

IgA Nephropathy

Immune pathogenesis · glomerular morphology · clinical correlation

Renal pathology teaching lecture

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Learning objectives

- Recognize the clinicopathologic definition of IgA nephropathy
- Trace the multi-hit mechanism from altered IgA1 to mesangial injury
- Interpret light microscopy, immunofluorescence, and electron microscopy
- Relate morphology to hematuria, proteinuria, and renal outcomes

Defining lesion: Mesangial IgA deposition

Pathologic identity

Prominent IgA deposits in the glomerular mesangial region are essential to its diagnosis.

Clinical expression

Recurrent hematuria is characteristic;
Proteinuria is often mild.

Why IgA nephropathy is a glomerulonephritis

Immune process

Deposited IgA or IgA-containing immune complexes initiate local injury.

Mesangial response

Mesangial cells proliferate and synthesize extracellular matrix.

Functional disturbance

Glomerular inflammation produces hematuria; Barrier injury may cause proteinuria.

Three biopsy modalities answer different questions

Method	Principal question	Expected clue
Light microscopy	What is the injury pattern?	Mesangial expansion ± proliferation
Immunofluorescence	Which immunoreactant deposits?	Dominant mesangial IgA
Electron microscopy	Where are the dense deposits?	Predominantly mesangial

IgA nephropathy in epidemiologic context

- It is the most common glomerulonephritis worldwide
- It may occur at any age, particularly older children and young adults
- Clinical presentation and long-term prognosis vary substantially

The cardinal presentation is hematuria

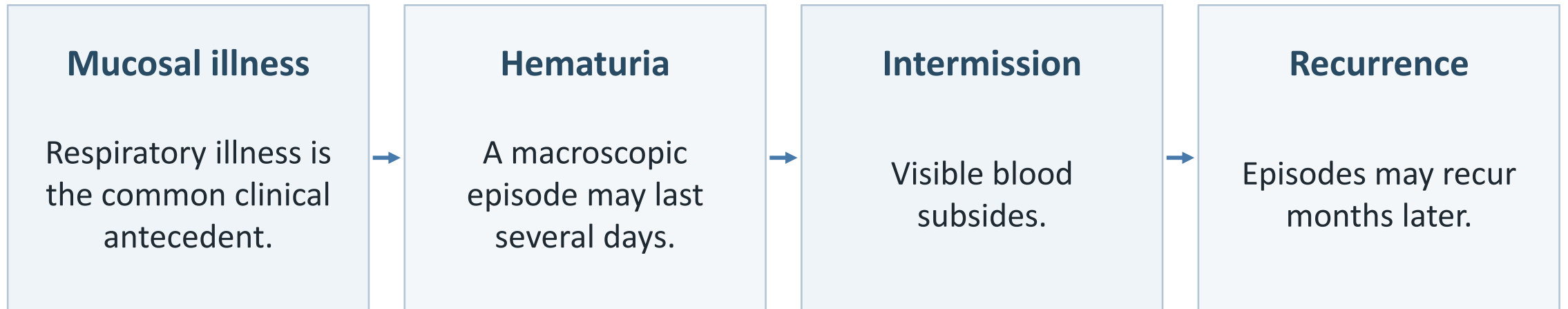
Macroscopic hematuria

Visible blood in urine may appear after a respiratory, gastrointestinal, or urinary infection.

Microscopic hematuria

Urine sediment abnormalities may be the only initial clue, sometimes with proteinuria.

Infection-associated hematuria is often recurrent



The infection association does not identify a single agent

- Respiratory and gastrointestinal exposure may stimulate production of abnormal IgA
- Viruses, bacteria, and food proteins have all been implicated
- The specific initiating antigen or antigens remain unknown

Microscopic hematuria may be the only clue

- Isolated or predominant microscopic hematuria in 30%–40%
- Proteinuria may accompany microscopic hematuria
- A relatively silent clinical presentation does not establish a specific biopsy pattern

Proteinuria reflects variable barrier injury

Typical proteinuria

Usually mild in IgA nephropathy.

Marked proteinuria

Can accompany more extensive glomerular injury and worsens prognostic assessment.

Nephrotic syndrome is not the dominant phenotype

- The nephrotic syndrome may occasionally arise
- Robbins relates such cases to widespread podocyte injury
- Podocyte injury adds a filtration-barrier component to mesangial disease

A minority present with acute nephritic syndrome

Acute nephritic presentation

5%–10% of patients with an acute nephritic syndrome.

Rapidly progressive presentation

Some severe cases show crescentic glomerulonephritis and an aggressive course.

Primary and secondary contexts must be separated

Usually renal-limited

Primary IgA nephropathy is typically an isolated kidney disease.

Potentially associated disease

Mesangial IgA deposits also occur in systemic conditions or secondary renal involvement.

Recognized secondary clinical associations

Liver disease

Impaired hepatobiliary clearance of IgA-containing complexes.

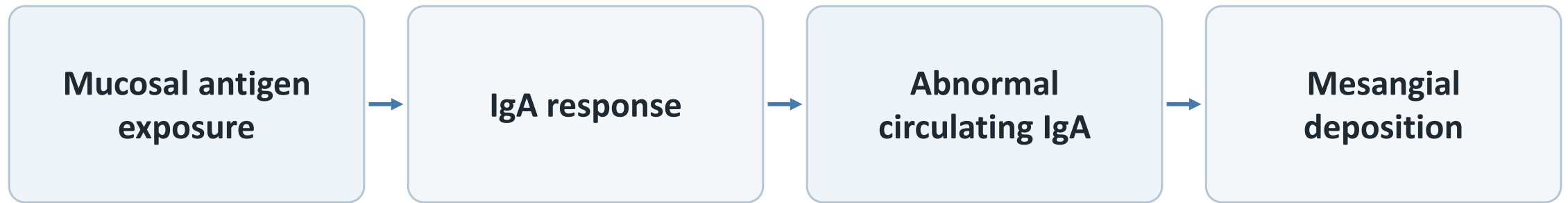
Gluten enteropathy

Altered intestinal mucosal integrity in celiac disease.

Staphylococcal infection

An infectious setting can be accompanied by secondary IgA-dominant glomerular injury.

IgA links mucosal immunity with renal deposition



Schematic — proposed link

Normal plasma IgA exists mainly as monomers

Mucosal IgA

IgA is the principal immunoglobulin in mucosal secretions.

Circulating IgA

Serum IgA is normally present mainly as monomers; Polymeric forms are cleared, including by the liver.

Polymeric IgA is increased but is insufficient alone

- Patients may have increased circulating polymeric IgA
- Polymeric IgA abundance by itself does not explain disease
- The molecular quality of IgA1 is central to the proposed pathogenesis

The IgA1 hinge region is a vulnerable target

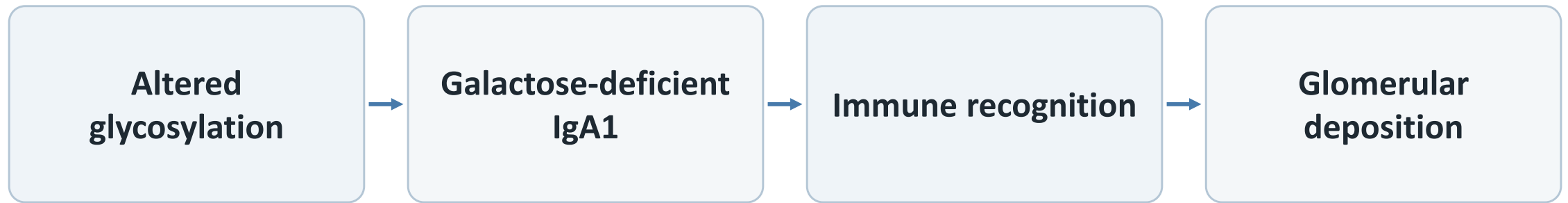
IgA1 architecture

O-linked glycans are attached to the hinge region of IgA1.

Abnormal IgA1

Defective assembly or attachment of galactose-containing glycans changes the molecule recognized by the immune system.

Abnormal O-glycosylation is a central hit



Conceptual pathogenesis

A multi-hit pathogenesis integrates several events

- 1 Production of galactose-deficient IgA1
- 2 Immune recognition of the altered IgA1 molecule
- 3 Formation or local assembly of immune complexes
- 4 Mesangial cell activation and glomerular injury

IgG autoantibodies recognize abnormal IgA1

Antigen

An abnormally glycosylated IgA1 molecule may become an autoimmune target.

Antibody response

IgG antibodies may bind altered IgA1 and create circulating immune complexes.

Immune complexes can form along two routes

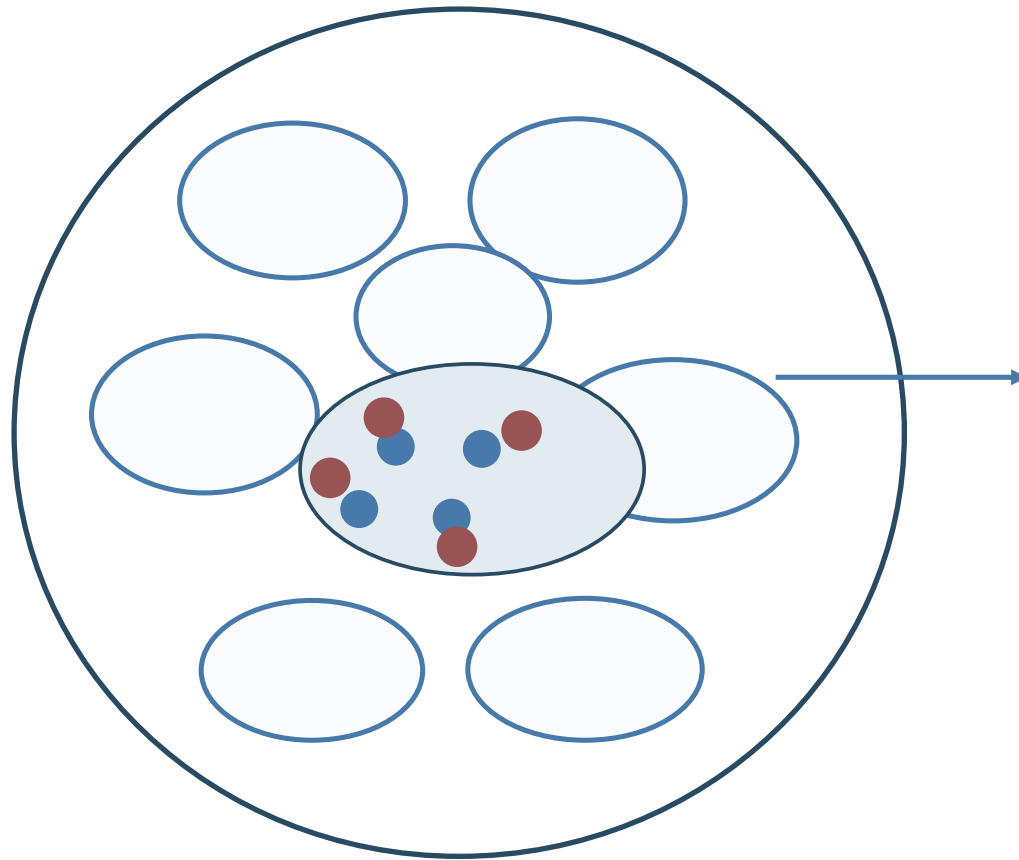
Circulating route

IgG antibodies bind abnormal IgA1 before glomerular deposition.

In situ route

Abnormal IgA1 deposits first; Immune complexes then form within the mesangial compartment.

The mesangium is the dominant deposition site

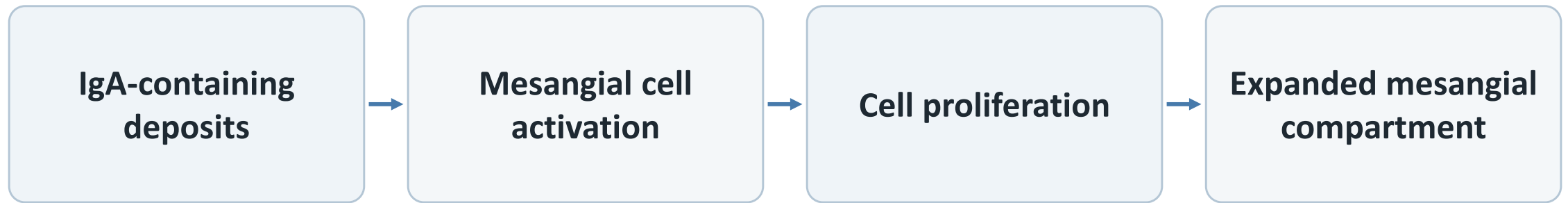


Mesangial immune deposits

Central supporting region of the glomerular capillary tuft

Schematic — not a specimen

IgA deposits stimulate mesangial activation



Native conceptual diagram

Mesangial matrix increases with inflammation

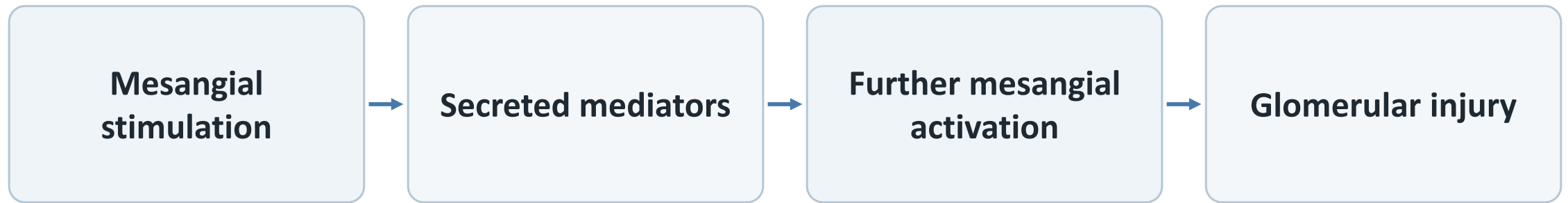
Cellular component

Activated mesangial cells proliferate and increase cellularity.

Matrix component

The same activated cells generate additional extracellular matrix.

Cytokines and growth factors amplify the response



Autocrine and paracrine effects

Inflammatory cells add to glomerular injury

Recruitment

Mesangial mediators may recruit inflammatory leukocytes into glomeruli.

Consequences

Leukocytes contribute to injury as well as clearance and repair of immune complexes.

Immune complex handling is both injurious and reparative

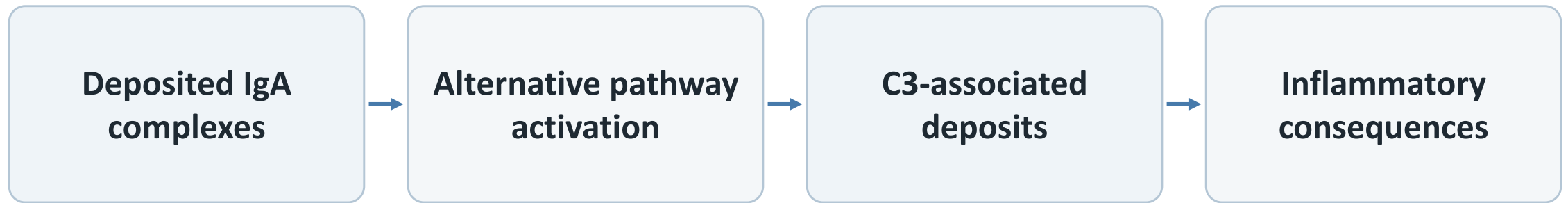
Potential harm

Complement and inflammatory cells can amplify tissue damage.

Potential resolution

Opsonization and immune-complex removal contribute to repair.

Alternative complement pathway is implicated



Complement pathway simplified

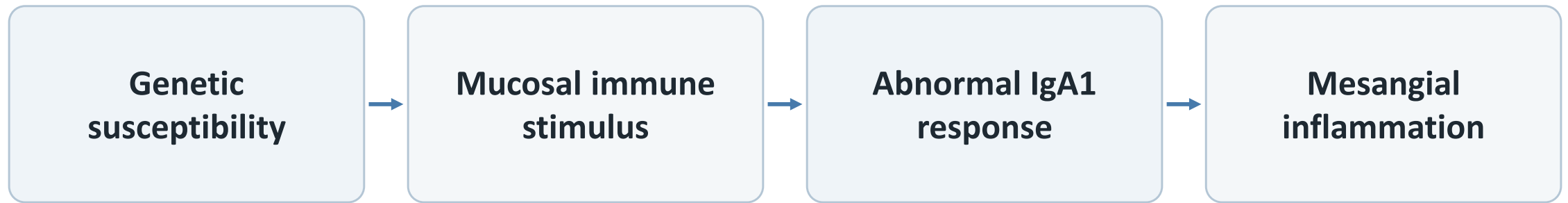
Complement staining is a mechanistic clue

Deposit	Robbins description	Interpretive role
IgA	Prominent mesangial staining	Defines deposited immunoglobulin
C3 / properdin	Frequently accompany IgA	Consistent with complement activation
C1q / C4	Usually absent	Early classical components not typical
IgG / IgM	May occur in lesser amounts	Ancillary deposits

Inherited susceptibility modifies disease risk

- Familial clustering and concordance in HLA-identical siblings are reported
- Some HLA and complement-related genotypes are associated with disease
- Genome-wide association studies implicate MHC class II regions

Environmental exposure acts on a susceptible host



Risk and response are not a deterministic sequence

The multi-hit model connects blood to biopsy

- 1 Mucosal immune stimulation in a susceptible host
- 2 Circulating polymeric, aberrantly glycosylated IgA1
- 3 IgG autoantibodies / IgA-containing complexes
- 4 Mesangial deposition, complement and cell activation
- 5 Proliferation, matrix expansion, inflammatory injury

Clinical and tissue findings need integration

Urine

Gross or microscopic hematuria; Often mild proteinuria.

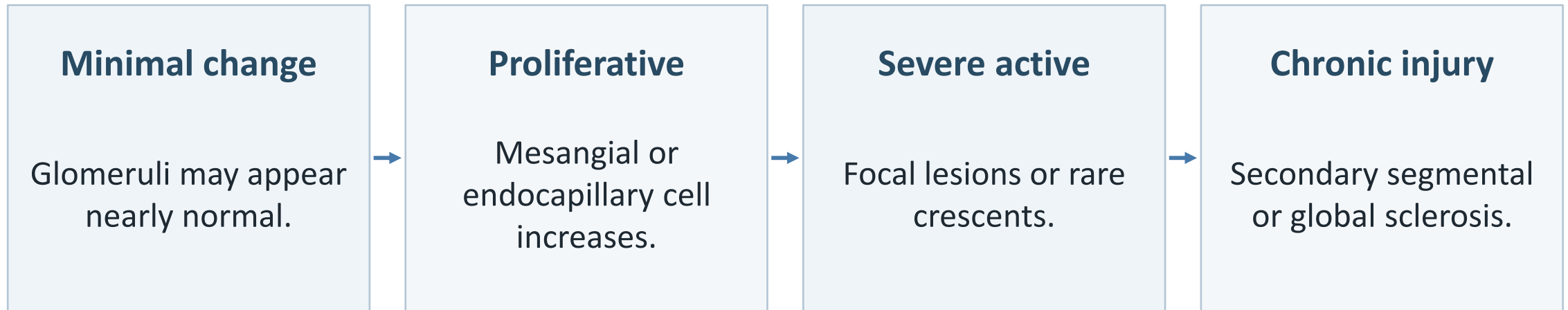
Light microscopy

Variable mesangial and proliferative patterns.

Immunopathology

Mesangial IgA deposition anchors diagnosis.

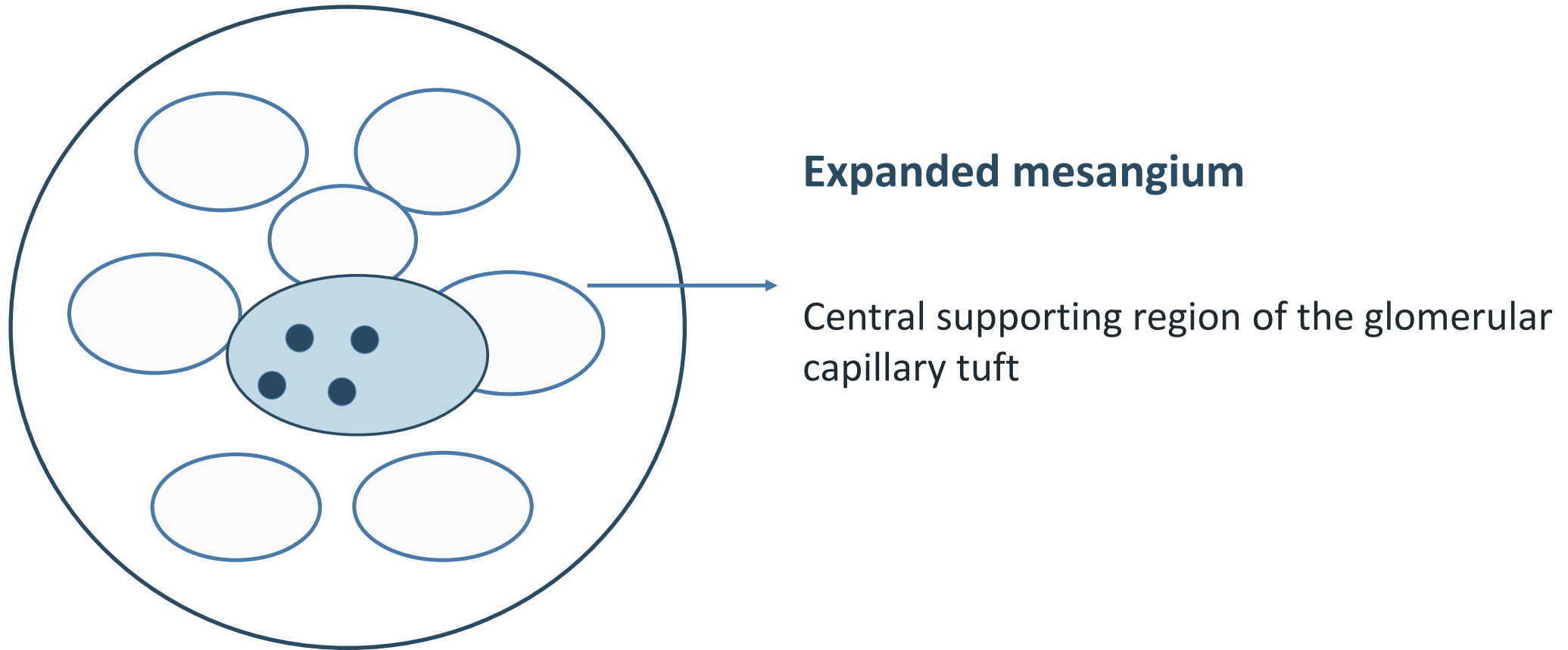
Light microscopy shows a wide spectrum



Normal-looking glomeruli do not exclude IgA disease

- IgA nephropathy may have few changes by light microscopy
- A visually subtle biopsy can still show prominent IgA on immunofluorescence
- Diagnostic correlation across light microscopy, IF, and EM is essential

Mesangial hypercellularity is a common active pattern



Schematic — not a specimen

Expanded mesangium has several contributors

Cells

Proliferation increases mesangial cell number.

Matrix

Extracellular matrix accumulation enlarges the compartment.

Deposits

Immune material may also contribute to widening.

Endocapillary proliferation changes capillary patency

Tissue finding

Cells within glomerular capillary spaces increase and may be accompanied by leukocytes.

Functional meaning

Inflammatory crowding can reduce filtration surface and contribute to nephritic manifestations.

Focal and segmental proliferation is possible

Focal

Only some glomeruli are affected by proliferative lesions.

Segmental

Within an affected glomerulus, only part of the tuft may show injury.

Crescentic IgA nephropathy is a severe pattern

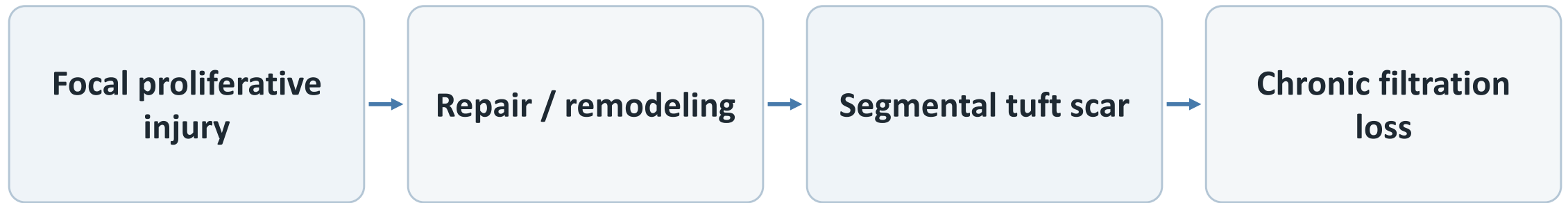
Morphology

Crescents may occur, although overt crescentic GN is uncommon in this source.

Clinical correlation

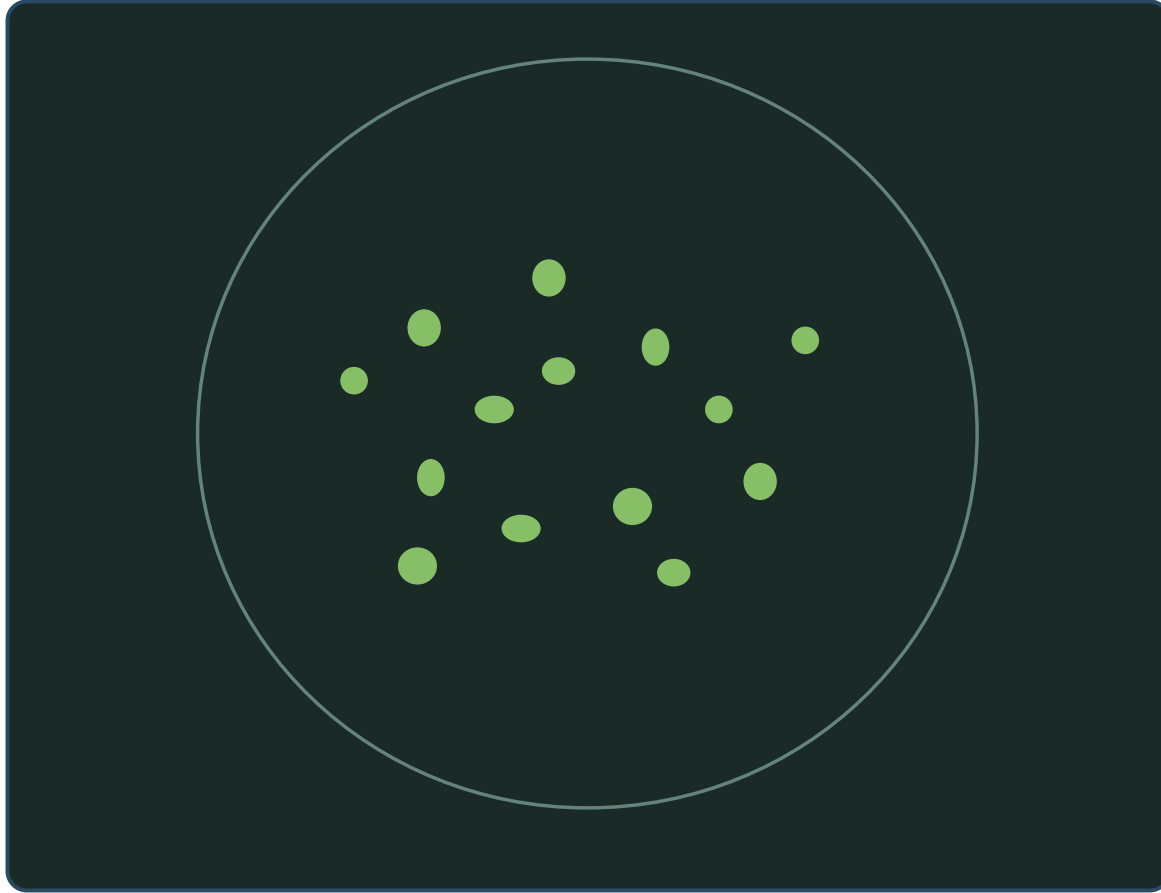
The severest presentations can include a rapidly progressive nephritic course.

Healing may leave focal segmental glomerulosclerosis



Chronic sequelae

Immunofluorescence demonstrates mesangial IgA



Schematic — not a specimen

Illustrative mesangial IgA distribution

- IgA localization is mesangial
- C3 and properdin often accompany IgA
- Early classical components usually absent

IgA staining must be interpreted with co-deposits

IgA

Mesangial pattern is diagnostic in the appropriate clinical setting.

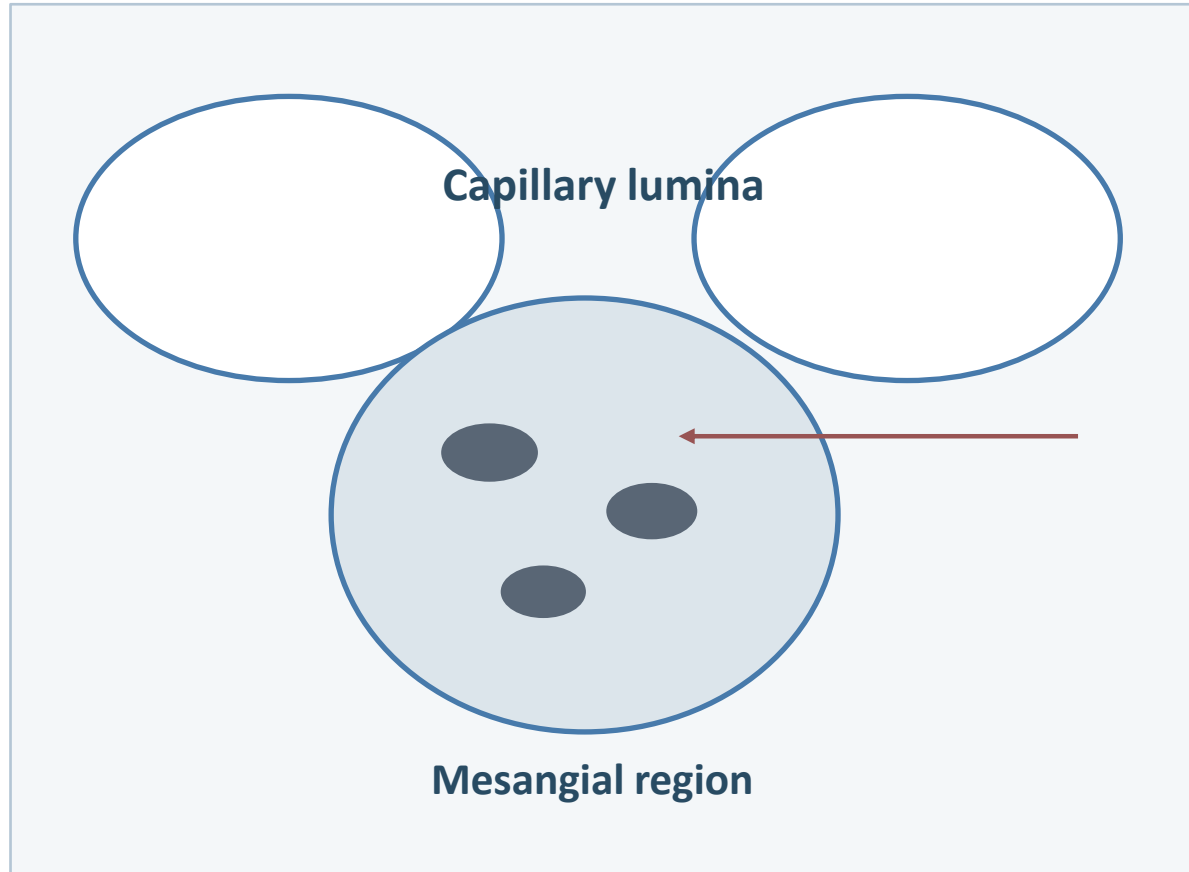
C3 / properdin

Common accompanying immune reactants.

IgG / IgM

May be present but are usually less prominent.

Electron microscopy localizes immune deposits



Electron-dense immune deposits

Predominantly mesangial; Capillary-wall deposits usually sparse when present

Schematic — not a specimen

Capillary-wall deposits are usually sparse

- Electron-dense deposits predominate in the mesangium
- Additional capillary-wall deposits, when present, are usually sparse
- The dominant mesangial location helps connect pathogenesis with immunofluorescence

The three modalities provide convergent evidence

Finding	Light microscopy	IF / EM corroboration
Mesangial expansion	More cells and / or matrix	Mesangial deposits on IF / EM
Endocapillary activity	Capillary crowding $\pm$ leukocytes	IgA immune deposits establish type
Segmental scarring	Chronic focal segmental sclerosis	IgA may remain detectable
Crescents	Severe extracapillary injury	Biopsy still requires immune typing

How morphology links to clinical phenotype

Pathologic process	Expected consequence
Mesangial + glomerular inflammation	Erythrocyte leakage → hematuria
Podocyte / barrier injury	Increased albumin passage → proteinuria
Active severe proliferation	Acute nephritic or rapidly progressive syndrome
Glomerular scarring	Loss of functioning filtration units

Biopsy IgA and circulating IgA are different measures

Circulating IgA

Elevated polymeric IgA may occur but is not sufficient for disease.

Deposited IgA

Glomerular IgA deposits are required to establish the biopsy diagnosis.

Henoch–Schönlein purpura has overlapping renal disease

IgA nephropathy

Usually an isolated renal process with mesangial IgA.

Henoch–Schönlein purpura

A systemic disorder of children may show a similar IgA-associated renal lesion.

Secondary IgA deposition requires clinical context

Liver disease

Consider defective IgA complex clearance.

Intestinal disease

Consider celiac disease and mucosal defects.

Staphylococcal infection

Consider an infection-associated immune process.

IgA nephropathy versus Alport-spectrum disease

Distinguishing feature	IgA nephropathy	Alport spectrum
Dominant mechanism	Mesangial immune deposits	Type IV collagen defect
IF pattern	Mesangial IgA	IgA deposition not defining
Ultrastructure	Mesangial electron-dense deposits	Irregular GBM thinning / splitting
Clinical clues	Recurrent hematuria after infection	Familial hematuria ± hearing / eye findings

The subsequent course is highly variable

Stable course

Some patients retain renal function for decades.

Recurrent activity

Hematuria episodes may recur repeatedly.

Progressive course

A subset develops chronic renal impairment.

Long-term progression is a substantive risk

- Chronic renal failure in 15%–40% over 20 years
- Risk is not uniform across patients
- Clinical and biopsy predictors help identify those more likely to progress

Clinical predictors of progression

At presentation

Older age at onset is associated with increased risk.

During follow-up

Heavy proteinuria and hypertension are unfavorable.

At biopsy

Greater glomerulosclerosis suggests chronic injury and risk.

Biopsy scarring has prognostic meaning

Active lesion

Mesangial or endocapillary proliferation reflects inflammation at biopsy.

Chronic lesion

Glomerulosclerosis indicates accumulated irreversible injury and is linked to worse prognosis.

IgA deposits often recur after transplantation

Pathologic recurrence

IgA deposits frequently reappear in renal allografts.

Clinical evolution

Similar slow progression in about 15% of those with recurrent IgA deposits.

Diagnostic reasoning begins with the phenotype

- 1 Recognize recurrent gross or persistent microscopic hematuria
- 2 Assess concomitant proteinuria and kidney dysfunction
- 3 Consider systemic and secondary IgA-associated conditions
- 4 Use biopsy morphology together with IgA immunofluorescence

Case study: Recurrent visible hematuria

Illustrative vignette

A young adult reports repeated short episodes of visible hematuria following respiratory illnesses. Between episodes, urine appearance normalizes.

Question

Which renal immune-deposit pattern would strongly support IgA nephropathy?

Case discussion: Hematuria after mucosal illness

Central clue

Recurrent gross hematuria after respiratory infections is a recognized presentation.

Pathologic answer

Mesangial IgA deposition by immunofluorescence; EM typically shows mesangial electron-dense deposits.

Case study: Silent urine abnormalities

Illustrative vignette

Routine testing reveals persistent microscopic hematuria and mild proteinuria without a history of visible blood in the urine.

Question

Can IgA nephropathy be present if the light microscopic biopsy appearance is subtle?

Case discussion: IF resolves subtle light microscopy

Interpretation

Yes. Some IgA nephropathy biopsies appear normal or nearly normal under light microscopy.

Diagnostic test

IgA staining in the glomerular mesangium is needed for diagnosis.

Case study: Rapidly declining kidney function

Illustrative vignette

A person with hematuria develops rapidly worsening renal function and a biopsy containing crescents.

Question

Does the presence of crescents exclude IgA nephropathy?

Case discussion: Severe active IgA disease

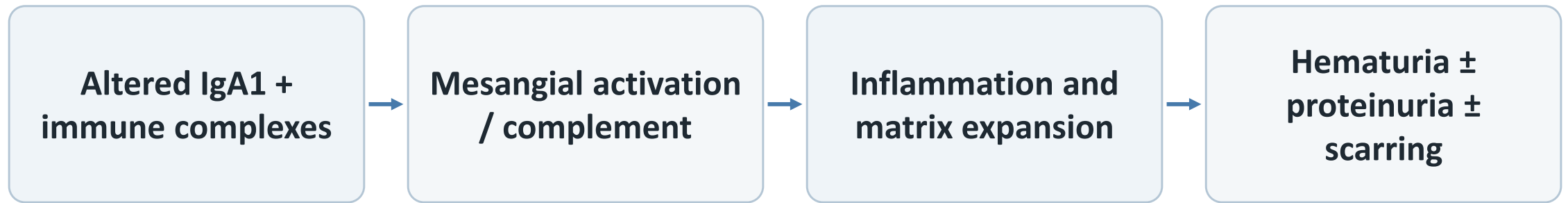
Interpretation

No. Crescentic glomerulonephritis is an uncommon but recognized IgA-associated pattern.

Required correlation

The biopsy still needs immunopathologic confirmation and clinical evaluation.

Integrated synthesis: Molecule to clinical outcome



Schematic integration

Core distinctions for pathology practice

- Light microscopy provides injury pattern; Immunofluorescence demonstrates the defining IgA deposits
- Most deposits are mesangial; C3 often accompanies them without typical C1q / C4
- Clinical behavior spans recurrent hematuria to progressive chronic renal failure
- Age, heavy proteinuria, hypertension, and sclerosis inform prognosis

References and source boundaries

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Chapter 20, The Kidney · pp. 836–837

Substantive section: “Other Glomerular Diseases” → “IgA Nephropathy”

Original native diagrams are conceptual schematics, not patient specimens.

No external treatment guideline, grading system, or uncited clinical image is included.