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Case Report

A Case of AL Lambda Amyloidosis with Severe Cardiac Impairment Whose Outcome was Unfavorable

Hannanse Mahunan Murielle Ahodakin[1*], Ngardjibem Djita[1], Pierre Bolarin Lawani[2], Ibrahima Sory Sylla[1], Noura Feniche[1]

[1]Department of Cardiology, Alençon-Mamers Intercommunal Hospital Center, Alencon, France;[2]Department of Cardiology, Dax Hospital Center-Silver Coast, Dax, France

ABSTRACT

Amyloidosis is an infiltrative pathology with a quasi-systemic manifestation. It can be a transthyretin infiltration (mutated or senile), a light chain AL infiltration that represents a therapeutic emergency or a type AA infiltration. The diagnosis is sometimes less obvious but is increasingly refined with tools and algorithms within the reach of practitioners. In some difficult cases, a myocardial biopsy is sometimes necessary. We report the case of one patient, followed in our cardiology department, in whom the diagnosis of AL amyloidosis was made late. Sadly, she died a few months later despite chemotherapy.

Keywords: Atrial Fibrillation; Electrocardiogram; Hypertension; Treatment; Prognosis

INTRODUCTION

Amyloidosis is a potentially underdiagnosed systemic pathology. They are caused by deposits and accumulation of "amyloid fibrils" in various tissues leading to progressive organ failure and death [1]. The infiltration and/or accumulation of these fibrillar proteins can affect: the heart, kidneys, liver, gastrointestinal system, nervous system, skin and hearing. The clinical manifestations depend on the organs affected. They are declined in neuro-sensory, dysautonomical, digestive manifestations; renal, cochleo-vestibular, cutaneous and cardiac (atrial fibrillation, isolated elevation of cardiac enzymes, conductive disorders, heart failure).

There are several types of amyloidosis, the presentations and even the basic diagnostic elements of which can be confusing. AL amyloidosis is linked to the excess production of a free light chain of the kappa or more often lambda type. They come within the framework of benign ("Monoclonal Gammapathy of Undetermined Significance", MGUS) or malignant (myeloma) gammopathies. They most often occur in between the ages of 60 and 80 but can appear at a younger age. Cardiac involvement is present in a percentage of the order of 70% to 80% of patients [2,3]. Cardiac biomarkers namely: NT-proBNP and Troponin have diagnostic (staging) but above all prognostic value [1,4]. The natural course is often of poor quality, hence the interest of an early diagnosis for a relatively suitable therapy. The severity of the cardiac involvement is a determining factor in the prognosis [5]. Management depends on the type of amyloidosis, knowing that AL amyloidosis represents a therapeutic emergency. This management in AL amyloidosis is based specifically on chemotherapy combining bortezomib (Velcade) + Cyclophosphamide (Endoxan) + Dexamethasone (VCD).

New therapeutic trials are under study, such as ANDROMEDA, which is a phase III trial with remarkable results in patients with severe organ damage, when daratumumab is combined with the standard VCD treatment [6]. This clinical case is of interest in the existence of potential difficulties in refining the diagnosis of AL amyloidosis, thus delaying specific therapeutic management.

CASE REPORT

This is a patient born on 01/08/1936, hospitalized for the first time in June 2016 in the cardiology department of Alençon Hospital Center for heart failure due to concentric hypertrophic heart disease. Several episodes of decompensations followed until September 2018, when he was transferred to a competence center.

His antecedents are marked by:

• Atrial Fibrillation (AF) reduced by electrical cardio version in March 2017; recurrence of AF after stopping amiodarone (due to diffuse iatrogenic interstitial lung disease)

Correspondence to: Hannansé Mahunan Murielle Ahodakin, Cardiologist, Department of Cardiology, Alençon-Mamers Intercommunal Hospital Center, Alencon, France, Tel: +33-758-30-5892; E-mail: ahodakinmurielle@yahoo.fr

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• Absence of arterial hypertension and aortic valve pathology

• Monoclonal Gammopathy of Undetermined Significance (MGUS) followed in hematology since June 2017, with elevation of lambda free light chains to 142 mg/L; Kappa at 16 mg/L, lambda peak at 12 g/L in February 2018.

Faced with this hypertrophic heart disease with several recurrences of cardiac decompensation and especially the presence of MGUS, a first biopsy of the salivary glands was taken in December 2017 and the results of which did not contribute to the diagnosis of AL amyloidosis. BENCE JONES proteinuria also came back negative.

She was seen in consultation for a post-hospital cardiological reassessment in February 2018. Clinically, she had stage 3 NYHA dyspnea, no nausea or vomiting. She reported alternating diarrhea/constipation. There was no macroglossia (Figure 1).The electrocardiogram was registered in regular sinus rhythm and a pseudo Q wave in anteroseptal. An echocardiographic check made found a concentric Left Ventricular Hypertrophy (LVH) (SIVd 17 mm, PVGd 16 mm), with shiny appearance of the myocardium, LVEF at 70%, restrictive mitral profile. Bi atrial dilation with left atrium at 52 ml/m2, OD 26 cm2, limits. The overall longitudinal strain is altered at -15%; Cockade aspect with apical sparing. Right Ventricular Hypertrophy (HVD) at 6 mm, longitudinal functions of the right ventricle normal. There was no pericardial effusion.

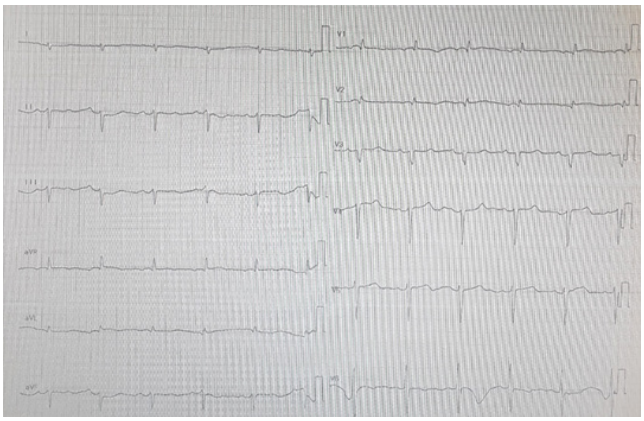

Figure 1: Regular sinus rhythm, Q aspect of antero-septal pseudo-necrosis, HBAG..

The cardiac biomarker assay found: very high NTproBNP at 13833 pg/ml; US troponin at 98 ng/L. A cardiac MRI performed subsequently confirms the LVH with good systolic function of the left ventricle and an appearance suggestive of cardiac amyloidosis. A first bone scan found no evidence for TTR amyloidosis. There was no cardiac fixation. The Myelogram showed a 5% plasma cell level without abnormalities.

In view of the results of these various assessments and the strong suspicion of AL cardiac amyloidosis, the patient was referred to the Heart Failure and Amyloidosis Unit of the CHU (University Hospital Center) Henri-Mondor in September 2018 where she was hospitalized several times for the assessment complementary to this amyloidosis.

The control cardiac ultrasound carried out in the expert center found: a typical appearance of cardiac amyloidosis with homogeneous biventricular hypertrophy, LVEF preserved but worsening of the alteration of the overall strain in the cockade (-9.2%) with apical sparing. A restrictive mitral profile and an infracentimetric non-compressive pericardial effusion over the postero-basal wall. The control of bone scintigraphy with diphosphonates will show an aspect compatible with cardiac amyloidosis of the TTR type. Heart/mediastinum ratio=1.45.

The TTR mutation taken and returned negative thereafter CRAB criteria: calcemia at 2.29 mmol/L; Creatinine at 95 µmol/L, Hb at 11 g/dl, unintended bone damage. A second salivary gland biopsy performed on 09/17/2018 returned later with a result in favor of AL lambda amyloidosis. Electrophoresis of the proteins shows a peak in the gamma globulin grass: monoclonal IgG lambda Myelogram 7% plasma cells. A cardiac biopsy taken on 10/05/2018: confirms the myocardial localization of AL amyloidosis.

The diagnosis of amyloidosis AL lambda stage 3b was finally made in view of the results of these various additional examinations. The file was discussed in a multidisciplinary consultation meeting (RCP) on 10/10/2020 with validation of the VCD treatment. The first treatment is carried out at CHU Henri-Mondor without major incident. Subsequent cures are carried out both at Henri-Mondor and the hematology service of CH Alençon.

After the first cures, there appeared a slight improvement in the haematological plan. In February 2019, the general condition begins to deteriorate. The patient becomes dependent on oxygen; reappearance of significant pleural effusion and new ascent of the Lambda peak. She will be hospitalized again in cardiology at the Alençon hospital for 2 successive episodes of cardiac decompensation. After discussion with the hematologist and the reference center in Mondor, on March 12, 2019, she completed her 5th cycle of chemotherapy with Velcade-Endoxan-Dexamethasone. Unfortunately, she died two months later post-operatively (discharge colostomy) from a tumor of the anal margin, the pathological examination of which concluded with presumed tumor necrosis.

DISCUSSION

This was cardiac amyloidosis AL lambda stage 3b in an 84-year-old patient with discordant initial assessment: presence of monoclonal gammopathy, a negative first salivary gland biopsy as well as testing for BENCE JONES proteinuria. Bone scintigraphy (controle) with diphosphonates showed fixation in favor of TTR amyloidosis and the second salivary gland biopsy performed returned positive for AL amyloidosis. The myocardial biopsy will then confirm the myocardial localization of AL amyloidosis.

In the literature, it is known that the diagnosis of AL amyloidosis can be difficult with the possibility of false negatives in biopsies at the onset of the disease; biopsy which will have to be repeated in case of persistent suspicion. It should also be remembered that the first bone scan performed at Alençon Hospital in this patient with MGUS was not contributing to the diagnosis of TTR amyloidosis. This examination was repeated at the CHU Henri-Mondor with very disturbing results. Could this positivity be due to an evolution of monoclonal gammopathy? or an initial misinterpretation?

This clearly demonstrates that any bone scintigraphy in the diagnostic process of cardiac amyloidosis must be interpreted according to the presence or not of gammopathy because AL amyloidosis can give myocardial fixations in about 10% of cases. A

scan suggestive of TTR amyloidosis will only be of good diagnostic value in the absence of monoclonal gammopathy. Thus in the diagnostic process of cardiac amyloidosis, it is imperative to perform at the same time as the bone scintigraphy, four examinations in search of monoclonal gammopathy, namely: electrophoresis of serum proteins, serum immunofixation, assay of free light chains , testing for BENCE JONES proteins in urine.

It should be remembered that the diagnosis of AL amyloidosis in our patient was late. However, any AL amyloidosis is a therapeutic emergency. This diagnostic delay conditioned the delay in the initiation of specific treatment. This fact clearly explains the unfavorable development that quickly led to the death of our patient. In fact, it took approximately 24 months to arrive at the diagnosis of a therapeutic emergency, which is AL amyloidosis in the case studied.

Severe cardiac involvement and classification to stage 3b before initiation of treatment was also a poor prognosis. For treated AL amyloidosis cases, the course is described as a function of the extent of cardiac involvement and the response to treatment. Prognostic criteria were established and based on the importance of the elevation of cardiac biomarkers (NT-proBNP; Troponin) with a hazar ratio for death of 11.1 (Table 1).

Table 1: Prognostic criteria about AL amyloidosis.

European 2015	cTNT ≥ 0.035 ng/ml TNT-hs ≥ 50 ng/L	NTproBNP ≥ 332 pg/ml BNP>81 ng/L	HR pour le décès (95%CI)
I	0	0	Ref [4]
II	1	des 2	56 ± 12
III-a	1	1	4.9 (3.6-6,8)
III-b	1	NTproBNP>8500 ng/L BNP>700 ng/L	11.1 (8.1-15.4)

Despite the risk of early mortality, overall survival has improved with advances in chemotherapy. Earlier diagnosis and treatment of AL cardiac amyloidosis is essential for best results. Conventional treatments for heart failure such as beta blockers, ACE inhibitors and Angiotensin II receptor blockers are poorly tolerated in cardiac amyloidosis and may also be aggravating factors. Our patient benefited from these treatments for two years before stopping them definitively once the diagnosis of AL cardiac amyloidosis was made. The treatment of cardiac decompensations is most often limited to the use of diuretics (Furosemide, Aldactone).

Atrial fibrillation arrhythmia is one of the telltale patterns of amyloid heart disease. This patient contraindicated to the beta-blocker could have benefited from a strategy of maintaining sinus rhythm or slowing heart rate improving the prognosis of heart failure. Unfortunately, he had developed interstitial lung disease with Cordarone prohibiting its use. The risk of recurrence of atrial fibrillation is therefore permanent and obvious and the cause of several cardiac decompensations.

To all these elements of bad omen comes a digestive surgery grafted on an extreme fragility definitely darkening the prognosis of the patient.

CONCLUSION

In view of this clinical case, we retain that:

• From a diagnostic point of view, the need for a minimum diagnostic assessment combining both bone scintigraphy and the search for monoclonal gammopathy (electrophoresis of serum proteins and serum immunofixation, assay of free light chains, search for proteins of BENCE JONES in the urine). Bone scintigraphy has excellent negative predictive value for AL amyloidosis in the absence of gammopathy.

• Salivary gland biopsy may be negative at first, and does not exclude the diagnosis.

• AL amyloidosis represents a diagnostic and therapeutic emergency. The sooner the diagnosis is made, better is the prognosis. Unfortunately our patient diagnosed late had an unfavorable prognosis.

CONFLICT OF INTEREST

None.

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