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Cardiac amyloidosis

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Cardiac involvement can be found in all types of amyloidosis, but is most frequent in AL amyloidosis. Severity of cardiac infiltration is by far the most relevant prognostic determinant. Once the heart is affected, amyloidosis carries a poor prognosis. Diagnosis is based on non-invasive testing such as ECG, echocardiography and cardiac MRI (CMR). However, endomyocardial biopsy is needed to unequivocally confirm cardiac infiltration and for immunohistochemical differentiation. Therapy primarily aims to reduce amyloid precursor proteins and treat end-organ failure. Specific cardiologic therapy is largely restricted to diuretics, anticoagulation and pacemaker implantation. In rare cases urgent heart transplantation followed by high-dose chemotherapy and stem cell transplantation can be considered.

Keywords: Cardiac amyloidosis, infiltrative cardiomyopathy, heart failure, diastolic dysfunction.

Introduction

Amyloid disease of the heart is the prototype of infiltrative heart diseases, a heterogeneous group of cardiomyopathies characterised by abnormal deposits causing ventricular wall thickening and progressively rigid walls that impede ventricular filling and result in diastolic dysfunction [1].

While other infiltrative cardiomyopathies usually affect children (e.g. Fabry disease, mucopolysaccharidosis), patients with cardiac amyloidosis most often present as adults and mostly beyond the fourth decade in age. Diastolic heart failure that results in dyspnoea and congestion is a leading symptom in all infiltrative cardiomyopathies. However, systemic involvement and thus morphological, cognitive and functional characteristics differ among disease entities.

Cardiac amyloidosis is characterised by the extracellular deposition and accumulation of relatively insoluble fibrillary proteins, with destruction of normal tissue structure and function [2–5]. There are at least 21 different precursor proteins for amyloid, and systemic organ involvement varies between the different types of amyloidoses [6]. Of these, light chain amyloidosis (AL), transthyretin amyloidosis (ATTR) and senile systemic amyloidosis (SSA) are most frequent. Secondary or reactive amyloidosis (AA) is not only more prevalent in developing countries due to the predominance of chronic infections [7], but is also associated with familiar Mediterranean fever and autoimmune diseases [8, 9].

Light chain amyloidosis (AL)

Light chain disorders are as frequent in women as in men and patients usually present beyond the fourth decade [10, 11]. Although almost any B-cell dyscrasia including lymphoma and macroglobulinaemia may result in AL amyloidosis, the majority of cases occur in the context of multiple myeloma [10]. Interestingly, most cases are associated with subtle and "benign" monoclonal gammopathies [10], and bone marrow aspirates of patients with AL amyloidosis usually show a 5–10% pool of clonal plasma cells. The paraprotein of these clones is misfolded and deposited in the tissue as amyloid. The ratio of kappa to lambda light chains (1:3) is nearly the reverse of the ratio usually seen for multiple myeloma (3:2) [7].

Being a systemic disease, AL amyloidosis can affect nearly every organ system and cardiac amyloidosis can be seen in up to 90% of patients [10]. Other organs affected are the kidneys (74%), liver (27%) and autonomic nervous system (18%) [7]. Involvement of the peripheral nervous system frequently results in carpal tunnel syndrome and painful sensory polyneuropathy. In rare cases relevant pulmonary involvement is reported [10, 12]. Purpura, especially periorbital ecchymoses as well as macroglossia, is less frequent but highly specific for the disease [13].

Transthyretin amyloidosis (ATTR)

ATTR amyloid deposits are derived from mutant transthyretin (mut-TTR) or wild-type transthyretin (wt-TTR), both originating in the liver [14]. There are about 100 different TTR mutations. Interestingly, the most common mutation, which is a substitution of isoleucin for valine (V122I), is almost exclusively recognised in African Americans [15, 16]. The predominant clinical manifestation of mut-ATTR is sensomotoric and/or autonomic neuropathy. Interestingly, symptoms of heart failure are often mild in mut-ATTR, even when severe

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cardiac infiltration is present [16]. It is therefore suspected that ATTR amyloid is less toxic than light chain deposits [17]. In patients with non-mutant wt-ATTR renal involvement is sparse and clinically relevant neuropathy is almost absent. Since this type of amyloidosis is frequently found in the elderly, it is commonly referred to as senile cardiac or senile systemic amyloidosis. Intriguingly, the male-to-female ratio for wt-ATTR is 20:1 [18].

Reactive amyloidosis (AA)

The precursor fibrils in AA are formed from the acute-phase reactant serum amyloid A and thus reactive amyloidosis is a sequela of chronic inflammation. It has become increasingly rare due to a decrease in chronic infections such as bronchiectasis, tuberculosis or leprosy [19, 20]. Nowadays, AA amyloidosis is primarily associated with rheumatoid arthritis, inflammatory bowel disease, sarcoidosis, seronegative spondyloarthropathy, as well as familial Mediterranean fever [21, 22]. In contrast to AL amyloidosis, cardiac infiltration with AA is unusual and although AA may result in heart failure and arrhythmias it rarely causes death [23].

Clinical manifestations

Cardiac amyloidosis primarily causes progressive biventricular diastolic dysfunction. Consequently, signs of heart failure, especially right heart failure are frequently found. Symptoms such as fatigue and dyspnoea on effort might be slight and unspecific in the beginning. Congestion leading to pulmonary effusion, elevated jugular venous pressure, hepatomegaly and profound peripheral oedema as well as ascites may follow later in the course of the disease. As the conduction system is usually affected, bradyarrhythmias resulting in dizziness or syncope and atrial fibrillation are typical findings. By contrast, complex tachyarrhythmias are rare, even in severe cases of heart failure with low systolic ejection fraction [24]. Also, systemic embolism is frequent, even in the absence of atrial fibrillation [25].

Non-cardiac findings are multiple and depend on the type of amyloidosis, with the most impressive appearance occurring in AL amyloidosis. Table 1 summarises cardiac as well as non-cardiac findings in amyloidosis.

Diagnosis of cardiac amyloidosis

Top priority in diagnosing cardiac amyloidosis is to remember to give it consideration, particularly when typical findings and organ manifestations are present (Fig. 1). A stepwise diagnostic approach including extended blood tests to search for monoclonal gammopathy is recommended whenever amyloidosis is suspected (Fig. 2). Since cardiac involvement is crucial for the prognosis and – in many cases – determines the therapeutic strategies, additional screening for cardiac amyloidosis is mandatory in all subtypes of amyloidosis.

Although electrocardiographic findings are not highly sensitive, they are typical and easily available. Pseudo-infarct pattern in anterior leads is a common finding (Fig. 1A). Low-voltage ECG along with left ventricular wall thickening is highly suspicious for infiltrative cardiomyopathies. Rhythm disorders such as atrial fibrillation or flutter, sinus arrhythmia and various degrees of AV block can be found. Reduced heart rate variability on 24-h holter ECG has been shown to be of prognostic value in AL and AA amyloidosis [26].

Echocardiography plays a key role in the diagnosis of infiltrative cardiomyopathy and reveals several typical findings in amyloid heart disease. Above all, concentric left ventricular wall thickening in the absence of arterial hypertension is highly diagnostic (Fig. 1B). A marked increase of the interventricular / interatrial septum, particularly when granular or sparkling appearance is evident, is typical and should sensitise to cardiac amyloidosis [27]. Except in severe stages, systolic left ventricular function is usually preserved. The hallmark of echocardiographic diagnosis is diastolic dysfunction, with a restrictive pattern on Doppler mitral inflow (Fig. 1C). Tissue Doppler is even more sensitive in detecting diastolic dysfunction and strain rate imaging is highly sensitive in detecting impaired longitudinal contraction, even in early stages [28, 29]. Biatrial dilatation, valvular thickening and pericardial effusion are more frequent later in the course of the disease [30]. Right ventricular dysfunction as determined by tricuspid annular plane systolic excursion (TAPSE) indicates disease

Tab. 1: Clinical, morphologic and laboratory findings in cardiac amyloidosis

Examination	Findings
Medical history	Chronic fatigue, weakness, dyspnoea, nocturia, dizziness, postural hypotension, resolution hypertension, syncope, peripheral polyneuropathic pain, chest discomfort, joint pain, diarrhoea and GI tract disturbance, family history of severe neuropathy, heart failure at young age
Physical examination & clinical presentation	Signs of heart failure: peripheral oedema, ascites, elevated venous pressure hepatomegaly, 3rd or 4th heart sound, skin lesions: petechia & bruising, nail dystrophy, "panda eyes", carpal tunnel syndrome, sensomotoric/autonomic polyneuropathy (ATTR) macroglossy, vitreous opacities
ECG profile	Low-voltage, pseudo-infarct pattern, sinus arrhythmia, atrial fibrillation/flutter, various types of AV block, reduced heart rate variability (24hour ECG), late after-potentials
Echocardiography	Wall thickening, granular "sparkling" appearance, thickened valves, thick interatrial septum, bi-atrial dilatation, normal to small ventricular chamber size, signs of diastolic heart failure: E/A ratio >2, reduced deceleration time (<150msec), reduced ventricular long axis shortening, normal to low systolic ejection fraction, pericardial & pleural effusion, atrial thrombi
MRI	Typical anatomic findings, normal or low ejection fraction, widespread delayed gadolinium enhancement including right ventricle and atria
Laboratory tests	Monoclonal gammopathy, free light chain elevation, plasma cell dyscrasia in bone marrow aspirates (AL), elevated serum troponin and/or BNP, proteinuria, renal impairment (nephrotic syndrome) coagulopathy, DNA analysis (familial types)

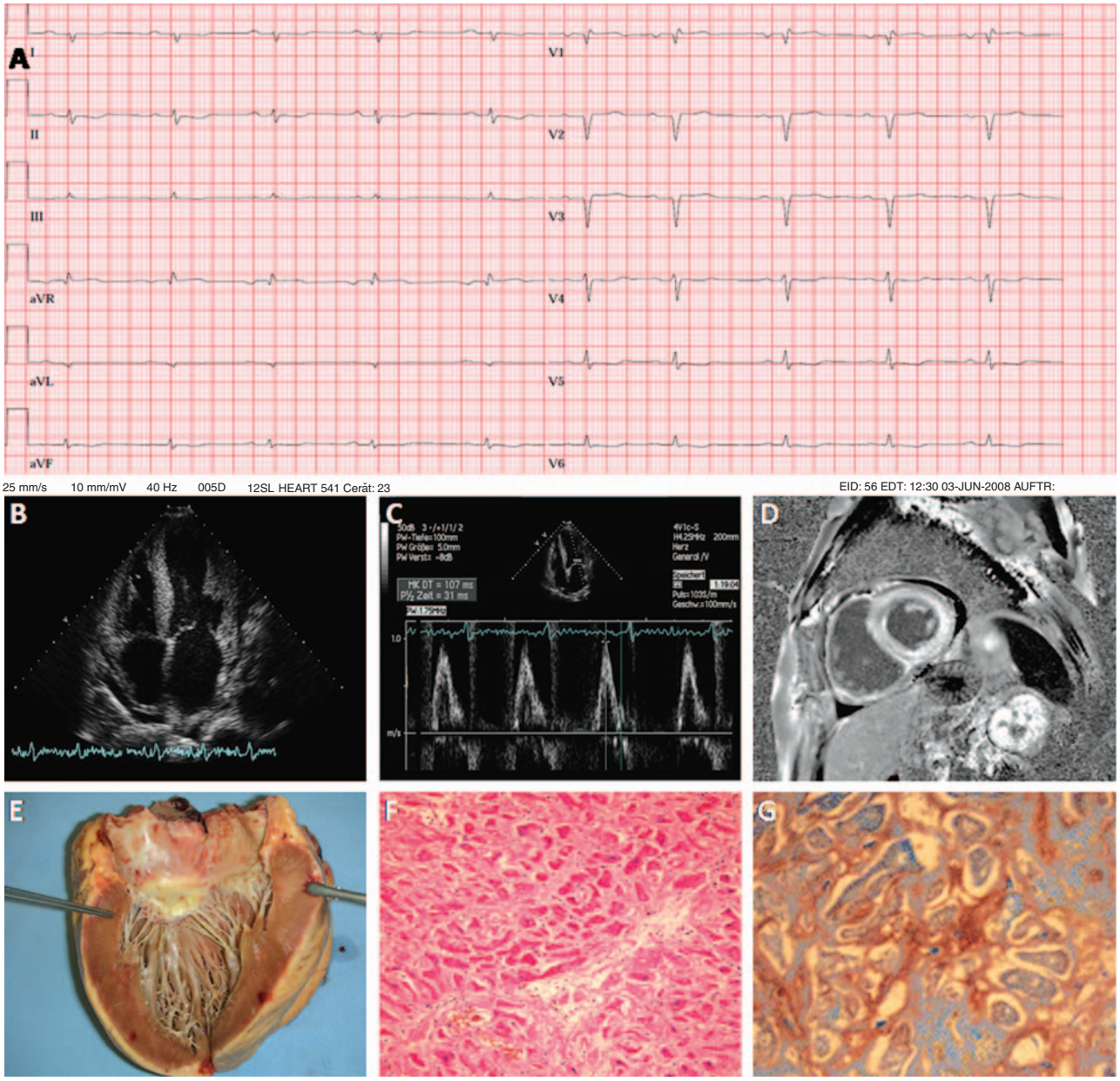

Fig. 1: Clinical and morphological findings in cardiac amyloidosis. (A) ECG: low-voltage and pseudo-infarct pattern. (B) Transthoracic echocardiography: four-chamber view with ventricular wall thickening, sparkling appearance and pericardial effusion. (C) Doppler echocardiography: E/A ratio >2, shortened E wave deceleration time in mitral valve inflow. (D) CMR at mid-ventricular level showing late enhancement, pericardial and pleural effusion. (E) Heart from autopsy showing marked left ventricular wall thickening. (F) Congo Red staining of endomyocardial biopsy with typical extracellular deposits. (G) Anti-κ immunoperoxidase staining of endomyocardial biopsy

progression and was shown to be associated with poor prognosis [31].

CMR is the gold standard in the armamentarium of non-invasive cardiac diagnostics. Cardiac amyloidosis has been shown to be associated with global and subendocardial, as well as localised or transmural late gadolinium enhancement in cardiac MRI (Fig. 1D) [32]. CMR provides excellent specificity, correlates with clinical findings or serological markers of heart failure and shows a high sensitivity in small cohorts [32–36].

Endomyocardial biopsy (EMB) should be performed whenever amyloid heart disease is suspected from non-invasive testing. EMB is safe in skilled hands, and its sensitivity in detecting amyloid is virtually 100% (Fig. 1F) [21]. It is of particular importance for the immunohistochemical evaluation of the underlying amyloid and hence plays a crucial role in therapeutic decision-making and risk stratification (Fig. 1G).

Prognosis and risk stratification

Although all types of amyloidosis may be associated with cardiac involvement, severity of cardiac symptoms and prognosis differ significantly between subtypes.

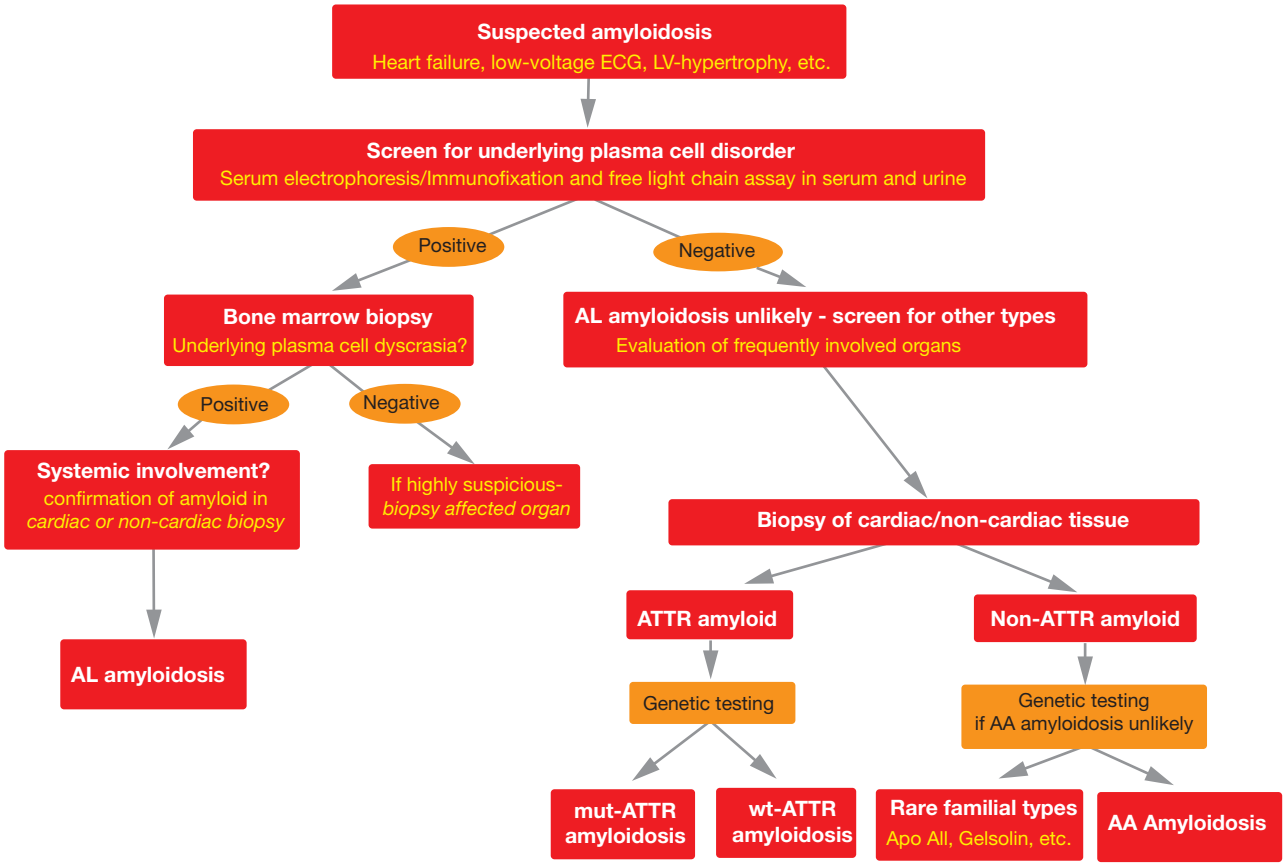

Fig. 2: Diagnostic algorithm outlining the evaluation of a patient with suspected cardiac amyloidosis; adapted from Falk 2005 [21]

Median survival of patients with symptomatic cardiac amyloidosis is less than two years, irrespective of the underlying subtype. AL amyloidosis clearly has the worst prognosis, with a median survival of less than six months after first manifestation of heart failure [37]. In AA amyloidosis prognosis is mostly related to the underlying disease, and the course in hereditary amyloidosis is distinctively associated with the underlying mutation [7, 10]. Reduction of left and/or right ventricular systolic function on echocardiography indicates poor prognosis [31]. Moreover, elevation of traditional risk factors such as BNP/NT-proBNP and troponins has been shown to be associated with poor outcome [38–40]. Staging of cardiac amyloidosis according to whether or not BNP and/or troponin are elevated is recommended [41]. Patients are at greatest risk (cardiac stage III) when troponin (TnT >0.035 µg/L or TnI >0.1 µg/L) and BNP (BNP >332 ng/L) are elevated. Patients are designated as being at medium risk (cardiac stage II) when they have at least one of the two markers above the cut-off, and patients with neither of the biomarkers elevated are considered to be at low risk (cardiac stage I) [41]. Most recently, the degree of late gadolinium enhancement in CMR was established as a potential risk marker [32].

Therapeutic options in cardiac amyloidosis

Therapy in cardiac amyloidosis aims to reduce amyloid precursor proteins and to treat end-organ failure.

AL amyloidosis

Reduction of amyloid precusor proteins is crucial for disease prognosis. During recent years various chemotherapeutic regimes were introduced for AL amyloidosis. Details on this issue are clearly beyond the scope of this review and can be found elsewhere in this issue. Basically, therapy is based on age, pre-existing organ dysfunction, performance state and organ involvement, in particular the presence of cardiac infiltration. Because of its eminent prognostic importance and the fact that cardiac involvement often limits therapeutic options, critical evaluation of cardiac function must always precede therapeutic decisions. In patients with significant cardiac involvement highly urgent heart transplantation followed by high-dose chemotherapy and stem cell transplantation seems to be the only virtually curative option [42]. Since this approach is associated with high morbidity, relevant multiorgan involvement must be excluded. Fig. 3 gives an algorithmic approach for therapeutic decisions in patients with AL amyloidosis For detailed information on available therapeutic options we refer to the corresponding article in this issue of the Journal.

ATTR amyloidosis

In ATTR amyloidosis the only specific treatment is liver transplantation. In rare cases of mut-ATTR amyloidosis concurrent transplantation of the heart and liver may be considered [42].

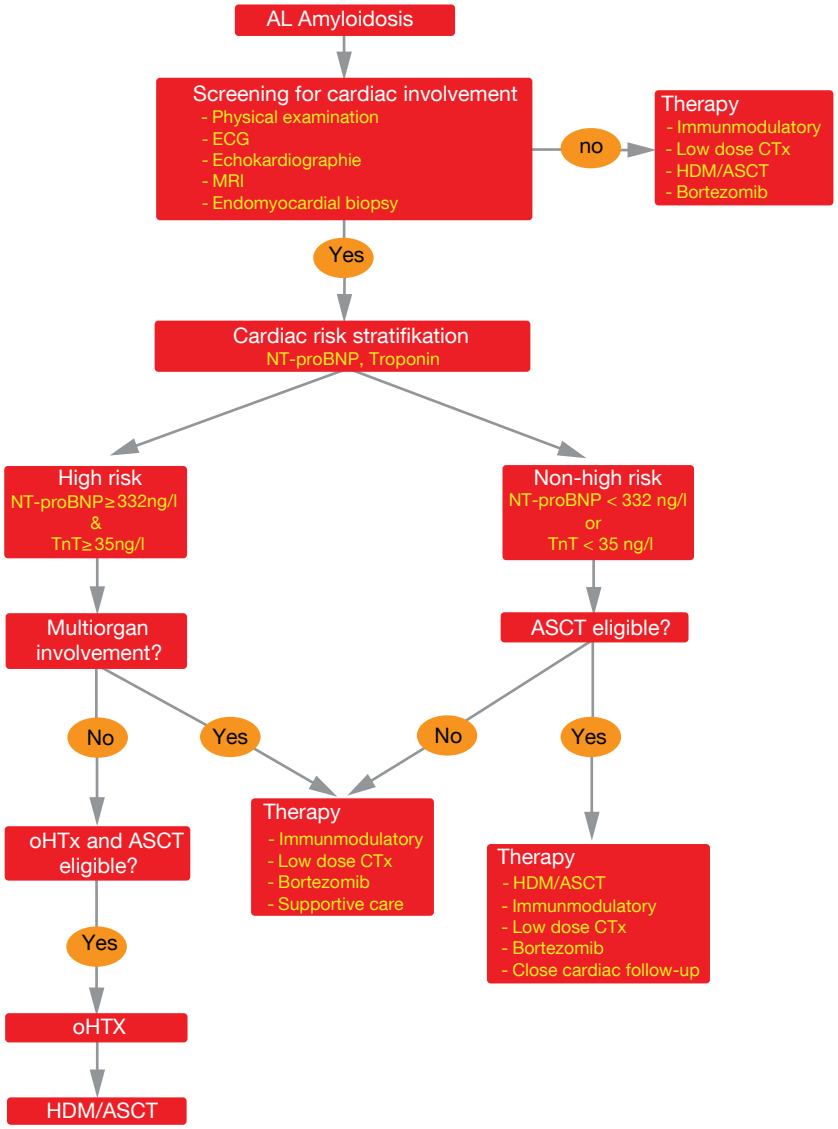

Fig. 3: Therapeutic algorithm in AL amyloidosis. CTx = chemotherapy; Immunmodulatory therapy = thalidomide, lenalidomide, pomalidomide; HDM/ASCT = high-dose melphalan and autologous stem cell transplantation; oHTx = orthotopic heart transplantation

Recently, green tea and its derivate epigallocatechin-3-gallate were suggested to reduce TTR amyloid deposits [43]. For patient convenience, polyphenol epigallocatechin-3-gallate is now also available in capsule form. Green tea may also be considered in AL amyloidosis, but must not be administered in parallel with chemotherapy [44]. Novel approaches including small-molecule ligands to stabilise transthyretin for prevention and therapy of ATTR amyloidosis are currently under investigation [16].

Secondary AA amyloidosis

Causal treatment in secondary amyloidosis aims to treat the underlying inflammatory disease. New biological agents that inhibit TNF-alpha or IL-1 potentially suppress the acute-phase response in rheumatoid arthritis, Crohn's disease or seronegative spondyloarthropathies [8]. In familial Mediterranean fever colchicine reduces the rate of AA amyloidosis [9]. Notably, the prognosis for AA amyloidosis is essentially better than for AL amyloidosis [16].

Cardiologic management

Therapy in cardiac amyloidosis differs substantially from standard heart failure treatment. Specific therapeutic options are rare and evidence from randomised trials evaluating standard heart failure therapy in this entity does not exist. Beta blocker therapy represents a cornerstone in heart failure treatment but seems not to be effective in amyloid heart disease. Beta blocker may be useful for controlling heart rate in atrial fibrillation but on the other hand may result in significant bradycardia based on pre-existing or developing infiltration of the conduction system. ACE inhibitors and angiotensin receptor blockers are usually poorly tolerated and even low dosages may cause severe hypotension. Also glycosides (digoxin, digitoxin), which are recommended in symptomatic

heart failure, are potentially harmful in cardiac amyloidosis. It has been shown that digoxin toxicity is increased because of interaction with amyloid fibrils, and even normal plasma levels may result in significant bradycardia [16]. Moreover, renal failure may further aggravate adverse effects. Considering the limited therapeutic options, symptomatic therapy with diuretics remains the cornerstone of cardiologic therapy in amyloid heart disease. Exact fluid management is challenging and close clinical follow-up as well as frequent adaptations of dosage is necessary to gain optimal balance between congestion, hypotension and renal impairment. Sequential nephron blockade with loop diuretics, thiazides and/or aldosteron antagonists are advised when progressive diuretic resistance ensues.

Due to the increased risk for cardioembolic events anticoagulation is advised, even in the absence of additional risk factors [21]. Basically, the indication for pacing is not different from that for other cardiac diseases, but the threshold for pacemaker implantation is often lower due to the progressive character of the disease. Sudden cardiac death is frequent in amyloidosis, although ventricular tachycardia may occur in the later stage of the disease. However, ICD implantation has not been shown to improve survival since death is usually due to electromechanical dissociation or progressive heart failure [24]. Heart transplantation as the final therapeutic option is limited to a select group of younger patients exclusive of multiorgan involvement.

Summary and perspectives

Cardiac involvement limits prognosis and therapeutic strategy in amyloidosis. Comprehensive cardiac assessment and risk stratification including biomarkers, non-invasive imaging and exact histopathologic definition of amyloid deposits are of paramount importance in the management of amyloidosis. Early diagnosis offers strategies with potential long-term survival like combined heart transplantation with concomitant high-dose chemotherapy followed by autologous stem cell transplantation in AL amyloidosis or combined liver and heart transplantation in ATTR amyloidosis. Novel chemotherapeutic regimens may offer improved prognosis, even in advanced stages of AL amyloidosis, and drugs to stabilise transthyretin may reduce disease progression.

Conflict of interest

The authors declare that there is no conflict of interest.

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