Renal AA Amyloidosis

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ABSTRACT

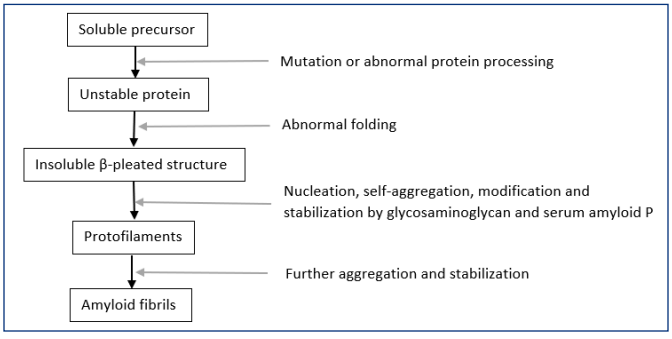
Amyloidosis is a rare systemic condition caused by extracellular deposition of misfolded fibrillary protein aggregates leading to progressive organ dysfunction. The kidney is a common site of amyloid deposition, with variable clinical presentations. Here, we will review pathophysiology, clinical manifestation, diagnosis and management of renal AA amyloidosis. Although significant progress has been made in understanding the disease pathophysiology and improving diagnostic yield, the treatment options remain limited, and the overall prognosis depends on the control of underlying inflammation.

KEYWORDS: Amyloidosis, serum amyloid A, chronic inflammation

INTRODUCTION

Amyloidosis is a rare but serious systemic disorder caused by deposits of pathogenic aggregates of misfolded proteins called amyloid in organs and tissues. Due to the conformational changes, soluble peptides in their normal configurations turn into a common insoluble fibrillar appearance with a structure rich in anti-parallel β-pleated sheet. The pathological process starts with a nucleation after a critical concentration of amyloid protein is reached, followed by aggregation and rapid expansion in the extracellular matrix, ultimately generates protofilaments that interact to form fibrils [**Figure 1**].[1] Both glycosaminoglycan and serum amyloid P can stabilize the structural changes in amyloid precursors to promote fibrillogenesis and prevent proteolysis/degradation.[2,3] Once formed, all amyloid proteins share a characteristic tinctorial property, showing an apple-green birefringence when observed under polarized light after Congo red staining or a yellow–green fluorescence after thioflavin S staining.

Figure 1. Amyloid fibril formation

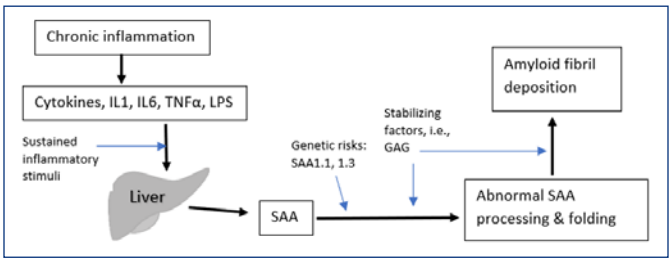


The origins of amyloid protein are quite diverse, with some resulting from genetic mutations and others due to deranged or dysregulated protein processing. Currently, at least 36 different amyloid proteins have been identified,[4] resulting in localized or systemic amyloidosis. They can be divided into the following types: AL (amyloid light-chain) amyloidosis, AH (amyloid heavy-chain), AA (amyloid A protein) amyloidosis, the familial or hereditary amyloidoses (i.e., TTR, apolipoprotein, fibrinogen A, lysozyme, cystatin, etc.), senile systemic amyloidosis, and dialysis-related β2-microglobulin amyloidosis. AL or AH amyloidosis is associated with plasma cell dyscrasia with increased light chain or heavy chain production. AA amyloidosis is associated with chronic inflammation from systemic autoimmune disease, infections and neoplasm. In familial amyloidoses, altered protein becomes amyloidogenic due to genetic mutations. TTR amyloidosis includes familial mutant transthyretin (ATTRm) amyloidosis, and senile systemic amyloidosis (SSA) involving wide-type TTR protein with amyloid deposit predominantly in the heart. Amyloidosis can also be categorized as being primary, secondary, hemodialysis-related, hereditary, senile, or localized.

RENAL AA AMYLOIDOSIS

The culprit of AA amyloidosis is a proteolytic fragment of serum amyloid A (SAA) protein, an acute-phase reactant made by liver whose expression dramatically increases in response to proinflammatory cytokines. Of the original 104 amino-acid SAA protein with a predominant α-helical structure, only the N-terminal fragments containing 66–76 amino-acid are commonly found in amyloid fibrils.[5] Therefore, both proteolytic action and a structural change adopting a cross-pleated sheet configuration are required for the development of AA amyloidosis. The fact that only a minority of patients with chronic inflammation and elevated blood SAA levels developed AA amyloidosis suggests a possible genetic predisposition.[5] Indeed, in patients with familial Mediterranean fever, SAA1 polymorphism (specifically a/a

Figure 2. Formation of AA amyloid



genotype) has a significant and independent association with renal amyloidosis.[6] Similar association between SAA1 gene polymorphism and AA amyloidosis was identified in a Japanese cohort with rheumatoid arthritis.[7] Sustained release of inflammatory cytokines stimulates liver to synthesize and release SAA protein, which turns into pathologic amyloid fibrils after abnormal protein processing and mis-folding. Glycosaminoglycans (GAG) can stabilize the mis-folded amyloid precursors and amyloid fibrils and inhibit their degradation. **Figure 2** shows the process of AA amyloid formation.

The kidney is the most common organ affected by AA amyloidosis due to its filtering property. Renal manifestations, typically as nephrotic range proteinuria and reduced renal function, occur in 80–90% of cases with amyloidosis and portend a poor prognosis. According to a Mayo clinic registry of biopsy proven AA amyloidosis, 100% had SAA amyloid deposit in the kidney. Among them, over 90% had proteinuria and/or renal insufficiency.[8] In another large case series, nephrotic syndrome was present in 39% of patients on presentation, whereas sub-nephrotic proteinuria with and without renal dysfunction was found in 42% and 20% of patients, respectively.[9] **Table 1** lists the patient characteristics and renal manifestations of AA amyloidosis from three large cohorts.

ETIOLOGIES

AA amyloidosis is considered to be reactive amyloidosis to chronic inflammation. As a result, inflammatory conditions including rheumatic/autoimmune diseases, autoinflammatory syndromes (i.e., Familial Mediterranean fever) and infections are commonly implicated. Malignancy has been linked to AA amyloidosis in less than 10% of cases.[10-12] Recently, obesity has been increasingly recognized as a potential cause of AA amyloidosis due to the presence of persistent low grade inflammation.[13-15] Overall, 15% of cases are considered "idiopathic" without an identifiable cause. In such cases, a hereditary form related to SAA gene mutation may be present and genetic testing should be pursued.[16]

PATHOLOGICAL DIAGNOSIS

Amyloid can be present anywhere inside the kidney, but the glomerular deposits are most prominent. Under light microscopy, these amyloid deposits appear as amorphous material. Inside glomeruli, capillary loop deposits can be segmental or global, and the mesangial deposits if extensive can lead to nodular formation resembling Kimmelstiel-Wilson lesions of diabetic nephropathy. In rare occasions, the amyloid deposits can lead to glomerular basement membrane dissolution and crescent formation. Crescents in amyloidosis is rare, and is usually associated with AA

Table 1. Renal manifestations and survival of AA amyloidosis

		Gertz, et al[8]	Ahbap, et al[9]	Bergesio, et al[28]
#, participants		64	121	86
Age, years		51/64(median, men/women)	43 (mean)	62 (mean)
Gender (men), %		59	69	42
Underlying diseases		Rheumatologic disorders (66%), chronic infections (17%), inflammatory bowel disease (9%), others (8%)	FMF (37.1%), TB (24.7%), chronic rheumatologic diseases (8.2%), COPD (6.6%), others or unknown (23.1%)	Not reported
Renal presentations		Median serum creatinine =2mg/dl, median urine protein =4.2 grams/day	Mean serum creatinine = 2.3 mg/dl, mean urine protein =6.7 grams/day	Mean serum creatinine = 2.0 mg/dl, mean urine protein =5.0 grams/day
Follow-up	**Renal outcomes**	Median follow up of the 17 survivors =42 months. 35% developed ESRD.	Mean follow up= 38.2 ± 37.2 months. 56.2% developed ESRD. Mean renal survival was 64.7 months. Renal survival rates at 1, 2 and 5 years were 81.7%, 67.3% and 46.1%, respectively	Median time of follow-up = 30 months. 47% developed ESRD
	Mortality	74% died, primarily as a result of renal failure. Median survival =24.5 months	41% died, primarily from complications of renal failure. Mean overall survival was 88.7 ± 7.8 months. Survival rates at 1, 2 and 5 years were 80.7%, 68.2% and 51.3%, respectively	40% died from complications of amyloidosis. Median survival =79 months. Cumulative survival at 2 and 5 years were 74% and 51% respectively

Abbreviations: TB: Tuberculosis; COPD: Chronic obstructive pulmonary disease; ESRD: End-stage renal disease.

amyloidosis.[17] Amyloid deposits can also involve extraglomerular vessels (i.e., arterioles) and tubulointerstitium, and sometimes be isolated to renal medulla eluding diagnosis if biopsy sample is superficial.[18] These deposits can be readily identified by their ability to bind Congo red or thioflavin-T, and confirmed by serum amyloid A stain via immunohistochemistry. It should be noted that AA amyloid deposits can sometimes trap immunoglobulin light chain leading to false positive immunofluorescent staining.[19] Under electron microscopy, classic amyloid fibrils should be seen, and immune complex–type deposits are typically absent.

CONGOPHILIC STAINING AND AMYLOID TYPING

Congo red dye, despite its strong affinity for β-sheet structures, can bind to non-amyloid proteins in tissue sections,[20] leading to a false-positive diagnosis. Furthermore, false-negative Congo red stains have also been documented,[21] further limiting its diagnostic utility. To overcome this limitation, Shehabeldin et al used Texas Red–filtered fluorescence microscopy to enhance the amyloid-specific congophilia, and reported an increased diagnostic yield and improved diagnostic specificity.[22] Once the tissue amyloid deposition is established, the amyloidogenic proteins can be further identified by mass spectrometry after laser-microdissection.[23]

MANAGEMENT AND OUTCOMES

The goal is to treat underlying inflammatory disease and suppress SAA production. Studies using agents targeting inflammatory cytokines including interleukin 6 and tumor necrosis factor-α have shown promising results.[24,25] Eprodisate, a novel therapeutic blocking the interactions between glycosaminoglycan and amyloidogenic proteins have also been developed, to reduce polymerization and promote breakdown of pathogenic amyloid fibrils. A phase II multicenter trial in patients with renal AA amyloidosis, showed that eprodisate significantly slowed down the rate of kidney function decline.[26]

In patients progressing to end-stage renal disease (ESRD), either hemodialysis or peritoneal dialysis can be offered, with potential complications including hypotension and peritonitis depending on the extent of extra-renal involvement of AA amyloidosis. Ultimately, kidney transplantation might be an effective therapeutic option although clinical experiences have been limited so far. A small study of living donor kidney transplant indicated that patient and graft survivals were similar in AA amyloidosis and matched non-amyloidotic controls.[27]

AA amyloidosis involving kidneys has been associated with high morbidity and mortality. Despite treatment, progression to ESRD is fairly common, with an extremely low rate of renal recovery.[9] In an Italian cohort of AA amyloidosis, the mean rate of glomerular filtration rate decline was 2.3 ml/min per month with a median renal survival of only 25 months after diagnosis. Overall, 47% progressed to ESRD in that cohort.[28] AA amyloidosis is also associated with reduced renal allograft survival and a high risk of disease recurrence after kidney transplantation.[29] Furthermore, serum creatinine concentration at presentation is also highly predictive of mortality in patients with AA amyloidosis.[9] Indeed, renal complications were found to be the main cause of death, with median survival ranging from 24 to 53 months after the diagnosis is established.[8,30] Once on dialysis, survival rates at one year ranged from 30% to 72% based on the observations from various cohorts.[9,31-33]

The overall prognosis is largely hinged upon the control of underlying inflammatory process. In a seminal study of 80 patients with AA amyloidosis who were followed prospectively for 12–117 months. Among those with controlled inflammation and normalized serum SAA concentrations, 60% had regressed tissue amyloid deposit, and 93% had stabilized or improved amyloidotic organ function. However, the amyloid disease burden increased, and organ function deteriorated in most of those whose SAA levels remained significantly elevated. Estimated patient survival at 10 years was 90% in patients with normalized SAA concentration, but only 40% in those with elevated SAA level (p=0.0009).[34]

Lastly, AA amyloidosis can recur after kidney transplantation. The risk of recurrence is closely associated with the presence of uncontrolled chronic inflammation or persistent infections. Therefore, it is essential for transplant nephrologists to thoroughly evaluate and rule out any ongoing inflammatory or infectious processes before proceeding with transplantation. Patients are generally advised to remain disease-free for a period of at least six months, although the optimal duration has not been definitively established.

CONCLUSION

Renal AA amyloidosis is a serious condition with variable clinical manifestations. Its diagnosis requires a high degree of clinical suspicion and timely recognition. Newer therapeutic agents have been studied to suppress systemic inflammation, generating hopes of targeted therapy with better tolerability and efficacy. Given the rarity of this disease and its potential to affect multiple organ systems, a specialized multidisciplinary care model has been adopted; however, data on the long-term outcomes of this approach are still needed.

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Disclosures

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