

Review

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Cardiac amyloidosis: the pathologist's point of view

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Abstract

Cardiac amyloidosis is a well-known entity recently recognized as a common etiology of heart failure. This infiltrative disease is caused by the deposition of misfolded proteins within the heart. The most common types of cardiac amyloidosis result from fibrils composed of monoclonal immunoglobulin light chains or transthyretin. Clinical presentation is usually elusive, and this can result in diagnostic delay. Diagnosis can be reached with non-invasive methods, but it often requires tissue sampling with pathological analysis. It is fundamental to determine the type of protein being deposited in order to indicate the specific treatment. In this article, we review the main features of cardiac amyloidosis with a focus on different pathological presentations of this rare disorder.

Keywords: Cardiac amyloidosis, cardiovascular pathology, histology

INTRODUCTION

Amyloidosis is a disorder caused by abnormal conformation and metabolism of proteins resulting in extracellular deposition of fibrillar material. These aggregates can alter tissue architecture and subsequently affect organ function throughout the body. The disease is usually classified according to the precursor proteins that undergo the misfolding and accumulation: more than 30 different human proteins have been recognized as precursors for the buildup of amyloid deposits. Nevertheless, only nine misfolded proteins can accumulate in the myocardium and be responsible for cardiac amyloidosis (CA)^[1]. Once considered a rare disease, CA is now acknowledged as an underrecognized cause of heart failure, with a variable



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prevalence of up to 32% in autopsy series in older populations^[2]. Since cardiac involvement is still the leading cause of morbidity and mortality in amyloidosis, early diagnosis remains critical for adequate therapeutical planning closely related to a better prognosis.

The aim of our paper is to review the available pathology literature on the gross and histological findings of cardiac involvement in amyloidosis, which are of potential value in interpreting laboratory and imaging data.

HISTORICAL NOTES

The term “amyloid” comes from the Latin *amylum* and the Greek *amylon*, meaning starch. This term was introduced in the medical field by Rudolf Virchow in 1854 to describe the small round deposits in the brain that stained pale blue on treatment with iodine and violet upon the subsequent addition of sulfuric acid. He was convinced that those structures were identical to starch and he named them “corpora amylacea”^[3]. The representatives of the French and British Schools instead considered amyloid to be more closely related to cellulose and they, respectively, used the name “lardaceous” (based on the bacon-like appearance of the tissue) and “waxy” (based on the homogeneity of the material)^[4]. Another historical term is the “sago spleen”, in cases of splenic involvement by amyloid, which can give a nodular appearance similar to sago starch grains. Only later observations led to the exclusion of starch and cellulose from the materials composing “amyloid”. The invention of the metachromatic stains in 1875 (particularly methyl violet stain) allowed for better detection of amyloid and localizing it in the extracellular tissue. The first description of amyloid in the cardiac tissue is reportedly the one by Soyka in 1876 who used this new method^[5]. A new dye originally used to stain textile fibers was then discovered and became widely used: Congo red staining^[6]. This stain was developed by the German chemist Paul Böttiger in 1884 and then sold to the Agfa company, which named it “Congo” for marketing purposes, reflecting geopolitical events of that time^[7]. However, only in 1922, the German chemist Bennhold discovered the capacity of Congo red to bind to amyloid, introducing it in the diagnostic process. Initially, Congo red was not used as a histological stain to obtain the diagnosis: it was administered to patients with suspected amyloidosis and its level in plasma was supposed to decrease in patients with amyloid due to systemic tissue binding. In 1959, the first observation of amyloid by electron microscopy was reported, demonstrating a fibrillar structure that was different from collagen and similar in different tissues^[8]. One of the first and most successful methods to extract amyloid from tissue was described in 1962 by Pras and colleagues (the so-called water extraction method), and it enabled the identification of the β -pleated sheet configuration of amyloid proteins and the discovery of the biochemical structure of those proteins^[9].

ETIOLOGY AND PATHOGENESIS

Amyloidosis is considered a rare disease with still few epidemiological studies published. Data on the epidemiology of CA are based mainly on single-center studies or population registries. Of the 36 thus far known precursor proteins, fewer than 10 can accumulate in the myocardium and cause significant cardiac disease^[10] [Table 1]. The most common types of CA result from fibrils composed of monoclonal immunoglobulin light chains (AL) or transthyretin (TTR), in either its hereditary or acquired form. AL-CA is the most frequent form with a reported prevalence of 6-10 per million^[11-13]. In recent times, an increase in AL amyloidosis has been observed, uncoupled with a similar rise in incidence. This was supposed to be explained by early diagnosis and a consequent improvement in overall survival^[14].

AL amyloidosis

AL amyloidosis (previously known as primary amyloidosis) results from the deposition of immunoglobulin light chains produced by a plasma cell dyscrasia. The clonal plasma cells in the bone marrow produce

Table 1. Amyloid fibril proteins and their precursors in humans. Modified from^[10]

| Fibril protein | Precursor protein | Acquired or hereditary | Target organs |
|----------------|--|------------------------|---|
| AL | Immunoglobulin light chain | A, H | All organs except CNS |
| AH | Immunoglobulin heavy chain | A | All organs except CNS |
| AA | (Apo) serum amyloid A | A | All organs except CNS |
| ATTR | Transthyretin, wild-type | A | Heart, lung, ligaments, tenosynovium |
| | Transthyretin, variants | H | PNS, ANS, heart, eye, leptomenynges |
| Aβ2M | β2-microglobulin, wild type | A | Musculoskeletal system |
| | β2-microglobulin, variants | H | ANS |
| AApoAI | Apolipoprotein A I, variants | H | Heart, liver, kidney, PNS, testis, larynx, skin |
| AApoAII | Apolipoprotein A II, variants | H | Kidney |
| AApoAIV | Apolipoprotein A IV, wild type | A | Kidney medulla and systemic |
| AApoCII | Apolipoprotein C II, variants | H | Kidney |
| AApoCIII | Apolipoprotein C III, variants | H | Kidney |
| AGel | Gelsolin, variants | H | Kidney, PNS, cornea |
| ALys | Lysozyme, variants | H | Kidney |
| ALECT2 | Leukocyte chemotactic factor-2 | A | Kidney, primarily |
| AFib | Fibrinogen α, variants | H | Kidney, primarily |
| ACys | Cystatin C, variants | H | CNS, PNS, skin |
| ABri | ABriPP, variants | H | CNS |
| ADan | ADanPP, variants | H | CNS |
| Aβ | Aβ precursor protein, wild type and variants | A, H | CNS |
| AαSyn | α-synuclein | A | CNS |
| ATau | Tau | A | CNS |
| APrP | Prion protein, wild type and variants | A, H | CJD, fatal insomnia, GSS syndrome |
| ACal | (Pro)calcitonin | A | C-cell thyroid tumors, kidney |
| AIAPP | Islet amyloid polypeptide | A | Islets of Langerhans, insulinomas |
| AANF | Atrial natriuretic factor | A | Cardiac atria |
| APro | Prolactin | A | Pituitary prolactinomas, aging pituitary |
| AIns | Insulin | A | Iatrogenic, local injections |
| ASPC | Lung surfactant protein | A | Lung |
| ACor | Corneodesmosin | A | Cornified epithelia, hair follicles |
| AMed | Lactadherin | A | Senile aortic media |
| AKer | Kerato-epithelin | A | Cornea, hereditary |
| ALac | Lactoferrin | A | Cornea |
| AOAAP | Odontogenic ameloblast-associated protein | A | Odontogenic tumors |
| ASem1 | Semenogelin 1 | A | Vescicula seminalis |
| AEnf | Enfuvirtide | A | Iatrogenic |
| ACatK | Cathepsin K | A | Tumor associated |
| AEFEMP1 | EGF-containing fibulin-like extracellular matrix protein 1 | A | Portal veins aging-associated |

CNS: Central nervous system; ANS: autonomic nervous system; PNS: peripheral nervous system; CJD: creutzfeldt–Jakob disease; GSS: gerstmann-Sträussler-Scheinker.

excessive quantities of immunoglobulin fragments, usually immunoglobulin light chains, leading to their accumulation and deposition. In rare cases, immunoglobulin heavy chains or both heavy and light chains are the components of the amyloid fibrils. AL amyloidosis is usually characterized by multiorgan involvement with non-specific clinical presentation: the combination of macroglossia and periorbital purpura is virtually pathognomonic, but it occurs in less than a third of cases. The average age at diagnosis is 63 years, and about 90% of patients are older than 50. Cardiac involvement is very frequent with an occurrence of about 50%-80% and kidneys are the second most involved organ (50%-60% of patients)^[15,16].

Immunoglobulin light chains can cause cardiac impairment both by mechanical stress due to deposition and by direct toxicity; this could explain the fact that sometimes AL-CA is clinically more severe than other types of amyloidosis given an apparently similar degree of amyloid deposition in the heart^[17-19]. Since patients affected by AL amyloidosis commonly have an underlying plasma cell dyscrasia ranging from monoclonal gammopathy of uncertain significance (MGUS) to multiple myeloma, the main treatment is chemotherapy to address the plasma cell proliferation, with regimens including bortezomib, cyclophosphamide, and dexamethasone. The aim of this strategy is to rapidly reduce the production of amyloidogenic light chains to limit the progressive damage to the involved organs, considering that the resolution of amyloid deposits is virtually impossible.

TTR amyloidosis

TTR amyloidosis (ATTR) occurs when dissociated TTR monomers misfold and assemble into amyloid fibrils. TTR is a tetramer protein produced primarily in the liver that becomes amyloidogenic when it dissociates into monomers. Two types of fibrils have been recognized as responsible for ATTR: Type A consists of C-terminal ATTR fragments and full-length TTR, whereas Type B consists only of full-length TTR. Every patient contains ATTR deposits of either Type A or B fibrils^[20]. Two distinct types of ATTR exist: hereditary or mutated (ATTRmt) and wild-type (ATTRwt), also referred to as senile systemic amyloidosis, age-related amyloidosis, or senile cardiac amyloidosis. Type A fibrils appear to occur in most TTR variants including ATTRwt, while Type B fibrils are seen in some ATTRmt mutations^[21]. ATTRmt is a rare autosomal dominant condition caused by mutations in the TTR gene. The most common mutation in ATTRmt is Val30Met. Clinical manifestations are mainly cardiovascular, neurological, or mixed^[22]. ATTRmt patients are usually younger than ATTRwt patients, with a median age at onset of 39. Phenotypic heterogeneity is wide and results from different factors: the different TTR mutations, the geographic region of the patient, and the Val30Met aggregation (endemic or nonendemic). The curative therapy for ATTRmt is orthotopic liver transplantation or combined heart-liver transplantation, which can provide a sort of surgical gene therapy in particular for amyloidotic cardiomyopathy^[23]. For patients with ATTR cardiomyopathy, new promising disease-modifying therapies have been developed, with specific targets including TTR silencing, TTR stabilization, and TTR disruption. TTR protein silencers (patisiran and inotersen) target the hepatic synthesis of TTR. Tafamidis and diflunisal are TTR stabilizers with the former being the only authorized drug for the treatment of ATTR cardiomyopathy. Other agents are under investigation for a role in TTR disruption (tauroursodeoxycholic acid and monoclonal antibodies), but their benefits are uncertain^[24].

CLINICAL DIAGNOSIS

CA diagnosis can be reached through invasive or non-invasive strategies, the latter available only for ATTR. The disease should be suspected when typical signs and symptoms appear, the so-called “red flags”: proteinuria (even mild), macroglossia, skin bruises, and carpal tunnel syndrome. For what concerns the heart, congestive heart failure coupled with unexplained left ventricular (LV) hypertrophy at imaging is a prominent feature. Additional signs that can suggest CA are persistent troponin elevation, disproportionately low QRS voltage at the electrocardiogram (ECG), or early conduction system disease. The presence of discrepancy between a low-voltage ECG and an increased LV wall thickness on two-dimensional echocardiography is highly suggestive of cardiac amyloidosis (particularly AL amyloidosis)^[25].

Non-invasive diagnosis (without histological sampling) is possible only for cardiac ATTR when a combination of clinical and imaging findings is documented: typical echocardiographic or cardiac magnetic resonance (CMR) findings need to be present in addition to positive scintigraphy [^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), or ^{99m}Tc-hydroxymethylene

diphosphonate (HMDP)] and negative search in those with plasma cell dyscrasia by serum-free light chain assay, serum, and urine protein electrophoresis. The importance of ruling out AL-CA is highlighted by studies that demonstrated cardiac uptake by ^{99m}Tc-DPD also in patients with AL-CA, with cardiac uptake associated with poorer cardiac function and outcomes^[26,27].

BIOPSY DIAGNOSIS

Diagnosis of CA can be reached by extracardiac biopsy coupled with typical imaging features of CA by echocardiography or CMR, in the absence of an alternative cause for increased LV wall thickness^[28]. A so-called “screening biopsy” of the rectum or salivary gland may be performed, but fatty tissue biopsy or aspiration is actually the easiest method to obtain a sample for amyloid diagnosis. The procedure of abdominal fat pad fine needle aspiration requires Congo red staining and is very simple and cheap. However, although the reported specificity is high, the diagnostic sensitivity varies widely among different studies^[29-31]. In particular, the use of fatty tissue aspiration is highly supported in systemic AL amyloidosis but demonstrates its limitations for diagnosis of ATTR amyloidosis, particularly ATTRwt amyloidosis, and generally cannot be used to exclude amyloidosis.

However, demonstration of amyloid fibrils in myocardial tissue through endomyocardial biopsy (EMB) remains the gold standard for the diagnosis of CA^[28]. The first step of CA diagnosis is the visual recognition of a homogenous, eosinophilic substance within the myocardial interstitium by hematoxylin-eosin staining. Although Congo red is commonly applied for histological analysis when clinical suspicion of CA is present, it requires the use of polarized light microscopy and a certain degree of expertise; moreover, the difficulty of detecting the diagnostic “apple green birefringence” of the dye can cause a low sensitivity. In addition to Congo red, probably the most widely used histochemical stain to detect amyloid by pathologists worldwide, other stains can be helpful in formalin-fixed paraffin-embedded (FFPE) tissues, such as thioflavin T and S, which bind with the amyloid proteins and exhibit fluorescence in dark-field microscopy^[32], and a slightly more complex to realize but highly specific histochemical dye, Sulfated Alcian Blu, which stains the mucopolysaccharide matrix associated with amyloid and gives a bright green appearance to the deposits^[33]. If available, confocal laser microscopy can increase sensibility and specificity of amyloid detection in Congo red- and thioflavin T-stained tissues [Figure 1]^[34].

Amyloid typing

After histological confirmation, amyloid typing is essential and can be obtained with different methods: antibody-based techniques and mass spectrometry are the most widely used. Both can be applied on FFPE tissue, avoiding the need for special handling of endomyocardial biopsy samples. Antibody-based methods consist of immunofluorescence (IF), immunohistochemistry (IHC), and immunoelectron microscopy. All three techniques require a broad panel of antibodies to accurately detect the abnormal protein. In addition, each technique has its own flaws: IHC has been reported as technically complex and difficult to interpret, IF requires fresh tissue, and immune electron microscopy is expensive and requires a longer turnaround time^[35]. This latter method is still used in highly specialized centers in Italy and is applied through the so-called immunogold labeling. This technique is useful for identifying biomarkers in tissues and is applicable for transmission electron microscopy and scanning electron microscopy.

Another technically complex but very specific technique is the proteomic method of the combination of laser microdissection with tandem mass spectrometry^[36]. This method, first used at the Mayo Clinic in the United States, utilizes FFPE specimens as source and is highly sensitive and specific in identifying the amyloid proteins. In addition, some reports demonstrated the possibility of detecting also the underlying genetic alterations^[37].

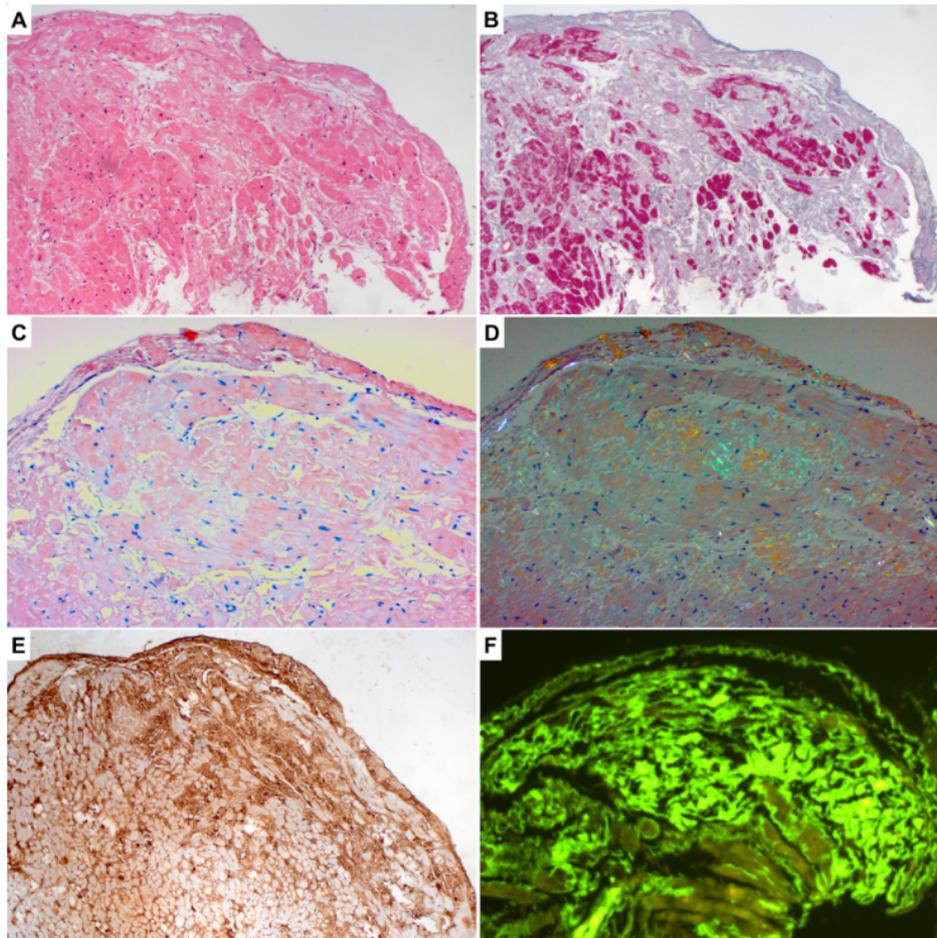


Figure 1. Endomyocardial biopsy diagnosis of cardiac amyloidosis: (A) traditional hematoxylin–eosin stain with evidence of eosinophilic interstitial deposits between cardiomyocytes; (B) Heidenhain trichrome stain highlighting amyloid in pale blue; (C,D) Congo red stain under light microscopy (C) and polarized light microscopy (D) with the typical apple-green birefringence; (E) immunohistochemical typing positive for TTR fibrils; and (F) thioflavin-T staining showing fluorescence in dark-field microscopy upon binding to amyloid fibrils. (A-F) Original magnification, $\times 100$.

CARDIOVASCULAR INVOLVEMENT IN AMYLOIDOSIS: THE STUDY OF WHOLE HEART SPECIMENS

Amyloid can accumulate in every district of the heart in addition to the ventricular myocardium, such as atria, vessels, valves, and pericardium^[35]. Whereas histological description of cardiac involvement by amyloid is well reported in the literature, comprehensive reports on whole heart specimens with detailed evaluation are rare, and their findings are summarized in [Table 2](#)^[38-43]. We reviewed the literature by searching for articles (excluding case report) published in the time interval 1980-2021 with the following keywords: amyloidosis, heart, pathology and histology, autopsy, and transplantation. Only articles including analysis of whole heart specimens were considered.

Gross features

The most evident macroscopic feature of CA is cardiomegaly, usually due to biventricular concentric hypertrophy. Asymmetric interventricular septal thickening can also occur^[35]. The use of the term ventricular “hypertrophy” in CA is historically accepted but controversial, owing to the interstitial nature of the amyloid deposition, unrelated to myocyte enlargement^[44]. The heart weight in CA can reach up to

Table 2. Whole heart-pathology studies on cardiac amyloidosis: literature review

| Author, year ^{ref} | Source | N. cases | Mean age, years (range) | Amyloid typing | Amyloid localization | Pattern of infiltration | Valvular involvement | Vascular involvement | Amyloid quantification | Clinical correlation |
|--|----------------|----------|---|---|---|--|--|---|------------------------|-----------------------------------|
| Roberts and Waller, 1983 ^[39] (including cases from ^[38]) | Autopsy | 54 | 64 (21-97) | ND | Interstitium and endocardium in all; always 1 or both atria | ND | At least 1 valve involved in all | No involvement in epicardial coronary artery Intramural vessels involved in all | ND | Hemodynamic in 16% Echo in 20% |
| Smith et al. ^[40] , 1984 | Autopsy | 47 | Primary 57.6 (35-83) Senile 83 (70-89) | Primary vs. senile | Endocardial 70% Pericardial 36% Left atrium 91% Right atrium 81% | Nodular 49% Perifiber 28% Mixed 17% | Mitral 60% Aortic 23% Tricuspid 50% Pulmonary 30% | Present in 19 primary and 1 senile (total 43%) | ND | ND |
| Leone et al. ^[41] , 2012 | Autopsy and HT | 9 | 56 (54-60) | 5 ATTR (unspecified) 4 AL | Computed analysis: trabecular and subendocardial layers most infiltrated | Diffuse 55.6% Segmental 22.2% Subendocardial 22.2% | ND | ND | Quantitative (%) | Echo in all CMR in 11% |
| Larsen et al. ^[42] , 2016 | Autopsy | 108 | 75 (31-89) | 60 ATTRwt 44 AL (32 λ, 12 κ) 2 AA 1 AApoAIV 1 AL + AH | Interstitium 85% Endocardium 41% | Pericellular 66% Nodular 28% | ND | Epicardial arteries 0% Epicardial vasa vasorum 18% Epicardial veins 48% Intramyocardial arteries 72% Intramyocardial veins 9% | Semi-quantitative | ND |
| Porcari et al. ^[43] , 2021 | Autopsy | 24 | 86 (84-91) | 12 AL 12 ATTR | Interstitium in 75% | LV non-diffuse 65% vs. diffuse 35% | ND | Vascular only in 25% | Semi-quantitative | Echo in 67% |

ND: Not disposable; HT: heart transplantation; echo: echocardiography; CMR: cardiac magnetic resonance; ATTR: transthyretin amyloid; AL: light chain amyloidosis; AA: serum amyloid A, apolipoprotein A-IV amyloidosis; AH: heavy chain amyloidosis.

1 kg^[45]. Hypertrophic cardiomyopathy is the major mimicker^[46,47], but amyloid hearts are usually firmer with additional atrial wall thickening and rugged appearance of the endocardial surface. In addition, the marker of interatrial septum thickening can help to distinguish CA from hypertrophic cardiomyopathy, particularly in the clinical setting^[48]. In some cases, hearts can be macroscopically normal^[39,40]. CA, in particular the AL form, is also associated with high frequency of intracardiac thrombi, most commonly localized in the atria and linked to the worst prognosis^[39,49]. Rough or irregular whitish patches on the external surface of the heart may indicate epicardial involvement.

Histological features

Ventricular myocardium

Deposition of amyloid in the myocardium can be quite variable. Infiltration has been described in terms of percentual or semiquantitative quantification, pattern, and localization. In whole hearts, the trabecular layer seems to be the most involved from the infiltration process^[41]. Amyloid patterns are non-homogeneously defined in different papers, with variable descriptions of segmental, nodular, perifer, pericellular, and diffuse deposition. Amyloid is variably associated with myocardial fibrosis, often described only as mild interstitial fibrosis but in some cases with significant extent, especially in cases with intramyocardial vascular involvement^[50,51]. Cardiomyocytes adjacent to amyloid deposits can show non-specific alterations such as perinuclear halos, cytoplasmic vacuolization, and cell atrophy^[52]. The presence itself of the misfolded proteins has been hypothesized as a cause of direct damage to the cardiomyocytes via apoptotic cell death, leading to cardiac dysfunction and subsequent heart failure^[19,53,54].

The presence of amyloid fibrils inside the myocardium can have a direct cytotoxic effect, for both AL and TTR fragments^[17,55]. This direct damage can contribute to the upregulation of an inflammatory response, positively correlating with disease severity. Histologically proven myocardial inflammation in CA has been linked with the worst prognosis in a large series of EMB, particularly in CA-AL^[56]. However, different studies reported variable results in terms of association of myocardial inflammation and amyloidosis: no stress about inflammation is put in the notable autopsy series^[38-42], whereas, in EMB papers, there is varied description of clusters of histiocytes, myocardial edema, and eventually plurifocal interstitial CD3+ lymphocytes in association with amyloid^[51,52,57]. Isolated reports on the concomitant presence of CA and acute myocarditis are quite frequent, including in the recent context of SARS-CoV-2-associated myocardial injury^[58-60].

Atria

Atrial involvement by amyloid deposits is very common. The buildup can be both intramyocardial and endocardial, the latter also being evident at gross analysis as a rugged or beadlike appearance, if very marked and diffuse^[39,40]. In ATTR as well, atrial infiltration by amyloid, in particular of the left atrium, has been linked to a progressive increase in stiffness correlating with poor prognosis^[61]. A different form of atrial involvement can be found in the so-called “isolated atrial amyloidosis” (IAA) caused by the accumulation of atrial natriuretic peptide or factor (ANF). IAA has typically fine deposits, unlike AL-CA and ATTR in which large plaques can occur^[62,63]. This form appears to be age-related and has been commonly associated with heart failure, in which ANF levels are usually very high^[64,65].

Vessels

Vascular involvement in CA is frequent and variegated. While epicardial main coronary vessels are typically spared from the condition (or limitedly involved without significant luminal obstruction), intramyocardial arteries, veins, and capillaries are usually involved in different grades by the deposits^[39,42,66]. The vasa vasorum of the epicardial coronary arteries also has considerable amyloid buildups. A peculiar phenotype of intramural vessel involvement by amyloid with vascular obstruction has been widely described, sometimes linked with myocardial necrosis as well as acute onset of heart failure mimicking acute myocarditis^[67-70]. This microvascular amyloid infiltration coupled with ischemic damage could explain the frequent elevation of troponin levels even in the absence of epicardial coronary lesions^[71,72]. Vascular involvement is far more frequent in CA-AL compared to ATTR, acting as a relevant prognostic factor as well^[40,50,73].

A different form of vascular amyloidosis is the isolated aortic amyloidosis caused by the buildup of a fibril different from light chains and TTR: the precursor is lactadherin and the accumulating fragment is called

medin. Lactadherin is expressed by several kinds of cells including vascular smooth muscle cells, and the amyloid deposits are commonly located in the aortic tunica media^[74-76]. This form is called AMed amyloidosis and has been demonstrated to also occur in some arterial vessels other than the aorta^[77]. However, the clinical relevance is not clear yet, and no casual relation between aortic amyloid and hypertension or aneurysms has been observed.

Valves

Many works describe the histological involvement by amyloid buildups in cardiac valves, particularly in aortic valves affected by dystrophic calcification causing stenosis^[78-82]. This deposition appears to be linked to the native degenerative pathology of the valve itself and the high hemodynamical stress^[81]. However, only limited demonstrations of amyloid fibrils in the valvular tissue by immunohistochemistry or electron microscopy exist, and they generally exclude the presence of the common AL and TTR deposits, suggesting a different subtype for this phenomenon^[83,84].

Conduction system

Typical ECG abnormalities in CA such as atrioventricular block or left anterior hemiblock prompted the detailed study of the conduction system in autopsy cases. Contrasting results were found by different authors on the localization of amyloid deposits in the specialized conduction tissue^[38,67,85,86]. Most often, the sinus node, the atrioventricular node, the bundle of His, and its major branches appeared to be spared from amyloid infiltration at histological analysis. The most creditable explanation for the discordance between ECG abnormalities and amyloid sparing was given by the presence of fibrosis found in the sinoatrial and atrioventricular node, in contrast to the non-CA control group^[67,86].

Pericardium

Pericardial involvement in CA is usually referred to as the presence of pericardial effusion in cases of congestive heart failure and a critical role in the prognosis^[87]. However, histological demonstrations of pericardial infiltration by amyloid are scarce. When examined in the context of the autopsy series, pericardial infiltration is present in about 50% of the patients affected by CA^[38,40]. In addition, a single intriguing report of isolated pericardial infiltration in AL-CA has been described but is surely an exception^[88].

CONCLUSION

CA is an underestimated cause of heart failure, usually with preserved ejection fraction and restrictive hemodynamics. The role of the pathologist is not only to provide a definitive diagnosis of CA through EMB but also to help in providing precise amyloid typing since this information is essential for prognostic and therapeutic purposes.

DECLARATIONS

Authors' contributions

Draft the manuscript: De Gaspari M

Complete and revise the paper: Finato N, Basso C

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Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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