병리 (Mini-Lecture)

Histopathology of ANCA-Associated Glomerulonephritis

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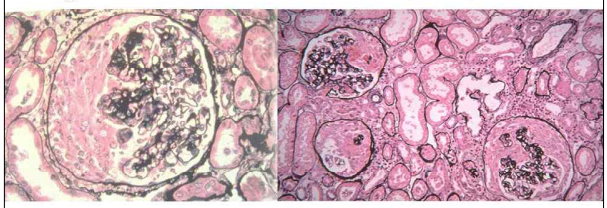
ANCA-associated pauci-immune crescentic GN

- Crescentic GN without anti-GBM antibody or immune complexes in glomeruli – Stiltmant et al. (1976)



- Crescentic GN (=Rapidly progressive GN)
  Anti-GBM antibody associated Immune complex associated Pauci-immune (complex)
- M/C cause of crescentic GN (61%) – Am J Kidney Dis 1994;24:130)
- ANCA in patients with pauci-immune crescentic GN with or without systemic vasculitis – Falk & Jennette (1988)

Antineutrophil cytoplasmic antibody (ANCA) – associated vasculitis (AAV)

- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA, Wegener's granulomatosis)
- Renal limited vasculitis (RLV)
- Eosinophilic GPA (EGPA, Churg-Strauss syndrome)

Definition of AAV (2012, Chapel Hill Consensus Conference)

Wegener's granulomatosis	**Granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels. Necrotizing glomerulonephritis is common.**
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and blood eosinophilia
Microscopic polyangiitis	Necrotizing small vessel vasculitis Necrotizing glomerulonephritis (90-100%) and pulmonary capillaritis (25-55%)

Etiology & Pathogenesis (1)

- Autoimmune disease – Autoantibodies made to neutrophil lysosomal components (ANCA)
  - T cell, macrophages
- Trigger for ANCA production
  - Unknown
  - Immune dysregulation
  - Genetic factor : PR-ANCA – HLA-DP, MOP-ANCA – HLA-DQ
  - Environmental factor : silica, infection (Staphylococcus aureus in GPA), Drug (prophylthiouracil, hydralazine)

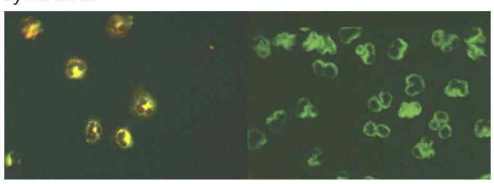
Etiology & Pathogenesis (2)

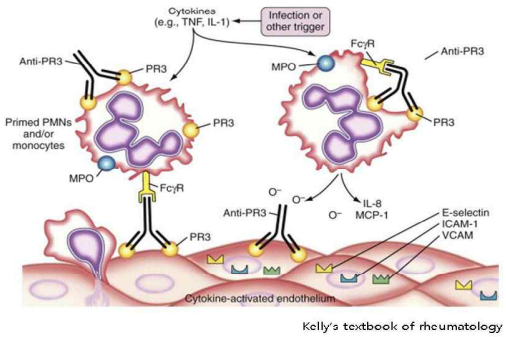
- Drugs (propylthiouracil, hydralazine, D-penicillamine, allopurinol) or cross-reactive microbial antigens induce ANCA
- Subsequent infection or other inflammatory stimuli – cytokines (TNF-α, IL-8, TGF-β) that cause surface expression of PR3 or MPO on neutrophils
- ANCAs-cytokine-activated cells either cause
  - direct injury (endothelial cells)
  - induce further activation of neutrophils, respiratory burst (oxygen free radicals)
  - signal transduction pathway for cell activation (FcR)
  - alternative complement pathway activation
- Measurement of ANCA titers useful in management

ANCA

- P(perinuclear)-ANCA
- MPO(myeloperoxidase)-ANCA
- Lysosomal constituent involved in generating oxygen free radicals
- Microscopic polyangiitis & Churg-Strauss syndrome

- C(cytoplasmic)-ANCA
- PR3(proteinase 3)-ANCA
- Neutrophil azurophilic granule constituent
- Wegener granulomatosis





Kelly's textbook of rheumatology

Frequency of Manifestations of ANCA-associated vasculitis

	Microscopic polyangiitis (%)	Wegener's granulomatosis	Churg-Strauss syndrome
Renal	90	80	45
Pulmonary	50	90	70
Cutaneous	40	40	60
ENT	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Clinical Presentation

- Rapidly progresseive GN with hematuria, proteinuria and elevated serum creatinine
- Necrotizing and crescentic GN
- Age : 2-92 years (56±20 years)
- Male:female ratio = 1:0.9
- Mean serum creatinine : 0.8-22.1mg/dL (6.5±4.0 mg/dL)
- Proteinuria : 0.11-18.00 g/dL (1.94±2.95 g/dL)
- Less severe than anti-GBM crescentic GN and more severe than immune complex crescentic GN

(Kidney Int 2003;63:1164)

Approximate Frequency of ANCAs in ANCA-associated vasculitis

	Wegener's granulomatosis (%)	Microscopic polyangiitis	Churg-Strauss syndrome	Renal-limited pauci-immune crescentic GN
MPO-ANCA	20	50	60	60
PR3-ANCA	75	40	10	20
ANCA-negative	5	10	30	20

AAV : Report from Korea

- Granulomatous and limited disease is prevalent in granulomatosis with polyangiitis (Wegener's granulomatosis)
- ANCA positivity : MPA (69-94%) > WG (56.6-68.9%)> EGPA (Churg-Strauss syndrome) (5.9-8.3%)
- C-ANCA/PR3-ANCA positivity in WG : 71.5-100%, P-ANCA/MPO-ANCA in MPA : 94-100%
- AAV among all patients with RPGN : 43.6%
- Decreased renal function with reduced GFR and elevated BUN and creatinine at baseline is significantly associated with increased mortality in ANCA-associated renal vasculitis.
- Patients with positive P-ANCA have higher mortality and poor renal outcome.
- Renal involvement or progression to ESRD was lower in Korean pts with WG and EGPA than in Caucasians with WG and EGPA (?)

Clin Exp Nephrol 2013;17:708-11

Pathologic Findings (1)

- Crescents and fibrinoid necrosis
  - irrespective of the presence or absence of associated systemic vasculitis
  - no significant difference in ANCA-positive and ANCA-negative pauci-immune GN
  - no difference in PR3-ANCA positive and MPO-ANCA positive pauci-immune GN
- Disruption of GBM & Bowman's capsule in Jones silver methenamine and periodic acid-Schiff (PAS)
- Periglomerular inflammatory infiltration (granulomatous with giant cells)
- Influx of neutrophils -> mononuclear leukocytes, macrophages
- Segmental or global sclerosis (MPO-ANCA > PR3-ANCA) : cellular -> fibrocellular -> fibrous crescent

Pathologic Findings (2)

- Necrotizing small vessel vasculitis in renal arteries, arterioles, and medullary vasa recta
  - interlobular arteries (M/C)
  - segmental fibrinoid necrosis and associated mural and perivascular infiltration of neutrophils or mononuclear leukocytes or both (eosinophils in Churg-Strauss syndrome, granulomas in Wegener's granulomatosis)
- Scarring

Pathologic Findings (3)

- Interstitial edema and focal tubular epithelial flattening
- RBCs in tubular lumen
- Tubulointerstitial vs periglomerular inflammation
- Interstitial fibrosis and tubular atrophy

Histopathologic Classification of ANCA-Associated GN

Class	Inclusion Criteria*
Focal	≥50% normal glomeruli
Crescentic	≥50% glomeruli with cellular crescents
Mixed	<50% normal, <50% crescentic, <50% globally sclerotic glomeruli
Sclerotic	≥50% globally sclerotic glomeruli

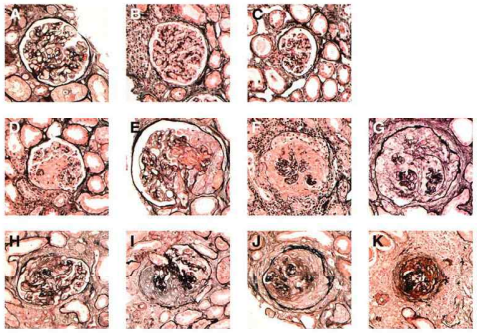
*Pauci-immune staining pattern on IF microscopy and ≥1 glomerulus with necrotizing or crescentic glomerulonephritis on LM are required for inclusion in all four classes.

Berden et al. J Am Soc Nephrol 2010;21:1628-36

Definitions

Total number of glom	The maximum number of glom in one of the sections excluding incomplete glom on the edges
Normal glom	Glom without vasculitic lesions or global sclerosis. Normal glom may show subtle changes as a result of ischemia or a minimum number of inflammatory cells (fewer than 4 neutrophils, lymphocytes, or monocytes) Exclusion criteria are synechiae local/segmental glomerulosclerosis extensive ischemic changes (splitting of Bowman's capsule, wrinkling of the GBM) any other lesion unrelated to vasculitis (e.g. amyloid, tram tracking)
Crescents	
Cellular	Purely cellular lesions or with cellular components
Fibrous	Fibrotic (sclerotic) lesion with fibroblasts filling Bowman's space
Global glomerulosclerosis	>80% of the glom sclerosed

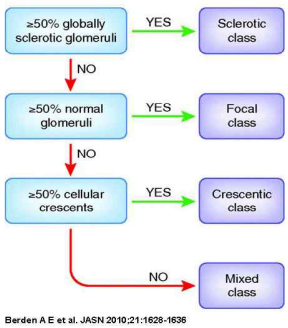
Typical examples of glomerular lesions in each of the four categories.



Berden A E et al. JASN 2010;21:1628-1636

JASN

Classification flowchart.



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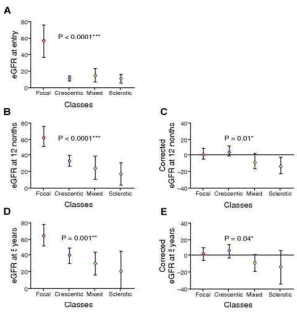
The histologic categories are strongly and independently correlated with renal function at baseline and during follow-up, with the phenotypical order of categories (focal, crescentic, mixed, and sclerotic) corresponding to the order of severity of renal fun...



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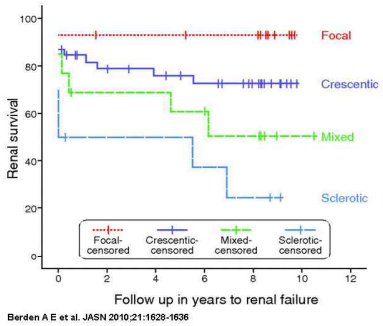
Renal survival (no development of end-stage renal failure) is depicted according to the four histologic categories.



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Recommendations for Reporting of Tubulointerstitial and Vascular lesions

- Dominance of any cell type in the infiltrate (plasma cells or eosinophils)
- High number of interstitial granulomas
- Extensive arteriolosclerosis

Outcomes of the Validation Studies Performed up to Date
(Curr Opin Nephrol Hypertens 2014;23:224-31)

	Berden et al. [15]	Iwakiri et al. [16]	Tagashi et al. [17]	Muso et al. [18]	Chang et al. [19]	Hilhorst et al. [20]	Ford et al. [21]	Ellis et al. [22]	Unlu et al. [23]
Renal function at baseline	Mean eGFR (±SD)	Median eGFR (IQR)	Mean eGFR (±SD)	Mean serum creatinine (±SD)	Mean eGFR (±SD)	Mean eGFR (±SD)	Median eGFR (range)	Mean eGFR ± SD	NR
Focal class	56.4 (36.8)	38.1 (22.5–57.4)	49.1 (26.2)	1.51 ± 1.49	55.3 (39.9)	39.3 (29.4)	31 (3.4–128)	50.2 (63.4)	NR
Crescentic class	11.2 (10.9)	12.0 (7.1–19.7)	12.4 (5.1)	2.42 ± 1.67	37.8 (63.7)	16.8 (14.7)	8 (2.5–108)	16.4 (10.3)	
Mixed class	15.4 (16.2)	16.5 (8.7–31.6)	17.4 (9.6)	2.37 ± 3.17	17.9 (17.7)	24.3 (19.5)	21 (5–60)	26.5 (23.3)	
Sclerotic class	10.8 (9.5)	12.4 (9.8–27.4)	13.3 (4.9)	7.52 ± 4.92	8.3 (8.1)	14.6	10 (1.9–45)	26.5 (15.0)	
eGFR 1-year	Mean (±SD)	Median (NR)	Mean (±SD)	NR	NR	Mean (±SD)	Median (range)	Mean (±SD)	NR
Focal class	63.3 (23.7)	45.7	52.9 (11.4)			54.5 (20.9)	42 (67.2–104)	70.8 (29.6)	
Crescentic class	32.8 (20.8)	24.5	25.5 (6.3)			41.0 (21.1)	26 (4.6–93)	42.1 (22.4)	
Mixed class	24.5 (21.4)	26.0	31.3 (20.4)			36.7 (18.6)	34 (6.1–102)	37.8 (19.8)	
Sclerotic class	16.6 (15.9)	16.9	15.5 (4.1)			–	8 (3.3–41)	22.7 (15.3)	
eGFR at 2 or 5-year follow-up	5-year	NR	2-year	NR	NR	2-year	NR	2-year	NR
Focal class	65.6 (20.3)		60.9 (17.6)			53.5 (20.8)		76.7 (29.5)	
Crescentic class	39.5 (22.5)		33.9 (9.4)			38.8 (22.3)		41.7 (18.1)	
mixed class	29.9 (19.7)		29.1 (9.2)			28.3 (19.9)		42.9 (21.9)	
Sclerotic class	20.4 (15.1)		7.4 (3.4)			–		37.8 (16.8)	
Renal survival at 1-year follow-up		NR				NR	NR	NR	NR
Focal class (%)	93		2	100	100				
Crescentic class (%)	84		22	86	73				
Mixed class (%)	69		11	96	83				
Sclerotic class (%)	50		33	35	29				
Renal survival at 2 or 5-year follow-up	5-year	NR	NR	5-year	5-year	5-year	NR	NR	NR
Focal class (%)	93			100	93	91			
Crescentic class (%)	76			86	60	64			
Mixed class (%)	61			96	72	69			
Sclerotic class (%)	50			29	29	–			
Development of ESRF or death	ESRF	ESRF	ESRF	NR	ESRF	NR	ESRF or death	NR	ESRF
Focal class [n (%)]	1/14 (7)	5/46 (4.3)	5/46 (4)		3/33 (9)		11/34 (33)		4/31 (13)
Crescentic class [n (%)]	11/45 (45)	9/32 (28)	9/32 (28)		15/53 (28)		14/33 (42)		20/69 (29)
Mixed class [n (%)]	6/13 (46)	8/18 (44)	8/18 (44)		4/24 (17)		13/33 (39)		10/29 (34)
Sclerotic class [n (%)]	7/10 (70)	4/6 (67)	4/6 (67)		8/11 (73)		16/20 (80)		8/12 (67)

eGFR, estimated glomerular filtration rate; ESRF, end-stage renal failure; IQR, interquartile range; NR, not reported.

Update

- The histopathological classification of ANCA-associated GN predicts renal outcome during follow-up, especially in patients with either a focal or sclerotic-class renal biopsy.
- There are conflicting outcomes with respect to the crescentic and the mixed-class renal biopsies.
- This could be due to differences in patients population, therapy, moderate inter-rater reliability, and lack of inclusion of tubulointerstitial lesions in the classification system.
- A large international validation study is currently being performed to address these issues.

(Rahmattulla et al. Curr Opin Nephrol Hypertens 2014;23:224-31)