
Other types of amyloidosis

Familial • dialysis-associated • localized • endocrine deposits

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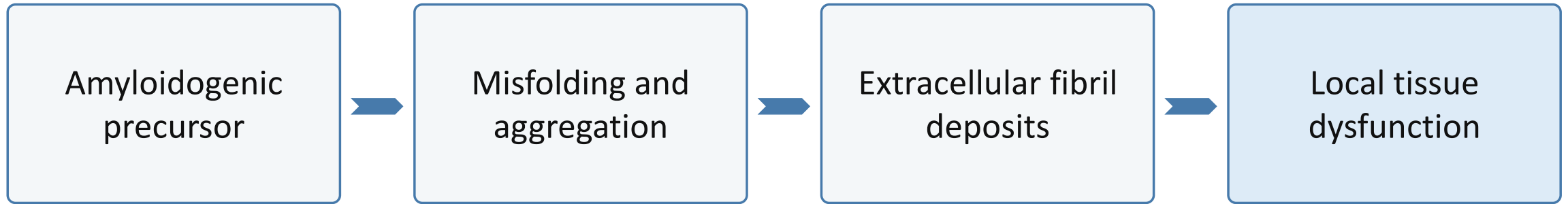
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Learning objectives

- Distinguish the principal uncommon amyloid syndromes by precursor protein and setting.
- Explain why familial Mediterranean fever produces AA—not variant-protein—amyloid.
- Connect dialysis-associated β_2 -microglobulin with musculoskeletal manifestations.
- Interpret localized and endocrine deposits without assuming systemic amyloidosis.
- Use morphology and protein typing to approach a suspected case.

Amyloid names describe fibril composition



- Morphologically similar deposits can contain different proteins.
- Correct typing therefore changes etiologic interpretation.

One structure, multiple clinical diseases

Shared tissue signature

- Extracellular amorphous deposits
- Cross- β fibrillar configuration
- Congo red binding and birefringence

Disease-specific features

- Different precursor molecules
- Different mechanisms of excess or misfolding
- Different organ distribution and clinical associations

Systemic and localized are different axes

Systemic disease

- Amyloid may deposit far from protein production.
- Multiple organs may be involved.
- Organ complications reflect deposit burden and sites.

Localized disease

- Deposits may remain restricted to one tissue.
- Nodules or microscopic deposits may occur.
- Absence of systemic involvement is part of the definition.

A practical map of the less common forms

FMF-associated

AA fibrils • inherited autoinflammation

Long-term dialysis

β_2 -microglobulin • musculoskeletal

Localized nodules

Often AL in some lesions

Endocrine deposits

Calcitonin or islet amyloid peptide

The clinical setting is a clue—not amyloid typing

- Congo red identifies amyloid, not its molecular species.
- Neither the affected organ nor the gross appearance reliably defines subtype.
- Link the clinical history to tissue findings and then identify the fibril protein.
- AA, AL and TTR may be distinguished with specific immunohistochemistry; Mass spectrometry can type amyloid.

Heredofamilial amyloidosis is heterogeneous

- Multiple rare familial amyloid syndromes.
- The fibril protein and dominant organs differ between families.
- Familial Mediterranean fever exemplifies hereditary inflammation with secondary AA deposition.
- Variant transthyretin amyloidosis is a separate inherited fibril-protein disorder.

Familial Mediterranean fever: Inheritance and phenotype

Underlying disorder

- Autosomal recessive hereditary syndrome
- Autoinflammatory rather than monoclonal plasma-cell disease
- Associated with abnormal regulation of inflammatory responses

Clinical attacks

- Recurrent fever
- Inflammation of serosal surfaces
- Potential progression to widespread AA amyloidosis

FMF attacks predominantly involve serosal tissues

Peritoneum

Inflammatory attacks may involve the abdominal serosa

Pleura

Inflammatory attacks may involve pleural surfaces

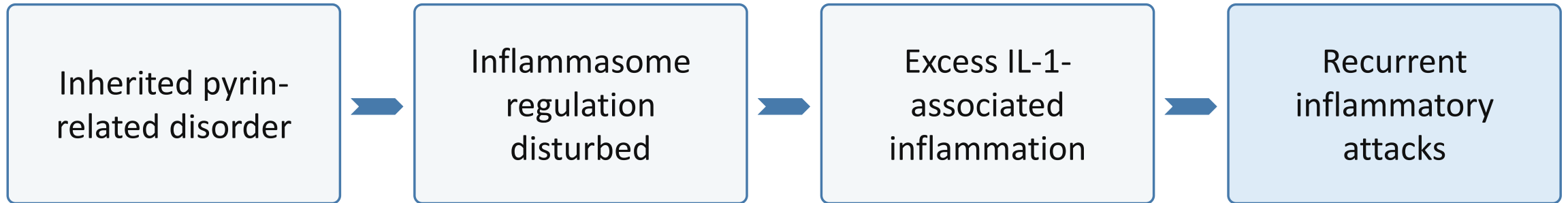
Synovial membrane

Joint-associated synovial inflammation

Systemic acute-phase response

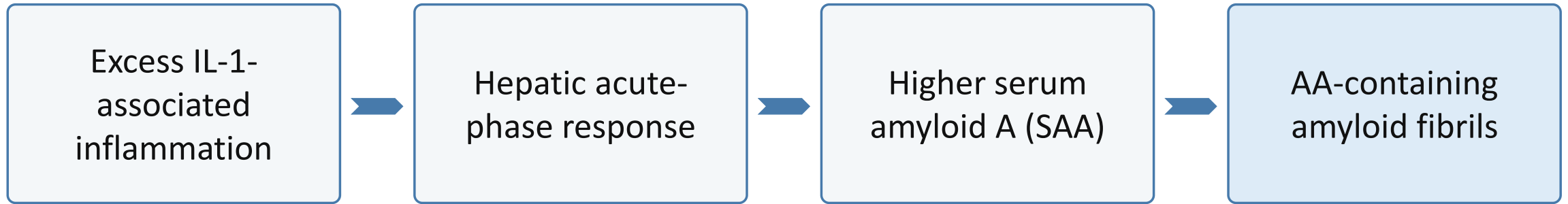
Repeated inflammation can sustain SAA production

Pyrin links the inherited defect to innate inflammation



- Pyrin participates in a protein complex regulating inflammatory reactions.
- The excerpt does not define a single mutation-specific molecular mechanism.

Inflammatory activity supplies the AA precursor



- The deposited AA fibril protein is derived from SAA.
- Amyloid is a downstream consequence of sustained inflammatory protein production.

FMF: Inherited disease, non-mutant fibril protein

FMF-associated AA

- Genetic defect affects inflammatory regulation.
- Excess cytokine activity increases SAA.
- Deposits contain AA protein.

Variant TTR amyloidosis

- The variant protein is itself amyloidogenic.
- TTR misfolds and forms deposits.
- The deposited protein is ATTRv.

FMF has a geographically clustered distribution

- Armenian, Sephardic Jewish, and Arabic ancestral groups.
- Population association supports clinical suspicion; It is not a diagnostic criterion.
- A family history and characteristic recurrent attacks strengthen the clinicopathologic context.
- Confirm amyloid and determine protein identity rather than inferring AA solely from ancestry.

Widespread AA amyloid can complicate FMF

Kidneys

Proteinuria or progressive renal dysfunction

Blood vessels

Vascular wall deposits

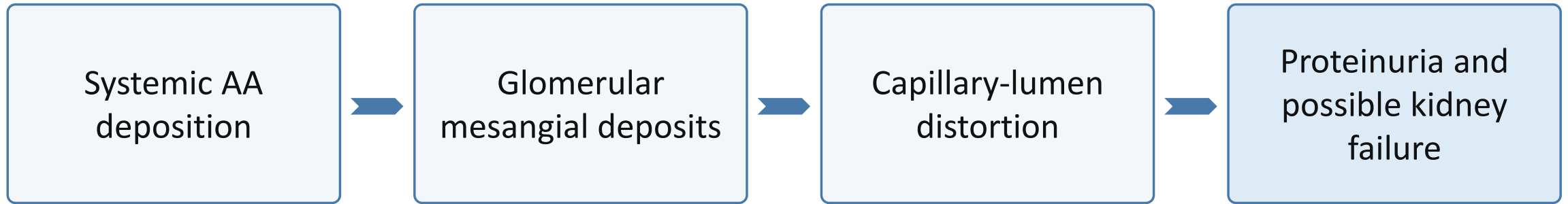
Spleen

Follicular or red-pulp involvement

Respiratory tract / liver

Possible respiratory involvement; Liver described as rare

Why the kidney matters in FMF



- Organ manifestations depend on deposit distribution and extent.
- The same renal mechanism also applies to other systemic amyloid types.

Contrast the two familial pathways

Feature	Familial Mediterranean fever	ATTRv amyloidosis
Inheritance	Autosomal recessive	Autosomal dominant
Proximal mechanism	Inflammatory IL-1 / SAA response	Variant TTR prone to misfolding
Fibril protein	AA	Variant transthyretin
Recognized pattern	Potentially widespread	Nerve or cardiac phenotypes

Case: Recurrent serositis and renal protein loss

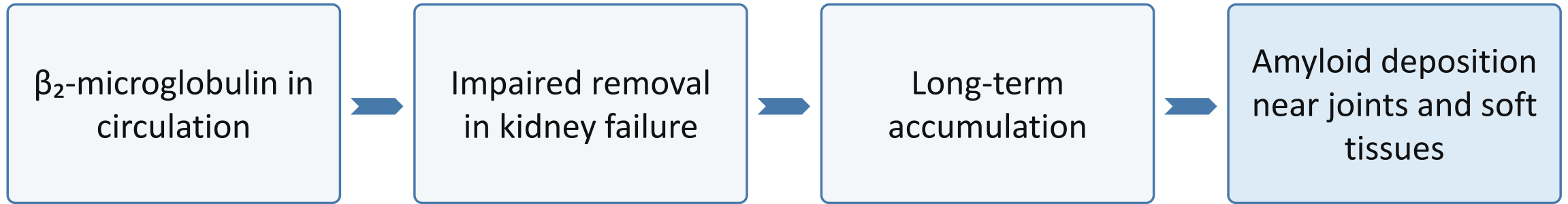
Clinical vignette

A patient has repeated episodes of fever with abdominal and pleural serosal inflammation. Later, marked proteinuria develops.

Which biochemical form of amyloid is most consistent with the Robbins-described syndrome?

Reasoned answer: AA amyloid, formed from SAA during sustained autoinflammatory activity.

Dialysis-associated amyloid has a distinct precursor



- β₂-microglobulin is a component of MHC class I molecules.
- This is not the AL, AA or transthyretin precursor.

β_2 -microglobulin belongs to MHC class I

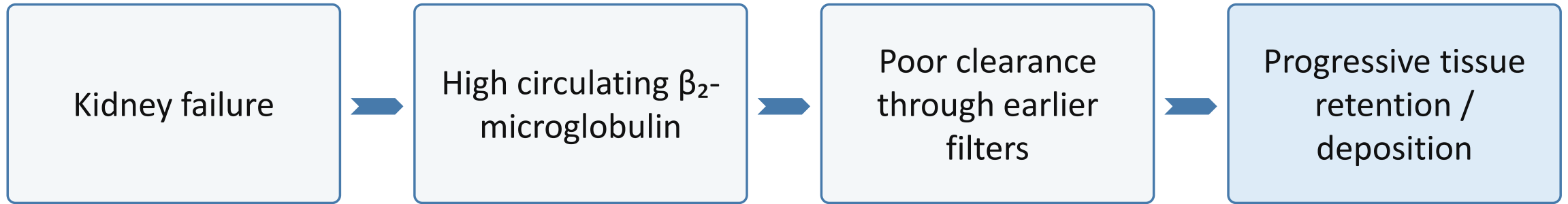
Physiologic context

- Component of MHC class I molecules
- Also present as a normal plasma protein

Pathologic context

- Can accumulate in kidney disease
- Fibrils may form in long-term dialysis
- Deposits target musculoskeletal and periarticular tissues

Historical dialysis membranes limited clearance



- The text links past dialysis membranes to retention of β_2 -microglobulin.
- Improved filters have substantially reduced this complication.

The distribution is predominantly musculoskeletal

Joints

Periarticular amyloid can contribute to symptoms

Tendons

Soft-tissue deposition

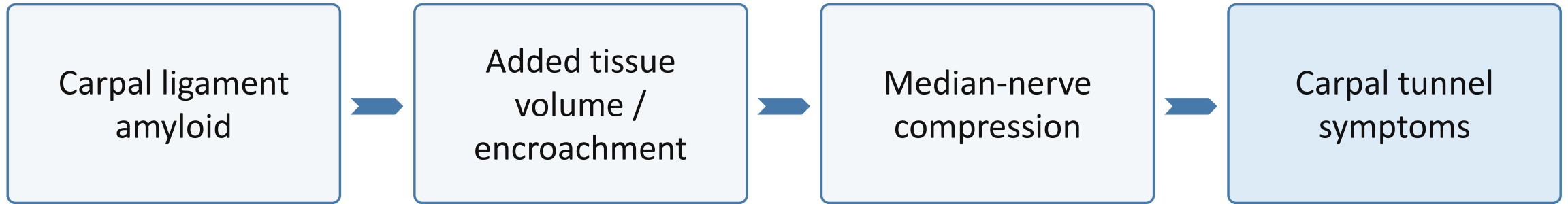
Ligaments

Particularly the carpal ligament

Muscles

Deposits may involve muscle tissue

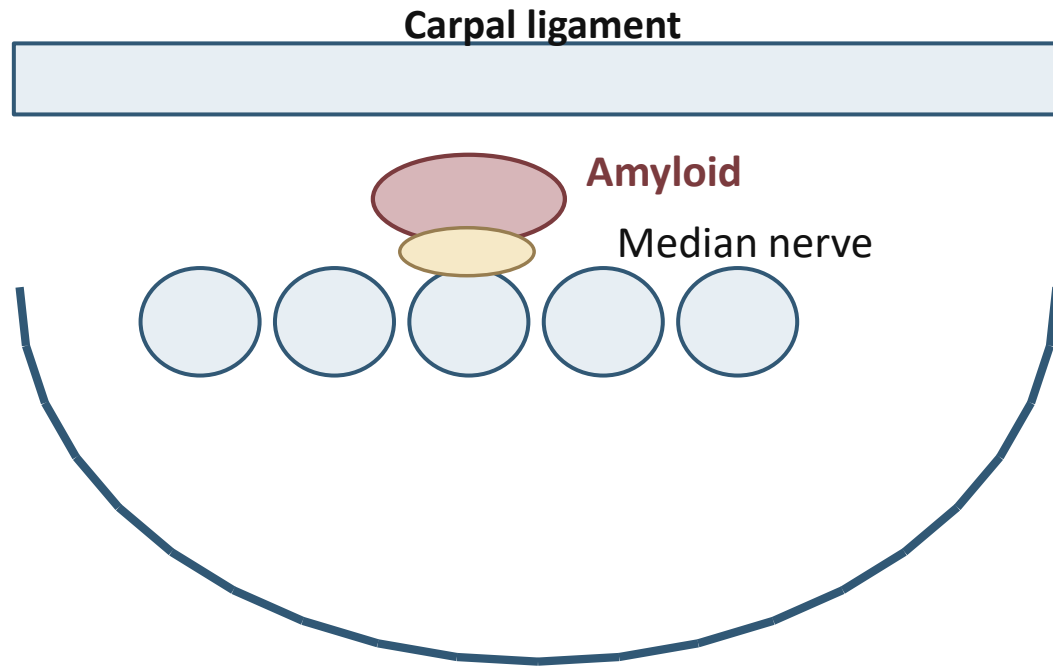
Carpal tunnel syndrome: A mechanical sequence



- Schematic causal sequence of the association.
- Clinical assessment still requires consideration of other causes of median neuropathy.

The carpal ligament is a key site

Simplified carpal tunnel cross-section



Schematic — not a clinical or histologic specimen

- Deposit in ligament and periarticular tissues
- Median nerve passes through a constrained space
- Nerve compression links anatomy to symptoms

Dialysis amyloid may extend beyond the wrist

- Joints, muscles, tendons and ligaments are listed deposit sites.
- Musculoskeletal symptoms do not specify the fibril type without tissue typing.
- A long history of dialysis changes the differential diagnosis.
- Pattern recognition is most useful when combined with a compatible specimen.

Improved dialysis filters changed the disease frequency

Earlier dialysis era

- Less effective β_2 -microglobulin clearance
- Circulating precursor retention
- Recognized musculoskeletal amyloid complications

More recent filters

- Improved precursor removal
- Substantial decline in the complication reported by Robbins
- Past history remains relevant to affected patients

Dialysis amyloid versus FMF-associated AA

Feature	Dialysis-associated	FMF-associated
Precursor	β_2 -microglobulin	SAA $\rightarrow$ AA
Clinical setting	Long-term hemodialysis	Autoinflammatory fever / serositis
Typical emphasis	Joints, tendons, ligaments	Potentially widespread systemic deposits
Illustrative symptom	Carpal tunnel syndrome	Proteinuria with systemic amyloid

Case: Chronic dialysis and hand symptoms

Clinical vignette

A patient on long-term hemodialysis develops wrist symptoms associated with median-nerve compression and periarticular deposits.

Which fibril precursor is most characteristic of this clinical setting?

Reasoned answer: β_2 -microglobulin, associated with dialysis-related musculoskeletal amyloid.

Localized amyloid is defined anatomically

Localized

- One organ or tissue is involved.
- A visible nodule or microscopic deposit may be present.
- The process does not necessarily imply systemic amyloidosis.

Systemic

- Multiple organs may harbor deposits.
- Deposits may occur away from synthesis of the precursor.
- Organ involvement is an important clinical staging question.

Localized deposits have two scales of presentation

Grossly apparent

Nodular amyloid masses

Microscopic only

Incidental small tissue deposits

Both patterns

Extracellular amyloid deposits

Interpretation

Examine the organ, distribution and precursor

Recognized sites of localized amyloid nodules

Lung / larynx

Respiratory tract

Skin / periocular region

Cutaneous and ocular-adjacent tissues

Urinary bladder

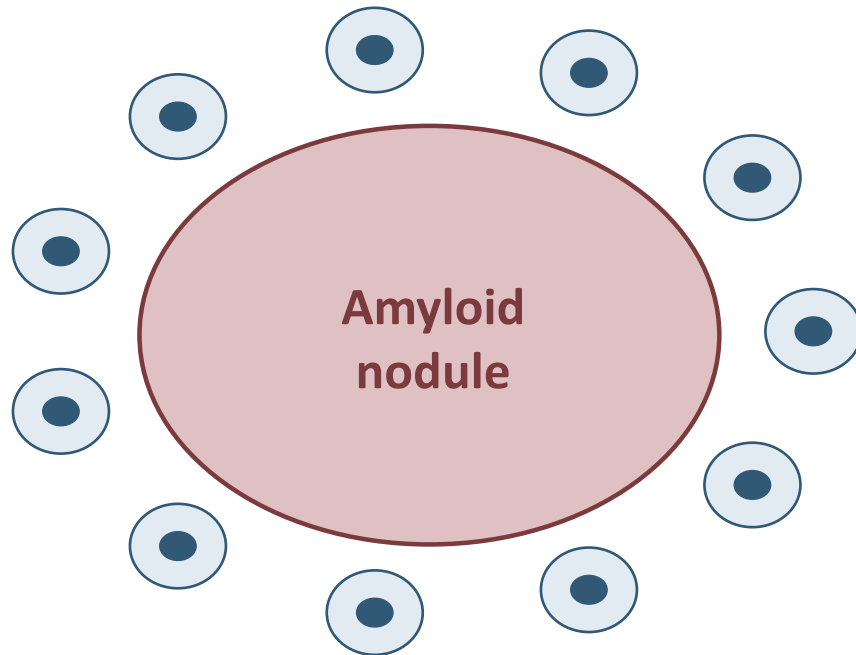
Urinary tract

Tongue

Oral soft tissue

Localized masses may have a plasma-cell rim

Central deposit with peripheral cells

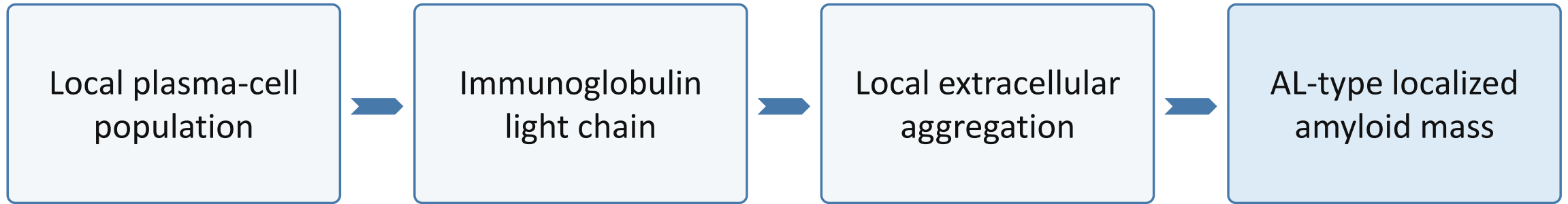


Peripheral inflammatory cells

Schematic — not a clinical or histologic specimen

- Amyloid forms a central extracellular nodule.
- Lymphocytes and plasma cells may lie at its edge.
- The cell infiltrate is an observation, not proof of systemic disease.

A subset of localized deposits consists of AL



- AL protein in at least some localized cases.
- Do not assume every localized amyloid nodule is AL.

The important distinction is extent, not appearance

- Microscopic amyloid can resemble systemic amyloid even when confined to one site.
- A nodular mass alone cannot establish localized versus generalized distribution.
- Protein typing identifies the deposited species.
- Clinical assessment addresses whether additional organs are involved.

Respiratory amyloid may be focal or diffuse

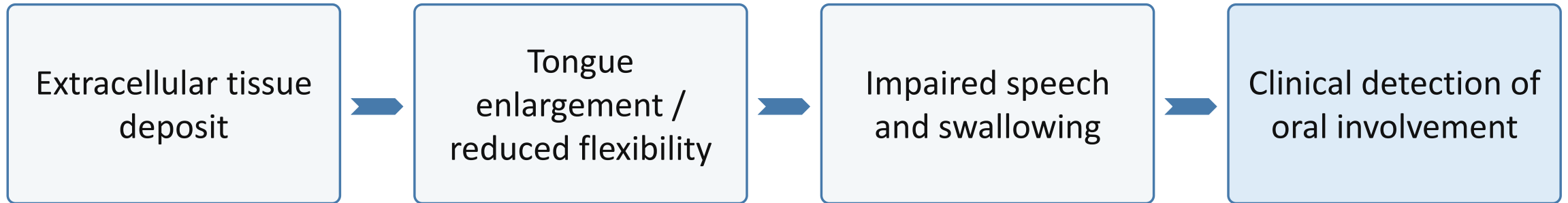
Focal pattern

- Nodular deposits can occur in the lung or larynx.
- A single mass may draw clinical attention.

Diffuse pattern

- Respiratory involvement down to small bronchioles.
- A broader airway distribution changes the clinicopathologic picture.

Tongue amyloid can create a mass effect



- The text describes tumor-forming amyloid and macroglossia.
- Mass-forming behavior does not by itself establish malignancy.

Case: A laryngeal amyloid nodule

Clinical vignette

Biopsy of a localized laryngeal nodule reveals Congo red–positive extracellular deposits with peripheral lymphocytes and plasma cells.

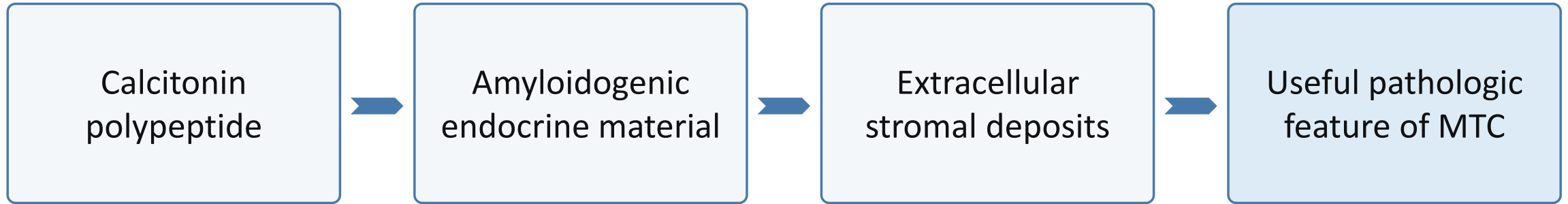
What inference is justified before completing the clinical workup?

Reasoned answer: A localized amyloid deposit is possible; Its AL composition and systemic extent remain to be established.

Endocrine amyloid is often microscopically localized

- Certain endocrine tumors contain amyloid deposits.
- Medullary thyroid carcinoma, pancreatic islet tumors and pheochromocytoma.
- Amyloid also occurs within islets in type 2 diabetes mellitus.
- The precursor differs by endocrine setting and should not be assumed to be AL.

Medullary thyroid carcinoma: Hormone-derived fibrils



- The classification table lists the fibril as ACal (calcitonin-derived).
- The presence of amyloid is helpful—not a standalone full diagnostic criterion.

Amyloid can aid recognition of medullary thyroid cancer

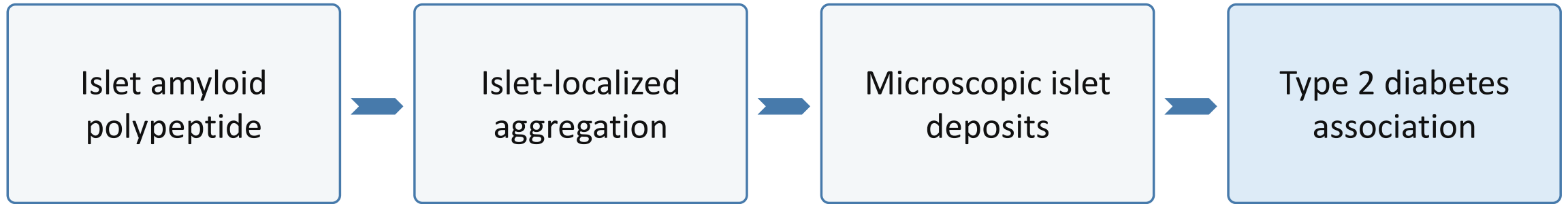
Microscopic observation

- Extracellular amyloid in the tumor stroma
- Congo red-compatible staining behavior

Diagnostic interpretation

- Supports medullary thyroid carcinoma in an appropriate lesion
- Correlate with cellular morphology and other diagnostic workup
- Do not identify a tumor solely from amyloid

Type 2 diabetes: Islet amyloid polypeptide



- The textbook table uses AIAPP for this fibril protein.
- Islet amyloid is an endocrine deposit, not a synonym for systemic amyloidosis.

Two endocrine deposits, two protein identities

Setting	Deposited protein	Anatomic site
Medullary thyroid carcinoma	Calcitonin-derived ACal	Tumor stroma
Type 2 diabetes mellitus	Islet amyloid polypeptide (AIAPP)	Islets of Langerhans
Other endocrine tumors	Protein not defined in this excerpt	Tumor-associated deposits

Additional localized categories in the source table

Alzheimer disease

A β from amyloid precursor protein

Isolated atrial amyloid

Atrial natriuretic factor (ANF)

Endocrine tumors

Hormone-related or other proteins

Localized AL nodules

Light chains in some lesions

Cerebral amyloid is a distinct organ pattern

Alzheimer disease

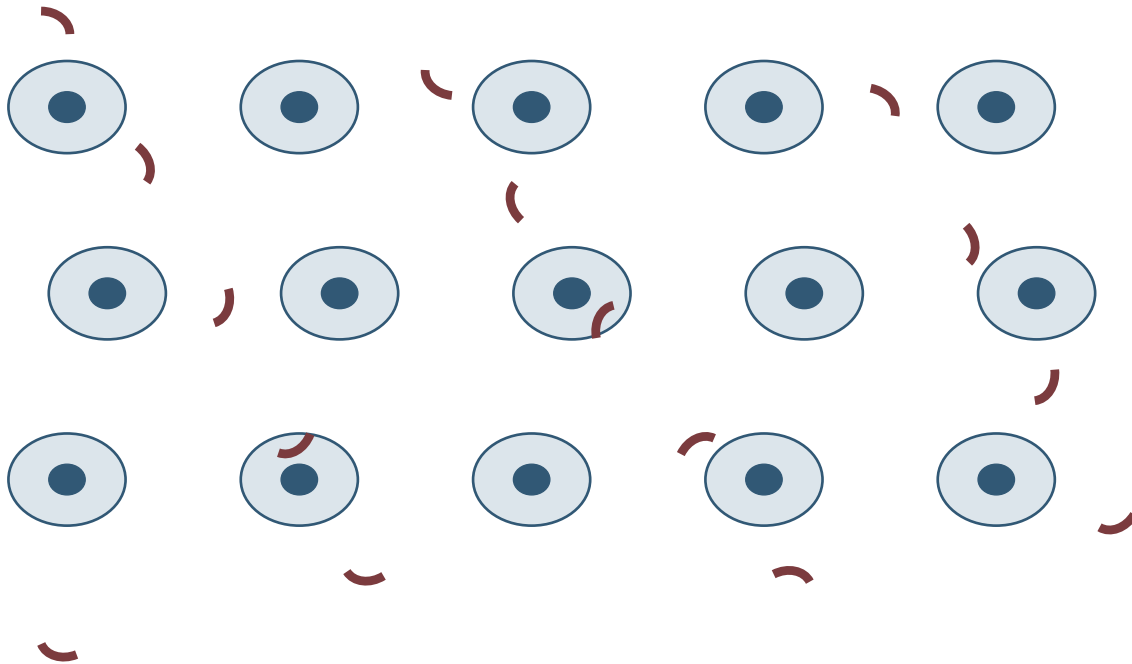
- A β deposition in cerebral plaques
- Also in walls of cerebral blood vessels
- Precursor: Amyloid precursor protein (APP)

Other amyloid types

- Have different fibril precursors
- May be localized or systemic
- Cannot be typed by Congo red color alone

Amyloid accumulates outside cells

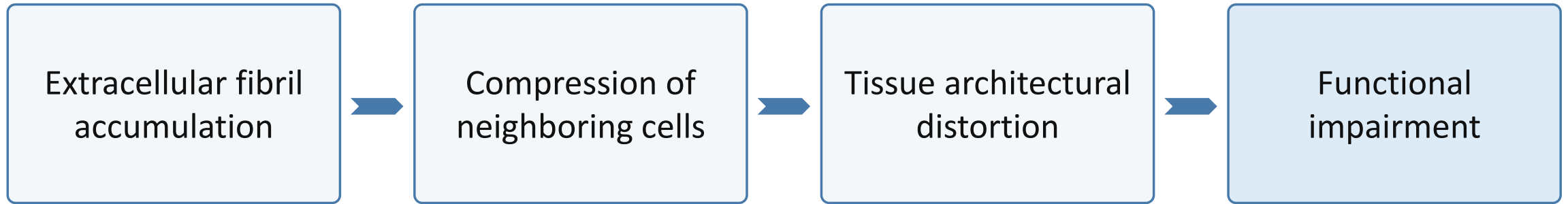
Extracellular amyloid around cells



Schematic — not a clinical or histologic specimen

- Deposits arise in extracellular interstitial spaces.
- They often form adjacent to basement membranes.
- Progressive accumulation displaces and damages cells.

Why amyloid produces pressure atrophy



- Tissue pressure and destruction.
- Extensive inflammation is not required to explain damage.

Grossly, extensive amyloid can be waxy and firm

Small deposits

- May be invisible on gross examination
- Require microscopic detection

Large deposits

- Organ often becomes enlarged
- Gray, waxy and firm cut surface
- Distribution depends on involved tissue

H&E morphology is suggestive, not specific

Typical appearance

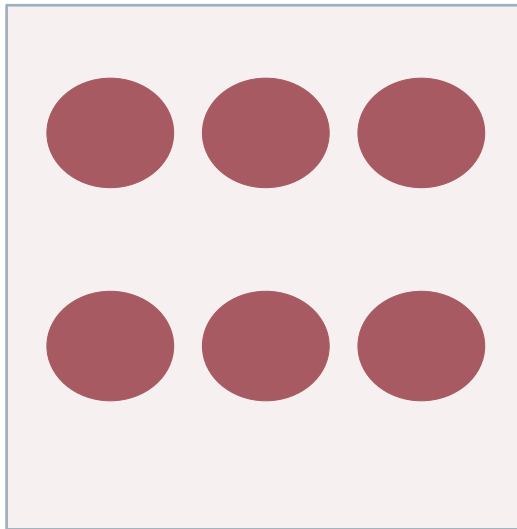
- Amorphous extracellular material
- Eosinophilic or hyaline quality
- Expansion of tissue compartments

Important limitation

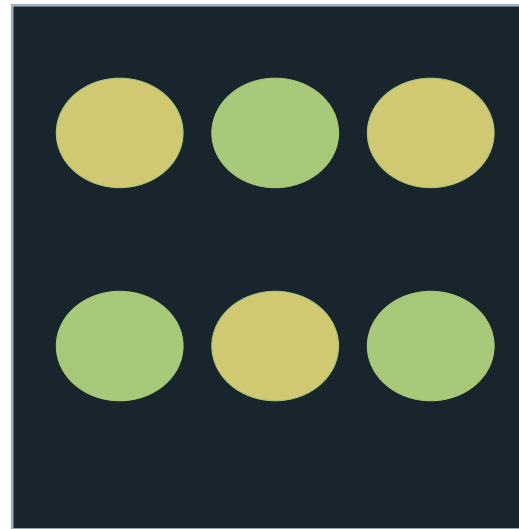
- Other hyaline materials may look similar
- Collagen and fibrin enter the differential
- A special stain establishes the characteristic reaction

Congo red: Ordinary versus polarized light

Same deposit under different illumination



Ordinary light

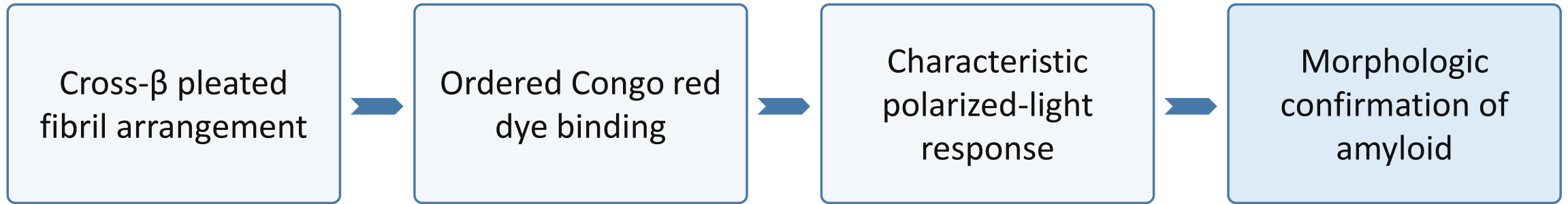


Polarized light

Schematic — not a clinical or histologic specimen

- Ordinary light: Pink-red amyloid deposits
- Polarized light: Characteristic apple-green / yellow-green birefringence
- The reaction reflects fibril cross- β organization

Birefringence reflects molecular organization



- The staining property is shared across chemically distinct amyloid types.
- It does not identify AA versus AL versus ATTR.

Electron microscopy shows thin nonbranching fibrils

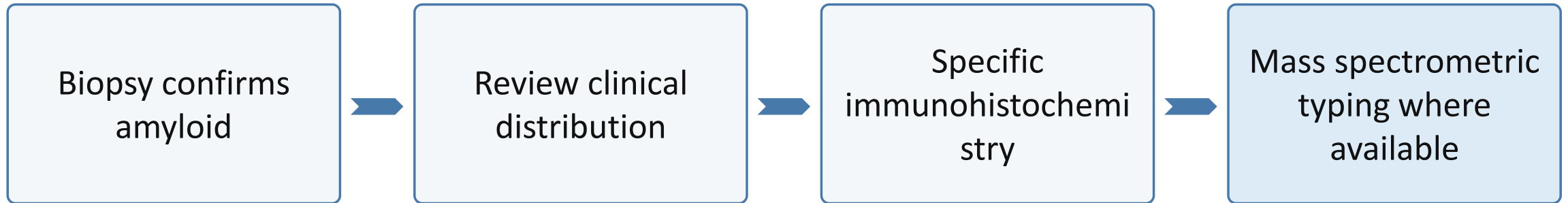
Nonbranching extracellular fibrils

- Approximately 8–10 nm fibrils are.
- Fibers are nonbranching and extracellular.
- Electron microscopy supports identity but does not supply protein type.

Schematic parallel fibrils

Schematic — not a clinical or histologic specimen

Typing the protein is a separate diagnostic step



- Immunohistochemistry for AA, AL and TTR.
- Its text reports mass spectrometry as capable of identifying amyloid types.

Organ distribution suggests—but does not prove—type

AA in chronic inflammation

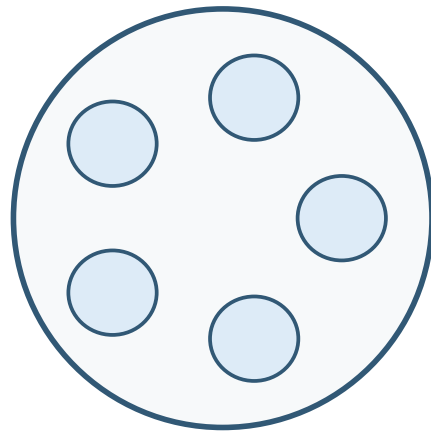
- Kidney, liver, spleen and lymph nodes often affected
- Adrenals and thyroid also described

AL with plasma-cell proliferation

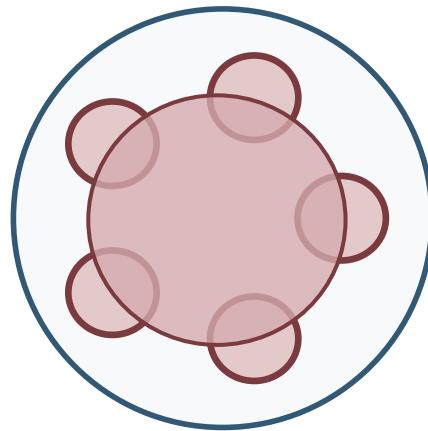
- Heart, GI tract and respiratory tract emphasized
- Peripheral nerves, skin and tongue often involved
- Overlap prevents diagnosis by anatomy alone

Renal amyloid begins in mesangium and capillaries

Schematic glomerulus: Progression of deposition



Early

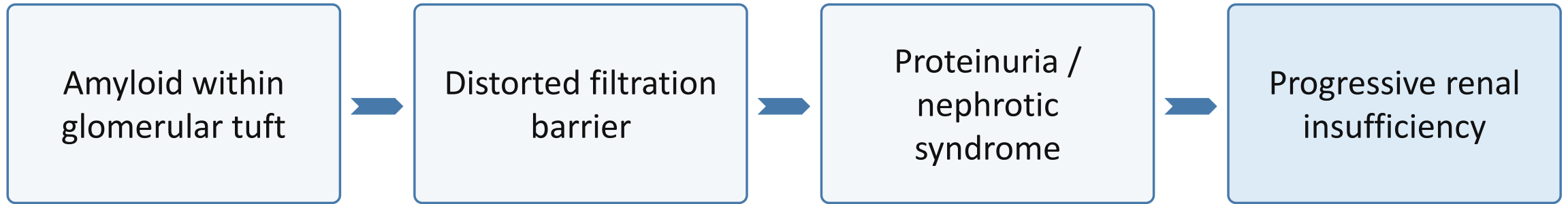


Advanced

Schematic — not a clinical or histologic specimen

- Early mesangial matrix expansion
- Uneven capillary basement-membrane thickening
- Progressive lumen narrowing and obliteration

Renal architecture explains proteinuria



- This is a shared organ-effect mechanism rather than a feature unique to FMF.

Splenic deposition has two named patterns

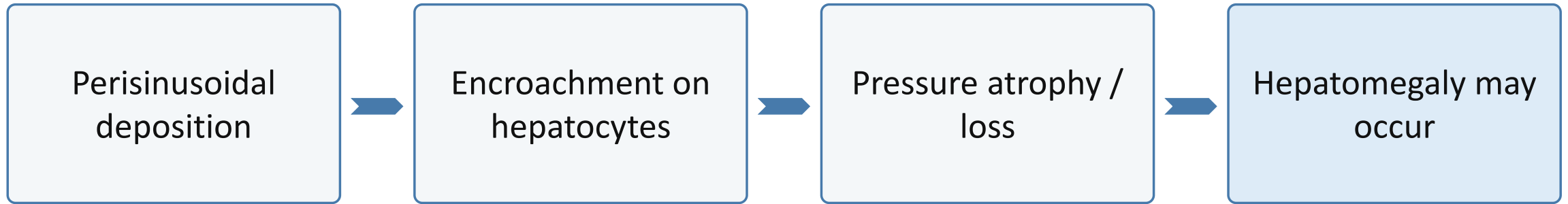
Sago spleen

- Amyloid largely in splenic follicles
- Small, tapioca-like gross granules

Lardaceous spleen

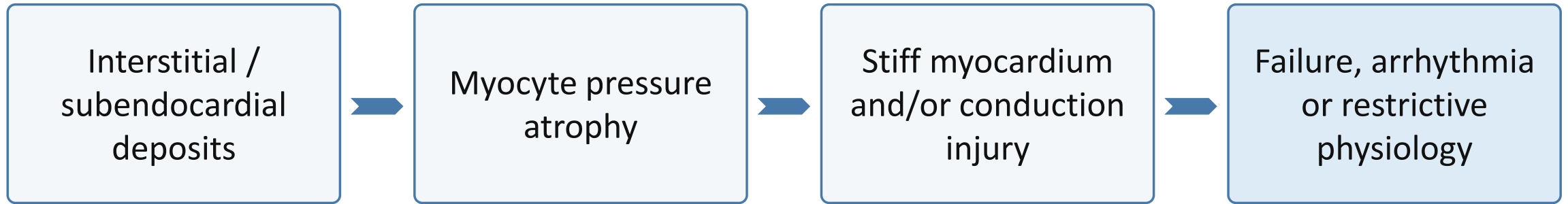
- Amyloid in red-pulp sinus walls and framework
- Coalescent map-like deposits
- Different appearance, same amyloid principle

Hepatic amyloid expands the space of Disse



- The source notes that liver function may remain preserved despite extensive deposits.

Cardiac amyloid compromises muscle and conduction



- Not all hearts show striking gross abnormalities.

Vessel-wall deposition can cause bleeding

Structural injury

- Amyloid infiltration can make vessels fragile.
- Bleeding may follow minor trauma or occur spontaneously.

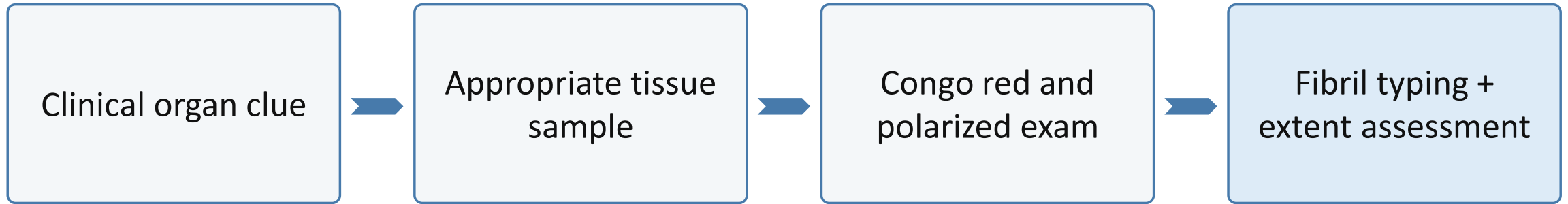
Specific AL-associated mechanism

- In some cases AL amyloid binds factor X.
- Factor X inactivation can aggravate bleeding.

Amyloidosis may present nonspecifically

- Early manifestations can include weakness or weight loss.
- Lightheadedness and syncope may occur.
- More informative findings arise from renal, cardiac, GI or nerve involvement.
- A normal-appearing organ does not exclude microscopic amyloid.

Biopsy establishes amyloid; Distribution frames the workup



- Kidney may be sampled in renal presentations.
- Other described sites include rectum, gingiva and abdominal fat aspirate.

Abdominal fat aspiration has a limitation

Potential utility

- Can support diagnosis of systemic amyloid
- Minimally invasive compared with organ biopsy

Important limitation

- Low sensitivity despite specificity
- A negative sample does not automatically exclude disease
- Interpret according to clinical suspicion

A suspected AL pattern requires clonal evaluation

- Serum and urine protein electrophoresis and immunoelectrophoresis are described.
- Bone marrow may show a monoclonal plasma-cell population.
- Systemic AL can exist even without overt multiple myeloma.
- These tests assess the source of AL, not the histologic staining reaction.

Diagnostic cases: Ask two distinct questions

Is amyloid present?

- Extracellular deposit morphology
- Congo red staining
- Polarized-light birefringence

Which amyloid and where?

- Protein typing: IHC or mass spectrometry
- Clinical setting and organ distribution
- Workup for the implicated precursor

Case: Endocrine amyloid in thyroid tumor

Clinical vignette

Histology of a thyroid neoplasm shows extracellular amyloid material within the tumor.

Which source-derived peptide should enter the differential, and what is the appropriate interpretation?

Reasoned answer: Calcitonin-derived ACal; A helpful finding in medullary thyroid carcinoma, not sufficient by itself to establish diagnosis.

Case: Amyloid in a single cutaneous nodule

Clinical vignette

A skin nodule contains Congo red–positive deposits with neighboring plasma cells. Examination has not established involvement elsewhere.

What should remain unresolved before labeling the disease?

Reasoned answer: Whether the deposit is localized or part of systemic amyloidosis, and whether the fibril is AL or another type.

Case: The protein determines classification

Clinical clue	Candidate protein	Reason
Recurrent familial serositis	AA	IL-1 response drives SAA
Long-term hemodialysis / carpal tunnel	β_2 -microglobulin	Reduced clearance / periarticular deposits
Medullary thyroid carcinoma	Calcitonin-derived ACal	Endocrine peptide source
Type 2 diabetes / islets	AIAPP	Islet amyloid polypeptide

Integrating pattern, protein and consequence

Predisposition

Inherited inflammation, dialysis retention or local peptide production

Protein

AA, β_2 -microglobulin, AL, ACal or AIAPP

Distribution

Systemic versus organ-limited

Damage

Compression, architectural distortion and organ dysfunction

Core distinctions to retain

- FMF: Hereditary autoinflammation with SAA-derived AA deposition.
- Dialysis: β_2 -microglobulin deposits in joint and soft tissues, especially around the wrist.
- Localized nodules: Distribution can be restricted; Some are AL and plasma-cell associated.
- Endocrine: Hormone / islet peptide-derived amyloid, including calcitonin in medullary thyroid carcinoma.
- Congo red confirms amyloid, while protein typing establishes subtype.

Primary source and study boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 6, “Amyloidosis,” particularly “Other Types of Amyloidosis,” pp. 230–235.
- The lecture also uses the adjacent primary-source sections on amyloid structure, classification, AL, ATTR and AA for essential context.
- Diagrams are original editable conceptual schematics. No diagnostic photomicrographs are reproduced because source figure files were not provided.