Serum Amyloid A Protein–Associated Kidney Disease: Presentation, Diagnosis, and Management

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Serum amyloid A protein (AA) amyloidosis, also known as secondary amyloidosis, is a known consequence of chronic inflammation and results from several conditions including inflammatory arthritis, periodic fever syndromes, and chronic infection. AA amyloidosis can lead to multiorgan dysfunction, including changes in glomerular filtration rate and proteinuria. Definitive diagnosis requires tissue biopsy, and management of AA amyloid kidney disease is primarily focused on treating the underlying inflammatory condition to stabilize glomerular filtration rate, reduce proteinuria, and slow potential progression to kidney failure. In this narrative review, we describe the causes, pathophysiology, presentation, and pathologic diagnosis of AA amyloid kidney disease using an illustrative case of biopsy-proven AA amyloid kidney disease in a patient with long-standing rheumatoid arthritis who had a favorable response to interleukin 6 inhibition. We conclude the review with a description of established and more novel therapies for AA amyloidosis including published cases of use of tocilizumab (an interleukin 6 inhibitor) in biopsy-proven AA amyloid kidney disease.

INTRODUCTION

Amyloid A protein (AA) amyloidosis results from chronic inflammation and is characterized by extracellular multiorgan deposition of serum AA protein fibrils leading to organ dysfunction.[1] AA amyloid kidney disease is the most common manifestation,[2] typically resulting in proteinuria and progressive decreased kidney function. The management of AA amyloidosis focuses on the treatment of the underlying inflammatory conditions, which include inflammatory arthropathies, familial Mediterranean fever and chronic infections.[3] Herein, we describe the causes, pathophysiology (including biopsy findings) and diagnosis of AA amyloid kidney disease using an illustrative case in a patient with long-standing rheumatoid arthritis who presented with nephrotic syndrome and acute onset chronic kidney injury. We conclude with a review of current literature on established and emerging therapies for AA amyloidosis, including a specific focus on the use of interleukin 6 (IL-6) inhibitors in biopsy-proven AA amyloid kidney disease.

CLINICAL PRESENTATION OF THE CASE

Consent was obtained before publishing the results of this case. A 58-year-old woman with a 40-year history of rheumatoid factor and anticyclic citrullinated peptide antibody-positive rheumatoid arthritis was referred to the nephrology clinic with progressive peripheral edema, new-onset dipstick-positive proteinuria (3 g/L, negative 1 year prior) without hematuria, and abnormal kidney function (creatinine increase from 0.89 mg/dL to 1.36 mg/dL over 4 months, corresponding to an estimated glomerular filtration rate [eGFR] of 43 mL/min/1.73 m^2).

Her disease-modifying antirheumatic regimen consisted of azathioprine and hydroxychloroquine, having previously failed to achieve symptom control with adalimumab. Upon initial assessment, she was otherwise asymptomatic apart from long-standing chronic pain from the arthritis and new pitting edema to the midshin bilaterally over the preceding months. She endorsed long-standing daily use of naproxen for her joint pain (although the dose had been decreased 3 months prior) and no other new prescription or herbal medications. She was normotensive, with no jugular venous distension and had pitting edema in both lower extremities. She had characteristic features of rheumatoid arthritis including metacarpophalangeal joint subluxation and ulnar deviation. The remainder of the physical examination was noncontributory.

Following her visit, the naproxen was immediately discontinued. A work-up for glomerulonephritis including hepatitis B and C, human immunodeficiency virus and syphilis serologies, antinuclear antibody, and vasculitis panels were negative. C3 and C4 were within normal limits. Serum albumin was 2.5 g/dL (normal, 3.4-5.4 g/dL), hemoglobin A1c was 6.1%, and a lipid panel revealed an low-density lipoprotein level of 126.5 mg/dL and high-density lipoprotein level of 75.4 mg/dL. Serum protein electrophoresis demonstrated no evidence of a monoclonal gammopathy. A 24-hour urine output collection confirmed 3.7 g of protein.

WHAT IS AA AMYLOIDOSIS?

Epidemiology

The history of amyloidosis dates back at least to the 1800s,[4] when pathologists noted abnormal infiltrative

proteins with an atypical uptake of iodine stain in autopsies of patients with chronic infection. It was not until the 1960s that the concept of "secondary amyloidosis" in patients with chronic inflammatory conditions was introduced and ultimately sequenced as AA protein.[5] Since then, determining an accurate prevalence of AA amyloidosis has been difficult, as a tissue diagnosis is not always performed and the management of chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease have evolved. Estimates in European studies describe an incidence of AA amyloidosis of 1 to 2 patients per million life-years.[6,7] Initially, AA amyloid was thought to be most prevalent in patients in their 40s; however, more recent studies have identified that the prevalence is highest among those aged 60 years or greater. Not only have the demographics at diagnosis changed, there has also been a relative decrease in the proportion of systemic amyloidosis thought to be secondary to AA amyloid protein, rather than primary or familial amyloidosis.[3]

Causes

There are a variety of conditions that have been found to be associated with systemic AA amyloidosis. These include chronic inflammatory arthropathies (rheumatoid arthritis being the most widely reported), chronic infections, periodic fever syndromes, inflammatory bowel disease and vasculitis.[2] A recent systematic review reported 48 different conditions with strong association to AA amyloidosis and 19 with a weak association.[8] There does appear to be some regional variability, with Western regions reporting the highest incidence of AA amyloidosis secondary to rheumatologic disease,[9] and Eastern regions showing higher rates of familial Mediterranean fever.[10] The proportion of AA amyloidosis caused by specific diseases is difficult to determine given the wide geographic variability; however, chronic inflammatory arthritis has been estimated as the underlying disorder in roughly 60% of cases.[2] There is also some suggestion that the predominant cause has changed over time. In a systematic review of infections and AA amyloidosis, the proportion of AA amyloidosis cases fell from >50% before the year 2000 to 20% after. This may reflect changes in the treatment of chronic infections, especially in developed countries where there may be better access to therapeutics.[3] Among chronic inflammatory arthropathies, rheumatoid arthritis and juvenile idiopathic arthritis appear to be the most common causes. In terms of AA amyloidosis secondary to infection, mycobacterium is most commonly implicated, especially in regions with higher rates of tuberculosis.[3]

Clinical Presentation

Systemic AA amyloidosis has been demonstrated to have multiorgan involvement, with biopsy-proven disease in the kidney, liver, gastrointestinal tract, peripheral nerves, lungs and skin, and soft tissue.[11] Presentations vary depending on specific organ involvement; however, new-onset proteinuria and progressive decreased kidney function appear to be by far the most commonly involved organ system, in some cases at over 90% of patients at presentation.[2] Lung involvement, presenting as a bilateral interstitial pattern and nerve involvement presenting as peripheral neuropathy appears to be less common.[2] While cardiac infiltration is well documented in other forms of amyloidosis, both the prevalence and clinical significance appear to be less in AA amyloidosis than amyloid light chain (AL) amyloidosis.[12] Other manifestations are much less common; however, diarrhea and hepatomegaly have also been reported in some studies. The highest-yield biopsy targets for diagnosis appear to be kidney, rectum, and abdominal fat pad based on published case reports.[13]

Specific to AA amyloid kidney disease, proteinuria is a common initial finding. Although many patients may have subnephrotic proteinuria on presentation, hypoalbuminemia and the nephrotic syndrome as presenting diagnoses are often reported.[14] In a prospective cohort of 374 patients with AA amyloidosis who were referred to a National Amyloidosis Center, median proteinuria was 3.9 g/day (interquartile range of 0-26.0), and 97% of patients had >500 mg/day of protein excretion, acknowledging that many of these patients were likely referred later in the course of their disease. The location of protein deposition varies in AA amyloid kidney disease and may dictate clinical presentation and course. Amyloid deposition isolated to the tubulointerstitium tends to present with less severe proteinuria, whereas glomerular involvement results in nephrotic-range proteinuria and more rapid decline in eGFR. One study reported progression to kidney failure in up to 85% in those with biopsy-proven glomerular disease, compared with 0% in those with vascular or tubular AA deposition.[15] Similar to proteinuria, changes in eGFR depend largely on the timing of the diagnosis. In the abovementioned prospective cohort study, the median creatinine clearance was 41 mL/min at presentation, and 59 out of 257 patients with a creatinine clearance >20 mL/min at baseline progressed to kidney failure. Specific to rheumatoid arthritis, mesangial proliferative glomerulonephritis, membranous kidney disease, thin basement membrane disease, and interstitial nephritis can occur.[16] Crescentic glomerulonephritis has also been reported but appears to be much more rare.[17] Although most cases of AA amyloidosis appear to have a more indolent presentation, a subset of patients with familial Mediterranean fever present with acute illness, massive proteinuria, elevated inflammatory markers, and rapid progression to kidney failure within weeks. These rare cases have been described as "amyloid storm" and are thought be precipitated by superimposed infections.[18]

Pathophysiology

The pathophysiology of AA-amyloid kidney disease involves the deposition of amyloid protein in the kidney parenchyma, resulting in proteinuria and a decline in

glomerular filtration. Mechanistically there appears to be a few reasons for proteinuria and the decline in kidney function.[14] The first involves physical disruption of tissue architecture from protein deposition, due to amyloid fibril self-aggregation. There is also evidence of direct tissue toxicity by amyloid precursor proteins supported by in vitro studies[19] and detection of protein aggregates in the absence of amyloid deposition. Serum AA, the precursor protein of AA amyloidosis, is an acute phase reactant and plays a role as an opsonin in bacterial phagocytosis. Its production by hepatocytes is mediated by tumor necrosis factor (TNF), IL-1, and IL-6. Serum AA circulates on plasma high-density lipoprotein and is cleaved to AA by macrophages.[20] Human serum AA genes have multiple alleles with polymorphisms, and it is this variability along with significant heterogeneity in the composition of high-density lipoprotein that likely explains the large spectrum of clinical presentations for AA amyloidosis.[21] Although the exact mechanism of serum AA cleavage leading to nephron AA deposition is unclear, there does appear to be correlation with serum AA levels. Gillmore et al[22] demonstrated that amyloid deposits, measured with amyloid P scintigraphy, regressed with improvement in serum AA levels. In addition, end organ dysfunction was more severe in those with serum AA concentrations >50 mg/L, and serum AA levels <10 mg/L were associated with almost 90% ten-year survival. In cases of AA amyloid kidney disease, serum AA levels were the strongest risk factor for the development of kidney failure. Fortunately, with effective treatment of systemic inflammation, serum AA levels do appear to decrease, and this, in turn, is also associated with improved long-term prognosis.[13]

Diagnosis and Pathologic Findings

The diagnosis of AA amyloid kidney disease should be suspected in any patient presenting with new proteinuria associated with a decline in kidney function, in the context of an underlying chronic inflammatory condition. Some have suggested (perhaps most importantly in rheumatologic disease, which is the most common underlying condition) that even the presence of >500 mg of proteinuria should prompt consideration of a kidney biopsy, although this approach is not substantiated by evidence. Although serum AA levels have shown correlation with severity of AA amyloidosis and may play a role in monitoring therapeutic response, they do not always correlate with the presence of amyloid deposits.[23] In addition, serum AA levels are often elevated in the presence of rheumatologic disease, therefore they are not sufficient to diagnose AA amyloid kidney disease in the absence of kidney biopsy.[24] Finally, assays for serum AA levels are not widely available, limiting their use for frequent testing or monitoring. ^{123}I-labeled serum amyloid P component scintigraphy has shown more promise as a noninvasive diagnostic test. Although the diagnostic sensitivity has been shown to be 90% for both AA and AL amyloidosis,[25] the degree of uptake may not correlate with the severity of clinical symptoms. The main barrier to routine diagnostic use of serum amyloid P scintigraphy appears to be access, as the required iodine isotypes are expensive and not readily available at all centers. Serum amyloid P scintigraphy has also been shown to be useful for monitoring therapeutic response[26] and as a result has been used in evaluating novel therapeutics for AA amyloidosis.

Biopsy remains the gold standard diagnostic test for AA amyloid kidney disease. Pathologically, amyloid protein is an amorphous extracellular material that is lightly eosinophilic, and sections with amyloid deposition will classically have affinity for Congo red stain.[14] Findings vary depending on histologic technique. Under light microscopy, findings of amyloid deposition are identical regardless of protein subtype. These include accumulation of acellular amorphous eosinophilic material on hematoxylin and eosin stain that are pale on periodic acid–Schiff stain. A nodular appearance of acellular amorphous expansion in the mesangial matrix is more commonly associated with AA amyloidosis but is not always seen.[27] Congo red stain can produce false-positives with overstaining; therefore it is recommended that results be confirmed under polarized light identifying green birefringence.[28] Electron microscopy may also be used as a confirmatory test for amyloid deposition; however, it is not able to differentiate between subtypes. Given the difficulty of distinguishing amyloid subtypes despite immunofluorescence, further analysis with mass spectrometry is recommended for definitive diagnosis. Gilbertson et al[29] demonstrated tandem mass spectrometry in addition to immunofluorescence increased the identification of specific amyloid protein in 94% of biopsies, with an 18% increase in pick-up rate compared with immunofluorescence alone. As a result, mass spectrometry is the preferred method for confirmation of AA amyloid deposition.

PATHOLOGIC FINDINGS OF THE CASE

Our patient underwent a kidney biopsy which revealed prominent expansion of the glomerular mesangium with homogeneous eosinophilic material (Fig 1A). The arteries showed foci of expansion by similar homogeneous eosinophilic material. These expanded areas stained salmon red with Congo red (Fig 1B) and showed apple green birefringence on polarization (Fig 1C). Four of 18 glomeruli were globally sclerosed. There was mild tubular atrophy with interstitial fibrosis, and mild arterial sclerosis. Electron microscopy showed glomerular basement membrane, mesangial and arteriolar expansion by randomly arranged fibrils, approximately 10 nm in diameter, consistent with amyloid (Fig 1D). Foot process effacement was noted in the examined glomerulus. Immunofluorescence showed 1+ mesangial IgM κ and λ and trace IgG and C3. Amyloid subtyping by liquid chromatography tandem mass spectrometry (Mayo Clinic) was consistent with AA amyloidosis.
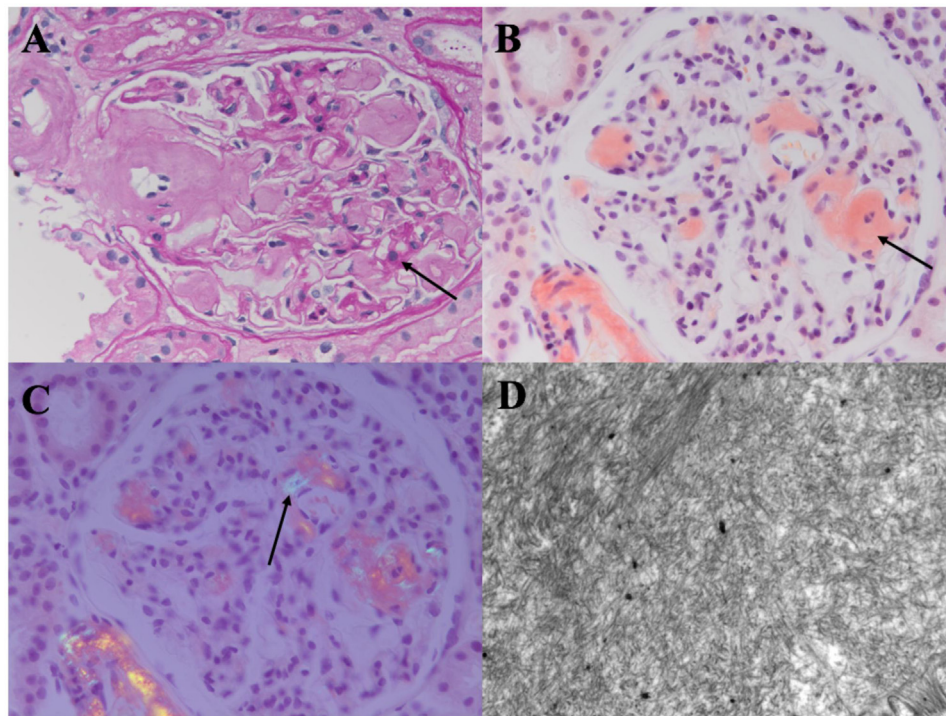
Figure 1. Kidney biopsy findings (clinical case). (A) Homogeneous weak material (arrow) in glomerular mesangium and arteriole. Periodic acid–Schiff stain. Original magnification, ×400. (B) Salmon red staining. Congo red stain (arrow). Original magnification, ×400. (C) Apple green birefringence (arrow). Congo red stain viewed under polarized light. Original magnification, ×400. (D) Randomly arranged fibrils, ~10 nm in diameter, in glomerular mesangium. Electron microscopy. Original magnification, ×10,000.

MANAGEMENT AND EMERGING THERAPIES

General Approach

The management of AA amyloid kidney disease involves suppression of systemic inflammation, in addition to pharmacologic treatment generally aimed at treating proteinuric kidney disease. Although formal studies are lacking, intuitively, the latter would include renin-angiotensin-aldosterone system inhibitors, and sodium/glucose cotransporter 2 inhibition. Furthermore, management of hyperlipidemia and edema may be required if the patient has high-grade proteinuria. Therapies targeted to decrease inflammation (and serum AA levels) should be tailored to a patient's underlying disease process. Examples of these strategies are outlined below.

Disease Specific-Approach

Rheumatoid and Inflammatory Arthritis

Treatment for AA amyloidosis in patients with rheumatoid arthritis has evolved with the increased use of biologics over the past 20 years. Initially, cyclophosphamide in combination with prednisolone had the best evidence for AA amyloidosis in patients with rheumatoid arthritis refractory to initial disease-modifying antirheumatic drug therapy.[30] Cyclophosphamide gradually became replaced by anti-TNF agents, especially after anticytokine therapy

was shown to be better tolerated and associated with improved survival. As the European Alliance of Associations for Rheumatology guidelines adopted anti-TNF agents as first-line therapy for rheumatoid arthritis,[31] anticytokine therapy as a treatment for AA amyloidosis was studied. When compared directly, etanercept was shown to be superior to cyclophosphamide in both preservation of eGFR and reduction in proteinuria.[32] In addition to etanercept, both infliximab[33] and adalimumab[34] have been used to treat AA amyloidosis, although there have been no head-to-head comparisons of anti-TNF agents. Beyond rheumatoid arthritis, anti-TNF agents have also been shown to be effective and well-tolerated during long-term follow-up in both inflammatory bowel disease and other inflammatory arthropathies as well.[35]

Familial Mediterranean Fever

As the mainstay of treatment, colchicine's impact on AA amyloid kidney disease secondary to underlying familial Mediterranean fever has been well documented.[36] Colchicine has been shown to reduce proteinuria and preserve kidney function. In one study, this effect did appear to be contingent on reaching a therapeutic dose of >1.5 mg per day and beginning treatment in patients with serum creatinine <1.5 mg/dL.[37] The presumed mechanism of action for colchicine's impact on amyloid

deposition and subsequent kidney disease is suppression of cytokines involved in serum AA production that are also targeted by other therapies. Colchicine inhibits neutrophil production, and therefore production of IL-1 and IL-8. In addition, it reduces the protein expression of TNF.[38]

Emerging Therapies

Tocilizumab

The management of AA amyloidosis continues to evolve as alternative cytokines involved in serum AA production are targeted. IL-6 is a proinflammatory cytokine that induces serum AA production via interaction with the signal transducer and activator of transcription protein.[39] Tocilizumab is a recombinant monoclonal antibody that blocks IL-6 signal transduction by targeting IL-6 receptor complex formation and has been shown clinically and in vitro

to decrease AA production.[40] IL-6 inhibitors have gradually become more widely used in the treatment of inflammatory arthropathies and as a result have been used in the treatment of AA amyloid kidney disease with a goal of reducing proteinuria and stabilizing kidney function.[41]

Outcomes of these cases vary; however, tocilizumab has been shown to decrease serum AA, as well as improve proteinuria and GFR, most notably in AA amyloidosis associated with inflammatory arthritis.

The earliest reports of tocilizumab for systemic AA amyloidosis appear to date back to 2006, when Okuda et al[42] reported improvements in serum AA amyloid levels, improvements in proteinuria, and histologic improvement in a 26-year-old woman with juvenile idiopathic arthritis. However, it was not until 2011 that case reports of biopsy-proven AA amyloid kidney disease responding to tocilizumab were

Table 1. Summary of Published Cases of Biopsy-Confirmed AA-Amyloid Kidney Disease in Patients With Rheumatoid Arthritis Treated With Tocilizumab and Reported Outcomes

Reference	Age (y)	Sex	Presentation	Treatment Dose (mg/kg/mo)	Treatment Duration (mo)	Concurrent Treatment	Response
Vinicki et al (2013)[45]	48	F	5.0 g/24 h proteinuria	8	24	None	0.5 g proteinuria/24 h
Matsui et al (2014)[46]	60	F	Progressive kidney dysfunction	8	36	None	Persistent deposition on biopsy, progression to kidney failure
Yamada et al (2014)[47]	71	F	Nephrotic syndrome, 4.3 g/24 h proteinuria	8	10	Losartan	Resolved proteinuria at 3 mo
Courties et al (2015)[44]	52	F	9.0 g/24 h proteinuria	8	8	Glucocorticoids	Progression to kidney failure within 20 mo
	70	F	8.4 g/24 h proteinuria	8	3	Glucocorticoids	Stable eGFR, 0.5 g/24 h proteinuria
	47	M	10.0 g/24 h proteinuria	8	6	Colchicine	Progression to kidney failure within 6 mo
	80	F	4.0 g/24 h proteinuria	8	34	Glucocorticoids	Improved eGFR, progression to 6.0 g/24 h proteinuria
	80	F	2.1 g/24 h proteinuria	8	32	Glucocorticoids	Stable eGFR, 0.09 g/24 h proteinuria
	73	M	8.0 g/24 h proteinuria	8	6	Glucocorticoids	Stable eGFR, 4.7 g/24 h proteinuria
Iijima et al (2015)[48]	51	F	Nephrotic syndrome, 5.2 g/24 h proteinuria and RPGN	8	18	None	Improved eGFR, 1.2 g/24 h proteinuria
Yamagata et al (2017)[49]	67	F	Urinary protein excretion of 7.5 g per gram urinary creatinine	Not reported	10	None	0.5 g/24 h proteinuria
Fukuda et al (2020)[50]	59	F	Nephrotic syndrome, 6.5 g/24 h proteinuria	8	24	None	1.1g/24 h proteinuria
	71	M	0.06 g/24 h proteinuria	8	60	None	Glomerular amyloid deposits unchanged on repeat biopsy (at 2 y)

Abbreviations: AA, serum amyloid A protein; eGFR, estimated glomerular filtration rate; F, female; M, male; RPGN, rapidly progressive glomerulonephritis.

Table 2. Summary of Published Cases of Biopsy-Confirmed AA-Amyloid Kidney Disease in Patients With Familial Mediterranean Fever Treated With Tocilizumab and Reported Outcomes

Reference	Age (y)	Sex	Presentation	Tocilizumab Dose (mg/kg/mo)	Treatment Duration (mo)	Concurrent Treatment	Response
Serelis et al (2015)[53]	32	F	Nephrotic syndrome and 9.0 g/24 h proteinuria	8	2	Colchicine 1 mg, lisinopril 5 mg twice a day	Resolution of nephrotic syndrome, 3.0 g/24 h proteinuria
Ugurlu et al (2017)[54]	36	M	12 g/24 h proteinuria	8	6	None	Resolved nephrotic syndrome, 2.1 g/24 h proteinuria
	44	M	Baseline Cr 2.58 mg/dL, 23.7 g/24 h proteinuria	8	5	None	Cr 1.85 mg/dL and 14.9 g/24 h proteinuria
	45	M	Baseline Cr 1.28 mg/dL, 4.7 g/24 h proteinuria	8	31	None	Cr 1.12 mg/dL and 4.4 g/24 h proteinuria
	47	F	Baseline Cr 0.79 mg/dL, 2.1 g/24 h proteinuria	8	31	None	Cr 0.83 mg/dL and 1.4 g/24 h proteinuria
	23	M	Baseline Cr 0.69 mg/dL, 3 g/24 h proteinuria	8	4	None	Cr 0.71 mg/dL and 1.4 g/24 h proteinuria
	35	M	Baseline Cr 1.18 mg/dL, 1.7 g/24 h proteinuria	8	28	None	Cr 1.39 mg/dL and 2.7 g/24 h proteinuria
	41	F	Baseline Cr 0.71 mg/dL, 3 g/24 h proteinuria	8	13	None	Cr 0.64 mg/dL and 1.9 g/24 h proteinuria
	39	F	Baseline Cr 0.43 mg/dL, 1.6 g/24 h proteinuria	8	32	None	Cr 0.54 mg/dL and 0.7 g/24 h proteinuria
	24	F	Baseline Cr 0.4 mg/dL, 6 g/24 h proteinuria	8	4	None	Cr 0.35 mg/dL and 4.7 g/24 h proteinuria
	22	F	Baseline Cr 0.38 mg/dL, 1.8 g/24 h proteinuria	8	20	None	Cr 0.5 mg/dL and 0.1 g/24 h proteinuria
	45	F	Baseline Cr 0.79 mg/dL, 7.1 g/24 h proteinuria	8	6	None	Cr 0.93 mg/dL and 5.7 g/24 h proteinuria
	21	M	Baseline Cr 0.83 mg/dL, 11.7 g/24 h proteinuria	8	4	None	Cr 0.85 mg/dL and 16.7 g/24 h proteinuria

Abbreviations: AA, serum amyloid protein; Cr, creatinine; eGFR, estimated glomerular filtration rate; F, female, M, male.

published. The first involved a patient presenting with nephrotic syndrome that was found to have biopsy-proven AA amyloid kidney disease in addition to underlying latent tuberculosis.[43] Subsequent treatment with tocilizumab lead to rapid improvement in proteinuria over a 9-week follow-up period; however, the patient experienced GFR decline because of gastrointestinal illness, ultimately leading to the need for hemodialysis. Since then, there have been several case reports regarding the efficacy of tocilizumab in chronic diseases, including Behcet disease, polyarteritis nodosa, psoriatic arthritis, and rheumatoid arthritis (Table 1[44-50]).

Specific to rheumatologic disease, Okuda et al[51] compared the effectiveness of tocilizumab to anti-TNF agents in 42 patients with AA amyloidosis. Patients in the tocilizumab group showed greater reduction in serum AA protein levels as well as improvements in kidney function and clinical disease activity. Notably, all patients had biopsy-proven gastrointestinal AA amyloid involvement, whereas only 3 patients in the study had biopsy-diagnosed AA amyloid kidney disease. Shortly after, a 2015 series of 6 cases of biopsy-proven AA amyloid kidney disease[44] also demonstrated the efficacy of tocilizumab in stabilizing GFR, reducing proteinuria, and improving inflammatory markers. Additional case series have focused on amyloid load measured with serum amyloid P scintigraphy in addition to patient quality of life and have demonstrated rapid reduction in amyloid deposition within 10 days that was sustained over almost 2 years of follow-up.[52]

Tocilizumab has also shown benefit in treating AA amyloidosis in a variety of other underlying conditions, including familial Mediterranean fever (Table 2)[53,54],

Table 3. Summary of Published Cases of Biopsy-Confirmed AA-Amyloid Kidney Disease in Patients Without Rheumatoid Arthritis or Familial Mediterranean Fever Treated With Tocilizumab and Reported Outcomes

Reference	Age (y)	Sex	Associated Condition	Presentation	Tocilizumab Dose	Duration (mo)	Concurrent Treatment	Response
Magro-Checa et al (2011)[43]	25	M	Latent tuberculosis	Nephrotic syndrome (18 g/24 h proteinuria)	8 mg/kg/mo	12	Isoniazid 300 mg	Improved proteinuria to 1.7 g/24 h. Unchanged colonic amyloid deposition on repeat biopsy (12 mo)
De La Torre et al (2011)[55]	14	F	Juvenile idiopathic arthritis	Nephrotic syndrome (7 g/24 h proteinuria)	8 mg/kg/2 wk	12	None	Improved proteinuria and kidney function
Hočevar et al (2013)[56]	33	M	Polyarteritis nodosa	3.6 g/24 h proteinuria	8 mg/kg/mo	10	Methylprednisolone 4 mg	Improvement in proteinuria to 1.0 g/24 h, regression of glomerular amyloid depositions on repeat biopsy at 6 mo
Redondo-Pachón et al (2013)[57]	51	F	Bechets	Nephrotic syndrome (9.5 g/24 h proteinuria)	8 mg/kg/mo	12	Colchicine 1 mg/d + isoniazid	Resolved nephrotic syndrome, improvement in proteinuria to 1.7 g/24 h
Pelegrin et al (2016)[58]	58	F	Seronegative polyarthritis	Nephrotic syndrome (11 g/24 h proteinuria)	480 mg/mo	60	None	Resolved nephrotic syndrome, stabilized eGFR
	46	M	Chronic osteomyelitis	Nephrotic syndrome (6 g/24 h proteinuria)	8 mg/kg/mo	8	None	Progression to kidney failure, increase to 11 g/24 h proteinuria
	56	F	Systemic sclerosis	Nephrotic syndrome (3 g/24 h proteinuria)	8 mg/kg/mo	5	None	Stable eGFR, progression to 6 g/24 h proteinuria
Ugurlu et al (2017)[54]	25	M	Latent tuberculosis	Nephrotic syndrome (18 g/24 h proteinuria)	8 mg/kg/mo	12	Isoniazid 300 mg	Improved proteinuria to 1.7 g/24 h, resolved nephrotic syndrome
Eriksson et al (2021)[59]	60	M	AS	0.52 g/24 h proteinuria	8 mg/kg/mo	52	None	Stability
	69	M	AS	urinary albumin-creatinine ratio 913 g/mol	8 mg/kg/mo	18	None	Stability, decreased protein
Giannese et al (2021)[60]	63	M	Sweet syndrome	10 g/24 h proteinuria	8 mg/kg/mo	23	None	Complete resolution of nephrotic syndrome, 1.5 g/24 h proteinuria

Abbreviations: AA, serum amyloid A protein; AS, ankylosing spondylitis; eGFR, estimated glomerular filtration rate; F, female; M, male.

multicentric Castleman disease and viral hepatitis (Table 3).[55-60]

Other Treatments

Eprodisate, thought to prevent amyloid deposition by directly targeting glycosaminoglycan-amyloid fibril complexes,[61] initially showed promise after demonstrating superiority to placebo in AA-amyloid kidney disease in a composite outcome of kidney function and/or death.[62] Unfortunately, a follow-up phase 3 clinical trial[63] did not meet its primary outcome of preserved kidney function, and further studies targeting this pathway are
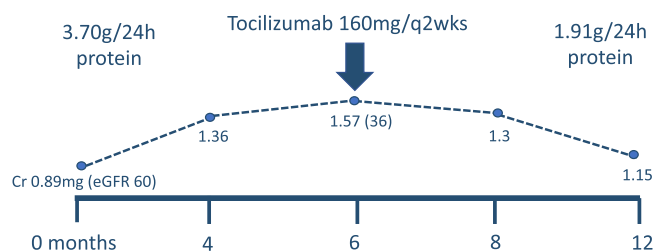
Figure 2. Treatment of biopsy-proven AA-amyloid kidney disease in a patient with rheumatoid arthritis using tocilizumab and subsequent response.

ongoing. In addition, efforts to target amyloidogenic precursor proteins (specifically their interaction with glycosaminoglycans)[64] are also in development. These treatments are not yet approved for use outside clinical trials. Anti-AA amyloid-specific monoclonal antibodies have also been developed and have been shown to be effective in specifically targeting amyloid deposition in small animal studies.[65] Although the hope is that fibril-specific monoclonal antibodies can remove pathologic amyloid deposits, this has yet to be demonstrated clinically. The role of IL-6 in systemic inflammation and AA amyloidosis has been targeted via a different route, namely an IL-6 binding protein that has shown sustained antagonism of the receptor in vivo.[66] Similar binding proteins have been used in ongoing studies for patients with hereditary amyloidosis as potential therapeutic options.[67]

MANAGEMENT AND OUTCOME OF THE CASE

At the time of her presentation, she was on lisinopril 5 mg daily. This was changed following the initial 24-hour urine output collection to candesartan because of cough (which resolved) but could not be up-titrated due to hypotension. In collaboration with the referring rheumatologist, in addition to conservative treatment with dietary salt reduction, she was prescribed tocilizumab (160 mg subcutaneously every 2 weeks). Before initiating treatment, serum creatinine peaked at 1.57 mg/dL (eGFR 36 mL/min/1.73 m^2). There was no evidence of cardiac amyloidosis on transthoracic echocardiography. Follow-up 6 months after starting anti-IL-6 therapy revealed a reduction in proteinuria to 1.91 g on a 24-hour collection improvement in serum creatinine to 1.15 mg/dL (eGFR 52 mL/min/1.73 m^2) and a fall in serum C-reactive protein from 15 mg/L at the time of diagnosis to <5 mg/L (Fig 2).

CONCLUSION

In conclusion, in cases of kidney disease in patients with long-standing underlying autoimmune conditions, chronic infection, or periodic fever syndromes, the diagnosis of AA-amyloid kidney disease should be considered. AA-amyloid kidney disease is associated most strongly with inflammatory arthropathies and familial Mediterranean fever and most commonly presents with proteinuria. Definitive diagnosis requires biopsy with additional mass spectrometry analysis. Treatment consists primarily of targeting the inflammatory condition. In addition, more contemporary therapies including IL-6 inhibitors have been shown to be effective at reducing serum AA production and improving/stabilizing proteinuria and eGFR.

ARTICLE INFORMATION

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