitial nephritis should be considered, as should bilateral renal vein thrombosis in patients with nephrotic syndrome.
(d) Rapidly progressive renal failure may be an expression of focal segmental or, more frequently, diffuse proliferative LN with segmental necrosis and extracapillary proliferation.

8.2.2 Clinical Renal Course During Follow-Up

The clinical picture during follow-up can be addressed and classified into three groups:

1. New onset or persistence of mild urinary abnormalities after induction therapy. Despite mild or silent clinical activity, ESRD may occur because of the persistence of smoldering immunological activity.
2. Moderate to severe proteinuria with or without nephrotic syndrome, paired with active urinary sediment. Hypertension is usually concomitant. This pattern has poor prognostic value, and ESRD is observed in 50 % of individuals after 10 years. Similarly as in the previous pattern, mild to moderate serological activity and systemic disease are usually observed, but with more aggressive features of systemic involvement, nephrotic syndrome, hypertension, and renal failure. These individuals have poor overall and renal survival rates after 2 years of follow-up due to the challenges related to controlling the systemic and renal disease.
3. The last group has an aggressive clinical course defined by resistant hypertension with malignant features (papilledema), encephalopathy, heart failure, and rapidly progressive renal failure. Thrombotic microangiopathy (TMA) is the most worrisome event [11–13].

8.3 Morphological Features

Approximately 50 % of patients with SLE develop LN, which increases the risk of renal failure, cardiovascular disease, and death. EULAR (European League Against Rheumatism), ACR (American College of Rheumatology), and ECS (European consensus statement on the terminology for the management of LN) have issued guidelines to optimize the management of LN [14–17].

8.3.1 Indications for Renal Biopsy in SLE

Any sign of renal involvement – in particular, urinary findings such as reproducible proteinuria ≥0.5 g/24 h, especially with glomerular hematuria and/or cellular casts – should be an indication for renal biopsy. Renal biopsy is indispensable as clinical, serological, or laboratory tests cannot accurately predict renal biopsy findings.

8.3.2 Pathological Assessment of Kidney Biopsy

The use of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (2003) is recommended, including an assessment of active and chronic glomerular and tubulointerstitial changes and of vascular lesions associated with antiphospholipid antibodies/syndrome [18]. The classification of LN has evolved over the past 40 years.

The current classification, which was proposed in 1982 and revised in 1995, reflects the understanding of the pathogenesis of the various forms of renal injury in SLE nephritis. The ISN/RPS classification introduces several important modifications, mainly concerning quantitative and qualitative differences in order to distinguish between class III and IV lesions. Glomerular immune deposits attributable to LN, as detected by immunofluorescence (IF), almost always contain dominant polyclonal IgG, as well as C3 and, in most instances, C1q, with variable co-deposits of IgA and IgM. The role of electron microscopy (EM) in the diagnosis and classification of LN cannot be underestimated and may be essential in some cases [19].

Class I

Class I (Fig. 8.1) is defined as mesangial immune deposits identified by IF and/or EM (Fig. 8.2), without glomerular alterations seen by light microscopy.

Class II

Class II (Fig. 8.3) is defined as mesangial proliferative LN characterized by any degree of mesangial hypercellularity (i.e., three or more mesangial cells per mesangial area in a 3 μm thick section) associated with mesangial immune deposits. IF or EM may show rare, isolated small immune deposits involving the peripheral capillary walls in some class II samples.

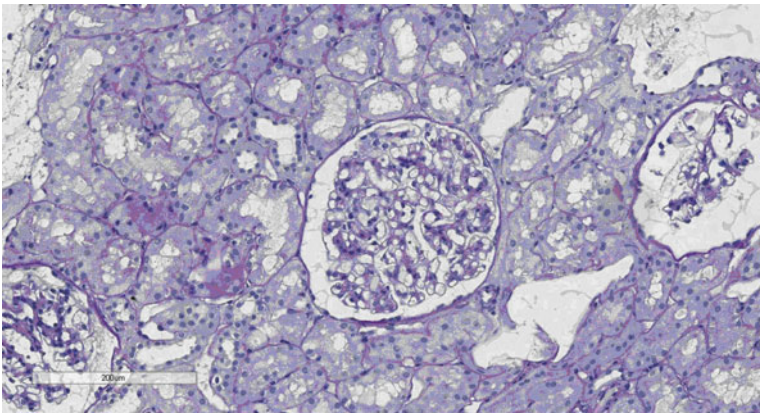

Fig. 8.1 Minimal mesangial LN (class I)

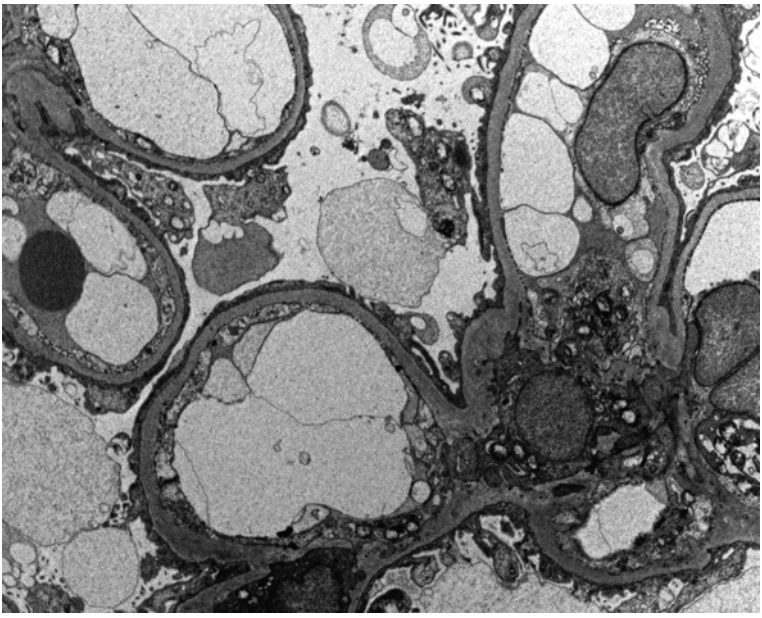

Fig. 8.2 Mesangial immune deposits identified by EM

Class III

Class III (Fig. 8.4) is defined as focal LN involving <50 % of all glomeruli. Affected glomeruli usually display segmental endocapillary proliferative lesions or inactive glomerular scars, with or without capillary wall necrosis and crescents, with subendothelial deposits. A specific diagnosis of combined class III and class V LN requires membranous involvement of at least 50 % of the glomerular capillary surface area in at least 50 % of glomeruli, as shown by light microscopy or IF.

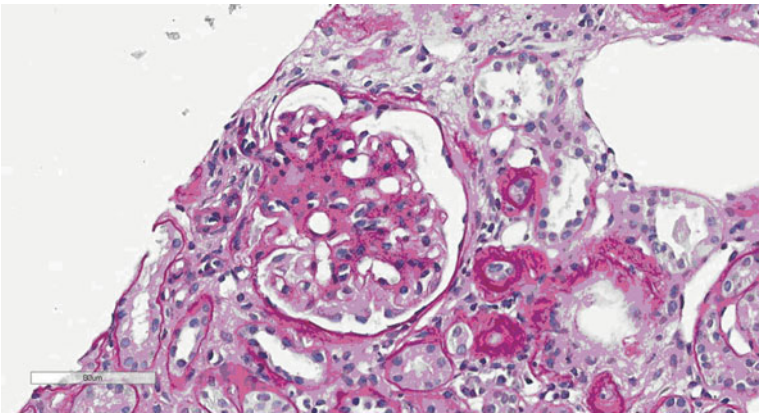

Fig. 8.3 Mesangial proliferative LN (class II)

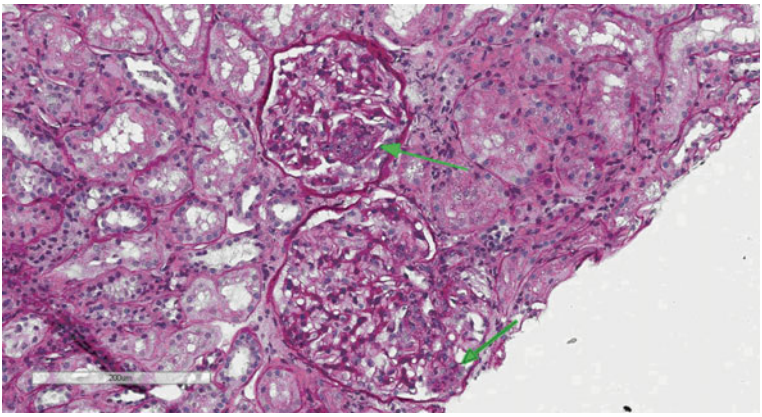

Fig. 8.4 Focal and segmental proliferative glomerulonephritis (class III)

Class IV

Class IV is defined as diffuse LN involving 50 % or more of glomeruli in the biopsy sample. In the affected glomeruli, the lesions as described below may be segmental, defined as sparing at least half of the glomerular tuft, or global, defined as involving more than half of the glomerular tuft. This class is subdivided into diffuse segmental LN (class IV-S) (Fig. 8.5) when <50 % of the involved glomeruli have segmental lesions and diffuse global LN (class IV-G) (Fig. 8.6) when >50 % of the involved glomeruli show global lesions. Class IV-S typically shows segmental endocapillary proliferation encroaching upon capillary lumen with or without necrosis and may be superimposed upon similarly distributed glomerular scars. Class IV-G is characterized by diffuse and global endocapillary, extracapillary, or mesangiocapillary proliferation or widespread wire loops. A diagnosis of combined class IV and class V is warranted only if subepithelial

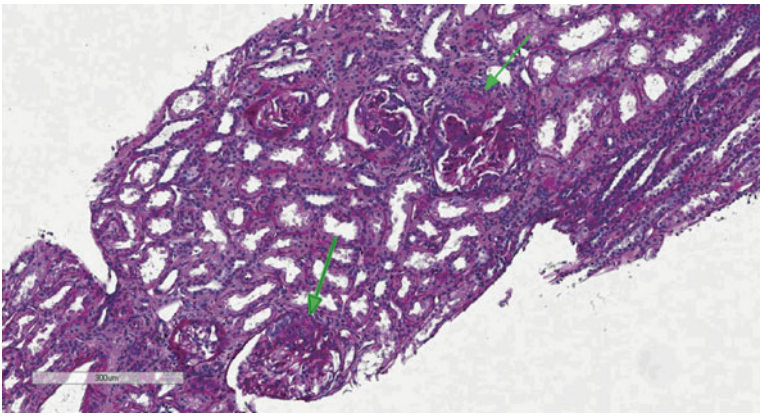

Fig. 8.5 Diffuse segmental LN (class IV-S)

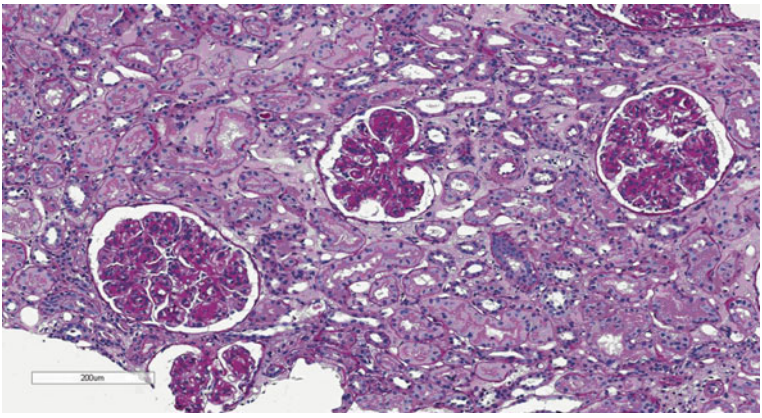

Fig. 8.6 Diffuse global LN (class IV-G) with >50 % of the involved glomeruli showing global lesions

deposits involve at least 50 % of the glomerular capillary surface area in at least 50 % of glomeruli as shown by light microscopy or IF. In assessing the extent of the lesions, both active and sclerotic lesions should be taken into account.

Class V

Class V (Fig. 8.7) is defined as membranous LN with global or segmental continuous granular subepithelial immune deposits, often with concomitant mesangial immune deposits. Any degree of mesangial hypercellularity may occur in class V. When a diffusely distributed membranous lesion is associated with an active lesion of class III or IV, both diagnoses are to be reported in the diagnostic line (Fig. 8.8).

Class VI

Class VI (Fig. 8.9) designates biopsies with >90 % global glomerulosclerosis, in which there is clinical or pathologic evidence that the sclerosis is attributable to LN.

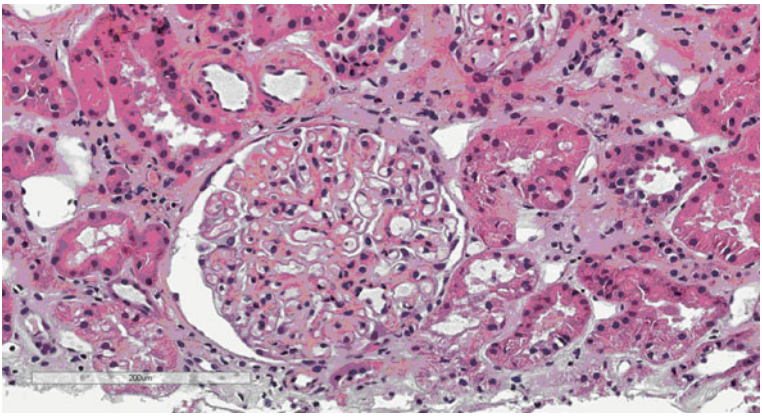

Fig. 8.7 Membranous LN with global or segmental continuous granular subepithelial immune deposits

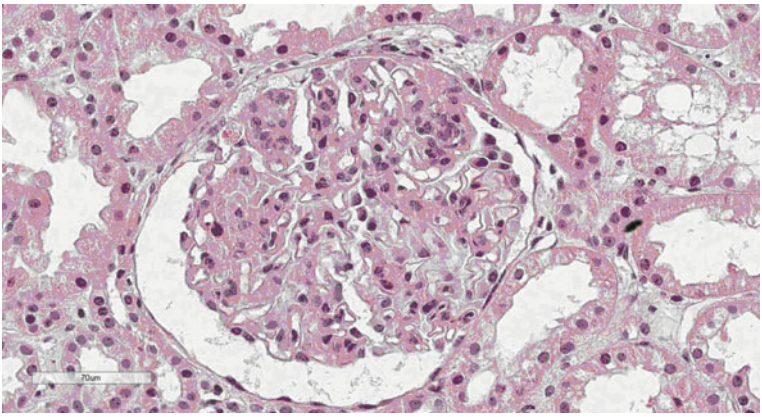

Fig. 8.8 Diffusely distributed membranous lesion associated with an active lesion of class III/IV

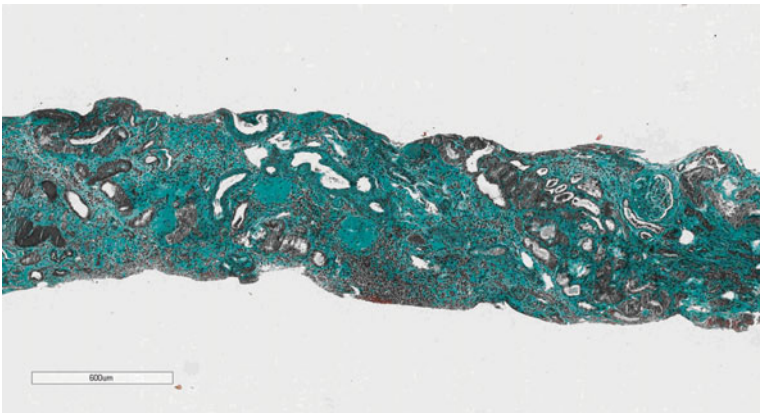

Fig. 8.9 Global glomerulosclerosis (class VI)

8.3.3 Histological Follow-Up

Histological transformation among different classes of LN has been reported in some studies [20]. However, those studies were mainly retrospective and included small cohorts of patients. Moreover, they were based on the previous WHO classification and therefore not comparable with the new criteria of ISN/RPS classification. They concluded that a single biopsy may not be sufficient to manage LN throughout the course of the disease. EULAR/ERA-EDTA guidelines support repeating the renal biopsy for the management of adult and pediatric LN. This may be the "gold standard" for the therapeutic follow-up in selected cases, such as individuals with persistent proteinuria lasting more than 1 year and/or worsening GFR, or at relapse. However, repeating kidney biopsy may also be considered in other clinical patterns, since a considerable percentage of patients are switched to different therapeutic strategies based on the results of their second biopsy [20]. Therefore, we suggest that complete remission should be declared only if no immunological activity is documented in the renal biopsy.

8.3.4 Clinical risk factors and prognosis

Caucasian race, low baseline proteinuria, early LN diagnosis, low serum creatinine (sCr) at diagnosis, stable sCr after 4 weeks of treatment, and class IV±V LN (WHO) are predictive of favorable outcomes. Conversely, African race, circulating anti-Ro antibodies, class III±V LN (WHO) with ≥50 % severe segmental glomerulonephritis, and refractory disease with the standard of care approach predict poorer outcomes [21]. These patients need closer follow-up and, if necessary, more aggressive therapeutic regimens. Further predictors of poor outcome that are generally identified at diagnosis include elevated sCr (≥2.4 mg/dl) and low hematocrit (<26 %) [22].

The previously mentioned clinical variables have to be considered when LN is overt; however, LN may occur in a subclinical manner called "silent LN." Although difficult to diagnose, the prognosis is encouraging. In 1996, a meta-analysis by Gonzales-Crespo et al. considered 193 patients affected with SLE who underwent renal biopsy despite no clinical signs of renal disease; 12 % of patients had no histological evidence of LN, 49 % had class II, 21 % had class III, 15 % had class IV lesions, and lastly, 3/191 had class V [23]. Although some histological classes with extensive proliferative features were included, outcomes were excellent, i.e., 98 % renal survival after 5 years.

As with other proliferative renal diseases, the first objective for clinicians is to obtain quick and complete remission of immunological activity and an early drop in proteinuria [24]. This approach is exhaustively discussed by Korbet et al. who reported a retrospective analysis that demonstrated how patients who were fully responsive to induction therapy had outstanding overall survival rates (95 %) at 5 and 10 years. Conversely, patients who were classified as refractory to standard treatment had overall survival rates between 65 % and 60 % at 5 and 10 years, respectively. Clearly, renal survival rates were influenced as well,

being as high as 94 % after 5 and 10 years of treatment in responders and 46 and 31 % in patients with resistant diseases [25]. Interestingly, individuals who achieved partial remission were more likely to evolve to ESRD as compared to those with complete remission: after 10 years of follow-up, those with evidence of class IV LN and partial renal response showed overall survival rates of 76 % compared to 94 % of complete responders and 19 % of nonresponders, while overall renal survival rate was 45 % (92 % complete responders, 13 % nonresponders) [26].

8.4 Diagnostic Approach

Early diagnosis should be obtained since it improves prognosis and supports clinical remission [27]. Therefore, a complete diagnostic approach should include the following:

- *Urine sediment*: direct observation should always be considered in order to investigate the presence of inflammatory casts, leukocytes, crystals or lipid droplets, and structural alterations of red cells. This latter finding is strikingly important: these cells are called "acanthocytes" (from the Greek word "akanthos" = spike) and define inflammation and blood leaking from glomeruli when ≥5 acanthocytes among 100 excreted erythrocytes are found in the urine (acanthocyturia). Red cells lose their ring shape and acquire round processes in the cellular membrane due to mechanical stress when they pass through inflamed capillary loops. Urine casts are frequently observed, especially granular ones, and are composed of red and/or white cells. Hyaline casts are not specific indicators of tubular injury and may be observed during remission phases. Positive hemoglobin reaction in the urine should be considered as an indirect sign of urinary hemolysis; this pattern should raise the suspicion of a concurrent TMA if it is associated with renal failure, anemia, and positive intravascular markers of hemolysis.
- *Proteinuria*: it is mainly an expression of glomerular involvement and should be accurately dosed. If 24 h proteinuria cannot be obtained due to technical limits, the proteinuria/creatininuria ratio (uPCR) is a useful tool.
- *Serum creatinine and estimation of glomerular filtration rate*: we suggest using sCr only for a gross evaluation of renal function. The real glomerular filtration rate (GFR) should be considered as the main parameter of renal function. GFR can be estimated (eGFR) by equations: in particular, the CKD-EPI equation is the most accurate. GFR can also be measured with expensive and less practical analyses that use inert substances filtered by glomeruli and that are not influenced by tubular input and output (e.g., iothalamate). No equations can precisely provide eGFR in individuals with ongoing acute kidney injury.

8.5 LN Treatment

8.5.1 General Principles

General SLE treatment is described elsewhere in this textbook.
Herewith, there are some general principles for LN therapy.
Three different therapeutic approaches are generally considered:

- General strategies against the progression to ESRD
  - Antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), in an effort to reduce proteinuria to below 1 g/day and blood pressure <130/80 mmHg
  - Lipid control with diet and/or drugs
  - Low-sodium diet (<4 g/day)
  - Low-protein diet, depending on the degree of proteinuria
  - Avoiding nephrotoxic drugs (e.g., NSAIDs)
  - BMI control
- Immunomodulating agents, especially in class III/IV LN with A or A/C activity indexes with or without class V, and class V alone (see below)
- Other immunomodulating agents that influence clinical response (e.g., hydroxychloroquine), but that do not achieve remission alone.

8.5.2 Outcome Measures in LN

No single parameter has high diagnostic accuracy in terms of both sensitivity and specificity in predicting a LN flare. Several composite measures to assess clinical response have been used in the past. In general, most clinicians define the clinical response of LN on the basis of the following criteria:

- *Complete response*:
  - sCr returns to previous baseline
  - Evidence of a declining uPCR (<500 mg/g)
- *Partial response*:
  - Stabilization (±25 %) or reduction of sCr without complete recovery
  - ≥50 % decrease in uPCR
  - If nephrotic-range proteinuria is present (uPCR ≥3000 mg/g), a ≥50 % reduction in uPCR and a uPCR <3000 mg/g may be expected.

Moreover, reduced immunological activity is empirically proven by the normalization of urine sediment. In particular, pyuria disappears (≤5 leukocytes per high-power field (HPF)) together with inflammatory casts and hematuria (≤5 dysmorphic red cells per high-field magnification, negative red cell casts, and hemoglobin in

stick urine test); C3 and C4 levels become nearly or completely normal, and the anti-DNA antibody titer decreases. These markers should especially be taken into account considering that chronic scarring may definitively alter the amount of proteinuria and renal function.

Another clinical problem lies in defining treatment failure. Some authors propose "*clinical deterioration*" as the criteria to switch to other therapeutic strategies. It is defined by a worsening of renal function, in particular of sCr, by more than 25 % from the beginning of the induction therapy. Other parameters, such as worsening proteinuria and renal biopsy after 3 months of therapy, have not yet been validated.

Minimal mesangial LN (class I)

No specific treatment is usually required in patients with class I LN. In general, this histological class is identified when investigating a suspicion of renal involvement in the context of a systemic flare or because of confounding variables (e.g., lower urinary tract hematuria and leukocyturia for infections).

Mesangial proliferative LN (class II)

As discussed for class I, it is an infrequent finding because most of the time it is clinically silent. Conversely, if a podocytopathy is concomitant with a high degree of proteinuria, therapy with steroids may be beneficial as is the case for minimal change disease.

Focal and segmental proliferative glomerulonephritis (*class III*) *and diffuse proliferative glomerulonephritis* (*class IV*)

In the last 10 years, the therapeutic approach to proliferative LN has progressively changed: cyclophosphamide (CYC)-based regimens that have dominated clinical practice despite being sustained by small randomized trials carried out in the 1980s are now shifting to less toxic solutions with proven equal efficacy. An aggressive approach is needed because unlike class I and II LN, class III and IV may evolve to ESRD. Renal biopsy is mandatory to plan the therapeutic approach which is mainly based on a two-step process: induction and maintenance therapy.

8.5.3 Induction and Maintenance Therapy of Proliferative LN

The role of the induction therapy is to provide a rapid resolution of the inflammatory state before permanent fibrotic changes replace the functional parenchyma. Induction therapy in LN bases on conventional and innovative agents.

Glucocorticoids (GCs) GCs alone are not effective at inducing remission of class III and IV LN, but they should be associated with almost every immunomodulating regimen (see below) [28].

- i.v. methylprednisolone 500–1000 mg/day for 1–3 days followed by prednisone 1 mg/kg/day, progressively tapered over 6–12 months

Cyclophosphamide-Based Regimens Before considering CYC-based regimens, a risk and benefit assessment is mandatory. Infections, infertility, and malignancies are the most worrisome short- and long-term side effects. CYC should be titrated based on renal function and cumulative dose (max. 36 g/lifetime) [29].

Two CYC-based regimens have been proposed:

- NIH regimen: i.v. CYC 500–1000 mg/m^2 monthly for 6 months + GCs as described above. Mean total cumulative dose: 8 g
- Euro-Lupus regimen (low CYC dose): i.v. CYC 500 mg + GCs as above, every 2 weeks for 3 months. Mean total cumulative dose: 3 g

In the 1990s, the need to reduce the incidence of CYC-related side effects, especially in patients with less aggressive forms of LN, prompted clinicians to modify the standard NIH regimen in favor of low-dose CYC regimens. The Euro-Lupus trial [30] was the response to this interest, demonstrating that after a median of 41 months, low-dose and high-dose groups had similar remission rates (71 % vs. 54 %, respectively) and renal flare rates (27 % vs. 29 %), while the high-dose group had an increased infection rate. The "quality" of remission (risk of ESRD and malignancy rate) was assessed in 2009 by the same authors after long-term follow-up (>73 months): only 7 % reached ESRD and the risk of malignancy was equal [24].

Although strongly debated, these promising response rates in class III and IV LN, especially in severe cases with necrosis and crescents, make CYC-based regimens the preferred approach by some authors when compared to mycophenolate mofetil (MMF). The low prevalence of ESRD in the Euro-Lupus trial may be explained by the persistence of GCs and/or immunomodulatory therapy for years in both groups. Based on clinical practice, some authors suggest that high-risk ethnicities, in particular non-Caucasian and non-Asian races, may benefit from prolonged high-dose CYC regimens, although MMF may be a valid alternative as shown in the post-hoc analysis of the ALMS trial [31].

However, in everyday clinical practice, LN is mostly diagnosed in young individuals in whom gonadal function should be preserved. We feel that in these cases, MMF should be preferred to CYC as a first approach.

Mycophenolate Mofetil Interest in MMF rose at the end of the 1990s, with the intent to apply the new knowledge on immunomodulating therapy in kidney transplant to native kidney diseases [32].

In 2005, for the first time, MMF proved to be better than i.v. CYC in inducing complete remission (22.5 % vs. 5.8 %), and considering combined partial and complete remission rates (52.1 % vs. 30.4 %), it was found to be better even in the short term (24 weeks) [33]. However, the trial was statistically underpowered to demonstrate the actual superiority of MMF compared to CYC. Later on, in 2009, the ALMS study, which included several ethnicities, showed that MMF was equal, but not superior to the NIH protocol (88 % and 83 % clinical response, respectively). Adverse events, including death and infection rates, did not differ significantly

between the two regimens [31]. Similar findings were documented in Chinese patients in the short- and long term [34, 35].

In crescentic LN, MMF seems to be as effective as CYC, though with higher complete remission rates (54 % vs. 27 %). In a study by Tang et al., MMF performed remarkably well considering that about 25 % of patients had sCr >3 mg/dlat baseline [36].

In summary, MMF may be used as an alternative to i.v. CYC, although some authors still have concerns regarding patients with severe proliferative LN. MMF is well tolerated by patients, especially after 1–2 weeks of intake. Unlike CYC, gonadal toxicity or bladder cancers are not observed [37].

Azathioprine (AZA) AZA is well tolerated and shows fewer side effects compared to CYC, but it has never been shown to be superior to MMF. Azathioprine preserves remission in pregnancy and has no fetal toxicity. AZA is as effective as CYC at inducing remission in proliferative LN and at reducing the incidence of ESRD. However, after 5 years, more relapses and short-term infections are observed in patients on AZA [38]. It is still under debate whether AZA may suffice to control a smoldering renal inflammation and if it is associated with an increased rate of progression to ESRD.

Cyclosporine A (CSA) The CYCLOFA-LUNE trial compared the use of CSA to a modified NIH regimen. Differences between arms were not significant after 9 and 18 months of follow-up [39]. The safety profile was similar, and as expected, CSA was more likely to result in a transient increase in creatinine, in hypertension, and in relapses after tapering. Like AZA, CSA is safe in pregnancy.

Multi-target therapy (MTT) MTT is defined as the association of tacrolimus (TAC), MMF, and GCs. MTT was superior to i.v. CYC in a Chinese study and showed a similar safety profile [40, 41]. MMT proved to be safe and effective in patients with both class IV and V LN and in those refractory to standard MMF regimens. MMT may be considered in individuals with relative or absolute contraindications to CYC.

Rituximab (RTX) RTX is a promising treatment for LN. However, the LUNAR study [42] showed that RTX in addition to standard of care therapy (MMF and GCs) failed to provide further benefits. Although RTX is not recommended as induction therapy by KDIGO guidelines, we suggest using RTX in class III and IV LN, with or without CYC in selected cases including young patients with pregnancy perspectives and subjects with relative/absolute contraindications or intolerance to CYC [43].

A RTX-based protocol (RA schedule) has been recently proposed as a steroid-sparing regimen including methylprednisolone (500 mg on days 1 and 15) in the induction phase and MMF as a long-term maintenance treatment (Rituxilup trial) [43].

A different approach, initially employed as a rescue therapy in refractory LN, has been proposed in order to minimize the long-term effects of both corticosteroids and the immunosuppressive agents used for remission maintenance. It was based on an intensified B-lymphocyte depletion consisting of "four (weekly) plus two (monthly) doses" of rituximab (375 mg/sm), associated with two i.v administrations of 10 mg/kg cyclophosphamide and three pulses of 15 mg/kg methylprednisolone, followed by oral prednisone tapered to 5 mg/day in 10 weeks, without further immunosuppressive maintenance therapy [44].

Maintenance Therapy The maintenance phase aims to avoid relapses once remission is achieved. The length of treatment is not predetermined and it is based on clinical status and history. The goal is to progressively titrate the immunomodulating agents until discontinuation or to reach the lowest possible dose needed to prevent relapses. Several drugs can be used to maintain remission in LN.

MMF is currently preferred. The maintenance phase of the ALMS trial [45] demonstrated that MMF is superior to AZA (16 % vs. 32 %) in reducing the clinical endpoints (death, ESRD, relapse, sustained doubling of sCr, need for rescue therapy). Conversely, the MAINTAIN [46] trial showed no differences between MMF and AZA in obtaining the primary endpoint, which includes time to renal flare, and safety profile. However, more relapses were observed in the AZA group. These data were confirmed in the long-term follow-up (5 years) [47].

CSA has a good safety profile and is as effective as AZA [48]. Therefore, CSA may be considered as an option in patients who do not tolerate AZA and MMF.

8.5.4 Therapy of Membranous LN (Class V)

Patients with pure class V LN should be aggressively treated if nephrotic-range proteinuria (>3.5 g/day) and increased sCr are present.

There is no clear consensus on the best strategy for pure class V. CSA achieved remission in 83 % of patients, followed by CYC (60 %) and GCs alone (27 %) in one study [48]. Conversely, as expected, relapse rates were more frequent in the CSA arm (60 % after 36 months) as compared to CYC (20 % after 50 months) [49]. Based on the ALMS cohort, MMF and CYC were equally effective after 24 weeks of treatment.

Patients with class V LN associated with proliferative changes should be treated according to the concomitant presence of class III and IV LN (see above) [50–52].

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