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ABSTRACT

Cardiac amyloidosis is an increasingly recognized entity that causes significant morbidity and mortality. Transthyretin amyloidosis (ATTR) is present in about 16% of patients with severe aortic stenosis and up to 17% of patients with heart failure with preserved ejection fraction[9,10]. Though the screening test of choice, echocardiography is not highly sensitive or specific, and it should not be relied upon to rule out cardiac amyloidosis, especially if clinical suspicion is high.

We present a case of a 58-year-old woman with a history of bilateral carpal tunnel syndrome who presented with paresthesia and syncope. Extensive workup for neurologic, infectious, and malignant etiologies was negative. EKG was remarkable for low voltage. Transthoracic echocardiogram (TTE) was not suggestive of infiltrative disease. Subsequent cardiac MRI demonstrated diffuse biventricular late gadolinium enhancement and technetium 99M pyrophosphate scan revealed diffuse (3+) uptake, which was in stark contrast to the TTE. The diagnosis of ATTR amyloidosis allowed for prompt initiation of treatment in this patient.

Syncope is an uncommon presentation of cardiac amyloidosis. Such significant cardiac burden of disease without appreciable changes on TTE or clinical heart failure, demonstrates the importance of clinical vigilance and thorough workup when suspicion for amyloidosis is high, particularly if characteristic signs and symptoms consistent with systemic disease are present, as timely treatment can significantly reduce the morbidity and mortality of this disease.

INTRODUCTION

The term "amyloidosis" describes a group of diseases characterized by the tissue deposition of amyloid fibrils - misfolded proteins or protein fragments that have aggregated and stabilized in primarily beta-pleated sheet configuration.[1] When this process involves cardiac tissue, it is known as cardiac amyloidosis. The subsets of amyloid most known for cardiac involvement are transthyretin amyloidosis (ATTR) and light chain amyloidosis (AL). Diagnosis of these diseases can be challenging as echocardiographic parameters lack specificity and sensitivity. Understandably, the involvement of cardiac tissue carries a high morbidity and mortality rate, making it an area of growing interest and research to this day. In this case report, we highlight a patient with cardiomyopathy caused by ATTR and emphasize the importance of maintaining a high index of suspicion for this disease.

CASE PRESENTATION

A 58-year-old female of Irish descent with a history of bilateral carpal tunnel syndrome and bilateral lower extremity paresthesias presented to the cardiology office with complaint of recurrent syncope. She had undergone an extensive evaluation by her primary care doctor and a neurologist. With negative workup, but continued episodes of syncope, she was referred to cardiology.

Her EKG was significant for low voltage and poor R-wave progression (**Figure 1**). Her review of systems revealed a 15-pound unintentional weight loss over the previous year, in addition to her paresthesias. Her family history was significant for a paternal grandfather who died of cardiac causes of unknown etiology. She had a normal stress echo 4 months prior to evaluation. Labs were unremarkable aside from a mildly elevated ferritin of 207 ng/mL (reference range 15-150 ng/mL).

A transthoracic echo showed normal left ventricular size and systolic function. Concentric remodeling but no left ventricular hypertrophy was present and there was borderline left atrial enlargement. Although there were technical limitations that precluded accurate assessment of global longitudinal strain, the overall strain was reduced but was not consistent with any diagnostic pattern. Assessment of diastolic function revealed a mildly reduced medial annular velocity of 6 cm/s but the lateral annular velocity was normal measuring 11 cm/s and the E/E ' was normal.

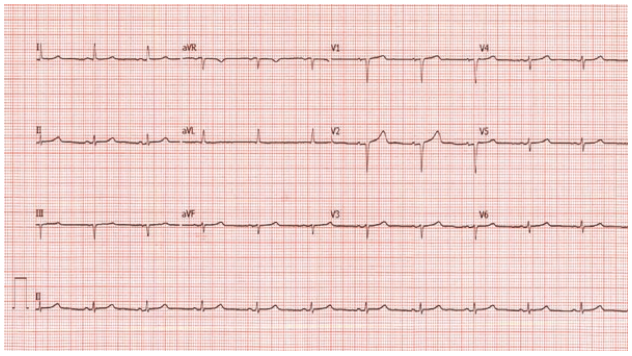

Figure 1: Patient's electrocardiogram showing low voltage and poor R-wave progression

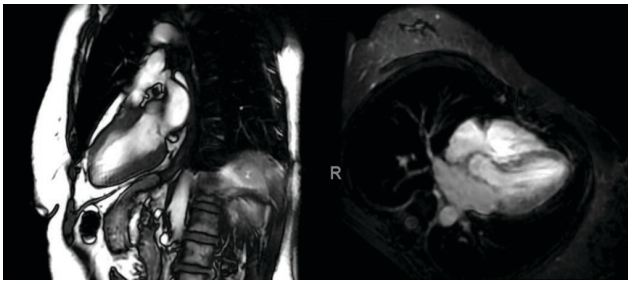

Figure 2: Cardiac MRI showing patchy late gadolinium enhancement of the entire left ventricle involving portions of the subendocardium, mid-myocardium and subepicardium

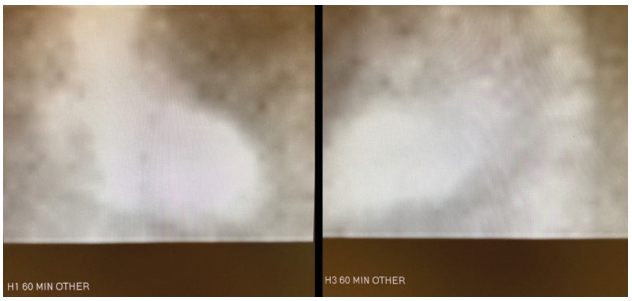

Figure 3: Nuclear PYP scan showing diffuse 3+ uptake

Given suspicion for infiltrative disease due to the patient's peripheral neuropathy and low voltage EKG, a cardiac MRI was ordered. The MRI showed patchy late gadolinium enhancement of the entire left ventricle involving portions of the subendocardium, mid-myocardium and subepicardial left ventricle, with additional enhancement of the right ventricle (**Figure 2**). These findings were highly concerning for amyloidosis and the diagnosis was confirmed by nuclear medicine scanning, which showed diffuse 3+ uptake of technetium 99 M pyrophosphate throughout the myocardium, consistent with TTR amyloidosis (**Figure 3**). To complete the workup, serum and urine immunofixation electrophoresis were checked, which were unremarkable.

Genetic testing confirmed the diagnosis of hereditary amyloidosis with a T80A mutation. At time of diagnosis her NT-proBNP was 331. She has since started on tafamidis and patisiran, which she is tolerating well. She currently has no clinical signs or symptoms of heart failure. She has consulted both with a heart failure specialist and a hepatologist regarding transplantation, which are not indicated at this time. She has a large extended family, and she has been educated on the importance of considering genetic and phenotype testing for them.

DISCUSSION

Transthyretin is a protein synthesized in the liver, that normally exists as a tetramer whose main functions include transport of vitamin A and thyroxine. There are two types of ATTR: hereditary (ATTR-FAP) and wild-type (ATTR-wt). ATTR-FAP is caused by inherited point mutations of the transthyretin protein, of which over 100 have been identified, leading to accelerated amyloid deposition. It usually displays autosomal dominant inheritance. ATTR-wt (previously known as senile or age-related systemic amyloidosis), is caused by normal TTR that becomes unstable, misfolds, and accumulates over time as amyloid deposits[1,2].

Due to the wide range of symptoms that ATTR can cause in different organ systems, its diagnosis is not straightforward and often delayed by years. Outside of the heart, amyloidosis can present with progressive symptoms in the nervous systems, eyes, kidneys, and gastrointestinal tract. The most common initial symptoms of ATTR-FAP are sensory-motor, such as peripheral neuropathy and carpal tunnel syndrome, and autonomic, such as GI motility disturbances and orthostatic hypotension. These manifestations can pre-date the diagnosis of amyloidosis by years[3].

Although there are characteristic findings on EKG such as low voltage and high-grade AV block, these are often not present and is usually a late manifestation of cardiac disease. In fact, less than 40% of patients with biopsy-proven ATTR have low voltage on EKG[4]. The first screening tool for diagnosis is most commonly a transthoracic echocardiogram (TTE). There are several characteristic TTE findings associated with cardiac amyloidosis. The most referenced phenotype is characterized by septal and left ventricular hypertrophy, usually with diastolic dysfunction and preserved to low ejection fraction. It is important to note that these characteristics are not specific to amyloidosis. Hypertrophic or hypertensive cardiomyopathy can have overlapping echocardiographic features. However, there have been some established studies showing more unique differentiating features. For example, two-dimensional speckle-tracking to show a relatively

sensitive and specific "apical sparing" longitudinal strain pattern is unique to amyloid cardiomyopathy[5,6].

If echocardiogram findings are suggestive of, or the clinical suspicion is high enough for cardiac amyloidosis, the next steps in workup include ruling out AL amyloidosis and in some cases obtaining a cardiac MRI. Once AL is ruled out, bone tracer cardiac scintigraphy is done to assess for ATTR. Endomyocardial biopsy is only needed if the scintigraphy grade is not sufficient to be diagnostic. Once the diagnosis of ATTR is made, genetic testing is used to identify hereditary ATTR[5]. This is particularly important because family members can be screened.

The treatment of cardiac amyloidosis is a continuously evolving field with the most recent developments being disease-modifying agents such as TTR stabilizers, silencers, and disruptors. Liver transplantation is an option to stop the progression of disease though it does not reverse already existing amyloid infiltration and related symptoms and is becoming less common as medical therapies improve[7,8].

In this case, we demonstrate how cardiac amyloidosis can have a varied presentation, requiring prompt recognition and diagnosis. Although TTE is the first screening test of choice, its imperfect sensitivity and specificity do not allow it to be used to rule out a diagnosis of CA. One must maintain a high index of suspicion and pursue further testing especially in situations where other organ systems are already involved[2]. Our patient had a history concerning for CA given her peripheral neuropathy, bilateral carpal tunnel syndrome, and syncopal episodes. She had low voltage on EKG but her TTE was not suggestive of infiltrative disease.

The patient's TTE was a stark contrast to the cardiac MRI and PYP scan, which showed extensive late enhancement and diffuse 3+ uptake throughout the myocardium, respectively. Such significant cardiac burden of disease without appreciable changes on TTE further demonstrates the importance of clinical vigilance and thorough workup when suspicion for amyloidosis is high.

Early detection is especially important given the progressive nature of ATTR and the fact that there are therapies with multiple different mechanisms of action available to halt the progression of this disease. These medications are most effective at minimizing the impact of the disease when initiated early, as the compounding effects of this disease over time are not reversible with pharmacologic therapy. Furthermore, cardiac involvement, when present, is the principal determinant of survival[5]. Our patient's diagnosis was fortunately confirmed before she had any significant heart failure symptoms, and she was initiated on treatment with tafamidis and patisiran early in her disease course.

ATTR has previously been considered a rare diagnosis. However, recent studies suggest that ATTR is present in about 16% of patients with severe aortic stenosis and up to 17% of patients with HFpEF[9,10]. This represents a significant percentage of patients with these two fairly common conditions, making accurate and early diagnosis even more crucial, especially given that pharmacologic therapies are most effective when initiated prior to the onset of significant cardiac involvement.

In conclusion, this case serves to emphasize the variation of clinical presentation in ATTR and specifically the limited sensitivity of echocardiography in diagnosis. It remains of high importance to consider and act early when there is clinical suspicion for amyloidosis in patients with a compatible history.

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