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Extensive Bi-Atrial Remodeling on Hypertensive Patient with Permanent Atrial Fibrillation Delayed Diagnosis of Fatal Cardiac Lambda Amyloidosis

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Abstract

Background: Amyloidosis is a disease characterized by the deposition of fibrillar proteins in tissues. The nature of the protein defines the type of amyloidosis. Cardiac involvement is most often secondary to deposits of transthyretin and immunoglobulin light chains. Treatment depends on the type of amyloidosis. Cardiac light chain amyloidosis is a medical emergency. **Aim:** To highlight the importance of an early diagnosis of cardiac light chain amyloidosis. **Case Presentation:** We report the case of an 88-year-old hypertensive female patient with sustained atrial fibrillation and recurrent heart failure, in whom echocardiography showed concentric left ventricle hypertrophy with mildly reduced left ventricle ejection fraction (LVEF) to 45%. Bone scintigraphy was normal. Serum analysis showed increased lambda free light chains. Accessory salivary gland biopsy revealed weak Kappa light chain staining and clear overexpression of lambda light chain deposits. The diagnosis of stage 3B cardiac amyloidosis secondary to lambda light chain myeloma was made. After a multidisciplinary meeting, it was decided to start treatment with DARATUMUMAB + LENALIDOMIDE. Patient's general condition deteriorated with the occurrence of febrile pancytopenia. Chemotherapy was stopped and management was limited to comfort care until the patient's death. **Conclusion:** Cardiac light-chain amyloidosis must be diagnosed early as it can be rapidly fatal.

Keywords

Myeloma, Cardiac Lambda Light Chain Amyloidosis, Monoclonal Gammopathy, Heart Failure

1. Introduction

Amyloidosis is caused by the deposition and accumulation of "amyloid fibrils" in tissues. They are responsible for progressive organ failure and death [1]. Amyloidosis can affect most tissues, including the heart, kidneys, liver, gastrointestinal tract, nervous system, skin, and hearing.

Amyloid infiltration of the myocardium is responsible for restrictive cardiomyopathy and heart failure [2]. Cardiac involvement is secondary to deposition of transthyretin, immunoglobulin light chains or, more exceptionally, serum amyloid A or beta-2 microglobulin or other very rare types.

The incidence of transthyretin cardiac amyloidosis is increasing in France, as cardiologists become more familiar with the disease [3]. In transthyretin cardiac amyloidosis, 20% to 25% of patients respectively have cardiac decompensation and a pacemaker before the disease is diagnosed [2].

Light chain amyloidosis is rare and under-diagnosed. The annual incidence is estimated at 5 - 13 cases per million patient-years. This corresponds to 1 - 2 cases of light chain amyloidosis per ten myeloma patients [4] [5].

In light chain amyloidosis, progressive and sustained exposure of tissues to high concentrations of free light chains (kappa or more often lambda) is accompanied by their precipitation and fibrillar degeneration in the tissues [6]. The cause may be gammopathy of undetermined significance or myeloma. Peak incidence occurs between the ages of 60 and 80. It is estimated that 70% to 80% of patients with light-chain amyloidosis have cardiac involvement. Symptoms and signs are non-specific. Manifestations vary with organs affected and extent of fibrillar infiltration. They are often interlinked, combining dysautonomia, cardiac manifestations (atrial fibrillation, isolated elevation of cardiac markers, arrhythmias and conduction disorders, heart failure), digestive, renal, cutaneous, and neurosensory signs, and cardioembolic events. NT-proBNP, BNP and Troponin are both diagnostic and prognostic markers. Light chain cardiac amyloidosis staging system has incorporated troponin and NT-pro-BNP levels [4]-[6]. Non-invasive methods for diagnosis of cardiac amyloidosis include electrocardiography (ECG), echocardiography with Doppler mode, cardiac MRI, and nuclear imaging. Many of these can be included in the diagnostic approach for suspected cardiac amyloidosis. Low QRS voltage is the most common ECG abnormality in light chain cardiac amyloidosis [4]-[6].

Classic echocardiography findings include thick-walled ventricles (septal thickness more than 12 mm without aortic valvular disease or significant systemic hypertension) with a granular or sparkling appearance, small left ventri-

cular chamber volume, atrial enlargement, valvular thickening, thickened interatrial septum, diastolic dysfunction, and signs of increased filling pressures (dilated vena cava, pericardial effusion) [4]-[13]. As echocardiograph findings of cardiac amyloidosis mimic hypertensive and hypertrophic cardiomyopathy, the diagnosis of cardiac amyloidosis is often delayed. Echocardiographic strain imaging is a reliable method for assessing and quantifying myocardial mechanical function and dysfunction [13]. In cardiac amyloidosis, there is severe impairment of basal longitudinal strain, but the strain in apical segments is preserved.

Cardiac Magnetic Resonance Imaging (CMR) is far superior for directly identifying amyloid infiltration using late gadolinium enhancement (LGE), even in patients with normal left ventricular wall thicknesses. If CMR findings do not support cardiac amyloidosis, the diagnosis is very unlikely. In the case that CMR findings are inconclusive, cardiac, or extracardiac histological demonstration of amyloid deposits is required to diagnose light chain cardiac amyloidosis [4]-[10] [13].

Technetium-phosphate derivatives such as 99mTechnetium-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD), 99mTechnetiumpyrophosphate (99mTc-PYP), and 99mTechnetium-hydroxymethylene diphosphonate (99mTc-HMDP) have been studied for diagnosis of cardiac amyloidosis. Unlike CMR, it was able to differentiate cardiac transthyretin amyloidosis from cardiac light chain amyloidosis (sensitivity: 90.9% - 91.5%; specificity: 88.6% - 97.1%) [13].

Histological confirmation is mandatory for the diagnosis of light chain amyloidosis. A definitive diagnosis requires confirmation through tissue (myocardial or other) biopsy and histology demonstrating a positive Congo red stain with apple-green birefringence under polarized light. Cardiac amyloidosis is diagnosed if one or both conditions are met, namely, a positive endomyocardial biopsy or a positive non-cardiac biopsy in a patient with clinical, laboratory, echocardiographic or CMR evidence consistent with amyloidosis [4]-[10] [13].

Treatment of light-chain amyloidosis is specifically based on "antiplasma chemotherapy". The various pharmacological agents include proteasome inhibitors (Bortezomib) with protocols combining Cyclophosphamide-Dexamethasone (CyBorD), alkylating agents (melphalan); immunomodulators (Lenalidomide); anti-CD38 monoclonal antibodies (daratumumab). Organ transplantation (bone marrow, heart, kidney, etc.) may complement treatment in some patients [7].

We report the case of an 88-year-old hypertensive patient with sustained atrial fibrillation and recurrent heart failure, in whom echocardiography showed concentric hypertrophy with mildly reduced left ventricle ejection fraction (LVEF) of 45%. Bone scintigraphy was normal. Serum analysis showed increased lambda free light chains. Accessory salivary gland biopsy revealed lambda light chain deposits. The diagnosis of stage 3B cardiac amyloidosis secondary to lambda light chain myeloma was made. After a multidisciplinary meeting, it was decided to start chemotherapy with DARATUMUMAB + LENALIDOMIDE.

2. Case Study

This is an 88-year-old hypertensive female patient with sustained atrial fibrillation since 2013. The patient lives alone and was autonomous in the acts of daily living before her hospitalization. She has a WHO performance score of 1. Her usual treatment combines Betaxolol 10 mg/day and Apixaban 2.5 mg twice daily (age and usual dry weight 58 kg). She previously was on telmisartan 80 mg/ day and amlodipine 10 mg/day.

She was hospitalized from 07/05/2023 to 07/21/2023 for a first decompensation of 50% LVEF heart disease associated with acute right-sided community-acquired pneumonia. Her condition improved after treatment with furosemide and amoxicillin + clavulanic acid. The patient was discharged on: Betaxolol 10 mg/d, Empaglifozine 10 mg/d; Apixaban 2.5 mg * 2/d, furosemide 60 mg/d with implementation of the Programme de retour au domicile pour l'Insuffisance cardiaque (PRADO).

The patient was hospitalized again from 09/07/2023 to 09/27/2023 for another cardiac decompensation. There was 07 Kg increase in weight despite compliance with treatment. She complained of fatigue, loss of taste and appetite, and tingling sensations in her fingers. Physical examination showed signs of heart failure (NYHA stage 4 dyspnea, lower limb oedema, bilateral crackles, bilateral pleural effusion, jugular vein dilation with hepato-jugular reflux) and irregular heartbeats. Blood pressure was 90/60 mmHg. Hemodynamic, respiratory, and neurological status were stable.

The electrocardiogram showed atrial fibrillation with narrow QRS at 75 bpm, right ventricular hypertrophy, diffuse repolarization abnormalities, low-voltage QRS discordant with echocardiographic bi-ventricular hypertrophy (**Figure 1**).

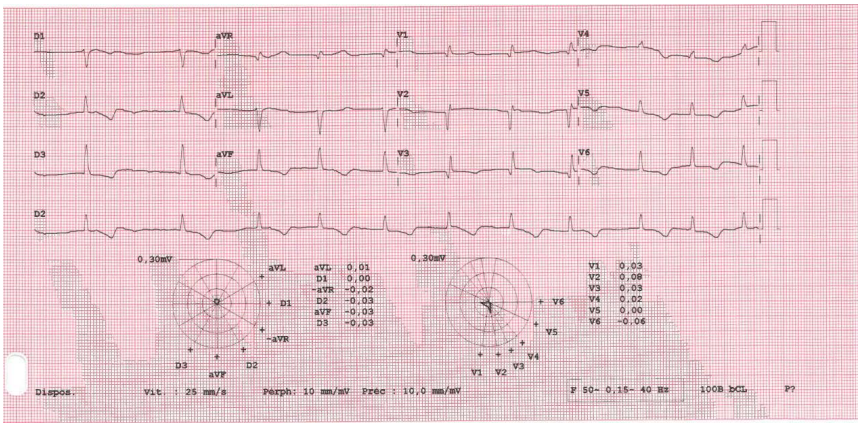

Figure 1. ECG: Atrial fibrillation, right ventricular hypertrophy, right axis deviation, diffuse abnormalities of repolarization, diffuse low voltage.

An in-bed chest X-ray showed a predominantly right pleural effusion and an enlarged cardiac silhouette (**Figure 2**).

Echocardiography showed concentric left ventricular hypertrophy (IVSd 13 mm, LVPWd 13 mm), shiny interventricular septum, LVEF 45% with Simpson

Biplan method, global longitudinal strain −8% (altered predominantly on the bases), significant bi-atrial dilation (Left Atrium, 38 cm^2 and 98 ml/m^2, Right Atrium 22 cm^2) with impairment of all left atrial's functions, hypertrophied right ventricle (07 mm), grade III left ventricular diastolic dysfunction with high filling pressures. Mean pulmonary arterial pressure on tricuspid regurgitation flow is 45 mmHg + 15, inferior vena cava is dilated noncompliant. There is millimetric pericardial effusion (**Figure 3**).

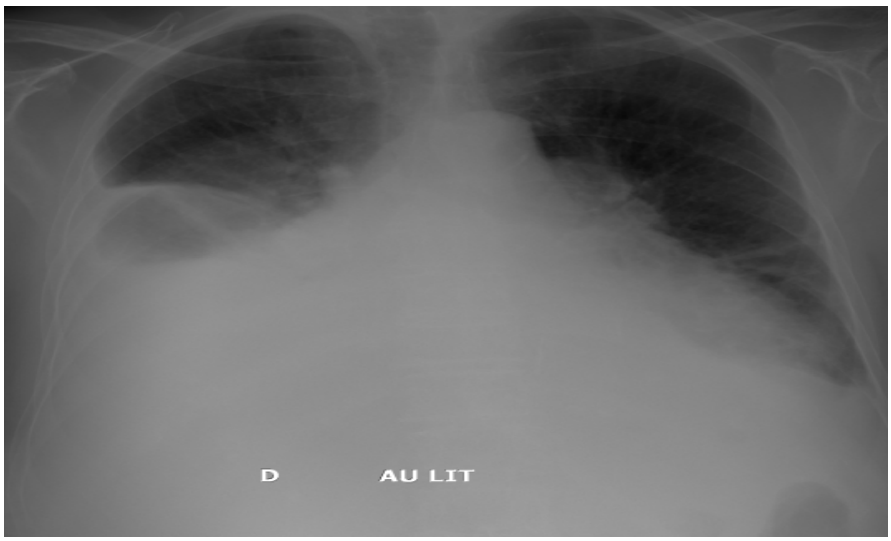

Figure 2. Chest: X-ray predominantly right pleural effusion and an enlarged cardiac silhouette.

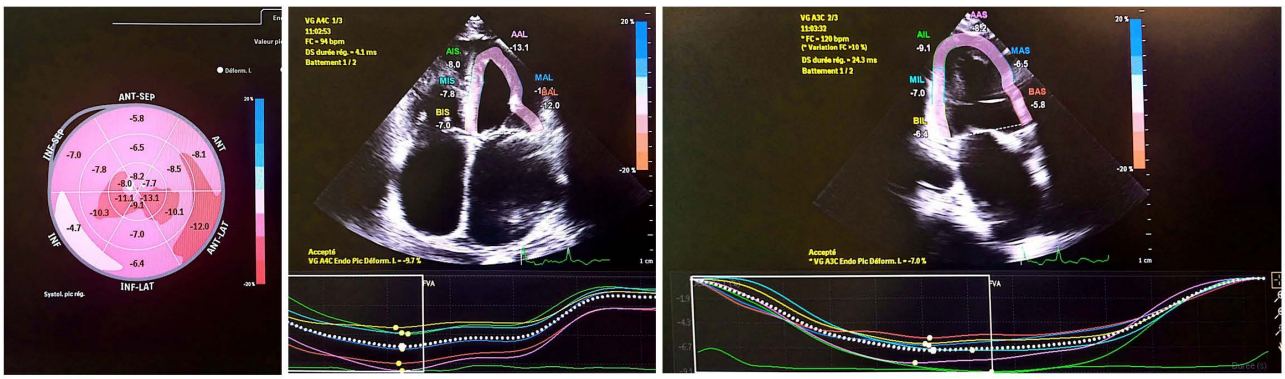

Figure 3. Increased ventricular wall thickness, abnormal GLS, bi-atrial dilation.

In view of the significant peripheral and visceral oedema, furosemide was increased to 250 mg/day. Empaglifozin and Betaxolol were stopped because of persistent hypotension (75/50 mmHg).

The recurrence of cardiac decompensation despite compliance, hypotension on previously hypertensive patient on (betaxolol, telmisartan and amlodipine), low voltage QRS on ECG, small ventricles volumes with increased wall thickness and diastolic dysfunction raised the suspicion of cardiac amyloidosis. Besides, patient complained of tingling sensations in her fingers possibly related to peri-

pheral neuropathy. In this context, bone scintigraphy with diphosphonates was done and showed no myocardial fixation (Perugini score 0). Then transthyretin cardiac amyloidosis was excluded.

Serum protein electrophoresis with immunofixation showed hypoalbuminemia at 31 g/l, hypo-gammaglobulinemia at 3.1 g/l, a monoclonal band migrating to the gamma position corresponding to a free lambda-type monoclonal peak at 1.1 g/l. Serum lambda free light chains concentration was 2053 mg/l with abnormal Kappa/Lambda ratio and abnormal difference in free light chain. Calcium, alkaline phosphatase, liver function tests, ferritin levels, transferrin saturation coefficient and thyroid-stimulating hormone (TSH) levels were normal. Renal function was impaired. 24-hour proteinuria was 0.87 g/24h, with a free lambda monoclonal chain on immunofixation (**Figure 4**).

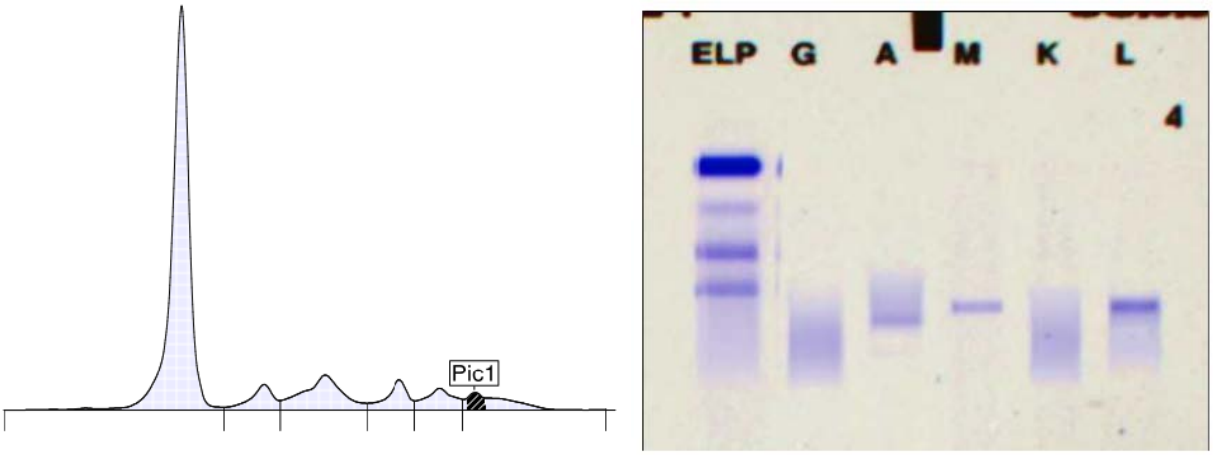

Figure 4. Capillary electrophoresis with serum protein immunofixation: free lambda monoclonal peak (anti-free lambda antibody on the IgM track of the gel).

Given these results, light chain cardiac amyloidosis was suspected. Accessory salivary gland biopsy performed on 09/20/2023 revealed amyloid deposits with a negative immunohistochemical phenotype for TTR, weak labeling for Kappa light chain and clear overexpression of lambda light chain deposits. Rectal biopsy performed on 09/25/2023, was negative for Congo red staining, no significant staining for Lambda and Kappa light chains on immunohistochemistry. Transthyretin staining was negative.

The myelogram performed on 22/09/2023 showed 49% plasmacytosis with rich smears invaded by large, sometimes binucleated plasma cells. The other lineages are poorly represented. Granular lineage: 28%, erythroblastic lineage: 10%, other lineage: 63%, plasma cells: 49%, lymphocytes: 13.5% (**Figure 5**).

Whole-body computed tomography revealed no bone involvement. Cardiac MRI could not be performed because of delay.

The diagnosis of stage 3B cardiac amyloidosis secondary to Lambda light-chain myeloma without bone involvement was made.

One week later, the patient presented a 30% increase in serum Lambda light

chains, probably due to high plasma cell activity.

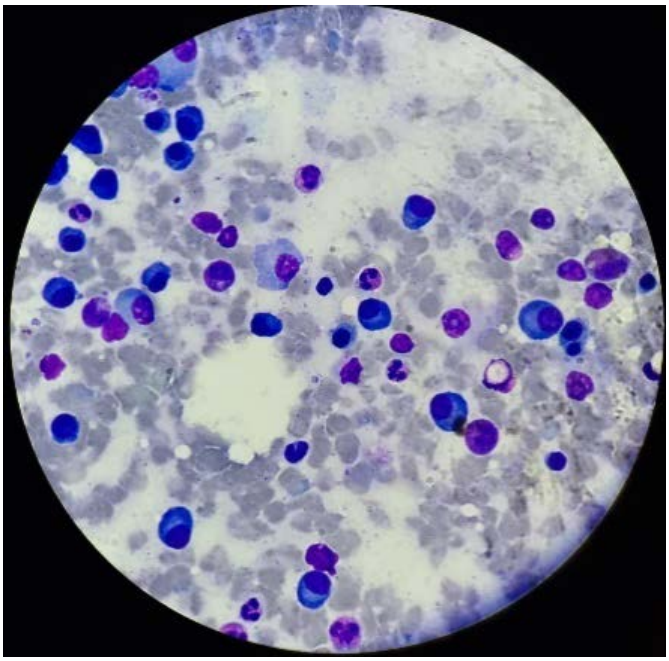

Figure 5. Large plasma cells.

Based on multidisciplinary staff decision, specific treatment with DARATUMUMAB + LENALIDOMIDE was initiated, with premedication with prednisone, cetirizine and paracetamol for the first daratumumab injections, and prophylaxis with Valacyclovir, Cotrimoxazole and amoxicillin.

After the second course of specific therapy, the patient was admitted to hospital again on 10/24/2023 (three months after the first cardiac decompensation). The patient developed febrile pancytopenia with increased inflammatory biomarkers that lead to septic shock. Management was limited to cessation of specific therapy and comfort care in accordance with patient's wishes. The patient died on October 26. (Table 1)

Table 1. Summary of laboratory exams performed.

Date	10/25/23	10/03/2023	09/27/23	09/20/23	07/21/23	07//05 23	Normal values
Hemoglobin	**11.6**		**11.6**	**12**	**13.2**	**13.2**	**11.8 - 15 g/dl**
Platelets	82		118	216	298	298	177 - 379 G/l
Calcium	**2.34**		**2.33**				**2.25 - 2.60 mmol/l**
Leukocytes	0.39		8	8	8	8	4 - 9 G/l
ASAT	23		23	23	23	23	0 - 35 UI/l
ALAT	13		13	13	13	13	0 - 35 UI/l

Continued

Serum Creatinin	**114**	**204**	**114**	**100**	**100**	**100**	**45 - 84 µmol/l**
Creatinin clearance (CKD-EPI) ml/min/1.73 m²	37	18	28	40	40	40	
CRP	144		144	2	2	2	0 - 5 mg/l
NT pro BNP (ng/l)	**>70,000**		**>70,000**	**41,000**	**18,000**	**18,231**	
Troponin I			**400**	**200**		**120**	0 - 16 pg/ml
Beta2 microglobulin				23			0 - 3 mg/l
Free Lambda			**2700**	**2053**			**3 - 19 mg/l**
Free kappa			19	19			6 - 26 mg/l
Ratio K/L			0.01	0.01			

3. Discussion

The occurrence of a second cardiac decompensation 45 days after the first led to the finding of lambda light chain multiple myeloma, without bone involvement, responsible for stage 3b cardiac amyloidosis.

In light chain amyloidosis, a plasma cell clone, or rarely a lymphoplasmacytic lymphoma, produces abnormal, toxic light chains which aggregate to form insoluble fibrils that deposit in tissues and disrupt their function [6]-[8].

All organs, except for the brain, can be affected. The heart and kidneys are most often affected. The clinical features therefore vary according to the nature of the organs affected, and the location and extent of amyloid infiltration within a single organ, such as the heart. Symptoms and signs are therefore not specific, which is likely to delay diagnosis. Screening extended to the general population lacks sensitivity. Suspiciousness remains the key to early diagnosis [9].

In our patient, the diagnosis was established 82 days after the first decompensation. Chemotherapy and immunotherapy were begun 07 days after histological diagnosis. This constitutes a diagnostic time-lag, emphasizing the need to suspect the diagnosis at an early stage. Mortality remains extremely high in patients with cardiac light-chain amyloidosis [10]. Serum protein electrophoresis was determinant because it showed monoclonal gammopathy that led to measuring serum free light chain. Serum electrophoresis and free light chain assessment should be systematically performed in patients with heart failure with red flags for amyloidosis.

Cardiac damage is a strong prognostic predictor. In many cases, sudden death or acute heart failure occurs within days or months following diagnosis and initiation of chemotherapy. Ideally, the diagnosis should be made within 02 weeks after the first signs, specific pharmacological treatment started immediately after diagnosis, and close monitoring of response to treatment made possible [10].

Clinical features, electrocardiogram, echocardiography, and cardiac MRI all

point to the suspicion of cardiac amyloidosis. Diagnosis is confirmed by applying an algorithm that includes a systematic search for monoclonal gammopathy by means of a complete protein work-up (serum and urine protein electrophoresis with immunofixation, serum free light chain assay with Kappa/Lambda ratio, dFLC) and disphosphonate scintigraphy. To diagnose cardiac light-chain amyloidosis, histological evidence of light-chain amyloid deposits in tissues (endomyocardial or extracardiac biopsy) is essential, after gammopathy has been discovered [10]-[12]. Symptoms could also guide the biopsy site to increase diagnostic sensitivity. Indeed, the loss of taste reported by the patient could be secondary to the infiltration of the oral area and would explain why only the biopsy of the accessory salivary glands was positive.

The severity of cardiac light chain amyloidosis is assessed by cardiac troponin (cTn) and natriuretic peptide values. Lambda and kappa light chains and the difference between these free light chains (dFLC) also have prognostic value [10]-[12]. In the patient's case, we observed a significant 30% increase in lambda free light chains within one week (prior to initiation of specific treatment). This suggests a remarkably high level of plasma cell activity, and hence the severity of the disease. Identification of the light chain type is mandatory for a definitive diagnosis of light chain amyloidosis. This is done by mass spectrometry, immunohistochemistry or immunoelectron microscopy [13].

Despite compliance with dietary and nutritional advice, a weight gain of 07 kg was noted at the second hospital admission. Indeed, patients with cardiac amyloidosis are highly prone to fluid retention and extremely sensitive to sodium intake. It is therefore particularly important that salt intake should ideally be less than 1500 mg/day [11].

In this patient, the outcome was rapidly fatal in 110 days (from the first cardiac decompensation to the second course of specific treatment). Diagnosis of cardiac light chain amyloidosis is an absolute emergency. The same applies to specific management (immune therapy, chemotherapy, organ transplantation in selected patients). It is of utmost urgency to look for light chain cardiac amyloidosis as soon as red flags are raised (renal failure, proteinuria, heart failure, carpal tunnel, orthostatic hypotension, peripheral neuropathy, hypothyroidism, macroglossia, periorbital purpura), blood pressure normalization in a previously hypertensive patient, when there is no obvious explanation for the heart failure, or when there are clinical, electrocardiographic or echocardiographic signs and elevated cardiac biomarkers. It is also crucial to systematically perform serum and urine protein work-up (electrophoresis with immunofixation, and serum free light chain assay) in the event of cardiac decompensation in a patient presenting symptoms and/or signs suggestive of the light chain amyloidosis.

Atrial fibrillation may be a revelatory feature of amyloid heart disease, but it may also predate or even be independent of the onset of cardiac light chain amyloidosis. Permanent atrial fibrillation since 2013 with extensive bi-atrial remodeling and previous hypertensive disease may have delayed diagnosis of car-

diac light chain amyloidosis. Global longitudinal strain (GLS) patterns might have helped if this had been performed at first hospitalization. GLS assessment should therefore be systematically performed in the event of cardiac decompensation when the conditions for doing so are met.

Severe cardiac damage and stage 3b classification prior to initiation of specific treatment are associated with a poor prognosis. In treated cases of light chain amyloidosis, prognosis is function of the extent of cardiac impairment and response to treatment. Prognostic criteria are based on the extent of elevation of cardiac biomarkers (NT-proBNP; Troponin), as shown in Table 2 below. Other prognostic markers such as global longitudinal strain, cardiac MRI, plasma cell clone percentage, Positron Emission Tomography/Computed tomography with amyloidosis-specific tracers could further be integrated into the prognostic evaluation. Cardiac biomarkers could also be adjusted in cases of end-stage renal disease [4] [14]-[16].

Table 2 below shows the validated markers for cardiac light-chain amyloidosis (CLCA).

Table 2. MAYO 2004 and EUROPEAN 2015 scores for ACCL [14]-[16].

MAYO 2004	cTnT ≥ 0.035 µg/l or HS-cTnT ≥ 50 ng/l	NTproBNP ≥ 332 pg/ml or BNP > 81 pg/ml	HR of death (95% CI)
I	0	0	Range
	1/2		2.5 (1.9 - 3.5)
III	1	1	6.7 (5.0 - 9.1)
EUROPEAN 2015	**cTNT ≥ 0.035 µg/l or TNT-hs ≥ 50 ng/l**	**NTproBNP ≥ 332 pg/ml or BNP > 81 pg/ml**	**HR of death (95% CI)**
I	0	0	Range
II	1/2		2.6 (1.9 - 3.5)
III-a	1	1	4.9 (3.6 - 6.8)
III-b	1	NTproBNP > 8500 pg/ml BNP > 700 pg/ml	11.1 (8.1 - 15.4)

Conventional heart failure treatments such as beta-blockers, converting enzyme inhibitors and Angiotensin II receptor antagonists are often poorly tolerated in cardiac amyloidosis and can also be worsening factors. Hypotensive treatment was discontinued in our patient. Treatment of cardiac decompensation is usually limited to diuretics.

4. Conclusion

This case study reminds us that cardiac light-chain amyloidosis can be rapidly fatal within a few months, especially when plasma cell activity is remarkably high. Cardiac light-chain amyloidosis is a medical emergency. Early detection of cardiac light chain amyloidosis is essential, and treatment is a race against time.

Diagnostic awareness is therefore crucial in the event of heart failure associated with a combination of symptoms and/or signs suggestive of amyloidosis. At a basic level, complete serum and urine protein testing are crucial. Bone scintigraphy has an excellent negative predictive value for light chain cardiac amyloidosis in the absence of gammopathy. The sensitivity of peripheral biopsies is low, sometimes requiring multisite and repeated biopsies to increase diagnostic utility. Endomyocardial biopsy is extremely sensitive and specific for cardiac light chain amyloidosis. In our patient, biopsy of the accessory salivary glands was decisive for the diagnosis. Unfortunately, our patient died quickly.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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