CASE REPORT

A challenging road to diagnosing transthyretin cardiac amyloidosis and using technetium-99m pyrophosphate bone scintigraphy in nuclear cardiology - A case report

Kavita Arumugam, MBBS[1,3], Muhammad Adib Abdul Onny, MMed[1], Subapriya Suppiah, MMed (Radiology)[1,2], Andik Fadilah Abdul Aziz, MMed[1], Hazlin Hashim, MMed[3], Raja Ezman Raja Shariff, MRCP[4], Chen Siew Ng, MRCP[1]

[1]Department of Nuclear Medicine, Institut Kanser Negara, Kementerian Kesihatan Malaysia, W.P. Putrajaya, Malaysia, [2]Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [3]Advanced Medical & Dental Institute, Universiti Sains Malaysia, Bertam, Kepala Batas, Pulau Pinang, Malaysia, [4]Department of Medicine, Faculty of Medicine, Universiti Teknologi Mara (UiTM) Sungai Buloh, Sungai Buloh, Selangor, Malaysia

SUMMARY

Cardiac amyloidosis (CA) is a rare form of protein deposition disease, leading to restrictive cardiomyopathy that often presents with signs and symptoms of unexplained heart failure with preserved ejection fraction (HFpEF). There are two main subtypes of CA, namely light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), which are conventionally confirmed by endomyocardial biopsy (EMB). The prognosis and treatment of the subtypes differ extensively, making it crucial to distinguish between the two. Although echocardiography (ECHO) and cardiac magnetic resonance imaging (CMR) are useful to aid in the diagnosis, they are unable to differentiate between the subtypes. Advantageously, the transthyretin cardiac amyloidosis (ATTR-CA) subtype can be diagnosed based on nuclear medicine bone scintigraphy imaging using Technetium-labelled bone-seeking radiotracers. We report a case of a previously well, elderly gentleman who presented with acute heart failure symptoms, whereby ECHO findings were suspicious for CA. Technetium-99m pyrophosphate (^{99m}Tc-PYP) bone scintigraphy performed with complementary single photon emission computed tomography/computed tomography (SPECT/CT) at three hours post-injection revealed radiotracer uptake in the myocardium that was higher than the skeletal bone uptake. This corresponded to Perugini score of 3 along with an increased heart to contralateral lung ratio (H:CL) of 1.69. The bone scintigraphy findings together with his symptoms, ECHO, CMR, and laboratory results enabled the diagnosis of ATTR-CA to be made. In summary, bone scintigraphy offers a reliable and non-invasive method for the diagnosis of ATTR-CA. We also highlight the diagnostic pitfalls and recommendations in reporting bone scintigraphy for the indication of typing cardiac amyloidosis.

INTRODUCTION

Cardiac amyloidosis (CA) is a rare condition that occurs when there is deposition of misfolded proteins that bind together to form amyloid fibrils in the myocardium.[1] CA is a part of a localised or systemic deposition of amyloid proteins that manifests as a rapidly progressive infiltrative, restrictive cardiomyopathy, which eventually leads to cardiac failure. CA can be further divided into light chain amyloidosis (AL) and the transthyretin amyloidosis (ATTR) subtypes. The cardiac amyloidosis of the ATTR subtype (ATTR-CA) if left untreated, can lead to death within 3-5 years from diagnosis, whereas the AL subtypes has a poorer prognosis with life expectancy of less than 6 months due to its direct toxicity to the cardiomyocytes.[2] The ATTR-CA can be further divided into the i) hereditary or familial autosomal dominant mutant type (ATTRm), whereas the age-related protein misfolding that occurs in the elderly above 65 years old, which was previously termed as senile CA, is known as the ii) wild type ATTR (ATTRwt).[1,2] The CA subtypes all eventually lead to heart failure with preserved ejection fracture (HFpEF), and patients often present with progressive fatigue, reduced effort tolerance, shortness of breath on exertion, and peripheral oedema.[3] In light of emerging treatment for ATTR-CA such as the FDA approved drug Tagamidis, which is a TTR protein stabilizer, there is a pressing need to distinguish between the two subtypes of CA.[4]

The gold standard for diagnosing CA is by performing endomyocardial biopsy (EMB). This procedure is invasive and carries a low but consequential risk of cardiac perforation.[5] Congo red dye viewed under polarized light or sulphated Alcian blue dye used to stain the biopsied specimen will give an apple-green birefringent appearance that is confirmatory for amyloidosis.[1] Currently, EMB is reserved for equivocal cases having discordant clinical and imaging findings. This is because there is a growing body of evidence regarding the role of i) transthoracic echocardiography (ECHO) with or without cardiac magnetic resonance imaging (CMR) having features suspicious of CA, in combination of results from ii) serum and urine electrophoresis (SEP and UEP, respectively) and immunofixation to detect light chain immunoglobulins pointing to a diagnosis of AL as well as iii) serum light chain assays to detect the presence of clonal plasma cells, together with iv) bone scintigraphy using Technetium-labelled bone-seeking radiotracers, for making the diagnosis and detecting the type of CA, which can obviate the need to perform EMB.[6] The elevation of cardiac enzymes and HF biomarkers, such as Troponin T and N-terminal prohormone of brain natriuretic

This article was accepted: 25 July 2021
Corresponding Author: Associate Professor Dr. Subapriya Suppiah
Email: subapriya@upm.edu.my

peptide (NT-proBNP) that are highly disproportionate to the degree of severity of HF symptoms may also point to a suspicion of ATTR-CA. Hence, the contemporary diagnosis of ATTR-CA is made from a high clinical index of suspicion based on the age of the patients, the presence of congestive heart failure and unexplained left ventricular wall thickening, the absence of light chain proteins on SEP and UEP, and a positive Technetium-labelled bone scintigraphy. Technetium-labelled bone scintigraphy, particularly using Technetium-99m pyrophosphate (^{99m}Tc-PYP) can aid in the non-invasive diagnosis of cardiac ATTR. This technique, used for a relatively rare condition, requires proper training for accurate interpretation and is not without pitfalls and limitations.

We report a rare case of an elderly Malay gentleman with acute heart failure and unexplained left ventricular hypertrophy, who had benefited from a bone scintigraphy at our nuclear medicine department at Institut Kanser Negara, Malaysia. Based on our imaging findings, we were able to make an early diagnosis of ATTR-CA. To the best of our knowledge, this is the first report in Malaysia that highlights the diagnostic pitfalls and recommendations in reporting bone scintigraphy for the indication of typing ATTR-CA.

CASE REPORT

An 81-year-old Malay gentleman was diagnosed with acute decompensated congestive heart failure (HF) at Institut Kanser Negara, Malaysia. He presented with reduced effort tolerance, shortness of breath on exertion, and bilateral upper and lower limbs oedema, for one month duration. He denied angina symptoms and his overall performance was categorized as NYHA Class II-III. The patient was an ex-chronic smoker (25 pack years) with no other underlying medical conditions. His blood pressure was within the normal range and cardiovascular system examination did not reveal any murmur. Plain radiograph of the chest showed evidence of left-sided pleural effusion and an apparent cardiomegaly. Electrocardiography (ECG) showed atrial arrhythmia with variable atrioventricular (AV) dissociation and broad QRS complexes suggestive of intraventricular conduction defect and bi-fascicular block. There was also low voltage ECG as evidenced by peak-to-peak QRS complex of <5 mm in the limb leads. There was, however, no evidence of acute ischaemic changes on ECG. ECHO revealed speckled, heterogeneously echogenic ('starry-sky' appearance) and thickened right and left ventricular walls, as well as dilated atria, with associated left-sided pleural effusion (Figure 1a). Tissue Doppler imaging (TDI) over the mitral annulus region demonstrated diastolic dysfunction as evidenced by restrictive filling pattern (Figure 1b). Reduced medial and lateral velocities were noted at this region, 0.02 cm/s and 0.03 cm/s, respectively (normal range early diastolic mitral tissue Doppler velocity is > 0.06 cm/s). The ejection fraction was relatively preserved i.e., 65%. In view of his elderly age, and ECHO features of HFpEF that was unexplained due to a lack of comorbid illness, the patient was suspected to have an infiltrative type of cardiomyopathy such as CA. A coronary angiogram done for this patient excluded the likelihood of atherosclerotic coronary artery disease. Biomarkers for cardiac ischaemia and heart failure were also investigated. The high-specificity Troponin T level was 78 mmol/L (normal range: < 14 mmol/L), and the NT-proBNP level was 2400 pg/mL (normal range: <450 pg/mL for age 75 years and above). Concurrently, serum and urine samples were sent for SEP and UEP, as well as serum assay for free light chain proteins, which all returned as negative. Thus, this made the diagnosis of AL type of CA unlikely.

Subsequently, CMR was performed for further assessment of infiltrative cardiac disease. Standard cine images using the steady state free precession cine sequence in (a) horizontal long axis, (b) vertical long axis and (c) short axis (SA) views that revealed thickened LV and RV myocardial walls (white arrows), bilateral atria dilatation, and a small left-sided pleural effusion (red star) (Figure 1 c, d, e). Then T1-mapping using the shortened Modified Look-Locker Inversion Recovery (shMOLLI) technique was performed. Axial T1 scouts in a single breath hold using double inversion recovery were performed to generate the dark blood sequence. The T1 maps of the basal, midventricular, and apical SA slices were performed at rest. Viability study using gadolinium contrast was done to look for late gadolinium enhancement (LGE) pattern, which is indicative of cardiac myocardial infiltration or ischemia, i.e., myocardial scarring. There was evidence of LGE at several foci of the myocardium in a subendocardial and transmural distribution (Figure 1 g). The T1-mapping revealed thickened LV myocardium and increased extracellular volume (ECV) (Figure 1 g). Furthermore, on the time inversion T1 scout images, there were foci of 'reverse nulling' pattern noted in the myocardium, i.e., the presence of low signal intensity nulling patterns that occurred before the onset of the dark blood pool, which was characteristic of CA (Figure 1 g).

Following these conventional cardiac imaging findings, the patient was referred to our nuclear medicine department for differentiation of the subtypes of CA, as there was a high index of clinical suspicion of the diagnosis of ATTR-CA. Bone scintigraphy was performed using ^{99m}Tc-PYP, based on the recommended protocol by Dorbala et al..[1] Planar imaging of the thorax in anterior, posterior, left anterior oblique (LAO) and left lateral views were performed at one hour post injection (p.i) using a ^{99m}Tc-PYP radiotracer dose of 15.67 mCi. The same static views were then repeated three hours p.i. A complementary single photon emission computed tomography/computed tomography (SPECT/CT) of the thorax was also performed to increase the accuracy of anatomical localization of the heart. Planar anterior and posterior views of the whole-body were also performed at 3 hours p.i.

At one-hour p.i. imaging, the planar images were reviewed. There was an abnormally increased radiotracer uptake at the lateral aspect of the left hemithorax in the region of the heart (H). Then a circular-shaped region of interest (ROI) was placed over the (H) region with similar ROI placed at the contralateral lung (CL) to yield the heart to contralateral lung (H:CL) ratio. The H:CL ratio was 1.69 (normal ratio is expected to be <1.5) (Figure 2 a). which gave a quantitative assessment that was highly indicative of ATTR-CA. Moreover, the whole-body scan at three hours p.i demonstrated that there was scoliosis noted in thoracolumbar spine along with

Table I: Multimodal imaging characteristics for making the diagnosis of cardiac amyloidosis

Imaging Modality	Echocardiography	CMR	^{99m}Tc-labelled bone scan
Characteristic features	• increased RV and LV wall thickness • heterogeneous echogenicity / speckled appearance of myocardium ('starry sky' appearance) • reduced LV cavity size • TDI: reduced myocardial relaxation velocities at the mitral annulus • Impaired global longitudinal strain (LS) showing reduced global strain with sparing of the apex ('cherry on top' appearance on the Bull's eye plot) or Apical/ mid-basal LS ratio that is > 1.0 • Increased LV filling pressure leading to atrial dilatation • small pericardial effusion • left-sided pleural effusion	• increased RV and LV wall thickness (≥12mm) • presence of septal thicknening (occurs in approx. 80% of ATTR-CA) • thickened valves • bi-atrial dilatation • 'reverse nulling' pattern of the myocardium on T1 mapping scout images • LGE of the myocardium in a subendocardial, transmural or diffuse pattern • small pericardial effusion • left-sided pleural effusion	• 1-hour planar scan having H:CL ratio of >1.5 (qualitative assessment) • 3-hour planar scan having Perugini Grade 2 or 3 cardiac uptake (semi-quantitative assessment)
Advantages	• relatively cost-effective investigation • does not involve ionizing radiation	• excellent soft tissue resolution of the myocardium • does not involve ionizing radiation • able to provide significant imaging findings to increase the likelihood of diagnosing CA	• able to distinguish between AL and ATTR-CA subtypes with a high degree of confidence • can be repeated for follow-up cases in order to quantitatively assess the response to treatment • able to provide significant imaging findings to increase the likelihood of diagnosing CA
Disadvantages	• operator dependant • unable to confirm the diagnosis or distinguish between AL and ATTR-CA	• relatively expensive and time-consuming investigation • requires highly trained experts for interpretation • unable to distinguish between AL and ATTR-CA subtypes with high degree of confidence	• involves a relatively small dose of ionizing radiation • may give falsely positive results if interpreted by inexperienced personnel who is unaware of the criteria that increased the pre-test likelihood for diagnosing ATTR-CA

Table II: Recommendations for interpreting and reporting Technetium-labelled bone scans in diagnosing ATTR-CA

No.	Points for concern	Recommendation
1.	Physicians may refer for a Technetium-labelled bone scan without performing other conventional imaging first or without performing biochemical tests to exclude the presence of light chain immunoglobulins	Put in place system prompts in the hospital medical information system when ordering a Technetium-labelled bone scan, to include serum and urine protein electrophoresis and clonal plasma cell analysis
2.	Wrong timing and wrong placement of ROI to measure the H:CL ratio, which may give a falsely positive or falsely negative result for diagnosis of ATTR-CA	To perform the H:CL ratio measurement during the 1-hour scan, which can confidently identify a value of > 1.5 to be diagnostic of ATTR-CA*. A SPECT/CT can also be performed to ensure the correct localization of the heart and avoid diagnostic pitfall.
3.	Wrong timing and wrong interpretation of radiotracer retention in the heart using the Perugini grading system, which may give a falsely positive result for diagnosis of ATTR-CA	To perform the semi-quantitative assessment at 3-hours to ensure adequate biodistribution of the of the blood pool tracer uptake. A SPECT/CT can also be performed to ensure the correct localization of the heart and avoid diagnostic pitfall.
4.	Referring clinicians and patients are not aware of how to proceed after receiving a Technetium-labelled bone scan report that is positive for the diagnosis of ATTR-CA*.	Reports of Technetium-labelled bone scans are required to include a recommendation for performing genetic testing when a positive scan is reported. This will enable the differentiation of ATTRwt from ATTRm. Those having ATTRm will require further family genetic counselling and an option for testing of other immediate family members because of its hereditary nature.

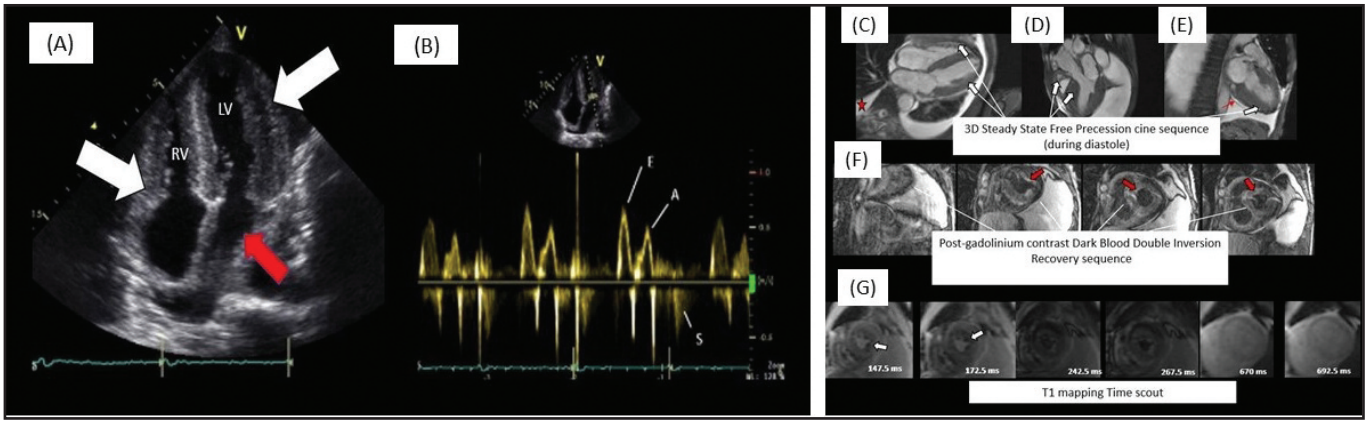

Fig. 1: Echocardiography and MRI images of the patient. (a) Echocardiography showed the 4-chamber view having thickened left ventricular (LV) and right ventricular (RV) walls (white arrow). There is also presence of dilated left atrium (red arrow). (b) Tissue Doppler imaging (TDI) demonstrated low myocardial relaxation velocities at the mitral annulus. (c,d,e) Cardiac magnetic resonance spectroscopy (CMR) of the 3D Steady State Free Precession cine sequence in the horizontal long axis, short axis, and vertical long axis views demonstrated thickened LV, RV and septal walls (white arrows). There is also a small pericardial effusion (thin red arrow) and left-sided pleural effusion (red star). (f) CMR in the post-gadolinium contrast dark blood double inversion recovery sequence demonstrated late gadolinium enhancement (LGE) in subendocardial, and transmural patterns (red arrow). (g) T1 mapping time scout identified the 'reverse nulling' pattern of the myocardium, whereby there was low signal nulling of the myocardial tissue (white arrows) that occurred before the nulling of the dark blood pool signal that is indicative of cardiac amyloidosis.

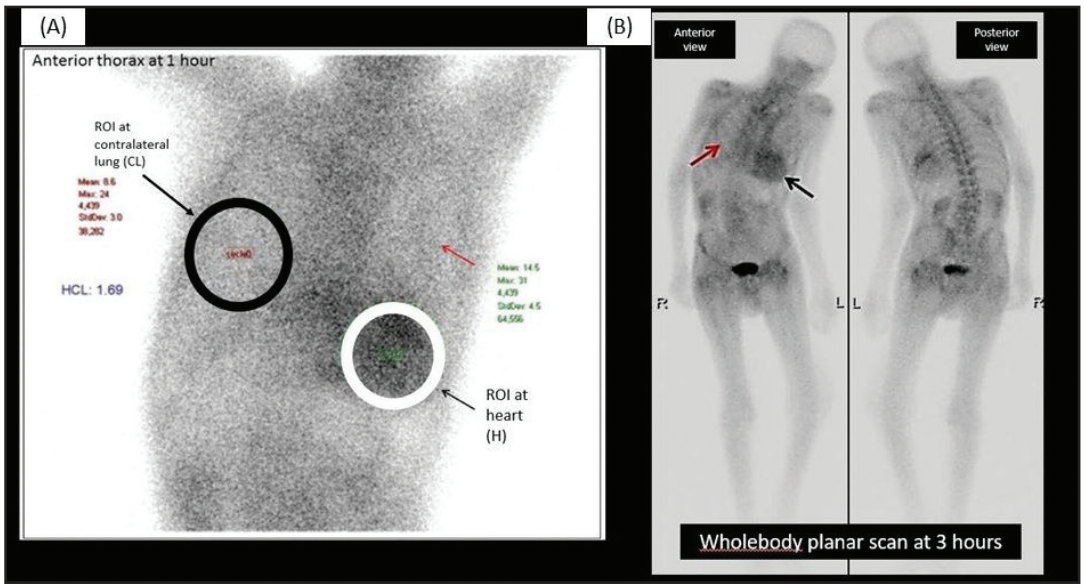

Fig. 2: (a) ^{99m}Tc-labelled bone scintigraphy with the anterior planar view of the thorax at 1-hour demonstrated increased radiotracer uptake at the region of the heart with H:CL lung ratio of 1.69, indicative of ATTR-CA within the given clinical context. (b) Anterior and posterior views of the wholebody bone scintigraphy scan demonstrated increased tracer uptake at the region of the heart (black arrow) with associated apparent attenuation of the skeletal bone uptake (red arrow), which was consistent with a Perugini Grade 3 scoring.

some mild degenerative changes of the joints, however there were no abnormal foci of radiotracer uptake in the bones. There was moderately increased diffuse tracer uptake in the (H) (thin black arrow), which was comparatively higher than the uptake seen on adjacent ribs and bones (thin red arrow) (Figure 2 b). This semi-quantitative assessment method using a visual scoring based on the Perugini grading system was used to compare the intensity of cardiac uptake with the skeletal uptake on planar images.2 Since the heart uptake was higher than the bones, hence a Perugini grade 3 scoring was given, which was consistent with a diagnosis of ATTR-CA.

Consequently, based on the overall picture of clinical restrictive cardiomyopathy, HFpEF, typical cardiac ECHO and CMR findings, biochemical laboratory tests that were negative for plasma-cell dyscrasia, as well as positive bone scintigraphy findings, a diagnosis of ATTR-CA was conclusively made. In view of the patient's old age and poor

performance status, conservative and supportive management were proposed. The family was counselled regarding the prognosis of the disease and the need for genetic testing to further identify the subtypes of ATTR-CA, i.e., ATTRwt or ATTRm.

DISCUSSION

ATTR-CA is a rare condition but is likely underdiagnosed due to the non-specific presentations that cause delays in performing the pertinent investigations. ATTRwt has been mostly detected in Caucasians and the ATTRm is prevalent among those of African American descent.[2] Thus, its detection in a Malaysian of Malay descent is very rare. Nevertheless, as this condition is likely to be underdiagnosed, there should be a high index of suspicion to further investigate elderly patients who present with sudden, unexplained HFpEF. Furthermore, this condition is frequently associated with a preceding history of carpal tunnel syndrome or lumbar spinal stenosis.[2] Thus, a thorough past medical and surgical history should be sought when investigating such patients.

Currently, there is great advancement in the expertise of nuclear cardiology to aid in the diagnosis and characterization of ATTR-CA. Apart from being a non-invasive investigation, is also relatively inexpensive to perform, with the ability to distinguish AL subtype of CA from the ATTR-CA subtype. Bone-seeking agents such as ^{99m}Tc-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), pyrophosphate(PYP), and methylene diphosphonates (MDP) have be shown to be taken up by the myocardium in patients with the ATTR-CA subtype.1 It has been postulated that the preferential binding of ^{99m}Tc-PYP to ATTR-CA is similar to those of ^{99m}Tc-MDP and ^{99m}Tc-HDP, which are more commonly available in Malaysia, may be attributed to the fact that TTR fibrils in the myocardium have higher calcium content.[7] This may be due to altered calcium metabolism that occurs due to the oxidative damage to the myocytes triggered by the abnormal deposition of the TTR fibrils.[3] Nevertheless, there may be 22-30% of cases that may have a mildly false positive bone scintigraphy result in cases of AL subtype of cardiac amyloidosis.

Hence, a diagnostic algorithm has been developed to improve the accuracy for detecting ATTR-CA using bone scintigraphy. These include using a semi-quantitative Perugini grading system of Grade 2 or 3 radiotracer uptake at post 3 hours imaging to indicate a positive scan, and together with a H:CL ratio of > 1.5 in the one-hour planar imaging to be diagnostic of ATTR-CA, provided that the clinical history, and ECHO with or without CMR findings suspicious of CA (Table I), together with laboratory tests to exclude AL have been performed.[6,7] The Perugini grading system is an assessment of the cardiac uptake on planar bone scintigraphy imaging, which can be visually score by comparing the intensity of the heart uptake with the adjacent ribs. This grading system can be evaluated as Grade 0: no cardiac uptake and normal bone uptake; Grade 1: cardiac uptake that is less intense than the bone signal, Grade 2: cardiac uptake with intensity similar to bone; and Grade 3: cardiac uptake that in higher than bone with relatively attenuated or absent bone signal.[8] Grade 0 corresponded to a negative predictive value (NPV) of 87% and Grade 3 corresponded to a positive predictive value (PPV) of 96% for ^{99m}Tc-PYP positivity.[8] The H:CL ratio of > 1.5 introduced by Bokhari et al., reported that this quantitative score along with diffuse intense myocardial radiotracer retention had a sensitivity and specificity of 97% and 100%, respectively with area under the curve (AUC) 0.992, for identifying ATTR-CA.[9] A meta-analysis of six bone scintigraphy studies involving 529 patients by Treglia et al., stated that bone scintigraphy had a sensitivity of 92.2% (95% CI: 89-95%), specificity of 95.4% (95% CI: 77-99%) for making the diagnosis of ATTR-CA, given that the relevant pre-scan criteria had been fulfilled.[10]

The limitations of bone scintigraphy for diagnosing ATTR-CA increases when only one method of assessment is used, e.g., only the Perugini grading system or the H:CL ratio alone. False positive results can be reported due to erroneous detecting of cardiac radiotracer uptake at an earlier scan times that in actual fact represents increased blood pool activity, or detecting of radiotracer uptake in adjacent rib fractures or the presence of aortic or mitral calcifications mistaken for cardiac myocardial tissue uptake.[4] Furthermore, the presence of acute or subacute myocardial infarction, hydroxychloroquine toxicity, and low cardiac output are among the causes of abnormal radiotracer uptake reported in the heart region on planar bone scintigraphy.[4] In particular the wrong placement of ROI or anatomical localization of the heart can be corrected by performing a targeted SPECT/CT scan at the thoracic region (Table II).

Another nuclear medicine radiotracer that can have a positive uptake in cardiac amyloidosis is ^{123}I meta-iodobenzylguanidine (MIBG). It cannot be used to conclusively diagnosed CA, however, as it can be positive in other types of conditions such as Parkinson's disease. Additionally, positron emission tomography (PET) radiotracers such as C11-PiB, F18-florbetapir and F18-florbetaben have been recently studied for the utility of diagnosing CA because they have high affinity and specificity to β-amyloid protein.[6] However, the limitation of these radiotracers cannot conclusively differentiate between ATTR-CA and AL subtype of CA.[6]

CONCLUSION

Technetium-labelled bone scintigraphy can be confidently used for the non-invasive diagnosis and subtyping of ATTR-CA (provided that there are supportive imaging findings from ECHO or CMR, and biochemical results that exclude the likelihood of AL). Clinical expertise is required to exclude the potential pitfalls and limitations in reporting the scans, to make it feasible for clinicians to forego invasive EMB when diagnosing ATTR-CA.

ACKNOWLEDGMENT

We would like to thank the patient for giving informed consent to use the anonymised data for preparing this article and the Director General of Health, Ministry of Health Malaysia for giving permission to publish this article.

DECLARATIONS

The authors declare no potential conflicts of interest with respect to the case report, authorship, and publication of this article.

CONSENT

Patient described in the above case report has given his written consent for the description of case, utilization of scan images and publication of this case report.

REFERENCES

1. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2—evidence base and standardized methods of imaging. J Nucl Cardiol 2019; 26(6): 2065-123.
2. Brunjes DL, Castano A, Clemons A, Rubin J, Maurer MS. Transthyretin Cardiac Amyloidosis in Older Americans. J Card Fail 2016; 22(12): 996-1003.
3. Mankad AK, Shah KB. Transthyretin Cardiac Amyloidosis. Curr Cardiol Rep 2017; 19(10): 97.
4. Gerber J, Miller EJ. Optimal interpretation of Tc99m PYP in 2020: Avoiding the million-dollar mistake. J Nuc Cardio 2021; 28(2): 503-6.
5. Chen W, Ton V-K, Dilsizian V. Clinical Phenotyping of Transthyretin Cardiac Amyloidosis with Bone-Seeking Radiotracers in Heart Failure with Preserved Ejection Fraction. Curr Cardiol Rep 2018; 20(4): 23.
6. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis. JACC Cardiovasc Imaging 2020; 13(6): 1368-83.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016; 133(24): 2404-12.
8. Marume K, Takashio S, Nishi M, Hirakawa K, Yamamoto M, Hanatani S, et al. Combination of Commonly Examined Parameters Is a Useful Predictor of Positive Labeled Pyrophosphate Scintigraphy Findings in Elderly Patients With Suspected Transthyretin Cardiac Amyloidosis. Circulation 2019; 83(8): 1698-708.
9. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Im 2013; 6(2): 195-201.
10. Treglia G, Glaudemans AWJM, Bertagna F, Hazenberg BPC, Erba PA, Giubbini R, et al. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. Eur J Nuc Med Mol Im 2018; 45(11): 1945-55.