AL Amyloidosis and Multiple Myeloma: Plasma Cell Dyscrasias and Renal Disease

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AL Amyloidosis and Multiple Myeloma: Plasma Cell Dyscrasias and Renal Disease

Learning Objectives

By the end of this module, you will be able to:

1. **Distinguish** AL amyloidosis from multiple myeloma despite shared pathogenic mechanisms
2. **Recognize** diagnostic delays and their catastrophic consequences
3. **Identify** renal manifestations and common misdiagnoses
4. **Apply** staging systems appropriate to each disease
5. **Understand** why treatment intensity differs despite similar drug classes

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Introduction: Two Diseases, Shared Origins

Shared Pathophysiology: - Both arise from clonal proliferation of bone marrow plasma cells - Both produce monoclonal immunoglobulin light chains - Both harbor some overlapping cytogenetic abnormalities - Both are plasma cell malignancies

Divergent Phenotypes: - AL amyloidosis: Light chains misfold into beta-pleated sheet fibrils, causing progressive organ infiltration - Multiple myeloma: Light chains cause direct toxicity through cast nephropathy and other mechanisms - Different organ involvement patterns - Dramatically different treatment approaches required

Epidemiologic Overlap: - 10-15% of myeloma patients develop AL amyloidosis - 10-18% of AL amyloidosis patients meet criteria for concurrent symptomatic myeloma

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The Critical Problem: Diagnostic Delay

Why AL Amyloidosis is Missed

Systemic Barriers: - Low disease awareness (most physicians see <1 case in career) - Nonspecific early symptoms (fatigue, weight loss, edema) - Multiple specialist visits before correct diagnosis

(average 3-4 physicians) - Symptoms misattributed to common conditions

Consequences of Delay: - Each month of diagnostic delay allows continued amyloid deposition - Progressive organ damage becomes irreversible - Cardiac involvement develops during diagnostic workup - Treatment becomes less effective

Impact on Survival: - Diagnosed <6 months from symptom onset: 48+ month median OS - Diagnosed 6-12 months: 24-36 month median OS - Diagnosed >12 months: 12-18 month median OS

Clinical Pearl: Diagnostic delay directly correlates with stage at diagnosis. Patients diagnosed within 6 months have significantly better survival regardless of cardiac stage at presentation.

Diagnostic Trap: Cardiac Amyloidosis Misdiagnosed as Heart Failure

Clinical Overlap Creating Confusion

Both cardiac amyloidosis and HFpEF present with: - Dyspnea - Fatigue - Peripheral edema - Elevated NT-proBNP/BNP - Left ventricular hypertrophy - Diastolic dysfunction

Key Distinguishing Features Often Missed

Feature	HFpEF/Hypertensive HD	Cardiac Amyloidosis
LV wall thickness	12-14 mm	>14 mm, often >16 mm
ECG voltage	Normal or increased	**Low voltage (paradox)**
Strain imaging	Global reduction	Apical sparing ("cherry on top")
Response to standard HF meds	Improves	Often worsens/no response
Hypotension with ACEi/ARB	Uncommon	Common (autonomic involvement)
Associated features	Hypertension history	Periorbital purpura, macroglossia, carpal tunnel

The Paradox: Marked LV hypertrophy with LOW voltage ECG is nearly pathognomonic for cardiac infiltrative disease, particularly amyloidosis.

Consequences of Misdiagnosis

- Standard heart failure medications may cause harm
- Digoxin binds amyloid fibrils ☐ toxicity at "therapeutic" levels

- Beta-blockers worsen cardiac output in amyloid-dependent hearts
- Diagnostic delay allows progression from Stage II to Stage III/IIIb
- Treatment intensity inadequate for amyloidosis

Diagnostic Trap: Renal Amyloidosis Misdiagnosed as Primary Glomerular Disease

The Diagnostic Error Pattern

Renal AL amyloidosis commonly misdiagnosed as: - Minimal change disease - Membranous nephropathy - Focal segmental glomerulosclerosis (FSGS) - Diabetic nephropathy

Why This Error is Catastrophic

Consequence of Empiric Immunosuppression: 1. Prednisone monotherapy (MCD regimen) inadequate — doesn't target plasma cell clone 2. Rituximab given for presumed membranous nephropathy — delays clone-directed therapy 3. Cyclophosphamide for presumed FSGS — wrong drug entirely 4. **Amyloidogenic clone continues producing toxic light chains** during diagnostic delay

Red Flags Suggesting AL Amyloidosis Rather Than Primary GN

Finding	Suggests AL
Age >50 with new nephrotic syndrome	Higher pretest probability
Nephrotic syndrome + unexplained cardiac symptoms	Multi-organ involvement
Nephrotic syndrome + carpal tunnel syndrome	Systemic amyloid deposition
Nephrotic syndrome + autonomic symptoms	Peripheral/autonomic neuropathy
Unexplained hepatomegaly + elevated ALP	Hepatic involvement
Periorbital purpura or macroglossia	**Pathognomonic for AL**
Monoclonal protein on SPEP/UPEP/FLC	Clonal plasma cell disorder

Screening Strategy for Nephrotic Syndrome >50 Years

Essential Workup BEFORE kidney biopsy for presumed primary GN: - Serum protein electrophoresis with immunofixation - Urine protein electrophoresis with immunofixation - Serum free light chain assay (abnormal ratio in 98% of AL) - NT-proBNP and cardiac troponin (screen for cardiac involvement)

If any abnormal: Perform fat pad aspiration/bone marrow biopsy with Congo red staining BEFORE starting immunosuppression for presumed glomerular disease.

Pathophysiologic Distinction: Two Types of Light Chain Toxicity

AL Amyloidosis: Fibril Deposition Toxicity

Mechanism: - Amyloidogenic light chains misfold into beta-pleated sheet structure - Form insoluble amyloid fibrils - Progressive extracellular accumulation in tissues - Cause organ dysfunction through mass effect and structural damage

Organ Involvement: - Heart (infiltrative cardiomyopathy) — 70-90% at diagnosis - Kidneys (glomerular deposition ☐ nephrotic syndrome) - Liver (progressive infiltration) - Peripheral/autonomic nerves (neuropathy)

Characteristic Feature: Relatively small plasma cell clones (<10%) produce highly amyloidogenic light chains

Light Chain Pattern: Lambda > kappa (75% vs. 25%) — opposite of myeloma

Multiple Myeloma: Cast Nephropathy (Myeloma Kidney)

Mechanism: - Excessive light chain filtration reaching distal nephron - Bind with Tamm-Horsfall protein (uromodulin) - Form obstructing intratubular casts - Trigger inflammatory response with giant cell reaction - Progressive tubular atrophy and interstitial fibrosis

Presentation: - Acute kidney injury (days to weeks) - Serum free light chains >500-1,500 mg/L - Bence Jones (tubular) proteinuria - Urine dipstick trace positive despite substantial protein (unusual)

Characteristic Feature: Large plasma cell clones (>10%) with aggressive tumoral biology

Light Chain Pattern: Kappa > lambda (opposite of amyloidosis)

Renal Manifestations Comparison

Feature	Cast Nephropathy (Myeloma)	Renal AL Amyloidosis
Primary site	Distal tubules, interstitium	Glomeruli, vessels
Presentation	Acute kidney injury	Nephrotic syndrome
Proteinuria type	Bence Jones (light chain)	Albumin-predominant
Urine dipstick	Trace or negative	3-4+ positive
Serum albumin	Usually normal	**Severe hypoalbuminemia**

Feature	Cast Nephropathy (Myeloma)	Renal AL Amyloidosis
Reversibility	Possible with rapid FLC reduction	Slow with sustained CR
FLC threshold	>500-1,500 mg/L typical	May be low (<500 mg/L)

Clinical Pearl: Approximately 50% of myeloma patients may have occult amyloid deposits on autopsy. Both pathologies can coexist—kidney biopsy remains gold standard for differentiation.

Diagnostic Approach and Staging

AL Amyloidosis Staging: Cardiac Biomarkers

Mayo 2012 Staging System (most current):

Incorporates three variables: 1. **NT-proBNP:** Threshold 1,800 pg/mL 2. **Cardiac troponin:** Threshold 0.025 ng/mL 3. **dFLC (involved minus uninvolved):** Threshold 180 mg/L

Stage	Criteria	Median OS
I	None elevated	94 months
II	One elevated	40 months
III	Two elevated	14 months
IV	All three elevated	6 months

Key Point: Cardiac involvement (NT-proBNP, troponin) predicts survival MORE powerfully than light chain burden. Stage IV disease has median OS of only 6 months untreated.

Multiple Myeloma Staging: Tumor Burden

Revised ISS (R-ISS) System:

Stage	Criteria	5-Year OS
I	ISS I + standard-risk cytogenetics + normal LDH	82%
II	Not I or III	62%
III	ISS III + high-risk cytogenetics or elevated LDH	40%

Key Point: In myeloma, staging reflects tumor burden (beta-2-microglobulin, albumin, cytogenetics). In AL amyloidosis, staging reflects end-organ damage (cardiac biomarkers). These are fundamentally different concepts.

Amyloid Typing: Critical for Treatment

Why Amyloid Typing Matters

Different Amyloid Types, Completely Different Therapies:

Amyloid Type	Treatment Approach	Prognosis
AL (light chain)	Clone-directed therapy (bortezomib-based)	Potentially curable with deep response
ATTR	TTR-stabilizing agents or gene therapy	Different natural history
AA (secondary)	Treat underlying inflammation	Different pathophysiology

Failure to Properly Type = Catastrophic Error

Using myeloma-intensity therapy (appropriate for AL) on ATTR amyloidosis patient ☐ toxicity without benefit

Diagnostic Methods

Gold Standard: Mass spectrometry-based proteomic analysis of laser-microdissected amyloid deposits (>98% accuracy)

Alternative Methods: - Immunofluorescence (higher false-positive/negative rates) - Immunohistochemistry (less accurate than mass spec)

Clinical Pearl: Always confirm amyloid type with mass spectrometry if tissue diagnosis made. Immunofluorescence alone insufficient for treatment decisions.

Survival Comparisons: Treatment Impact

AL Amyloidosis Survival

Untreated: - Median OS: 6-12 months overall - Stage I: 12-18 months - Stage IIIb: 2-3 months

Treated (Modern Era with Daratumumab): - Median OS: 5-6 years overall - Stage I: Not reached (long-term remission) - Stage IIIb: 18-24 months (from 3 months untreated)

Key Outcome: Complete remission patients have survival approaching age-matched controls; functional cure possible

Multiple Myeloma Survival

Untreated: - Median OS: 6-12 months

Treated (Modern Era): - Standard risk: 10+ years - High risk: 3-5 years

Key Difference: Myeloma shows linear survival decline over years; AL amyloidosis shows steep early decline followed by plateau for responders

Combined AL Amyloidosis and Multiple Myeloma

Prevalence: 10-18% of AL amyloidosis patients meet IMWG criteria for concurrent myeloma

Prognostic Challenge: Must stage BOTH diseases

Treatment Principles: 1. Stage using AL cardiac staging AND myeloma ISS 2. **Cardiac stage determines treatment intensity** (not myeloma burden) 3. Monitor BOTH myeloma (M-protein) AND AL parameters (dFLC, biomarkers) 4. Avoid myeloma-intensity therapy in organ-compromised patients

Survival: Worse than either disease alone (30-40 months vs. 60+ for AL alone or 80+ for MM alone)

Key Teaching Point: AL amyloidosis patients with >10% bone marrow plasma cells are at highest risk of receiving inappropriately intensive regimens. Cardiac function, not marrow burden, guides treatment intensity.

Practice Questions

Question 1: A 64-year-old presents with dyspnea, fatigue, edema, and 7 g/day proteinuria. Echocardiogram shows marked LVH (16 mm wall thickness) with low voltage ECG. Serum free light chains show kappa:lambda ratio 0.3 (involved lambda 180 mg/L). What is the most critical next step?

A) Refer to nephrology for kidney biopsy and presumed glomerular disease workup
B) Screen with serum protein electrophoresis, urine electrophoresis, and perform fat pad aspiration
C) Start prednisone for presumed immune-mediated nephrotic syndrome
D) Initiate ACE inhibitor and diuretics for heart failure

Correct Answer: B — The constellation of marked LVH with LOW voltage ECG (paradoxical), lambda predominance, and proteinuria suggests cardiac amyloidosis with renal involvement. Fat pad aspiration with Congo red staining will establish amyloid diagnosis before empiric immunosuppression. Correct diagnosis prevents catastrophic therapeutic errors.

Question 2: A 52-year-old with AL amyloidosis Stage II (one elevated cardiac biomarker) and 8% bone marrow plasma cells receives myeloma-dose bortezomib. Why is this treatment approach problematic?

A) AL amyloidosis is not responsive to proteasome inhibitors
B) Treatment intensity should be calibrated to cardiac function and organ involvement, not bone marrow burden
C) Eight percent plasma cells indicate this is actually myeloma, not amyloidosis
D) Bortezomib causes unacceptable cardiotoxicity in all AL patients

Correct Answer: B — AL amyloidosis with modest plasma cell burden but significant cardiac involvement requires careful dosing based on cardiac function/stage, not myeloma-intensity chemotherapy. A patient with 8% marrow burden could have Stage IV AL (all three cardiac biomarkers elevated, median OS 6 months) and cannot tolerate myeloma-dose therapy.

Question 3: A 58-year-old with renal AL amyloidosis receives 6 months of prednisone for presumed membranous nephropathy. Proteinuria remains 5.2 g/day. What is the most likely explanation?

A) Steroid-resistant membranous nephropathy requiring rituximab
B) AL amyloidosis was missed; prednisone inadequate because plasma cell clone still producing light chains
C) Patient has combined AL amyloidosis and membranous nephropathy
D) Therapy needs escalation to cyclophosphamide

Correct Answer: B — AL amyloidosis presenting as nephrotic syndrome often misdiagnosed as primary glomerular disease. Prednisone monotherapy does not target the plasma cell clone. The amyloidogenic clone continues light chain production during empiric immunosuppression. Correct diagnosis requires serum/urine free light chains, SPEP/UPEP, and fat pad aspiration before biopsy.

Clinical Pearls

1. **Cardiac amyloidosis ≠ heart failure** — low voltage ECG with LVH paradoxical finding
2. **Diagnostic delay = progressive organ damage** — each month matters
3. **AL is often missed** — maintain high suspicion with unexplained cardiac or renal disease
4. **Renal AL misdiagnosed as primary GN** — screen before kidney biopsy if >50 years
5. **Amyloid typing essential** — mass spectrometry gold standard
6. **AL vs. myeloma:** Different staging (cardiac vs. tumor burden), different treatment intensity
7. **Treatment intensity by cardiac stage, not clone size** — 8% plasma cells with Stage IV AL cannot tolerate myeloma-dose therapy

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See Also

Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Kidney Biopsy Essentials
- Glomerular Treatment Principles
- AKI Workup and Diagnosis

Clinical Reference (Primary Copies)

- Amyloid & Paraprotein Renal Disease — Knowledge Hub

- AL Amyloidosis & Multiple Myeloma — Full Clinical Review
- Cardiac Amyloidosis Case Report — Felton
- Inpatient AL Case Report 2026

Summary

AL amyloidosis and multiple myeloma, while both arising from plasma cell dyscrasias, present profoundly different diagnostic and therapeutic challenges. The most critical barrier to optimal AL amyloidosis outcomes is diagnostic delay, which allows continued amyloid deposition and progressive organ damage. Recognition of pathognomonic features (low voltage ECG with LVH paradox, periorbital purpura, lambda light chain predominance) enables rapid diagnosis. Renal AL amyloidosis frequently misdiagnosed as primary glomerular disease, with empiric immunosuppression delaying appropriate anti-plasma cell therapy. Treatment intensity must be calibrated to organ involvement (cardiac staging) rather than tumor burden (plasma cell percentage) — a critical distinction from myeloma. Modern therapies including daratumumab have transformed AL amyloidosis from uniformly fatal disease to one with meaningful long-term remission potential in many patients.