BEST OF THE JOURNAL

Amyloid Cardiomyopathy

Roy S. Small, M.D.
Medical Director Clinical Research
Penn Medicine Lancaster General Health

Editor's Note: *Amyloid cardiomyopathy is now recognized as a common cause of heart failure, so it is vital that clinicians consider the diagnosis, and arrange for proper workup and treatment. Dr. Small provided a comprehensive discussion of this entity in the Fall 2020 issue; because of its clinical importance, I have asked him to provide a synopsis of that article. Readers are referred to the original for a more detailed discussion.*[1]

Amyloid cardiomyopathy (CM) is a common "uncommon" disease that is easily overlooked. There are rarely specific physical findings that suggest it, and the initial complaints encountered by primary care providers are often the non-specific signs and symptoms of congestion.

When the etiology of dyspnea is not initially obvious, an echocardiogram is a primary tool. Although not diagnostic, characteristic echocardiographic finding of amyloid CM may heighten suspicion and include left ventricular hypertrophy (LVH), left and right atrial enlargement, and diastolic dysfunction. If cardiac strain measurements are available, they may reveal a pattern of "apical sparing" that is characteristic of amyloid CM.

Amyloid CM is a systemic disease with frequent neurological, renal, and gastrointestinal involvement. There are two types of amyloid CM which must be distinguished, as the treatment and prognosis are radically different.

AL AMYLOID

AL amyloid is due to the overproduction of free immunoglobulin light chains produced by clonal hematopoietic cells. Early diagnosis is imperative as untreated disease may be rapidly progressive. The abnormal immunoglobulins can be detected by serum and urine immunofixation and a free light chain assay. There is no longer a role for serum protein immunophoresis (SPEP) as it is too insensitive. An abnormal kappa/lambda ratio, even in the setting of mildly elevated kappa or lambda chains, is an indication for tissue biopsy which is required for the diagnosis of AL amyloid. A fat pad needle biopsy may be diagnostic (up to 90% sensitive), but an endomyocardial biopsy may be required if suspicion is high and the fat pad biopsy is not diagnostic.

If AL amyloid is diagnosed, a hematology evaluation is imperative. Multiple myeloma and other hematopoietic malignancies occur in about 10% of AL amyloid patients. The treatment of AL amyloid has dramatically improved with new chemotherapeutic regimens. Historically, life expectancy following diagnosis of AL amyloid had been a matter of months, but with early diagnosis and aggressive treatment, survival is now typically measured in years.

ATTR AMYLOID

ATTR amyloid is caused by the tissue deposition of disassociated tetramers of the hepatic produced protein, transthyretin (TTR). There are two types of ATTR amyloid: *wild type* (ATTRwt) and *mutant* (ATTRm).

ATTRwt is more common and is due to age-related changes in transthyretin production (also referred to as "senile" amyloidosis). Unlike ATTRm, there are no associated genetic mutations with ATTRwt. This distinction is important as the treatment options are different for these two entities.

ATTR amyloid (both ATTRm and ATTRwt) may be detected by technetium pyrophosphate

(^{99m}TcPYP) scanning which is highly sensitive and specific for ATTR cardiac amyloid. If positive, a genetic analysis is required to distinguish ATTRm from ATTRwt amyloid. Unlike AL amyloid, a tissue biopsy is rarely required if the ^{99m}TcPYP scan is clearly positive.

There are three pharmacological treatment strategies for ATTR amyloid: TTR silencers (by mRNA inhibition), TTR stabilizers, and TTR fibrillary disruption.

Tafamidis meglumine is a TTR stabilizer approved for both ATTRm and ATTRwt that slows progression of the associated polyneuropathy and cardiac manifestations of the disease. It is most effective in patients with early cardiac involvement (NYHA I-II), is administered orally, and is well tolerated with few side effects.

Diflunisal (an NSAID) and *doxycycline + tauroursodeoxycholic acid* (TUDCA, an over-the-counter dietary supplement) have TTR disrupting and stabilizing properties but are not FDA approved.

Patisiran is a small interfering mRNA which disrupts hepatic transthyretin production and is classified as a TTR silencer. It is administered parentally and is FDA approved for ATTRm with polyneuropathy.

Inotersen is an antisense oligodeoxynucleotide (TTR silencer) administered subcutaneously, which interferes with hepatic production of TTR. It is FDA approved for ATTRm with polyneuropathy. Both *patisiran* and *inotersen* are undergoing clinical trials evaluating safety and efficacy in patients with ATTRwt.

CONCLUSIONS

Of the total U.S. heart failure population of 6.2 million, approximately 50% have a normal (preserved) ejection fraction, and amyloid CM accounts for 10-20% of these (i.e. 5%-10% of all patients with heart failure). It is thus a common disease for which there are now effective treatments. A renewed awareness of this disease is warranted, as early recognition by primary care providers can substantially improve outcomes.

REFERENCES

1. Small RS. Amyloid cardiomyopathy – an update. *J Lanc Gen Hosp.* 2020; 15(3): 85-89. http://www.jlgh.org/Past-Issues/Volume-15-Issue-3/Small_Amyloid-Cardiomyopathy.aspx

Roy S. Small, M.D.
The Heart Group of Lancaster General Health
217 Harrisburg Ave.
Lancaster, PA 17603
717-544-8300
Roy.Small@pennmedicine.upenn.edu