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Review

AL amyloidosis – an update on diagnosis and treatment

Klara Gadó[1]*, Dóra Kicsi[2], Gyula Domján[3]

[1]Semmelweis University, Faculty of Health Sciences, Department of Clinical Studies, Budapest; Hungary

[2]St Rokus Hospital, Budapest; Hungary

[3]Semmelweis University, Faculty of Medicine, 1st Department of Medicine, Budapest; Hungary

***Corresponding authors**
Klara Gadó
Semmelweis University
Faculty of Health Sciences
Department of Clinical Studies,
Budapest; Hungarytnership
Felsoszentivan
Hungary
E-mail: gadok@freemail.hu

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Summary

Light chain (AL) amyloidosis is caused by a usually small plasma cell clone producing a misfolded light chain those deposits in tissues.
AL amyloidosis can affect several organs. Clinical presentation and outcome depend on the pattern and severity of organ involvement. Survival is mostly determined by the severity of heart involvement.
The diagnosis requires the demonstration of amyloid deposits in a tissue biopsy. Less-invasive biopsy sites (abdominal fat, minor salivary glands) are preferred. Amyloid deposits need to be characterized by reliable techniques to unequivocally identify amyloid type.
Screening of early organ damage based on biomarkers can help identify patients with monoclonal gammopathy of undetermined significance who are developing AL amyloidosis before they become symptomatic.
Late diagnosis results in approximately 30% of patients presenting with advanced, irreversible organ involvement and dying in a few months despite modern treatments. Thus, early diagnosis has an extremely great importance.
The treatment of AL amyloidosis has been solely based on anti-plasma cell chemotherapy for many years. By suppressing the plasma cell clone, chemotherapy reduces the concentration of toxic light chains, which is necessary to improve organ dysfunction and to prolong survival.
More recently, different approaches targeting the amyloid deposits and interfering with organ damage have been developed that are being tested in clinical trials.
Stratifying the patients by appropriate staging and risk assessment are important for applying individualised therapy. Tight follow-up and effective supportive treatment are also required.

Keywords: AL amyloidosis, immunoglobulin light chain, cardiac failure, renal amyloidosis, autologous stem cell transplantation, chemotherapy, bortezomib.thrombosis

Abbreviation: ASCT: autologous stem cell transplantation; AL amyloidosis: immunoglobulin light chain amyloidosis; B-type natriuretic peptide: NT-proBNP; FLC: free light chain; Immunoelectron microscopy: IEM; LC: light chain;

Introduction

Systemic amyloidosis is a heterogeneous group of rare disorders of protein folding characterized by extracellular tissue deposition of misfolded and aggregated proteins as β-pleated sheet fibrils [1].

Immunoglobulin light chain (AL) amyloidosis - also known as primary amyloidosis - is typically low-tumour-burden plasma cell disorder characterized by deposition of insoluble fibrils composed of immunoglobulin light (or rarely heavy) chains. It is the most common and severe form of systemic amyloidosis, accounting for approximately 70% of all amyloidosis patients [2]. The reported incidence in USA and in the Western countries of 10new cases per million people, and is probably underdiagnosed [3].It is caused by a plasma cell clone that infiltrates the bone mar-

row by less than 10% in half of the patients. The light chain protein, instead of a-helical configuration of most proteins, misfolds and forms a b-pleated sheet [1]. This insoluble protein deposits in tissues and interferes with organ function. The b-pleated sheet configuration is responsible for positive staining with Congo red when viewed under polarized light[4]. All organs, except for the central nervous system, can be affected by this process, that leads to irreversible, devastating organ dysfunction and death if unrecognized or treated ineffective [5].

Diagnosis requires demonstration of amyloid deposition and confirmation of the fibril protein type.

Evaluation of patients with AL amyloidosis includes definition of tumour/precursor protein burden, the extent and severity of organ involvement and co-morbidities.

Effective treatments exist, provided that they are started before irreversible organ damage has occurred. Treatment should be adapted to the stage of the disease. At present, the choice of up-front treatment lies between autologous stem cell transplantation (ASCT) and combination chemotherapy. Chemotherapy agents include dexamethasone, melphalan, cyclophosphamide, thalidomide, bortezomib, lenalidomide, bendamustine in various combinations. Because of the rarity of the disease, few randomized controlled trials have been performed in AL amyloidosis and treatment has been substantially based on clinical practice in multiple myeloma. It has become clear that the best prospects of survival and preservation or improvement in amyloid related organ function require as near complete suppression as possible of the underlying haematological disorder.

The cornerstones of the management of AL amyloidosis are early diagnosis, accurate typing, appropriate risk-adapted therapy, tight follow-up, and effective supportive treatment.

Clinical presentation

Clinical symptoms depend on the affected organs and so the clinical picture may be very diverse. Because of the general symptoms such as fatigue, lethargy, oedema formation the diagnosis is frequently delayed.

The most frequently affected organs are the kidney and the heart. Involvement of the liver and the peripheral and autonomic nervous systems and soft tissues is also common manifestation of AL amyloidosis [6]**Table 1**.

AL amyloidosis manifests with sign and symptoms resembling those of more common conditions of the elderly that makes setting up the diagnosis more difficult. General symptoms such as fatigue, lethargy, loss of appetite, weight loss are common but not specific for the disease. Involvement of the soft tissues with macroglossia, periorbitalpurpura, submandibular gland swelling is more specific but uncommon findings (**Figure 1., 2)**. Hoarseness of voice is observed in some patients due to amyloid deposition on the vocal cords. Patients with co-existing myeloma may have bone disease and a history of infections. Hepato/splenomegaly may occur, and hepatic or splenic infiltration may cause palpable organomegaly. Renal dysfunction is common, manifesting as nephrotic syndrome with associated peripheral oedema, hypo-albuminaemia and varying degrees of impaired glomerular filtration.

Organ	Frequency (%)
Heart	60-90
Kidney	74
Liver	27
peripheral/autonomic nervous system	22
Soft tissues	15
Macroglossia periorbitalpurpura	< 15

Table 1. Organ involvement in AL amyloidosis

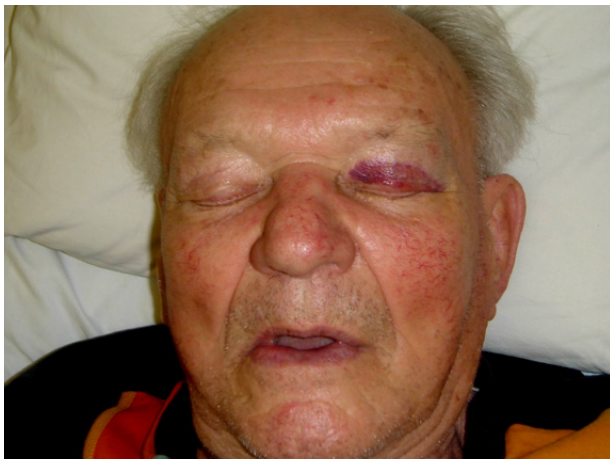

Figure 1. Periorbital bleeding in a patient with AL amyloidosis

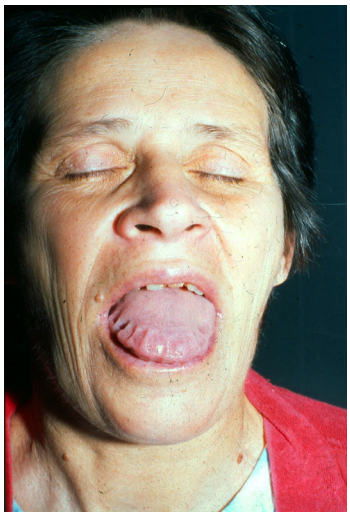

Figure 2. Macroglossia in a patient with AL amyloidosis

The main point of the right diagnosis is to think of amyloidosis: symptoms are so divergent that patients may appear at several points of the health care system (cardiology, nephrology or neurologicalsurgery) and diagnosis may be delayed while symptoms are progressing.

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Cardiac manifestation of amyloidosis

The heart is the most frequently affected by amyloid deposition. Cardiac involvement in AL amyloidosis is present in about 50-80 % of cases and is a key determinant of prognosis. Cardiac amyloidosis causes an infiltrative/restrictive cardiomyopathy. Usually it manifests with heart failure with preserved ejection fraction. Arrhythmias are common and can cause sudden death. Autopsy revealed that intra-cardiac thrombus is present in 50 % of cases. Pericardial fluid accumulation may also occur.

Early cardiac amyloidosis may be difficult to detect, but a history of rapidly diminishing exercise tolerance is a strong indicator. The symptoms of right-sided heart failure appear only in a relatively progressed stage of the disease and manifest in elevated jugular vein pressure and peripheral oedema.

After the international amyloidosis symposium in France in 2004, criteria for organ involvement and treatment response in AL amyloidosis were defined in a consensus paper [7] then it were revised in Rome at the 2010 meeting of the International Society of Amyloidosis. The criteria of cardiac involvement include an increase in mean wall thickness in end-ventricular diastole of ≥ 12 mm by echocardiography, with no other obvious cardiac cause, associated with an increase in the concentration of *N*-terminal pro-hormone of B-type natriuretic peptide (NT-proBNP) to > 332 ng/L(in absence of renal failure).

Electrocardiograms are abnormal in 90% of cases with cardiac involvement. The most common abnormalities are low voltage QRS complex and a pseudo-infarct pattern on the precordial leads in roughly 50% of the patients. Conduction abnormalities (such as second and third degree atrioventricular block), more frequently atrial fibrillation can be observed in about 15% of patients [8].

Echocardiography is a very useful method to identify the cardiac involvement of AL amyloidosis and assess the severity of cardiac dysfunction. The most characteristic aberrances are increased LV wall thickness ≥ 12 mm with 'brilliant' speckled appearance of the myocardium, normal or small LV cavity; preserved LV ejection fraction (LVEF) > 50%, abnormal mitral filling pattern, due to mild or moderate LV diastolic dysfunction, small pericardial effusion in 50% of cases, the presence of which is independently associated with worse survival [9].

Renal manifestations of amyloidosis

Renal manifestation is usually present as asymptomatic proteinuria or clinically apparent nephrotic syndrome. In some patients clinical presentation include impaired kidney function with no or mild proteinuria [10]. When the kidney is involved, renal insufficiency is common, accounting for 47% of cases [11]. Proteinuria has been reported in upwards of 73% of patients with Ig-related renal amyloid with full nephrotic syndrome in 25–68%. Histologically, AL amyloidosis can involve all renal parenchymal compartments, with the glomerulus being the most commonly affected [12].

Neurological manifestation of amyloidosis

Minor peripheral neuropathy is relatively common. It is axonal, predominantly sensory and centripetal. Patients may describe symptoms of paraesthesia or dysaesthesia typically in a 'glove and stocking' distribution reflecting the symmetrically ascending pattern of axonal neuropathy. Carpal tunnel syndrome and previous decompression surgery may precede the diagnosis. Autonomic neuropathy is also common usually asymptomatic, but may manifest as orthostatic hypotension, early satiety due to delayed gastric emptying, disturbances in bowel movements, and erectile dysfunction in males.

Diagnosis of AL amyloidosis

Laboratory diagnosis

A serum and/or urine monoclonal component is detectable by immunofixation and/or immunoelectrophoresis in 80–90% of patients. With the use of sensitive techniques, such as nephelemetric measurement of serum free light chain (LC), an abnormal concentration of serum free LC is found in > 90% of patients, with an over-representation of the lambda isotype compared with the kappa isotype [13].

Coagulation studies: many clotting system abnormalities have been described in AL amyloidosis. Prolongation of the prothrombin time and activated partial thromboplastin time may arise because of the binding of a clotting factor to the amyloid deposits. Renal amyloidosis presents with proteinuria. The 24-hour urinary protein level can be monitored not only at the time of diagnosis, but also thereafter to evaluate the response to chemotherapy. Liver and renal function studies are also required. Plasmocytosis is present in the bone marrow in > 50% of patients.

Histological diagnosis

Once amyloidosis is suspected, the diagnosis requires the demonstration of amyloid deposits in a biopsy. Histological findings using light microscopic examination, show amorphous extracellular Congo red positive deposits, which display characteristic dichroism and apple green birefringence under polarized light.

The abdominal fat aspirate is simple and minimally invasive. In combination with biopsy of the bone marrow stained with Congo red and/or biopsy of a minor salivary gland, it can yield a diagnostic sensitivity of approximately 90%, thus sparing organ biopsies.

If necessary, i.e. when tissue biopsies fail to demonstrate amyloid deposition, biopsy of a clinically affected organ (kidney, gastrointestinal tract or endomyocardial tissue) should be considered.

Biopsy of the liver should be avoided because of the high risk of

bleeding complications.

Electron microscopy may be useful to confirm the presence of amyloid deposits, which typically display the ultrastructural appearance of randomly arranged fibrils), 7–10 nm in external diameter.

Mass spectrometry techniques are now considered a diagnostic standard [14], but this complex and expensive technology is not yet available in most institutions.

The various forms of amyloidosis differ in pathogenesis and prognosis, but they usually show overlapping clinical manifestations, making their differentiation on clinical grounds very difficult. As the different types of amyloidosis require different treatment, amyloid typing is indispensable. The other reason for unequivocal amyloid typing is the high prevalence of a monoclonal component in patients with non-AL amyloidosis.

Immunoelectron microscopy (IEM) is a technique that combines immunohistochemistry and electron microscopy. Using gold-labelled secondary antibodies, IEM can co-localize the protein within amyloid fibrils and greatly reduce background staining, which is the most common cause of reduced specificity in immunohistochemistry. The sensitivity of IEM on abdominal fat is 76.1%, with 100% specificity and 99% correct classification of the amyloid type. Sensitivity is, however, higher in AL λ amyloidosis, the most frequent protein type [15].

Diagnostic criteria and the advised diagnostic procedures are summarized is **Tables 2 and 3.**

Using biomarkers

Screening of early organ damage based on biomarkers can help identify patients with monoclonal gammopathy of undetermined significance who are developing AL amyloidosis before they become symptomatic.

Biomarkers also play a central role in assessing the prognosis and evaluating the response to therapy in AL amyloidosis.

Cardiac involvement is the most serious manifestation of AL amyloidosis, and serum cardiac biomarkers have proved to be of great value in staging disease severity and response to chemotherapy agents. Increased concentrations of NT-proBNP are found in 100% of patients with cardiac AL amyloidosis, and precede symptoms and imaging alterations, allowing diagnosis at very early stages [16]. Cardiac troponin I or T is also valuable prognostic markers.

Renal involvement can be assessed using proteinuria and glomerular filtration rate [7].

Serum FLC measurement, a biomarker of plasma cell dyscrasias, is central for the management of AL amyloidosis and helps in identifying the underlying plasma cell dyscrasia, risk stratifying patients in combination with NT-proBNP and cardiac troponins.

Imaging technics

Beside echocardiography MRI is also a useful non-invasive method to assess the cardiac involvement in amyloidosis [17].

Risk stratification and staging

Proper risk stratification is necessary for choosing the most adequate therapeutic option for patients with AL amyloidosis. The most frequently applied among the several staging system is the Standard Mayo Clinic staging system [18] **Table 4**.

Low risk patients are those of NT-proBNP less than 5000 ng/L, troponins of less than 0.06 ng/ml, eGFR more than 50 ml/min per 1.73m, age less than 65 years, performance status of 0-2, NYHA class less than III, ejection fraction above 45%, systolic blood pressure above 90 mmHg standing and DLCO (Diffusing Capacity of the Lung for Carbon Monoxide) above 90%.

Intermediate risk patients are those of ineligible for ASCT and not worse than IIIa.

High-risk patients are those of stage IIIb, NYHA class III or above.

Adverse prognostic factors are: troponin T ≥0,025 ng/l, NT-proBNP ≥1800 pg/ml, and the difference between involved (amyloidogenic) and uninvolved FLCs is ≥180 mg/l [18].

Poor performance status, decreased GFR, progressed neuropathy, plasma cell ratio more than 20 % are also predict adverse prognosis.

Laboratory examinations	Total blood count Electrolytes, renal and liver function Haemostasis screening tests fX and von Willebrand factor if needed
	Serum and urine electrophoresis Immunofixation Serum and urine free light chain
	Proteinuria (24 hours urine) Creatinine clearance
	Troponin, B-type natriuretic peptide
	sTSH, cortisol
Bone marrow examination, Congo res staining and immunohistochemistry	
Cardiologic examination (included biomarkers, ECG, echocardiography and cardiac MRI)	
Electroneurography in case of neurological symptoms	
Abdominal ultrasound for detecting hepatomegaly and splenomegaly Endoscopic gastrointestinal in case of symptoms	
Respiratory functional tests if pulmonal involvement is suspected	

Table 2. Diagnostic examination for AL amyloidosis

Symptoms that refer to amyloidosis (cardiac, renal, liver, gastrointestinal, neurological symptoms)
Demonstration of amyloid deposition in any organ By tissue biopsy (subcutaneous fat, bone marrow, or affected organs) Staining with Congo red, or by electron microscopic examination
Demonstration of amyloid to be light chain By mass spectrometry or immuno-electronmicroscopy
Demonstration of plasma cell disease Presence of clonal plasma cells and abnormal free light chain κ/λ ratio

Table 3. Diagnostic criteria of AL amyloidosis according to the International Myeloma Working Group (IMWG).

Markers and thresholds	Stages	Outcomes
NT-proBNP> 332 ng/L	I. No markersabovethecutoff	I. Mediansurvival 26 monotreached
cTnT> 0.035 ng/mL (orcTnI> 0.01 ng/mL)	II. One marker abovethecutoff	II. Mediansurvival 11-49 mo
III. Both markersabovethecutoff	III. Mediansurvival 4-6 mo	

Table 4. Standard Mayo Clinic staging system for light chain amyloidosis [18].

Growth differentiation factor-15 (GDF-15) is a protein belonging to the transforming growth factor beta superfamily and acts as a pleiotropic cytokine. GDF-15 levels >7575 pg/ml proved to be associated with early death, shorter survival times and faster progression to dialysis [19].

These data could be useful to guide the choice of optimal treatment, moving toward a patient-tailored approach.

Treatment

Untreated AL amyloidosis patients have a mortality rate of approximately 80% over a two-year period. Treatment can result clinical improvement, with stabilization or regression of the amyloid deposits and preservation of organ function.

The main goals of treatment are to reduce the production of the amyloid precursor protein by eliminating the malignant plasma cell clone in the bone marrow and also to remove the amyloid deposits from the damaged organ tissues. AL amyloidosis results from a balance between amyloid deposition and clearance of deposits. The decrease or halting in the production of amyloidogenic proteins thanks to the treatment moves the balance towards the tissue catabolism of deposits [20]. Appropriate supportive treatment has essential importance.

More recently, different approaches targeting the amyloid deposits and interfering with organ damage have been developed that are being tested in clinical trials [21].

Before decision making a thoughtful clinical assessment of severity of organ disease, associated risks, and prognosis is pivotal for a balanced choice of the most effective treatment with acceptable risks. Patients also require of strict follow-up [22].

Eradicating the underlying plasma cell dyscrasia

For suppression the FLC producing plasma cell clone is basically done by using multiple myeloma protocols. High-dose melphalan followed by autologous stem cell transplantation (ASCT) for eligible patients has shown prolonged survival.This procedure is associated with a substantially higher risk of transplant-related mortality compared to multiple myeloma. ASCT is an option only for a minority of patients as low-risk patients represent approximately 15% of all subjects suffering from AL amyloidosis. With an adequate selection of transplant candidates in expertised haematological centers the outcome is excellent, with haematological response in 71% of subjects, complete response (CR) in 35-37% and overall median survival of 7.6 years [23].
Intermediate risk patients account for approximately 70% of patients with AL amyloidosis. They receive non-transplant chemotherapy. Until recently, a standard treatment for these patients has been oral melphalan and dexamethason. Novel drugs, such as thalidomide, bortezomib, lenalidomide, pomalidomide have shown clear effects, with the best effects in combination with dexamethasone [24]. Based on recent studies, bortezomib should be offered to intermediate-risk patients. For patients with peripheral neuropathybortezomib should be given only with great caution. It can be applied with or without melphalan and dexamethasone with best results with combination of the three agents[25, 26].

High-risk patients: bortezomib can be preferred due to a rapid onset of action or low-dose combination regimens are preferred as well.

Melphalan and Dexamethasone are the preferred regimen especially in the case of neuropathy or t(11;14) translocation. Cyclophosphamide with bortezomib and dexamethasone combination is a stem cell sparing regimen preferred in patients with renal failure and with 1q21 gain.

Young patients with isolated advanced cardiac involvement can be considered for heart transplant followed by ASCT.

There is no standard protocol for relapsed/refractory patients. Bortezomib-based regimen is advised. Carfizomib,daratumumab may also be an option for them [27, 28].

There is no evidence that maintenance therapy could be effective.

Patients should be carefully monitored at least in every two cycles of chemotherapy and in case of not appropriate improvementor progression an immediate switch to a second-line protocol should be carried out.

Therapeutic approaches targeting the amyloid deposits

Drugs that directly target deposited amyloid can be administered as combined treatment with plasma cell directed therapy or to patients who experience haematological response to previous systemic therapy but have persistent organ dysfunction.

Encouraging results by using anti–light chain monoclonal antibody having specificity for an amyloid-related epitope have been recently reported [29].

A monoclonal antibody (NEOD001) to a cryptic epitope on amyloid fibrils has been reported to target amyloid deposits. A randomized, placebo-controlled phase 3 trial is underway [30]. Preliminary results highlight that administration of NEOD001 can result in organ responses not solely attributable to haematological response [31].

Supportive care

Symptomatic measures and supportive care is necessary in patients with organ failure.

Dialysis should be considered for patients with end-stage renal failure without associated severe heart failure.

Diuretics are the mainstay of supportive care for cardiac AL amyloidosis in case of congestive heart failure, digitalis should be avoided. Usual treatments for cardiac failure (i.e. calcium inhibitors, β-blockers, angiotensin converting enzyme inhibitors) are inefficient or may be even dangerous. Amiodarone and pace-maker implantation should be considered in patients with rhythm or conduction abnormalities. [20].

Younger patients with advanced cardiac amyloidosis as the predominant or only clinical feature of amyloidosis should be considered for heart transplantation followed by chemotherapy +/− ASCT.

Bleeding should be managed with conventional supportive therapy (factor replacement, platelet transfusion and anti-fibrinolytic agents).

Patients at a high risk of a venous thromboembolism should be considered for prophylactic low molecular weight heparin.

The autonomic insufficiency can be difficult to manage, especially in patients with severe nephrotic syndrome or severe cardiomyopathy. The α-1 receptor agonist midodrine or the anticholinergic pyridostigmine can improve neurogenic orthostatic hypotension [32]. Patients with gastrointestinal symptoms should receive nutritional supplementation. Metoclopramide can help with gastric emptying.

Early response assessment

A huge international effort has established and validated criteria for assessment of hematologic, cardiac, and renal response to treatment that have been validated in independent series based on patients' outcomes. These criteria allow the identification of refractory patients in time. Response should be assessed at least every 2 cycles or 3 months after ASCT, measuring FLC and biomarkers of organ dysfunction. Patients who fail to rapidly achieve very good partial or complete response or organ response should be immediately switched to potentially effective second-line treatment. [33] **Table**

Prognosis

Patients with AL amyloidosis have a poor prognosis without treatment with an estimated median survival ranging from 6 months to 3 years depending on the patient population. Prognosis is strongly associated with cardiac manifestation and the severity of the heart disease. When symptomatic cardiac dysfunction is present, studies have found a median overall survival without treatment of ~6 months. Cardiac biomarkers, including N-terminal pro-brain natriuretic peptide [NT-proBNP] and cardiac troponins, have been used for assessing cardiac dysfunction severity and prognosis. MRI is also a useful non-invasive method to assess the cardiac involvement in amyloidosis. Recently, MRI feature-tracking peak systolic strain has been demonstrated to be associated with worse prognosis together with myocardial delayed enhancement [17] and non-contrast T1 mapping and also detection of myocardial extracellular volume [34].

Survival is strongly influenced by also the symptomatic hepatic and autonomic involvement [35].

In case of a good response to therapy, significant reduction of LC, reaching complete remission predicts longer survival especially when organ function is also improving.

Patients with gain of chromosome 1q21 have poorer outcome when treated with melphalan and dexamethasone, whereas translocation t(11;14) is associated with inferior survival in patients receiving cyclophosphamide-bortezomib-dexamethasone combination.

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