Overview of Cardiac Amyloidosis

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Advanced Heart Failure and Transplant Cardiology
Associate Program Director, Cardiology Fellowship
Scripps Clinic

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Disclosures

- No relevant faculty disclosures.

2

Important gateway for early identification
Red flag clinical clues

↓

Referral to Cardiology or Heart Failure Clinic

3

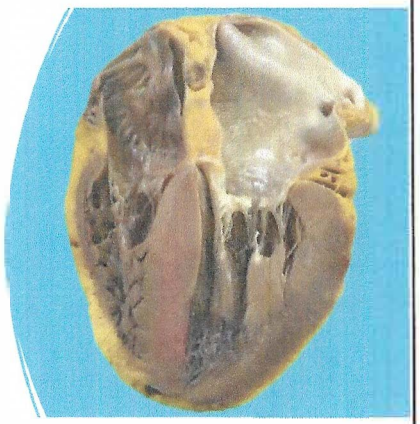
Objectives

- Progressive disease
- Early identification is key
- Multisystem disorder

4

What is Amyloidosis

- Disorder of protein misfolding
- Misfolded proteins deposit into organs resulting in dysfunction



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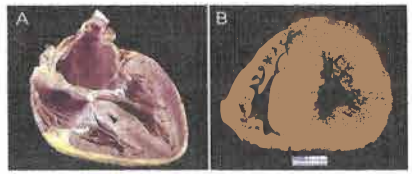
AL
Light chain amyloidosis

ATTR
Transthyretin amyloidosis



Maleszewski. Cardiovascular pathology. 2015

6

TABLE 2
Amyloid-specific pharmacotherapies

AL			ATTR		
Anti-plasma cell therapies	Alkylating agents	Melphalan	TTR silencers	siRNA	Patisiran
		Cyclophosphamide		ASO	Inotersen (ISIS-TTR$_{Rx}$)
	Proteasome inhibitors	Bortezomib	TTR stabilizers	Diflunisal	
		Ixazomib		Tafamidis	
	Immunomodulators	Pomalidomide		Tolcapone	
	Anti-CD38 monoclonal antibody	Daratumumab		AG10	
Anti-amyloid antibody	NEOD001		Fibril disruptors	Doxycycline + TUDCA	
				Green tea extract	
				Curcumin	
				Anti-amyloid antibody	PRX004
Ubiquitous Anti-Amyloid Fibril Antibody					
Monoclonal IgG1 anti-SAP antibody					

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Nativi-Nicolau, et al. JACC CardioOnc. 2021

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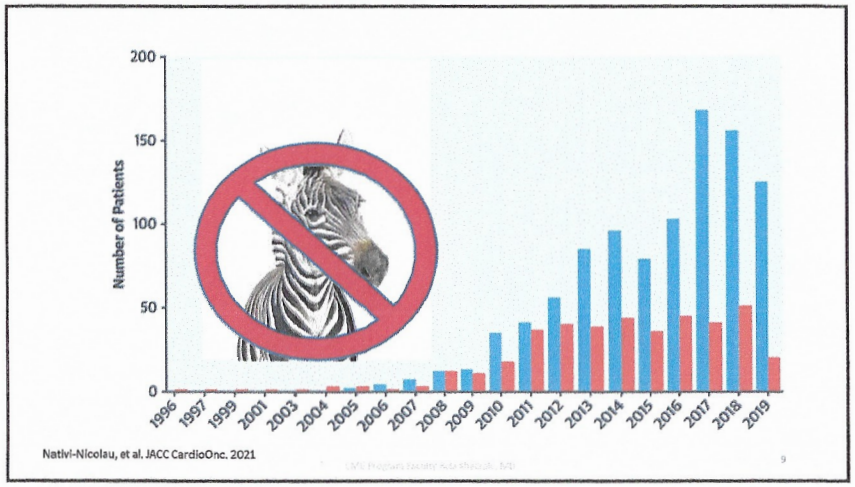

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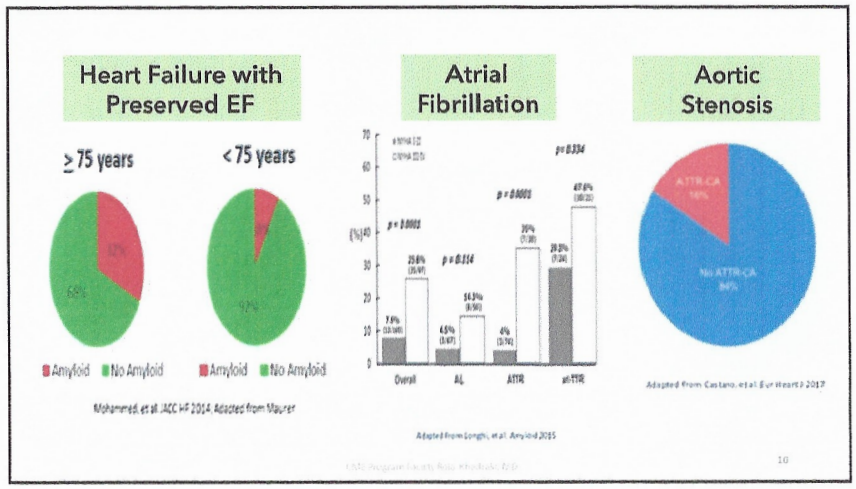

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Pathophysiology of Amyloidosis

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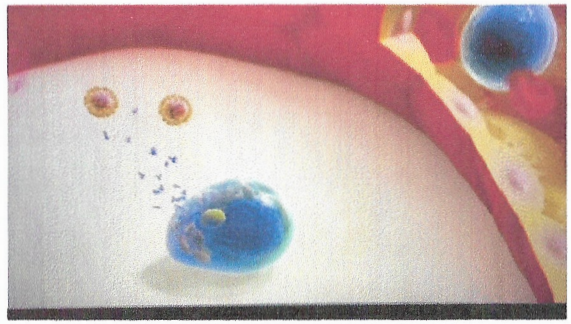
AL (Light-Chain) Amyloidosis

Amyloidosis Research Consortium



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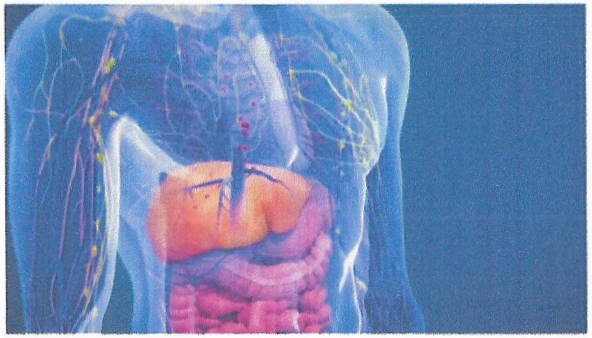
ATTR (Transthyretin) Amyloidosis

Amyloidosis Research Consortium



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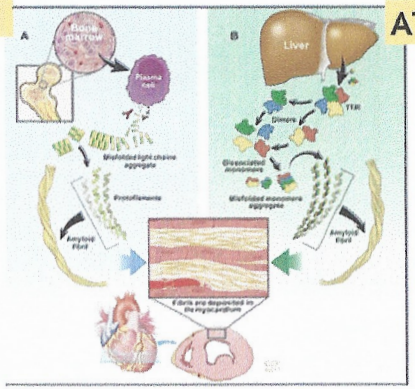
AL

ATTR



Donnelly J., Hanna, M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleveland Clinic Journal of Medicine. Dec 2017
https://www.ccjm.org/user/logout?current=node/2235

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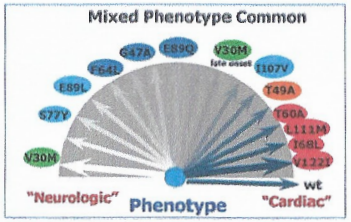
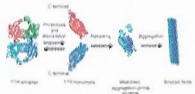
ATTR

Hereditary



Kristen, A. et al. https://doi.org/10.2217/nmt-2018-0033



Wild-Type

- Genetic sequence of TTR is normal
- Unclear why the wild-type protein becomes kinetically unstable and aggregates
- Appears to involve the aging process
- Males >> Females

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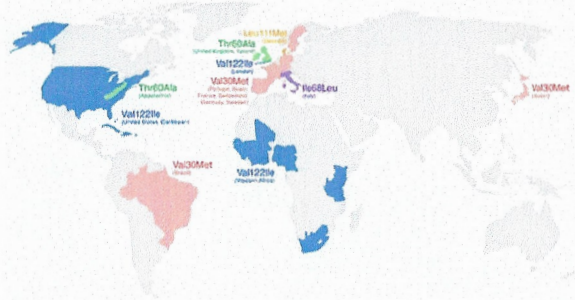
Epidemiology of Hereditary ATTR



https://journal.houstonmethodist.org/articles/10.14797/mdcvj.1066/

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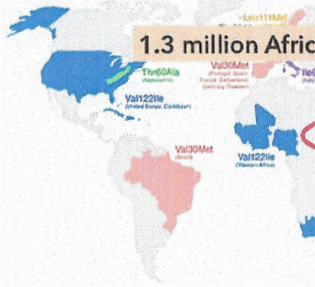
Epidemiology of Hereditary ATTR

>100 mutations in the TTR gene



1.3 million African American carriers in the US

V122I	Valine-to-isoleucine substitution at position 122	3.5% of the US African American population
V30M	Valine-to-methionine substitution at position 30	Portugal, Spain, France, Sweden Japan, South America with an incidence of 1:1000
T60A	Threonine-to-alanine substitution at position 60	Northwestern Ireland with a prevalence of 1%

https://journal.houstonmethodist.org/articles/10.14797/mdcvj.1066/

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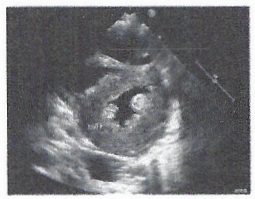
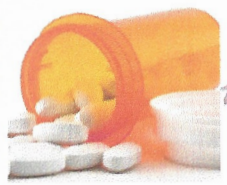
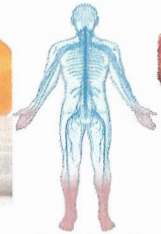
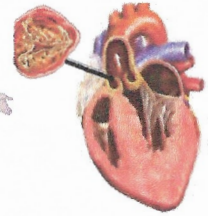
Red Flags for Amyloidosis









- Unexplained LVH
- "Hypertrophic cardiomyopathy" after age 60
- Progressive intolerance to antihypertensives
- Unexplained neuropathy
- LFLG AS

Donnelly J., Hanna, M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleveland Clinic Journal of Medicine. Dec 2017

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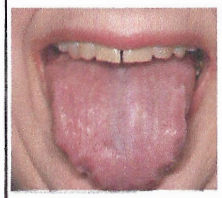
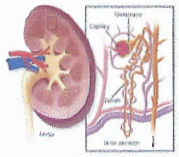
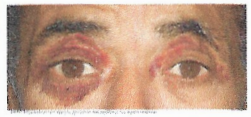
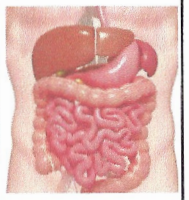
AL Amyloidosis









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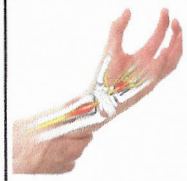
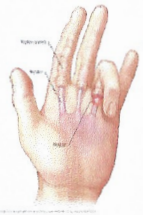
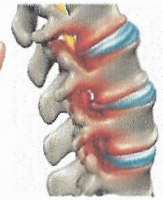
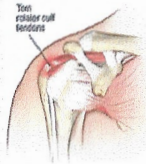
ATTR Amyloidosis









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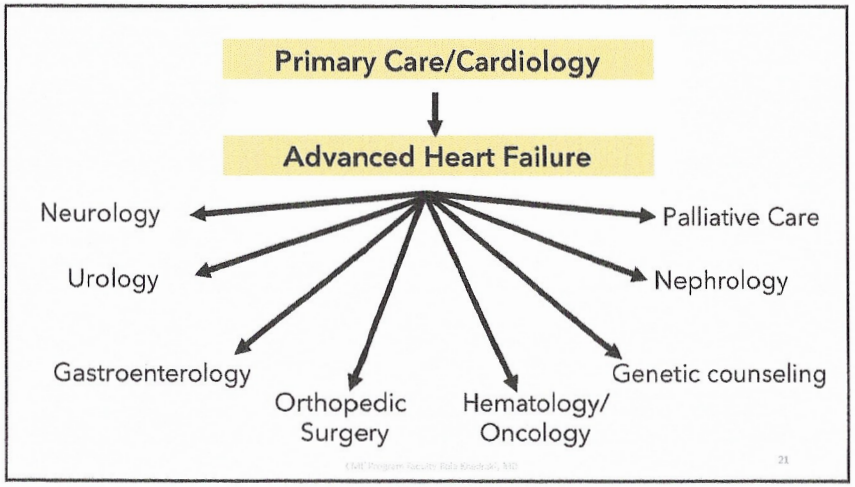

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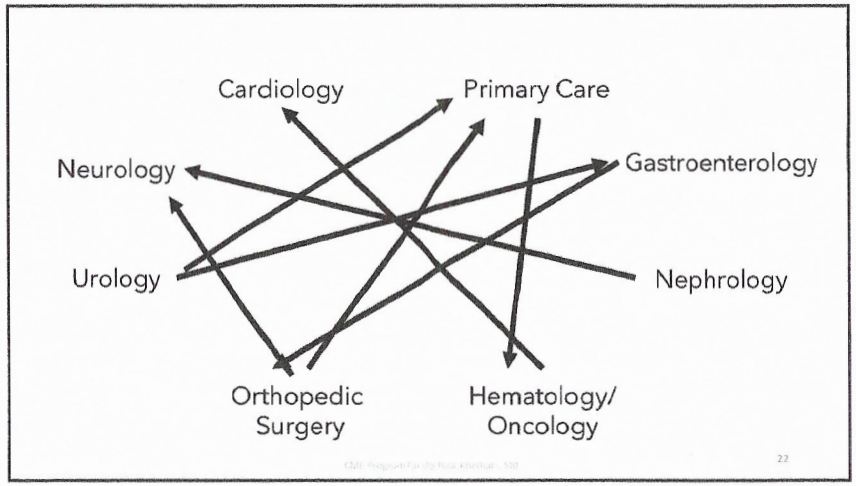

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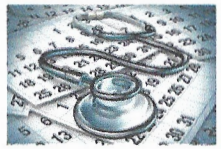
Diagnostic Delays Are Common!



ATTR

- Mean time to diagnosis **1.3 to 7.2 yrs**
- Misdiagnosis in 34-57% of patients

AL

- Mean time to diagnosis **2 years**
- 32% of patients reported seeing at least **5 physicians**

Delays have a large impact on quality of life and outcome

Rozenbaum et al. Cardiol Therp. 2021. Lousada, et al. Adv Ther. 2015

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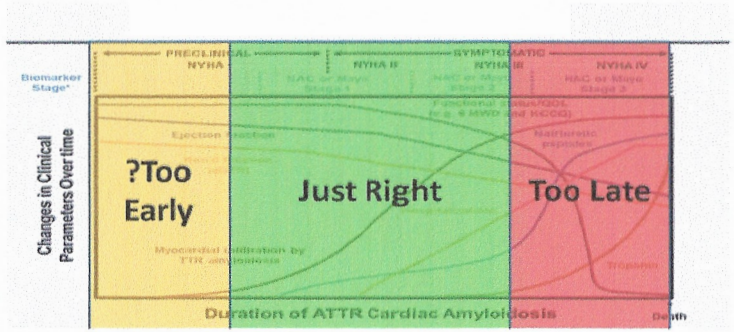
Timing of Therapy Is Key



Adapted from Maurer, M.

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Treatment

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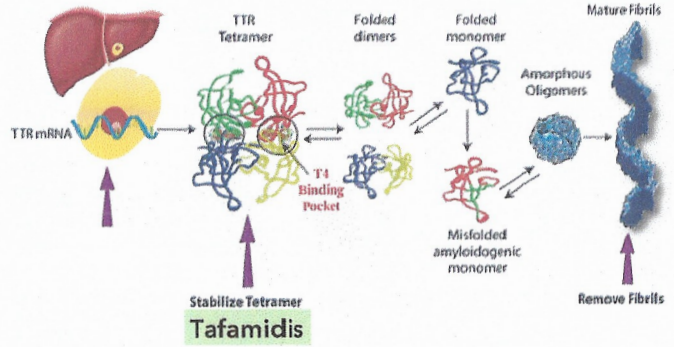
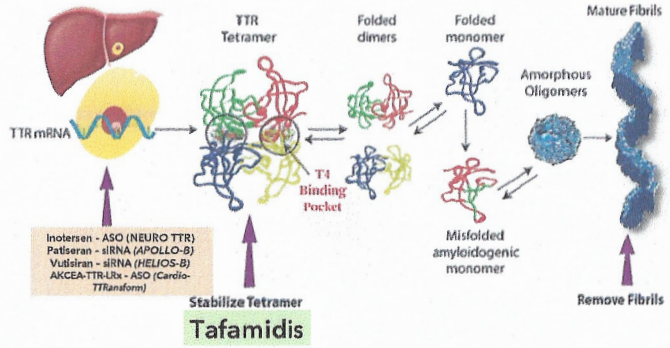
ATTR Amyloidosis Treatment



Hanna, M. Current Heart Failure Reports. 2014.

26

ATTR Amyloidosis Treatment



Hanna, M. Current Heart Failure Reports. 2014.

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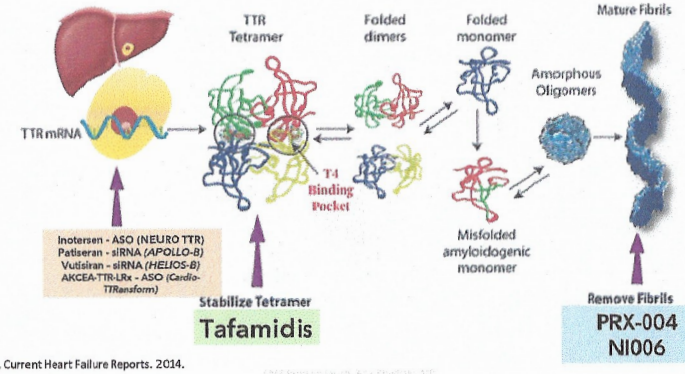
ATTR Amyloidosis Treatment



Hanna, M. Current Heart Failure Reports. 2014.

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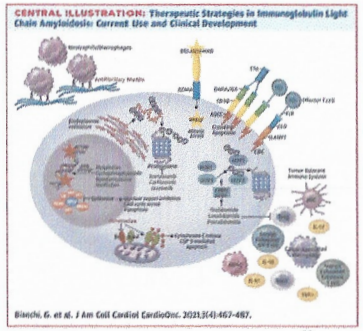
AL Amyloidosis Treatment

Goals:
Hematologic response
Organ response

Cybor-D
(Cyclophosphosphamide
Bortezemib, Dexamethasone)

Daratumumab
(CD38 monoclonal antibody)

**High dose melphalan +
Autologous Stem Cell Transplant**



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Cardiac Findings - ECG

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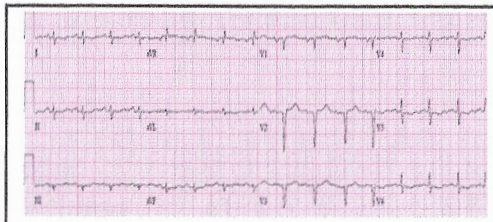
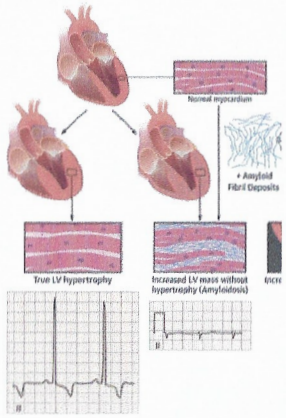


Low voltage defined as QRS amplitude:
→ <5mm in the limb leads and/or
→ <10mm in the precordial leads

EKG findings in amyloid:
- Low voltage or voltage:mass ratio
- Pseudo-infarct pattern
- Conduction abnormalities
- Tachyarrhythmias



Maurer et al. Circ, 2017. Dorbala et al. J Am Coll Cardiol Img. 2022;13(6):1368-83

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Cardiac Findings - Echocardiography

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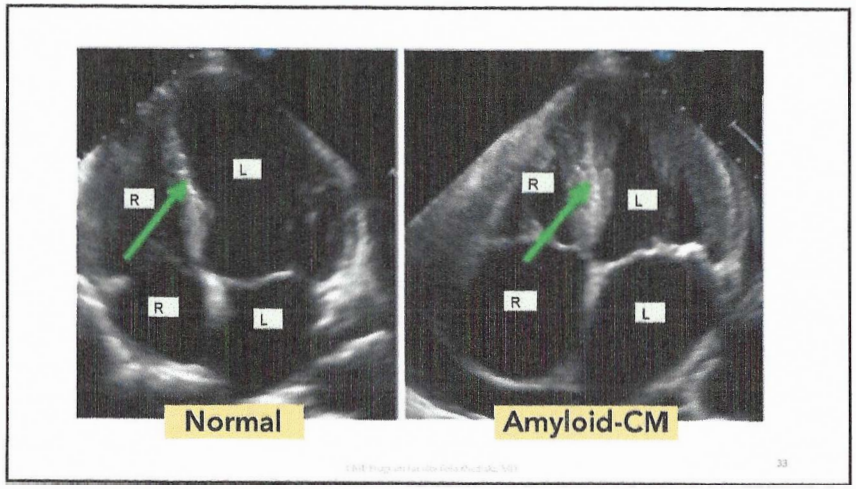
R
L
R
L
Normal
R
L
R
L
Amyloid-CM

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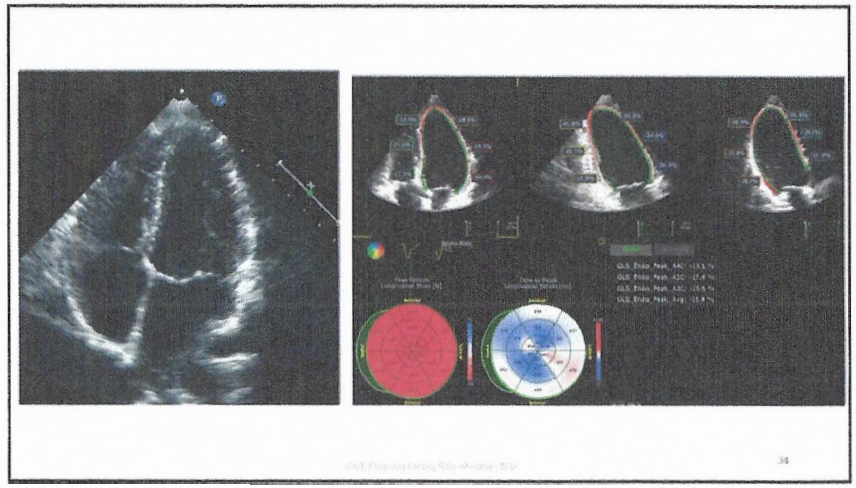

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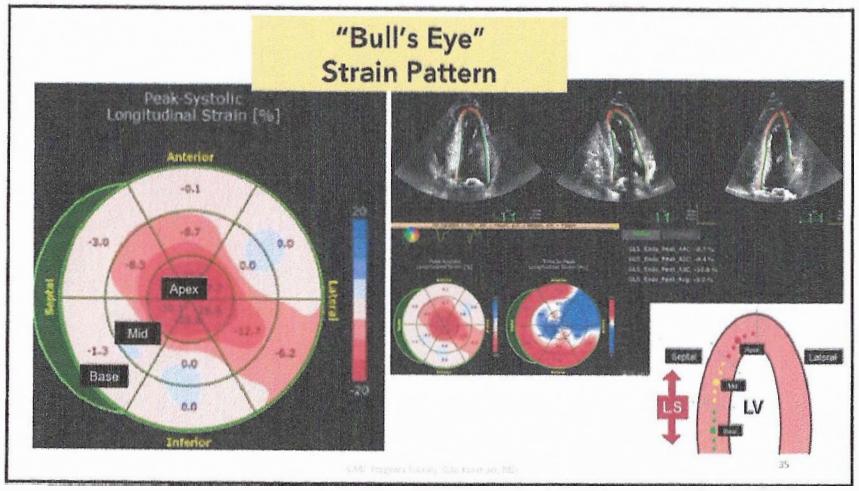
"Bull's Eye"
Strain Pattern
Peak-Systolic
Longitudinal Strain [%]
Anterior
Septal
Lateral
Apex
Mid
Base
Inferior
Septal
Lateral
LS
LV

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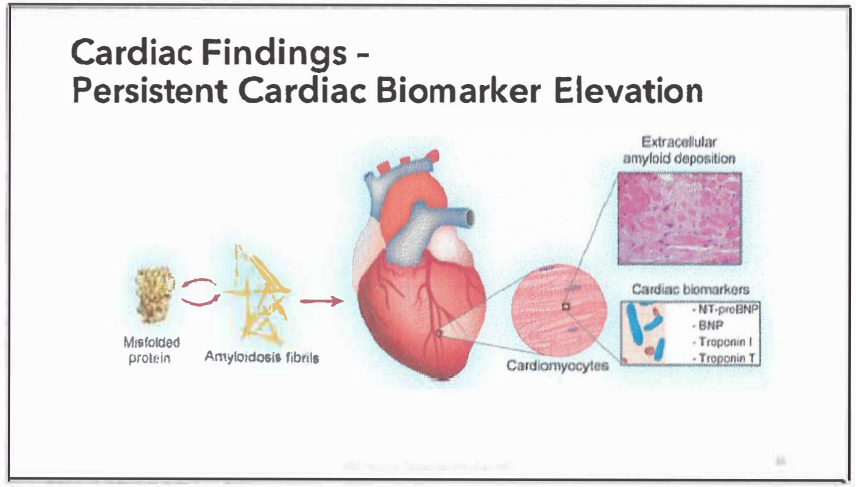
Cardiac Findings -
Persistent Cardiac Biomarker Elevation
Misfolded protein
Amyloidosis fibrils
Extracellular amyloid deposition
Cardiomyocytes
Cardiac biomarkers
- NT-proBNP
- BNP
- Troponin I
- Troponin T

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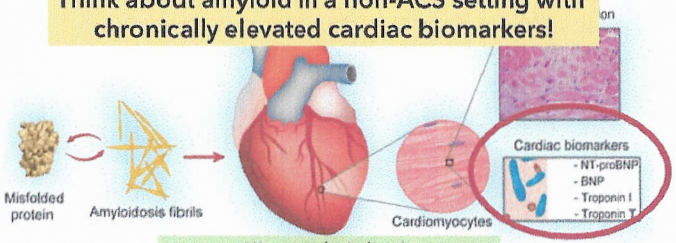
Cardiac Findings – Persistent Cardiac Biomarker Elevation

Think about amyloid in a non-ACS setting with chronically elevated cardiac biomarkers!



Microvascular ischemia
Toxic effects of the amyloid protein
Myocardial cell damage and membrane leak

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When to Suspect

The "Great Mimicker"

Extracardiac	Cardiac
Peripheral neuropathy	EKG
Carpal tunnel	Echo
Spinal stenosis	-Diffuse thickening
Biceps tendon rupture	-Diastolic
Dysautonomia	-Abnormal strain
GI symptoms	-Apical sparing
	-Pericardial effusion
	Persistent biomarker elevation

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Targeted Diagnostic Testing

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Labs

AL Amyloidosis	ATTR Amloidosis
• Serum free light chains • Serum/urine immunofixation	• No screening lab test • Genetic testing

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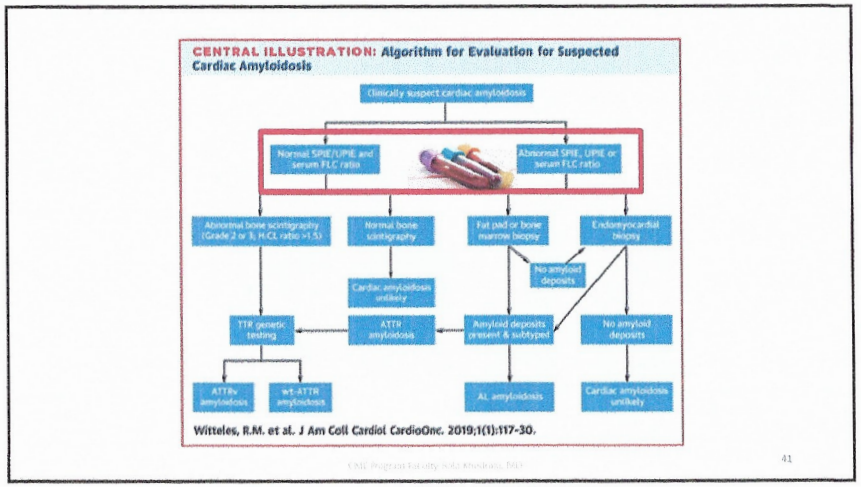

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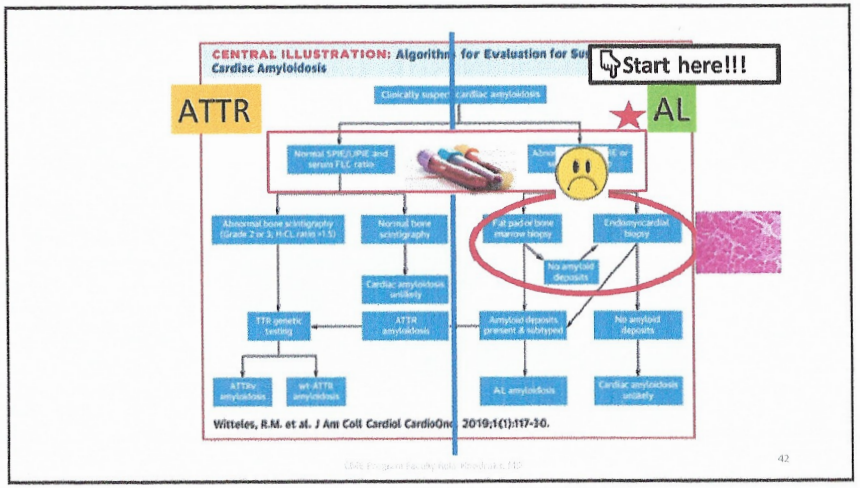

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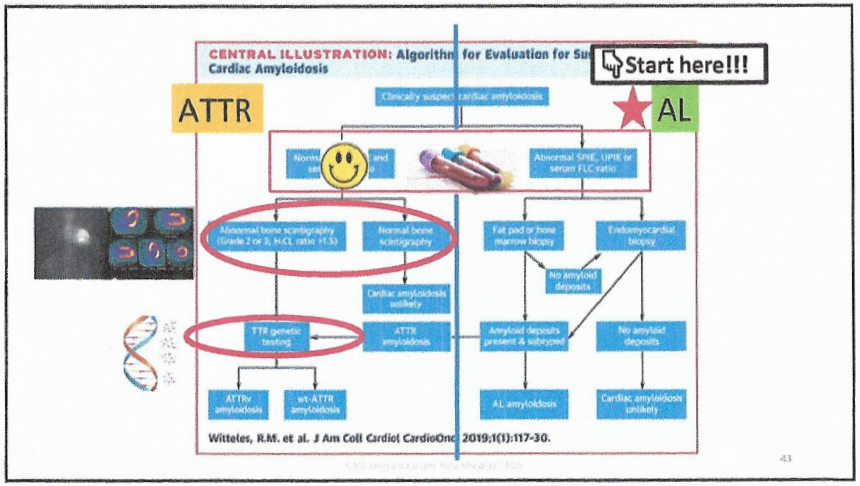

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Understanding Amyloid Laboratory Testing

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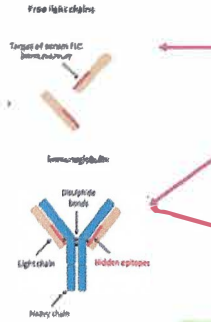
AL Amyloid Labs



1. Kappa / lambda free light chains
2. Electrophoresis with Immunofixation, Serum
   Electrophoresis (immunofixation if indicated),serum
3. Electrophoresis with immunofixation, Urine
   Electrophoresis (immunofixation if indicated),urine

>99% sensitivity for AL amyloidosis

Bebner. 2013. DOI: 10.3410/Mg-4

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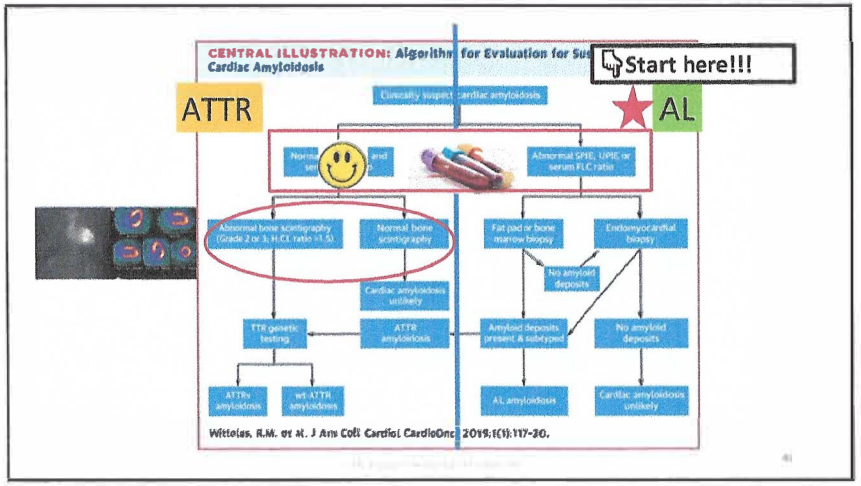

Witteles, R.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):117-30.

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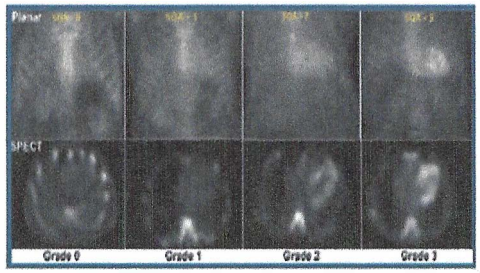
Bone Scintigraphy

Technetium Pyrophosphate Scan

- 99mTc-phosphate derivates originally developed for bone imaging
- Preferential binding to ATTR
- Grade 2 or 3 uptake
- Planar and SPECT/CT
- Uptake in AL is absent/minimal



https://www.nature.com/articles/s41569-020-0334-7

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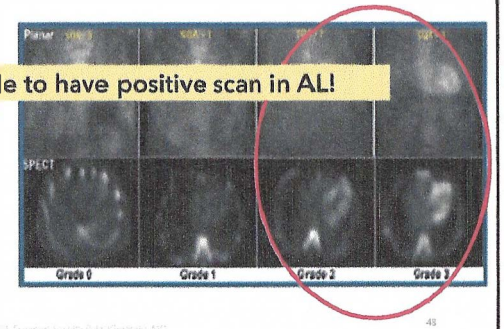
Bone Scinti

Technetium Pyroph

This is an ATTR Scan!
91% sensitivity and 100% specificity for ATTR amyloid

- 99mTc-phosphate derivates originally developed for bone imaging
- Preferential binding to ATTR
- Grade 2 or 3 uptake
- Planar and SPECT/CT
- Uptake in AL is absent/minimal

Still possible to have positive scan in AL!



https://www.nature.com/articles/s41569-020-0334-7

48

CAVEAT!!

ONLY USE PYP SCAN AFTER RULING OUT AL WITH FLC/IMMUNOFIXATION!

49

49

Non-ATTR causes of a false (+) 99mTc-PYP scan:

TABLE 2 Non-ATTR Causes of Positive Technetium-Labeled Cardiac Scintigraphy

1. AL-CM
2. Blood pool uptake (planar images)
3. Rib fracture (planar images)
4. Myocardial infarction (acute or subacute)
5. Hydroxychloroquine cardiotoxicity
6. Other rare forms of CA

Hanna et al JACC 2020

50

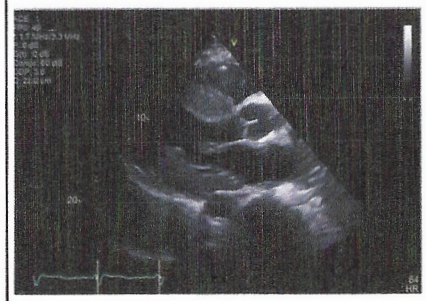
50

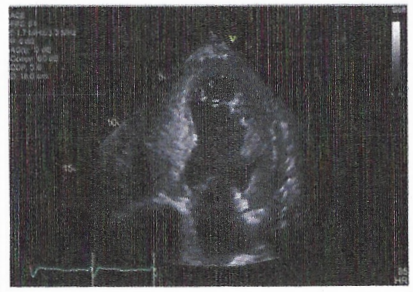
Case 1

51

51

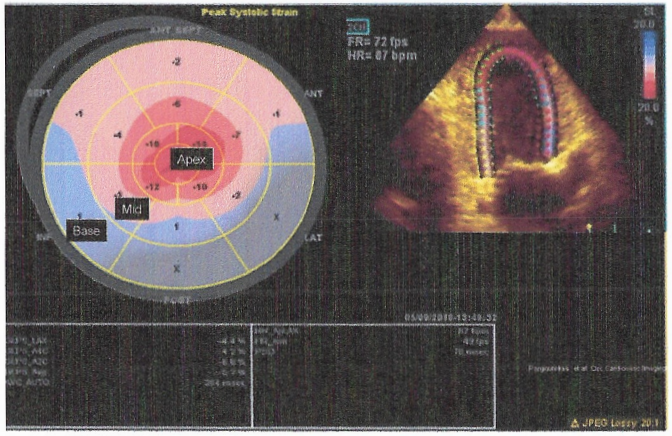
52-year-old African American male with longstanding cardiomyopathy due to "hypertensive heart disease," bilateral carpal tunnel syndrome



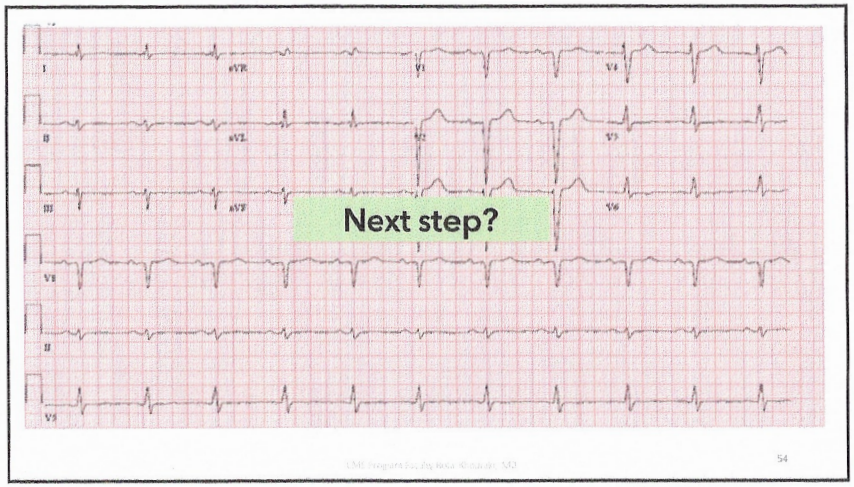


52

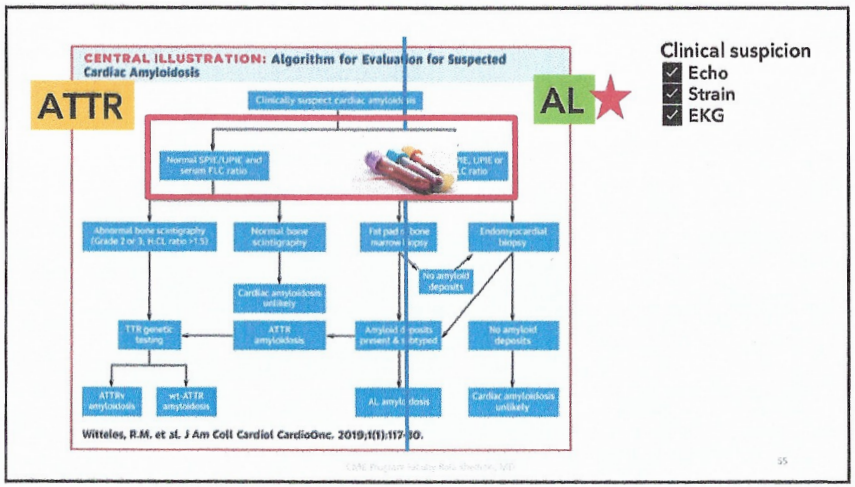
52


Peak Systolic Strain
FR= 72 fps
HR= 87 bpm
Apex
Mid
Base
JPEG Lossy 20:1

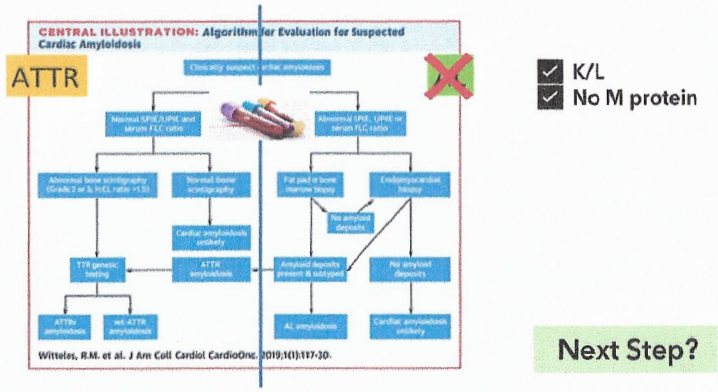
53


Next step?

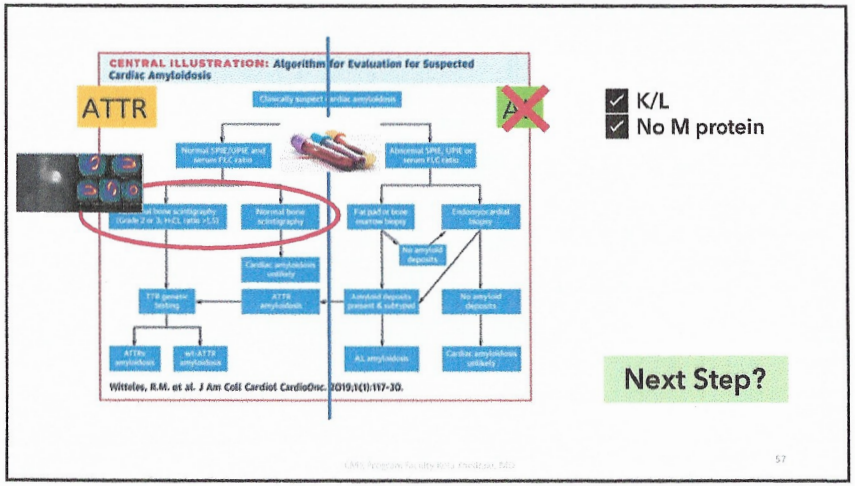
54


ATTR
AL
CENTRAL ILLUSTRATION: Algorithm for Evaluation for Suspected Cardiac Amyloidosis
Clinically suspect cardiac amyloidosis
Normal SPEP/UPEP and serum FLC ratio
Abnormal bone scintigraphy (Grade 2 or 3, H:CL ratio >1.5)
Normal bone scintigraphy
Fat pad or bone marrow biopsy
Endomyocardial biopsy
No amyloid deposits
Cardiac amyloidosis unlikely
TTR genetic testing
ATTR amyloidosis
Amyloid deposits present & typed
No amyloid deposits
ATTRv amyloidosis
wt-ATTR amyloidosis
AL amyloidosis
Cardiac amyloidosis unlikely
Witteles, R.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):117-30.
Clinical suspicion
Echo
Strain
EKG

55


ATTR
CENTRAL ILLUSTRATION: Algorithm for Evaluation for Suspected Cardiac Amyloidosis
Witteles, R.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):117-30.
K/L
No M protein
Next Step?

56



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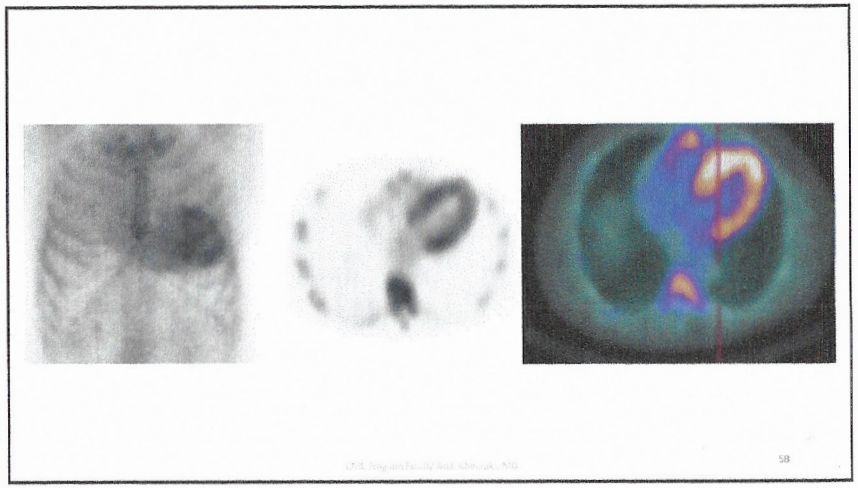
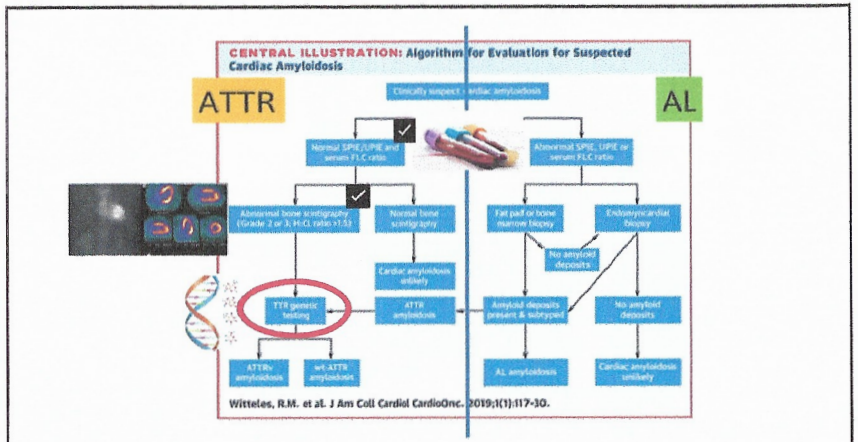


58

ATTR Amyloidosis

Next step?

59

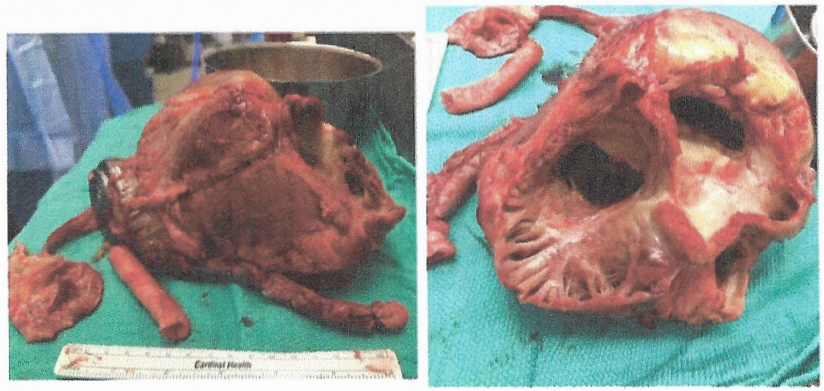


60

V122I
3-4% of those of African descent
↓
BEWARE of "hypertensive heart disease"

61

61



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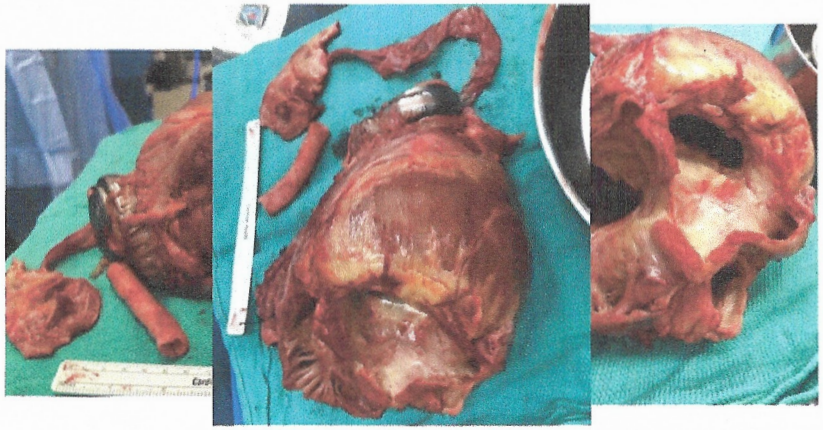


63

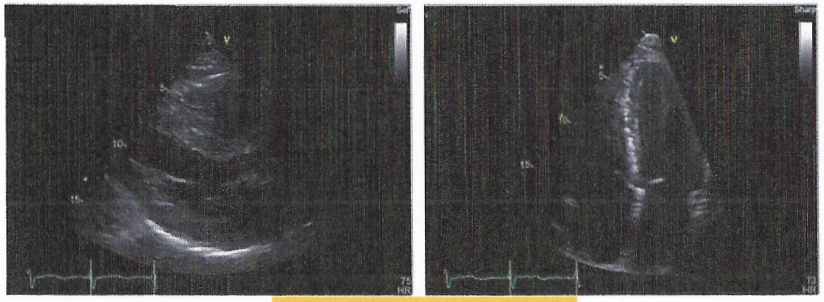
63

Case 2

64

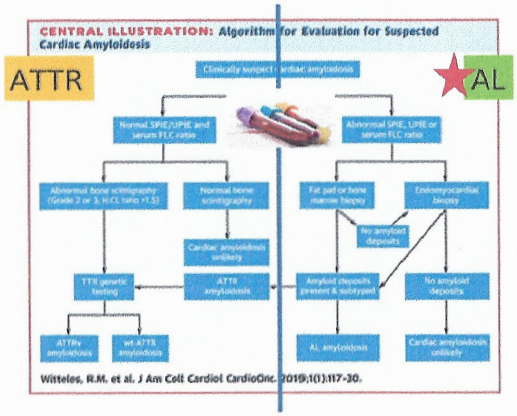
64

74 yo Caucasian male
Carpal tunnel syndrome w/bilat surgery in 2003, back surgery in 2008



IVS and PW thickness 1.8cm

65



66

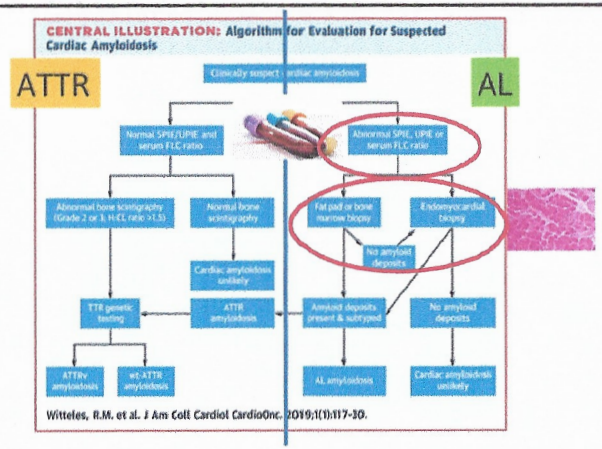
Labs

- Kappa: 114.3mg/L
- Lambda: 8.7mg/L
- K/L ratio: 13.14

- Immunofixation: IgM kappa monoclonal protein

Next step?

67



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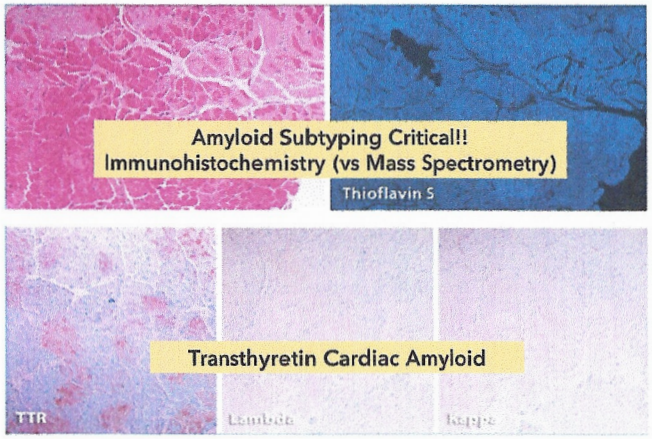

Cardiac Biopsy

69

Abnormal AL Labs!!

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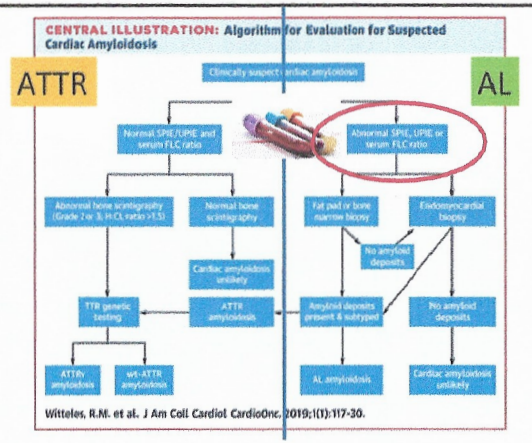
Final Diagnosis

ATTR cardiac amyloid
with incidental finding of Waldenstrom's

Next step?

71



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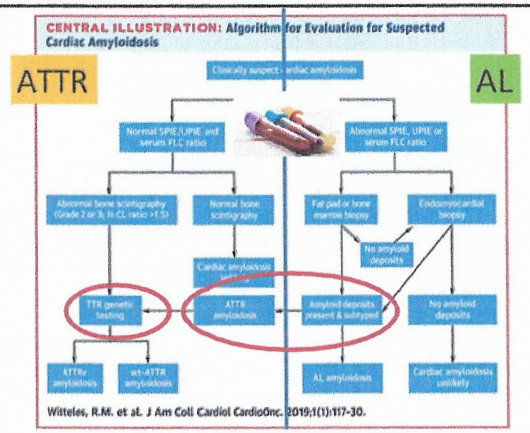

73

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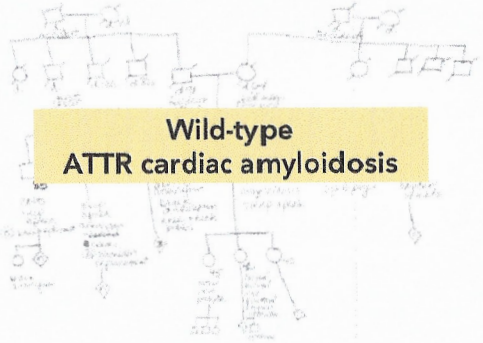
Genetic Testing



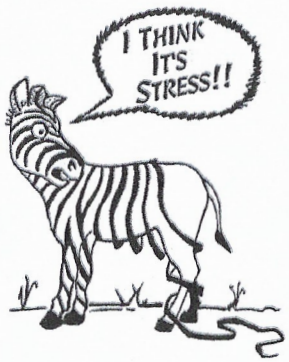
Wild-type ATTR cardiac amyloidosis

74

74

Learning Points

- More common than previously appreciated
- Look for cardiac and non-cardiac symptoms
- Always start with lab work up to rule out AL
- Many treatments and many more on the horizon!



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Carpal Tunnel Syndrome and Amyloidosis

Brett W. Sperry, MD

@BrettSperryMD

Advanced Heart Failure & Transplantation
Director, Cardiac Amyloidosis Program
Saint Luke's Mid America Heart Institute

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Disclosures

- Pfizer – speaker and research grant
- Alnylam – consultant
- BridgeBio/Eidos – consultant
- AstraZeneca – consultant

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Outline

- Non-cardiac manifestations
- Orthopedic issues and carpal tunnel syndrome

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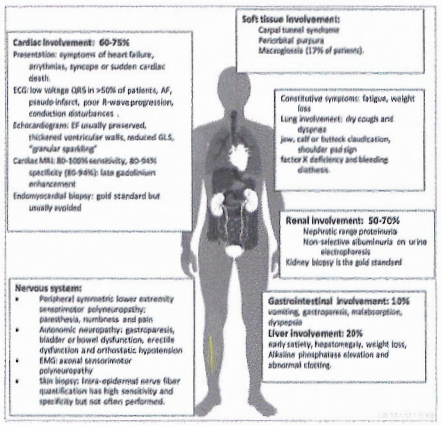

Systemic AL Amyloidosis

Current Approaches to Diagnosis and Management.

Fotiou D, Dimopoulos MA, Kastritis E. Hemasphere. 2020 Aug 10;4(4):e454.

Additional ATTR Amyloidosis Soft Tissue Manifestation

Spinal stenosis
Biceps tendon rupture
Rotator cuff pathology
Trigger finger

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Variable	AL (n=191)	ATTR (n=169)	P Value
Age, y	64.7±11.8	75.3±8.9	<0.001
Male	116 (61)	136 (81)	<0.001
White	157 (82)	112 (66)	<0.001
Body surface area, m^2	1.92±0.26	2.00±0.24	0.005
Hypertension	90 (47)	108 (64)	0.002
Hyperlipidemia	80 (44)	98 (58)	0.036
Diabetes mellitus	47 (25)	46 (28)	0.472
Smoking	92 (48)	93 (55)	0.197
Atrial fibrillation	65 (34)	93 (55)	<0.001
Anemia	80 (44)	80 (47)	0.525
CAD requiring PCI or CABG	33 (17)	42 (25)	0.091
NYHA class ≥3	122 (64)	104 (61)	0.743
eGFR, mL/min per 1.73 m^2	65.4±26.4	59.9±23.4	0.039
β-Blocker	73 (38)	97 (57)	<0.001
ACEI/ARB	61 (32)	74 (44)	0.022
Antihypertensive	118 (62)	126 (75)	0.013
Diuretic	158 (83)	139 (82)	1.000
Amyloid-specific treatment	135 (71)	44 (26)	<0.001

Sperry et al. Subtype-Specific Interactions and Prognosis In Cardiac Amyloidosis. J Am Heart Assoc. 2016 Mar 24;5(3):e002877.

AL
- Age 40s-70s
- Men = women
- Proteinuria
- Macroglossia, periorbital purpura, petechiae
- Carpal tunnel syndrome
- Orthostatic hypotension!
- GI involvement (diarrhea)

ATTR
- Age 60s-80s
- Men > women
- African Americans (V122I mutation)
- HFpEF
- Low-flow low-gradient AS
- Bilateral carpal tunnel syndrome
- Spinal stenosis
- Peripheral neuropathy (in some variants)

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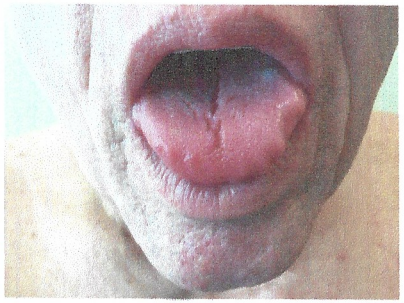
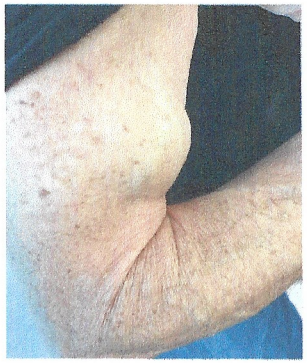
AL Amyloidosis



ATTR Amyloidosis



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Neuropathy in Amyloidosis

- Typically, sensory polyneuropathy
- AL amyloidosis: neuropathy from disease and potentially from treatment (proteasome inhibitors ie bortezomib)
- ATTR amyloidosis: neuropathy predominantly in hereditary ATTR - may have motor neuropathy component with certain variants

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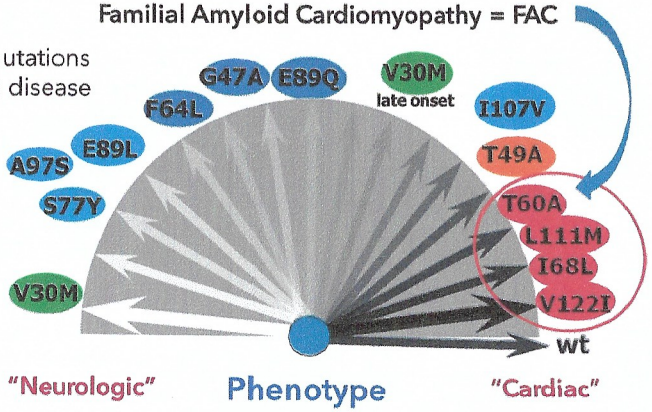
Familial Amyloid Cardiomyopathy = FAC

112+ mutations causing disease



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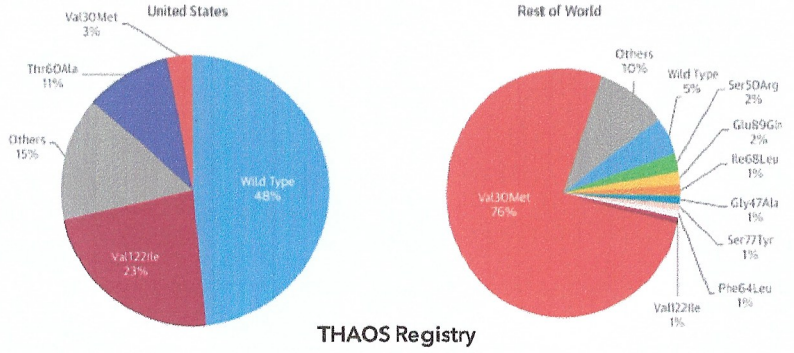

THAOS Registry

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Orthopedic Issues

- Carpal tunnel syndrome and trigger finger
- Spinal stenosis
- Biceps tendon rupture

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Ligaments and Tendons

- Biceps / rotator cuff → tendon
- Carpal tunnel / trigger finger → tendon
- Spinal stenosis → ligament

Ligaments connect bone to bone
Tendons connect muscle to bone and have a lining (tenosynovium)

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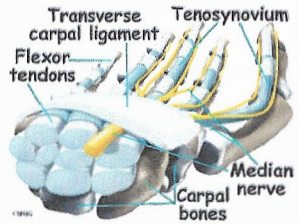
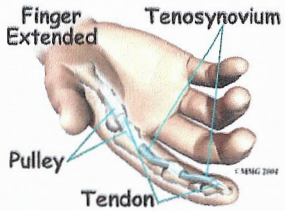
Tenosynovium - Hand

Surgeon cuts transverse carpal ligament in CTS and pulley in TF. Removes inflamed tenosynovium.

Carpal Tunnel Syndrome



Trigger finger



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Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release

Brett W. Sperry, MD,[1*] Bryan A. Reyes, MD,[1] Asad Ikram, MBBS,[1] Joseph P. Donnelly, MD,[1]
Dermot Phelan, MD, PhD,[2] Wael A. Jaber, MD,[2] David Shapiro, MD,[2] Peter J. Evans, MD, PhD,[2] Steven Maschke, MD,[2]
Scott E. Kilpatrick, MD,[3] Carmela D. Tan, MD,[3] E. Rene Rodriguez, MD,[3] Cecilia Monteiro, MD,[1]
W.H. Wilson Tang, MD,[2] Jeffery W. Kelly, PhD,[4] William H. Seitz, Jr. MD,[1] Maren Hanna, MD[1]

PROSPECTIVE STUDY

- 98 patients with idiopathic carpal tunnel syndrome
- Inclusion: men ≥ 50 and women ≥ 60 years old
- Intervention: tenosynovial biopsy at the time of carpal tunnel release surgery

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- 10% of patients had amyloid deposits in the tenosynovium
  - All had bilateral symptoms
- 8 with ATTR deposits and 2 with AL deposits
- 2 had previously unknown cardiac involvement
- 1 had previously unknown hATTR neuropathy (Leu58His)
- 1 had Ala81Thr mutation with negative PYP, but PYP+ at year 4

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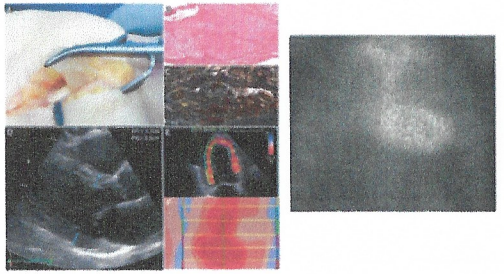

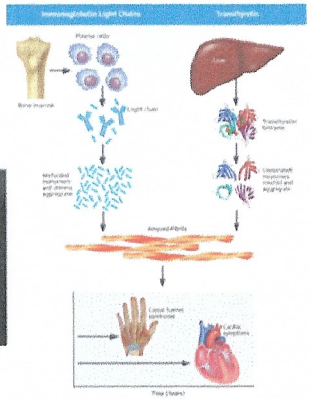

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Carpal Tunnel Syndrome – Additional Studies

- Takashio et al, Circ J 2023 → 700 patients biopsied, 37% positive for amyloid deposition. Screened 12 with PYP who met cardiovascular criteria of increased LV septal thickness, with 6 positive
- DiBenedetto et al, J Hand Surg Am 2022 → 185 patients biopsied, 29% positive for amyloid deposition
- Wininger et al, BMC Musc Dis 2021 → systematic review detailing deposition in carpal tunnel, hip/knee OA, spinal stenosis, and rotator cuff tears

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Trigger Finger – Tenosynovium

PROSPECTIVE STUDY

- 100 patients biopsied at the time of trigger finger release surgery
- Inclusion criteria: age > 50.
- Mean age 66 +/- 8 years

Sperry BW, Khedraki R et al. AJC 2021.

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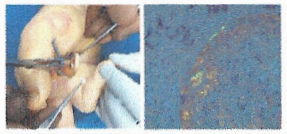

100 patients undergoing trigger finger release surgery

2 positive for amyloidosis in trigger finger samples

13 patients underwent concomitant carpal tunnel release

Patient 1
Fibrinogen A α-chain amyloidosis
- NTproBNP <50, troponin T < 0.010
- Echo: normal LV wall thickness
- ECG: normal sinus rhythm
- Urine Protein/Cr ratio 0.4

Patient 2
Undifferentiated amyloidosis
- NTproBNP 152, troponin T <0.010
- Echo: mild increased LV wall thickness
- ECG: normal sinus rhythm, Incomplete RBBB, first degree AVB
- TcPYP grade 0, no SPECT uptake
- K/L ratio normal, no M protein

2 patients with ATTR amyloid deposits on carpal tunnel sample but negative on trigger finger sample

Sperry BW, Khedraki R et al. AJC 2021.

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Spinal Stenosis

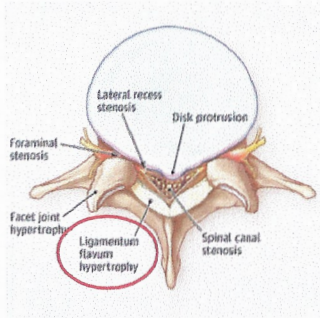

Image from: https://edhub.ama-assn.org/jn-learning/audio-player/18693675

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Spinal Stenosis – Ligamentum Flavum

- Variable rates of amyloid deposition in ligamentum flavum: 13-80%
- ATTR found in 13-65%
- Degree of amyloid deposition is correlated with presence of systemic disease

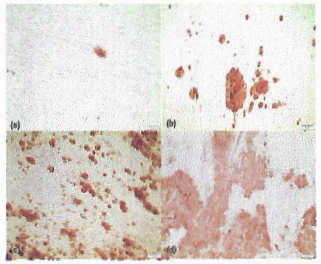

Fig. 1 *Visualization of the grading system of transthyretin amyloid deposits: (a), grade 1; (b), grade 2; (c), grade 3; and (d), grade 4. Amyloid deposits labelled with monoclonal antibody 7×. Bar = 50 μm.*

https://pubmed.ncbi.nlm.nih.gov/34263670/
https://pubmed.ncbi.nlm.nih.gov/37431662/
http://umu.diva-portal.org/smash/get/diva2:1527906/FULLTEXT02

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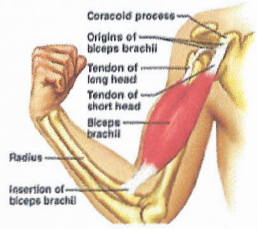
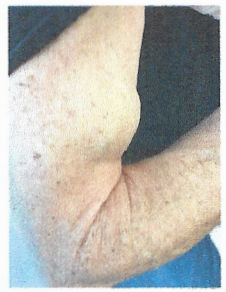
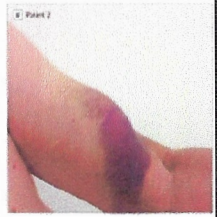
Biceps Tendon Rupture - Tenosynovium

Proximal – long head







Geller et al. JAMA 2017

Up to 1/3 of patients with wtATTR-CM may have BTR

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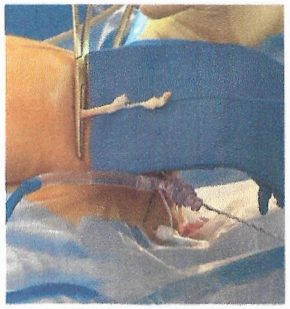
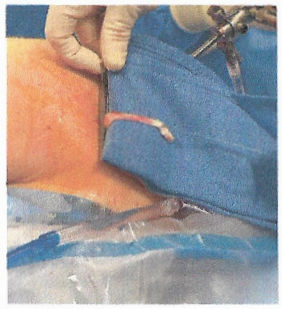
Partial Tear



Tenosynovitis



Long head of biceps tendon

Photos credit of Dr. Adam Meisel

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Reasons for Long Head of Biceps Pathology

- Long head of biceps tendon attaches to biceps anchor which then attaches to superior glenoid tubercle. Not a direct bony attachment like other tendons → prone to wear and tear
- Long head makes an acute turn over the bony ridge (lesser tuberosity) which creates friction
- May have stenosing tenosynovitis in the bicipital groove
- Amyloid involvement may speed up wear and tear

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How to Diagnosis Amyloidosis at the Time of Orthopedic Surgery?

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Biopsy

- Carpal tunnel syndrome: tenosynovial or TCL biopsy for patients > 50-60 years old.
- Spinal stenosis: ligamentum flavum biopsy at the time of surgery - consider more aggressive cardiac evaluation in patients with larger burden of deposition (ie Grade 2-4).
- Biceps tendon rupture: consider Congo red staining of tenosynovium or ligament if biceps tenodesis is done (reattachment of long head and removal of a portion of the tendon).

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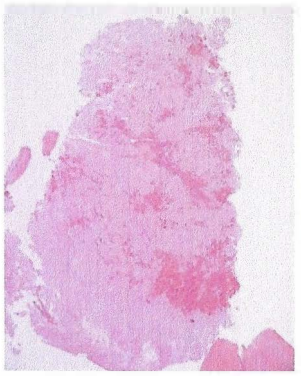

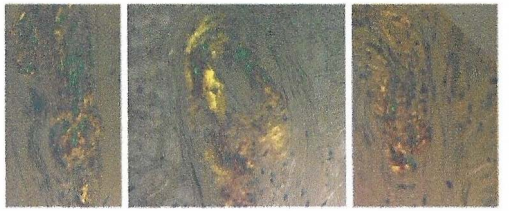

Congo red – Apple green birefringence

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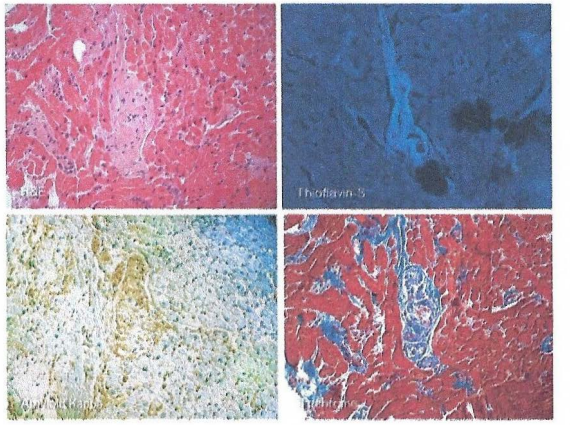

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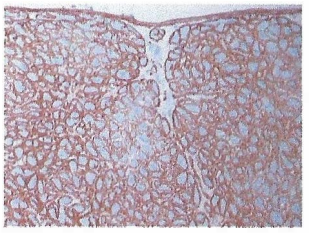
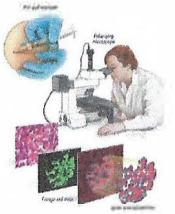
MUST SUBTYPE THE AMYLOID!!
Congo Red only tells you if it is amyloid
What type is it - AL? ATTR? Other?
Important for diagnosis, prognosis, treatment

Immunohistochemistry



Mass Spectrometry



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Summary

- Orthopedic manifestations of amyloidosis are typically caused by amyloid deposition in ligaments/tendons and tenosynovium, leading to wear and tear.
- 1 in 10 older patients will have amyloid deposits contributing to their carpal tunnel syndrome.
- Amyloid deposits are commonly found in the ligamentum flavum at the time of spinal stenosis surgery, and amount of deposition is associated with presence of systemic disease.
- Look for Popeye's sign → rupture of the long head of the proximal biceps tendon
- Consider biopsy at the time of orthopedic surgery in these conditions

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