

# The Pathology of Lupus Nephritis

Melvin M. Schwartz

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**Summary:** An international working group of clinicians and pathologists met in 2003 under the auspices of the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) to revise and update the 1982 and 1995 World Health Organization classification of lupus glomerulonephritis. This article compares and contrasts the ISN/RPS classification and the antecedent World Health Organization classifications. Although systemic lupus erythematosus is the prototypical systemic immune-complex disease, several non-immune-complex mechanisms of glomerular injury and dysfunction have been proposed, and this article summarizes the evidence supporting the pathogenic mechanisms of lupus vasculitis, glomerular capillary thrombosis, and lupus podocytopathy. The most significant and controversial feature of the ISN/RPS classification is the separation of diffuse glomerulonephritis into separate classes with either segmental (class IV-S) or global (class IV-G) lesions. Several groups have tested the prognostic significance of this separation, and this article discusses the implications of these studies for the ISN/RPS classification.

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Klemperer et al<sup>1</sup> were the first to describe the light microscopic renal pathology of systemic lupus erythematosus (SLE) glomerulonephritis (GN) with cellular proliferation, wire-loops, hematoxylin bodies, and fibrin thrombi in autopsied patients dying with the untreated disease. However, informed by pathogenetic insights and the newer techniques of immunopathology and electron microscopy, the interpretation and the prognostic and therapeutic implications of the pathology have evolved. Early in the renal biopsy era, the demonstration of immune deposits by fluorescence and electron microscopy led to the conclusion that all of the pathology observed in SLE renal disease was immune-complex mediated. However, despite the strong evidence supporting the existence of DNA-anti-DNA immune complexes in the circulation and aggregates containing DNA and anti-DNA antibodies in the glomeruli, other mechanisms of glomerular in-

jury have been described in patients with SLE. This article focuses on 2 aspects of the renal pathology of SLE that are of concern both to the clinician, who uses the renal biopsy to assess prognosis and to guide therapy, and to the investigator, who uses the biopsy findings to gain pathogenetic insight. The first is the recently proposed classification of lupus glomerular disease developed under the auspices of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS classification).<sup>2,3</sup> The second is the non-immune-complex pathogenetic mechanisms proposed to be operative in SLE renal disease.

## THE ISN/RPS CLASSIFICATION OF GLOMERULAR DISEASE

Early renal biopsy studies in SLE patients showed a spectrum of glomerular disease<sup>4</sup> and prognosis was a function of the underlying glomerular lesion,<sup>5</sup> and the glomerular pathology included segmental (focal), diffuse (global), and membranous forms of GN.<sup>6,7</sup> According to Weening et al,<sup>2,3</sup> Robert McCluskey codified the first histologic classification of lupus ne-

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Department of Pathology, Rush University Medical Center, Chicago, IL.  
Address requests for reprints to Melvin M. Schwartz, MD, Department of Pathology, Rush University Medical Center, 1753 W. Congress Pkwy, Chicago, IL 60612. E-mail: Melvin\_Schwartz@rush.edu  
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**Table 1. Comparison Between the Modified WHO (1982) and the ISN/RPS (2004) Classifications**

Class	Modified WHO (1982)	Critique of WHO 1982	ISN/RPS Classification (2004)
I	Normal glomeruli a) all techniques b) EM/FM deposits	No normal in pathologic classification	Minimal mesangial lupus nephritis. Normal by LM. EM/FM deposits
II	Pure mesangial alterations a) Mild hypercellularity b) Moderate hypercellularity	No shown clinical difference between classes a) and b)	Mesangial proliferative lupus nephritis with mesangial proliferation of any degree
III	Focal segmental GN*	1) Problem of focal global GN 2) No quantitative definition of focal	Focal lupus nephritis† <50% glomerular involvement
IV	Diffuse GN*	1) Category comprise widely distributed segmental and global lesions 2) No quantitative definition of diffuse	Diffuse lupus nephritis† ≥50% glomerular involvement a) IV-S ≥50% of glomeruli have segmental lesions b) IV-G ≥50% of glomeruli have global lesions <sup>3</sup>
V	Diffuse membranous GN a) Pure b) Plus class II c) Plus class III d) Plus class IV	1) No demonstrated clinical difference between classes a) and b) 2) Mixed classes combining membranous with active lesions in class III and IV confusing	Membranous lupus nephritis a) With or without mesangial proliferation or deposits b) In biopsies with mixed membranous and focal (class III) or diffuse (IV) GN, the glomerular lesions are diagnosed separately
VI	Advanced sclerosing GN	No quantitative definition of advanced	Advanced sclerosing lupus nephritis ≥90% global sclerosis without residual activity

\*Subcategories: active necrotizing, active and sclerosing, and sclerosing lesions.

†Subcategories: active, active and chronic, and chronic lesions.

phritis, and, after modification by the Pathology Committee of the International Study of Kidney Disease in Children, it was published in 1982 by the World Health Organization (WHO) (Table 1).<sup>8</sup> Although the WHO classification provided the pathologic context for many clinical studies, it was not universally accepted. The impetus to revisit the classification was the concern that the 1982 classification and the 1995<sup>9</sup> version with 6 classes and many subclasses were too cumbersome to apply, in certain aspects difficult to understand, and key terms were undefined.

Differences that are more fundamental were

the interpretation and clinical implications of the distinction between focal segmental (class III) and diffuse (class IV) GN in the WHO classification. To some, segmental GN represented a different form of glomerular pathology and a different pathogenetic mechanism from the diffuse global lesion seen in many cases of class IV lupus glomerulonephritis. Others believed that class III and IV lesions represented quantitative differences in the same pathologic process. Although distinguishing between classes III and IV by the proportion of glomerular involvement without considering sample size leads to misclassification of a significant number of biopsy

specimens,<sup>10</sup> the latter interpretation prevailed, and the ISN/RPS classification uses 50% glomerular involvement as the cut-off level between classes III and IV. The implications of this decision are discussed later (see section “Applying the ISN/RPS Classification”).

An international working group of clinicians and pathologists met under the auspices of the ISN and the RPS with “the major objective of standardizing definitions, emphasizing clinically relevant lesions, and encouraging uniform and reproducible reporting between centers.” The classification of lupus GN that was proposed is based on the 1982 WHO classification. **Table 1**, in which the 1982 WHO classification is compared with the ISN/RPS classification, lists specific criticisms and problems that were of concern to the working group. This is a morphologic classification of lupus GN that does not include coagulopathies, podocytopathy, or non-immunoglobulin-mediated glomerular capillary necrosis (vasculitis) (see later). If present, the working group recommends separate diagnoses for these glomerular lesions and nonglomerular vascular lesions, and tubulointerstitial nephritis. The salient features of the 6 classes of lupus glomerular pathology in the ISN/RPS classification are presented below and in **Table 1**, along with significant changes from the modified 1982 and 1985 WHO classifications.

### ISN/RPS Class I: Minimal Mesangial Lupus Nephritis

The glomeruli are normal by light microscopy, but they must have mesangial immune deposits by fluorescence microscopy or electron-dense deposits by electron microscopy. This definition eliminates the normal glomeruli by all morphologic modalities in category (IA) in the WHO classification, which is objectionable because a normal category should not be present in a pathologic classification.

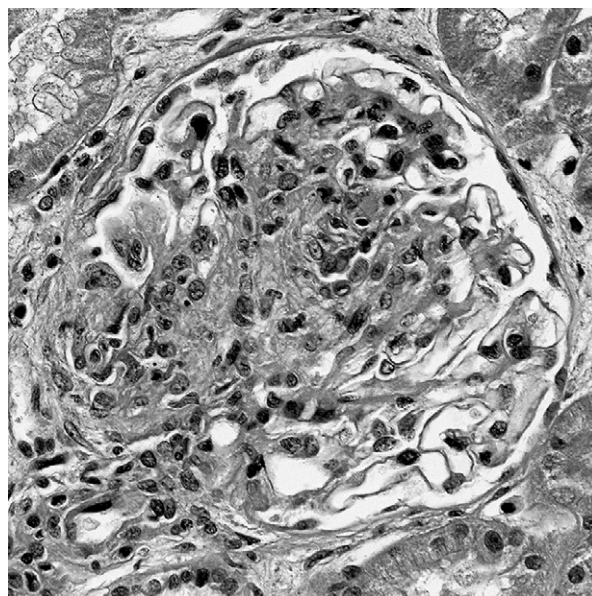
### ISN/RPS Class II: Mesangial Proliferative Lupus Nephritis

The glomerular pathology is limited to mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy with mesangial immune deposits seen by fluorescence microscopy or mesangial electron-dense

deposits seen by electron microscopy. This definition eliminates the distinction drawn between mild and moderate mesangial hypercellularity (categories IIA and IIB) in the WHO classification because clinicopathologic studies have produced no outcome data to support the separation of mesangial lupus nephritis based on the degree of mesangial cellularity.

### ISN/RPS Class III: Focal Lupus Nephritis

Class III is defined by the proportion of glomeruli with any active lesion or scar involving less than 50% of the glomeruli (**Fig 1**). It is not defined by the character of the pathology or its intraglomerular distribution. Although most of the active lesions seen in focal lupus nephritis are, in fact, segmental in their intraglomerular distribution, this strictly quantitative definition replaces the descriptive category III, “Focal segmental GN,” in the WHO classification. It should be noted that morphologically identical focal segmental GN may be distributed more widely, but when 50% or more of glomeruli are involved, the biopsy specimen is classified as diffuse lupus nephritis (see section “Class IV:



**Figure 1.** Focal segmental glomerulonephritis. There is a segmental proliferative lesion that obliterates the glomerular architecture and involves at least 50% of the tuft. The uninvolved glomerular lobules show mesangial expansion and normal cellularity. Only 2 of 32 glomeruli in the biopsy specimen were involved (ISN/RPS class IIIA). Hematoxylin and eosin, 66 $\times$ .

**Table 2. Active Glomerular Lesions in SLE**

Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction

Karyorrhexis

Fibrinoid necrosis

Rupture of glomerular basement membrane (breaks)

Crescents, cellular or fibrocellular

Subendothelial deposits identifiable by light microscopy (wire-loops)

Intraluminal immune aggregates (hyaline thrombi)

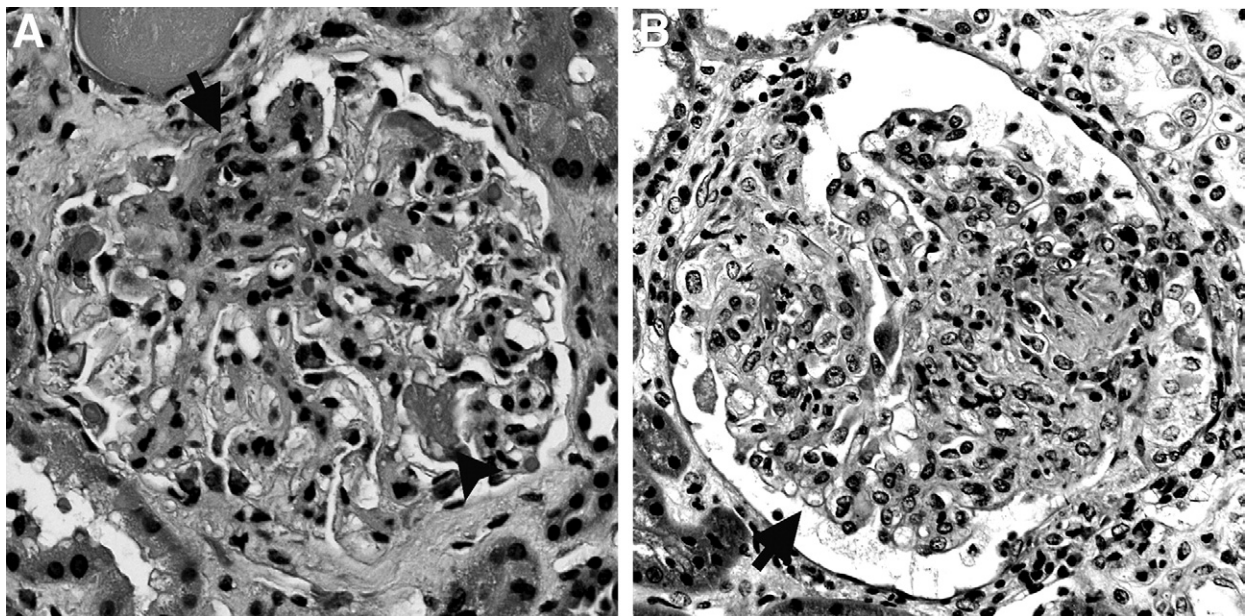
Hematoxylin bodies<sup>2</sup>

NOTE. Although hematoxylin bodies are a classic feature of active lupus glomerulonephritis, the ISN/RPS classification does not include them among the active lesions. Modified from Weening et al.<sup>2,3</sup>

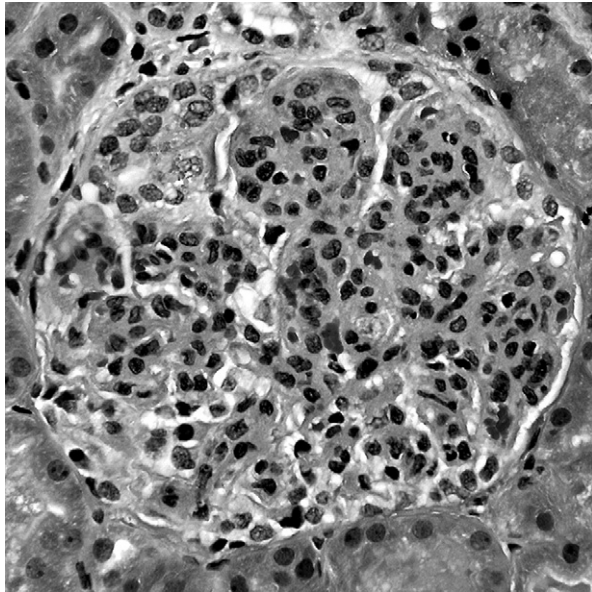
Diffuse Lupus Nephritis”). Class III has 3 subdivisions for active (III [A]), active and chronic (III [A/C]), and chronic (III [C]) lesions.

### ISN/RPS Class IV: Diffuse Lupus Nephritis

Diffuse lupus nephritis (ISN/RPS class IV) is defined by the proportion of glomeruli with any active lesion or scar (Table 2) involving 50% or more of the glomeruli. This class contains cases with global endocapillary and extracapillary (crescentic) proliferative GN involving 50% or more of the glomeruli and the rare cases with widespread subendothelial deposits (wire-loops), unaccompanied by significant endocapillary proliferation, seen by light microscopy. It also includes biopsy specimens with segmental lesions in 50% or more of the glomeruli. The ISN/RPS distinguishes between these 2 types of diffuse lupus nephritis and categorizes them separately as diffuse, segmental proliferative lupus nephritis (segmental lesions in  $\geq 50\%$  of glomeruli) (Fig 2), and diffuse, global proliferative lupus nephritis (global lesions in  $\geq 50\%$  of glomeruli) (Figs 2 and 3). The segmental glomerular lesions involve variable proportions of



**Figure 2.** Focal segmental glomerulonephritis. (A) There is a segmental proliferative lesion that involves 20% of the tuft (arrow) and a focal fibrin exudate (arrowhead). The uninvolved glomerular lobules show normal architecture with patent capillaries and a mild increase in mesangial matrix and cellularity. Similar lesions were present in 13 of 22 glomeruli (59%) in the biopsy specimen. This biopsy specimen is classified as ISN/RPS class IV-S (A) because more than 50% of the glomeruli are involved. Note the similarity of the lesion to Figure 1. (B) A proliferative lesion involves more than 80% of the tuft and similar lesions involved 30 of 35 glomeruli (85%) in the biopsy specimen. Despite the segmental nature of the process indicated by the uninvolved capillaries (arrow), this biopsy specimen is classified as diffuse global (ISN/RPS IV-G [A]) because of the involvement of more than 50% of the glomeruli and more than 80% of the tuft. (A and B) Hematoxylin and eosin, 66 $\times$ .



**Figure 3.** Diffuse global glomerulonephritis. The glomerulus shows a lobular pattern with every capillary showing endocapillary proliferation. This is a classic diffuse global glomerulonephritis (ISN/RPS class IV-G [A]), but contrast the pathologic process to the similarly classified lesion illustrated in Figure 2B. Hematoxylin and eosin, 66 $\times$ .

the tuft, but by definition the ISN/RPS limits and defines segmental involvement as less than 50% of the glomerulus. The distinction between classes IV-S and IV-G is based purely on the intraglomerular distribution of the lesion and not on the character of the inflammatory lesion. Classes IV-S and IV-G are each divided further, as are the focal lesions of category III, into 3 subdivisions for active (IV-S [A] and IV-G [A]), active and chronic (IV-S [A/C] and IV-G [A/C]), and chronic (IV-S [C] and IV-G [C]) lesions.

### ISN/RPS Class V: Membranous Lupus Nephritis

Global or segmental subepithelial immune deposits or light fluorescence or electron microscopic findings that are the result of antecedent subepithelial deposits define ISN/RPS class V. Small subendothelial deposits are allowed if wire-loops are not visible by light microscopy. In contrast to the modified WHO classification, class V may have any degree of mesangial proliferation, but when class III or IV lesions occur together with diffuse class V lesions (involving <50% of the glomeruli and  $\geq$ 50% of the glo-

meruli, respectively), they are diagnosed separately. For example, membranous GN in which 25% of the glomeruli have segmental proliferative lesions or scars would be diagnosed as membranous lupus nephritis (class V) and focal lupus nephritis (class III).

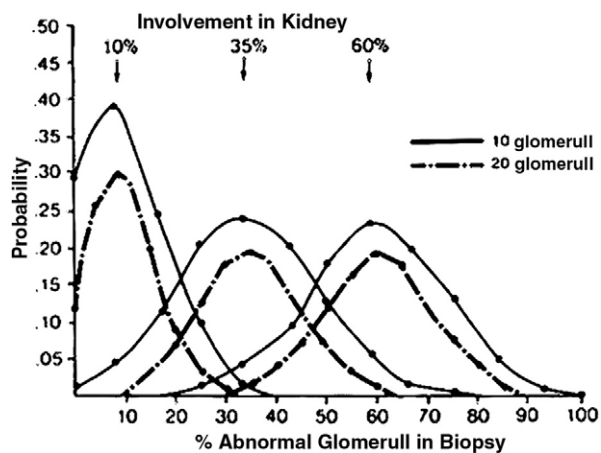
### ISN/RPS Class VI: Advanced Sclerosing Lupus Nephritis

This class has 90% or more of glomeruli globally sclerosed without residual histologic activity.

### APPLYING THE ISN/RPS CLASSIFICATION

The ISN/RPS classification is not simpler than the WHO classification. However, the pathology of SLE GN is heterogeneous, and 6 categories with subcategories are necessary to catalogue all cases of lupus GN. The authors of the ISN/RPS classification modified the 1982 and 1995 WHO classifications to remove ambiguity, to provide definitions of pathologic terms, and to eliminate categories that have not shown diagnostic or prognostic utility. For example, the category of normal by all modalities was removed from class I, the subclasses based on the degree of mesangial proliferation were removed from classes II and V, and segmental and diffuse proliferative GN were removed from class V. Although a predetermined proportion of glomerular involvement (50%) was chosen as an easy and reproducible criterion for separating class III from class IV, the statistical implications of this division require careful examination.

In SLE, glomerular inflammation (glomerulonephritis) may involve only some glomeruli (focal), leaving the remaining glomeruli uninvolved. The validity of the inference that the proportion of glomeruli with lesions seen in a biopsy specimen represent the proportion of involved glomeruli in the kidneys can be tested by representing the probability of finding 0, 1, 2, . . . , n abnormal glomeruli in a biopsy specimen as a binomial distribution (Fig 4). It follows from these statistical considerations that dichotomizing focal SLE GN with one class with less than 50% glomerular involvement and a second class with 50% or more glomerular involvement will lead to misclassification of 10% to 15% of the class III biopsy specimens as class



**Figure 4.** Binomial distribution of percentage of abnormal glomeruli in biopsy samples from kidneys with mild (10%), moderate (35%), and severe (60%) involvement. Reprinted with permission from S. Karger AG, Basel.<sup>10</sup>

IV, and the same proportion of class IV biopsy specimens will be incorrectly included in class III. These statistically based errors of classification will be exaggerated in biopsy specimens with small numbers of glomeruli. Furthermore, by including the most severe class III lesions in class IV and downgrading the least severe class IV lesions to class III, the prognosis of both groups will improve without changing the actual distribution of involved glomeruli in the kidneys or the overall outcome of the patients. This overlap in the distributions of biopsy categories is analogous to the Will Rogers phenomenon, which refers to misleading statistical outcomes resulting from "stage migration" in the classification of cancer patients.<sup>11</sup> To avoid erroneous classification, biopsy results must take into account these sampling problems. Practically speaking, a biopsy specimen with 10 glomeruli must have 8 involved glomeruli and a biopsy specimen with 20 glomeruli must have 14 involved glomeruli to ensure that 50% of the glomeruli in the kidneys will be involved. Users of the ISN/RPS classification should be aware of the problems associated with separating class III from class IV on the basis of the proportion of glomerular involvement and of the potential for misclassification of some biopsy specimens in this situation in which sample size is an important consideration.

The ISN/RPS diagnostic categories allow the inclusion of active lesions, representing current

inflammation, and scars, related to past episodes of disease activity. Classes III, IV, and V may contain active or chronic lesions or a mixture of both, and the active and chronic lesions have very different prognostic and therapeutic implications. Therefore, the clinician should observe the caveat that the abbreviated symbols for the ISN/RPS categories (eg, III, IV-S, and IV-G) are no substitute for an in-depth knowledge of the extent and nature of the glomerular inflammation and scars in the individual renal biopsy specimen. Therapeutic decisions and prognostication should be based on a pathology report that clearly states the number of glomeruli, the proportions of active and sclerosing glomerular lesions, the nature of the inflammatory lesion (proliferation, necrosis, thrombosis, crescents), and the distribution and pattern of immune deposits.

It was the consensus of the Working Group that the ISN/RPS classification is a work in progress, and the participants anticipated that testing of the classification would lead to validation of some and elimination of other categories and definitions. After discussing the pathogenetic implications of the renal biopsy findings, I present the studies that have appeared since the appearance of the ISN/RPS classification that investigate the prognostic and pathogenetic significance of classes IV-S and IV-G.

## PATHOGENESIS OF SLE GN

It is my thesis that multiple pathogenetic mechanisms are capable of causing glomerular injury in SLE, and this pathogenetic heterogeneity is reflected in the variable patterns of injury seen on renal biopsy and the different clinical presentations of patients with lupus renal disease. Abundant data have accumulated concerning the pathogenesis and etiology of lupus in experimental models, but I wish to consider only the implications of pathologic observations in human beings. I begin by presenting 2 generally accepted pathogenetic mechanisms in lupus nephritis and follow with evidence for 3 additional forms of glomerular injury.

### Circulating Immune-Complex Disease

Immune complexes deposited in the kidney from the circulation were the first pathogenetic

mechanism described in glomerular injury in SLE.<sup>12</sup> Serologic studies showing high levels of circulating immune complexes, double-stranded DNA, and other nuclear antigens and consumption of classic complement components (C1, C4, and C3)<sup>13,14</sup> support an immune-complex mechanism in patients with active lupus GN. Morphologic demonstration of glomerular immune reactants (immunoglobulins, complement components, and presumably antigens) and electron-dense deposits also are consistent with an immune-complex mechanism. Serologic findings associated with circulating immune complexes and activation of complement correlate best with large subendothelial deposits seen by light microscopy as wire-loops.<sup>15-17</sup> Although injection of preformed immune complexes into experimental animals gives, at best, mesangial immune deposits and never reproduces the massive subendothelial deposits of lupus glomerulonephritis,<sup>18</sup> this remains the most widely acknowledged form of glomerular injury in SLE. The histologic findings associated with immune-complex deposition including wire loops, hyaline (nonfibrin, immune reactant) capillary thrombi, and glomerular macrophages<sup>19,20</sup> are signs of active glomerular inflammation (Table 2) and are seen only in ISN/RPS classes III and IV.

Furthermore, morphologic evidence of an immune-complex mechanism is more compelling in ISN/RPS class IV-G (diffuse global) than IV-S (diffuse segmental). Najafi et al<sup>21</sup> compared the glomerular pathology of 35 biopsy specimens with diffuse SLE GN with 24 biopsy specimens with segmental GN in more than 50% of the glomeruli (this classification only roughly approximates ISN/RPS classes IV-G and IV-S; see Significance of the Distinction Between Diffuse Segmental [ISN/RPS Class IV-S] and Diffuse Global [ISN/RPS Class IV-G] GN). Wire-loops, hyaline thrombi, and massive subendothelial deposits seen by electron microscopy occurred with significantly greater frequency in class IV-G biopsy specimens. Mittal et al<sup>22</sup> compared biopsy specimens with ISN/RPS class IV-S with ISN/RPS class IV-G. Wire-loops and subendothelial deposits were observed more frequently in ISN/RPS class IV-G, but differences from ISN/RPS class IV-S were not statistically different.

Hill et al<sup>23</sup> observed that biopsy specimens from patients with ISN/RPS class IV-G (n = 31) were more likely to have glomerular hyaline thrombi, glomerular macrophage/monocytes, and subendothelial deposits than biopsy specimens from patients with ISN/RPS class IV-S (n = 15). These observations imply that subendothelial immune-complex deposits activate complement and mediate SLE GN, and this type of injury is most common in ISN/RPS class IV-G.

### In Situ Immune-Complex Disease

SLE membranous GN (MGN) (ISN/RPS class V) also is immune-complex mediated, but the deposits seen in SLE MGN are not usually associated with glomerular inflammation. In fact, the subepithelial and intramembranous immune deposits in SLE MGN are in the same location as the deposits seen in idiopathic MGN and the experimental model of MGN, Heymann nephritis, and in both of these conditions there is a heavy load of immune deposits in the capillary wall without significant glomerular inflammation. The mechanisms responsible for the subepithelial localization of immune complexes in some patients with SLE and the subendothelial localization in others are not understood completely, but the discrete patterns of immune-complex deposition have been attributed to differences in antibody and antigen characteristics and antigen location. However, there is considerable experimental evidence that the immune deposits in Heymann nephritis are the result of the in situ reaction of unbound antibody with antigen, and although the in situ mechanism is unproven in human beings, the weight of experimental evidence supports this mechanism in the pathogenesis of SLE MGN.<sup>24,25</sup>

Thus, there appears to be 2 discrete pathogenic mechanisms of glomerular immune-complex localization in SLE associated with the proliferative (principally ISN/RPS class IV-G) and membranous (ISN/RPS class V) forms of SLE GN. This dichotomy also is important clinically because the therapy and prognosis for glomerular pathology associated with these 2 forms of immune-complex disease are very different.

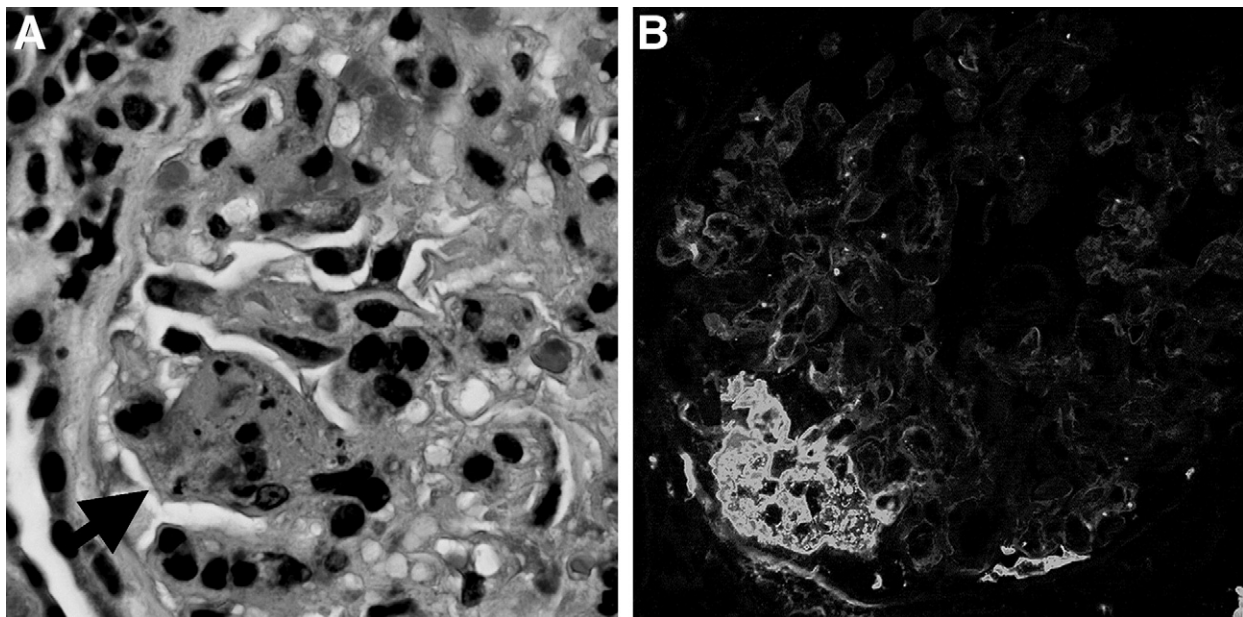
## Vasculitic Lupus GN

Glomerular involvement in the pauci-immune systemic vasculitides has a focal and segmental distribution, and these forms of GN are destructive inflammatory lesions that are frequently necrotizing and crescent-forming.<sup>26</sup> Likewise, a focal and segmental distribution of glomerular pathology is characteristic of many biopsy specimens from patients with lupus GN including most ISN/RPS class 3 (focal GN) and many in ISN/RPS class 4 (Fig 5).<sup>27</sup> Although the pathogenesis of focal segmental lupus GN has been attributed to glomerular mesangial immune deposits, glomerular capillary thrombosis also has been invoked. Churg and Sobin<sup>8</sup> noted that immune “deposits are found in nearly every case (of lupus glomerulonephritis) in the mesangium and less consistently in the capillary wall,” but the absence of deposits in the focal segmental glomerular lesions of focal lupus nephritis implies that they may not be produced by the same mechanism as the diffuse form. A non-immune-complex mechanism was suggested by the report of necrotizing and crescentic GN that occurred without significant glomerular immunoglobulin deposits.<sup>28</sup> In addition to the character

and distribution of the glomerular lesions, the presence of a positive antineutrophil cytoplasmic autoantibody (ANCA) in more than one third of patients with lupus GN, usually a P-ANCA supports a vasculitic mechanism in lupus GN. In these patients a P-ANCA correlates with histologic activity. The significance of this observation has been questioned because the target antigens are often different from myeloperoxidase that usually is seen in the systemic vasculitides and include cathepsin G and lactoferrin.<sup>29-31</sup> However, Hill et al<sup>23</sup> summarized the evidence concerning the pathogenesis of segmental proliferative SLE GN and concluded that the findings cast doubt on a classic immune-complex mechanism. Therefore, there is morphologic and serologic support for a pauci-immune, pathogenetic mechanism in lupus GN, which is separate and distinct from lesions that may result from antigen-antibody complex formation in the glomerular capillary wall.

## Thrombotic Microangiopathy

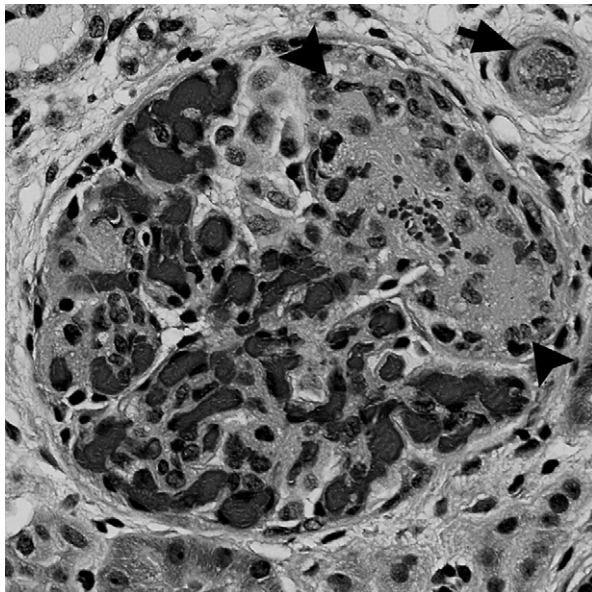
Glomerular fibrin thrombi are a histologic feature of proliferative lupus GN,<sup>32</sup> and in the presence of severe glomerular inflammation, thrombus forma-



**Figure 5.** Lupus vasculitis in a patient who had a positive P-ANCA (myeloperoxidase positive). (A) Several capillaries have undergone fibrinoid necrosis (arrow) without associated endocapillary proliferation, and they contain karyorrhectic debris. The uninvolved capillaries have normal architecture with thin delicate basement membranes, patent capillaries, and normal mesangial matrix and cellularity. Although there were mesangial immune deposits, they were not present around the periphery of the glomerular capillaries. (B) Fibrin in the same distribution as the lesions seen by light microscopy supports the segmental necrotizing nature of the lesion. (A) Hematoxylin and eosin, 163 $\times$ . (B) Fibrin, 66 $\times$ .



tion can result from endothelial activation or damage with activation of the intrinsic coagulation system. Thrombi also occur without other signs of glomerular inflammation in the thrombotic thrombocytopenic purpura (TTP)-like lesion that is a rare complication of systemic lupus erythematosus (Fig. 6).<sup>33</sup> Glomerular thrombosis also occurs in SLE in the absence of severe inflammation, and this suggests several additional pathogenetic mechanisms. A lupus anticoagulant or antiphospholipid antibody is present in a significant proportion of patients with systemic lupus erythematosus, and these autoantibodies, directed against the phospholipid elements in the intrinsic clotting cascade, may arise by mechanisms analogous to antinuclear antibodies.<sup>34</sup> With the onset of the antiphospholipid syndrome, the patients may develop thromboses in the arteries, veins, and glomerular capillaries. In addition, patients with SLE may acquire a deficiency of von Willebrand's factor-cleaving protease (ADAMTS-13), and the resulting large multimers of von Willebrand's factor lead to platelet aggregation and thrombosis.<sup>35</sup> Auto-antibody against ADAMTS-13 is a common cause of acquired von Willebrand's factor-protease



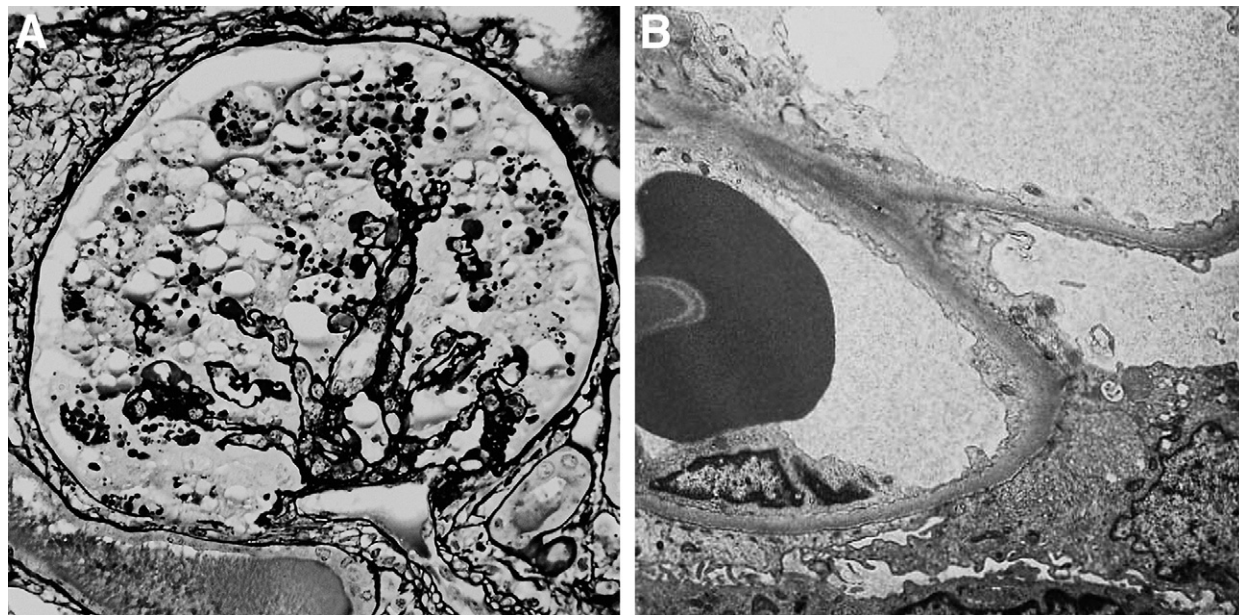
**Figure 6.** Thrombotic microangiopathy. There is a thrombus in the arteriole (arrow) that appears to extend into the glomerulus (between the arrowheads), and the glomerular thrombus contains fragmented red blood cells. The remaining capillaries are congested. Hematoxylin and eosin, 66 $\times$ .

deficiency in patients with TTP, and although immunoglobulin G anti-ADAMTS-13 antibody is unusual in patients with SLE,<sup>36,37</sup> the association remains a potential cause of thrombosis.

### Podocytopathy

The nephrotic syndrome is a sign of renal involvement in SLE, and it usually is attributed to glomerular inflammation or disruption of capillary wall function caused by immune deposits. However, there are cases of SLE in which the nephrotic syndrome occurs in the absence of inflammatory cell infiltrates, capillary wall immune deposits, and no or minimal mesangial deposits.<sup>38,39</sup> The glomerular pathology in these patients is usually minimal change disease, but there also are cases of collapsing focal segmental glomerulosclerosis (Fig 7).<sup>40,41</sup> The co-occurrence of 2 independent diseases, lupus and minimal glomerulopathy, could explain the nephrotic syndrome, but Hertig et al<sup>39</sup> showed that the nephrotic syndrome in this group of patients was much more frequent than could be explained by the chance association between minimal change glomerulopathy and SLE. Kraft et al<sup>40</sup> showed that diffuse foot process effacement is the only morphologic feature that distinguishes nephrotic and nonnephrotic range proteinuric SLE patients who did not have glomerular inflammation or necrosis or peripheral capillary-wall immune deposits. The investigators used the term *podocytopathy* to imply that non-immune-complex-mediated injury to the glomerular visceral epithelial cell (podocyte), rather than immune-complex-mediated glomerular injury, was responsible for nephrotic range proteinuria. These observations raise the intriguing possibility that in this group of SLE patients a primary pathologic process involving the glomerular visceral epithelial cell causes the nephrotic syndrome.

The cause of idiopathic minimal change glomerulopathy is unknown, but the Shalhoub<sup>42</sup> hypothesis holds that a product of aberrant T-cell function is responsible for glomerular epithelial cell injury resulting in diffuse podocyte effacement. There is growing evidence that activated T cells,<sup>43,44</sup> abnormal T-cell cytokine expression,<sup>45,46</sup> and an unidentified circulating factor of presumed T-cell origin<sup>47-49</sup> are in-



**Figure 7.** Lupus podocytopathy. (A) There is diffuse collapse of the glomerular capillaries with hypertrophy, vacuolization, and periodic acid-Schiff (PAS)-positive absorption droplets in the podocytes. Although there were mesangial deposits of immunoglobulin G, this pattern of glomerular injury is called the *cellular lesion of FSGS* or *collapsing glomerulopathy* rather than *diffuse proliferative glomerulonephritis*. (B) Electron micrograph of 2 glomerular capillaries from the biopsy specimen illustrated in A. There is diffuse foot process effacement, and there are no electron-dense deposits in the peripheral capillary wall. (A) Periodic acid-Schiff, 66 $\times$ . (B) Uranyl acetate and lead citrate, 7,000 $\times$ .

involved in the pathogenesis of podocyte diseases in human beings that result in proteinuria and the nephrotic syndrome. These findings raise the question of whether activated T cells could be implicated similarly in the pathogenesis of the podocyte lesion seen in some patients with SLE. T-cell activation seems to play an important role in the pathogenesis of SLE by altering the production of cytokines and the expression of cellular adhesion molecules, as well as inducing B cells to produce autoantibodies.<sup>50</sup> Therefore, one might speculate that the underlying mechanism of SLE-related podocytopathy, as proposed in idiopathic minimal-change glomerulopathy, could similarly be mediated by activated T cells. The concurrent presentation of clinical renal abnormalities (nephrotic syndrome) and evidence of active SLE in some patients supports this hypothesis.

These different pathogenetic mechanisms are recognized most easily when they occur in isolation. However, the glomerular pathology seen on renal biopsy often contains evidence of multiple types of injury, and it is important to consider the possibility that more than one

mechanism may be active at one time. For example, membranous lupus nephritis associated with subepithelial and intramembranous immune deposits (ISN/RPS class V) often co-exists with proliferative GN (ISN/RPS class IV-G [A]), which is associated with subendothelial immune deposits. In a similar fashion, the vasculitic lesions, podocytopathy, and thrombotic microangiopathy may be superimposed on immune-complex-mediated lupus GN and may contribute to the complexity of the pathology and the clinical manifestations.

#### SIGNIFICANCE OF THE DISTINCTION BETWEEN DIFFUSE SEGMENTAL (ISN/RPS CLASS IV-S) AND DIFFUSE GLOBAL (ISN/RPS CLASS IV-G) GN

The rationale for dividing ISN/RPS class IV into diffuse segmental and diffuse global lupus nephritis was based largely on the study presented by Najafi et al.<sup>21</sup> This was a 10-year follow-up evaluation of patients with severe lupus GN who participated in a prospective clinical trial conducted by the Collaborative Study

Group. There were 24 SLE patients with active segmental GN in 50% or more of the glomeruli and 35 SLE patients with diffuse GN. The clinical parameters at study entry were not different, and therapy was identical for the first 4 years.<sup>51</sup> After 10 years, the incidence of end-stage renal disease was significantly greater in patients with segmental GN of 50% or more compared with those with diffuse GN (9/24 [38%] versus 5/35 [14%],  $P = .05$ ), and the incidence of remission with stable renal function was greater in patients with diffuse GN (22/35 [63%] versus 9/24 [38%],  $P < .05$ ).

Three studies, focusing on the prognosis of classes ISN/RPS IV-S and IV-G, have appeared since the publication of the ISN/RPS classification,<sup>52</sup> and none was able to show a significant difference in any outcome between patients with diffuse segmental (IV-S) and diffuse global (IV-G) nephritis. Two of these studies had small numbers of patients, a relatively short follow-up period, and uncontrolled and variable treatment. However, it is possible that observed differences in outcome between Najafi et al<sup>21</sup> and these 3 studies result from differences in the way in which segmental and diffuse GN are defined and marked differences in treatment among these cohorts.

Segmental GN is characteristic of the pathology in some biopsy specimens from patients with lupus GN, and in the definition used by Najafi et al,<sup>21,53</sup> segmental GN could involve only one glomerulus or virtually all the glomeruli in a biopsy. Although there was no upper limit to the extent of involvement within the glomerulus, the segmental nature of the lesion was discerned readily, prospectively, by a panel of 4 experienced renal pathologists, in the preserved architecture and patent capillaries seen in a portion of the glomerulus.<sup>54</sup> Although the patients with segmental GN in 50% or more of the glomeruli and diffuse GN of Najafi et al<sup>21</sup> roughly correspond to ISN/RPS classes IV-S and IV-G, respectively, the categories are not congruent, chiefly because segmental GN involving more than 50% of the tuft and more than 50% of the glomeruli are included in ISN/RPS class IV-G, by definition, despite the clearly segmental nature of the pathology. As a result, ISN/RPS class IV-G contains all of Najafi et al's<sup>21</sup> diffuse

lesions and some of their segmental lesions that involve more than 50% of the glomeruli. The relegation of the most widely distributed segmental lesions to ISN/RPS class IV-G could easily conceal differences in outcomes between patients with class IV-S and IV-G lesions. Therefore, the arbitrary limits of glomerular involvement that define classes IV-S and IV-G in the ISN/RPS classification and that ignore the segmental nature of widely distributed segmental lesions that involve 50% or more of the glomeruli and more than 50% of the glomerular tuft may be incapable of detecting important clinical and biological differences between global and segmental forms of diffuse lupus GN.

## CONCLUSIONS

The ISN/RPS classification of lupus nephritis eliminated some ambiguities from the antecedent WHO classification. However, it adds the mathematic confusion of the meaning of an absolute percentage of abnormal glomeruli in a situation in which sample size is an important consideration. Because it is mainly a histologic and immune-deposit-based classification of glomerular pathology, the ISN/RPS classification does not include either non-immune-complex-mediated glomerular pathology or extraglomerular renal pathology of lupus. The appropriateness and prognostic use of separating diffuse segmental (IV-S) from diffuse global (IV-G) GN using the ISN/RPS definitions remain to be proven.

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