DIAGNOSING CARDIAC AMYLOIDOSIS USING ^{99M}TC-PYP AT DR. HASAN SADIKIN GENERAL HOSPITAL

Andi M. Iqbal[1]*, Erwin A Soeriadi[2], Achmad Hussein S Kartamihardja[3]
[1-3]Department of Nuclear Medicine and Molecular Theragnostic Dr. Hasan Sadikin General Hospital/Faculty of Medicine Universitas Padjadjaran Indonesia
Email: andiiqbalyusran@yahoo.com

ABSTRACT
Amyloidosis is an infiltrative disease characterized by the deposition of abnormal fibril proteins in various tissues and organ systems, including the heart. Cardiac amyloidosis is a very rare disease. The diagnosis of amyloidosis is highly dependent on the suspicion of a clinician. This disease is often asymptomatic until eventually advanced which will give symptoms and symptoms can vary widely. As a result, the patient's diagnosis is often delayed. Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when ^{99m}Tc-PYP scintigraphy shows Grade 2 or 3 myocardial uptake of Radiotracer. Once cardiac ATTR amyloidosis is confirmed, genetic counselling and testing should be performed to assess for the presence of TTR mutations in order to differentiate between ATTRwt and ATTRv. Genetic testing should be performed even in elderly patients, as a significant number can have TTR mutations. ^{99m}Tc-PYP can differentiate between CA types and specific for ATTR types. Imaging modalities other than nuclear imaging, cannot differentiate the types of amyloidosis

Keywords : Cardiac amyloidosis, ^{99m}Tc-PYP, Light Chain-Associated Amyloid (AL), Transthyretin-related Amyloidosis (ATTR)

INTRODUCTION
Cardiac amyloidosis is a disease that is rarely diagnosed in heart failure patients with a preserved ejection fraction which is often associated with high morbidity and mortality. The diagnosis of cardiac amyloidosis can be very challenging because the disease can mimic other heart conditions (such as hypertrophic cardiomyopathy, hypertensive heart disease) that are common in adults.[1] Cardiac amyloidosis is generally divided into two categories: Immunoglobulin Light Chain-Associated Amyloid (AL) and Amyloidosis. Transthyretin-related (ATTR). Clinical manifestations (progressive heart failure, sometimes accompanied by cardiac arrhythmias and chest pain) as well as from cardiac imaging are sometimes very difficult to distinguish between the two types. However, differentiating the type of cardiac amyloidosis is crucial, because the management and prognosis of the two types (AL and ATTR) differ greatly.[2]

One of the non-invasive examination modalities that can provide additional information in patients with suspected cardiac amyloidosis is scintigraphy examination in nuclear medicine, namely examination using ^{99m}Tc-Pyrophosphate (^{99m}Tc-PYP). This examination can provide an earlier diagnosis compared to echocardiography and CMR (cardiac magnetic resonance), better diagnostic

accuracy than CMR, and the ability to measure amyloid deposition, distinguish types between cardiac amyloid and provide prognostic information. Cardiac or chest SPECT and planar images are obtained one hour after injection of ^{99m}Tc-PYP. If persistent blood pool activity is noted on one hour images, delayed images may be obtained at 3 hours. Planar imaging is rapid, simple to perform, and useful for visual interpretation and quantification of the degree of myocardial uptake (see image interpretation) by heart to lung ratio or comparison to rib uptake. Whole body planar imaging may be helpful to identify uptake of ^{99m}Tc-PYP in the shoulder and hip girdles (a specific sign of systemic ATTR amyloidosis) and should be considered adjunctive and optional in addition to standard cardiac-centered imaging, based on local expertize.[3]

CASE REPORT

Case I

A 63-year-old man complains of shortness of breath, shortness of breath that worsens with activity and improves at rest. The patient complains of getting tired quickly when doing activities. The patient complained of swelling of the right and left limbs. Complaints accompanied by dizziness and feeling dizzy. Blood pressure, heart rate, and respiration rate were 130/80 mmHg, 82 beats/min, and 24 times/min, respectively. Echocardiography showed EF 52%, concentric remodelling with biatrial enlargement, normal LV systolic function with global normokinetic at rest, LVEF 52%. Mild MR, moderate TR, Intermediate probability of PH, PR, diastolic dysfunction, normal RV contractility. Minimal circumferential pericardial effusion. The patient was referred to Nuclear Medicine Department for cardiac radionuclide imaging. Conclusion of the examination results: Based on the 2019 ASNC criteria, this equivocal picture shows a Light Chain type Amyloidosis.

Case II

A 39-year-old female complains of shortness of breath, history of frequent syncope, heart rhythm disorders shortness of breath. Blood pressure, heart rate, and respiration rate were 140/90 mmHg, 80 beats/min, and 22 times/min, respectively. Echocardiography showed LV hypertrophy, moderate mR, mild TR, Pericardial effusion 1.2 cm on lateral LV and superior Additional examination performed is a biopsy examination which showed Idiopatic Hypertrophic Cardiomyopathy with diferntial diagnosis are infiltrative cardiacmyopathics e.c suspect with amyloidosis. Histochemistry (congo red stain) result is negative. The patient was referred to Nuclear Medicine Department for cardiac radionuclide imaging. Conclusion of the examination results: Based on the 2019 ASNC criteria, this picture is not typical (equivocal) for an ATTR amyloidosis. Areas that do not showed the radioactivity around the heart indicate a pericardial effusion.

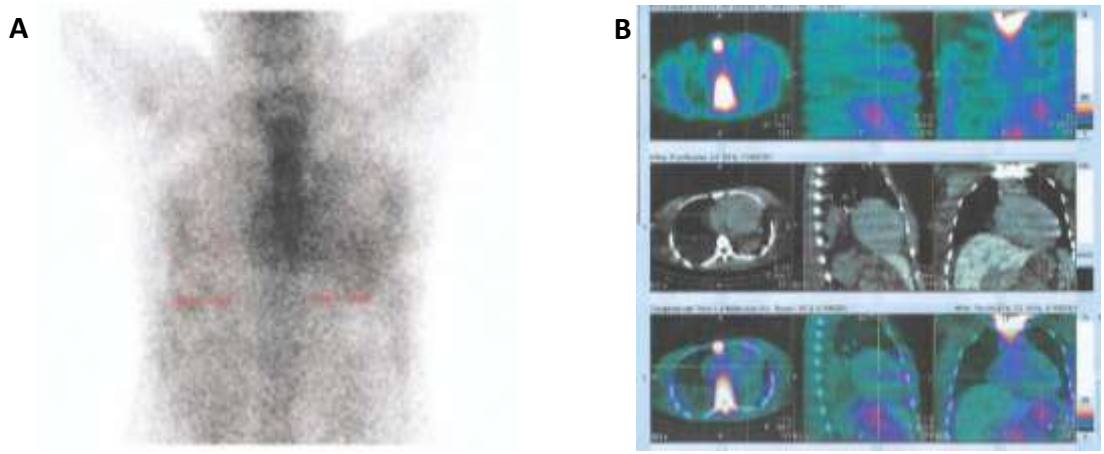

Figure 1 (**Case I)** Cardiac Radionuclide Imaging 1-Hour and 3-Hour Post Radiopharmaceutical Injection

A. Calculation of the ratio of Heart and Contralateral Lung on planar imaging 1 hour after injection of ^{99m}Tc-Pyrophosphate. H/CL ratio:1.28

B. SPECT imaging results at 3 hours post injection of ^{99m}Tc-Pyrophosphate show no radioactivity on cardiac projection.

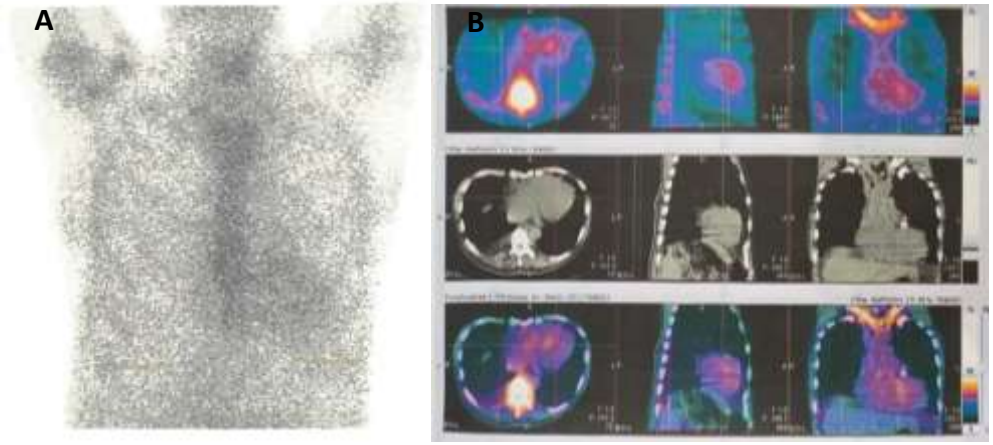

Figure 2 (**Case II)** Cardiac Radionuclide Imaging 1-Hour and 3-Hour Post Radiopharmaceutical Injection

A. Calculation of the ratio of Heart and Contralateral Lung on planar imaging 1 hour after injection of ^{99m}Tc-Pyrophosphate. H/CL ratio:1.33

B. SPECT imaging results at 3 hours post injection of ^{99m}Tc-Pyrophosphate shows diffuse radioactivity.

Case III

A 71-year-old man complains of shortness of breath, chest pain, tired easily. Blood pressure, heart rate, and respiration rate were 130/90 mmHg, 84 beats/min, and 24 times/min, respectively. Echocardiography showed LV GLS average -12.5% with apical, LV sparring pattern, RV free wall GLS -21%. Additional tests performed were CMR with suspicious results of cardiac amyloidosis. The patient was referred to Nuclear Medicine Department for cardiac radionuclide imaging. Conclusion of examination results: Based on the 2019 ASNC criteria, this picture is very supportive for a TTR amyloidosis. Areas that do not capture radioactivity around the heart indicate a pericardial effusion

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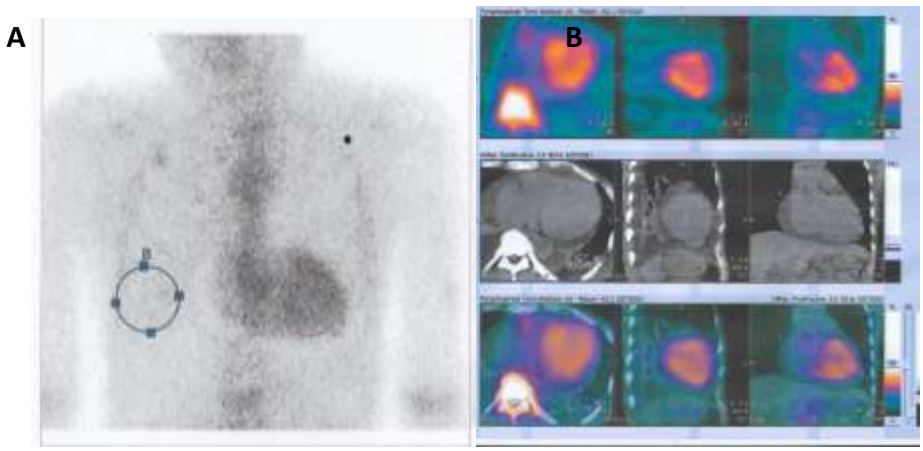

Figure 3 (Case III) Cardiac Radionuclide Imaging 1-Hour and 3-Hour Post Radiopharmaceutical Injection

A. Calculation of the ratio of Heart and Contralateral Lung on planar imaging 1 hour after injection of 99mTc Pyrophosphate. H/CL ratio:2.02

B. SPECT imaging results at 3 hours post injection of 99mTc Pyrophosphate show no radioactivity on cardiac projection.

Amyloidosis *light chain* (AL)

AL Amyloidosis is a disease of the bone marrow. A specific cell in the bone marrow, the plasma cell, normally produces proteins (antibodies) that help the immune system fight an infection. In AL amyloidosis, plasma cells do not function properly. These plasma cells produce abnormal amounts of antibody-producing proteins (light chains). This protein circulates in the blood and undergoes breakdown to form a buildup of amyloid deposits in various body tissues.[5]

AL amyloidosis is often associated with B-cell lymphoproliferative disorders and multiple myeloma-dyscrasias in plasma cells and occasionally occurs in malignant lymphoma and macroglobulinemia. Multiple myeloma along with AL amyloidosis occurs in up to 10-15% of cases and has a worse prognosis.[6] Apart from the heart, the kidney is the organ that often has symptoms, namely 74% apart from the liver 27%, peripheral nerves 22% and autonomic nerves 22%.[6] It is very important to

diagnose AL cardiac amyloidosis early because in addition to life-threatening disease, patients with cardiac involvement are more likely to have rapid disease progression.[2] The prognosis for AL is usually worse than with ATTR. [5,6]

***Amyloid transthyretin* (ATTR) amyloidosis**

Amyloid transthyretin (ATTR) amyloidosis is a disease caused by the presence of a precursor protein known as transthyretin (TTR), a serum transport protein in thyroid hormone and retinol which is mainly synthesized by the liver. ATTR amyloidosis is divided into two, namely wild-type (ATTRwt) and hereditary (ATTRv) which comes from genetic changes in the TTR gene.[9] ATTRwt can also be called senile systemic amyloidosis and ATTRv can also be known as mutant TTR (mTTR/ATTRm) or familial amyloid cardiomyopathy (FAC).[7,8]

Clinical symptoms usually occur in middle age or old age with a male to female presentation of 50:50. The main symptom of the mTTR mutation is generally cardiac and/or nervous system involvement. Manifestations from other organs are very rare, the presence of carpal tunnel syndrome is an early sign of this disease. Neuropathy is commonly seen as a sensory-motor and/or autonomic disturbance. Although cardiomyopathy is generally very severe prior to the presence of heart failure, it is very difficult to diagnose if the main symptom is neuropathy and echocardiography is not performed.[6] However, the age of onset and the appearance of clinical manifestations of this amyloidosis may vary among people with a mutated TTR.[9]

In senile systemic amyloidosis or wild type (ATTRwt) the transformation of 127-amino-amino acid protein to amyloid is stimulated by an unknown mechanism associated with the aging process.[3,13] ATTRwt is dominated by older people (especially those over 65 years of age) and in adult males.[6,14] ATTR amyloidosis may not be as rare as previously believed. In a recent study, wtTTR amyloidosis was detected in 13.3% of patients aged 60 years or older with heart failure with preserved ejection fraction (HFpEF) and LVH (≥12 mm). Amyloid deposits in wtTTR are generally found in the heart, although they can also be found in the gastrointestinal tract, liver, spleen, bone marrow, tongue and endocrine glands. Therefore, the presence of symptoms of congestive heart failure is always supported by a positive result on endomyocardial biopsy. [10,11]

DISCUSSION

Amyloidosis is a term for various groups of diseases in which the extracellular accumulation of insoluble protein fibrils (amyloid) infiltrates various tissues, resulting in organ dysfunction. This disease can be systemic or local.[5] Cardiac amyloidosis can be distributed in various anatomical tissues such as the atria, ventricles or perivascular spaces such as

valves or the conduction system in some cases.[6] Cardiac amyloidosis is generally classified as restrictive cardiomyopathy because of its pathophysiology.[7] Cardiac amyloidosis is a disease of the myocardium characterized by extracellular amyloid infiltration in the heart. This infiltration process results in thickening of the biventricular wall with concentric remodeling of the ventricles and results in decreased cardiac output. Increased pressure in the atria is associated with atrial dilatation. The intramyocardial vessels are often also infiltrated by amyloid, causing decreased myocardial perfusion. The conduction system may also be impaired, with atrial arrhythmias (fibrillation, flutter or atrial tachycardia) and atrioventricular delays frequently occurring. Ventricular arrhythmias may also occur, although prolonged ventricular tachycardia is rare.[8,16]

In recent years, researchers have focused on the use of nuclear medicine imaging in the detection of cardiac amyloidosis. Planar imaging alone or in conjunction with SPECT with non-specific amyloid pharmacokinetics, namely radiopharmaceuticals in bone fingerprint imaging (^{99m}Tc-DPD [3,3-diphosphono-1,2-propanodicarboxylic acid], ^{99m}Tc-MDP [methylene diphosphonate], ^{99m}Tc-HMDP [hydroxymethylene diphosphonate]], and ^{99m}Tc-PYP [pyrophosphate]) have been shown to be more effective in detecting myocardial TTR deposits. Amyloid-specific pharmacokinetics with the use of 18F- and 11C- positrons on PET imaging have been known to identify both AL and ATTR.[12,13]

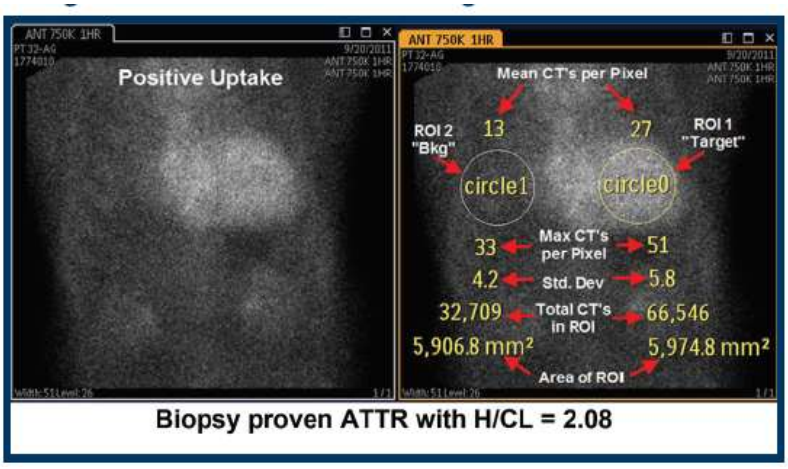

Figure 4. Quantitative assessment with H/C ratio.[20]

Based on ASNC criteria, interpretation of images can be done quantitatively or semi-quantitatively. The first quantitative method uses the heart to contralateral lung uptake ratio on planar image 1-hour post tracer injection. A positive result for ATTR amyloidosis is a heart to contralateral lung uptake ratio ≥ 1,5. The semi-quantitative method uses a visual score, which compares the tracer uptake between the myocardial and the rib. Visual score 0 is interpreted as absent of heart

uptake, visual score 1 as heart uptake less than ribs, visual score 2 as heart uptake similar to ribs, and visual score 3 as heart uptake higher than ribs. ATTR amyloidosis is positive if the tracer uptake of the heart is equal to the rib (visual score ≥ 2).[14,15]

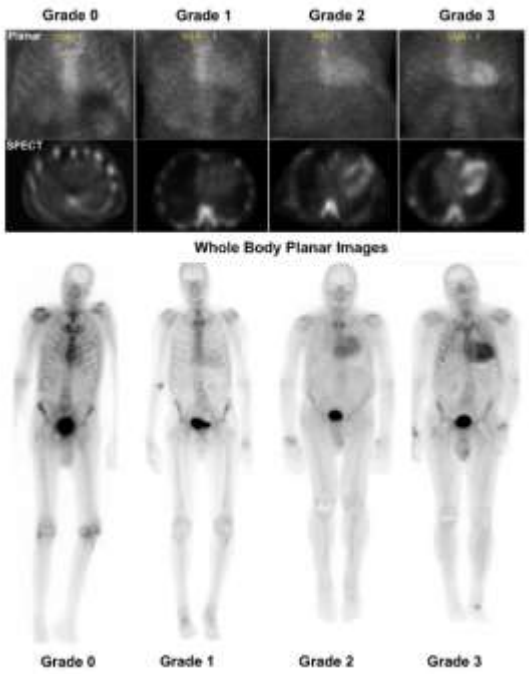

Figure 5. ^{99m} Tc-PYP capture on planar and SPECT imaging.[9,20]

Gillmore et al suggested that sensitivity could be >99% for ATTR in the presence of radioactivity capture, but specificity could be 68% due to low capture in some patients with AL amyloidosis. Specificity will increase to 97% only with high degree of radioactivity capture (Perugini score 2-3). In addition, high-grade arrest accompanied by a “triple negative” test (serum and urine immunofixation with serum free light chain) can achieve 100% specificity, thereby reducing the need for biopsy. [18,19]

With good sensitivity and specificity, this quantitative assessment of imaging also provides prognostic value. High retention of the myocardium can be associated with major cardiac events, acute heart failure and high mortality17 as well as rates of hospitalization for heart failure. ^{99m}TC-PYP imaging with a high H/CL ratio in cardiac amyloidosis ATTR is associated with lower survival rates.[20]

CONCLUSION

Amyloidosis fingerprinting using ^{99m}Tc PYP can differentiate cardiac ATTR from other types. Amyloidosis fingerprints using ^{99m}Tc PYP cannot be used to diagnose light chain type amyloid. Need a larger sample size to assess the diagnostic performance of ^{99m}Tc PYP in determining cardiac amyloidosis-TTR.

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