

Cardiac AL Amyloidosis (RCD code: III-3A.2a)

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Abstract

Primary systemic amyloidosis (AL amyloidosis) is the most common subtype of amyloidosis in developed countries. Amyloid fibrils deposition results from an abnormal secondary structure of immunoglobulin light chains produced by a plasma cell clone. The most common accompanying plasma cell dyscrasia is monoclonal gammopathy of undetermined significance, while multiple myeloma coexists in only 10–15% of patients. The kidneys and the heart are the most frequently affected organs. Patients usually present with concentric left ventricular concentric thickening displaying a restrictive filling pattern with well-preserved systolic function. Clinical suspicion of AL amyloidosis should be raised in older adults and elderly patients with diastolic heart failure accompanied by heavy proteinuria, upon detection of thick-walled heart on echocardiography with low-voltage QRS on ECG (“red-flags” for amyloidosis”), in non-diabetic subjects with peripheral neuropathy or autonomic neuropathy, commonly with severe postural hypotension. Classical clinical stigmata, i.e. periorbital purpura, macroglossia, carpal tunnel syndrome, are not frequent (10–20%) but can guide diagnosis. In the presence of typical echocardiographic features recommended diagnostic steps include identification of monoclonal gammopathy (serum and urine immunofixation and serum free light-chain kappa to lambda ratio) and confirmation of amyloid deposition, preferentially in a non-cardiac tissue such as periumbilical fat or minor salivary glands. Bone marrow biopsy, serum calcium assay and skeletal survey are mandatory to exclude multiple myeloma. Prognosis is mainly dependent on cardiac involvement, being determined by cardiac biomarkers and the difference between involved and uninvolved light chains. Intensive chemotherapy is the therapy of choice in intermediate-risk patients with AL amyloidosis. An improved overall survival was reported in patients with a complete haematological response and an adequate cardiac response, especially a fall in circulating levels of B-type natriuretic peptides. JRC D 2016; 2 (8): 245–253

Key words: rare disease, AL amyloidosis; restrictive cardiomyopathy; monoclonal gammopathy; plasma cell dyscrasia

Introduction and background

Amyloidosis is a rare group of diseases caused by the extracellular deposition of insoluble fibrils composed of misfolded proteins. Of these, primary systemic or AL amyloidosis is the most common subtype in developed countries and is characterized by the production of monoclonal immunoglobulin light chains or, more commonly, light chain fragments – usually due to an underlying plasma cell clone- which deposit in a variety of tissues and organs. An abnormal secondary structure of the light chain – enriched in β -pleated sheets – enhances its propensity to adopt an unstable molecular conformation and loss of water solubility with consequent aggregation of monomers and formation of amyloid fibrils. Extracellular amyloid deposition leads to multisystem involvement and organ damage with significant patient morbidity

and mortality. AL amyloidosis often has an insidious clinical onset resulting in delayed diagnosis. Significant organ involvement is noted, typically affecting the heart, kidneys, liver, peripheral nerves, soft tissue, and gastrointestinal system. Occasionally, AL amyloidosis may present as an isolated local disorder affecting a single tissue [1–3].

Upon diagnosis, patients with AL amyloidosis may present with a wide spectrum of clinical presentations. These include lethargy, fatigue, weight loss, peripheral edema, heart failure, kidney failure, diarrhea/constipation, peripheral or autonomic neuropathy, postural hypotension, or purpura, all of which contribute to the severity of the disease. However, it is extent of cardiac involvement that defines prognosis and governs treatment options within these patients and is of single greatest importance in patient evaluation [1–3].

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Table 1. Clinical features of cardiovascular involvement in AL amyloidosis

Clinical characteristics typical for AL amyloidosis	Mechanisms
Diastolic heart failure with initially peripheral venous congestion, rarely (20%) interstitial pulmonary oedema on chest X-ray	Left ventricle with thickened walls and preserved ejection fraction; thickened right ventricular free wall; biventricular involvement predisposes to right-sided heart failure owing to lower right ventricular filling pressures
Absent fourth heart sound; a third heart sound may be present	Coexistent atrial systolic dysfunction
Postural hypotension; resolution of hypertension in patients with a history of elevated blood pressure	Autonomic neuropathy; hypoalbuminemia
Limited use of standard medical therapy of heart failure (ACEI/ARB, β -blockers, aldosterone antagonists)	Autonomic neuropathy with hypotension; hypoalbuminemia, renal insufficiency
Digoxin considered relatively contraindicated	Binding of digoxin to cardiac amyloid deposits may lead to severe arrhythmias
Impaired response to diuretics	Proteinuria; renal insufficiency
Possible atrial thrombi despite preserved sinus rhythm	Atrial systolic dysfunction; rarely electro-mechanical dissociation with atrial standstill
Preferable dual-chamber pacemaker if bradyarrhythmia	Increased dependence of ventricular filling on atrial contribution due to an impaired ventricular compliance
Limited benefit from an ICD	Frequent electromechanical dissociation

Epidemiology

AL amyloidosis has an incidence of 8–10 per million inhabitants per year with 90% of cases presenting in patients over 50 years of age. Average age of diagnosis is 65 years with men being affected slightly more than women. AL amyloidosis is associated with such plasma cell dyscrasias as multiple myeloma [4] and monoclonal gammopathy of undetermined significance (MGUS) [5–9], while Waldenström's macroglobulinemia is rare. Owing to a high incidence of MGUS (about 3% and 5% for subjects over 50 and 70 years of age, respectively), this form of monoclonal gammopathy is the most frequent (about 80%) plasma cell dyscrasia found in patients with AL amyloidosis, whereas the respective prevalence of multiple myeloma is much lower, averaging averages only 10–15% [5–9].

Clinical presentation

Pathological cardiac involvement occurs in 40–60% of patients with AL amyloidosis, out of whom about 50% present symptoms of heart failure (Table 1) [3, 10]. Typical presentation involves signs and symptoms of heart failure, initially right-sided, in concordance with gradual progression of restrictive cardiomyopathy and diastolic dysfunction. About 60% patients present with dyspnea on exertion while more than 55% present with fatigue and weakness, all of which are the most common symptoms upon clinical evaluation [1]. Despite progressive peripheral edema (in over 80% and potential ascites (in about 15%; appears late in the course of the disease [10]), weight loss is common with more than 42% of patients experiencing a drop of 10 lbs of weight or more. Nearly 54% present with elevated jugular venous pressure [1] and a third heart sound is audible in about 20–30% [1] with a higher prevalence of a right ventricular third heart sound [10]. About 25% of patients report chest pain unrelated to exertion or stress; however, typical angina may occur owing to amyloid deposition in the wall of small coronary arteries and impaired coronary flow reserve. Nevertheless, this form of presentation is very rare in the absence

of left ventricular wall thickening on the echocardiogram, including only 1–2% patients with cardiac involvement [10]. Systolic murmurs are present in almost one-half of subjects with only 10% of patients presenting atrial fibrillation despite common findings of significant atrial dilation [1].

In about 2/3 patients with AL amyloidosis one or two organs are involved, whereas in 1/3 patients more than 2 organs are affected. Of note, clinically isolated cardiac disease is rare in AL amyloidosis (<5%), yet possible [1]. Most typically, kidney involvement occurs in 2/3–3/4 patients and presents usually with heavy proteinuria with predominant albuminuria and usually detectable monoclonal immunoglobulin light chain, nephrotic syndrome in about one-half of patients, usually without hematuria or hypertension [1, 5]. Renal insufficiency frequently coexists, with an estimated glomerular filtration rate below 60 ml/min per 1.73 m² body-surface area in about 25–40% of patients [5]. In about 10% of patients renal insufficiency develops without accompanying significant proteinuria, which is ascribed to amyloid deposition in renal vessels or tubulointerstitium [2]. Liver infiltration can manifest as hepatomegaly in 30–50% of cases and is described as being non-tender and “rock hard” [2, 10], while splenomegaly has been documented in more than 10% [1]. Patients experience carpal tunnel syndrome in 20–25% of cases involving cardiac amyloidosis. Approximately 15–20% of patients have autonomic neuropathy presenting with impotence, orthostatic hypotension, early satiety early satiety due to delayed gastric emptying, alternating diarrhoea and constipation, or voiding dysfunction not related to direct organ infiltration [1, 5].

Macroglossia, frequently with indented teeth, is identified in 10–20% of patients, while ecchymoses and petechiae are seen in 30–40%, including those in the periorbital area in about 10% [1]. Rarely, amyloid deposits can accumulate in endocrine glands, as adrenal insufficiency and hypothyroidism secondary to organ dysfunction have been previously documented [2].

Table 2. Diagnostic algorithm in cardiac AL amyloidosis**Suspected cardiac AL amyloidosis – “red-flags”**

- diastolic heart failure with proteinuria
- diastolic heart failure with monoclonal protein
- thick-walled heart on echocardiography with low-voltage QRS on ECG
- peripheral and autonomic neuropathy
- classical stigmata – not frequent (10–20%) but, if present, can guide diagnosis
 - periorbital purpura (“panda eyes”)
 - macroglossia
 - carpal tunnel syndrome

Biopsy of a non-cardiac tissue

- fine-needle aspiration of abdominal subcutaneous fat (positive in 60–75% of AL amyloidosis)
- labial salivary gland (positive in >50% patients with negative fat biopsy)
- rectal mucosa

Bone marrow aspiration

- to exclude multiple myeloma (clonal plasma cells $\geq 10\%$ in multiple myeloma) – usually 5–10% in AL amyloidosis
- positive Congo red staining for amyloid (in about 60–70% of AL amyloidosis)

Serum calcium assay and skeletal survey for lytic bone lesions (X-ray, computed tomography) are mandatory to exclude multiple myeloma.

Amyloid typing – classical stains

- apple-green birefringence under polarized light on Congo red staining
- alternative staining with metachromatic dyes
 - turquoise green on sulfated Alcian blue staining
 - bright pink on methyl violet or crystal violet staining
- pink (eosinophilic) on traditional hematoxylin and eosin staining

Amyloid typing – special techniques (rarely available)

- immunohistochemistry, immunofluorescence
- immunoelectron microscopy with gold-conjugated antibodies
- mass spectrometry after laser capture microdissection (LC-MS) (golden standard)

Caution: If both the fat and the bone marrows stain negative for amyloid, there is still a 15% chance that the patient has AL amyloidosis (!) [29]

Detection of monoclonal gammopathy**Detection of a monoclonal protein (M protein)**

- serum and/or urine protein electrophoresis
 - serum immunofixation (sensitivity: 69%)
 - urine immunofixation (sensitivity: 83%)
 - joint serum and urine immunofixation (sensitivity: 95%)
- Serum immunoglobulin free-light chains (abnormal κ/λ ratio: <0.26 or >1.65) (sensitivity: 91%)

If immunofixation negative and a normal κ to λ ratio – exclude AL amyloidosis (99%) [9]

Caution: M protein is positive and κ/λ ratio abnormal in about 25% and 10%, respectively, of patients with TTR amyloidosis [38] due to a high proportion of MGUS in the elderly.

Direct confirmation of amyloid deposition in the heart is not necessary if (all of the following):

- positive non-cardiac biopsy
- confirmed monoclonal gammopathy
- typical clinical features

Endomyocardial biopsy is rarely performed

- risk of hemorrhagic complications

Cardiac magnetic resonance (CMR) is the golden standard for non-invasive cardiac imaging

- **BUT: coexistent renal insufficiency is a frequent contraindication to gadolinium use**
- non-contrast T1 mapping is a novel technique proven useful in differentiating the commonest cardiac amyloidosis types (AL and TTR) from other causes of increased LV wall thickness

Consider genetic testing if all the following:

- positive Congo red staining for amyloid in biopsy
- unavailable special techniques of amyloid typing
- a normal κ/λ ratio by serum free light chain assay
- negative bone marrow biopsy

Mutant TTR or apoA₁

- Present – consider familial amyloidosis (due to a mutant TTR or apoA₁)
- Absent – probable wild-type TTR amyloidosis, i.e. senile systemic amyloidosis (SSA)

Organ involvement

Inclusion criteria for organ involvement in AL amyloidosis (updated at the XIIth International Symposium on Amyloidosis in Rome in 2010 [5]) were proposed earlier by Gertz et al. [6] and serve as a guide for evaluating the extent of systemic infiltration of amyloid. Kidney involvement is diagnosed when 24-h urine protein is greater than 0.5 g/day. Proteinuria frequently rapidly progresses to nephrotic syndrome with or without renal insufficiency. Heart involvement is identified when levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are greater than 332 ng/L in the absence of renal failure or atrial fibrillation, or when mean left ventricular wall thickness in end-diastole is greater than 12 mm during echocardiographic evaluation, in the absence of other conditions associated with left ventricular thickening, such as hypertension or aortic stenosis [5, 6]. Sometimes cardiac amyloidosis may be suspected when the magnitude of left ventricular thickening is disproportionate to the degree of coexisting abnormalities predisposing to hypertrophy.

Liver involvement is recognized when total liver span exceeds 15 cm in the absence of heart failure or when alkaline phosphatase is greater than 1.5 times the upper normal limit [5, 6].

Peripheral nerve involvement (in about 20% of patients) is recognized in the presence of symmetrical lower extremity sensorimotor peripheral neuropathy similar in presentation to diabetic neuropathy (paraesthesia, dysaesthesia) reflecting the symmetrical pattern of axonal ascending neuropathy [5, 8, 10]. With presentation of clinical signs, gastrointestinal tract or lung infiltration is evaluated by direct biopsy. Lung involvement may also be diagnosed with findings of interstitial lung disease on x-ray with no other suspected etiology. Bilateral pleural effusion is usually due to heart failure but occasionally may result from pleural infiltration with amyloid [10].

Soft tissue involvement encompasses macroglossia, submandibular gland enlargement (frequently accompanying macroglossia), nail dystrophy (brittle and slow-growing), joint symptoms (progressive symmetrical polyarthropathy), myopathy (muscular hypertrophy with pseudo-athletic appearance), or carpal tunnel syndrome [5]. The latter – even with a history of carpal tunnel decompression – is not uncommon and may even predate heart failure symptoms. Small vessel involvement and coagulation impairment (owing to factor X binding to amyloid) are responsible for a variety of skin lesions including easy bruising/bleeding and a highly-characteristic periorbital purpura.

Diagnosis of cardiac AL amyloidosis

Confirmation of amyloid deposition

Suspected AL amyloidosis is evaluated by identifying deposition of amyloid in tissue. Generally, abdominal fat pad biopsy with fine-needle aspiration provides sufficient amyloid deposits needed for diagnosis. Typical apple-green birefringence is appreciated when stained with Congo red under polarized light (Table 2) [3, 5, 10]. However, in cases where deposition is not demonstrated on biopsy or insufficient amounts of amyloid deposits are collected for assessment, biopsies of other superficially involved organs may be performed [10]. Rectal mucosa and minor salivary glands

Table 3. Wild-type transthyretin amyloidosis (systemic senile amyloidosis) – a diagnostic challenge

Suspected wild-type TTR amyloidosis (SSA, systemic senile amyloidosis)

- almost exclusively in elderly and especially very elderly men
- rarely extracardiac manifestations (!) (except for carpal tunnel syndrome)
- indistinguishable from cardiac AL amyloidosis on echocardiography
- usually normal QRS voltage on ECG; BUT: a frequent pseudo-infarction pattern
- frequently bifascicular block (RBBB+LAH) and atrial fibrillation

Diagnostic challenges

Biopsy of a non-cardiac tissue – lower diagnostic performance versus AL amyloidosis

- abdominal subcutaneous fat (positive Congo red staining in only 15–30%) (!) [39, 40]
- bone marrow (positive Congo red staining in about 30%) [40]

M protein/abnormal κ/λ ratio may be present [38] – high prevalence of MGUS in the elderly

Confirmation of amyloid deposition in the heart

- endomyocardial biopsy rarely performed
- CMR imaging with late gadolinium enhancement as a method of choice
 - the lack of renal involvement enables gadolinium use (contraindicated in AL amyloidosis in the presence of coexistent severe renal insufficiency)
- cardiac scintigraphy with bone-seeking tracers may be useful in screening for TTR amyloidosis (both wild-type and familial) and in differentiating from other types of cardiac amyloidosis

Prognosis / Management

- a slower progression compared to cardiac AL amyloidosis
- mainly supportive medical therapy
- better tolerance of ACEI / ARB compared to cardiac AL amyloidosis
 - no renal involvement
 - no autonomic neuropathy

provide alternate non-invasive points for evaluation of systemic amyloidosis. If clinical suspicion remains high despite persistent negative biopsy results, direct organ biopsy may be necessary to demonstrate disease. Endomyocardial biopsy is rarely performed because cardiac AL amyloidosis can be diagnosed in the presence of typical clinical features, confirmed amyloid deposition in the biopsy of a non-cardiac tissue and monoclonal gammopathy [10] (Table 2). In addition, the risk of hemorrhagic complications limits the use of cardiac, kidney or liver biopsy. However, cardiac biopsy may be necessary in exceptional situations, e.g. in wild-type transthyretin (TTR) amyloidosis (i.e. senile systemic amyloidosis) that frequently poses diagnostic problems due to a lower sensitivity of fat biopsy and rare extracardiac manifestations (Table 3) [10].

It is of clinical importance that amyloid typing be performed to identify the composition of deposits as this guides clinical approach and treatment. Using immunohistochemistry / immunofluorescence, samples can be analyzed for presence of immunoglobulin light chains within amyloid deposits, yet are rarely available. Immunoelectron microscopy with gold-conjugated antibodies or mass spectrometry-based proteomic analysis after laser dissection are currently only found in specialized centers, but bolster sensitivity and specificity compared to traditional approaches [5, 8, 10].

Detection of monoclonal gammopathy and diagnostics of plasma cell dyscrasia

Joint serum and urine immunofixation have been routinely used for identification of monoclonal light chains and provide approximately 90–95% sensitivity [9]. However, the introduction of serum free light-chain (FLC) assays has proven useful not only in the diagnosis of AL amyloidosis [7, 9], but also because FLC concentrations predict poor outcome [8]. In AL amyloidosis, κ/λ ratios < 0.26 or > 1.65 suggest the presence of monoclonal plasma cells producing excessive λ or κ light chains, respectively [9]. This is of particular importance in the presence of coexisting renal insufficiency when circulating levels of both κ and λ FLC are increased [10]. The use of FLC κ/λ ratio in conjunction with immunofixation of serum and urine samples have demonstrated a 99% sensitivity for AL amyloidosis, supporting its use in clinical settings [9].

In addition, an evaluation with regard to the presence of an underlying plasma cell dyscrasia is necessary and the extent of systemic infiltration should be defined. Once a monoclonal gammopathy has been identified, it is mandatory to perform a bone marrow biopsy to exclude (or confirm) multiple myeloma. In particular, percentage of clonal plasma cells should be evaluated as AL amyloidosis usually present with 5–10% of clonogenic plasma cells in the bone marrow. Other investigations, such as skeletal surveys by means of X-ray, computed tomography or positron emission tomography may help exclude bone lytic lesions owing to active multiple myeloma [8].

Electrocardiography

Presence of low QRS voltages, often in association with extreme right- or left-axis deviation, is a common finding in patients with cardiac amyloidosis (Table 4) [10]. Poor R-wave progression in precordial leads may also point to cardiac involvement and a pseudo-infarction pattern has been described in 45–70% of biopsy-proven cardiac amyloidosis [11–13]. Rahman et al. [13] reported a sensitivity of 72% and a specificity of 91% for cardiac amyloidosis for the combination of a low QRS voltage with inter-ventricular septal thickness ≥ 1.98 cm in 58 subjects with cardiac amyloidosis of various types confirmed by biopsy.

Right bundle-branch block is uncommon and left bundle branch block occurs extremely rare unless it is a manifestation of pre-existing conditions [10, 13]. Atrial standstill secondary to a lack of atrial excitability due to amyloid deposition in the atria is rare and can be suspected on the basis of a regular and slow heart rhythm without P waves with an escape rhythm of usually junctional origin with narrow QRS complexes.

Despite the lack of ischemic heart disease, ST-T abnormalities have been documented, including ST-segment depression and negative T-waves [12].

Recently, it has been shown in a small study group of 17 patients with biopsy-proven cardiac amyloidosis that echocardiographic left ventricular hypertrophy in the presence of a corrected QT interval (QTc) ≥ 440 ms and a Sokolow-Lyon index ≤ 1.5 mV to be 85% sensitive and 100% specific for cardiac amyloidosis and may serve to be a rapid diagnostic tool in suspected cases [14].

Table 4. Electrocardiographic abnormalities in cardiac amyloidosis [1, 11, 13]

ECG abnormalities in AL amyloidosis

Frequent

Low QRS voltage, in particular in the limb leads – 45–70%
A pseudo-infarction pattern – 45–75%, mainly in antero-septal leads
QTc prolongation > 440 ms – 45%
Left QRS axis deviation – 35%

Other

Right QRS axis deviation – 15%
First-degree AV block – 20%
Higher AV blocks – 5%
Atrial fibrillation or flutter – 10%
LVH – 15%; if present, usually in precordial leads; more frequent in senile amyloidosis
RBBB – 10%
LBBB – $< 5\%$

LBBB – left bundle branch block, RBBB – right bundle branch block, AV – atrioventricular, LVH – left ventricular hypertrophy

Table 5. Echocardiographic findings in cardiac amyloidosis

Echocardiographic abnormalities in AL amyloidosis

Left ventricular wall thickening

- usually symmetrical concentric LV thickening; rarely asymmetrical septal thickening (5%)
- “granular sparkling” – previously considered pathognomonic; currently of uncertain value
 - only 25–35% in more recent reports
 - previous reports largely before the onset of novel imaging techniques
- isolated cardiac involvement is very rare in AL amyloidosis ($< 5\%$) but possible
 - but: typical for senile systemic amyloidosis (SSA) – to be suspected in elderly men
 - if due to SSA – echocardiographic features similar to AL amyloidosis

Left ventricular function

- typically isolated diastolic dysfunction with normal or small LV size at the time of diagnosis
 - usually restrictive filling pattern (but low A-wave also due to atrial dysfunction)
 - low E' (< 8 cm/s by tissue Doppler) differentiates from pericarditis constrictiva
- usually normal EF at diagnosis; progressive EF decline in an advanced stage
- discrete impairment of longitudinal LV systolic function despite a normal EF
 - relative “apical sparing” at LV strain or strain-rate imaging

Other features

- pericardial effusion (45% – usually small)
- mitral/aortic leaflet thickening (30–50%); usually mild and without hemodynamic consequences
- thickened interatrial septum (30–40%)
- enlargement of the left atrium (45%) or both atria (45%) – usually mild-to-moderate
- RV – normal or mildly enlarged; frequently with free wall thickening (45%)
- Intra-atrial thrombus possible also in sinus rhythm (systolic dysfunction / mechanical atrial standstill)
 - TEE suggested to exclude an left atrial appendage thrombus
 - anticoagulation suggested if: A-wave peak < 0.2 m/s on TTE or atrial appendage emptying velocity < 0.4 m/s on TEE

TEE – transesophageal echocardiography, TTE – transthoracic echocardiography

Echocardiography

Cardiac amyloidosis is typically described as presenting with thickened left ventricular walls, right ventricular free wall, interatrial septum and valve leaflets (“pan-cardiac thickening”), sparkling granular myocardial appearance, and dilated atria (Table 5) [1, 3, 5, 10]. Patients exhibit concentric left ventricular thickening displaying a restrictive filling pattern with well-preserved systolic function as demonstrated by normal or near normal ejection fraction. Diastolic dysfunction is the earliest finding in cardiac amyloidosis. The use of 2D, M-mode, and Doppler studies has been beneficial in diagnosing cardiac involvement of systemic amyloidosis. A short deceleration time of the E wave (< 150 ms), and E/A ratio > 2.0, consistent with the restrictive filling pattern, are common findings in Doppler flow studies. The clear limitation associated with standard echocardiographic evaluation is that by the time a diagnosis is made, significant progression of cardiac involvement has usually developed in the absence of treatment.

Newer techniques have emerged to assess the severity of diastolic dysfunction prior to clinical appearance. Tissue-Doppler imaging (TDI) can characterize long-axis ventricular dysfunction by measuring early peak diastolic velocity at the lateral mitral annulus (E'). In cardiac amyloidosis, in which there is significant impairment of relaxation, E' is reduced (<8 cm/s) [12, 15]. In addition, left ventricular end-diastolic filling pressure and left atrial pressure are elevated, which is reflected by an elevated ratio of peak transmitral early filling velocity to the TDI-derived E' (E/E') usually over 15 [12, 15, 16].

Strain or strain-rate analysis by means of TDI or speckle tracking are additional approaches in the detection of early cardiac involvement even before distinctive symptoms of heart failure manifest clinically. While conventional echocardiography assesses systolic and diastolic dysfunction on the basis of wall movement, strain analysis assesses regional myocardial wall deformation. This allows for a higher sensitivity compared to tissue velocity imaging [17, 19, 20]. In one study, upon strain analysis, patients with non-cardiac systemic amyloidosis previously evaluated by traditional echocardiography and deemed to lack myocardial involvement were demonstrated to possess not only a lower TDI-derived E' but also impaired left ventricular longitudinal contraction upon strain analysis reflecting subtle systolic dysfunction by strain analysis [15]. Another study demonstrated reduced peak systolic longitudinal strain and strain-rate by TDI at the base and mid-ventricle in patients with cardiac AL amyloidosis but presenting normal fractional shortening and without heart failure symptoms, while tissue velocities were not impaired at that stage [21].

In summary, conventional methods of evaluating cardiac involvement using standard echocardiography may not be ideal in determining amyloid infiltration in patients with systemic amyloidosis. Nevertheless, whether novel echocardiographic techniques may be helpful in the clinical practice, requires further studies.

Magnetic resonance imaging

The use of cardiac magnetic resonance (CMR) in amyloidosis has recently been shown to serve as an alternative to echocardiography in determining the extent of myocardial involvement [22]. Unlike

echocardiography, CMR is able to differentiate the possible multiple etiologies of an increased left ventricular wall thickness. Left ventricular thickening may be the result of amyloid deposition or can be secondary to hypertension or other diseases, and MR imaging can differentiate between these conditions. Recently, late gadolinium enhancement (LGE) imaging has been proposed to be an alternative to endomyocardial biopsy as a non-invasive approach to diagnosis. One study showed that a characteristic LGE distribution (over the entire subendocardial circumference) was 80% sensitive and 94% specific in identifying cardiac involvement in 33 patients with biopsy-proven amyloidosis [22].

More recently, LGE was further evaluated in a larger population of 120 patients with cardiac amyloidosis, including 100 with AL amyloidosis. Out of 35 subjects with histologically verified cardiac involvement, 97% had abnormal LGE findings [23]. Of these, 83% presented with global transmural or global subendocardial LGE pattern associated with greater amyloid deposition. It was also discovered that LGE occurred preferentially in areas with amyloid deposition. Additionally, LGE was also present in 47% of patients without echocardiographically diagnosed cardiac amyloidosis. Despite these subjects having normal left ventricular thickness, they had worse prognosis based on clinical (NYHA functional class), ECG, and biomarkers (troponin T, NT-proBNP) profiles relative to those without LGE [23]. This provides evidence that CMR imaging of LGE may be useful in detecting early heart involvement before left ventricular thickening is evident on echocardiography.

Of note, LGE imaging requires the administration of gadolinium contrast that is contraindicated in severe renal insufficiency (frequently present in AL amyloidosis) due to the risk of nephrogenic systemic fibrosis. Therefore, T1 mapping offers an attractive alternative to LGE. The non-contrast T1 mapping has been proven useful in differentiating the commonest types of cardiac amyloidosis (AL and TTR) from other causes of increased left ventricular thickening [24].

Cardiac biomarkers

AL amyloidosis with heart involvement presents with significantly elevated NT-proBNP levels. NT-proBNP assessment during initial evaluation of patients aids in staging patients with AL amyloidosis thereby governing clinical approach [24–27]. Current criteria propose NT-proBNP levels >332 ng/L to be highly sensitive for cardiac amyloidosis, however, the value of this biomarker is limited owing to numerous conditions associated with elevated concentrations of B-type natriuretic peptides. Moreover, these levels depend on renal function, with renal insufficiency requiring higher cut-off values for appropriate evaluation [25]. Nonetheless, they serve also as strong predictors of survival and have been proposed to be superior to echocardiographic and clinical parameters as a marker of poor prognosis [24, 25, 27]. In fact, reductions in NT-proBNP levels following chemotherapy were associated with improvement of NYHA class in patients despite unchanged echocardiographic features [28]. Therefore, this marker plays an important role in the evaluation and monitoring of cardiac amyloidosis.

Cardiac troponins are another markers of myocardial damage. Elevated troponin levels occur in cardiac amyloidosis not due to ischemic changes, but owing to local destructive and/or toxic effects

of amyloid deposits surrounding myocytes [3]. Like NT-proBNP, serum troponin is a predictor of impaired long-term survival [24].

Treatment and Prognosis

Disease-modifying treatment

Disease-modifying treatment of AL amyloidosis is focused on chemotherapy regimens designed to eliminate the plasma cell clone secreting immunoglobulin light-chains. Amyloid has been demonstrated to undergo regression; therefore, eliminating further production of amyloid deposits favours long-term resolution of organ dysfunction and clinical symptoms. However, organ function restoration following treatment is not uniform. While hepatic deposits decrease significantly following 3 or 4 months of treatment, cardiac muscle infiltration persists even after several years [5]. Therefore, novel strategies are being pursued to deliver targeted therapy for affected organs in an effort to restore function and minimize systemic toxicities. The goal of treatment involves achievement of haematological response [6, 26]. Updated haematological response criteria define complete response occurring when there are negative urine and serum monoclonal immunoglobulins assessed via immunofixation electrophoresis and normal κ/λ ratio. Very good partial response occurs when monoclonal light chains are less than 40 mg/L as determined by the difference between involved and uninvolved free-light chains (dFLC) [26], while partial response has been traditionally classified as the decrease in dFLC by 50% or more [6]. However, partial response is no longer considered satisfactory and at least very good partial response is a minimum requirement [8].

Merlini et al. [8] and Gertz et al. [29] presented an update on patient classification and treatment options. In cases with good performance status where limited organ involvement is documented, renal function is relatively preserved, and NT-proBNP and troponin T levels are less than 5000 ng/L and 0.06 ng/mL, respectively, then patients are classified as low risk (Table 6). Low-risk subjects are best treated with combination of high-dose melphalan followed by autologous blood stem cell transplantation (HDM/SCT) [5, 8, 10, 29, 30]. To combat the risk of death, stringent inclusion criteria for HDM/SCT were proposed (Table 6) and this treatment is generally limited to those aged below 65–70 years without severe heart failure. However, it has been shown to be successful with no difference in toxicity or survival in those aged over 65 years meeting stringent criteria (median age: 68 years; range, 65–79 years) [31]. In light of the relatively severe potential complications associated with HDM/SCT, much focus is currently being placed on discovery of alternative treatments providing high responses with low risk and prolonged survival.

The majority of patients with AL amyloidosis are intermediate-risk subjects who are treated with chemotherapy regimens, including standard chemotherapy with melphalan and dexamethasone (MDex) or cyclophosphamide, thalidomide and dexamethasone (CTD). Lately, investigations into the proteasome inhibitor bortezomib have demonstrated it to be a novel promising front-line therapy in intermediate-risk patients with AL amyloidosis [16, 17, 28, 32] and several bortezomib-based regimens are currently wide-

Table 6. Risk stratification and therapeutic strategies in AL amyloidosis (modified on the basis of Merlini et al. [8]; Gertz et al. [29]; Wechalekar et al. [30])

Low-risk (15–20% of patients):

- < 65–70 years of age
- performance status 0–2 by Eastern Cooperative Oncology Group (ECOG)
- NYHA functional class <3
- systolic blood pressure on standing >90 mmHg
- LV ejection fraction >45%
- NT-pro-BNP <5000 ng/L
- troponin T <0.06 ng/mL
- <3 organs involved
- serum creatinine \leq 1.7 mg/L or creatinine clearance >30 mL/min
- no amyloid-related gastrointestinal bleeding
- no large pleural effusion
- no dependency on oxygen therapy

High-dose melphalan + autologous stem cells transplantation (ASCT)

Risk-adjusted high-dose melphalan + ASCT + bortezomib consolidation

Intermediate-risk (60–65% of patients):

- NT-pro-BNP <8500 ng/L
- no fulfillment of **all** low-risk criteria

Standard therapy

- MDex (Melphalan + Dexamethasone)
- CTD (Cyclophosphamide + Thalidomide + Dexamethasone)

Bortezomib-based therapy

- CyBorDex (Cyclophosphamide + Bortezomib + Dexamethasone)
- CVD (Cyclophosphamide + Bortezomib + Dexamethasone)
- Melphalan + Dexamethasone + Bortezomib

High-risk (15–20% of patients):

- NT-pro-BNP >8500 ng/L

Cautious chemotherapy

- reduced-dose bortezomib + reduced dose dexamethasone
- risk-adjusted CyBorDex (Cyclophosphamide + Bortezomib + Dexamethasone)

ly used, e.g. CyBorDex (cyclophosphamide + bortezomib + dexamethasone) (Table 6).

High-risk patients with NT-proBNP greater than 8500 ng/L are recommended to undergo close monitoring, symptomatic supportive management and cautious chemotherapy with reduced-dose bortezomib combined with reduced dose dexamethasone, or risk-adjusted CyBorDex (Table 6). However, a lack of prospective studies in these fragile subjects limit definitive recommendations [8].

Symptomatic management

In patients with cardiac involvement, symptomatic treatment is warranted. Despite their effectiveness in the treatment of cardiac failure, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and beta-blockers are poorly tolerated in cardiac AL amyloidosis with severe hypotensive episodes after even low doses. This results from frequent autonomic nephropathy, hypoalbuminemia and an impaired ability of the non-complacent left ventricle to increase stroke volume. In addition, coexistent renal insufficiency limits the use of ACEI and ARB (Table 1). Although diuretics remain the mainstay of symp-

tomatic therapy in patients with fluid overload, they also should be used cautiously to prevent excessive hypovolemia [3, 5, 10]. On the other hand, diuretic resistance is common in nephrotic syndrome. The alpha-agonist midodrin and compression stockings are useful in symptomatic postural hypotension, while fludrocortisone is poorly tolerated due to fluid retention. Anticoagulation is recommended not only in patients with atrial fibrillation or intra-atrial thrombus but also upon detection of echocardiographic features suggesting atrial systolic dysfunction [10] (Table 5). Digoxin is generally discouraged because this drug binds to amyloid fibrils, which predisposes to arrhythmias. Nevertheless, in patients with atrial fibrillation with rapid ventricular response digoxin may be used with caution to control heart rate. Verapamil and diltiazem are also considered contraindicated owing both to a negative inotropic effect and their ability to bind to amyloid.

Implantable cardioverter-defibrillators, although recommended in malignant ventricular arrhythmias, have produced a little survival benefit in cardiac amyloidosis as a high proportion of sudden deaths are due to electromechanical dissociation [10]. When pacemaker implantation is planned due to a bradyarrhythmia, dual-chamber pacing should be considered to preserve the stroke volume of the non-dilated stiff left ventricle. In contrast, single-chamber right ventricular pacing might predispose to left ventricular underfilling and cardiac output depression.

Selected high-risk subjects with severe cardiac involvement but without renal, autonomic, respiratory and gastrointestinal disease manifestations may be considered for orthotopic cardiac transplantation followed by high-dose chemotherapy and ASCT [33].

Prognosis

Once congestive heart failure presents clinically, median survival is less than 6 months in untreated patients. About 2/3 of patients die from cardiac causes, with a similar proportion of sudden cardiac death (typically due to electromechanical dissociation) and death from progressive congestive heart failure [1]. Concomitant gastrointestinal system involvement (but not renal or neurological involvement) has been shown to have a small yet significant impact on survival in 232 consecutive patients with cardiac AL amyloidosis [1]. The percentage of bone marrow plasma cells of $\geq 10\%$ is also a recognized correlate of early mortality [29].

According to a multivariate analysis incorporating multiple cardiac biomarkers, overall survival was dependent only on troponin T, NT-proBNP, and dFLC [34]. In accordance with the results, an updated criterion was proposed for risk stratification and prediction of long-term survival in cardiac amyloidosis. Each prognostic variable (dFLC ≥ 180 mg/L, troponin T ≥ 0.025 ng/mL, NT-proBNP ≥ 1800 ng/L) was assigned 1 point and the sum was divided amongst 4 stages (I, II, III, IV) with scores of 0, 1, 2, 3, respectively. Correspondingly, these values correlated with a 5-year survival of 68%, 60%, 27% and 14%, which was equivalent to a median overall survival from diagnosis of 94 months, 40 months, 14 months and 6 months, respectively [34].

As far as novel imaging techniques are concerned, the magnitude of LGE on CMR was associated with prognosis. The lowest and highest mortality risk was found in those with no LGE and a trans-

mural LGE pattern, respectively, whereas an intermediate risk was observed in the presence of a subendocardial LGE pattern [35].

In treated patients with cardiac AL amyloidosis, both haematological remission (at least very good partial response or, optimally, complete response) [26] and adequate cardiac response to therapy have a favorable prognostic effect. In 2004, classical criteria for cardiac response to treatment were proposed, including a decrease of mean interventricular septal thickness decreases by 2 mm, 20% improvement in ejection fraction, improvement by NYHA 2 classes without an increase in diuretic use, and no increase in wall thickness [6]. However, these parameters depend largely on echocardiographic evaluation which may not be evident for years following treatment. Therefore the above presented criteria were replaced by a more robust index, i.e. reduction in NT-proBNP by both $>30\%$ and >300 ng/L if baseline NT-proBNP was ≥ 650 ng/L [26] and the only remaining 2004 criterion is currently NYHA class response (\geq two-class decrease if baseline NYHA class 3 or 4) [26]. Haematological response to chemotherapy was associated with a simultaneous fall in NT-proBNP and better survival [36]. With regard to renal response, it can be diagnosed at a 50% decrease in proteinuria (at least ≥ 0.5 g/day) in the absence of a decrease in glomerular filtration rate by $\geq 25\%$ [26]. Recently, a 75% fall in 24-h proteinuria was associated with a longer overall survival, whereas a 50% reduction did not coincide with decreased mortality compared to those with a decrease in proteinuria below 50% [37].

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