

Light-Chain Cast Nephropathy (“Myeloma Kidney”)

Tubular obstruction, light-chain toxicity, and clinicopathologic diagnosis

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Learning objectives

Explain the two principal mechanisms of light-chain–mediated tubular injury.

Recognize cast morphology and the associated tubulointerstitial response.

Distinguish cast nephropathy from AL amyloidosis and light-chain deposition disease.

Integrate clinical presentation, urine findings, and the indication for renal biopsy.

The clinical entity is a tubulointerstitial disease

Filtered monoclonal immunoglobulin free light chains can damage renal tubular epithelium.

Their precipitation with urinary glycoprotein produces obstructive intratubular casts.

Tubular injury, inflammatory reaction, and interstitial fibrosis explain renal dysfunction.

Renal disease associated with nonrenal malignancy

Mechanism	Selected causes	Renal compartment
Direct invasion / obstruction	Renal parenchymal deposits; Ureteral obstruction	Parenchymal / postrenal
Systemic tumor complications	Hypercalcemia; Hyperuricemia	Tubular / interstitial
Abnormal proteins	Myeloma light chains; AL amyloid	Tubular or glomerular
Treatment / infection	Therapies, transplant, opportunistic infection	Variable

Myeloma kidney is not one lesion

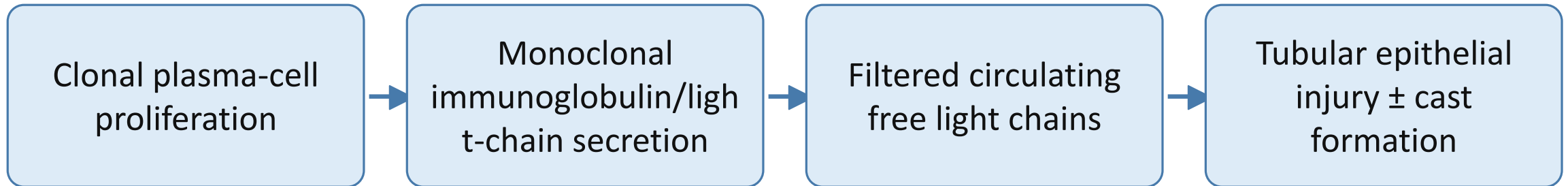
Cast nephropathy: Intratubular light-chain complexes and tubulointerstitial damage.

AL amyloidosis: Deposits of light-chain–derived amyloid.

Light-chain deposition disease (LCDD): Nonfibrillar deposits in glomerular and tubular basement membranes.

Hypercalcemia, hyperuricemia, infection, and treatment toxicity may coexist.

Where does the abnormal protein originate?



Conceptual sequence (simplified; Arrows indicate causal direction)

Bence-Jones proteinuria: The relevant substrate

Bence-Jones proteins are urinary immunoglobulin light chains.

The degree of light-chain proteinuria correlates with renal dysfunction account.

The intrinsic physicochemical behavior of the light chain affects its tubular toxicity.

Two parallel injury mechanisms

Direct epithelial toxicity

Some monoclonal light chains are injurious to tubular cells.

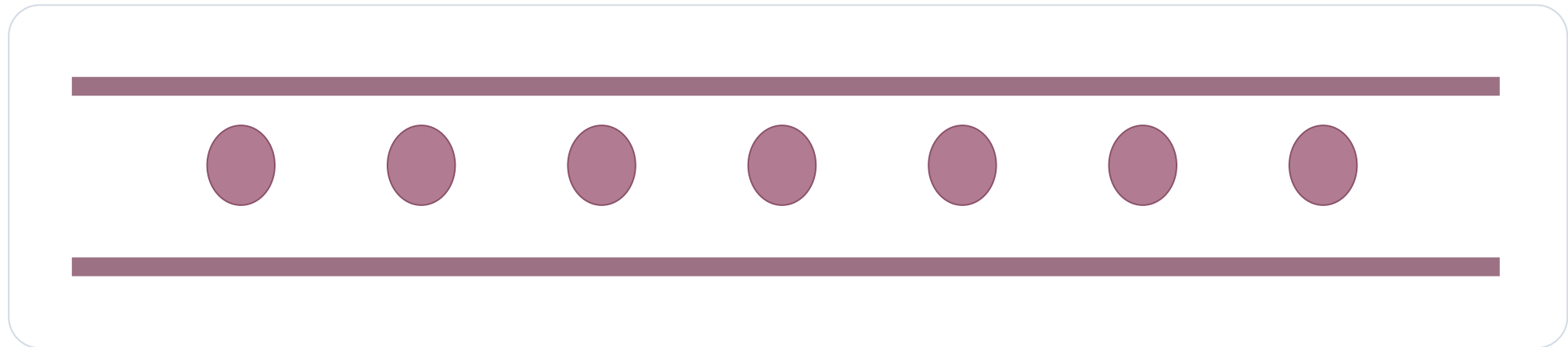
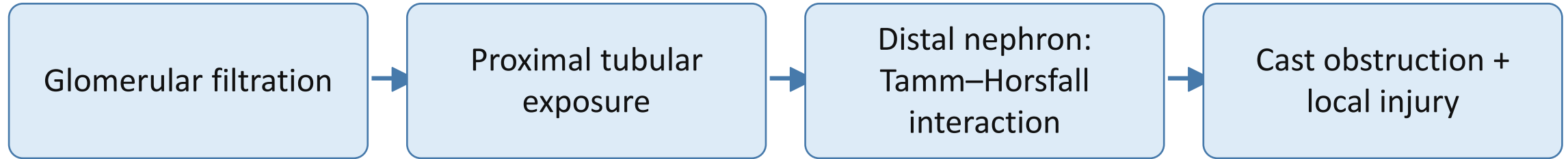
Toxicity varies with the properties of the individual protein.

Cast-mediated obstruction

Light chains combine with Tamm–Horsfall protein in urine.

Bulky intratubular casts obstruct flow and provoke inflammation.

Simplified nephron route of filtered light chains



Native PowerPoint schematic — not microscopy

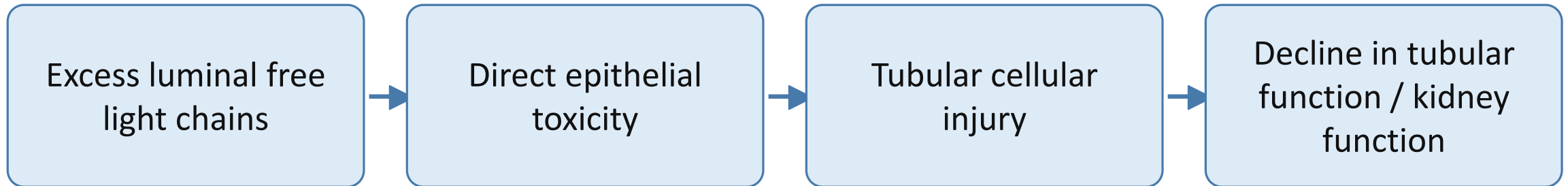
Why tubular light-chain exposure increases

A monoclonal plasma-cell disorder increases the circulating light-chain burden.

Light chains enter the glomerular filtrate and are delivered to the tubules.

A sufficiently large or nephrotoxic filtered load overwhelms normal handling.

Mechanism 1: Directly nephrotoxic light chains



Conceptual sequence (simplified; Arrows indicate causal direction)

Protein chemistry matters

Renal risk is not determined by the diagnosis of myeloma alone.

The amount of excreted light chain and its molecular behavior both matter.

Different light chains can preferentially produce casts, deposition, or amyloid pathology.

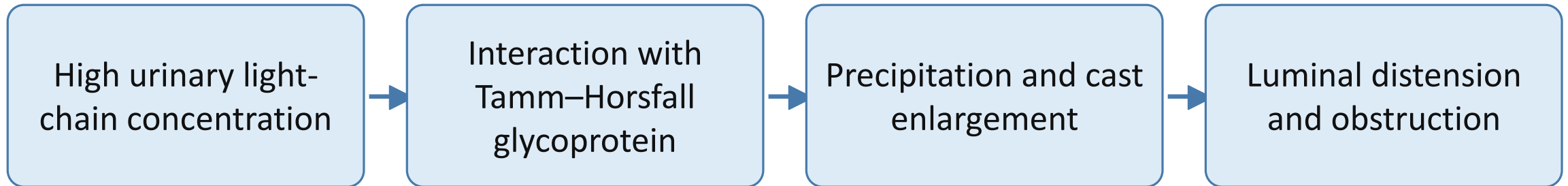
Tamm–Horsfall protein is the cast partner

Tamm–Horsfall urinary glycoprotein is also called uromodulin.

Light chains combine with this protein to form larger intratubular complexes.

The casts are a specific pathologic consequence of abnormal urinary protein interactions.

Mechanism 2: Development of an obstructive cast



Conceptual sequence (simplified; Arrows indicate causal direction)

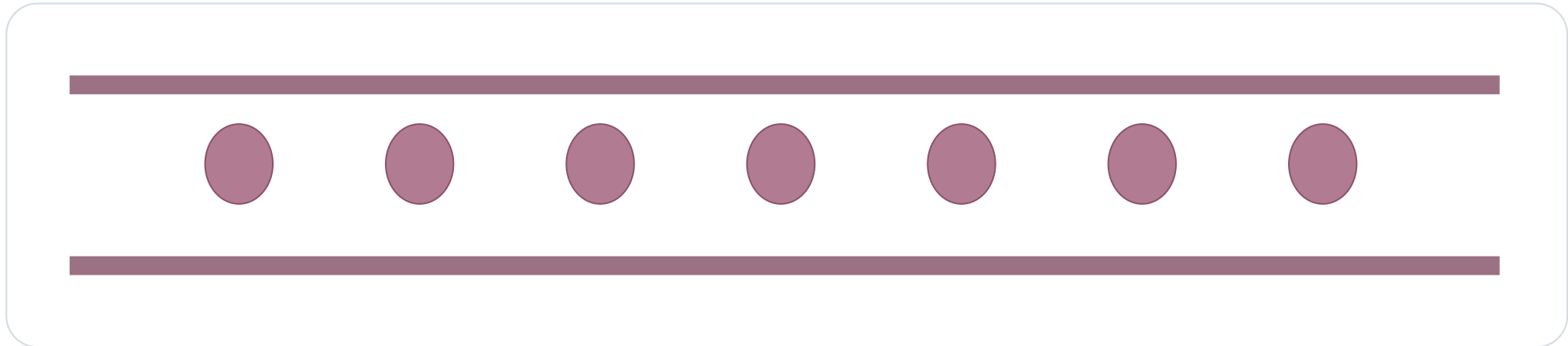
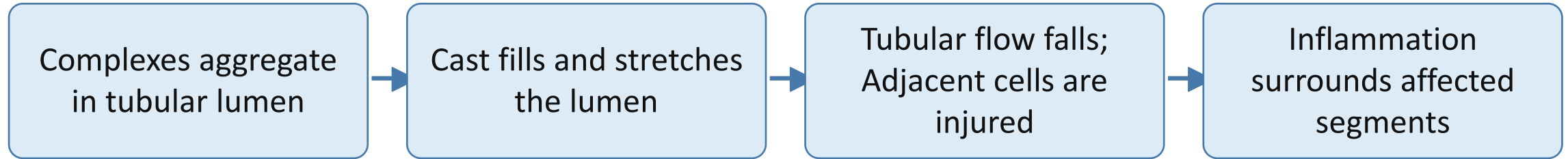
Why acidic urine promotes cast formation

Light-chain–Tamm–Horsfall aggregation under acidic conditions.

The resulting aggregates become large, histologically recognizable tubular casts.

Obstruction is coupled to local epithelial and inflammatory injury.

Tubular obstruction is more than a passive plug



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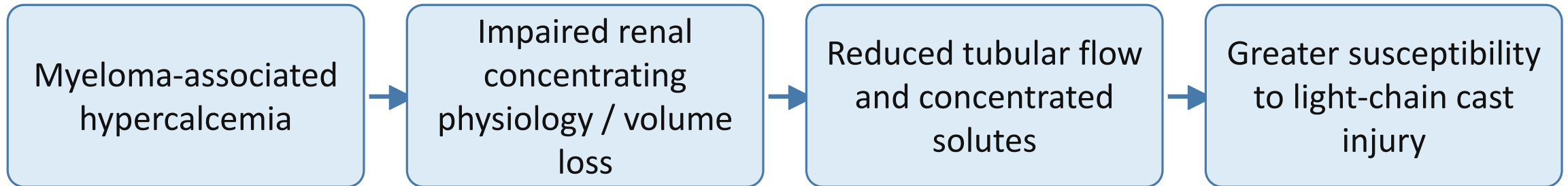
Why dehydration can precipitate injury

Reduced tubular water delivery concentrates the urinary light-chain load.

Concentrated luminal proteins are more likely to form obstructive aggregates.

Volume depletion can therefore convert a vulnerable kidney into abrupt renal dysfunction.

Hypercalcemia provides a second hit



Conceptual sequence (simplified; Arrows indicate causal direction)

Infection and drug exposure can trigger AKI

Acute infection is a textbook-listed precipitant of abrupt renal deterioration.

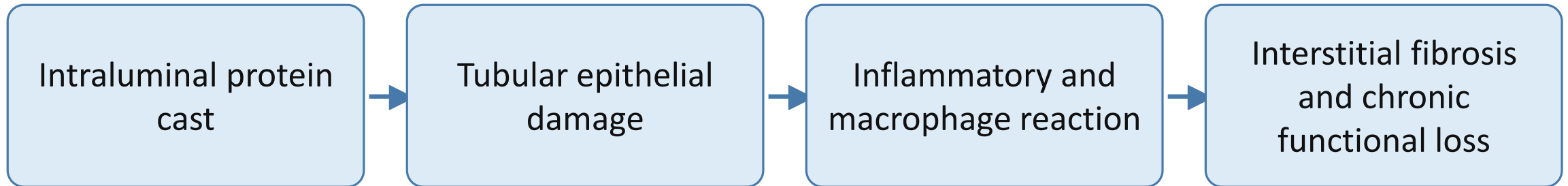
Nephrotoxic antibiotics are another documented trigger.

A superimposed insult may coexist with direct light-chain injury and tubular casts.

Renal hazards in a patient with myeloma

Hazard	Plausible renal effect	Clinical interpretation
Light-chain proteinuria	Tubular toxicity; Obstructive casts	Primary cast-nephropathy mechanism
Hypercalcemia	Volume / tubular disturbances	Amplifies susceptibility
Hyperuricemia	Additional tubular stress	Potential cofactor
Acute infection / antibiotics	Acute superimposed injury	May precipitate oliguria

From casts to interstitial scarring



Conceptual sequence (simplified; Arrows indicate causal direction)

The kidney can suffer several insults simultaneously

Tubular casts can coexist with AL amyloid, LCDD, or nephrocalcinosis.

Infection and treatment-related injury can modify the biopsy and the clinical course.

Attributing all renal impairment to “myeloma kidney” without phenotyping may be misleading.

Two clinical trajectories are described

Insidious chronic kidney disease can progress over months to years.

An abrupt presentation may manifest as acute kidney injury with oliguria.

The same systemic plasma-cell disorder can produce either trajectory.

Chronic versus acute presentation

Insidious decline

Renal function worsens over months to years.

Interstitial fibrosis can accompany sustained tubular injury.

Abrupt AKI

Oliguria may occur.

Consider dehydration, hypercalcemia, infection, and nephrotoxic antibiotics.

Chronic renal dysfunction: Morphologic correlate

Persistent tubular injury is followed by an interstitial inflammatory response.

Fibrosis within the tubulointerstitial compartment can accumulate.

This chronic change provides a structural basis for progressive renal impairment.

Acute oliguria: Identify the precipitant

Ask about recent fluid losses or reduced intake.

Review hypercalcemia, intercurrent infection, and nephrotoxic antibiotic exposure.

Interpret acute deterioration as potentially multifactorial rather than one isolated cast event.

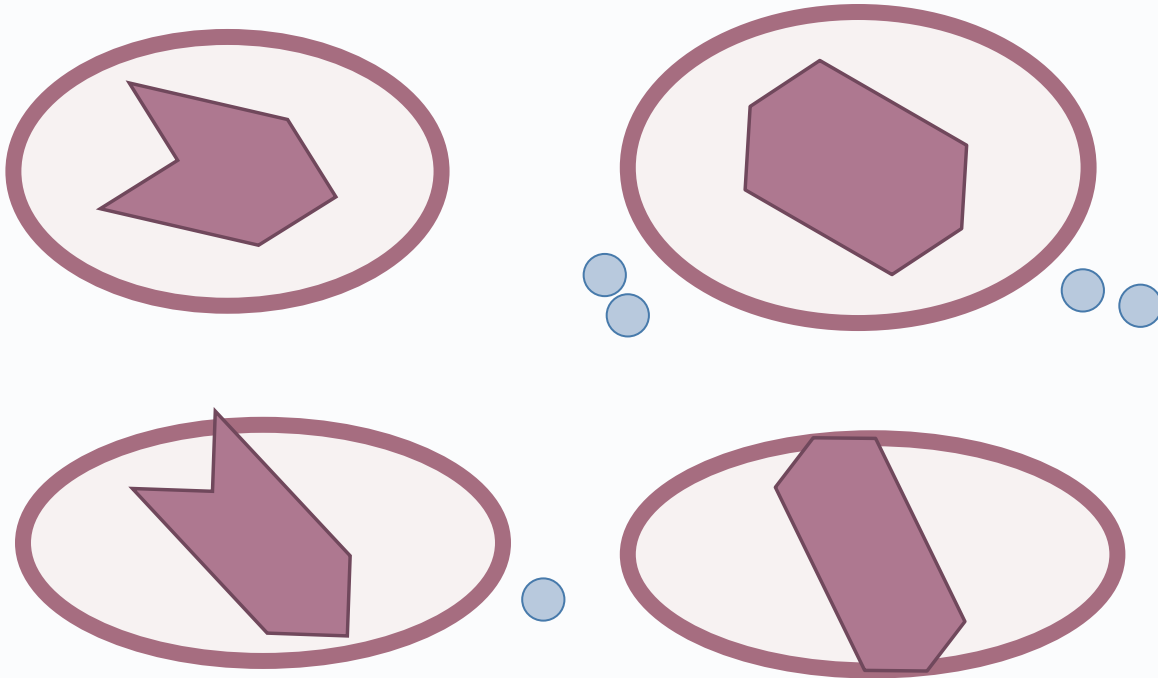
The biopsy target is principally tubular

The distinctive material is located inside tubular lumens.

The affected tubules become dilated or distended by casts.

Adjacent interstitial inflammation is a defining companion to the luminal lesion.

Morphology: Irregular casts inside distended tubules



Schematic — NOT a histologic specimen

Identify:

Amorphous intratubular material

Irregular / angulated outline

Luminal expansion

Epithelial boundary

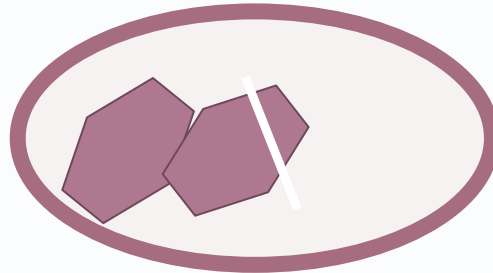
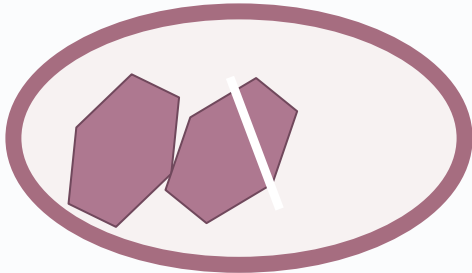
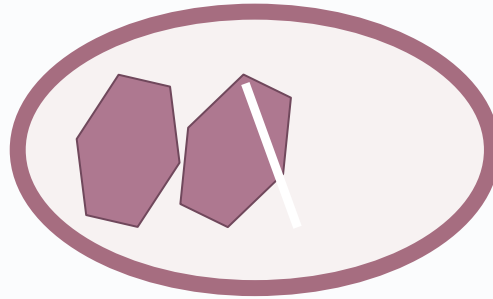
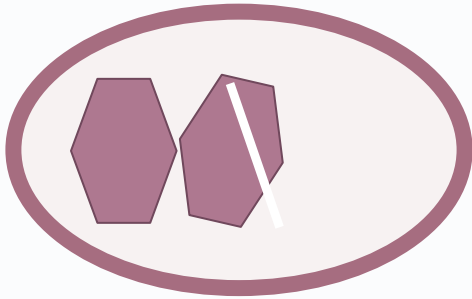
Cast color on routine histology

Bence-Jones casts as pink-to-blue amorphous masses.

Color may vary within or between casts; Do not require a single hue.

Location, contour, fracture pattern, and tissue reaction strengthen recognition.

Fractures and lamination are morphologic clues



Schematic — NOT a histologic specimen

Identify:

Angular fractured cast planes

Optional concentric lamination

Intraluminal location

Reactive cells outside tubule

Why “fractured” casts matter

Light-chain casts are often broken into irregular, angular segments.

Their brittle-appearing contours are a useful recognition clue on H&E.

Morphology must be interpreted alongside clinical monoclonal-protein evidence.

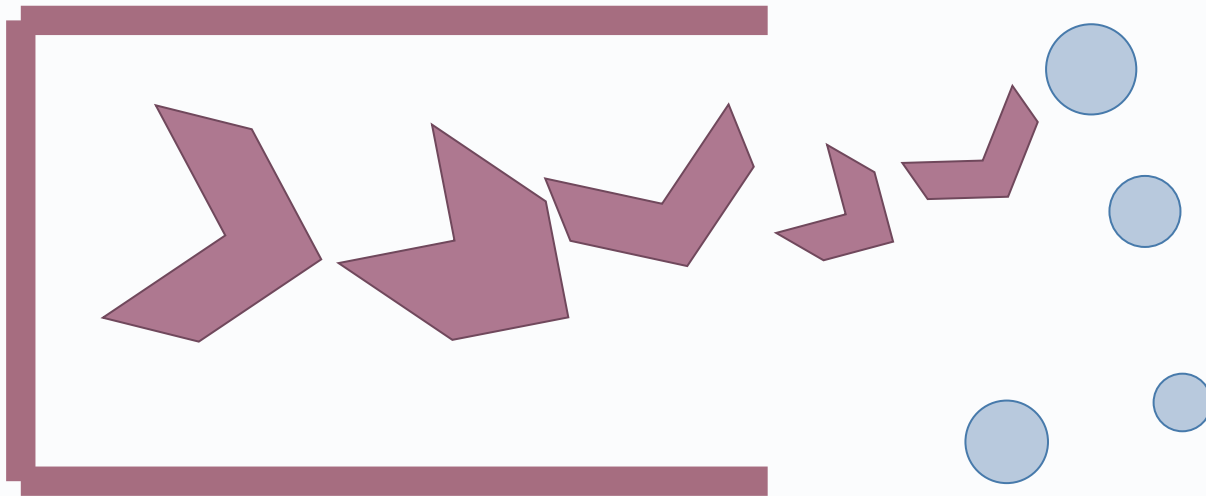
Macrophage reaction around casts

Activated macrophages can accumulate at affected tubules.

Some fuse into multinucleated giant cells surrounding cast material.

This reaction helps explain the striking tubulointerstitial inflammatory appearance.

Tubular rupture produces a granulomatous pattern



Tubular wall break

Schematic — NOT a histologic specimen

Identify:

- Cast-filled damaged tubule
- Tubular wall disruption
- Extravasated cast fragments
- Giant cells / macrophages
around leaked material

Tubular rupture intensifies tissue injury

Casts may breach a damaged tubular wall.

Extravasated material elicits a granulomatous inflammatory response.

Inflammation is therefore not limited to the lumen of an intact tubule.

Interstitial inflammation and fibrosis

Inflammatory cells commonly involve tissue adjacent to abnormal casts.

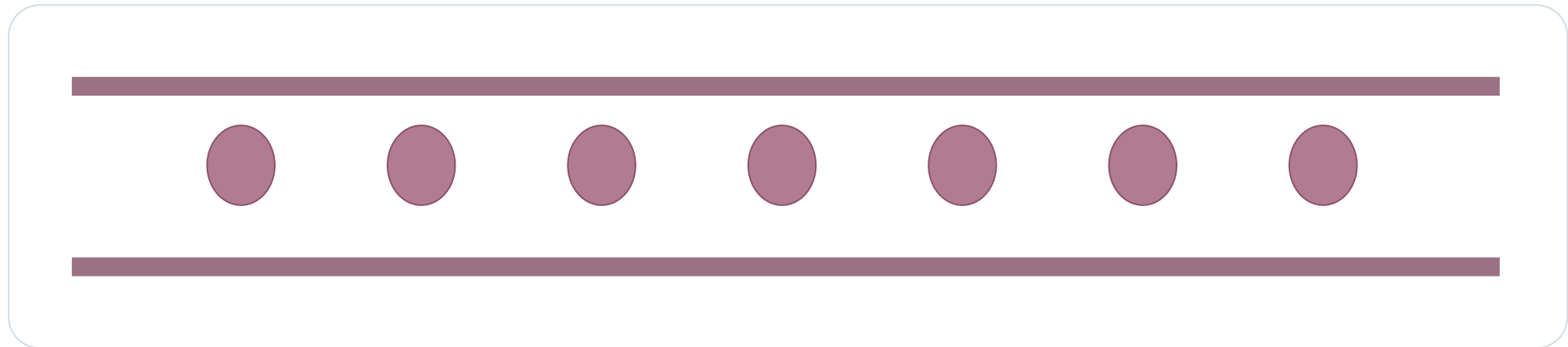
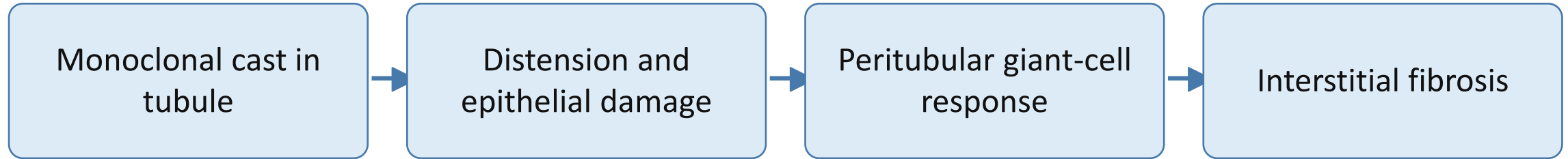
Interstitial fibrosis is often present in established disease.

The tubulointerstitial reaction contributes to lasting loss of renal function.

Read the renal biopsy systematically

Compartment	Examine for	Reason
Tubular lumens	Amorphous irregular fractured casts	Direct cast-related evidence
Tubular lining	Epithelial injury and luminal distension	Explains dysfunction
Interstitium	Inflammation, giant cells, fibrosis	Local response / chronicity
Glomeruli / vessels	Evidence of another concurrent lesion	Avoid single-cause attribution

Integrated lesion: Cast plus epithelial and interstitial damage



Native PowerPoint schematic — not microscopy

A fractured cast alone is not the complete diagnosis

Protein casts occur in other renal diseases.

A characteristic cast pattern is more convincing when paired with monoclonal light-chain evidence.

Correlate biopsy morphology with plasma-cell disease and the renal presentation.

Separate luminal casts from deposited light chains

Cast nephropathy: Aggregated protein occupies the tubular lumen.

LCDD: Nonfibrillar light-chain material deposits in basement membranes.

AL amyloidosis: Light-chain–derived amyloid forms a distinct tissue-deposit disease.

Three major myeloma-related light-chain lesions

Lesion	Principal material / site	Characteristic concept
Cast nephropathy	Light-chain–uromodulin casts in tubules	Obstruction + inflammation
AL amyloidosis	Amyloid from free light chains	Tissue amyloid deposition
LCDD	Nonfibrillar light chains in GBM, mesangium, TBM	Glomerular and tubular basement-membrane injury

AL amyloidosis: A different protein lesion

Renal amyloid in myeloma is usually derived from monoclonal free light chains.

An AL amyloidosis frequency of 6%–24% among individuals with myeloma.

This is a tissue-deposit mechanism, not synonymous with intratubular casts.

Light-chain deposition disease (LCDD)

Nonfibrillar light chains can deposit in GBM and mesangium.

The same process can involve tubular basement membranes.

LCDD produces a glomerulopathy and may contribute to tubulointerstitial nephritis.

The light-chain isotype pattern is a clue—not a rule

AL amyloidosis

Usually λ -type light chains description.

Confirm disease by actual deposition phenotype.

Light-chain deposition disease

Usually κ -type light chains description.

Do not diagnose LCDD from isotype alone.

Renal protein type helps localize the injury

The frequency of Bence-Jones light-chain proteinuria.

Substantial non–light-chain proteinuria (e.g., albuminuria) suggests AL amyloid or LCDD.

Protein pattern is a clinical clue; Overlapping lesions remain possible.

Textbook frequency statements: Interpret carefully

Textbook statement	Reported amount	Teaching interpretation
Renal insufficiency in myeloma / related disorders	About half	Overall renal involvement; Multiple mechanisms
Bence-Jones proteinuria in myeloma	About 70%	Urinary light chain, not proof of a cast lesion
AL amyloidosis in myeloma	6%–24%	Separately characterized renal/systemic lesion

A positive light-chain test does not locate a renal lesion

Urinary monoclonal light chains support the presence of a monoclonal protein burden.

They do not prove whether the kidney contains casts, amyloid, or basement-membrane deposits.

The pattern of proteinuria and, when indicated, biopsy clarify the renal phenotype.

Concurrent lesions are an expected diagnostic possibility

A patient may have cast nephropathy together with amyloid or LCDD.

Nephrocalcinosis and infection can also be present.

The final clinicopathologic assessment should identify all material contributors.

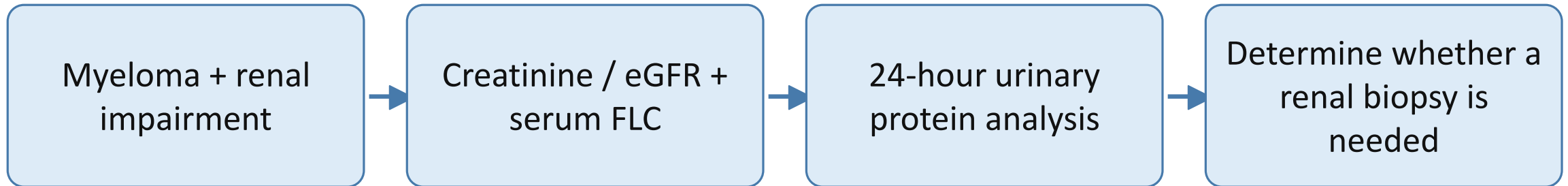
2023 IMWG: Basic assessment of renal impairment

Measure serum creatinine and estimate the glomerular filtration rate.

Obtain serum free light chains.

Obtain 24-hour urinary total protein, electrophoresis, and immunofixation.

2023 IMWG: Clinical diagnostic pathway



Conceptual sequence (simplified; Arrows indicate causal direction)

2023 IMWG: Why quantify albuminuria?

Predominant albuminuria raises suspicion of glomerular involvement.

AL amyloidosis and light-chain deposition disease are important alternatives.

The urine protein pattern changes the need to examine tissue directly.

2023 IMWG: When kidney biopsy is advised

Consider biopsy for nonselective proteinuria, mainly albuminuria.

Biopsy is advised when involved serum free light chains are below 500 mg/L and the cause remains uncertain.

Exclude other causes of renal impairment when applying the recommendation.

How to interpret the 500 mg/L recommendation

What it DOES indicate

Below 500 mg/L, biopsy has heightened importance when renal impairment is unexplained.

Interpret together with urine protein pattern and competing renal causes.

What it DOES NOT mean

It does not histologically define cast nephropathy.

It is not a guarantee that injury is absent above or below the value.

Why a renal biopsy changes the diagnosis

The renal lesions of monoclonal proteins are mechanistically different.

Biopsy can establish a tissue pattern when clinical/urine findings are ambiguous.

It can also identify fibrosis or a coexisting non–light-chain cause.

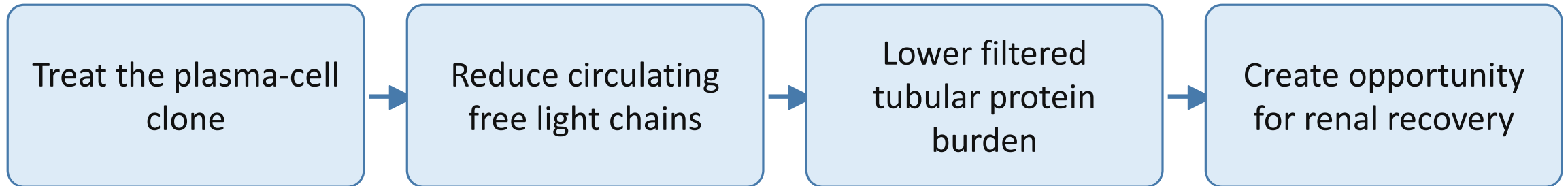
2023 IMWG: Early management priorities

Rapid suppression of the causal plasma-cell light-chain production is central.

Supportive care and high-dose dexamethasone are included in the IMWG recommendations.

Bortezomib-based regimens are a cornerstone of treatment in newly diagnosed renal impairment.

Therapeutic logic follows the mechanism



Conceptual sequence (simplified; Arrows indicate causal direction)

Correct reversible aggravating factors

Assess and correct dehydration when clinically appropriate.

Identify hypercalcemia, infection, and renal-toxic drug exposure.

Avoid interpreting oliguria without evaluating the combined renal insults.

2023 IMWG: Mechanical light-chain removal

Extracorporeal techniques can remove circulating light chains in selected settings.

IMWG reports that mechanical approaches do not improve overall survival.

Such techniques do not replace effective anti-myeloma treatment and supportive care.

What treatment can and cannot reverse

Potentially modifiable early injury

Lower light-chain delivery.

Correct hemodynamic and metabolic precipitants.

Potentially persistent injury

Established tubulointerstitial fibrosis.

Coexisting AL amyloid or light-chain deposits.

Clinical problem 1: Abrupt oliguria

A patient with known myeloma develops oliguria after dehydration and an acute infection. Which mechanisms should be considered?

- A. Only glomerular immune-complex disease
- B. Cast nephropathy plus superimposed precipitating factors
- C. Amyloid is the only possible renal mechanism

Instructor answer and rationale are in the speaker notes.

Case 1: Clinicopathologic reasoning

A large filtered light-chain burden makes tubular cast injury plausible.

Volume depletion concentrates tubular contents; Infection may add renal stress.

Urine studies and serum free light chains clarify the protein burden; Biopsy depends on the clinical picture.

Clinical problem 2: Marked albuminuria

A patient with monoclonal gammopathy has renal dysfunction and prominent albuminuria. Which diagnosis deserves particular consideration?

- A. AL amyloidosis or LCDD
- B. Pure cast nephropathy is proven
- C. All renal pathology is excluded

Instructor answer and rationale are in the speaker notes.

Case 2: Discriminating the lesion

Albuminuria suggests that the glomerular compartment may be importantly involved.

AL amyloidosis and LCDD have distinct deposited-protein pathology.

2023 IMWG recommends biopsy when nonselective proteinuria makes the lesion uncertain.

Morphology problem: Fractured casts

A biopsy description reports angulated, fractured intratubular material with multinucleated giant cells. Which entity is most strongly suggested?

- A. Light-chain cast nephropathy
- B. Minimal-change disease
- C. Ureteral obstruction alone

Instructor answer and rationale are in the speaker notes.

Morphology problem: What can coexist?

The biopsy may additionally show AL amyloid, LCDD, or nephrocalcinosis.

The adjacent interstitium may display both inflammation and established fibrosis.

An integrated report should not stop at the recognition of the cast material.

A high-yield differential of renal injury

Clinical / pathologic clue	Cast nephropathy	Alternative to consider
Fractured luminal casts, giant cells	Strongly supports	Other protein casts if context atypical
Substantial albuminuria	Not the classic isolated pattern	AL amyloid / LCDD
Nonfibrillar basement-membrane deposits	Not the defining cast lesion	LCDD
Abrupt AKI after dehydration	Compatible	Hemodynamic or toxic AKI also possible

Diagnostic traps to avoid

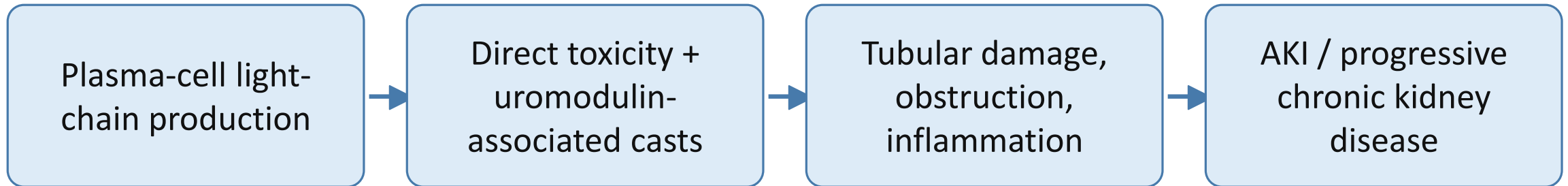
Do not call every light-chain–related renal disease “cast nephropathy.”

Do not regard Bence-Jones proteinuria alone as histologic confirmation.

Do not overlook albuminuria or competing causes of acute kidney injury.

Do not mistake the 500 mg/L IMWG biopsy recommendation for a histologic threshold.

Synthesis: Follow the causal chain



Conceptual sequence (simplified; Arrows indicate causal direction)

Five points to retain

Cast nephropathy is principally a monoclonal light-chain tubulointerstitial injury.

Renal dysfunction results from both direct light-chain toxicity and obstructive cast formation.

Fractured casts, giant cells, and adjacent inflammation are morphologic clues.

AL amyloid and LCDD are distinct, sometimes concurrent renal lesions.

Clinical evaluation must integrate protein pattern, FLC burden, and other renal insults.

Selected references

Reference	Role	Where to look
Robbins, Cotran & Kumar, 11th ed. (2026)	Primary pathology source	Chapter 20, pp. 850–851
Robbins, Cotran & Kumar, 11th ed. (2026)	Hematologic parent context	Chapter 13, pp. 553–554
Dimopoulos MA et al. Lancet Oncol. 2023	IMWG renal evaluation / treatment	doi:10.1016/S1470-2045(23)00223-1
Menè P et al. Int J Nephrol Renovasc Dis. 2022	Supplementary morphology / mechanism	doi:10.2147/IJNRD.S280179