4

Cardiovascular Complications in Patients with AL Amyloidosis

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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-β 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 subclincal involvement may be detected in almost every case at autopsy on endomyocardial biopsy. Laser micro dissection with mass spectrometry assessing the constituents of the Congophilic 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). Petecchiae, 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 wich 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 determing 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 in 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 α2-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 α2-antiplasmin, often secondary to complex formation with plasmin (18, 19).

Increased urokinase plasminogen activator activity also has been observed 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 ε-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 echocardiographyc 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 echocardiographyc 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 (TNR) 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) wich 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 reccomendations 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 lenalinamide 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 improvement s 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.

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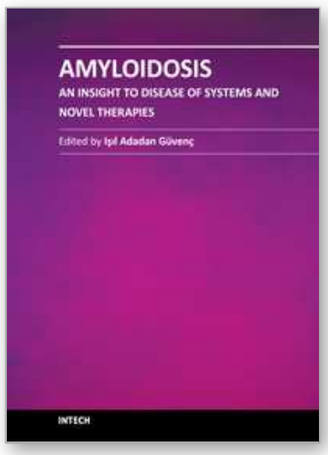

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Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of 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.

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