AL Amyloid

The Other Guys

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Disclosures

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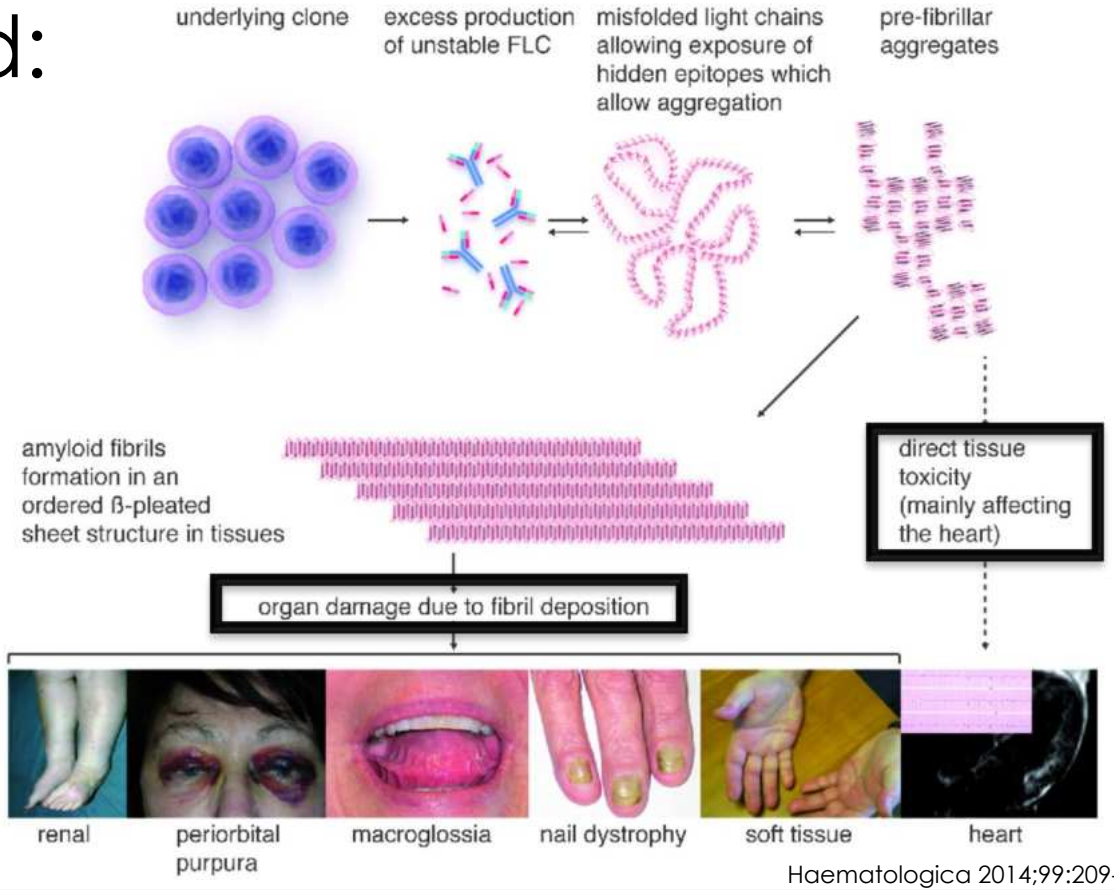
Objectives

- Review the presentation of AL amyloid including the conditions associated with it
- Differentiate the presentation & clinical course of AL amyloid from TTR-amyloid
- Discuss treatment options for AL amyloid

AL Amyloid: the Basics

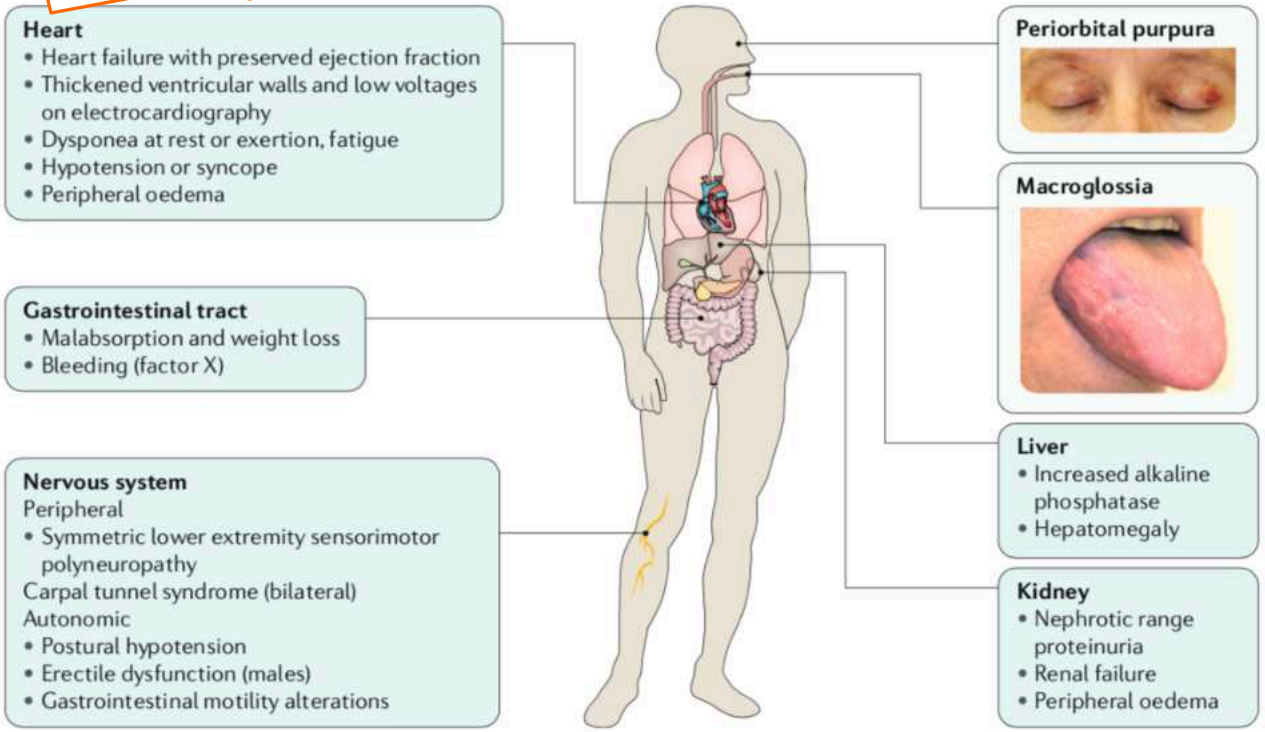
- Annual incidence ~10/1,000,000
- Prevalence ~50/1,000,000 py
- Mean age Dx 63
- 55% men
- Risk factors:
  - MGUS
  - Genetic predisposition?



Haematologica 2014;99:209-221

Death in >1/2 due to HF or arrhythmia

AL Amyloid: Clinical Presentation



Nat Rev Dis Primers 4, 38 (2018).

Clinical Clues Between Subtypes of Amyloid Cardiomyopathy

Amyloid Type	Systemic Amyloidosis	Transthyretin (TTR) Amyloidosis	
Subtype	**AL**	**ATTRm**	**ATTRwt**
Age range, yrs	50+	40+ (V122I, 60-65 yrs)	65+
Sex	55% male	Either, slight male dominance	Marked male predominance >15:1
Clinical cues	• Multiorgan involvement • Periorbital bruising or macroglossia are almost pathognomonic • Severe hypotension with ACE inhibitors	• African-American/ Caribbean origin (for V122I variant) • Left ventricular hypertrophy without presence of prior history of hypertension	• History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement

ACE, angiotensin-converting enzyme; AL, light-chain amyloidosis; ATTRm, mutated transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ECHO, echocardiogram; MRI, magnetic resonance imaging.

Comparison of Cardiac Amyloid Types

Amyloid Type	Systemic Amyloidosis	Transthyretin (TTR) Amyloidosis	
Subtype	**AL**	**ATTRm**	**ATTRwt**
Protein deposited	Light chain	Mutated TTR protein	wtTTR monomers
Disease etiology	Plasma cell dyscrasia with ↑ light chains	Familial mutation of TTR	Age-related TTR deposition - common in elderly aged >75 years
Specific features	Kidney, heart, nerves, GI tract, and liver affected	V122I common in African Americans	Carpal tunnel Male dominance
Median survival	1-3 years	2 years	4-6 years
Clinical course	HF can be fulminant, but may improve dramatically if rapid response to therapy	Similar to wt, but may be more rapid; may be dominated by neuropathy	Insidious, but easy decompensation

Free Light Chains in AL

- Primary pathogenic mechanism
  - Tissue deposition
  - Direct myocardial toxicity
- Biomarker useful for diagnosis and monitoring response to therapy
- Treatment target

Diagnostic Pitfalls in AL

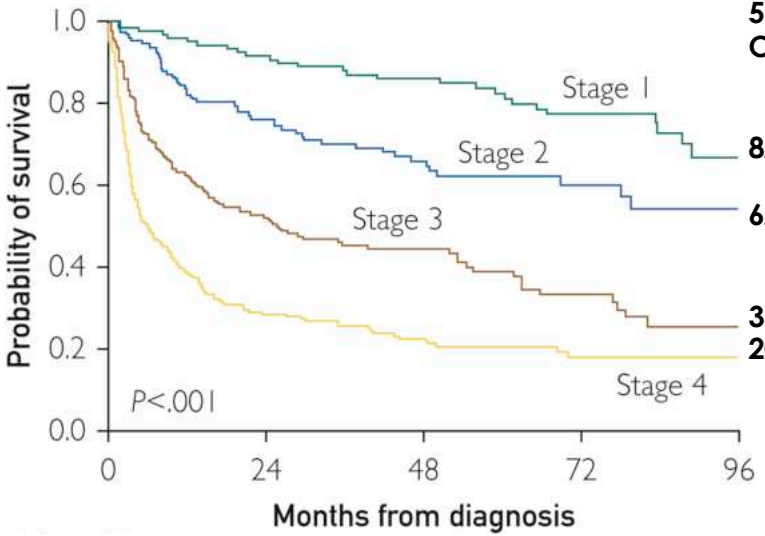
- Amyloidosis plus monoclonal protein does **not** necessarily equal AL amyloidosis unless immunofluorescence or mass spec demonstrates light chains in amyloid deposits

- *Conversely*, nuclear scintigraphy **cannot** differentiate between AL and ATTR in the presence of a monoclonal protein (FLC or SPEP/UPEP)

Prognosis in AL Amyloidosis

- Burden of amyloid deposition – cardiac biomarkers
  - Predicts early deaths (<1 year)
- Size and biology of plasma cell clone – dFLC, %BMPC, t(11:14)
  - Predicts late deaths
- Response to therapy

Prognosis in AL: Revised Mayo Staging



	5 yr OS	Median survival
Stage 1		
Stage 2	82%	94.1 mos
Stage 3	62%	40.3 mos
Stage 4	39%	14 mos
	20%	5.8 mos

dFLC ≥18 mg/dL

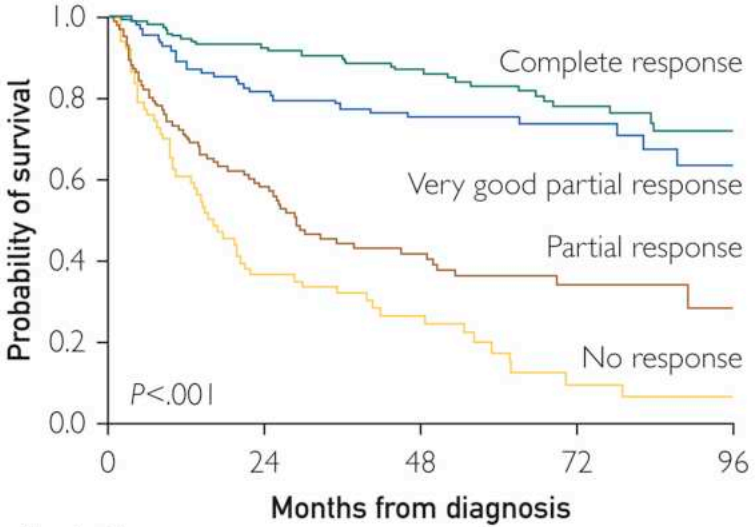
TnT ≥0.025

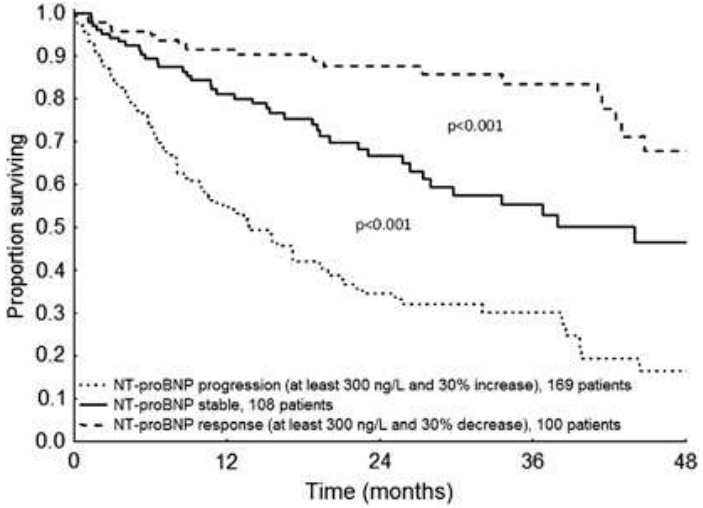
NT-proBNP ≥1800
or
BNP ≥400

Stage 1: 0/3
Stage 2: 1/3
Stage 3: 2/3
Stage 4: 3/3

Mayo Clin Proc. 2019;94(3):472-483

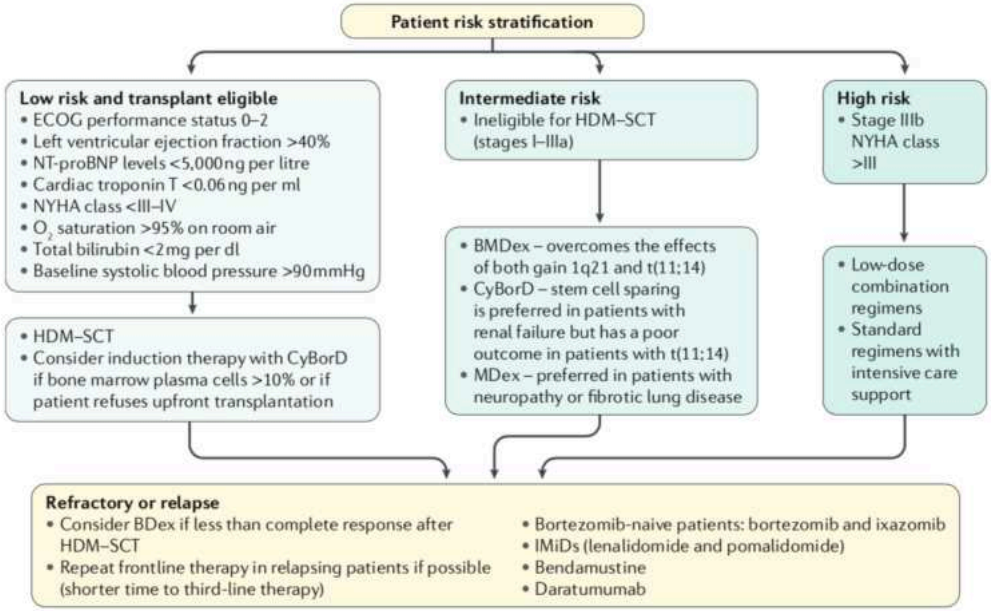
Prognosis in AL: Hematologic & Organ Responses





Mayo Clin Proc. 2019;94(3):472-483
Leukemia (2012) 26, 2317–2325

AL: Light chain-suppressive therapy



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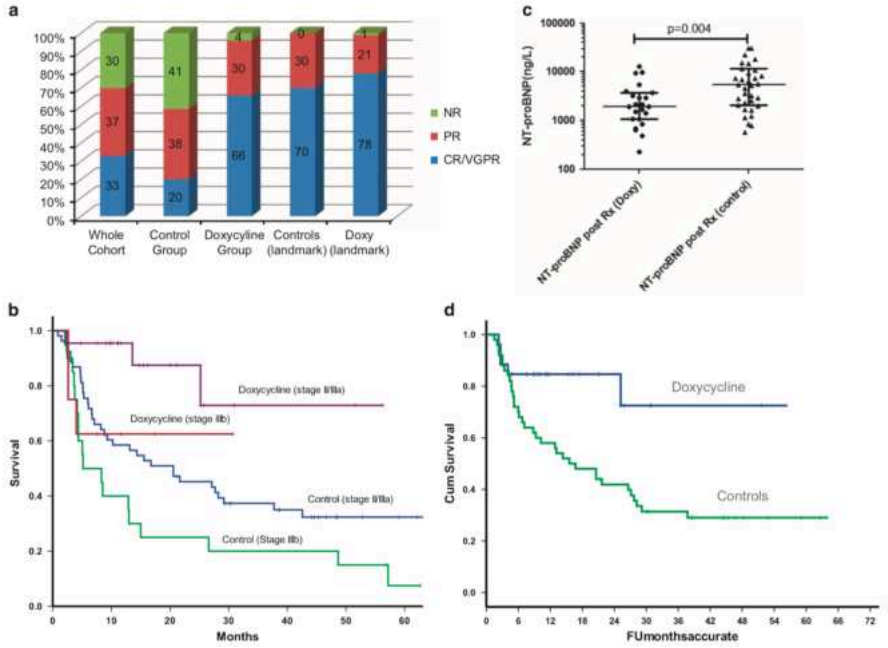
Doxycycline improves survival in patients receiving chemo for AL amyloidosis



Blood Cancer Journal (2017) 7, e546

Symptom-Directed Management

Congestive Symptoms
- Loop diuretics and thiazides in combination with mineralocorticoid receptor antagonist

Cardiomyopathy Medications
- Avoid β-blockers, ACEi, and ARB

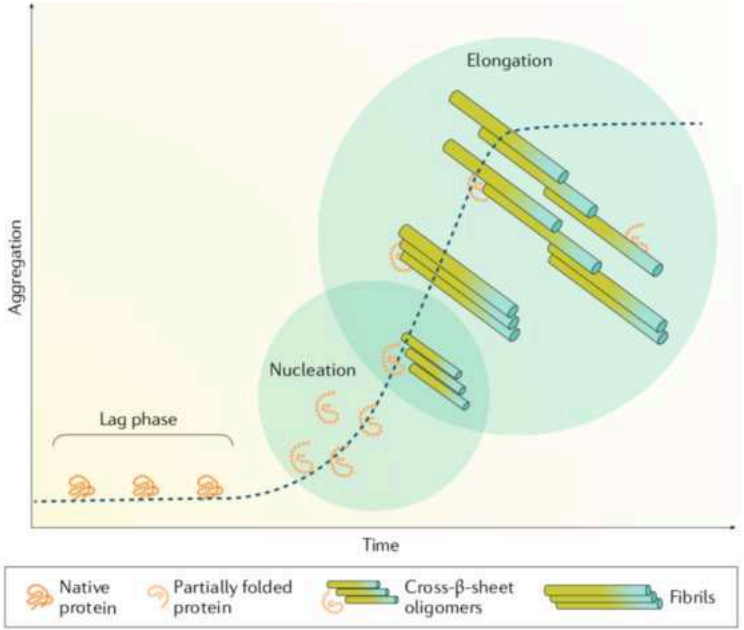
- Do not modify disease progression
- Can result in worsening fatigue and hypotension

Atrial Arrhythmias
- Amiodarone
- Catheter ablation

- Calcium channel blockers are contraindicated (bind to the amyloid fibrils)
- Digoxin can cause cardiac toxicity (progressive accumulation in amyloid-rich heart despite normal serum levels)
- Catheter ablation has high recurrence rate, necessitating AV ablation with permanent pacemaker placement in refractory cases

Hypotension
- α-1 blocker midodrine and compression stockings

Importance of early diagnosis and therapy



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Conclusions

- AL is a rare disease associated with multiorgan dysfunction and a very poor prognosis if not promptly treated
- Differentiation between AL, ATTR, and other causes of HFpEF is essential to ensure appropriate treatment
- Free light chains are the pathologic basis of the disease, a valuable tool in its diagnosis, and the primary treatment target
- Despite advances in therapy, advanced cardiac involvement is still associated with a poor prognosis
- Novel and developing therapies will hopefully change this prognosis in the future

Case Presentation

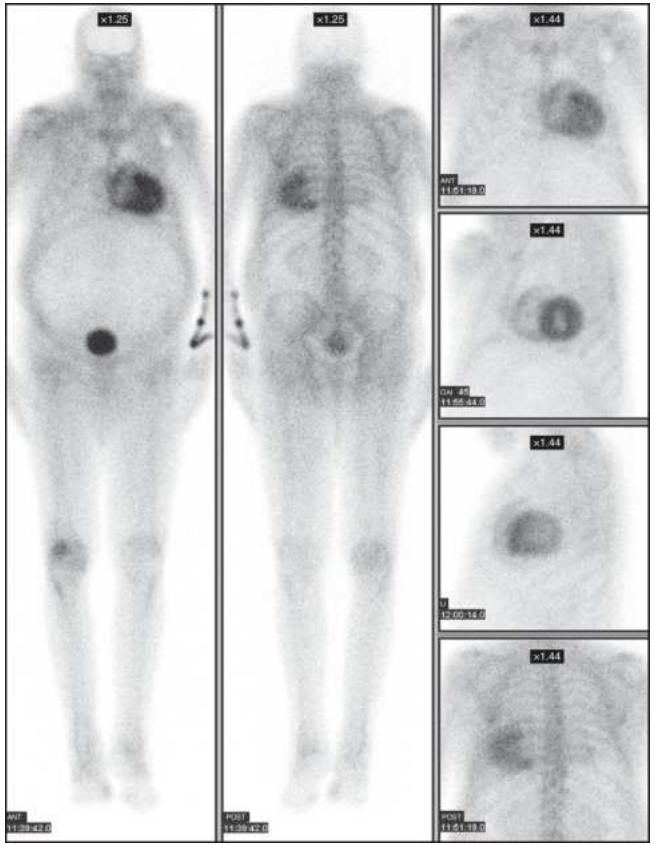
85 year old man referred for possible ATTR cardiac amyloidosis

- PMHx: HTN, DM2, CKD (GFR 30), Atrial fibrillation – diagnosed 2017, rate controlled
- Meds:
  - Ramipril 1.25 mg daily
  - Metoprolol 25 mg BID
  - Warfarin
  - Lasix 20 mg daily
  - Atorvastatin 20 mg daily
  - Trajenta

- Admitted with ADHF September 2018
  - Recently returned from trip, eating lots of salty food
  - Troponin 0.20 on presentation
- MIBI normal
- Echo in hospital:
  - Normal LV size, EF 39%
  - Dilated RV, normal function
  - Septum 15 mm, PW 11 mm, increased RV wall thickness
  - Biatrial enlargement
  - Mild-moderate MR and AR
  - Strain not reported

Tc-PYP scan

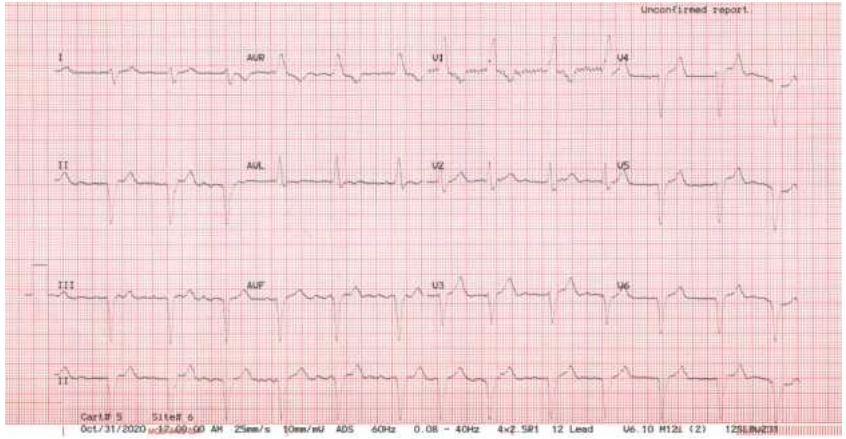
- Marked increased activity throughout the left ventricular myocardium, low grade activity within the right ventricle
- Diffuse activity typical of TTR cardiac amyloidosis



Clinic Evaluation

- NYHA 2
- No syncope
- No history CTS
- Numbness/paresthesias in arms/hands at night
- Intermittent foamy urine
- No macroglossia, change in taste, GI symptoms, weight loss. Bleeds but on OAC.

- Exam
  - 117/70; 81 bpm (irregular)
  - JVP 4 cm ASA, AJR+
  - No macroglossia
  - S1S2 irregular, no murmurs
  - Chest clear, trace edema
- BNP 364, TnI 0.07
- Cr 179, GFR 25, K 4.6, Na 142, Hb 139



Further Investigations

- SPEP: Normal pattern
- UPEP: Small band in gamma region
  - Immunofixation: small monoclonal free kappa light chain
- Serum free light chain assay
  - Kappa: 205
  - Lambda: 17.1
  - Ratio: 11.99

Audience response: What is the most appropriate next step?

- 1. Prescribe tafamidis 61 mg daily
- 2. Refer for liver transplant
- 3. Tissue biopsy
- 4. Refer for stem cell transplant
- 5. Suggest patient enroll in clinical trial of novel TTR-directed therapy

- Abdominal fat pad biopsy:
  - Negative for amyloid
- Bone marrow biopsy:
  - Mild increase (5-10%) in kappa restricted plasma cells. Histologic findings consistent with a diagnosis of a plasma cell neoplasm. No definite evidence of amyloid infiltrate by Congo red staining.
- Next?

Case summary

- Overall most consistent with ATTR with concomitant MGUS
  - Older age, male
  - AF for 2 years
  - Rapid recovery after ADHF episode
- Cannot rule out AL, given abnormal FLC and marrow
  - History of unexplained renal disease and lack of CTS also concerning
- Needs EMBx with mass spec to differentiate, as management vastly different for 2 diseases