Amyloidosis

AL, ATTR and AA · the red flags that should trigger the workup, and the one test sequence that must not be reversed

Type it
before you treat

WHEN TO SUSPECT IT *a multisystem disease that is diagnosed late because each organ looks like something commoner*

CARDIAC

Heart failure with thick walls but LOW ECG voltage is the classic mismatch, and it is the single most useful clue. Also: **intolerance of the usual heart failure drugs** (beta-blockers and ACE inhibitors cause hypotension), unexplained atrial fibrillation, and **apical sparing** on strain echocardiography.

RENAL

Nephrotic-range proteinuria with bland sediment, especially albuminuria out of proportion to the creatinine. In AL, the kidney and the heart are the two organs that determine prognosis.

THE GIVEAWAYS

Periorbital purpura and **macroglossia** are nearly specific for **AL**, though present in a minority. Also **bilateral carpal tunnel syndrome** and lumbar spinal stenosis, which often precede cardiac ATTR by years, plus autonomic neuropathy and unexplained weight loss.

THE TYPES *because the treatment is completely different*

Type	Precursor and setting	What it means
AL *light chain*	**Monoclonal light chain** from a plasma cell clone, usually small. Related to myeloma and MGUS but **does not require** myeloma criteria to be met	**The urgent one.** Untreated cardiac AL has a survival measured in months. Treatment targets the plasma cell clone
ATTR wild-type	**Normal transthyretin** misfolding with age. Predominantly **older men**, and much commoner than once believed	Increasingly recognized as a cause of **HFpEF**. Preceded for years by **bilateral carpal tunnel release** and biceps tendon rupture
ATTR hereditary	**Mutant transthyretin.** Cardiac, neuropathic or mixed depending on the variant	Needs **genetic testing and family screening**, which changes the plan for relatives as well as the patient
AA *serum amyloid A*	**Chronic inflammation**: poorly controlled rheumatoid arthritis, inflammatory bowel disease, chronic infection, familial Mediterranean fever	Predominantly **renal**. Treatment is **controlling the underlying inflammation**

DIAGNOSIS *the sequence matters more than any single test*

Step	Detail
1. Screen for a light chain never skip this	**Serum and urine protein electrophoresis WITH immunofixation, plus serum free light chains.** All three, because electrophoresis alone misses light-chain-only disease. This step exists to find or exclude **AL**
2. Prove amyloid	**Congo red staining with apple-green birefringence** under polarized light. Fat pad aspirate or bone marrow first, since they are low risk; involved-organ biopsy if those are negative and suspicion is high
3. TYPE it	**Mass spectrometry is the reference standard**, with immunohistochemistry as an alternative. **Typing is not optional**: the treatments have nothing in common, and a wrong type means a wrong drug
4. Cardiac imaging	Echo (thick walls, apical sparing) and cardiac MRI (diffuse late gadolinium enhancement). **Bone scintigraphy with 99mTc-PYP** takes up avidly in ATTR: a heart-to-contralateral ratio at or above **1.5** performed very well for ATTR in the validation work

⚠ THE ERROR THAT MATTERS: A POSITIVE PYP SCAN DOES NOT DIAGNOSE ATTR ON ITS OWN

PYP can be positive in AL amyloidosis too, and cases with strongly positive scans have turned out to be AL on biopsy. **A non-invasive ATTR diagnosis is only permissible when the light-chain screen is negative.** Calling ATTR on the scan alone in a patient who actually has AL starts the wrong treatment in the disease where delay is measured in months.

ORGAN INVOLVEMENT & PROGNOSIS *what to document, and what actually predicts survival*

Organ	How it presents	Assess with
Heart drives prognosis in AL	Restrictive physiology, heart failure, arrhythmia, conduction disease. **Low voltage with thick walls**	**NT-proBNP and troponin**, echo with strain, cardiac MRI. These two biomarkers plus the difference in free light chains form the **Mayo staging system**, which stratifies survival far better than symptoms do
Kidney	**Nephrotic-range proteinuria**, progressing to renal failure	**24-hour urine protein or a protein-to-creatinine ratio**, plus eGFR
Nerve	**Length-dependent sensory then motor neuropathy**, plus autonomic failure: orthostatic hypotension, early satiety, erectile dysfunction, alternating bowel habit	Clinical examination and orthostatic measurements. Autonomic involvement is **heavily under-recognized** and explains the falls
Liver and GI	**Hepatomegaly with a raised alkaline phosphatase** out of proportion to transaminases; malabsorption, bleeding, dysmotility	Liver function tests, imaging. Biopsy of an involved organ carries **a real bleeding risk** in amyloidosis
Soft tissue	Macroglossia, periorbital purpura, the **"shoulder pad" sign**, nail dystrophy, jaw claudication	Inspection. These cost nothing to look for and are frequently the finding that finally prompts the diagnosis

TREATMENT & PEARLS

- **AL: treat the clone, urgently.** Anti-CD38 antibody based regimens with a proteasome inhibitor, with autologous transplant in selected fit patients. **Response is followed by the free light chain level**, and organ recovery lags the hematologic response by months.
- **ATTR: stabilize the tetramer. Tafamidis reduces all-cause mortality and cardiovascular hospitalization** in ATTR cardiomyopathy. Gene-silencing therapies are also established for ATTR. Refer to a specialist center rather than managing it as ordinary heart failure.
- **The cardiac drug rules are inverted here.** These patients are **preload dependent with a stiff, small cavity**: they tolerate beta-blockers, ACE inhibitors and vasodilators badly, and the mainstay is **diuresis for congestion**. **Digoxin binds amyloid fibrils and is best avoided**. Anticoagulate atrial fibrillation, since the atrial thrombus risk is high even in sinus rhythm.
- **An MGUS in a patient with unexplained heart failure, neuropathy or proteinuria is not incidental** until AL has been excluded. That combination is the most commonly missed presentation of the whole disease.

References: Gillmore et al. non-biopsy diagnostic criteria for cardiac ATTR · 99mTc-PYP scintigraphy validation studies · ATTR-ACT (tafamidis) · ISA and Mayo consensus guidance on amyloidosis typing and management.