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RESEARCH ARTICLE

CARDIAC AMYLOIDOSIS RELATED TO WALDENSTROM'S DISEASE: CASE REPORT AND LITERATURE REVIEW

[1,*]Abdelmajid Bouzerda, [1]Amin Ahmindache, [1]Jawad Ngadi, [1]Ilyass Asfalou, [1]Zouhair Lakhal, [2]Mohammed Asseraji, [2]Laila Bendriss and [2]Ali Khatouri

[1]Department of Cardiology, Mohammed V Military Hospital, Rabat, Morocco
[2]Department of Cardiology Avicenne Military Hospital, Marrakech, University Cadi ayyad, Faculty of Medicine and Pharmacy, Marrakech, Morocco

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ABSTRACT

Amyloidosis is characterized by extracellular accumulation of insoluble protein fibrils in various tissues and organs. Cardiac involvement is the most serious localization and the leading cause of death, requiring early diagnosis that may be difficult. We report the case of a patient presenting Waldenstrom's disease complicated by cardiac amyloidosis and we review the cardiac involvement in immunoglobulin related amyloidosis.

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INTRODUCTION

Amyloidosis is a heterogeneous group of systemic disorders characterized by the extracellular deposit of insoluble protein fibrils. The most common is AL amyloidosis, linked to the deposit of light chains of immunoglobulins (Khan *et al*., 2001). It can be associated with myeloma or monoclonal gammopathy (Khan *et al*., 2001). Whose diagnosis is generally easy. Diagnostic may be difficult when myeloma or gammopathy are not known or when symptoms highly suggestive of amyloidosis are not present. The most frequently affected tissues are the kidneys (proteinuria, hypertrophy, renal failure), the liver (hepatomegaly, cholestasis), the digestive tract, the nervous system (peripheral neuropathy, dysautonomia) and the heart (restrictive heart disease with heart failure, disorders of conduction, coronary insufficiency) (Pavic *et al*., 2011). We report a case of cardiac amyloidosis complicating Waldenstrom's disease.

Case Presentation: A 56 year old male patient followed for 4 years for an asymptomatic Waldenstrom disease for which he is receiving no treatment.

Corresponding author: **Abdelmajid Bouzerda,**
Department of Cardiology, Mohammed V Military Hospital, Rabat, Morocco.

He presented de novoangina associated with NYHA Grade II-III exertional dyspnea. The ECG found a regular sinus rhythm at 87 bpm, a left deviated heart axis, a constant PR interval of 160 ms, Q waves in anteroseptal leads, flat T waves in high lateral leads and microvoltage in the peripheral leads (Figure 1). Cardiac ultrasound (Figure 2) showed a left ventricle (LV) mild hypertrophy predominantly on the septum whith agranular sparkling appearance, segmental and global kinetics are conserve dwith a left ventricle ejection fraction (LVEF) estimated at 63% and biatrial dilatation (surface of LA of 24 cm 2 and RA of 21cm2). The right ventricle (RV) was normal in size and contractility with good systolic function (TAPSE at 20mm and S-wave peak at 12 cm / s) with thickening of the free wall. Doppler examination noted a restrictive mitral profile with E / A ratio at 2.9 and high LV filling pressures. The inferior vena cava was small and compliant with a dry pericardium and novalvular abnormalities. Ultrasensitive troponin I was 50.4 ng/l. NT pro-BNP was 18500 pg/ml. An additional angiographic and hemodynamic assessment (Figure 3) showed no coronary involvement. The hypothesis of amyloid heart disease was therefore raised. MRI morphokinetic study in cine-Trufisp sequences, T2 study "black blood" and late enhancement (Siemens Avanto 1.5 T) study were performed. The morphological study revealed a hypertrophy of the left ventricle (LVH) walls and a pericardial

effusion, associated with biatrial dilatation (surface of LA of 24 cm2 and RA of 21 cm2). The LV study evaluated LVEF at 62% and an increased LV mass at 69 g/m2. The study of late enhancement (Figure 4) realized ten minutes after the injection revealed circumferential subendocardial enhancement without vascular systematization. The diagnosis of cardiac amyloidosis was therefore clarified. Periumbilical fat biopsy confirmed the presence of extracellular deposit of amyloid substance. Myocardial biopsy was not performed. Electrophoresis of serum proteins showed a monoclonal peak of Ig M lambda type (389.16 mg/l). The 24-hour Bence Jones Proteinuria was negative. Kidney function was normal. There was no digestive or neurological involvement. The diagnosis of cardiac amyloidosis secondary to Waldenstrom's disease was made. A combination of monoclonocal anti-CD20 antibodies (Rituximab) and Bendamustine was initiated which allowed improvement of cardiac symptoms with a relatively good clinical tolerance.

DISCUSSION

This case allows us todiscuss diagnostic criteria, treatment and the prognosis of cardiac amyloidosis. Cardiac amyloidosis include several clinical entities having in common the extracellular deposit of fibrillary proteins arranged in folded sheets. Cardiac amyloidosis is more common in AL (immunoglobulin related) amyloidosis and present a classic example of restrictive cardiomyopathy. Moreover, it is not an exceptional affection as there are between 1000 to 5000 new cases per year in the United States (Kyle *et al*., 1995). The diagnosis, most often made in adulthood, is based on the association of nonspecific clinical signs, serum and urine proteins electrophoresis abnormalities and histology on biopsies of accessory salivary glands, renal or digestive (Banypersad *et al*., 2012). Heart failure is the most common circumstance of discovery, affecting between 60 and 70% of cases (Cottin *et al*., 2015) and reflecting a severe and advanced form. Angina, as in the present case, is the second clinical manifestation, found in 25% of cases (Cottin *et al*., 2015). Cases of pseudo-necrosis have also been reported (Cottin *et al*., 2015). At last, orthostatic hypotension has been described in 16% of cases (Cottin *et al*., 2015). More than 90% of cases have a pathological electrocardiogram and can show: a micro voltage contrasting with LVH on ultrasound, a right or left axial deviation, atrial fibrillation andatrio-ventricular node conduction disorders. An aspect of anterior pseudo-necrosis is also common and may mislead to the diagnosis of coronary heart disease which may be reinforced by a frequent troponin elevation resulting in performing an angiogram as in our present case. Echocardiography remains the main examination demonstrating usually a predominantly septal LVH with a granular sparkling appearance (Dubrey *et al*., 2011) in the absence of aortic stenosis and/or hypertension. (Desport*et al*., 2012) and associated with a biatrial dilation and diastolic dysfunction. However, the ultrasound examination is limited in differentiating various restrictive heart diseases more or less associated with LVH (Mohty *et al*., 2013). The association of a restrictive profile and a pericardial effusion is highly suggestive of amyloidosis. Finally, it should be emphasized that intracardiac thrombosis are common and should be systematically sought out even in patients with sinus rhythm. Subtle analysis of the contractility using 2D strain is more sensitive than the LVEF. In amyloidosis, the LV 2D-strain is decreased predominantly in the basal segments and preserved in apical segments (Phelan *et al*., 2012).

Natriuretic peptides are essential for prognosis assessment and the follow-up of patients. The elevation of NT-pro-BNP greater than152 pmol/l has a prognosis value indicating an increased risk of mortality (Banypersad *et al*., 2012). On the other hand, its decrease by 30% after three cycles of chemotherapy marks therapeutic efficacy (Phelan *et al*., 2012). Troponins are likewise markers of cardiac involvement and have a prognostic value in AL amyloidosis (Dungu *et al*., 2012).

In addition to echocardiography, cardiac MRI, routinely used to differentiate between ischemic and non-ischemic conditions (Cummings *et al*.,), represents a powerful technique in the morphological and functional assessment of cardiac involvement in amyloidosis (Ruberg *et al*., 2009). First of all, it reveals signs of restrictive heart disease, with no specificity for the diagnosis of amyloidosis: concentric thickening of the LV wall, biatrial dilatation, decreased diastolic function and LVEF. It can also spot any pleural or pericardial effusions (Germans *et al*., 2008). More recently, imaging abnormalities specific to cardiac amyloidosis have been reported. These descriptions concern late myocardial enhancement sequences which are morphological sequences produced within 5 to 15 minutes after the injection of contrast media (gadolinium chelate) (Vogelsberg *et al*., 2008).

It is admitted that on these late sequences, myocardial enhancement may be related to cell death or accumulation of extracellular material (Ruberg *et al*., 2009). In the case of amyloidosis, two main aspects are found: The most specific aspect is a late circumferential subendocardial enhancement that is due to the accumulation of interstitial protein (Maceira *et al*., 2005) and may reflect its distribution within the myocardium (Ruberg *et al*., 2009). This aspect was found in the present case. Other localizations of the late enhancement were described as the atrial walls (Vogelsberg *et al*., 2008) or the papillary muscles (Maceira *et al*., 2005) which can also be infiltrated by amyloidosis. A diffuse heterogeneous late enhancement that would make the inversion recovery sequences difficult (Maceira *et al*., 2005). The prognosis utility of late enhancement has also been studied. Subendocardial enhancement alone is poorly correlated with survival in amyloid disease (Migrino *et al*., 2009).

The endomyocardial biopsy remains the method of diagnosis of certainty, its invasive nature and hard accessibility makes its clinical application sometimes difficult. The diagnosis can then be made by the combination of an evocative clinical picture, echocardiogram and a positive extracardiac biopsy. (Klemi *et al*., 1987) (Rectal, abdominal subcutaneous fat or accessory salivary glands biopsy). The histological diagnosis uses the particular and pathognomonic affinity of amyloid proteins for Congo red stain. The polarized light will show a red-green birefringence. It is always supplemented by immunohistochemical analysis to clarify the exact nature of the amyloid protein (Ancsin *et al*., 1999). In the present case, a biopsy of the periumbilical fat was performed and provided diagnostic confirmation.The search for other localizations, notably renal, must be systematic. In 50% of cases, there is a renal involvement which manifests most often as nephrotic syndrome or renal veins thrombosis. The second extracardiac localization is pulmonary with diffuse interstitial syndrome or nodular lesions on chest X-ray. Finally, digestive involvement is common with in particular macroglossia, dysphagia related to vegetative neuropathy or small intestines damage (Cottin *et al*., 2015).

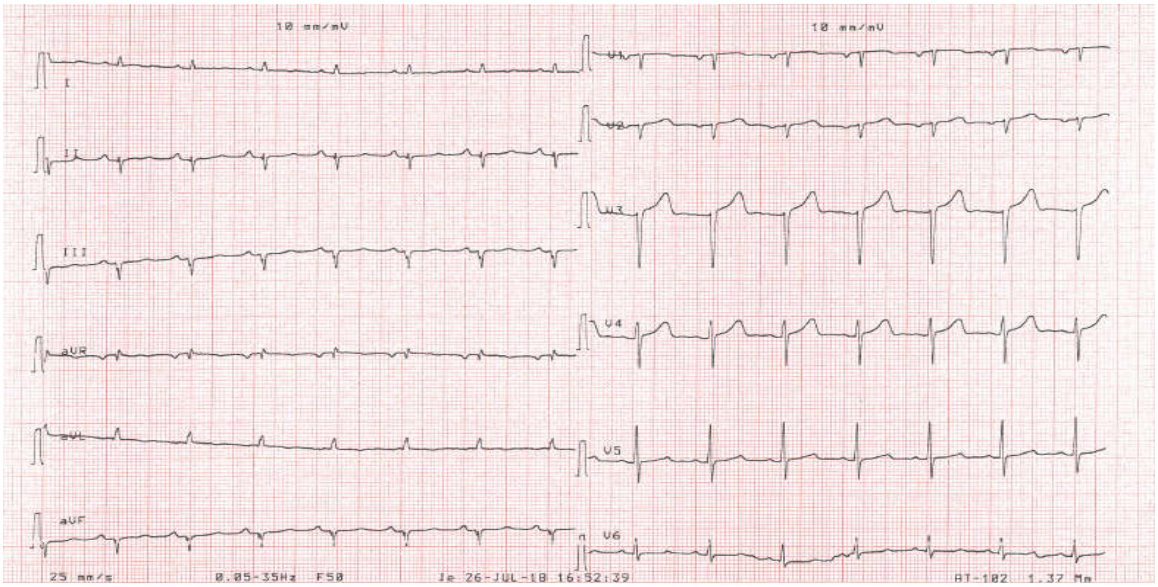

Figure 1. Electrocardiogram showing micro voltage in peripheral leads and pseudo necrosis in anteroseptal leads.

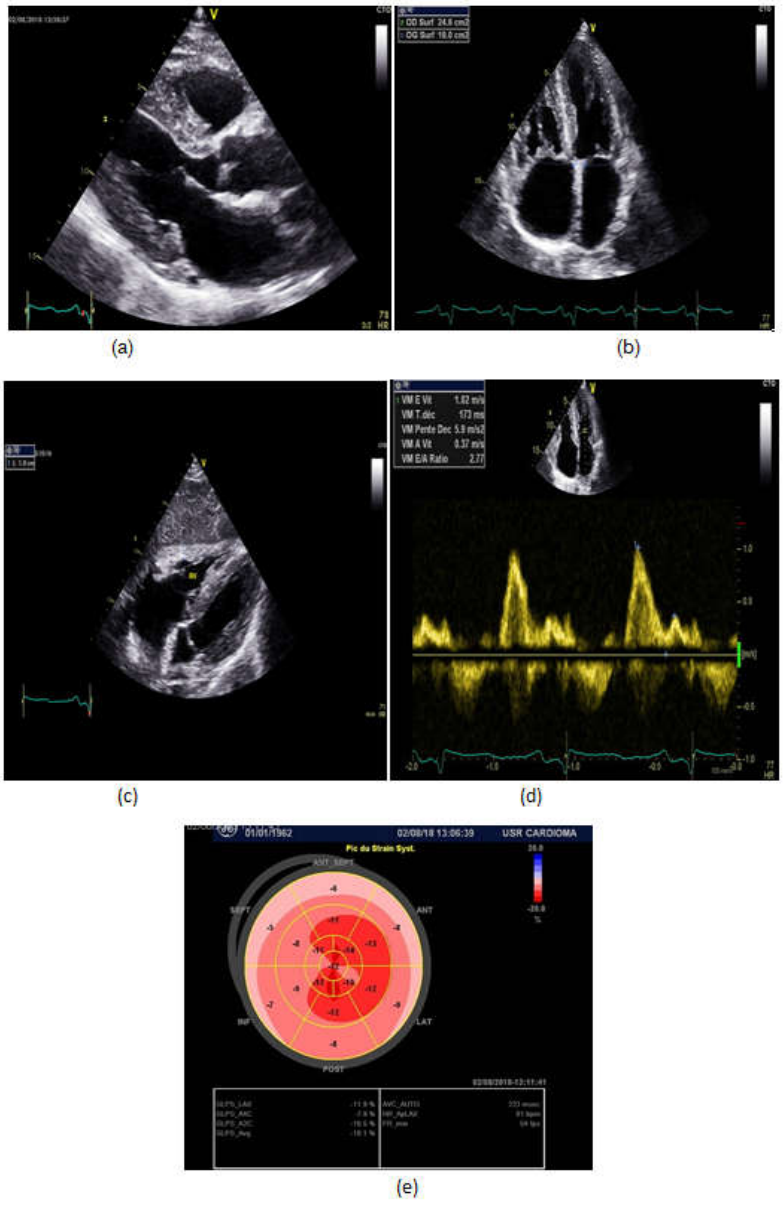

Figure 2: Ultrasound: (a): LV Myocardal hypertrophy. (b): Biatrial dilatation. (c) :RV free wall thickening. (d): Restrictive mitral inflow. (e): decreased global longitudinal strain and bull's eye pattern typical of amyloidosis . LV: left ventrile; RV: right ventricle

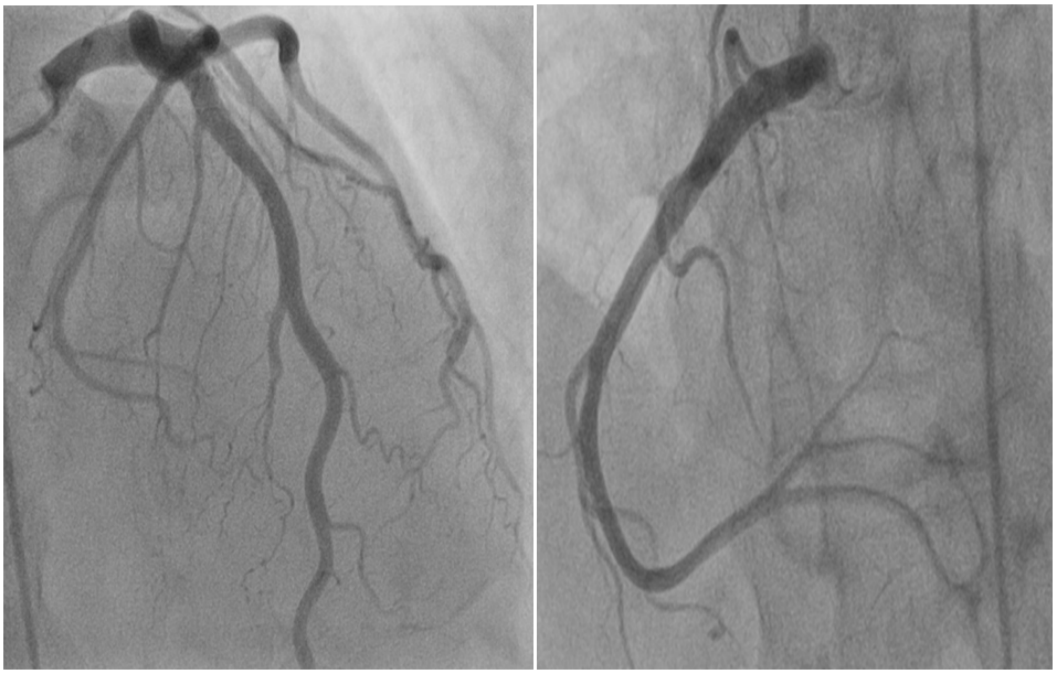

Figure 3. Coronary angiogram showing normal left (a) and right (b) coronary arteries

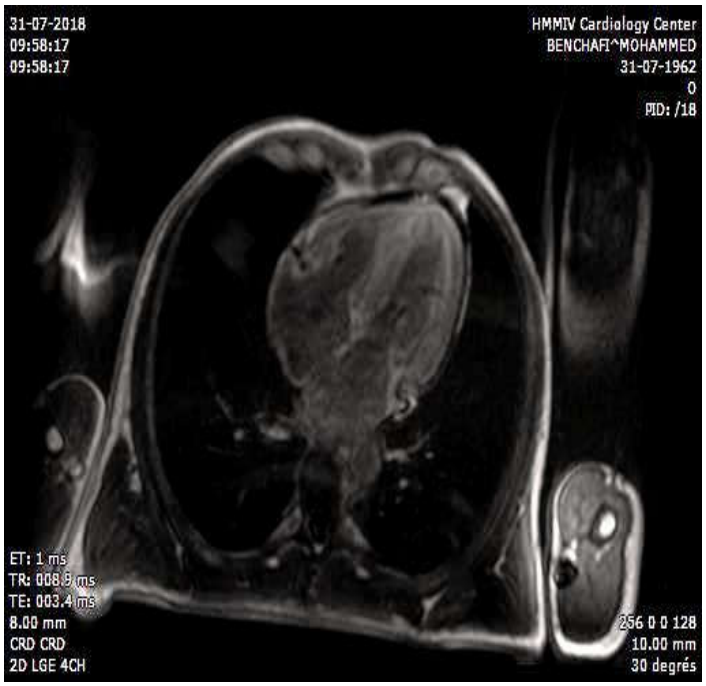

Figure 4. Cardiac MRI: global late gadolinium enhancement of the ventricle and atrias raising the diagnosis of an infiltrative cardiomyopathy

Many routinely used medications in cardiology are contraindicated or to be use with caution in cardiac amyloidosis. Beta-blockers because of their negative chronotropic effect, ACE inhibitors because of deep hypotension even in small doses and digoxin and calcium-channel blockers because of their potential bond with fibril deposits inducing high toxicity (Ruberg *et al*., 2012). Amiodarone remains the recommended treatment for rhythm disorders especially supraventricular arrhythmias and the loop diuretics for volume management. Defibrillator implantation has been considered to prevent cardiac sudden deathbut has been disappointing as sudden death is most often due to electromechanical dissociation (Ruberg *et al*., 2012).

The specific treatment of AL amyloidosis has evolved considerably and the use of new chemotherapies has greatly improved the prognosis of patients. Management of amyloidosis is a therapeutic emergency as the median survival is 13 months after diagnosis and only 6 months in case of cardiac involvement in the absence of treatment (Cottin *et al*., 2015).

The response to chemotherapy is associated with an improvement of symptoms, a decrease in biomarkers and light chains, an improvement of LV 2D strain and decrease of thickness of the walls (Thibaud Damy 2014).

Conclusion

The prevalence of cardiac amyloidosis is clearly underestimated, it affects adults of all ages depending on the different forms. Its diagnosis is often difficult and yet, it must occur as early as possible because of the poor prognosis in the absence of appropriate treatment. New imaging techniques can improve its screening that is still delayed. The development of new treatments will ultimately improve the prognosis of this disease.

Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images

Conflicts of interest: The authors declare that they have no conflicts of interest concerning this article.

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