AL Amyloidosis with Renal Involvement

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Key Words

Amyloid • AA amyloidosis • AL amyloidosis • Nephrotic syndrome • Stem cell transplantation • High-dose melphalan

Abstract

Primary (AL amyloidosis) is a systemic disease characterized by an amyloid deposition process in many organs, with unsatisfactory survival of patients. The monoclonal light chains form the fibrils that deposit and accumulate in tissues. Renal involvement is very frequent in AL amyloidosis and could lead to development of nephrotic syndrome followed by the renal failure in many cases. Classic therapeutic combination melphalan and prednisone has been supplemented with drugs with different mechanisms of action in this group of patients: high-dose dexamethasone, high-dose dexamethasone with melphalan, combination of vincristine, doxorubicin, and dexamethasone or newly high-dose melphalan supported by peripheral blood stem cell transplantation. This progressive therapy leads to the better survival and prognosis in the majority of patients. Alternative therapeutic approaches include thalidomide (alone or in combination with cyclophosphamide), lenalidomide, iododoxorubicin, etanercept and rituximab. The development of immunotherapy is expected in the near future. Copyright © 2007 S. Karger AG, Basel

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Introduction

AL amyloidosis is a result of the clonal plasma cell disorder with an incidence of about 10 persons per million per year [1]. It is the most common and most severe form of systemic amyloidosis. Amyloid deposits containing the light chain (LC) infiltrate the tissues and cause their dysfunction and failure. The most affected organs are kidneys (74%), heart (60%), gastrointestinal tract (10–20%), liver (27%) and autonomic nervous system (18%). 69% of patients had more than one affected organ at the time of diagnosis [2]. Without therapy the median survival is 10–13 months from the time of diagnosis assessment and the survival shortens to 6 months in the group of patients with cardiac involvement [1].

The optimal management of patients with AL requires early diagnosis, correct assessment of the type of amyloid, extent of organ involvement, effective treatment with supportive therapy and a very careful follow-up. The activity of the disease and the hematological response to the treatment could be monitored by plasma levels of monoclonal proteins (MP). Screening electrophoresis is inadequate, since 56% of patients do not have a detectable monoclonal spike. All patients might be screened by immunofixation. Unlike multiple myeloma, in which the majority of patients have a quantifiable amount of MP, many patients with AL amyloidosis do not have a measurable level of MP. The serum level of MP exceeds 1.5 g/l in only about 10% of AL patients. A new method for quantitative measurement of free light chains (FLC) has recently been developed for the detection of MP. This method, using the nephelometric assay, is able to detect

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Table 1. The most frequent types of amyloidosis (nomenclature, fibril proteins and precursors)

Amyloid protein	Precursor	Systemic (S) or localized (L) form	Syndrome or involved organs
A β	A β protein precursor (A β PP)	L	Alzheimer's disease
APrP	Prion protein	L	Cerebral amyloid angiopathy (Dutch type)
ABri	ABri protein	L (S)	Spongiform encephalopathies
ACys	Cystatin C	S	Familial dementia (British type)
A β_2 M	β_2 -Microglobulin	S	Cerebral amyloid angiopathy (Island type)
AL (AH)	Light (heavy) chains of immunoglobulins	S (L)	Dialysis associated
AA	Serum amyloid A	S	Primary amyloidosis (myeloma associated)
ATTR	Transthyretin	S	Secondary (reactive) amyloidosis
			Familial amyloid polyneuropathy
			Senile systemic
AApoAI	Apolipoprotein AI	S	Familial (kidney, liver, heart)
		L	Aorta
AApoAII	Apolipoprotein AII	S	Familial (kidney, heart)
AGel	Gelsolin	S	Familial (Finnish type)
ALys	Lysozyme	S	Familial (kidney, liver, spleen)
AIAPP	Islet amyloid polypeptide	L	Islets of Langerhans (diabetes mellitus, insulinomas)
AFib	Fibrinogen α -chain	S	Familial

Modified according to Westermark et al: Amyloid: toward terminology clarification. Report from the Nomenclature Committee of International Society of Amyloidosis. *Amyloid* 2005;12:1–4.

only small concentrations of FLC in patients with plasma cell disorders, including multiple myeloma and AL amyloidosis. The investigation of bone marrow is necessary to exclude the diagnosis of multiple myeloma or amyloid deposits in the bone marrow. Cardiac dysfunction may be characterized by increasing in concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponins [3].

Pathophysiology of Amyloid Formation

Amyloidoses represent a wide group of protein-folding disorders in which normally soluble proteins are deposited as insoluble fibrils in many organs, where they interfere with the structural integrity and function of targeted tissues. Amyloid deposits are composed of protein fibrils, the peptide subunits of which differ in different forms of amyloidoses. More than 20 different types of the fibrils form the basis for the classification of the clinical amyloidosis syndromes. Amyloidoses could be also divided into localized and systemic forms (table 1). Alzheimer's disease is the most common and typical repre-

sentative of the localized form of amyloidosis, with β -protein deposits found in the brain, while systemic forms of amyloidoses may affect all tissues except the brain.

Glycosaminoglycans (GAG), predominantly heparan sulfate and dermatan sulfate, are the second major components of amyloid deposits, which bind tightly, but non-covalently to the amyloid fibrils. Amyloid P component (AP) is a minor, but a very important part of amyloid deposits with glycoprotein non-fibrillar structure. AP is derived from a circulating precursor serum AP (SAP), which belongs to the acute phase proteins. SAP binds reversibly to all types of amyloid fibrils through a specific calcium-dependent receptor [4]. Apolipoproteins E and J and amyloid-enhancing factor complete the list of components forming amyloid deposits. Amyloid deposits infiltrate various tissues as hyaline eosinophilic material localized extracellularly and have a β -pleated sheet conformation.

The deposits in AL amyloidosis containing the fibrils consist of fragments of the variable portion of monoclonal LC. Although this disorder is associated with the single clone of proliferating plasma cells, most patients do not develop the malignant disease as multiple myeloma,

Fig. 1. Mesangial matrix of glomerulus affected by amyloid deposits. Congo red staining.

Fig. 2. Glomerular LC λ deposits in AL amyloidosis. Immunofluorescence with anti- λ antibody.

but have only monoclonal gammopathy, which is classified as monoclonal gammopathy of undetermined significance (MGUS). This observation indicates that some additional factors are required for development of amyloid deposits. One such property is the ability to be digested by macrophages, where intact LCs are metabolized to insoluble and unstable fragments with biochemical properties that allow them to form amyloid fibrils. The LC λ are more amyloidogenic than κ ones. LC κ have the tendency to form the granular tissue deposits resulting in so-called LC deposition disease [5].

Renal Involvement in Amyloidosis and Diagnosis

AL amyloidosis represents the systemic form of amyloidosis, in which the infiltration of kidneys by amyloid deposits occurs as an early and common event. Renal involvement in amyloidosis usually manifests as nephrotic syndrome in the majority of cases with normal renal function. The rate of progression to renal failure is usually slow, but depends directly on the intensity of proteinuria and extension of amyloid deposits, especially in the vessels and tubules. If the deposits are primarily localized to the vessels, there is little or no proteinuria but renal

insufficiency is commonly due to decreased glomerular perfusion.

A diagnosis of amyloidosis has to be assessed histologically from biopsy specimens. Positive staining for Congo red and fibrillar appearance by electron microscopy is the common property of all types of amyloidoses (fig. 1). Congo red-positive staining leads to the apple-green birefringence under the polarized light microscopy (fig. 2). Immunofluorescence microscopy is typically positive for monoclonal LC κ or λ in AL amyloidosis, while anti-AA antibody (typical for secondary AA amyloidosis) is negative (fig. 3). Deposition of predominantly variable, rather than the constant region explains why immunofluorescence microscopy with anti- λ or anti- κ LC antibodies is sometimes only weakly positive.

Light microscopy in renal amyloidosis typically reveals diffuse glomerular deposition of amorphous hyaline material, especially in the mesangium and also in capillary loops. Amyloid deposits could be seen in the small arteries, arterioles and later on also in the tubular basement membrane. Although radionuclide imaging methods using ^{99m}Tc aprotinin or iodinated SAP can be used to detect and image the deposits, these methods cannot replace the histological proof of amyloid deposits and are not widely available [6].

Fig. 3. Amyloid deposits in arterial wall and tubular basement membrane. Congo red under polarized microscopy.

Definition of Renal Involvement and Treatment Response in AL Amyloidosis

Kidney involvement is defined as presence of amyloid deposits in renal biopsy with clinical and laboratory evidence of kidney dysfunction or bioptically proven amyloid deposits in other organs from alternative biopsy specimens (abdominal fat, bone marrow, rectum, gingiva, etc.) associated with urinary protein excretion ≥ 0.5 g/day. Other causes of proteinuria (diabetes mellitus, uncontrolled hypertension or some autoimmunity) must be excluded. Renal response to the treatment is defined as 50% reduction (at least 0.5 g/day) of 24-hour urinary protein excretion (on the condition that urinary protein is >0.5 g/day initially) in parallel with the stable creatinine and creatinine clearance (both cannot worsen by 25% over baseline) [7].

Therapeutic Possibilities in AL Amyloidosis

There are several different targets which could be potentially influenced by our therapeutic interventions in the treatment of amyloidoses. First, there is the overproduction of structurally normal protein precursors or

quantitatively normal production of structurally abnormal proteins, which might be diminished. Second, the binding of SAP or GAG to the amyloid fibrils, affecting the formation of fibril aggregates, could be blocked.

Since AL amyloidosis develops as a result of neoplastic expansion of the plasma cell population synthesizing the amyloidogenic LCs, the primary therapeutic target remains to be the pathological clone. The crucial clinical endpoint in amyloidosis is organ response. It is clear that the amyloid in organs cannot resolve until the production of precursors has been diminished. After the discontinuation of MP production a slow resolution of amyloid deposits from the tissues (if the organ damage is not irreversible) can be observed [8].

Chemotherapy regimens in AL are based on those used in multiple myeloma despite the fact that the plasma cell dyscrasia in most AL patients is relatively benign and also less chemosensitive. The standard therapy used for more than 30 years is represented by the combination of melphalan (0.15–0.25 mg/kg) and prednisone (1 mg/kg) for 4 days, repeated every 28 days. This relatively myelotoxic therapy is recommended to be administered for a minimum of 12 months and a maximum of 24 months. Prolongation of treatment is accompanied by the dramatic increase in the incidence of acute leukemia and myelodysplastic syndrome [4]. The treatment with high-dose dexamethasone (40 mg of dexamethasone/day on days 1–4, 9–12 and 17–20) is less toxic than melphalan and prednisone with the similar response rate. The combination of high-dose dexamethasone with melphalan is more effective than the previous treatments for the patients ineligible for stem cell transplantation [9]. 67% of patients may achieve a hematological response and 33% of patients may achieve a complete hematological remission. In 48% of patients, functional/organ improvement can be observed after this treatment combination.

VAD (vincristine, doxorubicin, dexamethasone) or C-VAD (cyclophosphamide + VAD) have been reported in AL amyloidosis as a rescue therapy in severe forms of AL not indicated for stem cell transplantation (including those with myocardial involvement, despite doxorubicin itself being cardiotoxic) [4].

Many centers all over the world currently use high-dose chemotherapy with stem cell transplantation as the standard/basic treatment for patients with AL [10, 11]. The patients have to be carefully examined for eligibility for this procedure in order to minimize high peritransplant mortality. Patients at very high risk are those older than 65 years, with more than two affected organs, with significant hypotension (systolic blood pressure ≤ 90

mm Hg) or syncope, with ejection fraction of left ventricle <45% or thickness of interventricular septum ≥ 15 mm [12]. The dose of chemotherapy with melphalan is calculated according to the renal function, age and myocardial involvement (between 100 and 200 mg/m²). Despite the fact that cardiac, liver and kidney function in patients eligible for transplantation is relatively better (compared with those not selected), the treatment-related mortality in many centers recently oscillated around 10–15%. The response to the treatment is very important for the survival. Median survival for patients with more than two organs involvement at the time of transplantation is 21.5 months, and for those with involvement of only one organ exceeds 6 years [8, 13]. Longer survival in the group of patients undergoing the stem cell transplantation could be partly explained by strict patient selection. In a case-matched control study from Mayo Clinic on a cohort of 126 AL patients (63 patients with transplantation, 63 not undergoing transplantation; there was no difference between the groups in sex, age and organ involvement) a significantly longer survival in the group of patients undergoing peripheral blood stem cell transplantation compared with the control group (the majority of patients in this group were treated with alkylating chemotherapy) could have been demonstrated. One- and 4-year survival in the transplant and control group was 89 vs. 71 and 71 vs. 41% respectively [14].

Alternative therapeutic approaches include blockade of TNF- α (soluble receptor – etanercept) and blockade of plasma cells (anti-CD20 antibody rituximab). Thalidomide, that probably acts through the blockade of TNF- α , VEGF (vascular endothelial growth factor) and NF- κ B (nuclear factor- κ B) are reserved for high-risk patients, especially where stem cell transplantation failed [13]. These drugs are now being tested within different clinical trials. Also, drugs effective in multiple myeloma, bortezomib (proteasome inhibitor) and lenalidomide (similar effect as thalidomide), are usually active in AL amyloidosis [15].

I-DOX (4'-iodo-4'-deoxydoxorubicin), an iodinated anthracycline derivate, binds specifically and with high affinity to the natural fibrils and promotes their disaggregation. Its positive therapeutic effect has been observed predominantly in soft tissues as tongue, skin and genitals, with only a sparse effect in parenchymal organs – liver, kidneys and spleen [16].

Heart transplantation should be mentioned as the last therapeutic modality in patients with severe amyloid heart disease. This palliative procedure remains controversial due to a very high postoperative mortality (20%)

and 5-year survival not exceeding 30% [17]. Many centers additionally recommend the necessity of posttransplant treatment with high-dose chemotherapy and stem cell support during the 6-month period after heart transplantation [18].

Causal treatment for the renal involvement in AL amyloidosis is kidney transplantation, which might be accompanied by high-dose melphalan and autologous stem cell transplantation.

A very important role is played by supportive treatment in patients with AL amyloidosis due to the fact that specific treatment needs a certain time to take effect. Salt restriction is important in patients with congestive heart failure and nephrotic syndrome. Diuretic therapy and water restriction are sometimes controversial due to the intravascular water depletion and hypotension in this group of patients. Hypotension (multifactorial – heart failure, hypoproteinemia, autonomic nervous dysfunction, adrenal dysfunction) could be influenced by the use of midodrine or a small dose of mineralocorticoids. Patients with recurrent syncope may benefit from pacemaker implantation, and ventricular arrhythmias can be improved by administration of amiodarone. Anecdotal reports refer about treatment of diarrhea by octreotide [3].

Immunotherapy in AL Amyloidosis

For the future we can expect the rapid development of immunotherapy, both active and passive immunization. In active vaccination fragments of LCs or immunoconjugates of the amino-terminal part of fibril precursors may be used as antigen [19]. Passive immunization with amyloid-reactive antibodies might enhance clearance of amyloid deposits and rapid resolution of experimentally created AL amyloidosis in mice was shown [20].

Conclusion

AL amyloidosis, the most common type from the group of acquired amyloidoses, represents severe diseases with limited response to treatment and unsatisfactory outcome. Only early identification of the disease and aggressive treatment could lead to the remission. The new treatment modalities, including immunotherapy, represent a promising way with hope of better survival for patients.

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