Chapter

Lupus Nephritis: Clinical Picture, Histopathological Diagnosis, and Management

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect almost every organ of the body and presents with a great variety of clinical features. SLE effect on kidneys, mostly referred to as lupus nephritis, is of special interest for the rheumatologist and nephrologist for three reasons. First, lupus nephritis is one of the commonest types of organ involvement in this disorder, affecting as up to 45% of all patients with SLE. Second, it presents with a great variety of clinical and histopathological findings, and thus, therapy must be tailored accordingly. Third, it greatly affects the morbidity and mortality of SLE patients. Taking these facts into account, this chapter is centered on lupus nephritis from the perspective of the clinical nephrologist and renal pathologist. This chapter elaborates the diversity of clinical features of lupus nephritis, in relation to the different histopathological forms of the disease and the therapeutic options that are available to date, as well as the pathogenesis, natural history, and prognosis of patients with lupus nephritis.

Keywords: lupus nephritis, histopathology, prognosis, management

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with high heterogeneity. The hallmark of SLE pathogenesis is the production of autoantibodies [1], which results from a combination of genetic, epigenetic, environmental, hormonal, and immunoregulatory factors [2]. The heterogeneity is expressed with different clinical phenotypes that range from which organs are inflicted to the way that disease is caused at a specific organ and can be attributed to different autoantibody profiles, genetic variants, and interferon levels [3]. For example, there are two different phenotypes in patients with neuropsychiatric lupus [4], while there is a spectrum of different phenotypes concerning joint involvement in SLE [5]. This wide heterogeneity has even prompted researchers to question if SLE is a single disease [6] and highlights the difficulty of defining SLE. As a result, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have developed criteria to classify patients' disease as SLE. According to the most recent edition of these

criteria [7], all patients considered to be classified as SLE must have a positive antinuclear antibody test and must accumulate certain clinical and immunological criteria.

Kidney involvement in SLE is a common and potentially life-threatening form of the disease. There are diverse ways with which SLE can cause kidney disease, such as lupus podocytopathy [8], tubulointerstitial disease [9], and syndromes like thrombotic thrombocytopenic purpura [10], but the usual form of kidney involvement is lupus nephritis (LN). LN is a form of glomerulonephritis in patients with SLE [8], which is characterized by the presence of stains for immunoglobulin G (IgG), immunoglobulin M (IgM), C3, and C1q in the immunofluorescence (IF) [11]. Patients with LN have been shown to have higher rates of morbidity and mortality compared with patients without renal involvement. There are different classes of LN that present with different clinical signs and have different prognosis [8].

2. Epidemiology of lupus nephritis

SLE is a disease with a prevalence ranging between 30 and 50 cases per 100,000 people worldwide [12]. In the USA, the incidence of SLE is estimated between 5.5 and 7.4 cases per 100,000 persons-years [13]. In Europe, where there are discrepancies between different national SLE registries, the estimated incidence of SLE varies between 1.5 and 7.4 per 100,000 persons-years [14]. In South America, the incidence varies between 1 and 4.2 cases per 100,000 persons-years [14], while in Asia, incidence ranges between 2.8 and 8.6 cases per 100,000 persons-years; in Australasia, there are at least 11 cases per 100,000 persons-years [14]. These data showcase that the prevalence and incidence of lupus in a population is related to the ethnicity of the population. In the USA, it was shown [13] that SLE is commoner in African American, then in Hispanics, and is less common in Caucasian. It is widely known that 90% of patients with SLE are women [12]. In this regard, gender and ethnicity impact the incidence and prevalence of SLE.

The frequency of LN varies between different regions of the world and different ethnicities. Overall, 30–60% of patients with lupus and 70% of children with SLE develop LN [15]. It has been shown that LN is more frequent in the Black population with SLE than in Asians and Hispanic populations and less common in Caucasians [16]. The difference in frequency can be attributed to "high-risk" genotypes. For instance, a significant association between the known "high-risk" APOL1 alleles and LN has been shown [17]. These alleles can be found in Black patients, explaining the higher prevalence of LN in these patients. LN has a significantly higher frequency in male patients with SLE when compared to females [18–20]. Furthermore, LN is more common in patients with childhood onset lupus when compared with adult-onset lupus [21].

3. Pathogenesis of lupus nephritis

The pathogenesis of LN is complex with distinct factors (genetic, hormonal, and environmental) influencing the natural course of the disease [22]. The bottom line of LN pathogenesis is the production of autoantibodies against autoantigens, with double-stranded DNA being the commonest target [23]. There are two ways that anti-ds DNA antibodies exert their nephritogenic effect. First, immune complexes are formed in the circulation that are deposited to the glomeruli. Second, anti-ds DNA antibodies

are connected to the glomeruli *in situ* either by binding to exposed chromatin fragments connected to glomerular membranes and mesangial matrices or by binding to non-DNA structures connected to the glomerulus that cross-react with anti-ds DNA antibodies [22, 23]. All these models are required for the fragments of chromatin to be exposed for anti-ds DNA antibodies to be produced. Seredkina et al. [24] showed that this chromatin exposure is achieved in mice because of renal DNAse1 deficiency, leading to reduced clearance of apoptotic material. The surplus apoptotic material led to a surge of anti-ds DNA levels and the formation of mesangial immune deposits [25]. Reduced levels of renal DNAse1 have been observed in humans with LN as well [25]. It must be noted that not all anti-ds DNA antibodies are nephritogenic [26]; only a subset is able to get deposited in the kidney. It has been shown that autoantibodies against annexin-a2 [27] and autoantibodies against moesin [28], antigens found in the glomeruli, cause proliferative LN. At the same time, patients with membranous LN present with immune complexes consisted by exostosin-1/exostosin-2 antigens and autoantibodies [29] and immune complexes with neural cell adhesion molecule 1 [30]. It can be assumed that this great heterogeneity in SLE autoantibodies is the reason behind the different classes of LN.

The surplus apoptotic material described before activates dendritic cells, monocytes, and macrophages [22]. These cells, through the production of cytokines and the presentation of autoantigens, activate effector B cells by prolonging their survival and maturation process. This way, the number of autoreactive B cells, memory cells, plasma cells, and produced autoantibodies is increased [22]. Recently, a new function of B cells has been discovered. Besides their function as antibody-producing cells, B cells seem to aggregate in inflamed organs creating complex structures that are called tertiary lymphoid tissue [31]. This tissue form ranges from small clusters of lymphocytes to sophisticated structures reminiscent of lymph nodes. This tissue is observed on kidneys in a variety of different diseases from chronic pyelonephritis to autoimmune disease. Their role is to produce *in situ* autoantibodies and proinflammatory cytokines, activate T cells, and cause lymph angiogenesis [32]. Shen et al. [33] showed that intrarenal B cell infiltrates were found in 60% of patients with LN and were associated with LN class IV, greater activity and chronicity indices, and worse glomerular filtration rate (GFR). It can be deduced that B cell infiltrates in patients with LN are related to worse outcome.

Besides the proliferation of autoantibody-producing B cells, the surplus apoptotic material triggers innate immunity [8]. The surplus apoptotic material leads to the formation of neutrophil extracellular traps (NETosis) by neutrophils [34]. NETosis is a sequence of cellular events leading to the programmed death of neutrophils and the production of these "traps" (NETs). NETs are web-like DNA structures decorated with histones and cytotoxic proteins, and their role is to trap and destroy pathogens [35]. In sterile conditions, NETs, through their functions, can exacerbate inflammation. First, NETs are a potential source of autoantigens leading to the production of autoantibodies and the formation of immune complexes. Second, NETs serve as a platform for complement activation that leads to inflammation exacerbation and cellular damage. Third, NETs themselves contribute to kidney tissue damage by acting directly on kidney cells, creating microthrombi and releasing cytokines [36].

A critical step in the pathogenesis of LN is the activation of type I interferon system. It has been shown that NETs activate monocytes to produce cytokines such as interferon alpha [37]. However, most of the cytokines are produced by the plasmacytoid dendritic cells [38]. In lupus patients, these cells migrate to tissues (like renal

tissue) [38]. Then, immune complexes containing nucleic acids are internalized, reach the endosome, and stimulate the production of interferon alpha [39]. Under normal circumstances, type I interferons connect to type I interferon receptors that activate other pattern recognition receptors (like toll-like receptors 7 and 9). This cascade of events leads to the expression and stimulation of certain genes and their corresponding enzymes [38]. Some of the enzymes induced lead to the inhibition of viral reproduction [40] highlighting the role of the interferon system in antiviral immunity. At the same time, type I interferon enhances the cytotoxic abilities of natural killer (NK) cells and stimulates the maturation of dendritic cells to antigen-presenting cells [38]. In lupus patients, the overexpression of type I interferon leads to the overexpression of toll-like receptor 7. It has been shown in mice that this overexpression is related to clinically severe SLE [41]. Likewise, it has been shown that patients with nephritis present with an interferon signature and greater levels of interferon I [38].

Complement activation also plays a key role in LN pathogenesis. As already revealed, the first step in LN pathogenesis is the existence of surplus apoptotic material. Under normal circumstances, complement promotes apoptotic debris removal [42]. In patients with SLE, this complement's function is performed in a reduced rate. It has been found that many patients who develop LN present with anti-C1q antibodies [42]. These antibodies further reduce complement's capability of apoptotic debris removal and seem to induce a loop of activation of the classical pathway of complement. Then, the autoantibody mediated renal damage in LN seems to activate the complement via the classical and alternate pathway [43]. Moreover, complement factors like C3a and C5a attract neutrophils and potentiate their response (**Table 1**) [44].

4. Clinical phenotypes of lupus nephritis

The clinical phenotypes of LN are characterized by great heterogeneity, ranging from asymptomatic microscopic hematuria to nephrotic syndrome, to acute nephritic syndrome and rapidly progressive glomerulonephritis [18]. Specifically, Moroni et al. [45] showed that 49% of patients with LN present with isolated urinary

Mechanism	**Way of activation**	**Effect**
Surplus apoptotic material	Reduced renal DNAse1	Production of autoantibodies
Autoantibodies	Surplus apoptotic material	Activation of macrophages, dendritic cells
B cells	Cytokines by macrophages	Production of autoantibodies Aggregation for production of tertiary lymphoid tissue
NETs	Autoantibodies	Production of autoantigens Complement activation Tissue damage
Type I interferon	Plasmacytoid dendritic cells	Overexpression of toll-like receptor 7
Complement	Surplus apoptotic material Reduced ability of complement to remove apoptotic material	Tissue damage

Table 1.
Mechanisms related to pathogenesis of lupus nephritis.

abnormalities, 36% with nephrotic syndrome, 13% with acute nephritic syndrome, and 3% with rapidly progressive renal failure.

Despite the therapies that have been developed, a subset of patients reaches end-stage kidney disease (ESKD). The incidence of ESKD is estimated to be 2.3 patients per 1000 patient-years [46]. There are risk factors that help us identify patients at an elevated risk of developing end-stage renal disease. Some risk factors are demographic, like male sex, young age, and African or Hispanic ethnicity; some are clinical, like anemia, elevated serum creatinine, and hypertension on the biopsy time [47]; and some are histopathological, like proliferative nephritis (class III or IV) and high chronicity or activity indices [45]. It must be noted that the clinical phenotype cannot predict the class of LN. For example, in a series of 21 patients with SLE and isolated urinary abnormalities, the biopsies of 13 patients showed LN class III, IV, or V [48]. As a result, the EULAR proposed all patients with SLE and suspicion of renal involvement (glomerular hematuria and/or cellular casts, proteinuria >500 mg, or unexplained worsening of renal function) to be candidates for kidney biopsy [47].

5. Histopathology of renal involvement in patients with SLE

Lupus nephritis is an immune complex disorder of the kidney that may present with many faces, demonstrating a large diversity of clinical and pathological features among patients. Clinical features can range from asymptomatic urinary findings of microhematuria and mild proteinuria to full-blown nephrotic syndrome and/or rapidly progressive glomerulonephritis. Periods of remission and exacerbation are typically found during the course of the disease.

The pathological features can also be varied, including glomerular lesions, but also tubulointerstitial and vascular lesions. The major pathological findings are described in the LN Classification of 2003 by a consensus meeting of renal pathologists, nephrologists, and rheumatologists of the American Society of Nephrologists (ISN) and Renal Pathology Society (RPS), while previous classification schemes had been proposed by pathologists and nephrologists under the auspices of the World Health Organization.

The immune complex deposits can be found in mesangium and/or glomerular basement membranes, while sometimes deposits are recognized in tubular basement membranes and vessels walls. Therefore, a large diversity of immune-complex deposits can be found in LN, such as mesangial, subendothelial, and subepithelial, many times concurrently, while glomerular lesions can also be extremely varied, including mesangial, endocapillary, and/or glomerular basement membrane alterations. Glomerular pathological patterns can range from mesangial expansion and hypercellularity to endocapillary hypercellularity, membranoproliferative or membranous pattern, while in many instances, these patterns can coexist or overlap. Constant feature in all the classes of LN is the "full house" pattern in immunofluorescence examination, for example, expression of all immunoglobulins (IgG, IgA, and IgM) and complement components (C3 and C1q), as well as kappa and lambda light chains in the glomerular compartments. Additional findings revealed by electron microscopy (EM) examination include the common presence of "tubuloreticular" inclusions in endothelial cells and electron dense deposits within tubular basement membranes, while, sometimes, electron dense deposits can be found within small vessel walls. Uncommonly, organized mesangial deposits with tubulofibrillar substructure resembling seen in cryoglobulinemia or "fingerprint" laminated structures can also be encountered.

According to the distribution of glomerular tuft deposits that determines the type of proliferative response, the predominant resulting glomerular pattern, the extend of severity, any coexistence of glomerular patterns, and the presence of chronic lesions, LN is categorized in six classes according to the current classification (2003), while a few modifications have been proposed in 2016 and are discussed in detail later [49–51]. Electron microscopy (EM) examination is not required for defining the class of LN, since in many countries there is no EM facility. Data from light microscopy (LM) and immunofluorescence (IF) examination are usually enough for nephritis typing. On the other hand, EM can provide additional information, especially in some cases; thus, a small piece of tissue must be kept in glutaraldehyde for examination.

Class I is characterized by mesangial immune deposits in IF, but no morphological changes in light microscopy, according to the classification of ISN/RPS 2004. Urinary abnormalities are minimal and include microscopic hematuria with mild proteinuria, while renal function is normal. This is the mildest glomerular lesion in LN and is relatively rare, since these patients generally have no essential clinical renal abnormalities and are not referred to nephrologists for biopsy.

Class II is defined by purely mesangial hypercellularity of any degree, or mesangial matrix expansion by LM, with mesangial immune deposits. No subendothelial deposits visible by light microscopy are allowed for this class. Only few subendothelial or subepithelial deposits visible by IF or EM are allowed. Urinary abnormalities are mild and include microscopic hematuria with mild proteinuria, while renal function is usually normal. If nephrotic syndrome is observed, in an otherwise typical case of class II nephritis, with no subepithelial deposits, the possibility of lupus podocytopathy should be examined.

Class III includes active or inactive focal and segmental endocapillary and/or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits with or without mesangial alterations. Microscopic or macroscopic hematuria and severe proteinuria are usually seen. Lupus serologies are usually active.

Class IV includes active or inactive diffuse segmental and/or global endocapillary and/or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits with or without mesangial alterations. These patients have the most severe and active clinical renal presentation. Proteinuria can reach nephrotic level, and many patients (up to 50%) can present with nephrotic syndrome. Urine sediment is active, while red blood cell (RBC) casts are common. Renal insufficiency can be demonstrated by glomerular filtration rate (GFR), although serum creatinine can be normal, especially in young women with little muscle mass. Hypertension can be observed, while lupus serologies are active.

Class V includes membranous LN with global or segmental subepithelial immune deposits by LM and IF or EM, with or without mesangial alterations. Severe proteinuria or nephrotic syndrome is usually seen in many cases accompanied by microscopic hematuria. Renal insufficiency is uncommon.

Class IV includes advanced sclerosing LN. Urinary abnormalities consisted of proteinuria of varying degree with inactive sediment, while renal function is impaired. Hypertension is common, while lupus serologies may be inactive (i.e., "burnt-out" lupus).

There are also mixed classes in LN that include classes III and V and classes IV and V. In addition, an activity and chronicity index has been proposed [52] to determine the severity of disease, providing prognostic as well as therapeutic indications for patients' management.

Commonest classes in biopsies samples, according to various studies are classes III, IV, and V [53, 54]. Among the first five classes, classes III and IV have the worst prognosis. Classes III and IV are characterized by high activity. "Wire" loops (thickened eosinophilic glomerular membranes occupied by deposits), eosinophilic "hyaline" thrombi, and numerous inflammatory cells into capillary lumens including neutrophils, nuclear "debris," membranoproliferative pattern, glomerular crescents, and/or necrosis can be seen (see **Figures 1–4**). Numerous electron dense deposits in immunofluorescence and EM examination are usually seen in **Figures 5** and **6**.

Membranous LN is usually manifested with high proteinuria and nephrotic syndrome (up to 70%), while hematuria is found in up to 50% and renal insufficiency is uncommon (see **Figures 7** and **8**). On the contrary, high proteinuria with renal insufficiency and active urine sediment is common in mixed classes III and V or IV and V, so close pathological correlation with clinical data is required in every case.

In repeat biopsies, a "transformation" phenomenon has been described, from one class to another, usually after treatment, or spontaneously. Class III to class IV is a common transformation in repeat biopsies, but many authors prefer to interpret it as a transition along a disease continuum, rather than a true transformation. Mesangial proliferation is often seen after the treatment of class III or class IV LN, although ultrastructurally residual irregularities of the glomerular basement membrane consisted of resorbed and organized subendothelial deposits can be seen. Virtually, all directions of transformation have been described.

Some investigators have proposed that class IV-S is pathogenetically distinct from other LN. Schwartz et al. [55] described a category of "severe segmental

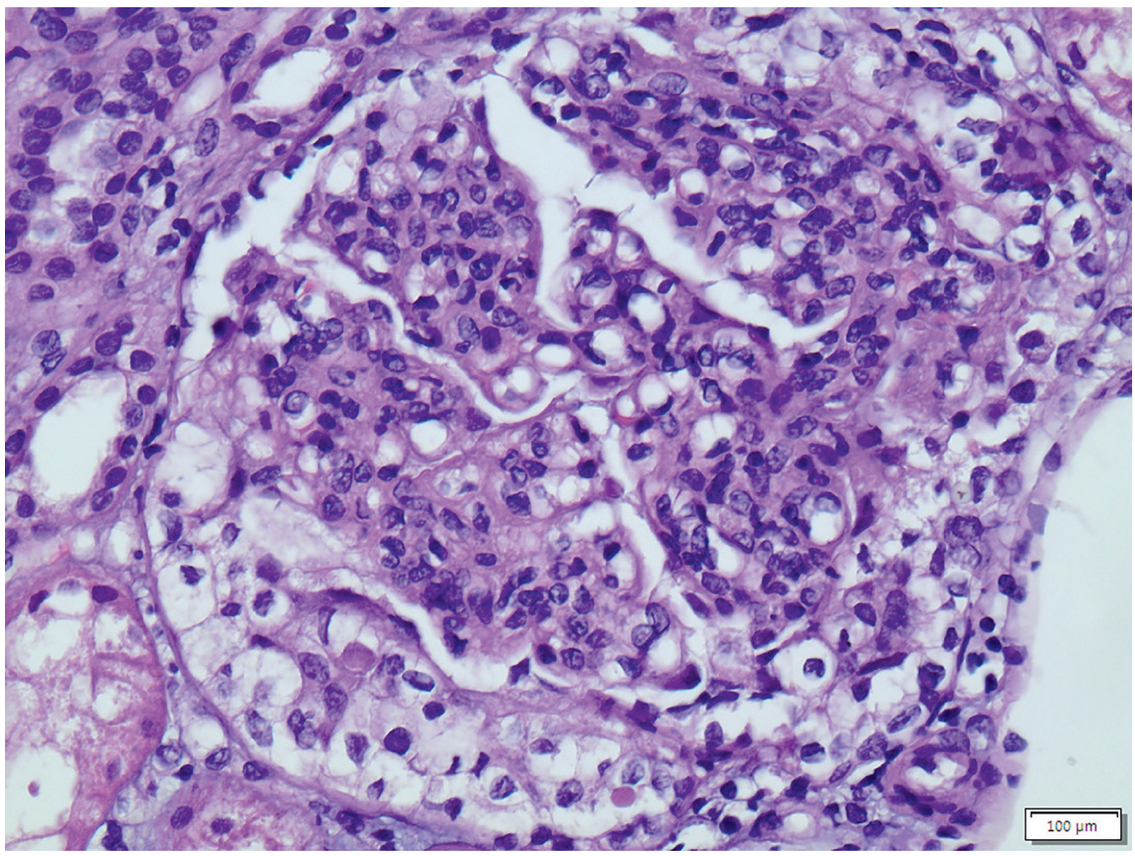

Figure 1.
Severe endocapillary cellularity/proliferation in association with crescent formation in the left corner [H&E X400].

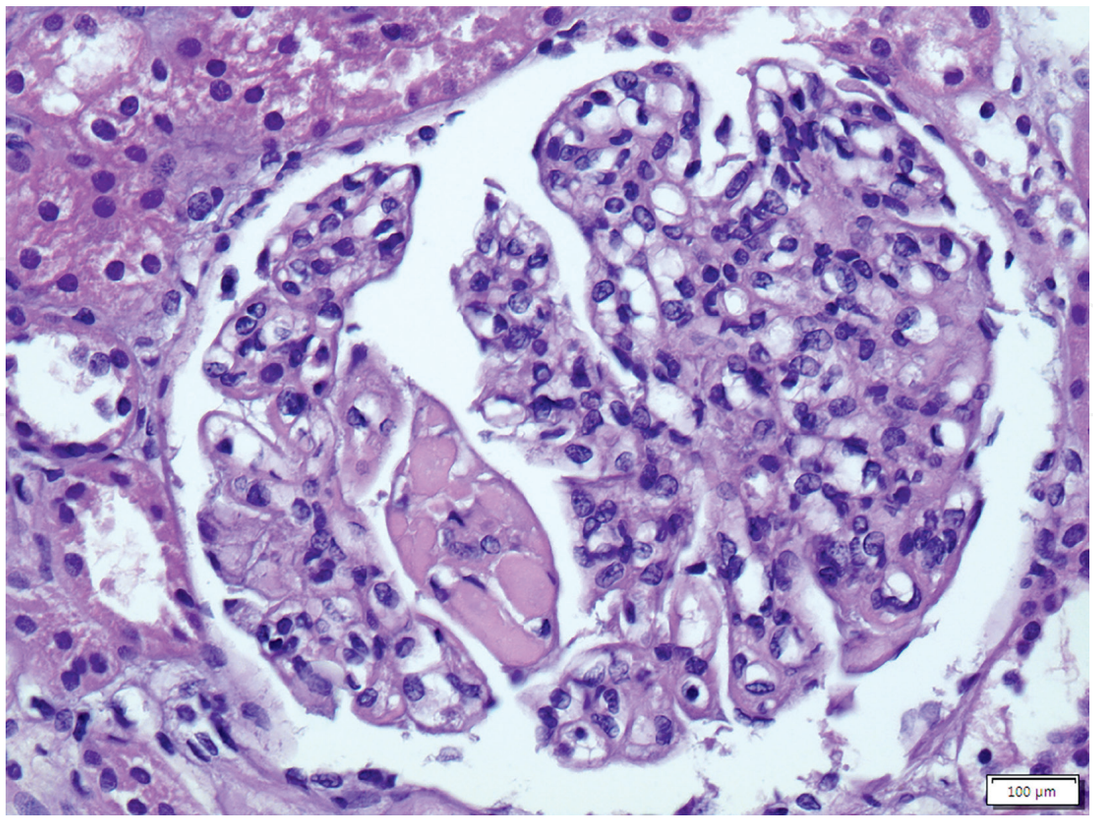

Figure 2.
Mesangial and endocapillary cellularity/proliferation in association with "hyaline" thrombi into glomerular lumens [H&E X400].

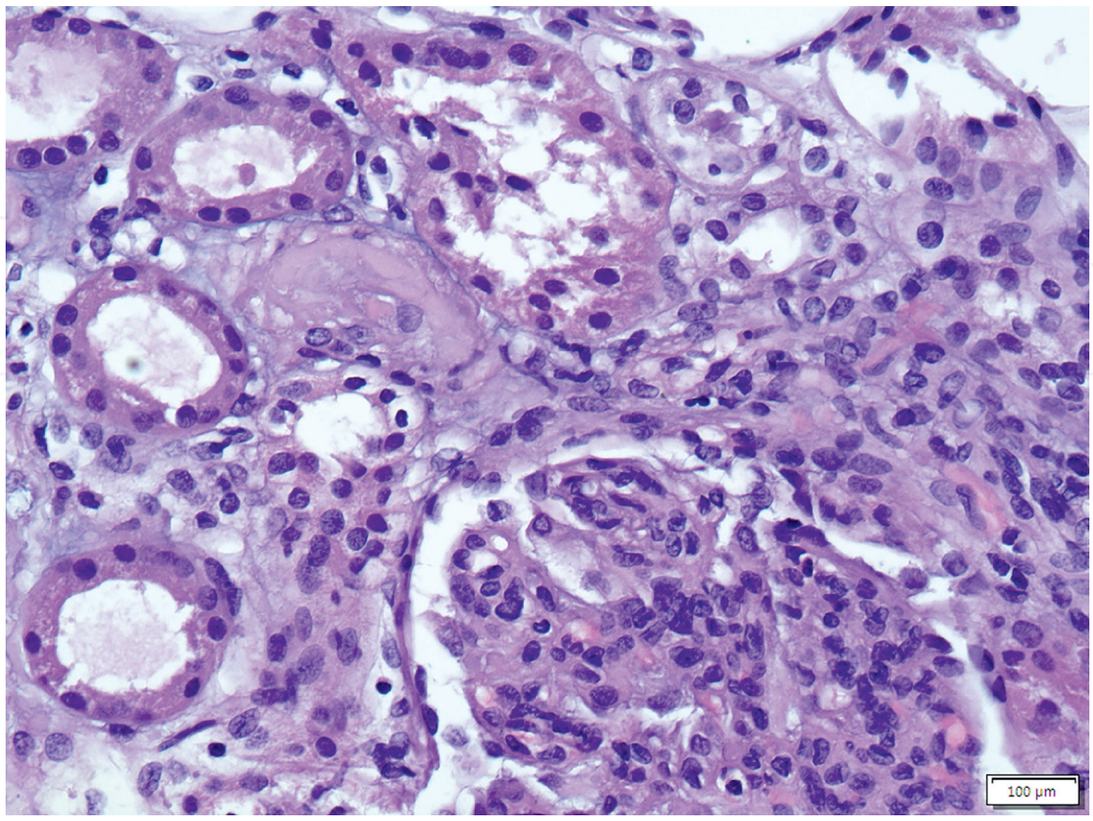

Figure 3.
Immune complex deposits in an arteriole, the so-called lupus "vasculopathy" [H&E X400].

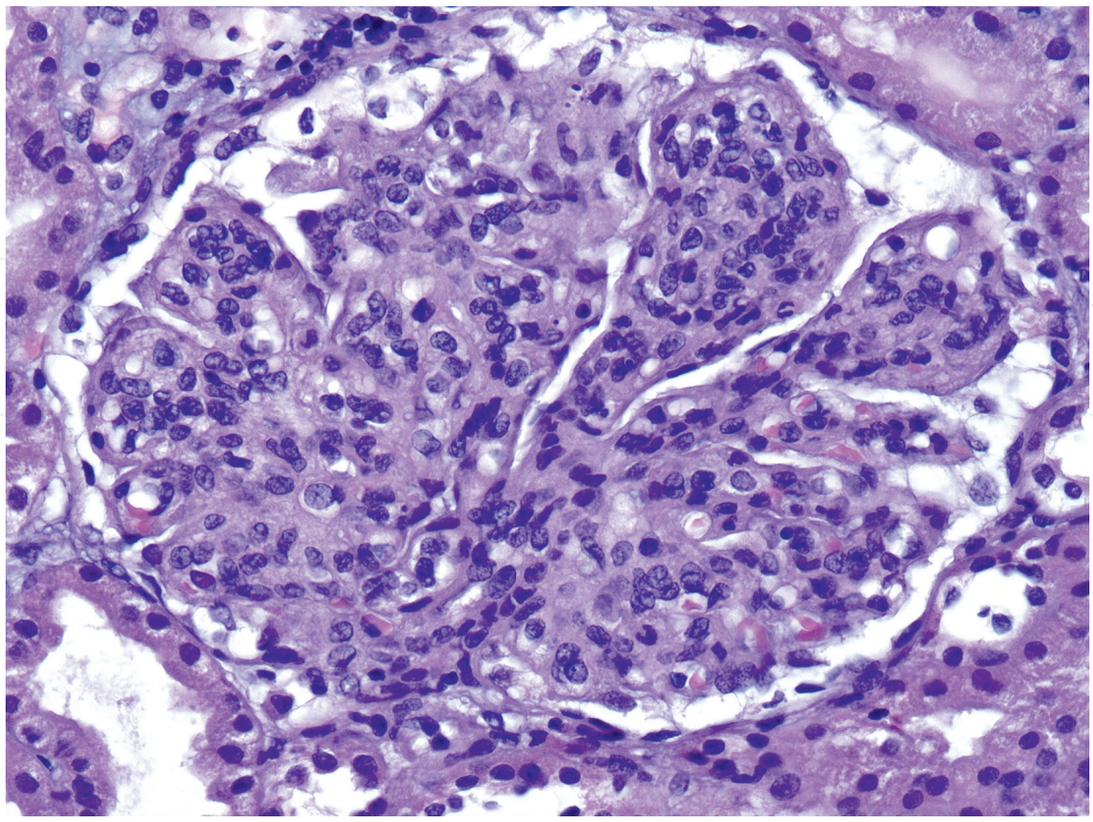

Figure 4.
Membranoproliferative pattern in LN [H&E X400].

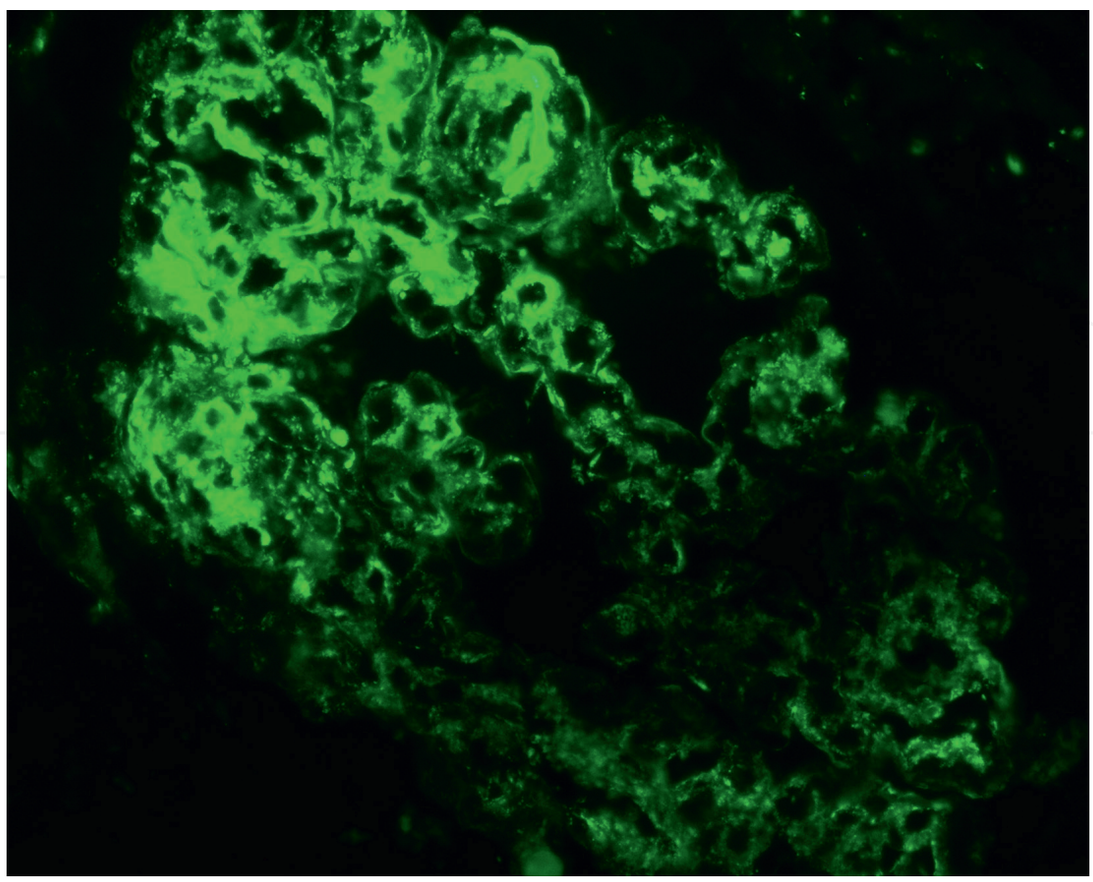

Figure 5.
Mesangial and large subendothelial deposits in immunofluorescence examination, in a case of class IV LN [C1q X400].

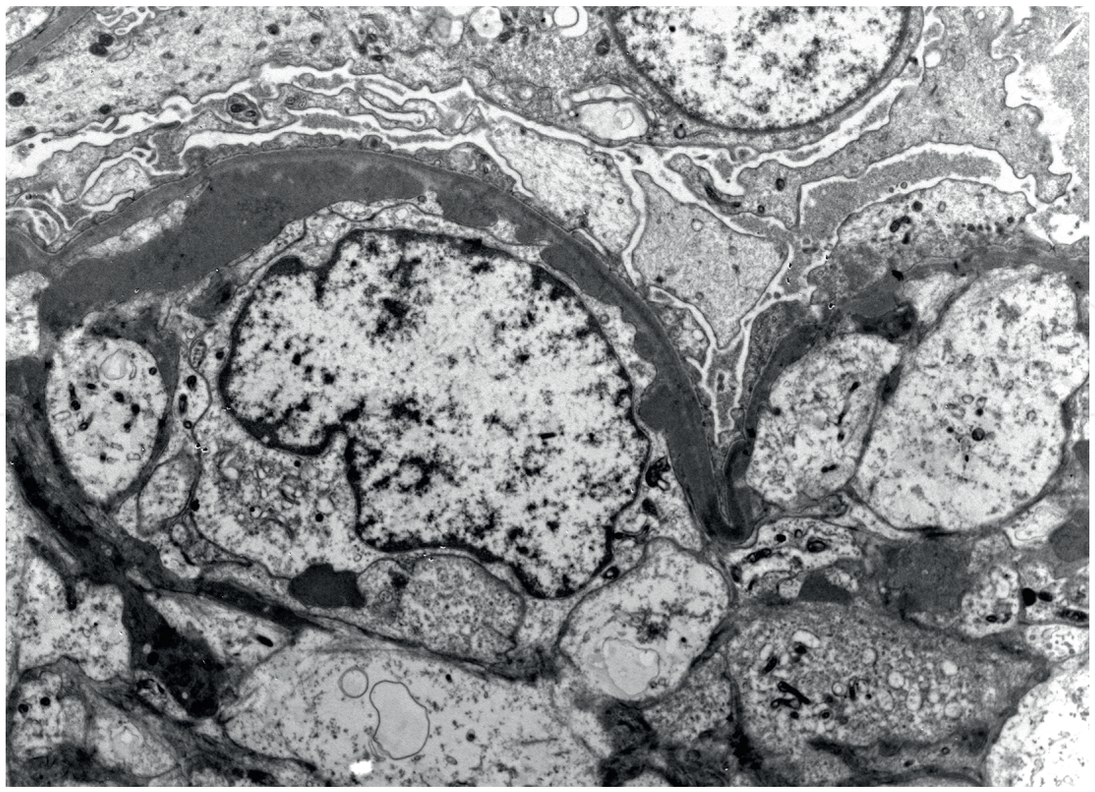

Figure 6.
Large subendothelial deposits in EM examination, in a case of class IV LN [uranyl acetate X 4400].

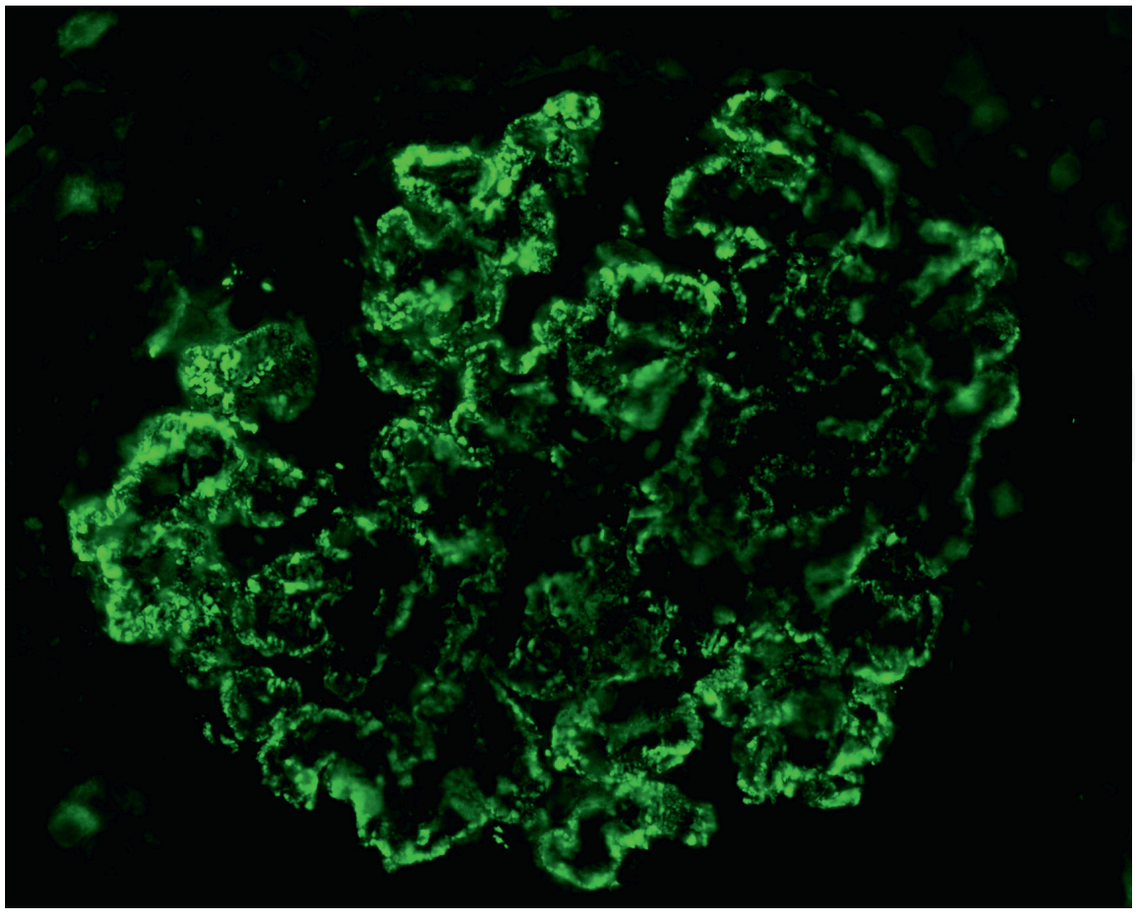

Figure 7.
Subepithelial deposits along glomerular basement membranes in a class V LN [immunofluorescence, IgGX400].

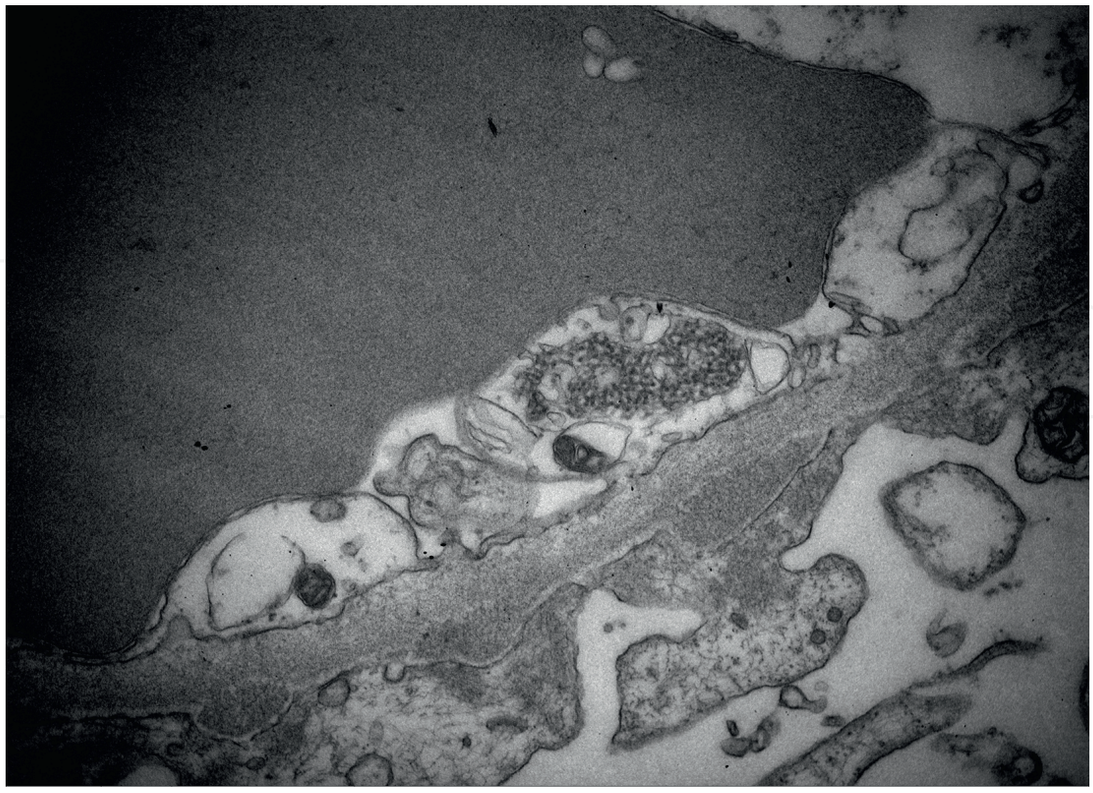

Figure 8.
Subepithelial deposits along glomerular basement membrane in association with a tubuloreticular inclusion in the cytoplasm of an endothelial cell, class V LN [uranyl acetate X 18000].

glomerulonephritis," in which the glomerular inflammation was predominantly segmental. This category is now designated as IV-S in the ISN/RPS classification. This category had an outcome measured in short-term renal survival that was intermediate between the classic focal and diffuse proliferative groups. The category IV-S was introduced because of evidence from the Chicago group that this subgroup has worse long-term outcome than IV-G, especially if associated with segmental necrotizing lesions and not endocapillary proliferation, possibly implicating pauci-immune necrotizing vasculitis mechanisms [56, 57]. In contrast, no difference in outcome was observed between these classes by the Boston group [58]. Typically, the subendothelial and mesangial deposits are larger and more abundant in class IV-G, as compared with classes III and IV-S, usually staining more intensely in immunofluorescence.

Clinical signs, such as proteinuria and hematuria, or creatinine level, as a solely marker are not enough to determine therapeutic options in LN, since it is well known that the discrepancy between the clinical and the pathological features in lupus patients, who are usually young, may compensate renal function. Furthermore, nephritis can be "silent" in lupus patients; that is an old observation. Thus, renal biopsy is necessary for disease control. Indications of biopsy include the confirmation of the disease, the confirmation of the kidney involvement in a patient with SLE, the determination of the type of involvement, the determination of disease severity, the determination of therapy, and prognostic implications. In addition, the extent of chronicity is evaluated in biopsy to determine if proteinuria or creatinine rising is due to activity or chronicity. If the latter predominates with no associated activity, unnecessary immunosuppression is avoided (see **Figure 9**).

According to a consent report by Bajema et al. [51] (after a meeting of 18 members of an International Nephropathology working group in Leiden, The Netherlands, in

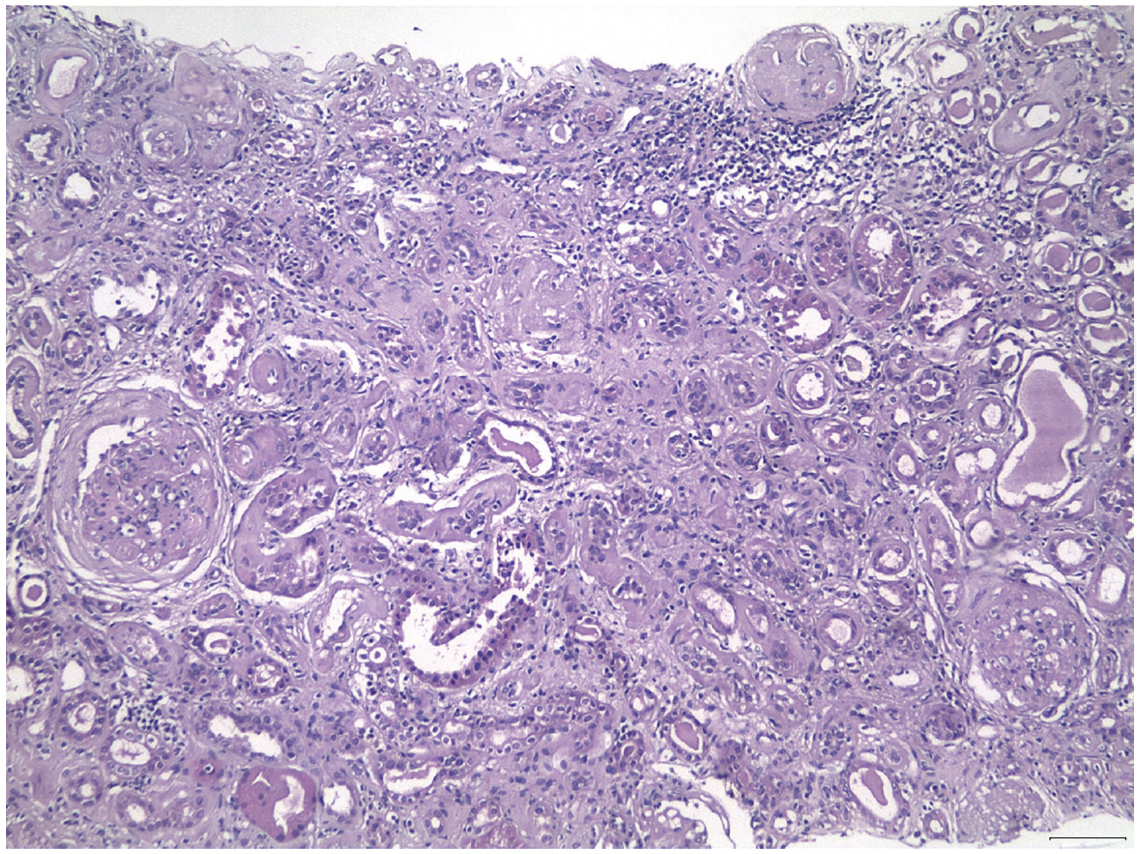

Figure 9.
Severe glomerulosclerosis, interstitial fibrosis, and tubular atrophy in a class VI LN [H&E X 100].

2016), the terms of segmental and global categories in class IV LN are eliminated. In addition, division in active/chronic categories for classes III and IV is replaced by an activity and chronicity score that should be provided in every pathology report. Fibrinoid necrosis is added in activity index, as an independent marker (activity index 0–24: endocapillary hypercellularity 0–3, neutrophils/karyorrhexis 0–3, hyaline deposits 0–3, fibrinoid necrosis 0–3 [x2], Cellular/fibrocellular crescents 0–3 [x2], and interstitial inflammation 0–3; chronicity index 0–12: total glomerulosclerosis 0–3, fibrous crescents 0–3, tubular atrophy 0–3, and interstitial fibrosis 0–3]. Other proposals of the same working group include an increase in the cutoff of mesangial hypercellularity from three to four mesangial cells (according to the definitions of Oxford Classification for IgA nephropathy), the replace of term endocapillary "proliferation" by the term endocapillary "hypercellularity," new definitions for crescents, etc.

Vascular lesions can also be encountered in LN, such as uncomplicated vascular immune deposits, noninflammatory necrotizing vasculopathy (lupus vasculopathy), thrombotic microangiopathy (that can be associated with hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, or antiphospholipid antibodies, or scleroderma/mixed connective tissue disease), and necrotizing vasculitis. In addition, "lupus podocytopathy" can also be seen in cases of severe proteinuria but without obvious glomerular alterations reminiscent of minimal change disease or focal segmental glomerulosclerosis, accompanied with or without mesangial deposits; therefore, LN can mimic almost every glomerular disease. Uncommonly, amyloidosis, fibrillary glomerulonephritis, other "nonlupus" nephritides, drug-induced LN, etc., have been reported.

According to Kudose et al. [59], five predominant features allow the distinction LN from other glomerular diseases: the full house pattern, intense C1q staining, extraglomerular deposits, combined subendothelial and subepithelial deposits, and endothelial tubuloreticular inclusions, with a high specificity and varying sensitivity.

Differential diagnosis includes glomerulonephritis with similar findings in light microscopy, but usually immunofluorescence examination (full house pattern), clinical history, and serology allow the distinction. Cryoglobulinemic glomerulonephritis is a major differential diagnosis, especially for class IV nephritis, since both can have a membranoproliferative pattern and "hyaline" deposits into glomerular loops, a situation complicating more by the fact that lupus can coexist with cryoglobulinemia or may show "organized" deposits by EM examination. In cryoglobulinemic glomerulonephritis, IgM usually predominates over other immunoglobulins, and there is no full house pattern in immunofluorescence, although exceptions have been described. In addition, EM examination may highlight structures of cryoglobulins in some cases. Furthermore, if necrosis and crescents predominate in histology without essential glomerular hypercellularity/proliferation, pauci-immune necrotizing vasculitis enters the differential diagnosis. Lupus serologies can provide important information in these cases, because sometimes in LN, antineutrophil cytoplasmic autoantibodies can be positive. Membranous nephropathy, especially in young women, should be examined carefully, since some cases may belong to lupus membranous. Serology may offer again some additional information, although sometimes the serology of lupus can be positive after years from the initial diagnosis of membranous. In these cases, a close follow-up is required.

In cases with mesangial proliferation with or without endocapillary proliferation, IgA nephropathy enters the differential diagnosis. Again, immunofluorescence examination will be the cornerstone for diagnosis. Notably, rheumatoid arthritis, a disease entity that can share common features with SLE, sometimes can be combined with IgA nephropathy, possibly due to rheumatoid factor related IgA. Uncommon glomerulopathies/glomerulonephritides, such as fibrillary or immunotactoid glomerulonephritis, may show mesangial expansion and positivity in immunofluorescence for IgG immunoglobulin, C3 complement component, or light chains. In these cases, EM examination has a pivotal role for diagnosis, by demonstrating the fibrils or microtubules accordingly. Interestingly, even uncommon diseases, such as fibrillary glomerulonephritis, have been described rarely in the literature, in the setting of LN. Podocytopathies, such as minimal change disease, have also been described in the context of SLE.

Rare cases of nonlupus nephritides with full house pattern in immunofluorescence examination mimicking LN have also been reported [60], including infection-related glomerulonephritis (such as endocarditis-related glomerulonephritis), cancer-associated membranous glomerulopathy, cryoglobulinemic glomerulonephritis, immune-complex-mediated glomerulonephritis lupus-like in HIV-infected patients, etc. If there is no convincing evidence of a specific etiology, the follow-up of the patients is required since some of these patients may develop positive lupus serology in the future.

However, even with the stringent criteria, rare examples of nonlupus glomerulopathies may exhibit characteristic features of LN. Furthermore, the ISN/RPS classification states that "it is important to realize that the kidney biopsy findings, per se, cannot be used to establish a diagnosis of SLE," requiring for this purpose a combination of clinical, serological, and histological data.

6. Management of lupus nephritis

The treatment of LN depends primarily on the histopathological findings of the kidney biopsy. Thus, not all histopathological classes need to receive immunosuppressive therapy. However, regardless of the need of immunosuppressive therapy, all patients with LN should be treated with antimalarial drugs, namely hydroxychloroquine [61].

6.1 Class I (minimal mesangial) and class II (mesangial proliferative)

Most patients with LN belonging to these two classes present with minor clinical findings, regarding kidney involvement. Their kidney function is normal, while they often present with mild subnephrotic proteinuria and/or microscopic hematuria. These patients have an excellent renal prognosis, and there is no reason to treat with immunosuppressive therapy [62] in the absence of extrarenal manifestations.

An exception is warranted for patients with nephrotic syndrome or nephrotic-range proteinuria, who have class I or II in histology. These patients probably have lupus podocytopathy. In this regard, electron microscopy is helpful to establish the diagnosis by demonstrating podocyte effacement. The usual treatment consists of oral prednisolone 1 mg/kg once daily (maximum dose of 80 mg) for one to four months followed by gradual tapering after achieving remission [63].

6.2 Class III (focal) and class IV (diffuse) lupus nephritis

Class III and IV LN is an aggressive disease that requires a quick and effective implementation of the therapeutic strategy. The therapeutic goal of patients with the above histological classes is the achievement of *complete response*, which translates to the recession of immunologic and inflammatory activity. The clinical criteria of defining a response to therapy are somewhat controversial and not universal, because a series of clinical studies and/or associations have defined different goals for a complete response. Nevertheless, all response criteria agree in the reduction of proteinuria and the improvement of the kidney function. We most commonly use the criteria published by the Improving Global Outcomes (KDIGO) Consensus Conference guidelines for glomerulonephritis, namely the reduction of proteinuria to <0.5 g/day measured by 24-hour urine collection or by the protein-to-creatinine ratio, the stabilization or improvement of the kidney function (±10% of the baseline) in a period of 6–12 months of therapy, as well the normalization of the urine sediment to red blood cells (RBCs) to ≤10 high-power field and absence of RBC casts [64]. Therapy must be initiated promptly after the acquisition of the diagnosis because a delay is related to irreversible kidney damage [65].

Traditionally, immunosuppressive therapy in patients with LN consists of two phases. The initial phase is the first phase with more intensive immunosuppressive, which usually lasts six months or until a remission is achieved. The second phase is a prolonged maintenance phase, which ensures the remission and the avoidance of a relapse [64]. With the most modern management of LN, we do not separate so strictly the two phases and we use an undivided approach, so that the duration of initial therapy varies; it can be as short as three months or as long as one year but averages approximately six months.

The immunosuppression of the initial phase includes two agents. The first one is always glucocorticoids combined with either mycophenolate mofetil (MMF) or

intravenous cyclophosphamide. There are a lot of commonly used dosing regimens for the glucocorticoids. We most commonly initiate the therapy with the administration of 0.5–1 mg/kg/day prednisolone (maximum dose 80 mg/day) followed by a gradual tapering at three to six months. When the clinical or histological findings are more severe (worsening of kidney function and crescents formation), then a therapeutic opening with intravenous daily pulses of 0.5–1 g methylprednisolone for three days is preferred [65, 66]. The use of intravenous cyclophosphamide was established as the standard of care in the 1980s after a series of trials evaluated its efficacy compared with monotherapy with glucocorticoids regarding the kidney prognosis and avoiding the development of ESKD [67]. The standard National Institute of Health (NIH) regimen consists of 0.5–1 g/m^2 monthly doses of intravenous cyclophosphamide for a period of six months [64]. The second option is the Euro-Lupus regimen, which consists of 500 mg intravenous cyclophosphamide every two weeks for a total period of three months, a remission-inducing regimen of low-dose IV cyclophosphamide (cumulative dose 3 g) that achieves clinical results comparable with those obtained with a high-dose regimen [68]. The alternative induction regimen consists of glucocorticoids plus MMF. The efficacy of this regimen compared with the one with cyclophosphamide was documented with the Aspreva Lupus Management Study (ALMS), where 370 patients with class III–V LN participated to open-label MMF (target dosage 3 g/day) or IV-cyclophosphamide (0.5–1.0 g/m^2 in monthly pulses) in a 24-week induction study. The study did not detect a significantly different response rate between the two groups: 104 (56.2%) of 185 patients responded to MMF compared with 98 (53.0%) of 185 to IV-cyclophosphamide. Moreover, no significant differences between the MMF and IV-cyclophosphamide groups with regard to rates of adverse events, serious adverse events, or infections were detected [69]. The dose of the MMF in this trial was 1.5 g twice daily. Enteric-coated mycophenolate sodium (EC-MPS) is an equivalent drug for patients who are unable to tolerate adequate doses of MMF due to gastrointestinal side effects (1 g of MMF is equivalent to 720 mg of EC-MPS). Although there are no clear guidelines regarding the selection of the initial induction therapy, MMF is preferred for younger patients with concerns about fertility since cyclophosphamide may adversely affect fertility. Nevertheless, in agreement with the EULAR recommendations, high-dose intravenous cyclophosphamide (0.5–0.75 g/m^2 monthly for six months) can be considered in patients with impaired renal function and/or histopathological factors [66]. The histopathological factors are included at the modified NIH activity index criteria, namely the endocapillary hypercellularity, karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular/fibrocellular crescents, and interstitial inflammation [70].

Rituximab, which is a monoclonal antibody that targets the CD20 antigen and depletes the B cells, is not used as initial therapy based upon data from a randomized trial, where 144 patients with class III or class IV LN treated concomitantly with MMF, and corticosteroids were randomized 1:1 to receive rituximab (1000 mg) or placebo and where no statistically significant difference in rates of complete or partial remission was found [71]. Yet, a systematic review of observational studies and case reports showed favorable results for patients with LN resistant to the standard care of MMF or cyclophosphamide [72].

The use of tacrolimus as part of a "multitarget" regimen in combination with MMF or intravenous cyclophosphamide is based on a series of Chinese trials, where the response rate regarding the reduction of the proteinuria was higher using the multitarget regimen. Overall, these limited data are insufficient to support the use of tacrolimus as first-line initial therapy for severe LN, and more studies are needed [73].

In the past few years, a new drug, belimumab, which is an IgG1-lambda monoclonal antibody that prevents the survival of B lymphocytes by blocking the binding of soluble human B lymphocyte stimulator protein to receptors on B lymphocytes, which results to the reduction of the autoimmune response, has been emerged, and it will probably play a role in the initial phase of treatment. In a recent clinical trial involving patients with active LN, the addition of belimumab to the standard induction therapy (MMF or cyclophosphamide) showed that more patients who received belimumab had a primary efficacy renal response than those who received standard therapy alone [74]. A post hoc analysis of this study [75] showed that the effect of belimumab on kidney response, time to kidney-related events, or death was related to the histological type of kidney nephritis. Specifically, patients with class III or IV lupus nephritis were benefited by the addition of belimumab, while patients with class V lupus nephritis or mixed class lupus nephritis (III + V or IV + V) reaped no benefit by the addition of belimumab. It was also shown that patients with a greater degree of proteinuria (UPCR>3 g/g) do not respond to the addition of belimumab. These results constitute a first step toward a more personalized treatment of lupus nephritis.

During the second phase of LN treatment, the prevention of a relapse is the main goal [76]. The duration of maintenance therapy is three to five years [77]. The optimal therapy consists of MMF at a dose of 1000 mg twice daily. The ALMS Maintenance Trial proved that MMF was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with LN who had a responded to initial therapy [78]. However, azathioprine is preferred for patients who want to become pregnant or for patients who cannot tolerate MMF. The dose of azathioprine is 2 mg/kg per day to a maximum of 150–200 mg/day. Low-dose oral prednisolone (0.05–0.2 mg/kg) is continued in most patients on maintenance therapy.

Patients with focal or diffuse LN resistant to initial therapy are treated with the alternative therapy. Patients resistant to CYC are switched to MMF, and patients resistant to MMF are switched to CYC [65]. In cases of a relapse, we most commonly treat patients with the same regimen that led to the initial remission. Concerns regarding the cumulative dose of CYC and the development of toxicity or infertility can lead sometimes to the alternative choice of MMF [79].

6.3 Class V (lupus membranous nephropathy)

The majority of patients with this histological class are presented with nephrotic syndrome or nephrotic-range proteinuria. Lupus patients with nephrotic syndrome due to membranous nephropathy should receive immunosuppression. Patients with nephrotic-range proteinuria despite the use of renin-angiotensin system blockers and/or patients with worsening of their kidney function should also receive immunosuppressive therapy [64, 80].

The general scheme consists of glucocorticoids plus either MMF or CYC or a calcineurin inhibitor or rituximab. All of the above treatments have shown comparable efficacy, although MMF probably is showing a better safety profile [69, 81]. Calcineurin inhibitors that is, cyclosporin or tacrolimus, should be given cautiously in patients with impaired kidney function considering its potential for nephrotoxicity. According to the KDIGO and the EULAR guidelines, MMF is a reasonable first line of choice in these patients. However, if MMF is proven ineffective, cyclophosphamide may be used for six months in an effort to induce long-term remission [82]. Long-term calcineurin inhibitor or rituximab may also be tried if the patient had prior significant exposure to cyclophosphamide or if there are other contraindications.

The dose of MMF and CYC is the same as for the treatment of class III and IV LN. Cyclosporine, when used, is started at 3–5 mg/kg/day in two divides doses and tacrolimus at 0.05–0.1 mg/kg/day in two divided doses. Consequently, we measure whole blood trough cyclosporine or tacrolimus levels, and 2 hours after receiving dose [C2] levels for cyclosporine to navigate through therapy. The desired trough levels range from 100 to 200 ng/ml for cyclosporine and 4–6 ng/ml for tacrolimus, whereas it is 600–800 ng/ml for C2 cyclosporine levels.

Patients who have concurrent lupus membranous nephropathy and focal or diffuse LN are treated with the same approach as used for those with focal or diffuse LN alone (**Table 2**) [64].

6.4 Class VI (advanced sclerosing lupus nephritis)

Class VI disease is characterized by global sclerosis of more than 90% of glomeruli. The immunosuppressive therapy is highly unlikely to benefit them, and it will only produce adverse effects. Hence, these patients need to be treated as chronic kidney disease to control the blood pressure, to reduce the proteinuria by using renin-angiotensin system blockers, and to prepare for the next step, when it is needed, the kidney replacement therapy.

6.5 General management

General supportive measures in all patients with LN, as with other patients with glomerulonephritis, include the restriction of dietary sodium intake to <2 g/day, the restriction of protein intake to 0.8 g/kg/day for patients with chronic kidney disease with a GRF < 60 ml/min/1.73 m^2, blood pressure control with a goal of <120–130/80 mmHg, the use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to maximally tolerated or allowed daily dose for the minimization of proteinuria and for the concomitant control of the blood pressure, the treatment of hyperlipidemia with lifestyle modifications (exercise, weight reduction, and smoking cessation), and the use of statins when needed, thrombosis prophylaxis for patients with nephrotic syndrome, and prophylaxis for *Pneumocystis jirovecii* pneumonia with trimethoprim/sulfamethoxazole, and the minimization of bone loss and osteoporosis prophylaxis due to the long-term glucocorticoid treatment [64].

6.6 Management of ESKD

Patients who develop ESKD can be managed with kidney transplantation, hemodialysis, or peritoneal dialysis. As with the other causes of ESKD, kidney transplantation is the best modality, with the best overall prognosis and survival, and so is preferred over hemodialysis or peritoneal dialysis [83]. A preemptive transplantation may be carried out when the extrarenal manifestations do not bear any contraindication for surgery [84]. The recurrence rate of LN at the kidney allograft was examined using the United Network for Organ Sharing files, and it was found in 2.4% (167 of 6780 patients) [85]. Among the patients who are on hemodialysis or peritoneal dialysis, there is no difference regarding the survival rates and mortality [86]. It must be noted, interestingly, that the development of ESKD and the initiation of a kidney replacement therapy are in the majority of patients associated with a complete or partial remission of the extrarenal manifestations of systemic lupus erythematosus [87].

Treatment	Dosage	Line of treatment	References
Cyclophosphamide (NIH)	0.5–1 g/m^2 monthly for six months	First line	KDIGO [64]
Cyclophosphamide (Eurolupus)	0.5 g every two weeks for three months	First line	Houssiau et al. [68]
Mycophenolate	3 g/day	First line	Appel et al. [69]
Glucocorticoids	0.5–1 mg/kg/day—tapering for three to six months	First line	Esdaile et al. [65]; Boumpas et al. [66]
Tacrolimus	4 mg/day	Part of multitarget therapy	Liu et al. [73]
Belimumab	10 mg/kg per 28 days	Added on regular therapy	Furie et al. [74]

Table 2.
Induction therapy of lupus nephritis class III, IV, III + V, or IV + V.

7. Prognosis of LN and risk factors for progression

The percentage of patients that achieve a complete remission within six months of therapy is 30% [88, 89]. Although the rates over the last decades have been becoming better, up to 20% of patients with LN will ultimately develop ESKD [90]. Thus, the ability to predict the long-term renal outcome is of vital importance. A better long-term prognosis is associated with attaining the complete response of active LN. What favors the long-term renal outcome is the early decrease of proteinuria levels over six months of treatment compared with patients with persistently high-grade proteinuria [91]. Probably, the most reliable predictor of good long-term renal outcome is proteinuria levels <0.7–0.8 g/day at one year after the initiation of treatment [92]. Regarding the demographic risk factors, Caucasians have the best prognosis and Africans the worst, whereas Asians have an intermediate prognosis. Black patients present worse outcomes with increased rates of ESKD and mortality [93]. The main clinical risk factors for the development of chronic kidney disease are baseline hypertension, nephrotic-range proteinuria, young age, anemia, and elevated serum creatinine at the time of biopsy [94]. There is a well-established link between histopathological findings on kidney biopsy and the clinical course of LN, with mesangial nephritis (class II) carrying the best renal prognosis while proliferative nephritis (classes III and IV) carrying the worst with a more aggressive course. Membranous (class V) nephritis is considered relative mild [45]. What is also very important are the high activity and chronicity indexes, which are independent predictors of ESKD [95]. To be more specific, cellular crescents, extracapillary proliferation, and interstitial fibrosis in the renal biopsy have the highest predictive value [95].

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