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Review Article

Sudden death in lambda light chain AL cardiac amyloidosis: a review of literature and update for clinicians and pathologists

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Abstract: Light chain (AL) amyloidosis is the most common type of systemic amyloidosis, affecting around 10 people per million per year. In Europe, approximately 5000 new diagnosis per year are reported. Deposition of amyloid fibrils derived from antibody light chains are key pathogenic agents in AL amyloidosis. They can be deposited in multiple organs but cardiac involvement carries a major risk of mortality. The prognosis is poor in cases associated with multiple myeloma. The average survival is around 1 year. Up to half of all patients with cardiac amyloidosis die suddenly; 75% ofthose deaths are due to heart failure. Ventricular arrhythmia is also associated with cardiac amyloidosis and unexpected death. It is crucial to make a diagnosis and start treatment at an early stage. Recent data suggest that cardiac amyloidosis has become a treatable and curable condition with a combination of agents targeting multiple steps of the amyloid cascade. ICD implantation may not be as effective for the therapy of light chain (AL) cardiac amyloidosis as supposed earlier. In cases of unexpected and sudden death, autopsy may show unknown conditions and is valuable to assess existing risks for family members. Even after careful autopsy, a proportion of sudden deaths, ranging from 2 to 54%, remain unexplained and this broad range of values is likely due to the heterogeneity of autopsy protocols. Post mortem diagnosis of cardiac amyloidosis still represents a challenge for forensic pathologists. Detailed morphologic study of the heart and a complete histopathologic study are mandatory. Immunohistochemistry is essential for amyloid subclassification. A review of existing literature is performed by the authors and a methodological approach in post mortem diagnosis of light chain AL cardiac amyloidosis is proposed. Both macroscopic and microscopic findings are discussed.

Keywords: Cardiac amyloidosis, light chain amyloidosis, sudden death, autopsy, immunohistochemistry, post-mortem diagnosis

Introduction

Amyloidosis is a rare disorder characterized by the abnormal extracellular deposition of misfolded amyloid proteins in various organs. These proteins polymerize into fibrils that are insoluble and resist degradation with a characteristic β-pleated sheet structure, which stabilizes the fibrils to form amyloid. Amyloid accumulates in various organs (particularly kidneys, heart, gastrointestinal tract, liver, skin, peripheral nerves and eyes), resulting in architectural disorganisation, cellular damage, and functional failure [1]. Amyloid deposition can be systemic (more frequent) or localized at specific sites; it can either be acquired or inherited [2-4]. The incidence is thought to be equal in males and females. Cardiac amyloidosis is classified into several types: AL (immunoglobulin light chain), AA (historically known as secondary), isolated atrial amyloidosis (IAA) and transthyretin amyloidosis (ATTR) (**Table 1**). Most cases of cardiac amyloidosis are caused by one of two proteins: light chain (AL) or transthyretin (TTR). Light chain AL amyloidosis is the most common type of systemic amyloidosis. It is due to a dyscrasia of a type of white blood cell in the bone marrow with misfolding of immunoglobulin light chains (LCs) - which are constituents of natural antibodies - and production of an abnormal light

Table 1. Cardiac amyloidosis is classified into several types: AL (immunoglobulin light chain), AA (historically known at secondary), isolated atrial amyloidosis (IAA) and transthyretin amyloidosis (ATTR)

Type	Protein	Systemic or Localized	Organs involved	Clinical phenotype	Sex	Age	Survival
AL	Light chain	S and L	Kidney, Heart, Liver, PNS, ANS	Primary or in association with multiple myeloma (5-15%)	Male/Female	After 40 years old	6 months-4 years
AA	AA serum protein	S	Kidney, Liver, ANS	Secondary in association with chronic inflammatory disease (5-9%)	Male/Female	Also children	5-10 years
ATTR	Transthyretin	S	PNS, Heart, ANS	Senil systemic	Male	After 60 years old	12 years

chain protein [5]. A precondition is a clonal B cell disorder, such as multiple myeloma, which elevates the concentration of one monoclonal LC in the serum [6]. AA amyloidosis is derived from the inflammatory serum protein amyloid A and occurs in association with chronic inflammatory disease such as rheumatic diseases, familial Mediterranean fever, chronic inflammatory bowel disease, tuberculosis, or empyema. Secondary amyloidosis (AA) occurs in less than 5% of individuals with these conditions. Hereditary amyloidosis is a rare type of amyloidosis caused by an abnormal gene. The most common type of hereditary amyloidosis is called ATTR and is caused by mutations in the transthyretin (TTR) gene. Age related amyloidosis is due to amyloid derived from wild-type transthyretin. It is a slowly progressive disease that affects the hearts of elderly men and it is called ATTR wt amyloidosis. It is probably more common than AA amyloidosis, but considerably underdiagnosed. Cardiac amyloidosis should be considered as part of a systemic disease and not an isolated condition. Amyloid deposits in the myocardial interstitium are associated with progressive heart failure and ventricular arrhythmia. Polymorphic ventricular tachycardia or ventricular fibrillation are recorded in fatalities. Up to half of all patients with undiagnosed cardiac amyloidosis die suddenly.

Light chain AL cardiac amyloidosis: a systematic review

Light chain AL amyloidosis is a rare condition with a reported incidence of 5.1-12.8 per million persons per year [7-9]. In AL amyloidosis, manifestations of a plasma cell dyscrasia are found in 98% and multiple myeloma is co-diagnosed in 5-15% of the cases. AL amyloidosis may have minimal or severe cardiac involvement with 50% of patients showing cardiac amyloidosis. In AL amyloidosis, renal, neural and/or dermatologic involvement often coexists with heart involvement. Less commonly, symptomatic hepatic and gastrointestinal infiltration may occur. Cerebral involvement is not reported. AL amyloidosis is a hematologic disorder of plasma cells closely related to multiple myeloma. It is caused by the proliferation of an abnormal clone of plasma cells that overproduce lambda or, less commonly, kappa light chains with a ratio of 3:1 approximately. Approximately 5 to 10% of patients with AL amyloidosis have evidence of overt multiple myeloma and a similar proportion of multiple myeloma patients will have AL amyloidosis. Clinically isolated AL cardiac amyloidosis is infrequent but not rare and probably was underestimated in the past due to the rapid progression to death in undiagnosed patients. Cardiac involvement with AL light chains deposits is associated with high mortality. Early diagnosis and management are crucial for survival as the AL type cardiac amyloidosis is associated with a bad prognosis [10, 11]. Untreated, the median survival from onset of heart failure is approximately of 6 months but modern therapies can put the disease into a prolonged remission and extend life by many years [9, 12]. AL amyloidosis has both toxic and infiltrative effects [13]. It was demonstrated that physiologic levels of amyloidogenic light chains caused an increase in cellular reactive oxygen species and up-regulation of heme oxygenase in rat cardiomyocites, with associated impairment in contractility and relaxation. This toxic effect was blocked by antioxidants [14, 15]. The initial response at a subcellular level to toxixicity of AL chains is lysosomal dysfunction with impaired autophagy culminating in elevated ROS, cellular dysfunction, impaired calcium homeostasis and cellular death [16]. Although much emphasis has been placed on toxicity in AL amyloidosis, recent data suggest cardiotoxic effects of the amyloid fibrils themselves binding to the surface of cardiomyocytes and producing a disturbance of cellular metabolic activity [17]. Clinically, patients with AL cardiac amyloidosis present progressive diastolic heart failure [18]. Up to 50% of AL patients with cardiac involvement also have conduction abnormalities [19]. Amyloid deposits in the atrium result in atrial dysfunction, and thrombus formation may occur. Valvular involvement is rarely clinically severe.

Persistent cardiac troponin elevation is a feature of AL cardiac amyloidosis due to myocardial ischemia from small vessel occlusion or from the direct toxic effects of AL light chain. Elevated N-terminal pro brain natriuretic peptide (NT-pro-BNP) and troponin levels, diastolic dysfunction, and the extent of extracellular bolum and late gadolinium enhancement on MRI are considered adverse prognostic factors [20].

Myocyte contractility and calcium release are impaired by AL amyloid, which increases oxidative stress [21]. Cardiac inflammation and sep-

aration of myocytes induced by deposition of amyloid fibrils explains conduction abnormalities. The conduction system is involved in all forms of cardiac amyloidosis. Normal sinus node function is generally preserved in AL cardiac amyloidosis, while conduction defects in the His-Purkinje system are more commonly reported and associated with AV block [22, 23]. Postural hypotension and syncope resulting from autonomic dysfunction are a common findings in patients with AL amyloidosis. A higher incidence of ventricular arrhythmias is described in AL cardiac amyloidosis. In a study of 195 patients with AL amyloidosis, 24 hour Holter recordings revealed non sustained ventricular tachycardia (VT) in 27% of patients with advanced AL cardiac amyloidosis with a mortality rate of 88% [24].

Diagnosis depends on symptoms (fatigue, dyspnea on exertion, orthopnea, palpitations, and syncope), physical examination (mitral or tricuspid regurgitation), laboratory (BNP > 400 pg/mL and high immunoglobulin levels) and imaging [19, 25]. Electrocardiogram (EKG) findings include non-specific low voltage in limb leads seen in up to 50% of the patients, but patients may have a left bundle or right bundle branch block with pseudo-infarct Q-waves [26]. Low voltage EKG often precedes heart failure and may be present before an increase in left ventricular wall thickness is apparent on echocardiogram. Transthoracic echocardiograph is the non-invasive test of choice to diagnose cardiac amyloidosis. Findings are diastolic dysfunction with a high ejection fraction and increased left ventricular wall thickness [27]. The echocardiogram typically shows concentric left ventricle (LV) thickening, often with right ventricular thickening. Disproportion of low voltage on EKG with left ventricular hypertrophy on echocardiography is suspect for cardiac amyloidosis [28]. Magnetic resonance imaging shows global transmural to subendocardial late gadolinium enhancement [29]. Cardiac biopsy represents the gold standard for diagnosis [19, 30, 31].

Light chain AL cardiac amyloidosis and sudden death: a diagnostic challenge?

AL amyloidosis is frequently undiagnosed or detected at autopsy. Sudden death is far more common in AL cardiac amyloidosis and can be the presenting event [32-35]. The estimated rate of sudden cardiac death in amyloidosis without evidence of heart failure is 15% to 23% [36]. Sudden death in patients with AL amyloidosis is usually attributed to pulseless electrical activity, followed by ventricular arrhythmias, but may result from thromboembolic complications or bradyarrhythmias and conduction system disease secondary to amyloid infiltration or autonomic dysfunction [37]. Despite advances in therapeutic regimens the frequency of sudden death within ≤90 days of diagnosis remains at 25%-30%. All unexplained sudden death victims should undergo post-mortem expert examination to investigate whether a cardiac origin should be suspected [38]. Unfortunately, even when an autopsy is performed, a proportion of sudden deaths, ranging from 2 to 54%, remain unexplained: this broad range of values is likely due to heterogeneity of the autopsy protocols. Postmortem diagnosis of cardiac amyloidosis is rare and needs a rigid protocol of macroscopic and microscopic investigations. Elevated standards for autopsy, heart examination, and histologic sampling are needed.

Gross examination of *in toto*, formalin-fixed heart is suggested (**Figure 1A**, **1B**). Thickening of ventricular walls is pathognomonic of cardiac deposits of amyloid fibrils [6]. Occasionally, in patients with mild cardiac amyloidosis, left ventricle hypertrophy can be absent. Nodular deposits of amyloid may also be present on pericardium, cardiac conduction tissue and valves. According to Sattar et al., hypertrophic cardiomyopathies like left ventricular outflow tract (LVOT) obstruction is one of the rare presentations of disease. It is due to the systolic anterior motion of the mitral valve and irregular septal hypertrophy secondary to amyloid deposits [39]. The amyloid deposits expand the extracellular space and stiffen the heart without producing compensatory dilatation, which result in a restrictive pathophysiology involving both ventricles. A review of current literature reveals the increasingly important role attributed to right ventricular (RV) assesment in cardiac amyloidosis [40, 41]. RV features include increased wall thickness, dysfunction and chamber enlargement [42-44].

A standard histologic examination of the heart should include mapped labelled blocks of myocardium from representative transverse slices

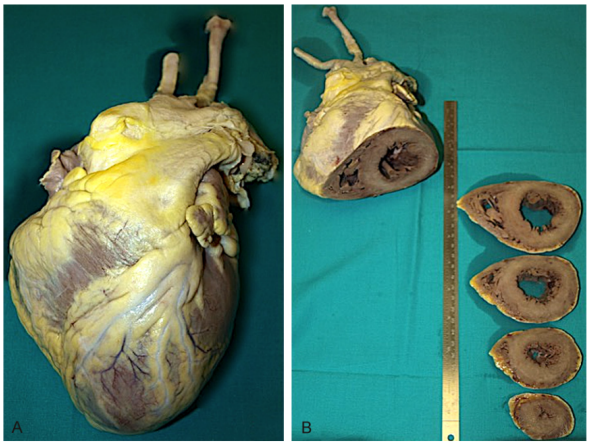

Figure 1. A. Autopsy specimen of the heart of a 58 year old man with multiple myeloma. Mascroscopic study was delayed after fixation in formalin. Heart was normal in shape, increased in weight (560 grams) and volume. Coronary tree was unremarkable. B. Section of the heart according to the inflow-outflow method with thickening of ventricular walls.

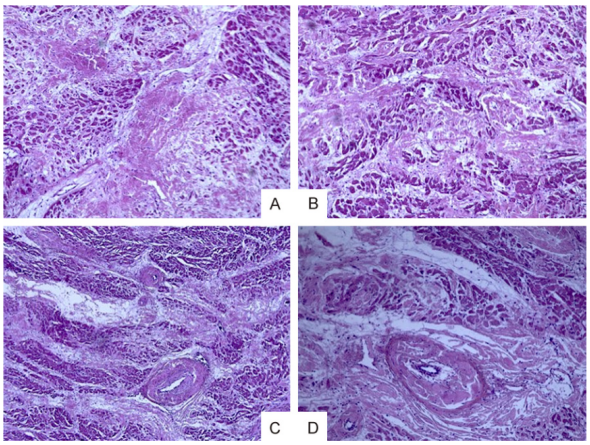

Figure 2. Cardiac samples stained with hematoxylin and eosin. A, B. Extensive amorphous light pink extracellular amyloid deposits compress the cardiomyocytes. C, D. Amyloid surrounds small vessels.

of both ventricles. Appropriate staining of heart samples is critical for a correct diagnosis. Cardiac specimens stained with hematoxylin and eosin show the deposition of amorphous, light pink fibrillar proteinaceous material in the extracellular space of the heart and perivascularly (**Figure 2A-D**). A greater number of diffuse pericellular, endocardial, and arterial and/or arteriolar deposits are observed in AL amyloidosis than in ATTR [45]. Subendocardial amyloid depositions can also damage the conduction system and cause arrhythmias [46]. This appearance, although consistent with amyloid deposition, requires more specific stains.

Congo red staining has a sensitivity of 70-90% for the diagnosis of AL amyloidosis [46, 47]. Congo red will stain the amyloid red-pink with apple-green birefringence when viewed with polarized microscopy (**Figure 3A-D**). The green refractility of the samples stained by Congo Red is typical of all forms of amyloidosis and is due to the conformation of the amyloid fibrils that form β-crossed sheets. Many studies have shown that immunohistochemistry is a feasible and highly sensitive and specific tool for amyloid subclassification [48]. Immunohistochemistry can usefully identify fibril type in about 60-70% cases [49]. Amyloid deposits can be reliably subtyped in cardiac specimens using immunohistochemistry such as AL-lambda, AL-kappa (**Figure 4A-D**) [50]. However, availability of antibodies for detection of all amyloid subtypes can be limited. Proteomic typing of amyloid by mass sprectrometry can represent a straightforward option [51, 52]. Analysis of pathologic amyloid protein depositions by MALDI IMS (matrix-assisted laser desorption/ionization imaging mass spectrometry) may represent a good option, as signal to noise ratio is expected to be high [53]. Mass spectrometry has been associated with detection of amyloid deposition in an earlier stage than Congo red staining. Diagnosis of amyloidosis with mass spectrometry is based

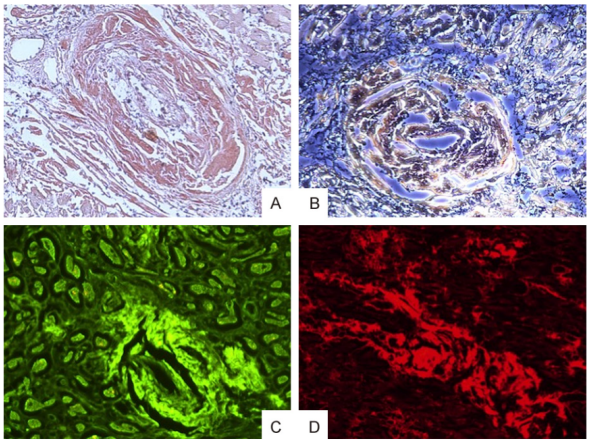

Figure 3. Cardiac specimens stained with Congo Red. A. Perivascular red-pink deposits of amyloid. B. Amyloid deposition by phase contrast examination. C. Amyloid stained with Congo red shows an apple-green birefringence when viewed with polarized microscopy. D. Congo red with rhodamine fluorescence.

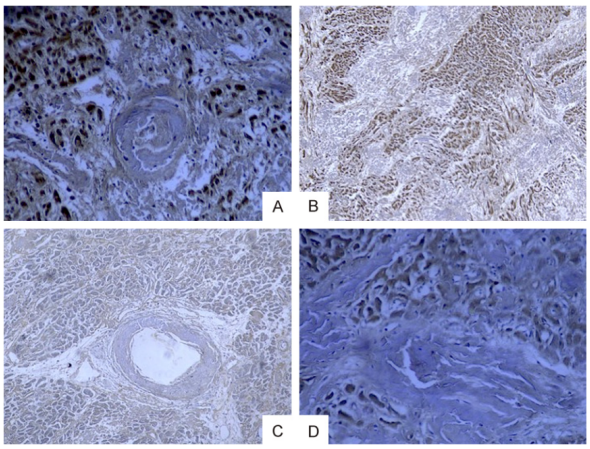

Figure 4. Immunohistochemistry with monoclonal antibodies directed against lambda light chain and kappa light chain. Immunostaining of the amyloid deposits with anti-lambda chain antibodies was strongly positive (A, B), whereas staining with anti-kappa chain antibodies was negative (C, D) confirming AL amyloidosis.

on the detection of proteins which are linked to AL and AA amyloidosis like serum amyloid P component, apoliproprotein E, vitronectin, and perlecan [54-56]. The next generation approach to immunohistochemistry proposes a combination of immunohistochemistry with mass spectrometry, based on the laser-mediated mass spectrometry detection in the tissues of metal-labelled antibodies [57]. Scanning mass cytometry and multiplexed ion-beam imaging use the mass spectrometry technique for detection of secondary ions released by the use of a laser beam. Finally, vibrational spectroscopy technology may be used to detect changes in biochemical composition at the cellular level [58, 59].

Conclusion

Light chain AL cardiac amyloidosis can be first diagnosed after a complete post mortem investigation. Diagnosis of cardiac amyloidosis still represents a challenge for forensic pathologists and a rigorous methodologic approach is mandatory. When cardiac amyloidosis is suspected, standard histologic stains such as hematoxylin and eosin (H&E) cannot be considered complete to confirm diagnosis. Congo red stain is mandatory and immunohistochemical reaction with anti light chain antibody is necessary for subclassification. Combining mass spectrometry technique with immunohistochemistry may become a routine procedure for pathology laboratories. Cost balancing and promising results constitute the next challenge.

Disclosure of conflict of interest

None.

Abbreviations

AL, immunoglobulin light chain; AA, historically known at secondary; IAA, isolated atrial amyloidosis; ATTR, transthyretin amyloidosis; ROS,

Reactive oxygen species; NT-pro-BNP, N-terminal pro brain natriuretic peptide; MRI, Magnetic resonance imaging; VT, Ventricular tachycardia; EKG, electrocardiogram; LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle; H&E, hematoxylin and eosin; MALDI IMS, matrix-assisted laser desorption/ionization imaging mass spectrometry.

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