CLINICAL VIGNETTE

Treatment of Amyloidosis in a Geriatric Patient

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Case Report

A 79-year-old African American man with prediabetes, carpal tunnel syndrome, osteoarthritis and neuropathy presented for routine follow-up after an ER visit for proctocolitis. He was found to have irregular pulse on exam and ECG showed atrial fibrillation. He had no shortness of breath, palpitations, chest pain or edema. Family history included diabetes in his father and pancreatic cancer in his mother. He was a retired warehouseman who had a remote smoking history and no alcohol use. He was an avid boxer and still trained at the gym. An echocardiogram showed severe concentric left ventricular hypertrophy with increased left ventricular wall texture consistent with infiltrative disease, as well as global hypokinesis of the left ventricle with an ejection fraction of 20-25%. He was started on rivaroxaban for anticoagulation and a cardiac MRI with and without contrast showed findings suggestive of advance infiltrative disease, particularly amyloidosis. Nuclear medicine myocardial infarct and amyloidosis imaging (Tc99m PYP) scan demonstrated diffusely increased myocardial tracer activity suggestive of amyloid transthretin (ATTR) amyloidosis. Work up also included a normal SPEP, UPEP, serum IFE, free light chains and quantitative immunoglobulins. An abdominal fat pad biopsy was negative for amyloid. Genetic testing for hereditary ATTR returned positive for the V142I mutation confirming ATTR amyloidosis. EMG and NCS showed bilateral moderate median neuropathy. The patient was initiated on Patisiran infusion therapy. He was also recommended to take doxycycline and green tea extract (catechins).

Discussion

Amyloidosis is a disease of misfolded proteins in which insoluble amyloid fibrils deposit extracellularly in the heart and various other tissues and organs, leading to organ impairment and failure. There are more than 30 extraceullar amyloid fibril proteins in humans, per 2014 nomenclature.[1,2] Amyloidosis can be either systemic or localized. Systemic amyloidosis frequently involves the heart, with heart involvement being the most important prognostic factor.[1,3]

The major subtypes of amyloidosis include light chain (AL) amyloidosis, amyloid A (AA) amyloidosis, dialysis-related amyloidosis, hereditary (transthyretin mutant type) amyloidosis (ATTR-m), transthyretin wild type amyloidosis (ATTR-wt) which is also known as age-related (senile) systemic amyloidosis (SSA), and organ specific amyloidosis. Treatment strategies vary per diagnosis and the correct diagnosis is crucial to determining potential therapies. The prognosis depends upon the extent of tissue involvement and type of amyloid deposited. The majority of clinically significant cardiac amyloidosis is a result of AL and ATTR subtypes.[4,5] The median survival for untreated amyloid cardiomyopathy is 11 months for those with AL amyloid and 2.5-3.6 years for ATTR.[5]

AL amyloidosis is due to immunoglobulin light chain fragments and is a complication of plasma cell dyscrasia. Cardiac involvement is common in AL amyloidosis patients with 33-50% having clinically significant heart disease.[6] In the treatment of AL amyloidosis, chemotherapy is used to target clonal plasma cells, reduce light-chain production and slow disease progression. The treatment for AL amyloidosis mirrors treatment for multiple myeloma and includes alkylators (e.g. melphalan, cyclophosphamide), steroids (e.g. dexamethasone), proteasome inhibitors (e.g. bortezomib), immunomodulators (e.g. pomalidomide), and anti-CD38 monoclonal antibody (e.g. daratumumab). Chemotherapy has improved survival outcomes.[2,3,7] Select AL amyloidosis patients may be eligible for autologous stem cell transplant.[8]

Hereditary amyloidosis (ATTR-m) can result from various mutations and often leads to neurologic and cardiac disease. Age-related (senile) systemic amyloidosis (ATTR-wt) results from normal (wild-type) protein deposition. For ATTR, chemotherapy has no current role but there are clinical trials and emerging therapies available including fibril disruptors (e.g. doxycyline), Transthyretin (TTR) stabilizers (e.g. diflunisal, tafamidis, AG10), and TTR silencers (e.g. Patisiran, Inotersen).[2,3,9,10] Treatment of ATTR with tafamidis was associated with reduction in all-cause mortality and cardiovascular-related hospitalizations in addition to reduction in functional decline and improvement in quality of life;[11] Tafamidis has recently been FDA approved for use in the U.S. A different study using Inotersen, which inhibits hepatic production of transthyretin in patients with ATTR-m, also showed improvement in quality of life in addition to modifying the course of neuropathy.[12] Patisiran, which also inhibits hepatic synthesis of transthyretin, has been shown to improve neuropathy in patients with hereditary ATTR.[13] In patients with hereditary ATTR with polyneuropathy, treatment with patisiran was more effective than tafamidis.[14] Transplant may be a possible option in select ATTR-wt patients. Patients who are better candidates for heart transplants are those younger than 60 years old without associated plasma cell dyscrasias or other

major organ involvement.[15] In a retrospective cohort study by Rosenbaum et al. 2018, 7 patients with ATTRwt underwent heart transplant between 2007-2015 (mean age was 66+/-9); 3 year survival rate was 100% and these patients did well postoperatively with low incidence of rejection.[15] Liver transplant may be considered in select patients with ATTR-m.

Supportive treatment is similar across all subtypes of cardiac amyloidosis and includes management of volume overload and arrhythmias. Diuretics and sodium and fluid restriction are used for congestive heart failure symptoms. Beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers often need to be avoided as they are poorly tolerated and can lead to hypotension.[3,9] Since cardiac amyloidosis is a restrictive heart disease, stroke volume is limited and cardiac output is heart rate dependent.[3,7,9] Rhythm control with antiarrhythmics therapy may contribute to normal atrial contractility, improve diastolic filling, and preserve stroke volume.[9] Digoxin should be avoided since it binds to amyloid fibrils and can cause toxicity. However, if needed, low dose digoxin can be cautiously used for rate control with close monitoring.[7]

Conclusion

Like the disease itself, current treatment strategies for amyloidosis are heterogeneous. Therapeutic considerations rely upon accurate diagnosis and subtyping of the amyloidosis, and new treatment modalities are actively emerging. This patient who suffers from both cardiac and neurologic manifestations of hereditary (ATTR) amyloidosis was started on patisiran prior to the FDA approval of tafamidis. With so many novel treatment options in the pipeline, it is prudent for clinicians to keep the varied amyloidosis subtypes in their differential diagnosis of patients who present with symptoms of this diverse condition.

REFERENCES

1. **Flodrova P, Flodr P, Pika T, Vymetal J, Holub D, Dzubak P, Hajduch M, Scudla V**. Cardiac amyloidosis: from clinical suspicion to morphological diagnosis. *Pathology*. 2018 Apr;50(3):261-268. doi: 10.1016/j.pathol.2017.10.012. Epub 2018 Feb 12. Review. PubMed PMID: 29448998.
2. **Hanna M, Huded C, Rodriguez ER, Phelan D, Kwon D, Jaber W, Valent J, Tong MZ**. Progress in diagnosing and managing cardiac amyloidosis. *Cleve Clin J Med*. 2019 Jan;86(1):29-37. doi: 10.3949/ccjm.86gr.18004. Review. PubMed PMID: 30624188.
3. **Witteles R**. Cardiac Amyloidosis. American College of Cardiology [Internet]. American College of Cardiology; 2019 [updated 2016 July 7; cited 2019 May 23]. Available from: http://www.acc.org/latest-in-cardiology/articles/2016/07/07/14/59/cardiac-amyloidosis.
4. **Alexander KM, Singh A, Falk RH**. Novel pharmacotherapies for cardiac amyloidosis. *Pharmacol Ther*. 2017 Dec;180:129-138. doi: 10.1016/j.pharmthera.2017.06.011. Epub 2017 Jun 22. Review. PubMed PMID: 28648829; PubMed Central PMCID: PMC5832446.
5. **Harikrishnan P, Yandrapalli S, Aronow WS, Lanier GM, Jain D**. Novel drug therapies for cardiac amyloidosis. *Expert Opin Investig Drugs*. 2019 Jun;28(6):497-499. doi: 10.1080/13543784.2019.1619695. Epub 2019 May 21. PubMed PMID: 31084448.
6. **Donnelly JP, Hanna M**. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med*. 2017 Dec;84(12 Suppl 3):12-26. doi: 10.3949/ccjm.84.s3.02. Review. PubMed PMID: 29257735.
7. **Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, Grogan M, Hayman SR, Kapoor P, Leung N, Fonder A, Hobbs M, Hwa YL, Gonsalves W, Warsame R, Kourelis TV, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Kyle RA, Rajkumar SV, Dispenzieri A**. Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. *Blood*. 2017 Apr 13;129(15):2111-2119. doi: 10.1182/blood-2016-11-751628. Epub 2017 Jan 26. PubMed PMID: 28126928; PubMed Central PMCID: PMC5391625.
8. **Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW, Miller WL, Maleszewski JJ, Dispenzieri A**. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol*. 2016 Sep 6;68(10):1014-20. doi: 10.1016/j.jacc.2016.06.033. Erratum in: *J Am Coll Cardiol*. 2017 Jun 13;69(23):2882. PubMed PMID: 27585505.
9. **Pereira NL, Grogan M, Dec GW**. Spectrum of Restrictive and Infiltrative Cardiomyopathies: Part 1 of a 2-Part Series. *J Am Coll Cardiol*. 2018 Mar 13;71(10):1130-1148. doi: 10.1016/j.jacc.2018.01.016. Review. PubMed PMID: 29519355.
10. **Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, Grogan M, Selby VN, Jacoby D, Hanna M, Nativi-Nicolau J, Patel J, Rao S, Sinha U, Turtle CW, Fox JC**. Transthyretin Stabilization by AG10 in Symptomatic Transthyretin Amyloid Cardiomyopathy. *J Am Coll Cardiol*. 2019 Jul 23;74(3):285-295. doi: 10.1016/j.jacc.2019.03.012. Epub 2019 Mar 15. PubMed PMID: 30885685.
11. **Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators**. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med*. 2018 Sep 13;379(11):1007-1016. doi: 10.1056/NEJMoa1805689. Epub 2018 Aug 27. PubMed PMID: 30145929.
12. **Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH 3rd, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceição I, Schmidt HH, Vita G,**

Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *N Engl J Med*. 2018 Jul 5;379(1):22-31. doi: 10.1056/NEJMoa1716793. PubMed PMID: 29972757.

13. **Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH 3rd, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB**. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med*. 2018 Jul 5;379(1):11-21. doi: 10.1056/NEJMoa1716153. PubMed PMID: 29972753.
14. **Planté-Bordeneuve V, Lin H, Gollob J, Agarwal S, Betts M, Fahrbach K, Chitnis M, Polydefkis M**. An indirect treatment comparison of the efficacy of patisiran and tafamidis for the treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy. *Expert Opin Pharmacother*. 2019 Mar;20(4):473-481. doi: 10.1080/14656566.2018.1554648. Epub 2018 Dec 12. Review. PubMed PMID: 30489166.
15. **Rosenbaum AN, AbouEzzeddine OF, Grogan M, Dispenzieri A, Kushwaha S, Clavell A, Daly RC, Edwards BS**. Outcomes After Cardiac Transplant for Wild Type Transthyretin Amyloidosis. *Transplantation*. 2018 Nov;102(11):1909-1913. doi: 10.1097/TP.0000000000002240. PubMed PMID: 29677073.