Primary (AL) Amyloidosis in Plasma Cell Disorders

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Key Words. AL amyloidosis • Proliferative plasma cell disorder • Light chain multiple myeloma

Introduction: AL Amyloidosis Is a Multifaceted Clonal Plasma Proliferative Disorder

Amyloidosis is a rare systemic disorder of protein metabolism with progressive extracellular deposition of insoluble fibrillary protein, disorganization of tissue architecture, and subsequent organ dysfunction [1]. In Western countries, the estimated age-adjusted incidence for the most frequent form, the primary systemic immunoglobulin light chain (LC) primary (AL) amyloidosis, is 5.1–12.8 per 1,000,000 persons per year, with 1,275–3,200 new cases annually in the U.S. [2, 3]. In AL amyloidosis, fibrils derive mostly from the N-terminal amino acid residues of LC immunoglobulin variable regions [1, 4], which are synthesized by a

Abstract

Primary (AL) amyloidosis is the most common form of systemic amyloidosis. The morbidity arises from extracellular deposition of immunoglobulin light chain (LC) fibrils in major organs, such as the kidneys, heart, and bowel. Organ dysfunction contributes to a high mortality and poor prognosis, with a median survival time of 1–2 years from diagnosis. Here, we present a 46-year-old man with an exceptional clinical course of an LC multiple myeloma with generalized amyloidosis, causing renal insufficiency, congestive heart failure, and complete intestinal necrosis. We have summarized recent knowledge on AL amyloidosis, its association with monoclonal gammapathies, clinical presentations, diagnostic tools, and treatment strategies. Our comprehensive overview of this rare and often fatal disease aims to increase the awareness of AL amyloidosis. This may facilitate earlier diagnosis, and thus allow initiation of prompt and specific therapies, which are indispensable in order to improve disease prognosis. The Oncologist 2006;11:824–830
monoclonal plasma cell population. Hence, although bone marrow (BM) infiltration can be remarkably subtle [2], AL amyloidosis shares numerical chromosomal changes with monoclonal gamopathy of undetermined significance (MGUS) and multiple myeloma (MM), particularly 13q14 deletions [2] and t(11;14), and belongs to the spectrum of clonal plasma proliferative disorders [5]. Recently, a number of deregulated genes and pathways in AL plasma cells have been described that appear to feed into a common loop related to protein processing and folding, suggesting an association with deregulated protein clearance, degradation, intercellular folding, and increased fibrillogenesis [6]. However, the exact mechanisms of pathogenesis, along with specific differences between MM with and without amyloidosis, have not yet been clearly elucidated.

**AL AMYLOIDOSIS CAN BE ASSOCIATED WITH MM, LC-MM, AND NONSECRETORY-MM**

AL amyloidosis can occur as a primary phenomenon or in association with different forms of plasma cell disorders, such as MGUS or MM [4, 15], with 10%–15% of MM patients developing an AL amyloidosis of vital organs [7–10]. In AL amyloidosis, only 18% of patients have >20% plasma cells in the BM, while the majority (60%) have <10% [6]. By means of immunofixation and electrophoresis of serum and urine, monoclonal immunoglobulins or LCs are detected in ~90% of cases [4, 7]. In those patients without a detectable M-protein, BM immunohistochemistry can verify a monoclonal plasma cell proliferation in approximately another 50%. Contrary to MM, the detectable M-protein consists mostly of \( \lambda \)-LC (70%). The AL \( \lambda \) variant of the monoclonal gamopathy particularly predisposes to the development of manifest amyloidosis (Reinhold P. Linke, personal communication). In contrast, ~80% of MM patients have M-protein in their serum or urine at diagnosis. The remaining patients have LC-MM, which is characterized by the presence of excess immunoglobulin LC (Bence Jones protein) [11], or nonsecretory (NS)-MM [4, 12], which is diagnosed through the demonstration of BM plasma cells >10% and disease-related organ damage, without evidence of a monoclonal protein [12–15]. However, with the introduction of novel LC assays, fewer cases of NS-MM are being observed, because two thirds of patients with NS-MM based on immunofixation have detectable monoclonal free LC (FLC) [15], and these are now better defined as “oligosacerratory myelomas” or LC-MM [12], which is in accordance with immunohistochemical studies revealing cytoplasmic M-proteins within BM plasma cells in ~85% of patients with NS-MM [12]. AL amyloidosis is usually associated with secretory MM or MGUS, whereas amyloidosis in NS-MM has rarely been reported.

**DIAGNOSTIC PROCEDURES AND INTRODUCTION OF THE NOVEL FLC ASSAY**

Diagnosis of amyloidosis is made on the basis of congophilic staining. In addition, most AL patients have serum or urine immunoglobulin abnormalities detectable by electrophoresis or immunofixation. Because of the comparably low sensitivity of electrophoresis, ~20% of patients have no measurable circulating immunoglobulin protein [1, 16, 17]. Immunofixation is more sensitive and can detect free immunoglobulin LC in the urine in up to 80%–90% of patients, but the results are not quantitative and depend on renal function (reabsorptive capacity of the proximal renal tubules and glomerular filtration) [1, 11, 16, 17]. The nephelometric assay Freelite™ (The Binding Site Ltd., Birmingham, England, http://www.thebindingsite.co.uk) provides a sensitive and quantitative method for detection and monitoring of monomer- or dimer-FLC [18]. This assay is particularly useful in NS-MM and LC-MM, with a sensitivity of 68%–86% even in patients with negative electrophoresis and immunofixation [12, 16] and because of the short half-life of serum FLC (2–4 hours) compared with immunoglobulins (IgG half-life 20–25 days), allows a rapid assessment and monitoring of the disease [11, 17, 19]. In AL amyloidosis, a >100-fold greater sensitivity compared with standard electrophoresis methods has been achieved [12, 19].

**CASE REPORT**

Here, we present the exceptional course of LC-MM in a 46-year-old man who was admitted to our intensive care unit because of rapidly deteriorating health, severe weight loss (30 kg in 3 weeks), persistent nausea, fever >39°C, and acute renal failure. Shortly before admission he had consulted a neurologist because of generalized weakness and muscle pain. Because of prolongation of the distal motor neuron latency and a sensory deficit of the median nerve, carpal tunnel syndrome was diagnosed (Table 1).

On admission, he presented with oliguria and nephrotic syndrome (proteinuria, 5.8 g/day; serum creatinine, 3.4 mg/dl; urea, 131 mg/dl), hypercalcemia (2.85 mmol/l), anemia (hemoglobin, 8.5 g/dl), and hypogammaglobulinemia. His heart rate was 160–180 bpm, and the electrocardiogram (ECG) showed nonspecific ST-segment depression in leads II, III, aVF, and V3–V6. Transthoracic echocardiography revealed normal left ventricular function (left ventricular ejection fraction [LVEF], 55%), thickening of both ventricles, with an end diastolic interventricular septal thickness of 14 mm and posterior wall thickness of 14 mm. Brain natriuretic peptide (NT-proBNP) was highly elevated at 31,000 pg/ml (normal, <125 pg/ml). BM cytology and histology showed a dense \( \kappa \)-LC restricted atypical plasma cell infiltration of 70% (Fig. 1A, B), and fluorescence in situ
hybridization (FISH) showed deletion of chromosome 13 (13q14). Renal biopsy revealed a tubular LC, “cast,” nephropathy with tubular epithelial necrosis but minimal glomerular changes. Tubular protein casts were immuno-reactive for \( \kappa \)-LC. Urine immunofixation demonstrated \( \kappa \)-LC and Bence Jones proteinuria (5.6 g/day). Serum FLC quantification (Freelite\textsuperscript{TM}) showed \( \kappa \)-LC >1,700 mg/l (normal range, <19.4). The diagnosis of \( \kappa \)-LC-MM stage IIIB was made, and plasmapheresis and high-dose dexamethasone treatment (20 mg/m\textsuperscript{2} on days 1–4, 9–12, and 18–20)
were immediately initiated. After 5 days of persisting, therapy was escalated with the addition of two i.v. pulses of cyclophosphamide (1 g/week). Despite this treatment, the patient’s condition progressively deteriorated. He developed generalized sepsis with *Enterococcus faecium* bacteremia and *Pseudomonas aeruginosa* pneumonia, requiring catecholamine support and invasive ventilation. Moreover, he suffered from diarrhea and gastrointestinal bleeding. Gastroscopy showed multiple erosive lesions at the cardiosophageal junction and in the first part of the duodenum. A computerized tomography (CT) scan of the abdomen revealed a paralytic ileus, thickened wall of the intestine, and free air. Laparotomy exposed several perforated jejunal lesions, requiring extensive segmental resection. With continuing clinical deterioration, repeat laparotomy 5 days later demonstrated complete ischemic intestinal necrosis (Fig. 2). Despite maximal support, the patient died. Autopsy was refused; however, histology of the ischemic intestinal lesions revealed massive amyloid deposits (Fig. 3A–D). Moreover, examination of all available biopsies showed interstitial and vascular congophilic amyloid deposits in the kidney, vasculature of the BM (Fig. 1C), and interstitium of the gastric mucosa. Although a cardiac biopsy was not obtained, the clinical presentation with tachycardiac arrhythmias, left-ventricular thickening, an NT-proBNP increasing to >105,700 pg/ml, and a serum troponin T rising from 0.63 ng/ml initially to >2.0 ng/ml made cardiac amyloidosis highly likely.

**Clinical Features: AL Amyloidosis Is a Multigorgan Disease**

Morbidity results from infiltration of amyloid fibrils and subsequent dysfunction of major vital organs, with renal failure reported in 28%, congestive heart failure (CHF) in 17%, carpal tunnel syndrome in 21%, polyneuropathy (PNP) in 17%, and orthostatic hypotension in 11% of patients at diagnosis [4]. In addition, purpura, particularly in the periorbital and facial area, is common (15%).

**Cardiac Disease**

Death occurs most commonly in amyloidosis as either a result of progressive congestive cardiomyopathy or sudden death from ventricular fibrillation or asystole. CHF in amyloid cardiomyopathy is usually rapid in onset and progression and is associated with a median survival duration...

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**Figure 1.** Bone marrow (BM) biopsy at diagnosis (histological sections). (A): Giemsa staining: dense plasma cell infiltration accounting for 60%–70%. (B): Positive immunohistochemistry reaction (κ-antibody) of densely infiltrating plasma cells. (C): Congo red staining: amyloid deposits in BM vasculature.

**Figure 2.** Small bowel resection specimen (macro sections). (A): Small bowel resection specimen with large areas of peritonitis surrounding a focus of transmural perforation (arrow). (B): Cut section showing glassy aspect of submucosa resulting from massive amyloid deposition. (C): Mucosal surface with confluent zones of ischemic and hemorrhagic enteritis.

**Figure 3.** Intestinum; resected jejunum (histological sections). (A): Hematoxylin and eosin staining: intestinal necrosis. (B): Congo red staining: massive extracellular and perivascular amyloid deposits. (C): Congo red staining: massive extracellular and perivascular amyloid deposits. (D): Congo red staining: perivascular amyloid deposits.
of only 6 months [1]. The diagnostic gold standard for cardiac amyloidosis is a cardiac biopsy, but clinical tests can be highly indicative: echocardiography usually reveals hypertrophic ventricles with an interventricular septal thickness >12 mm [20] and a low normal to mildly reduced LVEF [3], with CHF being considered a predominantly diastolic phenomenon [21]. ECG frequently shows either low voltage in the limb leads or characteristics consistent with anteroseptal infarction, such as loss of anterior forces, without evidence of infarction at autopsy. Cardiac rhythm disturbances, such as atrial fibrillation, atrial or junctional tachycardia, or heart block, are common [3, 4]. Serum troponin T, a sensitive marker for ischemic cardiac injury, and NT-proBNP, which has been shown to correlate with LV dilatation, dysfunction, and CHF in a nonamyloidosis setting, have been shown to be powerful predictors of survival in amyloidosis, and were feasible even in the setting of end-stage renal disease [20].

Renal Involvement

Renal involvement is common in AL amyloidosis, manifest as proteinuria in 73%, renal insufficiency in ~50%, and nephrotic syndrome or renal failure in 28% of patients [4]. Urinary excreted LCs first deposit in the mesangium of the glomerulus and later extend along the basement membrane [4]. Hypercalcemia, dehydration, infection, nonsteroidal anti-inflammatory agents, and radiographic contrast media may contribute to renal failure. In more than half of the patients, renal function may recover within the first few months [22]. However, 18% of patients with AL amyloidosis require dialysis, which is associated with a median survival time of <1 year [23]. In MM, plasma exchange has been reported to be efficient in removing the underlying monoclonal LCs, and may restore renal function [10]. However, its role and potential benefit—if at all present—seem transient, and thus, it is controversially discussed, has not been validated in prospective randomized trials, and has scarcely been addressed in the specific setting of AL amyloidosis.

Gastrointestinal Amyloidosis

Localized or diffusely spread amyloid involvement of the submucosa, the muscularis mucosa, and subserosa, as well as the vasculature of the gastrointestinal (GI) tract, is frequently observed [9, 22]. It is usually asymptomatic or associated with nonspecific symptoms, such as anorexia, nausea, diarrhea, abdominal pain, weight loss, or malabsorption [22] and pseudo-obstruction [3]. Motor dysfunction of the bowel may result from extensive mucosal amyloid deposition but is more often attributable to autonomic dysfunction [4]. Rare cases of bleeding, from a localized ulcerous amyloid lesion or diffusely, both from the upper and the lower GI tract, have been reported [22]. This may be aggravated by a high prevalence of coagulation defects, including deficiencies of factor X, antithrombin III, factor IX, and inhibitors of the thrombin time [22]. Amyloid obstruction of larger vessels can result in infarction and subsequent perforation of the intestinal wall. This, however, is exceedingly uncommon and has only been reported in isolated cases [24].

Amyloidosis of the Nervous System

Autonomic and sensory neuropathy are relatively common features of AL amyloidosis. Sensorimotor PNP is usually distal, symmetric, and progressive, and may be extremely troublesome. Another frequent manifestation of neuronal amyloidosis is carpal tunnel syndrome, which may precede the final diagnosis of the disease by more than a year. Severe autonomic dysfunction can lead to symptomatic postural orthostatic hypotension and disturbances in gastrointestinal motility [3, 4].

BM and Peripheral Blood

Congo red staining of a BM biopsy demonstrates amyloid deposits in ~60% of patients [1] and when present is usually located in blood vessel walls only [25]. There are no distinctive features in peripheral blood (PB). Anemia is not a prominent feature in AL amyloidosis, but when present, MM, renal insufficiency, and GI bleeding are the most common causes. Thrombocytosis may be observed and is a consequence of functional hypersplenism from amyloid replacement of the spleen, as manifested by detection of Howell-Jolly bodies [4].

TREATMENT AND PROGNOSIS

Prognosis of AL amyloidosis varies depending on the extent of organ involvement, with cardiac and multiorgan involvement having the most adverse impact on outcome. In addition, predictive relevance has been reported for BM plasmacytosis >30%, circulating plasma cells in the PB, Howell-Jolly bodies, increased β2-microglobulin, and circulating cardiac biomarkers (troponins, NT-proBNP) [26]. Whether cytogenetic changes, such as 13q14 deletions determine the clinical course and correlate with prognosis in AL amyloidosis, as seen in MM [27–29], is as yet unclear [2]. Previously, the median overall survival (OS) time in AL amyloidosis was reported as being approximately 8.5 months [4]. With the use of melphalan, cyclophosphamide, dexamethasone, and prednisone, the median OS has increased to 12–18 months, with no difference between melphalan plus prednisone and vincristine, carbamustine, melphalan, cyclophosphamide, and prednisone [16, 30]. Phase II and retrospective analyses of high-dose
chemotherapy with autologous PB stem cell transplantation (auto-PBSCT) have suggested that OS has improved in selected patients [20]. Unfortunately, the rarity and rapid progression of the disease often delay diagnosis until multiorgan involvement limits the ability to treat patients specifically and aggressively [3]. Treatment-related mortality (TRM) for AL amyloidosis patients undergoing auto-PBSCT had initially been approaching 50%, but, with more stringent patient selection, it is now ~15%–25% [20]. Most recently, risk-adapted, high-dose melphalan schedules have been shown to further reduce TRM to 4.4% [31], which prompts hope to possibly achieve TRM rates similar to those of other myeloma patients undergoing auto-PBSCT.

**Conclusion and Discussion**

Despite the unequivocal correlation between AL amyloidosis and monoclonal gammopathies with plasma cell proliferation, there are marked differences with regard to organ involvement, clinical course, and outcome. Although plasma cell infiltration of the BM and the absolute rate of monoclonal immunoglobulin synthesis are generally low in AL amyloidosis, LC products possess a high propensity to form amyloid fibrils with strong tissue affinity [6, 32].

We believe that our case of an LC-MM patient with generalized amyloidosis identifies several important clinical features: (a) An exceedingly rare complication of LC-MM, presenting with severe intestinal and generalized amyloidosis, multiple ischemic perforations, and subsequent complete necrosis of the bowel, was observed. Likewise, tubular LC, cast, nephropathy is a distinctly unusual phenomenon in AL amyloidosis. (b) Despite deteriorating health with signs of multiorgan failure, the diagnosis of the underlying cause was challenging because there was no serum M-protein and the urine diagnostic was delayed with oligo- to anuria under continuous venous hemodialysis. The high neoplastic protein load was therefore best detected in the serum (and consecutively in the urine) via FCL assay. Diagnosis was confirmed by BM cytology and histology, which showed an extraordinarily high plasma cell infiltration. (c) As in our patient, most AL amyloidosis patients present with manifest organ dysfunction at diagnosis. Symptomatic treatment of organ failure may be required acutely but has no direct influence on the underlying plasma cell proliferation. (d) While MM and AL amyloidosis may have a rather chronic clinical course, AL amyloidosis is frequently aggressive, with generalized organ involvement and rapid clinical deterioration despite maximal therapeutic intervention.

In conclusion, AL amyloidosis should be suspected in patients presenting with nephrotic renal insufficiency, CHF, peripheral neuropathy, or nonspecific signs such as obscure hemorrhage or inexplicable abdominal symptoms. A substantial proportion of AL amyloidosis patients have no obvious M-protein, which makes serum electrophoresis and immunofixation alone insufficient to exclude a clonal plasma cell dyscrasia. Use of serum FLC assays on a routine basis should identify patients earlier. Because there is no other routinely administered diagnostic blood test, radiograph, or scan procedure, awareness of the diagnosis and its clinical features is essential to correctly identify these patients. Early diagnosis is critical to enable patients to obtain timely access to therapeutic interventions, and to potentially improve their prognosis in this otherwise uniformly fatal disease.

**Acknowledgement**

We are grateful to Prof. R. Mertelsmann and Prof. C. Bode for their support and thank Prof. Bradwell and Prof. Linke for valuable suggestions and insightful comments. We would also like to thank the entire staff of the intensive care unit Heilmeyer II, Department of Cardiology and Angiology of the Freiburg University Medical Center for their outstanding patient care, and Teresa Leigh for proofreading this paper.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.

**References**


