Amyloidosis – a rare cause of refractory heart failure in a young female

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Abstract

Cardiac amyloidosis may occur in any type of systemic amyloidosis. The clinical picture is often characterized by restrictive cardiomyopathy. We report the case of a 41-year-old female patient admitted to the Department of Cardiology with clinical signs of right heart failure: congested jugular veins, hepatomegaly, peripheral edema, ascites associated with atrial fibrillation, low values of arterial blood pressure and oliguria. Echocardiographic findings were helpful for the diagnosis of cardiac amyloidosis: enlarged atrial cavities, normal size ventricles, thickened ventricular septum and posterior left ventricle wall with normal left ventricular ejection fraction, mitral and tricuspid regurgitation. Two-dimensional echocardiography revealed additional features: thickened papillary muscles and a specific "granular sparkling" appearance of the thickened cardiac walls – probably due to the amyloid deposit. Gingival biopsy showing amorphous eosinophilic material located in the vessel walls and the specific dichroism and "apple-green" birefringence under polarized light on Congo red stained slides completed the diagnosis of systemic amyloidosis. We recommend cardiologists to take into account a possible cardiac amyloidosis in a patient with unexplained refractory heart failure and a typical pattern of restrictive cardiomyopathy revealed by echocardiographic examination. We also emphasize the fact that the complete diagnosis cannot be set without a biopsy that should reveal the presence of amyloid. Although endomyocardial biopsy, completed with histochemical and immunohistochemical stains, is a valuable diagnostic method, in cases with advanced cardiac failure, the best site for this biopsy may be the gingiva.

Keywords: amyloidosis, restrictive cardiomyopathy, gingival biopsy.

Introduction

Amyloidosis is defined as a condition in which extra-cellular deposits of fibrillary proteins are responsible for tissue damage and functional compromise [1]. The term "amyloidosis" has its root in Greek (*amylon*, starch + *eidos*, resemblance + *osis*, abnormal proliferation) [2], but it is incorrect as there is virtually no carbohydrate in amyloid deposits, which instead are composed of protein [3].

From a pathological point of view, the affected organs may show a "waxy" texture to their cut surface, a feature that led earlier pathologists to refer to this condition as "waxy degeneration" or "lardaceous disease" [4].

On microscope examination, amyloid is an amorphous extracellular eosinophilic material deposited in various body tissues and organs that shows an "apple-green"-positive birefringence in polarized light after staining with Congo red dye, has a characteristic fibrillar non-branching ultrastructure [5] and is predominantly composed of abnormal fibrillar proteins in a *β*-pleated sheet confor-mation [4, 5]. The fibrillar deposits bind a wide variety of sugar groups, which give them the staining characteristics that were thought to resemble starch [1].

The *Nomenclature Committee of the International Society of Amyloidosis* (ISA) met during its 14th Symposium, in 2014, to assess and formulate recommendations for the nomenclature of amyloid fibrillary proteins and for the clinical classification of amyloidoses [6]. The Committee concluded that there are 31 extracellular fibrillary proteins in humans, two of which are iatrogenic in nature and nine of which have also been identified in animals [7].

Amyloidosis should be classified taking into conside-ration its clinical and biochemical features. As such, the disease can be systemic (generalized) involving several organs, or localized, when deposits are limited to a single organ, such as the heart. Also, systemic amyloidosis is sub-classified into primary amyloidosis, usually of the AL (protein A light chains) type, when it is associated with monoclonal plasma cell proliferation, which produces an

abnormal protein, and secondary or reactive amyloidosis, when it occurs as a complication of an underlying chronic inflammatory process (mainly tuberculosis, osteomyelitis, syphilis, bronchiectasis) [1], but also after the onset of non-infectious chronic inflammatory disorders, *e.g.*, rheumatoid arthritis [8]. Hereditary or familial amyloidosis constitutes a separate, heterogeneous group, with several distinctive patterns of organ involvement [1]. Hereditary amyloidoses, *e.g.*, with ATTR (transthyretin amyloidosis) or AFib (fibrinogen amyloidosis) proteins, are the result of a mutation in the fibril protein gene itself, while other amyloidoses, *e.g.*, AA (amyloid A) amyloidosis, may occur in a familial setting due to mutations in genes expressing non-amyloid proteins [7].

Taken into consideration the type of protein constituting the amyloid fibrillar protein and the predominant organs involved, the common types of amyloidoses are: AL amyloidosis (localized or systemic), which involves the kidney, heart, nervous system, liver and soft tissue; familial (mutant transthyretin), involving the nervous system and the heart; senile (SSA – senile systemic amyloidosis) (wild type transthyretin) involving the heart; secondary amyloidosis (SAA – secondary amyloid A) in relation with acute phase reactant involving the liver and kidney; isolated atrial amyloid (IAA), the main constituent of which is atrial natriuretic peptide, involving the atrial wall [9]. However, the chemical identity of the protein should be unambiguously characterized by protein sequence analysis when possible.

Some authors considered that cardiac amyloidosis is a complication of any type of the systemic amyloidoses and the predilection for the heart varies considerably among the specific types, with some very rarely involving this organ, whereas others do so almost exclusively [10]. Others said that cardiac involvement may occur in the three main types of amyloidosis (acquired monoclonal light-chain, hereditary transthyretin and senile amyloidosis) and has a major impact on prognosis [11].

The disease is often characterized by restrictive cardiomyopathy although the particular signs and symptoms depend in part on the underlying cause [10]. Also, dilated cardiomyopathy has been reported as a manifestation of cardiac amyloidosis [12].

In this paper, we report a rare case of systemic amyloidosis, in which the patient was admitted with refractory heart failure after a 10-year history of atrial fibrillation considered earlier of unknown etiology, but the gingival biopsy revealed the diagnosis.

⌻ Case presentation

A 40-year-old female patient was admitted to the Department of Cardiology with clinical symptoms and signs of predominantly right-side cardiac failure: weakness, shortness of breath, 3rd degree turgescent jugulars, hepatomegaly, ascites, and deep lower limb edema. She also showed signs of low cardiac input: systolic blood pressure values less than 100 mmHg, oliguria, and low skin temperature. In her personal history, we could not find any cardiovascular risk factor or any significant pathological event until the age of 30 when she was diagnosed with unresponsive atrial fibrillation, despite sinus rhythm conversion attempts. At the age of 33, she began to

experience ascites, which raised the suspicion of hepatic disease; though, all the functional explorations performed in the Department of Gastroenterology ruled out a hepatic cause for the ascito-edematous syndrome (the viral markers were negative). The patient said that she had received treatment for her cardiac failure (*Digitalis*, diuretics and beta-blockers), without a significant clinical improvement, and that she had been admitted to the hospital many times in the later years, especially due to right heart decompensation.

On her physical examination, she was ill looking, but conscious, and had a "mitral" face, lower limb edema, reduced fat tissue, and bilateral basal dullness with vesicular murmur abolition. The cardiovascular system examination revealed irregular heart sounds (atrial fibrillation), apparently without organic murmurs, 2nd degree turgescent jugulars, and hypotension (90/60 mmHg blood pressure values). The patient had enlarged abdomen due to ascites, and painful hepatomegaly extending 3 cm below the costal line, but impalpable spleen.

The laboratory tests on admission showed: normal blood count, normal renal function, dyselectrolytemia (sodium 119 mmol/L, potassium 5.6 mmol/L), initially considered to be an event in the context of the diuretic treatment, prothrombin index 75%, cholesterol 115 mg%, triglycerides 66 mg%, total proteins 74 g/L, normal albumin and normal aminotransferases.

The electrocardiogram confirmed the atrial fibrillation diagnosis with medium ventricular aspect, the patient being under anti-arrhythmic treatment, without any repolarization stage modifications (Figure 1). The thoracic radiography on admission confirmed the presence of bilateral pleural effusion in medium quantity.
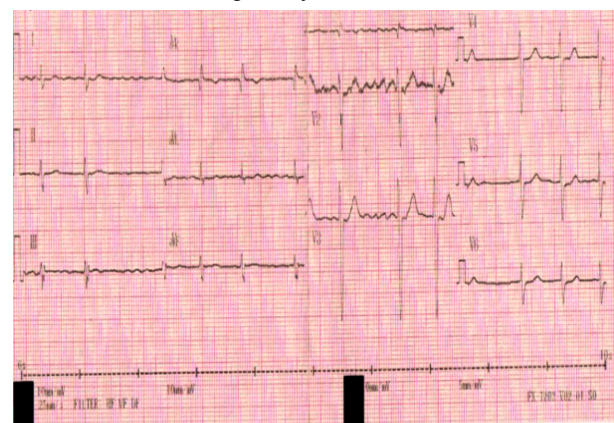

Figure 1 – *The electrocardiogram revealed the atrial fibrillation with medium ventricular rhythm.*

The abdominal ultrasound scan showed the presence of ascites in high quantity, liver with irregular structure and stasis aspect, normal intrahepatic bile ducts, non-dilated portal vein, normal pancreas, spleen and kidneys.

The biochemical analysis of the ascites fluid extracted through puncture proved the fluid to be a transudate and excluded the tuberculous or neoplastic etiopathogenesis of the ascites. The peripheral venous blood pressure of over 200 mmH$_2$O also supported the assumption of the cardiac etiology of the ascito-edematous syndrome.

The echocardiographic examination on the second hospitalization day showed features compatible with the diagnosis of restrictive cardiomyopathy: normal ventricular

cavities, normal left ventricle kinetics, 55% ejection fraction, posterior pillar hypertrophy, dilated atria (left atrium 50/63 mm, right atrium 50/62 mm), without intracavity thrombi, hypertrophic walls [interventricular septum (SIV) 15 mm, posterior wall of the left ventricle (PPVS) 13 mm] with a light granular aspect, shinning, suggesting cardiac amyloidosis diagnosis (Figure 2, a–d). Second degree mitral valve and 1st degree tricuspid valve regurgitations were also accompanied by a systolic blood pressure value in the pulmonary artery of 37 mmHg, dilated inferior vena cava with inspiratory collapse and a significant stasis in the suprahepatic vessels. The echo-

cardiographic aspect excluded the diagnosis of valvulopathy, constrictive pericarditis or congenital cardiac disease as possible causes of cardiac failure in a young patient.

Gingival biopsy was performed on the fourth hospitalization day and revealed gingival epidermoid mucosa fragments with several of the medium-sized vessels exhibiting abnormally thickened walls due to intramural deposition of a homogeneous eosinophilic material on Hematoxylin–Eosin (HE) staining slides and "apple-green" birefringence when examined in polarized light after Congo red staining. The histopathological features were suggestive of amyloidosis (Figure 3, a and b).
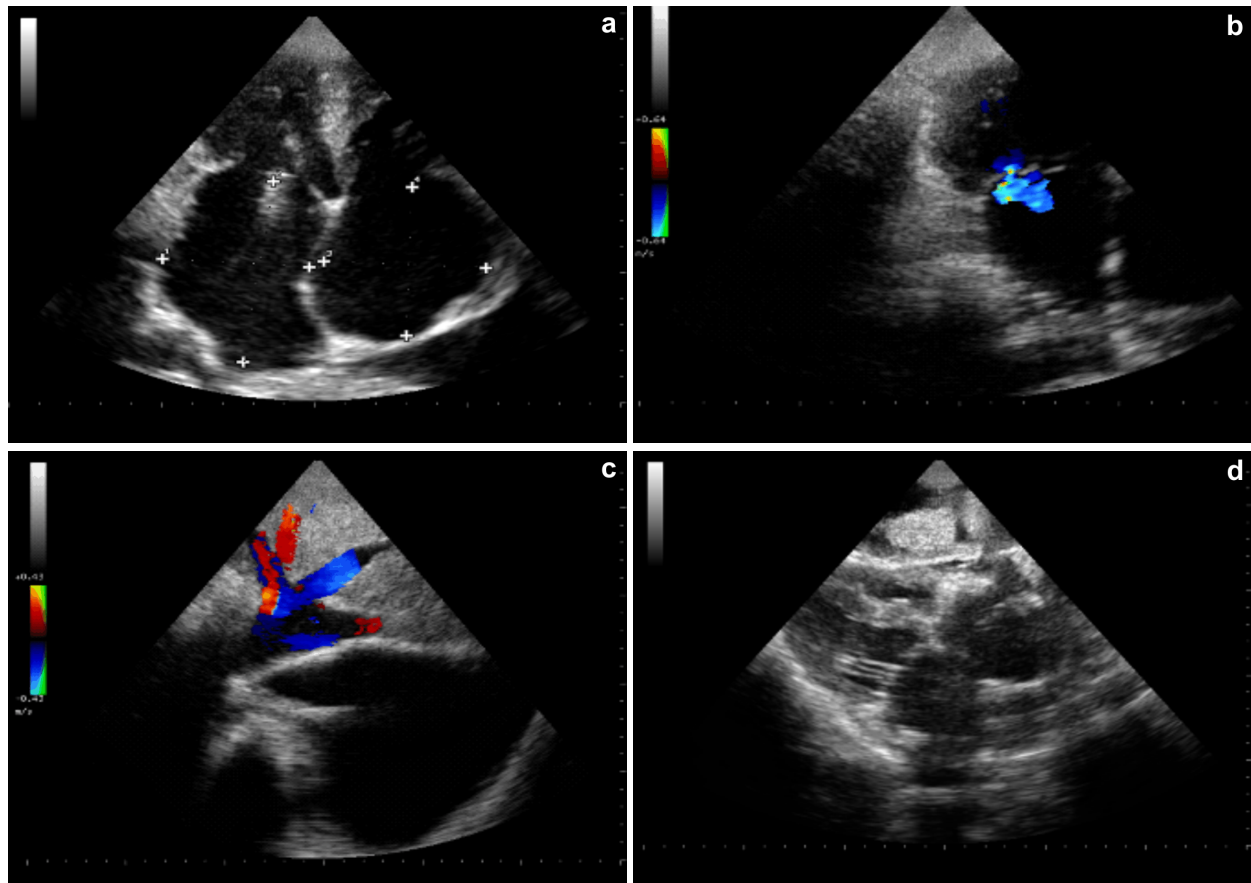

Figure 2 – *Two-dimensional (2D) echocardiographic examination revealed: (a) Dilated atria; (b) The presence of mitral valve regurgitation; (c) Suprahepatic vein stasis; (d) Small ventricles with hypertrophied walls and light granular and shinning ventricular myocardium.*
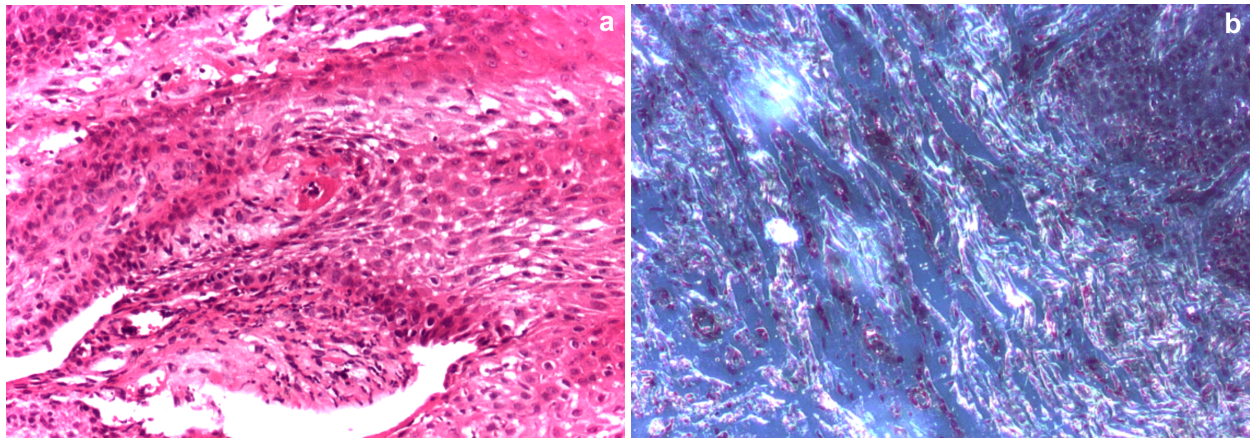

Figure 3 – *The gingival biopsy showed: (a) Typical amorphous eosinophilic material deposited in the walls of the vessels located in lamina propria of gingival orthokeratinized epithelium (HE staining, ×200); (b) Characteristic dichroism and "apple-green" birefringence under polarized light of the same deposits (Congo red staining, ×100).*

The final diagnosis was: systemic amyloidosis; amyloid restrictive cardiomyopathy; permanent atrial fibrillation; chronic global cardiac failure; low cardiac output syndrome.

Diuretic treatment, dopamine positive inotrop support, small-dose beta-blockers and correction of electrolyte imbalances were the measures taken. The *Digitalis* drugs were taken out of the treatment scheme, as they are not recommended in amyloidosis. The arterial hypotension did not allow the addition of conversion enzyme inhibitors. The patient's conditions worsened, as she did not respond to treatment. Due to the advanced state of the patient's cardiac decompensation, no further investigations were attempted and she was discharged on her wish.

⊟ Discussion

Amyloidosis is one of the first pathological entities described. Although originally named differently, the main features of this condition were well known to dissectors. Although we do not know it exactly, some authors consider that clear entities with amyloid were described in autopsies carried out in 1657 by Thomas Bartholin (1616–1680), in works by Théophile Bonet (1620–1689), Marcello Malpighi (1628–1694), Giovanni Battista Morgagni (1682–1771) and others. They described a unique substance, which accumulated in organs (spleen, liver, and kidney) or muscles of the heart or tongue, causing their hypertrophy and making them abnormally firm [9]. For example, Malpighi recognized "sago spleen" and other investigators later spoke of "lardaceous or cholesterin disease" (*Speck- oder Cholesterin-krankheit*) [13] to refer to the distinct macroscopic appearances of two variant patterns of amyloid deposition [8].

Nonetheless, the term "amyloid" was first coined and used in Botany by the German botanist Matthias Jakob Schleiden (1804–1881), in his book entitled "*Grundzüge der wissenschaftlichen Botanik*", published in 1842–1843. He used the term "amyloid" to refer to a "starch-like" substance, which he described as "*a normal amylaceous constituent in plants, and representing a cartilaginosus, but moist, gelatinous, clear, transparent body, soluble in boiling water, strong acids, and caustic alkalies. It is coloured blue by iodine*" [14].

In medicine, the Austrian pathologist Carl Freiherr von Rokitansky (1804–1878), was the first who described, in 1842, a form of amyloidosis which he named "*lardaceous disease of the spleen, liver and kidney*" that would be classified today as secondary amyloidosis and made the autopsy description of amyloid when he identified "waxy" liver and splenomegaly [15].

However, the German pathologist Rudolf Ludwig Karl Virchow (1821–1902) was the first who introduced the term "amyloid" in medical literature. He used the word in 1854, in his publication "*Über eine im Gehirn und Rückenmark des Menschen aufgefundene Substanz mit der chemischen Reaction der Cellulose*", to describe the small round deposits in the nervous system that stained pale blue on treatment with iodine, and violet on the addition of sulfuric acid, as typical to starch [16]. Convinced that those structures were identical to starch, Virchow named them "*corpora amylacea*", using the name employed by Schleiden. Virchow later applied the iodine sulphuric acid test to other tissues infiltrated with amyloid [14].

Cardiac amyloid deposit, which usually results in infiltrative/restrictive cardiomyopathy, is a common feature of amyloidosis. Cardiac involvement is primarily encountered in immunoglobulin (AL) and ATTR (hereditary/familial and senile). Although the latter variants could be indolent, untreated AL amyloidosis with clinical cardiac involvement is a rapidly fatal disease [17].

Cardiac amyloidosis may be the visible feature of the disease or it may be discovered while examining a patient with non-cardiac amyloidosis [9]. In early cardiac amyloidosis, patients may be asymptomatic, but patients with advanced disease have the typical clinical manifestation of restrictive cardiomyopathy [18] due to infiltrative deposits of amyloid into the myocardium. As such, the patients complain of weakness, dyspnea, and deep edema, including peripheral edema, hepatomegaly, ascites and anasarca. Physical examination is notable for an elevated jugular venous pulse, often with the Kussmaul sign, and a rising jugular pressure during inspiration [19].

The common clinical feature of the various forms of cardiac amyloidosis is the presence of congestive heart failure associated with non-dilated left ventricle, thickened walls, and a normal or slightly reduced left ventricular ejection fraction. Since the disease impairs all parts of the heart, biventricular heart failure is usually present, although the presenting feature is often severe right heart failure. Peripheral edema may be deep and ascites is often present in advanced disease. Careful physical examination is important in order not to miss the cardiac etiology of the presenting symptoms. When heart failure results in ascites or congestive hepatomegaly, the jugular venous pressure is always elevated, often to the angle of the jaw. However, if attention is not paid to the upper neck veins, the diagnosis of heart failure may initially be missed, particularly if the physician is misled by the report of abnormal ejection fraction.

Nevertheless, cardiac amyloidosis diagnosis setting may be difficult and take a long time even when these clinical manifestations exist. Therefore, electrocardiography and transthoracic echocardiography are important diagnostic and prognostic tools in patients with cardiac involvement [11].

Electrocardiograms (ECGs) are abnormal in 90% of the cases and typically show low voltage and pseudo-infarction pattern with Q waves simulating a myocardial infarction in the precordial leads. Arrhythmias, especially atrial fibrillation, are common (30% of patients), and a sick-sinus syndrome may be present [18].

Murtagh *et al.* investigated the largest cohort of patients with AL and biopsy-proven cardiac involvement [20] and reported that the two most common abnormalities were low voltage QRS complex (defined as all limb leads <5 mm in height) and a pseudo-infarction pattern on the precordial leads, which were detected in almost 50% of the patients included in the research. Other researchers also found conduction abnormalities (such as second and third degree atrio-ventricular block), and atrial fibrillation in about 15% of the patients [21].

In cardiac amyloidosis, echocardiography typically demonstrates thickened and sparkled ventricular walls,

thickened interatrial septum, mitral and tricuspid valves, with restrictive cardiomyopathy and a marked decrease in the diastolic function [11].

In 1981, Siqueira-Filho et al. [22] performed an echocardiography examination on 28 patients with cardiac amyloidosis whom he examined as follows: 26 by M-mode and 13 by two-dimensional studies. All of them had heart failure and biopsy-proven amyloidosis. M-mode features included: normal left ventricular (LV) dimension in all; thickened ventricular septum (88%), LV posterior wall (77%), and right ventricular (RV) anterior wall (79%); decreased thickening of ventricular septum (96%) and of LV posterior wall (65%) and reduced LV global function (62%); left atrial enlargement (50%) and pericardial effusion (58%). 2D echocardiography provided additional features: thickened papillary muscles; thickened valves; thickened RV wall; and a specific "granular sparkling" appearance of the thickened cardiac walls − probably due to the amyloid deposit. The authors concluded that M-mode echocardiography is helpful in recognizing cardiac amyloidosis and 2D echocardiography showing thickened cardiac walls with a "granular sparkling" appearance in patients with unexplained cardiac failure revealed the diagnosis of cardiac amyloidosis. More recently, Bonow et al. did not consider the sparkling appearance alone to be suggestive of cardiac amyloidosis as this feature could also be a sign of other conditions such as hypertension (especially in patients with renal failure) or glycogen storage disease [19]. In our patient, the echocardiogram suggested amyloid heart disease when it showed thickened ventricular walls, small or normal sized left ventricle, normal ejection fraction, dilated left and right atrium, mitral and tricuspid regurgitation. 2D echocardiography added substantial diagnostic information and defined the extent of cardiac involvement in a young female patient with unexplained congestive heart failure, revealing a diffuse hyper-refractile "granular sparkling" appearance of the ventricular walls, which are virtually suggestive of amyloid heart disease.

In the case we reported here, with the patient being in a poor condition, a gingival biopsy was made and revealed the diagnosis of systemic amyloidosis. However, if heart imaging suggests the presence of cardiac amyloid deposits, confirmation by biopsy is required, although endomyocardial biopsy is generally not necessary [23]. The rectal biopsy was the diagnostic method the most commonly employed in the past; however, other sites of the gastro-intestinal tract were also biopsied: duodenum and jejunum mucosa. Some authors suggested labial and gingival biopsy as routine systemic amyloidosis investigations. Actually, all these sites were replaced by abdominal subcutaneous fat aspiration, due to its greater feasibility in clinical practice, low cost and lack of complications [24].

On heart biopsy examination, the pathologist sees the amyloid protein infiltrating the myocardium [17] and also conduction system impairment. In 1970, Buja et al. [25] described a clinical and necroptic study based on 15 patients with cardiac dysfunction due to amyloidosis. The researchers considered that the most obvious anatomic indicator of clinically significant cardiac amyloidosis was a firm rubbery noncompliant myocardium on gross examination. Also, some patients showed narrowed intra-mural coronary arteries due to amyloid and no significant coronary atherosclerosis. In 1977, Ridolfi et al. [26] found that cardiac amyloidosis was frequently associated with major electrocardiographic conduction disturbances due to infiltrative destruction of the conduction system by the amyloid, but the connection has not been elucidated yet. They investigated the conduction systems in an autopsy study conducted on 23 patients with cardiac amyloidosis and found that most of them had experienced life-long abnormalities of conduction or rhythm. Only three of the 23 patients had extensive amyloidosis of the conduction system; in all three, ECGs showed first-degree atrio-ventricular block and left anterior hemi-block. Common morphological abnormalities of the conduction system were severe sino-atrial node fibrosis and idiopathic atrophy and fibrosis of the bundle branches.

Immunohistochemistry may be used for amyloid typing, in addition to standard histological technique and histochemistry, since it is able to identify amyloid deposits by binding antibodies directed against most of the amyloid molecules identified to date [27].

AL amyloidosis, in which amyloid is derived from monoclonal light chains (either intact light chains or, more commonly, light chain fragments), is associated with clinical cardiac involvement in about half of all cases, although subclinical involvement may be detected in almost every autopsy or endomyocardial biopsy.

Cardiac amyloid deposits are characteristically extensive and cause myocardial dysfunction manifested as congestive heart failure, which ultimately leads to death. About one-third of the patients with amyloidosis suffer a cardiac-related death.

In our case, the cardiac amyloid deposit may account for the long-term progress of the disease in the absence of a certain diagnosis and an adequate treatment, for the extremely severe progress towards refractory cardiac failure, and for the appearance of a rhythm disorder resistant to any cardioversion attempt when the patient was in her fourth decade of life.

The absence of any specific electrocardiographic changes, i.e., microvoltage, is the distinctive feature of this case. Also, the presence of arterial hypotension raised the suspicion of amyloid polyneuropathy with effects on the autonomic nervous system.

In many amyloidosis cases, there are no specific laboratory findings or symptoms, and unless one considers amyloidosis in the differential diagnosis, the condition may go undiagnosed, as was the case with our patient.

However, when a diagnosis of extracardiac amyloidosis is already set, the occurrence of symptoms attributable to a heart disease should guide medical judgment towards cardiac amyloidosis. Unfortunately, when cardiac amyloidosis is an isolated disorder, the diagnosis is often late in the course of the disease. The different types of systemic amyloidoses tend to progress at different speeds, but in most cases, the prognosis is determined by the presence and severity of cardiac involvement [6].

Cardiac amyloidosis treatment depends on the underlying etiology. Therapies include conservative management, chemotherapy, autologous stem cell transplantation and solid organ transplantation [13].

The expected survival of patients with cardiac amyloidosis is generally poor. In particular, survival has been reported to be 4–12 months for patients with congestive heart failure due to amyloid light chain amyloidosis [12].

⊟ Conclusions

Amyloidosis is a well-known but uncommon disease. We recommend cardiologists to be very suspicious of cardiac amyloidosis in a patient with unexplained refractory heart failure and a typical pattern of restrictive cardiomyopathy revealed by echocardiography examination in order to make a timely diagnosis. We also emphasize the fact that the complete diagnosis cannot be set without a biopsy that should reveal the presence of amyloid. Although endomyocardial biopsy, complemented by histochemical and immunohistochemical stains, is a valuable diagnostic method, in cases with advanced cardiac failure the best site of biopsy may be the gingiva.

Conflict of interests

The authors declare that they have no conflict of interests.

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