Penn Medicine

CLINICAL BRIEFING™

Cardiovascular Medicine • Amyloidosis Program

Treatment of TTR Amyloid Cardiomyopathy and Heart Failure

Cardiologists at Penn Medicine are treating patients for the cardiovascular sequelae of wild-type and familial amyloidosis as part of an institutional, multidisciplinary effort in coordination with the Penn Amyloidosis Program to treat transthyretin (TTR) amyloid disease.

Amyloidosis is a heterogeneous collection of protein folding diseases characterized by the extracellular deposition and accumulation of insoluble amyloid fibrils in tissue (Figure 1). Amyloidosis is considered a rare disease by the National Institutes of Health. However, recent data suggests the disease may be more common than previously appreciated.

Amyloid Disease Effects on the Heart

Of the multiple subtypes of amyloid disease, each with unique clinical features and natural histories, three have effects in the cardiovascular system:

- **AL AMYLOIDOSIS** (primary amyloidosis), the most common variant, and most widely diagnosed. A systemic plasma cell dyscrasia, AL may occur alone or with other plasma cell dyscrasias (e.g., multiple myeloma).
- **TWO VARIANTS** arising from an association with the transport protein transthyretin (TTR). Both affect specific populations and both are identified with cardiomyopathy, heart failure, and other effects.
  - » **Familial amyloidosis (ATTRm)** has a genetic component (>130 TTR mutations have been described) is known to affect African American, Swedish and Portuguese communities, among others, and is associated with peripheral and autonomic neuropathies and carpal tunnel syndrome (parasthesias, orthostatic symptoms).
  - » **Wild-type amyloidosis (ATTRwt)** occurs primarily in elderly men as a result of age-related protein instability (carpal tunnel syndrome, spinal stenosis, and tendon rupture occur with this type).

It should be noted that both AL and the TTR variants cause diastolic dysfunction, restrictive cardiomyopathy, arrhythmias, and heart failure. However, the natural history of these events varies widely by disease subtype. AL amyloidosis has systemic effects, can occur at an earlier age than TTR amyloid disease, and progresses more rapidly. Onset and extent of sequelae vary between the TTR subtypes, as well.

Management of TTR Amyloid Disease at Penn Medicine

ATTR is diagnosed and treated within the comprehensive Amyloidosis Program at Penn Medicine.

Diagnosis of TTR Amyloid Disease

Because AL progresses much more rapidly than TTR amyloidosis and is treated differently, it is critical to identify the amyloid subtypes promptly and accurately. Today at Penn Medicine, this is achieved by a combination of readily available serum and urine studies. If these tests

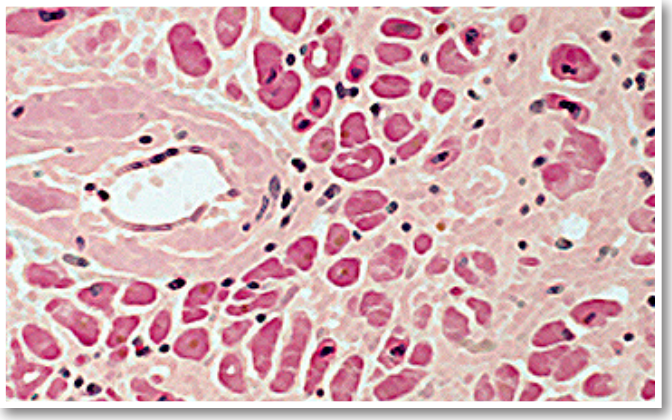

Figure 1: Amyloidosis is characterized by the accumulation of insoluble amyloid fibrils in tissue with concordant conformational changes.

are negative, AL amyloidosis can be excluded with virtual certainty, and a second, noninvasive technique, technetium pyrophosphate (^{99m}Tc-PYP) cardiac imaging can then be used to confirm TTR amyloid disease. When combined with other clinical clues, a grade 2 or 3 scan (Figure 2, back page) is essentially diagnostic.

Treatment

At Penn Medicine, the treatment of TTR amyloid disease involves disease modification with the FDA approved agents, tafamidis, inotersen and patisiran. Note that these medications act by slowing the progress of amyloid disease but are not a cure.

Tafamidis binds to the TTR tetramer to slow disease progression; inotersen and patisiran work by cleaving to and disabling amyloid messenger RNA, a mechanism known as RNA silencing (siRNA). siRNA drugs produce a reduction in circulating familial and wild-type TTR of ~80%. RNA inhibition is quickly becoming a standard investigational approach in other disease states.

Clinical Research

Penn Cardiology is conducting a study of molecular imaging of the underlying mechanisms of cardiotoxicity in patients with light chain amyloidosis using two types of positron emission tomography (PET/CT).

Elsewhere, clinical trials are ongoing to develop new drugs for patients with TTR Cardiac Amyloidosis. These include new siRNA drugs (Vutrisiran and AKCEA-TTR-LRx) and TTR stabilizers (AG10).

In addition, in studies, there is some evidence that existing agents, including doxycycline and tauroursodeoxycholic acid (TUDCA, an ambiphilic bile acid), have promise in fibril degradation and reabsorption.

(See Case Study, back page)

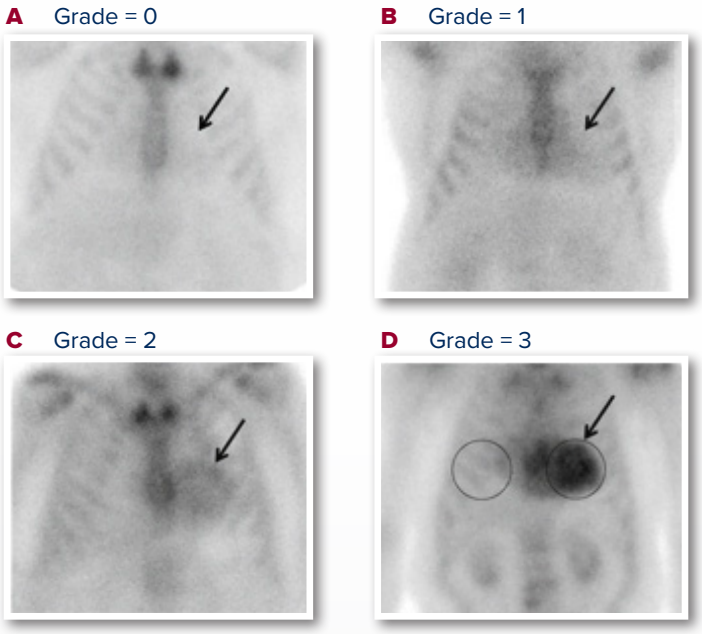

Figure 2: Images of tracer uptake in TTR cardiac amyloidosis patients. Arrows point to cardiac region. Circles represent region of interest in the cardiac area and contralateral right chest wall for quantitative analysis. **(A)** Non visualization of cardiac uptake in a patient without TTR involvement: Grade 0. **(B)** Mild uptake less than bone: Grade 1. **(C)** Moderate uptake equal to bone: Grade 2. **(D)** High uptake greater than bone: Grade 3. *Images: Chen W, Ton V-K.*

CASE STUDY

Mr. R, a 70-year-old man, visited his physician for an evolving set of symptoms over several months that included dyspnea and palpitations. In retirement, Mr. R was moderately overweight (BMI 26kg/m^2) and sedentary, but in otherwise relatively good health. A review of his medical and surgical history was exceptional only for carpal tunnel syndrome in both wrists, for which Mr. R had surgery 5 and 7 years previously.

An echocardiogram revealed mild left ventricular hypertrophy. Mr. R was administered an ACE inhibitor and diuretic and counseled to lose weight and exercise. In the next 18 months, however, Mr. R experienced a confusing set of symptoms, including weight-loss, scrotal edema and ascites. Revisiting his physician, he was referred for paracentesis, which was inconclusive. Mr R's diuretic was replaced by furosemide. By now alarmed, he asked to be referred to a hematologist-oncologist, where a metabolic panel excluded liver cancer, leukemia and primary amyloidosis.

Six months later, feeling increasingly ill, Mr. R self-referred to Penn Cardiology, where his history came to the attention of Brian Drachman, MD, Co-Director of the Amyloidosis Program, and an investigator in the ATTR-ACT trial that preceded the FDA approval of tafamadis for ATTR. Recognizing the combination of age, carpal tunnel syndrome, ascites and cardiovascular effects as precedents for ATTR, Dr. Drachman ordered a workup that confirmed transthyretin amyloid disease.

Mr. R had aggressive treatment of his heart failure and started taking tafamidis 80 mg daily. Within six months, he noted a substantial improvement in quality of life and capacity to perform the tasks of daily living. At two years, his disease is stable, and he remains in the community.

About the Penn Amyloidosis Program

At Penn Medicine, the treatment of amyloidosis involves the dedicated efforts of seven Divisions, including Cardiology, Renal Electrolyte and Hypertension, Hematology, Hematology-Oncology, Medical Oncology, Neurology and Pathology. The mission of the Amyloidosis Program is to diagnose and treat amyloidosis in all its manifestations.

Treating Amyloid Cardiomyopathy at Penn Medicine

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