

# Educational Case: Lupus Nephritis as an Example of Immune Complex–Mediated Glomerulonephritis

Deborah Jebakumar, MD<sup>1</sup> and Kathleen A. Jones, MD<sup>1</sup> 

*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/2374289517715040>.<sup>1</sup>*

## Keywords

pathology competencies, organ systems pathology, kidney, renal syndromes, immune-mediated renal disease, lupus nephritis, systemic lupus erythematosus

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## Primary Objective

*Objective UTK5.3: Immune-Mediated Renal Disease.* To compare and contrast the mechanisms of immune complex and antibody-mediated glomerulonephritis.

Competency 2: Organ Systems Pathology; Topic UTK: Kidney; Learning Goal 5: Renal Syndromes.

## Patient Presentation

A 25-year-old woman presents to the nephrology clinic for follow-up of recently discovered proteinuria and hematuria. She has a history of systemic lupus erythematosus, initially diagnosed 6 years ago, that has manifested as flares of acute serositis and musculoskeletal pains. She has been hospitalized twice in the past 5 years for lupus-related symptoms and has received immunosuppressive therapy. On a visit to her rheumatologist a week ago, she was discovered to have new-onset proteinuria and hematuria on dipstick urinalysis. She denies any history of gross hematuria or dysuria and has not noticed decreased urine output. She has been taking up to three 200-mg ibuprofen each day for joint pain but discontinued those a week ago on the advice of her rheumatologist. She is currently on

oral steroids, hydroxychloroquine, and azathioprine, in addition to oral contraceptives and a multivitamin. She is married and has no children. She does not smoke or drink alcohol. She denies a family history of autoimmune or kidney disease.

## Diagnostic Findings: Part I

On physical examination, her temperature is 98.6°F (37°C), pulse is 76 beats per minute, blood pressure (supine) is 150/91 mm Hg, and respiratory rate is 12 breaths per minute. Her height is 5'4" (1.62 m), weight is 145 pounds (65.8 kg), and her body mass index is 24.9 kg/m<sup>2</sup>. Physical examination reveals a well-appearing woman who is pale and in no acute distress.

<sup>1</sup> Department of Pathology and Laboratory Medicine, Baylor Scott & White Medical Center, Temple, Texas A & M College of Medicine, Temple, TX 76508, USA

## Corresponding Author:

Kathleen A. Jones, MD, Department of Pathology and Laboratory Medicine, Baylor Scott & White Medical Center, Temple, 2401 S. 31st St., Temple, TX, 76508, USA.

Email: [kathleen.jones1@BSWHealth.org](mailto:kathleen.jones1@BSWHealth.org)



Examination of the head reveals a mild, red to purple rash involving the cheeks and bridge of the nose, with sparing of the nasolabial folds. Examination of the eyes, ears, nose, and throat are unremarkable. Cardiac examination reveals a normal S<sub>1</sub> and S<sub>2</sub> with no murmurs, gallops, or rubs. Respiratory examination reveals that the lungs are clear to auscultation. Abdominal examination reveals no organomegaly or fluid wave. Examination of the upper extremities reveals 1 ring-shaped, scaly, red lesion on the left forearm. Examination of the lower extremities finds mild (1+) edema bilaterally. No other skin rashes are noted. Neurological examination reveals no significant findings, specifically with no proximal or distal weakness noted in the extremities.

## Questions/Discussion Points: Part I

### *What Is the Differential Diagnosis Based Upon History and Physical Findings?*

In a patient with systemic lupus erythematosus and hypertension who is found to have proteinuria and/or hematuria, there is a concern that these findings indicate renal glomerular involvement by lupus nephritis. Lupus nephritis is classified according to the clinical and renal biopsy findings. Some patients have mild renal involvement that is manifested by milder degrees of proteinuria and hematuria. Other patients may have more significant renal involvement by lupus, up to and including acute kidney injury (AKI)/acute renal failure with or without nephritic syndrome or nephrotic syndrome.<sup>2</sup> Some lupus patients may present with vascular disorders, such as thrombotic microangiopathy, necrotizing lupus vasculitis, or even antiphospholipid antibody syndrome, all of which can affect the kidney. These should be considered as diagnostic possibilities in this patient.<sup>3</sup>

Patients with other autoimmune disorders, such as mixed connective tissue disease, can present with clinical features similar to those seen in this patient, although proteinuria with a membranous nephropathy picture is a more common glomerular injury pattern in this population. Patients with rheumatoid arthritis may present in a manner similar to this patient, although proteinuria with subsequent detection of amyloidosis or treatment-related renal injury (various patterns) is more commonly seen.<sup>3</sup> Overlap in the autoimmune disorders does exist. So, this patient's diagnosed systemic lupus erythematosus may not represent a "pure" disorder, and other autoimmune disorders should be considered in the differential diagnosis of her presentation.

Given this patient's recent use of nonsteroidal anti-inflammatory drugs and other medications, acute tubulointerstitial nephritis is also a diagnostic consideration,<sup>4</sup> although associated use of steroids might attenuate the degree of renal injury and inflammation caused by nonsteroidal anti-inflammatory drugs. Of note, patients with Sjogren syndrome may present with renal impairment and findings of chronic tubulointerstitial nephritis.<sup>3</sup>

Although lupus-related lesions are high on the differential diagnostic list, patients with lupus can have renal disorders unrelated to lupus, such as postinfectious glomerulonephritis or IgA nephropathy. Therefore, consideration must be given to a variety of renal lesions in this patient, as appropriate to the clinical presentation.<sup>2</sup>

### *What Are the Best Next Steps in Diagnostic Evaluation of This Patient?*

Review and comparison of previous laboratory studies to current laboratory studies should determine the degree of proteinuria, confirm the presence of hematuria, evaluate for renal functional impairment, and determine the presence of any specific renal syndromes.

- Blood urea nitrogen (BUN) and serum creatinine are indicated to evaluate renal function and/or determine if this patient has a reduced glomerular filtration rate (GFR).
- Serum electrolytes and/or a comprehensive metabolic profile will assist in determining the level of renal functional impairment, if present.
- A complete urinalysis (including macroscopic, chemical, and microscopic evaluation) will confirm the presence of proteinuria and hematuria and will also inform the differential diagnosis, relative to the presence of other pathologic urine findings that might indicate glomerular versus tubular dysfunction (presence of red blood cell casts, presence of tubular epithelial cell casts, etc.).
- A quantitative urine study or use of urine protein:creatinine ratio will help determine the degree of proteinuria.
- A complete blood count (CBC) may be indicated to determine the effect her current medications have, if any, on bone marrow function.

If renal impairment is confirmed, and findings point to a glomerular lesion, studies such as serum complement levels (C3 and C4) and serum antinuclear antibody test may be helpful. Active lupus nephritis can cause decreased serum complement levels, as can other proliferative glomerular lesions, such as postinfectious glomerulonephritis and membranoproliferative glomerulonephritis.

## Diagnostic Findings: Part 2

The patient's laboratory findings on presentation to the nephrology clinic, including results from a complete metabolic profile, CBC, and urinalysis, are shown in Table 1. Review the findings and determine what abnormalities are present.

- Review of her chart reveals that the patient's BUN and serum creatinine were 20 and 0.8 mg/dL, respectively, 2 months ago at her annual physical examination.

**Table 1.** Laboratory Findings.

Laboratory Parameter	Patient Result	Reference Range
<b>Chemistry—complete metabolic profile</b>		
Serum creatinine	2.3 mg/dL	0.50-1.30 mg/dL
Blood urea nitrogen	31 mg/dL	7-22 mg/dL
Serum sodium	142 meq/L	136-145 meq/L
Serum potassium	4.0 meq/L	3.5-5.3 meq/L
Serum chloride	111 meq/L	97-111 meq/L
Carbon dioxide	22 meq/L	22-30 meq/L
Serum calcium	9.6 mg/dL	8.6-10.5 mg/dL
Glucose	91 mg/dL	70-100 mg/dL
Total protein	6.4 g/dL	6.0-8.0 g/dL
Albumin	3.0 g/dL	3.4-5.2 g/dL
Total bilirubin	0.3 mg/dL	0.2-1.2 mg/dL
Alkaline phosphatase	62 IU/L	34-130 IU/L
SGOT (AST)	19 IU/L	0-40 IU/L
SGPT (ALT)	14 IU/L	0-68 IU/L
Estimated GFR	15 mL/min/1.73m <sup>2</sup>	>60 mL/min/1.73m <sup>2</sup>
<b>Hematology—complete blood count</b>		
WBC	3.5 × 10 <sup>9</sup> /L	4.8-10.8 × 10 <sup>9</sup> /L
RBC	3.96 × 10 <sup>12</sup> /L	4.70-6.10 × 10 <sup>12</sup> /L
Hemoglobin	11.4 g/dL	14.0-18.0 g/dL
Hematocrit	33.6%	42.0-52.0%
MCV	91.9 fL	80.0-94.0 fL
MCH	29.5 pg	27.0-34.5 pg
MCHC	32.1 g/dL	32.0-36.5 g/dL
RDW	12.9%	11.0-15.0%
Platelet count	250 × 10 <sup>9</sup> /L	150-450 × 10 <sup>9</sup> /L
MPV	10.2 fL	7.4-12.0 fL
<b>Urinalysis</b>		
Color	Light brown color	Yellow
Appearance	Hazy	Clear-hazy
Specific gravity	1.025	1.005-1.030
pH	6.5	5.0-8.0
Glucose	Negative	Negative
Protein	2+	Neg-Trace mg/dL
Ketones	Trace	Negative
Blood	3+	Negative
Bilirubin	Negative	Negative
Urobilinogen	<2 IU/L	<2 IU/L
Nitrite	Negative	Negative
Leukocyte esterase	1+	Negative
Microscopic	Dysmorphic RBCs, 1-2 RBC casts/low power field	None
RBCs	40-50 RBCs/high power field	0-2/high power field
WBCs	10-15 WBCs/high power field	0-2/high power field

Abbreviations: GFR, glomerular filtration rate; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; RBC, red blood cell; RDW, red cell distribution width; SGOT (AST), serum glutamic-oxaloacetic transaminase (aspartate transaminase); SGPT (ALT), serum glutamic pyruvic transaminase (alanine transaminase); WBC, white blood cells.

- A 24-hour urine collection study reveals total protein excretion of 2433 mg.
- Serum complement levels are both below the reference ranges: 62 mg/dL for C3 (normal reference range: 90-180 mg/dL) and 9 mg/dL for C4 (normal reference range: 10-40 mg/dL).

## Questions/Discussion Points: Part 2

*What Significant Laboratory Abnormalities Are Present in This Patient? Do the Clinical and Laboratory Findings in This Patient Support the Presence of a Specific Syndrome?*

This patient has impaired renal function that is relatively acute (rise in serum creatinine from 0.8 up to 2.3 mg/dL within 2 months), as well as hypertension. On urinalysis, she has proteinuria, hematuria (including dysmorphic red blood cells), and red blood cell casts. She does not report oliguria but does have other findings that suggest the presence of nephritic syndrome. Nephritic syndrome is typically defined by the presence of hypertension, hematuria, often with red blood cell casts in urine, elevated BUN/serum creatinine (azotemia) and oliguria, indicating reduced GFR, and some degree of proteinuria. Since her decline in renal function has happened relatively quickly, she could also be classified as having AKI.

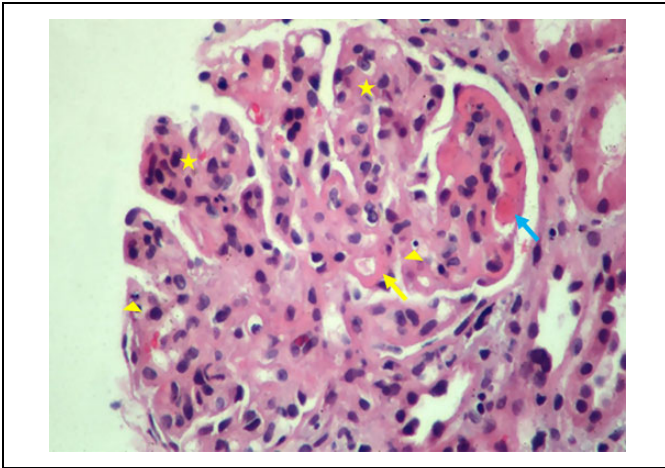
The presence of red blood cell casts on urinalysis suggests glomerular injury, while the absence of renal tubular epithelial cells or renal tubular epithelial cell casts in her urine argues against the presence of acute tubular/tubulointerstitial injury. Results of her other laboratory studies (quantitative urine study and comprehensive metabolic panel) do not suggest the presence of nephrotic syndrome, although she does have subnephrotic range proteinuria (less than 3.5 g urine protein excretion/24 h).

This patient has leukopenia and anemia, as demonstrated on her CBC results. This finding is likely related to her autoimmune disease, as systemic lupus erythematosus commonly affects the bone marrow.

*What Is the Differential Diagnosis Now, Given the Initial Laboratory and Diagnostic Studies?*

The differential diagnosis includes glomerular lesions that cause hypertension, renal functional impairment, proteinuria, and hematuria, including red blood cell casts (more nephritic presentation than nephrotic presentation). Since she has a history of lupus, lupus nephritis is highly likely, although other glomerular lesions (such as postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, and IgA nephropathy) could be considered in the differential.

The presence of hypocomplementemia implies that consumption of complement is occurring in this patient, thereby helping to narrow the differential to glomerular diseases that cause hypocomplementemia. Given her relatively acute course, diagnoses under the umbrella of rapidly progressive glomerulonephritis should also be considered. These include anti-glomerular basement membrane (GBM) antibody-mediated disease, immune complex disease (of many types), and pauci-immune glomerulonephritis. If her disease is severe and classified as rapidly progressive, then immune complex disease is most likely, particularly in light of her history of autoimmune disease.



**Figure 1.** Glomerulus demonstrating global endocapillary hypercellularity (indicated by yellow stars), neutrophil infiltration and nuclear dust (indicated by yellow arrowheads), wire loops (indicated by yellow arrow) and rare hyaline thrombus (indicated by blue arrow; light microscopy, hematoxylin–eosin stain, original magnification  $\times 400$ ).

### What Additional Studies Are Indicated to Arrive at the Diagnosis for This Patient?

The differential diagnosis is now narrowed to include disorders that cause renal lesions, and specifically glomerular lesions, so a renal biopsy is indicated, to include light microscopy, immunofluorescence microscopy, and electron microscopy.<sup>4</sup> For this patient, the decline in renal function has been relatively acute. She has hematuria (including dysmorphic red blood cells and red blood cell casts) and proteinuria is not the leading symptom (although present). Therefore, given her history, an active, proliferative lupus lesion is favored.

### Diagnostic Findings: Part 3

A renal biopsy is obtained from the patient. Ultrasound-guided biopsy is performed by the nephrologist with on-site gross evaluation by the pathologist to assure that adequate tissue is obtained. The representative images from light, immunofluorescence, and electron microscopic findings for this patient's renal biopsy were reviewed (Figures 1–5). The biopsy findings were described. A detailed description of the renal biopsy findings is found in the following sections:

- **Light microscopy:** Approximately 80 glomeruli are present, none of which are globally sclerosed. Essentially, all glomeruli demonstrate global endocapillary hypercellularity. Many glomeruli are infiltrated by neutrophils and focal glomerular necrosis is seen. Focally prominent wire loops and scattered intraluminal hyaline-type thrombi are noted (Figures 1 and 2). No cellular or fibrocellular crescents are identified. The interstitium shows a mild to moderate chronic inflammatory infiltrate composed chiefly of lymphocytes. Neither significant numbers of eosinophils are noted nor is

evidence of acute tubular injury identified. The blood vessels outside of glomeruli are patent without significant pathological changes. The periodic acid–Schiff (PAS) stains highlight intraglomerular wire loops and hyaline-type thrombi, with essentially no tubular atrophy. The trichrome stains show minimal cortical interstitial fibrosis with no fibrous glomerular crescents noted. The silver stains highlight intraglomerular wire loops with apparent subendothelial deposits).

- **Direct immunofluorescence microscopy:** Approximately 20 glomeruli are present. IgA, IgG (Figure 3), and IgM show strong deposition within all glomeruli in both the mesangium and along the peripheral capillary loops (2+), with a granular morphology. Similarly, C1q, C3, and C4 are deposited within the mesangium and along the peripheral capillary loops of virtually all glomeruli, with a granular morphology. C3 is the most intense (2+) of the complement components.  $\kappa$  and  $\lambda$  show a similar distribution with moderate intensity (2+). No fibrin thrombi are noted.
- **Electron microscopy:** Numerous, relatively large, and focally confluent aggregates of electron-dense deposits are noted in the subendothelial areas of most glomerular capillary loops. Similar-appearing mesangial electron-dense deposits are noted (Figure 4). A few scattered subepithelial electron-dense deposits are present. Scattered tubuloreticular bodies are seen within endothelial cell cytoplasm (Figure 5).

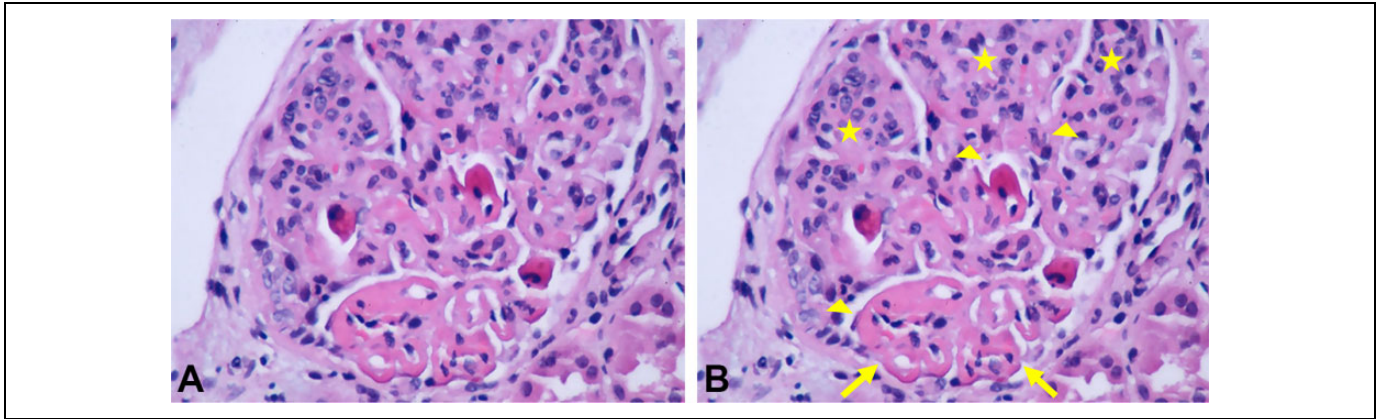
### Questions/Discussion Points, Part 3

#### What Is This Patient's Diagnosis, Based on the Light, Immunofluorescence, and Electron Microscopic Findings?

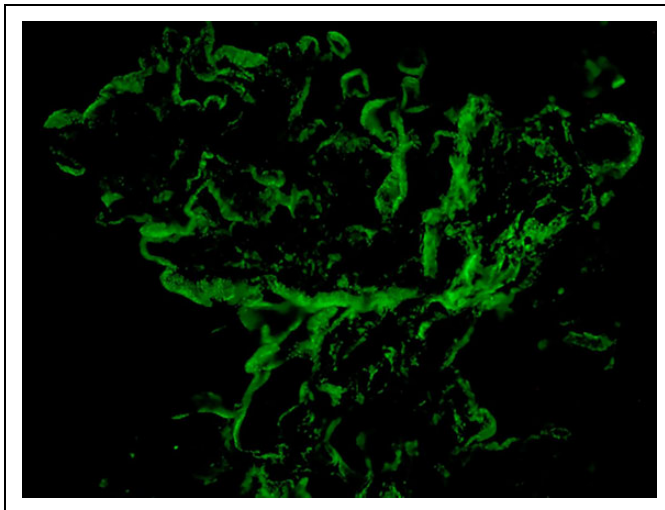
This patient's findings on renal biopsy are consistent with a diagnosis of lupus nephritis. Endocapillary hypercellularity and glomerular inflammation are present, indicating a proliferative glomerulonephritis. By immunofluorescence, Ig and complement components are found within glomeruli (granular deposits in mesangium and along capillary loops), and there are many subendothelial electron-dense deposits, in addition to electron-dense deposits in other glomerular locations (mesangium). Tubuloreticular bodies are also present within the endothelial cell cytoplasm. These features all support a diagnosis of lupus nephritis, as a type of immune complex-mediated glomerulonephritis, in this patient.

#### Briefly Describe How Lupus Nephritis Is Classified

Typically, lupus nephritis is classified on renal biopsy using the World Health Organization (WHO) classification scheme. This scheme takes into account the location, type, and degree of hypercellularity within glomeruli, immunofluorescence features, and the presence and location of electron-dense



**Figure 2.** Glomerulus (unannotated, panel A) demonstrating global endocapillary hypercellularity, neutrophil infiltration and nuclear dust, and prominent wire loops. Panel B (annotated) shows a glomerulus demonstrating global endocapillary hypercellularity with occluded capillary loops (indicated by yellow stars), neutrophil infiltration and nuclear dust (indicated by yellow arrowheads), and prominent wire loops (indicated by yellow arrows) (light microscopy, hematoxylin–eosin stain, original magnification  $\times 400$ ).

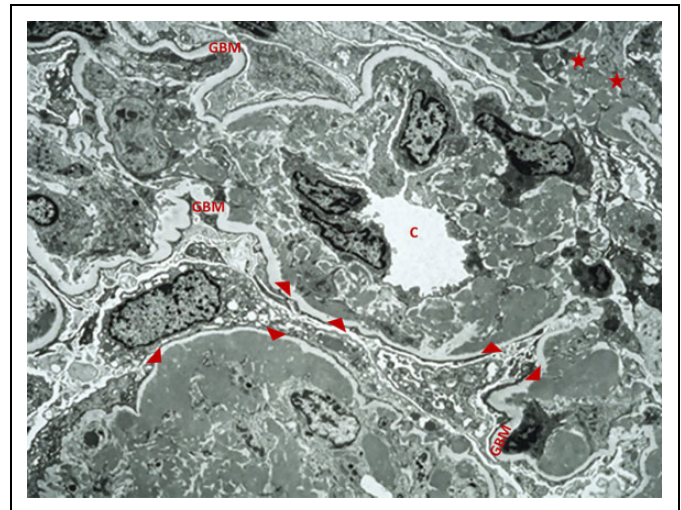


**Figure 3.** Glomerulus depicting granular capillary loop and mesangial staining on anti-IgG stain (immunofluorescence microscopy, anti-IgG, original magnification  $\times 400$ ).

deposits. Table 2 summarizes the key features for classification of lupus nephritis.<sup>5</sup>

### Based on This Classification Scheme, Which WHO Class Is Represented in This Patient's Biopsy?

Using the WHO classification scheme, this patient has class IV, diffuse lupus nephritis. She has glomerular hypercellularity that is endocapillary in nature. She has neutrophilic infiltration of glomeruli and wire loops, which typically indicate the presence of relatively large subendothelial immune-type deposits. Her immunofluorescence studies detect deposition of Ig and complement components within the mesangium and along the capillary walls of glomeruli. By electron microscopy, many large subendothelial electron-dense deposits are present within



**Figure 4.** Glomerulus with extensive subendothelial electron-dense deposits (indicated by red arrowheads) and some mesangial electron-dense deposits (indicated by red stars; transmission electron microscopy, approximate original magnification,  $\times 1500$ ). C indicates capillary lumen and GBM, glomerular basement membrane.

the glomeruli, accompanied by mesangial electron-dense deposits. These features fit best with a class IV lupus lesion.

### What Is the Underlying Pathophysiologic Mechanism for Lupus Nephritis, as an Example of Immune Complex–Mediated Glomerulonephritis?

In approximately 50% of patients with systemic lupus erythematosus, renal manifestations will be evident.<sup>4</sup> Certain populations have a higher incidence of more severe and progressive lupus nephritis,<sup>2</sup> and there is evidence to suggest that this may be linked to certain higher risk genetic markers.<sup>4</sup> In these patients, certain autoantibodies are more prevalent (anti-Ro,

anti-Sm, and anti-RNP), and these have been linked to a higher likelihood of lupus nephritis.<sup>4</sup>

Given the autoimmune nature of lupus, the inciting antigens are typically those related to nuclear components of the patient's cells. Some studies have shown that neutrophils can be a source of the nuclear material to which patients develop autoantibodies. Specifically, as neutrophils die, they can release neutrophil extracellular traps, composed of nuclear components and proteins, which then prompt autoantibody production.<sup>4</sup> As autoantibodies are formed against these nuclear antigens (recognize self-antigens as foreign) and the antibodies bind to the antigens, circulating antigen-antibody (Ag-Ab) complexes are then formed. There is also evidence to support that patients who have autoantibodies to C1q have more active and severe lupus nephritis.<sup>4,6</sup>



**Figure 5.** Endothelial cell with tubuloreticular body (inclusion) present near nucleus (inclusion indicated by red arrow; transmission electron microscopy, approximately original magnification,  $\times 15\ 000$ ).

Renal injury in lupus nephritis is mediated through deposition of Ag-Ab complexes within the glomeruli, through a type III hypersensitivity reaction.<sup>5</sup> Specifically, deposition of circulating Ag-Ab complexes that have formed elsewhere (outside of the glomerulus) typically prompts an inflammatory response within the glomerulus, which leads to glomerular injury. This inflammatory response involves activation of the complement pathway (classical), which can promote direct glomerular injury and prompt influx of inflammatory cells into glomeruli, thereby indirectly contribute to glomerular damage.<sup>4</sup> When the C1 complex binds the Ig portion of the immune complexes in the glomerulus, C3b is ultimately produced, which serves as an opsonin to promote clearance of the immune complexes from the glomerulus.<sup>6,7</sup> This binding of complement also results in the production of chemotactic factors, including C5a, which recruit inflammatory cells to the kidney (glomerulus). The action of these inflammatory cells can produce direct destruction through the release of enzymes and production of reactive oxygen species.<sup>6,7</sup> There is also some evidence to suggest that the alternative complement pathway plays a role in the pathogenesis of lupus nephritis.<sup>8</sup>

### *Describe Some Morphological Features of Immune Complex-Mediated Glomerulonephritis (for Example, in Lupus Nephritis) as They Relate to the Pathophysiologic Mechanism*

Since the kidney is a vascular organ and serves as a filter, the Ag-Ab complexes become localized to different parts of the glomerulus (mesangial, subendothelial, and subepithelial), depending upon the characteristics of the Ag-Ab complexes and hemodynamic factors within the glomerulus. Given their nature, these complexes will typically be manifested on immunofluorescence as granular deposits since they are aggregates of already-formed Ag-Ab complexes that lodge in the

**Table 2.** ISN/RPS 2003: Classification of LN.<sup>5</sup>

Class	Glomerular Hypercellularity	Associated Light Microscopic Findings	Immunofluorescence Features*	Location of Electron-Dense Deposits
Class I: minimal mesangial LN	None or minimal	None	Mesangial deposits	Mesangial (rare)
Class II: mesangial proliferative LN	Yes; mesangial	None	Mesangial deposits	Mesangial (some to many)
Class III: focal LN	Yes; segmental or endocapillary	Focal glomerular involvement† (<50% glomeruli)	Focal capillary wall and mesangial deposits	Focal subendothelial and mesangial
Class IV: diffuse LN	Yes; endocapillary	Diffuse glomerular involvement † (>50% glomeruli)	Diffuse capillary wall and mesangial deposits	Diffuse subendothelial and mesangial
Class V: membranous LN	None or minimal	Global or segmental capillary wall thickening	Finely granular, capillary wall deposits	Subepithelial and mesangial
Class IV: advanced sclerosing LN	Variable	More than 90% of glomeruli globally sclerosed	Variable	Variable

Abbreviation: LN, lupus nephritis.

\* All classes typically have immunoglobulin (IgG, IgM, IgA,  $\kappa$ , and  $\lambda$ ) and complement (C3, C1q) components deposited within the glomeruli, with a granular morphology. A differentiating feature is the location of these deposits.

† Class III/IV LN show varying degrees of endocapillary hypercellularity, inflammatory cell infiltration (neutrophils), karyorrhexis, fibrin deposition, and hyaline pseudothrombi. Crescents and wire loops may be present, more often in class IV. Diffuse and global involvement is often more evident in class IV.

glomerulus. By electron microscopy, these Ag-Ab complexes are electron-dense and aggregate in clumps or groups in various locations.<sup>3</sup>

In order to explain how immune complex-mediated glomerulonephritis can present differently in different lupus patients, a few examples follow, noting that Table 2 briefly summarizes the WHO classification scheme for lupus nephritis.

- Sometimes, these Ag-Ab complexes lodge within the mesangium and do not elicit a significant inflammatory response (eg, in class II lupus nephritis).
- In other cases, these Ag-Ab complexes lodge in a sub-endothelial location and prompt an inflammatory response, as in the patient presented in this case. In these circumstances, proliferation by mesangial or endothelial cells (or even visceral or parietal epithelial cells) promotes a hypercellular appearance in a segment of (segmental) or the entire glomerulus (global). Endothelial cell swelling may also contribute to the “full” appearance of glomeruli in these cases.<sup>9</sup> In such instances, chemotactic factors that are released from Ag-Ab complex activation (through complement) also recruit inflammatory cells into the glomerulus, further causing inflammation and potential glomerular damage (necrosis and fibrin deposition).<sup>6</sup> This response is relatively typical of class III and class IV lupus nephritis.
- Finally, in some cases, although not in this patient’s case, the circulating immune complexes are primarily deposited on the subepithelial side of the GBM, resembling a primary idiopathic membranous nephropathy. In these instances, the inflammatory response is less profound, and patients may present with more proteinuria and less inflammatory changes (more nephrotic than nephritic picture). This is typical of class V lupus nephritis.<sup>3</sup>

Regardless of the class or histologic type of lupus nephritis, a unifying pathophysiologic mechanism is one of the deposition of already-formed, previously circulating Ag-Ab complexes within the glomerulus.

Although this patient has immune complex-mediated lupus nephritis (glomerular injury), other manifestations of renal injury can be seen in systemic lupus erythematosus, including vascular lesions, tubulointerstitial injury, and thrombotic microangiopathy, as mentioned previously.<sup>2</sup> These forms of renal injury contribute to varying degrees to the development of chronic kidney disease in lupus patients. In addition, treatment-related renal injury should also be considered in patients with longstanding lupus and a history of long-term therapy.<sup>10</sup>

### **Compare and Contrast the Mechanisms of Immune Complex-Mediated Glomerulonephritis and Antibody-Mediated Glomerulonephritis**

As mentioned previously, in immune complex-mediated glomerulonephritis (lupus nephritis as an example), the deposition

of circulating, already-formed Ag-Ab complexes within the glomerulus incites glomerular dysfunction and injury. The degree of dysfunction and patterns of glomerular injury depend upon the location of immune complex deposits and the extent of activation of inflammatory pathways.

In contrast, injury in antibody-mediated glomerulonephritis (anti-GBM antibody-mediated glomerulonephritis as an example) is due to the formation of an autoantibody to antigens that are present within the GBM. The autoantibodies circulate systemically and then bind to the GBM antigen *in situ* (within the kidney). This underlying pathogenetic mechanism affects the way anti-GBM antibody-mediated disease is manifested on the microscopic evaluation, specifically with a linear morphology detected along GBMs on immunofluorescence microscopy (vs a granular morphology detected in immune complex-mediated diseases).

### **What Therapeutic Approaches Are Employed in Treating Lupus Nephritis? Why?**

The classification of a patient’s lupus nephritis through renal biopsy is typically used to guide therapy.<sup>4</sup> Ongoing efforts by clinicians worldwide are focused on continuing to revise and standardize the classification and nomenclature used to diagnose lupus nephritis, through evidence-based diagnostic, therapeutic, and outcome studies.<sup>2,9</sup> It is important to prevent renal injury, to the greatest extent possible, since the development of chronic kidney disease in patients with systemic lupus erythematosus is linked to higher mortality risk.<sup>8</sup>

Once the severity and activity of lupus nephritis and the extent of chronic damage to the kidney has been determined,<sup>9</sup> anti-inflammatory and immunosuppressive agents are a mainstay of therapy. Anti-inflammatory agents can help attenuate the immune response to the deposition of Ag-Ab complexes in the kidney and other affected organs, thereby reducing inflammation and hopefully preventing long-term organ damage. Corticosteroids should be used judiciously, however, since they can also cause significant harmful effects.<sup>8</sup> More intense immunosuppression serves to quickly attenuate inflammation during a flare of lupus nephritis (induction), while lower dose immunosuppression over a longer term can help a patient maintain a flare-free state.<sup>8,10</sup> Immunosuppressive agents can help decrease inflammation and attenuate the autoimmune response overall, thereby decreasing the number of circulating Ag-Ab complexes that form and that are available to be deposited within the kidney and other organs.<sup>4</sup>

### **Teaching Points**

- Immune-mediated mechanisms are a significant cause of pathologic kidney injury.
- Clinical history and physical findings inform development of an appropriate differential diagnosis for patients with renal disorders. They also aid in categorizing and classifying renal disease in a given patient.

- Often, results of laboratory diagnostic studies (serum electrolyte studies, BUN, and serum creatinine, comprehensive metabolic profile, complete blood count, and urinalysis) support an appropriate diagnostic evaluation of patients with renal disorders.
- Nephritic syndrome is typically defined by the presence of hypertension, hematuria, red blood cell casts in urine, elevated BUN/serum creatinine (azotemia), and oliguria. Proteinuria may be present to varying degrees.
- Renal biopsy is helpful and often indicated to determine the nature and extent of renal injury in patients with renal disorders, including glomerular disorders that present with nephritic or nephrotic syndrome.
- Disorders causing nephritic syndrome typically incite damage to glomeruli through immune-mediated mechanisms. Immune complexes (Ag-Ab complexes) that circulate in plasma may deposit within the glomeruli. In contrast, circulating antibodies that are formed against native intraglomerular antigens may bind to the antigen within the kidney (*in situ*). In either case, glomerular dysfunction may ensue.
- Deposition of Ag-Ab complexes within glomeruli and formation of Ag-Ab complexes within glomeruli can both trigger inflammatory pathways that cause proliferation of intraglomerular cells and recruit inflammatory cells into glomeruli. This can result in significant glomerular injury, up to and including crescent formation and glomerular necrosis.
- In lupus nephritis, immune complexes may deposit in the glomerular mesangium, subendothelium, and/or subepithelial space. The location and extent of deposition of these immune complexes affect the light, immunofluorescence, and electron microscopic findings for a given patient. The location and extent of immune complex deposition also importantly affect the nature and severity of the patient's clinical presentation.
- Regardless of location, the immune complexes in lupus nephritis (and in most cases of immune complex-mediated disease) have a granular morphology when detected by immunofluorescence. This is in contrast to anti-GBM antibody-mediated glomerulonephritis, in which a linear staining pattern is noted along GBMs by immunofluorescence.
- Since immune mechanisms underlie many glomerular lesions, anti-inflammatory agents and immunosuppressive therapy are often used to treat these glomerular disorders.


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## ORCID iD

Kathleen A. Jones  <https://orcid.org/0000-0001-8420-1894>

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