Essentials for the Diagnosis of Amyloidosis

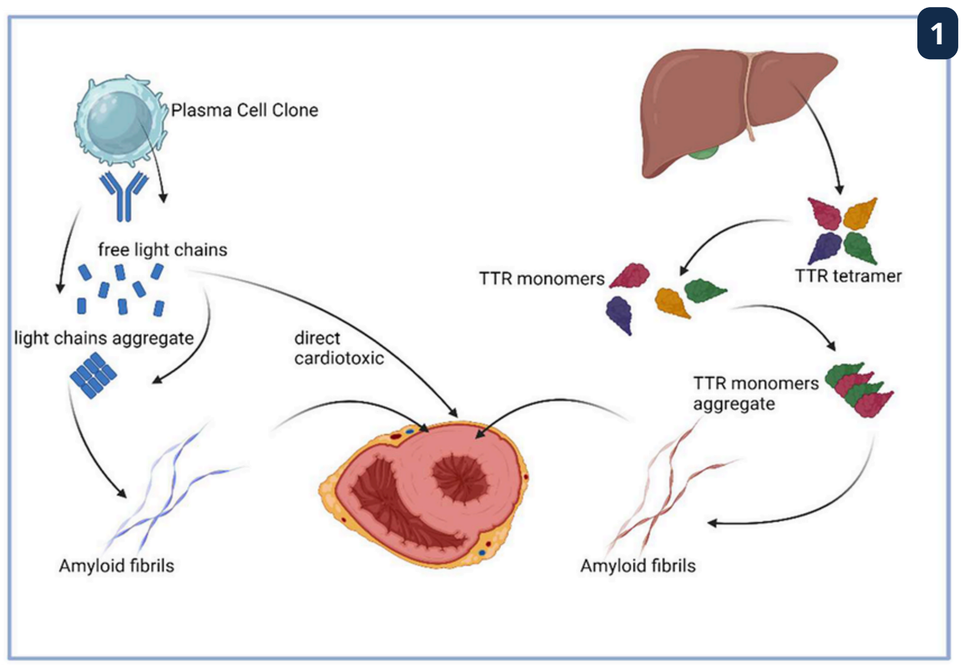
When to Suspect and Useful Clinical Tools for Investigation

What Is Cardiac Amyloidosis?

It is a disorder of insoluble fibrils formed from abnormal misfolded proteins that deposit into tissues, particularly the cardiac muscle resulting in cardiomyopathy. There are two major types: AL and ATTR

AL Amyloidosis

AL amyloidosis is a type of plasma cell dyscrasia with or without multiple myeloma. It is the result of **misfolded immunoglobulin light chains, resulting in fibril formation.** These fibrils infiltrate the myocardium, leading to impairment of myocardial contractility and relaxation.

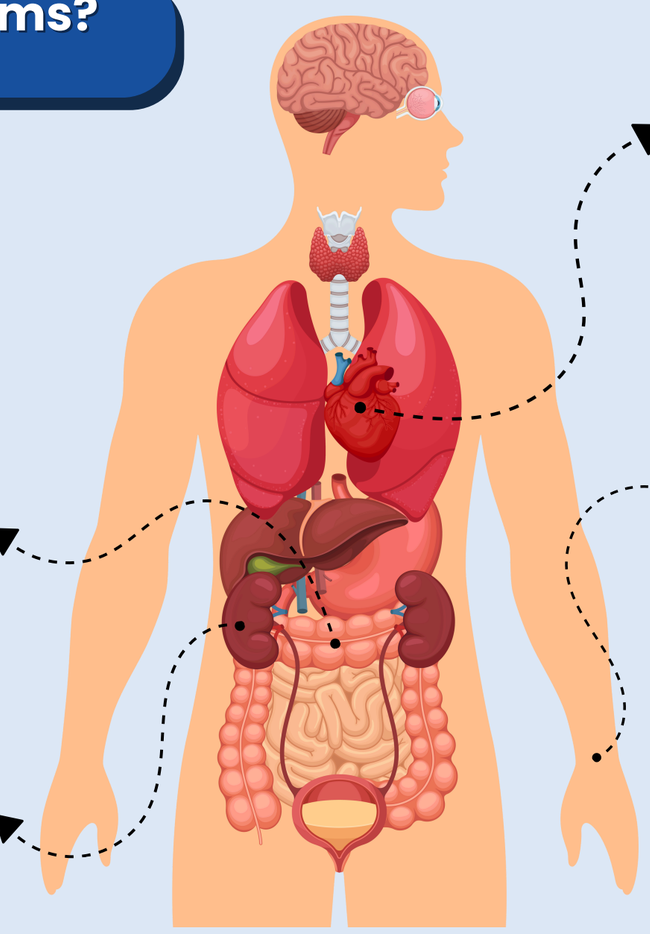


ATTR Amyloidosis

ATTR amyloidosis results from transthyretin (TTR), a protein produced by the liver that transports thyroid hormone and vitamin A. **TTR misfolds, resulting in fibril formation and deposition in tissues.** The cardiac and peripheral nervous system are commonly affected.

What Are the Signs and Symptoms?

Multiple or only one sign may be present



Nervous System

- Peripheral neuropathy, sensory/motor (numbness/weakness in hands/feet)
- Autonomic dysfunction (e.g., orthostasis, intolerance to vasodilator medication, erectile dysfunction)

Cardiovascular

- Symptoms of HF (fatigue, edema, dyspnea)
- Cardiomyopathy (thick ventricular walls)
- Arrhythmia (atrial fibrillation, conduction disorders)
- Association with aortic stenosis (ATTR)

Gastrointestinal

- Dysmotility (e.g., early satiety, constipation, diarrhea, nausea, vomiting)
- Unexplained weight loss

Orthopedic

- Spinal Stenosis
- Carpal tunnel syndrome (especially bilateral)
- Ligamentous rupture (e.g., bicep tendon rupture)

Renal

- Acute and chronic renal insufficiency
- Proteinuria

Others

- Periorbital purpura (AL)
- Macroglossia (AL)
- Hepatomegaly

How Do We Make the Diagnosis? 2

Clinical Suspicion of Cardiac Amyloidosis

- Left ventricular hypertrophy w/o hypertension or other causes
- Unexpected cardiac biomarker elevation

Obtain 3

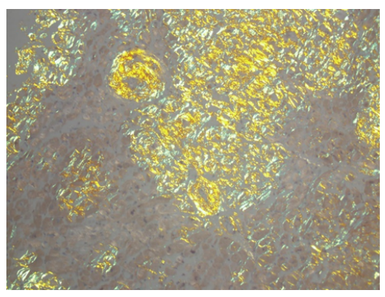
- Serum kappa and lambda free light chains
- Serum and 24-hour urine electrophoresis and immunofixation

in order to exclude monoclonal protein production

ABNORMAL

Monoclonal protein detected

- Consult hematology
- Tissue biopsy :
  - Bone marrow
  - Affected organ
  - Abdominal fat pad biopsy
- Pathology:
  - Congo red stain
  - Tissue typing by mass spectrometry



Congo red, positive apple green birefringence

NORMAL

No monoclonal protein

Obtain technetium PYP scan

Negative

Unlikely ATTR amyloidosis.
However, if the clinical suspicion remains high and PYP scan is negative or equivocal, consider an endomyocardial biopsy.

Positive

Grade 2/3 uptake
Abnormal Heart Lung ratio

ATTR amyloidosis is likely.
Obtain genetic testing (wild type vs hereditary).

References:

1· Diagnosing AL and ATTR Amyloid Cardiomyopathy: A Multidisciplinary Approach. Fabian aus dem Siepen, Timon Hansen. (2024). Journal of Clinical Medicine. DOI: 10.3390/jcm13195873
2· AL Amyloidosis for Cardiologists Awareness, Diagnosis, and Future Prospects. Ashutosh D. Wechalekar, Marianna Fontana, C. Cristina Quarta, Michaela Liedtke. (2022). JACC CardioOncol DOI:10.1016/j.jaccao.2022.08.009
3· How to Screen for Monoclonal Gammopathy in Patients With a Suspected Amyloidosis. Samuel Rubinstein, Keith Stockerl-Goldstein. (2021). JACC CardioOncol. DOI: 10.1016/j.jaccao.2021.07.001.

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