



Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

AL Amyloid

The Other Guys

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Disclosures

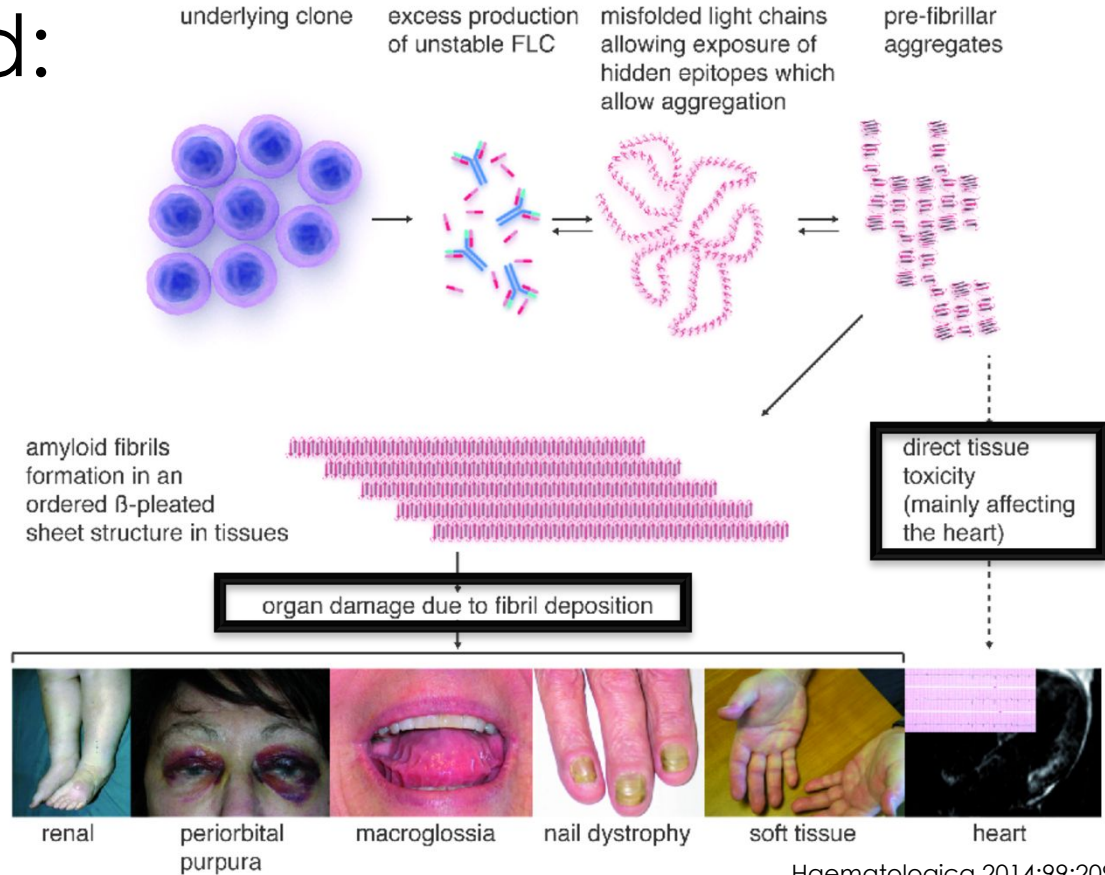
- Consultancy/speaking fees: Janssen, Novartis, Boehringer-Ingelheim, Takeda, Pfizer, Akcea, Alnylam, Amgen, Ferring, TerSera
- Grant funding: Pfizer, Takeda, Boehringer-Ingelheim, Servier, Akcea

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?



Death in >1/2 due to HF or arrhythmia

AL Amyloid: Clinical Presentation

Heart

- Heart failure with preserved ejection fraction
- Thickened ventricular walls and low voltages on electrocardiography
- Dyspnoea at rest or exertion, fatigue
- Hypotension or syncope
- Peripheral oedema

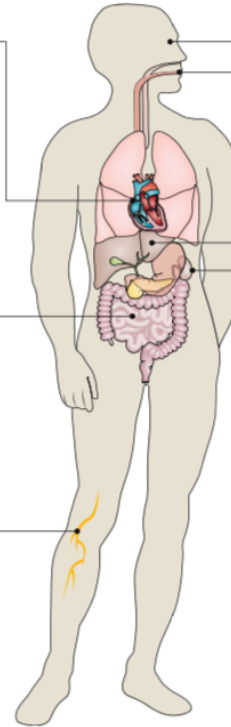
Gastrointestinal tract

- Malabsorption and weight loss
- Bleeding (factor X)

Nervous system

Peripheral

- Symmetric lower extremity sensorimotor polyneuropathy
 - Carpal tunnel syndrome (bilateral)
- ### Autonomic
- Postural hypotension
 - Erectile dysfunction (males)
 - Gastrointestinal motility alterations



Periorbital purpura



Macroglossia



Liver

- Increased alkaline phosphatase
- Hepatomegaly

Kidney

- Nephrotic range proteinuria
- Renal failure
- Peripheral oedema

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	<ul style="list-style-type: none"> Multiorgan involvement Periorbital bruising or macroglossia are almost pathognomonic Severe hypotension with ACE inhibitors 	<ul style="list-style-type: none"> African-American/Caribbean origin (for V122I variant) Left ventricular hypertrophy without presence of prior history of hypertension 	<ul style="list-style-type: none"> History of carpal tunnel syndrome 5-10 yrs earlier, with no other organ involvement

Comparison of Cardiac Amyloid Types

Amyloid Type	Systemic Amyloidosis		Transthyretin (TTR) Amyloidosis
Subtype	<u>AL</u>	<u>ATTR_m</u>	<u>ATTR_{wt}</u>
Protein deposited	<u>L</u> ight chain	<u>M</u> utated TTR protein	<u>w</u> tTTR 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

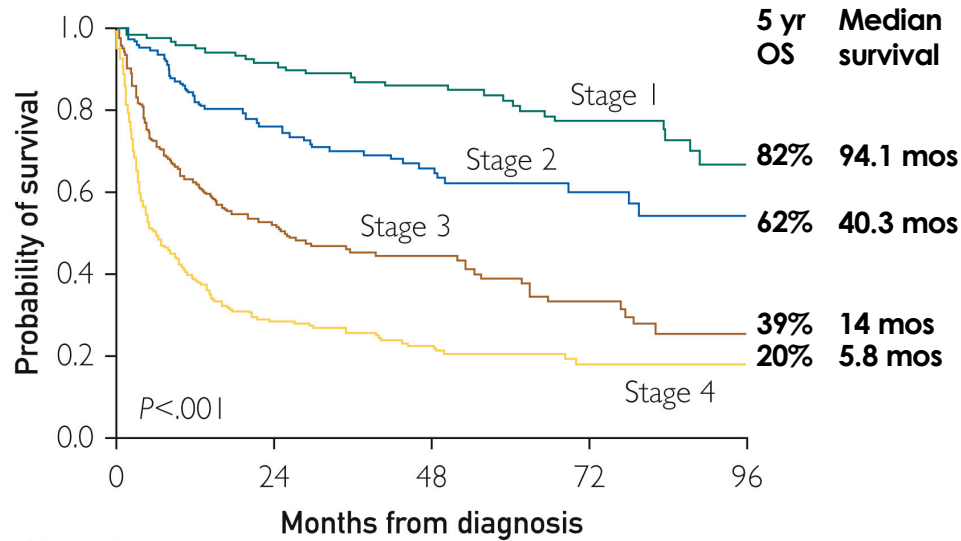
Diagnostic Pitfalls in AL

- 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



dFLC ≥ 18 mg/dL

TnT ≥ 0.025

NT-proBNP ≥ 1800
or
BNP ≥ 400

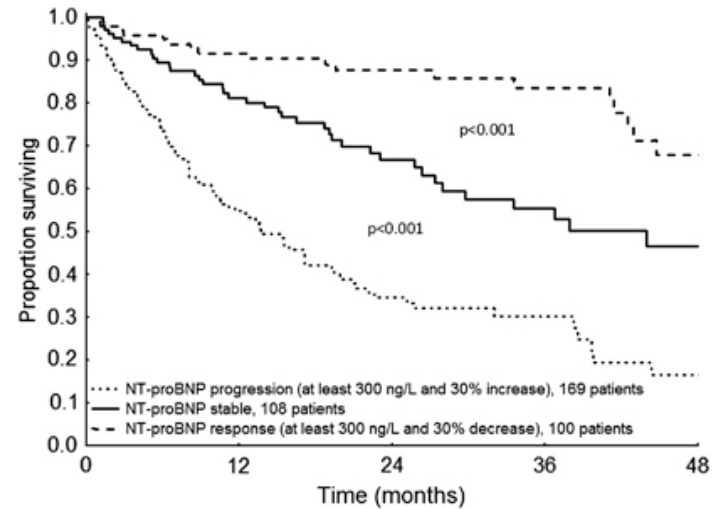
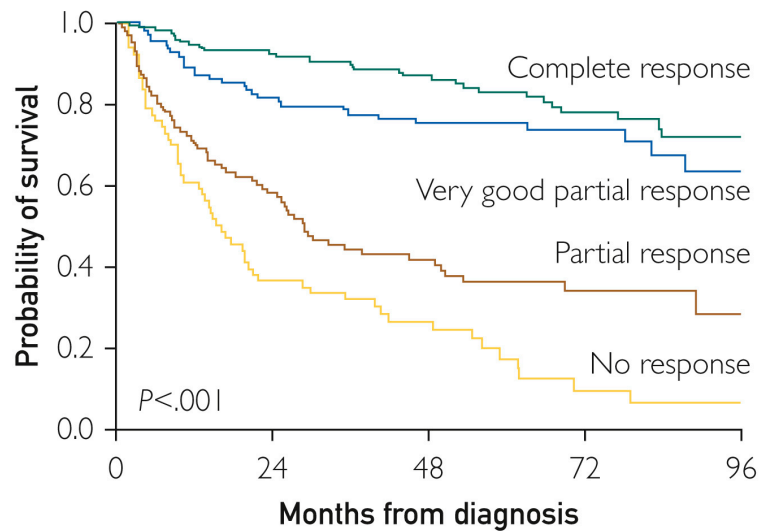
Stage 1: 0/3

Stage 2: 1/3

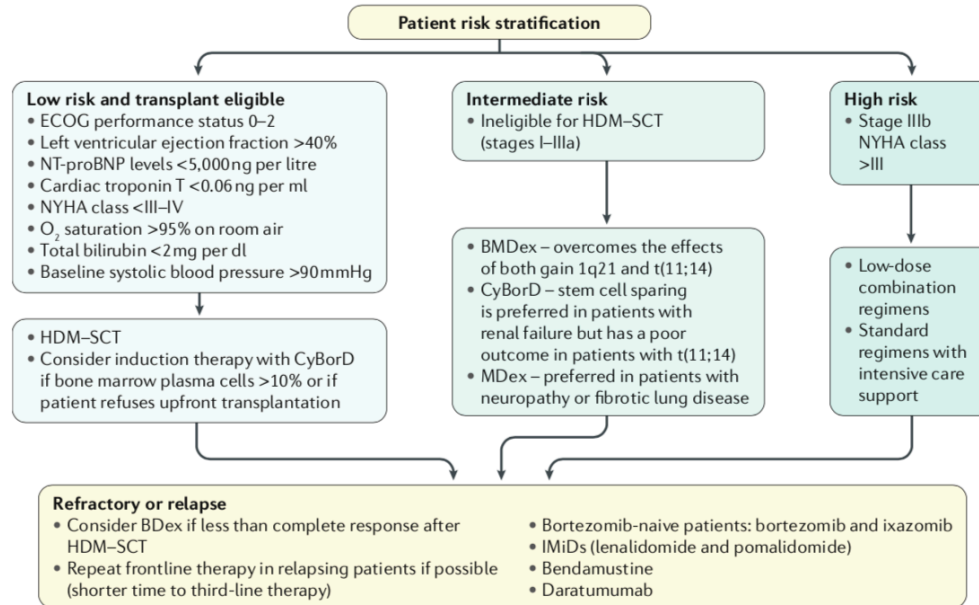
Stage 3: 2/3

Stage 4: 3/3

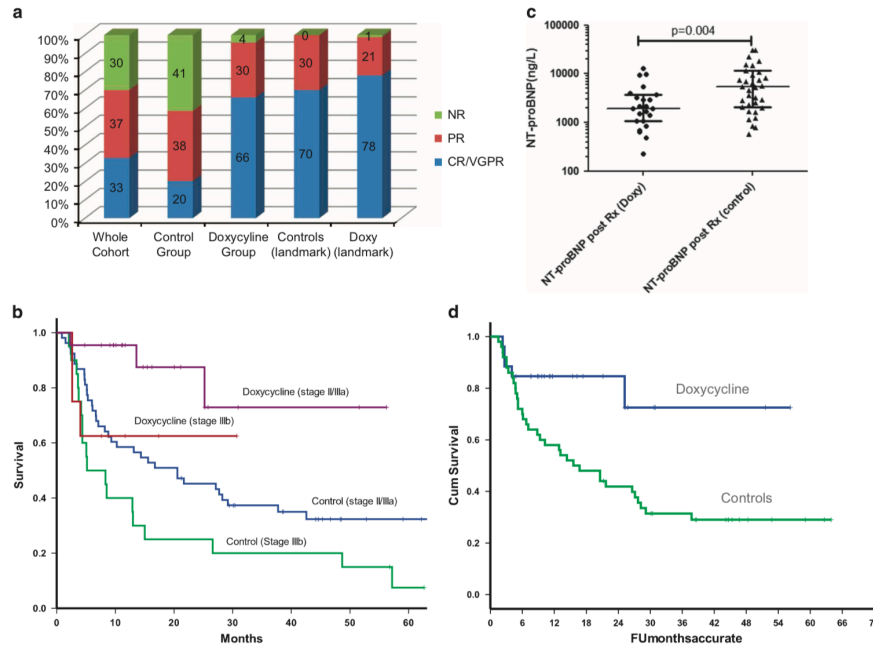
Prognosis in AL: Hematologic & Organ Responses



AL: Light chain-suppressive therapy



Doxycycline improves survival in patients receiving chemo for AL amyloidosis



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

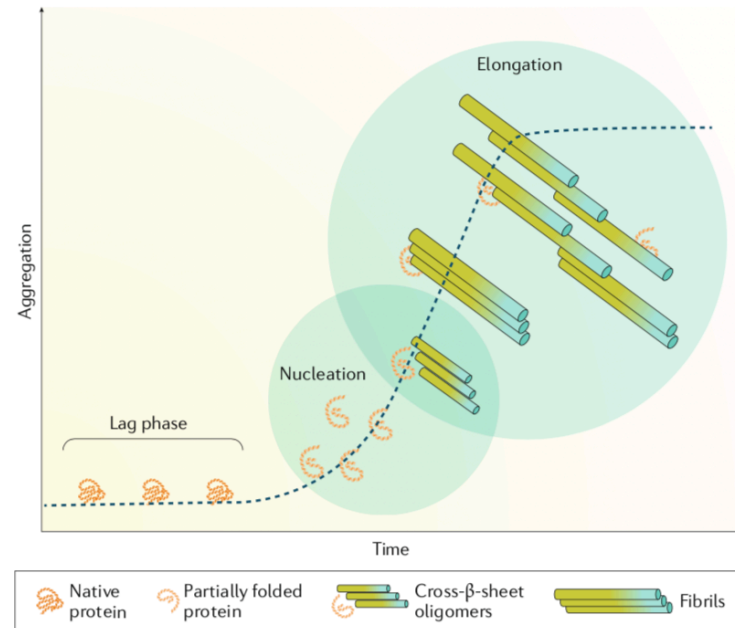
- Amiodarone
- Catheter ablation

- 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



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

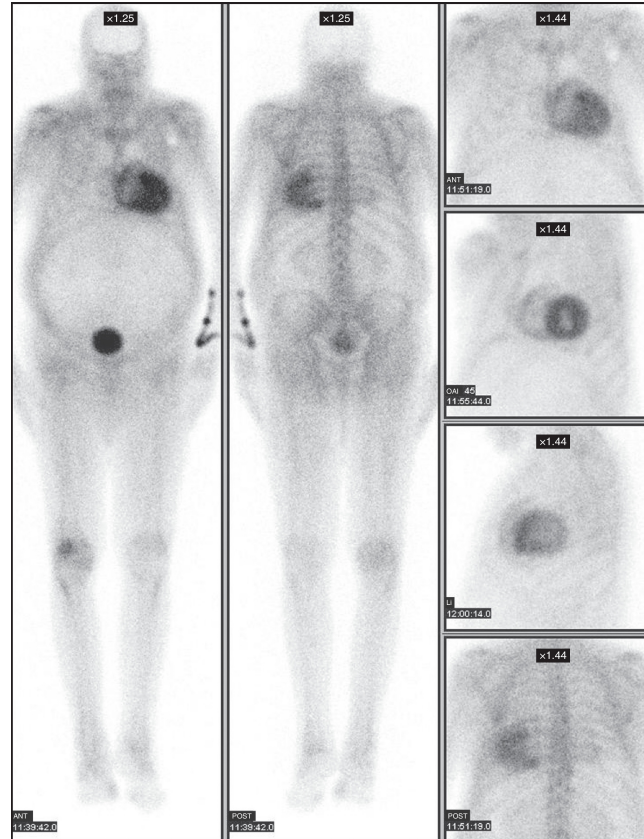
Case Presentation

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

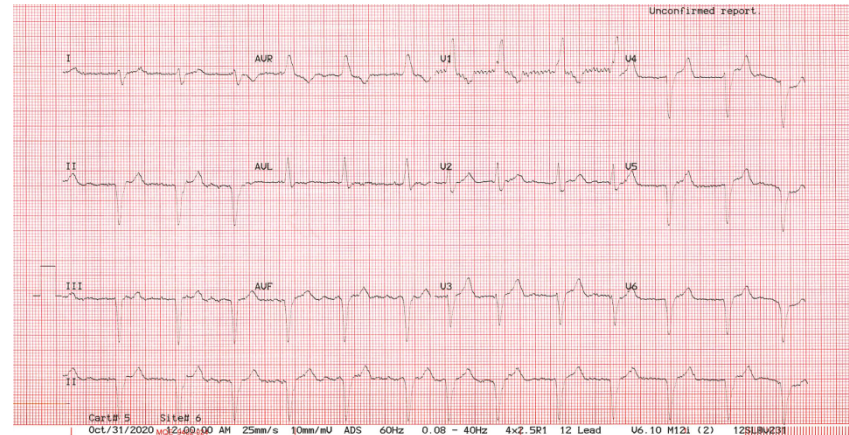
Tc-PYP scan

- 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, Tnl 0.07
 - Cr 179, GFR 25, K 4.6, Na 142, Hb 139

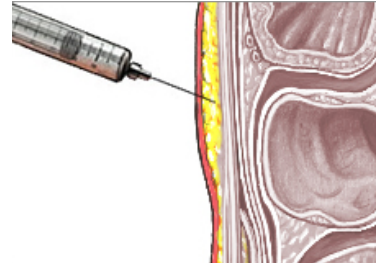


Further Investigations

- 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