CHAPTER

53 Renal Involvement in Systemic Lupus Erythematosus

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The kidney is affected in a clinically important way in about 38% of patients with systemic lupus erythematosus (SLE), although renal involvement varies considerably by race and ethnicity. Caucasians (European, European Americans) have an incidence of renal lupus of 12% to 33%, whereas black (African American, Afro-Caribbean), Hispanic, or Asian patients have a 50% or greater incidence.[1–4] Of the patients who eventually have clinical renal involvement, 40% to 60% have overt findings of kidney disease at the time of initial diagnosis of SLE.[1,2,4]

Kidney damage in SLE is most often due to lupus nephritis (LN) in which glomerular immune complex accumulation leads to an inflammatory response that damages glomeruli and eventually the renal interstitium. LN is associated with a worse outcome in SLE, in part due to the development of chronic kidney disease (CKD) or end-stage renal disease (ESRD).[5,6] The incidence of ESRD attributed to LN in adults from 1996 to 2004 was 4.4 to 4.9 cases per million in the general population according to the United States Renal Data Service.[7] However, in blacks and Hispanics, the incidence of ESRD was 6 to 20 per million compared to Caucasians (2.5 per million). Similarly, in the United Kingdom 19% of Caucasians versus 62% of blacks with LN progressed to ESRD.[3] The prevalence of CKD in patients with SLE is difficult to estimate, but because current therapies induce complete remission in 50% or fewer LN patients, CKD is likely to be high in the lupus population.

LN is generally treatable. Presently this requires intense, nonspecific immunosuppression, which confers considerable risk of severe infection and other morbidities. Efforts are under way to develop new LN therapies that have greater efficacy and less toxicity. These new therapies are based on our current understanding of the pathogenesis of LN.

THE PATHOGENESIS OF LUPUS NEPHRITIS

Overview

SLE occurs when there is a loss of tolerance to self-antigens, and autoantibodies to these antigens are produced. Although the exact etiology of SLE remains unknown, a number of pathogenic mechanisms are thought to be involved. These include defects in the clearance of cellular debris and immune complexes (IC) that lead to enhanced self-antigen presentation, HLA-based polymorphisms that reduce the tolerogenic presentation of self-antigen, defects in B and T lymphocytes that facilitate their activation, and overproduction of cytokines that affect lymphocyte activation. In addition to their role in breaking tolerance, many of these pathways also directly contribute to the clinical manifestations of SLE.

The pathogenesis of LN mirrors, in many respects, the pathogenesis of systemic lupus, particularly immune complex (IC)-driven inflammation. Inflammatory kidney injury occurs following intrarenal IC accumulation. However, there appears to be qualitative differences between the 30% and 40% of the SLE patients who develop LN and those who do not. Most patients without kidney involvement in the first few years of the disease will never develop LN, and younger age has been shown to be a risk factor for LN. Thus, certain aspects of the pathogenic pathways of SLE are manifested only in the subset of SLE patients that develop LN. The following discussion will highlight some of these aspects, focusing in particular on what is known about human LN, with animal models of LN cited for support where appropriate.

Autoantibodies and Immune Complexes

One of the earliest demonstrations of loss of tolerance in SLE was the discovery of autoantibodies in lupus, in particular antinuclear and anti–double-stranded (ds)DNA antibodies.[8] Antinuclear antibodies (ANAs) are the most prevalent, appearing in over 95% of SLE patients. However, over 100 self-antigens have been identified in SLE patients that are targets of autoantibodies, including dsDNA, single-stranded (ss)DNA, nucleoproteins, RNA-protein complexes, ribosomes, phospholipids, carbohydrates, cell cytoplasm and cell surface molecules, blood components, and endothelial cells.[9] The fact that autoantibodies to all of these antigens are not present in every patient suggests that autoantibody specificities may define which organs are affected. Two antibody specificities seem to be particularly relevant to LN

pathogenesis, those against dsDNA and those against the complement component C1q.

Two lines of evidence have historically suggested a specific role for anti-dsDNA in the development of LN. First, numerous studies found an association of high titer anti-dsDNA with active LN.[10] Second, anti-dsDNA antibodies can be isolated from the glomeruli of LN patients.[11] Why these antibodies, and IC containing these antibodies, target renal tissue is not completely clear, although two main mechanisms are proposed that focus on the nature of the dsDNA antigen. One mechanism involves nucleosomes, which are composed of DNA in association with a core of positively charged histone proteins. Nucleosomes are released by cells undergoing apoptosis, and can be trapped in the glomeruli, perhaps facilitated by interactions between the positively charged histones and the negatively charged glomerular basement membrane.[12] Anti-dsDNA can recognize the DNA in nucleosomes, and the binding of anti-dsDNA in lupus renal tissue occurs at the site of glomerular nucleosome deposition.[13] Another mechanism is based on cross-reactivity between anti-DNA and one or more renal tissue antigens. Many potential tissue antigens have been implicated, and two of the more relevant candidates are alpha-actinin expressed in both glomerular podocytes and mesangial cells,[14] and annexin II on mesangial cells.[15] Regardless of which mechanism predominates, the result is localized anti-dsDNA-containing IC with the potential to drive local tissue inflammation. Anti-dsDNA autoantibodies appear to be predominantly immunoglobulin G1 (IgG1)[16] which is an inflammatory IgG subtype due to its ability to activate complement and engage Fc receptors for IgG.

Antibodies to C1q, the first component of the classical complement pathway, have been strongly associated with LN in so many studies[17] that some investigators feel they are required for active nephritis.[18] However, this does not seem to be true in all cases.[19] Nevertheless, the high prevalence of anti-C1q antibodies in active LN patients suggests an important pathogenic role. Anti-C1q does not appear to cause an acquired deficiency of circulating C1q because anti-C1q binding requires a neoepitope formed when it becomes fixed to its target substrate. Rather, injury is likely related to interaction of anti-C1q with C1q already present in the kidney, such as in IC bound to nucleosomes.[20,21] The resulting C1q/anti-C1q IC could focus on inflammatory response to renal tissue, similar to anti-dsDNA/nucleosome IC, leading to nephritis. It should be noted, however, that unlike anti-dsDNA antibodies, most anti-C1q antibodies appear to be IgG2,[22] which is a poor activator of complement and binds Fc receptors with low affinity. Other IgG subtypes (mainly IgG1) can be present in these IC, so the role of anti-C1q in LN pathogenesis may depend on the relative amounts of each anti-C1q IgG subtype.

The Complement and Fcγ Receptor Systems

The formation of IC leads to the activation of both the complement cascade and cells bearing Fc receptors for IgG (known as Fcγ receptors, or FcγR). The activation of complement and FcγR by IC can provide protective effects against SLE, mainly by promoting proper clearance of circulating IC. However, once IC are deposited in tissue, both of these pathways can drive tissue inflammation and damage, either through direct effects on tissue (complement membrane attack complex) or by activating cells to produce proinflammatory cytokines and toxic mediators.

Complement is thought to provide protection from SLE in a few different ways. First, classical complement activation by IC results in a more soluble, less phlogistic form of IC that is less likely to be trapped in tissue.[23] Second, complement contributes to clearance of apoptotic debris through opsonization by C1q, thus removing a highly immunogenic source of self-antigen.[24] Third, IC opsonization by other complement components (C4b and C3b/bi) that result from complement activation promotes IC clearance through C4b/C3b/C3bi receptors.[25] The type one complement receptor (CR1, CD35), which binds C4b, C3b and C3bi and acts as a regulator of complement activation, is expressed in the circulation predominantly on erythrocytes (E-CR1), and mediates the binding of complement-opsonized IC to erythrocytes (a process known as immune adherence).[26] This binding allows erythrocytes to shuttle IC through the circulation, minimizing glomerular trapping of IC, and promoting IC delivery to the liver and spleen for safe removal.[26] The evidence that all of these complement functions protect against SLE include studies showing that individuals with homozygous deficiencies of classical pathway components have an increased risk for developing SLE and SLE-like diseases,[27] and that E-CR1 levels are decreased in SLE and fluctuate in chronically active disease.[28,29]

In contrast, several observations suggest complement-mediated inflammation and direct tissue damage contribute to the pathogenesis of LN:

- Circulating levels of C3 and C4 are lower in active LN compared to inactive LN or nonrenal SLE, indicating ongoing complement activation.[30,31]
- Complement components, including the membrane attack complex, are deposited in LN kidneys.[30,32,33]
- Longitudinal assessment of circulating C3 and C4 levels during SLE flare showed that levels decrease significantly at the time of a renal flare, but not at nonrenal flare, even if the nonrenal flare occurred in patients with a history of LN.[29]
- Renal tubular production of C3 and complement factor B occurs in LN patients but not healthy controls.[34,35]
- The inflammatory receptor for C3a (C3aR), absent from healthy kidneys, becomes expressed in glomerular endothelium in association with IC deposits in LN, and the expression level correlates with LN severity.[36]
- The inflammatory receptor for C5a (C5aR), although present in normal kidneys, is greatly upregulated in the mesangium and podocytes of LN kidneys.[37]
- The expression of CR1 is decreased in LN glomeruli, compared to its normal expression on podocytes.[38]

- The expression of another complement regulator, decay accelerating factor (DAF, CD55), is also reduced in LN patients from its normal expression in the juxtaglomerular apparatus, and appears de novo in the renal vasculature, interstitium, and mesangium.[39]

Although there have been no human studies of complement inhibition in LN to verify its pathogenic role, such experiments have been done in experimental animals. For instance, in the NZB/NZW murine lupus model, anti-C5 antibody blocks the development of glomerulonephritis, suggesting C5a and/or the membrane attack complex are critical nephritic factors.[40] In the MRL/lpr mouse model of SLE, the administration of a rodent inhibitor of complement activation (Crry) was effective at protecting against glomerulonephritis.[41] Interestingly, nephritis in the MRL/lpr model appears to be dependent on the alternative pathway of complement activation, as deleting either the factor B or factor D genes significantly reduced the degree of renal injury.[42,43] The alternative complement pathway is an amplification pathway that is tightly regulated, suggesting that renal damage in LN is due to amplified complement activation occurring in the face of inadequate or overwhelmed complement regulation.

The role of FcγR in the pathogenesis of LN, although perhaps not as complex as complement, is similarly confounding. Like complement, IC activation of FcγR can provide protection by mediating IC phagocytosis and clearance, but can also induce inflammatory responses by activating the cells expressing FcγR.[44] Studies of polymorphic forms of FcγR have clarified which role has the most influence in SLE pathogenesis. There are three classes of FcγR (FcγRI, FcγRII, and FcγRIII), with different genes that produce full length products for FcγRII (FcγRIIA, FcγRIIB, FcγRIIC) and FcγRIII (FcγRIIIA and FcγRIIIB). Single nucleotide polymorphisms (SNPs) that affect the peptide sequence have been identified in some of these genes that influence binding affinity for IgG, including the FcγRIIA 491G>A SNP (amino acid 131R>H) and the FcγRIIIA 559T>G SNP (amino acid 158F>V).[45,46] Although not unequivocal, most studies have reported that the lower affinity forms of FcγRIIa (R131) and FcγRIIIa (F158) are associated with SLE, and particularly with LN.[47,48] The fact that the forms of these receptors that bind IC more efficiently are associated with protection against SLE suggest that their overall function is to promote IC clearance rather than drive tissue inflammation, and that relative deficiencies in this function contribute to LN.

It should be noted that there is an extensive body of work in mouse models of SLE that suggests IC inflammation is mainly FcγR-mediated, with little contribution from the complement system.[49] This includes nephritis in the NZB/NZW model, where deleting the signaling unit of FcγRI and FcγRIII, which also prevents expression of these FcγR, significantly reduces proteinuria, and increases survival time.[50] Although these studies support the potential of FcγR to drive inflammation, they do not negate the contributions of complement to this process. Caution must also be taken in their interpretation, as the relative contribution of complement and FcγR to mouse models of IC inflammation, including LN, depends on the mouse strain that is being tested.[51,52] Finally, if the role of FcγR, particularly FcγRIIIa, in lupus and LN is mainly to drive inflammation, higher affinity forms of the receptor should be associated with worse IC inflammation and LN. However, the studies in human lupus discussed previously demonstrate the opposite; higher affinity forms of FcγRIIIa and FcγRIIa are associated with protection against SLE and LN. Thus the extent to which these models recapitulate the complex nature of human SLE and LN must be considered.

Renal Chemokines, Cytokines, and Cellular Infiltrates

The presence of IC and the activation of the complement system are key initiators of inflammation that define LN. One consequence of complement activation is the deposition of the membrane attack complex, which directly induces cell membrane damage through the formation of transmembrane pores.[33] Another consequence of IC and complement activation is more indirect, and is mediated by the induction of chemokines and cytokines that induce infiltration and activation of proinflammatory cells. These chemokines and cytokines can be initially produced by renal parenchymal tissue, including glomerular endothelial cells, mesangial cells, podocytes, and tubular epithelium.[53] Once leukocytes containing chemokine receptors are drawn into the kidney, inflammation is accelerated through leukocyte secretion of additional chemokines and inflammatory cytokines. Some notable examples of upregulated chemokines and cytokines in kidneys of LN patients include monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1-alpha (MIP-1α); interleukin (I)L-6, IL-10, IL-12, IL-17, IL-18; interferon (IFN)-gamma (IFN-γ); tumor necrosis factor (TNF)-alpha (TNF-α); and Eta-1/osteopontin.[53–57]

In support of a role for chemokines and cytokines in the pathogenesis of LN, deletion or inhibition of their expression substantially reduces kidney injury in mouse models of lupus. For example, deletion of the genes for MCP-1 or its receptor (CCR2) in the MRL/lpr mouse,[58,59] or predisease treatment of the mouse with a MCP-1 antagonist,[60] reduced infiltration of macrophages and T cells and attenuated clinical and histologic measures of injury, despite accumulation of renal IC comparable to wild-type animals. In both MRL/lpr and NZB/NZW mice, anti-IL-6 antibody treatment reduced anti-dsDNA antibodies and glomerulonephritis, as reflected by near normal renal function and glomerular histology.[61,62] Anti-IL-18 antibodies, induced in MRL/lpr mice through IL-18 cDNA vaccination, attenuated LN.[63] Anti-TNF-α treatment of NZB/NZW mice reduced proteinuria, renal inflammatory infiltrates, and glomerulosclerosis, despite increasing circulating anti-dsDNA levels.[64] These data suggest that the renal expression of proinflammatory chemokines and cytokines is an integral step in the pathogenesis of LN.

Some of these may specifically mediate kidney damage (e.g., MCP-1 and TNF-α), whereas others may predispose to kidney injury through general effects on autoimmunity.

Infiltrating neutrophils and monocytes/macrophages can cause direct renal tissue damage by secreting mediators like reactive oxygen species and proteolytic enzymes. The effect of infiltrating T cells is less direct, and is reflected by the cytokine profile of these T cells. During proliferative LN the intrarenal production of Th1 cytokines appears to predominate over Th2 cytokines and correlates with histologic activity. Th1 responses are associated with activated macrophages, and with the production of IgG capable of activating complement and FcγR pathways. Specifically, relatively high levels of IL-12, IFN-γ, and IL-18 are present, although IL-10, a Th2 cytokine, has also been shown to increase. This leads to an overall higher Th1/Th2 cytokine ratio.[55,56,65,66] Th1-dominant expression can also be observed in serum, urine, and circulating T cells of LN patients.[66] The Th1 dominance displayed in LN patients, both locally in the kidney and systemically in the circulation, suggests that this may be an important prerequisite for developing LN.

IL-17 may also play a particularly important role in the pathogenesis of LN. As mentioned previously, IL-17 is found in the kidney in LN, and two major cell sources of IL-17, Th17 cells and CD4-CD8 T cells, have been observed in renal biopsies of LN patients.[57] Local production of IL-17 may drive inflammatory cytokine and chemokine expression by resident glomerular and tubular cells having the IL-17 receptor,[67] leading to activation of neutrophils and monocytes.[68] The presence of IL-17-producing cells in the LN kidney may also represent a shift away from natural regulatory T cells capable of suppressing immune responses.[69] The role of regulatory T cells is discussed later.

Although not usually prevalent, infiltrating B cells have also been described in LN kidneys. Their presence may directly target autoantibodies to the kidney, as has been shown in NZB/NZW mice.[70] B cells in renal tissue may also present kidney antigens to intrarenal T cells. Recent work has shown that intrarenal B and T cells associate with various degrees of organization, including structures resembling germinal centers with central follicular dendritic cells.[71] Interestingly, these structures appear to occur mainly outside of the glomeruli, and are associated with tubular basement membrane IC.[71] These may contribute specifically to tubulointerstitial inflammation in LN.

Intrinsic Regulatory T Cells

Human regulatory T cells (Treg), characterized as $CD4^+$ $CD25^{hi}FoxP3^+$, inhibit immune responses through effects on T and B cells, and particularly autoantibody production.[72,73] Studies in the NZB/NZW mouse suggest a role for Tregs in lupus pathogenesis, with an inverse correlation between circulating Treg numbers and circulating anti-dsDNA levels,[74] and suppression of lupus-like disease activity, including glomerulonephritis by adoptive transfer of Tregs.[75] More than 25 studies have been done on human SLE and the majority of these indicate lower circulating levels of Tregs in SLE, although there is no clear consensus.[76] With regard to the role of Tregs in human LN, one study demonstrated an increase in Treg markers following rituximab-induced B cell depletion in LN patients (n = 7) that correlated with clinical remission,[77] whereas a second study showed no relationship between circulating Treg numbers or function and active LN.[78] Although Tregs are likely involved in SLE pathogenesis, the specific nature of that involvement, especially with respect to LN, remains to be determined.

Interferon-α and Plasmacytoid Dendritic Cells

IFN-α has recently taken a central role in the proposed paradigms of SLE pathogenesis.[79] This pathway is initiated when IFN-α is produced in response to a variety of stimuli, most involving nucleic acids. Plasmacytoid dendritic cells (pDCs) are the major sources of IFN-α following engagement of their endosomal toll-like receptors 7 and 9 (TLR7, TLR9) by ssRNA and unmethylated CpG in DNA, respectively.[80,81] Both TLRs are intracellular. Other cell types can produce IFN-α following engagement of different receptors, such as TLR3 in myeloid dendritic cells, or non-TLR pattern recognition receptors such as the helicases RIG-I and MDA5 in a variety of cells.[82] All these receptors sense various viral and bacterial nucleic acids and activate signaling cascades that end in the production of IFN-α. The effects of IFN-α on the immune response includes driving maturation of conventional dendritic cells into potent antigen presenting cells,[83] inducing B cell differentiation to plasma cells,[84] and contributing to the development of CD4 helper T cells[85] and CD8 central memory T cells.[86]

The IFN-α response receptors theoretically are important in discriminating between self and nonself. For example, TLR7 shows specificity for guanosine/uridine rich ssRNA such as viral ssRNA, whereas TLR9 shows specificity for unmethylated CpG that occurs mainly in nonmammalian DNA. Both receptors also can recognize mammalian nucleic acid in the form of IC containing RNA/protein (e.g., anti-RNP IC) or anti-dsDNA containing IC.[87] The presence of autoantibody may be crucial for this recognition, as RNA and DNA in the form of IC allow phagocytosis of the nucleic acids via FcγRIIa expressed on pDCs.[88] By generating increased IFN-α through this mechanism, an enhanced immune response can occur that may break tolerance to RNA and DNA-containing antigens, resulting in the types of autoantibody that are prevalent in SLE. Initiation of SLE strictly by this mechanism would require a baseline level of IgG against nucleic acids, which is reasonable as ANA positivity occurs in >1% of the general population.[89] Whether the IFN-α /pDC pathway initiates SLE or not, evidence suggests that the pathway is important to the pathogenesis of SLE. This evidence includes the observation that patients treated with IFN-α can develop a lupuslike disease,[90,91] the identification of a number of IFN-α-related

genes as susceptibility genes for SLE onset,[79] an increase in IFN-α induced gene expression (the IFN-α signature) associated with active SLE,[92] and the number of known SLE autoantigens that can drive IFN-α secretion.

There is also evidence that IFN-α may be particularly involved in the pathogenesis of LN. Serum levels of IFN-α correlate directly with anti-dsDNA and inversely with C3 levels,[93,94] markers that are associated with LN. Peripheral blood cell levels of the IFN-α signature are associated with LN patients.[92,95] IFN-α-inducible chemokines, including MCP-1, correlate negatively with C3 levels, and are associated with active LN,[94] and with risk for renal flare.[96] During severe LN pDC disappear from the circulation and accumulate in glomeruli, due in part to glomerular expression of IL-18 and pDC expression of the IL-18 receptor.[97] It is plausible that the presence of renal IC containing dsDNA (e.g., nucleosomes) could drive glomerular pDCs to produce IFN-α, thus amplifying the autoimmune response to local glomerular antigens and contributing to the formation of local germinal centers. Studies in mouse models also generally support a role for IFN-α in LN pathogenesis. Experimental LN is reduced by deletion of the IFN-α receptor or by administration of TLR7 or TLR9 antagonists, whereas LN is worsened by administration of an IFN-α-producing vector or an agonist of TLR7 or 9.[98] One exception is seen in the MRL/lpr model, in which LN is significantly worsened following deletion of the IFN-α receptor,[99] suggesting that IFN-α protects against LN in this mouse strain.

The realization of the importance of the IFN-α pathway in SLE pathogenesis has reinvigorated the concept of microbial pathogen involvement in SLE pathogenesis. The activation of TLRs and other sensors that stimulate IFN-α by viral and bacterial nucleic acids may be important in initiating the break in tolerance, or in accelerating the autoimmune response.

The Genetics of Lupus Nephritis

Much effort has gone into identifying the basis for genetic susceptibility to SLE, using genomewide and candidate gene studies.[100] Over 30 genes have been identified that appear to be related to specific pathogenic pathways in SLE. These include IC clearance/inflammatory pathway genes, immune response genes, and IFN-α signaling and response genes. A number of these impart particular susceptibility to LN.[101] Examples include genetic variation in the FcγRIIA and FcγRIIIA genes described previously, in which the higher affinity variants are associated with protection against LN.[47,48] Two cytokines previously discussed as important for cell infiltration into the kidney, the chemokine MCP-1 for monocytes/T cells and IL-18 for pDCs, have promoter polymorphisms that influence expression levels. The MCP-1 variant that results in higher expression levels is associated with LN.[102] Similarly, the IL-18 variant that causes higher expression is associated with diffuse proliferative LN.[103] Also of interest, the HLA DR3 allele (DRB1*0301) correlates with renal disease,[104] and with anti-dsDNA antibodies,[104] supporting a genetic contribution to a type of autoantibody that may target renal tissue. For the IFN-α pathway, STAT4, which is important for transmitting the IFN-α signal, has a genetic variant that is associated with increased STAT4 RNA levels, and with SLE, particularly LN.[105]

Genome studies have identified six quantitative trait loci (QTLs) that are linked to LN, supporting the fact that LN has a specific genetic component.[106,107] Three of these regions are linked to LN in European Americans, and three are linked to LN in African Americans. One of the loci for European Caucasians occurs on chromosome 4, at q13.1, a region that contains the gene for IL-18. This may account for the relationship between this QTL and LN.

A Composite Picture of Lupus Nephritis Pathogenesis

Considering all of the LN-specific "traits" of the various pathways that contribute to SLE pathogenesis, a picture emerges as to what may be the important steps that culminate in clinical LN (Fig. 53.1). Clinically active LN is always associated with IC accumulation and complement deposition in the kidneys, and often with corresponding evidence of systemic complement activation. The IC that are perhaps most relevant to LN are those containing nuclear antigens. These can arise due to deficiencies in clearance of IC containing nuclear antigens from microbes or apoptotic debris. Deficiencies in the clearance of apoptotic debris may also lead to glomerular accumulation of self-antigen, such as nucleosomes, that can target autoantibody directly to renal tissue. Initial accumulation of glomerular IC sets the stage for an escalating cascade of events that includes local complement activation and chemokine/cytokine production, leading to infiltration and activation of inflammatory (monocytes, neutrophils) and immune cells (pDCs, T cells), and a heightened intrarenal Th1-dominant immune response with significant Th17 contributions. This then leads to an escalation of autoantibody production targeted to the kidney, and inflammation driven primarily by complement and FcγR activation. Many of the mediators derived from this activation contribute to kidney injury, including direct tissue damage by complement proteins and toxic factors produced by inflammatory sells, such as reactive oxygen species and proteolytic enzymes. Continued inflammation can lead to matrix expansion, fibrosis, scarring, and eventually ESRD.

Why LN occurs only in some SLE patients remains an unknown, although the data discussed previously point to the existence of specific LN genes, including those that favor inefficient IC clearance, exuberant chemokine/cytokine production, and loss of tolerance and activation of T and B cells. Environmental contributions such as exposure to certain microbial infections may also be involved in the development of LN. As the specifics of how genetic

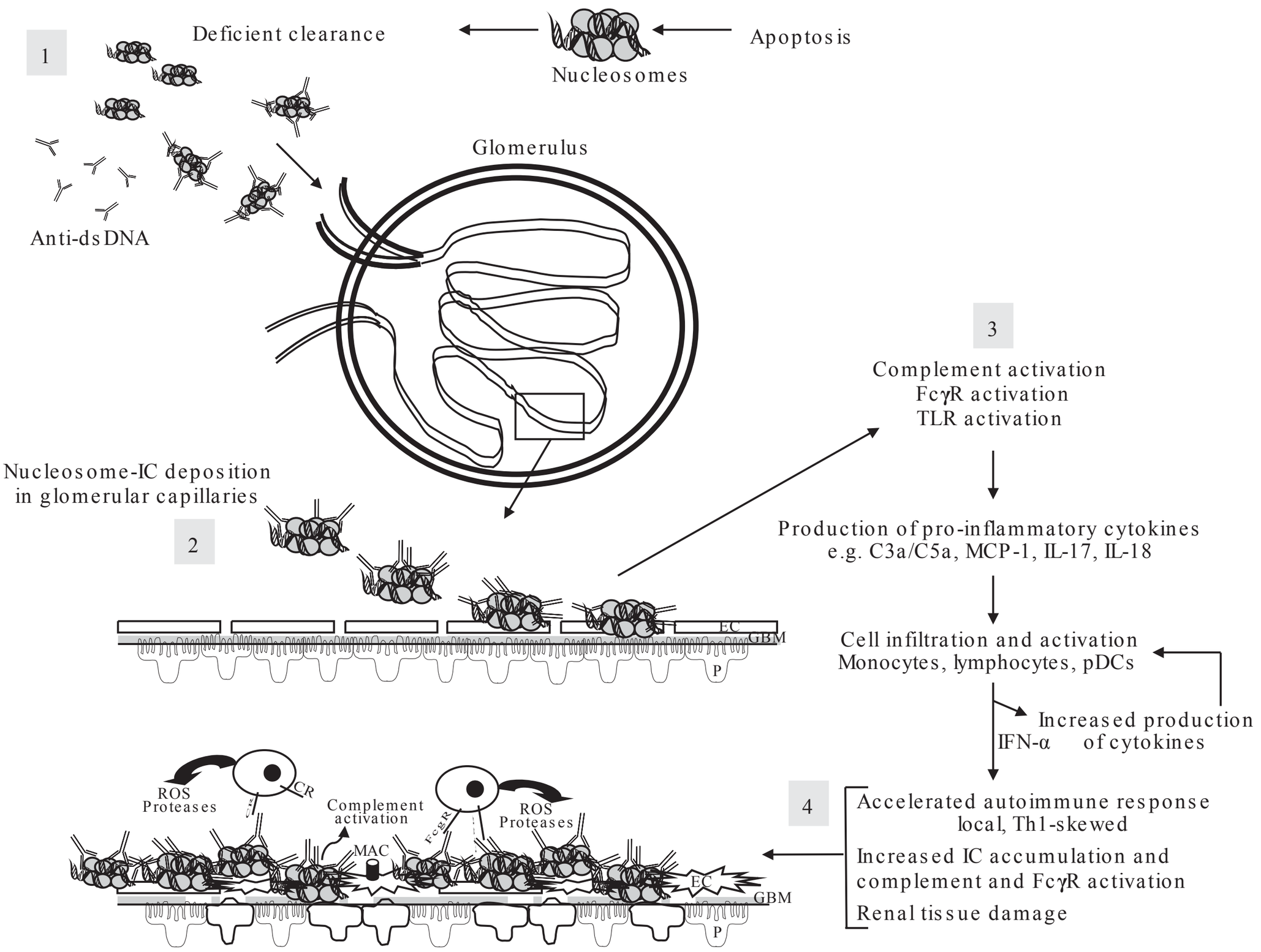


FIGURE 53.1 A paradigm for lupus nephritis pathogenesis. The onset of lupus nephritis likely begins with initial accumulation of self-antigen and immune complexes. In the model presented in the figure, the self-antigens are nucleosomes that can persist due to deficient clearance or overwhelming production, and which in turn can drive anti-dsDNA production (step 1, in shaded box). The resulting immune complexes (IC) are prone to deposit in the renal vascular beds (step 2), in part due to the positively charged core histones of the nucleosome. Once deposited, the IC can activate the complement system, activate circulatory leukocytes via expressed FcγR, and activate resident cells expressing TLRs (step 3). This establishes a cascade of inflammatory cytokine and chemokine production that recruits and activates inflammatory cells, lymphocytes, and pDCs. These infiltrating cells further amplify the production of cytokines and chemokines in the kidney microenvironment. The result is a locally driven and accelerated autoimmune response with Th1 characteristics, and increased IC accumulation and accompanying complement and FcγR activation. This response culminates in the production of inflammatory mediators of tissue damage (step 4). One immediate consequence is destruction of the glomerular filtration barrier through the damaging effects on glomerular endothelial cells (EC), glomerular basement membrane (GBM), and podocytes (P), which leads to proteinuria and hematuria, the hallmark clinical manifestations of active lupus nephritis. *CR*, complement receptor; *MAC*, complement membrane attack complex.

and environmental factors interact and contribute to LN become clearer, so too will our understanding of the pathogenesis of LN.

DIAGNOSIS OF LUPUS NEPHRITIS

Preservation of kidney function in patients with LN is best achieved with early diagnosis and treatment.[108–110] This requires a high index of suspicion for renal involvement in all patients with SLE. Although some patients may present with overt clinical signs of renal disease, such as edema secondary to nephrotic syndrome, or severe hypertension, it is more likely that the initial evidence of kidney involvement will be an abnormality of serum creatinine and/or the urinalysis. An approach for evaluating the SLE patient for kidney involvement is presented in Figure 53.2. Considering serum creatinine, it is important to recognize that a normal range value may be abnormally high for a woman with small-moderate muscle mass and low rates of creatinine production. Also, hypoalbuminemic patients with severe nephrotic syndrome may have increased tubular creatinine secretion, lowering serum creatinine, and leading to an impression of better renal function than in actuality.[111] Finally, in addition to LN, SLE patients may develop acute renal insufficiency because

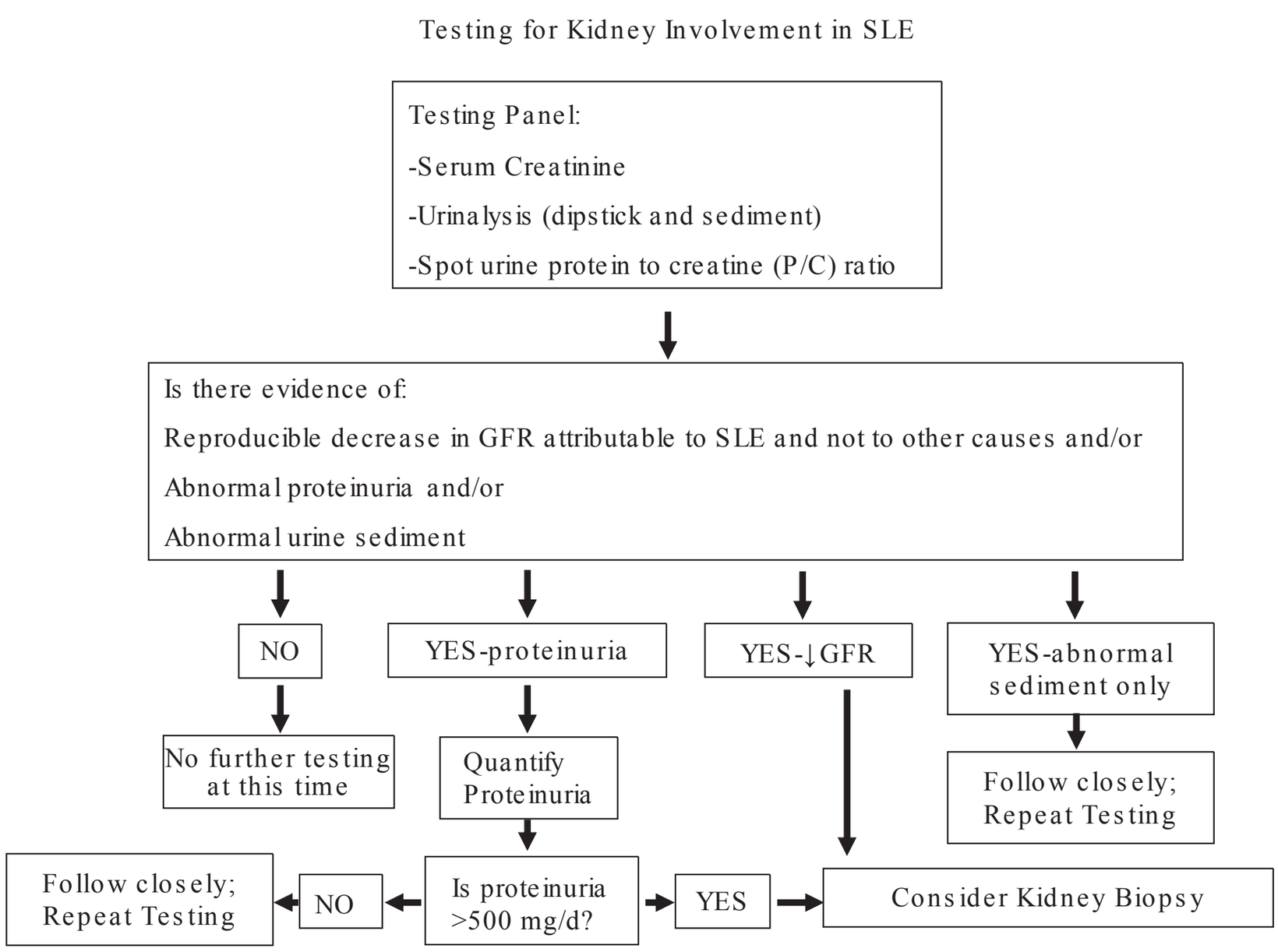


FIGURE 53.2 An algorithm for the evaluation of the kidney in patients with systemic lupus nephritis. Note that patients with a history of lupus nephritis and previous kidney biopsy may not need a repeat biopsy (see text). Kidney biopsy should be done for all new diagnoses of kidney involvement.

of infection, medications, nephrotoxins, hemolysis, thrombosis, and cardiac failure.

Urinalysis is a useful screening test for patients with SLE. A urine dipstick positive for blood and/or protein suggests possible LN; however, a systematic study of the accuracy of the urine dipstick as a screening tool found a false-negative rate in up to 30% of SLE patients and a false-positive rate in about 40% of patients.[112] Therefore the urine sediment should be evaluated for evidence of glomerulonephritis. Glomerular bleeding is suggested by acanthocytes and/or red blood cell (RBC) casts. White blood cells (WBCs) and white blood cell casts in the absence of infection are indicative of renal inflammation, and support a diagnosis of glomerulonephritis.

Proteinuria is a key indicator of kidney injury in SLE. It has prognostic importance because proteinuria may injure the kidney, and it is used as a clinical biomarker of relapse, remission, and successful treatment. Therefore accurate measurement of protein excretion is crucial to the ongoing management of LN.

Random spot urine protein-to-creatinine (P/C) ratios can be used in addition to urine dipsticks to screen patients, but are not accurate enough to be used to make therapeutic decisions or to follow changes in proteinuria magnitude in response to therapy. The most reliable method to quantify proteinuria is to measure the P/C ratio of a 24-hour urine collection, or an intended 24-hour collection that is at least 50% complete.[113] Measuring the P/C ratio reduces confounding the assessment of proteinuria by errors in collecting the 24-hour urine. A 12-hour overnight urine collection that includes the first morning void urine also provides an accurate measure of proteinuria magnitude, and may be easier for patients to collect.[114]

Ultimately a kidney biopsy is essential for the optimal diagnosis and management of most cases of LN. A biopsy is not necessarily required if the only abnormalities are isolated hematuria, or low level proteinuria in the absence of hematuria and an active urine sediment. A biopsy should be considered when proteinuria is above 500 mg per day, as this degree of proteinuria has been associated with significant renal injury.[115–117]

There is some controversy surrounding the utility of kidney biopsies in LN. The main argument against biopsy is a prevalent notion that most patients can be treated with mycophenolate mofetil (see later), and biopsy information would not change the approach to therapy.[118] There are, however, several important reasons to obtain a biopsy:

- Not all kidney disease in SLE patients is classic, IC-mediated glomerulonephritis (LN), so one therapy does not fit all patients. For example non-LN glomerular diseases have been reported in SLE patients.[119–121] This literature is mostly case reports, but in a series of 252 patients, 5% were found to have changes consistent

with focal segmental glomerulosclerosis, minimal change disease, thin glomerular basement membrane disease, hypertensive nephrosclerosis, and amyloidosis.[119] The incidence of podocytopathies in lupus patients appears to be greater than in the general population, suggesting a causal link to the immune dysregulation of SLE.[122,123] Amyloid A (AA) amyloidosis has also been reported frequently in some series.[120,121] Finally, there are other important kidney lesions found in SLE patients that are treated differently than LN, such as interstitial nephritis without glomerulonephritis[121] and thrombotic microangiopathy with or without LN.[124,125]

- The kidney biopsy, especially if performed serially, assesses the degree of chronic kidney injury, and therefore the risk of progressive renal failure that is not related to active LN. If extensive scarring is the dominant process found on biopsy even with some areas of active inflammation, the risk of immunosuppression may outweigh its benefits in terms of renal survival. Such patients may be more appropriately treated with kidney-protective therapies alone.
- In the context of LN therapeutics, kidney biopsies can and should be exploited in novel ways to better inform future drug development. For example, leukocyte subsets can be analyzed by specific staining in lupus kidneys and may yield new insights on renal inflammation.[126] Proteomic techniques can be used to look for patterns of protein expression in LN.[127,128] Gene expression in biopsies can be analyzed with microarray techniques.[128,129] These technologies are just being applied to kidney biopsies, but have the potential to greatly enhance the amount of information available from renal tissue.

KIDNEY PATHOLOGY IN SYSTEMIC LUPUS ERYTHEMATOSUS

Although the gold standard for the exact diagnosis and classification of LN is the renal biopsy, it should be emphasized that LN is not a renal biopsy diagnosis. Renal biopsy changes, although characteristic, are not specific and the diagnosis of LN cannot be made unless the patient fulfills the American College of Rheumatology criteria for SLE. In the absence of a concurrent clinical diagnosis of SLE, only a diagnosis of immune complex glomerulonephritis can be made, with the suggestion that the glomerulonephritis, in the appropriate clinical setting, could be associated with SLE.

The clinical utility of the kidney biopsy depends on obtaining an adequate sample of renal cortex (at least 10 glomeruli) and examination by a renal pathologist.[130] In as much as every biopsy is a clinicopathologic correlation, the nephropathologist must be given all relevant clinical information in order to properly interpret the tissue and integrate the microscopic findings with the clinical data. Furthermore, it is essential that the clinician and pathologist review the findings together before initiation of therapy to ensure that specific clinical concerns have been addressed and that the lesions have been contextualized appropriately.

The first renal biopsy of a patient with LN, although important diagnostically and therapeutically, has somewhat limited prognostic value because most of the active lesions are reversible with treatment. However, a follow-up biopsy performed after several months or years may provide important prognostic information.[131–133] If the degree of chronic injury in the follow-up biopsy does not change substantially, and the patient had a good response to treatment, outcome is likely to be favorable. In contrast, if the degree of chronic injury is substantially more prominent in a follow-up biopsy, a progressive decline in the disease course can be anticipated.

Classification Schemes for Lupus Nephritis

Renal biopsy findings in LN involve the entire spectrum of renal pathology. Therefore, it became necessary to develop a pathologic classification of LN. A first attempt was made in 1974 by a group of pathologists under the auspices of the World Health Organization (WHO), and was later designated as the WHO classification. This was further modified in 1982 and 1995.[134] The original WHO classification was relatively simple, with five classes of LN (Table 53.1). Subsequent modifications made the WHO classification more complicated and cumbersome to use, leading a group of nephrologists and pathologists to develop a new classification of LN (Table 53.1) in 2003 under the auspices of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS).[135]

Similar to the previous WHO classification, the ISN/RPS classification is based primarily on characteristic light microscopic patterns of glomerular injury:

- Mesangial hypercellularity. Mesangial hypercellularity is almost always present in LN, except in Class I (Fig. 53.3), and is the basic, and probably the earliest LN lesion which is later combined with other pathologic patterns of injury.
- Endocapillary hypercellularity. Endocapillary hypercellularity is the hallmark lesion in forms of proliferative LN (Figs. 53.4 and 53.5). Intracapillary cells usually are infiltrating inflammatory cells (including monocytes/macrophages, polymorphonuclear leukocytes, lymphocytes, and rarely eosinophils or basophils). There may also be a component of endothelial cell proliferation.
- Extracapillary hypercellularity. Extracapillary proliferation results in crescent formation (Fig. 53.6), and is common in proliferative forms of LN. It is frequently associated with glomerular capillary rupture, Bowman's capsular basement membrane rupture, fibrin in Bowman's space, and fibrinoid necrosis of the glomerular capillary tuft.
- Karyorrhexis with or without associated fibrinoid necrosis of the glomerular capillary tuft (Figs. 53.7 and 53.8). Karyorrhexis in glomeruli usually reflects apoptosis, a common finding in LN. The apoptotic cells may be infiltrating inflammatory cells or native glomerular cells. Hematoxylin bodies (Fig. 53.9), seen occasionally in

53.1 Classification of Lupus Nephritis

	Original World Health Organization Classification	Simplified ISN/RPS Classification
Class I	Normal: No pathologic findings, no glomerular IC	Minimal mesangial LN: Mesangial IC
Class II	Mesangial LN: Mesangial IC, normal or hypercellular mesangium	Mesangial proliferative LN: Mesangial IC, hypercellular mesangium
Class III	Focal LN (<50% of glomeruli) Glomerular lesions mainly segmental	Focal LN (<50% of glomeruli) – III (A): active lesions – III (A/C): active and chronic lesions – III (C): chronic lesions
Class IV	Diffuse LN (>50% of glomeruli) Glomerular lesions mainly global	Diffuse LN (≥50% of glomeruli involved, lesions may be segmental [S] or global [G]) – IV (A): active lesions IV-S(A); IV-G(A) – IV (A/C): active and chronic lesions – IV-S(A/C); IV-G(A/C) – IV (C): chronic lesions IV-S(C); (IV-G(C)
Class V	Membranous LN	Membranous LN
Class VI		Advanced sclerosing LN

IC, immune complex; LN, lupus nephritis.

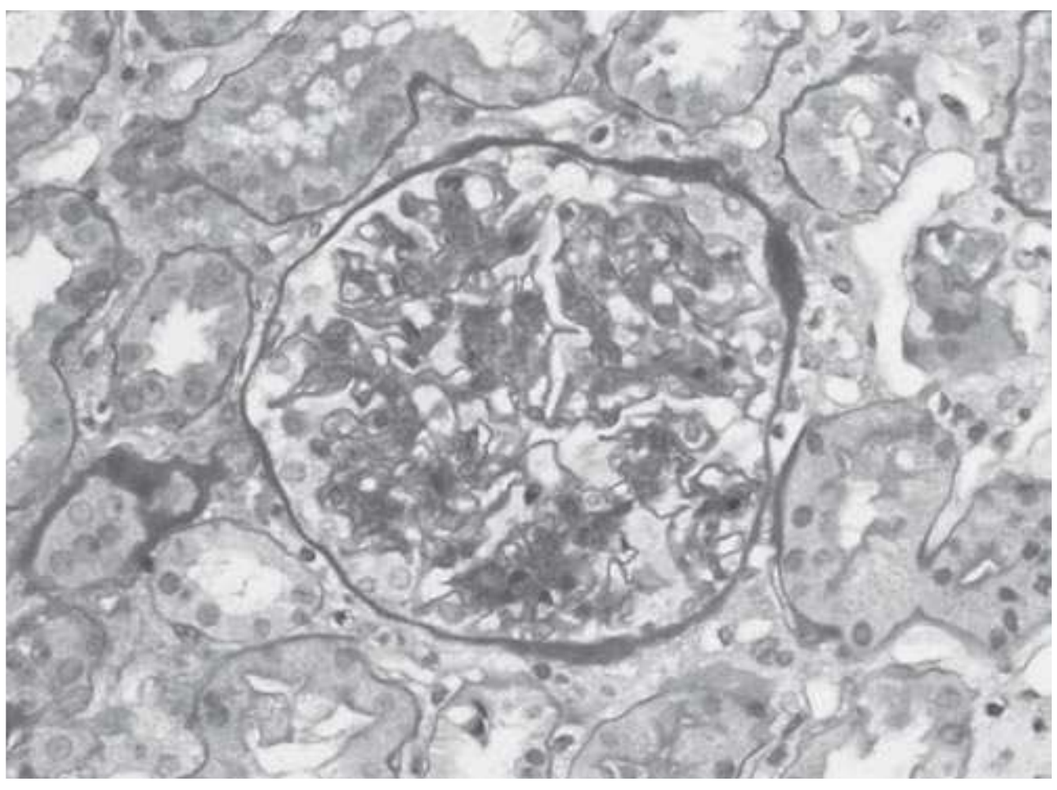


FIGURE 53.3 Mesangial hypercellularity in a case of class II lupus nephritis. Note that the glomerular capillaries are patent. (Periodic acid-Schiff [PAS] ×400.)

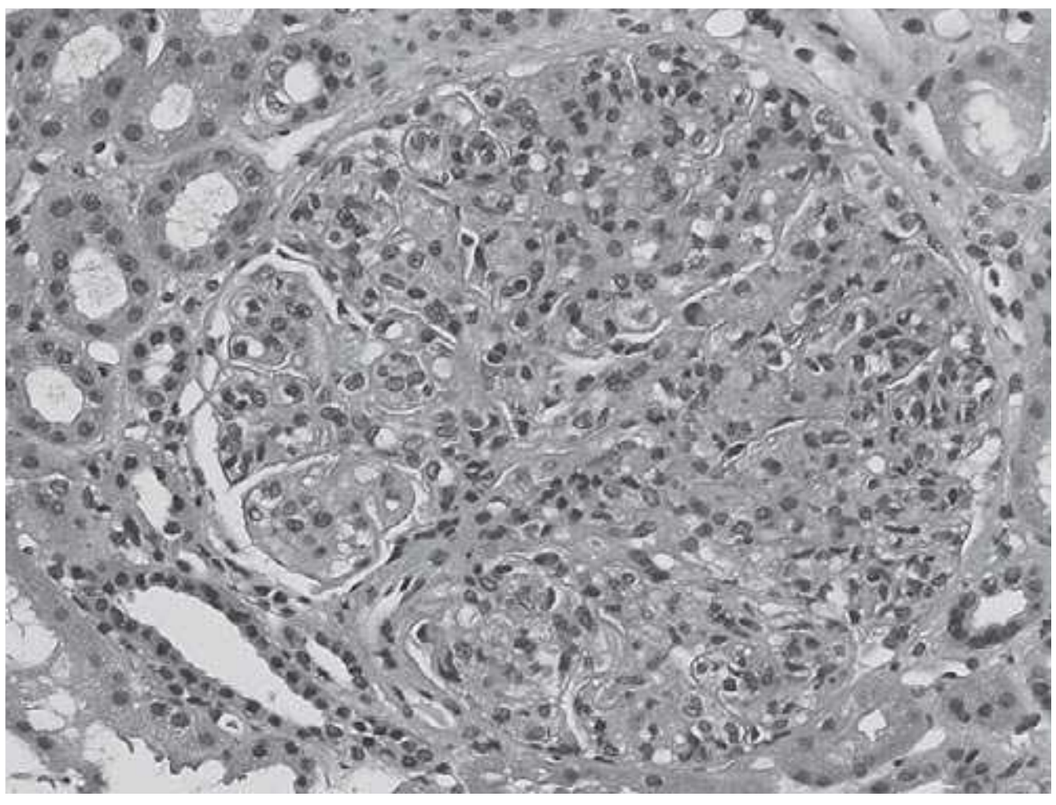


FIGURE 53.4 Global endocapillary hypercellularity with obliteration of the glomerular capillaries in a case of class IV lupus nephritis. The hypercellularity is the result of infiltrating inflammatory cells, including occasional polymorphonuclear leukocytes, as well as proliferating glomerular cells, including endothelial cells and mesangial cells. (Hematoxylin and eosin [H&E] ×400.)

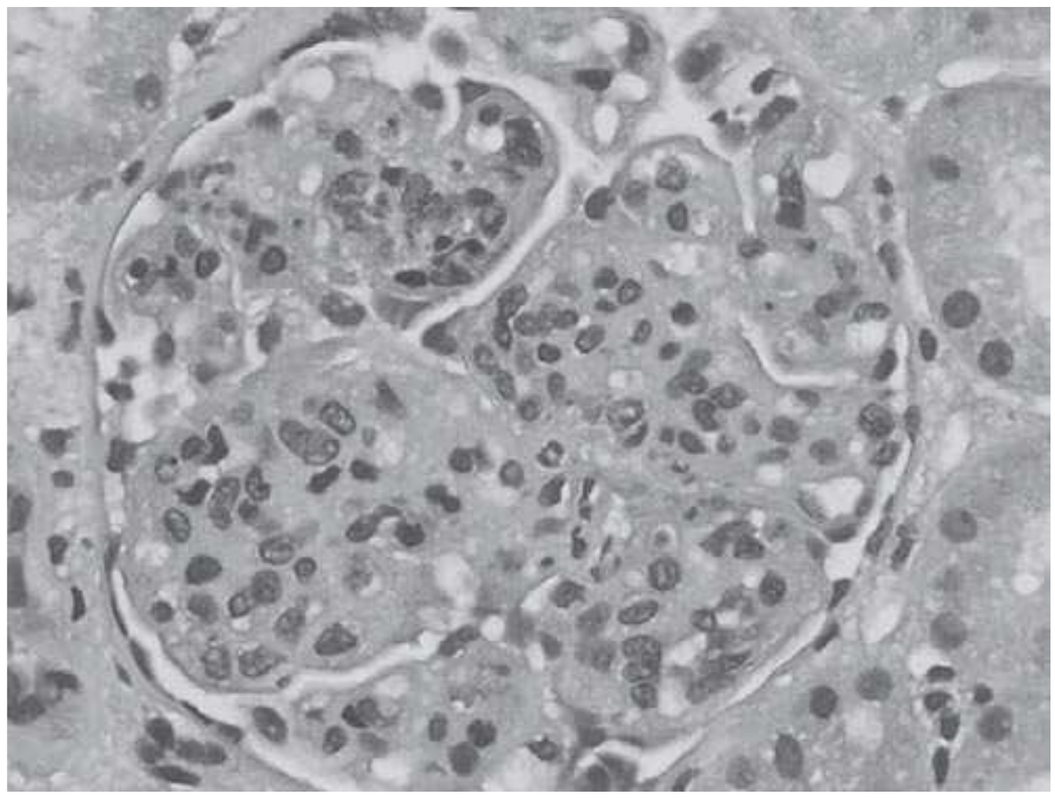


FIGURE 53.5 Global endocapillary hypercellularity with accented lobularization of the glomerular capillary tuft, resembling a membranoproliferative glomerulonephritis in a case of class IV lupus nephritis. (H&E, ×400.)

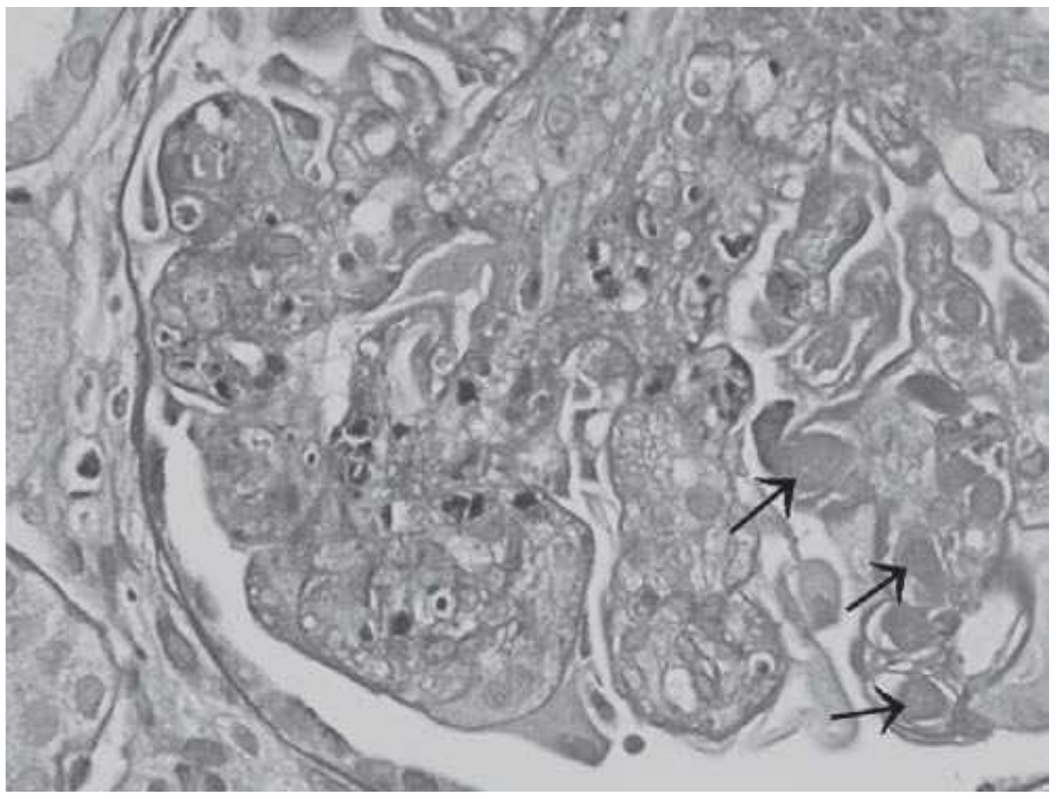


FIGURE 53.7 Apoptotic debris (karyorrhectic nuclei) in the glomerular capillaries in a case of class IV lupus nephritis. In this glomerulus, large subendothelial deposits ("wire loop" lesions) and intracapillary hyalin thrombi (*arrows*) are also present. (PAS ×600.)

biopsies, most likely represent a tissue equivalent of the LE cell phenomenon.

- Wire loop lesions. These lesions are due to large subendothelial immune complex deposits, visible even with light microscopy (Fig. 53.10). If these subendothelial deposits are large enough, they may occlude the entire glomerular capillary lumen and appear as "hyalin thrombi" (Figs. 53.7 and 53.10). Wire loop lesions are positive for periodic acid-Schiff (PAS), negative with methenamine silver stain, and red with Masson's trichrome stain. Wire loop lesions are much more common in LN with global glomerular hypercellularity than with biopsies showing mainly segmental hypercellularity and/or necrosis.
- Spikes. Diffuse uniform glomerular capillary loop thickening with "spike" formation on methenamine silver stain (Figs. 53.11 and 53.12) is the main light microscopic pattern of injury if the immune complex deposits are subepithelial in membranous lupus nephritis.

The ISN/RPS classification (Table 53.1) retained the main subclasses of the modified WHO classification, but introduced several modifications: The ISN/RPS classification

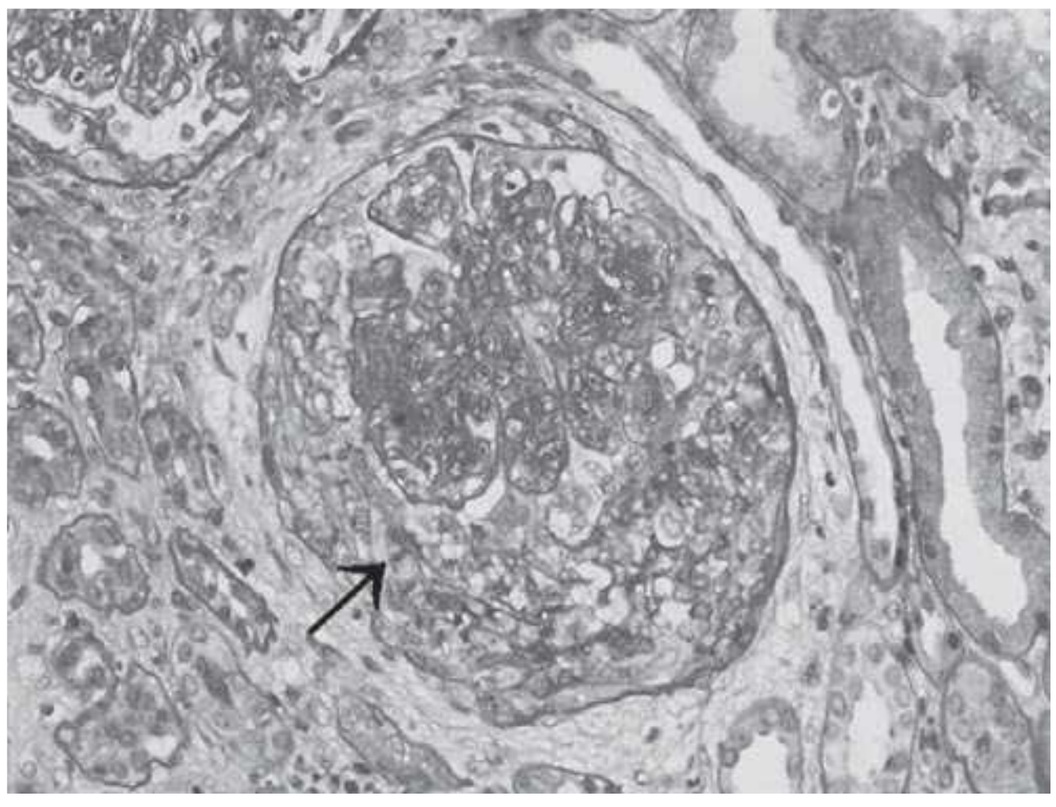


FIGURE 53.6 A cellular crescent in a case of class IV lupus nephritis. Note the compressed glomerular capillary tuft and the rupture in the Bowman's capsule (*arrow*). (PAS ×400.)

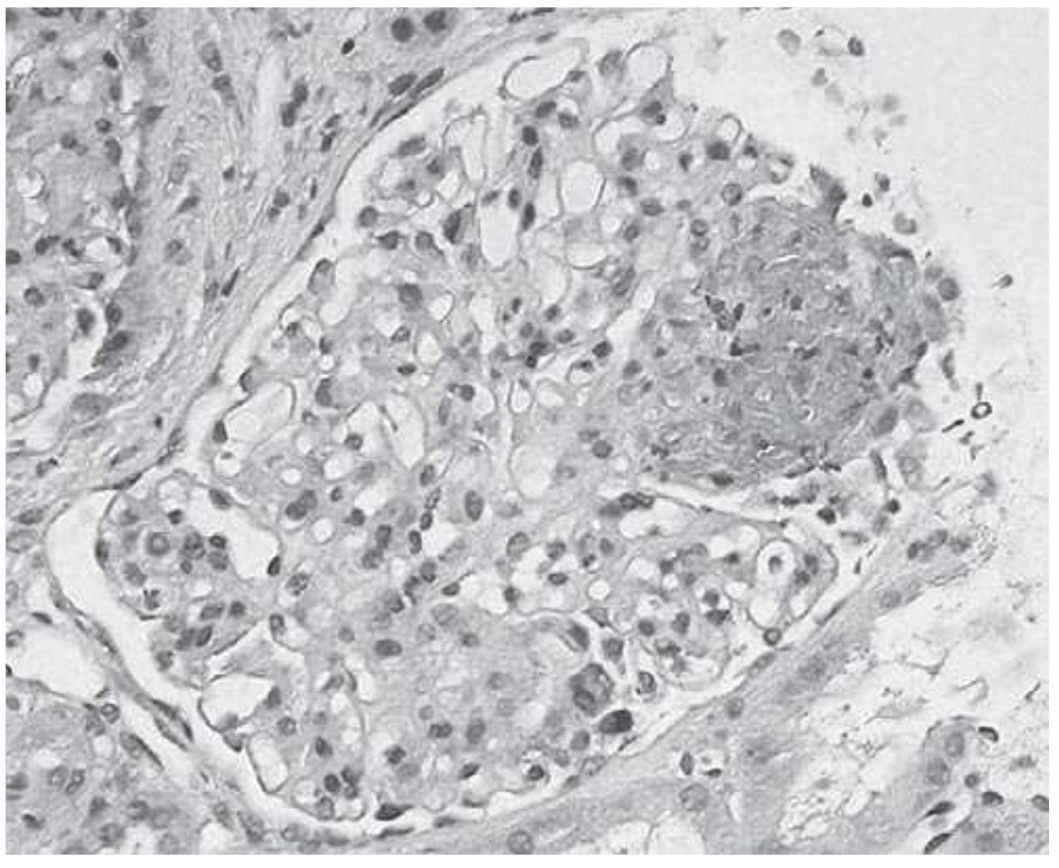


FIGURE 53.8 Segmental glomerular capillary tuft necrosis associated with karyorrhectic/apoptotic debris in a case of focal lupus nephritis. (H&E ×400.)

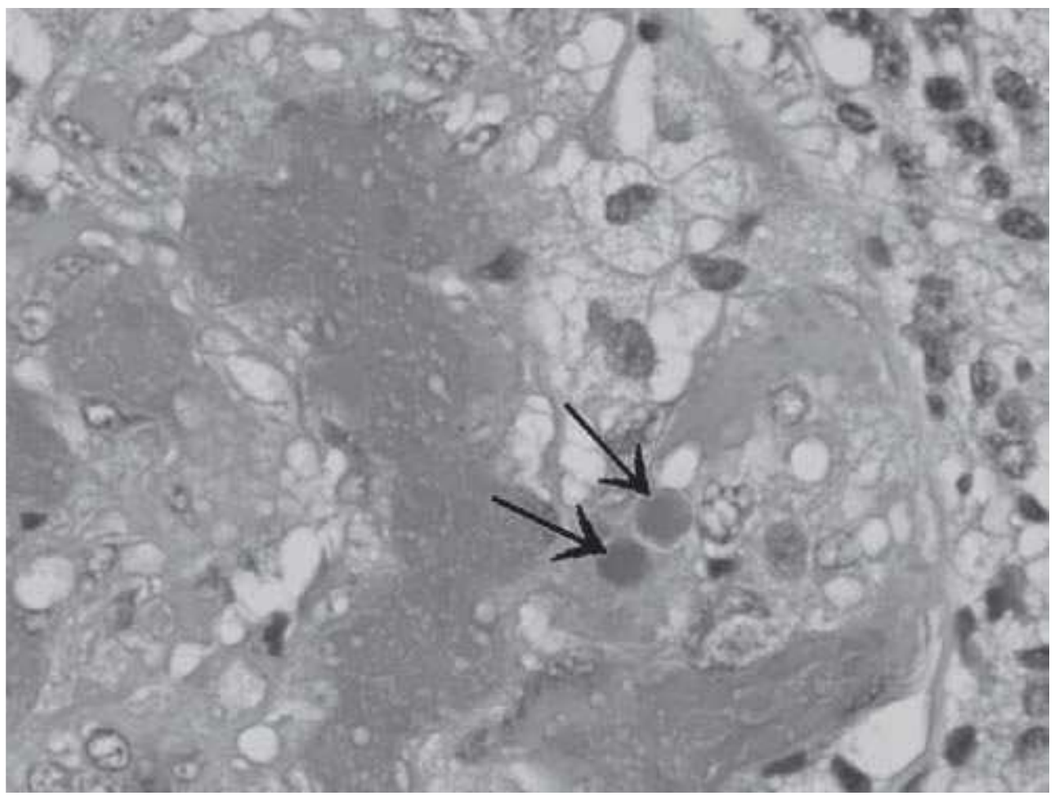


FIGURE 53.9 Hematoxylin bodies in a glomerular capillary (*arrows*) in a case of active class IV lupus nephritis. (H&E ×1000.)

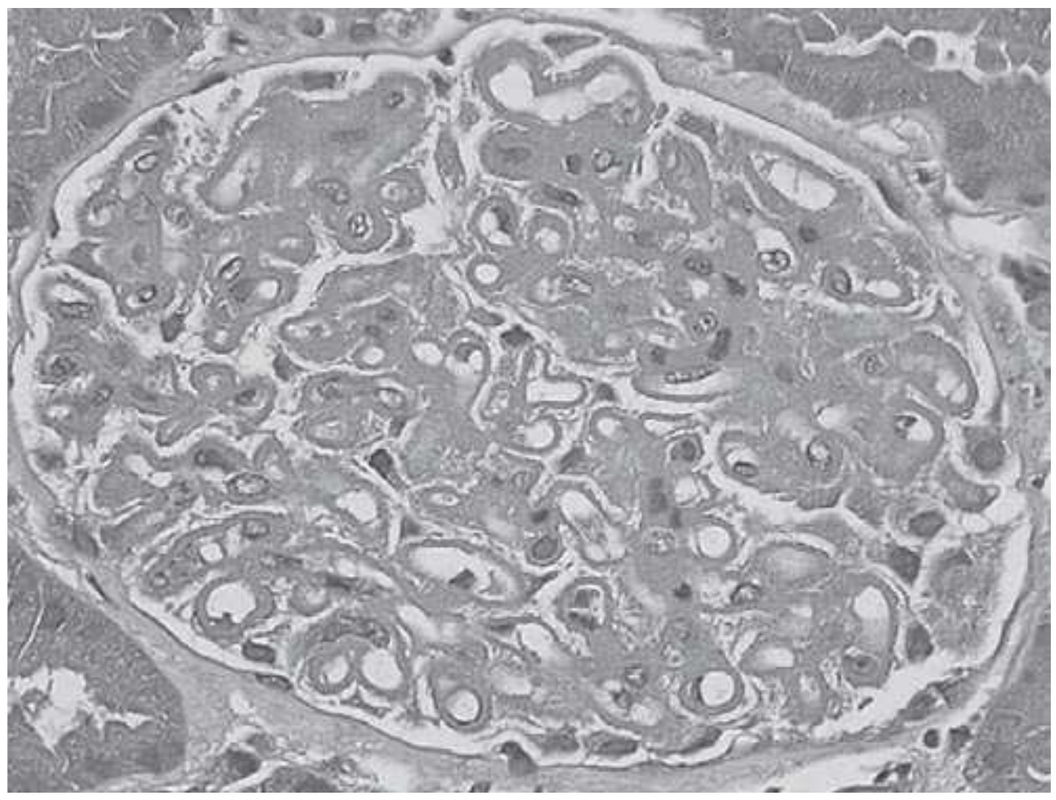


FIGURE 53.11 Diffuse uniform glomerular capillary thickening without hypercellularity in a case of membranous class V lupus nephritis. (H&E ×400.)

differentiates active (A) and chronic (C), and segmental (S) and global (G) glomerular lesions. Active glomerular lesions include glomerular endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction, karyorrhexis, fibrinoid necrosis, rupture of the glomerular basement membrane, cellular or fibrocellular crescents, wire loop lesions, and large intraluminal immune complexes (hyalin thrombi) (Figs. 53.4 to 53.8 and 53.10). Chronic lesions include glomerular sclerosis (segmental or global), fibrous adhesions, and fibrous crescents (Figs. 53.13 to 53.15). Segmental lesions involve less than half of the glomerular capillary tuft area; global lesions involve more than 50% of the glomerular capillary tuft area.

Class I: Minimal Mesangial Lupus Nephritis

In class I LN, the glomeruli appear entirely normal by light microscopy. However, immunofluorescence and electron microscopy reveal obvious mesangial immune complex deposits (Fig. 53.16).

Class II: Mesangial Proliferative Lupus Nephritis

In class II LN, there is pure mesangial hypercellularity (Fig. 53.3) without glomerular endocapillary hypercellularity or crescents. Immunofluorescence and electron microscopy reveal mesangial deposits (Figs. 53.17 and 53.18) as in class I LN. By electron microscopy a few isolated glomerular capillary deposits may be seen. If many peripheral

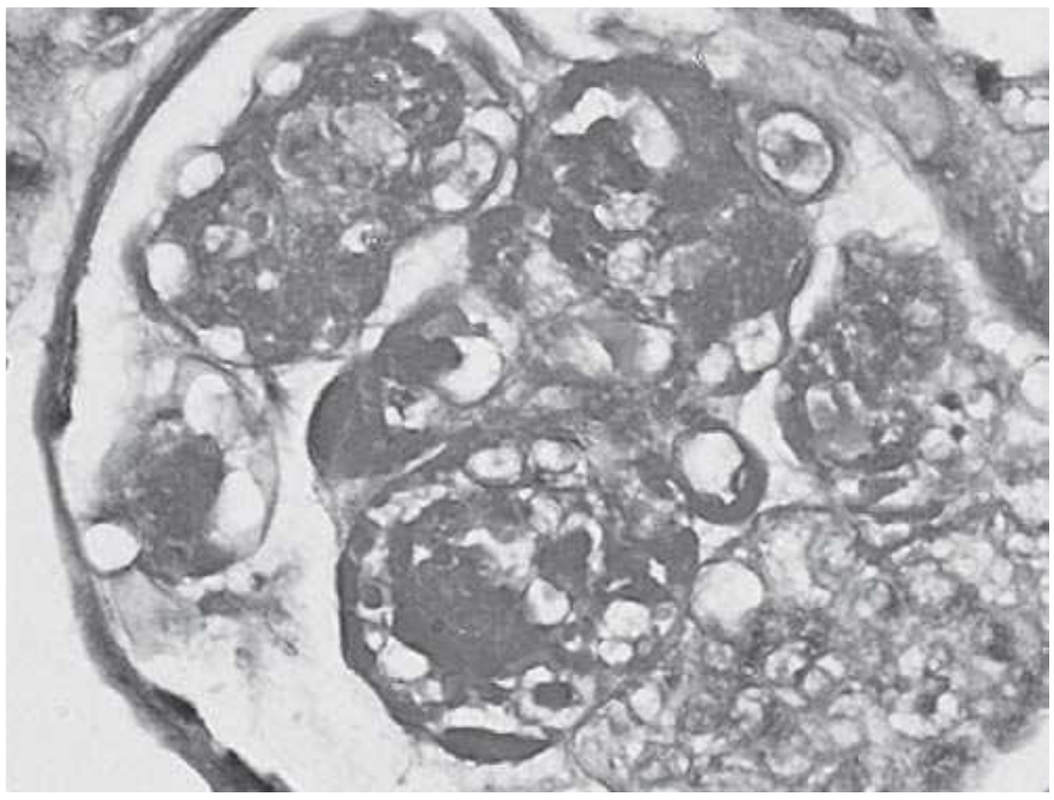


FIGURE 53.10 Large PAS positive deposits along the glomerular capillary loops ("wire loop" lesions) as well as extensive mesangial deposits and glomerular capillary hyalin thrombi in a case of class IV lupus nephritis. (PAS ×600.)

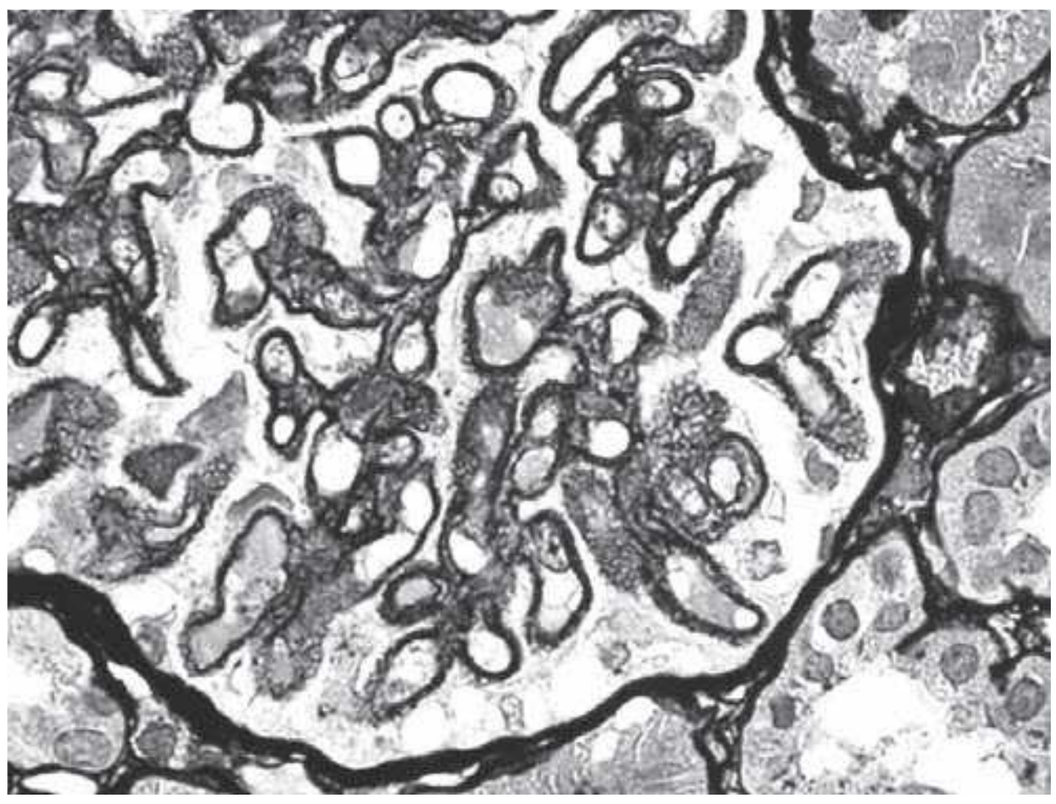


FIGURE 53.12 Methenamine silver stain reveals extensive spike formation along the glomerular capillary loops in the same biopsy shown in Figure 53.11. (Jones' methenamine silver ×600.)

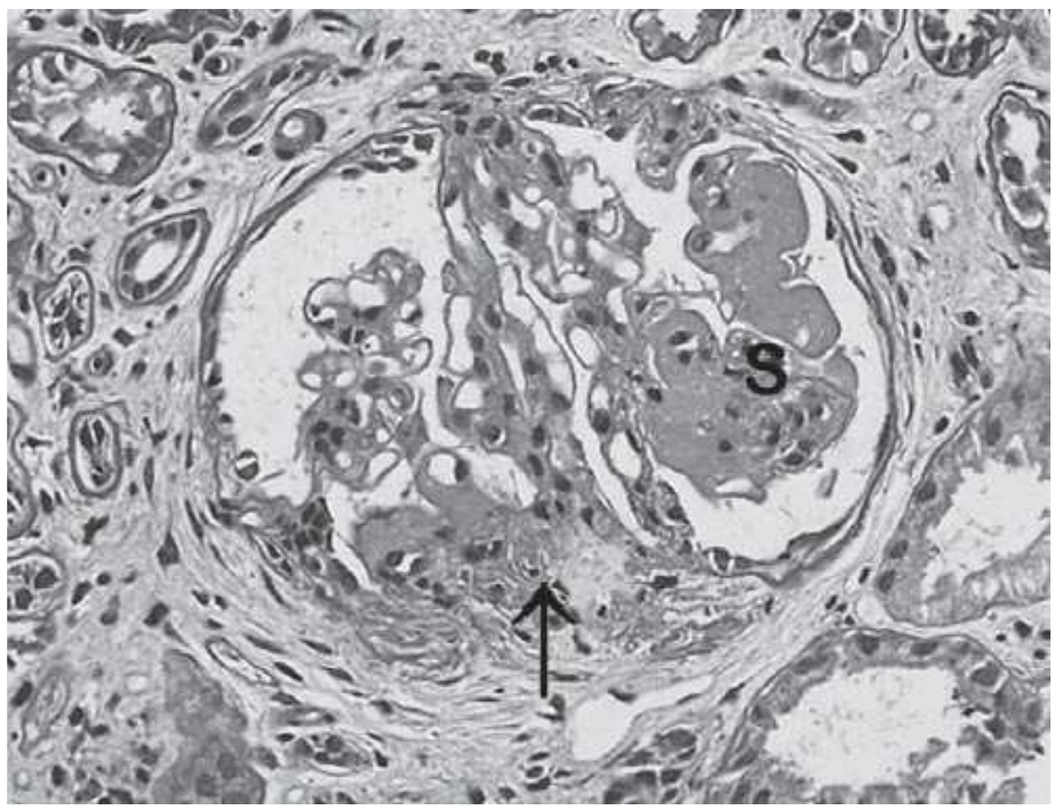


FIGURE 53.13 Segmental sclerosis (*S*) and glomerular capillary adhesion (*arrow*) in a glomerulus from a biopsy with class III lupus nephritis. (PAS ×400.)

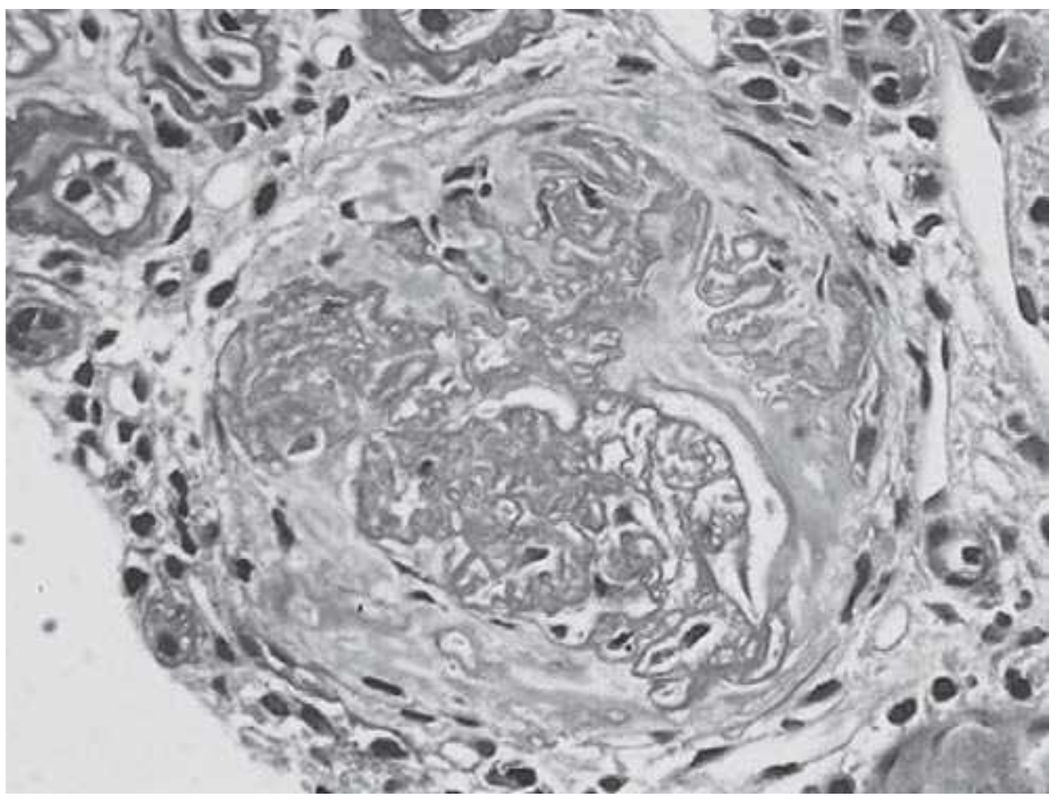


FIGURE 53.15 A fibrous crescent from biopsy with class IV lupus nephritis with moderate to advanced chronicity and mild activity. Note the disrupted Bowman's capsule and the separation of sclerosing glomerular lobules by faintly PAS positive interstitial type collagen. (PAS ×400.)

glomerular capillary immune complex deposits are present, the diagnosis of class II LN should not be made.

Class III: Focal Lupus Nephritis

In class III LN, obvious endocapillary or extracapillary (crescents) proliferative lesions are seen (Figs. 53.7, 53.8, and 53.19), but in less than 50% of all glomeruli, including sclerotic glomeruli, which are also taken into account. Glomerular lesions in focal LN are almost always segmental (Fig. 53.8). By immunofluorescence and electron microscopy, abundant mesangial immune complex deposits are seen, usually associated with segmental glomerular capillary deposits (Fig. 53.20). There are three possible subclasses of focal LN.

- In class III (A) there are only active lesions (focal proliferative LN).
- In class III (A/C) both active and chronic lesions are present (focal proliferative and sclerosing LN). In such cases, focal or segmental sclerosing glomeruli coexist with glomeruli with active proliferative/necrotizing lesions.

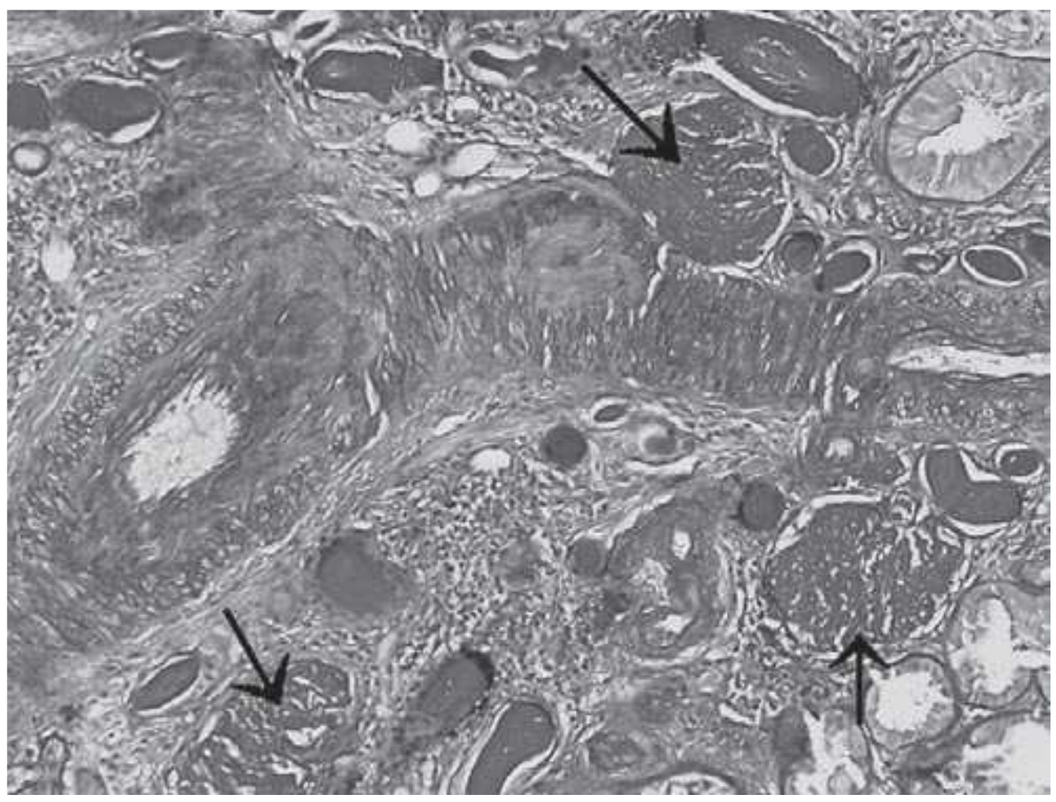


FIGURE 53.14 Globally sclerotic glomeruli (arrows) in a biopsy with advanced sclerosing (class VI) lupus nephritis. (PAS ×200.)

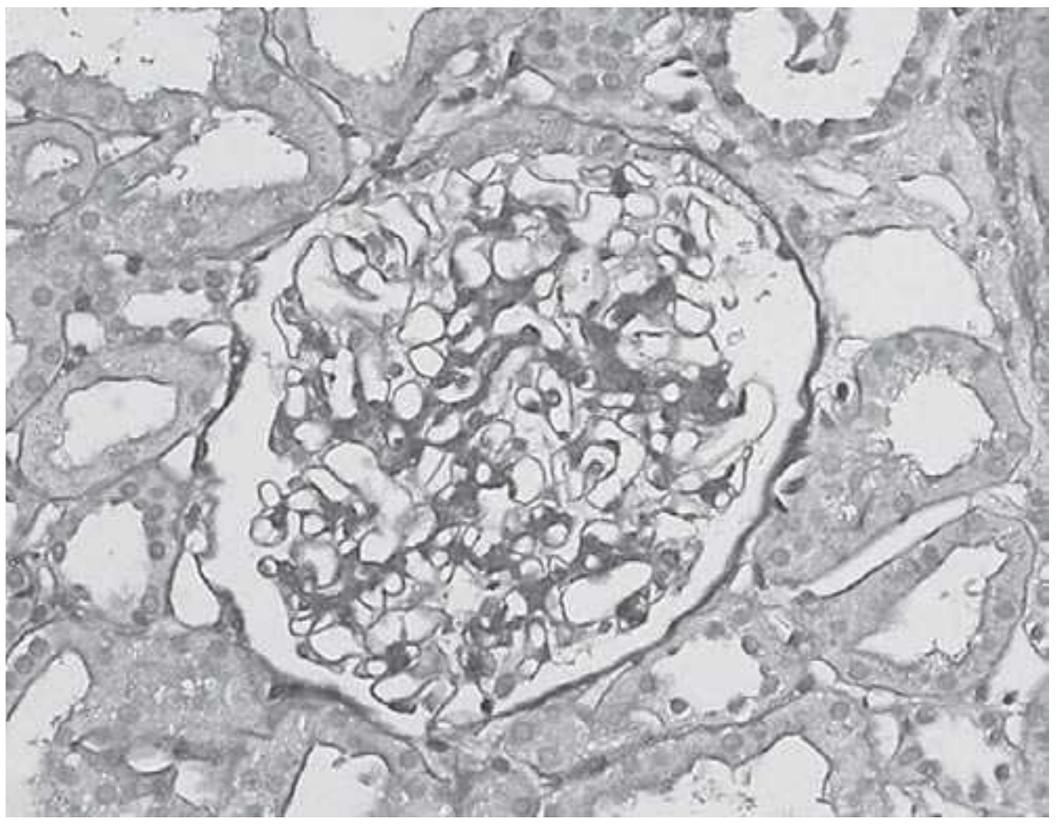


FIGURE 53.16 A light microscopically unremarkable glomerulus in a biopsy with class I lupus nephritis. Immunofluorescence and electron microscopy revealed mesangial immune complex deposits. (PAS ×400.)

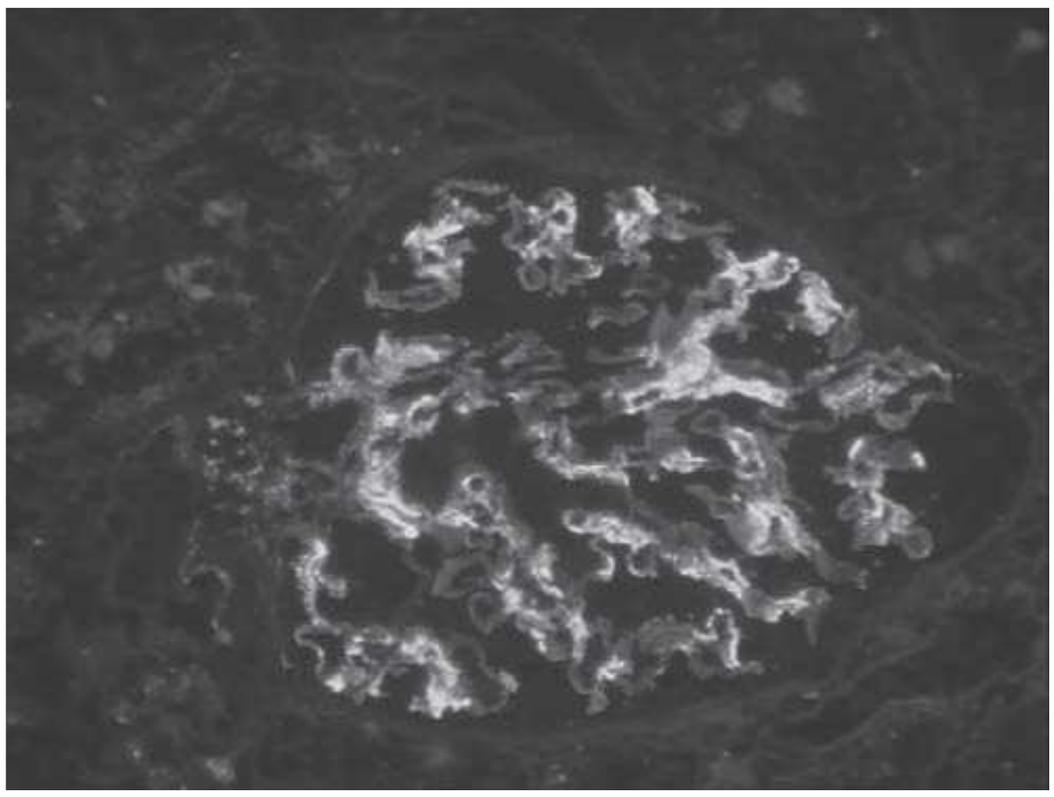


FIGURE 53.17 Mesangial immune complex deposits in a case of class II lupus nephritis. (Direct immunofluorescence with an antibody to IgA, ×400.)

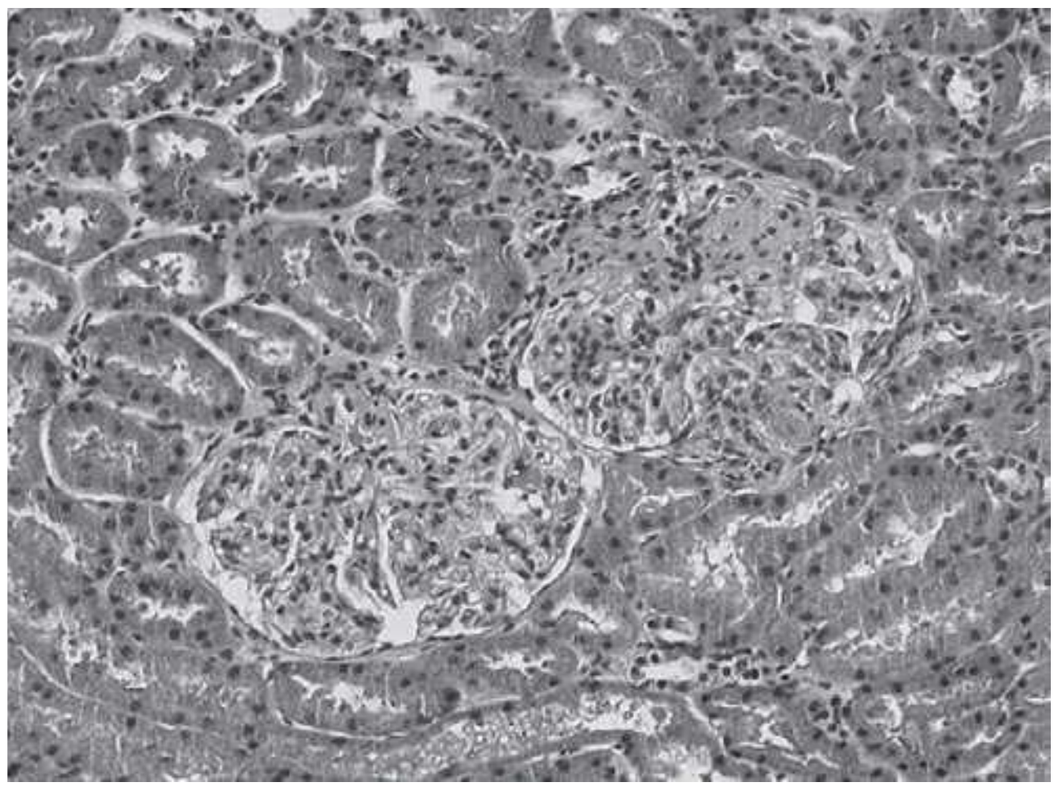


FIGURE 53.19 Two glomeruli from a biopsy with class III lupus nephritis. Note that the left lower glomerulus is light microscopically unremarkable whereas the right upper glomerulus reveals segmental proliferative lesions. (H&E, ×200.)

- In class III (C) only focal sclerosing glomerular lesions are noted with glomerular scars and segmental or global sclerosis (focal sclerosing LN). Active lesions are not seen.

Class IV: Diffuse Lupus Nephritis

In this class of LN, segmental or global endo- or extracapillary glomerular proliferative lesions are seen in more than 50% of all glomeruli (Figs. 53.4 to 53.8). Large subendothelial deposits, visible under the light microscope (wire loop lesions) (Figs. 53.7 and 53.10), are common. In class IV LN, the glomerular lesions can be global or segmental. Also, active and chronic glomerular lesions are evaluated separately. Immunofluorescence and electron microscopy reveal abundant glomerular mesangial and capillary loop deposits. The glomerular capillary loop deposits are mainly subendothelial, and frequently quite large (Figs. 53.21 and 53.22). Scattered intramembranous and subepithelial deposits are common. Therefore, there are six possible subclasses of diffuse LN.

- Class IV-S(A) indicates active diffuse segmental endocapillary or extracapillary proliferative glomerular lesion or necrosis involving more than 50% of the glomeruli.
- Class IV-G(A) shows diffuse global LN with active endocapillary or extracapillary proliferative glomerular

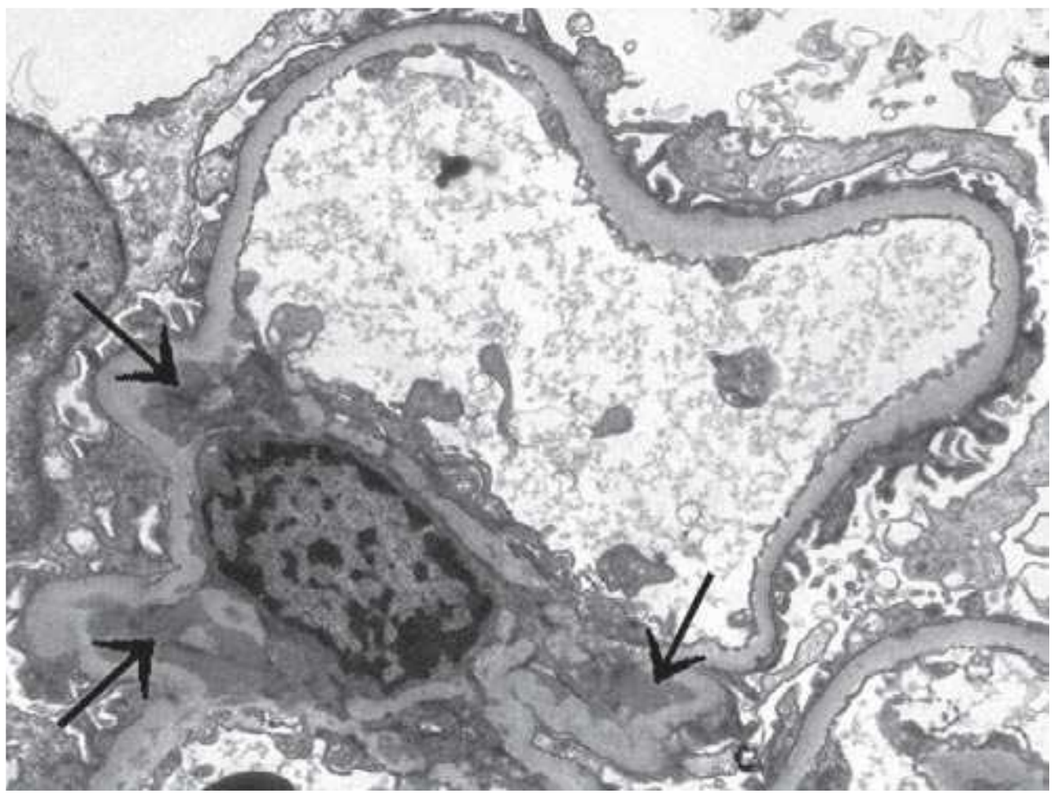


FIGURE 53.18 Mesangial electron dense immune type deposits (*arrows*) in a case of class II lupus nephritis. (Uranyl acetate, lead citrate ×8000.)

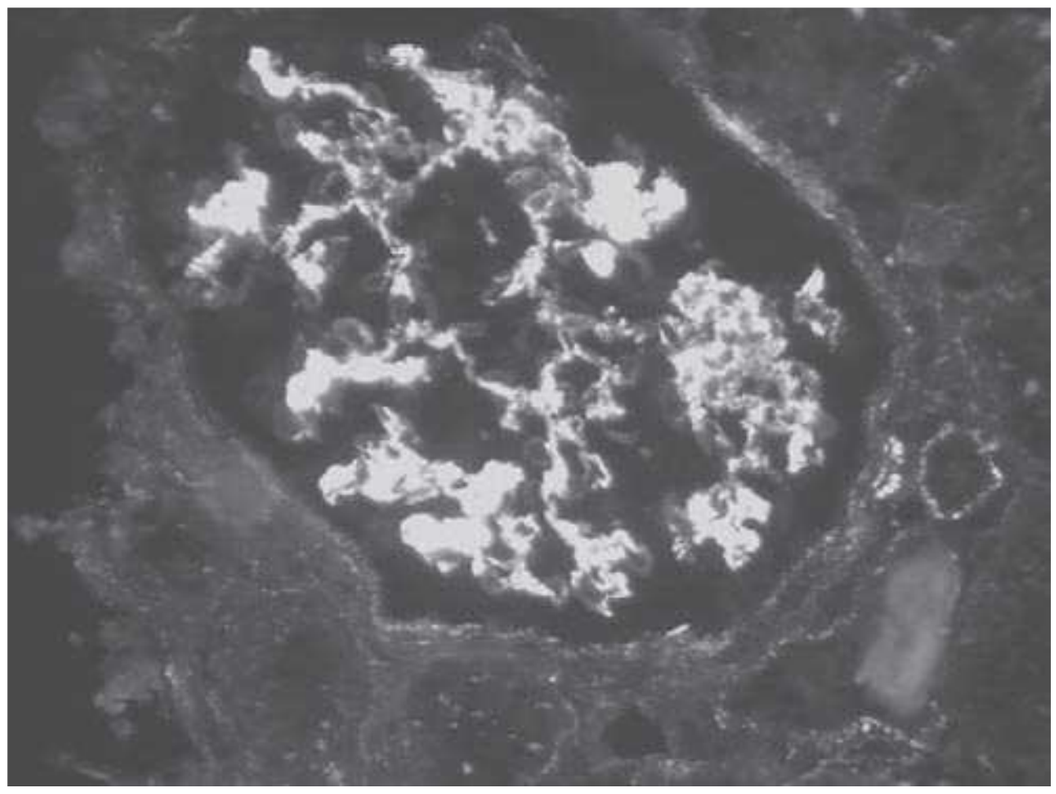


FIGURE 53.20 Granular mesangial and segmental glomerular capillary loop deposits in a case of class III lupus nephritis. Also note the subtle granular tubulointerstitial staining. (Direct immunofluorescence with an antibody to IgG, ×400.)

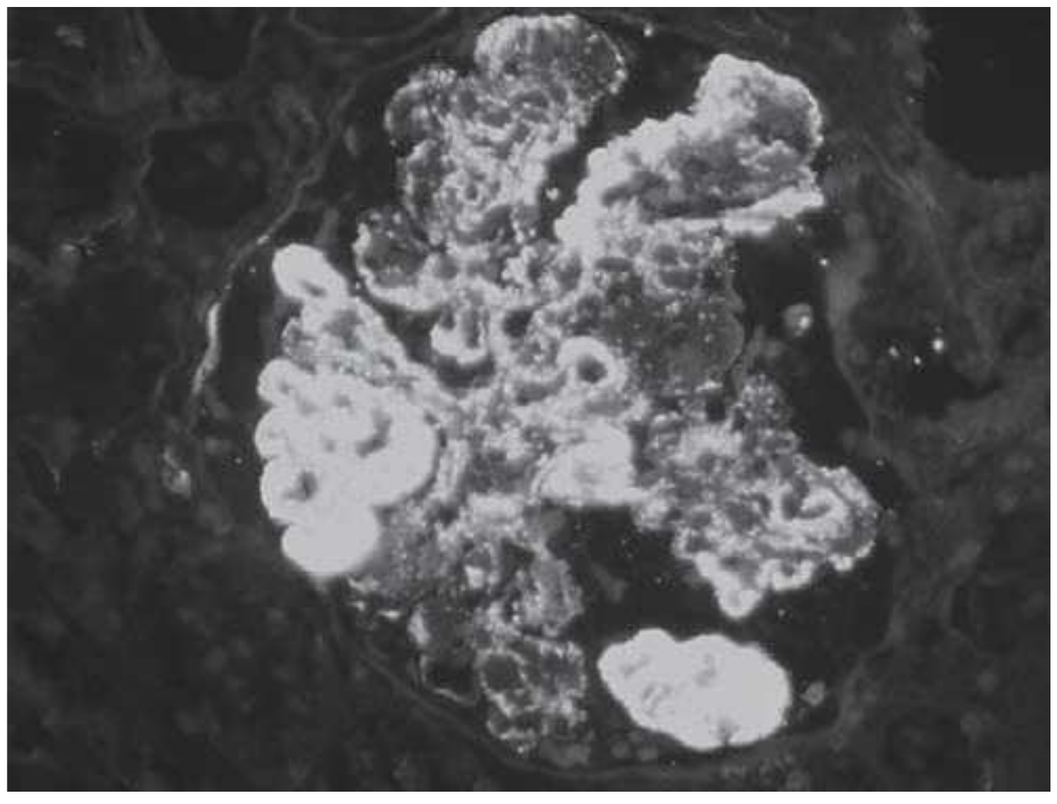


FIGURE 53.21 Diffuse granular glomerular deposits with large subendothelial deposits ("wire loop" lesions) in a case of class IV lupus nephritis. (Direct immunofluorescence with an antibody to IgG, ×400.)

lesions and/or necrosis involving more than 50% of glomeruli.

- Class IV-S(A/C) indicates diffuse segmental proliferative and sclerosing LN. In such biopsies, active segmental proliferative lesions coexist with chronic sclerosing glomerular lesions.
- Class IV-G(A/C) indicates diffuse global proliferative and sclerosing LN. These biopsies show active global proliferative lesions with chronic sclerosing glomerular lesions.
- Class IV-S(C) indicates diffuse segmental sclerosing LN. In this subclass, no active lesions are present; only inactive, mainly segmental glomerular lesions are seen, such as segmental sclerosis/scarring.
- Class IV-G(C) shows diffuse global sclerosing LN. In such biopsies, glomeruli reveal global sclerosis or scarring with or without fibrous crescents, involving more than 50% of all glomeruli, in the absence of active proliferative lesions.

Class V: Membranous Lupus Nephritis

In class V LN the glomeruli do not reveal endocapillary hypercellularity; the mesangium may be normocellular or hypercellular. The glomerular capillaries are uniformly and diffusely thickened (Fig. 53.11), except in very early stages of the disease. Spike formation on methenamine silver stain is common, just like in idiopathic membranous glomerulonephritis (Fig. 53.12). Glomerular subepithelial immune complex deposits involve over 50% of the glomerular capillary tufts (Figs. 53.23 and 53.24). In contrast to idiopathic membranous glomerulonephritis, in class V LN the immunofluorescence frequently, shows a "full house" pattern (see later text), and the IgG deposits contain mainly IgG1 and IGg3 as opposed to IgG2 and IgG4 (see later). However, we encountered several cases of class V LN with IgG4 predominant glomerular capillary deposits. Mesangial immune complex deposits are almost invariably present. A few small subendothelial deposits are possible. Electron microscopy usually reveals endothelial tubuloreticular inclusions (TRIs) (Fig. 53.25).

Class VI: Advanced Sclerosing Lupus Nephritis

In class VI LN over 90% of the glomeruli are globally sclerosed without residual activity (Fig. 53.14). There has to be clinical or morphologic evidence that the advanced glomerular

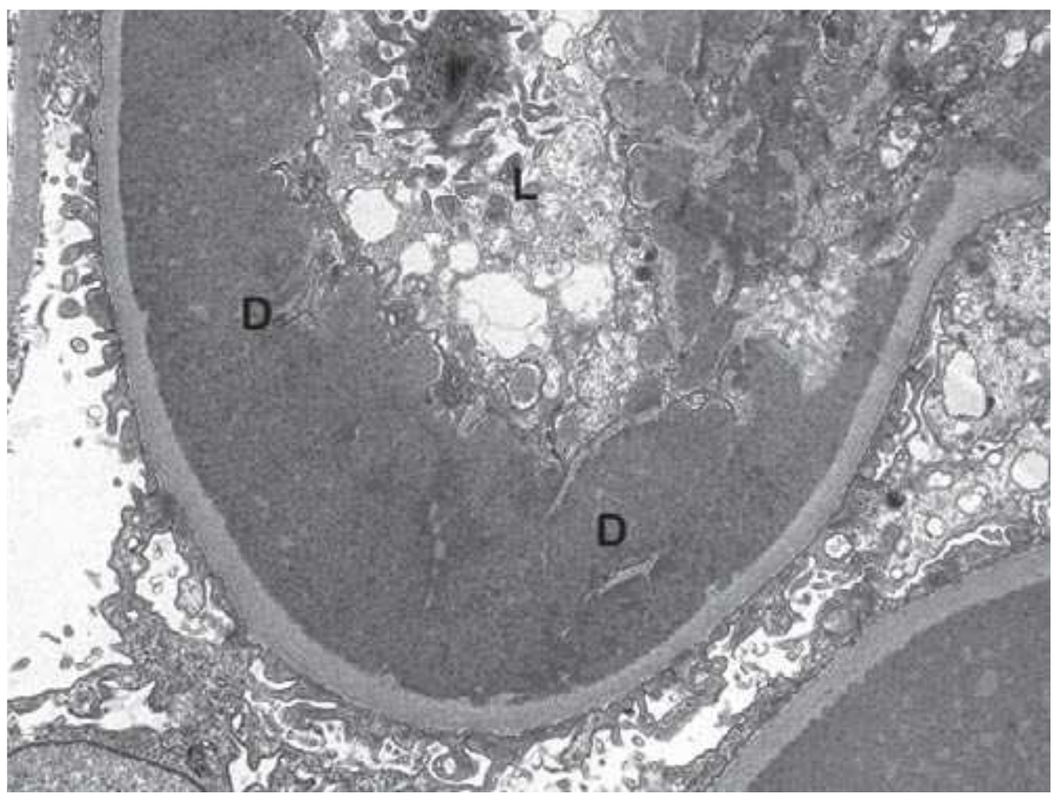


FIGURE 53.22 This electron micrograph shows a large subendothelial electron dense deposit (*d*) in the same biopsy shown in Figure 53.21. *L*, glomerular capillary lumen. (Uranyl acetate, lead citrate, ×8,000.)

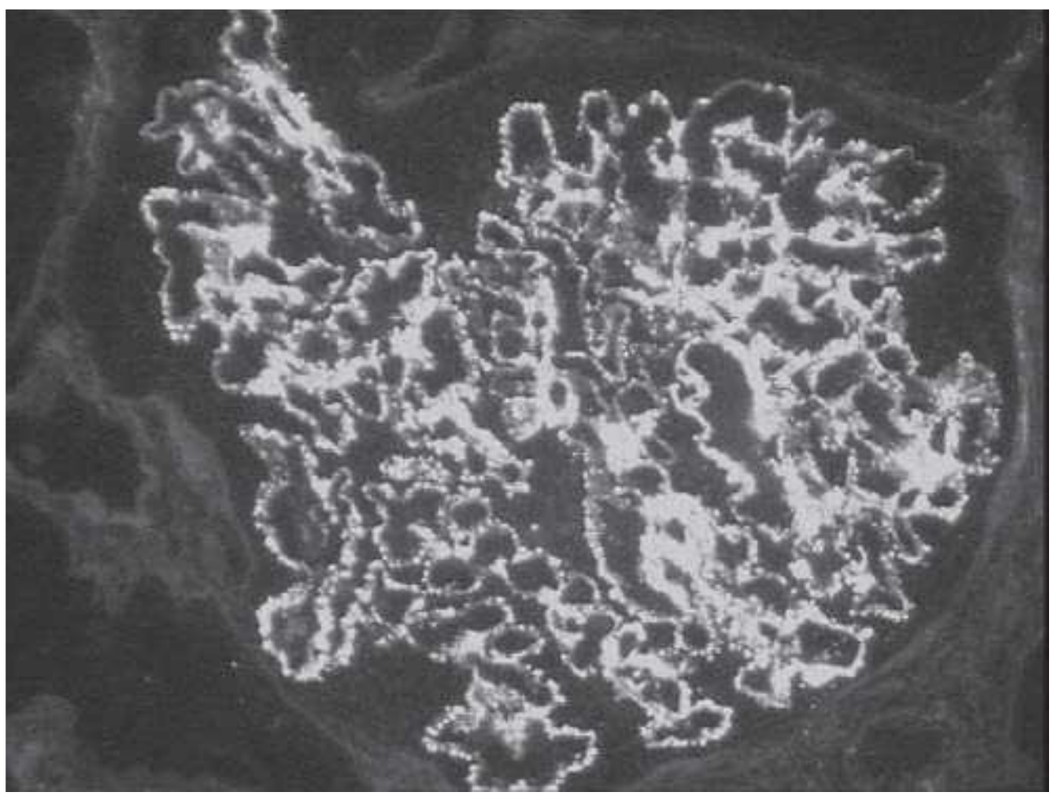


FIGURE 53.23 Granular mesangial and glomerular capillary fluorescence with an antibody to IgG in a case of membranous (class V) lupus nephritis. Note that over 50% of the glomerular capillaries contain granular deposits. (Direct immunofluorescence, ×400.)

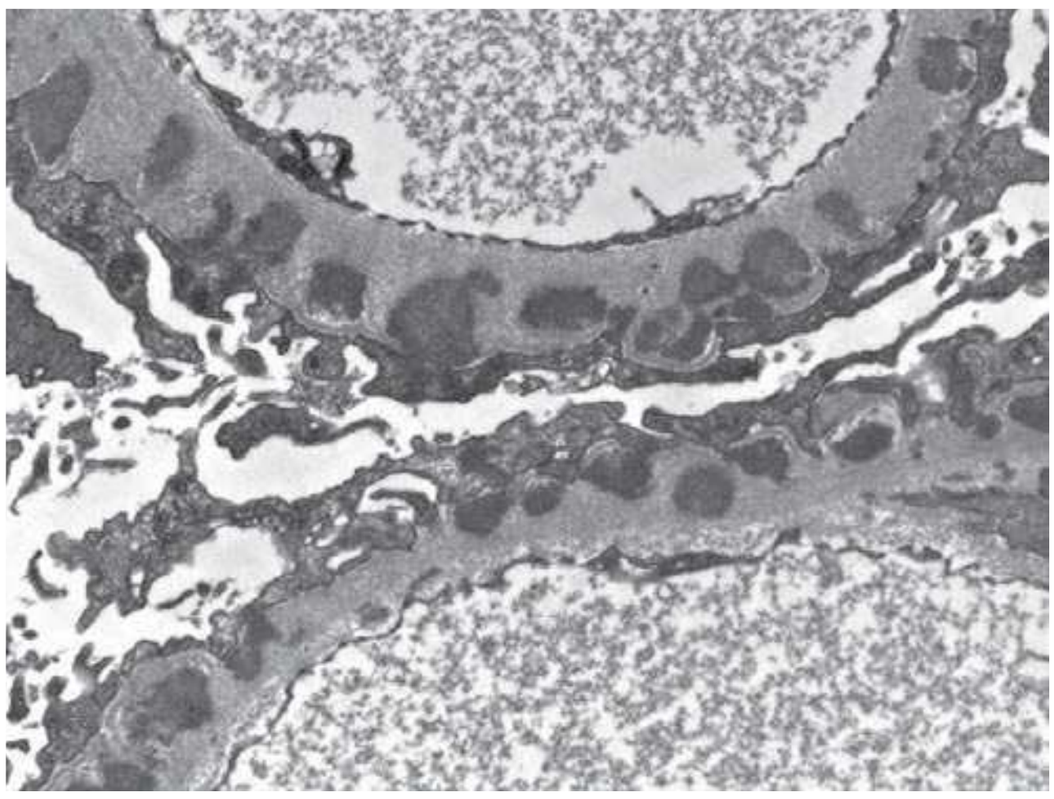


FIGURE 53.24 Subepithelial electron dense immune type deposits along the glomerular basement membrane in a case of class V(membranous) lupus nephritis. Note that occasional deposits are already completely incorporated into the glomerular basement membrane. (Uranyl acetate, lead citrate ×15,000.)

sclerosis is secondary to LN. Immunofluorescence and electron microscopy still frequently reveal mild glomerular immune complex deposits in the few nonsclerotic glomeruli.

Controversies with the ISN/RPS Classification

Although several follow-up studies emphasize the benefits of the ISN/RPS classification of LN,[136,137] not all investigators share this enthusiasm.[138,139] The classification is based purely on morphologic findings and arbitrary definitions. For example, the classification of proliferative LN into focal and diffuse forms is based on an arbitrary cut off value of 50% glomerular involvement. It is hard to imagine that a patient with LN and 40% glomerular involvement would be treated and respond differently than a patient with 60% glomerular involvement.

The definitions of segmental and global lesions are even more controversial. A segmental lesion is defined by involvement of less than 50% of the glomerular surface area in the tissue section. In contrast, a global lesion is defined as involvement of more than 50% of the glomerular surface area. The degree of involvement in a given tissue section depends on the plane of the section through the glomerular tuft. Thus, depending on the level of the cut, a segmental lesion could appear to involve more or less than 50% of the glomerular capillary surface area.

Furthermore, some investigators argue that the pathogenesis of LN with true global lesions is different from LN with segmental glomerular lesions, and that this affects outcomes, and may require different treatment.[139–142] Class IV LN cases with segmental lesions involving more than 50% of the glomerular tuft area (classified as class IV-G) appear to have a worse outcome than true global proliferative LN with 100% involvement of the glomerular capillary tuft area (also classified IV-G by ISN/RPS), and class IV-S with less than 50% glomerular tuft involvement.[139] In contrast, others did not find any difference in outcome between patients with class IV-S and class IV-G LN,[143–146] but this may be because cases of class IV-G with segmental lesions involving more than 50% of the glomerular tuft were generally not separated out from class IV-G with 100% tuft involvement.[139,142,147] At the present time, these concerns remain unresolved.

Immunofluorescence Findings in Lupus Nephritis

Most renal pathology laboratories perform immunofluorescence with a panel of antibodies to IgG, IgA, IgM, kappa and lambda light chains, complement components C1q, C3, C4, fibrinogen, and albumin. The distribution of glomerular immune complexes in the various classes of LN was addressed previously. Interestingly, glomerular immune complex deposits in LN often show a "full house" pattern, meaning that all or almost all immunoreactants (IgG, IgA, IgM, kappa and lambda light chains, C1q, C3) are present. This is unusual in other forms of glomerulonephritis. However, the absence of full house immunofluorescence does not exclude LN. In membranous LN the full house pattern may be absent, and even in proliferative LN, it is not always evident. C1q staining is usually quite prominent in LN and may show the most intense staining among all antigens. Such strong C1q staining is rare in other forms of glomerulonephritis. Another characteristic immunofluorescence feature in LN biopsies is the frequent deposition of extraglomerular immune complexes (Fig. 53.26). Extraglomerular immune complexes are most commonly seen along the tubular basement membrane, but they are also common in the interstitium, particularly along the basement membranes of peritubular capillaries. Bowman's capsule immune complexes are also common. In our experience, if

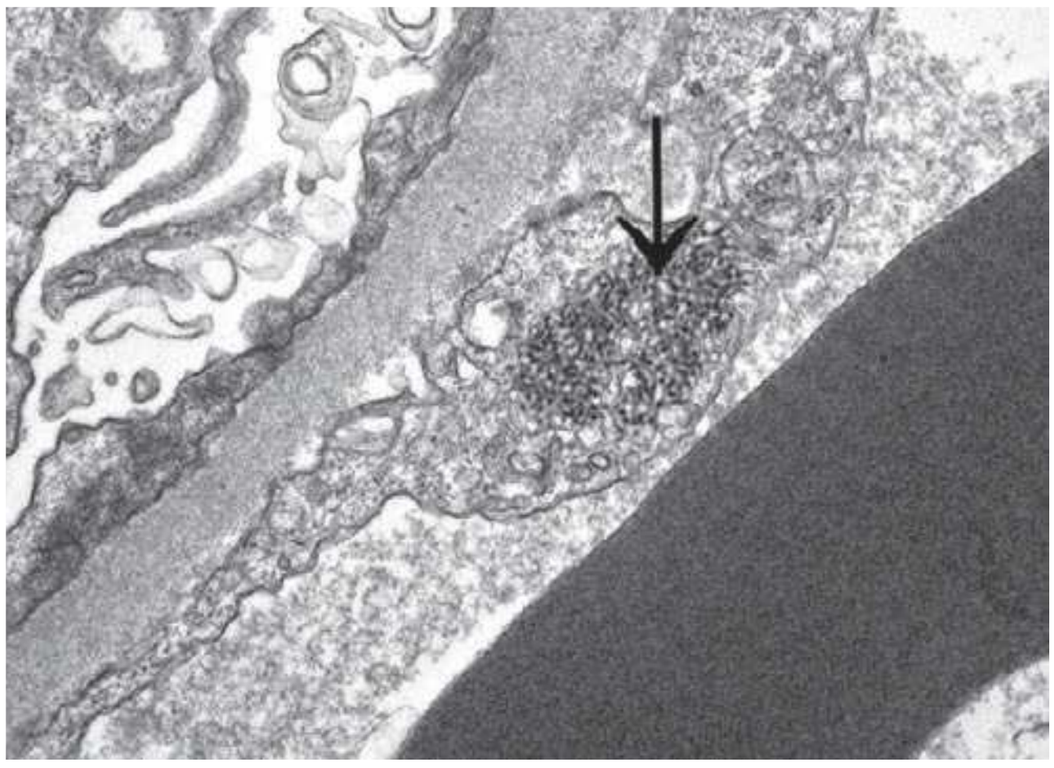


FIGURE 53.25 A large, tubuloreticular inclusion in a glomerular capillary endothelial cell (*arrow*). (Uranyl acetate, lead citrate, ×20,000.)

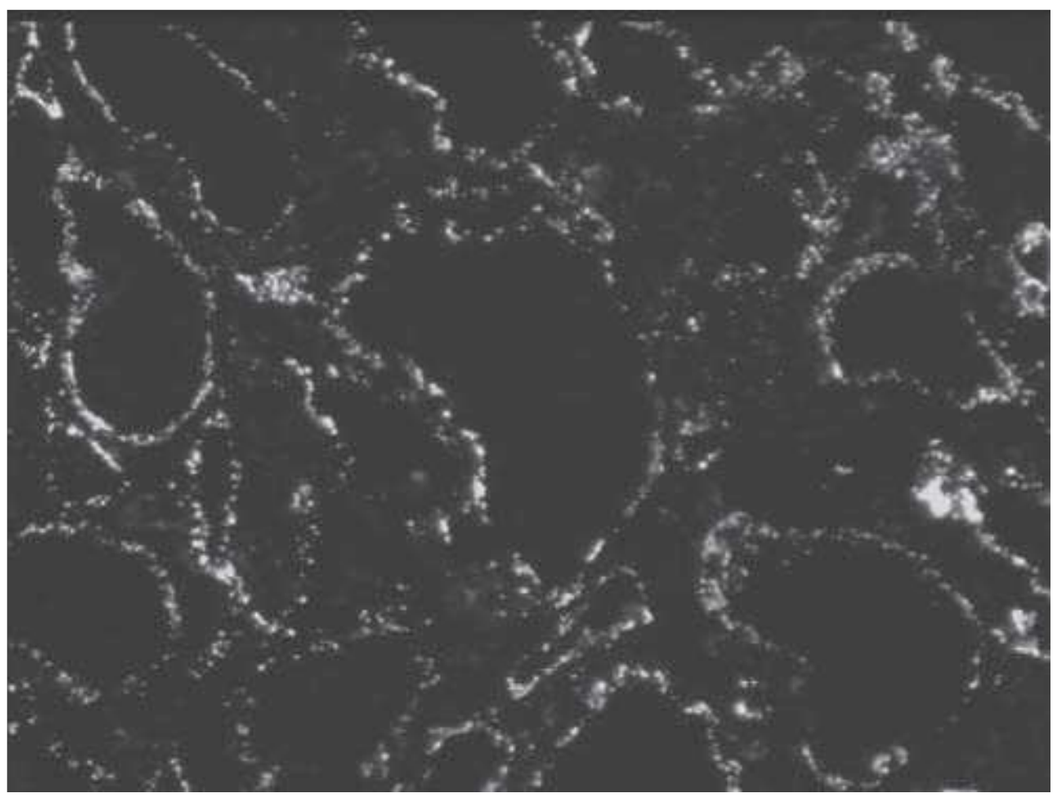


FIGURE 53.26 Prominent granular tubular basement membrane and interstitial immune complex deposits in a case of class IV lupus nephritis. (Direct immunofluorescence with an antibody to C1q, ×400.)

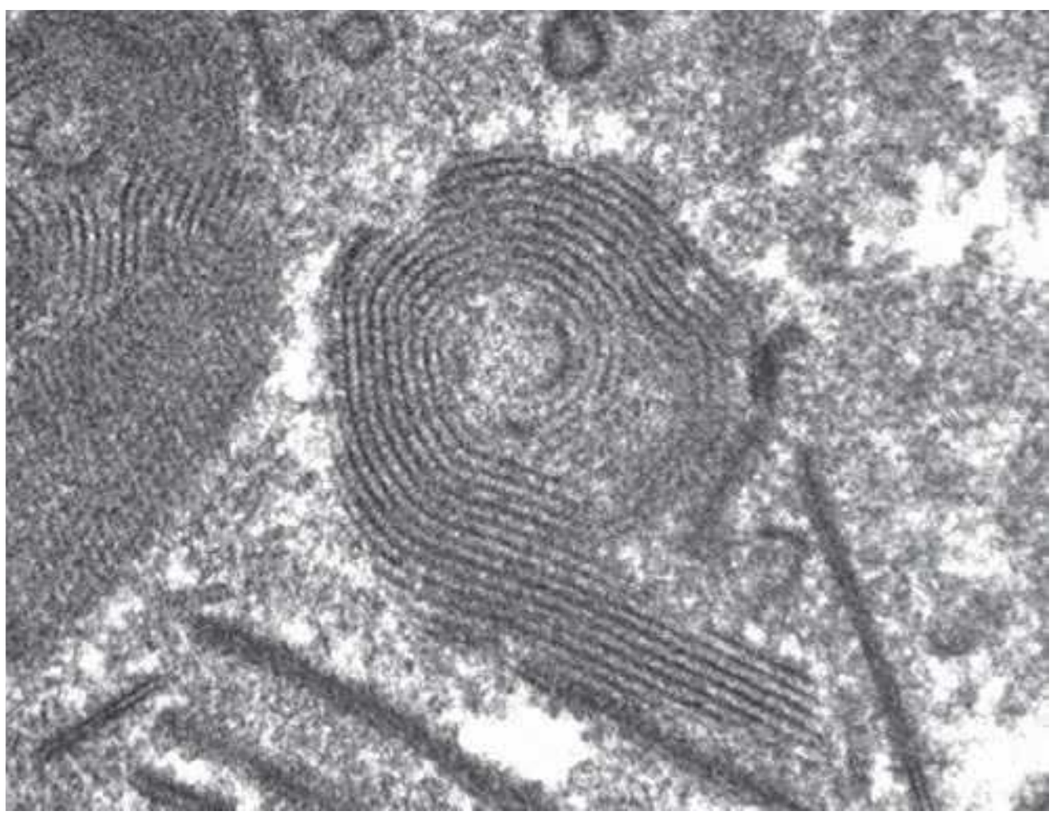


FIGURE 53.28 Subendothelial electron dense deposits with so-called fingerprint substructure. Such fingerprint substructure in the deposit is quite characteristic of lupus nephritis (LN). (Uranyl acetate-lead citrate, ×50,000.)

there are tubulointerstitial immune complex deposits, it is quite common to see vascular (arterial/arteriolar) immune complex deposits as well (Fig. 53.27). Superficially, the composition of glomerular and extraglomerular immune complex deposits appears similar; however, we found that glomerular and extraglomerular deposits frequently have different IgG subclass distributions.[148] In general, most cases of LN immune complexes contain IgG1 and IgG3, less IgG2, and minimal IgG4. The differences in IgG subclass distribution in different renal compartments raise the possibility that glomerular and extraglomerular immune complex deposits have a different pathogenesis.

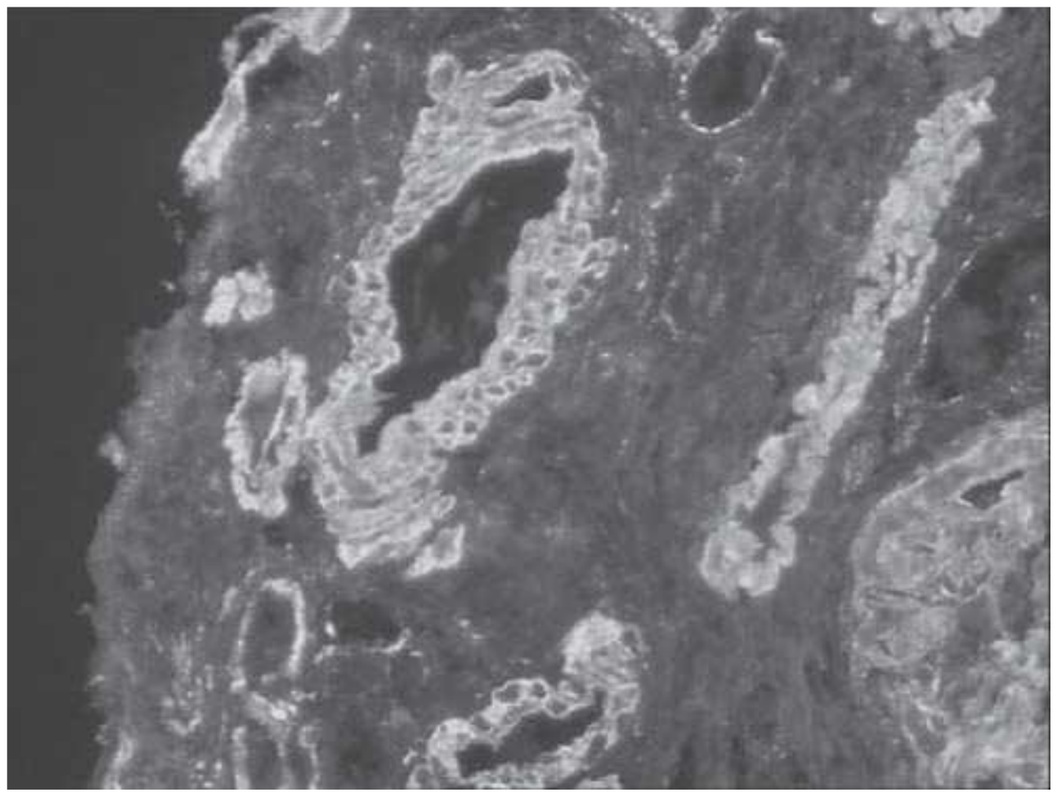


FIGURE 53.27 Arterial and arteriolar staining with an antibody to IgG in a biopsy with class IV lupus nephritis. (Indirect immunofluorescence ×200.)

Electron Microscopy in Lupus Nephritis

Ultrastructural examination practically always reveals mesangial immune complex deposits in any form of LN (Fig. 53.18). Sometimes, the electron dense deposits may have a "fingerprint" substructure (Fig. 53.28). TRIs seen mainly in endothelial cells are a very common ultrastructural finding in LN (Fig. 53.25). Although not diagnostic of LN, TRIs reflect high interferon levels in patients with active SLE; therefore, they are also called interferon footprints. TRIs are present all over the body, not only in renal endothelial cells.

Tubulointerstitial Lesions in Lupus Nephritis

Light microscopic lesions in the tubulointerstitium are nonspecific. Interstitial inflammatory cell infiltrates may or may not be present in biopsies with LN (Fig. 53.29). They are more common in patients with proliferative LN (class III or IV) and indicate an active disease process. Interestingly, the degree of interstitial inflammatory cell infiltrate does not correlate with the degree of tubulointerstitial immune complex deposition.[148,149] In later stages of LN, interstitial fibrosis and tubular atrophy appear and indicate progressive chronic injury (Fig. 53.30). Interstitial fibrosis and tubular atrophy may or may not be associated with active inflammatory cell infiltrate in the same biopsy specimen.

Arterial/Arteriolar Lesions in Lupus Nephritis

Although any type of vascular pathology may occur in a patient with SLE, there are four basic vascular patterns of injury that are attributed to SLE.[150]

- Uncomplicated arterial/arteriolar immune complex deposits (Fig. 53.27). This is the most common pattern of vascular pathology related to SLE and is frequently

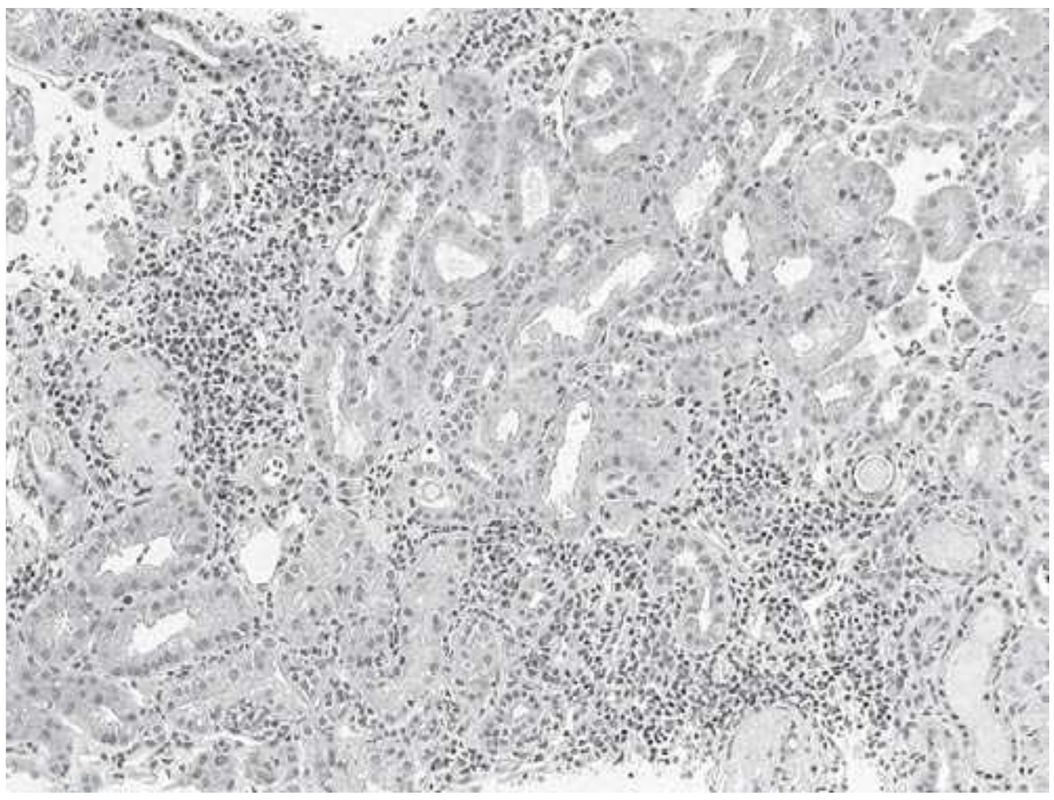


FIGURE 53.29 Interstitial inflammatory cell infiltrate in a case of class III lupus nephritis. The interstitial inflammatory cells are mainly mononuclear cells, but scattered eosinophils are also present. Occasional polymorphonuclears may also be seen. (H&E ×200.)

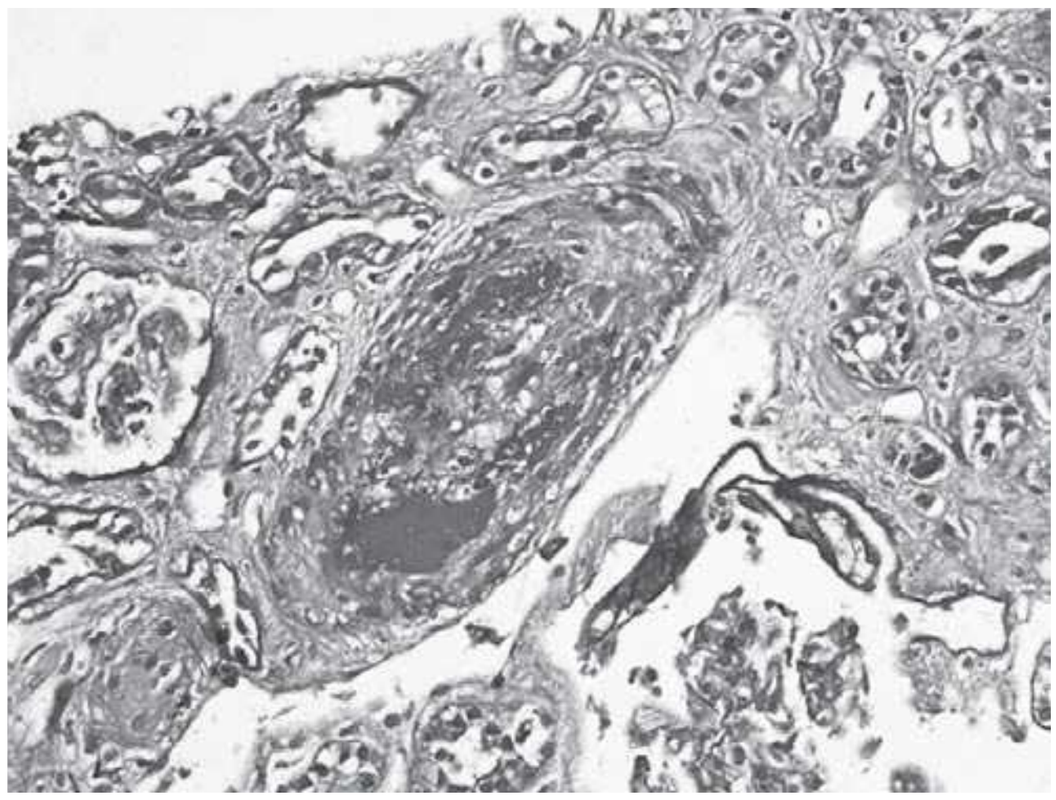


FIGURE 53.31 A small interlobular artery occluded by amorphous material, including fibrin (*bright red color*), in a patient with systemic lupus erythematosus, antiphospholipid antibodies, elevated d-dimers, and thrombotic microangiopathy. Immune complex deposits were not seen in this biopsy. (Masson's trichrome, ×400.) (See Color Plate.)

seen in biopsies with LN. There is no correlation between vascular inflammation and the degree of arterial/arteriolar immune complex deposition; by light microscopy, the arterial/arteriolar walls are usually normal.

- Thrombotic microangiopathy (TMA). TMA is a rare but serious complication of SLE and is particularly common in patients who have circulating antiphospholipid antibodies and high d-dimer levels.[151] The biopsy findings are similar to those seen in other forms of TMA (Fig. 53.31), and include arterial/arteriolar fibrin thrombi with or without fibrinoid necrosis of the vessel wall, fragmented RBCs in the fibrin thrombi or embedded in the thickened loosened arterial/arteriolar walls, and mucoid subendothelial widening of the arteries/arterioles. In more chronic stages, concentric thickening (onion skinning) of the arterial/arteriolar walls may develop. Arterial/arteriolar immune complex deposits may or may not be present. The glomerular changes include fibrin thrombi and/or prominent thickening of the glomerular capillaries, secondary to subendothelial electron lucent widening between the glomerular capillary basement membrane and the swollen endothelium (seen on electron microscopy). Because of the capillary wall thickening, the glomerular capillary lumen is narrowed and many of these glomeruli appear "bloodless." Fragmented RBCs are not unusual in the glomerular capillaries. In some glomeruli, the dominant feature is ischemic wrinkling of the capillaries, particularly if there is severe obliteration of arterial/arteriolar lumen.
- Noninflammatory necrotizing lupus vasculopathy (Fig. 53.32). This is a somewhat controversial vascular pattern of injury in patients with SLE. In such cases, there is necrosis of the wall of the small arteries/arterioles without obvious thrombus formation and inflammatory cell reaction. The lesion is thought to be related to abundant vascular immune complex deposits and is very difficult to differentiate from TMA.
- True lupus vasculitis. It is very rare to see true lupus vasculitis in a renal biopsy specimen, probably because of sampling issues. The morphology of lupus vasculitis is similar to other forms of vasculitis and includes fibrinoid necrosis of the wall of arteries with an associated active mixed inflammatory cell infiltrate (Fig. 53.33). This vascular wall necrosis/inflammation may or may not be associated with secondary thrombus formation.

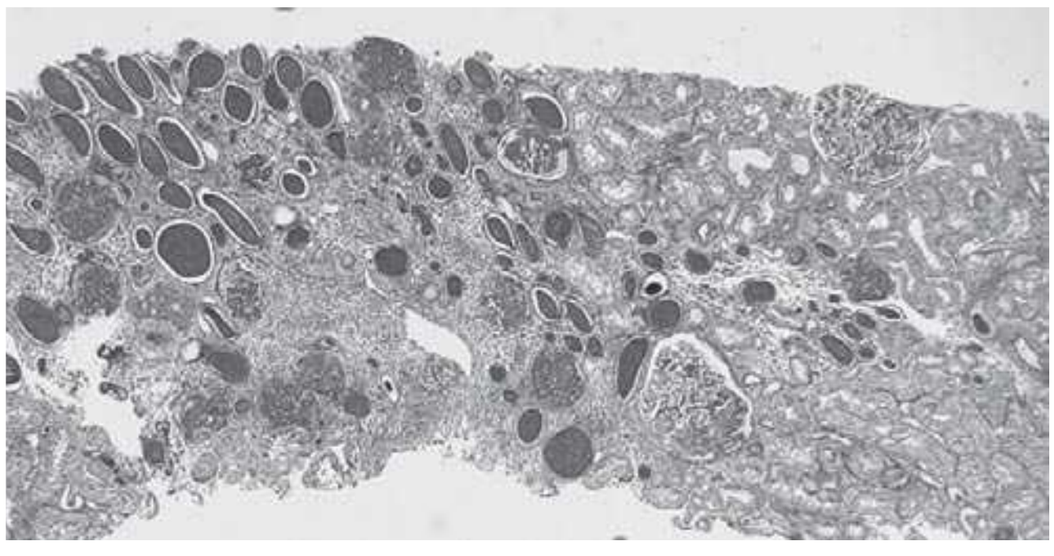


FIGURE 53.30 Zonal renal cortical scarring in a patient with class III lupus nephritis. This patient also had antiphospholipid antibodies. Note that the left part of the image shows completely scarred renal parenchyma with thyroidization of the tubules. Such zonal renal cortical scarring with tubular thyroidization is not unusual in patients with antiphospholipid antibodies, in our experience. (PAS ×100.)

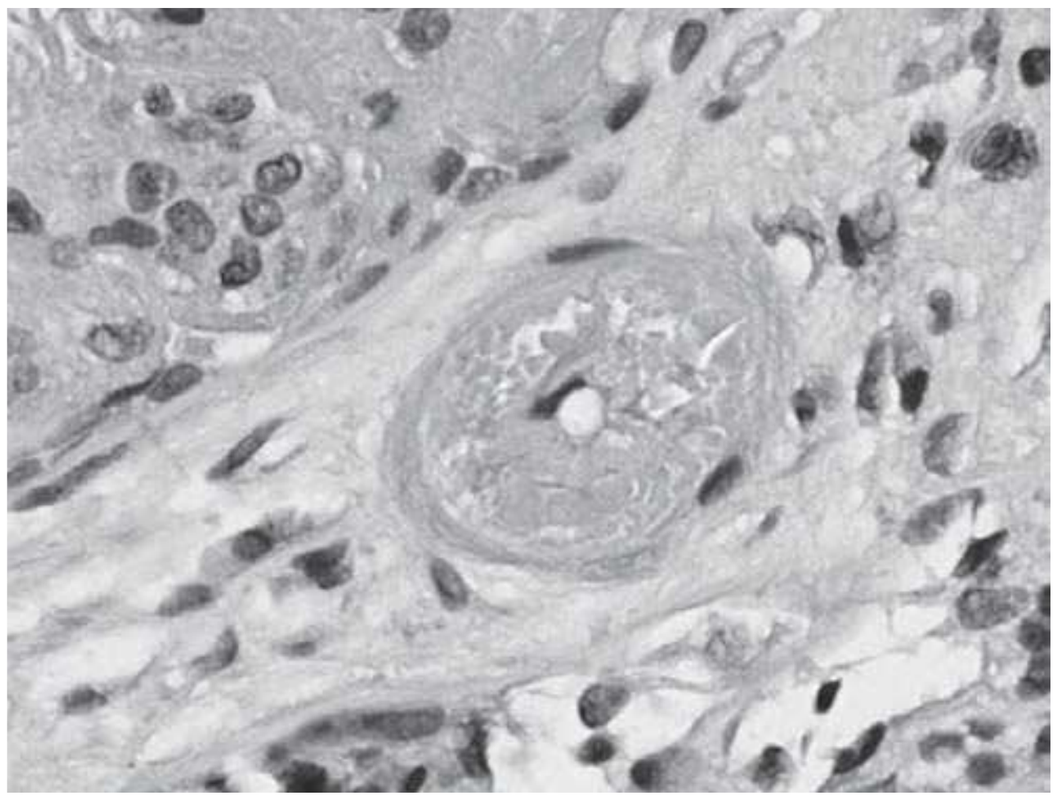


FIGURE 53.32 An arteriole with extensive subendothelial deposition of eosinophilic material (immune complexes) in a biopsy with noninflammatory necrotizing lupus vasculopathy. Interestingly, inflammatory cell infiltrate is usually absent in such arteries. (H&E ×600.)

Combination of Different Classes of Lupus Nephritis

Mild LN with only mesangial deposits (classes I and II) is the basic lesion of LN; therefore, we do not diagnose combinations of classes III, IV, or V + class I or II. By ISN/RPS definition, classes III and IV cannot combine. Class V LN is common in combination with class III or class IV LN. In these combined patterns of injury the proliferative component is listed first (such as classes III+V or classes IV+V).

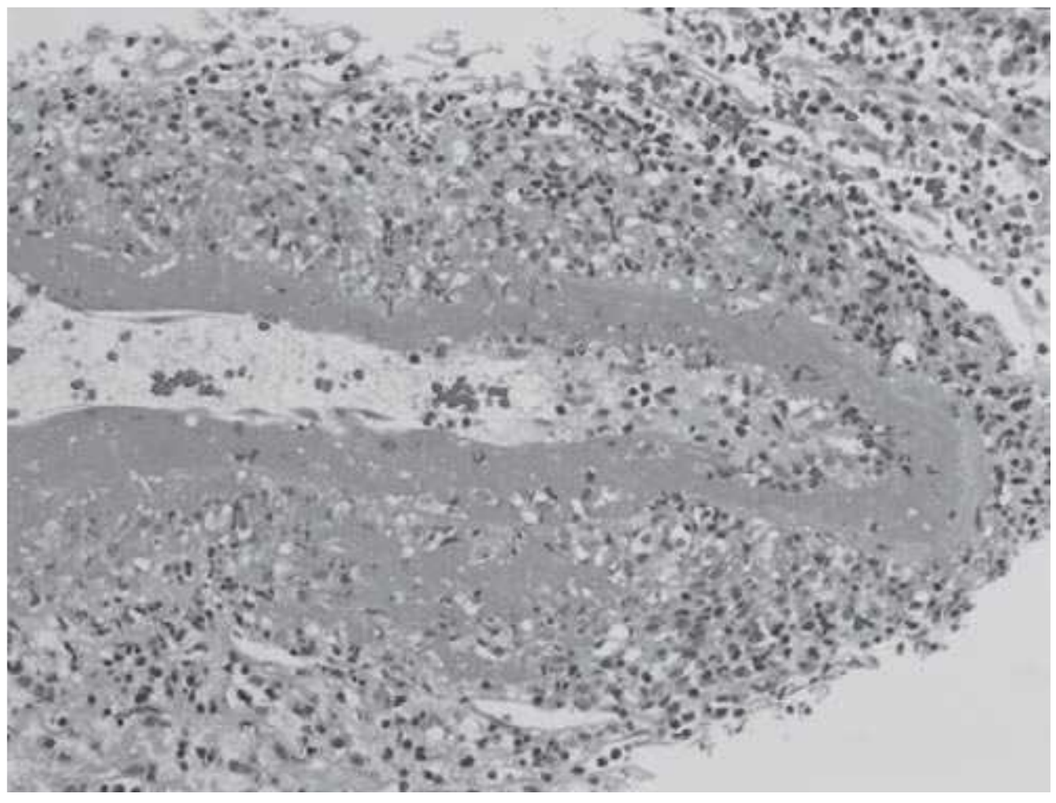


FIGURE 53.33 An arcuate artery with widespread fibrinoid change of the media and transmural inflammatory cell infiltrate. Such true vasculitic lesions are rare in kidney biopsies with lupus nephritis. (H&E ×200.)

Class Transformation in Lupus Nephritis

Follow-up biopsies of LN often show a class different from the initial biopsy.[133,134] If the initial biopsy reveals class I or II LN, the follow-up biopsy commonly shows focal, diffuse proliferative, or membranous LN. Another common transformation is for focal proliferative LN (class III) to evolve into diffuse proliferative LN (class IV). Classes I, II, III, or IV may transform into membranous (class V) LN. In cases of proliferative LN this transition usually reflects a combination of proliferative and membranous LN. Any class can turn into class VI (advanced sclerosing) LN eventually. It is less common for a higher class LN to turn into a lower class LN in a renal biopsy because this kind of transformation usually reflects a good response to treatment and most centers would not perform a repeat biopsy in this situation. Membranous (class V) LN on initial biopsy may turn into combined proliferative and membranous LN.

Less Common Patterns of Glomerular Injury Associated with Systemic Lupus Erythematosus

- Minimal change disease. Occasional patients with SLE develop acute onset nephrotic syndrome and kidney biopsy reveals only minimal change disease without immune complex deposits or with only mild mesangial immune complex deposits. Considering the autoimmune nature of lupus, it is likely that immunologic podocyte damage can occur and induce minimal change-like disease responsive to corticosteroids.[122]
- Collapsing glomerulopathy. It has been reported that occasionally glomerular changes of collapsing glomerulopathy may develop in patients with SLE.[152] The pathogenesis is unclear.
- Pauci-immune proliferative glomerulonephritis. This may rarely occur in patients with SLE.[153,154] Biopsies show active proliferative lesions, including occasional crescents, in the absence of relevant glomerular immune complex deposits. Antineutrophil cytoplasmic antibody (ANCA) is negative in such patients. If ANCA is positive and necrotizing proliferative lesions are present, it is likely that the patient with SLE also developed ANCA-associated crescentic and necrotizing glomerulonephritis.[140]
- Lupus patients rarely can develop renal diseases not related to SLE, such as diabetic nephropathy, hypertensive nephrosclerosis, or infection-related glomerulonephritis.

Activity and Chronicity Indices in Lupus Nephritis

Because renal biopsy findings provide important guidance to treatment of patients with LN, but the renal biopsy interpretation can be quite individual, an attempt was made to standardize the scoring of active and chronic lesions in biopsies with LN.[154a] The value of the activity and chronicity indices is debated, but they provide guidelines as to what to look for while evaluating renal biopsies (Table 53.2).

53.2 Active and Chronic Lesions in Lupus Nephritis

Activity (score: 0–24)
- Crescents[a]
- Glomerular necrosis/karyorrhexis[a]
- Glomerular polymorphonuclear leukocytes
- Endocapillary hypercellularity
- Large subendothelial deposits ("wire loops")
- Interstitial inflammation

Chronicity (score: 0–12)
- Glomerular sclerosis
- Fibrous crescents
- Tubular atrophy
- Interstitial fibrosis

[a]The scores for renal lesions are doubled.
Lesions are scored on a semiquantitative scale from 0–3 (0 absent, 1 mild, 2 moderate, 3 severe).

Clinicopathologic Correlations

There is a reasonable correlation between clinical presentation and the class of LN in many patients (Table 53.3). Usually patients with active proliferative forms of LN have severe proteinuria, hematuria, and low complement levels. However, these clinicopathologic correlations are far from perfect and the degree of activity and chronicity cannot be determined based on clinical presentation alone. As mentioned earlier, the prognostic value of active lesions in the biopsy is poor; however, a follow-up biopsy may reveal important prognostic information. For example, advanced chronic injury in a biopsy specimen, just as in any other renal disease condition, indicates poor renal outcome. Follow-up biopsies in LN are not yet universally done, but many clinicians are beginning to think of these as part of the standard of care for LN patients.

53.3 Clinicopathologic Correlations in Lupus Nephritis, Simplified

Class I:	Usually no clinical kidney abnormalities; often normal serum complement
Class II:	Normal kidney function, mild hematuria and/or proteinuria, often normal serum complement
Class III:	Normal or impaired kidney function, nephritic sediment, proteinuria (may be nephrotic), often low serum complement
Class IV:	Normal or impaired kidney function, nephritic sediment, proteinuria (may be nephrotic), often low serum complement
Class V:	Normal kidney function, often nephrotic syndrome, microscopic hematuria, often normal serum complement
Class VI:	Chronic renal failure

MANAGEMENT OF LUPUS NEPHRITIS

The treatment of LN should be based on biopsy findings, and historically has been tied to the pathologic class of the kidney lesion. However, within each ISN/RPS lupus class there is considerable clinical variation (severity of proteinuria and renal dysfunction) and severity of kidney injury (proliferation, necrosis, crescents, fibrosis/sclerosis). These variations should be taken into account to individualize the application of the aggressive immunosuppressive regimens outlined later.

In addition to the protocols described subsequently, all patients receiving moderate to high dose immunosuppression should be treated with a sulfa antibiotic or dapsone if sulfa-allergic for Pneumocystis prophylaxis. All LN patients should be treated with hydroxychloroquine unless there is a contraindication. Anti-malarials have activity against TLR7 and 9, which may be important in the pathogenesis of SLE and LN.[155a] Hydroxychloroquine may protect against vascular thrombosis,[155] kidney damage,[156] renal flares,[157] ESRD,[158] and has a favorable impact on lipid profiles. Finally, the renoprotective measures discussed elsewhere in this book should be used in LN patients at risk of progressive kidney injury, including control of blood pressure with antiproteinuric antagonists of the renin-angiotensin-aldosterone system.

Most of the evidence-based protocols for LN were designed to treat proliferative or membranous LN (classes III, IV, V). An overview of generally accepted approaches to management of LN is shown in Figure 53.34. Class I is rarely diagnosed because there are no or few clinical renal manifestations that would warrant a biopsy. Patients with class II LN may have glomerular hematuria and proteinuria (usually nonnephrotic), but kidney function is normal.[159] The immunomodulatory regimens used to treat extrarenal SLE are generally sufficient for class II (and I), along with renoprotective measures for hypertension and proteinuria as clinically indicated. At the other end of the spectrum of kidney function, inactive sclerosing LN, such as class VI, and advanced stage sclerosing class III (C) or class IV (C) are clinically associated with severe chronic kidney disease (CKD). When LN has reached this stage, the therapeutic strategy should shift from an immunosuppression focus, except as needed for extrarenal SLE, to a renal protection focus. The goal of renoprotection in inactive sclerosing LN is to prolong kidney function and avoid ESRD requiring renal replacement therapies for as long as possible.

Proliferative Lupus Nephritis

Proliferative LN (class III or IV) can be an aggressive disease that requires intense therapy. Corticosteroids have historically been the backbone of all approaches to class III and IV

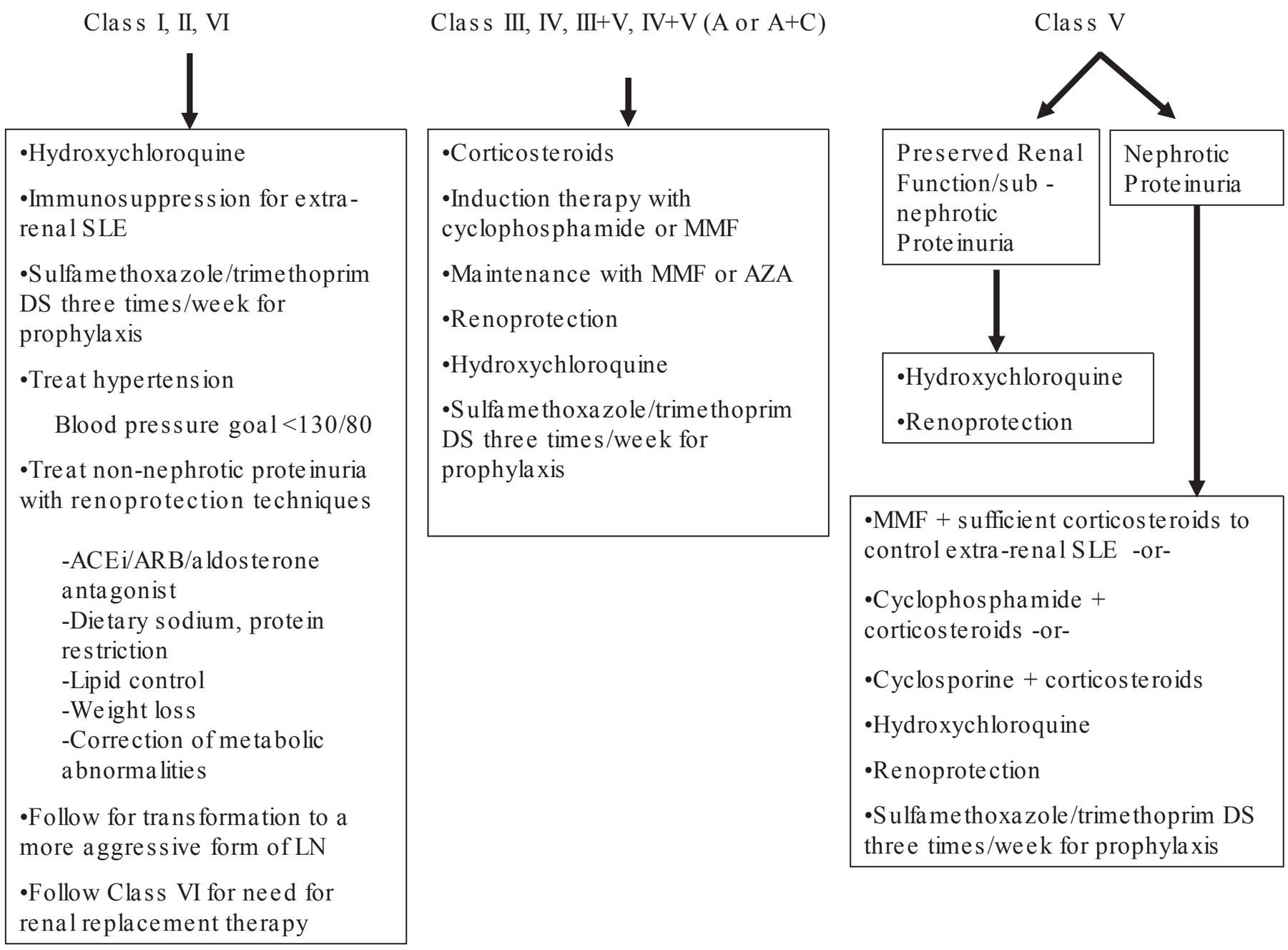


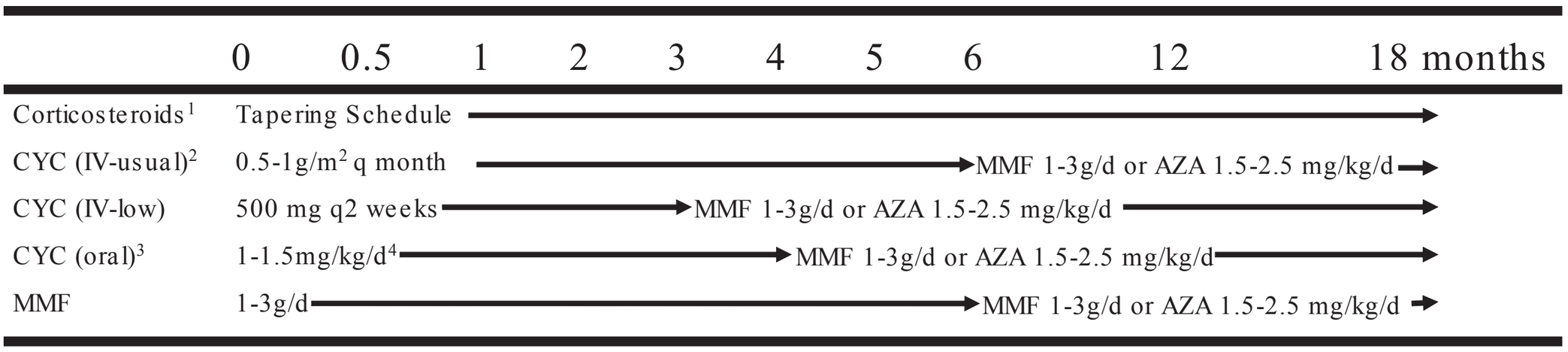
FIGURE 53.34 An approach to the treatment of lupus nephritis. See text for details of the recommended approaches.

LN. Pioneering randomized clinical trials at the National Institutes of Health (NIH) showed that, although corticosteroids were effective in controlling proliferative LN, combination with cytotoxic agents at treatment initiation decreased the frequency of renal relapse and the development of future CKD or ESRD.[160,161] Importantly, the beneficial effect of cytotoxic agents to preserve kidney function was only apparent after 5 years of follow-up.[160–162] This finding has implications for assessing the benefits of new therapies.

As a result of the NIH trials, high-dose corticosteroids and cyclophosphamide, given intravenously every month, followed by quarterly boluses for an extended time (18 months or more), became the prevalent practice. Because of associated toxicities, trials were done limiting cyclophosphamide to 6 months, but this resulted in an increase in renal relapses.[161] These findings were consistent with a need for maintenance therapy after initial treatment with steroids and cyclophosphamide. The role of cyclophosphamide as maintenance was successfully challenged by a prospective study of proliferative LN that compared six to seven monthly pulses of cyclophosphamide followed by maintenance azathioprine (AZA) or mycophenolate mofetil (MMF), to six monthly pulses of cyclophosphamide followed by quarterly cyclophosphamide pulses for 1 year after remission.[163] Over 72 months patients treated with maintenance AZA or MMF were significantly less likely to reach the composite endpoint of death or CKD than the cyclophosphamide-only group, and experienced fewer adverse side effects. Thus the prevalent treatment strategy for proliferative LN became an initial (also called induction) treatment phase of high-dose corticosteroids plus cyclophosphamide for 6 months, followed by substitution of an antimetabolite, usually AZA or MMF for cyclophosphamide, for a prolonged maintenance phase (Fig. 53.35).

Intravenous cyclophosphamide has dominated proliferative LN protocols, although oral cyclophosphamide shows comparable efficacy along with ease of administration and generally less cost.[160,164–168] Oral cyclophosphamide was originally associated with increased toxicity, especially cystitis,[160] but many of the early studies were done using very high doses (up to 2.5 mg/kg/day) for 6 or more months. However lower dose, shorter duration oral cyclophosphamide (Fig. 53.35) is effective, well-tolerated, and results in a cumulative cyclophosphamide exposure similar to 6 months of pulse therapy.[169]

Important caveats with any cyclophosphamide regimen include dose reduction by 20% to 30% in patients with moderate-severe renal insufficiency,[170] and dose-adjustment to keep the neutrophil count $\geq$2000 cells per μl. To protect fertility women should be offered prophylaxis with leuprolide and men testosterone while cyclophosphamide is being given.[171,172] Sperm banking and ovarian tissue cryopreservation are additional options. To avoid increasing risk of future malignancy, lifetime cumulative exposure to cyclophosphamide should be limited to 36 grams or less.[173,174]



[1]An Example of a Prednisone Tapering Schedule

Week	Prednisone Dose-Severe Disease
0-2	1 mg/kg/day Ideal Body Weight (IBW, maximum 80 mg/d, 2 divided doses)In very severe disease this may be preceded by 500-1000 mg/d methylprednisolone intravenously for 3 days
2-4	0.6 mg/kg/d
4-8	0.4 mg/kg/d
8-10	30 mg/d
10-11	25 mg/d
11-12	20 mg/d
12-13	17.5 mg/d
13-14	15 mg/d
14-15	12.5 mg/d
15-16	10 mg/d
16-	IBW < 70 kg: 7.5 mg/d IBW 70 kg: 10 mg/d

Week	Prednisone Dose-Moderate Disease
0-2	0.4-0.6 mg/kg/day (IBW, maximum 50 mg/d, 2 divided doses)
2-4	0.3-0.4 mg/kg/d
4-6	20 mg/d
6-7	15 mg/d
7-8	12.5 mg/d
8-9	10 mg/d
9-	IBW: <70 kg: 7.5 mg/d IBW: 70 kg: 10 mg/d

[2]Cyclophosphamide, intravenous

[3]Treat for 2-4 months, depending on response

[4]Maximum dose 150 mg/d

FIGURE 53.35 Induction and maintenance regimens for proliferative lupus nephritis.

In an effort to reduce cyclophosphamide exposure in LN, a low-dose cyclophosphamide induction regimen (Fig. 53.35) was designed and compared to six monthly pulses followed by two quarterly pulses of cyclophosphamide.[175,176] This low-dose regimen was termed "Euro-lupus," and after 10 years of follow-up the endpoints of death, ESRD, and doubling of the serum creatinine were similar in both groups, suggesting that low-dose cyclophosphamide can be used successfully in proliferative LN. Importantly, the Euro-lupus patient population was mostly Caucasian, and the proliferative LN was of mild-moderate severity.

To completely eliminate the undesirable side effects of cyclophosphamide, non-cyclophosphamide containing protocols have been evaluated. The regimen that has achieved widespread utilization used MMF for both initial treatment and maintenance of LN (Fig. 53.35). The Aspreva Lupus Management Study (ALMS) prospectively compared MMF + corticosteroids to intravenous pulse cyclophosphamide + corticosteroids, looking for superiority in response at the end of a 6-month induction period.[177] This endpoint was not achieved. The ALMS induction trial showed the response to MMF and pulse cyclophosphamide was equivalent at 6 months. There was a similar incidence of adverse events, serious infections, and deaths for both MMF and cyclophosphamide, and although not statistically significant, withdrawals due to adverse events were almost double in the MMF arm. A provocative result from the ALMS trial was found in a post hoc analysis after stratifying response by race and ethnicity. Black or mixed-race patients who received intravenous cyclophosphamide did worse than those who received MMF, and the response rate among Hispanic patients was greater with MMF. These findings suggest that black and Hispanic patients, generally considered to have more resistant LN,[178] may respond better to MMF than intravenous cyclophosphamide. This will need to be verified in an independent prospective trial.

Other alternatives to cyclophosphamide induction have been tried. Intravenous cyclophosphamide was compared prospectively to AZA plus corticosteroids. Repeat biopsy showed more chronic damage in the AZA group, and those treated with AZA had a higher incidence of renal relapse and doubling of the serum creatinine.[179] However, in some areas of the world AZA may be the only option because of cost or availability, and at least some large retrospective studies have shown long-term responses similar to initial treatment with cyclophosphamide.[180]

Calcineurin inhibitors have recently been tested as an alternative to cyclophosphamide for initial therapy in proliferative and mixed proliferative plus membranous LN. In a prospective, randomized noninferiority trial, 81 patients were

treated either with pulse intravenous cyclophosphamide and corticosteroids, or tacrolimus (TAC) and corticosteroids.[181] At 6 months there was no difference between groups in terms of complete or complete plus partial remissions, but long-term follow-up was not available. Nine patients with class IV LN, refractory to treatment with prolonged cyclophosphamide, received TAC and corticosteroids and 78% showed improvement with two complete remissions.[182] Another small (n = 40) randomized, controlled study compared 9 months of cyclosporin A (CSA) followed by a 9-month taper to an unusual 9-month course/dosing regimen of intravenous cyclophosphamide followed by 9 months of maintenance with oral cyclophosphamide.[183] At the end of 18 months there were no differences between the two treatments. Long-term follow-up (40 months) continued to show no difference between treatments; however, this was determined retrospectively, and maintenance therapy after 18 months was not protocol-prescribed. Additionally, patients had only mild renal insufficiency because of concern over reductions in glomerular filtration rate (GFR) by CSA, but had rather high renal biopsy chronicity scores. In summary, calcineurin inhibitors may have a role in treating proliferative LN, but that role remains to be determined based on long-term prospective randomized trials.

Leflunomide is a drug that blocks lymphocyte proliferation, T cell activation, and suppresses production of cytokines such as interleukin-2. It is currently used to treat rheumatoid arthritis. There have been two small trials from China using leflunomide to treat LN.[184,185] Response rates were similar to those of cyclophosphamide. Interestingly, in one study repeat biopsies at 6 months showed a large increase in the chronicity index,[184] but this was not seen in repeat biopsies from the second study.[185] Thus long-term trials will be required to determine if leflunomide preserves kidney function over time as well as cyclophosphamide.

Because the renal response rate for class III and IV LN with any of the initial therapies discussed is only about 60% at 6 to 12 months (see later), an add-on strategy was employed in a randomized controlled trial to determine if rituximab plus MMF and corticosteroids could improve this outcome.[186] This was based on several small, open-label, uncontrolled trials that suggested rituximab may be effective in proliferative LN, either for refractory disease or as initial therapy.[187–190] At 12 months, however, there were no differences between the rituximab and placebo groups in terms of complete or partial remissions. Thus rituximab cannot be recommended as adjunctive initial therapy.

The choice of initial therapy for proliferative LN is currently between a cyclophosphamide-containing regimen and an MMF-only regimen. The patients in the two largest studies of MMF versus cyclophosphamide generally had less severe LN, according to the level of proteinuria and kidney function,[191,192] than the patients in some of the randomized clinical trials of cyclophosphamide.[162] Thus, in severe class III/IV LN, a cyclophosphamide-containing protocol for initial therapy may be preferred. Low-dose cyclophosphamide could be considered in Caucasians with moderate LN.

The goal of long-term preservation of kidney function should also be considered when choosing an initial therapy. As mentioned earlier, the superiority of cyclophosphamide plus corticosteroids versus corticosteroids alone on preservation of kidney function was only apparent after 3 to 5 years of follow-up.[160–162] In a long-term study of initial therapy with MMF compared to initial therapy with cyclophosphamide, there were no significant differences in renal function between the groups after a median of 64 months.[168] However, more patients in the MMF group had relapses, prolonged proteinuria >1 g per day, and persistent serum creatinine >2 mg per dL. These combined clinical findings have been associated in other studies with deterioration of kidney function over time. Similarly, after the initial 6 month treatment period, the ALMS trial was extended (see later) for 3 years to evaluate maintenance therapy with either MMF or AZA.[193] Although not designed to compare the long-term efficacy of initial therapy on kidney function, there was a (nonsignificant) trend toward fewer treatment failures in those who received cyclophosphamide as initial therapy as opposed to MMF. This result was independent of whether maintenance therapy was AZA or MMF. Thus it cannot yet be stated with certainty that initial therapy with MMF is equivalent to cyclophosphamide for proliferative LN with respect to long-term preservation of kidney function.

Maintenance therapies after the initial treatment of proliferative LN are outlined in Figure 53.28. AZA and MMF have received the most evaluation as maintenance agents. The MAINTAIN trial prospectively compared MMF to AZA as maintenance therapy in a predominantly Caucasian population after initial treatment with the low-dose Euro-lupus cyclophosphamide protocol, regardless of whether patients had achieved remission.[194] The primary endpoint was time to renal relapse, and after at least 3 years of follow-up, MMF and AZA were found to be statistically equivalent, although MMF was numerically better.

The ALMS trial Extension Phase[193] prospectively compared MMF and AZA as maintenance therapies after the 6-month initial treatment period with either MMF or cyclophosphamide. Patients entered this extension phase only if they achieved a complete or partial remission with initial therapy. Over 3 years the composite treatment failure endpoint (death, ESRD, renal flare, sustained doubling of serum creatinine, or requirement for rescue therapy) was reached in 16% of maintenance MMF-treated patients compared to 32% of maintenance AZA-treated patients (P = .003). The superiority of MMF over AZA was not dependent on initial therapy (MMF or cyclophosphamide) or race of the patient.

A pilot randomized clinical trial in 69 patients with class III/IV LN suggested that 2 years of CSA may be as effective as 2 years of AZA for maintenance after initial treatment with prednisone and oral CYC, in terms of relapse prevention and reduction of proteinuria.[195] Another randomized clinical trial showed CSA was as effective as AZA in terms of tapering maintenance corticosteroids in severe systemic lupus, but only 29% of the patients had LN.[196]

From these studies it is difficult to make a definitive recommendation for a maintenance drug. Individualizing by patient-specific factors such as desire for pregnancy or occurrence of side effects may be considered when making this choice.

Few patients reach complete remission by 6 months, and kidney biopsies after 6 months of initial therapy have shown that although active inflammation tends to improve, complete resolution of pathologic changes is unusual.[197–200] Consistent with this, clinical improvement in class III/IV LN continues well beyond 6 months and into the maintenance phase of therapy.[166,169,175,201,202] Thus, unless there is clear evidence for deterioration of renal status (rising serum creatinine, worsening proteinuria, increased activity of the urine sediment) at 6 months, the initial treatment plan should be maintained. A recent reanalysis of the ALMS data showed that for patients treated with MMF or cyclophosphamide, a reduction in proteinuria of ≥25%, or a normalization of complement components C3 and/or C4 by week 8 of therapy was prognostic of a renal response by 6 months.[203] The positive predictive value of these variables was about 70%, and therefore they could be helpful in guiding treatment decisions.

There are no specific guidelines for duration of maintenance therapy. In seven randomized clinical trials, immunosuppression was continued for an average of 3.5 years.[160,161,165,168,175,176,201] A repeat biopsy study found that after 2 years of immunosuppressive therapy only 40% of patients with class III/IV reverted to class II, consistent with the need for a prolonged maintenance phase.[179] It is reasonable to consider slowly tapering immunosuppressive therapy after patients have been in complete remission for a year. If a patient has a history of renal relapses it may be prudent to extend maintenance therapy. Although there is no standard definition of complete remission for LN in the literature, for preservation of kidney function the most important clinical variable currently available is proteinuria. Proteinuria less than 0.5 g per day should be the target for complete remission.[204] Serum creatinine should improve to a patient's pre-LN baseline if known. A caveat is that serum creatinine may be increased (acceptably) by renoprotective therapies. Thus, a stable serum creatinine should be the minimum requirement for complete remission. Urine sediment should not have any RBC or WBC casts, but hematuria may persist for months.[205] Finally, at remission normalization of serologic markers of lupus activity, such as complement and double-stranded DNA antibodies is expected, but there are several caveats regarding lupus serologies (see later).

Immunosuppression should be continued indefinitely for patients who achieve only a partial remission, and renoprotective therapies intensified. This is supported by the finding of continued activity in biopsies taken 2 or more years after initial therapy when significant proteinuria or an abnormal serum creatinine is still present.[206] Although the strategy of trying to convert a partial remission to a complete remission by increasing corticosteroids or using alternative immunosuppressive agents is not supported by evidence, it is often tried. A repeat kidney biopsy may be useful to determine the level of pathologic activity, which if severe could provide a rationale for re-induction therapy.

Membranous Lupus Nephritis

Membranous LN (class V) is a nonproliferative glomerulopathy that can be seen alone or with superimposed proliferative LN. Patients with mixed membranous and proliferative LN are treated as for the proliferative component, but may have a less favorable prognosis.[207] Alternatively, in a small randomized, controlled trial from China in patients with mixed class IV and V LN, the combination of TAC (4 mg per day), MMF (1 g per day), and oral corticosteroids was compared to pulse monthly intravenous CYC (0.75 g per m^2 for 6 months) plus oral corticosteroids. At 6 months 90% of patients treated with this lower dose, "multitarget" therapy and 45% of patients treated with CYC achieved either complete or partial remission ($P = .002$).[208]

Pure membranous LN occurs in 8% to 20% of patients with LN.[207,209,210] It is generally regarded as a less aggressive form of LN but long-term follow-up suggests a 20% incidence of chronic kidney disease, and ESRD develops in about 8% to 12% of patients.[207,209–211] In addition to renal insufficiency, the heavy proteinuria characteristic of membranous LN, if chronically present, predisposes to hyperlipidemia and atherosclerosis, contributing to cardiovascular morbidity and mortality.[212,213] Heavy proteinuria can also lead to a hypercoagulable state and arterial and venous thromboses.[213,214] Thrombotic events occur in 13% to 23% of lupus patients, and have been linked to the presence of antiphospholipid antibodies, and/or the nephrotic syndrome.[207,209,215] Spontaneous remission of heavy proteinuria occurs in only a minority of membranous LN patients.[216,217] Thus, membranous LN, although indolent compared to proliferative LN, can be associated with important morbidities and therefore warrants therapy.

Renoprotective and antiproteinuric therapies should be used for pure membranous LN with low level proteinuria. In addition to renoprotective and antiproteinuric measures, class V LN patients with nephrotic-range proteinuria and/or renal insufficiency should be considered for immunosuppression. A single prospective, randomized clinical trial showed that the addition of cyclophosphamide (six intravenous pulses of 0.5 to 1 g per m^2 every other month) or cyclosporin A (5 mg/kg/day for 11 months) to corticosteroids was superior to corticosteroids (prednisone 1 mg per kg every other day for 8 weeks, then taper) alone, but within a year of finishing treatment 40% of the cyclosporin group had relapsed.[218] Relapses were not seen in the cyclophosphamide group for 48 months posttreatment.[218] MMF (2 to 3 g per day) was found to be as efficacious as cyclophosphamide when subgroup analysis of class V LN was performed on data collected prospectively in two trials of MMF versus cyclophosphamide for classes III, IV, and V LN.[219] This is consistent with a number of smaller, nonrandomized, retrospective, or open-label studies of MMF

and AZA (1 to 2 mg/kg/day) with or without corticosteroids in class V LN.[215,220–222]

Therefore, MMF plus corticosteroids may be tried initially to induce remission and, if that fails, a switch in immunosuppression to cyclophosphamide or cyclosporin A plus corticosteroids in patients with membranous LN and heavy proteinuria appears justified (Fig. 53.34).

TREATMENT OUTCOMES IN LUPUS NEPHRITIS

Treatment objectives for LN include remission in the short term, and prevention of relapse, CKD, ESRD, or death in the long term. The first 6 months of LN treatment is generally considered induction.[177,223] Although the term induction carries an expectation of remission, the number of complete responses at 6 and 12 months is low.

It is difficult to make direct comparisons of short-term outcomes among studies because treatment regimens differ, and the definitions of response and complete remission are not uniform. To generalize, a complete response requires normalization, improvement, improvement to baseline, or stabilization of serum creatinine and a reduction of proteinuria to ≤0.5 g per day. A partial response requires a stable or improved serum creatinine and a reduction of proteinuria by 50% and to below nephrotic range. Individual studies applied these criteria more or less rigorously, and some included improvement in the urinalysis in the definition of response. A survey of six studies of class III and IV LN[163,169,175,177,192,224] showed a median (range) 6-month complete response rate of 8.6% (7.4% to 25%), and an overall (complete plus partial) response rate of 53.5% (18% to 85%). The median (range) response 12 months after initiation of therapy was 60.5% (32% to 85%). These studies were done in black, Hispanic, and Caucasian patients, and used corticosteroids plus low or usual-dose intravenous cyclophosphamide, oral cyclophosphamide, or MMF. Interestingly, in four studies of Chinese SLE patients,[164–167] the median complete response at 12 to 24 months was 71% (57% to 81%), and the median overall response was 90% (73% to 95%). It is not known why Chinese patients respond so much better than most groups to initial therapy. These patients were, however, more often treated with oral cyclophosphamide than intravenous cyclophosphamide, and their genetic and environmental differences may have contributed to response rates.

For membranous LN, treatment trials suggest that the addition of an immunosuppressive to background corticosteroid will yield a complete response in the neighborhood of 40% to 60% of the patients within 6 to 12 months.[215,218,221,222,225] Response may be more rapid with calcineurin inhibitors, but the risk of relapse is high.

The long-term outcomes for proliferative LN in most studies were death, doubling of serum creatinine, ESRD, and renal relapse. Considering five studies[163,164,166,224,226] that included black, Hispanic, Caucasian, and Chinese patients, observed for a median (range) of 6 years (3 to 10 years), the rate of mortality and ESRD were 5% (0% to 20%) and 4% (0% to 10%), respectively. Doubling of serum creatinine occurred in 7.2% (0.04% to 18.2%) of patients, and renal relapse in 23% (0.04% to 42%). Similarly, 25% of patients reached a composite endpoint of death, doubling serum creatinine, or ESRD in 10 years of follow-up after treatment with the low-dose (Euro-lupus) cyclophosphamide protocol.[176]

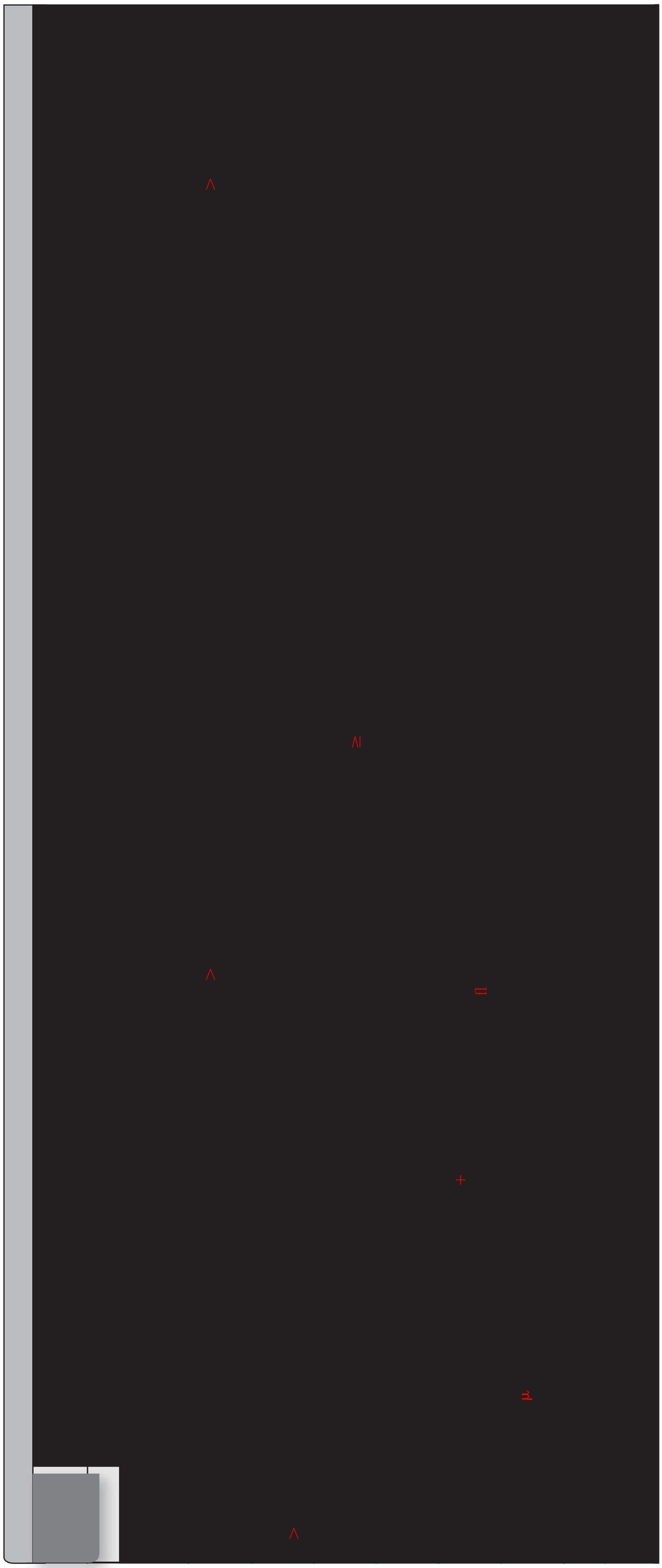
In univariate analyses, a large number of risk factors for treatment outcomes of proliferative LN have been reported. However, multivariate analyses demonstrated that many were not independent risk factors. Independent risk factors for LN outcomes from several multivariate analyses.[164–166,178,179,202,203,226–228] are shown in Table 53.4. Among these studies, only serum creatinine at the beginning of treatment appears to reach consensus as a biomarker of future remission, renal relapse, CKD, or ESRD. It is interesting that failure to achieve a complete remission was identified by only a few investigations to be a significant risk factor for relapse, CKD, ESRD, or mortality,[166,229,230] especially considering that for most proteinuric kidney diseases resolution of proteinuria is the strongest predictor of renal survival.[213,231,232] It is possible that if a more rigorous definition of complete remission had been applied, more studies would have found achieving a complete remission to be an important factor in long-term renal preservation. Finally, few studies included socioeconomic status in their analyses, which may have affected the strength of race and ethnicity as independent risk factors.

There is far less information on risk factors for the outcome of membranous LN after treatment. By multivariate analysis, the only independent predictor of failure to achieve remission was initial proteinuria over 5 g per day, and failure to achieve sustained remission was a risk factor for decline in kidney function.[218] Race or ethnicity did not appear to affect response.

FOLLOWING PATIENTS WITH LN

After successful initial treatment of LN, patients must be carefully followed because LN relapses. Renal flares in LN patients who had participated in randomized clinical trials occurred in 40% of complete responders within a median of 41 months of remission, and 63% of partial responders within a median of 11.5 months of response.[233] Putative risk factors for renal relapse are listed in Table 53.4, but there is no consensus on what predisposes patients to flare. It is important to recognize and treat flares because, with each episode of active LN, the kidney sustains chronic damage as demonstrated by repeat biopsy studies that showed an increase in the renal chronicity index at the second biopsy.[179,197,199,200,208,234] LN relapses may thus culminate in CKD or, eventually, ESRD.

Renal flare is diagnosed by increases in activity of the urine sediment, amount of proteinuria, and serum creatinine. Consensus definitions for SLE and LN flares have



53.5 Criteria for Diagnosis and Classification of Severity of SLE Renal Flare[a]

Mild Renal Flare	Moderate Renal Flare	Severe Renal Flare
↑ in glomerular hematuria from <5 to >15 RBC/hpf, with ≥2 acanthocytes/hpf and/or recurrence of ≥ 1 RBC cast, WBC cast (no infection), or both	If baseline creatinine is: <2.0 mg/dL, an ↑ of 0.20–1.0 mg/dL ≥2.0 mg/dL, an ↑ of 0.40–1.5 mg/dL and/or If baseline Pr/Cr is: <0.5, an ↑ to ≥1.0 0.5–1.0, an ↑ to ≥2.0, but < absolute ↑ of 5.0 >1.0, an ↑ of ≥ twofold with absolute Pr/Cr <5.0	If baseline creatinine is: <2 mg/dL, an ↑ of >1.0 mg/dL ≥2 mg/dL, an ↑ of >1.5 mg/dL and/or an absolute ↑ Pr/Cr >5.0

[a]Remission of nephritis is defined as stabilization or improvement of serum creatinine to baseline or better, and a return of proteinuria to baseline or better.
hpf, high-power field; Pr/Cr, protein/creatinine; RBC, red blood cell; WBC, white blood cell.

recently been published,[235,236] and one way of operationalizing these as criteria is shown in Table 53.5.[237] Other findings that support a diagnosis of renal flare, but are not necessarily always present (see later) include a fall in serum complement levels and a rise in anti–double-stranded DNA antibody titers. Flares are less likely to occur in patients who have been highly immunosuppressed. Depressed serum immunoglobulin levels may indicate overt immunosuppression; however, in severe nephrotic syndrome due to LN flare, serum immunoglobulins can also be low. Non-LN causes of an increase in creatinine or an increase in proteinuria must be excluded (see also page 1528). Increases in proteinuria can occur with pregnancy, uncontrolled hypertension, and increased sodium intake. An approach to flare therapy based on flare severity is given in Figure 53.36.

Complement components 3 and 4 (C3, C4) and anti–double-stranded DNA antibodies have been used to support the diagnosis of renal flare and also to anticipate impending flare. However, these serologies have low sensitivity (49% to 79%) and specificity (51% to 74%) for concurrent renal flare, and do not reliably predict impending flare even when measured serially, with sensitivities and specificities around 50% and 70%, respectively.[238–240] In one cohort the positive predictive values for C3 and C4 to forecast impending flare were 7.4% and 5.5%, respectively.[238]

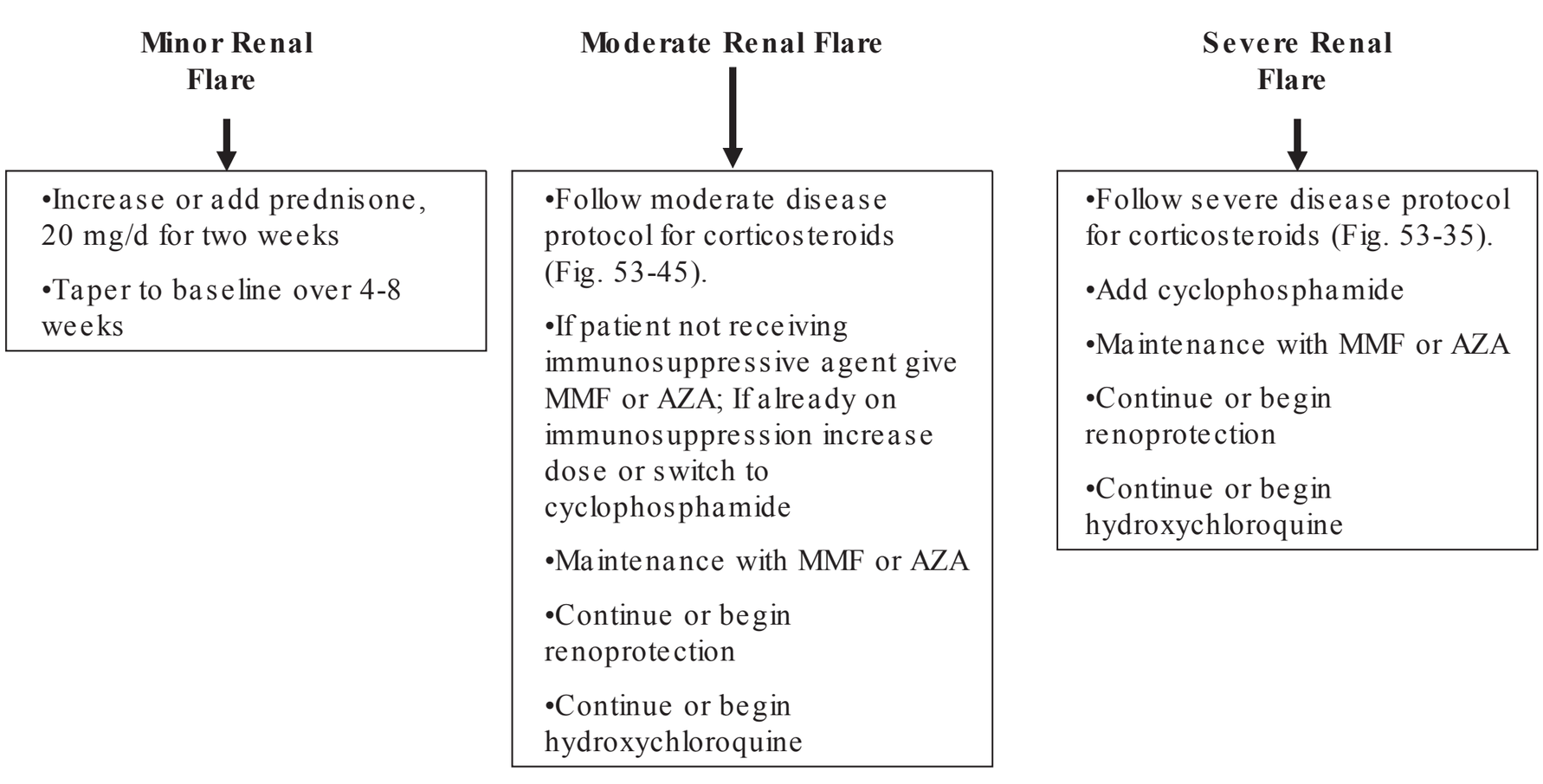


FIGURE 53.36 Severity-based approach to renal flare therapy.

Being able to anticipate imminent renal flare and potentially start therapy preemptively could attenuate the development of chronic kidney injury and minimize exposure to cytotoxic agents. Similarly, modification of drug dose and duration of therapy based on biomarkers that predict outcome of a flare would be expected to improve treatment efficacy and reduce toxicity. Finally, because kidney biopsies are not repeated at every flare, a noninvasive surrogate of renal pathology would be very useful in choosing therapy. This approach to LN treatment represents a fundamental change from a reactive to a proactive paradigm, and will require biomarkers that accurately predict SLE nephritis activity, pathology, and prognosis to guide therapeutic decisions. Efforts are under way to identify such novel biomarkers. A major focus has been on developing urine markers[241,249a] because urine generally reflects intrarenal events. Several urine biomarker candidates[237,242–249,249a] have been found (Table 53.6). None of these candidates has, to date, been validated in a large, independent, prospectively followed lupus cohort, although such studies are anticipated.

THROMBOTIC INJURY TO THE KIDNEY IN SYSTEMIC LUPUS ERYTHEMATOSUS

The most common clotting events that affect the kidney in SLE occur as a manifestation of the antiphospholipid syndrome (APS). The incidence of renal APS is about 30% in SLE, usually in conjunction with LN, but also alone.[125,250] Serologic studies show that lupus anticoagulant is present in 30% to 52% of cases of renal APS, anticardiolipin antibodies in 72% to 95% of patients, but up to 15% had neither.[124,125] Thrombi or evidence of past clotting may be found in any of the kidney blood vessels. The term APS nephropathy describes renal injury due to thrombi or their consequences in glomeruli and small intrarenal blood vessels, and characteristically presents a histologic picture of a thrombotic microangiopathy.[251] Although renal artery occlusion and renal vein thrombosis due to APS can be diagnosed with imaging studies, APS nephropathy requires a kidney biopsy. Failure to treat APS, and especially APS nephropathy, can lead to insidious CKD or ESRD despite adequate treatment of LN with immunosuppression, because APS results in noninflammatory occlusions of renal blood vessels and renal ischemia. Renal APS is treated with chronic anticoagulation therapy plus hydroxychloroquine.

Thrombotic thrombocytopenic purpura (TTP) may also occur in the setting of SLE and is associated with a high mortality.[252] TTP is treated with plasma exchange in addition to high-dose steroids. Because of the high associated mortality, it is important to consider this diagnosis and treat early.

PREGNANCY AND LUPUS NEPHRITIS

SLE affects women during their reproductive years, so pregnancy concerns are very common. In several retrospective analyses the risk of fetal loss in SLE patients with LN was not higher than SLE patients with no history of LN.[253,254] If LN is in remission, fetal losses of 8% to 25% have been reported,[254–257] but in active LN, fetal loss can be considerably higher, around 35% to 59%.[254,257] In addition to the clinical activity of LN, hypocomplementemia appears to be a risk factor for fetal loss, whereas the use of low-dose aspirin may be protective.[255]

53.6 Novel Candidate Biomarkers for Monitoring LN

Forecast Impending LN Flare	Predict Development of CKD	Predict Renal Pathologies
uMCP-1[a]	uLFABP[c]	uGlycoproteins[f]
uNGAL[b]	mEPCR staining on kidney biopsy[d]	uCXCL10 mRNA[g]
uTransferrin	uFOXP3 mRNA[e]	CD29 on T cells[h]
uHepcidin		uMCP-1 + serum creatinine[i]

[a]MCP-1, monocyte chemoattractant protein-1, a proinflammatory chemokine upregulated in lupus nephritis; u, urine as the source.
[b]NGAL, neutrophil gelatinase-associated lipocalin, an antibacterial protein, that also transports iron and is an epithelial growth factor.
[c]LFABP, liver-type fatty-acid binding protein, produced by human proximal tubular cells.
[d]mEPCR, membrane endothelial protein C receptor, found on cortical peritubular capillaries in lupus nephritis kidney biopsies.
[e]FOXP3, forkhead transcription factor, important in development of regulatory T cells.
[f]Serum glycoproteins excreted in urine; for example, α-1 acid glycoprotein, α1 microglobulin, and zinc α-2 glycoprotein.
[g]CXCL10, a TH-1 chemokine upregulated in lupus nephritis.
[h]CD29, a T-cell β1 integrin.
[i]A composite biomarker of interstitial inflammation.
CKD, chronic kidney disease; LN, lupus nephritis.

There is also risk to the kidneys in patients with LN who become pregnant. One study noted that renal flares and progressive renal dysfunction were not different between pregnant and nonpregnant patients with LN.[253] In other studies, renal flares were found to be higher in patients who became pregnant and had only achieved partial remission of the LN, or who had more than 1 g per day proteinuria or renal insufficiency.[255,257] Renal flare rates of 10% to 69% have been reported during or directly following pregnancy.[253,255–257] Hydroxychloroquine may be protective again SLE flares in general, and/or in the setting of pregnancy.[254]

To protect the kidneys and the fetus, it is recommended that SLE patients with kidney involvement be advised to wait at least 6 months after complete renal remission before trying to become pregnant. Cytotoxic drugs such as cyclophosphamide and MMF, and anti-hypertensive/renoprotective agents like angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should not be used during pregnancy. Hydroxychloroquine should be continued, and corticosteroids and AZA may be used if needed to control SLE activity.

RENAL REPLACEMENT THERAPIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

ESRD occurring as a result of SLE requires renal replacement therapy with either dialysis or transplantation. There has been concern that SLE patients do not do as well as other patients with renal replacement therapies; however, available evidence, although limited and mainly retrospective, does not suggest this is completely warranted.

SLE patients receiving hemodialysis were found to have similar outcomes as patients with other causes of ESRD,[258] but SLE patients on peritoneal dialysis appeared to have a higher mortality and more infectious complications.[259,260] In contrast, a small study suggested 5-year survivals were similar for the two modalities.[258,261]

There is no consensus on extrarenal SLE activity in patients receiving renal replacement therapy. This may be due, in part, to lack of a consistent definition of flare. Consequently, some investigations have shown significant improvement in extrarenal lupus and reduced need for immunosuppression, whereas in other investigations, despite 3 or more years of dialysis, SLE activity remained prevalent (40% to 50%), or worsened in peritoneal dialysis recipients.[258,259,262,263]

Kidney allograft survival in transplant recipients with SLE appears to be close to that of non-SLE ESRD patients, according to multivariate analyses of the United States Renal Data Service (USRDS) and the United Network for Organ Sharing (UNOS) databases.[264,265] These large studies looked at information from 43,000 to 93,000 transplant recipients, 2,000 to 3,000 having been transplanted for ESRD due to LN. Analysis of the USRDS lupus patients who received deceased donor kidneys showed lower allograft and patient survival rates than a diabetic ESRD reference group, but the hazard ratios were small at 1.14 and 1.3, respectively.[264] The analysis of UNOS showed that compared to non-SLE recipients in general, recipients with SLE had the same rate of patient and allograft survival.[265] Additionally, in smaller studies SLE recipients did not seem to have a higher frequency of acute rejection episodes,[264] except in one study where the hazard ratio for acute rejection in recipients of living (but not deceased donor) kidneys was slightly increased at 1.19.[265] Posttransplant treatment with MMF reduced allograft loss in lupus patients who received deceased donor kidneys and improved patient survival.[265,266] Finally, a common finding was that SLE recipients had a higher rate of thrombotic events than non-SLE recipients.

The recurrence of LN in transplanted kidneys was found to be in the range of 2.4% to 11%.[266–270] One surveillance biopsy study found a 54% recurrence rate, but most of these were class II, and only 12% were class III, IV, or V.[271] Although some studies did not find recurrent LN to affect allograft loss,[268–270] in the largest investigation,[267] which examined 6,850 SLE recipients, recurrent LN was independently associated with allograft loss (hazard ratio 4.09; 95% CI 3.41–4.92). The attributable risk for allograft loss was low, however, because the recurrence rate of LN was so low (2.4%). Recurrent LN did not affect patient survival.[266,267]

In summary, lupus patients who come to ESRD should be offered the option of a kidney transplant. Before transplantation SLE should be quiescent. Additionally, because of the higher incidence of cardiovascular disease in lupus, patients need to be carefully evaluated for this before surgery. Living donor transplants and an MMF-containing antirejection regimen are preferred. There are no data regarding prophylaxis for thrombotic events—a high index of suspicion is warranted. If dialysis is needed before transplantation, hemodialysis may be the preferred modality. While on dialysis, even though lupus can become quiescent, vigilance for extrarenal flares is appropriate, and treatment for active lupus with immunosuppression may be necessary.

THE FUTURE DIRECTION OF LUPUS NEPHRITIS TREATMENT

The need for new approaches to the treatment of LN is highlighted by the low complete remission rate, the modest overall remission rate, and the high occurrence of side effects from current therapies. The therapeutics now under development and in various phases of clinical trial assessment attempt to target cytokines or cells specifically involved in the pathogenesis of SLE. This will presumably result in less overall immunosuppression but increased efficacy.

Figure 53.37 summarizes the relationship of these novel biologic agents to pathogenic mediators in SLE and LN. Targeted B cell therapies have received the most attention because the B cell has such a wide array of relevant functions including autoantibody production, antigen presentation, and regulation of T and dendritic cells.

The most widely studied anti-B cell agent is rituximab, a monoclonal antibody to the B cell antigen CD20. Rituximab

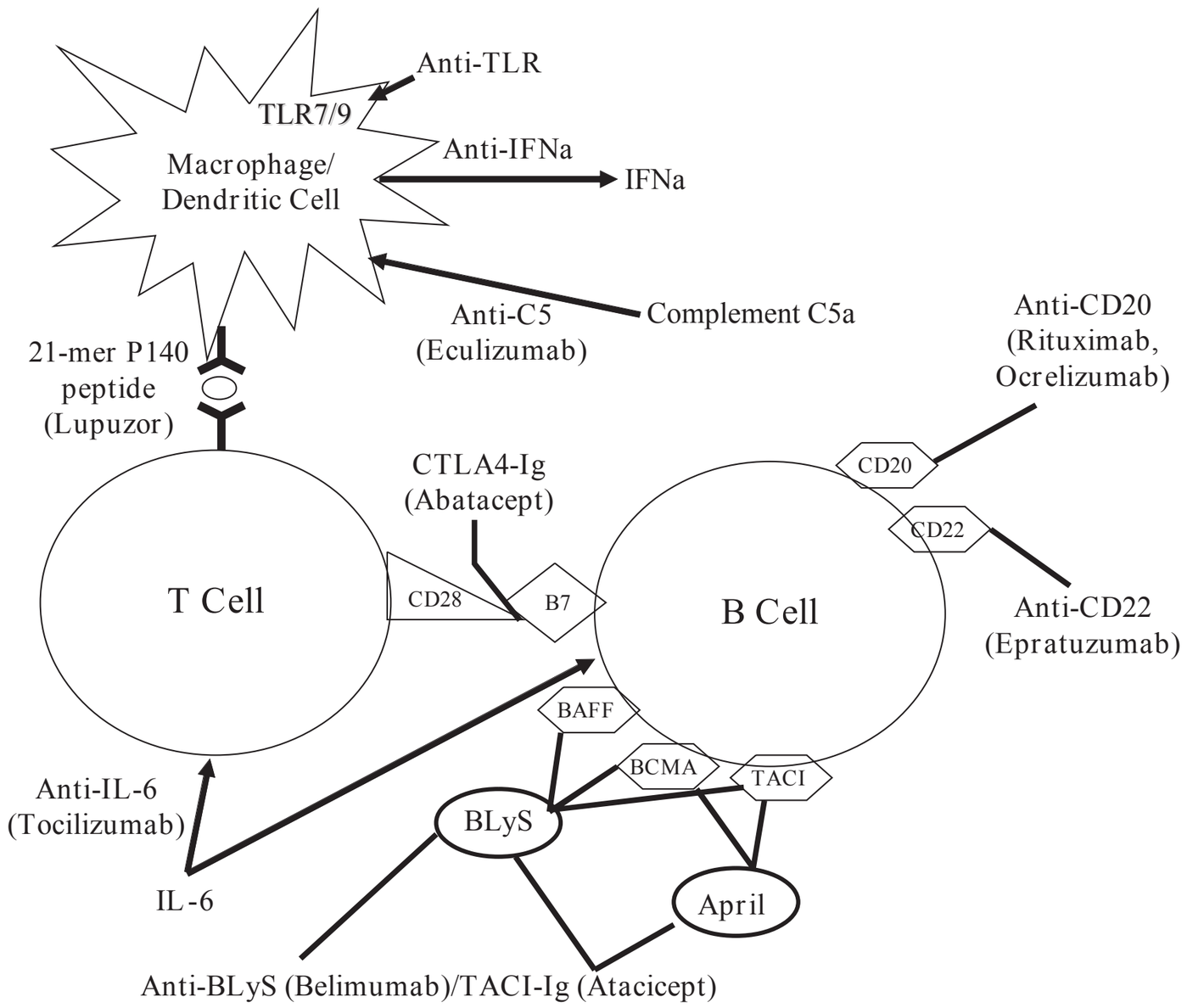


FIGURE 53.37 Novel therapies for lupus nephritis that are being developed or are in clinical trials.

causes profound depletion of circulating B cells that lasts for several months. A number of small, open-label, uncontrolled trials have suggested that rituximab is effective in proliferative LN, either for refractory disease or as induction therapy.[188–190,272] An equally small (n = 8) longer term study of refractory LN treated with rituximab suggested poor efficacy, but half of the patients did achieve complete or partial remission.[273] However, in a large, prospective, double-blind controlled study of rituximab versus placebo added to MMF plus corticosteroids for proliferative LN, there was no difference in complete or partial responses at 12 months between groups.[186] The niche for rituximab in the therapy of LN thus remains unclear.

Epratuzumab is a humanized monoclonal antibody that targets the B cell antigen receptor coreceptor, CD22. Epratuzumab partially depletes B cells, but may also interfere with their proliferation and activation in lupus. Although few LN patients (n = 4, published) have been treated with epratuzumab, 75% showed some improvement in BILAG scores.

B cells require the cytokines BLyS and APRIL for survival and proliferation. Drugs that inhibit these factors including belimumab, an anti-BLyS monoclonal antibody and atacicept, a soluble receptor that binds to BLyS and APRIL, are being evaluated in SLE. Although belimumab has not been used specifically for LN, two phase III trials in SLE were recently completed and at 12 months successfully met the composite endpoint of improvement in the Systemic Lupus Erythematosus Disease Activity Index, no worsening of physician's global assessment of disease activity, and no new BILAG organ occurrences.[274,275]

Autoreactive B cells communicate with and activate T cells through interaction of B7.1/B7.2 receptors with CD28 on T cells. Recombinant CTLA4 fused to IgG heavy chain components (abatacept) blocks the interaction between CD28 and B7.1/B7.2, and has been shown to reduce proteinuria in a rodent model of LN.[276] Abatacept is currently approved for rheumatoid arthritis and is being tested in human LN.

Autoreactive T cells from SLE patients bind and proliferate to a peptide containing residues 131 to 151 of the 70K spliceosomal protein within the U1 small nuclear RNP. A phosphorylated analog called P140 (lupuzor) prevents T cell proliferation and induces secretion of the anti-inflammatory cytokine interleukin-10. This peptide may tolerize T cells, and in a human SLE phase II trial had minimal side effects and a reduction in anti–double-stranded DNA antibody levels by over 20%, suggesting possible utility in treatment.[277]

As previously discussed, a number of cytokines have been implicated in the pathogenesis and/or tissue damage of SLE and LN. Of these, antagonists of IFN-α, IL-6, complement component C5, and TLR7 and 9 or their receptors have been developed, and are at various stages of preclinical or clinical testing.[274]

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