CLINICAL VIGNETTE

Amyloid Cardiomyopathy and Autonomic Dysfunction in a 75-Year-Old Male

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Case Report

A 75-year-old male with congestive heart failure due to restrictive cardiomyopathy, hypertension, and atrial fibrillation was hospitalized for decompensated heart failure. He presented with syncope and recurrent dizziness. Echocardiogram showed ejection fraction of 40% which was reduced from 50-55% the prior year. Left and right heart catheterizations showed increased filling pressures and cardiac MRI was suggestive of restrictive cardiomyopathy. The patient underwent endomyocardial biopsy which revealed amyloid, specifically concerning for transthyretin amyloid cardiomyopathy (ATTR-CM). His medications were optimized, however, diuresis was limited by persistent orthostatic hypotension and autonomic dysfunction. Midodrine was started and all blood pressure medications were discontinued. However, he remained orthostatic with ongoing risks for syncope and was counseled on precautions. Due to deconditioning and weakness, he was discharged to a skilled nursing facility for rehabilitation. His rehabilitation progress was limited by persistent orthostatic hypotension despite titration of medications including midodrine and the addition of fludrocortisone. All blood pressure medications remained on hold, and diuretics were further reduced. Cardiology recommended tafamadis but availability was delayed due to high cost for non-formulary status and after a prolonged trial he had limited progress and lost coverage and was discharged home to continue home health therapy. Outpatient tafamadis was delayed and his condition deteriorated with limited clinical benefit of tafamdais due to frailty. He declined additional management trials and eventually transitioned to home hospice care.

Discussion

Transthyretin amyloidosis (ATTR) is a progressive adult-onset disorder resulting from tissue amyloid deposition of transthyretin that affects various nerve fibers associated with autonomic function and regulation. Approximately 40-60% of individuals with amyloidosis experience orthostatic hypotension and other disabling manifestations of autonomic dysfunction. Orthostatic hypotension is caused by impaired norepinephrine release from sympathetic neurons due to the amyloid deposition.[1] Transthyretin amyloid cardiomyopathy (ATTR-CM) is one type of systemic amyloidosis where the transthyretin protein is deposited in the myocardium. ATTR-CM may progress to advanced stages present with minimal initial signs which may overlap with more typical signs of heart failure. It can progress rapidly and is associated with poor prognosis.

Transthyretin (TTR) is a circulating protein mainly synthesized in the liver that functions as a carrier protein for retinol and thyroxine. It has a tetrameric structure of four beta-sheet monomers. Structural changes can cause the protein to misfold and aggregate, depositing into different tissues. The myocardium and peripheral tissues are the most common sites for deposition of the misfolded TTR protein, which leads to axonal neuropathy, conduction blocks and hypertrophic restrictive cardiomyopathy.[1] Amyloid deposits initially affect the small nerve fibers that regulate thermalogic sensations associated with autonomic phenomenon. Eventually, they impair the larger nerve fibers, resulting in further sensory losses, gait unsteadiness, imbalance, and motor deficits.[2] Peripheral autonomic nerves are affected before motor nerve impairment due to morphologic characteristics Unmyelinated, small myelinated and large fibers become impaired in that order.

The two types of misfolded TTR proteins in amyloidosis include wildtype (wATTR) and hereditary (hATTR) which can cause the clinical phenotype of amyloid cardiomyopathy. wATTR is the more common type of ATTR cardiomyopathy and is seen predominantly in older males.[3] Autopsy studies have shown an increased incidence of wATTR deposits with advancing age.[4,5] One study also reported a higher prevalence of amyloid cardiomyopathy in older males with heart failure and left ventricular hypertrophy.[6]

Cardiac amyloidosis can cause recurrent heart failure exacerbations, and result in peripheral congestive symptoms including lower extremity edema, hepatic congestion and ascites. Initially, the compromised compliance causes diastolic dysfunction, but eventually results in more global systolic dysfunction.[7] In advanced states, cardiorenal syndrome may occur. Cardiac arrhythmias are also present, most commonly atrial fibrillation, in 40-60% of patients at the time of diagnosis. Atrial fibrillation is poorly tolerated due to the restrictive impact of cardiac amyloidosis. The deposition of amyloid in the interstitial space also disrupts the conduction system of the heart. Patients may develop varying degrees of heart block and some may require a permanent pacemaker.[8] The most dangerous manifestation is the cardiovascular autonomic neuropathy that can manifest with life-threatening arrythmias and sudden death. Warning signs include heart rate variability and reduced baroreflex sensibility with dysregulated blood pressures and orthostatic hypotension. Sudden death has been reported in patients with ventricular

arrythmias and orthostatic hypotension even without prior underlying cardiac abnormalities.[7,8]

ATTR amyloidosis also manifest as various types of autonomic dysregulation, affecting multiple organs, including cardiovascular, gastrointestinal, and genitourinary systems. Autonomic dysfunction is seen in early stages of the disease, usually before motor impairment but will eventually impair function and quality of life. Orthostatic hypotension in amyloidosis can be related to heart failure from amyloid cardiomyopathy or volume depletion from drug effects. If neither are present, orthostatic hypotension is usually neurogenic from reduced norepinephrine release due to neuronal amyloid deposition.

Management/Treatment

Autonomic dysregulation is commonly associated with cardiac amyloidosis and can have a major impact on the quality of life. Management approach requires balancing periodic symptomatic screening with consideration of medication side effects and co-morbidities. The goal of treatment may not necessarily be normalization of standing blood pressure, but to reduce symptoms, improve quality of life and reduce morbidity and mortality associated with orthostatic hypotension. Management can be challenging due to the limited options in achieving and maintaining euvolemia. Beta blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are not well tolerated, and diuretics deplete intravascular volume which can further worsen the orthostatic symptoms. Management of arrhythmias is crucial due to the high incidence of conduction system disease. Prompt pacemaker evaluation may be required for those who meet criteria.

Several pharmacologic agents target ATTR amyloid cardiomyopathy, including transthyretin stabilizers and RNA interference medications.[1] Tafamidis was FDA approved for use in cardiac amyloidosis in May 2019. Tafamidis binds to the thyroxine binding sites of TTR and stabilizes the tetrameric form, reducing amyloid formation. Treatment should be started early to see clinical benefits. Although it can slow the progression of the disease, it cannot reverse it. Also, the overall effect of tafamidis on orthostatic hypotension remains unclear and additional studies are needed. Early identification and management are advised as delays in treatment can lead to poorer prognosis and outcomes.

There are other newly developed RNA-based therapies approved in the US and Europe targeting the production of transthyretin which improve polyneuropathy in amyloidosis. Although these drugs can mitigate the autonomic side effects, the full impact of these disease-modifying drugs on neurogenic causes requires further investigation. More studies are needed to evaluate their effect on orthostatic hypotension in those with TTR amyloidosis.

Lastly, there are agents aimed more at amyloidosis neurogenic orthostatic hypotension. Droxidopa is a synthetic norepinephrine precursor that is converted to norepinephrine. Earlier studies in Japan showed that droxidopa increased blood pressure and norepinephrine levels which improved orthostatic tolerance in patients with amyloidosis. This medication later became FDA approved for symptomatic orthostatic hypotension associated with Parkinson's disease, multiple system atrophy, and autonomic neuropathies including hereditary TTR amyloidosis. There have been positive reports on droxidopa use in for neurogenic orthostatic hypotension. It is approved in the US and Asia, although additional studies are needed.[9]

Conclusion

Transthyretin amyloidosis is a disease characterized by adult-onset sensory, motor and autonomic neuropathy. Specifically, ATTR amyloid cardiomyopathy is caused by deposition of the abnormally folded TTR protein on the heart. Autonomic dysfunction and orthostatic hypotension can be associated with amyloidosis and cause disabling manifestations affecting quality of life. If untreated, cardiac amyloidosis can cause progressive heart failure, arrhythmias, conduction system diseases and even sudden cardiac death. Quality of life and function also decline significantly with each heart failure exacerbation and hospitalization. Early detection and anticipation of symptoms are critical. Management includes a balanced supportive and multimodal approach with management of volume status, arrythmias and consideration for transthyretin-targeting therapies, if applicable. Management of autonomic dysfunction and orthostatic hypotension is important but can be challenging due to the inherent nature of pharmacotherapies that may further exacerbate hypotension and orthostatic symptoms. Additional clinical trials are needed to further understand the phenomenon and management options.

Our patient had cardiac amyloidosis with severe symptoms of orthostatic hypotension and autonomic dysregulation, preventing the use of diuretics and guideline-directed medical therapies. He was prescribed a transthyretin-targeting therapy, tafamidis; however, due to cost and formulation availability issues, delayed starting this medication, which may have limited the overall clinical benefit. Due to clinical and functional decline from disease progression, the patient opted for more palliative goals and deferred further pharmacologic therapies.

This case illustrates the importance of understanding amyloidosis, and the sequelae of the disease if not detected and managed promptly. ATTR amyloid cardiomyopathy should be on the differential in older patients with recurrent heart failure exacerbations and autonomic dysfunction. Early detection, diagnosis and management are important to optimize outcomes and reduce further disease progression and decline. Unfortunately, prognosis can be poor in those with delayed detection and treatment.

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