Renal aspects of amyloidosis

D. Heininger

Department of Internal Medicine IV, Medical University of Innsbruck, Innsbruck, Austria

Received 7 November, 2011; accepted 23 February 2012

The term “amyloidosis” covers a group of conditions characterised by extracellular protein deposits in the form of insoluble fibrils with a beta-pleated sheet structure. Systemic amyloidoses very often involve the kidney, as the primary AL (Ig light chains), the secondary AA (amyloid A), but also some hereditary forms of amyloidosis. The main renal symptom of amyloidosis is proteinuria. In addition to histological work-up using light microscopy, immunohistochemistry and electron microscopy, diagnosis often calls for amyloid classification by means of DNA sequencing or laser microdissection with mass spectrometry. The therapeutic approach depends on the underlying primary disease but especially in AL amyloidosis new chemotherapeutic options and interesting data from bone marrow as well as solid organ transplantation have recently become available.

Keywords: Amyloidosis, proteinuria, renal biopsy, hemodialysis, renal transplantation.

Abbreviations: AA (amyloid A), AApo AII (apolipoprotein AII), AApo AI (apolipoprotein AI), AFib (fibrinogen A-alpha chain), AH (Ig heavy chains), AL (Amyloidosis associated with Ig light chains), ALys (lysozyme), ATTR (transthyretin), ESRD (end-stage renal disease), FMF (familial Mediterranean fever), HCT (hematopoietic cell transplantation), HDM (high dose melphalan), PAS (periodic acid Schiff), RAS (renin-angiotensin system), SAA (serum amyloid A), sFLC (serum free light chain).

Introduction

The term “amyloidosis” covers a group of conditions characterised by extracellular protein deposits in the form of insoluble fibrils with a beta-pleated sheet structure. Depending on the precursor protein of the fibrils, this can lead to localised or systemic forms of amyloidosis with increasing organ dysfunction. When untreated, renal amyloidosis progresses to end-stage renal disease (ESRD) necessitating renal replacement therapy.

Currently more than 20 proteins are known that are able to cause amyloidosis. Initially, as the result of a misfold-

ing event, insoluble intermediate forms are produced that have a strong tendency for autoaggregation and that form fibrils by producing protofilaments [1]. The type of amyloidosis is classified from the underlying protein and the fibril distribution pattern and is designated “A” followed by the abbreviation for the precursor protein.

Systemic amyloidosis frequently involves the kidney, especially in the primary AL (Ig light chains) and the rare AH (Ig heavy chains), the secondary AA (amyloid A), but also in the hereditary forms of amyloidosis such as AFib (fibrinogen A-alpha chain), AApo AI (apolipoprotein AI) und AApo AII (apolipoprotein AII) as well as ALys (lysozyme) and rarely ATTR (transthyretin) [2].

Clinical presentation

The major renal symptom of amyloidosis is proteinuria, which (depending on the localisation of the amyloid deposits) is mostly of glomerular origin in amyloidosis and does albuminuria. It ranges from subnephrotic range to a nephrotic syndrome, for which reason amyloidosis should always be considered as a possible differential diagnosis in patients presenting with proteinuria, especially in the presence of systemic signs of amyloidosis. For proteinuria in the nephrotic range (>3.5 g/d, predominantly albumin) an intraglomerular localisation of the amyloid deposits is probable. The nephrotic syndrome is accompanied by dysproteinemia with hypoalbuminemia with pronounced edema, hyperlipidemia, reduced kidney function (optional) and increased likelihood of thrombosis. If the deposits are found predominantly in the tubulointerstitium, proteinuria is commonly less pronounced (Bence Jones proteinuria). Deposits located in the vessel walls can cause hypertension, which is otherwise rare in amyloidosis [10]. Other complications are nephrogenic Diabetes insipidus accompanying deposits in the collecting ducts [3] and Fanconi syndrome when the proximal tubule epithelium is damaged [4]. A predominance of amyloid deposits in the medulla, as is seen for apo AI amyloidosis and less frequently also for AA amyloidosis, can be difficult to diagnose because renal biopsy cylinders rarely contain medulla. Crescentic glomerulonephritis with mesangial amyloid deposits and nephritic sediment is a very rare form, seen mostly in AA amyloidosis secondary to rheumatoid arthritis [5].

Independent of the specific symptoms induced by amyloid deposits, as in any kidney disease a number of factors such as

Correspondence: Dorothea Heininger, MD, Department of Internal Medicine IV, Medical University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.
 E-mail: Dorothea.heininger@uki.at

dehydration, nephrotoxic medication, infections or thrombosis of the renal veins make the kidney more vulnerable and can cause acute renal insufficiency.

Diagnosis

Diagnosis of renal amyloidosis is performed by renal biopsy [6]. Assessment of the biopsy specimen must include light microscopy, immunohistochemistry and electron microscopy. On light microscopy amyloidosis can be suspected in the presence of nodular glomerulopathy with amorphous, cell-poor weak PAS- and methenamine silver-positive material seen not only in the mesangial area but also in the glomerular capillary loops, tubular basement membranes or the vessel walls of small arteries and arterioles (Fig. 1). Diagnostic proof is obtained with a positive Congo Red stain, i.e. a salmon pink stain of the amyloid fibrils, which under polarised light occurs apple-green (Figs. 2 and 3).

Fig. 1: Light microscopy: weakly PAS-positive material in a glomerulus, expanding the mesangium and producing a nodular appearance. This amorphous material is also evident in the wall of the arteries and arterioles. Image courtesy of H. Hopfer

Fig. 2: Light microscopy/Congo Red stain: salmon-red amyloid in the interstitium under nonpolarized light. Image courtesy of H. Hopfer

Fig. 3: Light microscopy/Congo Red stain: amyloid-defining stain that shows an apple green birefringence under polarised light. Image courtesy of H. Hopfer

If renal biopsy is not possible or if additional tissue is needed for amyloid classification, abdominal fat aspiration can be performed. Sensitivity of Congo Red staining of abdominal fat is approx. 80–90% for AL, 65–75% for AA amyloidosis and lower for hereditary forms [7].

Since amyloid deposits are often scantily distributed in renal tissue, they can be missed by light microscopy. Electronmicroscopic assessment is therefore essential for the diagnosis or exclusion of amyloidosis (Fig. 4). Here, fibrils with a diameter of approx. 8–10 nm are found in the mesangium, basal membranes, interstitium and vessels, with various precursor proteins influencing pattern as well as localisation of deposits [8]. Very sparse deposits can also be missed by electron microscopy and the renal disorder can thus be misdiagnosed as minimal change nephropathy.

However, since the various forms of amyloid cannot be differentiated by light microscopy or electron microscopy, immunohistochemistry should be performed with specific antibodies in order to determine the amyloid type. AL amyloidosis is optimally seen to have a monoclonal positivity for one of the Ig light chain isotypes (lambda-kappa). However, the background staining often prevents definitive

Fig. 4: Electron microscopy: Amyloid fibrils in the basement membrane of a glomerulus. Image courtesy of H. Hopfer

Fig. 5: Immunohistochemistry/Amyloidtyping: Strong positivity for AA amyloid. Image courtesy of H. Hopfer

assessment of the stain, and not even a negative stain permits exclusion of AL amyloidosis [9]. AA amyloidosis, on the other hand, is usually reliably detected with the commercially available antibodies against AA protein [10] (Fig. 5).

For assessment of prognosis and above all for therapy planning depending on the underlying disorder, precise determination of the amyloid type is essential. The study by Lachman et al. showed that approx. 10% of those patients in whom AL amyloidosis was suspected (80% of whom showed monoclonal gammopathy in serum and/or urine electrophoresis and immunofixation) were ultimately seen to have a hereditary form, which underscores the importance of a precise workup [11].

When AL amyloidosis is clinically suspected, but immunohistology of the biopsy specimen shows no clonal light chains (lambda or kappa), classification must be performed by serum free light chain assay in combination with paraprotein in serum protein electrophoresis (98% screening sensitivity) plus urinary screening with immunofixation as well as confirmation of clonal plasma cells in bone marrow. If negative, other forms of amyloidosis must be excluded [12]. Also AA amyloidosis must be immunohistologically proven, because if negative other forms have to be excluded.

Hereditary amyloidosis is probable in patients with positive family history, but variable penetrance can also mean that no affected individual can be identified. Diagnosis of a hereditary amyloidosis can be confirmed by DNA sequencing. The current gold standard for typing of amyloid is laser microdissection with mass spectrometry analysis, enabling amyloid identification in 98% of cases [13].

Therapy

Planning of the treatment regimen requires a precise diagnosis of the amyloid type as well as a meticulous, standardised assessment of the involved organ systems, above all the heart [14].

Besides therapy directed against the underlying disorder the general basis of renal therapy is to treat complications such as the nephrotic syndrome by means of RAS

blockers, diuretics, low-salt diet and, if necessary, anti-hypertensive as well as anticoagulant therapy and if necessary planning for and performance of renal replacement therapy.

AL amyloidosis

Standard first line therapy options are melphalan/dexamethasone or high-dose melphalan followed by autologous or allogeneic hematopoietic cell transplantation (HDM/HCT) with not only high rates of hematological and organ response, but also high treatment-associated mortality (10–15%) for HCT. The outcome of the treatment with HDM/HCT was not superior to the outcome with standard dose melphalan/dexamethasone [15]. Severity of proteinuria is an independent predictor of renal response after HCT, patient survival is superior in those who achieve renal response, which is a cumulative effect to the benefit of hematologic response [16]. Risk-adapted approaches with adaptation of the melphalan dose to patient age and risk status show improved early survival and reduced treatment-associated mortality. Acute renal failure occurs in 20% of patients following high-dose melphalan; these patients needed dialysis significantly more often and showed poorer 90-day survival, but no difference in long-term survival [17].

Novel agents for therapy of AL amyloidosis are thalidomide/dexamethasone as adjuvant post-HCT therapy [18], cyclophosphamide/thalidomide/dexamethasone [19], as well as lenalidomide/dexamethasone [20], pomalidomide/dexamethasone [21] and bortezomib/dexamethasone [22] or new combinations such as bortezomib/melphalan/dexamethasone.

The presence of lambda light chains predicts the increased likelihood of renal involvement - those patients with lambda light chains had greater urinary protein loss than did those with kappa light chains. Baseline proteinuria and serum creatinine predict, which patients will require dialysis [23]. The extent of the serum free light chain (sFLC) reduction by treatment is associated with outcome, and serial measurements of sFLC are a good form of therapy monitoring [24].

Prognosis for AL amyloidosis largely depends on the extent of cardiac involvement; median survival of untreated or non-responding patients with symptomatic cardiac AL amyloidosis is six months, the biomarkers troponin T or I and NT-proBNP are highly sensitive for cardiac involvement and prognosis with regard to survival [25]. So the treatment outcome should be assessed by monitoring the serologic and the organ response.

AA amyloidosis

The therapeutic approach for AA amyloidosis is to treat the underlying infection, autoimmune disorder or malignancy in order to reduce the excessive production of the acute-phase reactant serum amyloid A (SAA) and thus AA amyloid formation as well as to stabilize renal function and reduce proteinuria. In rheumatoid diseases biologics as antagonists of TNF alpha, IL-6 or IL-2 might be helpful [26]. In patients with familial Mediterranean fever (FMF) as the underlying disease colchicine can prevent disease progression [27].

Hereditary amyloidosis

Orthotopic liver transplantation is the therapy of choice for ATTR. Proteinuria did not change significantly, but renal function remained stable for several years [28]. Combined liver-kidney transplantation is curative for AFib [29]. Liver transplantation is not an option for ALys, because lysozyme is produced by polymorphonuclear leukocytes and macrophages, nor for AAI, because apolipoprotein AI is formed in the liver and intestine.

Renal replacement therapy in amyloidosis

End-stage renal disease can be treated with dialysis or renal transplantation. Time from diagnosis to dialysis is shorter for AL than for AA amyloidosis. Mean time to dialysis in AL amyloidosis was 15 months, mean survival on dialysis was 24 months; mortality is significantly higher in patients with AL than with AA amyloidosis [30]. Hemodialysis in AL amyloidosis is complicated by a strong tendency towards intradialytic hypotension due to cardiac involvement, continuous ambulatory peritoneal dialysis by peritonitis [31].

HDM/HCT is possible in dialysis patients, with hematologic response rates and peritransplant mortality being comparable with those in the overall population of patients undergoing this treatment. Renal transplantation in AL-amyloidosis shows a one- and 5 year patient survival of 95% and 67% [32].

Experience with renal transplantation is available also for AA amyloidosis. Graft survival is comparable with that of a control group with different underlying disorders, but patient survival is lower. Recurrent amyloid deposition occurs because of a persistence of the underlying disorder.

Conclusion

The diagnosis of Amyloidosis should be considered if proteinuria in combination with systemic disease is evident. Workup should include a correct typing of the amyloid protein involved. On this basis a risk-adapted therapy regimen can be introduced. In case of renal failure organ transplantation is a possibility in selected patients.

Conflict of interest

The author declares that there is no conflict of interest.

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