Crescentic Lupus Nephritis

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- Renal involvement is common in patients with SLE, it occurs in approximately 60 percent of patients.
- The clinical presentation of lupus nephritis is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive GN, and the occurrence of kidney disease is the most important predictor of morbidity and mortality in patients with SLE.

Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices

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Class I: Minimal mesangial lupus nephritis

- Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.

Class II: Mesangial proliferative lupus nephritis

- Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits.
- A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.

Class III: Focal lupus nephritis*

- Active or inactive focal, segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.

Class IV: Diffuse lupus nephritis†

- Active or inactive diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations.
- This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.

Class V: Membranous lupus nephritis

- Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations.
- Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed.
- Class V lupus nephritis may show advanced sclerosis.

Class VI: Advanced sclerotic lupus nephritis

- ≥90% of glomeruli globally sclerosed without residual activity.

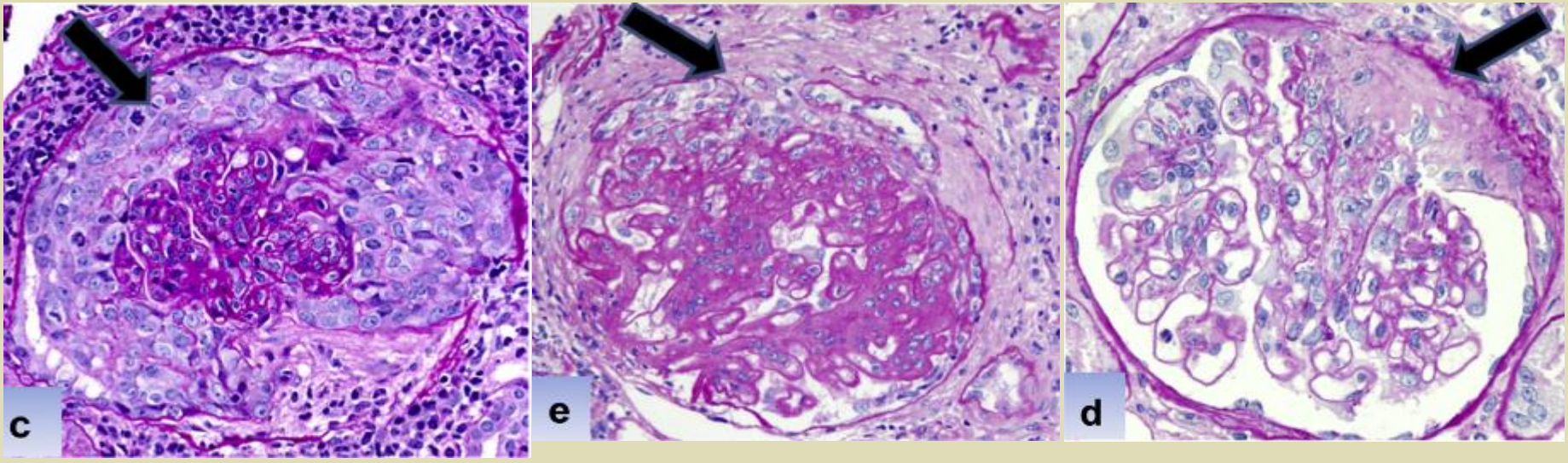
- The term “crescent” is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells:

1. epithelial proliferation
2. monocytes and/or macrophages
3. variable mixture of cells
4. Fibrin and fibrous matrix

- The ISN/RPS criterion of a crescent involving :

1. 25% or more of the glomerular capsular circumference
2. more than 2 cell layers

- Some glomeruli may have more than 1 type of crescent.



c) cellular crescent, (e) fibrocellular crescent, d) fibrous crescent,

Update on Lupus Nephritis: Core Curriculum 2020

Samir V. Parikh, Salem Almaani, Sergey Brodsky, and Brad H. Rovin

Systemic lupus erythematosus is a multisystem autoimmune disease that commonly affects the kidneys. Lupus nephritis (LN) is the most common cause of kidney injury in systemic lupus erythematosus and a major risk factor for morbidity and mortality. The pathophysiology of LN is heterogeneous. Genetic and environmental factors likely contribute to this heterogeneity. Despite improved understanding of the pathogenesis of LN, treatment advances have been few and risk for kidney failure remains unacceptably high. This installment in the Core Curriculum of Nephrology provides an up-to-date review of the current understanding of LN epidemiology, pathogenesis, diagnosis, and treatment. Challenging issues such as the management of LN in pregnancy, timing of transplantation, and the evolving role of corticosteroid use in the management of LN are discussed. We review the currently accepted approach to care for patients with LN and highlight deficiencies that need to be addressed to better preserve long-term kidney health and improve outcomes in LN.

Complete author and article information provided at end of article.

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Epidemiology

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that predominantly affects women of childbearing age and often involves the kidneys. Lupus nephritis (LN) occurs in ~50% of patients with SLE and is the most common, but not the only, cause of kidney injury in SLE. Men with SLE tend to have more aggressive disease with higher rates of renal and cardiovascular involvement and are more likely to

Mortality associated with lupus is significantly higher in those with LN compared with those without LN, and death directly attributable to kidney disease occurs in 5% to 25% of patients with proliferative LN within 5 years of onset. Furthermore, 10% to 30% of patients with LN progress to kidney failure requiring kidney replacement therapy (KRT). Patients with proliferative forms of LN (class III, IV, or III/IV + V) are at highest risk for requiring KRT. Achieving a complete clinical

The Core Curriculum aims to give trainees in nephrology a

Table 2. 2003 ISN/RPS LN Histopathologic Classification, NIH Injury Indexes and Proposed Changes

Classification	Category	Description	Proposed Modification
ISN/RPS	Class I	Normal glomeruli by LM, mesangial immune complexes on IF or EM	No changes recommended
ISN/RPS	Class II	Pure mesangial hypercellularity with mesangial immune deposits; mesangial matrix expansion seen by LM	Definition for mesangial hypercellularity is provided; ≥4 nuclei surrounded by matrix in the mesangial area
ISN/RPS	Class III	Focal segmental or global disease involving <50% of all glomeruli III (A): active lesions III (A/C): active and chronic lesions III (C): chronic inactive lesions	1. Endocapillary proliferation is replaced by endocapillary hypercellularity 2. Crescent >10% of Bowman capsule circumference (cellular crescent, >75% cells, <25% fibrous matrix; fibrocellular crescent, 25%-75% cells and fibrin, remainder is fibrous matrix; fibrous crescent > 75% fibrous matrix, <25% cells) 3. Adhesion defined as an area of isolated continuity of ECM material between tuft and capsule; fibrinoid necrosis is fibrin associated with basement membrane disruption and/or lysis of mesangial matrix 4. Eliminate global and segmental designations from class IV LN 5. Indicate whether tubulointerstitial lesions occur in presence or
ISN/RPS	Class IV	Diffuse segmental (S) or global (G) disease involving ≥50% of all glomeruli IV-S: ≥50% glomeruli with segmental lesions IV-G: ≥50% glomeruli with global lesions IV-S(A), IV-G(A): active lesions IV-S(A/C), IV-G(A/C): active and chronic lesions IV-S(C), IV-G(C): chronic inactive lesions	

NIH activity indexes	a) Glomerular endocapillary hypercellularity b) Glomerular leukocyte infiltration c) Glomerular fibrinoid necrosis, karyorrhexis d) Glomerular subendothelial deposits-wire loop lesions e) Glomerular cellular crescents f) Interstitial inflammation	Active lesions scoring: 0-24 Each lesion scored 0-3: 1+: <25% of glomeruli 2+: 25%-50% of glomeruli 3+: >50% of glomeruli involved For interstitial lesions: 1+: <25% interstitial leukocytes 2+: 25%-50% interstitial leukocytes 3+: >50% interstitial leukocytes Fibrinoid necrosis and crescents are double the weight (0-3 × 2)	Modified NIH injury indexes reported with each biopsy and replaces active and chronic designations for proliferative (class III/IV lesions) Active Lesion Proposed Changes: 1. Separate fibrinoid necrosis from karryhorhexis 2. Fibrocellular recognized with cellular crescent as active lesion 3. Leukocyte infiltration is removed
NIH chronicity indexes	a) Glomerular sclerosis b) Glomerular fibrous crescents c) Tubular atrophy d) Interstitial fibrosis	Chronic lesions scoring: 0-12 Each lesion scored 0-3: 1+: <25% of glomeruli 2+: 25%-50% of glomeruli 3+: >50% of glomeruli For tubulointerstitial lesions: 1+: <25% tubular atrophy and/or interstitial fibrosis 2+: 25%-50% tubular atrophy and/or interstitial fibrosis 3+: >50% tubular atrophy and/or interstitial fibrosis	Modified NIH injury indexes reported with each biopsy and replaces active and chronic designations for proliferative (class III/IV) lesions Chronic lesions: create a total glomerular sclerosis score (global + segmental)

Abbreviations: ECM, extracellular matrix; EM, electron microscopy; GBM, glomerular basement membrane; IF, immunofluorescence; ISN/RPS, International Society of Neurology/Renal Pathology Society; LM, light microscopy; LN, lupus nephritis; NIH, National Institutes of Health.

Redefining lupus nephritis: clinical implications of pathophysiologic subtypes

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Abstract | Systemic lupus erythematosus (SLE) is associated with a broad spectrum of clinical and immunologic manifestations, of which lupus nephritis is the most common cause of morbidity and mortality. The development of nephritis in patients with SLE involves multiple pathogenic pathways including aberrant apoptosis, autoantibody production, immune complex deposition and complement activation. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system for lupus nephritis was widely accepted with high intraobserver and interobserver concordance to guide therapeutic strategy and provide prognostic information. However, this classification system is not based on the underlying disease

- The mechanisms that drive the formation of crescents in lupus nephritis are not fully understood.
- A 2009 study showed that natural killer T cells accentuated disease severity in a model of crescentic glomerulonephritis.
- Thus, targeting CX3CL1/CX3CR1 pathway, which regulates the activation of invariant natural killer T cells, might represent a promising treatment approach with fewer adverse effects than general immunosuppressive therapies .

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REVIEW ARTICLE

CX3CL1/CX3CR1 Axis, as the Therapeutic Potential in Renal Diseases: Friend or Foe?

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Abstract: The fractalkine receptor chemokine (C-X3-C motif) receptor 1 (CX3CR1) and its highly selective ligand CX3CL1 mediate chemotaxis and adhesion of immune cells, which are involved in the pathogenesis and progression of numerous inflammatory disorders and malignancies. The CX3CL1/CX3CR1 axis has recently drawn attention as a potential therapeutic target because it is involved in the ontogeny, homeostatic migration, or colonization of renal phagocytes. We performed a Medline/PubMed search to detect recently published studies that explored the relationship between the CX3CL1/CX3CR1 axis and renal diseases and disorders, including diabetic nephropathy, renal allograft rejection, infectious renal diseases, IgA nephropathy, fibrotic kidney disease, lupus nephritis and glomerulonephritis, acute kidney injury and renal carcinoma. Most studies demonstrated its role in promoting renal pathopoiesis; however, several recent studies showed that the CX3CL1/CX3CR1 axis could also reduce renal pathopoiesis. Thus, the CX3CL1/CX3CR1 axis is now considered to be a double-edged sword that could provide novel perspectives into the pathogenesis and treatment of renal diseases and disorders.

Keywords: Fractalkine, CX3CL1, Chemokine receptor, CX3CR1, Renal disease, Kidney transplantation.

1. INTRODUCTION

1.1. CX3CL1/CX3CR1 Axis

Chemokine (C-X3-C motif) Receptor 1 (CX3CR1) is ubiquitously expressed in most tissues on mononuclear and circulatory lymphatic leucocytes [1]. Fractalkine, also known

granzyme B and death-signaling Fas ligand, which could help leukocytes undergo transendothial migration to infiltrate into inflamed tissues [5].

In humans, CX3CL1 is mainly expressed on the tubular epithelium, especially during inflammation. Concomitantly

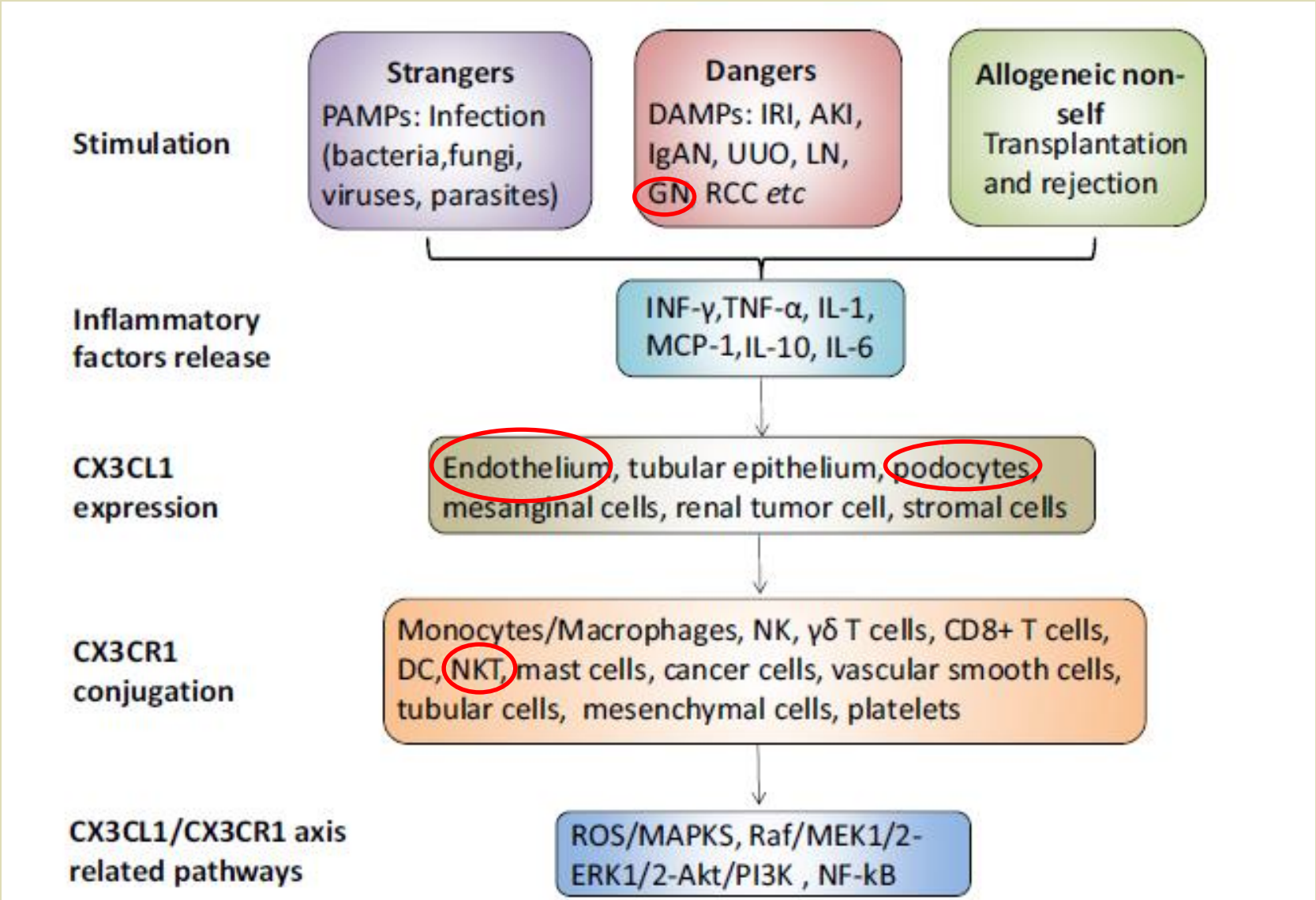
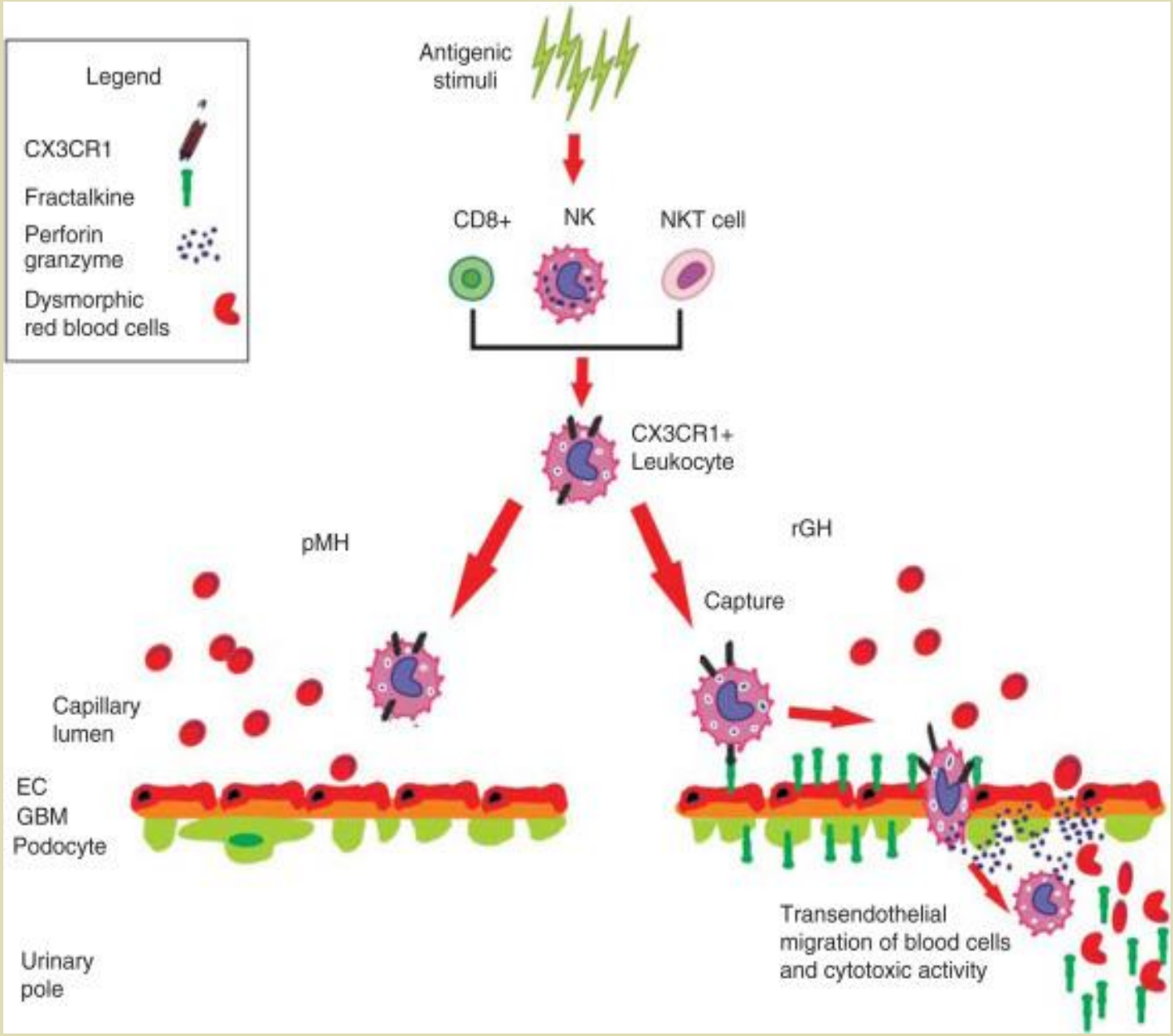
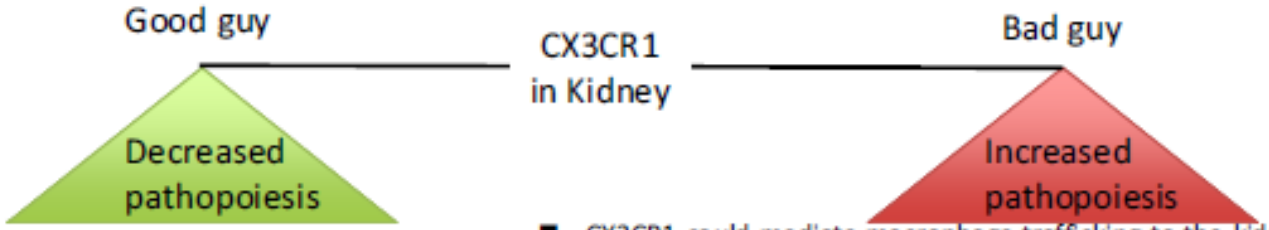


Fig. (1). The general process of CX3CL1/CX3CR1 axis cascade. (1) Stimulation process: stranger pattern (microbes), danger pattern (injuries) and allogeneic non-self pattern stimulate the kidney. (2) Inflammatory factors release process: INF-γ,TNF-α, IL-1, MCP-1, IL-10, IL-6 are produced by (1). (3) CX3CL1 expression process: fractalkine is produced and increasingly expresses by endothelium, tubular epithelium, podocytes, mesangial cells, renal tumor cell, and stromal cells. (4) CX3CR1 conjugation process: fractalkine would conjugate with CX3CR1+ cells such as monocytes/macrophages, NK, γδ T cells, $CD8^+$ T cells, DC, NKT, mast cells, cancer cells, vascular smooth cells,


Legend
CX3CR1
Fractalkine
Perforin granzyme
Dysmorphic red blood cells
Antigenic stimuli
CD8+
NK
NKT cell
CX3CR1+ Leukocyte
pMH
rGH
Capture
Capillary lumen
EC
GBM
Podocyte
Urinary pole
Transendothelial migration of blood cells and cytotoxic activity



- CX3CR1 reduced the inflammation-induced proliferation of TGF-β producing renal macrophages (*eg.* UUO and fibrosis)
- CX3CR1 helped to synthetize and secrete anti-inflammatory mediators, such as IL-1ra and prostaglandin E2 (*eg.* Sepsis)
- Sepsis could suppress CX3CR1 expression via NF-kB pathway (*eg.* Sepsis)
- CX3CR1 attracted NK cell to eliminate tumor cells (*eg.* RCC)

- CX3CR1 could mediate macrophage trafficking to the kidney (*eg.* IRI)
- CX3CR1 promoted profibrotic macrophages survival, maintenance and monocytes migration or differentiation (*eg.* UUO and fibrosis, Lupus nephritis, allograft rejection)
- CX3CR1 helped monocytes interact with neutrophils to produce proinflammatory cytokines like TNF-α and IL-1 (*eg.* Glomerular injury)
- CX3CL1/CX3CR1 endothelium is a key site of CMV latency and reactivation (*eg.* CMV infection)
- CX3CR1 helped CD1c+ DC produce TGF-β and collagen type 1(*eg.* Fibrosis)
- CX3CR1 helped tumor cells adhesion via PI3K/Akt and MEK1/2/ ERK1/2 signaling pathways (*eg.* RCC)
- CX3CR1 promoted mesangial ECM synthesis (*eg.* diabetic nephropathy)
- CX3CR1 helped leukocytes release perforin granzyme to cause transendothelial migration of blood cells and cytotoxic activity (*eg.* IgA nephropathy)

Fig. (3). CX3CR1 as enhancers and regulators of pathopoiesis in kidney disease.

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www.lupus-journal.com

REVIEW

Antineutrophil cytoplasmic autoantibodies in systemic lupus erythematosus

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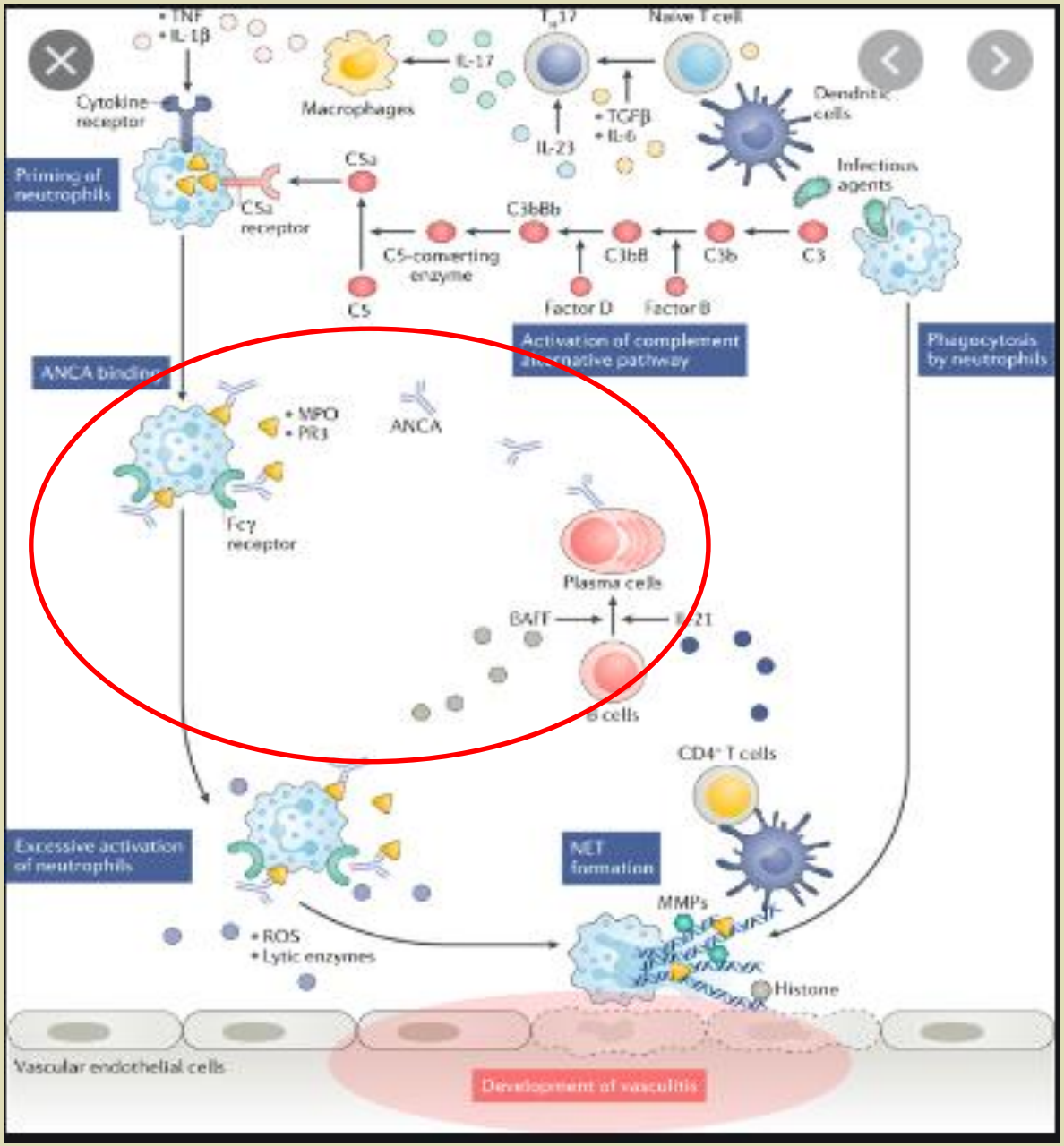
Although antineutrophil cytoplasmic antibodies (ANCA) were first associated with the primary vasculitides, it is now clear that 15–20% of patients with lupus have detectable ANCA. In this short review we confirm that the major link is with perinuclear ANCA (pANCA) but not cytoplasmic ANCA (cANCA). ANCA to myeloperoxidase are associated with drug-induced lupus. There may be a link between pANCA levels and disease activity in some patients although the links to specific organ involvement are not proven. ANCA in lupus must be interpreted cautiously with particular attention

- Some studies reported a correlation between the serum ANCA status (atypical perinuclear ANCA, such as anti-cathepsin G antibodies) and the presence of crescents in patients with lupus:
- ANCA bind directly to vascular endothelium containing neutrophil-released myeloperoxidase (MPO) and proteinase 3 (PR3), to release granules and generate ROS.
- Apoptosis of neutrophils leading to the expression of antigens for ANCA and further ANCA binding.


• TNF
• IL-1β
Cytokine receptor
Priming of neutrophils
Macrophages
IL-17
T_H17
Naive T cell
Dendritic cells
• TGFβ
• IL-6
IL-23
Infectious agents
C5a
C5a receptor
C3bBb
C5-convertase enzyme
C3bB
C3b
C3
C5
Factor D
Factor B
Activation of complement alternative pathway
Phagocytosis by neutrophils
ANCA binding
• MPO
• PR3
ANCA
Fcγ receptor
Plasma cells
BAFF
IL-21
B cells
CD4+ T cells
Excessive activation of neutrophils
NET formation
MMPs
• ROS
• Lytic enzymes
Histone
Vascular endothelial cells
Development of vasculitis

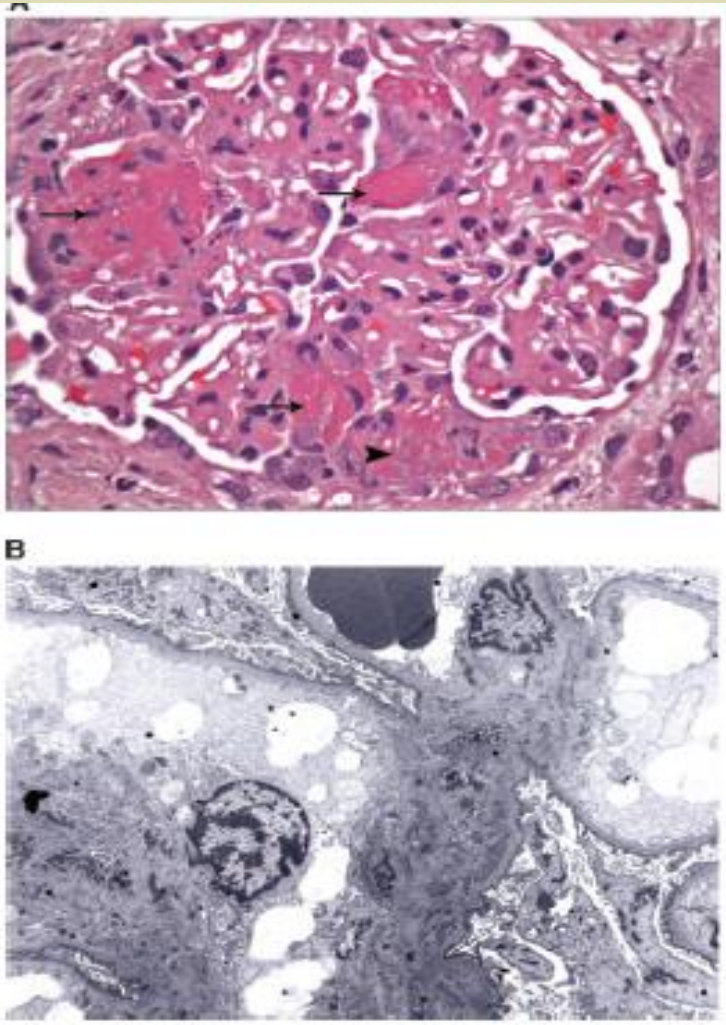


Figure 1. Lupus nephritis (LN) III with antineutrophil cytoplasmic antibody (ANCA)-associated necrotizing and crescentic glomerulonephritis. (A) A glomerulus from patient 10 exhibits three separate foci of fibrinoid necrosis (arrows), one of which is associated with a segmental small cellular crescent (arrowhead). Mild global mesangial proliferation and expansion are seen. (B) Ultrastructural evaluation reveals solely mesangial electron-dense deposits. No subendothelial or subepithelial deposits were identified. Magnifications: ×600 in A (hematoxylin and eosin); ×3000 in B.

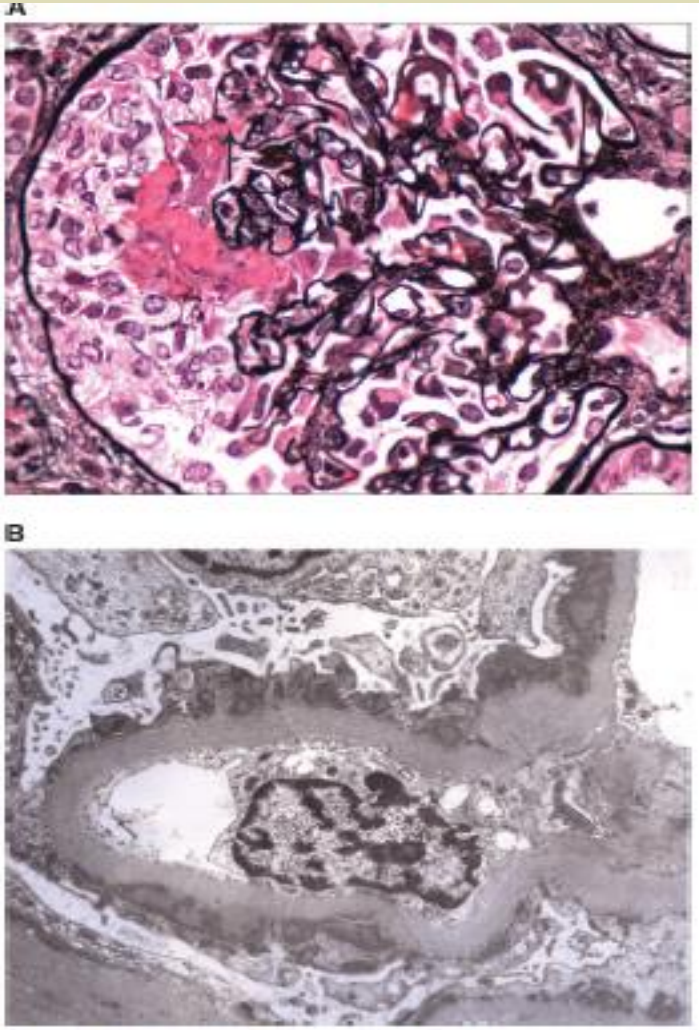


Figure 3. LN V with ANCA-associated necrotizing and crescentic glomerulonephritis. (A) A glomerulus from patient 2 exhibits segmental fibrinoid necrosis, rupture of the glomerular basement membrane (arrow), and an overlying cellular crescent. There is also mild thickening of the glomerular basement membrane. (B) Ultrastructural evaluation reveals global subepithelial electron-dense deposits with focal small intervening spikes. No subendothelial deposits were identified. Magnifications: ×600 in A (Jones methenamine silver); ×6000 in B.

Positive antineutrophil cytoplasmic antibody serology in patients with lupus nephritis is associated with distinct histopathologic features on renal biopsy

OPEN

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Class IV-S lupus nephritis is often associated with more necrosis and fewer subendothelial immune deposits compared to class IV-G lupus nephritis, suggestive of necrotising glomerular inflammation found in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. ANCAs are present in a significant proportion of patients with lupus nephritis. Here we determine whether ANCAs are associated with distinct clinical and histopathologic features of lupus nephritis. Thirty-two ANCA-positive biopsies were compared to 222 ANCA-negative biopsies from patients with lupus nephritis. The majority (82%) of ANCA-positive patients had antimyeloperoxidase antibodies. Class IV-S lupus nephritis and glomerular necrosis were significantly more common (36% vs. 16% and 35% vs. 15%, respectively) and isolated

KEYWORDS: ANCA; glomerulonephritis; renal pathology; systemic lupus erythematosus

The classification of lupus nephritis (LN) was revised with the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification in 2003,[1] which subdivides Class IV LN into segmental (IV-S) and global (IV-G) subclasses based on whether endocapillary involvement in diffuse proliferative LN is predominantly segmental (involving <50% of the glomerular tuft) or global

- 32 ANCA-positive biopsies were compared to 222 ANCAnegative biopsies from patients with lupus nephritis.
- The majority (82%) of ANCA-positive patients had antimyeloperoxidase (MPO)antibodies.
- Class IV-S lupus nephritis and glomerular necrosis were significantly more common(36% vs. 16% and 35% vs. 15%, respectively).
- ANCA+ patients with LN tended to have a more segmental and necrotizing Pattern of immune deposits.

- ANCA-positive patients had significantly higher :

1. dsDNA titers (335u/ml vs. 52u/ml),
2. lower serum C4 (0.125g/L vs. 0.15g/L)
3. higher serum creatinine (130mmol/L vs. 84mmol/L) at the time of biopsy.

- The lower serum C4 in this group suggests that they had increased consumption of complement components by circulating immune complexes.
- It is therefore not surprising that these patients had evidence of immune complex deposition on renal biopsy rather than a pauci-immune phenotype.

BASIC RESEARCH www.jasn.org

The IL-23/Th17 Axis Contributes to Renal Injury in Experimental Glomerulonephritis

Hans-Joachim Paust,* Jan-Eric Turner,* Oliver M. Steinmetz,* Anett Peters,* Felix Heymann,† Christoph Hölscher,‡ Gunter Wolf,§ Christian Kurts,† Hans-Willi Mittrücker,‖ Rolf A.K. Stahl,* and Ulf Panzer*

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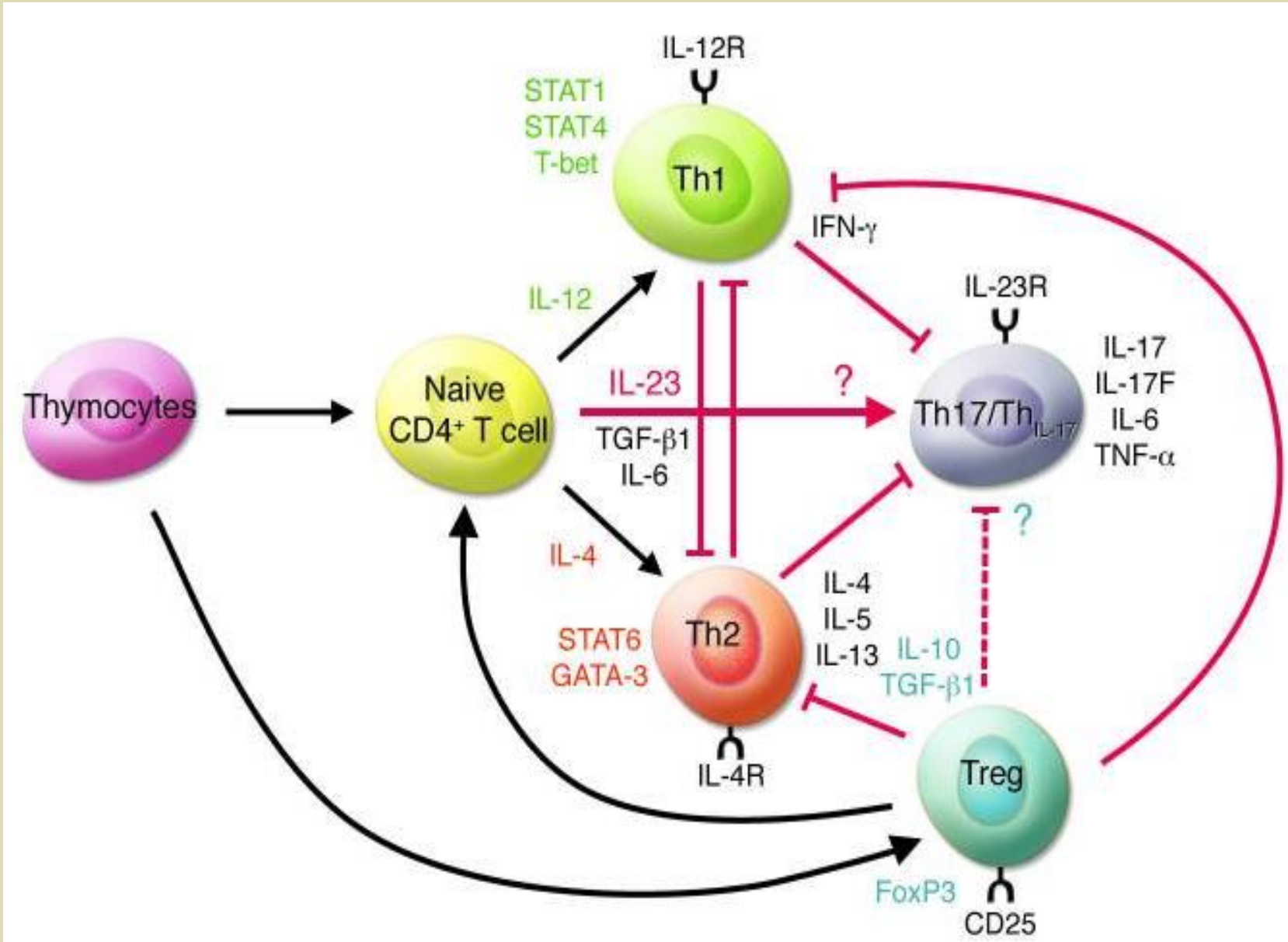
ABSTRACT

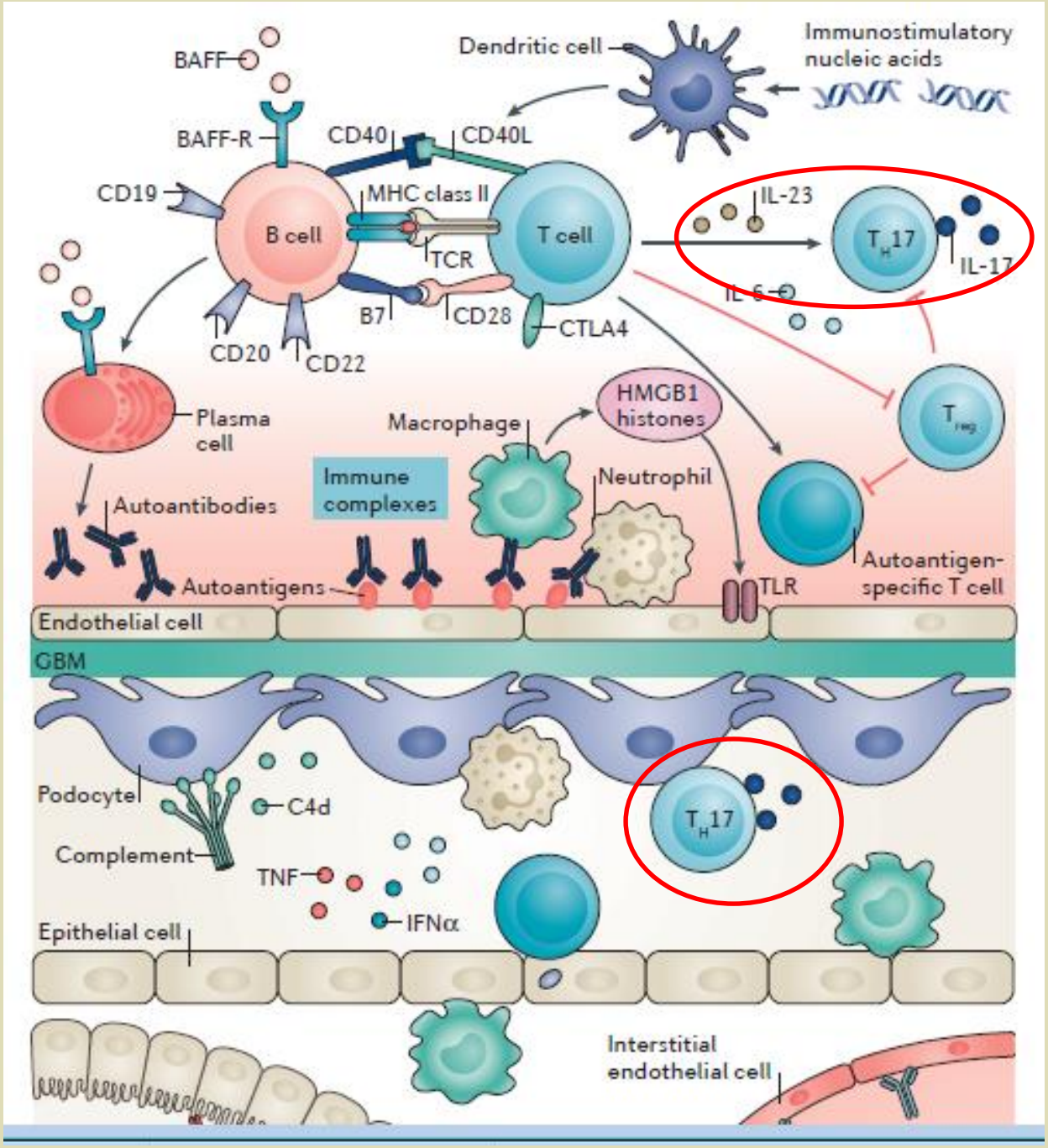
T cells infiltrate the kidney in both human and experimental glomerulonephritis, and several lines of evidence indicate that T cell-mediated tissue damage plays an important role in the immunopathogenesis of renal inflammatory diseases. However, the functions of the different T cell subsets, particularly the recently identified interleukin-17 (IL-17)-producing T cells (Th17 cells), are incompletely understood in glomerulonephritis. Here, we identified renal IL-17-producing T cells in the T cell-mediated model of nephrotoxic nephritis in mice. *In vitro*, IL-17 enhanced the production of the proinflammatory chemokines CCL2/MCP-1, CCL3/MIP-1α, and CCL20/LARC, which are implicated in the recruitment of T cells and monocytes, in mouse mesangial cells. To determine the function of Th17 cells in renal inflammation, we induced nephrotoxic nephritis in IL-23 p19$^{-/-}$ mice, which have reduced numbers of Th17 cells, and in IL-17$^{-/-}$ mice, which are deficient in the effector cytokine IL-17 itself. In comparison with nephritic wild-type mice, IL-23 p19$^{-/-}$ mice demonstrated less infiltration of Th17 cells, and both IL-23 p19$^{-/-}$ and IL-17$^{-/-}$ mice developed less severe nephritis as measured by renal function, albuminuria, and frequency of glomerular crescent formation. These results demonstrate that the IL-23/IL-17 pathway significantly contributes to renal tissue injury in experimental glomerulonephritis. Targeting the IL-23/Th17 axis may be a promising therapeutic strategy for the treatment of proliferative and crescentic glomerulonephritis.

J Am Soc Nephrol 20: 969–979, 2009. doi: 10.1681/ASN.2008050556

- The Th1/Th2 paradigm has been challenged by identification of a third IL-17-producing CD4 effector T cell subset termed Th17.
- IL-23, a member of the IL-12 family, is dispensable for differentiation but important for Th17-cell expansion.
- Th17 cells appear to be critical to the enhancement of host protection against extracellular bacteria and fungi, which are not efficiently cleared by Th1 and Th2 responses.


IL-12R
STAT1
STAT4
T-bet
Th1
IFN-γ
IL-12
IL-23R
IL-17
IL-17F
IL-6
TNF-α
Thymocytes
Naive
CD4+ T cell
IL-23
?
TGF-β1
IL-6
Th17/Th17
IL-4
?
IL-4
IL-5
IL-13
STAT6
GATA-3
Th2
IL-10
TGF-β1
IL-4R
Treg
FoxP3
CD25

- Animal models studies have also demonstrated that the IL-23/IL-17 pathway contributes to renal injury in experimental GN ; thus, blocking IL-23 production and/or the subsequent recruitment of IL-17 producing effector T cells can be a therapeutic method.
- IL-17RE was highly expressed by CD4+ TH17 cells, and loss of IL-17RE expression prevented the TH17 responses and subsequent tissue injury in crescentic GN.


BAFF
BAFF-R
CD19
B cell
CD20
CD22
CD40
CD40L
MHC class II
TCR
B7
CD28
CTLA4
T cell
Dendritic cell
Immunostimulatory nucleic acids
IL-23
T_H17
IL-17
IL-6
T_{reg}
Plasma cell
Autoantibodies
Autoantigens
Immune complexes
Macrophage
HMGB1 histones
Neutrophil
TLR
Autoantigen-specific T cell
Endothelial cell
GBM
Podocyte
C4d
Complement
TNF
IFNα
Epithelial cell
Interstitial endothelial cell

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original article

Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis

Feng Yu[1,2,3], Ying Tan[1,2,3], Gang Liu[1,2,3], Su-xia Wang[1,2,3], Wan-zhong Zou[1,2,3] and Ming-hui Zhao[1,2,3]

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There are few clinicopathologic and outcome data on patients with crescentic lupus nephritis, therefore, we determined factors of the disease by retrospectively reviewing the records of 327 patients diagnosed with lupus nephritis. Of these, 152 cases were regrouped as class IV-G, including 33 patients with crescentic glomerulonephritis. Significantly, all patients with crescentic glomerulonephritis had acute kidney injury as compared with only about a quarter of the patients without the disease. On pathological evaluation, activity scores, chronicity indexes, relapse rates,

Renal involvement is common in patients with systemic lupus erythematosus (SLE). The clinical presentation of lupus nephritis is highly variable, ranging from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis, and the occurrence of kidney disease is the most important predictor of morbidity and mortality in patients with SLE.[1]

Concerning the classification of lupus nephritis, a new classification was proposed by the International Society of Nephrology and Renal Pathology Society (ISN/RPS) in 2003[2] to rectify some of the problems that have arisen over the

- In 327 patients with lupus nephritis, 152 cases were regrouped as class IV-G, including 33 (21.7%) patients with crescentic GN (10.1% total LN).
- In Crescentic GN group:

❖ all of theses patients had AKI as compared with only about a quarter of the patients without the disease.

❖ Activity scores, chronicity indexes, relapse rates, and the frequency of positive serum ANCA were each significantly higher.

❖ complete remission rates and renal outcomes, over a mean follow-up of 4 years, were significantly poorer in patients with crescentic glomerulonephritis.

- More interestingly, we identified lower levels of IgG, IgA, IgM, C3, C1q and fibrin in crescentic biopsy samples than in non-crescentic biopsy samples, suggesting further similarities between crescentic IV-G samples and ANCA vasculitis.

Laboratory data			
Number of patients	33	119	
Hemoglobin (mean ± s.d.) (g/l)	84.61 ± 19.46	95.03 ± 21.97	0.015
Urine protein (mean ± s.d.) (g/24 h)	6.25 ± 3.54	5.85 ± 3.89	0.598
Serum creatinine (mean ± s.d.) (mg/dl)	3.74 ± 2.68	1.61 ± 1.57	<0.001
Creatinine clearance rate (mean ± s.d.) (ml/min)	25.83 ± 26.28	64.52 ± 31.26	<0.001
Serum albumin (mean ± s.d.) (g/dl)	2.54 ± 0.67	2.71 ± 0.42	0.563
Positive ANA, *n* (%)	33 (100)	119 (100)	1.0
Positive anti-ds-DNA, *n* (%)	25 (75.8)	91 (76.5)	1.0
Positive anti-Sm, *n* (%)	5 (15.2)	27 (22.7)	0.471
Positive anti-SSA, *n* (%)	14 (42.4)	53 (44.5)	0.846
Positive anti-SSB, *n* (%)	6 (18.2)	15 (12.6)	0.403
Positive anti-RNP, *n* (%)	4 (12.1)	36 (30.3)	0.044
Anti-cardiolipin antibody, *n* (%)	1/20 (5)	7/78 (9)	1.0
C3 (mean ± s.d.) (g/l)	0.38 ± 0.16	0.38 ± 0.16	1.0

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PAPER

Lupus nephritis: a challenging cause of rapidly progressive crescentic glomerulonephritis

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The outcomes of 32 lupus patients with rapidly progressive crescentic glomerulonephritis were studied. Lupus nephritis accounted for 51.6% (32/62) of all patients with biopsy proven rapidly progressive crescentic glomerulonephritis during a six year observation period that includes 961 consecutive native kidney biopsies. Median entry serum creatinine was 221 μmol/1. All patients received induction therapy with pulse methylprednisolone ($n=27$) or intravenous cyclophosphamide ($n=5$). Maintenance therapies included prednisolone alone (group 1), prednisolone plus intermittent pulse intravenous cyclophosphamide (IVCY) (group 2) and prednisolone plus daily oral cytotoxic drugs (group 3). Twelve patients eventually had uremia. Seven further patients died of infection during therapy. One patient still had renal insufficiency and twelve patients had favorable clinical outcome (serum creatinine < 200 μmol/1). Patients in group 3 were more likely to have favorable clinical outcome than group 2 ($P=0.01$; Fisher's exact test). Survival analysis found that the three year survival of 'group 2' was 27.6% while that of 'group 3' was 83.3%. Our results suggest that lupus nephritis is not an infrequent cause of crescentic glomerulonephritis.

- In this study, a high proportion of lupus (32/62 or 51.6%) as a cause of RPGN in all patients with biopsy proven crescentic GN.

❖ Their finding that the crescent score was not a significant predictor of renal outcome.

❖ Their results suggest that the renal prognosis of lupus patients who have only segmental crescent can be as bad as those with severe or extensive crescents.

❖ Incidence of oliguria in the patients (25%) was much high in patients with crescentic lupus.

❖ The incidence of hypertension in their crescentic lupus patients (78%) appears high.

Update on Lupus Nephritis: Core Curriculum 2020

Samir V. Parikh, Salem Almaani, Sergey Brodsky, and Brad H. Rovin

Systemic lupus erythematosus is a multisystem autoimmune disease that commonly affects the kidneys. Lupus nephritis (LN) is the most common cause of kidney injury in systemic lupus erythematosus and a major risk factor for morbidity and mortality. The pathophysiology of LN is heterogeneous. Genetic and environmental factors likely contribute to this heterogeneity. Despite improved understanding of the pathogenesis of LN, treatment advances have been few and risk for kidney failure remains unacceptably high. This installment in the Core Curriculum of Nephrology provides an up-to-date review of the current understanding of LN epidemiology, pathogenesis, diagnosis, and treatment. Challenging issues such as the management of LN in pregnancy, timing of transplantation, and the evolving role of corticosteroid use in the management of LN are discussed. We review the currently accepted approach to care for patients with LN and highlight deficiencies that need to be addressed to better preserve long-term kidney health and improve outcomes in LN.

Complete author and article information provided at end of article.

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Epidemiology

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that predominantly affects women of childbearing age and often involves the kidneys. Lupus nephritis (LN) occurs in ~50% of patients with SLE and is the most common, but not the only, cause of kidney injury in SLE. Men with SLE tend to have more aggressive disease with higher rates of renal and cardiovascular involvement and are more likely to

Mortality associated with lupus is significantly higher in those with LN compared with those without LN, and death directly attributable to kidney disease occurs in 5% to 25% of patients with proliferative LN within 5 years of onset. Furthermore, 10% to 30% of patients with LN progress to kidney failure requiring kidney replacement therapy (KRT). Patients with proliferative forms of LN (class III, IV, or III/IV + V) are at highest risk for requiring KRT. Achieving a complete clinical

The Core Curriculum aims to give trainees in nephrology a

Table 3. Induction and Maintenance Treatment Regimens for Management of Proliferative Lupus Nephritis

Medication Name	Treatment Regimen	Dosing
LN Induction: First-Line Therapies		
CYC	IV CYC (NIH)	0.75-1 g/m^2 monthly × 6 doses; reduce dose by 25% for GFR < 20 mL/min
	IV CYC (low dose)[a]	500 mg every 2 wk × 6 doses
	Oral CYC	1.5 mg/kg/d × 3-6 mo; reduce dose by 25% for GFR < 20 mL/min
MMF or mycophenolate sodium (myfortic)	Oral MMF[a]	MMF: 1,000-1,500 mg 2×/d × 6 mo Myfortic: 720 mg 2×/d × 6 mo
LN Induction: Emerging Therapies		
Rituximab	IV rituximab	1,000 mg on d 1 and 14 × 2 doses
Multitarget regimen	Tacrolimus or cyclosporine plus MMF	0.05 mg/kg/d tacrolimus (target trough level 4-6 ng/mL) *or* 3-5 mg/kg/d cyclosporine (level is not well established) *plus* MMF 500-1,000 mg 2×/d × 6 mo
LN Maintenance Regimens		
MMF[a]	—	500-1,000 mg 2×/d[b]
Azathioprine	—	1.5-2 mg/kg/d

Abbreviations: CYC, cyclophosphamide; GFR, glomerular filtration rate; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; NIH, National Institutes of Health.

[a]First-line treatment choice for induction and maintenance therapy.

Initial treatment

- In class III-IV LN, an updated Cochrane systematic review suggested similar efficacy of MMF/MPA compared with CY, however:

1. MMF potentially being more efficacious in African–Americans.
2. The low-dose regimen CY has been used in non-European populations.

- Consequently, both MMF/MPA and low-dose CY are recommended as *first-line* options for initial (*induction) treatment.*

- High-dose intravenous CY (0.75–1 g/m2 monthly for 6 months) can be considered in patients with adverse clinical:

1. nephritic urine sediment and impaired renal function with GFR between 25 and 80 mL/min)
2. histological (crescents or necrosis in >25% of glomeruli)

2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis

Antonis Fanouriakis ,[1,2] Myrto Kostopoulou,[3] Kim Cheema,[4] Hans-Joachim Anders,[5] Martin Aringer ,[6] Ingeborg Bajema,[7] John Boletis,[8] Eleni Frangou,[9] Frederic A Houssiau ,[10] Jane Hollis,[11] Adexandre Karras,[12] Francesca Marchiori,[13] Stephen D Marks,[14] Gabriella Moroni ,[15] Marta Mosca,[16] Ioannis Parodis ,[17] Manuel Praga,[18] Matthias Schneider,[19] Josef S Smolen,[20] Vladimir Tesar,[21] Maria Trachana,[22] Ronald F van Vollenhoven ,[23] Alexandre E Voskuyl,[24] Y K Onno Teng,[25] Bernadette van Leew,[26] George Bertsias,[27] David Jayne,[4] Dimitrios T Boumpas [1,28]

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Initial treatment		
4.3 For patients with class III or IV (±V) LN, MMF(target dose: 2 to 3 g/day, or MPA at equivalent dose)	1a/A	9.84 (0.37)
or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses)	1a/A	
in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.		
4.4 Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria.	1a/B	9.32 (0.93)
4.5 Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4,	2b/B	8.88 (1.56)
but high-dose ntravenous CY (0.5–0.75 g/m^2 monthly for 6 months) can also be considered.	1a/B	
4.6 To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months.	2b/C	9.48 (0.90)

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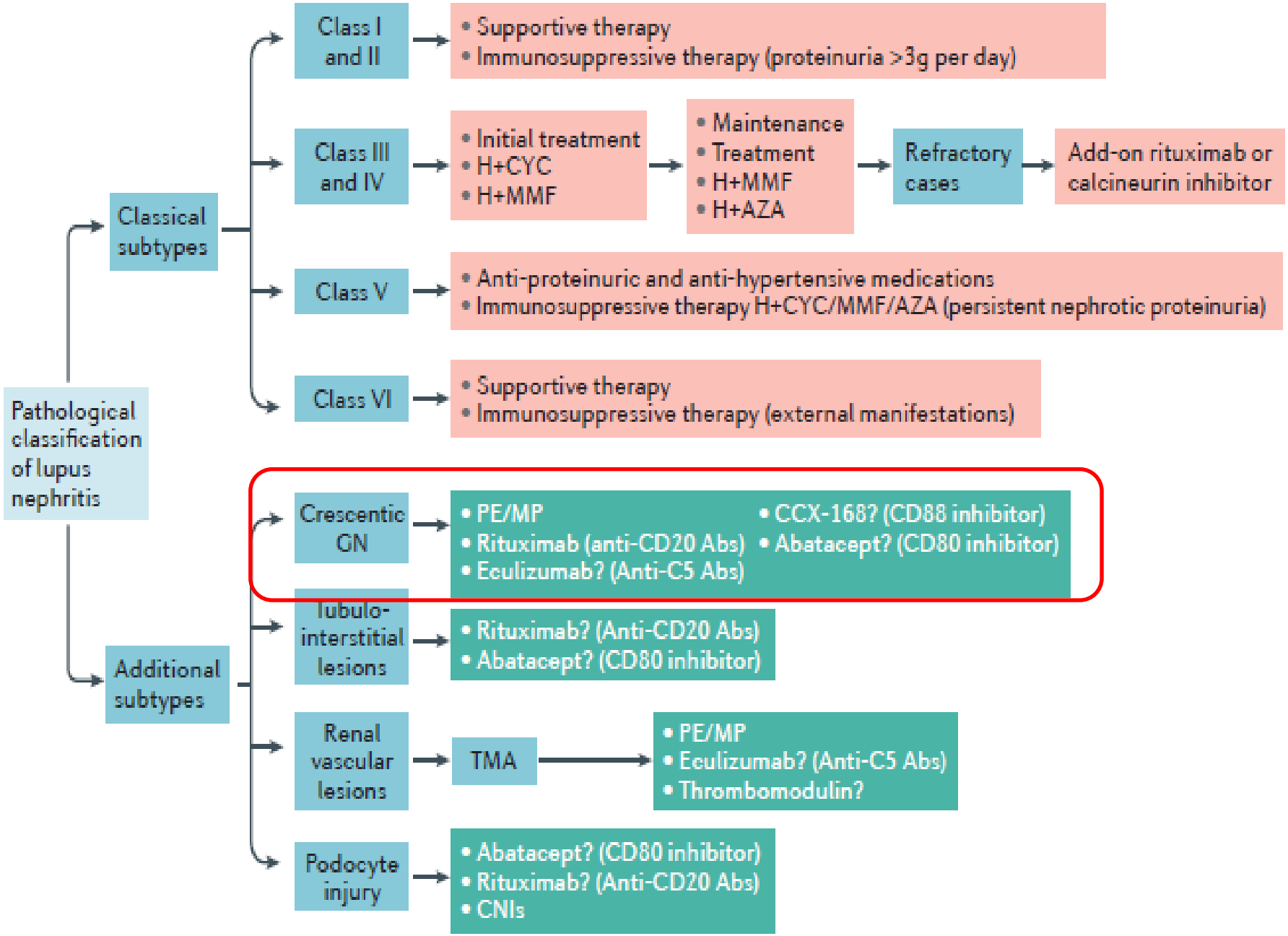
Redefining lupus nephritis: clinical implications of pathophysiologic subtypes

Feng Yu[1,2], Mark Haas[3], Richard Glassock[4] and Ming-Hui Zhao[1,5]

Abstract | Systemic lupus erythematosus (SLE) is associated with a broad spectrum of clinical and immunologic manifestations, of which lupus nephritis is the most common cause of morbidity and mortality. The development of nephritis in patients with SLE involves multiple pathogenic


Pathological classification of lupus nephritis
Classical subtypes
Class I and II
• Supportive therapy
• Immunosuppressive therapy (proteinuria >3g per day)
Class III and IV
• Initial treatment
• H+CYC
• H+MMF
• Maintenance
• Treatment
• H+MMF
• H+AZA
Refractory cases
Add-on rituximab or calcineurin inhibitor
Class V
• Anti-proteinuric and anti-hypertensive medications
• Immunosuppressive therapy H+CYC/MMF/AZA (persistent nephrotic proteinuria)
Class VI
• Supportive therapy
• Immunosuppressive therapy (external manifestations)
Additional subtypes
Crescentic GN
• PE/MP
• Rituximab (anti-CD20 Abs)
• Eculizumab? (Anti-C5 Abs)
• CCX-168? (CD88 inhibitor)
• Abatacept? (CD80 inhibitor)
Tubulo-interstitial lesions
• Rituximab? (Anti-CD20 Abs)
• Abatacept? (CD80 inhibitor)
Renal vascular lesions
TMA
• PE/MP
• Eculizumab? (Anti-C5 Abs)
• Thrombomodulin?
Podocyte injury
• Abatacept? (CD80 inhibitor)
• Rituximab? (Anti-CD20 Abs)
• CNIs

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Clinicopathological characteristics and outcomes of patients with crescentic lupus nephritis

Feng Yu[1,2,3], Ying Tan[1,2,3], Gang Liu[1,2,3], Su-xia Wang[1,2,3], Wan-zhong Zou[1,2,3] and Ming-hui Zhao[1,2,3]

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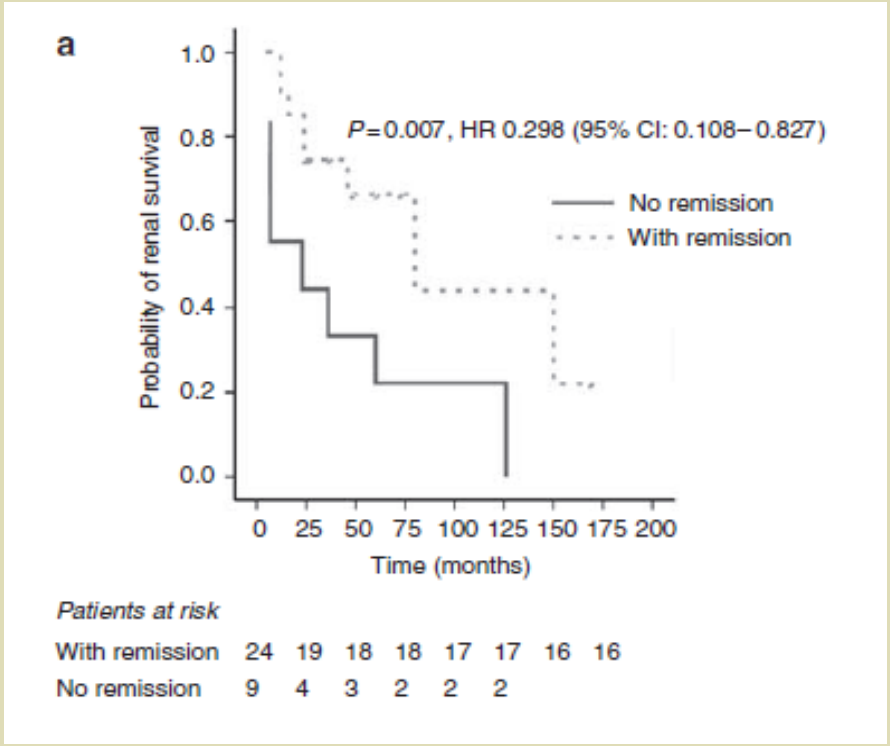

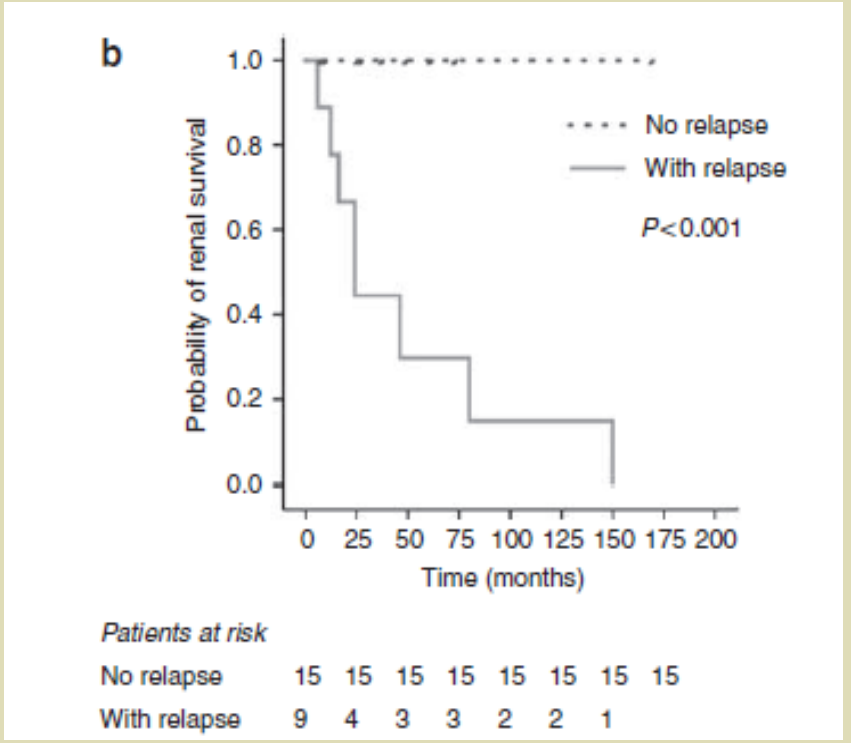

Figure 1 | Renal outcome in crescentic glomerulonephritis group. (**a**) Comparison of renal outcomes between patients with remission and no remission in crescentic glomerulonephritis group. (**b**) Comparison of renal outcomes between patients with relapse and no relapse in the crescentic glomerulonephritis group.

Kidney International (2009) 76, 307–317

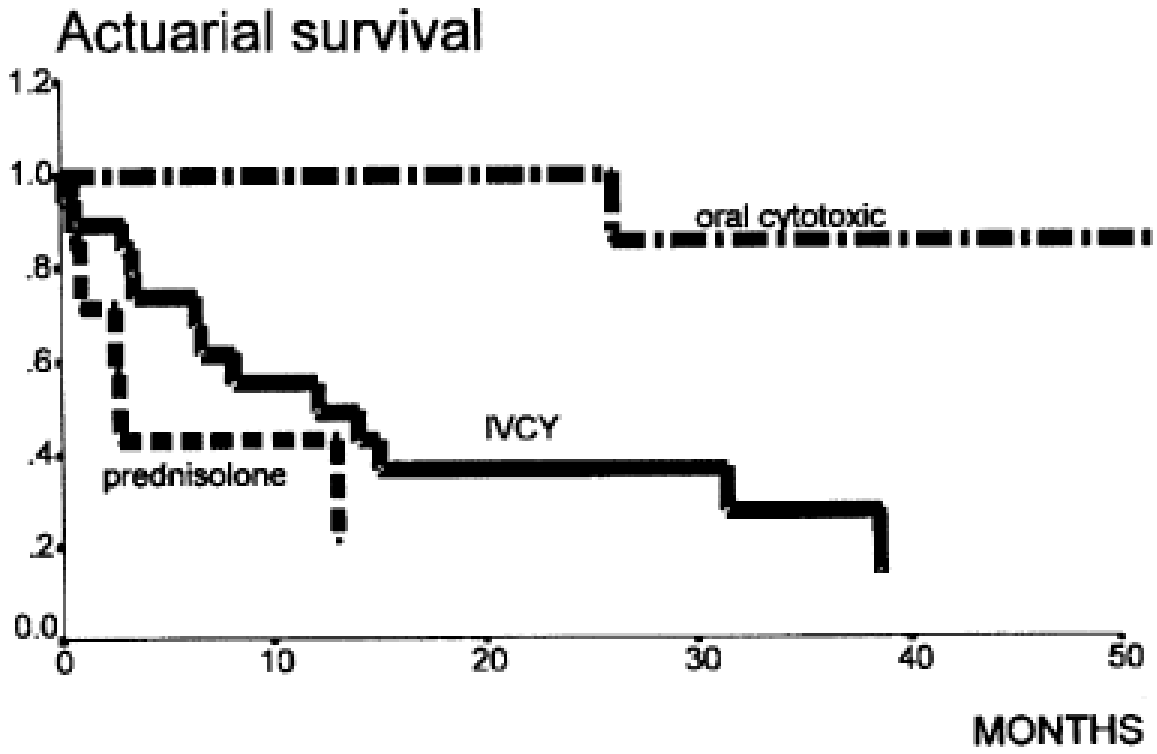

Figure 1 The actuarial survival rate of all patients in according with treatment regimen.

- Death before uremia occurred in an unexpectedly high proportion (7/32) of our patients.

- The outcome of the patients was made worse by the finding that there were seven nonrenal deaths (all were infectious complication) during therapy. This led to an awareness that crescentic lupus patients may be more immunocompromised than other patients with crescentic glomerulonephritis.