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Case Report

Diagnostic challenges in cardiac amyloidosis: a case report of negative initial endomyocardial biopsy

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Abstract: Cardiac amyloidosis (CA) is a challenging acquired heart disease caused by the deposition of β-pleated amyloid proteins, often leading to nonspecific symptoms that complicate the diagnosis. This case report describes an 83-year-old male patient presenting with chest pain and cough, revealing significant cardiomegaly and pericardial effusion on imaging. Initial diagnostic modalities, including echocardiography and endomyocardial biopsy (EMB), have yielded inconclusive results. Despite a negative EMB result, further investigation using positron emission tomography/computed tomography ruled out cardiac sarcoidosis. A second EMB was performed to confirm the diagnosis of CA. This case underscores the importance of combining clinical symptoms with paraclinical assessments and advocating additional testing when discrepancies arise, highlighting the complexities in diagnosing CA. This case report emphasizes the necessity for clinicians to integrate clinical symptoms with diagnostic findings when assessing for cardiac amyloidosis. This illustrates the potential for false-negative biopsies and the importance of considering further testing to ensure an accurate diagnosis, ultimately enhancing diagnostic accuracy and patient management in cases of suspected cardiac amyloidosis.

Keywords: Cardiac amyloidosis, endomyocardial biopsy, positron emission tomography/computed tomography, diagnosis

Introduction

Amyloidosis is a common disorder characterized by extracellular accumulation of insoluble fibers from altered gene-encoded or misfolded proteins. Accumulation of β-pleated amyloid proteins in the myocardium causes cardiac amyloidosis (CA), an acquired heart disease. CA is caused by immunoglobulin light chain (AL) and transthyretin amyloidosis (ATTR) [1].

Due to its rarity and nonspecific clinical manifestations, CA is difficult to diagnose. The illness has nonspecific symptoms and different diagnostic approaches, making diagnosis difficult [2]. As infiltrative cardiomyopathies, CA and cardiac sarcoidosis (CS) might have similar symptoms but unique features. Carpal tunnel syndrome (CTS) or lumbar spinal stenosis may indicate CA; however, the early symptoms are typically non-specific and similar to heart failure with maintained ejection fraction. This similarity can delay the diagnosis by 22 months and necessitate more than five specialist consultations [2].

Methodologies for evaluating patients with suspected CA have advanced significantly in recent years. The diagnosis of cardiac amyloidosis begins with clinical suspicion based on symptoms, such as heart failure, increased left ventricular wall thickness, low electrocardiography (ECG) voltage, conduction issues, and elevated cardiac biomarkers (e.g., troponin). Laboratory tests, including serum-free light chain assays and immunofixation electrophoresis, are used to rule out AL by detecting monoclonal proteins; their absence excludes AL amyloidosis with high accuracy. If monoclonal proteins are present, biopsy is needed to confirm AL amyloidosis. Noninvasive imaging, particularly bone scintigraphy with radiotracers such as ^{99m}Tc-PYP, which has strong cardiac uptake, confirms the condition without the need for a biopsy if mono-

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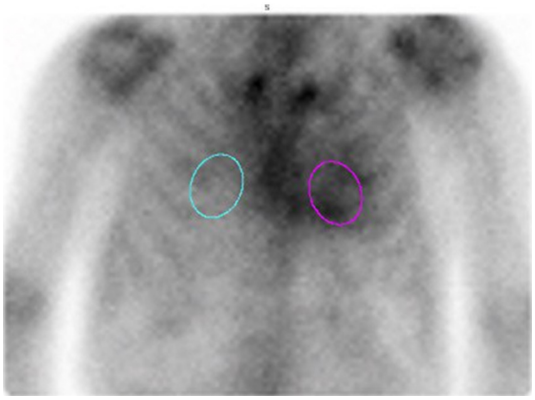

Figure 1. ^{99m}Tc-PYP images in grade 2 borderline for cardiac ATTR amyloidosis.

clonal proteins are absent. Echocardiography (echo) and cardiac magnetic resonance imaging (MRI) provide supportive evidence of wall thickening, diastolic dysfunction, and tissue abnormalities [3]. Nevertheless, the guidelines state that endomyocardial biopsy (EMB) is regarded as the definitive method for diagnosing CA, offering virtually 100% accuracy when conducted and analyzed properly [4]. Therefore, a negative biopsy could rule out CA. However, in the current study, we reported a sporadic case of CA with cardiac MRI diagnostic for CS and a false negative biopsy. Also, we discussed the proper approach after observing a negative biopsy in this case.

Case presentation

An 83-year-old man with chest trouble and cough visited Stony Brook University Hospital. The chest pain started three months before presentation and intensified thereafter. Shortness of breath and a pressure-like sensation in the center of the chest, which extended to the left arm and jaw, were common symptoms, particularly when exerting effort. Resting and sometimes sitting relieved pain. His cough worsened over a period of two weeks, accompanied by yellowish phlegm. No fever, chills, nausea, vomiting, diarrhea, hemoptysis, accidental weight loss, or nocturnal perspiration was recorded. No palpitations, weariness, dizziness, or leg/abdominal swelling were reported.

The patient's medical history included type 2 diabetes mellitus, non-obstructive coronary artery disease (CAD), chronic kidney disease (CKD), CTS, hypertension, hyperlipidemia, pancreatic insufficiency, and gastroesophageal reflux disease.

A physical examination revealed mild jugular venous distention and rales in the lung bases. There was no evidence of bilateral lower extremity edema. An electrocardiogram showed low-voltage QRS complexes with no ischemic change.

Laboratory tests, including cardiac biomarkers, were within normal limits.

A chest computed tomography (CT) scan showed pleural thickening in a partially lobulated left pleural effusion with adjacent parenchymal consolidation consistent with left lower lobe pneumonia (PNA) and an increase in mild to moderate pericardial effusion compared to the last CT five years prior. Moreover, cardiomegaly and pericardial effusion increased, suggesting echo. The echo showed a 45% ejection fraction (EF), down from 59% one month earlier, with no tamponade physiology. After 5 days, follow-up echocardiography indicated a 40% EF and significant posterior pericardial effusion, indicating early tamponade physiology requiring pericardial window installation and biopsy.

Given reduced EF compared to the previous Echo, the patient underwent an ischemic workup, which was negative for obstructive CAD. Given characteristics of HF, and negative ischemic work up, there was suspicion for CA and a ^{99m}Technetium-pyrophosphate scintigraphy (^{99m}Tc-PYP) was performed.

The patient's ^{99m}Tc-PYP scan was reported grade 2 as borderline for ATTR and considered equivocal with a grade of 2 (**Figure 1**), along with an inconclusive qualitative assessment of myocardial uptake.

On the other hand pericardial biopsy result was positive for amyloid deposition to vascular wall (**Figure 2A**, **2B**). Also, the patient had elevated serum-free light (kappa and lambda), which is typical in patients with CKD. Also, no abnormal band was found in serum and urine immunofixation. Therefore, we ordered an EMB for more evaluation and also may be necessary to differentiate between AL and ATTR amyloidosis.

The patient underwent cardiac catheterization for EMB for a definitive diagnosis. However,

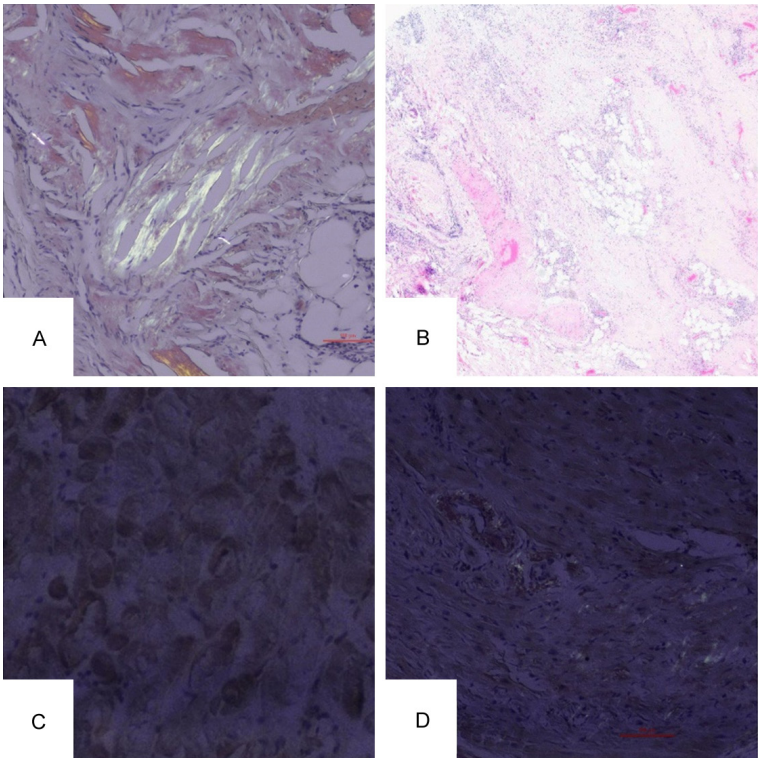

Figure 2. Amyloid deposits in the endomyocardial biopsy sample. A. Congo red staining of pericardial cells demonstrated apple-green birefringence under polarized light, indicative of vascular wall amyloid deposition. B. Hematoxylin-eosin staining showing evidence of eosinophilic interstitial deposits between the epicardial cells. C. Congo red staining of endomyocardial cells without apple green birefringence under polarized light indicated negative cardiac amyloidosis. D. Congo red stain of second endomyocardial biopsy cells showing apple-green birefringence under polarized light diagnostic for cardiac amyloidosis.

EMB revealed a negative for amyloid (negative Congo red) (**Figure 2C**). Consequently, the patient underwent cardiac MRI for further evaluation to ensure no evidence of infiltrative cardiomyopathy and to determine the patient's EF more precisely. EF was 43%, and the scar pattern was thought to be most suggestive of CS (**Figure 2D**).

Therefore, a full-body positron emission tomography/computed tomography (PET/CT) to evaluate extracardiac findings of sarcoidosis, which was negative for CS, and repeated echo was in favor of CA (**Figure 3A**, **3B**).

Given the case's complexity and paradoxical data, a decision was made to repeat the EMB.

Finally, the second EMB demonstrated myocardial and pericardial amyloid deposition and confirmed the diagnosis of CA (**Figure 3C**).

Discussion

This case report describes an unusual presentation of CA in an 83-year-old male, characterized by both endomyocardial and pericardial involvement, which initially mimicked CS on cardiac MRI. The diagnosis was confirmed only after a second EMB following a negative initial biopsy, highlighting the diagnostic challenges inherent in CA when standard tests yield misleading or inconclusive results.

CA and CS, both infiltrative cardiomyopathies, share overlapping clinical features including heart failure symptoms (e.g., dyspnea, fatigue, and edema) and arrhythmias due to myocardial infiltration. However, accurate differentiation is essential because these conditions differ significantly in terms of treatment and prognosis. CS is frequently associated with atrioventricular (AV) block, typically progressing from the first-degree to complete heart block, whereas CA more commonly presents with atrial fibrillation [5]. Demographically, CS predominantly affects younger individuals (mean age ~50 years) and females, as evidenced by a systematic review of 83 patients [6], while CA, particularly ATTR, is more prevalent in older males, consistent with the patient's profile. Echocardiographic findings in CS often include segmental wall motion abnormalities and variable septal thickness due to patchy granulomatous infiltration [1], features absent in this case, which instead showed concentric hypertrophy more suggestive of CA.

The diagnostic process was confounded by negative initial EMB and cardiac MRI findings, suggestive of CS. Although EMB is the gold standard for CA diagnosis, with nearly 100% accuracy when properly executed [4], false-negative results can occur because of sampling variability, as amyloid deposits may be

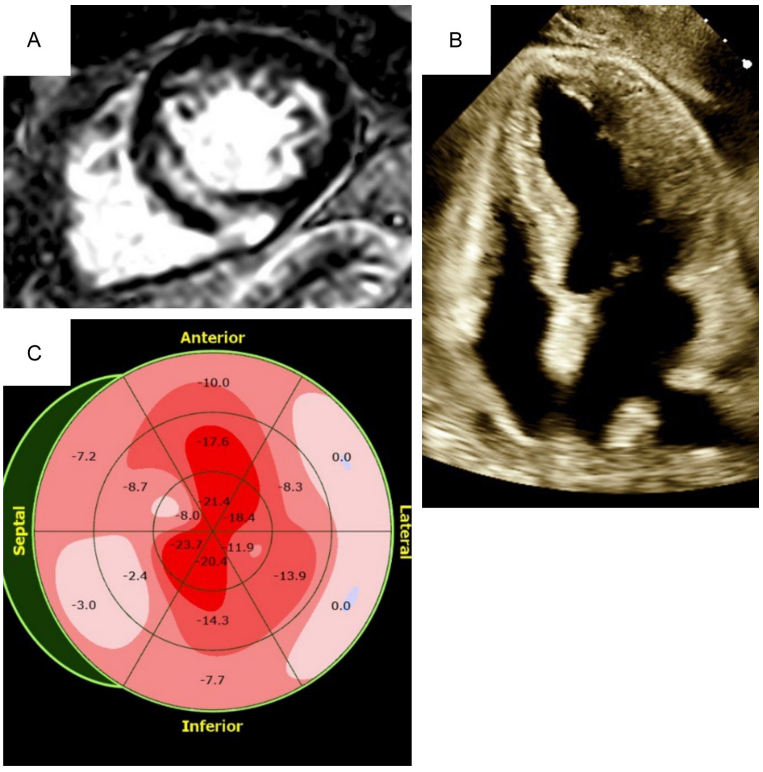

Figure 3. Echocardiographic findings in cardiac amyloidosis. A. Short axis view extensive patchy areas of late gadolinium enhancement throughout myocardium characteristic of cardiac amyloidosis. B. Transthoracic echocardiogram four-chamber view showing moderate concentric left ventricular hypertrophy. C. Apex-sparing distribution pattern of peak left ventricular longitudinal systolic strain by transthoracic echocardiogram, characteristic for cardiac amyloidosis.

patchy, especially in early disease stages [7-9]. Technical factors such as prolonged formalin fixation or inadequate tissue sectioning may also obscure detection. In this case, the initial EMB likely missed the affected myocardial regions, whereas the cardiac MRI displayed a scar pattern interpreted as consistent with CS. However, no imaging modality, including cardiac MRI or PET/CT, is pathognomonic of CS. Furthermore, CS typically involves extracardiac organs, most commonly the lungs [5], yet a whole-body PET/CT scan in this patient revealed no systemic sarcoidosis, casting doubt on the CS hypothesis.

Clinical suspicion of CA persisted despite these discordant findings, driven by the patient's advanced age, history of CTS, a known association with ATTR amyloidosis, and positive Congo red staining in the pericardium. Notably, amyloidosis involving the pericardium is rare, with prior reports linking it primarily to AL rather than to ATTR; however, no evidence of AL was found in this case. Although pericardial biopsy demonstrated positive amyloid deposition within the vascular wall, this observation alone was insufficient to confirm the diagnosis of CA. Amyloid deposits located in the pericardium or vascular walls do not necessarily imply myocardial involvement, which is crucial for a definitive diagnosis of CA. The gold standard for confirming CA is the identification of amyloid deposits within the myocardium, typically achieved through EMB. The EMB directly samples the myocardial tissue, allowing for histological confirmation via Congo red staining and amyloid typing [9, 10]. This distinction necessitated a second EMB, which ultimately identified amyloid deposits in both the myocardium and pericardium, thus confirming CA.

The diagnostic challenges in this case highlight the limitations of relying solely on a single EMB or imaging results. To enhance accuracy and avoid the false-negative EMBs, clinicians should obtain multiple biopsy fragments, ensure prompt tissue processing, and complement histological findings with confirmatory tests such as mass spectrometry or genetic testing for transthyretin mutations [11-14]. Non-invasive tools, including echo (e.g., apical sparing patterns) and cardiac MRI, can guide biopsy targeting and support repeat testing when initial results conflict with clinical suspicion [15, 16].

In summary, this case illustrates the complexity of diagnosing CA when the initial tests are inconclusive or suggest alternative conditions such as CS. This emphasizes the importance of integrating clinical presentation, such as age, comorbidities (e.g., CTS), and histopathological clues, with diagnostic findings. When discrepancies arise, as they did here, additional or repeated procedures such as a second EMB

may be warranted to achieve an accurate diagnosis, ultimately improving patient management in suspected CA cases.

Conclusion

In conclusion, we present a rare case with a difficult to diagnose due to imaging examination and initial biopsy mismatching the patient's clinical complaints. Therefore, specialists should compare patients' clinical presentations with their paraclinical assessments. If they do not match, additional or repeated diagnostic procedures may be needed.

Disclosure of conflict of interest

None.

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