Amyloid cardiomyopathy

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Amyloidosis is a heterogeneous group of diseases characterized by the deposition of amyloid. It is caused by extracellular deposition of insoluble fibrils with beta-pleated sheet configuration. The protein misfolding abnormalities result in amyloid fibrils and may manifest as primary, secondary, or familial amyloidosis. Amyloid deposition can occur in multiple organs (eg, heart, liver, kidney, skin, eyes, lungs, nervous system) resulting in a variety of clinical manifestations. Cardiac involvement can occur as part of a systemic disease or as a localized phenomenon. Cardiac involvement in all types of amyloidosis represents a major negative prognostic factor. Early diagnosis, multi-disciplinary cooperation and proper therapy are key aspects of care for patients with amyloid cardiomyopathy. Early diagnosis is crucial, especially in AL amyloidosis, as patients with advanced heart disease are unsuitable candidates for modern, effective hematological treatment including autologous stem cell transplantation. Despite signal development in diagnostics and therapy, the prognosis for patients with advanced cardiac involvement remains poor. This article is an overview of amyloidosis, providing information about the characteristics of cardiac amyloidosis, and present a structured approach to diagnosis, treatment and prognosis of this condition.

Key words: amyloidosis, amyloid cardiomyopathy, heart diseases, heart failure, restrictive cardiomyopathy

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DEFINITION, PATHOPHYSIOLOGY AND CLASSIFICATION

Amyloidosis is a heterogeneous group of diseases characterized by the deposition of amyloid - an insoluble fibrillar protein with β-sheet conformation, relatively resistant to proteolysis. Amyloid masses are deposited extracellularly in tissues, resulting in their disorganization with consequent disruption of organ function. More than 30 different amyloidogenic proteins have so far been identified.

Amyloidosis is principally differentiated into systemic and localized types depending on the degree of involvement, and acquired and hereditary types according to the character of transmission[1-3]. The majority of systemic amyloidoses is associated with multi-organ involvement. Cardiac involvement is very frequent in AL (amyloid light chain), transthyretin and senile systemic amyloidosis, but less frequent in cases of AA (secondary) and lipoprotein amyloidosis. Isolated involvement of cardiac atria is found in AANF (atrial natriuretic peptide) amyloidosis, where the atrial natriuretic peptide represents the precursor protein.

Amyloid cardiomyopathy diagnosis is based on 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 of LV hypertrophy with a positive non-cardiac biopsy.

AL amyloidosis is the most commonly diagnosed form of amyloid disease in developed countries. It belongs to the group of monoclonal gammopathies and is associated with multiple myeloma or Waldenström's macroglobulinemia in approximately 10–20% of cases. It represents more than 70% of cases of all amyloidosis types. The disease is characterized by deposition of fibrils formed from fragments or complete molecules of monoclonal light immunoglobulin chains produced by the clonal plasma cell population. Imbibition of tissues with amyloid leads to the progressive involvement of organs – most often the kidneys, heart, liver and peripheral nervous system. Macroglossia and periorbital purpura ("panda" or "raccoon eyes"), specific features of AL amyloidosis, are present only in a minority of cases. In addition to the infiltration of tissues by amyloid, direct toxic effect of light chains on cells is also common, via oxidative stress mechanisms.

The kidneys are the most frequently affected organ, with a clinical picture of renal insufficiency and excessive proteinuria, frequently accompanied by advanced nephrotic syndrome[4-6]. Cardiac involvement is detected in 50–60% of patients, and 20–35% of patients present clinical signs of cardiac involvement at the time of diagnosis. Isolated cardiac involvement is seen in less than 5% of patients. Cardiac involvement represents the most significant prognostic factor in patient survival and the severity of cardiac involvement influences the choice of therapeutic strategy[7,8].

Hereditary transthyretin amyloidosis (ATTR, mATTR) belongs among the less frequent amyloidoses (7–9%), in which the amyloid fibrils are formed by transthyretin (prealbumin) molecules. Prealbumin is primarily generated

Table 1. Classification of amyloidoses.

Amyloid type	Amyloidogenic protein	Site of production	Heart Involvement
AL	Immunoglobulin light chains	Bone marrow	Frequent and severe
TTR	Transthyretin molecules	Liver	Frequent and severe with particular mutation
SSA	Wild-type (non-mutant) transthyretin	Liver	Possible
AA	Amyloid protein A	Liver	Rare
AANF	Atrial natriuretic peptides	Atria	Possible in elderly patients

AL - light chain amyloidosis, TTR - transthyretin, SSA - senile systemic amyloidosis, AA - secondary amyloidosis

by the liver and the disease is characterized by mutations in the prealbumin gene with autosomally dominant type of heredity with variable penetration. The most frequent disease type is familial amyloid polyneuropathy (FAP) type I, characterized by a Val30Met mutation. The primary symptom is progressive peripheral sensomotoric polyneuropathy. Dominant cardiac involvement with minimal neurological deficit is characteristic for patients carrying the Val122Ile mutation (familial amyloid cardiomyopathy, FAC). The disease is characterized by progressive cardiomyopathy and onset in patients after the age of 60 (ref.[9-12]).

Senile systemic amyloidosis (SSA) is an acquired type of the disease, in which the fibril aggregates are composed of native transthyretin (wild-type, wtATTR) molecules. The dominant clinical symptom is usually cardiac involvement – most often in the form of a restrictive or hypertrophic cardiomyopathy. Symptoms include congestive heart failure, arrhythmias, and conduction defects. The disease is typical in males older than 65 years. As a rule, carpal tunnel syndrome is present. The diagnosis of SSA is problematic (there are no biomarkers and disease identification requires the exclusion of all other types of systemic amyloidosis). The final diagnosis is usually based on a positive endomyocardial biopsy and identification of the type of amyloid masses. Exclusion of hereditary forms by genetic analysis of the TTR (transthyretin) gene is also required[13,14].

The clinical progression of TTR cardiac amyloidosis depends on the fibril type (wild-type versus variant), specific mutation and age of onset. Untreated, TTR disease is associated with significantly longer median survival than AL amyloidosis but progresses to refractory heart failure and death from systolic heart failure or dysrhythmia.

Secondary amyloidosis (AA) accompanies chronic inflammatory diseases, usually difficult to control with therapy (rheumatoid arthritis, Bechterew disease, inflammatory bowel diseases). Serum amyloid A (SAA), an acute phase protein synthesized in the liver, is the etiological agent of amyloid deposits. It represents 4–7% of all amyloidoses. Dominant involvement is most often that of kidneys, in the form of the nephrotic syndrome and/or renal failure but cardiac involvement is rare (2–3%) (ref.[3,13,14]).

AANF represents a localized amyloidosis type affecting cardiac atria. Atrial natriuretic peptide is the precursor protein. Unlike SSA, AANF predominantly affects older women. Finding of this amyloidosis type is predominantly sectional due to the unacceptably high risk of wall perforation during endomyocardial biopsy of the thin atrial wall[15] (Table 1.).

CLINICAL SYMPTOMS AND DIAGNOSTICS

The initial clinical symptoms of amyloid cardiomyopathy are non-specific, because amyloid deposition in the myocardium leads to only a gradual thickening of the walls, which primarily affects cardiac filling, while left ventricular ejection fraction (LVEF) is preserved for a relatively long time. The advanced clinical picture includes progressive congestive cardiac failure with dominant right-sided symptomatology. The patient complains of fatigue, weakness, weight loss (particularly with SSA). Dyspnea is initially exertional, but in late stages, in cases of global cardiac failure development, manifests also at rest. Physical examination usually reveals lower extremity edemas, ascites, hepatomegaly with blood stasis and pleural exudates. Peripheral edemas are often also enhanced by hypoalbuminemia with advanced nephrotic syndrome. Chronic hypotension is often detected, frequently of orthostatic character, with reduced cardiac output and vegetative nervous system involvement. Autonomous dysfunction is also associated with the reduction or loss of heart rate variability. Palpitations or syncope may be the manifestation of supraventricular arrhythmias, mainly due to dilatation of the left ventricle with chronically increased left ventricular pressure. Prothrombogenic risk is often enhanced by the presence of nephrotic syndrome with hemostasis cofactor deficiency (antithrombin III). Valvular defects (mitral and tricuspid insufficiency) are relatively frequent with infiltration of the valvular and suspensory system. Chronic refractory cardiac failure and sudden death due to electromechanical dissociation or arrhythmogenic states are among the most frequent causes of death[7,8,16-23].

A thorough physical examination may indicate the possible presence of amyloidosis. Most patients have multiple organ involvement with an array of clinical symptoms (nephrotic syndrome, cardiac failure, hypotension, polyneuropathy, macroglossia, periorbital purpura).

Determination of AL amyloidosis diagnosis itself necessarily requires a complex examination including evidence of monoclonal immunoglobulin or structural subunits – 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)

Table 2. Clinical symptoms of amyloidosis.

Cardiovascular system involvement:	Notes
Right-sided heart failure	elevated jugular venous pressure
	third heart sound
	lower extremity edema
	hepatomegaly
Presyncope/syncope, postural hypotension	caused by low cardiac output
Angina-like pain	amyloid infiltration of the coronary vessels
Tricuspid or mitral regurgitation murmur	in patients with valvular infiltration of amyloid
Sudden cardiac death	
Nervous system involvement	**Notes**
Presyncope/syncope, postural hypotension	adrenal dysfunction, loss of cardiac frequency variability
Carpal tunnel syndrome	20% of all patients, an early sign
Painful polyneuropathy	10-20% cases
Other clinical features	**Notes**
Macroglossia	Due to infiltration, teeth indentation marks often visible on lateral borders of tongue, abnormal phonation
Periorbital purpura	"raccoon or panda eyes", a result of vascular fragility
Proteinuria	
Cachexia	Due to gastrointestinal tract involvement

- and organ screening (echocardiography or cardiac MRI, ultrasound of the kidneys and liver, proteinuria, cardiac biomarkers and alkaline phosphatase activity assays) (ref.[7,17,23-25]). Conclusive proof of the diagnosis requires tissue sample collection with histological evidence and consequent determination of the amyloid mass type. Non-targeted biopsies are used primarily (rectum, tongue, subcutaneous fat), with a targeted biopsy of the involved organ system being performed (biopsy of the kidney, liver or endomyocardium) only in case of negative and inconclusive result and lasting suspicion. In cases of AL amyloidosis, provided that amyloid from non-targeted or extracardial biopsy is verified, endomyocardial biopsy is not necessary for the verification of amyloid cardiomyopathy diagnosis.

The principal morphological method for amyloid proof is a special Congo red stain showing specific birefringence with dichroism in polarized light. Proof of amyloid deposition is most often found by an indirect immunohistochemical method and direct immunofluorescence. Both methods are based on the principle of reaction of an antibody with an antigen – amyloidogenic protein epitope (light chains, transthyretin, SAA) with a standard visualization by the avidin-biotin complex technique on slices of formaldehyde-fixed tissue cast in paraffin blocks.

Another test allowing identification of the amyloid deposits is amyloid typing mass spectrometry which provides information about the presence or absence of amyloidogenic proteins in tissue. This technique is used on formalinfixed, paraffin-embedded tissue. The analysis usually begins with visual identification of amyloid deposits, followed by their dissection under the microscope (laser microdissection). The specimen is then digested with trypsin, resulting in the generation of peptide fragments. Mass spectrometry is then used to analyze these peptide fragments, resulting in an m/z spectrum. The specific m/z characteristics of the different peaks are compared to those in databases, leading to the identification of the peptide fragments in the amyloid digested by trypsin. These peptide fragments are quantified and the higher the number of peptide fragments originating from a particular amyloidogenic protein, the higher the degree of confidence that the particular protein is a component of the amyloid[20,22]. (Table 2., Fig. 1.)

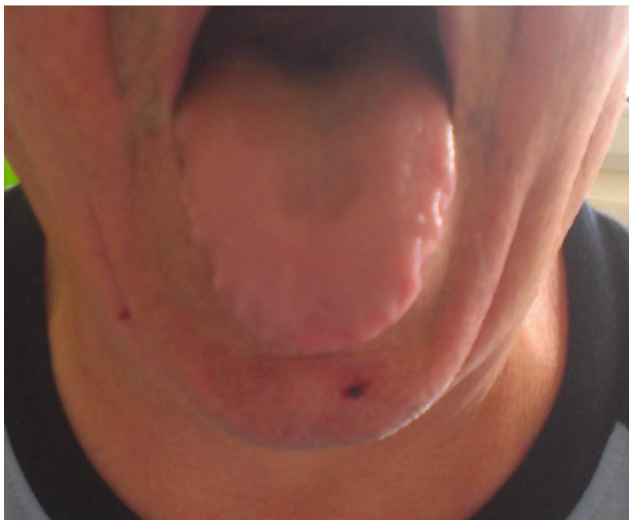

Fig. 1. Macroglossia with teeth indentation marks on lateral borders of tongue in patient suffering from AL amyloidosis.

CARDIAC BIOMARKERS

Cardiac biomarker assay is a necessary part of the diagnostic algorithm in amyloidosis patients. Troponin T (TnT)/troponin I (TnI) and N-terminal pro-brain natri-

uretic peptide (NT-proBNP) levels are usually tested. TnT levels are a sensitive indicator of myocardial involvement, and the levels determined at the time of diagnosis are used as a prognostic parameter. TnT (TnI) levels, in addition to their prognostic significance, are used with NT-proBNP levels as discrimination parameters in a widely used staging system published by the Mayo Clinic group, which not only enables a stratification of patients into 4 risk groups, but also helps to a certain degree in determining the apropriate therapy. This stratification system has been further modified and supplemented by the parameter of free light chain level assay representing the amyloidogenic protein burden. Troponin levels correlate with the LVEF value and interventricular septum thickness Likewise, the effect of chemo(immuno)therapy is associated with decrease of these levels. It is known that steady or increasing troponin levels indicate continuing loss of cardiomyocytes[24-29].

Serum NT-proBNP assay is routinely used in the care of patients with cardiac involvement. Analogous to those of troponin, NT-proBNP levels enable prognostic stratification of AL amyloidosis patients (332 ng/L), while normal levels practically rule out amyloid cardiomyopathy. Elevated NT-proBNP levels are an early marker of cardiac involvement in amyloidosis, but the elevation frequently does not correspond with the degree of cardiac dysfunction. The NT-proBNP assay is currently used as part of the above mentioned Mayo Clinic stratification system[25,26,30]. The change of NT-proBNP levels correlates with the dynamics of free light chain levels, i.e. circulating amyloidogenic precursors, and effective therapy is associated with decrease in absolute values. Change of NT-proBNP levels is currently used as a criterion for the evaluation of cardiac remission[31-34]. (Table 3., 4.)

ELECTROCARDIOGRAPHY

Electrocardiography (ECG) is one of the basic examination methods used in daily clinical practice. Low amplitude of the QRS complex < 0.5 mV in the limb leads and/or < 1.0 mV in the precordial leads is a typical finding in amyloid cardiomyopathy, present in approximately 2 out of 3 patients with AL amyloidosis.

A QS pattern in at least two precordial chest leads ("a pseudo-infarct pattern") and an inversion or depression of the T or ST section in the lateral chest leads can be seen in some patients[35-39].

The Holter ECG shows episodes of ventricular and supraventricular arrhythmia in a large number of asymptomatic patients. Another finding is the decrease or absence of heart rate variability, a sign of autonomous nervous system dysfunction[40-42]. (Fig. 2.)

ECHOCARDIOGRAPHY

Transthoracic echocardiography represents the imaging method of first choice in the diagnostics and monitoring of cardiac involvement in amyloidosis. However, echocardiography cannot confirm diagnosis in isolation and is also unable to distinguish between various types of amyloidosis. A finding typical for infiltrative affection of the myocardium is end-diastolic thickness of the interventricular septum or left ventricular wall > 12 mm[35]. The use of the term "hypertrophy" is, in this case, incorrect, as the condition is not caused by the hypertrophy of cardiomyocytes, but by amyloid deposition. Nevertheless, the finding of "concentric hypertrophy" of the left ventricle in a routine echocardiography in the absence of hypertension or another cause explaining myocardial hypertrophy should lead to a consideration of the presence of amyloidosis. Amyloid infiltration of the myocardium can be also indicated by a "granular sparkling" texture, as the amyloid deposits have a higher echogenicity than normal myocardium. The left ventricular cavity is reduced. LVEF is preserved, particularly in early stages (LVEF > 50%),

Table 3. Staging System for Light Chain Amyloidosis.

Stage	Cardiac biomarkers	Median overall survival (months)
I	TnT < 0.035 μg/L or TnI < 0.1 μg/L NT-proBNP < 332 ng/L	26.4
II	TnT > 0.035 μg/L or TnI > 0.1 μg/L or NT-proBNP > 332 ng/L	10.5
III	TnT > 0.035 μg/L or TnI > 0.1 μg/L and NT-proBNP > 332 ng/L	3.5

Table 4. Revised Staging System for Light Chain Amyloidosis.

Risk factors	Revised Prognostic Stage	Median overall survival (months)	Five-year survival
0	I	94	59%
1	II	40	42%
2	III	14	20%
3	IV	6	14%

The number of risk factors:
Difference between serum free kappa and lambda light chains: 0 points FLC under 180 mg/L, 1point FLC 180 mg/L or higher
Troponin T (cTNT): 0 points cTNT under 25 ng/L, 1 point cTNT 25 ng/L or higher
NT-proBNP: 0 points NT-proBNP under 1800 ng/L (< 213 pmol/L), 1 point NT-proBNP1800 ng/L (213 pmol/L) or higher

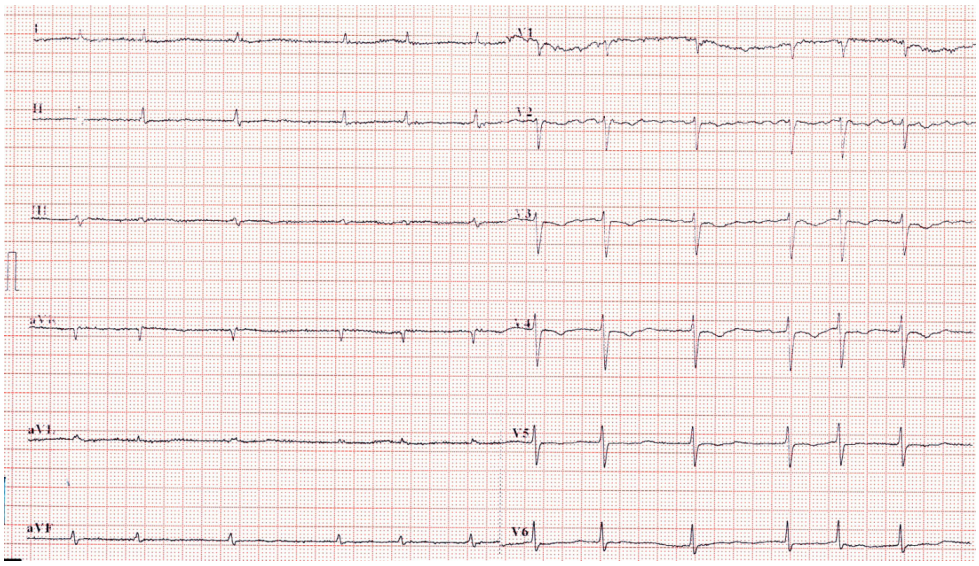

Fig. 2. Low voltage complexes (QRS amplitude ≤ 0.5 mV in limb leads or ≤ 1.0 mV in all precordial leads) are seen in 46% of cases.

but a dominant disorder of longitudinal contractility typical for amyloidosis, particularly of the basal segments of the left ventricle, is visible earlier by an examination with tissue Doppler (S and Em wave reduction of the septal and lateral edge of the mitral annulus) (ref.[43-47]). There are regular findings of left ventricular diastolic dysfunction, from a mild diastolic relaxation disturbance to the clinical image of a severe restrictive disorder (E/A ratio > 2) with high left ventricular filling pressures (elevated E/Em), and atrial dilatation in later stages (diameter > 23 mm/m^2, area > 20 cm^2 or maximal volume > 28 mL/m^2, and small A wave due to atrial dysfunction) (ref.[47]). Thickening of the free right ventricular wall and its dysfunction, as well as thickening of the valves, also indicate that these structures are damaged by amyloid. Pericardial effusion is present in about 50% of patients. This is usually small and of minor hemodynamic significance, but is associated with a worse prognosis; large effusion with the possibility of a tamponade is found only exceptionally[47].

As a quantitative technique to estimate myocardial function and contractility we use strain and strain rate imaging. Strain and strain rate measurements are more sensitive and accurate than tissue velocity imaging for evaluating regional longitudinal myocardial function. This echocardiographical technique can even detect early regional myocardial dysfunction in amyloidosis before the onset of chronic heart failure. A specific pattern of longitudinal strain characterized by worse longitudinal strain in the mid and basal ventricle with relative sparing of the apex may help distinguish left ventricular infiltration due to amyloid from true ventricular hypertrophy of hypertensive heart disease or hypertrophic cardiomyopathy. Abnormal longitudinal strain also predicts worse survival in patients with AL amyloidosis. The use of this diagnostic technique in routine clinical practise is unfortunately limited due to the technical demands involved[48-50]. (Table 5, Fig. 3-4)

SCINTIGRAPHY

SAP scintigraphy uses radiolabeled serum amyloid P component (SAP) to visualize the whole body amyloid burden. SAP forms a part of all amyloid deposits, regardless of amyloidogenic protein type and is a normal plasma protein that binds reversibly to amyloid deposits of any type. SAP scintigraphy is used for assessing the distribu-

Table 5. Transthoracic echocardiography abnormalities in amyloid cardiomyopathy.

Abnormality	Notes
Left ventricular thickening in the absence of hypertension	not specific for amyloidosis
Granular or sparkling appearance of LV myocardium	seen only in 26% of cases
Preserved LVEF	reduced LV systolic function late in the course of the disease
Normal or small LV cavity dimensions	
Diastolic dysfunction, restrictive mitral in-flow filling pattern on Doppler evaluation	
Left atrial enlargement	biatrial enlargement late in the course of the disease
Thickened interatrial septum, thickened atrioventricular valves	
Small pericardial effusion	

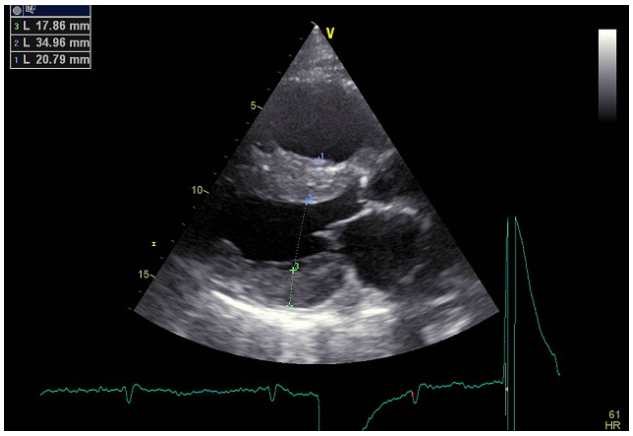

Fig. 3. An echocardiogram of a patient with amyloid cardiomyopathy. In amyloidosis, the walls of the heart are thickened and the left ventricle reduced in size. A granular sparkling texture of the myocardium is visible.

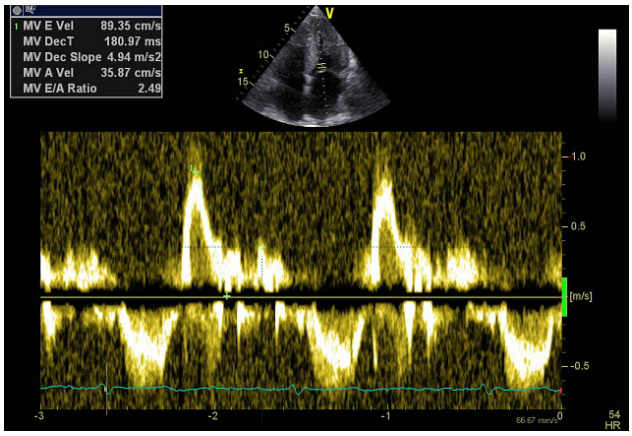

Fig. 4. PW dopplerometry of transmitral flow - severe diastolic dysfunction of the left ventricle, a serious restrictive condition (E/A ratio > 2) with atrial dilatation.

tion and degree of involvement, as well as for monitoring the treatment response. It is not suitable for myocardial visualization because of the distribution of radiopharmaceuticals in the blood compartment of the moving heart and frequent accumulation in the spleen[51,52].

^{99m}Tc-3,3-diphosphono-1-2-propanodicarboxylic acid (DPD) scintigraphy. ^{99m}Tc-DPD is selectively taken up in the myocardium by TTR amyloid deposits. This is advantageous not only for the diagnostics and assessment of heart involvement in mTTR and SSA, but also for the differential diagnostics of AL, where the accumulation of the radiopharmaceutical is very low or absent[53,54]. (Fig. 5.)

MAGNETIC RESONANCE

Cardiac magnetic resonance imaging (MRI) enables a more accurate morphological and functional imaging of the heart compared to echocardiography. The findings are the same as with echocardiography: hypertro-

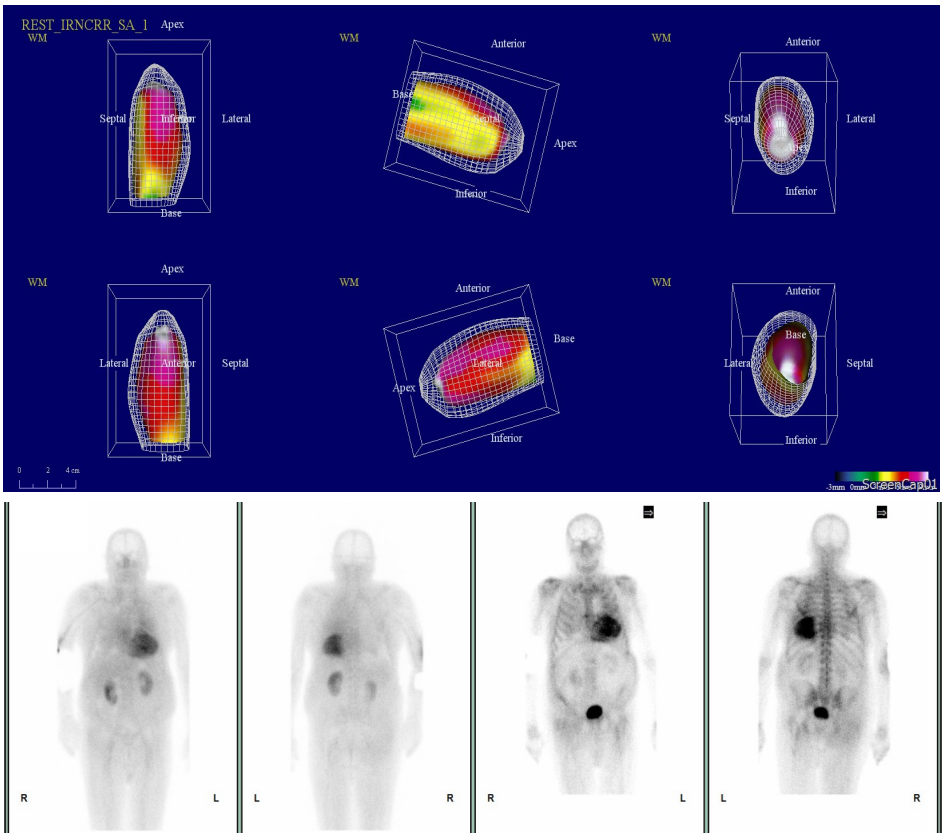

Fig. 5. 99m Tc-DPD is taken-up globally in the myocardium, mostly in the interventricular septum, a typical finding of TTR amyloidosis. (Courtesy of prof. M. Kaminek M.D., Department of Nuclear Medicine, Olomouc University Hospital)

phy of ventricular walls and interventricular septum, atrial dilatation, preserved or reduced ejection fraction of a non-dilated left ventricle with decreased longitudinal contraction of the walls; pericardial effusion is often present. The possibility of tissue characterization by the late gadolinium enhancement (LGE) method represents a major contribution to the evaluation of amyloid cardiomyopathy. Gadolinium kinetics are abnormal in cardiac amyloidosis, with a faster washout of gadolinium from myocardium and blood pool compared to non-amyloid control subjects. Late gadolinium enhancement images are typically obtained about 5 minutes after infusion of 0.1 to 0.2 mmol/kg of gadolinium injection; global subendocardial LGE is most often found in amyloid cardiomyopathy. These findings, found in 80% of patients, are typical and pathognomonic for amyloid cardiomyopathy[55-59].

T1 mapping techniques may identify cardiac involvement at an earlier stage compared to LGE images. On T1 mapping, if the myocardium crosses the null point at a T1 time point prior to the blood pool, it indicates the presence of diffuse global hyperenhancement and is characteristic of cardiac amyloidosis. Native (pre-contrast) T1 times in patients with cardiac amyloidosis were significantly prolonged compared to hypertrophic cardiomyopathy and healthy subjects[60]. Native T1 mapping techniques may be particularly helpful in patients with renal dysfunction (due to risk of gadolinium toxicity).

Direct quantification of the volume of distribution of gadolinium (myocardial extracellular volume, ECV) by CMR is determined by pre and post contrast R1 (1/T1) for the blood and myocardium taking into account serum hematocrit (Hct). In AL amyloid patients, ECV correlated directly with LV mass, TDI "S" wave, brain natriuretic peptide (BNP) and troponin levels, suggesting that ECV may represent a marker of amyloid burden in the heart[61].

Late gadolinium enhancement, T1 prolongation, and extracellular volume expansion may be observed in amyloidosis, other infiltrative diseases, inflammation, and fibrosis. Certain LGE patterns, T1 times and ECV values are sensitive to a diagnosis of amyloidosis but are not specific and cannot exclusively obviate the need for a definitive histological diagnosis. (Fig. 6.)

HISTOLOGICAL FINDINGS

Endomyocardial biopsy (EMB) is considered the gold standard in the diagnosis of amyloid cardiomyopathy. Amyloid tissue, when stained with Congo red, appears as an amorphous pink deposit under light microscopy and has a green birefringence under polarized ligh. EMB has great sensitivity (almost 100%) due to the diffuse cardiac involvement and is a safe procedure in experienced hands. It is also of great value in differentiating cardiac amyloidosis from other infiltrative myocardial conditions.

Rectal submucosal biopsy was traditionally used in the past. It has a sensitivity of greater than 75% for detecting amyloidosis but carries a risk of bleeding and rectal perforation.

Abdominal fat biopsy is a simple and commonly performed procedure in patients suspected of having amyloidosis with a sensitivity of approximately 75%. If positive, it obviates the need for a cardiac biopsy. It is informative in the diagnosis not only of amyloidosis AL, but of amyloidosis AA. The great advantage of the method is the lack of contraindications and no risk of complications[62]. Although EMB is more commonly required to establish the diagnosis of SSA, noncardiac biopsy or fat aspiration could be considered as initial testing in patients evaluated for ATTR cardiac amyloidosis with characteristic echocardiography findings.

Bone marrow biopsy is useful in AL amyloidosis to assess the plasma cell burden and to exclude myeloma and other disorders. The identification of a monoclonal population of plasma cells using immunohistochemical techniques on bone marrow core biopsy specimens sometimes is difficult because of the low number of plasma cells present.

TREATMENT OF CARDIAC AMYLOIDOSIS

Cardiac amyloidosis therapy focuses both on influencing cardiac-related complications due to amyloid deposition (which is similar regardless of the specific type of amyloid) and on treatment of the underlying disease to suppress new amyloid formation (which is targeted for each specific form).

Heart failure therapy

Loop diuretics and aldosterone antagonists are the mainstay of heart failure therapy. In patients with severe

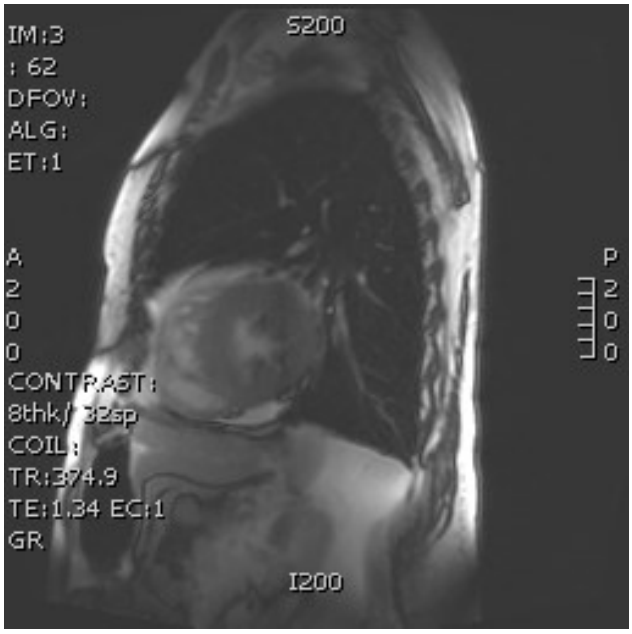

Fig. 6. MRI of a 74-years old patient suffering from TTR amyloidosis showing diffuse thickening of myocardium and widespread late gadolinium enhancement. (Courtesy of Z. Tüdös M.D., Department of Radiology, Olomouc University Hospital)

congestion and/or nephrotic syndrome, high doses of diuretics are usually necessary. 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 . Therefore, significant attention should be paid to fluid balance, with daily weight measurements and careful adjustment of diuretic dosage. Hypotension is common especially in AL cardiac amyloidosis. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are mostly poorly tolerated and the dose must be administered titrated and with great caution because even very low doses may cause severe hypotension, particularly in AL amyloidosis. Nevertheless, low doses of these agents may be beneficial as afterload reducing agents, particularly in cases of co-existing hypertension, to improve forward cardiac flow and renal perfusion.

As amyloid infiltration markedly impairs diastolic filling and reduces stroke volume, tachycardia is a compensatory mechanism that maintains cardiac output. Therefore high-dose betablockers are also not a standard part of heart failure therapy in cardiac amyloidosis as they may aggravate symptoms of cardiac failure in amyloidosis patients, whose cardiac output depends on heart rate with low fixed stroke volume, and may also worsen hypotension. Calcium channel blockers of the verapamil and diltiazem type are counterindicated in cardiac failure.

Due to its binding to amyloid fibrils, digoxin often leads to manifestation of digitalis toxicity even at therapeutic serum levels, and therefore is not recommended in amyloidosis patients.

Patients with severe cardiac amyloidosis are at high risk of intracardiac thrombus development and are indicated for appropriate anticoagulation treatment after individual assessment of hemorrhage risk. Anticoagulation treatment is indicated not only for intracardiac thrombi and patients with atrial fibrillation but also in cases of sinus rhythm and atrial hypocontractility detectable in echocardiographic examination[6-9,63].

Treatment of the Underlying Condition

To prevent disease progression, it is critical to address the abnormality that leads to the production of the amyloid protein. The treatment for AL amyloidosis is entirely different from that for TTR or SSA.

AL Amyloidosis

The aim of specific therapy is to eliminate the production of abnormal light chains by the plasma cells. This can be achieved by a variety of chemotherapy drugs and related agents. Because each patient is different, the dosage and choice of agent requires careful assessment by a hematologist skilled in the management of AL amyloidosis, in cooperation with a cardiologist who can make sure that any adverse side effects are treated and minimized. It is known that patients with advanced cardiac involvement have a very unfavorable prognosis. An initial therapy is often changed if there is no clear response over the first 2 to 3 cycles. In some cases of relatively mild AL cardiac amyloidosis, a patient may be offered high-dose chemotherapy with autologous stem cell transplantation. This is currently the most effective but toxic therapy, and very careful patient selection is needed, as it can be offered safely to only about 20% of patients due to old age, organ involvement and other comorbidities[64-66]. Growth factor administration during graft collection for autologous transplantation may be accompanied by aggravated congestive heart failure or worsened hypotension, and the transfer of stem cells itself may be associated with ventricular arrhythmia due to the toxic effect of the cryoprotective dimethyl sulfoxide[67-70].

Heart transplantation may be considered in young patients with advanced isolated cardiac involvement. Heart transplantation alone or a transplantation followed by chemotherapy is associated with five-year survival in 20–36% of patients. If, however, a high-dose therapy with autologous stem cell transplantation follows heart transplantation, one-year survival is as high as 75% (ref.[71,72]).

TTR Amyloidosis

Liver transplantation represents a very effective therapy in neuropathic forms of mTTR. It is known, however, that cardiac involvement often further progresses in the non-Val30Met forms despite liver transplantation, apparently due to the continuing deposition of native transthyretin. Therefore, a combined heart and liver transplantation should be considered in mTTR with cardiac involvement[73].

Tafamidis is a preparation bound by TTR in the blood. This binding stabilises the transthyretin tetramers, making them less amyloidogenic. This has recently been approved in Europe, but only for polyneuropathy caused by hereditary ATTR amyloid. Tafamidis has not yet received approval for cardiac ATTR amyloidosis but studies evaluating its effect in mTTR with dominant cardiac involvement are presently underway. Diflunisal, a non-steroid anti-inflammatory drug, has an identical effect and a combination of tauroursodeoxycholic acid (TUDCA) with doxycycline has an effect on the disruption of amyloid masses. Clinical studies are in progress[74-78].

SSA Amyloidosis

Appropriate therapy based on symptomatology is the cornerstone of SSA treatment.

CONCLUSION

Cardiac involvement in all types of amyloidosis represents a major negative prognostic factor. Early diagnosis, multi-disciplinary cooperation and prooper therapy are key aspects of care for patients with amyloid cardiomyopathy. Confirmation of amyloid type is now possible in most cases, using different modern methods. Unlike other causes of heart failure, supportive treatment is usually very limited. Early diagnosis is crucial, especially in AL amyloidosis, as patients with advanced heart disease are unsuitable candidates for modern, effective hematological treatment including autologous stem cell transplanta-

tion. Despite important development in diagnostics and therapy, the prognosis of patients with advanced cardiac involvement remains poor.

Search strategy and selection criteria

We examined studies and articles from various resources (e.g. PubMed, MEDLINE). The search terms used included amyloidosis, amyloid cardiomyopathy, heart diseases, heart failure, restrictive cardiomyopathy. Citation from journals with high impact factors were given special weight.

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