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Přehledový článek | Review article

Cardiac amyloidosis: A comprehensive review

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ABSTRACT

Cardiac amyloidosis is characterized by clinically significant extracellular amyloid infiltration of the heart that is usually, but not always, associated with the involvement of other organs depending on the type of amyloid. Cardiac involvement represents the most important prognostic factor especially in AL amyloidosis and thus early diagnosis of amyloid heart disease is of utmost importance influencing further management of the patients. This review aims to broadly discuss pathogenesis, manifestation and complex diagnostics of amyloidosis with the main focus on amyloid cardiomyopathy. Also, the summary of current therapeutic options that have great potential to improve existing poor prognosis of affected individuals is given.

SOUHRN

Srdeční amyloidóza je charakteristická klinicky významnou extracelulární depozicí amyloidu v srdečních tkáních, která bývá obvykle doprovázena i postižením dalších orgánů v závislosti na konkrétním typu amyloidového proteinu. Srdeční postižení je nejdůležitějším prognostickým faktorem přežívání nemocných, a to především s AL amyloidózou. Časná diagnostika srdeční amyloidózy je tak zcela zásadní pro volbu dalšího terapeutického postupu. Tento přehledový článek si klade za cíl informovat podrobně o patogenezi, projevech a metodách diagnostiky srdeční amyloidózy. Zároveň uvádí přehled současných terapeutických možností, které mají velký potenciál zlepšit dosud poměrně špatnou prognózu postižených jedinců.

Introduction

The amyloidoses are a group of diseases which are caused by extracellular deposition of a similarly appearing morphologically indistinguishable material called amyloid. Amyloid consists of approximately 95% of fibrils formed by an aggregation of misfolded insoluble proteins, the remaining 5% being the P component (pentameric protein, member of the pentraxins family of serum proteins) and other glycoproteins such as proteoglycans and sulfated glycosaminoglycans [1]. The protein fibrils can be made of more than 28 different unrelated proteins which misfold in parallel or as an alternative to physiologic folding.

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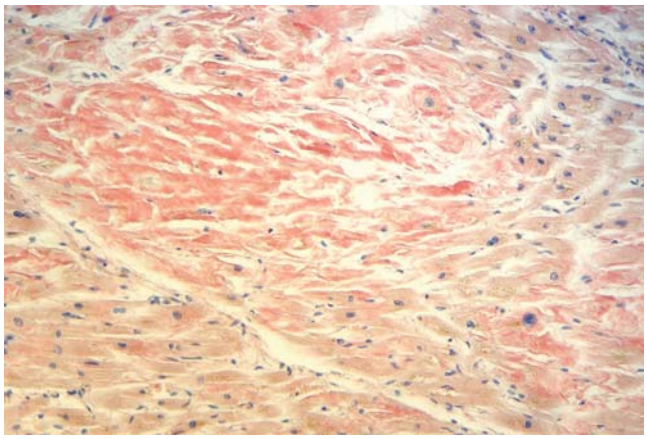

Fig. 1 – Amyloid infiltration of the myocardium (Congo red stain, original magnification × 200).

P component may contribute to amyloid deposition by stabilizing the fibrils and decreasing their clearance [2–4].

Under the light microscope the amyloid appears as an eosinophilic amorphous substance in hematoxylin-eosin stained sections. Amyloid binds Congo red dye and when stained produces apple green birefringence under polarized light, which is used as "gold" standard in diagnosis (Fig. 1) [1]. The affinity to Congo red dye is caused by special β-pleated sheet confirmation of amyloid, as could be seen by X-ray crystallography. Ultrastructurally, randomly oriented fibrils with a diameter of 7.5–10 nm can be shown by electron microscopy (Fig. 2). Thioflavin T is another molecule which binds amyloid fibrils but is less frequently used than Congo red. The Congo red staining and ultrastructural examination is used for routine histopathologic diagnosis; however, it cannot differentiate between amyloid subtypes [5].

The classification of amyloid is based on the immunohistolabeling techniques with a panel of antibodies against known amyloidogenic proteins or proteomics techniques (Fig. 3) [6–8].

Types of amyloidosis and heart involvement

Based on the spectrum of involved organs amyloid diseases can be divided into systemic amyloidosis, where amyloid deposits can be found in different organs and tissues, and localized forms with the deposits present in only one particular tissue or organ [9]. The nature of the diversity of organ and tissue involvement still remains unclear [10]. The heart is frequently the predominant organ affected; however, in some types of amyloidosis, isolated heart involvement can occur. Amyloid deposition in the heart may occur in all anatomical distributions, including the atria, ventricles, and perivascular space as well as valves and conduction system in some cases [11]. Regardless of the type of systemic amyloidosis, the presence and severity of amyloid cardiomyopathy is the major factor influencing prognosis of affected subjects [11–13]. According to consensus opinion from the 10th International Symposium on Amyloidosis, cardiac involvement is described as either a positive cardiac biopsy demonstrating amyloid infiltration or as an increased left ventricular (LV) wall thickness > 12 mm in the absence of arterial hypertension or other potential causes

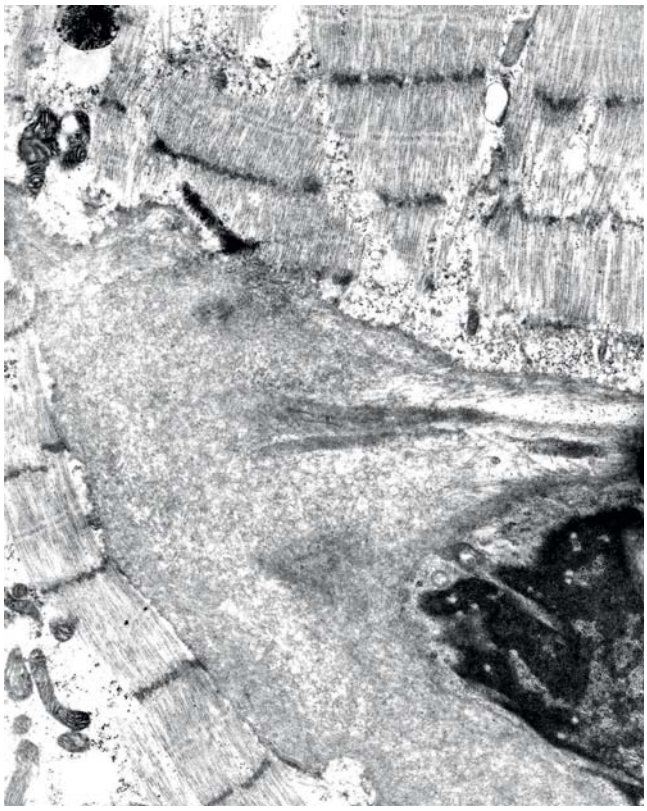

Fig. 2 – Electron microscopy of the myocardial specimen. A mesh formed from randomly oriented amyloid fibrils is located within the myocardium (original magnification × 6000).

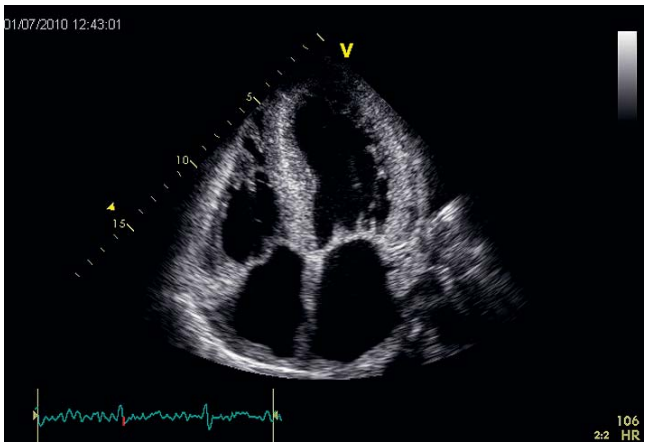

Fig. 3 – Transthoracic echocardiography demonstrating typical morphological findings in a patient with amyloid cardiomyopathy: the walls of non-dilated LV are concentrically thickened with increased echogenicity of the myocardium; thickening of RV free wall as well as of both dilated atria and interatrial septum is also seen; considerable thickening of mitral and tricuspid valve cusps is present (apical 4-chamber view). LV – left ventricle; RV – right ventricle.

of true LV hypertrophy with a positive non-cardiac biopsy [14]. Among amyloid types the ones affecting the heart are light-chain (AL) amyloidosis, familial amyloidoses, senile systemic amyloidosis (SSA), isolated atrial amyloidosis (IAA) and secondary (AA) amyloidosis (Table 1). The prognosis and treatment strategies are distinct for each of the dif-

Table 1 – Common systemic amyloidoses affecting the heart.

Type	Protein	Site of production	Organ involvement
Light chain (AL)	Light chain κ or λ	Bone marrow	Kidneys, heart, gastrointestinal tract, liver, nervous system, soft tissues
Familial	Mutant transthyretin	Liver	Nervous system, heart
Senile	Wild type transthyretin	Liver	Heart
Secondary (AA)	Serum amyloid A	Liver	Kidney, gastrointestinal tract, liver, spleen, nervous system (rarely heart)
Isolated atrial amyloid	Atrial natriuretic peptide	Atria	Atria

ferent types of amyloidosis. Therefore, precise diagnostics of the type of infiltrating amyloid is crucial with respect to further management of the patient.

Light chain (AL) amyloidosis

Light chain (AL) amyloidosis is the most commonly diagnosed form of amyloid disease in developed countries [15,16]. Both genders are nearly equally affected (with slight predominance of men over women) and the disease is usually diagnosed at the age of 55–60 years [17]. AL amyloidosis is associated with various B cell lymphoproliferative disorders encompassing the multiple myeloma-plasma cell dyscrasia spectrum and, on occasion, with malignant lymphomas and macroglobulinemia [9]. Rare forms of amyloid from heavy chain have also been reported [18]. Multiple myeloma coexists with AL amyloidosis in around 10–15% of cases and this scenario is associated with poorer prognosis [12]. In AL amyloidosis, monoclonal plasma cell population produces abnormal monoclonal light chains or more frequently their fragments which misfold to form amyloid. In vast majority of cases (69%), there is a systemic organ involvement in AL amyloidosis. Other than heart, kidneys are affected in approximately 74% of subjects, liver in 27%, peripheral nerves in 22% and autonomic nerves in 18%; nevertheless, virtually any tissue may be affected [6]. Macroglossia and periorbital purpura ("panda" or "raccoon eyes") represent typical and rather specific features of AL amyloidosis; however are present only in minority of cases [9]. Approximately 20% patients have symptomatic heart amyloidosis at the time of diagnosis; however, amyloid deposits may be found in autopsy or on endomyocardial biopsy in almost every affected subject. On the other hand, clinically isolated cardiac involvement is seen in less than 5% of cases [17]. The presence of amyloid heart infiltration portends the worst prognosis as compared to other organ involvement [13]. Although myocardial dysfunction is generally understood as a result of infiltration by extracellular amyloid deposits, there is experimental evidence that amyloidogenic light chains may also be inherently cytotoxic, possibly due to oxidative stress [19,20]. The diagnosis of AL cardiac amyloidosis is based either on the presence of typical noninvasive echocardiographic or on the cardiac magnetic resonance (CMR) findings together with the bioptic proof of amyloid in extracardiac tissue, or on the positive endomyocardial biopsy in patients with less clear results of the above mentioned imaging methods. Standard laboratory investigations include serum and urine protein electrophoresis and immunofixation as well as serum free light chain assay which quantify the aberrant circulating κ and λ free light chains (FLC). In AL amyloidosis, λ chains prevail over κ chains in a ratio of 3 : 1, which is different from multiple myeloma where this ratio is reversed to 2 : 3 [21]. Bone marrow biopsy plays an important role in determining the presence of multiple myeloma. Furthermore, plasma cell number and degree of clonality, together with the quantity of light chain and light chain isotype are related to prognosis [12,13,17].

Familial amyloidoses

Familial or hereditary systemic amyloidoses represent a group of autosomal dominant diseases with variable penetrance [12]. Vast majority of cases are associated with mutations in the gene for the plasma protein transthyretin (mTTR). Transthyretin is predominantly synthesized in liver with small portion being produced in choroid plexus. So far, more than 100 amyloidogenic missense point mutations have been identified, out of which 44 are associated with heart involvement [12]. Clinically apparent disease usually presents in middle or old age, with male to female ratio of 50 : 50 [22]. The majority of mTTR mutations are associated with cardiac and/or nervous system involvement [23]. Other organ manifestation is very rare, although carpal tunnel syndrome may be an early sign of the disease. Neuropathy is usually seen as a progressive sensorimotor and/or autonomic neuropathy and its clinical aspects predominate in majority of patients. Although cardiomyopathy is usually severe even before heart failure symptoms develop, it may not be diagnosed if the leading clinical manifestation is neuropathy and echocardiography is not performed [22]. The definite diagnosis of cardiac involvement in this type of amyloidosis requires the demonstration of pathological myocardial infiltration by endomyocardial biopsy. The two most commonly encountered mTTR mutations are methionine for valine at position 30 (Val 30 Met) which is present almost worldwide and isoleucine for valine at position 122 (Val 122 Ile). The latter mutation may be found in about 4% of the African American population and results predominantly in progressive severe amyloidotic cardiomyopathy with minimal or no neuropathy with onset in the late 60's in affected individuals [24,25].

Rare effects of familial non-transthyretin amyloidoses are caused by mutations in genes coding for fibrinogen, gelsolin, lysozyme and apolipoproteins A1 and A2. Fibrinogen and apolipoprotein mutations lead predominantly to amyloid renal disease, although in some patients, especially affected by apolipoprotein A1 mutation, progressive cardio-

myopathy and severe heart failure may occur [26]. Interestingly, gelsolin mutations, which are endemic in Finland and occur sporadically worldwide, are almost exclusively associated with cardiac conduction system disorders [27].

Senile systemic amyloidosis (SAA)

Wild type TTR/prealbumine (wTTR) represents the precursor protein of this type of amyloidosis [28]. It is a disease affecting almost exclusively men older than 65 years. The deposition of wTTR occurs predominantly in the heart [29]. Although this type of amyloidosis as already its name suggests is a systemic disease with deposits being found in the gastrointestinal tract, liver, spleen, bone marrow, tongue and endocrine glands, other clinically significant manifestations than cardiac amyloidosis and carpal tunnel syndrome are very rare. Therefore, presenting features are almost always considered to be symptoms of congestive heart failure and final diagnosis is usually based on positive endomyocardial biopsy. According to autopsy studies, 22–36% of individuals older than 80 years will have demonstrable amyloid deposits in the heart, but in the amount not sufficient to cause apparent myocardial dysfunction [30].

Isolated atrial amyloidosis (IAA)

In IAA, atrial natriuretic peptide is a precursor protein for amyloid formation and deposition, which occurs only in atria. This disease is the representative of a true localized form of amyloidosis not affecting any other organ [12]. Isolated atrial amyloidosis is thus a diagnosis that is almost always diagnosed only by autopsy as performing endomyocardial biopsy from the thin atrial wall is associated with unacceptably high risk of wall perforation. In contrast to SSA, it is usually a disease of elderly women [29]. The prevalence of IAA increases with age and reaching 95% in subjects of 81–90 years of age according to one autopsy study [29,31]. In spite of its high prevalence IAA does not represent a clinically significant type of amyloidosis, not-being usually responsible for eventual heart failure. However, some studies suggest its potential role in the development of atrial conduction defect and atrial fibrillation in older patients [32,33].

Secondary systemic (AA) amyloidosis

AA amyloidosis, formerly known as secondary amyloidosis, is an infrequent complication of chronic inflammatory states like rheumatoid arthritis, inflammatory bowel diseases, familial Mediterranean fever or chronic infective conditions such as tuberculosis. The amyloid fibrils are made of acute phase reactant protein, serum amyloid A (SAA), which is synthetized by liver. Renal disease represents the major clinical feature of AA amyloidosis. Although myocardial deposits may be often found in histology, clinically apparent cardiac involvement is very rare, occurring in about 2% of the affected subjects [34].

Clinical presentation and diagnosis of amyloid heart disease

As stated previously, cardiac involvement is associated with very ominous prognosis in almost all types of amyloidosis [12]. Making an early diagnosis of amyloid heart disease and its type is thus crucial with respect to subsequent management of affected individuals including the choice of therapeutic strategy as well as its efficiency, especially in AL amyloidosis. With an earlier diagnosis and less cardiac involvement, more aggressive treatment can be employed resulting in better long-term outcome for the patient [9].

Clinical features

The clinical findings in patients with cardiac amyloidosis may be divided into two groups: those directly arising from cardiac involvement and the features being the manifestation of extracardiac amyloid deposition. The presence of non-cardiac signs and symptoms may help a clinician not only to suspect amyloidosis to be possible underlying disorder but may also indicate the type of amyloidosis.

In AL amyloidosis, there is a tremendous amount of possible extracardiac findings, which may first seem to be completely unrelated and are a huge challenge for the diagnosing physician to join all of them into one correct diagnosis. Macroglossia is almost pathognomic for AL amyloidosis, but is present only in about 10% of cases [35]. Periorbital purpura and petechial lesions of eyelids are the result of vascular fragility. Carpal tunnel syndrome, peripheral and autonomic neuropathy, nail dystrophy, cutis laxa, weight loss, disturbance of bowel movements and general weakness and fatigue represent other typical, although nonspecific systemic symptoms [12]. Kidney and liver involvement is common in AL amyloidosis. Heavy proteinuria should always raise suspicion for amyloid renal disease [36]. On the other hand, neuropathy and/or cardiomyopathy are two predominant manifestations of familial transthyretin amyloidosis as mTTR preferentially affects the heart and nervous system [37]. Nephropathy is very rarely present. Neural involvement results in a progressive sensorimotor neuropathy, sometimes with some degree of autonomic neuropathy. As mentioned before, neurological symptoms often dominate the clinical picture in familial transthyretin amyloidosis because of the absence of heart failure symptoms despite severe myocardial infiltration [38]. In senile systemic amyloidosis, carpal tunnel syndrome represents the only common accompanying, clinically apparent extracardiac manifestation [22]. Other systemic features like renal and pulmonic involvement are exceptional. Secondary AA amyloidosis is associated with chronic inflammatory conditions and thus the signs and symptoms of this underlying disorder initially form the clinical picture. Renal involvement manifesting by proteinuria dominate in AA amyloidosis and cardiac dysfunction is very rarely seen [9,34].

The classical clinical presentation of cardiac amyloidosis represents the signs and symptoms of congestive heart failure. Myocardial deposition of amyloid causes progressive thickening of ventricular walls that primarily results in the deterioration of ventricular filling with later worsening of global systolic function in advanced stages. As the disease affects both ventricles, biventricular heart failure is usually present although the features of right-sided heart failure almost always predominate [22]. Peripheral edema, congestive hepatomegaly and elevated jugular pressure together with some degree of dyspnea and fati-

gue are common presenting signs and symptoms of amyloid cardiomyopathy. Ascites is often present in advanced disease. Pleural effusion may be a result of congestion as well as of amyloid infiltration of the pleura which may be indicated by its frequent recurrences [39]. Typically, tendency to low blood pressure and postural hypotension is present in affected patients. This is due to low cardiac output together with the peripheral vasomotor dysfunction caused by autonomic neuropathy [40]. The appearance of syncope or palpitations should lead to investigation for their arrhythmic origin as amyloid deposition also occurs in the conduction system. Atrial arrhythmias, most commonly atrial fibrillation, are detected in 10–15% of patients and tend to occur late in the disease [22,33]. Atrial fibrillation is associated with a very high incidence of thromboembolism and its onset may also lead to rapid hemodynamic deterioration. In advanced stages, atrial thrombi may even form despite the presence of the sinus rhythm. This is due to atrial standstill which is the result of atrial electromechanical dissociation in the setting of severe infiltration of atrial walls [34,41,42]. The amyloid deposition in small coronary vessels may result in the impairment of myocardial flow reserve that rarely manifests as chest pain [43]. The two most often causes of death in patients with cardiac AL amyloidosis are progressive heart failure and sudden cardiac death [9]. The latter one is usually due to electromechanical dissociation rather than ventricular arrhythmia [11,44–46].

Echocardiography

Echocardiography plays a key role in diagnosing cardiac amyloidosis as it provides comprehensive morphological and functional assessment of the heart. However, one should always remember, that "classical" features of amyloid cardiomyopathy are present only in advanced phases of the diseases [9,47]. There is a wide spectrum of echocardiographic findings out of which none is itself specific and thus they should be interpreted in the context of the clinical picture and other investigations. Echocardiography cannot confirm diagnosis in isolation and also is not able to distinguish between various types of amyloidosis [11].

Amyloid infiltration typically leads to the thickening of ventricular walls (Fig. 3). Usually there is a concentric pattern of increased wall thickness but sometimes, at early stages, only interventricular septum may be thickened. Because LV cavity is not dilated, the term "concentric hypertrophy" is incorrectly used as the pathological process is amyloid deposition, not myocyte hypertrophy [48–50]. Thickening of the LV wall has of course poor specificity for amyloidosis as it also occurs in other conditions, such as hypertensive heart disease, hypertrophic cardiomyopathy and other infiltrative cardiomyopathies. The contemporary presence of RV wall thickening and, more importantly, the absence of high ECG voltages favors the diagnosis of infiltrative disorder, of which amyloidosis is the most common [51].

Increased echogenicity of thickened ventricular myocardium, also referred to "granular" or "sparkling" appearance, has been reported in several studies [52–54]. However, this phenomenon can occur in other causes of LV hypertrophy and its specificity is probably not sufficiently high. Moreover, this granular pattern is seen only on standard echocardiographic imaging, because scanning with tissue harmonic frequencies imparts increased echogenicity of myocardium in general [9].

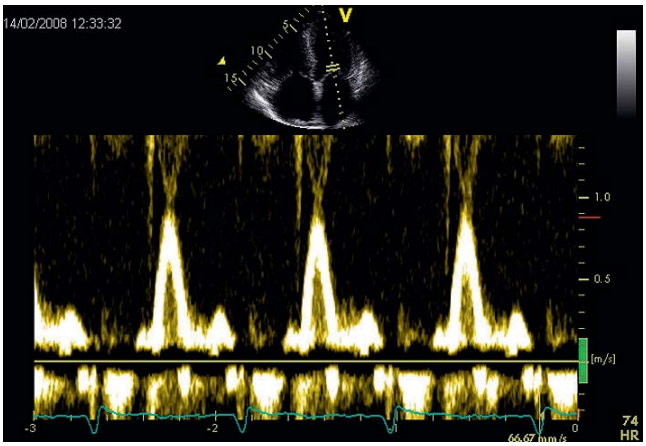

Fig. 4 – Transthoracic echocardiography demonstrating LV restrictive filling pattern in a patient with amyloid cardiomyopathy. The dominance of early mitral inflow velocity with decreased deceleration time < 150 ms is seen (apical 4-chamber view).

Diastolic dysfunction is the hallmark of amyloid heart disease [55–57]. Traditionally, restrictive pattern of left ventricular filling indicating increased ventricular stiffness with high filling pressures is regarded as pathognomic for amyloid cardiomyopathy (Fig. 4). However, this most severe impairment of diastolic function is present in advanced stages of myocardial infiltration [50]. Mild to moderate LV diastolic dysfunction may be detected earlier in the course of the disease. Therefore, the absence of restrictive filling pattern type as such should not lead the cardiologist to exclude the diagnosis of amyloidosis if other echocardiographic and clinical features and investigations, for example low voltage ECG, are present. In agreement with this, according to the current European classification of cardiomyopathies, amyloid cardiomyopathy may be regarded either as hypertrophic or restrictive cardiomyopathy based on the severity of diastolic filling impairment [58].

Global LV systolic function as assessed by ejection fraction is usually normal until the more severe stages of the disease are present [9,11]. However, longitudinal contractile dysfunction that can be evaluated either by mitral annular displacement or velocity or by deformation imaging is present early in the course of amyloid cardiomyopathy. Importantly, decreased longitudinal contractile function of LV walls is disproportionately severe compared to other types of LV hypertrophy with preserved ejection fraction [59–61].

The dilatation of atria caused by high ventricular filling pressures is often present, but it is not specific for amyloid cardiomyopathy [49]. As mentioned earlier, thrombi may form within the atria due to their standstill. High LV filling pressures lead to significant postcapillary pulmonary hypertension and this may result in right ventricular cavity enlargement.

As amyloid deposition occurs in the whole heart, thickened valves and interatrial septum may be noted in some

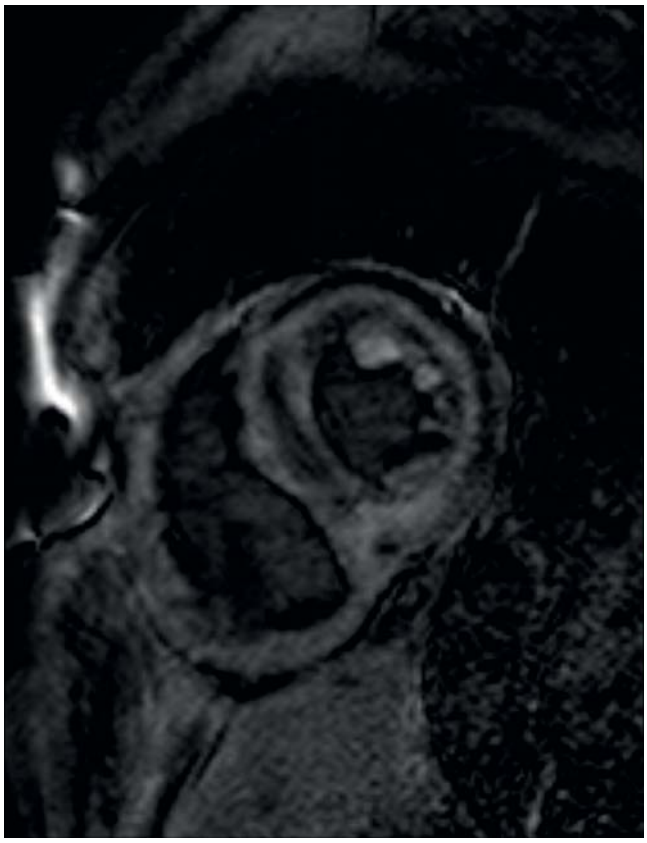

Fig. 5 – Magnetic resonance imaging of amyloid cardiomyopathy. A typical global subendocardial late gadolinium enhancement of the LV walls is present together with enhancement of RV free wall (short axis view). LV – left ventricle.

patients, especially in more advanced disease [62]. The thickening of valve leaflets does not lead to hemodynamically significant regurgitant lesions [12]. There are some case reports in the literature on the occurrence of systolic anterior motion of anterior mitral leaflet in amyloid cardiomyopathy, resulting in dynamic LV outflow obstruction; however, this phenomenon is definitely exceptional in this disease [63]. Pericardial effusion is found in 40–60% of patients [64]. It is usually small and reflects high right atrial pressure although pericardial infiltration by amyloid may also play a role.

To summarize, echocardiography can provide many features suggesting amyloid heart disease though none of them are absolutely specific. The presence of several echocardiographic findings increases the likelihood of the diagnosis, especially the combination of markedly increased walls of nondilated LV with restrictive filling pattern, biatrial enlargement, thickened valves and pericardial effusion [65]. However, most useful approach is to combine echocardiographic findings with results of other investigations like ECG and CMR.

Magnetic resonance imaging

In the last few years, CMR has emerged as very useful imaging modality in diagnosis of cardiac amyloidosis. Compared to echocardiography, CMR more accurately measures the thickness and volumes of both ventricles. It is also able to assess biatrial dilatation, interatrial septal thickness, the presence of pericardial effusion and, by using phase-velocity mapping, to evaluate LV filling [66]. However, major and unique advantage of CMR is the possibility of tissue characterization by late gadolinium enhancement (LGE). First study interested in the use of

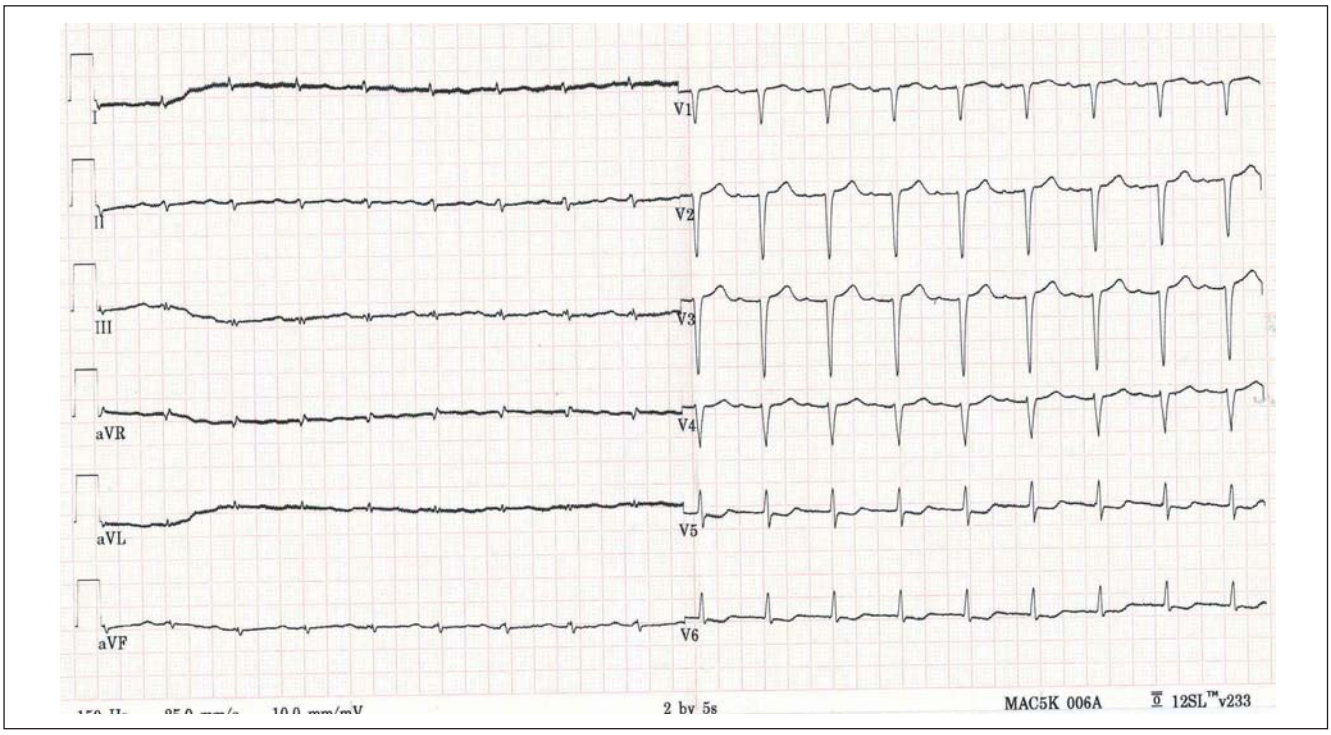

Fig. 6 – A typical ECG in the patient with amyloid heart disease. Low voltage of QRS complexes with amplitude ≤ 0.5 mV in limb leads and pseudo-infarct pattern in precordial leads.

LGE in patients with cardiac amyloidosis has suggested the global subendocardial LGE pattern to be pathognomic pattern for amyloid heart disease (Figs. 5 and 6) [67]. Nevertheless, other authors have shown that several LGE patterns, localized or diffuse, and subendocardial or transmural may be present in patients with amyloid cardiomyopathy [68,69]. The histological basis for LGE is interstitial expansion from amyloid infiltration as demonstrated by Maceira et al. [67]. The prevalence of LGE in patients with cardiac amyloidosis has been reported from 69% to 97% [67–69]. Based on the results of the studies published so far one may summarize that global subendocardial to transmural LGE pattern is most common, being present in 80–85% of affected individuals, and represent unique CMR feature that may noninvasively "phenotype" cardiac amyloidosis. Myocardial and blood pool kinetics of gadolinium uptake are also unusual in patients with cardiac amyloidosis with similar myocardial and blood T1 relaxation values as a result of high myocardial uptake and fast blood pool washout. Therefore, blood pool has atypically dark appearance in LGE images and the selection of the appropriate inversion time may be difficult [67,69,70]. If suboptimal "nulling" of the hypertrophied myocardium occurs, amyloid infiltration shall be suspected. Future studies shall prove if highly sensitive LGE imaging may help to discover subclinical early cardiac involvement that cannot be depicted by echocardiography, however, first results are promising [69].

ECG

In 46–71% of patients with AL cardiac amyloidosis, ECG shows typical picture of low voltage of QRS complexes defined as QRS voltage amplitude $\leq$ 0.5 mV in all limb leads or $\leq$ 1.0 mV in all precordial leads [12,71]. This contrasts with marked increase in LV wall thickness seen by imaging techniques, which is, however, caused by extracellular amyloid deposition and not a result of true myocyte hypertrophy as in hypertensive heart disease or hypertrophic cardiomyopathy. Therefore, as stated previously, the combination of increased LV wall thickness on the echocardiogram with low ECG voltage is highly suggestive for infiltrative process, especially AL or familial amyloidosis [17,22,51]. Pseudo-infarct pattern may be present in half of affected subjects, most often in anterior precordial leads. Both low ECG voltage and pseudo-infarct pattern are expressed in about 25% cases [12,71]. Surprisingly, sinus rhythm is present in majority of patients, although atrial fibrillation and conduction system disease may occur. On the other hand, the patients with senile systemic amyloidosis may have normal ECG voltage, often with left anterior hemiblock pattern [9], and atrial fibrillation and flutter are common [22]. Also, conduction disorders requiring an implantation of permanent pacemaker are frequent in these individuals [22]. In patients with AL cardiac amyloidosis, signal-averaged ECG is often abnormal and heart variability on 24-h ECG monitoring is reduced, both of which may be related to the risk of sudden death [72,73].

Right heart catheterization

Because of sufficient amount of data derived from imaging methods such as echocardiography and magnetic resonance with which cardiac morphology and function is described with high accuracy, invasive cardiologic examination is currently performed only when endomyocardial biopsy is indicated or in rare unclear cases, typically in order to differentiate constrictive pericarditis as the other cause of congestive heart failure [11]. In typical advanced stages of amyloid cardiomyopathy, left and right heart catheterization confirms the presence of restrictive hemodynamics. This is characterized by rapid and sustained elevation of diastolic ventricular pressures (so called dip-and-plateau configuration or "square root sign") with equalization of ventricular and atrial pressures at end-diastole [74]. Similar pattern is also seen in constrictive pericarditis. However, the difference between left and right ventricular end-diastolic pressures is less than 5 mmHg, right ventricular systolic pressure is less than 50 mmHg and the ratio of right ventricular end-diastolic to systolic pressure is more than 1/3 all favors constriction. The most important hemodynamic sign, that differentiates restriction from constriction, is concordant behavior of systolic ventricular pressures during respiration in restriction, while in constriction respiratory discordance of left and right ventricular pressure curves is seen in systole due to increased ventricular dependence [75].

Laboratory examination and biomarkers

Standard blood tests represent an essential part of examinations in suspected amyloidosis and shall include the assessment of urea and creatinine levels, liver enzymes, glucose, thyroid function tests, CRP, full blood count and blood clotting tests together with the analysis of serum and urine for the presence of an abnormal monoclonal immunoglobulin. Unfortunately, standard serum protein electrophoresis does not detect a monoclonal band in many cases of AL amyloidosis as the amount of paraprotein is small [11,12]. Immunofixation is more sensitive than plain electrophoresis and should always be performed [12,14]. However, even with immunofixation, in about 20% of affected subjects the circulating paraprotein will not be detected [12,35].

Today, a serum immunoglobulin free light chain (FLC) assay has become most useful laboratory method not only for establishing the diagnosis, but also for prognostic and follow-up of AL amyloidosis [76,77]. The quantitative analysis of κ and λ FLCs levels is declared to be 10 times more sensitive than immunofixation electrophoresis for the detection of circulating paraprotein [78,79]. Normal FLCs values basically disprove the diagnosis of AL amyloidosis [12]. Importantly, the ratio of κ to λ should always be assessed. With renal impairment, serum levels of both κ and λ FLCs are increased and their ratio remains unchanged. On the contrary, monoclonal production of paraprotein κ or λ significantly alters FLC ratio. Compared to multiple myeloma, the predominance of λ over κ chains is more common in AL amyloidosis leading to λ to κ ratio approximately 3 : 1 [80]. When examining monoclonal protein one must be aware that abnormal FLC assay is not specific for AL amyloidosis. Monoclonal FLCs are found in about 50% of patients with monoclonal gammopathy of unknown significance (MGUS), which is present in 5–10% of elderly individuals [11,81]. Nevertheless, the FLC ratio is generally much less abnormal in MGUS then in AL amy-

loidosis [82]. Of course, all patients with multiple myeloma express monoclonal FLCs.

Cardiac biomarkers represented by troponins and N-terminal of BNP (NT-proBNP) are elevated in patients with amyloid heart disease. In AL amyloidosis, NT-proBNP levels are often elevated disproportionately to the severity of symptoms of congestive heart failure [83]. This may be due to the fact that elevation of NT-proBNP levels is not only a result of heart failure but may reflect hormone production by myocytes that are compressed by extracellular amyloid deposits [84]. Troponins and NT-proBNP or BNP provide important prognostic information in AL amyloidosis and are currently used for staging the severity of organ involvement in AL amyloidosis and in connection with this for stratification of patients regarding their suitability and risk for high-dose chemotherapy and autologous stem cell transplantation (ASCT) [85–88]. Importantly, NT-proBNP levels seem to be useful for monitoring of disease progression and response to therapy. Palladini et al. have shown that significant reduction in NT-proBNP levels by 30% early in the course of chemotherapy has been associated with improved event-free survival of patients with AL amyloidosis [89]. However, the exact value of serial monitoring of cardiac biomarkers has yet to be determined by further studies.

Extracardiac and endomyocardial biopsy

The diagnosis of amyloidosis requires histologic demonstration of amyloid deposits and subtyping of amyloid. Because of safety reasons, extracardiac biopsy shall be the first step. In practice the specimen may be taken either non-specifically from rectal mucosa or abdominal fat or biopsy is targeted to the presumably involved organ or tissue like kidney, liver or peripheral nerve. The positivity of extracardiac biopsy together with the presence of typical echocardiographic or MRI findings, especially in otherwise unexplained thickening of LV walls, makes the diagnosis of amyloid heart disease almost certain and cardiac biopsy is not necessary [77,90]. Nevertheless, this applies almost exclusively for the diagnosis of AL amyloidosis because of its common systemic nature and in the case of rarely performed peripheral nerve biopsy also for familial mTTR amyloidosis. If extracardiac biopsy is negative and the results of other examinations are suggestive for amyloid cardiomyopathy, then endomyocardial biopsy must be performed [7,91,92]. The presence of amyloid deposits in any biopsy specimen is firstly confirmed or excluded by Congo red dye and in the case of positivity with apple-green birefringence when placed under polarized light. In case of small scarce deposits other techniques such as modified Sirius red staining could be used [93]. As an additional technique, electron microscopy examination is usually performed [94].

Once the presence of amyloid is confirmed, it is absolutely necessary to determine the type of amyloid as this determined the treatment [95]. The next step is then the classification of amyloid based on the immunohistolabeling techniques with panel of antibodies against known amyloidogenic proteins (usually initial and secondary panel). Immunoperoxidase staining used with formalin-fixed paraffin embedded tissue and immunofluorescence staining typically performed on fresh frozen tissue are used. Since there are reports of low success rates of immunoperoxidase staining with commercially available antibodies mainly in case of light chains, the use of immunofluorescence technique is recommended [96].

Whenever AL amyloidosis is diagnosed, the bone marrow biopsy is routinely performed to exclude the coexistence of multiple myeloma.

Scintigraphy

Radiolabelled serum amyloid P component (SAP) scintigraphy is a method capable of evaluating the whole-body-amyloid-burden [38]. Serum amyloid P component is a plasma glycoprotein of the pentraxin family which is specifically concentrated in amyloid deposits of all types [1,10]. If 123 I-labelled P component is supplied intravenously, it distributes between the circulating and the amyloid-bound SAP pools in proportion to their size and can be imaged and quantified on a gamma camera [97]. This method thus provides the information on the distribution as well as the extent of amyloid deposits throughout the body. Also regression of amyloid infiltration may be documented by SAP scintigraphy when the supply of the culprit amyloid precursor protein is significantly reduced [98]. Unfortunately, SAP scintigraphy is not able to image in the moving heart due to blood pool uptake [99]. Another disadvantage of the use of radiolabelled P component arises from its possible infectious risk as SAP is obtained from blood donors [38,98]. Currently, SAP scintigraphy is used only in few centers, mainly in Great Britain. 99m-Tc-aprotinin has been shown to be fairly specific for cardiac amyloidosis; however, the experience with its use is limited [100].

Recently, Perugini et al. have demonstrated, that 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid, a bone scanning agent, is significantly taken up by the myocardium infiltrated by transthyretin amyloid [101]. As shown also by other authors, dicarboxypropane diphosphonate (DPD) scintigraphy may thus serve as very elegant noninvasive test for the presence of transthyretin cardiac amyloidosis and help to differentiate it from AL amyloidosis, in which myocardial uptake of DPD is minimal [102,103].

Therapy

Therapeutic approach to cardiac amyloidosis is generally twofold: supportive care including therapy of congestive heart failure and treatment to abrogate the amyloid process with the aim to prevent further deposition of amyloid.

Congestive heart failure and other cardiac therapy

Restricted salt intake and loop diuretics together with aldosterone antagonists like spironolactone or eplerenone are the mainstay of heart failure therapy [9,11,22]. In patients with severe congestion and/or nephrotic syndrome, high doses of diuretics are usually necessary [9]. However, their use may lead to under-filling of small and stiff LV with further reduction of already compromised cardiac output and consequently to hypotension, vertigo, syncope as well as prerenal worsening of renal function [9]. Therefore, significant attention shall be paid to fluid

Table 2 – The consensus criteria for hematologic and organ response in AL amyloidosis according to the 12th International Symposium on Amyloidosis [114].

Response type	Criteria
Hematologic response	
Complete response	Negative serum and urine immunofixation electrophoresis normal κ/λ ratio
Very good partial response	dFLC < 40 mg/L
Partial response	dFLC decrease ≥ 50%
No response	Other
Organ response	
Heart	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in LVEF, improvement by two NYHA classes without an increase in diuretic use, and no increase in wall thickness and/or a reduction (≥ 30% and ≥ 300 ng/L) of NT-proBNP in patients in whom the eGFR is ≥ 45 mL/min/1.73 m^2
Kidney	50% decrease in 24-hour urinary protein excretion in the absence of a reduction in eGFR ≥ 25% or an increase in serum creatinine ≥ 0.5 mg/dL
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm

dFLC – difference in concentration between involved and uninvolved free light chains; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association.

balance, with daily weight measurements and careful adjustment of diuretic dose. Hypotension is common especially in AL cardiac amyloidosis [22]. This is due to low cardiac output, autonomic neuropathy or to impaired vascular tone caused by amyloid infiltration. Ortostatic hypotension accompanied by peripheral edema may respond to thigh-high support stockings [12]. Midodrine, an α-agonist, can be effective if autonomic neuropathy is present [104]. On the other hand, fludrocortizone is not recommended because of its sodium retaining effect that worsens congestion [22]. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are generally poorly tolerated as they can lead to profound hypotension namely in AL amyloidosis because vascular tone is disproportionately dependent on angiotensin receptors due to impaired sympathetic nervous system function in this condition [9,11]. Beta-blockers are also not a standard part of heart failure therapy in cardiac amyloidosis as they may worsen hypotension and decrease myocardial contractility due to their negative inotropic effect [11,22]. One possible exception for use of cautiously dosage beta-blockers represents rate control of atrial fibrillation. Recently, an interesting study has been published demonstrating a positive effect of carvedilol treatment on mTTR deposition in a familial amyloidotic polyneuropathy mouse model [105]. Digoxin and some calcium channel blockers bind to amyloid fibrils thus increasing susceptibility to digoxin toxicity and to negative inotropic effects of calcium blockers [106,107]. Therefore, these drugs are contraindicated in cardiac amyloidosis, again with possible exception for low dose and carefully monitored digoxin therapy in atrial fibrillation with rapid ventricular response. Amiodarone seems to be relatively well tolerated when used for rate-control therapy in patients with atrial fibrillation [108]. In some studies in AL amyloidosis, amiodarone has been given with aim to prevent ventricular arrhythmias, but so far no solid data exist whether its use in this indication is of any significance in amyloid heart disease [109]. Rhythm-control of atrial fibrillation either with amiodarone or with catheter ablation techniques is ineffective due to abnormal atrial electrical properties [108]. Anticoagulation therapy using warfarin is absolutely indicated in patients with atrial fibrillation and flutter or after cardioembolic episode. Importantly, anticoagulation shall be administered also in the setting of sinus rhythm, when echocardiographic signs of minimal or absent atrial mechanical activity are present as the prevalence of atrial thrombi and the risk of embolic event are considerably high [41,110]. The presence of advanced atrioventricular block necessitates the implantation of permanent pacemaker. Although not an indication supported by current guidelines, strong consideration should be given to biventricular pacing as conventional right ventricular pacing may lead to LV dyssynchrony and thus further decrease the stroke volume [9,22,111]. Most cases of sudden cardiac death in amyloidosis are due to electromechanical dissociation and thus implantation of cardioverter-defibrillator is less successful in prevention of fatal arrhythmic events [44,46,112,113]. The study from Mayo Clinic clearly showed that despite high rate of appropriate shocks in patients with cardiac amyloidosis, mainly AL, this therapy did not lead to survival benefit [46].

Specific treatment of systemic amyloidoses

AL amyloidosis

Early diagnosis is a key prerequisite for effective therapy of AL amyloidosis allowing stabilization or even reversal of the organ damage and minimization of treatment toxicity. Current therapies are targeted to eradicate the pathologic plasma cells and to eliminate misfolded free light chains [114]. This can lead to regression of amyloid deposits with consequent organ improvement and extended survival. The efficacy of a treatment is assessed by hematologic response, which reflects reduction in the burden of plasma cell disease, and by organ response representing improvement in the organ function. The consensus criteria for hematologic and organ response were recently updated at the 12th International Symposium on Amyloidosis and are summarized in Table 2 [114].

The extent of cardiac involvement is the major determinant of prognosis in amyloidosis. Echocardiographic features like LV wall thickness, severity of diastolic dysfunction and reduced systolic function are associated with a poor outcome [11]. The prognostic value of new promising parameters derived from echocardiographic deformation imaging as well as the presence and extent of late

gadolinium enhancement must be confirmed in larger trials [115,116]. Cardiac biomarkers, troponins I or T and BNP or NT-proBNP, have been shown to be most important predictors of outcome in patients with AL amyloidosis [38,87]. Troponins provide a quantitative measure of myocardial damage and natriuretic peptides reflect cardiomyocyte stress. By using these biomarkers, a staging system has been developed. The patients are classified to be at stage III if both biomarkers are elevated with mean survival of 3.5 months, stage II when one of the biomarkers is abnormal (survival 10.5 months) and stage I characterized by normal levels of troponins or NT-proBNP (survival 26 months) [85]. The staging system based on the evaluation of cardiac biomarkers together with the assessment of FLC levels and markers of plasma cell burden is important in clinical management with respect to optimization of therapy, monitoring its success and minimizing its toxicity [114].

Treatment of AL amyloidosis has been largely based on experiences gained with the therapy of multiple myeloma. Today, high-dose melphalan followed by autologous stem cell transplantation (HDM/SCT) represent a standard front-line therapy for patients with AL amyloidosis who are suitable candidates for this aggressive treatment. Although the very first clinical trials clearly demonstrated HDM/SCT efficacy in achieving significant hematologic and organ response, the toxicity of this approach has been also soon recognized [117,118]. Treatment-related mortality in the 90's reached 40% in some centers and advanced age together with cardiac involvement has been recognized to identify the most fragile population [119]. Since stem cell preparation requires administration of high-dose of granulocyte-colony stimulating factor, patients with cardiac involvement and autonomic dysfunction are particularly susceptible to hypotension and fluid shifts induced by this factor. Also, patients with cardiac amyloidosis may experience life-threatening arrhythmias during stem cell infusion presumably related to dimethyl sulfoxide preservative toxicity [120]. The above mentioned cardiac staging system represented a significant improvement in careful selection of patients for HDM/SCT. The data from experienced centers show that hematologic response may be achieved in more than three quarters of patients including 39% with complete response and with treatment-related mortality about 10% [121,122]. Complete hematologic response has been consistently documented as the strongest predictor of outcome. The median survival of patients achieving complete hematologic response may be more than 10 years compared to a few dozen months in those with no hematologic response [123]. In patients with no or partial response to HDM/SCT, regimens combining dexamethasone with either thalidomide or bortezomib have been successfully tested, especially with the latter one [124,125].

Because of the risk of such aggressive treatment, current indication criteria for HDM/SCT are strict and comprise age < 65 years, ≤ 2 organs involved, NT-proBNP and troponin I levels < 35 ng/l and < 0.1 μg/l, respectively, LV ejection fraction > 45%, creatinine clearance ≥ 50 ml/min, diffusion lung capacity for carbon monoxide > 50% and systolic blood pressure > 90 mmHg [126]. That is why only about 25% of patients with Al amyloidosis are suitable candidates for this effective therapy.

In individuals not eligible for HDM/SCT, melphalan combined with high-dose dexamethasone (MDex) became a standard of care. Studies evaluating this therapeutic regimen in patients ineligible for HDM/SCT demonstrated that hematologic response was achieved in two thirds of patients and complete hematologic response in about 30% [127,128]. Similar to HDM/SCT, the survival was much longer for patients who responded to the therapy. Lower response rates and outcome was again documented in subjects with advanced cardiac involvement, with median survival rate of 10.5 months [129]. Current trials are testing the efficacy of MDex combined with the third agent like thalidomide, lenalidomide or bortezomib [130,131]. However, even patients with severe cardiac disease may benefit from palliative melphalan therapy [132].

So far, there has been only one randomized trial comparing the efficacy of HDM/SCT and MDex. In the Intergroupe Francophone du Myélome trial, 100 patients were randomized in 29 centers to either chemotherapy using MDex or HDM/SCT [133]. Interestingly, hematologic response rates were similar in both groups (67% vs. 68%) and the median overall survival was significantly better in the MDex arm (57 vs. 22 months). Although this trial has failed to demonstrate higher effectiveness of HDM/SCT approach, one must be well aware of the limitations of this study. Treatment related mortality was surprisingly high in HDM/SCT arm (24%) suggesting that these patients were not suitable candidates for stem cell transplant. Also, 26% of individuals in the transplantation arm did not complete HDM/SCT and thus a number of patients who underwent stem cell transplant was small and likely insufficient for correct analysis of treatment efficacy. Moreover, the study was conducted in multiple centers, out of which some had limited experience in caring for patients with amyloidosis.

As already mentioned, novel agents have been recently introduced in the treatment of AL amyloidosis. Thalidomide and lenalidomide have been combined with dexamethasone and with dexamethasone plus melphalan or cyclophosphamide. Hematologic responses have ranged generally between 40% and 50%; however, considerable treatment toxicity has been documented including most worrying myelosupression induced by lenalidomide [130]. Bortezomib, a reversible proteasome inhibitor, has been successfully tested either as a single agent or in combination with dexamethasone or mephalan and dexamethasone (BMDex) [131]. The therapeutic regimens using bortezomib seem to be very promising. High rates of hematologic responses as well as organ improvement were achieved rapidly in conducted trials and overall treatment was safe with mild to moderate neurotoxicity being the most common adverse effect. After being tested in randomized trials, the BMDex regimen has the potential to become a standard of care for newly diagnosed patients with AL amyloidosis.

Immunotherapeutic strategies that target amyloid deposits, precursor protein or pathologic plasma cells are extensively investigated. A novel compound, CPHPC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1yl]-6-oxo-hexanoyl] pyrrolidine-2 carboxylic acid) binds to circulating SAP to form complexes which are subsequently cleared by the liver [134]. CPHPC combined with a fully humanized mono-

clonal anti-human SAP IgG antibodies acting on residual bound SAP has the potential to clear amyloid deposits of all kind and is currently tested in early clinical trials. Monoclonal antibodies targeting the κ and λ chain are being explored in animal models with promising results [132]. Immunotherapeutic approaches directed at the pathologic plasma cell are also being investigated, mainly therapeutic strategies acting through cancer testis antigen that is expressed on the plasma cells of patients with AL amyloidosis [135].

As amyloid cardiomyopathy represents the most important prognostic factor, the issue of correct indication of a patient with AL amyloidosis for heart transplantation has been debated already for decades and continuously evolves with both experiences gained in transplant medicine as well as with improvements in specific chemotherapy and SCT. The majority of patients with AL amyloidosis have significant involvement of other organs excluding them from cardiac transplantation. Cardiac transplantation alone does not affect the underlying plasma cell dyscrasia and the deposition of amyloid thus continues unless hematologic disorder is treated. This was exactly the problem of early attempts at cardiac transplantation in AL amyloidosis, when short-term improvement was followed by death from progressive amyloidosis in most patients [136]. Also, adjunctive chemotherapy did not lead to improvement in a poor survival of transplanted patients with AL amyloidosis as compared to heart transplantation from other indications [26]. Therefore, cardiac transplantation with subsequent chemotherapy and autologous stem cell transplantation performed within 6–12 months of heart transplant in order to prevent further amyloid deposition is currently recommended in highly selected patients [137]. Although no precise criteria have been stated, there is a general consensus that the disease must be isolated to the heart in the time of cardiac transplantation, with no significant proteinuria, neuropathy or hepatic involvement [22]. Recently, successful single-center experience with cardiac transplantation using the so-called extended donor criteria was reported [138]. The definition of extended donor criteria means advanced donor age, concomitant nonobstructive coronary artery disease, inability to obtain a cardiac catheterization, mild left ventricular hypertrophy, prolonged ischemic time, or positive donor serology for hepatitis C. The use of such hearts shortens the waiting time, although the post-transplant survival is highly likely decreased. However, a very poor prognosis of patients with cardiac amyloidosis seems to justify this transplant approach. Nevertheless, whether or not the extended donor criteria are used, precise selection of the suitable candidate for heart transplantation with subsequent chemotherapy and SCT is the most important issue.

Familial amyloidoses

Congestive heart failure is usually easier to control in patients with familial amyloidosis as compared to AL amyloidosis. Low doses of ACE-inhibitors and beta-blockers are better tolerated in these patients if autonomic neuropathy is not present [22]. To date, the only specific therapy for TTR, fibrinogen and apolipoprotein hereditary amyloidoses is organ transplantation. In TTR-associated familial amyloid neuropathy, orthotopic liver transplantation represents causal and highly effective treatment [139]. However, in many patients with nonVal30Met TTR an accelerated progression of cardiac amyloidosis was observed after liver transplantation [140]. This is probably due to continued deposition of wTTR in the heart [141]. Therefore, combined heart and liver transplantation shall be considered for patients with familial TTR amyloidosis involving the heart [142].

New drugs on the basis of small molecule ligands that are able to stabilize tetrameric structure of TTR are investigated. Diflunisal is a non-steroidal anti-inflammatory agent which reduces tetramer dissociation and subsequent misfolding and amyloid formation; however, it may worsen renal function and lead to fluid retention [143]. Another drug with similar effect is tafamidis, with which successful clinical trial that demonstrated the slowing of progression of neuropathy in ATTR amyloidosis has been recently conducted [144]. Currently, multicenter trial exploring the efficacy of tafamidis in cardiac mTTR amyloidosis is under way.

Senile systemic amyloidosis

Treatment is symptomatic with diuretics being the mainstay. Carefully monitored therapy often leads to significant improvement with long-term freedom from recurrence of congestion. Similar to familial TTR amyloidosis, the patients with senile amyloidosis usually tolerate ACE-inhibitors and low doses of beta-blockers. Atrial fibrillation is common and electrical or pharmacological cardioversion shall be strongly considered as atrial arrhythmia may lead to substantial worsening of heart failure [22]. Amiodarone is generally used to maintain the sinus rhythm. Anticoagulation is mandatory if atrial fibrillation or flutter persists as the thromboembolic risk is very high. The implantation of permanent pacemaker is common because of considerable occurrence of advanced conduction system disorder with high-degree AV blocks. The treatment of senile systemic amyloidosis with tafamidis is also being tested in currently conducted clinical trials.

Secondary amyloidosis

The treatment is primarily orientated to control the underlying chronic inflammatory disorder. Immunomodulating agents like TNFα-inhibitors or IL-1-inhibitors are increasingly used; however, financial aspects limit greater use of this therapeutic approach. Recently, eprodisate, a molecule that binds to glycosaminoglycan-binding sites on SAA and inhibits fibril polymerization, has been successfully tested in a randomized clinical trial which has demonstrated slowing down the progression of renal failure in patients with AA amyloidosis [145].

Conclusions

Cardiac amyloidosis may or may not be associated with involvement of other organs and represents a major negative prognostic factor in all types of amyloidosis. The presence of various typical features derived from imaging techniques and ECG shall always rise suspicion for the disease and lead to stepwise diagnostic process that

translates into the confirmation of the amyloid heart disease and assessment of other organ involvement together with precise histological verification of the type of infiltrating amyloid. Early diagnosis is critical especially in most common AL amyloidosis, because patients with advanced heart disease are not suitable candidates for modern and effective hematologic treatment regimens including intensive chemotherapy and autologous stem cell transplantation. In patients with advanced amyloid cardiomyopathy, diuretics with aldosterone antagonists remain the mainstay of the therapy. Heart transplantation may be offered only to a minority of patients with isolated cardiac involvement. In familial transthyretin amyloidosis, combined heart and liver transplantation represents a therapeutic method of choice. Novel pharmacological agents like tafamidis are being tested in clinical trials in treatment of transthyretin-related amyloidosis.

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