Crescentic Glomerulonephritis Overview/Update

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Objectives:

- Definition
- Pathophysiology, Origin
- Classification, Immunopathologic Features
- Review of glomerular diseases in which crescents constitute the main histologic feature.
- prediction renal prognosis

Rapidly Progressive Glomerulonephritis/ Crescentic Glomerulonephritis

Only integrating all results from clinical phenotyping, standard laboratory tests, and specific immunological exams can ultimately clarify the diagnosis underlying CGN.

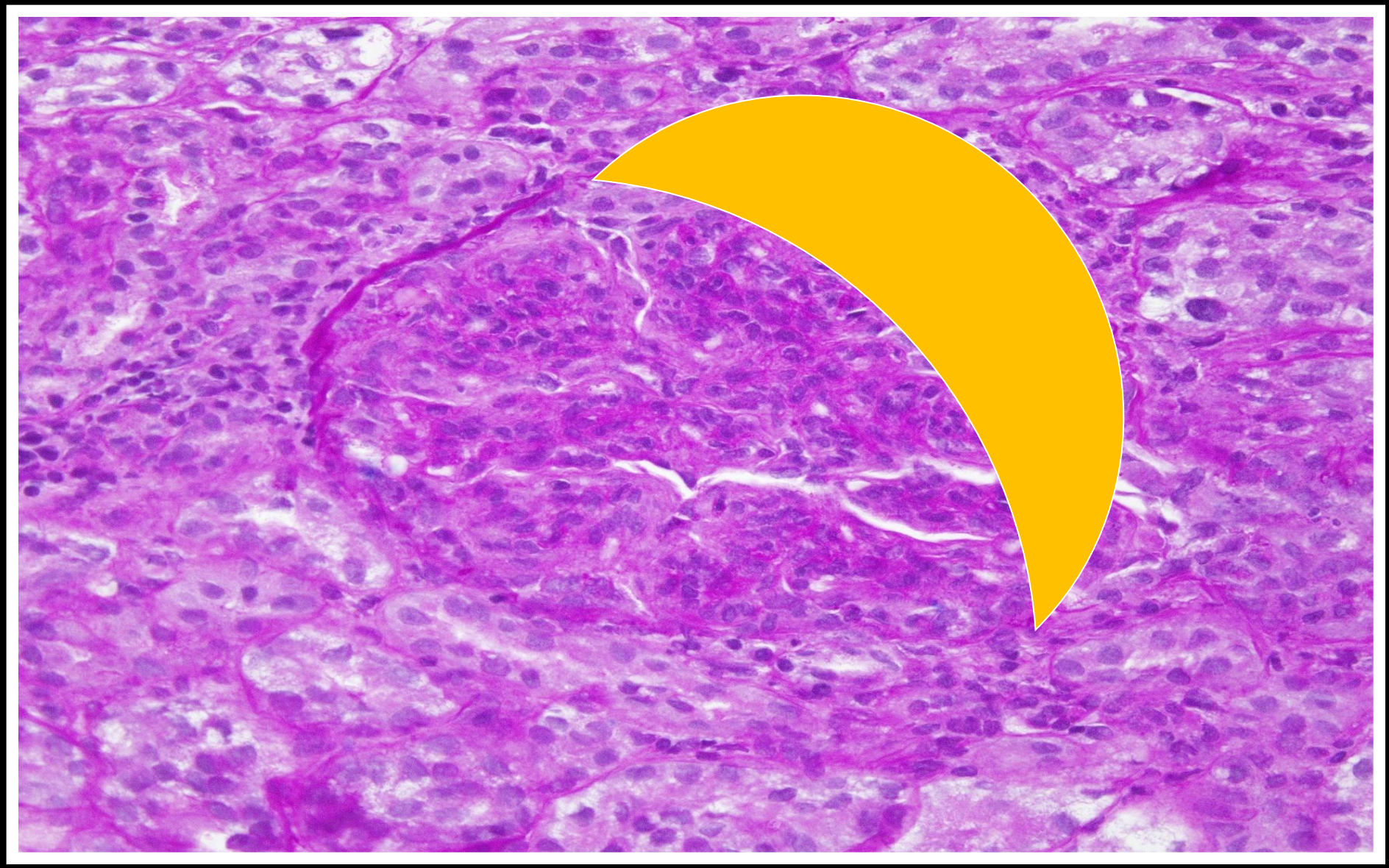
glomerulonephritis is used interchangeably with the Pathologic term crescentic glomerulonephritis.

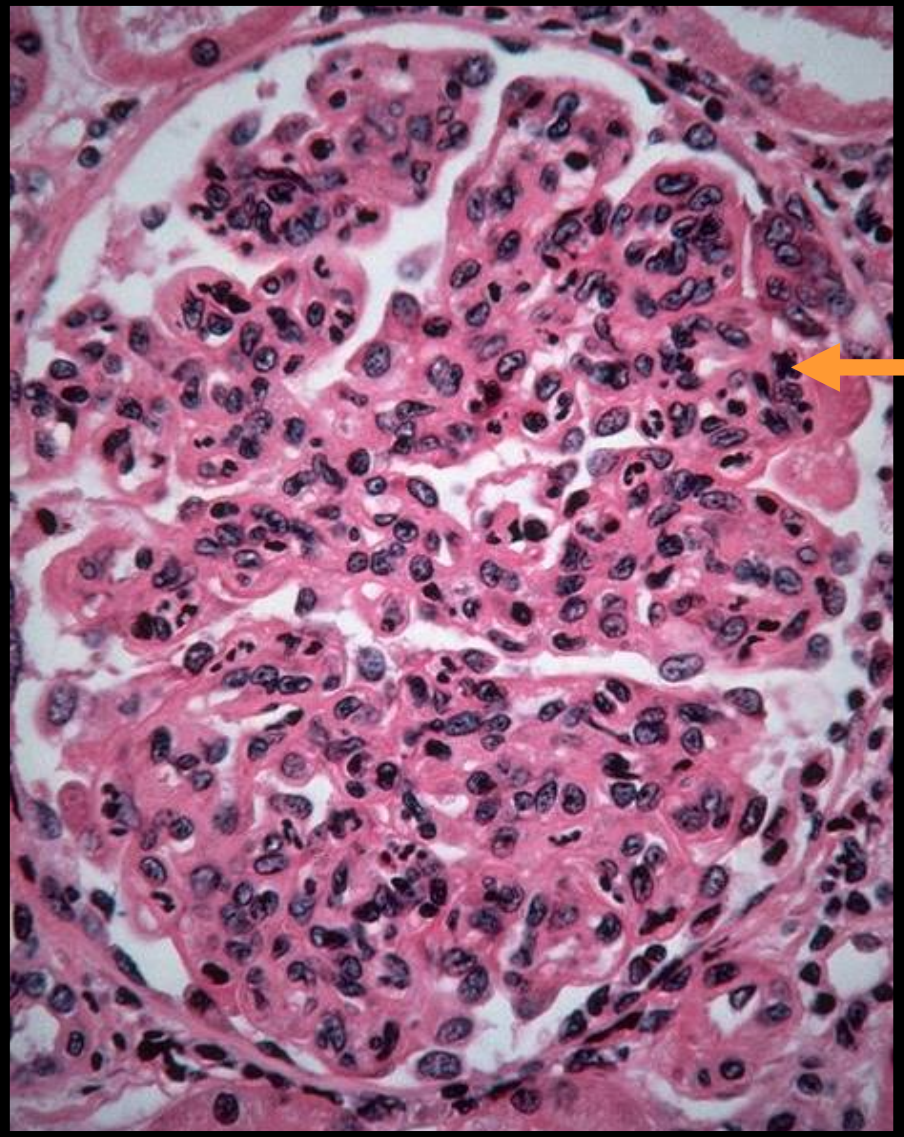
Crescentic Glomerulonephritis
Definition

- Proliferative extracapillary glomerulonephritis (GN) or crescentic GN is not a specific disease, but a histologic manifestation of severe glomerular damage.

On histological examination it has the presence of numerous glomerular crescents (usually greater than 50%).

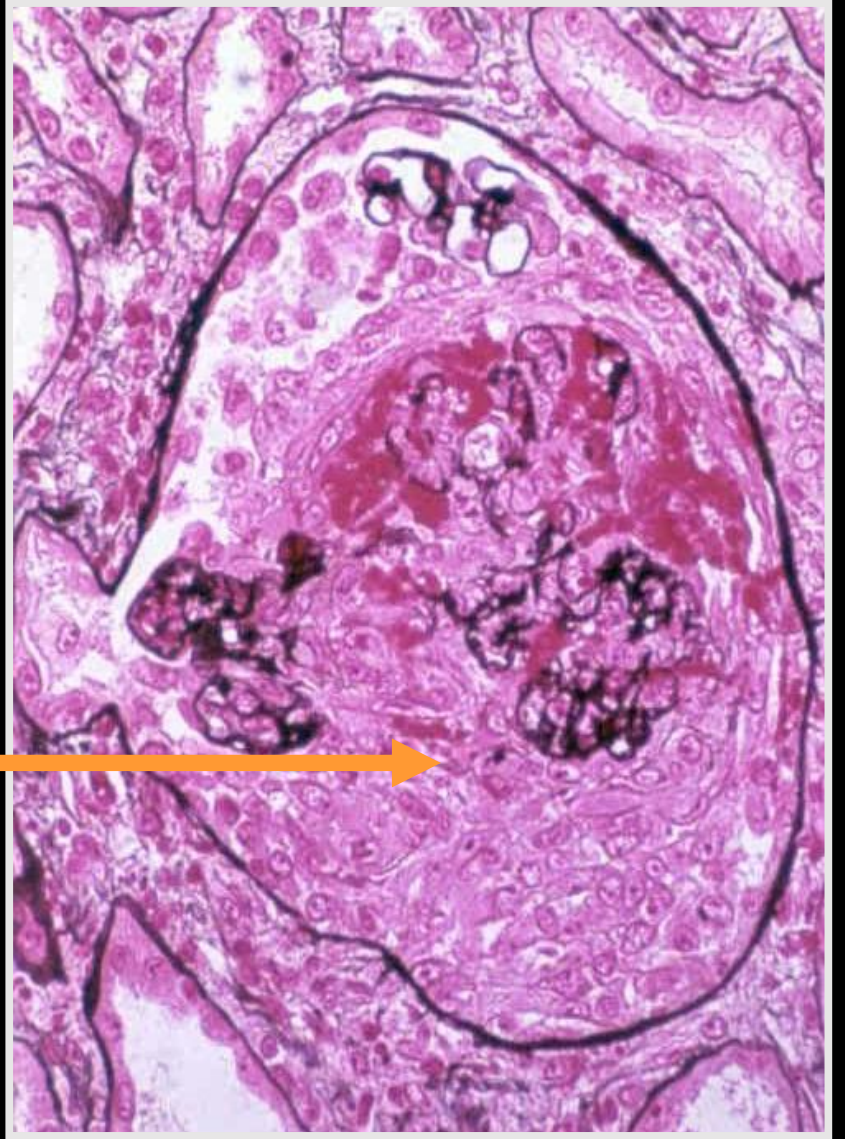
to enter Bowman's space, where they induce epithelial cell proliferation and macrophage influx and maturation that together produce cellular crescents

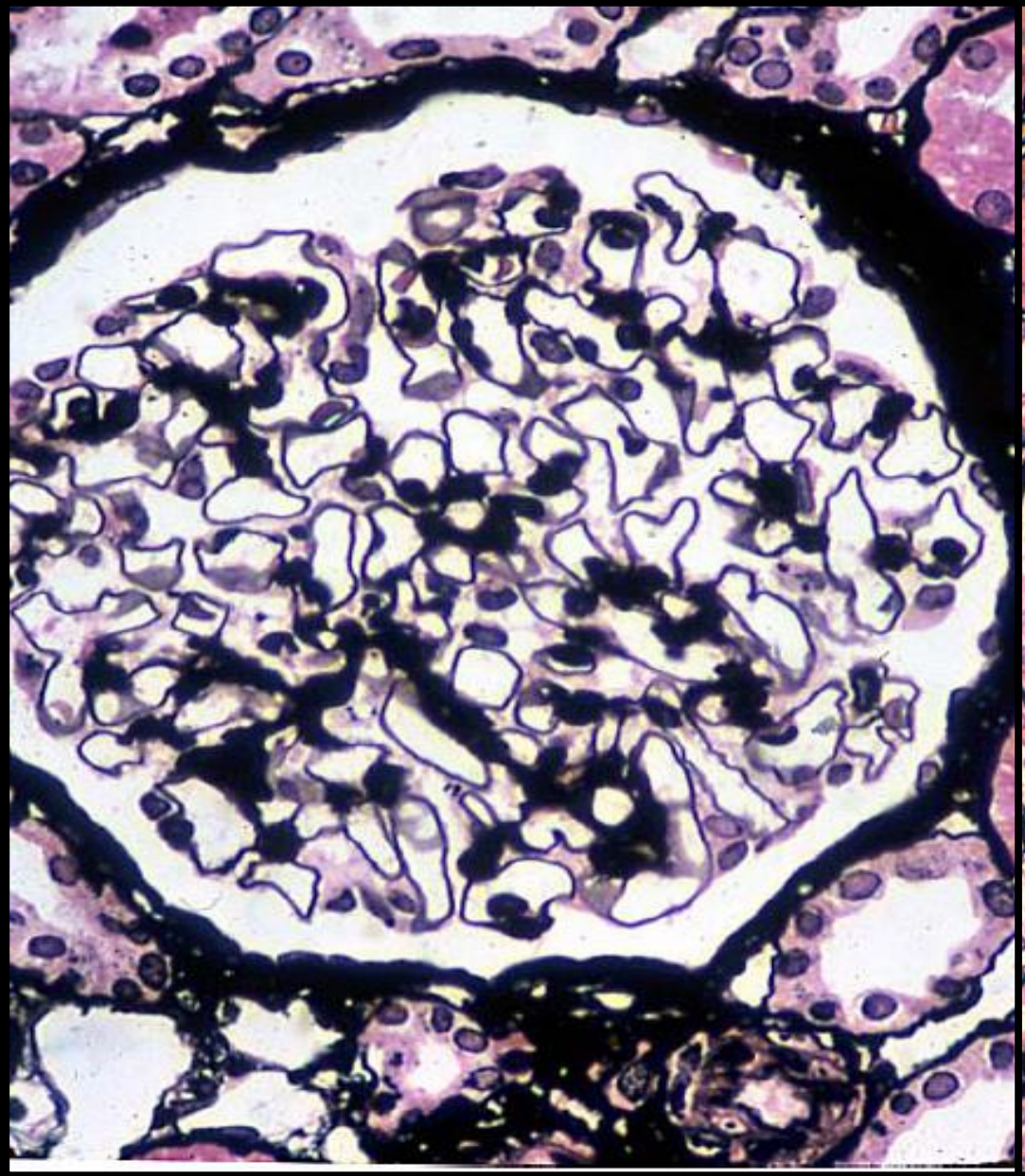




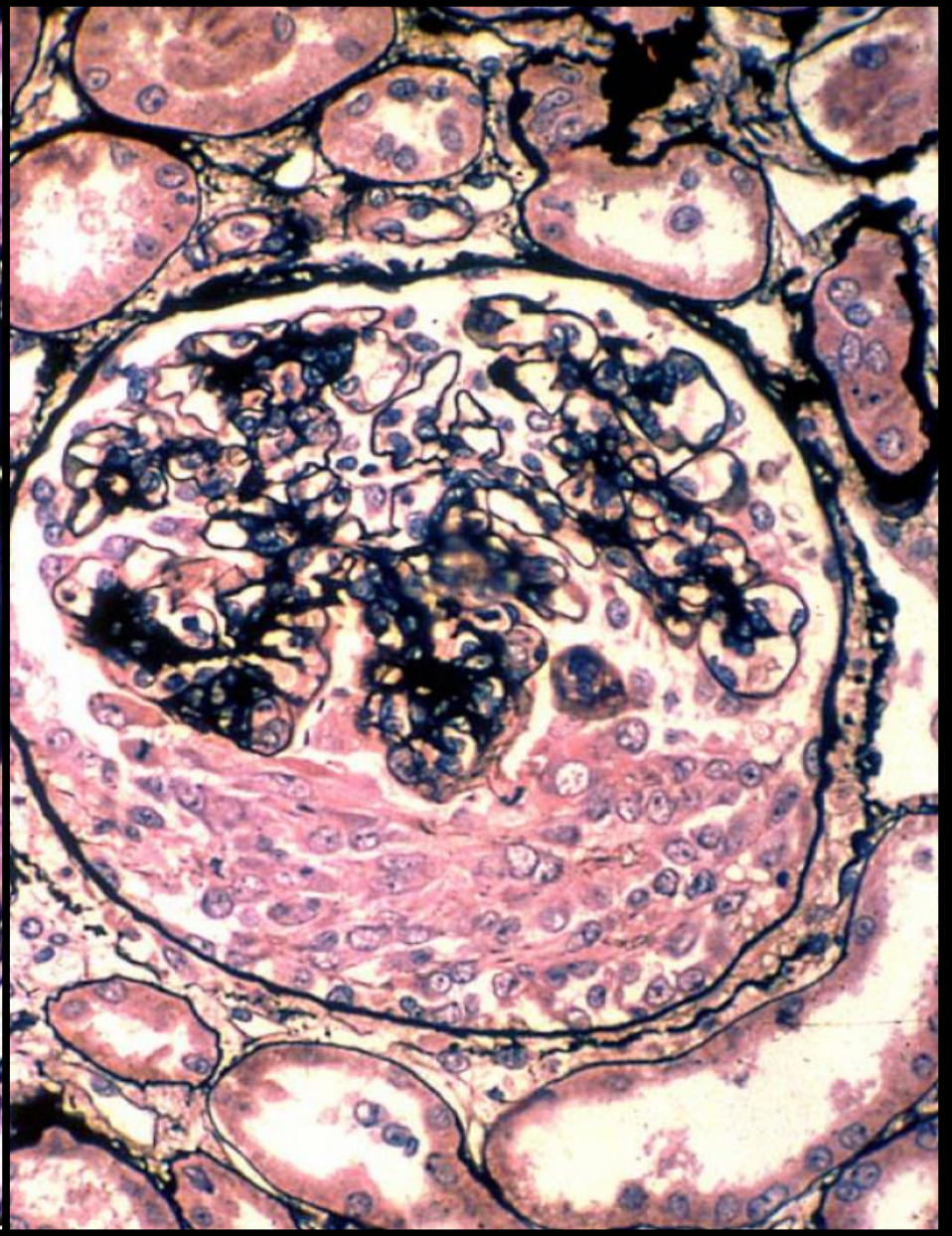
INTRACAPILIARY
(WITHOUT CRESCENT)

EXTRACAPILLARY
(WITH CRESCENT)





Normal



Crescentic

www.kidney-international.org

meeting report

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

Ingeborg M. Bajema[1], Suzanne Wilhelmus[1], Charles E. Alpers[2], Jan A. Bruijn[1], Robert B. Colvin[3], H. Terence Cook[4], Vivette D. D'Agati[5], Franco Ferrario[6], Mark Haas[7], J. Charles Jennette[8], Kensuke Joh[9], Cynthia C. Nast[7], Laure-Hélène Noël[10], Emilie C. Rijnink[1], Ian S.D. Roberts[11], Surya V. Seshan[12], Sanjeev Sethi[13] and Agnes B. Fogo[14]

Kidney International (2018) 93, 789–796

Table 1 | Phase 1 recommendations for lupus nephritis classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region (A)	Cuttoff for mesangial hypercellularity unclear
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved. Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C) Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D) Fibrocellular crescent: 25%–75% cells and fibrin and the remainder fibrous matrix (E)	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents
	Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis (F)	There was no definition for an adhesion
	scoring system (Table 2) to be used instead of the currently used A, C, and A/C parameters	considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis	Lack of cut-off values for reporting the severity of tubulointerstitial lesions

A–F refer to typical examples of glomerular lesions in Figure 1.

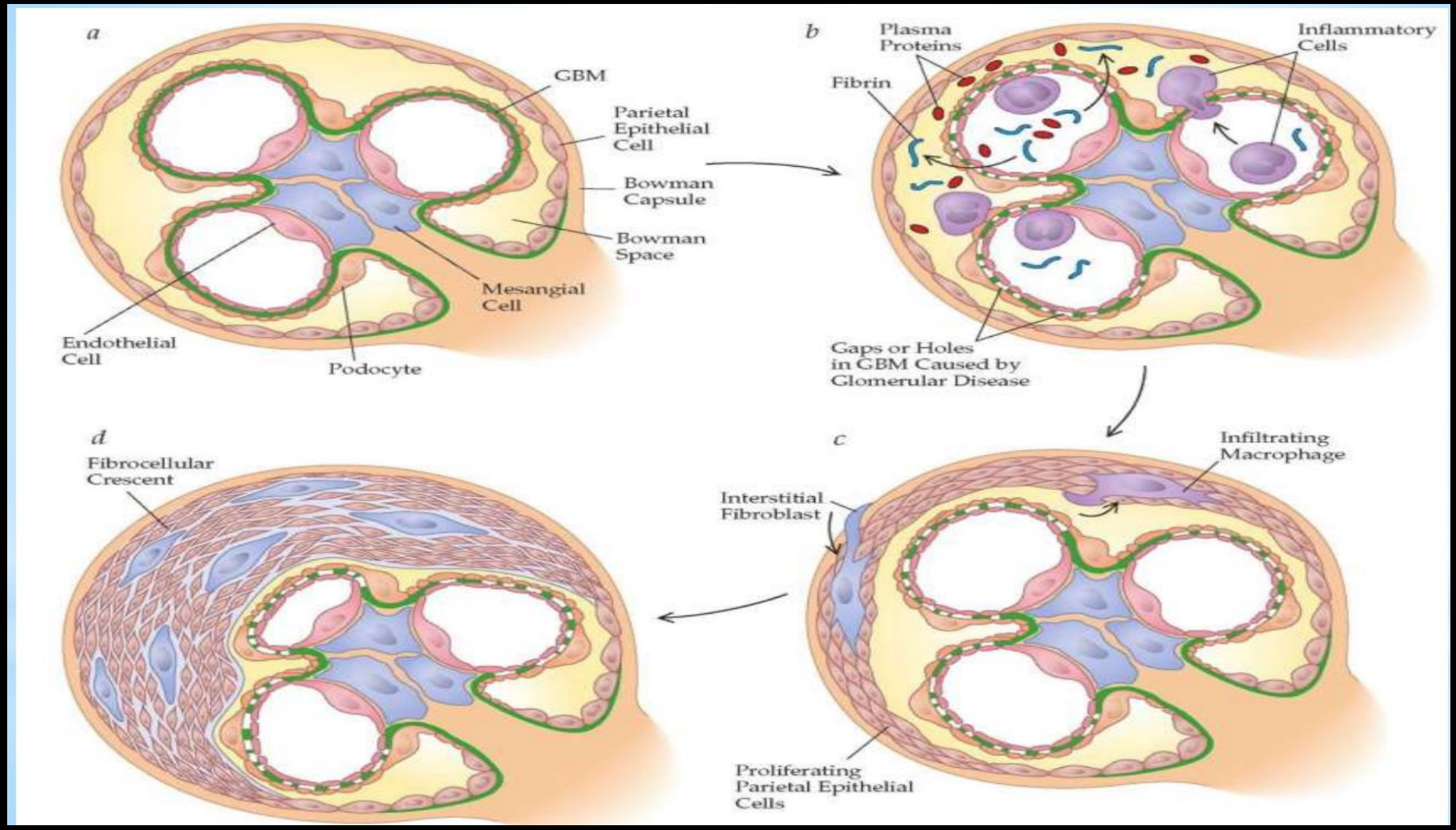
Crescents should be composed of more than 2 cell layers in order to distinguish them from apposition of the single layers of hypertrophied visceral and parietal cells

Kidney International (2018) 93, 789–796

Origin of extracapillary proliferation

- Crescents are associated to rupture of capillary walls and fibrin in the urinary space. This fibrin and other proteins of the plasma seem to have the capacity to stimulate Parietal epithelial cells (PECs)
- In addition, the mediators released by monocytes and platelets would contribute to the cellular proliferation and, probably, to posterior fibrosis.
- Crescents may evolve to fibrosis (fibrous crescent) or disappear (by apoptosis).
- Fibrosis is mediated by infiltration of fibroblasts from the periglomerular interstitium through spaces in the Bowman's capsule.

Origin of Extracapillary Proliferation



Classification of Crescentic GN according to Immunopathologic Features I:

- **Type I:** Produced by anti-glomerular basement membrane (GBM) antibodies.
- **Type II:** Due to immune complexes deposited in glomeruli.
- **Type III:** Without deposits of immunoglobulins or complement in glomeruli, *pauci-immune*. This group has been subdivided in: Associated to antineutrophil cytoplasmic antibodies (ANCA):

1-microscopic polyangiitis

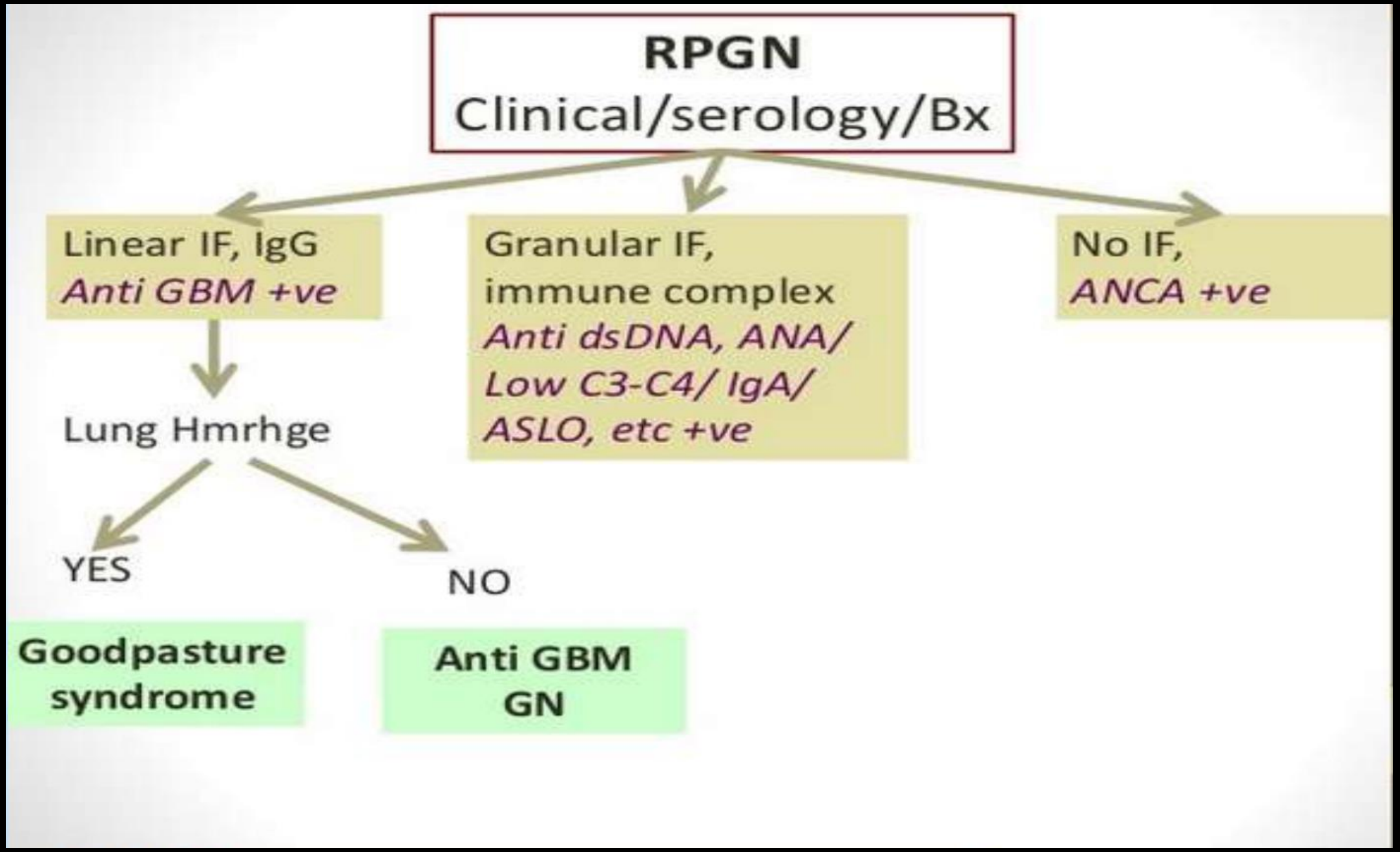
2- granulomatosis with polyangiitis (Wegener)

3- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Classification of Crescentic GN according to Immunopathologic Features II:

- or renal-limited vasculitis; and not associated to ANCA (idiopathic crescentic GN).

- type IV: has been proposed for those cases in which coexistence of anti-GBM disease and ANCA-associated GN is documented.


RPGN
Clinical/serology/Bx
Linear IF, IgG
Anti GBM +ve
Granular IF,
immune complex
Anti dsDNA, ANA/
Low C3-C4/ IgA/
ASLO, etc +ve
No IF,
ANCA +ve
Lung Hmrhge
YES
NO
Goodpasture syndrome
Anti GBM GN

- Crescentic GN corresponds to <10% of all the biopsies with GN diagnosis.
- According to the three defined types the distribution is approximately thus:
- anti-GBM disease: 20%
- immune complexes mediated: 40%
- pauci-immune: 40%.

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

SPECIAL ARTICLE

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

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Introduction

The goals of the first International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC1994) were to reach consensus on names for the most common forms of vasculitis and to construct a specific definition for each (1). An effort was made to adopt names and definitions that were already widely accepted. Because of advances in our understanding of vasculitis, another International Chapel Hill Consensus Conference (CHCC2012) was convened to improve the CHCC1994 nomenclature, change names and definitions as appropriate, and add important categories of vasculitis that were not included in CHCC1994. As in the original CHCC, the emphasis was on making changes only when justified. Herein we report the CHCC2012 revised nomenclature for vasculitides.

CHCC is a *nomenclature system* (nosology). It is neither a *classification system* that specifies what findings must be observed in a specific patient to classify that patient for clinical research nor a *diagnostic system* that

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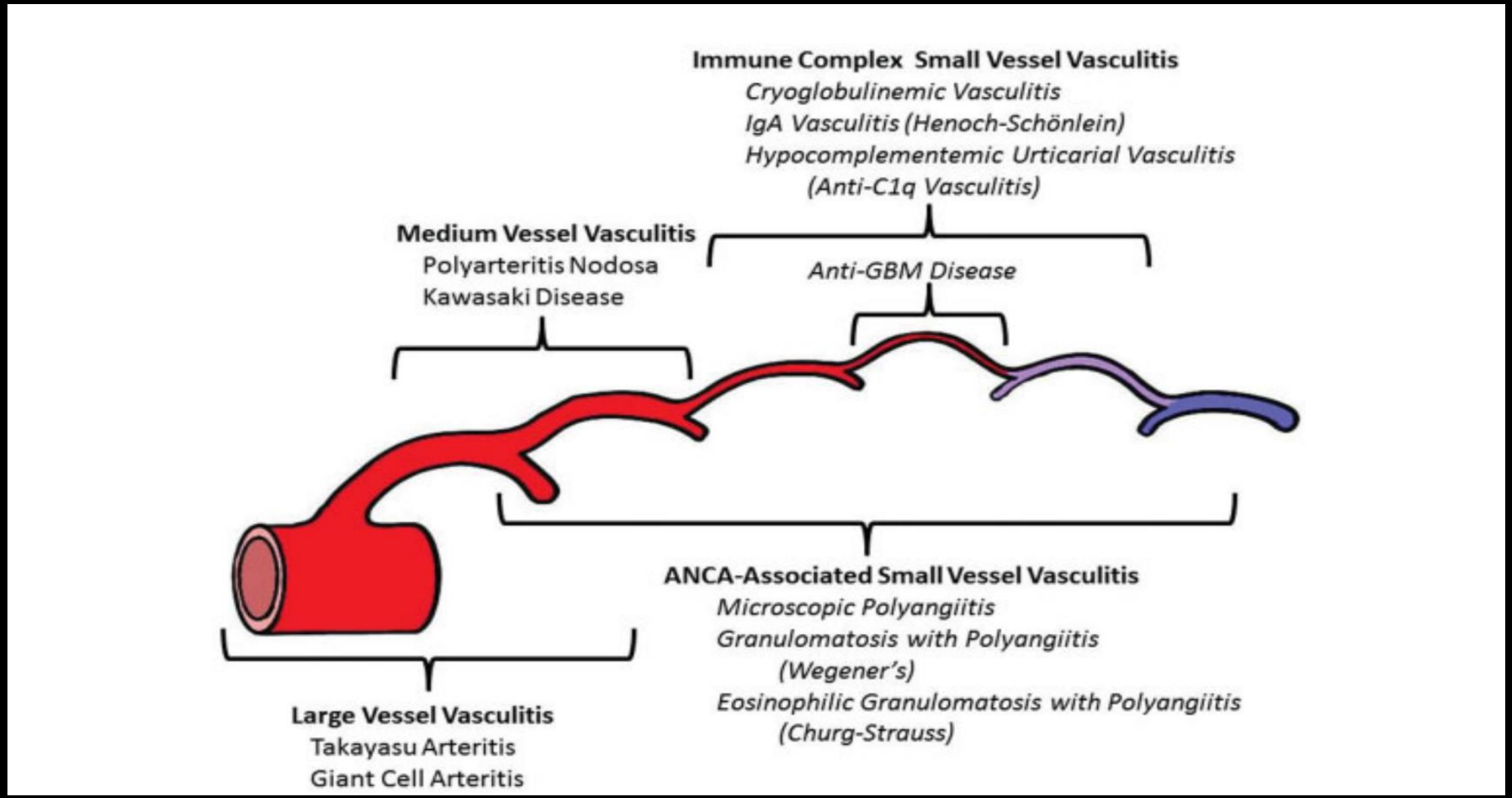


ARTHRITIS & RHEUMATISM Vol. 65, No. 1, January 2013

REVIEW

OPEN

CURRENT OPINION

The glomerular crescent: triggers, evolution, resolution, and implications for therapy

Lidia Anguiano[a], *Renate Kain*[b], *and Hans-Joachim Anders*[a]

Purpose of review

Crescents are classical histopathological lesions found in severe forms of rapidly progressive glomerulonephritis, also referred to as crescentic glomerulonephritis (CGN). Crescent formation is a consequence of diverse upstream pathomechanisms and unraveling these mechanisms is of great interest for improving the management of patients affected by CGN. Thus, in this review, we provide an update on the latest insight into the understanding on how crescents develop and how they resolve.

The glomerular crescent... Anguiano et al –nephrol hypertension 2020

Anti-GBM disease

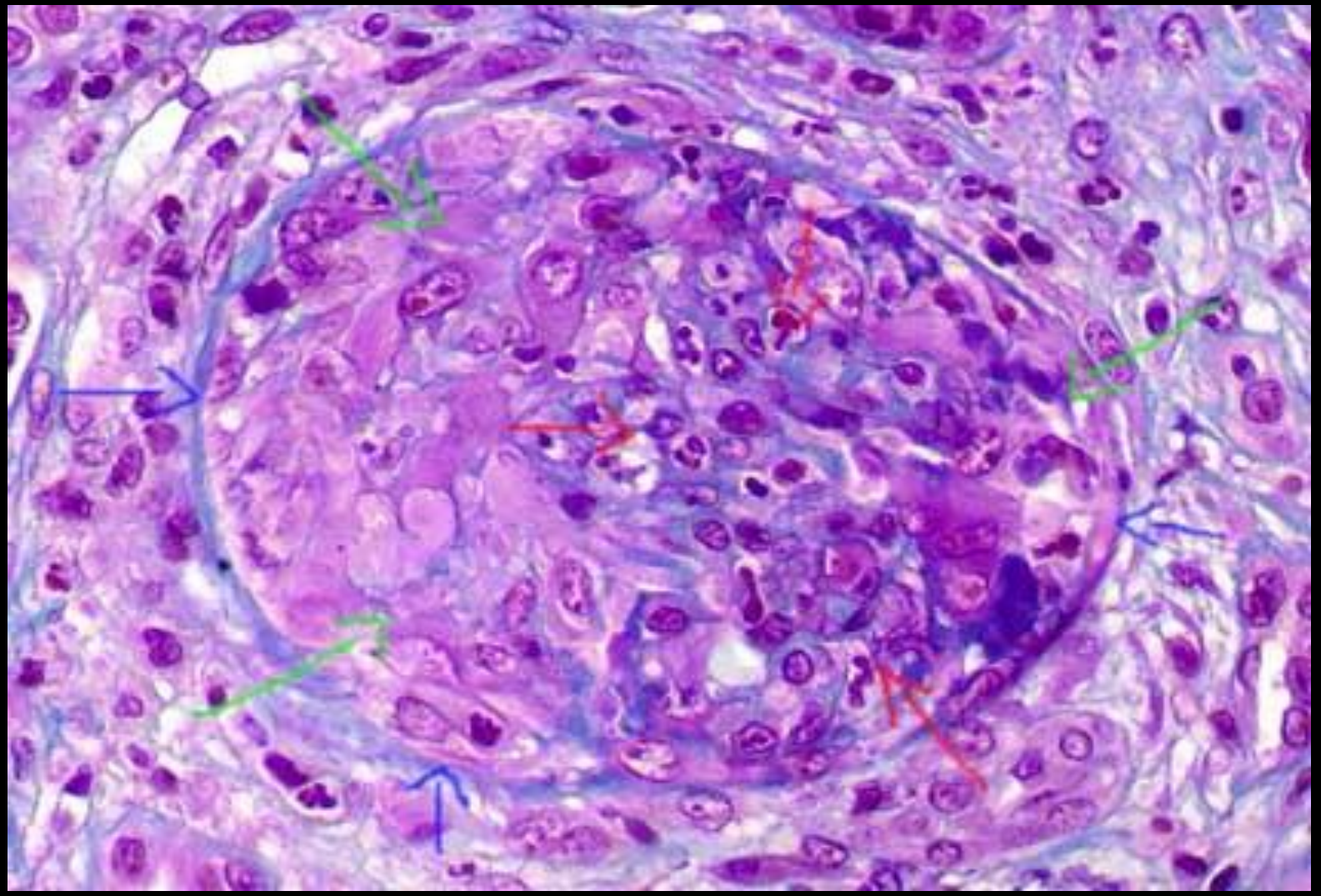
- Anti-GBM disease is rare, affects people of any age, but it is commonest in 20-40 years of age. There is greater frequency in men than in women.
- This disease frequently appears like a pulmonary-renal syndrome, characterized by severe hemoptysis, pulmonary alterations, and rapidly progressive GN (RPGN).
- The eponym is "Goodpasture disease" (or Goodpasture syndrome)
- All the patients with anti-GBM antibodies do not present Goodpasture disease: in some patients there is not pulmonary involvement.

Anti-GBM disease

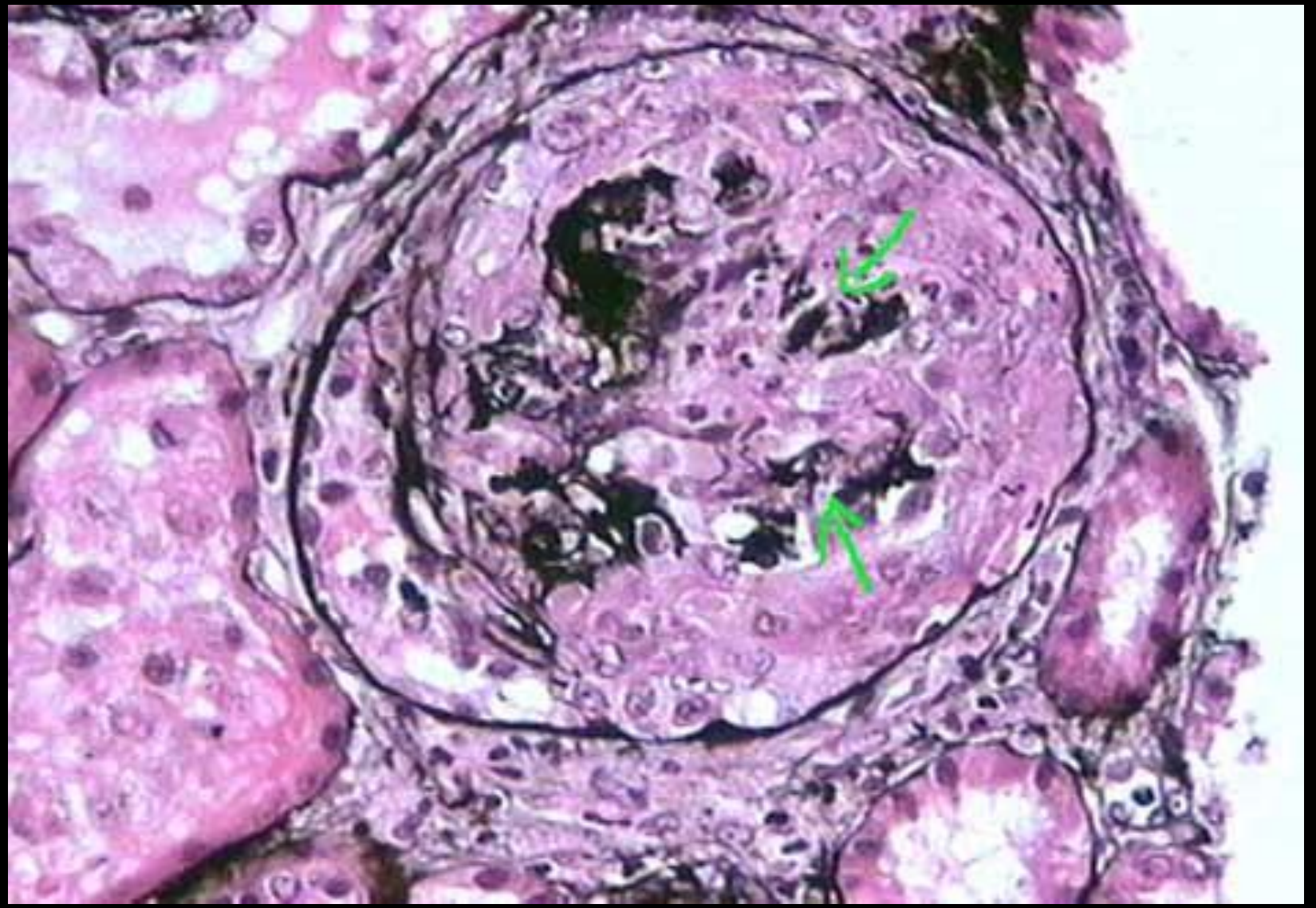
- The anti-GBM antibodies are directed against the alpha-3 chain in the C-terminal non-collagenous domain of type IV collagen (alpha-3 [IV] chain of NC1 domain).
- In most of patients with anti-GBM disease serum antibodies (anti-GBM) can be detected, but it is a difficult technique in which there are false negatives.
- The target antigen is in kidney, lung, and other tissues, such as choroids plexus and choclea.

Anti-GBM disease

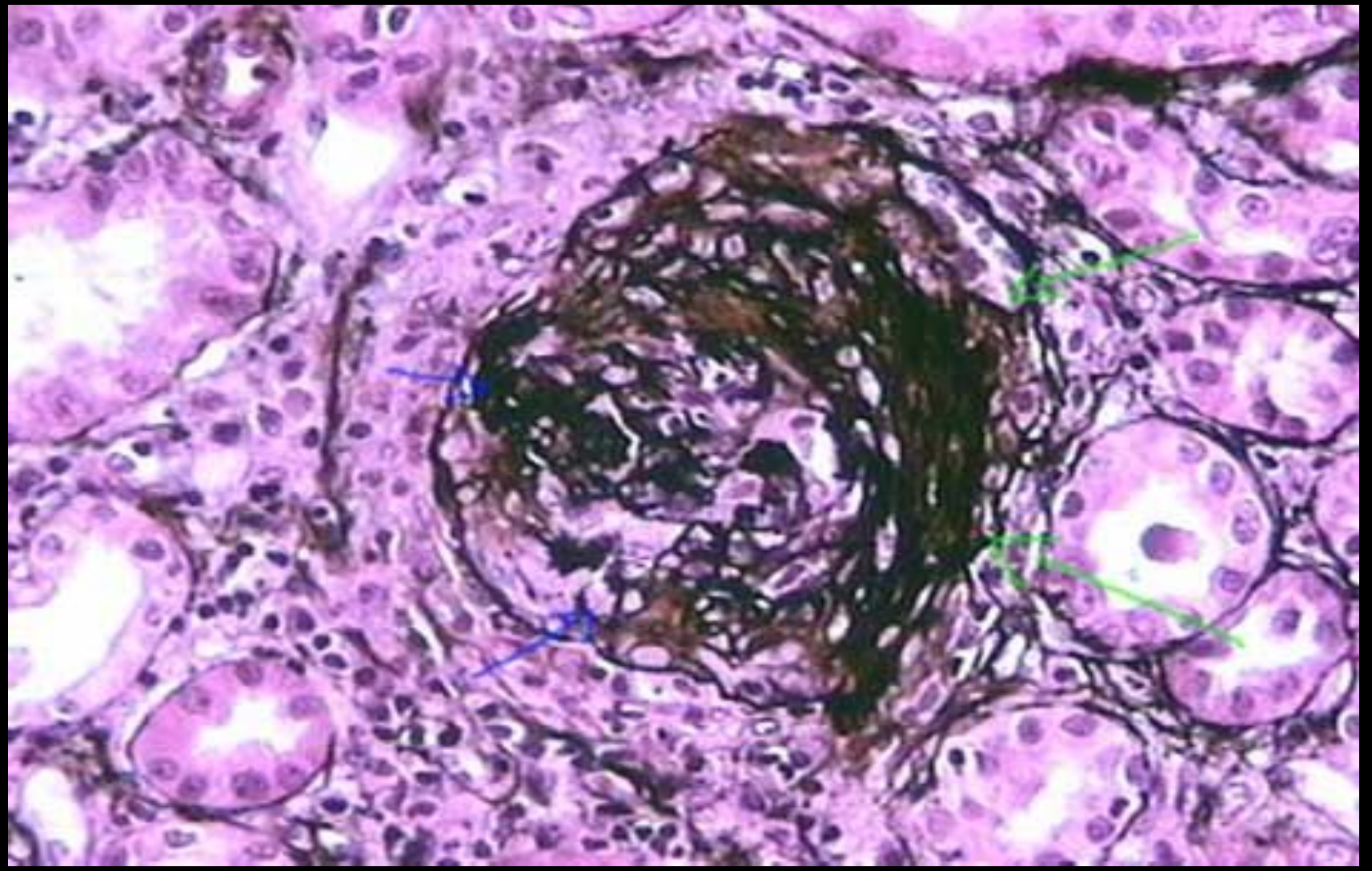
- Anti-GBM disease has worse prognosis than immune complexes GN and pauci-immune GN.
- Around half of the patients will develop terminal renal failure.
- After a complete remission recurrence of active disease is uncommon but may occur even many years later.
- The disease also can recur in renal allografts, but this is uncommon if transplantation is delayed until anti-GBM antibodies are undetectable.



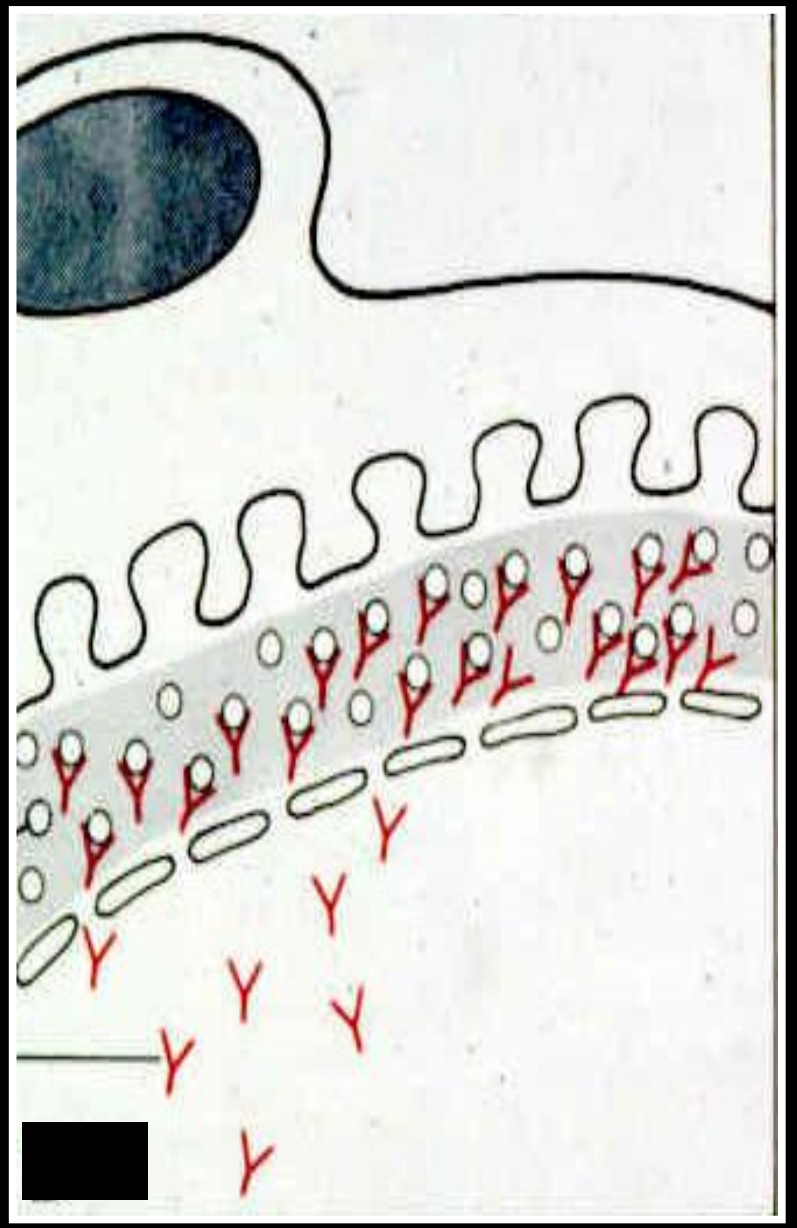
This case corresponds to a 58-years-old patient with rapidly progressive GN. See proliferation of cells occupying the entire Bowman's space (green arrows) and compressing the tuft (red arrows). The Bowman's capsule is indicated by the blue arrows. This is the characteristic aspect of an epithelial crescent, in this case circumferential. Cells forming the crescent may be epithelial, monocytes or other inflammatory cells. (Masson's trichrome, X400).



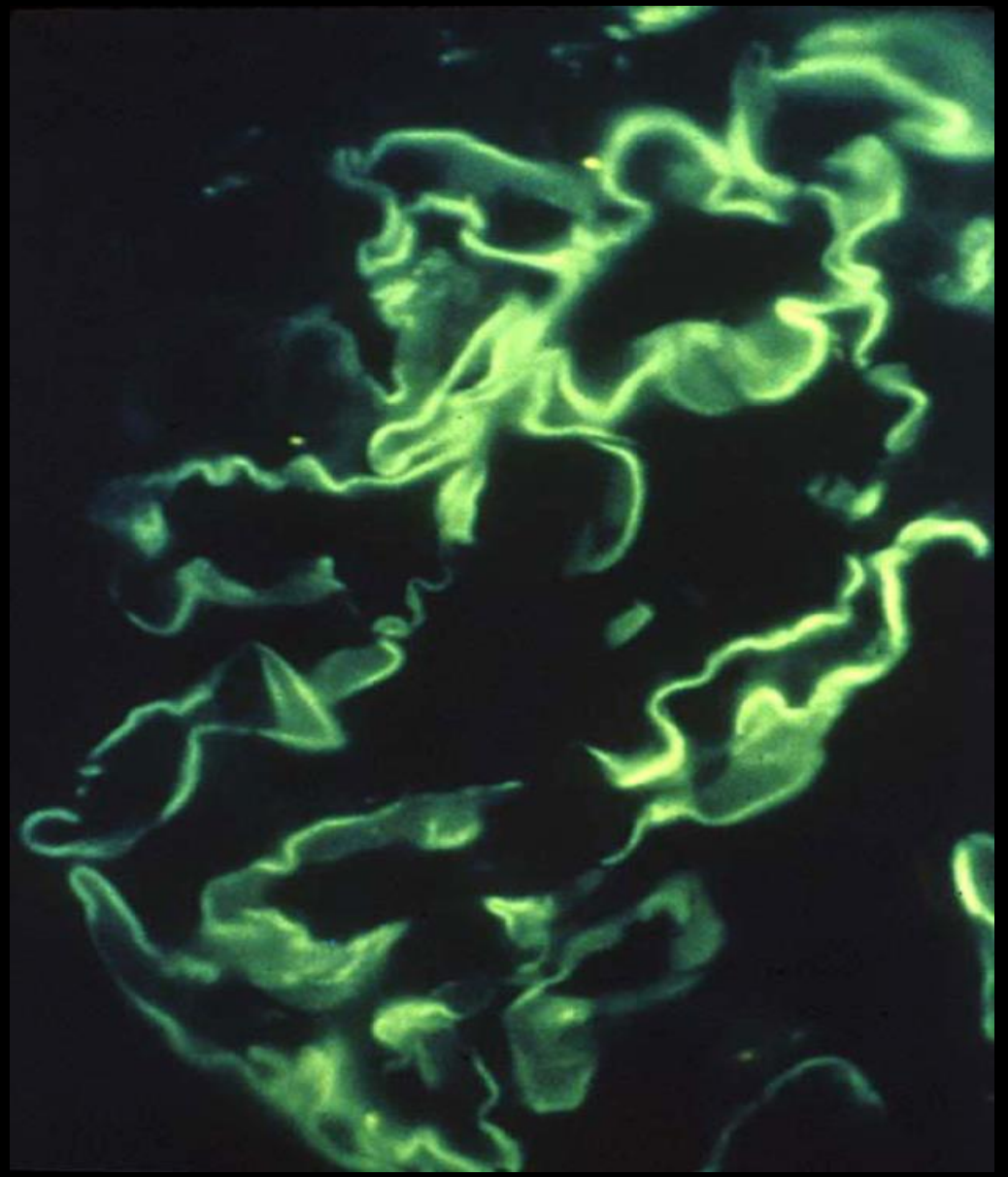
Methenamine-silver stain emphasizes the compressed tuft and rupture of capillary walls (arrows). This capillary damage is an important pathogenic phenomenon in the generation of the extracapillary proliferation. (Methenamine-silver, X400).



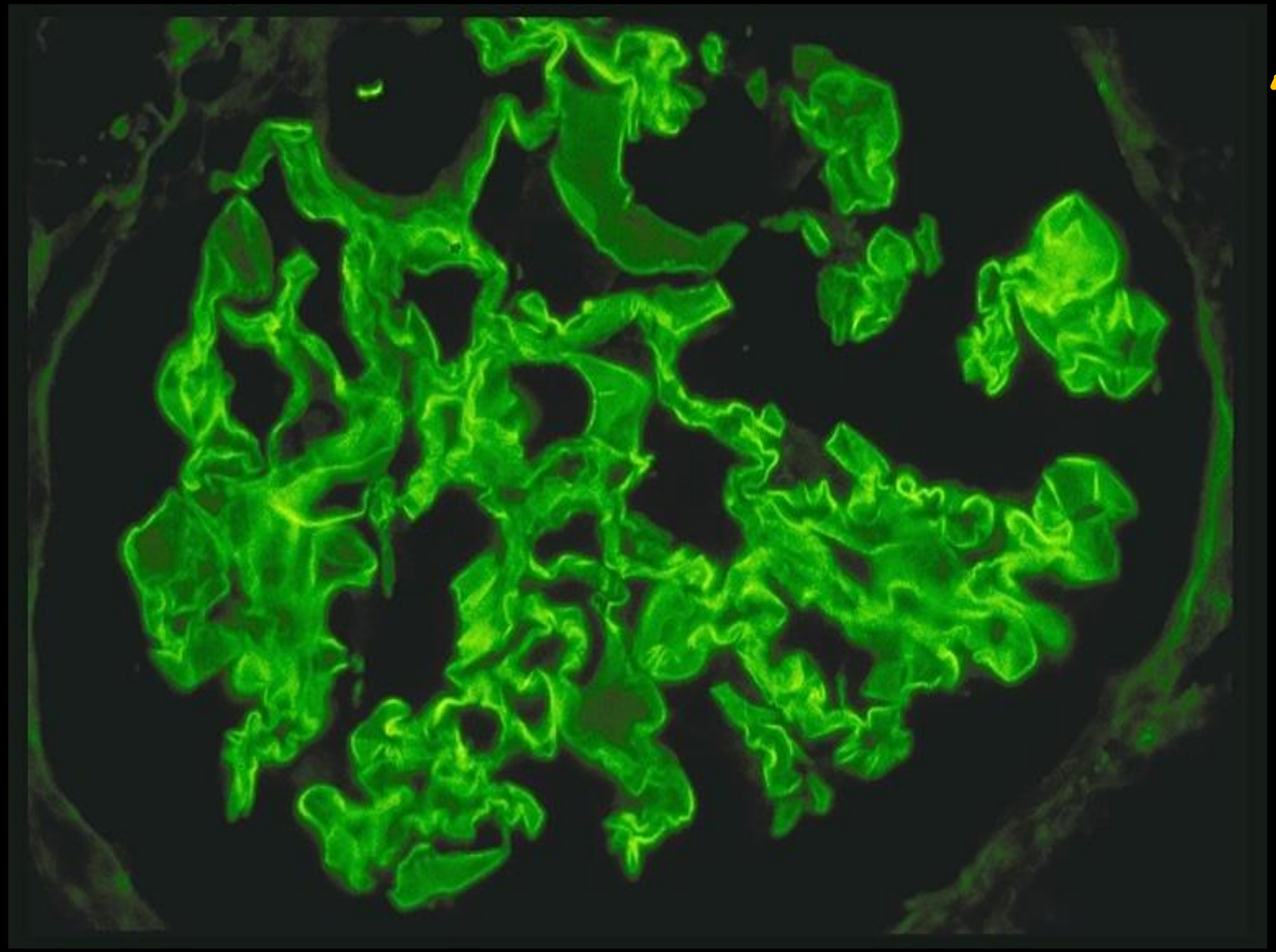
When advancing the destructive process of glomeruli the crescent becomes more fibrous (or scarred) and the cells composing it diminish progressively until disappearing, being replaced by fibroblasts. Stains for fibrous tissue, like trichrome and silver, emphasize this component (green arrows), in this case without epithelial component; the blue arrows indicate remains of glomerular tuft. (Methenamine-silver, X400).



IC : in situ – fixed Ag



Linear IF



Anti-GBM Disease

Pauci-Immune Proliferative Extracapillary GN

- Crescentic GN without immunoglobulins or complement deposition is called pauci-immune.
- The disease may be part of a systemic vasculitis and, since affects glomerular capillaries, it would be called small vessel vasculitis.
- When it is not part of a systemic disease and there is only renal involvement, it is also known with the names idiopathic crescentic GN, primary crescentic GN, or vasculitis limited to the kidney.

Pauci-Immune Proliferative Extracapillary GN

- Approximately 90% of patients with pauci-immune crescentic GN have ANCAs.
- Cases of idiopathic crescentic GN not associated to ANCAs, immune complexes nor anti-GBM antibodies are very rare (approximately 5%).
- Pauci-immune crescentic GN is the most frequent cause of rapidly progressive GN and the pulmonary-renal syndrome.
- The differential diagnosis in crescentic pauci-immune GN is: Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and idiopathic crescentic GN.

Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing GN is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. MPO-ANCA
Granulomatosis with polyangiitis (Wegener)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small-to-medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing GN is common. PR3-ANCA
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when GN is present.MPO-ANCA

Pauci-Immune Proliferative Extracapillary GN

- There is clinical or morphologic evidence of renal involvement in 90% of patients with microscopic polyangiitis, 80% of patients with Wegener and 45% of patients with Churg-Strauss.
- ANCAs are detected in 80-90% of patients with Wegener's granulomatosis and microscopic polyangiitis, and in 60% of patients with Churg-Strauss syndrome
- The levels of ANCA antigens correlate with the degree of activity of the disease

SPECIAL ARTICLE www.jasn.org

Histopathologic Classification of ANCA-Associated Glomerulonephritis

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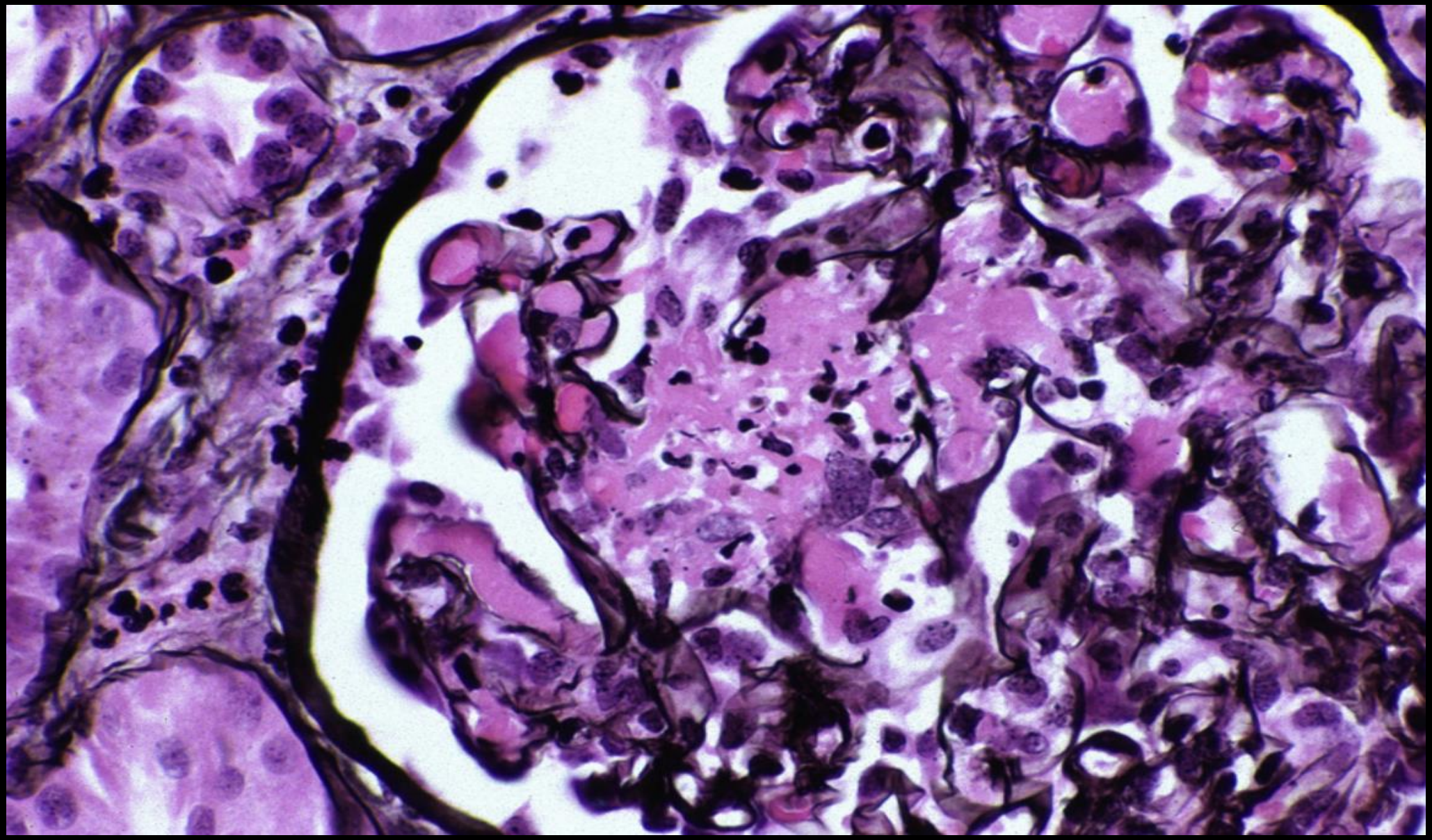
J Am Soc Nephrol 21: 1628–1636, 2010

Histopathologic Classification Schema for ANCA-Associated Glomerulonephritis

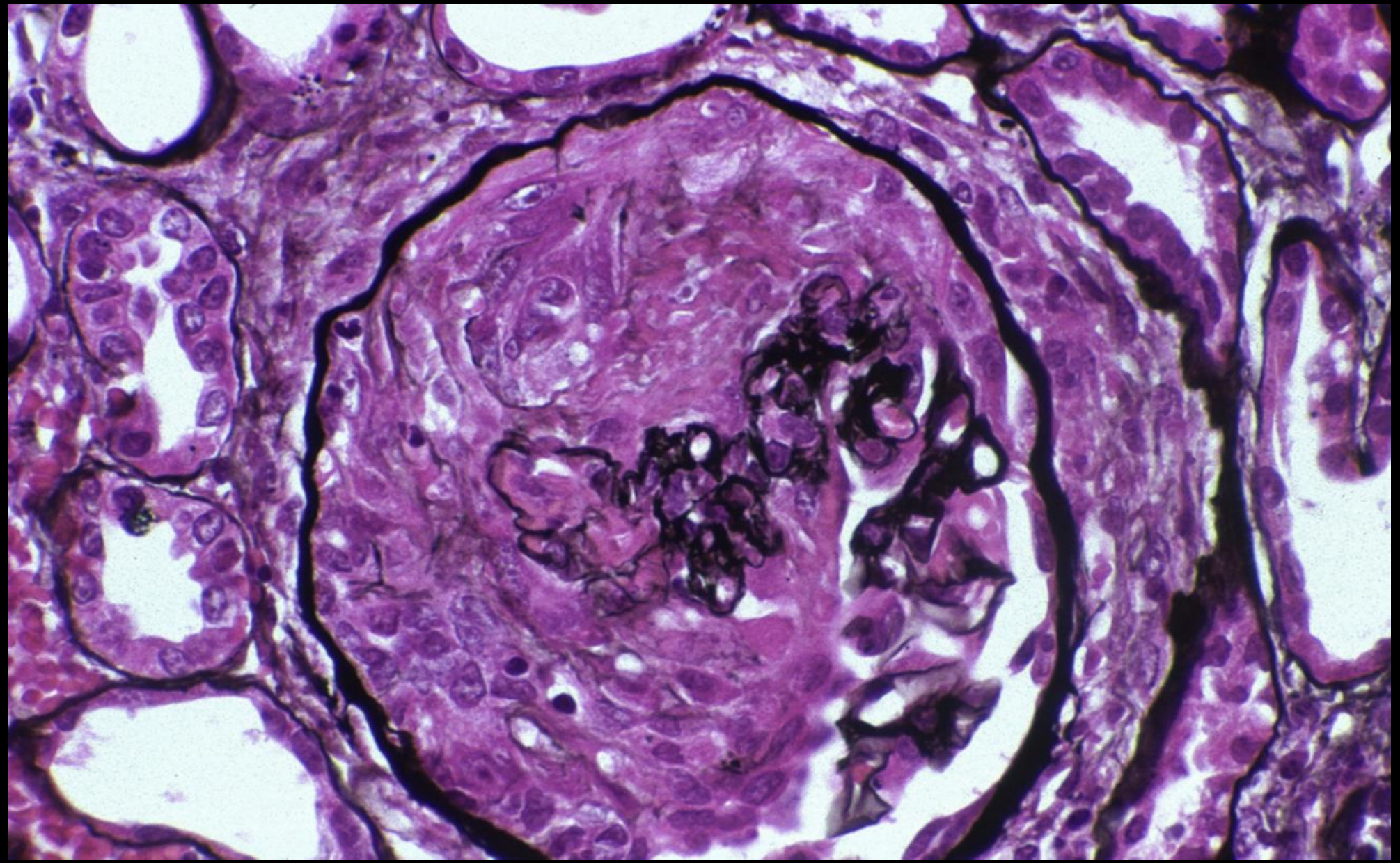
- **Focal**: ≥50% normal glomeruli.
- **Crescentic**: ≥50% glomeruli with cellular crescents.
- **Mixed**: <50% normal, <50% crescentic, <50% globally sclerotic glomeruli.
- **Sclerotic**: ≥50% globally sclerotic glomeruli.

This classification is of aid in the **prognostication** of patients at the time of diagnosis and facilitates **uniform reporting** between centers.

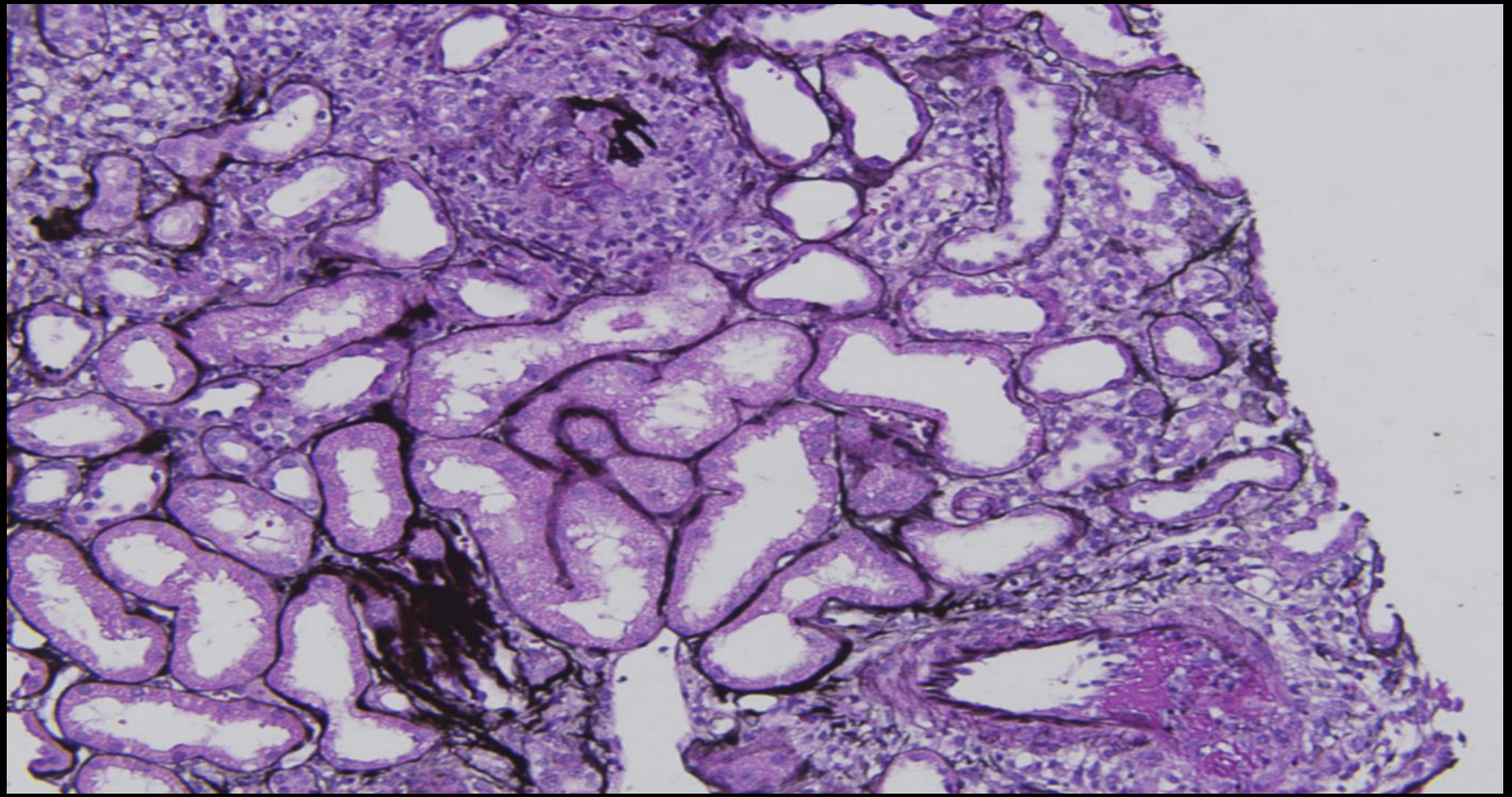
J Am Soc Nephrol 21: 1628–1636, 2010



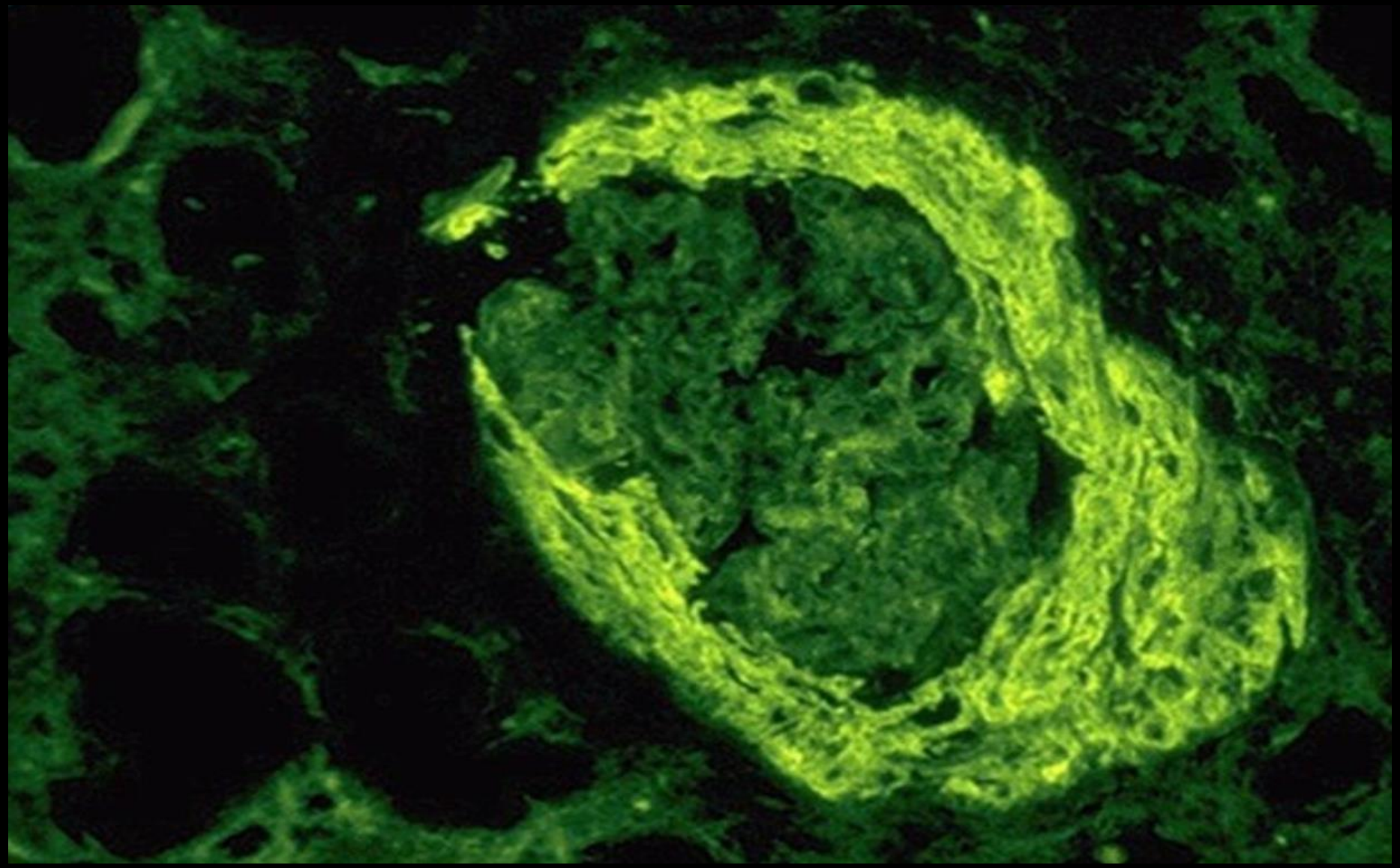
Pauci-immune necrotizing crescentic glomerulonephritis with fibrinoid necrosis, nuclear debris, and glomerular basement membrane break (Jones silver stain)



Pauci-immune necrotizing crescentic glomerulonephritis with cellular crescent and collapse of the glomerular tuft with fibrinoid necrosis (Jones silver stain).



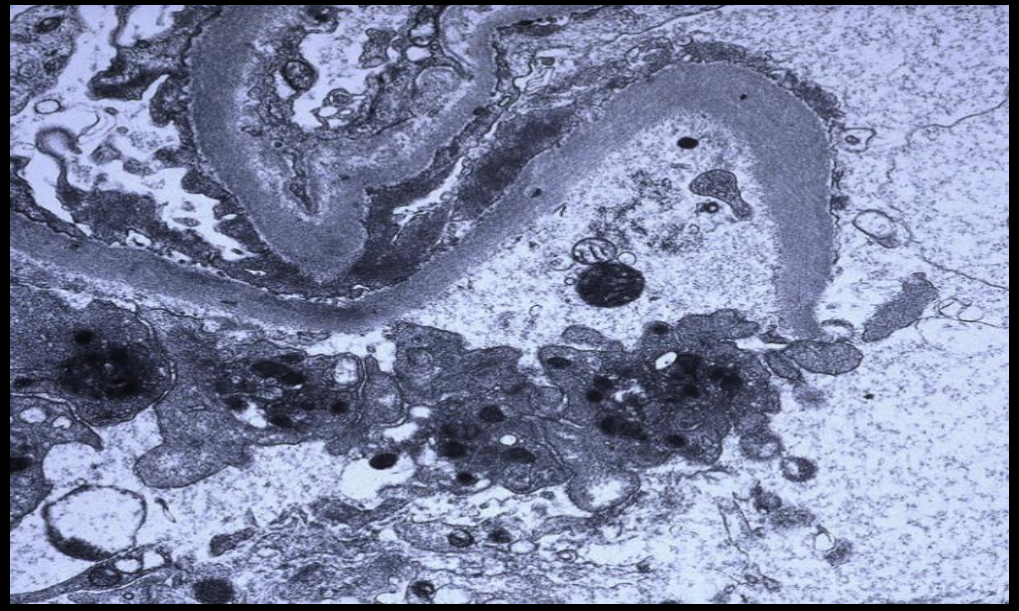
Pauci-immune necrotizing crescentic glomerulonephritis with cellular crescent, collapse of the glomerular tuft, and disruption of Bowman capsule (upper center). Also present is an artery with fibrinoid necrosis (lower right; Jones silver stain)



The crescent show positivity for fibrinogen.

Electron microscopy

- In anti-GBM disease and pauci-immune GN the findings are very similar: rupture of GBM and Bowman's capsule, focal effacement of podocyte foot processes, fibrin in urinary space and tuft, and fibrinoid necrosis.
- It must not have electron-dense deposits indicating immune complexes disease.



Observational Study

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Clinical outcomes of IgA nephropathy patients with different proportions of crescents

Wang Zhang, PhD[a], Qian Zhou, MSc[a], Lingyao Hong, MSc[a], Wenfang Chen, PhD[b], Shicong Yang, PhD[b], Qiongqiong Yang, MD, PhD[a], Wei Chen, MD, PhD[a,*], Xueqing Yu, MD, PhD[a]

Abstract

Crescents involving more than 50% of glomeruli in IgA nephropathy (IgAN) signify a rapid deterioration of renal function. However, little is known about the prognosis of IgAN patients presenting crescents in less than 50% of glomeruli. We aimed to investigate the clinicopathological characteristics and outcomes of IgAN patients with different proportions of crescents.

From January 2000 to December 2011, biopsy-proven primary IgAN patients with histological crescents formation were enrolled in this retrospective cohort study. The patients were divided into 4 groups on the basis of crescent proportion as follows: <5%, 5% to 9%, 10% to 24%, and ≥25%. The primary endpoint was defined as the doubling of baseline serum creatinine (SCr) and/or end-stage renal disease (ESRD), and the secondary endpoint was death.

A total of 538 crescent-featured IgAN patients were followed up and included in the analysis. The median crescent proportion was 8.0%. An increasing crescent proportion was associated with a reduced estimated glomerular filtration rate (eGFR), decreased level of hemoglobin, and increased amount of urine protein excretion. After a median follow-up period of 51 months (range 12–154 months), the endpoint events-free survival rate of the above 4 groups were 69.9%, 47.7%, 43.8%, and 40.6%, respectively (Log rank=13.7, P= 0.003), when we incorporated death with renal outcome as a composite endpoint. Multivariate Cox regression analyses adjusting for eGFR, hypertension, proteinuria, and the Oxford-MEST classification demonstrated the predictive significance of an increasing crescent proportion with renal survival and mortality (each increase by 5% [log-transformed]: HR=1.51, 95% CI 1.08–2.11, P=0.02). Further comparisons of patients with small proportions of crescents (<5%) and those absent of such pathological lesion showed that the 2 groups of patients had comparable prognosis.

An increasing crescent proportion was identified as an independent predictor for unfavorable clinical outcomes in IgAN. Therefore, a small proportion of crescents, over 5% particularly, should be paid more attention in clinical practice.

Zhang et al. Medicine (2017) 96:11 Medicin

Conclusion

The present study showed that an increasing crescent proportion in IgAN was independently associated with unfavorable outcomes, even after adjusting for clinical factors and Oxford-MEST pathological parameters.
The prognostic value of the crescent proportion remains to be further consolidated considering the influence of immunosuppression
and needs to be assessed in larger prospective studies.

Research Article

Analysis of Various Types of Glomerulonephritis with Crescents at a Single Center

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Conclusions

In cases of glomerulonephritis with at least one crescentic lesion, global sclerosis and eGFR calculated using the creatinine value at renal biopsy were independent factors for exacerbated renal prognosis, regardless of the underlying disease,

We also suspect that the formation of at least one crescentic lesion led to the development of these predictive factors, regardless of the type of glomerular disease and degree of crescent formation.

Key Points

- CGN is not a diagnosis and only points towards a set of differential diagnoses that require further diagnostic work up.
- Classification of Crescentic GN Is according to Immunopathologic Features
- Histopathological presentation in renal tissue is similar for anti-GBM and pauci-immune crescentic GN.
- The clinical presentation of the Wegener's granulomatosis and microscopic polyangiitis does not allow making a precise differential diagnosis; this is possible only demonstrating presence of granulomas
- Interstitial granulomas not associated to glomeruli indicate Wegener's granulomatosis.
- Cellular crescents can be reversible, but when multilevel growth of PECs associate with an epithelial-mesenchymal transition-like change in cell phenotype, fibrous crescents form, and crescents become irreversible also in terms of GFR recovery.
- suggesting that the formation of at least one crescentic lesion led to the development of predictive factors.


Thank you For Your Attention