

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



## Cardiovascular Complications in Patients with AL Amyloidosis

Maurizio Zangari<sup>1</sup>, Tamara Berno<sup>2</sup>,  
Fenghuang Zhan<sup>1</sup>, Guido Tricot<sup>1</sup> and Louis Fink<sup>3</sup>

<sup>1</sup>University of Utah, Division of Hematology, Myeloma Program, Salt Lake City, Utah;

<sup>2</sup>University of Padua;

<sup>3</sup>Laboratory Medicine, Nevada Cancer Institute, Las Vegas, Nevada;

<sup>2</sup>Italy

<sup>1,3</sup>USA

### 1. Introduction

Amyloidosis is a disease characterized by aberrant precursor molecules whose misfolded intermediate forms aggregate and are deposited as interstitial fibrils. The most common type of systemic amyloidosis is immunoglobulin light-chain amyloidosis (AL). Less common types of systemic amyloidosis are the transthyretin (ATTR) types caused by either mutant (hereditary) variants or wild-type ("senile systemic") transthyretin. Although rare in developed countries secondary amyloidosis is associated with autoimmune or inflammatory diseases, chronic infections and malignancies. Different precursor proteins can coexist in the same patient as in the African-American population, which has a 4% incidence of an hereditary ATTR variant (Val122Ile) and a significant incidence of monoclonal gammopathy (1, 2).

The amyloids are highly ordered cross- $\beta$  sheet protein with extra cellular deposition in single or multiple organs. Cardiac deposition, leading to an infiltrative/restrictive cardiomyopathy, is a common feature and may be present at the diagnosis or discovered while investigating a patient presenting with non-cardiac amyloidosis.

AL amyloidosis, is associated with clinical cardiac involvement in about half of all cases, although subclinical involvement may be detected in almost every case at autopsy on endomyocardial biopsy. Laser micro dissection with mass spectrometry assessing the constituents of the Congoophilic deposits is now the gold standard for amyloid typing, obtaining protein type identification in over 98% of cases (3).

Evaluation for cardiac involvement is a critical step of the initial staging of amyloidosis. Criteria for the assessment of organ involvement at baseline and after treatment have been standardized (4). In systemic AL amyloidosis the extent of cardiac involvement has prognostic indications, with a median survival of 6 months for untreated or non-responding patients (5, 6).

### 2. Clotting alterations

The cardiovascular complications observed in patients with amyloidosis range from myocardial involvement to haemostatic dysfunctions leading to thrombotic or hemorrhagic

complications. At presentation, 15-40% of patients with AL amyloidosis experience hemorrhagic manifestations (7, 8). Petechiae, purpura in periorbital and facial areas ecchymosis and bleeding tendencies are common clinical features and severe hemorrhages may contribute to worsening the clinical course and lead to death. Increased fragility of blood vessels and impaired vasoconstriction, caused by deposition of insoluble fiber, are frequent causes of bleeding (9, 10). Acquired coagulation factor deficiency, most commonly factor X, is a unique feature of AL amyloidosis. In a reported large series of patients with primary amyloidosis, 8.9% showed factor X deficiency (defined as factor X activity < 50%); about half of them experienced bleeding episodes and the severity and frequency of these episodes was most pronounced with the lowest factor X levels(11). Absorption of the coagulation factor by AL fibrils, primarily in the liver and spleen is the proposed pathogenetic mechanism. Deficiency of factor X in patients with splenic amyloid in some cases has been corrected by splenectomy which can produce resolution of the bleeding diathesis (12). Normalization of factor X levels has been reported after oral melphalan chemotherapy. Resolution of the bleeding episode was also described in five of 10 patients treated with high dose melphalan followed by autologous stem cell transplantation although bleeding complications in the peritransplant period were fatal in two patients (13). Perivascular amyloid deposition, inhibition of fibrinogen conversion to fibrin, and specific deficiencies of factor X, IX, and V along with circulating heparin-like anticoagulants play important roles in determining the haemostatic abnormalities.

Prolongation of pro-thrombin time (PT), thrombin time (TT), reptilase time (RT) and Russell's viper venom time (RVVT) are the most common coagulation abnormalities. Abnormal fibrinogen and/or elevated fibrinogen/fibrin degradation products (FDP) are considered to be the main factors that affect both TT and RT. It has been postulated that inhibitors must be present in plasma of patients with AL amyloidosis and the inhibitory activity persists in the supernatant even after fibrinogen precipitation (14). Several pathologic conditions other than the presence of a plasma thrombin inhibitor could explain the prolongation of aPTT and PT in AL patients e.g. malabsorption associated with amyloid deposits in the gastrointestinal tract, reduced food intake due to macroglossia or vomiting, liver failure and plasma deficiencies of some clotting factors due to their affinity for amyloid deposits.

Although TT and RT prolongations are peculiar features of AL Amyloidosis, they do not predict bleeding manifestations. Other coagulation abnormalities such as factor X deficiency, enhanced fibrinolysis, and amyloid angiopathy seem to correlate better with clinical symptoms (15).

Deficiencies in specific coagulation factors have long been recognized and along with factor X, acquired deficiencies in factor IX, factor II and factor VII have also been described (16). Hypofibrinogenemia has also been observed in systemic AL amyloidosis in association with disseminated intravascular coagulation and increased fibrinolysis (17).

Hyperfibrinolysis related to a reduced level of  $\alpha$ 2-antiplasmin or to a complex formed with plasmin can be associated with either bleeding manifestations or abnormal coagulation tests in patients with amyloidosis. Bleeding diathesis associated with a shortened clot lysis time and elevated FDP is pathognomonic. The pathogenesis appears to be related to a reduced level of  $\alpha$ 2-antiplasmin, often secondary to complex formation with plasmin (18, 19).

Increased urokinase plasminogen activator activity also has been observed in a patient with primary amyloidosis. Immunoprecipitation studies showed that single-chain urokinase plasminogen activator was the main fibrinolytic agonist in the patient's plasma. Treatment

with  $\epsilon$ -amino-caproic acid was effective in controlling bleeding symptoms in some patients, even when accelerated fibrinolysis is not demonstrable (20). Standard chemotherapy and new novel agents can also induce bleeding complications by multiple mechanisms. Drugs with anti-angiogenic activity may be associated with vascular complications in amyloidosis patients and their use should be closely monitored as these patients could have pre-existing haemostatic abnormalities associated with their paraproteins.

### 3. Cardiac amyloidosis

Definition of cardiac involvement (cardiomegaly, pleural effusions, and Kerley B lines on the chest radiograph) (21) over the past three decades has been supplanted by echocardiography. A granular sparkling appearance with wall thickening, diastolic relaxation abnormalities, right ventricular dysfunction and abnormal echocardiography strain have all been shown to be associated with prognosis (22). Serum cardiac biomarkers have been recently introduced and serum troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) are now widely available. Using a cutoff value of 0.035 mcg/L Troponin T and 332 pg/mL NT-proBNP, patients can be classified into three stages: Stage I both biomarkers low (33% incidence); Stage II, only 1 marker high (37%); Stage III both values high (30% incidence). The reported median survivals are 26.4, 10 and 3.5 months, respectively for Stages I, II, III (23).

The cardiac biomarkers values have been validated in different cohorts of patients treated with either conventional chemotherapy or stem cell transplantation (SCT) (24). Stage III patients are at high mortality risk in SCT studies and also are poor candidates for clinical trials of standard agents (25).

Echocardiography is one of the earliest tests employed in the investigation of suspected heart disease. The specificity of the echocardiographic findings increases in the presence of the clinical manifestations suggestive of myocardial amyloidosis. The earliest finding in cardiac amyloidosis is suggested by reduced diastolic mitral inflow velocities upon Doppler imaging (26, 27).

A granular sparkling texture of the myocardium with increased thickness is strongly suggestive of cardiac amyloid infiltration with a specificity approaching 81%. The addition of the finding of increased septal diameter remarkably increases the specificity of ventricular wall thickness parameter; an interventricular septum thickness of more than 15 mm is also considered a poor prognostic sign (28). The thickness of the left ventricular walls correlates with reduced survival. Low voltage/mass ratio strongly favors the diagnosis of amyloid myocardial infiltration (29). Typical clinical presentation of cardiac amyloidosis with specific echocardiographic findings such as dilated atria, interatrial septal hypertrophy > 7 mm, thickened valves and right ventricular free wall has been proposed as diagnostic of cardiac amyloidosis even without an endomyocardial biopsy (30).

The diagnosis can be confirmed by endomyocardial biopsy and the extent of involvement appears as the most important determinant of clinical outcome as cardiac troponin and NT-proBNP have been shown to be potent prognostic indicators, the suppression of amyloidogenic serum light chains by treatment and reductions in NT-proBNP have been associated with improved outcome.

Circulating amyloidogenic light chains interact with cardiac cell membrane constituents and other local matrix components. Extracellular space amyloid deposition causes myocardial damage by direct cell toxicity mediated by the formation of light chain oligomers (31). The

pathologic features are thickening of all four chambers, biatrial dilatation, a normal or mildly dilated right ventricle and a left ventricular cavity that is normal or small. Myocardial cells are separated and distorted by amyloid deposition. Intramyocardial vessels are frequently infiltrated by amyloid, resulting in impaired vasodilatation, which may result in myocardial ischemia. Rarely amyloid deposits have been found in epicardial vessels resulting in obstructive coronary artery disease indistinguishable on coronary angiography from cholesterol-laden plaques. The predominant manifestation of amyloid heart disease is congestive failure (32).

Accumulation of amyloid in the myocardial interstitium results in late gadolinium enhancement, often with a predominant diffuse, global and subendocardial distribution that matches the distribution of amyloid on histology although other more focal patterns have also been reported. This is associated with substantial alteration in gadolinium kinetics, with faster washout of gadolinium from blood and myocardium than normal (33). Some studies have suggested that gadolinium kinetics may be even more predictive than echocardiography or serum markers. The value of the Cardiovascular Magnetic Resonance (CMR) measurements may in part be due to the fact that cardiac amyloid burden cannot be measured satisfactorily by other techniques, and therefore CMR may offer a fundamental new window into the cardiac pathology in this disease (34). Recognition that T1 mapping in cardiac amyloidosis may be significantly more predictive of poor prognosis than the other currently used measures, its use may be justified when early and more intensive chemotherapy is planned.

A number of the gadolinium kinetics parameters have been significantly associated with mortality, but the one with greatest discriminatory value was the intra-myocardial T1 gradient after gadolinium injection, with 95% accuracy at a threshold value of 23 ms (Kaplan Meier analysis  $P = 0.002$ ). Although further experience and reproduction of these results by other centers is necessary, the technique is in principle straightforward and could be implemented on most 1.5T scanners (35).

#### **4. Gene expression and cytogenetic abnormalities**

Gene expression profiling studies have revealed subsets of genes associated with the development of amyloidosis. A unique molecular profile for AL amyloidosis may be relevant to the development of disease.

The comparison of gene expression profiles between AL, normal BM and myeloma plasma cells has revealed that AL plasma cells had an intermediate transcription profile. A few genes may be of particular relevance in understanding the differences in the pathobiology of these two disease entities. One of these, TNFRSF7, a member of the tumor necrosis factor (TNF) receptor superfamily which codes for CD27, a marker expressed on memory B cells and is important in controlling maturation and apoptosis of plasma cells, has a higher average expression in AL plasma cells. CD27 has been postulated to be important in the oncogenesis of myeloma, since MM plasma cells (PC) do not express this marker, whereas normal PCs do, and the expression of CD27 declines with the more advanced stages of MM. CD27 interacts with its ligand CD70, and this interaction is thought to be important in the differentiation of plasma cells. Interestingly, the tail of CD27 binds a proapoptotic protein, Siva, and CD27-70 interaction may activate a death signal that determines the life span of PCs.

CD27 expression is progressively down regulated in the transition from normal plasma cells to MGUS to MM to myeloma cell lines suggesting that molecular mechanism in AL disease



is an early event. Another gene that was significantly different between AL and MM was the chemokine SDF-1, which is comparatively more highly expressed in AL PCs. However, SDF-1 levels in normal PCs are higher than those expressed in AL (36, 37). Whereas over expression of SDF-1 has been implicated in preventing apoptosis, promoting proliferation and metastatic spread in a number of neoplastic diseases through interactions with CXCR4, it is apparent that the relatively high levels of SDF-1 in normal and AL PCs have a paradoxical effect. This paradox can be explained by the binding of SDF-1 to CXCR4 which results in activation of the suppressors of cytokine signaling (SOCS) proteins, in particular, SOCS-3, which can negatively regulate CXCR4 function without interfering with surface receptor expression.

Clonal AL plasma cells express recurring cytogenetic abnormalities, including t(11,14), gain 11q, del 13q, and gain 1q. Interestingly, t(11;14) was associated with worse overall survival in a recent study of AL patients (38). Over expression of cyclin D1 (CCND1 located on chromosome 11q13) in purified AL plasma cells occurs in one-half of AL patients and is associated with unique pathobiologic characteristics at diagnosis: including high frequencies of light-chain only M proteins and kappa light chains, increased cardiac biomarker levels, and poorer overall survival (39).

## 5. Therapy

The therapy aim for AL amyloidosis is to eliminate the clonal plasma cells producing the toxic precursor protein. Once a case of amyloidosis is recognized, it is vital to precisely determine the type of amyloid as the prognosis and treatment differ considerably among the various types. The management of heart failure in patients with amyloidosis remains challenging. Judicious diuretics use and salt restriction with avoidance of intravascular volume depletion remains the mainstay of the treatment. Angiotensin-converting enzyme inhibitors and Angiotensin-II receptor blockers are poorly tolerated in cardiac amyloidosis. The role of calcium channel blockers and digoxin is limited and probably detrimental. This is due to an exaggerated negative inotropic effect. A high incidence of sudden death in patients treated with digoxin has been reported (40).

Heart transplantation remains a controversial option because of the systemic involvement and the potential recurrence of graft Amyloidosis (41). In primary amyloidosis, heart transplantation is only a palliative procedure and consequent supportive chemotherapy should be considered. The long-term prognosis is poor (39% survival at 4 years in one study and 30% at 5 years in another, even with adjuvant chemotherapy. Sequential heart and autologous stem cell transplantation for primary amyloidosis has been reported (42).

Active agents in the treatment of the amyloid include corticosteroids (prednisone, dexamethasone), alkylating agents (melphalan, cyclophosphamide), immunomodulatory drugs (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib). Conventional chemotherapy based on melphalan and prednisone was introduced in 1972 can achieve a median survival of 12 to 18 months and in patients with severe cardiac failure, continuous, oral, daily melphalan has been used as palliative method (43). Based on the observation that dexamethasone as single agent was able to produce hematological and organ responses, melphalan and dexamethasone have been later used in combination in this setting (44). Melphalan and dexamethasone is still now considered a front-line therapy, inducing a hematological response of 67% of the time with a 33% of CR and an organ response rate of 48% in a phase II study of 45 patients. A 5-year follow-up the study showed a median PFS of

3.8 years and OS of 5.1 years. Subsequent studies have later confirmed the efficacy of this combination (45).

Amyloid therapy remained unchanged until the introduction of stem cell transplantation (SCT) which was designed to target rapidly the amyloidogenic light chain production by the clonal plasma cell populations. High rates of hematological and organ response have now been documented in multiple centers with long-term data reported and median survivals of over a decade for SCT patients achieving complete response. The high rate of treatment-related mortality (5 to 10% even at experienced centers) would explain the failure to show a survival advantage when compared to standard therapy in a large prospective randomized trial (46). Risk-adapted SCT, which tailors the melphalan dose according to age and risk status of the patient, may improve early survival (47). To compensate for the loss of efficacy due to attenuated conditioning, adjuvant therapy post SCT for patients not achieving a CR has been tested. Thalidomide and dexamethasone or bortezomib and dexamethasone has been used as adjuvant therapy post SCT with CR rates at 12 months post SCT of 39% and 65% of evaluated patients (48).

The propensity for sudden cardiac death, the frequency of multi-organ involvement and the problem of progressive organ disease and drug-related side effects has limited clinical research in amyloid. The first novel agent to be tested in relapsed AL was thalidomide. Initially it was poorly tolerated at high doses but showed efficacy at moderate doses in combination with dexamethasone and alkylating agents (melphalan or cyclophosphamide) resulting in hematological and organ responses. Current recommendations suggest to start with thalidomide at a dose of 50 mg daily and it can be increased if tolerated (49).

Lenalidomide has been combined with dexamethasone in two studies with hematological response of 41% and 67% respectively. Several phase I/II combining Lenalidomide and dexamethasone with an alkylating agent (melphalan or cyclophosphamide) have been recently completed. In a phase 1/2 dose-escalation study of lenalidomide in combination with melphalan and dexamethasone. A complete hematological response was achieved in 42% at the dose of 15 mg of lenalidomide per day. After a median follow-up of 19 months, estimated 2-year overall survival (OS) and event-free survival (EFS) were 80.8% and 53.8% respectively (50).

In a preliminary report on a phase II study of the thalidomide derivative pomalidomide with weekly dexamethasone in AL amyloidosis patients previously treated with SCT and alkylating agents lenalidomide or thalidomide one-third achieved a hematological response by 6 months, highlighting the promising anti amyloid effect of this potent immunomodulatory drug (51).

Bortezomib is a selective inhibitor of the 26S proteasome, a protein complex involved in the regulation of degradation of aberrant proteins as well as for the regulation of other proteins involved in the regulation of apoptosis, and cell-cycle progression.

Single agent Bortezomib in a phase I dose escalation study achieved hematological responses in 50% of patients and CR in 20%. A multicenter study of 94 AL amyloid patients treated with bortezomib with or without dexamethasone has reported hematological responses in 71% and CR in 25% of patients; cardiac response was documented in 29% of subjects (52). Bortezomib is currently being evaluated in combination with melphalan and dexamethasone in 2 trials in Europe and USA.

The past decade has seen significant advances in the treatment of patients with AL, leading to improvements in both quality of life and survival. The novel agents have significantly

expanded the armamentarium against AL. The central challenges of this decade will be how to combine these agents and how to bring forth new ones for approval.

## 6. References

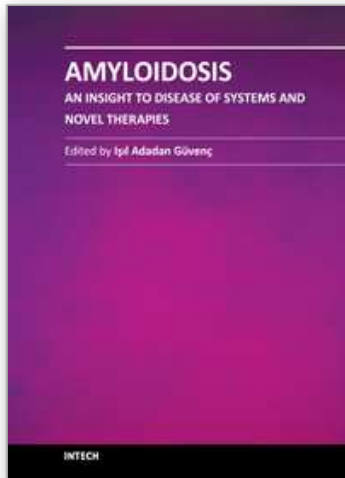
- [1] Lachmann HJ, Booth DR, Booth SL, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med*. 2002;346:1786-1791.
- [2] Comenzo RL, Zhou P, Fleisher M, Clark B, Teruya-Feldstein J. Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. *Blood*. 2006;107:3489-3491.
- [3] Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3d, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114:4957-4959.
- [4] Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10<sup>th</sup> International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Haematol*. 2005;79:319-328.
- [5] Lebovic D, Hoffman J, Levine BM, et al. Predictors of survival in patients with systemic light-chain amyloidosis and cardiac involvement initially ineligible for stem cell transplantation and treated with oral melphalan and dexamethasone. *Br J Haematol*. 2008;143:369-373.
- [6] Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32:45-49.
- [7] Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32:45-59.
- [8] Mumford A, O'Donnell J, Gillmore J, et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. *Br J Hematol*. 2000;110:454-460.
- [9] Sucker C, Hetzel GR, Grabensee B, et al. Amyloidosis and bleeding: pathophysiology, diagnosis and therapy. *Am J Kidney Dis*. 2006;47(6):947-55.
- [10] Hoshino Y, Hatake K, Muroi K, et al. Bleeding tendency caused the deposit of amyloid substance in the perivascular region. *Intern Med*. 1993;32(11):879-881.
- [11] Choufani E, Sanchowarala V, Ernst T, et al. Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high dose chemotherapy. *Blood*. 2001; 97:1885-1887.
- [12] Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in primary amyloidosis: resolution after splenectomy. *N Engl J Med*. 1979;301(19):1050-1051.
- [13] Rosenstein ED, Itzkowitz SH, Penziner AS, et al. resolution of factor X deficiency in primary amyloidosis following splenectomy. *Arch Intern Med*. 1983;143(3):597-599.
- [14] Gamba G, Montani N, Anesi E, et al. Clotting alterations in primary systemic amyloidosis. *Haematologica*. 2000;85(3):289-92.
- [15] Galbraith PA, Sharma N, Parker WL, et al. Acquired factor X deficiency. Altered plasma antithrombin activity and association with amyloidosis. *JAMA*. 1974;230(12):1658-1660.
- [16] Korsan-Bengsten K, Hjort PF, Ygge J. Acquired factor X deficiency in a patient with amyloidosis. *Thromb Diath Haemorrhag*. 1962;7:558-566.



- [17] McPherson RA, Onstad JW, Ugoretz RG, Wolf PL. Coagulopathy in amyloidosis: combined deficiency of factors IX and X. *Am J Hematol.* 1977;3:225-35.
- [18] Liebman H, Chinowsky M, Valdin J, et al. Increased fibrinolysis and amyloidosis. *Arch Intern Med.* 1983; 143(4):678-82.
- [19] Takahashi H, Koike T, Yoshida N, et al. Excessive fibrinolysis in suspected amyloidosis: demonstration of plasmin-alpha 2-plasmin inhibitor complex and von Willebrand factor fragment in plasma. *AM J Hematol.* 1986;23(2):153-66.
- [20] Liebman HA, Crfagno MK, Weitz IC, et al. Excessive fibrinolysis in amyloidosis associated with elevated plasma single-chain urokinase. *Am J Clin Pathol.* 1992; 98(5):534-541.
- [21] Desai HV, Aronow WS, Peterson SJ, Frishman WH. Cardiac amyloidosis: Approaches to diagnosis and management. *Cardiol Rev.* 2010;18:1-11.
- [22] Koyama J, Falk RH. Prognostic significance of strain Doppler imaging in light-chain amyloidosis. *JACC Cardiovasc Imaging.* 2010;3:333-342.
- [23] Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: A staging system for primary systemic amyloidosis. *J Clin Oncol.* 2004;22:3751-3757.
- [24] Kumar S, Dispenzieri A, Gertz MA. High dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med.* 2008;358:91.
- [25] Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. *Blood.* 2007; 109:465-470. Epub 2006 Sep 28.
- [26] Cueto-Garcia L, Tajik AJ, Kyle RA, et al. Serial echocardiographic observations in patients with primary systemic amyloidosis: an introduction to the concept of early (asymptomatic) amyloid infiltration of the heart. *Mayo Clin Proc.* 1984;59:589-97.
- [27] Koyama J, Ray-Sequin PA, Davidoff R, et al. Usefulness of pulsed tissue Doppler imaging for evaluating systolic and diastolic left ventricular function in patients with AL (primary) amyloidosis. *Am J Cardiol.* 2002;89:1067-71.
- [28] Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. *J Am Coll Cardiol.* 2007;50:2101-10 [PubMed]
- [29] Kothari SS, Ramakrishnan S, Bahl VK. Cardiac Amyloidosis- An Update. *Indian Heart J.* 2004;56:197-203.
- [30] Simons M. Amyloid cardiomyopathy in Updateonline 12.3
- [31] Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler Echocardiography in patients with AL (primary) Cardiac amyloidosis. *Circulation.* 2003;107:2446-2452.
- [32] Maceira Am, Joshi J, Prasad SK, et al. Cardiovascular Magnetic resonance in cardiac amyloidosis. *Circulation.* 2005;111:186-193.
- [33] Sueyoshi E, Sakamoto I, Okimoto T, Hayashi K, Tanaka K, Toda G. Cardiac amyloidosis: typical imaging findings and diffuse myocardial damage demonstrated by delayed contrast-enhanced MRI. *Cardiovasc Intervent Radiol.* 2006;29:710-2.
- [34] Cheng AS, Banning AP, Mitchell AR, Neubauer S, Selvanayagam JB. Cardiac changes in systemic amyloidosis: visualisation by magnetic resonance imaging. *Int J Cardiol.* 2006;113:E21-3.

- [35] Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hyperthrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2003;41:1561-7.
- [36] Guikema JE, Hovenga S, Vellenga E, et al. CD27 is heterogeneously expressed in multiple myeloma: low CD27 expression in patients with high-risk disease. *Br J Haematol* 2003;121:3643
- [37] Zhan F, Barlogie B, Arzoumanian V, Huang Y, Williams DR, Hollmig K, Pineda-Roman M, Tricot G, van Rhee F, Zangari M, Dhodapkar M, Shaughnessy JD Jr. Gene-expression signature of benign monoclonal gammopathy evident in multiple myeloma is linked to good prognosis. *Blood.* 2007 15;109(4):1692-700.
- [38] Bochtler T, Hegenbart U, Cremer FW, et al. Evaluation of the cytogenetic aberration pattern in amyloid light-chain amyloidosis as compared with monoclonal gammopathy of undetermined significance reveals common pathways of karyotypic instability. *Blood.* 2008;111:4700-4705
- [39] Comenzo RL, Hofman JE, Hassoun H, Landau H, Iyer L, Zhou P. Pathobiologic associations of plasma cell (PC) overexpression of *Cyclin D1 (CCND1)* in systemic AL amyloidosis (AL) [abstract]. *Amyloid.* 2010;17(s1):61.
- [40] Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation.* 2005;112:2047-60. [PubMed]
- [41] Shan KB, Inoue Y, Mehra MR. Amyloidosis and the heart. A comprehensive review. *Arch Intern Med.* 2006;166:180-1813. [PubMed]
- [42] Kholová I, Kautzner J. Current treatment in cardiac amyloidosis. *Curr Treat Options Cardiovasc Med.* 2006;8:468-473. [PubMed]
- [43] Kyle RA, Bayrd ED. Amyloidosis: Review of 236 cases. *Medicine.* 1975;54:271-299.
- [44] Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood.* 2004;103:2936-2938. Epub 2003 Dec 18.
- [45] Palladini G, Russo P, Nuvolone M., et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood.* 2007; 110:787-788.
- [46] Mhaskar R, Kumar A, Behera M, et al. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: A systematic review. *Biol Blood Marrow Transplant.* 2009;15:893-902. Epub 2009 Apr 2.
- [47] Cohen AD, Zhou P, Chou J, et al. Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light chain amyloidosis: results of a phase II trial. *Br J Haematol.* 2007;139:224-233.
- [48] Landau H, Hassoun H, Bello C, et al. Adjuvant bortezomib and dexamethasone following risk-adapted melphalan and stem cell transplant in systemic AL amyloidosis [abstract]. *Amyloid.* 2010;17(s1):80.
- [49] Palladini G, Perfetti V, Perlini S, et al. The combination of thalidomide and intermediate-dose dexamethasone is an effective but toxic treatment for patients with primary amyloidosis (AL). *Blood.* 2005;105:2949-2951.
- [50] Moreau P, Jaccard A, Benboubker L, et al. Lenalidomide in combination with melphalan and dexamethasone in patients with newly AL amyloidosis: a multicentre phase I/II dose escalation study [abstract]. *Blood.* 2010 Dec 2;116(63):4777-82. Epub 2010 Aug 19.

- [51] Dispenzieri A, Gertz MA, Hayman SR, et al. A pilot study of pomalidomide and dexamethasone in previously treated light chain amyloidosis patients [abstract 3854]. *Blood*. 2009;114.
- [52] Kastiris E, Wechalekar AD, Dimopoulos MA, et al. Bortezomib with or without dexamethasone in primary systemic (light-chain) amyloidosis. *J Clin Oncol* 2010; 28:1031-1037. Epub 2010 Jan 19.
- [53] Wechalekar AD, Lachmann HJ, Offer M, et al. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. *Haematologica*. 2008;93:295-298.



## **Amyloidosis - An Insight to Disease of Systems and Novel Therapies**

Edited by Dr. Işıl Adadan Güvenç

ISBN 978-953-307-795-6

Hard cover, 194 pages

**Publisher** InTech

**Published online** 16, November, 2011

**Published in print edition** November, 2011

Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Maurizio Zangari, Tamara Berno, Fenghuang Zhan, Guido Tricot and Louis Fink (2011). Cardiovascular Complications in Patients with AL Amyloidosis, *Amyloidosis - An Insight to Disease of Systems and Novel Therapies*, Dr. Işıl Adadan Güvenç (Ed.), ISBN: 978-953-307-795-6, InTech, Available from: <http://www.intechopen.com/books/amyloidosis-an-insight-to-disease-of-systems-and-novel-therapies/cardiovascular-complications-in-patients-with-al-amyloidosis>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen