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# Amyloid Cardiomyopathy in African Americans and the Transthyretin Linkage Associated with Macroglossia: A Rare Presentation

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**Abstract** We report a case of a 63 year old African American female with congestive heart failure, poorly controlled hypertension, and end stage renal disease admitted for STEMI (ST Elevation Myocardial Infarction) and hypertensive crisis. Macroglossia was noticed during hospitalization and an echocardiogram was suggestive of cardiac infiltrative disease. Protein electrophoresis and immunofixation were negative. Although macroglossia is a common finding in light chain (AL) amyloidosis, there are reported cases in transthyretin (ATTR) amyloidosis. Learning objective: To highlight a rare presentation of transthyretin amyloidosis, and to raise awareness of this disease and its particular prevalence in the African American and African Caribbean populations.

***Keywords:*** *amyloidosis, African-American, african-caribbean, transthyretin amyloidosis, macroglossia; congestive heart failure*

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## 1. Introduction

Amyloidosis has a wide variety of non-specific clinical findings. Cardiac involvement is most commonly seen in AL and familial or senile ATTR amyloidosis. Macroglossia is usually linked with AL amyloidosis, although it can also be evident in ATTR amyloidosis [1,2,3]. The ATTR variant has a high prevalence in African American populations and should be suspected in any African American adult with unexplained heart failure and echocardiogram findings suggestive of infiltrative disease. Therefore, we present a suspected case of ATTR amyloidosis in an African American female with heart failure and macroglossia.

## 2. Case Presentation

A 63-year-old African American female with known history of congestive heart failure, poorly controlled hypertension and end stage renal disease on hemodialysis presented with shortness of breath for several days associated with chest tightness. She had previous multiple admissions for hypertensive crisis attributed to medication noncompliance. On admission, she was hypoxic and in hypertensive crisis with a blood pressure of 290/112 mmHg. General appearance was apparent for moderate respiratory distress. Further examination revealed jugular venous distension and bibasilar crackles. Cardiac evaluation revealed grade 3/6 systolic murmur over the apex radiating to the axilla. No appreciable S3 nor S4 gallop. Hemogram revealed anemia (10g/dL). Renal function panel showed blood urea nitrogen and creatinine of 69mg/dL and 5.4mg/dL respectively. She had mild troponinemia of 0.075ng/mL and elevated BNP greater than 5000pg/mL. Electrocardiogram demonstrated sinus tachycardia (104 bpm), left ventricular hypertrophy, and ST elevations in anterolateral leads. Chest radiograph showed bilateral consolidations and worsening pulmonary congestion. Transthoracic echocardiogram revealed right ventricular systemic pressure of 60mmHg, lipomatous hypertrophy of the interatrial septum, severe concentric biventricular hypertrophy, and dense myocardial speckling. The patient was admitted with a diagnosis of STEMI, CHF, and hypertensive crisis and treated accordingly. During her stay in the ICU she developed upward gaze, confusion and jaw trismus, which progressed to nonresponsiveness to verbal stimuli. Macroglossia was noticed during intubation. EEG revealed nonconvulsive status epilepticus refractory to all antiepileptic medications. She eventually required tracheostomy and PEG tube placement. Three days later she had a cardiac arrest and was revived. A repeat TTE showed an EF of 55% and a moderate concentric LVH with speckled pattern (Figure 1) and Tissue Doppler velocities consistent with reduced longitudinal systolic shortening (reduced S' velocity) and diastolic dysfunction (reduced E' velocity) suggestive of infiltrative disease (Figure 2). Protein electrophoresis and immunofixation were normal. Genetic testing for ATTR was discussed with the family, but the family declined. After two weeks in ICU she became more alert and was transferred to the floors, but then developed a tracheostomy related ventilatory compromise which eventually lead to her demise. Autopsy was declined by family.

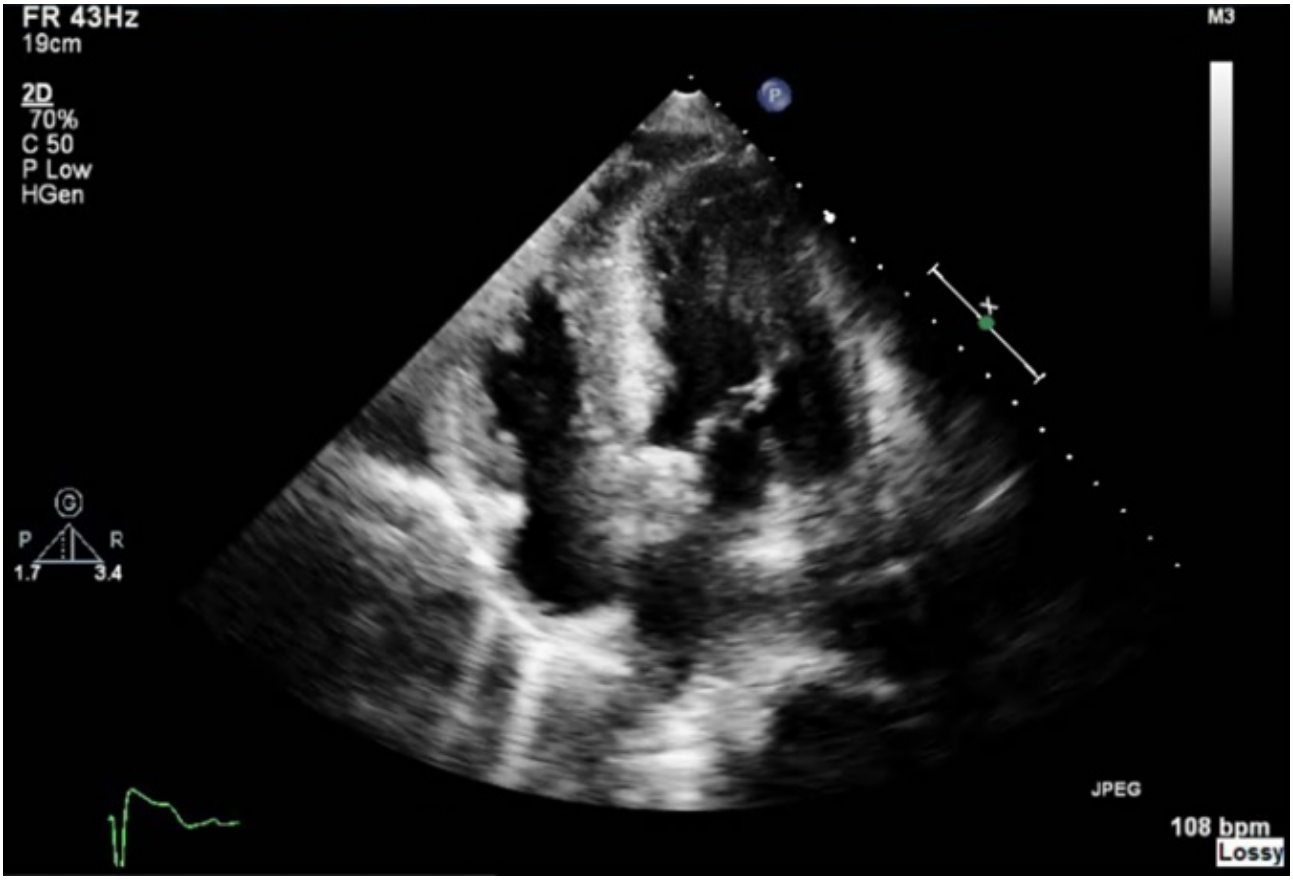


**Figure 1.** Echocardiographic appearance of cardiac amyloidosis. Four chamber view, increased biventricular wall thickness and interatrial septal thickness

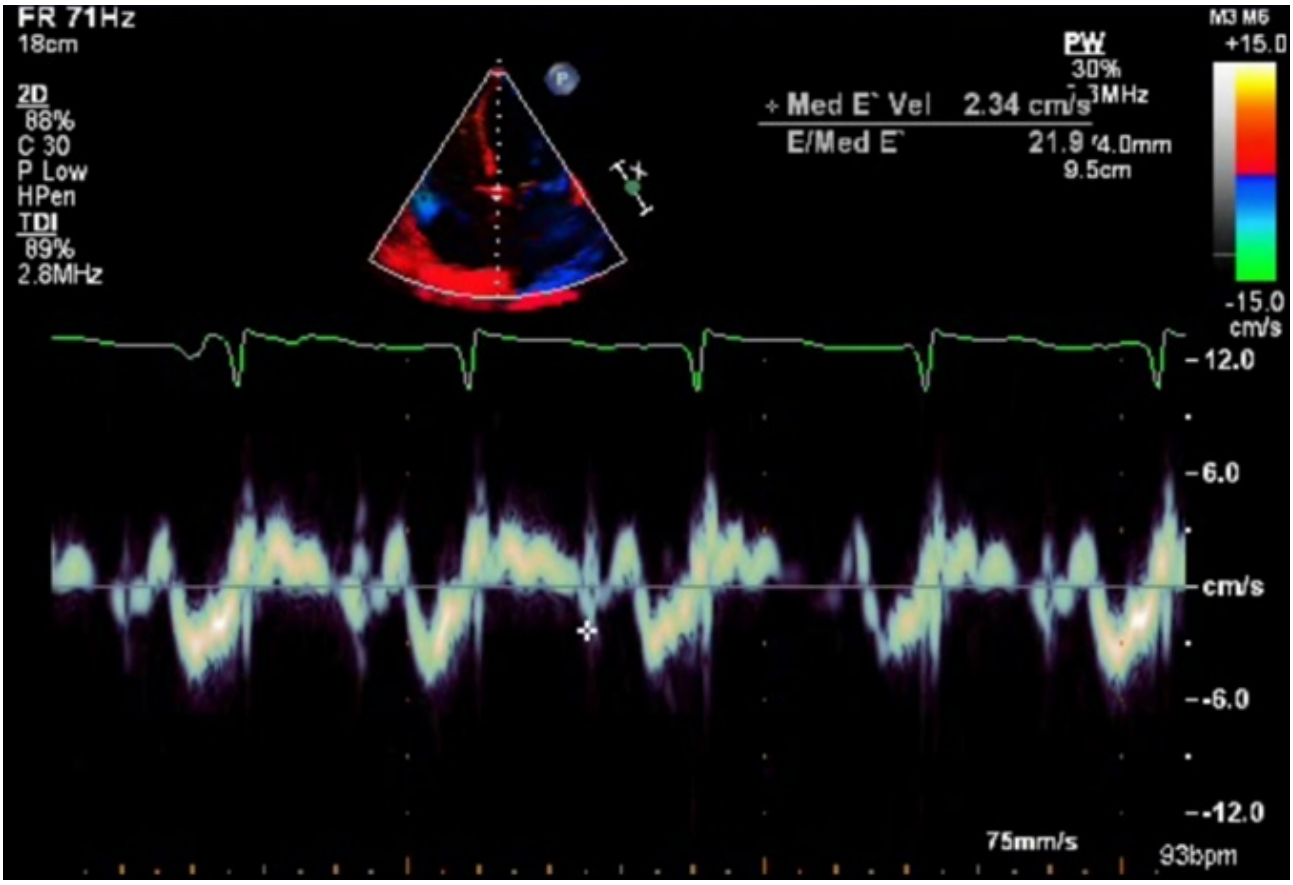


**Figure 2.** Tissue Doppler velocities consistent with reduced longitudinal systolic shortening (reduced S' velocity) and diastolic dysfunction (reduced E' velocity)

**Table 1. Differences between AL and ATTR V122I**

| | AL | ATTR |
|---|---|---|
| Etiology | Plasma cell dyscrasia | Mutation V1221 |
| Organs affected | Heart, kidneys, tongue, skin, GI tract | Heart, PNS, tongue (rare) |
| Signs/symptoms | Nephritic syndrome, hepatomegaly, neuropathy, macroglossia, periorbital purpura | CHF, neuropathy, macroglossia (reported cases) |
| Ethnic group | No difference | African-American and African-Caribbean |
| Age | 40-50 yo | 60-70 yo |
| Stroke | (+++) | (+) |
| Low QRS voltage inECG | 46-60% | 25-40% |
| Cardiac conduction abnormalities | Rare | Often |
| IVST in Echocardiogram | >12 mm | >15 mm |
| BNP (fg/ml) | 500-600 | >1000 |
| Treatment | Chemotherapy | Liver transplant |
| Survival if untreated | <1 year | 27 months |
| Abbreviations: V1221. Valine 122 lsoleucine; PNS. Peripheral nervous system, CHF. Cardiac heart failure; GI. Gastrointestinal; IVST. Interventricular septal thickness; BNP. Beta natriuretic perptide. | | |

## 3. Discussion

Amyloidosis is a systemic condition that results from the deposition of proteins in different tissues, which is often diagnosed at an advanced stage due to non-specific symptoms. Cardiac involvement in amyloidosis may be the predominant feature or may be found on investigation of a patient presenting with another major organ involvement. Macroglossia was the first sign suggestive of infiltrative disease in this patient and considered to be a pathognomonic feature of AL amyloidosis. However, up to 8 percent of patients with ATTR cardiac amyloidosis can present with macroglossia [3]. The three most common types of amyloidosis are AL, familial or senile ATTR and secondary (AA) amyloidosis. AL and ATTR are more commonly associated with amyloid cardiomyopathy [4]. AA is associated with different chronic inflammatory disorders, but AA amyloidosis rarely produces heart disease [1]. Cardiac involvement is most commonly seen in AL amyloidosis. Fifty percent of AL patients have clinically significant cardiac involvement, but there is limited data on ATTR [5]. This patient had a previous history of heart failure and this is the most common cardiac manifestations in both AL and ATTR amyloidosis. Atrial fibrillation and poor atrial mechanical function have been reported also. ATTR is typically associated with milder clinical manifestations, slower progression and a more benign prognosis than AL amyloidosis, although patients are more prone to develop atrial fibrillation and the disease presents later in life [6]. The most common ATTR amyloid cardiomyopathies in the United Stated are caused by the Val122Ile allele mutation [7]. Our patient was African-American and the ATTR variant has a prevalence of 3 to 4 percent in the African-American and African-Caribbean population, with an estimated homozygote prevalence of 10 percent in those patients [8]. Based on most recent United States census statistics, ≈1.5 million African Americans carry the Val122Ile mutation and are at risk for the development of ATTR amyloidosis [9]. The other ATTR amyloidosis type is called “wild-type ATTR,” most commonly known as senile systemic amyloidosis. In the majority of these cases, amyloid deposits are of no clinical significance. Only a small proportion of patients in which the ventricular deposition is massive develop heart failure [7].

Echocardiography is the initial noninvasive test of choice although hypertensive cardiomyopathy can give a similar appearance. The most common findings in amyloidosis are increased left ventricular wall thickness and diastolic dysfunction as well as increased echogenicity, described as “sparkling” or “granular”. Most studies report increased wall thickening in ATTR compared to AL amyloidosis, but longitudinal strain impairment is similar and does not have adequate sensitivity or specificity to distinguish between types. A small study found a difference in ratio of BNP and left ventricular mass index that was higher in AL patients [10]. These differences, among others, are described in Table 1. Cardiac Magnetic Resonance (CMR) produces high-resolution images of the heart and several studies have shown high sensitivity of late gadolinium imaging in cardiac amyloidosis although there was no difference in the amyloid deposition pattern between different subtypes. Nuclear cardiac imaging has emerged as an imaging modality with high sensitivity, particularly in the ATTR subtype. Definitive diagnosis of cardiac amyloidosis is confirmed by amyloid deposits in endomyocardial biopsy or other tissues. The genetic test for ATTR is helpful in differentiating between the ATTR hereditary type and wild type. Cardiac amyloidosis should be considered in any adult with unexplained heart failure and an echocardiogram showing increased wall thickness. The ATTR type in particular is likely underdiagnosed in elderly Afro-American and Afro-Caribbean populations and should be suspected in any adult patient of this descent who has unexplained left wall thickening on echocardiogram with or without macroglossia. Increased awareness of this entity will identify more patients with cardiac amyloidosis, thereby allowing timely institution of appropriate treatment.

## Conflict of Interests

The authors declare that they have no conflict of interest.

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