

## SYMPTOMS TO DIAGNOSIS

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# A 50-year-old man presents with shortness of breath

A 50-YEAR-OLD MAN with a history of bilateral carpal tunnel syndrome presented with progressive shortness of breath on exertion for the previous 3 months. Cardiovascular physical examination showed jugular venous distention to the middle neck at 30 degrees, a palpable maximal impulse displaced inferiorly and laterally with a prominent S4 heart sound, and bilateral bronchovesicular lung sounds. Tinel sign was present, as noted by a tingling sensation following percussion over the median nerve on both wrists. Further investigation revealed a serum creatinine level of 1.4 mg/dL (reference range 0.74–1.35) with undetectable troponin T enzyme, elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) of 2,145 pg/mL (reference range < 125 pg/mL), and electrocardiogram (ECG) with low voltage, normal sinus rhythm, and Q waves in the anterior leads.

**1** Which of the following diagnostic studies is the most appropriate to obtain next?

- Echocardiography
- Chest radiography
- Exercise stress testing
- Coronary angiography

## DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis for a patient who presents with dyspnea on exertion, abnormal ECG findings, and negative cardiac enzymes includes heart failure, myocardial ischemia, pericardial effusion, and noncardiac etiologies.<sup>1</sup>

Chest radiography would be beneficial to determine lung involvement and evaluate cardiac silhouette to screen for any abnormalities. However, cardiovascular abnormalities seen on chest radiography such

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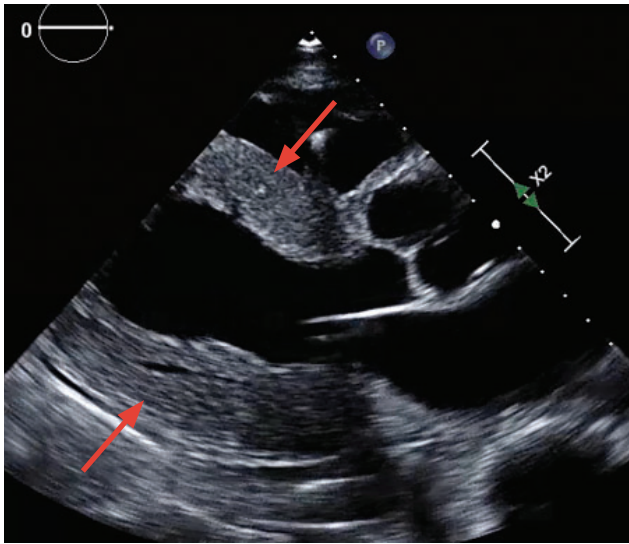
as altered shape or widened mediastinum would be nonspecific in this patient, and there are better imaging studies for heart function and anatomy. Additionally, in the context of abnormal physical examination findings, including abnormal heart sounds, elevated jugular venous pressure, and NT-proBNP elevation, a cardiac manifestation is more likely.

The cardiac stress test is a common diagnostic modality for patients with chest pain who are at risk for obstructive coronary artery disease. The patient's lack of cardiovascular risk factors and younger age make ischemia less likely, particularly if the chest discomfort is not thought to be an angina-equivalent. Similar reasoning can be used as to why a coronary angiogram would not be the ideal initial study to obtain. The patient has Q waves on the ECG, yet although an ischemic etiology is imperative to remain within the differential, in the context of no other findings suggestive of angina-equivalent symptoms, coronary angiography would not be the next step in management.

The best diagnostic study for this patient would be an echocardiogram to accurately assess the structure and function of the patient's heart. This will allow the clinician to narrow the potential reasons for the patient's presentation. According to the American College of Cardiology/American Heart Association appropriate use criteria, there are numerous indications for an echocardiographic evaluation, including suspicion of heart failure, as in our clinical presentation.<sup>2</sup>

## CASE CONTINUED: IMAGING RESULTS

Echocardiography showed a left-ventricular ejection fraction of 55% and concentric left-ventricular wall hypertrophy with a wall thickness of 15 mm (Figure 1). Echocardiography with strain imaging



**Figure 1.** Parasternal long-axis view on echocardiography demonstrates diffuse concentric left ventricular hypertrophy (arrows).

to evaluate function of the myocardium revealed longitudinal impairment with apical sparing, ie, the “cherry-on-top” appearance. There was no pericardial effusion.

**■ RED FLAGS FOR CARDIAC AMYLOIDOSIS**

At this time, infiltrative and hypertrophic pathologies should be considered (Table 1) such as Fabry disease, Danon disease, mucopolysaccharidosis, and hypertrophic cardiomyopathy.<sup>1</sup> However, in the context of this patient’s presentation it is important to consider cardiac amyloidosis, a type of infiltrative cardiomyopathy.

In this patient, red flags for cardiac amyloidosis include the ECG findings accompanied by a history of carpal tunnel syndrome and evidence of renal dysfunction.<sup>1</sup> ECG findings generally include a discordance in ECG voltage, which may be reduced or normal, and the degree of hypertrophy on imaging. Cardiac amyloidosis typically demonstrates abnormal global longitudinal strain with apical sparing, which helps differentiate this disease process from other etiologies of hypertrophy.<sup>3</sup> A history of carpal tunnel syndrome is common in patients with systemic amyloidosis as protein deposition can occur in both cardiac and non-cardiac organ systems.<sup>1</sup>

Amyloidosis is an infiltrative disease due to the accumulation of misfolded precursor proteins that make up amyloid.<sup>1,4,5</sup> Two major types of amyloidosis include light chain amyloidosis (AL) and transthyre-

tin amyloidosis (ATTR), which is further subdivided into hereditary (hATTR) and wild-type (ATTRwt). While cardiac amyloidosis has been historically thought to be a rare disease, emerging imaging and other advancements in medicine have revealed a greater prevalence of ATTR than what was previously believed. This may be due to the phenotypic heterogeneity in the presentation of the disease.<sup>1,4,5</sup> A survey of patients with ATTR and their caregivers showed that 57% of patients with hATTR and 39% of patients with ATTRwt received a misdiagnosis, 17% sought care from 5 different physicians before proper diagnosis, and those who were misdiagnosed received treatment for the wrong disease 75% of the time.<sup>4</sup>

Patients typically do not receive appropriate care owing to similarities of clinical presentation of cardiac amyloidosis with other etiologies of heart failure, the relatively advanced age of the patient population, misconceptions pertaining to the disease process, and common misdiagnosis.<sup>1,4,5</sup> Arrhythmias and bilateral carpal tunnel syndrome commonly precede heart failure symptoms in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) by many years.<sup>1,6,7</sup> It is also important to identify the myriad noncardiac manifestations that can be affected by the disease. For instance, patients tend to have a degree of renal dysfunction, neuropathies, and tendinopathies, including unprovoked tendon rupture, autonomic dysfunction,<sup>8</sup> lumbar spinal stenosis,<sup>9</sup> need for early joint replacements, issues with bowel motility,<sup>10</sup> and even retinal deposition of the misfolded protein.<sup>1,5</sup> A thorough history from the patient and care team along with a high suspicion for ATTR-CM is essential for a clinician to piece together the diagnosis.

**2** What diagnostic studies should be performed early in the suspicion of cardiac amyloidosis?

- Fat pad biopsy
- Monoclonal protein testing with free light chain analysis
- Genetic testing
- Endomyocardial heart biopsy

In a patient with high suspicion for cardiac amyloidosis, the clinical priority is differentiating between an etiology of AL or ATTR, and genetic testing would not provide a definitive diagnosis.<sup>5,11</sup> Genetic testing is warranted once ATTR is discovered to determine the form of disease being hATTR or ATTRwt<sup>5</sup>; hATTR indicates that first-degree relatives are at higher risk for the development of this pathology.<sup>5</sup> Fat-pad biopsies can be used to evaluate for amyloid deposition,

**TABLE 1**  
**Findings that may warrant cardiac amyloidosis workup**

Extracardiac manifestations	Cardiac manifestations	Imaging findings
Bilateral carpal tunnel syndrome	Persistent mildly elevated troponin levels	Echocardiography: increased thickness of left ventricle, right ventricular free wall, atrioventricular valves, interatrial septum
Unprovoked biceps tendon rupture	Symptomatic hypotension or orthostasis in response to hypertensive medication	Electrocardiography: discrepancy in QRS voltage and left ventricular thickness
Lumbar stenosis	Unexplained atrioventricular block, heart block, or bundle branch block	Strain echocardiography: longitudinal impairment with apical sparing
Sensorimotor polyneuropathy	Elevated N-terminal-pro-brain natriuretic peptide not proportionate to severity of heart failure	Cardiac magnetic resonance imaging: increased extracellular volume or late enhancement
Autonomic dysfunction	Family history of cardiomyopathy	Chest radiography: cardiomegaly

yet the sensitivity for ATTR is approximately 50%, leading to unnecessary pain for the patient and potential false-negative results.<sup>5,12</sup> Endomyocardial biopsy would be warranted after conflicting or equivocal findings of another less-invasive test.<sup>5,12</sup>

### ■ PATHOGENESIS OF CARDIAC AMYLOIDOSIS

Two of the primary types of systemic amyloidosis include ATTR amyloidosis, in which the liver produces an excess amount of protein that ultimately misfolds and deposits in various tissues, and AL amyloidosis, which is primarily a bone marrow dyscrasia in which monoclonal proteins are overproduced and deposit in the various tissues.<sup>1,5</sup> These two conditions can have similar presentations but their treatment pathways are completely different, so it is of the utmost importance to rule out AL early in disease stage.<sup>5,11-13</sup> With a 6-month median survival of patients from time of diagnosis with AL, an urgent hematology-oncology evaluation is warranted.<sup>13</sup> Sensitivity of over 99% for AL is achieved when combining serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum light chain concentration.<sup>12</sup> Serum plasma electrophoresis has an inferior sensitivity of approximately 70% and should be avoided.<sup>12</sup> These three tests should be ordered before or simultaneously with diagnostic imaging to avoid delay of targeted treatment.

Amyloidosis involves the misfolding and subsequent deposition of precursor proteins, infiltrating numerous organ systems within the body.<sup>5,11-13</sup> Transthyretin is a

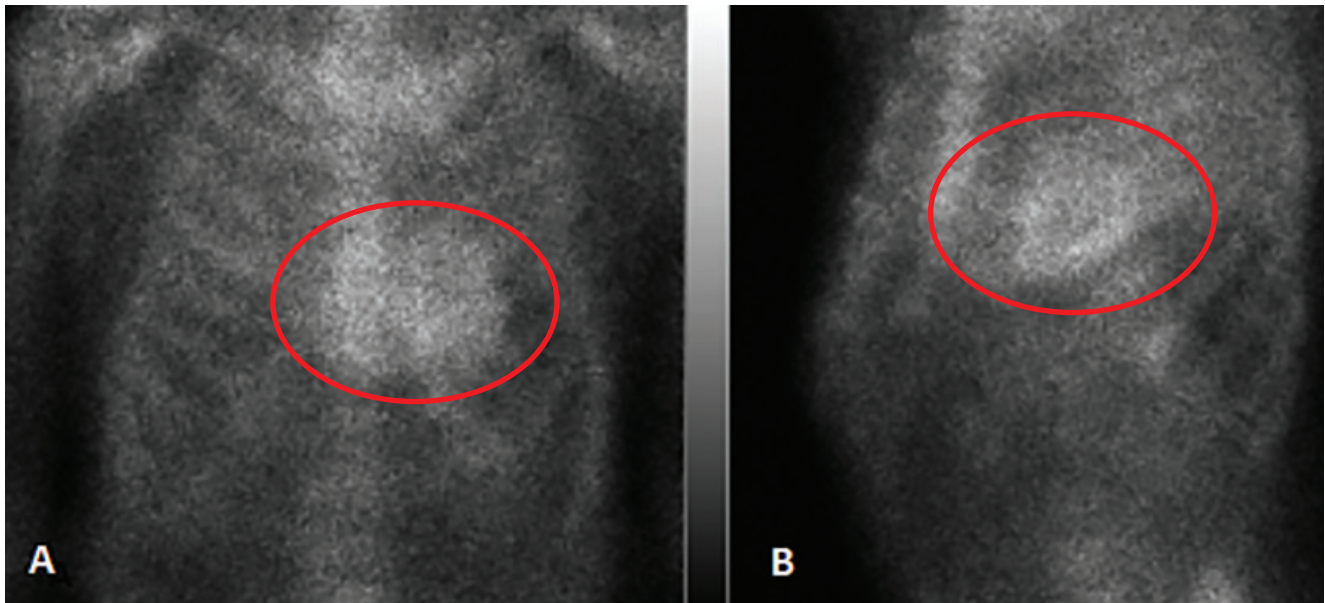
tetramer that acts as a tertiary carrier protein for thyroxine and holo-retinol binding protein and is mostly secreted from the liver into the blood.<sup>12</sup> In hATTR, a single amino acid mutation occurs on chromosome 18 where the transthyretin gene is found, causing aggregation to be more efficient.<sup>5,11,12</sup> In ATTRwt, the wild-type protein becomes unstable without any evidence of damage to the genetic sequence.<sup>5,11</sup>

**3** What is the next step in confirming suspicion of ATTR?

- Cardiac magnetic resonance imaging (MRI)
- Fluorodeoxyglucose-positron emission tomography (FDG-PET)
- Technetium-99m pyrophosphate scintigraphy
- Endomyocardial heart biopsy

Cardiac MRI would be beneficial in this patient if echocardiography was inconclusive and further investigation was warranted. Cardiac MRI would not give a definitive diagnosis for ATTR but may be useful when excluding other pathologies such as hypertrophic cardiomyopathy or a different infiltrative process. It can be suggestive of amyloidosis but not diagnostic. FDG-PET is used to detect sarcoidosis or malignancy but would not be useful in the diagnosis of cardiac amyloidosis.

Although endomyocardial biopsy still has a role in certain clinical conditions, it would be an invasive and more aggressive modality to help make the diagnosis compared with more conventional imaging modalities.



**Figure 2.** Technetium-99m pyrophosphate scintigraphy. (A) Anterior and (B) left anterior oblique views in our patient demonstrated grade 2 to 3 myocardial uptake of the radiotracer (circles) 3 hours after injection, thus meeting diagnostic criteria for transthyretin amyloid cardiomyopathy.

**■ DIAGNOSIS OF AMYLOIDOSIS**

Technetium-99m pyrophosphate scintigraphy is the recommended diagnostic tool for ATTR-CM. It is cost-effective, noninvasive, and relatively widely available.<sup>14,15</sup> The radiotracer used in this scan is generally absorbed by bone structures and amyloid deposition in the myocardium, and therefore the degree of uptake in the myocardium is generally compared with that of the contralateral ribs.<sup>14,15</sup> In normal myocardium, no uptake would be present, but in patients with ATTR-CM, radiotracer uptake is usually comparable to or exceeds that of the contralateral ribs based on the severity of the disease process. Due to the diffuse deposition of amyloid throughout the myocardial tissue, the sensitivity of endomyocardial biopsy for the diagnosis of cardiac amyloidosis is nearly 100%.<sup>14</sup> Nonetheless, the risks of the procedure and limited access make it the less favorable option. When observing 103 patients undergoing diagnostic endomyocardial biopsy for ATTR-CM, a radiotracer uptake of grade 2 to 3 had sensitivity of 94% and specificity of 89%, with 100% specificity for grade 3.<sup>15</sup>

While false-positive results may occur with this test, further investigations are recommended to diminish the likelihood of this.<sup>14,15</sup> To distinguish blood-pooling from myocardial uptake, single-photon emission computed tomography is necessary after technetium-99m pyrophosphate scintigraphy has

shown evidence of ATTR-CM.<sup>12,15</sup> Once blood-pooling and AL amyloidosis have been ruled out, ATTR-CM will meet diagnostic criteria if scintigraphy shows grade 2 to 3 cardiac uptake 3 hours after injection, as seen in our patient (**Figure 2**).<sup>14</sup> ATTR should only be established after AL has been ruled out with serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum light chain concentration.<sup>12,15</sup>

**4** What is the best disease-modifying medical treatment for cardiac amyloidosis?

- Doxycycline
- Tafamidis
- Inotropes
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

**■ MANAGEMENT OF CARDIAC AMYLOIDOSIS**

Although doxycycline and NSAIDs have been used historically in the treatment of cardiac amyloidosis, there are no data to support their ability to alter the disease process or to show a survival benefit.<sup>5,12</sup> These treatments were used on the premise of having efficacy in other inflammatory and infectious cardiac etiologies.<sup>5</sup> Inotropes and diuretics may improve the quality of life for patients with specific types of cardiomyopathies but will not change the progression of the disease.<sup>16</sup> The pathogenesis of ATTR-CM involves

TABLE 2

**Disease-modifying therapies for transthyretin amyloidosis (ATTR) approved by the US Food and Drug Administration**

Drug	Indication	Effect on transthyretin
Tafamidis	Wild-type or hereditary ATTR cardiomyopathy	Stabilizer
Vutrisiran	Hereditary ATTR with neuropathy	Silencer
Patisiran	Hereditary ATTR with neuropathy	Silencer
Inotersen	Hereditary ATTR with neuropathy	Silencer

the deposition of proteins. Therefore these methods would not alter the disease course.

The goal of drugs that target ATTR is to slow the progression of the disease. However, cardiac and extracardiac manifestations of ATTR must also be managed. Due to the low stroke volume of the heart in ATTR-CM, beta-blockers should be avoided, though they may be necessary for rate control of arrhythmias that commonly occur owing to atrial involvement of the disease.<sup>16</sup> Referral to a neurologist may be necessary as the patient may experience polyneuropathy and autonomic instability evidenced by orthostatic hypotension.<sup>16</sup>

Disease-modifying therapies for ATTR-CM target transthyretin through silencing, stabilization, and disruption (**Table 2**). Tafamidis is the first treatment approved by the US Food and Drug Administration for ATTR-CM and is used in both the wild-type and hereditary subtypes.<sup>17,18</sup> The mechanism of this medication is to stabilize the transthyretin protein in its tetrameric configuration, ultimately preventing breakdown into unstable monomers that infiltrate various organ systems. In the ATTR Tafamidis in Transthyretin Cardiomyopathy Clinical Trial,<sup>17</sup> patients randomized to tafamidis therapy not only had a decrease in cardiovascular-related hospitalizations but also showed less decline in functional capacity and reduced all-cause mortality. Over a 30-month span of treatment with tafamidis, therapy was tolerated well with safety profiles similar to those with placebo.<sup>17</sup> Furthermore, patients randomized to tafamidis experienced less worsening of their general health, reduced or no worsening in heart failure symptoms, and improved quality of life.<sup>18</sup> Other transthyretin-stabilizing drugs such as diflunisal have been shown to improve survival

in patients with cardiac ATTR.<sup>19</sup> Further research targeting ATTR through silencing and disruption shows promising results: medications like patisiran and inotersen have reduced the production of transthyretin by up to 80%, ultimately stabilizing or partially relieving peripheral neuropathy in patients included in the trial.<sup>20</sup>

**The goal of drugs that target ATTR is to slow the progression of the disease, but cardiac and extracardiac manifestations must also be managed**

**5** This patient was initiated on tafamidis therapy, but 2 years later he was noted to have a reduced left ventricular ejection fraction of 35%, small left ventricle cavity size, worsening symptoms of heart failure, and a negative coronary angiogram. What treatment option should be considered at this juncture?

- Left ventricular assist device
- Heart transplantation
- Addition of diuretics to tafamidis treatment
- Hospice or palliative care

**■ FURTHER MANAGEMENT IN AMYLOIDOSIS PATIENT**

Left ventricular assist devices (LVADs) are used for patients with end-stage heart failure with reduced ejection fraction. LVADs have demonstrated survival and quality-of-life benefits among select patient populations. Patients with cardiac amyloidosis tend to have small ventricle sizes as a result of hypertrophy, which will likely preclude successful LVAD implan-

tation, and no study has demonstrated improvement in morbidity or mortality in this patient population.<sup>21</sup> Therefore, LVAD therapy would not be an ideal option for our patient.

Diuretics are an adjunct to traditional guideline-directed therapies in patients with reduced ejection fraction. Although diuretics improve symptoms by way of decongestion, they do not increase survival and will not modify disease progression in heart failure with reduced ejection fraction. Hospice or palliative care may be an option for a patient with ATTR-CM who elects not to proceed with more invasive treatments or would not be able to tolerate them.

The age of the patient and lack of other significant comorbidities should warrant consideration for heart transplantation as the next step in management.

### CASE CONCLUSION

The patient was ultimately considered for and underwent successful orthotopic heart transplant without complications.

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### TAKE-HOME POINTS

- Amyloidosis involves the misfolding of precursor proteins, resulting in an infiltrative pathology of protein deposition involving numerous organ systems, including the heart.
- Amyloidosis is a multisystem disease; therefore, clinicians should be aware of extracardiac involvement that may raise suspicion for the diagnosis.
- Once a high suspicion of cardiac amyloidosis has been established, prioritization of differentiation between AL-CM and ATTR-CM is of utmost importance, as treatment differs drastically, and disease course may progress rapidly without intervention.
- Although cardiac amyloidosis is considered rare, data demonstrate a much higher prevalence than previously thought, giving emphasis to the need to screen patients with clinical features consistent with ATTR.

### DISCLOSURES

Dr. Wolinsky reports consulting with Alnylam Pharmaceuticals and Pfizer, and consulting, teaching, and speaking with Akcea Therapeutics and Astellas Pharma US. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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