Pocket Guide

^{99m}Tc PYP Scan for Diagnosis of ATTR-CM

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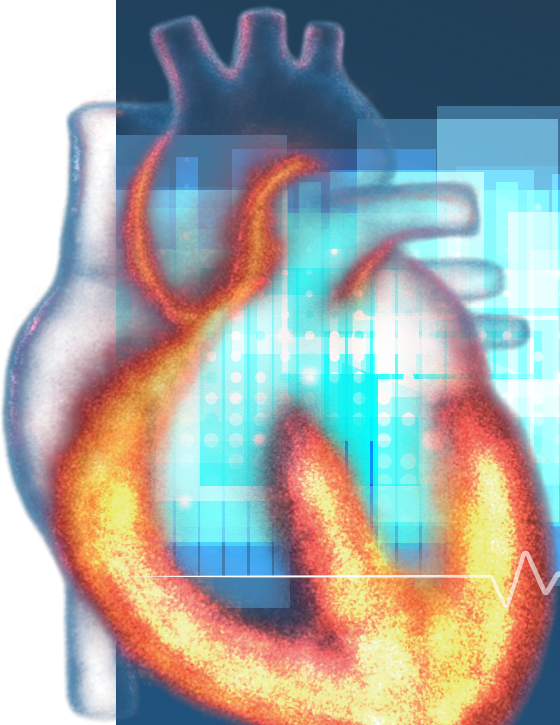

Pfizer

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Preface

Transthyretin cardiac amyloidosis (ATTR-CM) is a progressive and serious disease that is still often missed or diagnosed too late. This means many patients lose the chance to receive treatment early enough to truly change their outcome and quality of life.

Over the past few years, ^{99m}Tc-PYP scan has become an important tool in diagnosing and differentiating ATTR-CM from other forms of cardiomyopathy, without the need for invasive procedures. When performed carefully and interpreted with expertise, it allows timely and accurate diagnosis, enabling better treatment planning. As nuclear medicine physicians, our work goes far beyond reading images as we are part of each patient's journey toward the right diagnosis and better care.

This pocket guide was prepared especially for nuclear medicine physicians, drawing on the latest local expert consensus. It offers practical imaging protocols, interpretation guidance, and real-world cases contributed by colleagues who face these challenges in daily practice. Our purpose is not only to guide good practice but also to remind ourselves that every scan we do and every report we sign, there is one shared goal: to truly help the patients who place their trust in us.

I sincerely thank all the experts and colleagues who contributed their time and expertise to make this guide possible. Your dedication reflects the best of our field as we work together to enhance patient care. I also encourage every member of our society to stay closely connected to clinical practice, to collaborate with clinicians and multidisciplinary teams, and to deeply understand the needs of the patients we serve, ensuring that nuclear medicine is not just about producing images, but about delivering care that makes a meaningful difference.

With commitment to our patients,

Yuh-Feng Wang

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Abbreviations

^{99m}Tc	^{99m}Technetium
A97S	p.Ala117ser, p.A117S
AF	Atrial Fibrillation
AL	Amyloid Light Chain
AL-CA	Amyloid Light Chain Cardiac Amyloidosis
Alpha-GAL	Alpha-Galactosidase A
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
ATTR	Transthyretin Amyloid
ATTR-CM	Transthyretin Amyloid Cardiomyopathy
ATTRv	Variant Transthyretin Amyloidosis
ATTRwt	Wild-type Transthyretin Amyloidosis
AV	Atrioventricular
BUN	Blood Urea Nitrogen
CK-MB	Creatine Kinase-MB
CMR	Cardiac Magnetic Resonance
CPK	Creatine Phosphokinase
CPV	Cardiac Pyrophosphate Volume
CXR	Chest X-Ray
ECV	Extracellular Volume
eGFR	Estimated Glomerular Filtration Rate
EKG/ECG	Electrocardiogram
EMB	Endomyocardial Biopsy
FLC	Free Light Chain
H/CL	Heart-to-Contralateral Lung
Hb	Hemoglobin
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HR	Heart Rate
hsCRP	High-Sensitivity C-Reactive Protein
hs-TnT	High-Sensitive Troponin T
IFE	Immunofixation Electrophoresis
Inorganic P	Inorganic Phosphate
LA	Left Atrial
LAO	Left Anterior Oblique
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVIDd	Left Ventricular Internal Diameter in Diastole
LVIDs	Left Ventricular Internal Diameter in Systole
LVPWd	Left Ventricular Posterior Wall Dimension
IVSd	Interventricular Septal Thickness in Diastole
MI	Myocardial Infarction
NT-proBNP	N-Terminal Pro B-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Peritoneal Dialysis
PLT	Platelet
PYP	Pyrophosphate
RA	Right Atrial
ROI	Region of Interest
RT	Radiation Therapy
RV	Right Ventricle
SNMROC	Society of Nuclear Medicine of the Republic of China
SPECT/CT	Single-Photon Emission Computed Tomography/Computed Tomography
TSOC	Taiwan Society of Cardiology
TTR	Transthyretin
WBC	White Blood Cell

What is **Cardiac Amyloidosis?**

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy caused by the extracellular deposition of misfolded amyloid fibrils, leading to myocardial stiffness, diastolic dysfunction, and progressive heart failure.[1]

The two most common types of CA account for over 95% of all CA diagnosis.[2]

- **AL-CA** results from monoclonal immunoglobulin light chains produced by clonal plasma cells, and often progresses rapidly. Patients who present with heart failure and who are not treated survive less than 6 months. [2,3,4] Therefore, accurate differentiation between ATTR-CM and AL amyloidosis is critical for appropriate management to achieve optimal patient outcome.
- **ATTR-CM** is due to misfolded transthyretin (TTR) protein and includes two forms[5]
  - **Wild-type (ATTRwt)**, associated with aging, typically manifests after age 65 with heart failure symptoms. [6]
  - **Variant (ATTRv),** caused by TTR gene mutations, often presents earlier and may include neuropathic features. [1, 3] In Taiwan, **A97S (p.Ala117Ser)** is the most common variant. [7-9]

The role of ^{99m}Tc-pyrophosphate (PYP) scintigraphy
Accurate differentiation between **ATTR-CM** and **AL amyloidosis** is critical for appropriate management.

AL-CA, Amyloid light chain cardiac amyloidosis. ATTR-CM, Transthyretin amyloid cardiomyopathy. AL, Amyloid light chain

PYP scan has become a **cornerstone in the non-invasive diagnosis** of ATTR-CM.

In the landmark study by **Gillmore et al.**, PYP scan with **grade 2–3 uptake** demonstrated **>99% sensitivity** and **86% specificity** for ATTR-CM; when combined with the **absence of monoclonal protein**, specificity and positive predictive value of ATTR-CM reached **100%** [10].

Thus, **PYP scan** is considered to be a suitable alternative to **EMB** in many cases[1, 3].

Current **Taiwan Society of Cardiology (TSOC)** and **Society of Nuclear Medicine of the Republic of China (SNMROC)** consensus recommends[3](Fig. 1)

- Performing **PYP scan** alongside **serum and urine monoclonal protein testing** (free light chains, immunofixation).
- **ATTR-CM** diagnosis can be made with a typical PYP result (**grade ≥2**) and **no monoclonal protein**.
- If monoclonal protein is present, **biopsy** remains necessary.

In addition to diagnosis, emerging evidence suggests **PYP scan** may serve as a **tool for monitoring treatment response**, as signal intensity decreases following **stabilizer** or **silencer therapies** [11-14].

Given its **high diagnostic accuracy, non-invasiveness**, and **potential for disease monitoring, PYP scan** is now considered an **essential component** of the modern diagnostic algorithm for CA[15, 16].

Reference

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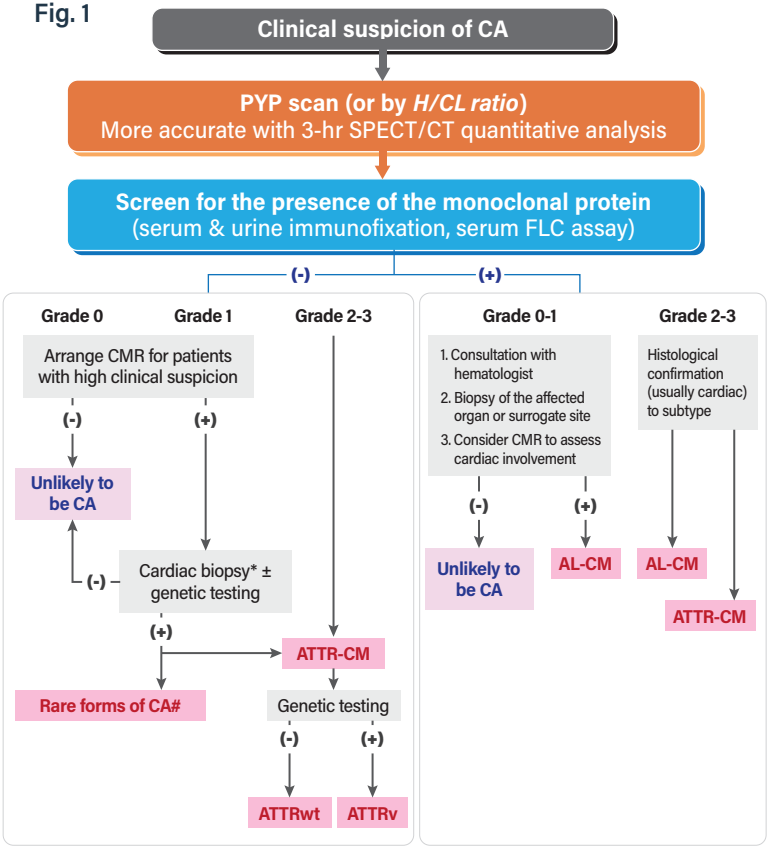
Diagnostic Algorithm of Suspected Cardiac Amyloidosis

Fig. 1



*Cardiac biopsy in patients with grade 1 and negative hematology tests should only be performed after a thorough risk-benefit assessment and detailed discussion with the patient.
#Rare forms of CA, such as Apo AI, AIV amyloidosis or Phe64Leu ATTRv, frequently present with grade 0 or 1 on PYP scan.

^{99m}Tc-Pyrophosphate Scintigraphy

Image acquisition procedures

Diagnosis of ATTR-CM

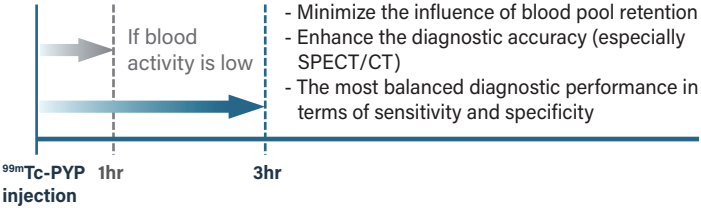
Planar imaging

- **Anterior planar**
- Left anterior oblique (LAO)
- Left lateral

SPECT/CT

- Exclude blood pool activity
- Highlight differences in myocardial uptake patterns (e.g., absent, focal, diffuse, focal-on-diffuse)

Timing



Strongly recommended

- Minimize the influence of blood pool retention
- Enhance the diagnostic accuracy (especially SPECT/CT)
- The most balanced diagnostic performance in terms of sensitivity and specificity

Key considerations

- The imaging should **include both bilateral shoulders** to evaluate musculoskeletal manifestations of amyloid deposition (e.g., shoulder pad sign, joint swelling).
- To enhance myocardial signal detection, **symmetric renal counts in planar images should be minimized.**

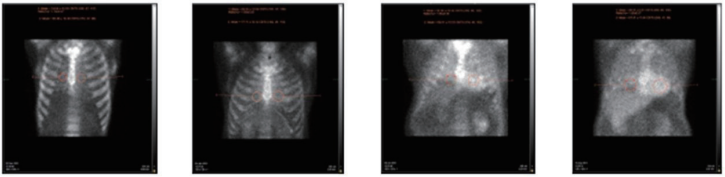
Visual grading scale

Grade	The relative tracer uptake in the myocardium compared to the ribs		^{99m}Tc-PYP scan result
	Myocardial uptake	Rib uptake	
0	Absent	Normal bone uptake	(-)
1	<		Further assessment is required if there is strong clinical suspicion of ATTR-CM.
2	=		(+)
3	>	(Mild or absent)	(+)

If the visual grading of planar and SPECT images is **inconsistent**, it is recommended to rely on the visual score obtained from the **SPECT images**.

^{99m}Tc-Pyrophosphate Scintigraphy

Planar ^{99m}Tc-PYP visual scoring:

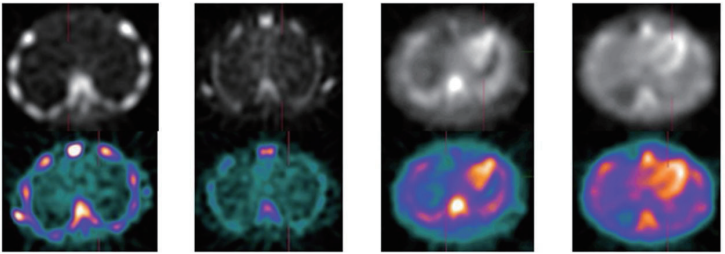


Grade 0 Grade 1 Grade 2 Grade 3

Heart-to-contralateral lung (H/CL) ratios:

H/CL = 1.14 ± 0.27 H/CL = 1.08 ± 0.25 H/CL = 1.35 ± 0.30 H/CL = 1.42 ± 0.27

SPECT ^{99m}Tc-PYP visual scoring:

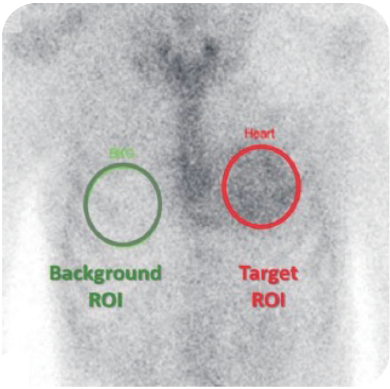


Grade 0 Grade 1 Grade 2 Grade 3

Case examples of planar and SPECT visual grading for ATTR-CM.
Reproduced with permission from Schockling et al.
This research was originally published in Journal of Nuclear Medicine Technology.
Schockling EJ, Farrell MB, Embry-Dierson M, Warren J, Jerome S. Cardiac Amyloidosis Imaging, Part 2: Quantification and Technical Considerations.
J Nucl Med Technol. 2023;51(2):90–98. © SNMMI. DOI: https://doi.org/10.2967/jnmt.123.265416

H/CL ratio

Determining ROI on anterior planar images



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Heart ROI

- Select **a circular or elliptical region** that encompasses the myocardium uptake area
- Avoid the sternum and subdiaphragmatic organs

Contralateral Lung ROI

- Mirroring the heart ROI, the background ROI is positioned over the contralateral lung region
- Exclude the subdiaphragmatic organs
- **Similar size to the heart ROI**

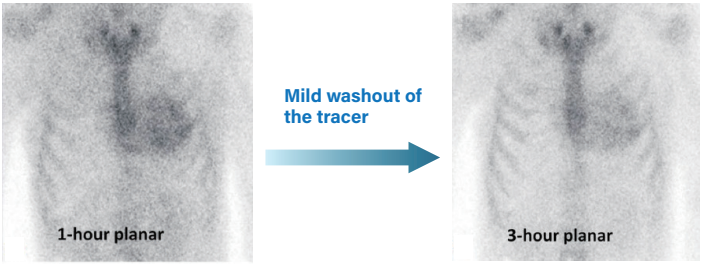
ROI, Region of Interest. H/CL, Heart-to-Contralateral Lung.

^{99m}Tc-Pyrophosphate Scintigraphy

H/CL ratio

Indicators of a positive PYP scan

	H/CL ratio (= mean counts of the heart ROI / mean counts of the CL ROI)
1-hour images	>1.5
3-hour images	≥1.3



H/CL ratio = 1.99

H/CL ratio = 1.92

- If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is **NOT recommended.**
- **Interpretation should not rely solely on H/CL ratios**, since they do not provide enough sensitivity alone; combining with visual scores improves specificity, particularly at the 3-hour image.

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Utilizing ^{99m}Tc-PYP Scan and SPECT/CT for ATTR-CM with Acquisition Parameters (1/2)

Patient selection	Indications	- HF symptoms, especially HFpEF. - Unexplained LVH or suspected CA - Consider in older adults with ATTRv or ATTRwt.
Image procedure	Dose of ^{99m}Tc-PYP	20 mCi
	Time interval between injection and acquisition	3-hour planar and SPECT or SPECT/CT (Optional: 1-hour planar and SPECT)
General imaging parameters	Field of view	Cardiac or chest
	Position of planar and SPECT	
	Energy window	140 keV, 15-20%
	Collimators	Low energy, high resolution
	Matrix	- Recommended: 128 x 128 for SPECT - Minimum required: 64 x 64 for SPECT, 256 x 256 for planar
	Pixel size	2.3-6.5 mm (may change with different matrix)
Planar imaging specific parameters	Number of views	Anterior, lateral, LAO
	Detector configuration	180 degrees
	Image duration	750,000 counts
	Magnification	1.45-1.5

HF, Heart Failure. HFpEF. Heart Failure with Preserved Ejection Fraction. LVH, Left Ventricular Hypertrophy. LAO, Left Anterior Oblique.

Utilizing ^{99m}Tc-PYP Scan and SPECT/CT for ATTR-CM with Acquisition Parameters (2/2)

SPECT imaging specific parameters	Angular range	360 degrees
	Detector configuration	180 degrees
	Number of views/detectors	32-64
	Time per stop	20 seconds
Quantitative and semi-quantitative analysis	H/CL ratio	- On the anterior planar image, define a ROI over the heart and contralateral lung. - May consider ATTR-CM if H/CL ratio ≥ 1.3 on the 3-hr image.
Diagnosis and interpretation	Positive for ATTR-CM	- Visual grade is 2 or 3 - H/CL ratio meets the positive threshold - If visual grading and H/CL results are inconsistent, it is recommended to rely on the visual score
	Equivocal or negative results	If results are equivocal, consider additional modalities like CMR or repeating the scan for further clarification.
Reporting and documentation		The report format can be referenced from the **Standardized Reporting of ^{99m}Tc-PYP scan for CA**
Follow-up and monitoring		- A reduction in H/CL ratio suggests a decrease in amyloid burden, while stable or increased values may indicate disease progression or suboptimal therapeutic response. - May also be used to monitor early-stage (e.g., grade 1) ATTR-CM.

Typical Case 1

Grade 0

Patient Profile

70 y/o Asian Male

162 cm

77 kg

Symptoms

- Arrhythmia
- Exertional dyspnea

Past History

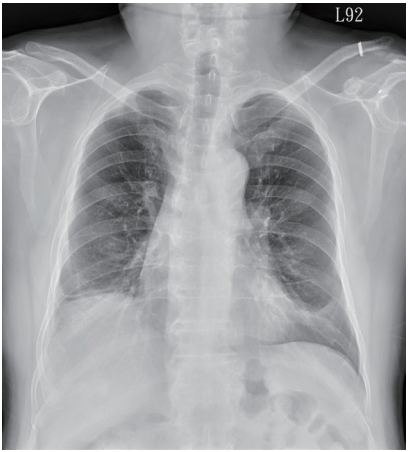
- Wolff-Parkinson-White syndrome
- Coronary artery disease status post ballon angioplasty and stenting of the left anterior descending artery

Raising Suspicion

Lab Data

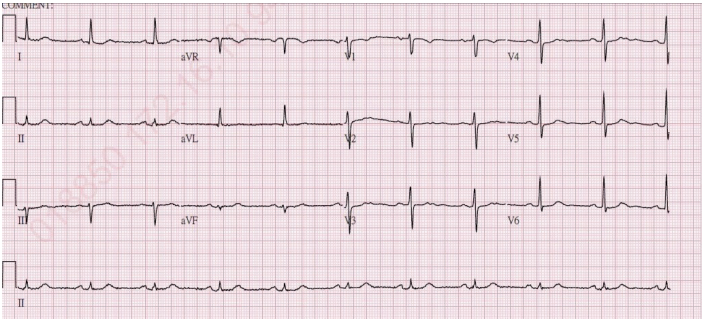
Cardiac	NT-proBNP	108 pg/ml
	hs-TnT	7.21 ng/L
Renal	BUN	19.9 mg/dL
	Creatinine	1.3 mg/dL
	Uric Acid	4.5 mg/dL
	eGFR	58.0 ml/min/1.73m^2
Hepatic	Albumin	4.7 g/dL
	ALT	21 U/L
Electrolytes	Na	139 mEq/L
	K	5.2 mEq/L
Inflammation	hsCRP	0.55 mg/dL

CXR



Raising Suspicion

Electrocardiogram

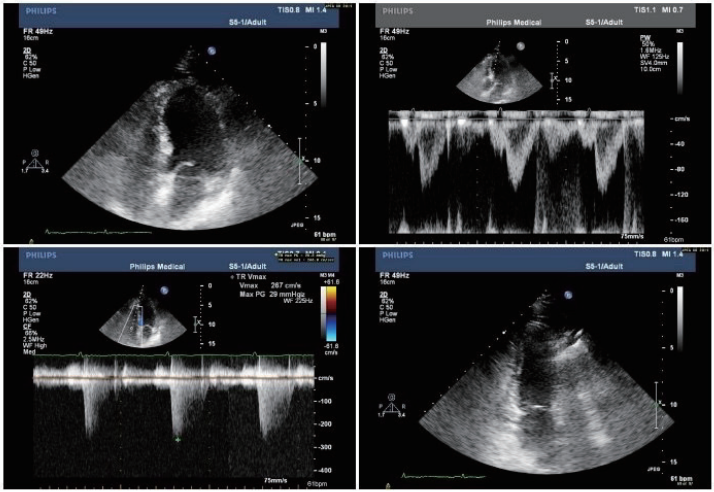


No remarkable EKG findings

Raising Suspicion

Echocardiography

- **LVIDd 48 mm**
- **LVIDs 30 mm**
- **IVSd 12 mm**
- **LVPWd 11 mm**
- **LVEF 68.5 %**
- **LA 35mm**
- **Aortic regurgitation, moderate**



LA, Left Atrial. LVIDd, Left Ventricular Internal Diameter in Diastole. LVIDs, Left Ventricular Internal Diameter in Systole. LVPWd, Left Ventricular Posterior Wall Dimension. IVSd, Interventricular Septal Thickness in Diastole.

Differential Diagnosis

Testing for AL

Serum	Free kappa	25.6 mg/L
	Free lambda	22.20 mg/L
	Kappa/lambda ratio	1.1532
	IFE	Shows no monoclonal gammopathy.
Urine	IFE	Shows no Bence Jones proteins.

Testing for Fabry

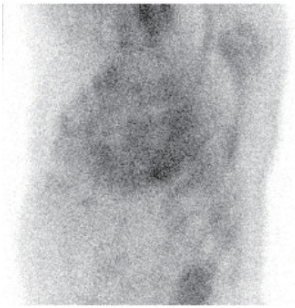
Blood	Alpha-GAL	5.13 umol/hr.

AL amyloidosis and Fabry disease were ruled out.

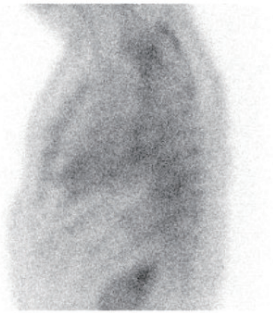
Alpha-GAL, Alpha-Galactosidase A. IFE, Immunofixation Electrophoresis.

Differential Diagnosis with ^{99m}Tc-PYP Scan

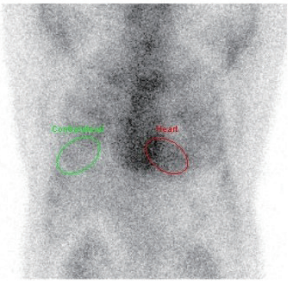
3-hr Planar Images



LAO



Left lateral



Anterior

H/CL ratio interpretation

3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

H/CL ratios < 1.3 are classified as ATTR-CM (+).

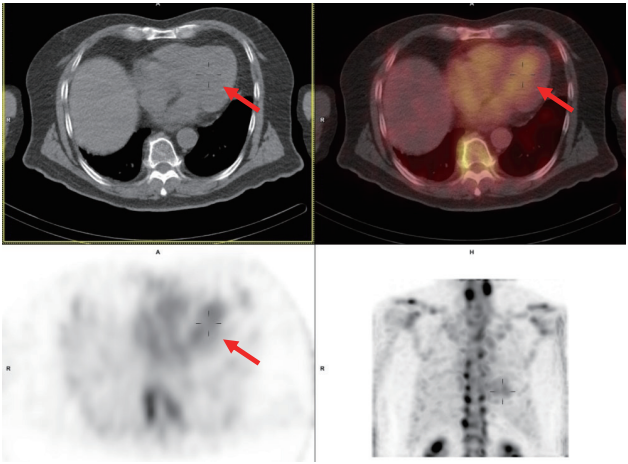
If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

H/CL ratio = 1.67

Typical Case 1

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr SPECT/CT Images



Visual grading = 0

Imaging demonstrated uptake within the cardiac chambers (blood pool).

Visual intepretation

Visual scores ≥ 2 on planar or SPECT images are classified as ATTR-CM positive.

Grade 0: No myocardial uptake and normal bone uptake

Grade 1: Myocardial uptake < rib uptake

Grade 2: Myocardial uptake = rib uptake

Grade 3: Myocardial uptake > rib uptake

Key Messages

- ✓ Planar imaging and H/CL ratio alone are **insufficient** for diagnosis of ATTR-CM.
- ✓ **SPECT is necessary** to identify myocardial uptake.
- ✓ Visual grading on planar and SPECT imaging is the primary method for diagnosis of ATTR-CM.

to Take Away

Typical Case 2

Grade 1

Patient Profile

57 y/o Asian Male

Symptoms

- Bilateral carpal tunnel syndrome presented as both hand numbness 2 years ago

Past History

- Familial amyloidosis polyneuropathy (FAP)

Raising Suspicion

Lab Data

Vital Sign	HR	80 bpm
	BP	109/66 mmHg
Cardiac	NT-proBNP	50 pg/ml
	Troponin I	<0.10 ng/ml
CBC	Hb	14.9 g/dL
	WBC	5,700/ul
	PLT	214,000/mm^3
Renal	BUN	15 mg/dL
	Creatinine	1.3 mg/dL
	Uric Acid	8.2 mg/dL
Electrolytes	Na	143 mEq/L
	K	3.7 mEq/L
	Ca	9.6 mg/dL
	Inorganic P	3.1 mmol/L

Gene Test

Molecular genetic testing revealed TTR **A97S** gene mutation

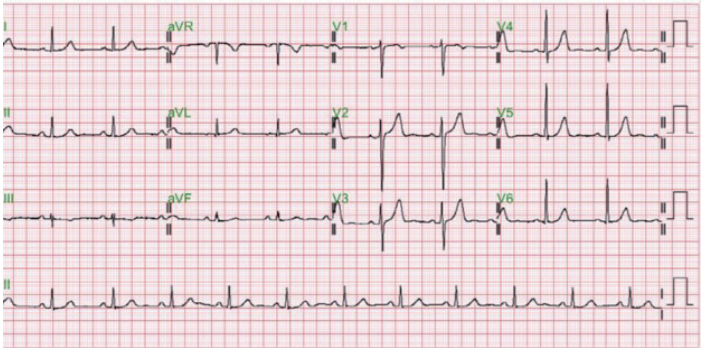
Testing for AL

Serum	Free kappa	17.32 mg/L
	Free lambda	10.98 mg/L
	Kappa/lambda ratio	1.58

AL amyloidosis was ruled out.

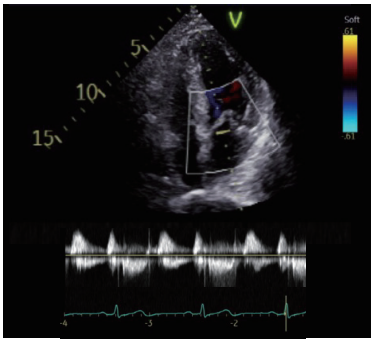
Raising Suspicion

Electrocardiogram



Sinus rhythm, r/o LVH, anterior ST elevation likely secondary to LVH

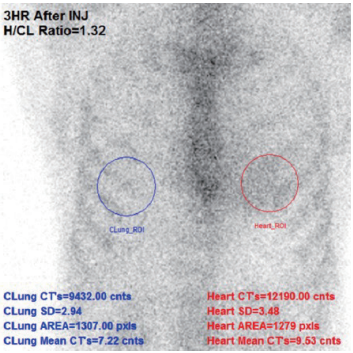
Echocardiography



- **Normal LV size**
- **IVSd 9 mm**
- **LVEF 60 %**

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr Planar & SPECT/CT Images



H/CL ratio interpretation

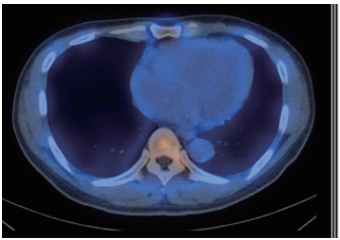
3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

H/CL ratios < 1.3 are classified as ATTR-CM (+).

If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

H/CL ratio was just around the cutoff



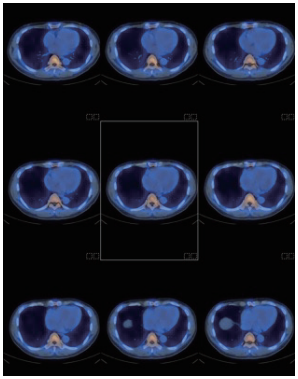
Visual grading = 1

Equivocal PYP scan: myocardial uptake < rib

Typical Case 2

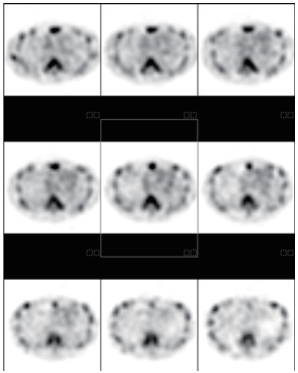
Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr SPECT/CT Images



Sometimes, it is still hard to differentiate blood pool activity from myocardial uptake even reading all slices in the fusion images especially in cases of equivocal uptake.

3-hr SPECT Images



When looking at the entire slices in the SPECT, interpretation for the myocardial uptake is more confident.

Key Messages

✓ In case with equivocal uptake, a single slice may be hard to differentiate myocardial uptake or blood pool activity. Sometimes, it is also difficult to judge even after looking at all SPECT/CT slices. **Pure SPECT (non-fusion SPECT images)** may help in this situation. **Read all obtained images all the time before making a report for PYP scan.**

to Take Away

Typical Case 3

Grade 2

Patient Profile

58 y/o Asian Male

Symptoms

- Off & on dropped beat felt with cough.

Examinations

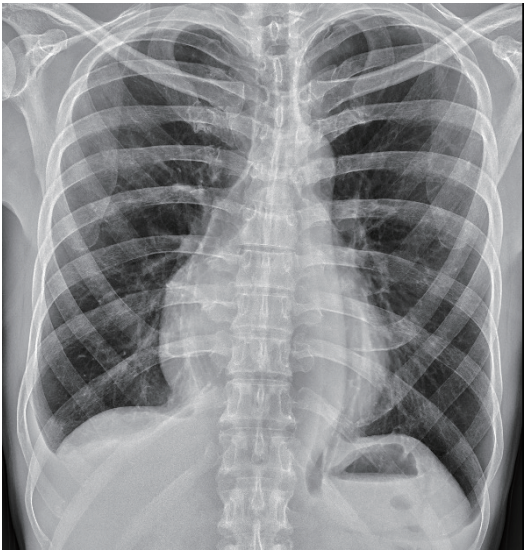
- CXR showed cardiomegaly.

Raising Suspicion

Lab Data

Cardiac	NT-proBNP	498 pg/ml
	hs-TnT	38.7 ng/L
	CPK	108 U/L
	CK-MB	43 U/L
Renal	BUN	16 mg/dL
	Creatinine	1.00 mg/dL

CXR

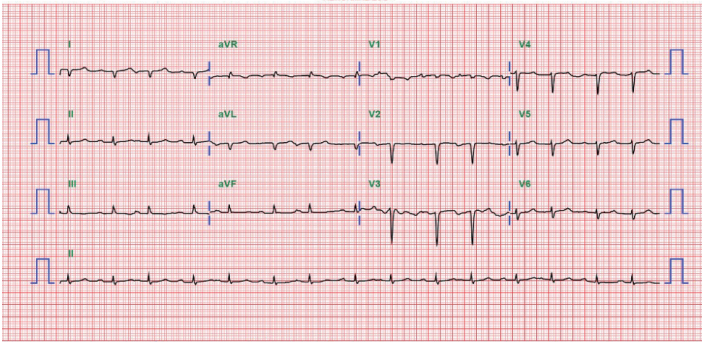


Typical Case 3

Raising Suspicion

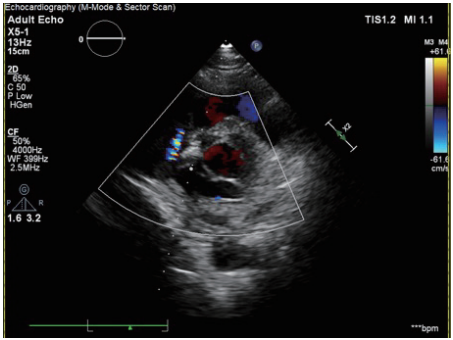
Electrocardiogram

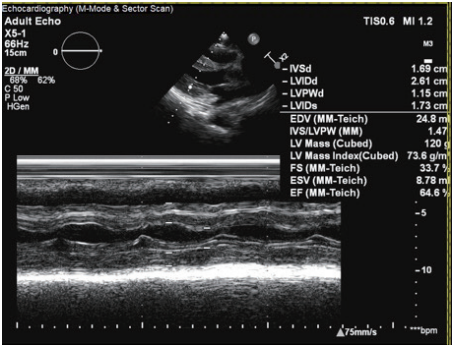
- **Old anterolateral myocardial infarction**
- **Borderline prolonged QTc**
- **First-degree AV block**
- **Sinus rhythm with supraventricular bigeminy**



Echocardiography

- **LVIDd 26 mm**
- **LVIDs 17 mm**
- **IVSd 16 mm**
- **LVPWd 14 mm**
- **LVEF 66 %**
- **LA 30 mm**



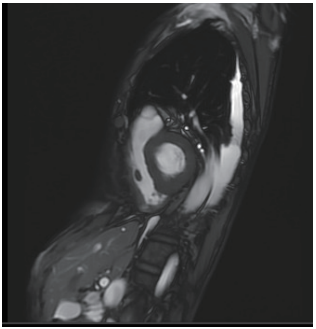


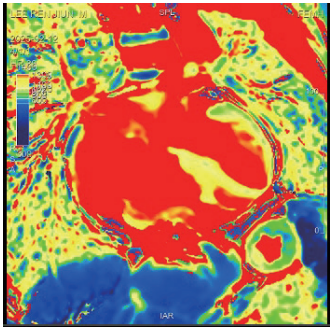
Typical Case 3

Raising Suspicion

CMR

- Marked **late gadolinium enhancement (LGE)** involving LV, RV, and RA: endocardial enhancement of LV; transmural enhancement of RV and RA.
- Relative sparing of LV basal and free wall with less enhancement.
- **Native T1 markedly elevated** (mean: 1,292 ms).
- **ECV significantly increased** (mean: 68%).
- LVEF 51.5 %





The elevated native T1 , enhances ECV and specific LGE pattern suggested CA.

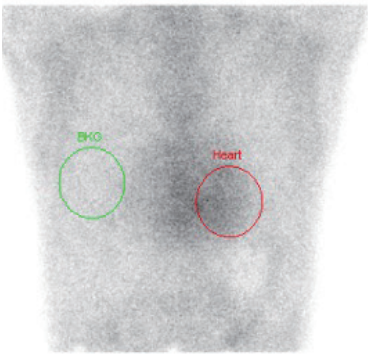
Testing for AL

Serum	Free kappa	16.3 mg/L
	Free lambda	16.4 mg/L
	Kappa/lambda ratio	0.994

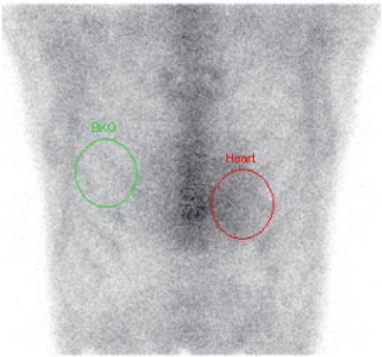
AL amyloidosis was ruled out.

Differential Diagnosis with ^{99m}Tc-PYP Scan

Planar Images



1-hour planar



3-hour planar

H/CL ratio at 1-hr is 2.22; at 3-hr is 1.80.

H/CL ratio interpretation

3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

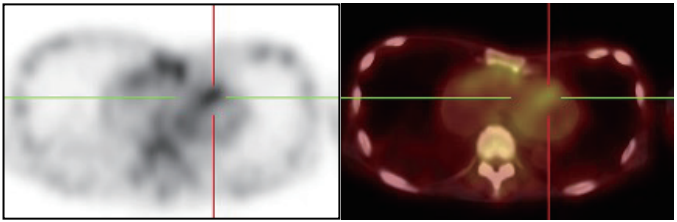
H/CL ratios < 1.3 are classified as ATTR-CM (+).

If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

Typical Case 3

Differential Diagnosis with ^{99m}Tc-PYP Scan & Biopsy

3-hr SPECT/CT Images



Visual grading = 2

Diffuse myocardial uptake with focal uptake in the septum and RV.

Visual intepretation

Visual scores ≥ 2 on planar or SPECT images are classified as ATTR-CM positive.

Grade 0: No myocardial uptake and normal bone uptake

Grade 1: Myocardial uptake < rib uptake

Grade 2: Myocardial uptake = rib uptake

Grade 3: Myocardial uptake > rib uptake

Diagnosis

CA by EMB:

Congo red stain demonstrates apple-green birefringence using polarized microscopy.

Differential Diagnosis with Biopsy

Key Messages

- ✓ EMB may be needed in equivocal cases or discordant data.
- ✓ Key recommendations emphasized: 3-hour acquisition (planar and SPECT/CT) and comprehensive interpretation integrating visual grading, H/CL ratios, and quantitative metrics.

to Take Away

Typical Case 4

Grade 3

Patient Profile

97 y/o Asian Male

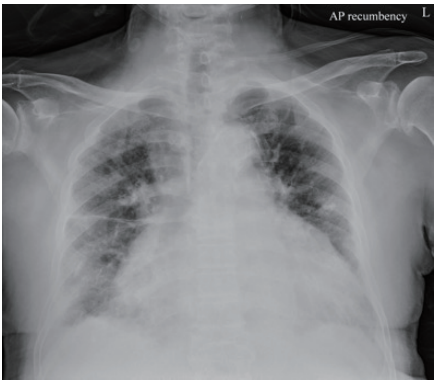
Present Illness

- Heart failure with mildly reduced ejection fraction (HFmrEF)
- Atrial fibrillation with repeated stroke.

Lab Data

Cardiac	NT-proBNP	3219 pg/ml
	hs-TnT	61.27 ng/L
Renal	BUN	20.0 mg/dL
	Creatinine	1.2 mg/dL
	Uric Acid	5.2 mg/dL
	eGFR	59.7 ml/min/1.73m^2
Hepatic	Albumin	4.1 g/dL
	ALT	23 U/L
Electrolytes	Na	138 mEq/L
	K	4.4 mEq/L
Inflammation	hsCRP	1.10 mg/dL

CXR

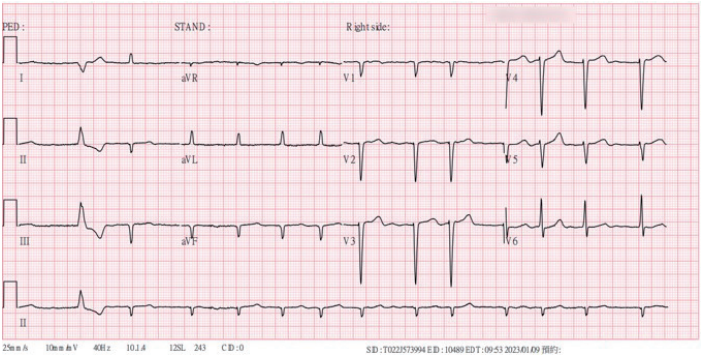


Typical Case 4

Raising Suspicion

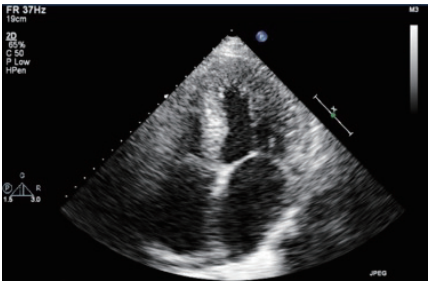
Electrocardiogram

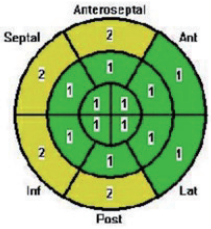
- **Atrial fibrillation**
- **Left axis deviation**
- **r/o, Inferior infarct and anterolateral infarct**



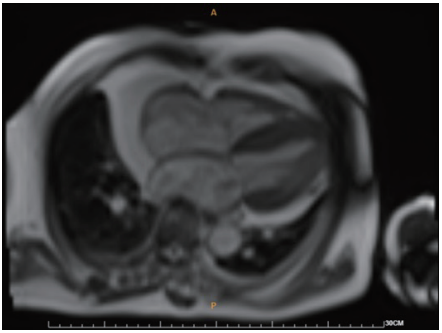
Echocardiography

- **IVSd 17 mm**
- **LVPWd 16 mm**
- **LVEF 42.9 %**
- **Regional wall motion abnormality over basal segments**





CMR



- Concentric LVH
- Large amount pericardial effusion

Differential Diagnosis

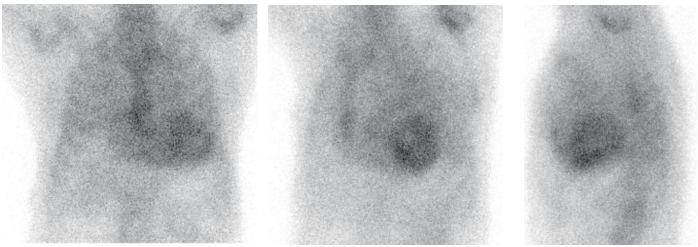
Testing for AL

Serum	Free kappa	34.78 mg/L
	Free lambda	22.65 mg/L
	Kappa/lambda ratio	1.536
	IFE	Shows no monoclonal gammopathy.
Urine	IFE	Shows no Bence Jones proteins.

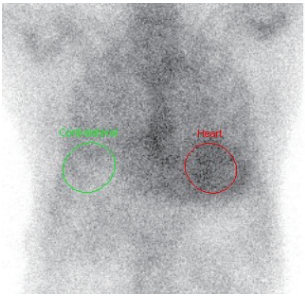
AL amyloidosis was ruled out.

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr Planar Images



Marked myocardial uptake greater than rib activity



H/CL ratio interpretation

3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

H/CL ratios < 1.3 are classified as ATTR-CM (+).

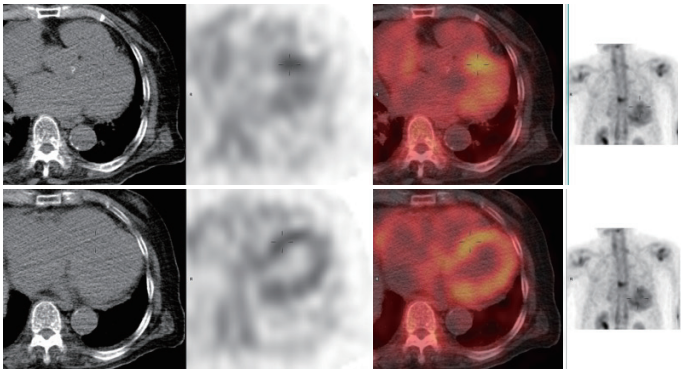
If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

H/CL ratio is 1.7089.

Typical Case 4

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr SPECT/CT Images



Visual grading = 3

SPECT/CT also showed diffuse myocardial uptake, greater than rib activity.

Visual intepretation
Visual scores ≥ 2 on planar or SPECT images are classified as ATTR-CM positive.
Grade 0: No myocardial uptake and normal bone uptake
Grade 1: Myocardial uptake < rib uptake
Grade 2: Myocardial uptake = rib uptake
Grade 3: Myocardial uptake > rib uptake

Differential Diagnosis with Biopsy

Diagnosis

ATTR-CM

Key Messages

✓ SPECT/CT can further confirm tracer localization in myocardium.

to Take Away

Special Case 1

Grade 1 - Sarcoidosis

Patient Profile

54 y/o Asian Male

Symptoms

- Persistent dyspnea on exertion despite medical treatment

Past History

- Complete atrioventricular block, s/p Permanent pacemaker (PPM).

Examination

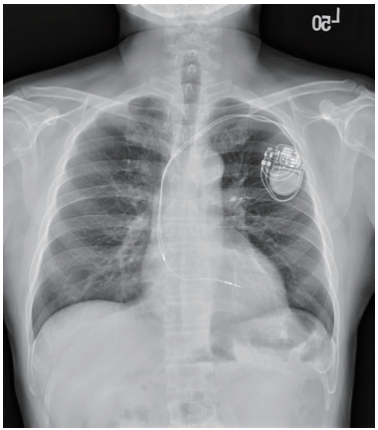
- Coronary angiography : patent arteries

Raising Suspicion

Lab Data

Cardiac	NT-proBNP	662 pg/ml
	hs-TnT	24.73 ng/L
Renal	BUN	24.4 mg/dL
	Creatinine	1.3 mg/dL
	Uric Acid	6.1 mg/dL
	eGFR	60.9 ml/min/1.73m^2
Hepatic	Albumin	4.1 g/dL
	ALT	23 U/L
Electrolytes	Na	144 mEq/L
	K	4.0 mEq/L
Inflammation	hsCRP	0.12 mg/dL

CXR

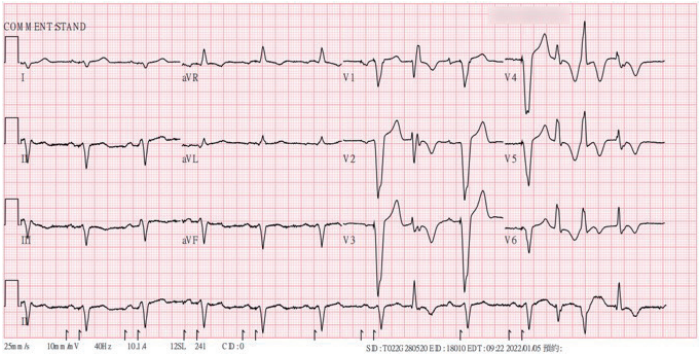


Special Case 1

Raising Suspicion

Electrocardiogram

Atrioventricular dual paced rhythm

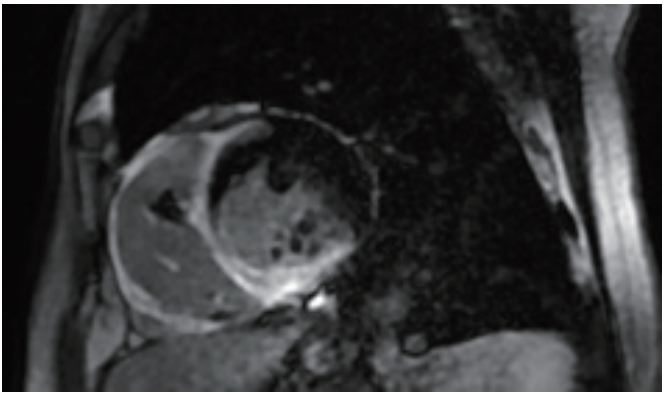


Echocardiography

- **IVSd 13 mm**
- **LVPWd 12 mm**
- **LVEF 43 %**
- **Apex and basal septal regional wall motion abnormality.**

CMR

- **Diffuse LGE**
- **Myocardial edema**
- **Elevated T1 value and ECV**



Diffuse LGE

Differential Diagnosis

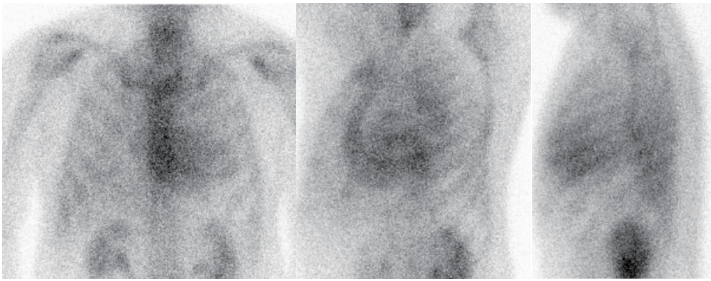
Testing for AL

Serum	Free kappa	15.34 mg/L
	Free lambda	16.89 mg/L
	Kappa/lambda ratio	0.908
	IFE	Serum IFE shows no monoclonal gammopathy.
Urine	IFE	Urine IFE shows no Bence Jones proteins.

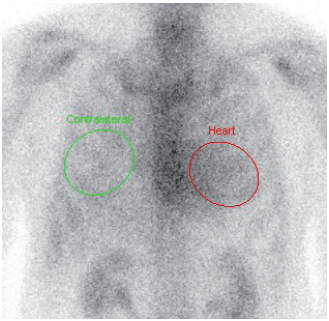
AL amyloidosis was ruled out.

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr Planar Images



Presence of cardiac activity, slightly less than rib activity



H/CL ratio interpretation

3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

H/CL ratios < 1.3 are classified as ATTR-CM (+).

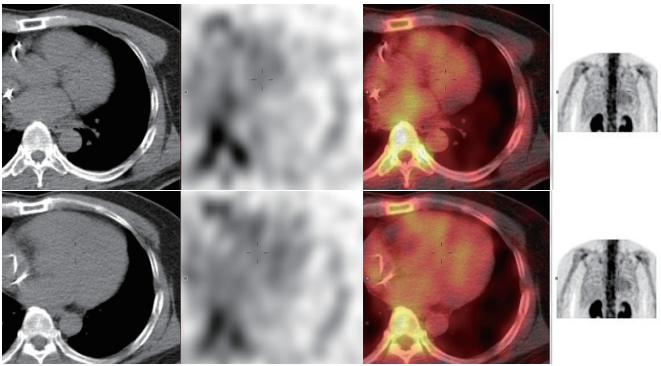
If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

H/CL ratio is 1.35.

Special Case 1

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr SPECT/CT Images



Visual grading = 1

Patchy myocardial uptake over apex, basal septum, basal inferior wall, generally less than rib activity.

Visual intepretation

Visual scores ≥ 2 on planar or SPECT images are classified as ATTR-CM positive.

Grade 0: No myocardial uptake and normal bone uptake

Grade 1: Myocardial uptake < rib uptake

Grade 2: Myocardial uptake = rib uptake

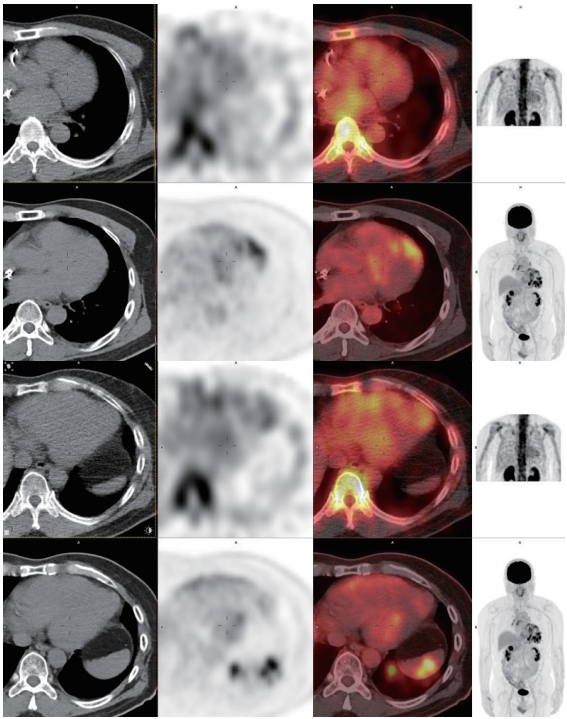
Grade 3: Myocardial uptake > rib uptake

Differential Diagnosis with Biopsy & ^{99m}Tc-PYP Scan

Diagnosis

EMB: Granulomatous inflammation, Acid-fast statin (AFS) negative
→ Cardiac sarcoidosis

Inflammation scan (lower row) showed inflammation at myocardium, spleen, and mediastinal nodes



Key Messages

- ✓ Planar images with SPECT/CT better separate myocardial uptake from blood pool activity.
- ✓ Patients with visual grade 1 require further work-up.

to Take Away

Patient Profile

60 y/o Asian Male

Symptoms

- Paroxysmal nocturnal dyspnea
- Orthopnea

Present Illness

- HFpEF with LVEF 58.2% (NYHA II)

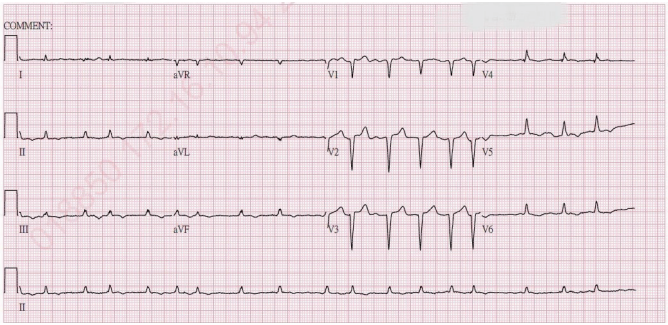
Raising Suspicion

Lab Data

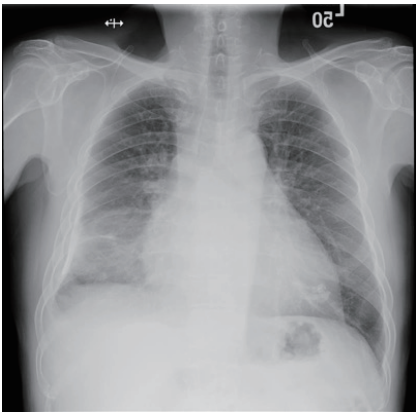
Cardiac	NT-proBNP	1375 pg/ml
Renal	BUN	22.7 mg/dL
	Creatinine	1.1 mg/dL
	Uric Acid	10.0 mg/dL
	eGFR	72.6 ml/min/1.73m^2
Hepatic	Albumin	3.5 g/dL
	ALT	21 U/L
Electrolytes	Na	139 mEq/L
	K	4.0 mEq/L
Inflammation	hsCRP	0.18 mg/dL

Electrocardiogram

- **R/o out Anteroseptal infarct**
- **AF with rapid ventricular response**
- **Low voltage QRS**



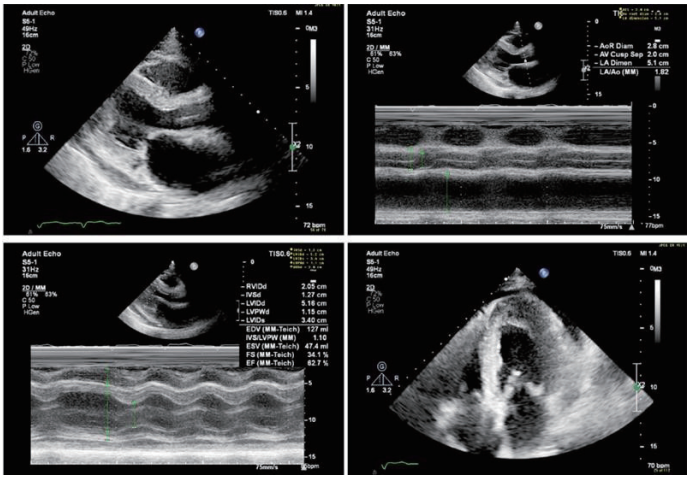
CXR



Raising Suspicion

Echocardiography

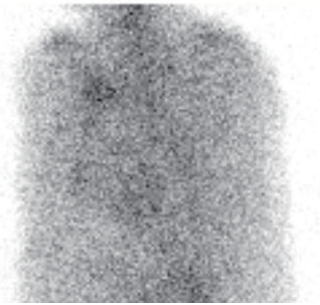
- **LVIDd 52 mm**
- **LVIDs 36 mm**
- **IVSd 12 mm**
- **LVPWd 12 mm**
- **LVEF 59.8 %**
- **LA 51 mm**
- **Pericardial effusion, moderate**
- **Mitral regurgitation and Tricuspid regurgitation, mild-moderate**



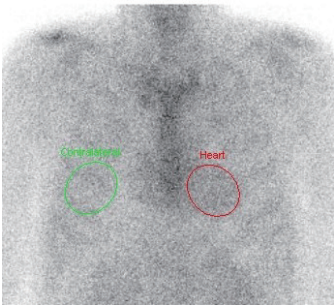
Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr Planar Images

60 degree



90 degree



H/CL ratio is 1.22

H/CL ratio interpretation

3-hour images:

H/CL ratios ≥ 1.3 are classified as ATTR-CM (+).

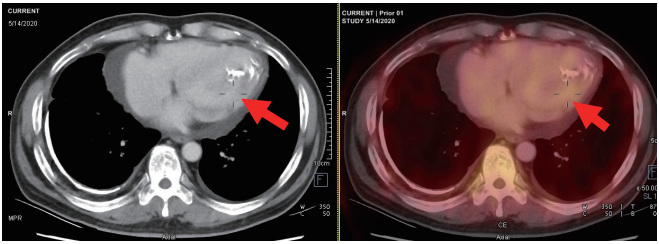
H/CL ratios < 1.3 are classified as ATTR-CM (+).

If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

Special Case 2

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr SPECT/CT Images



Visual grading = 2

Visual intepretation

Visual scores ≥ 2 on planar or SPECT images are classified as ATTR-CM positive.

Grade 0: No myocardial uptake and normal bone uptake

Grade 1: Myocardial uptake < rib uptake

Grade 2: Myocardial uptake = rib uptake

Grade 3: Myocardial uptake > rib uptake

Testing for AL

Serum	Free kappa	12.90 mg/L
	Free lambda	1120.00 mg/L
	Kappa/lambda ratio	0.0115
	IFE	Shows no monoclonal gammopathy.
Urine	Free kappa	13.00 mg/L
	Free lambda	768.00 mg/L
	Kappa/lambda ratio	0.0169
	IFE	Shows a very dense band of lambda light chain Bence Jones proteins.

Abnormal monoclonal proteins were demonstrated by urine immunoelectrophoresis, and light chain CA was subsequently impressed.

Diagnosis

Mixed myeloma and familial systemic AL amyloidosis , status post bone marrow biopsy proven.

Key Messages

✓ **AL-CA must be excluded** with laboratory screening in every patient with suspected CA (AL-CA can sometimes cause grade 2 or 3 uptake on PYP scan)

to Take Away

Special Case 3

Grade 3
Hyperphosphatemia-Related False-Positive

Patient Profile

30 y/o Asian Male

Present Illness

- ESRD, on peritoneal dialysis since age 22
- Hypertension documented concurrently with his ESRD, under medical treatment

Symptoms

- Exertional dyspnea for 2 months

Raising Suspicion

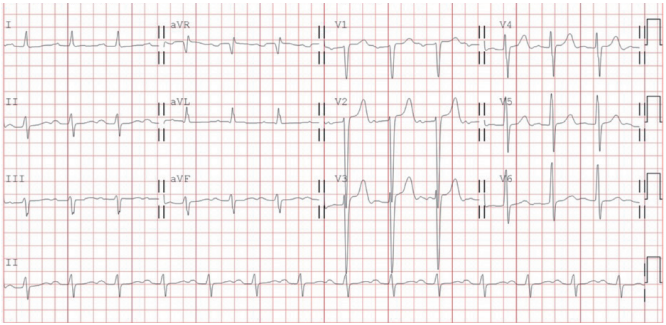
Lab Data

Vital Sign	HR	65 bpm
	BP	146/112 mmHg
Cardiac	NT-proBNP	429471.0 pg/ml
CBC	Hb	7.8 g/dL
	WBC	5,140/ul
	PLT	162,000/mm^3
Renal	BUN	87 mg/dL
	Creatinine	12.71 mg/dL
	Uric Acid	6.5 mg/dL
Electrolytes	Na	135 mEq/L
	K	4.38 mEq/L
	Ca	9.6 mg/dL
	Inorganic Phosphate	7.8 mmol/L
	iPTH	488 pg/ml

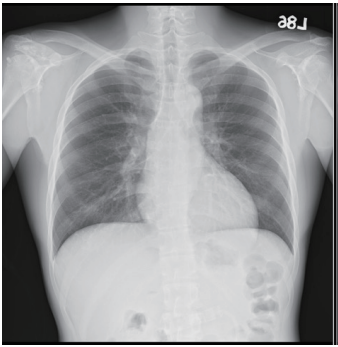
Findings reflect ESRD on long-term peritoneal dialysis with anemia, hyperphosphatemia, and secondary hyperparathyroidism managed by erythropoietin and calcium acetate.

Electrocardiogram

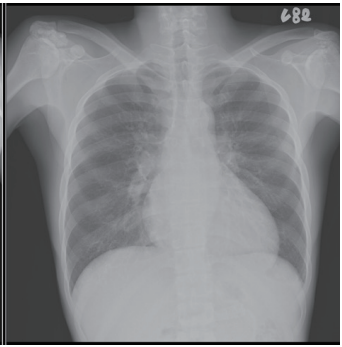
LVH and first-degree AV block



CXR



CXR obtained 4 years ago

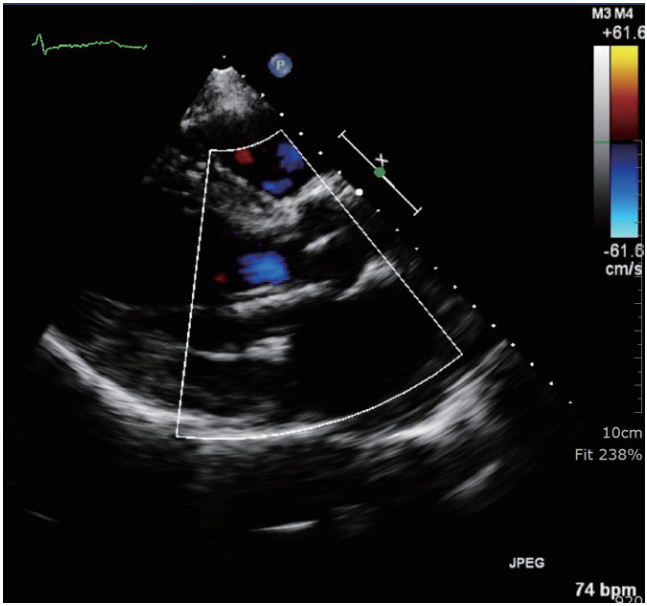


Current CXR:
Interval cardiomegaly is noted

Raising Suspicion

Echocardiography

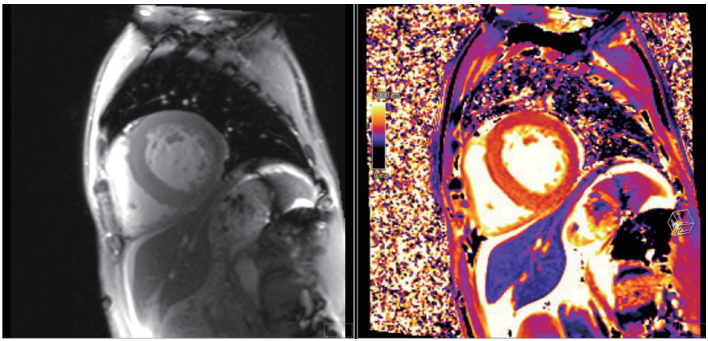
- **IVSd 18 mm**
- **LVEF 36 %**
- **Mild mitral annular calcification**
- **Minimal pericardial effusion**



Raising Suspicion

CMR

- **Moderate depressed LV systolic function.**
- **Dilated LV is noted with diffuse hypokinesis of LV.**
- **T1 mapping showed normal native T1 over left ventricle.**
- **LGE was not performed due to ESRD.**



Testing for AL

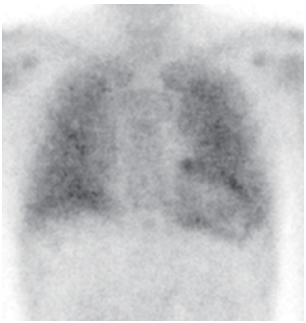
Serum	Free kappa	201.36 mg/L
	Free lambda	209.49 mg/L
	Kappa/lambda ratio	0.96
	IFE	Shows no monoclonal gammopathy.

AL amyloidosis was ruled out.

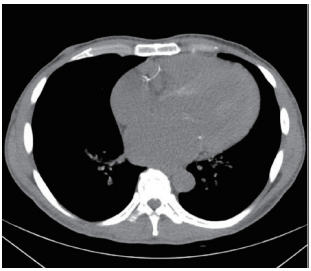
Special Case 3

Differential Diagnosis with ^{99m}Tc-PYP Scan

3-hr Planar Images



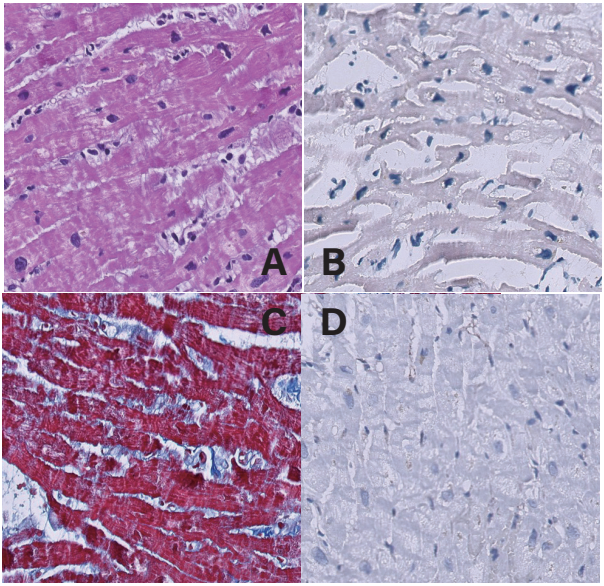
3-hr SPECT/CT Images



- **Myocardial uptake > rib (Perugini score 3)**
- **Hyperdense basal septum with intense uptake; diffuse lung uptake**
- **Clinical criteria met for ATTR-CM; TTR gene mutation negative**

Differential Diagnosis with Biopsy

EMB



RV endomyocardial biopsy performed

(A) H&E: hypertrophied cardiomyocytes, preserved structure

(B) Congo red: no amyloid (no apple-green birefringence)

(C) Masson's trichrome: no significant fibrosis

(D) Immunostaining: transthyretin negative

LVH was due to cardiomyocyte enlargement, not fibrotic remodeling or amyloid deposition.

Special Case 3

Documented False-Positive of PYP Scan

Documented False-positive Causes of Myocardial Scan with Bone Tracers for the Diagnosis of ATTR-CM :

- Acute myocardial infarction
- History of radiation therapy[1]
- Recent iron infusion [2]
- Cardioversion (DC shock) [3]
- Usage of cardiotoxicity drugs[4-5]
- Hyperphosphatemia[6]

The patient had no history of AMI and had never received radiotherapy, cardioversion, and he did not have recent iron infusion. All the drugs he took in the past years were just antihypertensive drugs and those common medications used in ESRD management; no drugs of cardiotoxicity had ever been used. The false-positive result of the PYP scan in this patient was most likely related to hyperphosphatemia related metastatic calcification myocardium.

Reference:

1. George O. Ajene, D. D., Christian A. Inchaustegui, Ajith Nair. ACC.23/WCC.
2. Lades, G., et al. J Nucl Cardiol **29: 2051-2052**.
3. Pugh, B. R., et al. Circulation **54: 399-403**.
4. Wakfie-Corieh, C. G., et al. Clin Nucl Med **46: e188-e189**.
5. Chang, I. C. Y., et al. Circ Cardiovasc Imaging **11: e007059**.
6. Enevoldsen, L. H., et al. Clin Physiol Funct Imaging **37: 131-136**.

Key Messages

- ✓ There should be an explainable reason in a false-positive PYP scan.
- ✓ Common causes of false-positive in a PYP scan include AMI, post-RT, recent iron-infusion, cardioversion, and drugs of cardiotoxicity. **Hyperphosphatemia** is a less commonly mentioned but important cause of false-positive PYP scan.
- ✓ EMB is important when clinical profile or examinations are inconsistent.

to Take Away

Standardized Reporting of ^{99m}Tc-PYP Scan for CA (1/3)

Standardized Reporting of ^{99m}Tc-PYP Scan for Cardiac Amyloidosis

Recommended items for cardiologists to submit with PYP scan requests

Reasons for Test

Lab Data findings :

NT-proBNP :_____pg/ml BNP :_____pg/ml
Troponin I :_____ng/ml Troponin T :_____ng/ml
BUN :_____mg/dl Creatinine :_____mg/dl eGFR :_____ ml/min/1.73m2
Others :_____

Echocardiography findings :

Increased LV wall thickness : Septum _____mm Posterior wall _____mm
LVEF :_____%
☐ Increased LV mass ☐ LV longitudinal strain pattern ☐ Mitral annular TDI <5 cm/s
☐ Biatrial enlargement ☐ Small A wave in sinus rhythm ☐ Pericardial and/or Pleural effusions

Cardiac MRI findings :

☐ Diffuse or global LGE pattern ☐ Significantly increased ECV ☐ Elevated Native T1 values
☐ Increased LV wall thickness ☐ Increased LV mass ☐ Pericardial and/or Pleural effusions

Other Reasons for Test :

☐ Abnormal ECG (e.g., Low QRS voltage, MI ...) ☐ Family history of FAP
☐ Others : _____

Standardized Reporting of ^{99m}Tc-PYP Scan for CA (2/3)

PYP Methods

Dose：_____ mCi Scan technique：☐ Planar ☐ SPECT ☐ SPECT/CT

Interval between injection and scan：_____ hour

PYP Findings

Image Quality：☐ Good ☐ Fair ☐ Poor

Visual Interpretation (Required)：

3-hr Visual Grade：☐ 0 ☐ 1 ☐ 2 ☐ 3 1-hr Visual Grade：☐ 0 ☐ 1 ☐ 2 ☐ 3

Pattern：☐ Diffuse ☐ Focal ☐ Others:_____

Comments：_____

Visual interpretation Definition：

- Evaluate for cardiac uptake on both planar and myocardial uptake on SPECT or SPECT/CT images.
- If SPECT images show radiotracer uptake in the myocardium, proceed with visual grading.
- In the absence of any myocardial tracer uptake on SPECT, assign a visual grade of 0.

Grade 0 = No myocardial uptake Grade 1 = Myocardial < rib uptake (mild)

Grade 2 = Myocardial ≈ rib uptake (moderate) Grade 3 = Myocardial > rib uptake (severe)

If the visual grading of planar and SPECT images is inconsistent, it is recommended to rely on the visual score obtained from the SPECT images.

Semi-Quantitative Findings (Optional; recommended for positive scans)：

H/CL Ratio：_____

3-hr：☐ <1.3 (Negative) ☐ ≥1.3 (Positive) 1-hr：☐ ≤1.5 (Negative) ☐ >1.5 (Positive)

If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is not recommended.

AL evaluation

☐ AL excluded ☐ AL cannot be excluded ☐ AL not yet evaluated

Causes of False Positives and False Negatives of PYP Scan in ATTR-CM Diagnosis

False Positives		
AL amyloidosis	Hydroxychloroquine cardiac toxicity	Blood pool activity
ApoAIV, Aβ2M amyloidosis	Recent myocardial infarction (<4 weeks)	
	Rib fractures and Valvular/Annular calcifications	
False Negatives		
Phe84Leu hATTR	Delayed or Premature acquisition	
Ser97Tyr hATTR	Early-stage disease progression	

Standardized Reporting of ^{99m}Tc-PYP Scan for CA (3/3)

PYP Imaging Impression

☐ Strongly suggestive of ATTR-CM (Visual grade 2 or 3)
☐ Not suggestive of ATTR-CM (Visual grade 0)
☐ Equivocal (Visual grade 1 or uncertain between grade 1 & 2)

Definitions

Strongly suggestive:

Diffuse myocardial uptake of ^{99m}Tc-PYP visually confirmed, with a visual grade of 2 or 3.

Not suggestive:

Visual grade of 0.

Equivocal:

Diffuse myocardial uptake of ^{99m}Tc-PYP visually confirmed, with a visual grade of 1, or interpretive uncertainty between grade 1 and grade 2.

Additional Recommendation：

☐ Hematology consult ☐ Repeat imaging ☐ Follow-up labs

若符合以下任一情況，建議進一步轉介血液科或類澱粉沉積症專家：

✓ 心臟超音波（Echo）或心臟磁振造影（Cardiac MRI）高度懷疑心臟類澱粉沉積症，但本次影像檢查結果為「不支持」或「不確定」。
✓ AL 檢測結果異常或無法排除。

評估結果應結合臨床表現與既往檢查，以利後續診斷與治療規劃。

Reporting Physician：_____

Date：_____

Clinical Laboratory Reference Ranges

Category	Test Item	Unit	Reference Range
Cardiac	NT-proBNP	pg/mL	<125 (non-acute), <300 (acute HF)
	hs-TnT	ng/L	<14
	Troponin I	ng/mL	<0.04
	CPK	U/L	30 – 223
	CK-MB	U/L	< 24
Renal	BUN	mg/dL	7 – 25
	Creatinine	mg/dL	0.6 – 1.3
	Uric Acid	mg/dL	Male: 4.4 – 7.6, Female: 2.3 – 6.6
	eGFR	mL/min/1.73m^2	≥ 90
Hepatic	Albumin	g/dL	3.5 – 5.7
	ALT	U/L	<41
Electrolytes	Na	mEq/L	136 – 145
	K	mEq/L	3.5 – 5.1
	Ca	mg/dL	8.6 – 10.2
	Inorganic P	mmol/L	2.5 – 4.5
Inflammation	hsCRP	mg/dL	< 0.3
CBC	Hb	g/dL	Male: 13.1 – 17.2, Female: 11.0 – 15.2
	WBC	/μL	3250 – 9160
	PLT	/mm^3	150,000–378,000
AL	Free kappa (serum)	mg/L	3.3–19.4
	Free lambda (serum)	mg/L	5.7–26.3
	Kappa/lambda ratio	—	0.26–1.65
	Free kappa (urine)	mg/L	< 32.9
	Free lambda (urine)	mg/L	< 3.79
Fabry	Alpha-GAL	μmol/hr	> 1.5

Source: National Taiwan University Hospital, Far Eastern Memorial Hospital, Taipei Veterans General Hospital

Acknowledgement

This pocket guide was collaboratively written and edited by five dedicated nuclear medicine specialists in Taiwan. With their collective expertise, this guide integrates clinical knowledge with practical case examples to support diagnostic decision-making in daily practice.

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These experts not only contributed to the organization of the content but also shared valuable clinical cases to aid in the diagnosis of cardiac amyloidosis. Their practical contributions are truly instrumental in helping clinicians navigate complex diagnostic scenarios.

MEMO

^{99m}Tc PYP Scan for Diagnosis of ATTR-CM