

Cardiac Amyloidosis : Mini Review and a Case Report

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Abstract: Amyloidosis is a rare heterogeneous group of systemic disorders, which result due to extra cellular deposition of an insoluble, amorphous, eosinophilic, substance known as amyloid. The disease is often characterized by a restrictive cardiomyopathy with a poor prognosis and survival. The treatment of cardiac amyloidosis depends on the underlying etiology. However, the diagnosis of the type of cardiac amyloidosis is not always straightforward. We present here a case of cardiac amyloidosis and we discuss the different forms.

Keywords: Cardiac amyloidosis, Restrictive cardiomyopathy, Heart failure, Primary amyloidosis.

INTRODUCTION

Amyloidosis is a rare systemic disease and heart is involved in some cases. It refers to the extra-cellular tissue deposition of fibrils composed of low molecular weight subunits. More than 20 distinct low molecular weight proteins are recognized to form amyloid fibrils. These fibrils have a specific configuration and can be identified on biopsy specimens both by their characteristic appearance on electron microscopy, and by their ability to bind Congo red [1].

Cardiac involvement is seen in approximately 60 percent of patients and is typically characterized by symptoms and signs of restrictive cardiomyopathy. Therapeutic approach depends on the type of amyloidosis, but it is known the poor prognosis of cardiac amyloidosis [2].

We present a patient with presumed cardiac amyloidosis and we review the different forms.

CASE DESCRIPTION

An 83 year-old Caucasian man was admitted to our department with dyspnea associated with chest discomfort without the characteristics of angina, fatigue and lower limb edema. The patient had no family history of cardiovascular disease and the medical history showcased dementia. His personal story begins two months ago, where he was hospitalized due to peptic ulcer and in the context of laboratory examinations was found pleural effusion (transudate). He was discharged with a recommendation for conducting echocardiogram on a regular basis while the medication included furosemide, carvedilol and proton-pump inhibitors (PPIs).

Upon discharge, on physical examination he was ill-appearing, afebrile, with a blood pressure of 110/70 and heart rate of 80bpm. He was breathing at a rate of 22 breaths per minute and his oxygen saturation was 96% on FiO₂ 21%. His jugular venous was slightly distended and a positive hepatojugular reflux was present. Cardiac exam revealed a regular rate and rhythm, with systolic murmur audible at the apex of the heart. On lung exam, he had bilateral rales at the bases and his abdomen was slightly distended.

Table 1: Laboratory Values on Admission

| Exams | Value |
|----------------------------|-------------------------|
| GLU | 92mg/dl |
| UREA | 55mg/dl |
| CREA | 1.39 mg/dl |
| Na | 136 mmol/dl |
| K | 4.64 mmol/dl |
| AST | 36 IU/L |
| ALT | 30 IU/L |
| ALP | 82 IU/L |
| LDH | 583 IU/L |
| CK | 63 IU/L |
| CKMB | 56 IU/L |
| TROPONINE-T High Sensitive | 67.97 pg/ml |
| CRP | 8.7 mg/dl |
| TKE | 107 |
| WBC | 10.82 |
| NEU | 73.7% |
| LYM | 17.2% |
| HCT | 40.1 |
| HGB | 13.6 g/dl |
| PLT | 547×10 ³ /μL |

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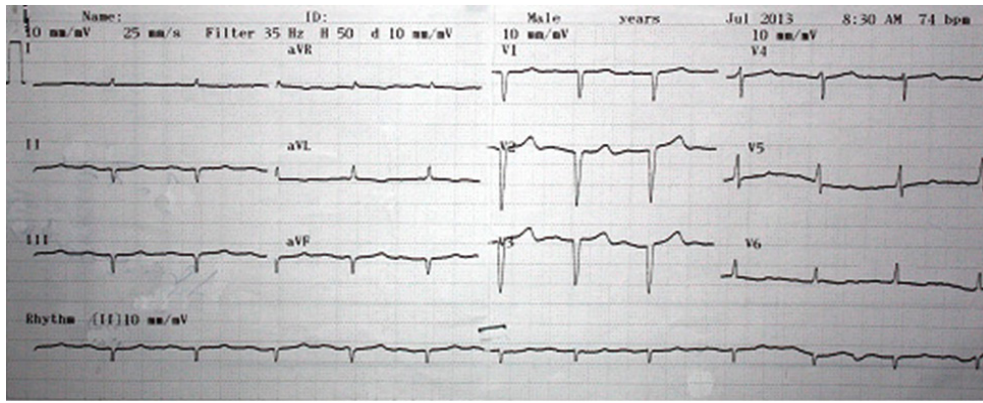


Figure 1: ECG. First degree AV block, low QRS voltage in limb leads, Q wave in inferior leads and in V1-V3.

Laboratory values on admission are shown in Table 1. The ECG revealed sinus rhythm, with ventricular rate 74 bpm, first degree AV block, low QRS voltage in precordial and lower leads and a pseudo-infarct pattern without signs of left ventricular hypertrophy [Figure 1]. The chest X-ray on admission showed minimal pleural effusion on the right base [Figure 3, 4].

Two-dimensional trans-thoracic echocardiogram revealed a small left ventricular cavity with evidence of left and right ventricular hypertrophy. The left ventricular ejection fraction was 50%. Both the left and right atria were moderately dilated. Four-chamber views of the ventricles and atria suggested the possibility of a restrictive cardiomyopathy [Figure 4]. There was reported a moderate mitral regurgitation [Figure 5]. Right ventricular systolic pressure was estimated at 30 mmHg while a severe diastolic dysfunction was present ($E/E' > 13$) [Figure 6].



Figure 2: Face X-ray. Pleural effusion on the right base.

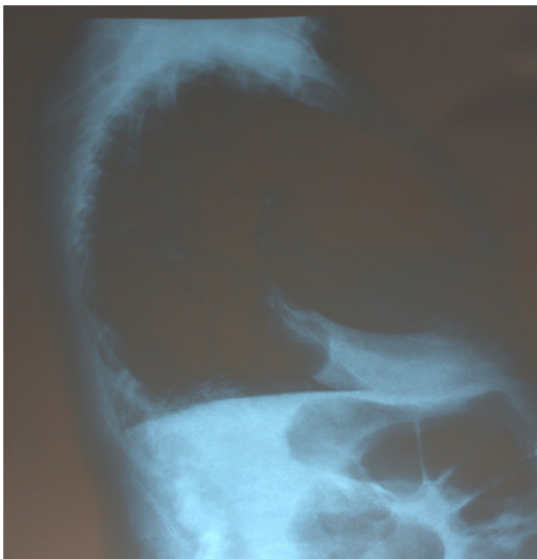


Figure 3: Profile X-ray.

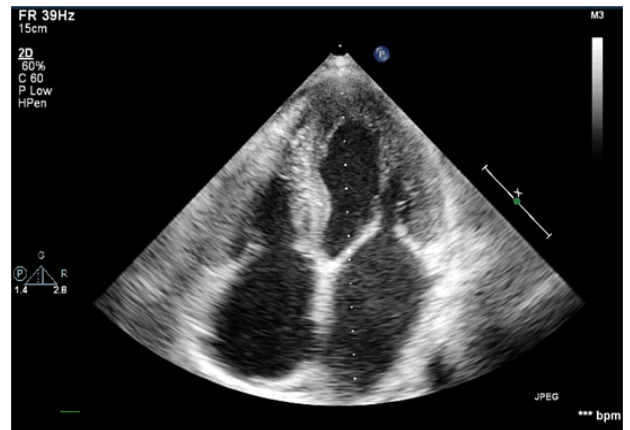


Figure 4: Four chambers view – “sparkle” myocardium.

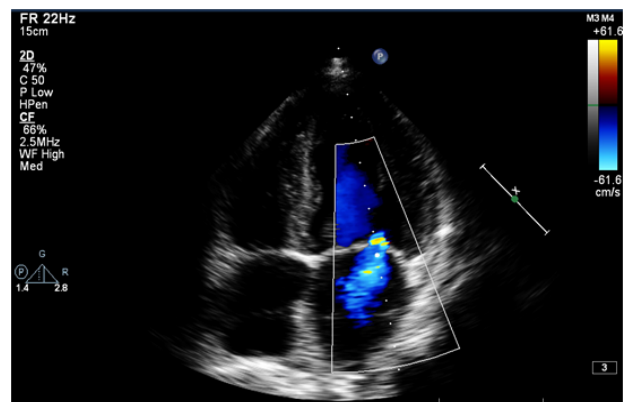


Figure 5: Moderate mitral regurgitation.

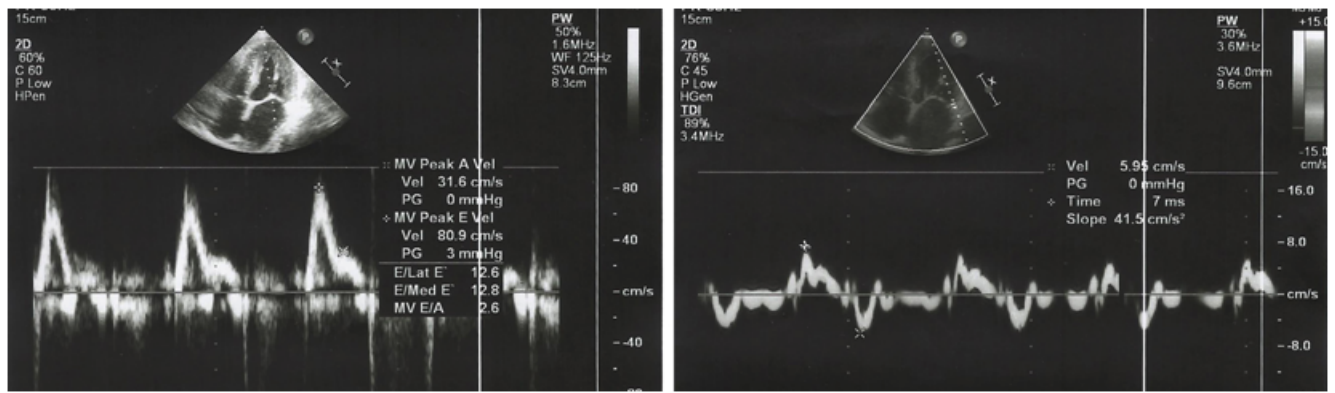


Figure 6: Severe diastolic dysfunction.

Taking into consideration of the severe diastolic dysfunction of left ventricular, the “sparkle” myocardium in two-dimensional trans-thoracic echocardiogram [Figure 7], the elevated values of three digiterthrocyte sedimentation rate and a pseudo-infarctpattern in the ECG, we further examine the patient byconducting a subcutaneous fat pad biopsy and a bonemarrow biopsy.

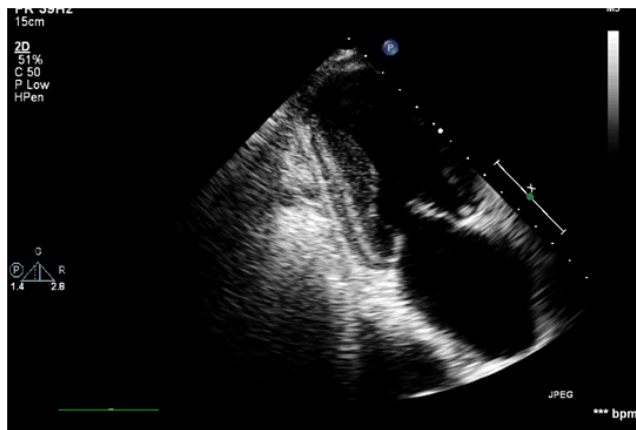


Figure 7: Two chambers view– “sparkle” myocardium.

Bone marrow biopsy was performed on the fifth hospital day and amyloid deposition proved positive associated with myeloma multiple. Immunohistochemical examination with antibodies against the antigens CD20, CD3, CD138, CD56, of light and heavy chains of immunoglobulins showed plasma cells mature type CD138+ CD56+/-, cyclin D1, with lambda light chain, which are developed by forming tendency summations. The cell infiltrate that was estimated account at 12-15%.

A subcutaneous fat pad biopsy, was performed on the sixth hospital day, and it was positive for detection of amyloid in the vessel wall, and diffusible in the tissue (Congo red positive).

The patient was treated with cortisone (prednisone) under continuous hematological monitoring.

DISCUSSION

Amyloidosis is a rare systemic disease characterized by amyloid deposition in different organs and tissues. There are several types of amyloidosis: primary amyloidosis (AL), secondary amyloidosis (AA), familial amyloidosis, senile systemic amyloidosis and Beta-2 Micro globulin Amyloidosis (Abeta2m).

TYPES OF AMYLOIDOSIS

The most frequent types of amyloidosis are the AL (primary) and AA (secondary) types.

AL Amyloidosis

Deposition of immunoglobuline light chains (kappa or lambda) indicates this type of amyloidosis. Monoclonal immunoglobulin light chain, is produced in the bone marrow, and usually is found in the blood or urine. AL amyloidosis can occur alone, in association with multiple myeloma or, much less often, Waldenström’s macroglobulinemia or non-Hodgkin lymphoma.

AL amyloidosis, can appear with a variety of symptoms or signs, including heavy proteinuria, edema, hepatosplenomegaly, and unexplained heart failure.

It is an uncommon systemic disorder, and in United States, the occurrence appears to be 6 – 10 cases per million [1].

There is a male predominance in this disorder and the median age of diagnosis is at 64 years of age [2].

The prognosis for patients with AL amyloidosis is, poor. Median survival is 13 months without treatment, and can be extended to 17 months with cyclic oral melphalan and prednisone therapy [3].

Only 5% of patients survive for more than 10 years [4].

The 85% of patients with AL amyloidosis will have circulating monoclonal proteins in serum or urine. As a result, patients with a presumed cardiac amyloid infiltration, but no evidence of a monoclonal gammopathy, will require an endomyocardial biopsy [5, 6].

The diagnosis of primary AL amyloidosis, is not certain, considering that up to 3% of patients over the age of 70, have a monoclonal gammopathy of undetermined significance (MGUS) [7].

The clinical presentations depend on the organs affected, while in many patients it is possible to identify a dominant organ affected. Renal involvement occurs, in approximately 70 percent of the cases with asymptomatic proteinuria as a chance finding. Cardiac involvement leads to systolic and diastolic dysfunction, with symptoms of heart failure [8]. In addition, there can be angina or infarction, due to accumulation of amyloide in coronary arteries. Peripheral neuropathy is present in 20% of patients with AL. Frequently are present, paresthesia and findings of orthostatic hypotension. Purpura and other skin manifestations (ecchymoses, subcutaneous nodules), are highly characteristic of AL amyloidosis [9].

In general, therapy involves the administration of chemotherapy and/or autologous stem cell transplantation (ASCT). The most common chemotherapy, regimens used, include melphalan plus dexamethasone, or bortezomib-based regimens, such as bortezomib, cyclophosphamide, and dexamethasone. ASCT involves administration of high-dose melphalan, followed by stem cell rescue. Patients with symptoms of heart failure, are excluded of stem cell transplantation.

In immunoglobulin light chain (AL) amyloidosis, amyloid fibril deposits, derived from immunoglobulin light chains, produced by a clonal plasma cell dyscrasia, accumulate in tissues and damage vital organs. Treatment regimens used in multiple myeloma can be effective in AL amyloidosis; however, patients

with this disease, often tolerate these regimens poorly, because of multisystem organ dysfunction. Thalidomide and lenalidomide as a single agent, and in combination with dexamethasone, have both been shown to be effective in myeloma.

In newly diagnosed patients, who are not candidates for high-dose chemotherapy with peripheral blood stem cell transplantation, the combination of lenalidomide and dexamethasone, may be an option as either first, or second-line therapy. For patients who have relapsed after other treatments, the lenalidomide and dexamethasone combination, is a viable choice [10].

Stem cell transplantation (STC), for primary systemic amyloidosis, is applicable to a minority of patients, such as those with limited organ disease, and no significant cardiac involvement. Response rates with SCT appear to be higher, than those seen in patients treated with traditional melphalan and prednisone. Morbidity and mortality are clearly higher, than in patients with multiple myeloma or other hematologic malignancies undergoing autologous SCT. An unusually high rate of significant gastrointestinal tract hemorrhage, and cardiac complications including arrhythmias, are prevalent. SCT for AL will remain controversial, until there is either a multicenter phase 3 trial, comparing it to standard therapy in newly diagnosed patients, or a multicenter phase 2 trial using a risk-adapted approach, showing reduced treatment-related mortality. We anticipate that, improved patient selection, peri-transplantation management, and adoption of a risk-adapted approach to melphalan dosing based on organ involvement, and age, will accelerate the acquisition of the expertise needed for the conduct of multicenter SCT trials, and will enhance the impetus for early diagnosis and timely treatment of AL.

AA Amyloidosis

AA amyloidosis, the most common form in developing countries may complicate chronic diseases such as rheumatoid arthritis (RA), spondyloarthropathy, or inflammatory bowel disease, chronic infections, or periodic fever syndromes [11]. As a result of chronic inflammation, serum amyloid A (protein in acute phase), composes the fibrils. AA amyloidosis at the beginning affects the kidneys, but other organs can be involved.

Familial Amyloidosis

Deposition of transthyretin in myocardium and other tissues, has been referred to as Systemic Senile Amyloidosis (SSA) [12]. A mutation in the transthyretin (TTR) gene that produces abnormal transthyretin protein, is typical in familial amyloidosis. The abnormal TTR protein, accumulates as amyloid fibrils: thus, it is termed ATTR amyloidosis. Symptoms of disease are usually, neuropathy and cardiomyopathy, and occur in mid to late life. Treatment is a liver transplant; however, newer treatments with targeted inhibitors, are in clinical trials. Compared with patients with AL amyloidosis, those with the senile systemic disease, survive longer (75 versus 11 months), despite having ventricular free wall and septal thickening, due to amyloid accumulations [13].

However, less common than AL amyloidosis, is a familial form associated with a point mutation in the transthyretin molecule (ATTR). The clinical presentation is usually polyneuropathy and/or cardiomyopathy, and more than 100 variant transthyretin proteins with single amino acid substitutions, have been described, most of which are amyloidogenic. Patients with ATTR amyloidosis who have cardiac involvement, may have an echocardiographic appearance indistinguishable from patients with AL cardiac amyloidosis but with a significantly longer survival time. A mutation in ATTR is not a prerequisite for the formation of transthyretin-associated amyloid fibrils. In elderly patients, wild-type transthyretin, may be come structurally unstable, resulting in the development of misfolded intermediates that ultimately aggregate and precipitate as amyloid [14]. These fibrils form in many different organs, but they have a predisposition for the heart [15]. Although cardiac deposits of wild-type transthyretin amyloid are not uncommonly found in small amounts at autopsy in elderly patients who had few or no cardiac symptoms, wild-type transthyretin may occasionally be deposited in massive amounts in the heart. When this occurs, congestive heart failure occurs and senile cardiac amyloidosis is found to be present [15].

Dialysis-Related Amyloidosis

Is associated with deposition of beta-2 microglobulin, which accumulate in patients with end-stage renal disease, who are being treated with dialysis.

In conclusion, cardiac amyloidosis, is a serious disease with a poor prognosis. The clinical cardiologist, should suspect cardiac amyloidosis in a patient, with symptoms of right heart failure and walls of left ventricle with restrictive pattern of diastolic dysfunction, coupled with low dynamic ECG. Tissue biopsy (subcutaneous fat pad biopsy, bone marrow biopsy), will put the final diagnosis.

ABBREVIATIONS

primary amyloidosis (AL), secondary amyloidosis (AA), monoclonal gammopathy of undetermined significance (MGUS), autologous stem cell transplantation (ASCT), systemic senile amyloidosis (SSA), transthyretin (TTR), proton-pump inhibitors (PPIs), stem cell transplantation (STC).

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