Congestive Heart Failure: A Case of Protein Misfolding

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Abstract

This article describes an interesting case of a patient presenting with congestive heart failure found to have restrictive cardiomyopathy with initial laboratory evaluation showing hypogammaglobuminemia without a monoclonal band on serum and urine electrophoresis. This case highlights the clinically significant cardiac manifestation caused by protein misfolding, a defect in protein homeostasis. In addition, the utility of a relatively newer laboratory test, serum free light chains as well as the importance of clinical and pathophysiologic correlation is also discussed. We present a relatively uncommon cause of heart disease, cardiac amyloidosis in a patient with a systemic plasma cell dyscrasia, and multiple myeloma.

Keywords

congestive heart failure, cardiac amyloidosis, multiple myeloma, serum free light chains

Case History

A 65-year-old man presented to his primary care physician complaining of shortness of breath, dyspnea on exertion (DOE), and swelling of his legs and ankles. His past medical history included coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, and a history of prostate cancer surgically treated 10 years prior. He was referred to cardiology and underwent a thallium stress test which showed a decreased ejection fraction of 41% (Normal range 55-65%) and a cardiac catheterization which showed 90% ostial left anterior descending stenosis that was stented. During the course of a year he had repeat cardiac studies which showed ejection fraction of 50-55% with moderate left ventricular hypertrophy as well as a repeated elevated E/E' (early filling/early diastolic mitral annular velocity ratio) of 34 and 22 (Normal range <15%). Other findings on echocardiogram were moderate mitral regurgitation, mild tricuspid regurgitation, and pulmonary artery systolic pressure (PASP) 30 mmHg (Normal range <30 mmHg), left atrial end systolic diameter (LAESD) 4.0 (Normal range 2.0 - 4.0cm), left ventricular end diastolic diameter (LVEDD) 4.2 (Normal range 3.5-5.6 cm), and left ventricular end systolic diameter (LVESD) 2.9 (Normal range 2.0 - 4.0). EKG studies revealed low voltage. These findings were suggestive of diastolic dysfunction. Throughout this time he had no chest pain and no other EKG abnormalities. Subsequently, he developed worsening pleural effusion that was not responsive to diuresis and worsening of his DOE. Lab studies showed elevated serum brain natriuretic peptides (BNPs) in the 300 - 400 ng/L range (RI <100 ng/L) with normal alanine aminotransferase (ALT), and a normal calculated glomerular filtration rate (GFR) with creatinine ranging between 97.1 - 114.9 μmol/L (RI 44.2-106.1μmol/L). Based on the overall clinical findings the differential diagnosis of an infiltrative myocardial process causing a restrictive cardiomyopathy was considered. A cardiac MRI was done to evaluate for constrictive or infiltrative disease. There was diffuse endocardial enhancement suggesting an infiltrative process.

A workup for cardiomyopathy was performed which included a serum protein electrophoresis (SPEL), and urine protein electrophoresis (UPEL). The SPEL was abnormal showing hypogammaglobuminemia thus prompting further evaluation including immunofixation electrophoresis (IFE), immunoglobulin levels, as well as serum free light chains. The serum IFE did not show any monoclonal immunoglobulin bands but the serum free kappa/lambda light chain quantitation showed an elevated kappa free light chain of 561.6 mg/L (RI 3.3 - 19.4 mg/L), a low lambda free light chains of 4.2 mg/L (RI 5.7 - 26.3) as well as a markedly elevated serum free kappa/lambda ratio of 134.67 (RI 0.26 to 1.65). Serum IgG, IgM, and IgA levels showed decreased values. Neither UPEL nor IFE revealed any monoclonal immunoglobulin. Concurrently, an abdominal fat pad biopsy was performed which showed a positive Congo red stain for amyloid. A bone marrow biopsy revealed more than 30% plasma cells expressing kappa light chain restriction (by immunohistochemical staining and flow cytometric analysis) as well as amyloid deposits. The patient declined autologous hematopoietic stem cell transplant and treatment for amyloidosis was initiated including bortezomib and dexamethasone. Initially, the patient improved clinically with decreased shortness of breath and DOE. However, despite treatment the patient gradually deteriorated clinically and he expired 6 months after being diagnosed with amyloidosis. Permission for an autopsy was not obtained.

Discussion

Restrictive cardiomyopathy is the least common form of cardiomyopathy and one of the causes is secondary infiltrative myocardial diseases.[1] In the United States, amyloidosis is the most common cause of restrictive cardiomyopathy.[2] Amyloidosis is a relatively rare systemic disease caused by deposition of misfolded protein in a variety of tissues and organs including the heart.[3]

Heart disease due to abnormalities of protein homeostasis involving misfolding (giving rise to fibril formation amyloidosis) portends a high degree of morbidity with poor prognosis. The misfolded proteins may arise within the myocardium or may be imported from external entities (eg, immunoglobulin light chains). The former category of misfolding consists of mutations in desmin or its chaperones.[4] Accumulation of mutant proteins which have the potential to misfold is in part due to defects in intracellular proteolysis involving systems of

ubiquitin-proteasome and/or autophagy.[5] Twenty seven precursor soluble proteins with organ infiltrative properties which have the potential to form proteolysis resistant extracellular insoluble β -fibril aggregates are known.[6] The transformation of the precursor proteins to initiate amyloidogenesis may involve intrinsic β-pleated sheet secondary structure with excessive production, selective proteolysis and/or mutations.

In our patient, the initial serum protein electrophoresis showed hypogammaglobuminemia which prompted quantitation of immunoglobulins IgG, IgA, and IgM, serum immunofixation and urine studies. Interestingly, serum and urine protein electrophoresis and immunofixation revealed no evidence of a monoclonal gammopathy, however the serum free light chain ratio was markedly elevated. As this case demonstrates, the relatively new serum free light chain assay, while not determining monoclonality, has been shown to be a valuable addition to the work up of patients suspected of having a plasma cell dyscrasia such as amyloidosis.[7] In the study by Katzmann, et al, a small percentage (2%) of patients with amyloid-light chain (AL) amyloidosis had only an elevated serum free light chain ratio with no monoclonal protein detected on serum and urine protein electrophoresis or IFE as in our case. In addition, a study by Drayson, et al, has shown that 68% of non-secretory multiple myeloma patients were found to have an abnormal serum free light chain ratio.[8]

There are primary and secondary causes of hypogammaglobuminemia. Secondary hypogammaglobuminemia can be caused by a number of conditions including diseases of immunoglobulin loss or impaired production, high stress, drug induced states, as well as certain malignancies.[9] Diseases causing immunoglobin loss include protein-losing enteropathies and chronic renal disease, and impaired production can be seen in certain malignancies such as chronic lymphocytic leukemia (CLL), lymphoma, and multiple myeloma. Drugs implicated in causing secondary hypogammaglobuminemia include anti-rheumatic drugs, systemic steroids, phenytoin, carbamazepine, as well as androgen replacement therapy. Obtaining a good history and clinical assessment of the patient can help direct appropriate laboratory studies. When no other clinical cause for hypogammaglobulinemia is found, primary hypogammaglobilinemia must be considered. In adults, the most common primary cause is common variable immune deficiency (CVID) and selective IgA deficiency.[9] Laboratory evaluation includes immunoglobulin studies as well as evaluation of the lymphocyte immunophenotyping. Clinical presentation consists primarily of frequent recurrent respiratory tract infections. In this patient, the clinical history and initial lab findings were pivotal in directing further laboratory assessment related to our patient's cardiac findings of CHF with diastolic dysfunction, followed by MRI findings of an infiltrative process causing a restrictive cardiomyopathy. This case study describes misfolding of a circulating amyloidogenic immunoglobulin κ light chain which is targeted to myocardium, giving rise to an infiltrative cardiac amyloidosis. This is a relatively rare disorder. The overall incidence of amyloidosis is approximately 0.5-1.3 per 100,000. Of all patients with amyloidosis approximately 80% is AL or primary systemic amyloidosis, the type in which cardiac deposition and manifestations are most commonly seen. In the US, there are between 2000-2500 cases of AL amyloidosis diagnosed annually.[10] The diagnosis was established by characteristic findings obtained in EKG, echocardiogram, cardiac MRI, and elevated serum BNP followed by histologic studies of biopsy specimens obtained from abdominal fat pad and bone marrow. The bone marrow aspirate was subjected to flow-cytometry. All of these studies along with an elevated serum BNP level were consistent with the diagnosis of infiltrative amyloidosis cardiomyopathy due to κ-light chain amyloidosis.[11,12,13] Serum and urine protein electrophoresis and immunofixation electrophoresis did not reveal the presence of any clearly discernible monoclonal band, which if present is considered as surrogate marker for the presence of a monoclonal immunoglobulin. Hypogammaglobulinemia and an abnormal serum free light chain ratio suggested amyloid or multiple myeloma (light chain, non-secretory, or oligosecretory) and the bone marrow studies showing 30-35% plasma cells confirmed the diagnosis of kappa AL with myeloma. Factors that may contribute to the absence of any detectable urinary κ-light chain include a very small quantity of monoclonal kappa secretion as well as the propensity of aggregation of the kappa light chains. The elevated serum free light chain ratio and clinical manifestations of an infiltrative cardiomyopathy are consistent with κ-light chain amyloidosis. Despite treatment for κ-light chain amyloidosis, the patient's cardiac function deteriorated and death occurred after 6 months of the initiation therapy.

This case highlights several educational observations which includes evaluating for causes of hypogammaglobuminemia, the value of serum free light chain assay, the importance of clinical pathologic correlation, as well as the interesting pathophysiologic mechanism of a defect in protein homeostasis leading to significant clinical manifestations. Amyloidosis is a diverse group of disorders of protein misfolding giving rise to β-sheet fibrils. A preferential cardiac organ targeting by amyloidogenic mutant λ-light chains has been previously reported.[14]

Conclusion

This case study describes a fatal heart disease caused by an abnormality in protein homeostasis resulting in protein misfolding, namely amyloidogenic κ-light chains targeted to cardiac tissue. The characteristic hypogammaglobulinemia and elevated serum free kappa/lambda light chain ratio despite the absence of Bence-Jones proteinuria along with clinical and histopathologic studies are consistent with a systemic plasma cell dyscrasia with infiltrative cardiac amyloidosis.

Conflict of Interest

None of the authors identify a conflict of interest.

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