

CLINICAL CASE CHALLENGES

Mistaken Identity



Using Bone Scintigraphy to Diagnose Cardiac Amyloidosis in Patients With a Monoclonal Gammopathy

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Cardiac amyloidosis (CA) occurs when amyloid fibrils infiltrate the myocardial interstitium, resulting in stiffened myocardium and a restrictive cardiomyopathy. More than 95% of CA is due to systemic light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR). AL amyloidosis arises from a clonal plasma cell dyscrasia that produces amyloidogenic monoclonal immunoglobulins. These immunoglobulins then misfold and deposit in various organs, such as the heart, kidneys, liver, gastrointestinal tract, and peripheral nerves (1). ATTR amyloidosis arises when transthyretin (2), a liver-derived transporter of thyroid hormone and retinol proteins, undergoes tetramer dissociation, misfolds, and forms amyloid fibrils in various distant organs (3).

Differentiating between AL and ATTR amyloidosis is crucial because their respective clinical courses and treatments differ significantly. Delays in diagnosis lead to poorer outcomes as continued amyloid deposition causes further organ dysfunction. Moreover, diagnostic confusion may delay initiation of amyloid-directed treatment.

Thus, having a high index of clinical suspicion coupled with appropriate diagnostic sequencing can ensure a timely and accurate diagnosis of CA. We report a case of a patient that highlights the challenges stemming from inappropriate use of ^{99m}Tc-pyrophosphate scintigraphy (^{99m}Tc-PYP) scanning to diagnose ATTR-CA in a patient with suspected CA and a plasma cell dyscrasia.

CASE DESCRIPTION

A 63-year-old man with a history of bilateral carpal tunnel syndrome presented to an outside hospital with dyspnea on exertion, positional lightheadedness, and chest pain. During his first episode of chest pain, he was found to have a mildly elevated troponin I level of 0.23 ng/mL (reference range: 0-0.09 ng/mL). His N-terminal pro-B-type natriuretic peptide level was 510 pg/mL (reference range: <100 pg/mL). An electrocardiogram revealed sinus rhythm, a right bundle branch block, and Q waves in leads II, III, and aVF. An echocardiogram revealed a left ventricular ejection fraction of 55%, bi-atrial enlargement, concentric left ventricular hypertrophy, and grade II diastolic dysfunction. Coronary angiography was negative for obstructive coronary artery disease. The patient was diagnosed with heart failure with preserved ejection fraction secondary to hypertension and was started on furosemide, metoprolol, lisinopril, and spironolactone. However, metoprolol was soon discontinued due to hypotension, and he was subsequently started on midodrine. Despite medical therapy, the patient had multiple outpatient visits and repeat hospitalizations for dyspnea and chest pain.

Two years later, the patient underwent a repeat ischemia evaluation. An exercise treadmill test was negative for inducible ischemia but notable for paroxysmal supraventricular tachycardia and rare premature ventricular contractions during exercise. A subsequent Zio Patch (iRhythm Technologies, Inc) study revealed episodes of nonsustained ventricular tachycardia, with the longest lasting 39 beats. A repeat coronary angiogram was again

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negative for obstructive coronary artery disease. Cardiac magnetic resonance (CMR) imaging was then performed to further investigate the cause of the patient's non-ischemic cardiomyopathy. CMR imaging revealed a left ventricular ejection fraction of 39%, mild concentric left ventricular hypertrophy, and diffuse late gadolinium enhancement with an inability to null the blood pool, which were all concerning for CA.

After these findings, hematologic testing for a monoclonal gammopathy and a ^{99m}Tc -PYP scan were pursued in parallel, as recommended in the CMR report. Serum electrophoresis with immunofixation detected an abnormal immunoglobulin G lambda monoclonal protein. Serum free light chains revealed a serum free lambda of 152.03 mg/L (reference range: 5.71-26.30 mg/L), serum free kappa of 8.91 mg/L (reference range: 3.30-19.40 mg/L), and a kappa:lambda ratio of 0.06 (reference range: 0.26-1.65). Taken together, these results are consistent with a lambda monoclonal gammopathy. During this time, the patient also underwent a ^{99m}Tc -PYP scan, which revealed a heart/contralateral lung ratio of 1.47 and was read as grade 2 myocardial uptake (myocardial tracer uptake equals rib uptake) (Figure 1). However, single-photon emission computed tomography (SPECT) imaging was inconclusive for clear myocardial uptake. Based on the ^{99m}Tc -PYP scan and TTR genetic testing negative for a variant, his team diagnosed him with wild-type ATTR amyloidosis.

**ABBREVIATIONS
AND ACRONYMS**

^{99m}Tc -PYP = 99m -technetium pyrophosphate scintigraphy

AL = light chain amyloidosis

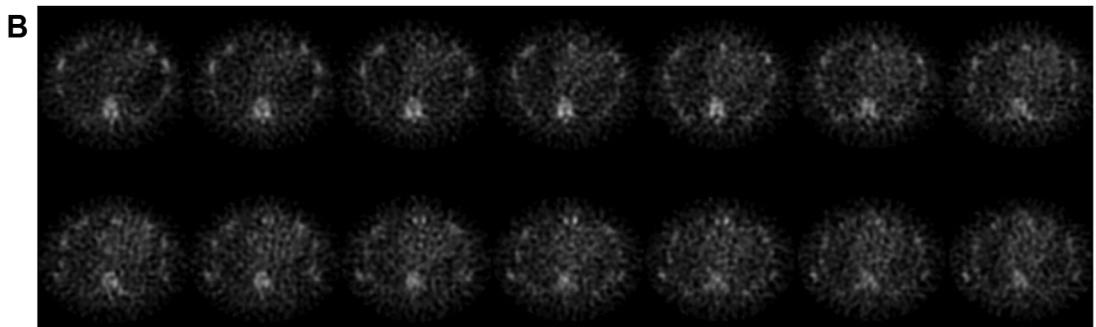
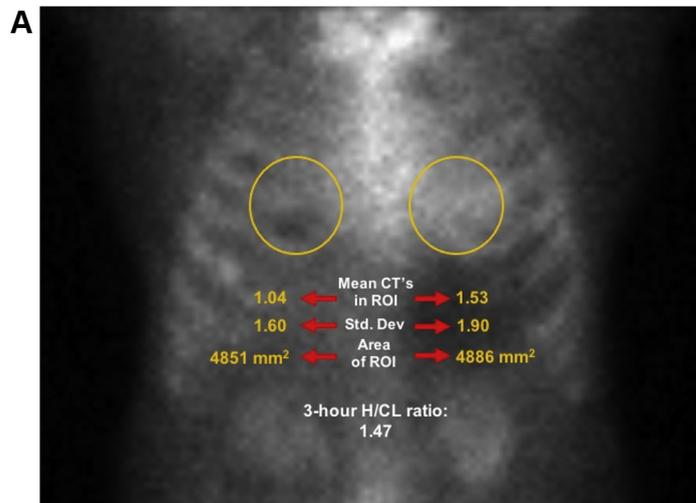
ATTR = transthyretin amyloidosis

CA = cardiac amyloidosis

CMR = cardiac magnetic resonance

SPECT = single-photon emission computed tomography

FIGURE 1 Technetium Pyrophosphate Scan



^{99m}Tc Technetium pyrophosphate scintigraphy scan planar (A) and single-photon emission computed tomography (CT) (B) images. Three-hour post-injection heart/contralateral lung (H/CL) ratio = 1.47. Single-photon emission computed tomography images without conclusive myocardial uptake. ROI = region of interest.

The patient was referred to our center for further management. Given the presence of a monoclonal gammopathy, the patient underwent an endomyocardial biopsy (2 months after the ^{99m}Tc -PYP scan), which confirmed CA. Amyloid subtyping by mass spectrometry found a peptide profile consistent with AL (lambda)-type amyloid deposition rather than ATTR amyloidosis. A subsequent bone marrow biopsy revealed 10% to 20% lambda-restricted plasma cell population. Thus, the patient was ultimately diagnosed with AL-CA. Inappropriate use and interpretation of ^{99m}Tc -PYP imaging led to an initial misdiagnosis of ATTR-CA. This resulted in a 3-month delay between the initial detection of a monoclonal gammopathy and initiation of chemotherapy for AL-CA.

The patient was started on anti-plasma cell therapy with bortezomib, cyclophosphamide, and dexamethasone. Daratumumab was subsequently added. The patient was able to achieve a complete hematologic remission. Despite the hematologic remission, he still experienced significant limitations due to his cardiac status (New York Heart Association functional class III heart failure symptoms and orthostasis, requiring midodrine).

DISCUSSION

This case highlights a potential pitfall of inappropriate ^{99m}Tc -PYP scan use and interpretation during an evaluation for CA. It also emphasizes the importance of early diagnosis and treatment in AL-CA to reverse the effects of light chain toxicity and fibril deposition on the myocardium. Bone scintigraphy has emerged as an important noninvasive alternative to endomyocardial biopsy for diagnosing ATTR amyloidosis. Endomyocardial biopsy is the historic gold standard for histological confirmation of ATTR amyloidosis. This procedure, however, can cause complications, such as tamponade and valvular damage, and is limited to clinical practices with procedural experience. In contrast, bone scintigraphy is easier to perform and more readily available in most clinical practices. As such, bone scintigraphy can improve access to diagnosing ATTR amyloidosis, which is historically an underdiagnosed but treatable cause of heart failure (2).

Importantly, when ordering a bone scintigraphy scan, expert guidelines and consensus recommendations emphasize the need to exclude AL amyloidosis because >20% of patients with AL-CA will have grade 2 or 3 radiotracer uptake (4,5). If a monoclonal gammopathy is excluded through serum and urine testing, then grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy has a specificity and positive predictive value for ATTR-CA of 100% (6). In addition to ruling out AL amyloidosis, it is important to obtain SPECT images for bone scintigraphy scans. False-positive findings on scans can occur with planar scintigraphy if radiotracer blood pooling occurs and is mistaken for myocardial uptake (7). In patients with grade 2 uptake on planar images, the false-positive rate has been shown to be 64% due to blood pooling or lack of myocardial uptake, as determined by follow-up SPECT imaging (8).

In cases in which a monoclonal gammopathy is present, biopsy (eg, endomyocardial) should be pursued instead of a ^{99m}Tc -PYP scan to confirm the presence of CA and accurately define the amyloid subtype. Therefore, given that many older patients with ATTR-CA can also have an unrelated monoclonal gammopathy, biopsy is still needed in many instances in lieu of a ^{99m}Tc -PYP scan to make a definitive diagnosis of ATTR-CA (9).

Diagnostic guidelines are important to ensure that a complete, accurate evaluation for CA occurs (10). In particular, as ATTR-CA has become more recognized and ^{99m}Tc -PYP scans are more widely used, understanding the appropriate use and caveats of interpreting bone scintigraphy will be imperative to avoid misdiagnosis. Consensus recommendations call for screening for CA when there is a clinical suspicion for CA based on history, electrocardiography, echocardiography, CMR imaging, or biomarkers. The patient in our case had many clinical clues, such as intolerance to heart failure medications and orthostatic hypotension requiring midodrine. In addition, he had bilateral carpal tunnel disease and a persistently low-level positive troponin measurement. Although there was suspicion for ATTR, the first step remains to evaluate for the presence of a monoclonal gammopathy, as detecting a monoclonal protein would warrant an endomyocardial biopsy to avoid missing AL amyloidosis. Screening for a monoclonal gammopathy and undergoing ^{99m}Tc -PYP can occur in tandem; however, a positive ^{99m}Tc -PYP scan must be interpreted in the setting of ruling out AL amyloid. Moreover, in our patient, ^{99m}Tc -PYP planar images revealed grade 2 tracer uptake, but SPECT imaging did not show clear myocardial uptake, raising the concern for a false-positive finding due to blood pool uptake. Because the ^{99m}Tc -PYP scan revealed radiotracer uptake, the patient was incorrectly diagnosed with ATTR-CA,

despite the presence of a gammopathy. The true diagnosis of AL amyloidosis was made only after a subsequent endomyocardial biopsy and amyloid subtyping according to mass spectrometry.

CONCLUSIONS

Endomyocardial biopsy is necessary for the correct evaluation for CA in patients with evidence of a monoclonal gammopathy. Bone scintigraphy imaging is a promising, noninvasive tool that has the potential to improve the diagnosis of ATTR-CA, an underrecognized but now treatable cause of heart failure. However, a clear framework for CA evaluations is key to avoiding diagnostic delays and improving outcomes. This is particularly relevant for AL-CA, which if untreated has a median survival of 6 months (11). Our case illustrates some potential pitfalls of inappropriate use and interpretation of bone scintigraphy imaging for CA, and it emphasizes the importance of evaluating for an underlying plasma cell dyscrasia. As awareness grows of CA and novel therapies, it will be essential for providers to pursue a systematic diagnostic approach to avoid unnecessary financial burden and diagnostic delay.

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