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Mini Review

Amyloidosis: Diagnosis and Treatment

Mishi Bhushan*

Department of Hematopathology, Medical City Dallas, Medical City Children's Hospital, Dallas, Texas, USA

ABSTRACT

Amyloidosis is a heterogenous acquired or hereditary collection of disease entities that presents as a localized disease or multisystemic disorder due to the abnormal deposition of beta-sheet fibrillar protein aggregates in tissue. Classification depends on amyloid type and pathophysiology is multifactorial. Diagnosis by tissue biopsy, immunohistochemistry, gene sequencing, mass spectrometry, and electron microscopy as well as demonstration of congo red staining with apple-green birefringence under polarized light is characteristic. Imaging with echocardiogram, EKG, MRI and CT scan illustrate the degree of organ damage. Treatment is variable and usually depends on the type of amyloidosis. We discuss the ethical dilemmas of diagnosis and treatment of amyloidosis.

Keywords: Amyloidosis; Tissue biopsy; Multisystemic disorder

INTRODUCTION

Amyloidosis is characterized by deposition of globular, soluble proteins that undergo misfolding and aggregate into insoluble fibrils that deposit in various tissues, leading to organ dysfunction and eventually death. Classification of amyloid is based on amyloid protein type, of which 26 have been identified. The most common causes of amyloidosis are the immunoglobulin-light chain (AL), ATTR amyloidosis, and reactive amyloidosis (AA) due to chronic inflammatory diseases. Primary systemic or light chain (AL) amyloidosis is characterized by the presence of monoclonal plasma cells and deposition of immunoglobulin light chain-derived amyloid deposits in various organs. AL amyloidosis is the most common form of systemic amyloidosis in the developed world and is acquired, while AA is the most common type of systemic amyloidosis. In AA amyloidosis, the fibrils are derived from serum amyloid a protein, an acute phase reactant. ALECT2 accounts for 2.7T %-10% of patients with renal amyloidosis and accounts for 54% of amyloid diagnosis in Mexican Americans and fibrils are derived from leukocyte chemotactic factor. Hereditary amyloidosis are relatively rare and are associated with variants of apolipoproteins and mutations in the TTR gene. Alzheimer's disease is a localized subtype of amyloidosis that results from the deposition of amyloid plaques and neurofibrillary tangles [1-13].

CLINICAL PRESENTATION

Amyloidosis can present in various ways: heart failure with left ventricular hypertrophy, hepatomegaly, nephrotic syndrome, macroglossia, orthostatic hypotension, ecchymosis, autonomic and peripheral neuropathy, carpal tunnel syndrome, jaw claudication, and articular deposits. Secondary amyloidosis can present with hepatosplenomegaly, proteinuria, renal failure, and orthostasis. ATTR amyloidosis presents in midlife with peripheral and autonomic neuropathy, cardiomyopathy, and vitreous opacities. Localized amyloid beta-amyloidosis to the central nervous system presents as Alzheimer's disease. Amyloidosis is also found in familial Mediterranean fever in patients with the MEFV genotype and SAA1 and MICA polymorphisms [14,15].

Physical exam findings include hypertrophied shoulder pads, amyloid purpura, and raccoon eyes secondary to bleeding from factor-X dysfunction/deficiency [16].

HISTOPATHOLOGY AND DIAGNOSIS

Amyloid deposits are formed by 10-12 nm wide non-branching fibrils that display a cross-B fiber diffraction pattern as observed by electron microscopy and an affinity for congo red staining with birefringence under polarized light [2,17].

Correspondence to: Mishi Bushan, Department of Hematopathology, Medical City Dallas, Medical City Children's Hospital, Dallas, Texas, USA, Tel: +14698359354; E-mail:Bhushanm0214@gmail.com

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Tissue biopsy of subcutaneous fat aspirate has about 80% diagnostic sensitivity in AL amyloidosis, and biopsy of minor salivary glands can be diagnostic when fat aspirates are negative[18]. Serum and urine electrophoresis with immunofixation and free light chains are useful to rule out plasma cell diseases. If monoclonal light chains are not present, bone marrow biopsy can establish the diagnosis. Fluorescence in Situ Hybridization (FISH), immune electron microscopy and a skeletal survey also aid in diagnosis. Mass spectrometry can be used to identify amyloidosis variants. Gene sequencing is recommended to rule out hereditary amyloidosis. Organ involvement and staging is essential to establish the management plan with echocardiogram, NT-proBNP, troponins, EKG, cardiac MRI, 24-hour urinary protein, eGFR, liver function tests and hepatic imaging. A staging system incorporating cardiac biomarkers and level of amyloid genic light chain synthesis can aid in predicting prognostic outcomes and the development of treatments [19].

As transthyretin amyloidosis is challenging due to its heterogeneous presentation, it can often be misdiagnosed. While cardiac and peripheral nervous systems are most frequently involved in ATTR amyloidosis, patients can experience gastrointestinal or other systemic manifestations. Misdiagnosis can lead to delays in treatment, and thus tools such as diagnostic algorithms are needed to raise suspicion of this life-threatening disease [20]. Diagnosis of amyloidosis, specifically in the use of biomarkers and genetical testing for Alzheimer's disease, presents an ethical dilemma. Alzheimer's disease is due to accumulation of amyloid and tau proteins and neurodegeneration. Disclosing a diagnosis has risks and rewards: rewards include social support, while risks include stigma and discrimination [21-27].

TREATMENT

AL amyloidosis referred to as Primary Amyloidosis is one of the more treatable amyloidosis. Prognosis is dependent on stage and prognostic factors. Patients with cardiac amyloidosis have expected survival of less than one year. Treatment consists of chemotherapeutic agents, steroids, and monoclonal antibody. Bone marrow transplant with high dose chemotherapy is the treatment of choice in eligible patients. Supportive therapy helps to maintain quality of life and prevent further organ dysfunction [19, 28-31].

As transthyretin is a protein predominantly synthesized in the liver, liver transplant can reduce levels of mutant transthyretin in those with ATTR amyloidosis. As current and future therapies are expensive, the cost-effectiveness of these treatments comes into question. This creates an ethical dilemma of equitable delivery and access to life-prolonging treatments [32].

All amyloidosis treatments pose a significant financial burden including medication copays and coinsurance, and out of pocket costs. Patients are particularly vulnerable to financial toxicity due to the use of novel treatments and extended treatment duration. Financial toxicity negatively impacts quality of life and can hinder delivery of care. One study of 266 patients with multiple myeloma found that 32% of patients depleted their savings, 22% borrowed against or used money from retirement, and 35% reported cutting their grocery expenses. The desire to reduce medical expenses also led to some patients to treatment non-adherence, as 5% reported skipping dosages of medicine at least sometimes and 6% postponed filling prescriptions. Patient-reported Financial Toxicity (FT) using the EORTC Quality of Life questionnaire (QLC-C30) in 5,667 patients in multiple myeloma trials reported that 14% of patients had worse FT at both 3 and 6 months. Another survey using the 11-item COST measure in individuals with multiple myeloma found that 36% reported applying for financial treatment, 46% used savings to pay for treatment, and 21% borrowed money to pay for medications [33-35].

The effectiveness of Autologous Stem Cell Transplant Marrow Transplant (ASCT) in AL amyloidosis is variable and poses yet another ethical dilemma as it is associated with a high risk of Early Mortality (EM). A retrospective multicenter study of 1536 patients with AL who underwent ASCT found that centers with high volumes had superior survival outcomes [36]. Furthermore, the study found that mortality at 30 and 100 days progressively declined over successive time periods, demonstrating that post-transplant survival in AL has improved, with significant reduction in early post-transplantation mortality and high 5-year survival [37].

CONCLUSION

The ethics of amyloidosis resides in the challenge in making a definitive diagnosis, financial toxicity to patients and their families, and uncertain long-term cost-effectiveness of efficacy of treatments. The challenge in therapies lies in affordability for the target population. A framework for the responsible pricing guided by value-based assessments to assure broad access is necessary to provide equitable and just healthcare. Targeted therapies would have to have cost reduction of more than 90 percent to be cost-effective. Careful selection of patients and transplant centers are also crucial factors in patient outcomes, as patients who undergo ASCT at high-volume centers were shown to have higher overall survival and lower mortality.

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