

The Clinical Presentation and Diagnosis of Primary Cardiac Amyloidosis

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ABSTRACT

A 67-year-old woman presented to her family physician with a five month history of progressing shortness of breath and fatigue. The patient was referred to cardiology who saw her two weeks later. An echocardiogram revealed normal biventricular systolic function, pulmonary hypertension, and mild tricuspid regurgitation. Clinically, the patient had bilateral pedal edema, evidence of pleural effusion, and an elevated jugular venous pressure (JVP). Five weeks later she was admitted to hospital for further testing as there was a marked change in her condition. In hospital, a series of investigations were performed, including a pulmonary angiogram, thoracentesis, chest computed tomography (CT), venous Doppler of lower extremities, and an endomyocardial biopsy. The endomyocardial biopsy demonstrated interstitial and vascular positivity for amyloid. The patient was diagnosed with systemic primary (AL) amyloidosis with cardiac involvement. Primary amyloidosis results from an accumulation of immunoglobulin light chains due to a clonal B cell disorder such as multiple myeloma. Patients with primary amyloidosis, with heart involvement, progress rapidly and have a median survival of six months. The signs and symptoms of congestive heart failure (CHF) can be recognized with ease; however, establishing the underlying cause can be more difficult. Determination of the underlying cause of heart failure is essential as it will influence the management of the patient. Early intervention can have a significant impact on the patient's response to treatment, especially when the underlying condition involves a malignancy or infiltrative disorder.

KEYWORDS: *primary amyloidosis, cardiac involvement, shortness of breath, fatigue, congestive heart failure, comfort care*

INTRODUCTION

Symptoms and signs of congestive heart failure (CHF) are present in 6–10% of patients over the age of 65 years.¹ There are many causes of CHF, including coronary artery disease, myocardial infarction, hypertension, pulmonary heart disease (cor pulmonale), and chronic anemia. Other causes include infiltrative, storage, and metabolic disorders.^{1,2} The cause of CHF remains unknown in 20–30% of affected patients.¹ While the signs and symptoms of CHF can be easily recognized and commonly encountered, further investigations should be performed in an attempt to determine the cause. While some causes of heart failure are idiopathic and respond well to typical medications (β -blockers, ACE inhibitors, and diuretics), other causes may

require additional treatment in order to slow or halt progression of the disease. Depending on the underlying cause of the heart failure, this additional treatment may consist of chemotherapy, surgery, or transplantation.

CASE REPORT

History of Presenting Illness

A 67-year-old female first presented to her family physician with a five month history of progressive shortness of breath and fatigue. At the time of this visit she was able to perform her daily activities and was able to ride a stationary bike five miles, three times per week. However, she did state that her exercise tolerance on a flat surface was affected mainly by fatigue. She had no paroxysmal nocturnal dyspnea and no orthopnea. Her medical history included a cerebral vascular event likely secondary to an eight year history of hypertension. At this time it was discovered that she had a left bundle branch block on ECG. Since this incident, she had well controlled blood pressure.

A chest x-ray showed small bilateral pleural effusions, and she was given a bronchodilator. The patient was seen by cardiology two weeks later. The cardiologist noted that she looked depressed, and the patient stated that she was losing weight. Her blood pressure was 110/60 mmHg, (sitting, right arm) and

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her heart rate was 60 bpm and regular. She now had marked bilateral pedal edema and an elevated jugular venous pressure (JVP). Her chest was clear to auscultation. The provisional diagnosis was hypothyroidism or another systemic process that was resulting in hypoproteinemia. However, due to the marked change in her condition since she had been seen by her family physician, a series of investigations were performed (Table 1). The chest x-ray was now consistent with mild CHF and moderate bilateral pleural effusions. There was borderline left ventricular (LV) hypertrophy and pulmonary hypertension with a PA systolic pressure of 50 mmHg on echocardiogram (normal PA systolic pressure varies from 15–25 mmHg). Serum lactate dehydrogenase and transaminases were mildly elevated. She was treated with fluvastatin (Lescol®) 20 mg PO daily, furosemide (Lasix®) 80 mg PO daily with added potassium, amlodipine (Norvasc®) 2.5 mg PO daily, and acetylsalicylic acid (Aspirin®) 81 mg daily.

The patient was seen again by her cardiologist five weeks later. At this time she was no longer able to ride the stationary bike and was more fatigued. She appeared unwell and complained again of shortness of breath and bilateral leg swelling. Upon examination the cardiologist noted:

1. Blood Pressure 150/110 mmHg (sitting, right arm)
2. Heart Rate 110 bpm and regular (sinus tachycardia)
3. JVP markedly elevated
4. Heart sounds were distant on auscultation
5. Marked bilateral pedal edema
6. Mild bilateral periorbital purpura
7. No heart murmurs were detected
8. No ascites, no organomegaly were present

The patient's problems now included new onset pulmonary hypertension, severe pedal edema, pleural effusions, and an

Test	Results (Normal Ranges in Brackets)
Blood Tests	Normal CBC and differential Alkaline phosphatase 115 (40–120) Lactate Dehydrogenase 821 (300–600) AST 100 (10–40) GGT 198 (10–65) Creatinine normal
Serum Protein Electrophoresis	Total 53 (60–80) Albumin, alpha 1, alpha 2, and β -globulin normal Gamma globulins 3 (5–17) No monoclonal peak identified
Pulmonary Function Tests	FVC 87% of predicted FEV ₁ 71% of predicted No change with bronchodilators
Chest x-ray	Mild congestive heart failure Moderate pleural effusions bilaterally
Transthoracic Echocardiogram	Borderline left ventricular hypertrophy Mild tricuspid regurgitation PA pressure 50 mmHg No evidence of pericardial fluid No evidence of RV failure
Chest and Abdominal Ultrasound	Large bilateral pleural effusions Pericardial effusion present No ascites, no abnormalities with organs

CBC-complete blood count, AST-aspartate aminotransferase, GGT-gamma-glutamyl transpeptidase, FVC-forced vital capacity, FEV₁-forced expiratory volume in one second, RV-right ventricular.

elevated JVP. She was admitted to hospital for further diagnostic investigations.

Diagnostic Tests

In hospital, the patient underwent another series of investigations (Table 2). These investigations demonstrated pulmonary hypertension, concentric LV hypertrophy, mild global LV systolic dysfunction, severe diastolic dysfunction, mild to moderate mitral regurgitation, and normal coronary arteries. Bilateral pleural effusions were present. An ECG showed decreased voltage in all leads. A pulmonary angiogram revealed elevated pulmonary artery pressure and an ejection fraction of 50% (normal 55–70%). One month later the patient had an endomyocardial biopsy.

Pathology-Endomyocardial Biopsy

The endomyocardial biopsy showed patchy widespread accumulation of material in the interstitium that stained positively with Congo red and showed apple green birefringence in polarized light. These findings are consistent with amyloid protein deposits. The interstitial amyloid appeared to be strangulating certain groups of cardiac myocytes. Amyloid deposition was also prominent in the vessel walls of the small intramyocardial arteries.

Definitive Diagnosis

The pathology findings from the endomyocardial biopsy demonstrated features of cardiac amyloidosis. Detection of free immunoglobulin lambda light chains in the serum confirmed the diagnosis of primary (AL) amyloidosis. A bone marrow biopsy was not performed as it would not have influenced treatment.

Treatment

The patient was treated with a trial of chemotherapy which consisted of melphalan (Alkeran®) 10 mg PO daily for four days and prednisone (Deltasone®) 100 mg PO daily for four days. This treatment was given at intervals of four weeks. The patient was deteriorating quickly, and further treatment options were not explored. Rather, comfort care was initiated. She was also treated with a potassium supplement, nitroglycerine (Minitran®) patch daily, fluvastatin (Lescol®) 20 mg PO daily, quinapril (Accupril®) 5 mg PO daily, furosemide (Lasix®) 120 mg PO daily, and digoxin (Lanoxin®) 0.625 mg PO daily.

Other treatment options for primary cardiac amyloidosis may include cardiac transplantation and bone marrow transplantation. Cardiac transplantation is rarely offered as the transplanted heart becomes infiltrated with amyloid protein. Roig *et al.* (2009) reviewed the outcome of heart transplant patients with primary amyloidosis and found the five year survival rate was 36%.³ As post-surgical mortality rates remain high, measures should be taken to reduce the amount of new infiltration of amyloid protein. Recent studies have shown that the survival of patients who receive cardiac transplantation followed by autologous stem cell transplantation (ASCT) was 60% at seven years compared to 39% at four years when no ASCT was provided after cardiac transplantation.⁴

Outcome

The patient passed away five and a half months from the time of her first visit to her family physician and 10 weeks after a definitive diagnosis was made.

Table 2. Investigations in Hospital.

Test	Results	Ruled Out
Pulmonary Angiograms and Pressure	Elevated pulmonary artery pressure	Pulmonary thromboembolism
Thoracentesis	No malignant cells No acid-fast bacilli, culture negative	Infection Malignancy
Arterial Blood Gases with Exertion	Pre-exercise: SpO ₂ = 96%, HR 88 bpm, no shortness of breath Post-exercise (3 min later): SpO ₂ = 98%, HR = 89 bpm, pH = 7.46, PaCO ₂ = 38, PaO ₂ = 83, HCO ₃ ⁻ = 27	
Venous Doppler of Lower Extremities	Normal	DVT
Coronary Angiogram/Cardiac Catheterization	Ejection fraction 55% Moderate mitral regurgitation Pulmonary hypertension Global LV hypokinesis Coronary arteries normal	
Chest CT	Bilateral pleural effusions Intralobular septa thickening in the right apex and medial aspects of the lingula	Constrictive pericarditis Lymphangitis carcinomatosa
Anti-hepatic Serology	Non-reactive	Infectious hepatitis
ECG	Sinus rhythm with left axis deviation and left bundle branch block. All leads showed decreased voltage.	
2 nd Transthoracic Echocardiogram	Concentric LV hypertrophy Enlarged left and right atria Estimated EF = 40–50% Moderate pulmonary HTN Severe mitral regurgitation	
Transesophageal echocardiogram (recommended after the echocardiogram was performed to determine the degree and etiology of mitral regurgitation)	Concentric LV hypertrophy Small pericardial effusion Mild mitral regurgitation Dilated pulmonary artery Diastolic dysfunction: restrictive cardiomyopathy	

SpO₂-oxygen saturation, PaO₂-partial pressure of oxygen in arterial blood, DVT-deep vein thrombosis, CT-computed tomography, ECG-electrocardiogram, LV-left ventricular, EF-ejection fraction, HTN-hypertension.

DISCUSSION

Three types of amyloidosis that can affect the heart are primary amyloidosis (also known as immunoglobulin light chain amyloidosis), senile systemic amyloidosis, and familial amyloidosis.⁵ Rarely, secondary (AA) amyloidosis can involve the heart.⁵ Secondary amyloidosis may result from chronic infectious or inflammatory states. Primary amyloidosis, which results from various plasma cell disorders, most frequently leads to amyloid deposition in the heart.

Primary amyloidosis affects 4.5 of 100,000 individuals.¹ It often occurs in patients over the age of 40, and the median survival of individuals with primary amyloidosis who present with heart failure is six months.^{1,6} Primary amyloidosis is caused by the accumulation of monoclonal immunoglobulin light chain (AL) fragments that deposit as misfolded amyloid fibrils into various tissues.⁷ These light chain fragments arise from clonal B cell disorders. 20 percent of patients with light-chain amyloidosis have multiple myeloma while the rest have other B cell disorders such as B-cell lymphoma or Waldenström macroglobulinemia.^{1,8} The deposition of the amyloid fibrils leads to organ dysfunction. Amyloidosis is diagnosed histologically by means of a biopsy from the affected tissue. In the heart (Figure 1), amyloid deposits appear as amorphous pink material in the interstitium or walls of intramyocardial blood vessels on routinely stained slides. With special histochemical stains, such as the Congo red stain, amyloid

appears salmon-coloured in ordinary light but shows apple green birefringence in polarized light. Because amyloid can be caused by deposition of a number of different proteins, additional studies, including immunohistochemical stains on the tissue biopsy, are needed to distinguish them.^{9,10} The infiltration of amyloid fibrils in the heart leads to a restrictive cardiomyopathy.^{8,10} The ventricles stiffen resulting in diastolic dysfunction which leads to an increase in the pulmonary pressures and an elevated JVP. CHF may result from this process. If the amyloid fibrils deposit within the cardiac conduction system, arrhythmias and heart block may result.⁹ Along with the signs of CHF (Table 3), the patient may also exhibit dyspnea and fatigue as a result of a decreased cardiac output.⁹

CONCLUSION

Early recognition may improve the poor prognosis of these individuals.^{5,10} Studies have found that cardiac amyloidosis should be considered when the patient presents with rapidly progressing dyspnea, a non-dilated cardiomyopathy with thickening of the LV wall on echocardiogram, and low voltage ECG (in contrast to high voltage usually seen with ventricular thickening) with or without a pattern that resembles a myocardial infarction.¹⁰ Myocardial biopsies must be performed for a definitive diagnosis to be made. Primary amyloidosis with cardiac symptoms is a devastating disease where symptoms progress rapidly, and patients often only

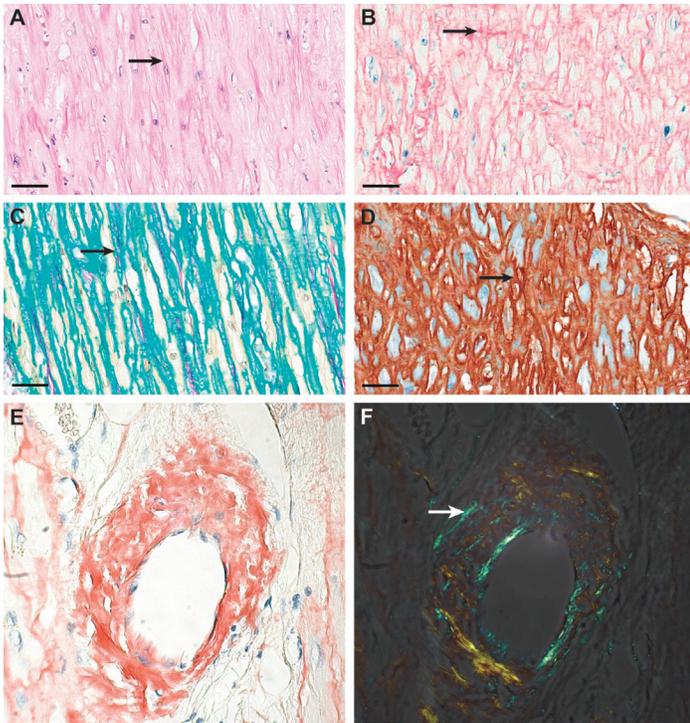


Figure 1. Representative photomicrographs of left ventricular myocardium affected by AL amyloidosis. (A) Cardiac myocytes are surrounded by pink material (Hematoxylin and Eosin, Arrow) (B) that stains positively with Congo red (red-orange color, Arrow) and (C) Sulfated Alcian Blue (greenish-blue color, Arrow) stains. (D) Immunohistochemical staining shows strong positivity for lambda (λ) light chain proteins (Arrow) with no positivity for kappa (κ) light chains or protein A (not shown). (E) The Congo red stain is also prominently positive in the vascular walls in the myocardium and when viewed under polarized light, (F) the amyloid exhibits characteristic “apple-green” birefringence (Arrowhead). Scale bar is 75 μ m. Images are not from the patient presented in this case.

Table 3. Signs and Symptoms of Congestive Heart Failure.^{2,11}

Right-Sided Failure	Left-Sided Failure
Elevated jugular venous pressure	Exertional dyspnea
Ascites	Cough
Peripheral Edema	Fatigue
Hepatomegaly	Orthopnea
	Paroxysmal nocturnal dyspnea
	Pulmonary crackles
	Gallop rhythm
	Pulmonary venous congestion
	Pulmonary edema

live for months. There is little that can be done to treat cardiac amyloidosis, but continued research provides hope for patients and families affected by this tragic illness. While the prognosis remains poor, early recognition of the underlying cause of heart failure of unknown origin will facilitate management of a patient with cardiac amyloidosis and aid in attempts to improve the outcome of the patient. 

DEDICATION

To the most beautiful, compassionate, and supportive woman that I have known. You showed great strength throughout your life, and this did not falter in the last few months as you fought this illness. You continue to teach us today. We will miss you always.

SOAP Note.

Subjective

Progressive shortness of breath and fatigue
Bilateral leg swelling

Objective

Marked bilateral pedal edema
Elevated JVP
Mild bilateral periorbital purpura
Heart sounds distant on auscultation
Bilateral pleural effusions on chest x-ray
Pulmonary hypertension and global left ventricular hypokinesis on cardiac angiogram
ECG - decreased voltage in all leads
Diastolic dysfunction on transesophageal echocardiogram
Amyloid protein deposits in endomyocardium biopsy

Assessment

Symptoms, signs, and diagnostic results consistent with systemic primary amyloidosis with cardiac involvement

Plan

- Comfort Care
- Melphalan (Alkeran®), 10 mg PO daily for 4 days (intervals of 4 weeks)
 - Prednisone, 100 mg PO daily for 4 days (intervals of 4 weeks)
 - Potassium supplement
 - Nitroglycerine (Minitran®) patch daily
 - Fluvastatin (Lescol®) 20 mg PO daily
 - Quinapril (Accupril®) 5 mg PO daily
 - Furosemide (Lasix®) 120 mg PO daily
 - Digoxin (Lanoxin®) 0.625 mg PO daily

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