Kidney Medicine

Case Report

AL Amyloidosis Presenting With Crescentic Glomerulonephritis

Ann A. Wang, Yashpal S. Kanwar, Vikram Aggarwal, and Anand Srivastava

Kidney amyloidosis typically presents with nephrotic-range proteinuria. Rare cases of crescentic glomerulonephritis have been reported in patients with kidney amyloidosis but most cases were in the setting of patients with AA amyloidosis from long-standing inflammation and malignancy. We present a case of a previously healthy man in his 70s who was admitted with severe acute kidney injury, nephrotic-range proteinuria, and nephritic urinary sediment. Initial serologic testing for causes of rapidly progressive glomerulonephritis were negative. Kidney biopsy demonstrated the presence of active cellular and fibrocellular crescents with Congo red–positive staining in glomeruli and microvasculature on light microscopy and amyloid fibrils in glomerular basement membrane on electron microscopy. Urinary protein electrophoresis revealed monoclonal λ light chains, leading to a diagnosis of kidney AL amyloidosis, which was confirmed with bone marrow biopsy. Our case illustrates that AL amyloidosis can present with findings suspicious for rapidly progressive glomerulonephritis and crescent formation on kidney biopsy specimens.

Complete author and article information provided before references.

Kidney Med. 3(4):644-648. Published online April 20, 2021.

doi: 10.1016/j.xkme.2021.02.009

INTRODUCTION

AL amyloidosis is a disorder of plasma cell clonal proliferation that results in the formation of amyloid from excess light chain fragments. AL amyloid can deposit in any organ in the body outside of the central nervous system and affects the kidneys in 50% to 80% of cases.[1] In the kidney, insoluble amyloid fibrils typically collect in glomeruli but can also deposit in the interstitium, tubules, and blood vessel walls.[1,2] Patients with AL amyloidosis and kidney involvement typically have albumin-predominant nephrotic-range proteinuria.[1,2] However, acute kidney injury (AKI), nephrogenic diabetes insipidus, and Fanconi syndrome may also be present.[1] Further testing usually uncovers the presence of monoclonal or polyclonal proteins with abnormal elevations in κ or λ light chains in serum or urine.[1,2]

On kidney biopsy, Congo red–staining amyloid deposits on light microscopy, 8- to 10-nm nonbranching amyloid fibrils on electron microscopy, and monoclonal light chains on immunofluorescence studies are classic findings.[1] While monoclonal gammopathies cause a diverse spectrum of pathologic and clinical disease in the kidneys, nephritic syndrome concerning for rapidly progressive glomerulonephritis (RPGN) is not a typical presentation of AL amyloidosis.[1,2]

We present a case of AL amyloidosis diagnosis in an elderly patient who initially presented with a clinical picture suspicious for RPGN and whose kidney biopsy revealed active cellular crescents alongside glomerular and vascular AL amyloid deposition.

CASE REPORT

A man in his 70s was admitted to the hospital after routine laboratory tests showed an elevated serum creatinine level to 4.0 mg/dL from his previous baseline of 1.3 to 1.5 mg/dL obtained 1 year before admission. His medical history was remarkable for a 4-year history of microscopic hematuria and a 3-year history of chronic kidney disease stage 3 with trace proteinuria. Urology performed multiple cystoscopies to evaluate his microscopic hematuria in the past, which found no abnormalities. One year before this admission, he saw a nephrologist to evaluate his elevated creatinine level and minimal proteinuria, but kidney biopsy was deferred at that time and the patient was asked to follow-up with his primary care physician.

On admission, the patient reported no symptoms. He took no medications besides occasional ibuprofen for chronic lower back pain. Physical examination findings were remarkable only for trace bilateral lower extremity edema, which the patient reported was chronic. The patient had microscopic hematuria, new nephrotic-range proteinuria (urinary protein-creatinine ratio of 7.07 g/g creatinine), and urinary sediment with dysmorphic red blood cells (RBCs) on phase contrast microscopy. Other remarkable laboratory results included elevated serum potassium level (5.2 mEq/dL) and anemia (hemoglobin, 10.8 mg/dL).

A 3-day course of pulse-dose steroids was started due to concern for RPGN in the setting of severe AKI with an unclear trajectory, new proteinuria, and dysmorphic RBCs on urine microscopy. Urgent kidney biopsy was scheduled, and a full serologic and urine workup was obtained.

Kidney biopsy specimens evaluated 40 glomeruli under light microscopy (Fig 1A-D), which revealed glomeruli with 10% active cellular crescents, 20% fibrocellular crescents, 15% small hilar nodules, and homogenous pink material in the arterial walls. Approximately 50% of glomeruli were globally sclerosed; the rest showed

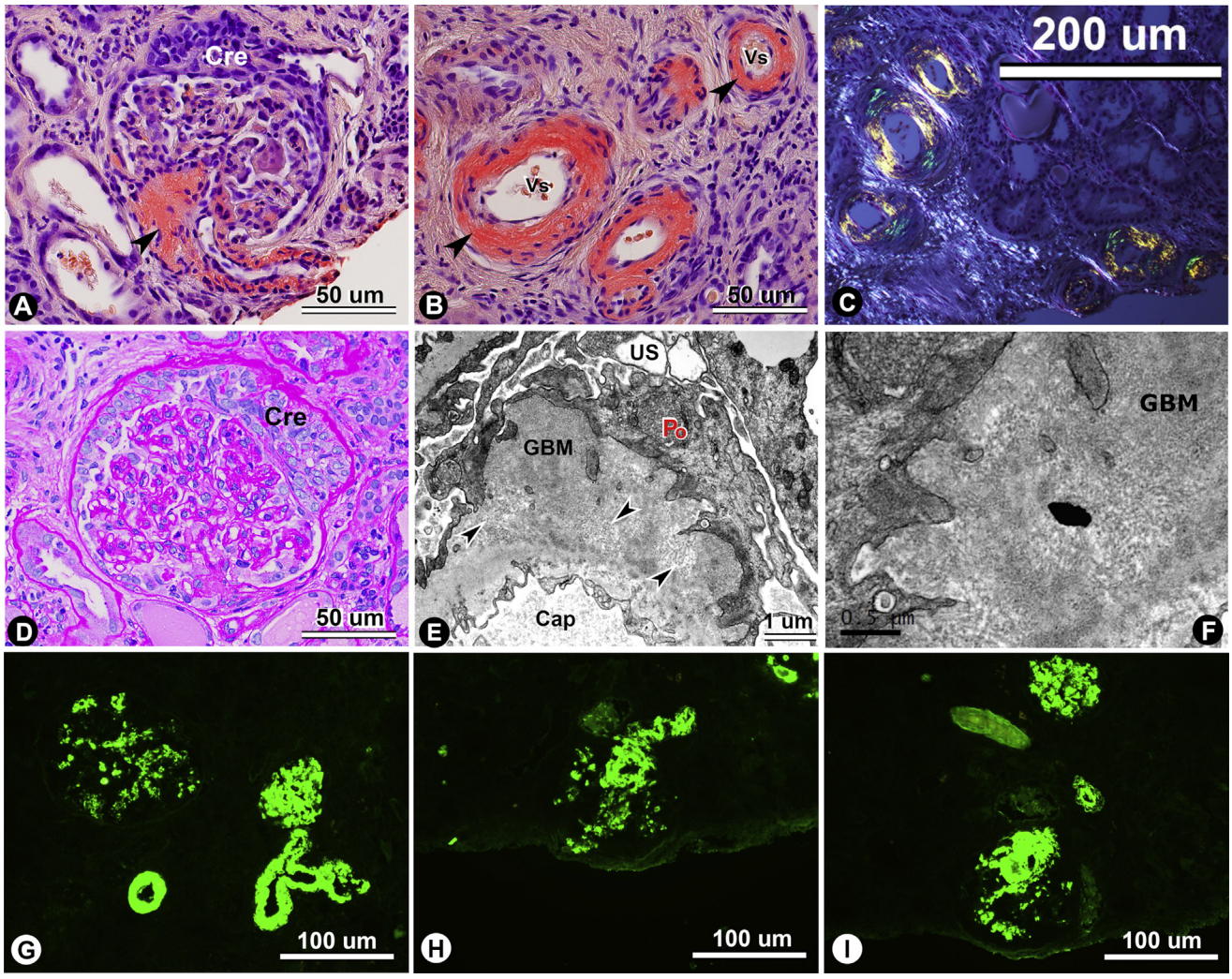

Figure 1. Photographs show morphologic features of glomeruli and blood vessels. Light micrograph shows (A) a glomerulus with a small crescent (Cre) and deposition of Congo red–reactive material (amyloid) in the hilar mesangium and feeding arteriole (black arrowhead), (B) amyloid deposits (black arrowhead) in walls of intrarenal blood vessels (Vs), (C) apple green birefringence as demonstration of amyloid in kidney blood vessels, and (D) a well-developed Cre (periodic acid–Schiff stain). (E) Electron micrograph shows amyloid fibrils (black and white arrowhead) in the substance of glomerular basement membrane (GBM). (F) High-resolution electron micrograph shows GBM amyloid fibrils. (G) Immunoglobulin G (IgG), (H) κ light chain, and (I) λ light chain immunofluorescence staining in smudgy pattern in mesangium and vessel walls. Abbreviations: Cap, capillary lumen; Po, podocyte; US, urinary space.

moderate proliferation of mesangial and endothelial cells with mild influx of leukocytes. There was approximately 50% to 60% interstitial fibrosis and tubular atrophy. Congo red staining confirmed the presence of amyloid deposition in glomeruli and blood vessels. Electron microscopy (Fig 1E and F) demonstrated fusion of podocyte foot processes. Glomerular basement membranes (GBMs) appeared thickened and wrinkled in many areas in which there were fibrillary subepithelial deposits with fibril width of 10 to 12 nm. These fibrils were also observed in the mesangium and small blood vessels. Immunofluorescence studies (Fig 1G-I) stained 4+ positive to immunoglobulin G (IgG), κ, and λ in a smudgy pattern in the mesangium and blood vessels. Although both κ and λ staining were reported as 4+, the kidney pathologist noted there was a mild predominance of λ compared with κ.

Results of the serologic and urine workup are shown in Table 1. Laboratory investigations were notable for monoclonal free λ light chain present in serum and urine and a low serum κ:λ free light chain ratio.

AL amyloidosis was diagnosed and the patient with initiated on treatment with bortezomib and steroids. A bone marrow biopsy obtained before initiation of therapy demonstrated 10% plasma cells with a λ-restricted monotypic plasma cell population, and Congo red stain identified focal amyloid deposits in vessel walls, confirming the diagnosis of AL amyloidosis.

The patient was discharged with close nephrology and hematology-oncology follow-up. His serum creatinine level peaked at 5.2 mg/dL 1 month after discharge and subsequently improved with a presumed new baseline of

Table 1. Laboratory Results

Laboratory Test	Result	Reference Range
ANA titer, pattern	1:80, speckled	
Complement C3, mg/dL	100	75-170
Complement C4, mg/dL	27	10-40
Cytoplasmic ANCA titer	<1:40	
Perinuclear ANCA titer	<1:40	
Anti-GBM IgG, AI	<1.0	<1.0
Rheumatoid factor, IU/mL	<10	0-14
Hepatitis B surface antigen	Not detected	
Hepatitis B surface antibody	Nonreactive	
Hepatitis B core antigen	Not detected	
Hepatitis B core antibody	Nonreactive	
Hepatitis C antibody	Nonreactive	
HIV 1,2 antigen/antibody	Nonreactive	
Syphilis antibody	Negative	
Cryoglobulin	Negative	
Serum protein electrophoresis		
Total protein, g/dL	5.5	6.4-8.9
Albumin, g/dL	3.2	3.5-5.7
Interpretation	No restricted bands seen in the γ region	
Serum immunofixation	Possible monoclonal free λ light chain	
Random urinary protein electrophoresis		
Urinary protein, mg/dL	353	0-10
Urinary albumin, mg/dL	223.5	0-10
Interpretation	Restricted band seen in the γ region	
Random urine immunofixation	Monoclonal free λ light chain	
Serum free light chains		
Free κ light chain, mg/dL	3.47	0.33-1.94
Free λ light chain, mg/dL	17.1	0.57-2.63 mg/dL
Free κ:λ light chain ratio	0.20	0.26-1.65

Abbreviations: ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; IgG, immunoglobulin G.

4.0 mg/dL. The patient underwent 7 cycles of treatment with bortezomib with methylprednisolone that resulted in adequate bone marrow response and plateau of his light chains. He transitioned to carfilzomib, cyclophosphamide, and methylprednisolone therapy. Six months after his initial presentation, the patient's kidney function worsened and he initiated dialysis.

DISCUSSION

Kidney AL amyloidosis classically presents as isolated nephrotic syndrome, though patients may also have proteinuria below nephrotic range with or without AKI.[1,2] Our patient's clinical presentation suspicious for RPGN with a kidney biopsy that showed glomerular crescents is atypical for kidney AL amyloidosis.[1,2]

Co-existence of crescentic glomerulonephritis and kidney amyloidosis has been previously described in few case reports and retrospective analyses,[3-10] summarized in Table 2. The true prevalence of kidney amyloidosis with glomerular crescents is unknown because prior retrospective studies report glomerular crescents in a wide range of pathologic specimens (1.1%-13.3%).[3,4] Most case reports demonstrating kidney amyloidosis with glomerular crescents or nephritic urinary sediment describe patients with AA amyloidosis secondary to malignancy or long-standing rheumatoid arthritis.[4-9] Although a large retrospective case series identified 3 patients with AL amyloidosis who had crescent formation,[3] no detailed clinical information is available regarding the presentation of these patients. Detailed clinical information for patients with AL amyloidosis who presented with findings suspicious for crescentic glomerulonephritis has been described in only 2 prior case reports.[10,11]

In 1 case report, a man in his mid-70s had AL amyloidosis diagnosed after initially presenting with a nephritic urinary sediment.[11] Kidney biopsy revealed widespread amyloid deposits in glomeruli and mesangial tissue but there were no glomerular crescents or other signs of inflammation or proliferation that could explain his hematuria and RBC casts.[11] Another case report described a 67-year-old man with a 5-year history of AL amyloidosis with known kidney and cardiac involvement who presented with AKI and hematuria 1 month after having multiple myeloma newly diagnosed.[10] The patient's kidney biopsy showed segmental necrotizing lesions, cellular crescents, and amyloid deposits in the mesangium and capillary walls.[10] Although the authors argued that the patient's long-standing AL amyloidosis caused glomerular crescent formation, it is not clear whether this was a rare presentation of multiple myeloma.[12]

We contribute to the existing literature by sharing a case of newly diagnosed AL amyloidosis with an initial presentation suggestive of RPGN and an accompanying native kidney biopsy with crescent formation. Although we suspected RPGN on presentation, we cannot exclude that the patient had more chronic kidney injury because the last serum creatinine measured was 1 year before presentation. However, RPGN can occur over a period of months,[13] which may have been sufficient time for the development of significant chronic histopathologic injury. Although serum, urine, and bone marrow testing were suggestive of AL amyloidosis, we acknowledge that laser microdissection followed by liquid chromatography/mass spectrometry amyloid typing of kidney biopsy tissue would have been ideal to address equal staining for κ and λ light chains by immunofluorescence.[14,15] Our patient's negative antineutrophil cytoplasmic antibody, negative anti-GBM IgG and absence of linear IgG staining of GBM, and absence of granular electron-dense deposits in glomeruli on electron microscopy argued against the presence of concurrent pauci-immune crescentic

Table 2. Summary of Relevant Previous Literature: Kidney Amyloidosis With Presentation Concerning for Crescentic Glomerulonephritis

Study	Study Type	Patient Presentation/ Study Population	Diagnosis	Kidney Biopsy Findings/Study Findings	Outcome
Murakami et al[7] (1998)	Case report	43 F with 8-y history of RA presenting with hypertension, proteinuria, hematuria, pyuria, and AKI	AA amyloidosis	70%-80% fibrocellular crescents and moderate amyloid deposits	Death
Bernheim and Bernheim[6] (1999)	Case report	80 F with history of RA presenting with nephrotic syndrome and rapidly progressive kidney failure	AA amyloidosis	Amyloid deposition staining positive with anti-amyloid A antibody with fibrocellular and fibrous crescents, interstitial fibrosis, focal lymphocytic infiltration, and tubular atrophy	Not reported
Nagata et al[4] (2001)	Retrospective analysis	105 kidney specimens (44 biopsies, 61 autopsies) with amyloidosis	N/A	Of 105 specimens with any amyloidosis, 14 (13.3%) demonstrated crescents; of these 14, the associated disease in 11 specimens was RA; there was 1 case of each of the following: macroglobulinemia, plasma cell dyscrasia, multiple myeloma	N/A
Schafernak et al[5] (2005)	Case report	62 F with RA, insulin-dependent type 2 diabetes mellitus, hypertension, coronary artery disease, and hypothyroidism presenting with AKI and proteinuria	AA amyloidosis	Amyloid deposition in mesangium, 60% fibrocellular crescents, diffuse proliferative hypercellular lesions rich in polymorphs and monocytes, 11% glomerular sclerosis, moderate tubular atrophy, and scattered interstitial cellular infiltrates with lymphocytes, monocytes, and plasma cells	Hemodialysis-dependent after 17 mo
Crosthwaite et al[10] (2010)	Case report	67 M with history of AL amyloidosis with known kidney and cardiac involvement and recently diagnosed with IgG κ multiple myeloma presenting with AKI and hematuria	AL amyloidosis and multiple myeloma	Amyloidosis with segmental necrotizing lesions and cellular crescents	Remained on hemodialysis until death after 6 mo
Said et al[3] (2013)	Retrospective analysis	474 kidney biopsy specimens with amyloidosis in single academic center 2007-2011	N/A	Of 474 specimens, 5 (1.1%) demonstrated crescents; of the 384 specimens with AL amyloidosis, 3 (0.8%) demonstrated crescents	N/A
Liangos et al[11] (2015)	Case report	73 M with history of MGUS presenting with fever and multiorgan dysfunction featuring kidney failure with nephrotic-range proteinuria and microhematuria with erythrocyte casts.	AL amyloidosis	AL amyloidosis and tubular atrophy; no crescents or evidence of GN or vasculitis	Kidney function recovery

Abbreviations: AKI, acute kidney injury; GN, glomerulonephritis; IgG, immunoglobulin G; MGUS, monoclonal gammopathy of unknown significance; N/A, not applicable; RA, rheumatoid arthritis.

glomerulonephritis, anti-GBM disease, or immune complex glomerulonephritis, respectively. Together with previous reports, our case demonstrates that AL amyloidosis can present as crescentic glomerulonephritis.

The mechanisms underlying glomerular crescent formation in kidney amyloidosis remain unclear. Prior literature suggests that amyloid deposition likely causes rupture of the GBM, leading to leakage of proteinaceous material and cellular contents into Bowman space.[5,10,11] This theory is supported by observations that amyloid deposits were more frequently identified near areas of GBM rupture.[5] In AL amyloidosis, excess light chain fragments may also directly damage the GBM.[12] Processes upstream to amyloid deposition, such as mesangial cell uptake of amyloid precursors, may also play a significant role in crescent formation.[16] Further study is needed to evaluate the pathogenesis of crescent formation in kidney amyloidosis.

Although a rare presentation, our case illustrates that AL amyloidosis with crescentic glomerulonephritis should remain on the differential diagnosis for patients who present with features suspicious for RPGN. Taken together with the prior literature, our case demonstrates that the pathophysiology, histopathologic features, and clinical presentation of amyloidosis are more diverse than previously described.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Ann A. Wang, MD, Yashpal S. Kanwar, MD, PhD, Vikram Aggarwal, MD, and Anand Srivastava, MD, MPH.

Authors' Affiliations: Graduate Medical Education, Northwestern University Feinberg School of Medicine (AAW); and Department of Pathology (YSK), Division of Nephrology and Hypertension (VA, AS), and Center for Translational Metabolism and Health, Institute for Public Health and Medicine (AS), Northwestern University Feinberg School of Medicine, Chicago, IL.

Address for Correspondence: Anand Srivastava, MD, MPH, 633 N St Clair St, Ste 18-083, Chicago, IL 60611. Email: anand.srivastava@northwestern.edu

Support: Dr Kanwar is supported by National Institutes of Health (NIH) grant R01DK060635. Dr Srivastava is supported by NIH grant K23DK120811 and core resources from the George M. O'Brien Kidney Research Center at Northwestern University (NU-GoKIDNEY) P30DK114857.

Financial Disclosure: Dr Srivastava received honoraria from Horizon Therapeutics, PLC, and AstraZeneca and consulting fees from CVS Caremark. The remaining authors declare that they have no relevant financial interests.

Patient Protections: The authors declare that they have obtained consent, from a relative with appropriate authority, for publication of the information about the patient reported in this article and any associated supplementary material.

Peer Review: Received September 14, 2020. Evaluated by 3 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form February 15, 2021.

REFERENCES

1. Dember LM. Amyloidosis-associated kidney disease. *J Am Soc Nephrol*. 2006;17(12):3458-3471.
2. Bridoux F, Leung N, Hutchison CA, et al. Diagnosis of monoclonal gammopathy of renal significance. *Kidney Int*. 2015;87(4):698-711.
3. Said SM, Sethi S, Valeri AM, et al. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. *Clin J Am Soc Nephrol*. 2013;8(9):1515-1523.
4. Nagata M, Shimokama T, Harada A, Koyama A, Watanabe T. Glomerular crescents in renal amyloidosis: an epiphenomenon or distinct pathology? *Pathol Int*. 2001;51(3):179-186.
5. Schafernak KT, Chugh SS, Kanwar YS. Co-existent crescentic glomerulonephritis and renal amyloidosis: a case report and literature review. *J Nephrol*. 2005;18(5):616-622.
6. Bernheim J, Bernheim J. The patient with two renal diseases: crescentic glomerulonephritis and renal AA amyloid. *Nephrol Dial Transplant*. 1999;14(5):1315-1316.
7. Murakami H, Ura N, Nagao K, et al. Rheumatoid arthritis associated with renal amyloidosis and crescentic glomerulonephritis. *Intern Med*. 1998;37(1):94-97.
8. Moroni G, Banfi G, Maccario M, Mereghetti M, Ponticelli C. Extracapillary glomerulonephritis and renal amyloidosis. *Am J Kidney Dis*. 1996;28:695-699.
9. Zuckerman JE, Peng F, Karl BE, Schulze CE, Sisk A. Cancer-associated AA amyloidosis presenting as crescentic glomerulonephritis. *Kidney Int Rep*. 2019;4:882-887.
10. Crosthwaite A, Skene A, Mount P. Rapidly progressive glomerulonephritis complicating primary AL amyloidosis and multiple myeloma. *Nephrol Dial Transplant*. 2010;25(8):2786-2789.
11. Liangos O, Buettner-Herold M, Ketteler M, Madias NE. Atypical case of AL amyloidosis with urinary erythrocyte casts. *Clin Nephrol Case Stud*. 2015;3:19-24.
12. Moscoso-Solorzano GT, Madureira-Silva MV, Balda C, Franco MF, Mastroianni-Kirsztajn G. Crescentic glomerulonephritis in IgA multiple myeloma: a case report. *Nephron Extra*. 2011;1(1):69-72.
13. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis*. 1988;11(6):449-464.
14. Sethi S, Vrana JA, Theis JD, et al. Laser microdissection and mass spectrometry-based proteomics aids the diagnosis and typing of renal amyloidosis. *Kidney Int*. 2012;82(2):226-234.
15. Leung N, Bridoux F, Batuman V, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol*. 2019;15(1):45-59.
16. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet*. 2016;387(10038):2641-2654.