

AA amyloidosis

Inflammation-associated systemic amyloid deposition

Mechanisms · morphology · clinicopathologic interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Connect persistent inflammation with hepatic SAA production and AA fibril deposition.
- Recognize the major associated diseases and organ distribution.
- Explain renal and systemic morphology and its clinical consequences.
- Distinguish confirmation of amyloid from identification of its biochemical type.

Clinical starting point

A patient with long-standing inflammatory arthritis develops increasing urinary protein excretion. Kidney tissue shows extracellular amyloid deposits.

1. Which precursor protein is implicated by this clinical setting?

2. Why must a biopsy still establish amyloid type?

A clinical association guides suspicion; It does not prove AA composition.

Amyloidosis: A disorder of extracellular deposits

- Amyloid comprises insoluble fibrillar aggregates derived from amyloidogenic proteins.
- Deposits accumulate in extracellular tissues and can impair organ architecture.
- The term “amyloidosis” encompasses chemically distinct disorders with similar morphology.
- Identifying a deposit is a different task from identifying its precursor.

AA: The biochemical identity



Precursor and fibril are not interchangeable terms.

SAA is the circulating hepatic acute-phase precursor; AA names the deposited amyloid fibril protein.

Systemic rather than localized disease

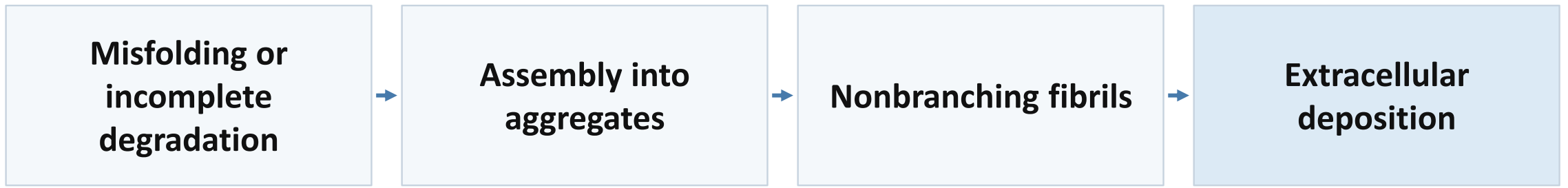
Systemic AA amyloidosis

- SAA originates predominantly in liver cells.
- Deposits arise at multiple distant tissue sites.
- Renal and other organ dysfunction may coexist.

Localized amyloidosis

- Deposits are restricted to a tissue or site.
- May have an unrelated amyloid precursor.
- The term does not designate AA automatically.

A shared amyloid architecture



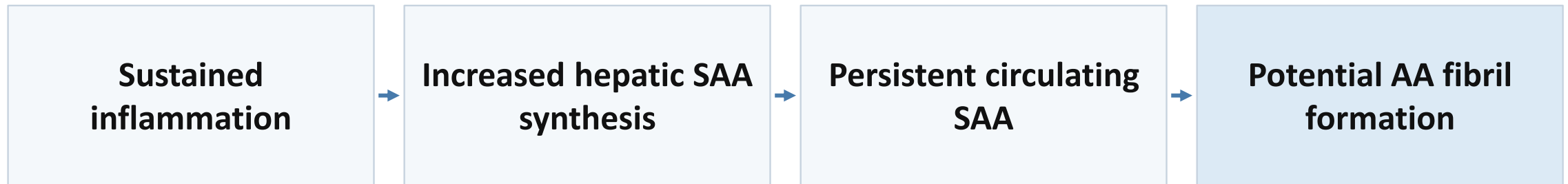
This is a generic amyloid sequence, applied here to SAA-derived protein.

Distinct precursor proteins converge on a similar fibrillar configuration.

Physical structure of amyloid

- Amyloid fibrils have a characteristic cross- β -pleated organization.
- Electron microscopy shows continuous, nonbranching fibrils approximately 8–10 nm in diameter.
- This shared structure underlies Congo red staining and birefringence.
- Appearance under routine stains alone cannot determine the chemical type.

The AA precursor belongs to an acute-phase response



The clinical disease supplies the inflammatory stimulus.

Increased SAA is required for this pathway but is not sufficient by itself for deposition.

Classification by deposited protein

Category	Fibril protein	Precursor / setting
AA	AA	SAA; Chronic inflammatory conditions
AL	Immunoglobulin light chain	Monoclonal plasma-cell proliferation
ATTR	Transthyretin	Wild-type or variant transthyretin

Why “secondary amyloidosis” is an older name

Historical terminology

- “Secondary” reflected an associated inflammatory disorder.
- It described a clinical context rather than fibril chemistry.

AA terminology

- Identifies the deposited amyloid A protein.
- Allows direct comparison with AL and ATTR by composition.

Historical infectious associations

- Tuberculosis was once a prominent underlying condition.
- Bronchiectasis and chronic osteomyelitis were also important associations.
- Their relative contribution declined after effective antibiotic therapy.
- The pathogenic connection is persistent inflammation, not infection of amyloid deposits.

Present-day inflammatory associations

Inflammatory setting	Examples named by Robbins
Inflammatory arthritis	Rheumatoid arthritis; Ankylosing spondylitis
Inflammatory bowel disease	Crohn disease; Ulcerative colitis
Persistent infection	Historically TB, bronchiectasis, osteomyelitis
Inflammation from injection-related lesions	Chronic skin infections after subcutaneous heroin injection

Rheumatoid arthritis: Principal association

- Rheumatoid arthritis is the most frequently associated condition account.
- Its chronic inflammatory activity supplies a sustained acute-phase stimulus.
- AA deposition is a systemic complication, not primary articular amyloid formation.
- Renal abnormalities in such a patient require tissue and amyloid typing.

Interpreting the rheumatoid arthritis figure

~3%

Textbook-reported occurrence of amyloidosis in rheumatoid arthritis

About one-half of affected patients have clinically significant amyloidosis. These are textbook contextual estimates, not a claim about present-day risk.

Other connective-tissue inflammation

- Ankylosing spondylitis is explicitly named among associated connective-tissue disorders.
- The shared factor is prolonged inflammatory signaling and acute-phase protein production.
- A specific inflammatory diagnosis does not imply that every patient forms amyloid.
- Duration and intensity of inflammation create biologic exposure, not a standalone diagnostic criterion.

Inflammatory bowel disease

Crohn disease

- Recognized AA-associated inflammatory bowel disorder.
- Inflammation can persist or recur for extended periods.

Ulcerative colitis

- Also included among recognized associations.
- AA is not inferred solely from the IBD label.

Subcutaneous narcotic injection and AA



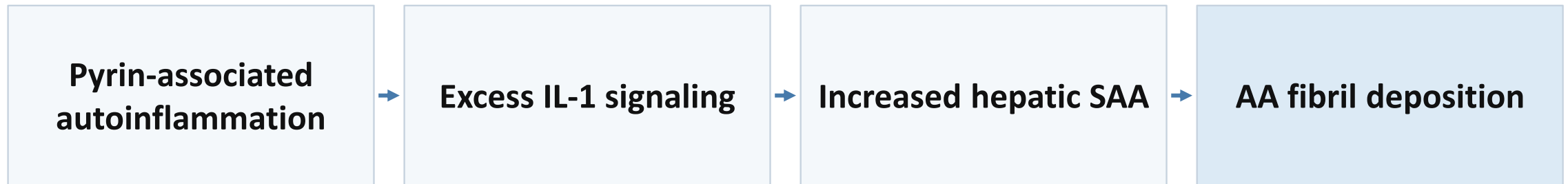
“skin-popping” to generalized AA via chronic skin infection.

The associated infection is the explanatory driver; Avoid assuming direct drug-to-fibril toxicity.

Neoplastic settings mentioned with AA

- AA amyloidosis can accompany certain solid tumors and lymphoid neoplasms.
- Renal cell carcinoma is identified as the most common associated solid tumor.
- Hodgkin lymphoma is another association named in the source.
- The chronic inflammatory milieu remains central to the AA mechanism.

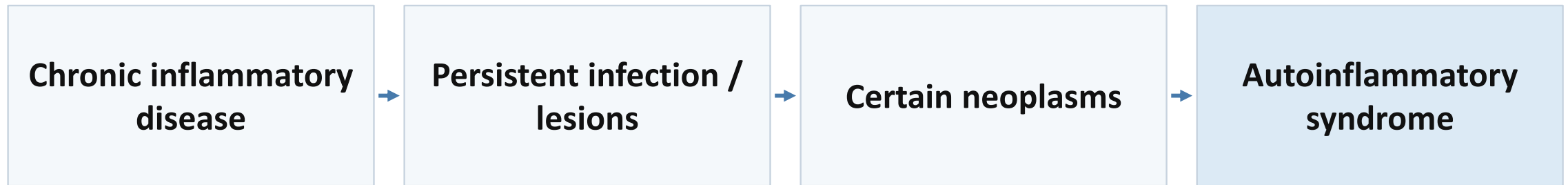
Familial Mediterranean fever: A related AA pathway



A hereditary inflammatory syndrome can produce the same AA fibril type.

The inherited disorder and the fibril biochemical identity are separate axes of classification.

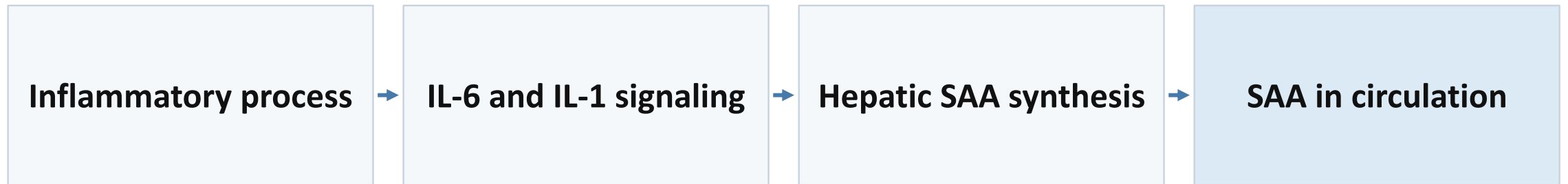
Etiologic groups share one downstream precursor



Different causes converge on inflammatory SAA stimulation.

Each box represents an association; It is not a quantitative comparison.

Cytokine-mediated hepatic stimulation



IL-6 and IL-1 are named examples, not a complete cytokine inventory.

Liver cells as the principal SAA synthesis site.

Inflammation changes hepatic protein production

- SAA is an acute-phase reactant made by liver cells.
- Its synthesis rises during inflammatory signaling.
- Long-standing inflammation maintains SAA at elevated concentrations.
- The precursor response is systemic even when the inflammatory lesion is localized.

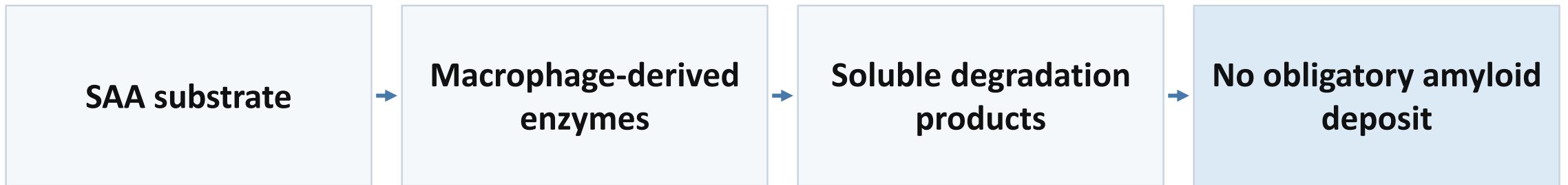
Circulating SAA and lipoproteins



Circulating SAA is described as bound to high-density lipoproteins.

A transport association is not itself proof that an individual will develop AA amyloidosis.

Normal SAA handling: Soluble degradation



Normally, extracellular protein handling prevents accumulation.

This normal catabolic pathway explains why a rise in SAA alone is insufficient.

Why elevated SAA alone is insufficient

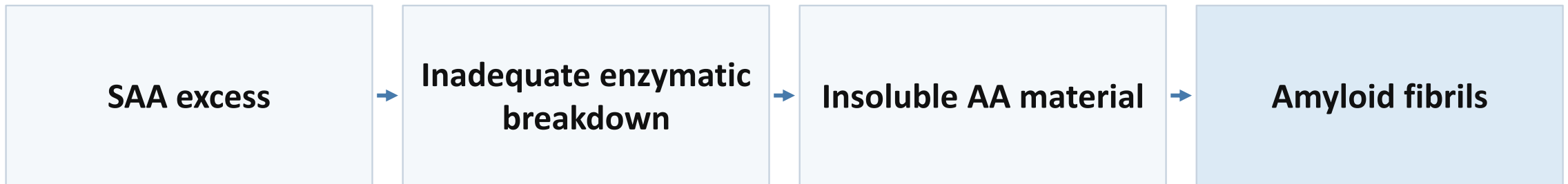
Increased input

- Inflammation amplifies SAA production.
- Precursor concentrations may remain raised.

Required additional failure

- SAA must escape effective degradation.
- Amyloidogenic material must become insoluble and aggregate.

Proposed mechanism: Incomplete proteolysis



An enzyme defect as a possible explanation, not an established universal mechanism.

Do not equate a proposed individual susceptibility mechanism with a clinically proven test.

Proposed mechanism: SAA structural variation



A genetically determined SAA abnormality is another hypothesis in the source.

The excerpt does not supply a specific variant or molecular test.

What the source establishes—and what it proposes

Robbins statement	Epistemic status
Inflammation induces SAA through IL-6/IL-1	Described mechanism
SAA is normally enzymatically degraded	Described normal pathway
High SAA alone cannot explain deposits	Explicit conclusion
A degradation-enzyme defect predisposes	Proposed explanation
SAA structural abnormality resists breakdown	Alternative proposed explanation

From prolonged inflammation to tissue damage



A mechanistic synthesis from the textbook; Susceptible intermediate steps are not fully resolved.

An arrow shows the explanatory sequence, not a patient-specific deterministic prediction.

Proteostasis as a general amyloid mechanism

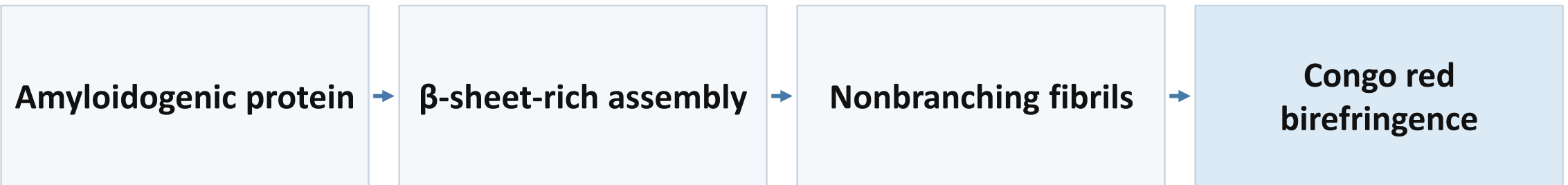
Normal safeguards

- Misfolded intracellular proteins undergo proteasomal degradation.
- Extracellular proteins can be processed by macrophages.

Amyloid setting

- Quality-control pathways fail to prevent aggregation.
- Insoluble fibrils accumulate outside cells.

Cross- β fibrils create a shared phenotype



Congo red confirms amyloid architecture; It does not establish AA chemistry.

AL, AA and ATTR differ in precursor despite shared staining behavior.

Extracellular deposits distort organs



Progression is mainly mechanical and architectural.

Deposits can injure tissues without eliciting a proportionate local inflammatory response.

Organs commonly affected in reactive systemic disease

Kidneys

Glomeruli; Vessels

Liver

Space of Disse

Spleen

White or red pulp

Lymph nodes

Systemic deposits

Adrenals

Systemic deposits

Thyroid

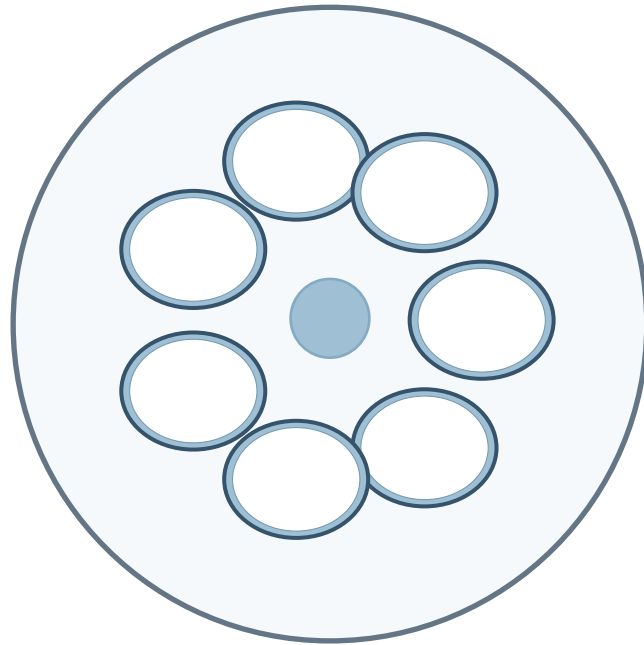
Systemic deposits

Kidney: The major clinicopathologic target

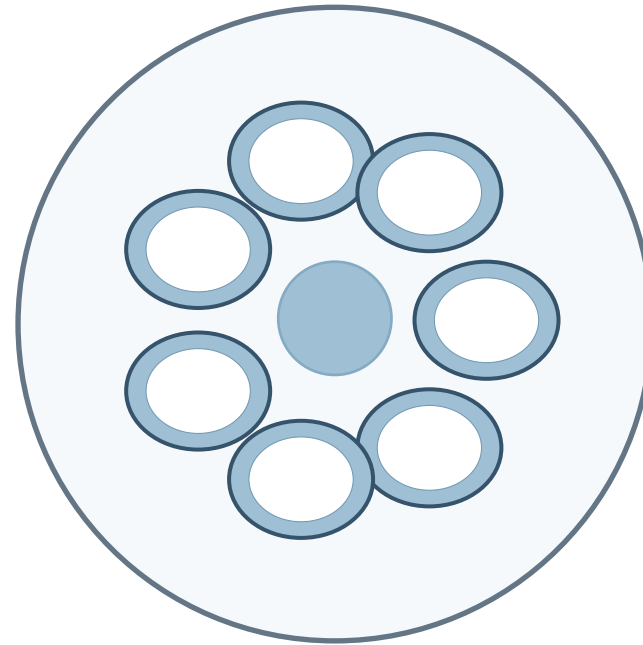
- Renal amyloid is among the most consequential patterns of systemic deposition.
- Glomeruli are a principal site; Vessels and interstitium may also be involved.
- Early deposition changes mesangial matrix and glomerular capillary walls.
- Later glomerular obliteration explains protein loss and renal failure.

Early glomerular amyloid

Schematic — not a histologic specimen



Earlier burden

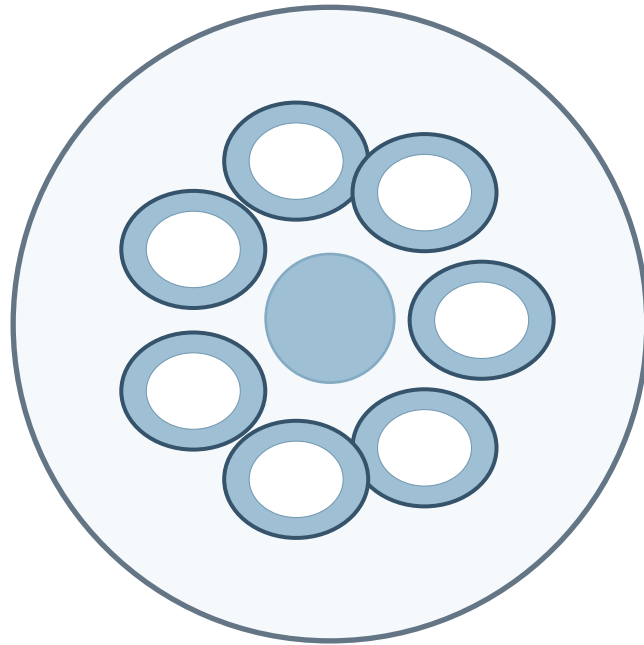


More extensive burden

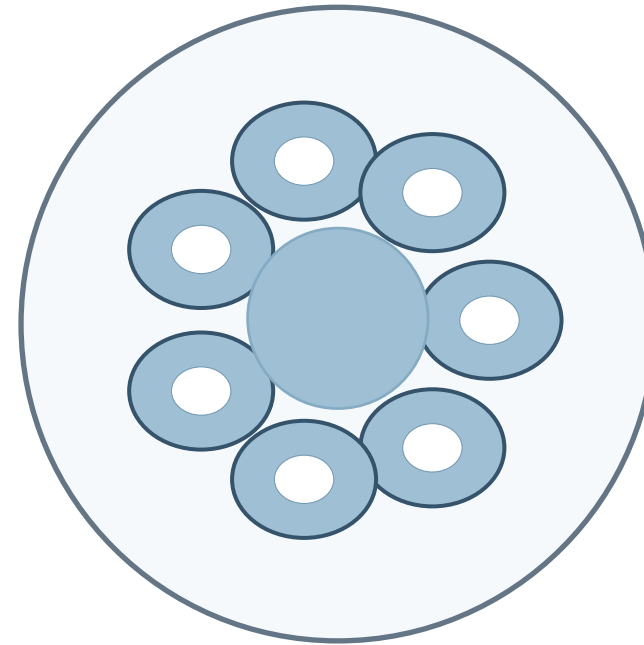
The early morphologic changes can be subtle before the vascular tuft is extensively distorted.

Progressive glomerular capillary narrowing

Schematic — not a histologic specimen



Earlier burden

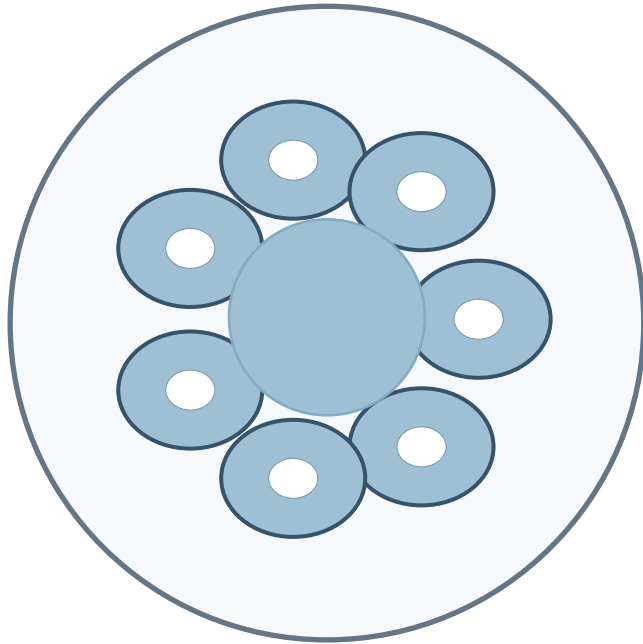


More extensive burden

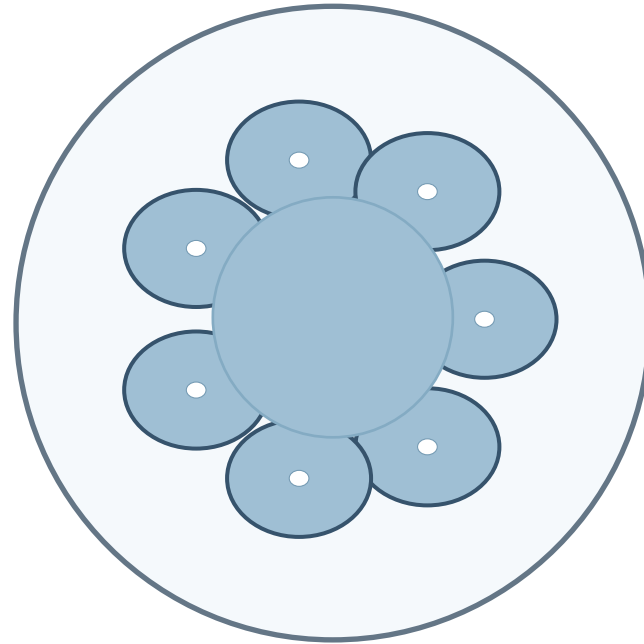
Mesangial expansion and capillary-wall involvement progressively interfere with the filtration apparatus.

Advanced glomerular obliteration

Schematic — not a histologic specimen



Earlier burden



More extensive burden

Broad masses of deposited amyloid may efface the tuft, creating an obsolescent glomerulus.

Renal vascular deposits and gross appearance

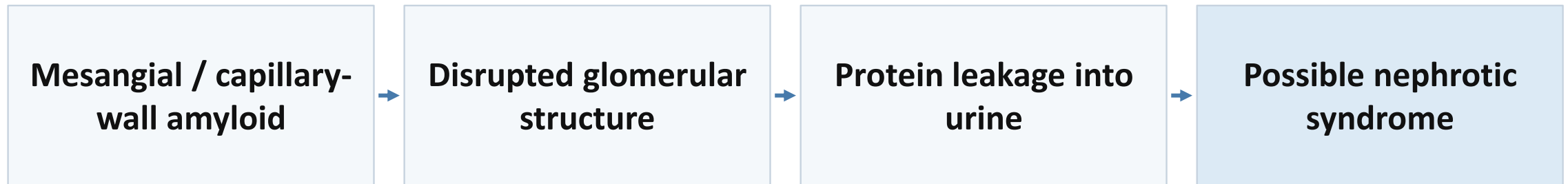
Gross appearances

- Kidneys can initially appear normal in size and color.
- Advanced vascular narrowing may produce ischemic shrinkage.

Microscopic compartments

- Glomerular deposits predominate.
- Arterioles, arteries, and peritubular interstitium may also be involved.

Glomerular injury explains proteinuria



Proteinuria is a clinical consequence, not evidence of a particular amyloid fibril type.

Severity depends on the functional impact of renal deposition.

Advanced renal injury and kidney failure



Kidney failure is a serious systemic amyloidosis outcome.

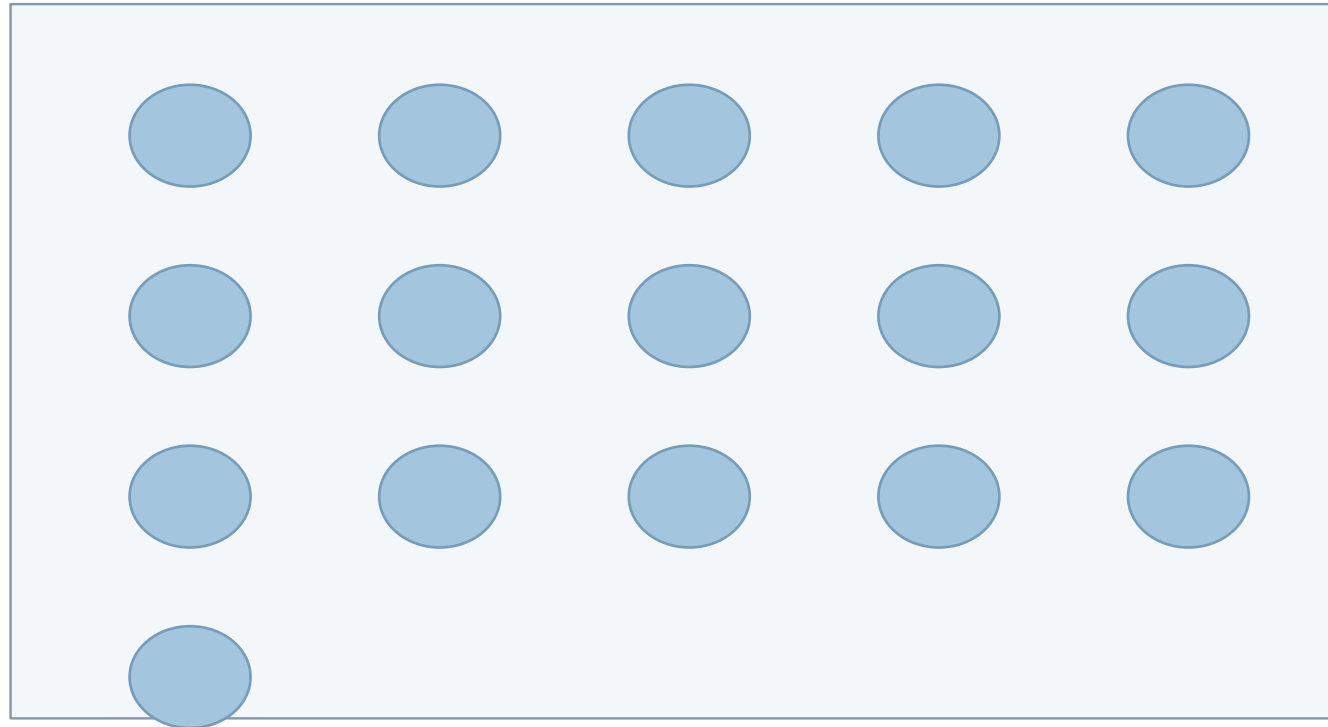
Kidney failure as a common cause of death in systemic amyloidosis.

Spleen: Two morphologic deposition patterns

Pattern	Predominant compartment	Classic gross descriptor
Sago spleen	Splenic follicles	Tapioca-like granules
Lardaceous spleen	Sinus walls and red-pulp connective framework	Confluent map-like deposits

Sago spleen: Follicular distribution

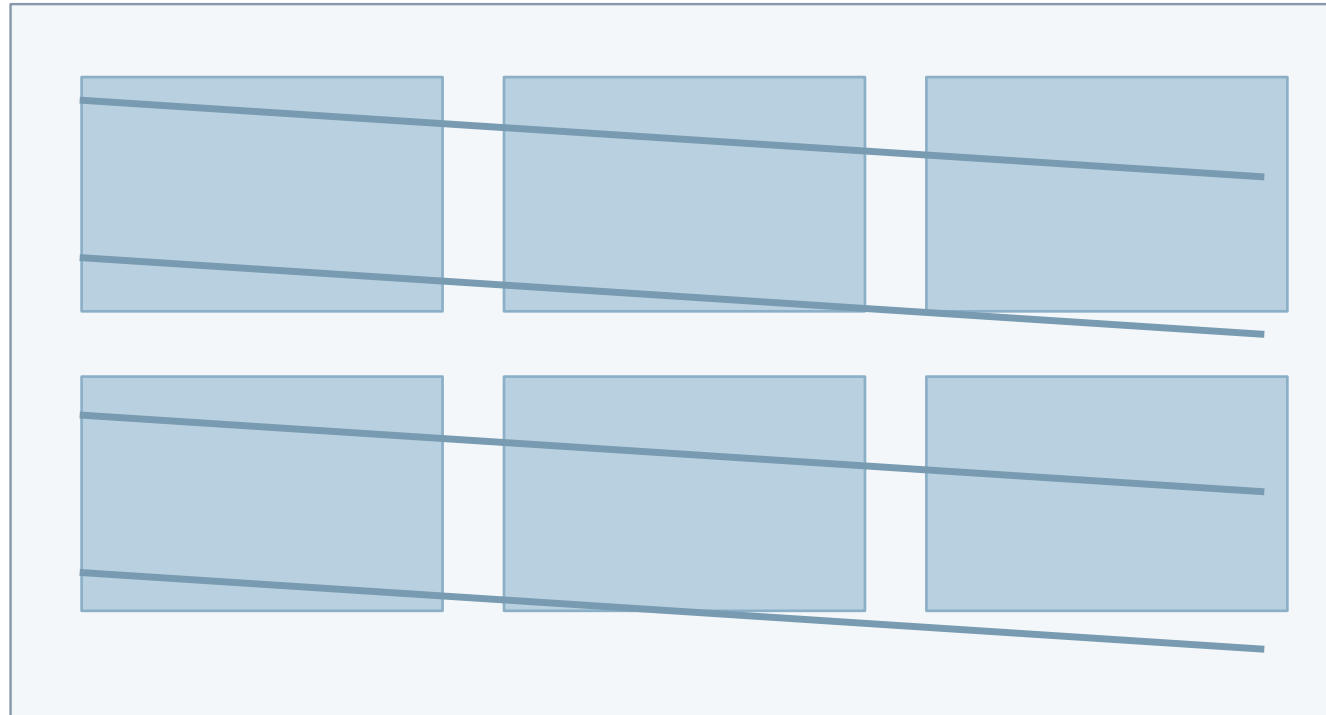
Schematic — compartment emphasis only



The classic tapioca-like granularity reflects localization to splenic follicles.

Lardaceous spleen: Red-pulp distribution

Schematic — compartment emphasis only



Confluence of deposits around sinuses and connective tissue produces a map-like pattern.

Liver: Deposition begins in the space of Disse



This is the microscopic evolution described for hepatic amyloid.

Vascular deposits can accompany sinusoidal involvement.

Extensive hepatic amyloid may preserve function

- Liver enlargement can accompany substantial amyloid deposition.
- Sinusoidal deposits compress and distort hepatocytes.
- Hepatocyte loss can be striking on microscopic examination.
- Nevertheless, liver function is often relatively preserved description.

Systemic distribution is variable

Usually mentioned in reactive AA

- Kidneys, liver, spleen.
- Lymph nodes, adrenals and thyroid.

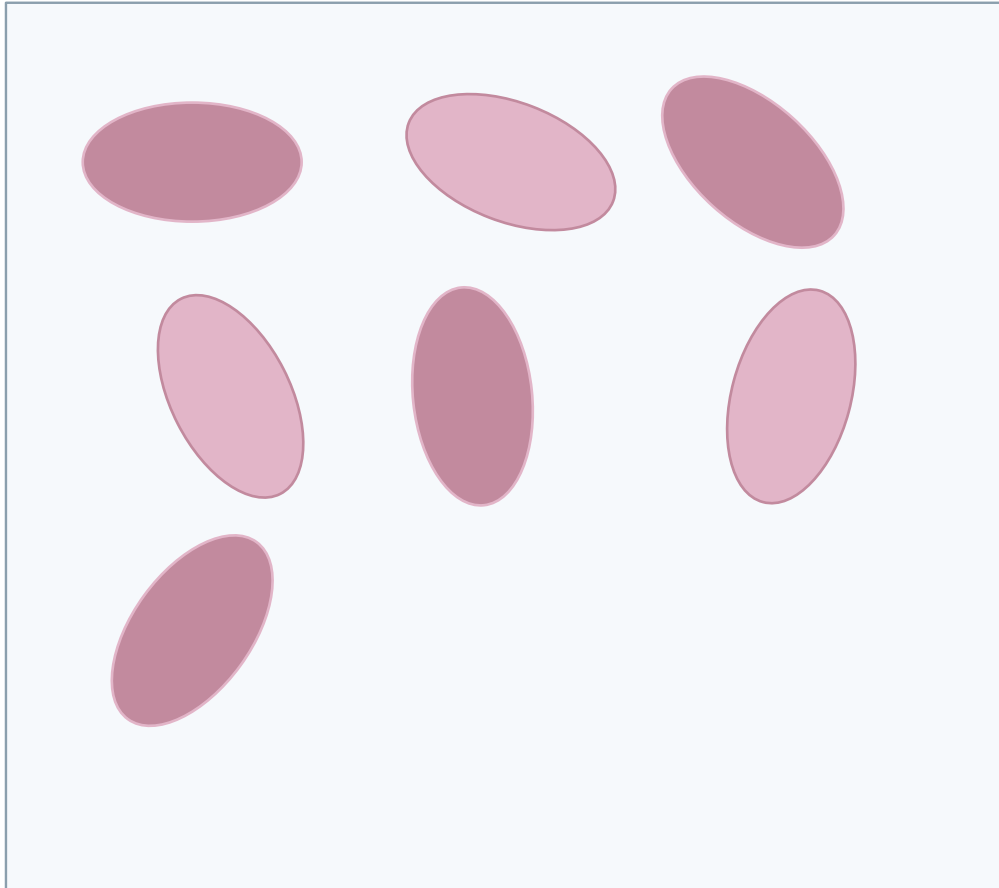
Interpretive caution

- Patterns overlap with other systemic amyloid types.
- Distribution alone cannot type the fibril protein.

Gross morphology may be silent or waxy

- Even widespread amyloid may not be macroscopically conspicuous.
- When deposits are extensive, organs may be enlarged and firm.
- Tissues may have a gray, waxy appearance.
- Histology is needed to recognize and characterize the deposit.

Routine H&E: Extracellular hyaline material



Conceptual H&E schematic — not a histologic photomicrograph.

- Amorphous and eosinophilic extracellular material.
- Often adjacent to basement membranes.
- Morphology suggests amyloid but is not definitive.

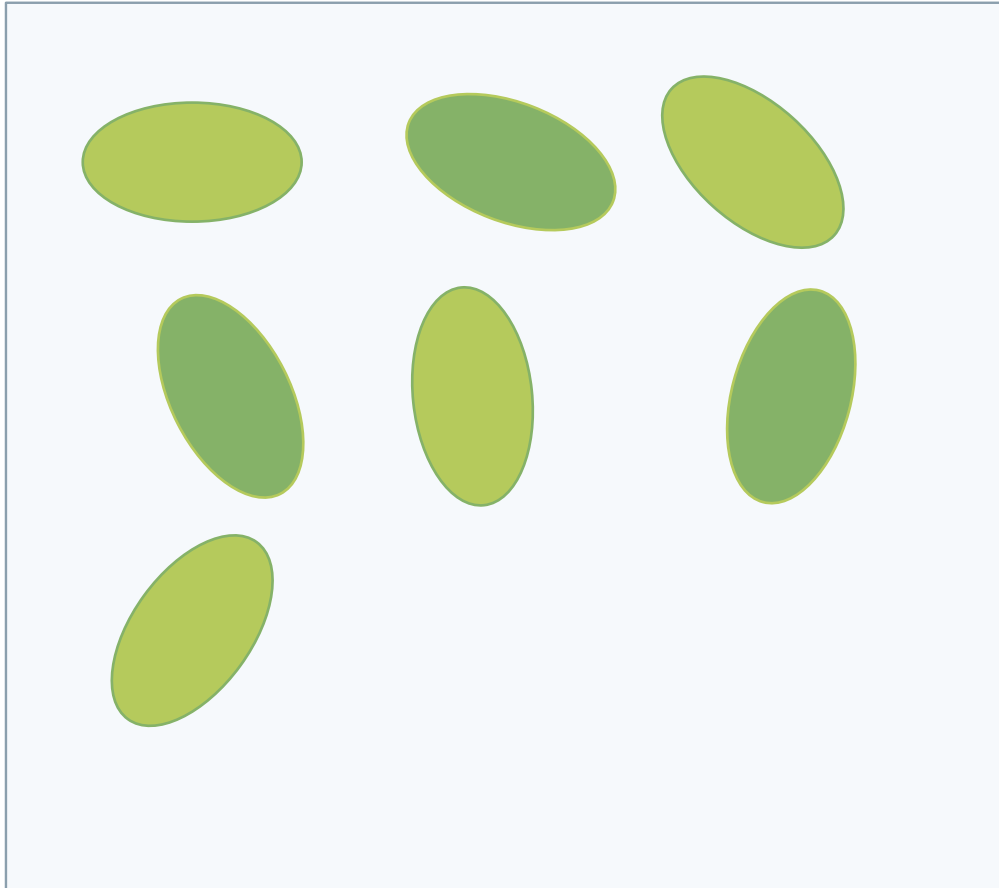
Congo red in ordinary transmitted light



Conceptual stain schematic — not a microscope image.

- Deposits take up pink-to-red Congo red stain.
- This supports the presence of amyloid.
- Confirm the expected optical property under polarized light.

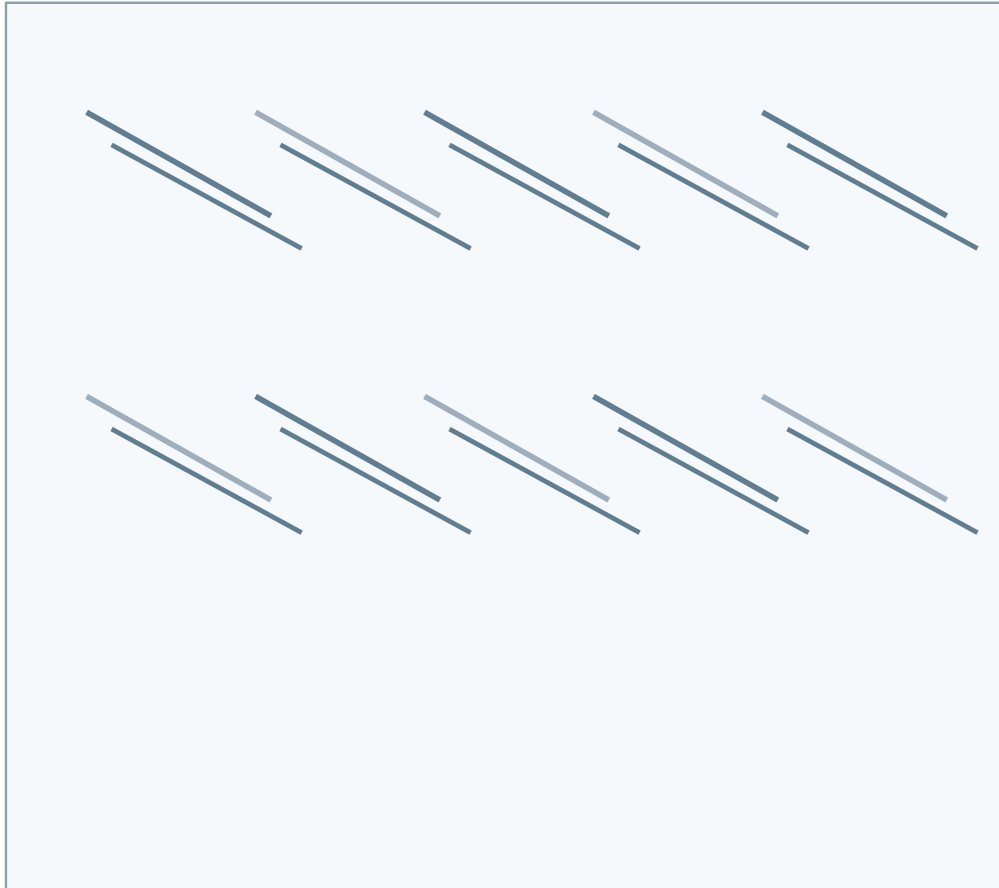
Congo red under polarization



Conceptual optical schematic — not observed polarized microscopy.

- Characteristic yellow-green / apple-green birefringence.
- Depends on the cross- β fibrillar structure.
- Shared by AA, AL, ATTR and other amyloid types.

Electron microscopy: Amyloid fibrils



Original vector schematic — not an electron micrograph.

- Thin continuous fibrils lack branching.
- Diameter is approximately 8–10 nm in the source.
- Ultrastructure supports amyloid, not its biochemical subtype.

Sampling tissues to demonstrate amyloid

Approach named by Robbins	Diagnostic role / qualification
Kidney biopsy	Common when renal manifestations are present
Rectal or gingival tissue	Possible sites when systemic disease is suspected
Abdominal fat aspirate	Congo red can detect deposits; Sensitivity is low

A negative fat aspirate does not exclude disease

- Congo red examination of abdominal fat as quite specific.
- Its sensitivity is low: A negative result does not rule out systemic amyloidosis.
- Persistent suspicion warrants clinicopathologic reassessment and appropriate tissue sampling.
- A positive Congo red result still requires fibril typing.

Finding amyloid $\neq$ identifying AA

Presence of amyloid

- Congo red staining and birefringence.
- Characteristic fibrils on electron microscopy.
- Confirms a fibrillar deposit.

Amyloid type

- Specific immunohistochemistry where validated.
- Mass spectrometry when available.
- Establishes protein composition.

Immunohistochemistry for amyloid type

- Specific immunohistochemical stains can help distinguish AA, AL and TTR amyloid.
- The tissue distribution cannot reliably perform this classification.
- Stain interpretation is distinct from generic Congo red positivity.
- Typing should inform clinicopathologic attribution rather than merely restating the associated disease.

Mass spectrometry identifies the deposited protein



Mass spectrometry as a method able to identify all amyloid types.

Availability is described as restricted to some centers in the source.

AA-oriented diagnostic reasoning



The arrows are a teaching sequence, not a prescriptive clinical guideline.

Do not classify amyloid as AA from rheumatoid arthritis history alone.

AA, AL and ATTR: Discriminating features

Feature	AA	AL	ATTR
Typical mechanism	Inflammation / SAA	Plasma-cell light chains	Transthyretin aggregation
Precursor	SAA	Ig light chain	TTR
Amyloid detected by Congo red?	Yes	Yes	Yes
Chemical typing needed?	Yes	Yes	Yes

Common diagnostic pitfalls

- Treating Congo red positivity as sufficient evidence for AA amyloidosis.
- Assuming renal disease plus rheumatoid arthritis establishes the fibril composition.
- Misreading eosinophilic extracellular material as amyloid without confirmatory stain.
- Excluding systemic amyloidosis solely because abdominal fat aspiration is negative.

Clinical manifestations reflect affected organs

Compartment	General systemic amyloid consequences
Renal	Proteinuria → nephrotic syndrome → kidney failure
Hepatic	Hepatomegaly; Often preserved function despite deposition
Systemic	Weakness, weight loss, lightheadedness may precede specific signs
Vascular / gastrointestinal	Fragility-related bleeding; GI manifestations depend on site

Case application: Analyze the kidney biopsy

A patient with persistent rheumatoid arthritis has progressive proteinuria. Glomeruli contain amorphous extracellular material, confirmed by Congo red with birefringence.

1. What has been demonstrated with confidence?

2. What additional step identifies the cause of the deposits?

Think in two layers: Presence of amyloid; Biochemical identity of amyloid.

Case answer: What can be concluded?

Supported conclusion

- Systemic amyloidosis is plausible.
- Tissue staining establishes amyloid deposits.
- Renal involvement explains the proteinuria.

Not yet demonstrated

- That the fibril protein is AA.
- That rheumatoid arthritis alone explains the biopsy.
- That other systemic amyloid types have been excluded.

Therapeutic implication: Control the driver



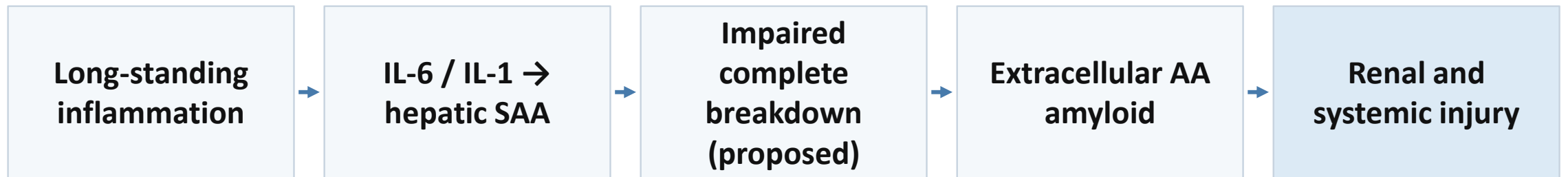
This is a mechanistic rationale; No drug regimens or contemporary guidelines are inferred.

Decreasing AA prevalence with more effective treatment of inflammatory disorders.

Prognosis depends partly on inflammatory control

- Reactive systemic amyloidosis has a somewhat better outlook than AL discussion.
- Outcome depends in part on the degree of control of the associated disease.
- Already established tissue deposits may not promptly resolve when inflammation is controlled.
- Resorption after treatment is reported, but described as rare.

AA amyloidosis: Integrated causal chain



Solid clinical association + proposed susceptibility mechanisms should be distinguished.

The central, source-supported biological axis is inflammation → SAA → AA fibrils.

Five high-yield distinctions

- SAA is the circulating precursor; AA is the deposited fibril protein.
- The inflammatory condition is an association, not tissue proof of amyloid chemistry.
- High SAA production alone is not sufficient for deposition.
- Congo red identifies amyloid; Further typing identifies the fibril.
- Kidney involvement links extracellular deposition to proteinuria and failure.

Self-assessment: Apply the framework

A patient with inflammatory bowel disease has renal proteinuria and Congo red-positive extracellular deposits. A second patient has a plasma-cell neoplasm and Congo red-positive deposits.

1. Can the two tissues be distinguished reliably by Congo red alone?

2. Which protein precursors must be considered in each context?

Use precursor chemistry—not the generic staining reaction—to name the amyloid type.

Self-assessment: worked interpretation

Shared finding

- Both patients have histologically demonstrable amyloid.
- The Congo red reaction derives from amyloid fibril architecture.

Different candidate precursors

- Inflammatory bowel disease: SAA-derived AA is plausible.
- Plasma-cell neoplasm: immunoglobulin light-chain AL is plausible.
- Typing is required for attribution.