Primary systemic amyloidosis in a 66-year old Filipina presenting with extracardiac uptake on Tc-99m pyrophosphate (Tc-99m PYP) scintigraphy

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ABSTRACT

This is a case of a 66-year-old, Filipina, who presented with persistent proteinuria diagnosed with renal amyloidosis. In the presented case, the equivocal cardiac and incidental extracardiac findings in the Tc-99m pyrophosphate (Tc-99m PYP) scan aided in the diagnosis of primary systemic light chain amyloidosis (AL amyloidosis). Tc-99m PYP scan with single photon emission computed tomography (SPECT) is currently used as a non-invasive imaging modality to diagnose Transthyretin amyloidosis (ATTR amyloidosis) however its role in diagnosing AL amyloidosis is not well documented. The case highlights its role in detecting extracardiac amyloid burden and suggests possible biopsy sites. The researchers recommend an additional whole-body planar scan with possible SPECT/CT on the 3rd hour delay to survey other areas with possible amyloid protein deposit.

Keywords: *Light chain amyloidosis, Tc-99m pyrophosphate, Philippines, case report*

INTRODUCTION

Primary or light chain amyloidosis is a relatively rare non-cancerous condition brought about by protein misfolding and metabolism leading to organ dysfunction. It has a worldwide incidence of 5 to 13 cases per million per year and a 20-year prevalence was estimated at 51.27 people per million [1]. It is more common in males (3:2 ratio), with a median age of 64 years old with no apparent ethnic or geographic specificity. An unchanged median survival of 5 months from the time of diagnosis [2] suggests there continue to be significant delays in diagnosis [3].

The following case report will delve into how nuclear medicine played a role in diagnosing a case of systemic amyloidosis which was managed in a tertiary referral institution in the Philippines.

PURPOSE

Our objective is to describe how the incidental findings in Tc-99m pyrophosphate cardiac scintigraphy findings aided in the diagnosis of primary systemic amyloidosis.

CASE PRESENTATION

The patient presented with a 6-month history of generalized body weakness, early satiety, bloatedness, intermittent bipedal edema, paresthesia, and weight loss of approximately 10 kgs. Laboratory work-up revealed elevated creatinine and proteinuria, and she was referred to a nephrologist with a working impression of glomerulonephritis. Due to the increasing trend of creatinine and persistent proteinuria, a renal biopsy was performed in a different tertiary institution which revealed renal amyloidosis.

In the interim, she noted progressive generalized body weakness associated with exertional dyspnea, hence admission. A series of laboratory and imaging tests (Table 1) were ordered based on the diagnostic algorithm of patients suspected of systemic amyloidosis (Figure 1).

TABLE 1. Summary of imaging and laboratory findings

Renal function tests	Serum creatinine: 6.43 mg/mL (NV: 0.55-1.02 mg/L) Urinalysis: Proteinuria (+3), Glucosuria (+2), and Hematuria (+3) Random urine protein: 810.5 mg/dL (NV: 0-11.9 mg/dL)
Liver function tests	Whole abdominal ultrasound: Hepatomegaly, minimal perihepatic ascites SGPT/ALT 79 U/L (NV: 10-49 U/L) SGOT/SGPT 100 U/L (NV: 0-34 U/L) Alkaline phosphatase 706 U/L (NV: 46-116 U/L)
Cardiac function tests	ECG: Atrial fibrillation with controlled ventricular response, non-specific ST-T changes, long QT, abnormal R wave progression and low voltage complexes in limb leads
	2D Echocardiogram: Concentric left ventricular hypertrophy with increased ventricular mass index and increased relative wall thickness. Hypokinesia of the anterolateral, inferolateral, and inferior left ventricular free walls from base to mid. EF of 44.4%
Serum FLC	Free kappa: 55.70 mg/L (NV: 4.7- 21.54 mg/L) Free Lambda: 332.5 mg/L (NV: 7.61-23.5 mg/L) Ratio: 0.17 (NV: 0.5-1.12) Positive for monoclonal serum free lambda light chains
Serum protein electrophoresis	Hypogammaglobulinemia with a suspicious peak distortion

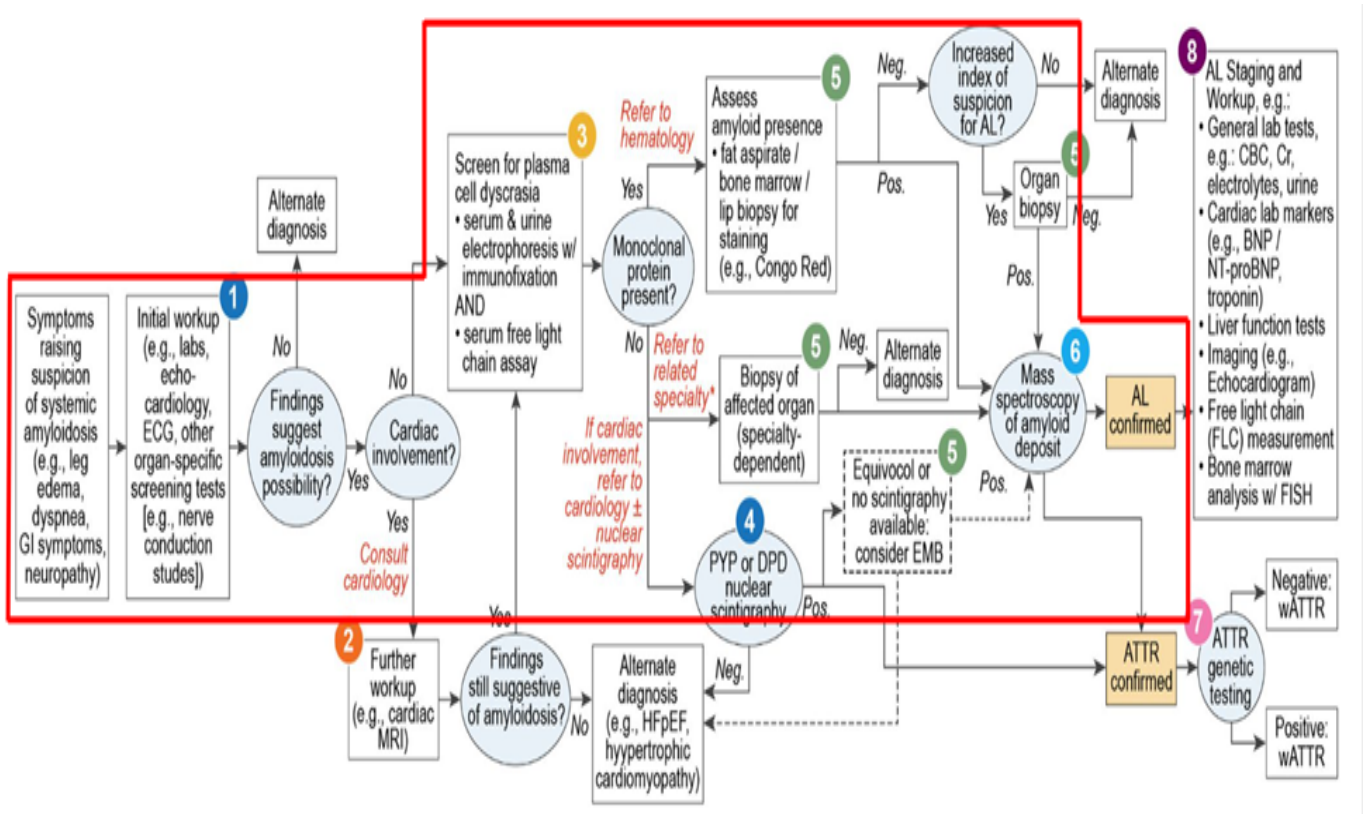

FIGURE 1. Comprehensive diagnostic algorithm for suspected systemic amyloidosis.[4]

The patient was initially for contrast-enhanced cardiac MRI. However due to the worsening creatinine levels, a cardiac scintigraphy with SPECT using Tc-99m pyrophosphate (Figure 2) was done to rule out ATTR amyloidosis. The images show mild myocardial Tc-99m PYP uptake less than the rib with a heart-to-contralateral lung ratio of 1.33. Mild diffuse Tc-99m PYP uptake is noted in the liver with diffusely intense activity noted in the spleen. The results showed equivocal findings for ATTR cardiac amyloidosis, considerations were AL amyloidosis or early ATTR cardiac amyloidosis [5].

Incidental extracardiac findings noted in the Tc-99m PYP scan suggested other organ involvement, hence the liver biopsy. On the 5th hospital day, the patient had intermittent episodes of hypotension for which she was started on inotropes. On the 14th day of admission, the patient was referred for encephalopathy and was transferred to the ICU. STAT ECG showed atrial fibrillation in controlled ventricular response (87 bpm) prolonged QT, later that day the patient had pulseless ventricular tachycardia and eventually expired with fatal arrhythmia as the immediate cause of death and cardiac amyloidosis as the antecedent cause of death. Unfortunately, the results of the serum free light chain and serum electrophoresis were released during the critical period of illness and specific chemotherapy treatment could not be initiated.

The liver biopsy and partial autopsy reports confirmed the presence of amyloid deposits involving the kidney, liver and heart with mass spectroscopy confirming the diagnosis of AL type of amyloidosis

DISCUSSION

Amyloidosis is a rare protein misfolding disease caused by the deposition of amyloid fibrils that self-assemble in β-sheet conformation in almost any organ in the body. The precursor protein of AL amyloidosis is a monoclonal immunoglobulin light chain causing cellular toxicity, oxidative damage, disrupting the organ architecture

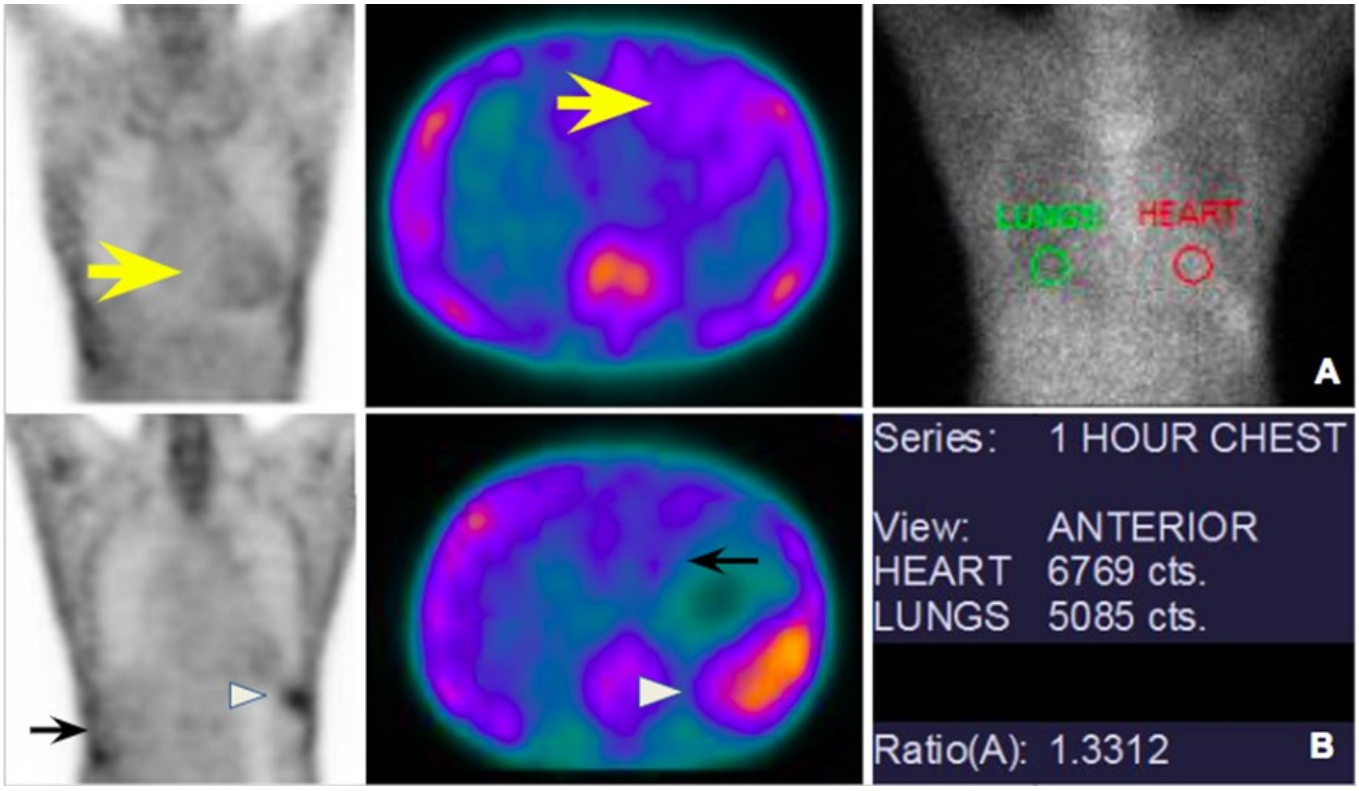

FIGURE 2. Technetium-99m pyrophosphate cardiac scan. Planar and SPECT imaging were obtained 1 hour and 3 hours after intravenous administration of Tc-99m pyrophosphate. Semi-quantitative SPECT images show grade 1 myocardial uptake (yellow arrows) with extracardiac findings of mild diffuse uptake in the liver (black arrows) and intense uptake in the spleen (white arrowheads). Quantitative analysis was performed by drawing regions of interest over the planar images of the heart and contralateral lung (A). The calculated heart-to-contralateral lung ratio is 1.33 (B). A ratio of ≥1.5 at one hour is classified as ATTR positive.

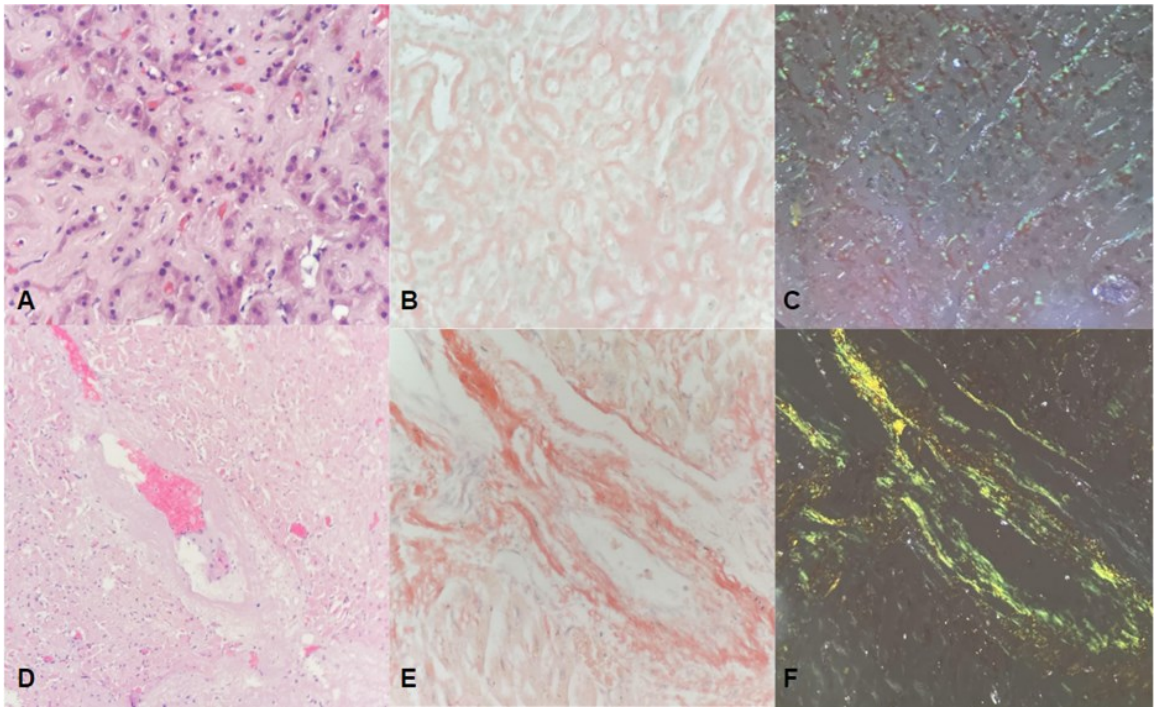

FIGURE 3. Histopathologic images with immunohistochemical staining of the liver and heart. Histopathologic images of the liver (A) and heart (D) with positive congo red staining under normal light (B and E) and apple green birefringence (C and F).

leading to organ dysfunction. The prognosis depends on the type and amount of accumulated fibril deposition on the affected organ upon diagnosis. Early diagnosis and reduction of circulating amyloid fibrils upon diagnosis are the mainstay of management [6].

Amyloidosis can either be localized, involving one organ, or systemic when it involves more than one organ. Primary systemic amyloidosis is usually of the AL type with 76% of patients have cardiac involvement, with renal (53%), liver (18%), and nerve (24%) involvement, with cardiac involvement being the best predictor of mortality and morbidity compared to other organs [7]. Clinicians should identify symptoms that raise suspicion of amyloidosis. Diagnostic work-up includes confirmation for multi-organ involvement. Some cases show negative or equivocal laboratory results which necessitate clinicians to proceed with a tissue biopsy of the suspected organ involved. Scintigraphy with Tc-99m radiolabelled with bisphosphonate bone-seeking tracers offers a non-invasive approach to diagnosing ATTR amyloidosis without proceeding to endomyocardial biopsy. A case of ATTR amyloidosis reported by Takahashi, K. (2021) noted persistently increased PYP uptake in the heart and abdominal walls which aided the clinician to identify an alternative possible biopsy site to confirm the diagnosis [8]. Similarly, extracardiac findings in the Tc-99m PYP scan suggested multiple organ involvement and provided the clinician with a possible biopsy site.

Other bisphosphonate-derivative radiotracers may used for diagnosing ATTR amyloidosis such as Tc-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) and Tc-99m hydroxymethylene diphosphonate (HMDP), as suggested by the American Society of Nuclear Cardiology [5]. A study by Khor, Y.M, et.al (2023) noted increased hepatic and splenic HMDP uptake exclusively seen in the AL type of amyloidosis and increased DPD liver uptake in both ATTR and AL amyloidosis. The presence of extracardiac HMDP/DPD activity suggests a large amyloid burden in other organs and determines disease extent [9]. A similar study conducted by Malka, N., et al. (2020) concluded that in the background of increased cardiac uptake, extra-cardiac findings are highly diagnostic and prognostic in amyloidosis patients [10].

A similar case of systemic amyloidosis was reported locally with the patient initially presenting with cardiac arrhythmia and a pancreatic head mass. An incidental finding of mild, diffuse hepatic uptake in the total body bone scintigraphy using Tc-99m methylene diphosphonate (MDP) or hydroxydiphosphonate (HDP) was noted suggesting amyloidosis. On partial autopsy, systemic AL amyloidosis was confirmed to affect the heart, lungs, liver, and kidneys [11].

CONCLUSION

Due to its rarity, amyloidosis remains the least considered diagnosis for patients with non-specific signs and symptoms. Early detection remains the key to a better prognosis however tissue biopsy remains the gold standard in confirming the diagnosis and a prerequisite in treatment planning. Tc-99m pyrophosphate scan with SPECT is currently recommended as the non-invasive diagnostic modality to confirm ATTR diagnosis; however, its role in AL amyloidosis is very limited. The case underscores its diagnostic role in evaluating extracardiac amyloid burden and suggests possible biopsy sites. The researchers recommend an additional whole-body planar scan with possible SPECT/CT on the 3rd hour delay to survey other areas with possible amyloid protein deposit.

ETHICAL CONSIDERATIONS

Written informed consent was obtained from the patient's next of kin for the publication and presentation of this case report and any accompanying images. This report was conducted in adherence to the Principles of the Declaration of Helsinki [12] and the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP), E6 (R2), other ICH-GCP 6 (as amended), and National Ethical Guidelines for Health and Health-Related Research [13].

REFERENCES

1. Kumar, N., Zhang, N.J., Cherepanov, D. et al. (2022). Global epidemiology of amyloid light-chain amyloidosis. Orphanet J Rare Dis 17, 278. https://doi.org/10.1186/s13023-022-02414-6.2020 Feb 28. PMID: 32108413; PMCID: PMC8030094.
2. Baker K. R. (2022). Light Chain Amyloidosis: Epidemiology, Staging, and Prognostication. Methodist DeBakey cardiovascular journal, 18(2), 27–35. https://doi.org/10.14797/mdcvj.1070.
3. Hasib Sidiqi, M., & Gertz, M. A. (2021). Immunoglobulin light chain amyloidosis diagnosis and treatment algorithm 2021. Blood cancer journal, 11(5), 90. https://doi.org/10.1038/s41408-021-00483-7.
4. Jimenez-Zepeda, V. H., Bril, V., Lemieux-Blanchard, É., Royal, V., McCurdy, A., Schwartz, D. A., & Davis, M. K. (2023). A comprehensive multidisciplinary diagnostic algorithm for the early and efficient detection of amyloidosis. Clinical Lymphoma, Myeloma & Leukemia, 23 (3), 194–202. https://doi.org/10.1016/j.clml.2022.12.013.
5. Miller, E. J., Campisi, R., Shah, N. R., McMahon, S. R., Cuddy, S., Gallegos-Kattan, C., Maurer, M. S., Damy, T., Slart, R. H. J. A., Bhatia, K., & Einstein, A. J. (2022). Radiopharmaceutical supply disruptions and the use of 99mTc-hydroxymethylene diphosphonate as an alternative to 99mTc-pyrophosphate for the diagnosis of transthyretin cardiac amyloidosis: An ASNC Information Statement. Journal of Nuclear Cardiology, 29(5), 2748–2760. https://doi.org/10.1007/s12350-022-03059-5.
6. Witteles, R., & Liedtke, M. (2019). AL amyloidosis for the cardiologist and oncologist. JACC: Cardiooncology, 1(1), 117–130. https://doi.org/10.1016/j.jaccao.2019.08.002.
7. Senecal, J., Abou-Akl, R., Allevato, P. A., Mazzetti, I., Hamm, C., Parikh, R., & Woldie, I. (2023). Amyloidosis: a case series and review of the literature. Journal of Medical Case Reports, 17(1). https://doi.org/10.1186/s13256-023-03886-1.
8. Takahashi, K., Sasaki, D., Sakaue, T., Enomoto, D., Uemura, S., Okura, T., Ikeda, S., Yamamoto, D., Kono, T., & Yamamura, N. (2021). Extracardiac accumulation of Technetium-99M-Pyrophosphate in transthyretin cardiac amyloidosis. JACC: Case Reports, 3(7), 1069–1074. https://doi.org/10.1016/j.jaccas.2021.02.015.
9. Khor, Y. M., & Dorbala, S. (2023). Extra-cardiac uptake on technetium-99m pyrophosphate (Tc-99m PYP) scan: not just a matter of the heart. Journal of Nuclear Cardiology. https://doi.org/10.1007/s12350-023-03341-0.
10. Malka, N., Abulizi, M., Kharoubi, M., Oghina, S., Galat, A., Bras, F. L., Moktefi, A., Guendouz, S., Molinier-Frenkel, V., Fanen, P., Funalot, B., Lefaucheur, J., Blanc-Durand, P., Deux, J., Audard, V., Bodez, D., Itti, E., & Damy, T. (2020). Extracardiac soft tissue uptake, evidenced on early 99m Tc-HMDP SPECT/CT, helps typing cardiac amyloidosis and demonstrates high prognostic value. European Journal of Nuclear Medicine and Molecular Imaging, 47(10), 2396–2406. https://doi.org/10.1007/s00259-020-04753-7.
11. Asuncion, Bernadette, , Giron, Danilo M, Orillaza, Marissa A, Tan, Carmela D, & Templo, Felipe S, (2003). Primary systemic amyloidosis in a 52-year old male presenting with cardiac arrhythmia: An autopsy report. Philippine Heart Center Journal, 2003: 10:72-80.
12. World Medical Association (2013). World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA, 310 (20), 2191–2194. https://doi.org/10.1001/jama.2013.281053.
13. Philippine Health Research Ethics Board (2017). National Ethical Guidelines for Health and Health-related Research. DOST - PCHRD. https://ethics.healthresearch.ph/index.php/2012-04-19-05-10-10/297-2017-nationalethical-guidelines-revision.

ANNEX A

PROTOCOL FOR CARDIAC TTR AMYLOIDOSIS IMAGING

EQUIPMENT, MATERIALS AND SUPPLIES:

Planar Gamma Camera with SPECT/CT

LEHR- low energy high resolution collimator

Tc-99m PYP- Tc-99m Technetium Pyrophosphate

IMAGE ACQUISITION:

1. Administer 10-20 mCi (370-740 MBq) of Tc-99m PYP and wait 1 hour before the first scan.
2. Position the patient on the scanner bed, supine with both arms over the head.
3. Move the bed towards the detectors and set the region of interest (ROI) to include the heart. Position the detectors as close as possible to the patient.
4. Remind the patient to neither move nor sleep during the scan.
5. Acquire anterior, lateral, and left anterior oblique planar images of the chest at 140 keV (15-20% window) in a 256 x 256 matrix, detector configuration at 90°, for 750,000 counts.
6. Acquire SPECT images of the heart in a 128 x 128 matrix with angular range of 360° and detector configuration of 180°, 25 seconds per stop for 40 views per detector, and a zoom factor of 1.00.
7. Advise the patient to return 2 to 3 hours for the delayed imaging. 3-hour delayed imaging is recommended if excess blood pool activity is noted in the initial images.
8. For the delayed imaging, retrieve the previous patient data. Position the patient and detectors in the same manner as with the initial imaging. Acquire planar and SPECT images using the same imaging parameters.