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Kidney Biopsy Corner

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# Kidney Biopsy Corner: Amyloidosis

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**Keywords**
Amyloidosis · Intravenous drug use · AA amyloidosis · Kidney biopsy · Mass spectrometry

**Abstract**
Amyloidosis is an infiltrative disease caused by misfolded proteins depositing in tissues. Amyloid infiltrates the kidney in several patterns. There are, as currently described by the International Society of Amyloidosis, 14 types of amyloid that can involve the kidney, and these types may have different locations or clinical settings. Herein we report a case of AA amyloidosis occurring in a 24-year-old male with a history of intravenous drug abuse and provide a comprehensive review of different types of amyloids involving the kidney.



## Case Presentation

The patient is a 24-year-old male with a past medical history of intravenous drug abuse for 3 years and no other significant clinical or family history. He presented 3 months prior with edema and heavy proteinuria but left against medical advice before a kidney biopsy could be performed. At that time, his 24-h urine protein collection showed 20,261 mg. He had trace-positive cryoprecipitate. His C3 was 84 mg/dL (normal range 75–175 mg/dL), and his C4 was 19 mg/dL (normal range 15–45 mg/dL). He had negative testing for HIV, ANA, and ANCA. He followed up as an outpatient, and focal segmental glomerulosclerosis secondary to drug abuse was the leading differential diagnosis. He re-presented to the hospital 3 months later with continued peripheral edema and proteinuria. At this time, he was noted to have bilateral edema in the extremities as well as extensive wounds on his arms bilaterally. Bilateral pleural effusions and a pericardial effusion were noted on imaging. Pertinent laboratory data included a serum creatinine of 1.67 mg/dL with a reported baseline of 1 mg/dL. Urinalysis showed 3+ protein and 1+ blood. Albumin was 0.9 g/dL. Hepatitis C antibody was positive, but the RNA PCR for the hepatitis C virus was negative. Hepatitis B surface antigen and antibody testing were negative. Complement levels were normal, and double-stranded DNA testing was negative. ASO was 151 Todd units (normal range <200 Todd units). Blood cultures were negative. Serum protein electrophoresis was equivocal. The clinical differential diagnosis for this patient's ongoing heavy proteinuria was focal segmental glomerulosclerosis associated with drug use, infection-related glomerulonephritis, and cryoglobulinemic glomerulonephritis.

## Kidney Biopsy Findings

The patient underwent renal biopsy which showed kidney cortex and medulla with up to 7 glomeruli, none of which were globally sclerosed. The glomeruli showed diffuse infiltration of the mesangium by acellular, amorphous, PAS-pale material (Fig. 1a–c). Silver stain showed segmental subepithelial spikes along capillary walls (Fig. 1d). The material was Congo red positive with apple green birefringence, consistent with amyloid (Fig. 2a, b). The Congo red-positive amyloid material was also seen in the interstitium, vascular wall, and tubular

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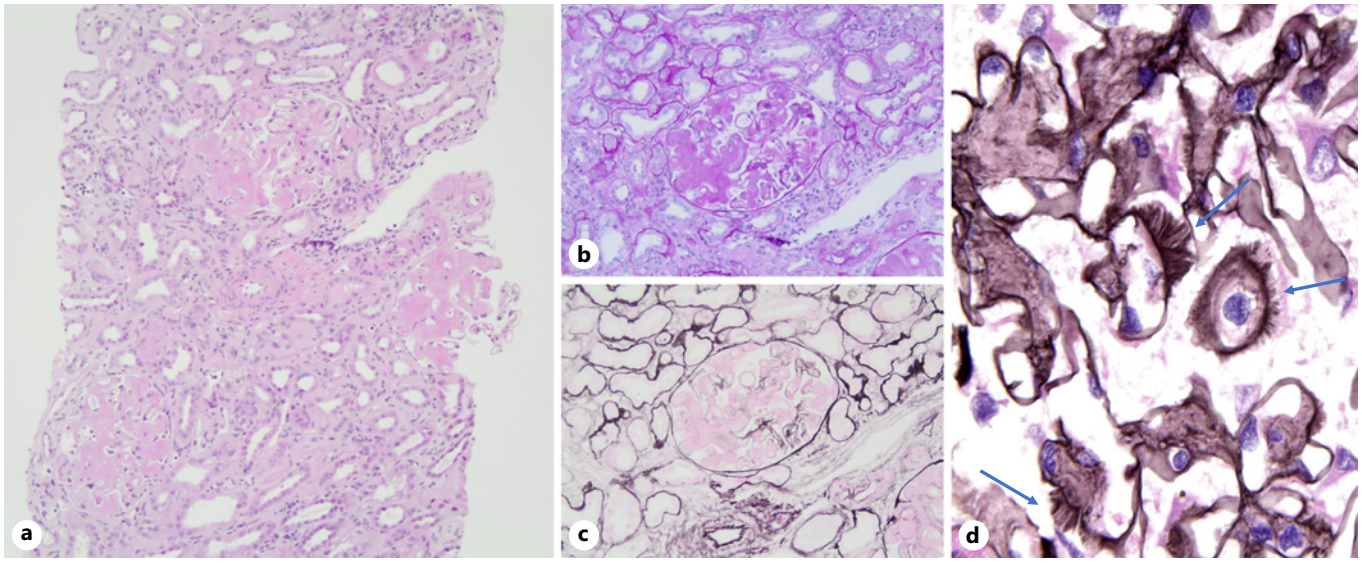


**Fig. 1.** Amyloid A amyloidosis (AA). **a** H&E stain showing diffuse infiltration of the glomeruli by amorphous material (×10). **b** PAS stain showing the material is weakly PAS-positive material (×20). **c** Silver stain: the material is silver negative. **d** Classic "spikes" or "spicules" (arrows) seen on the subepithelial aspect of the basement membranes on silver stain (×60).

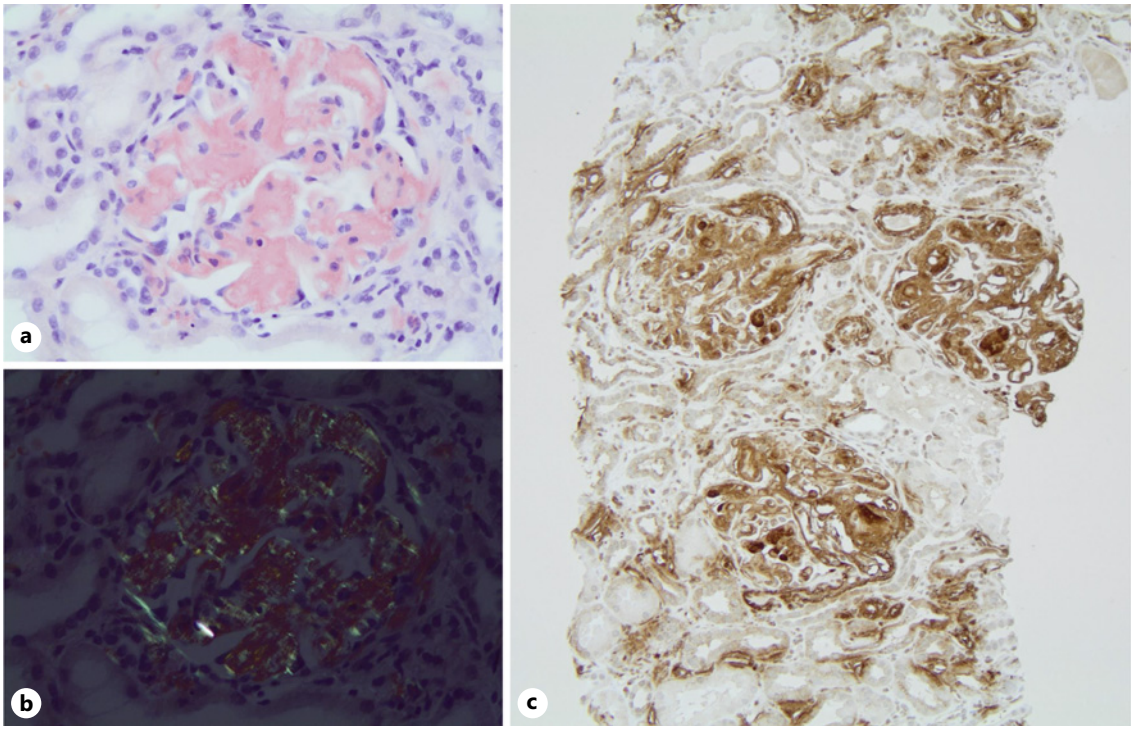


**Fig. 2.** Amyloid A amyloidosis (AA). **a** Positive Congo red special stain (×40). **b** Apple green birefringence on polarization (×40). **c** Amyloid A immunohistochemical stain showing diffuse staining in the glomeruli, vessels, and mesangium (×10).

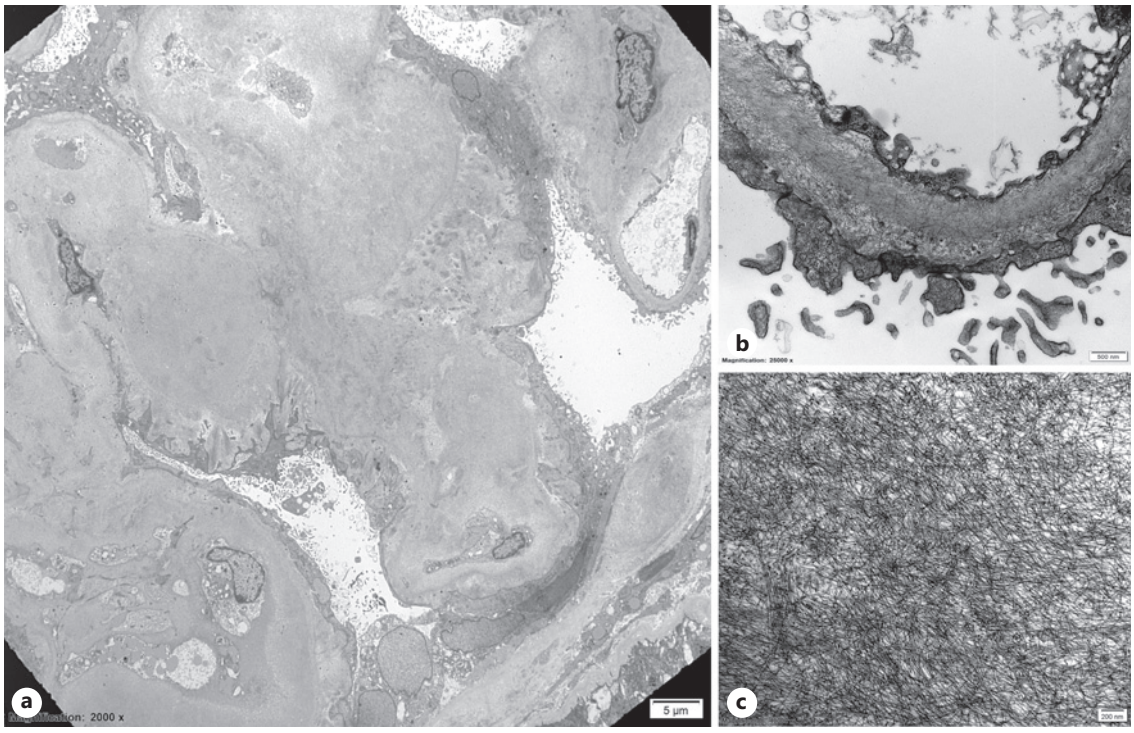


**Fig. 3.** Amyloid A amyloidosis (AA). **a** Electron microscopy showing fibrils expanding and replacing the mesangium. **b** Fibrils extending along the glomerular capillary loop basement membranes. **c** Non-branching, randomly arranged fibrils with an average diameter of 10.43 nm.

**Table 1.** Amyloid type involvement of kidney compartments

| Amyloid type | Kidney compartment involvement | | |
|---|---|---|---|
| | glomeruli | tubulointerstitium | vessels |
| AL/AH/ALH | Yes | Yes | Yes |
| AA | Yes | Yes | Yes |
| AFib | Yes; replaces the glomeruli | Not usually | Not usually |
| AGel | Yes; usually dominant glomerular involvement | Not usually | Not usually |
| ALECT2 | Not usually | Yes; dominant interstitial involvement | Yes |
| ATTR | Yes | Yes, may be cortical and medullary | Rarely; may see more with certain mutations |
| ALys | No specific pattern described | | |
| AApoAI | Rarely; may see dominant glomerular involvement with certain mutations | Yes; dominant interstitial involvement in the inner medulla | Yes |
| AApoAII | Yes; may replace the glomeruli and may show giant cells | Yes; much less than the glomeruli | Yes; much less than the glomeruli |
| AApoAIV | No | Yes; medulla only with cortical sparing | Not usually |
| AApoCII | Yes; nodular expansion of the mesangium | Rarely | No |
| AApoCIII | Yes; moderate | Yes; moderate | Yes; abundant |

AL, amyloidosis light chain; AH, amyloidosis heavy chain; ALH, amyloidosis light and heavy chain; AFib, fibrinogen amyloidosis; AGel, gelosin amyloidosis; ALECT2, LECT2 amyloidosis; ATTR, transthyrettin amyloidosis; ALys, lysozyme amyloidosis; AApoAI, apolipoprotein AI amyloidosis; AApoAII, apolipoprotein AII; AApoAIV, apolipoprotein AIV; AApoCII, apolipoprotein CII; AApoCIII, apolipoprotein CIII.

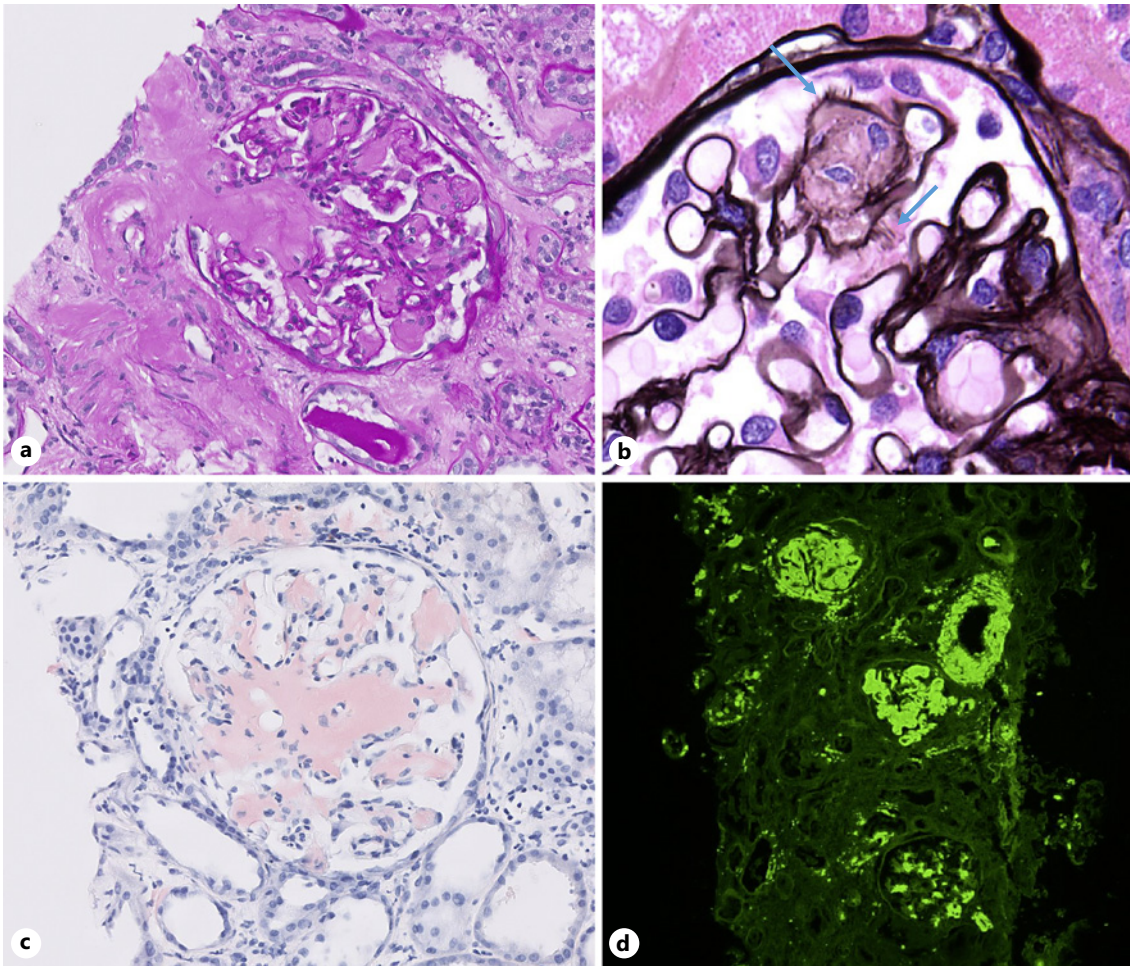


**Fig. 4.** Light chain amyloidosis (AL). **a** Amyloid involving the glomeruli, interstitium, and vessels (PAS stain; ×20). **b** Spikes (arrows) in the basement membrane (silver stain; ×60). **c** Congo red stain highlighting amyloid in the glomeruli (×20). **d** Lambda light chain immunofluorescence highlighting bright staining amyloid material in the glomeruli, interstitium, and vessels (×10).

basement membranes. Immunofluorescence showed moderate (2+) nonspecific reactivity for IgM but no significant dominance for either kappa or lambda light chain or other heavy chains. Electron microscopy showed non-branching randomly arranged fibrils with an average diameter of 10.43 +/− 2.18 nm (Fig. 3). Immunohistochemical staining for protein A was positive (Fig. 2c); transthyretin/prealbumin was negative. Liquid chromatography-tandem mass spectroscopy (LC-MS) performed at the Mayo Clinic confirmed the presence of AA amyloid. Additional history taken from the patient following histologic diagnosis confirmed no history of inflammatory disorders and no family history of amyloidosis or renal disease. Therefore, the amyloidosis was attributed to his intravenous drug abuse.

## Pathology Differential Diagnosis

In advanced cases, the diagnosis of amyloidosis is relatively easy to make. However, especially in early cases or cases with an unusual distribution pattern, the diagnosis can be challenging. On histology, amyloid is amorphous, acellular material that is classically silver and PAS-pale. It is characterized by positive staining on Congo red with "apple green" birefringence [1]. On histology, even with the help of a Congo red stain, early amyloids may be difficult to detect by light microscopy alone, and examination under fluorescence with a filter set for detecting fluorescein isothiocyanate increases the sensitivity of the stain and may help in detection of subclinical amyloidosis [2]. Some amyloids, such as

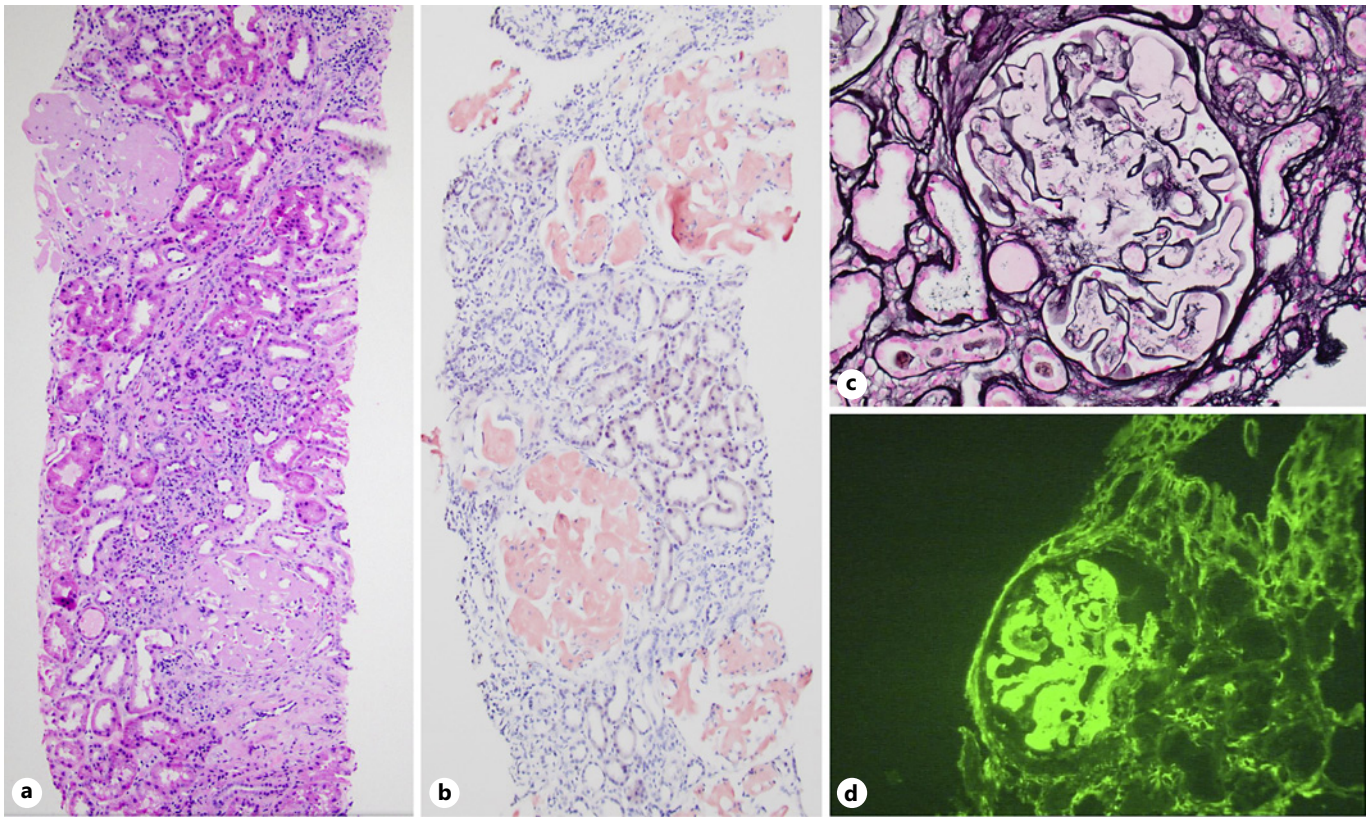


**Fig. 5.** Fibrinogen A α amyloidosis (AFib). **a** Amorphous amyloid material completely replacing the glomeruli (H&E, ×10). **b** Congo red stain highlighting the amyloid with a strikingly glomerular distribution (×10). **c** Silver-negative amyloid material with no spike formation in the glomeruli (×40). **d** Bright staining for fibrinogen on immunofluorescence (Fibrinogen immunofluorescence, ×20).

Apolipoprotein CII amyloidosis, may only show weak staining by Congo red, at which point thioflavin or crystal violet can be used to highlight the amyloid material [3, 4]. Amyloid deposits on crystal violet stain are metachromatic magenta or pink-violet in color, and thioflavin T will fluoresce at 450 nm [3, 5].

In the interstitium, especially in the deep medulla, dense fibrosis may mimic amyloid deposition but is easily distinguished by Congo red stain. In the glomeruli, the biggest differential of amyloidosis is fibrillary glomerulonephritis. Fibrillary glomerulonephritis is nearly always negative for Congo red, though rare cases of fibrillary glomerulonephritis are congophilic [6]. However, fibrillary glomerulonephritis will not show the characteristic glomerular subepithelial "spikes" or "spicules" in the glomeruli seen in amyloidosis (Fig. 1d). Notably, this feature is not seen in all amyloid cases. The size of the fibrils is also an important differentiating factor with amyloid fibrils ranging in size from 8 to 12 nm and fibrillary glomerulonephritis fibrils measuring slightly larger with an average size range of 10–30 nm. Amyloid staining on immunofluorescence depends on the type of amyloid present, but fibrillary glomerulonephritis is usually positive for polyclonal IgG, and subclass staining will usually show dominance for IgG4 with or without IgG1 staining. Rarely, monoclonal fibrillary glomerulonephritis cases are seen, but they are often polyclonal when stained after antigen retrieval [7]. If the differentiation between the two entities remains unclear, immunohistochemical staining for DNAJB9 can be performed and will be positive in cases of fibrillary glomerulonephritis and negative in amyloidosis [8].

Once a diagnosis of amyloidosis has been established, the type of amyloid must be determined. There are, as currently described by the International Society of Amyloidosis, 14 types of amyloid that can involve the kidney, and these types may have different locations or clinical settings [9]. Morphologically, all forms of amyloidosis

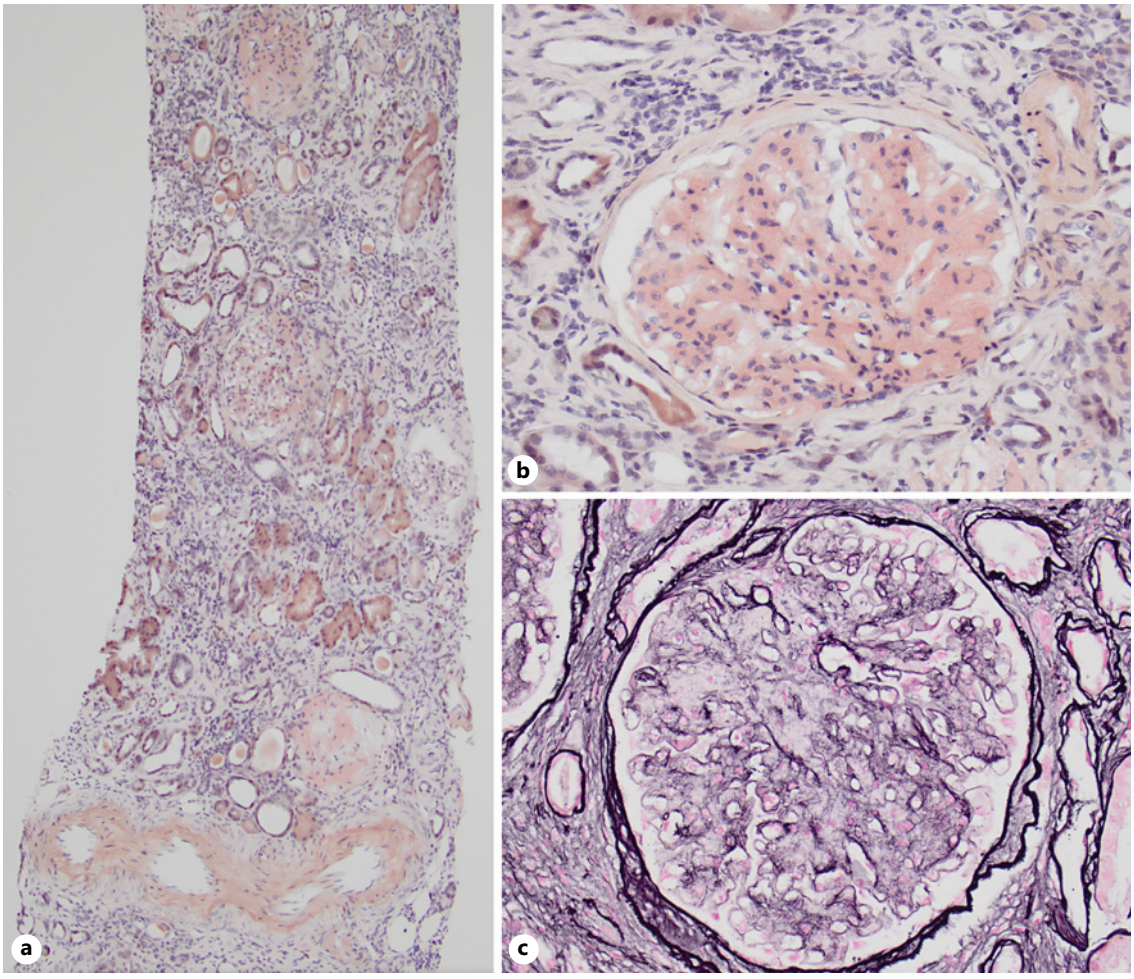


**Fig. 6.** Gelosin amyloidosis (AGel). **a** Congo red-positive amyloid involving the glomeruli and vessels (×10). **b** Congo red-positive amyloid involving the glomeruli and an arteriole (×40). **c** Silver-negative amyloid without distinct spike formation (silver stain, ×40).

show similar histologic and ultrastructural features: eosinophilic, amorphous, Congo red-positive, acellular material consisting of randomly arranged fibrils on ultrastructure. However, although amyloid can deposit in any of the compartments of the kidney, some amyloid types show an affinity for a specific compartment of the kidney. Additionally, immunofluorescence and immunohistochemistry may help to distinguish certain forms of amyloidosis. Notably, in non-AL forms of amyloidosis, a diagnostic pitfall arises in cases with higher background staining for a given light chain. Because amyloid may show nonspecific reactivity for all immunoglobulins and light chains, higher serum levels for a given light chain can result in brighter background staining in the immunofluorescence tissue, which may artifactually appear as dominant light chain staining. Many examples of hereditary amyloidosis, including transthyretin, apolipoprotein AI, and lysozyme, are misdiagnosed as AL amyloidosis, likely due at least in part to this reason [10]. This pitfall can be avoided by looking at the renal tissue in areas uninvolved by amyloid to compare the background staining. Confirmation of the suspected amyloid type using immunohistochemistry can be performed in many cases. If any doubt remains, LC-MS can be performed for diagnosis confirmation. LC-MS has become the gold standard for amyloid identification with excellent sensitivity and specificity [11, 12]. If the type of amyloid is undetermined by LC-MS, additional ancillary testing including genetic testing can be performed to evaluate it further [11, 13]. Although confirmation with ancillary studies such as immunofluorescence,

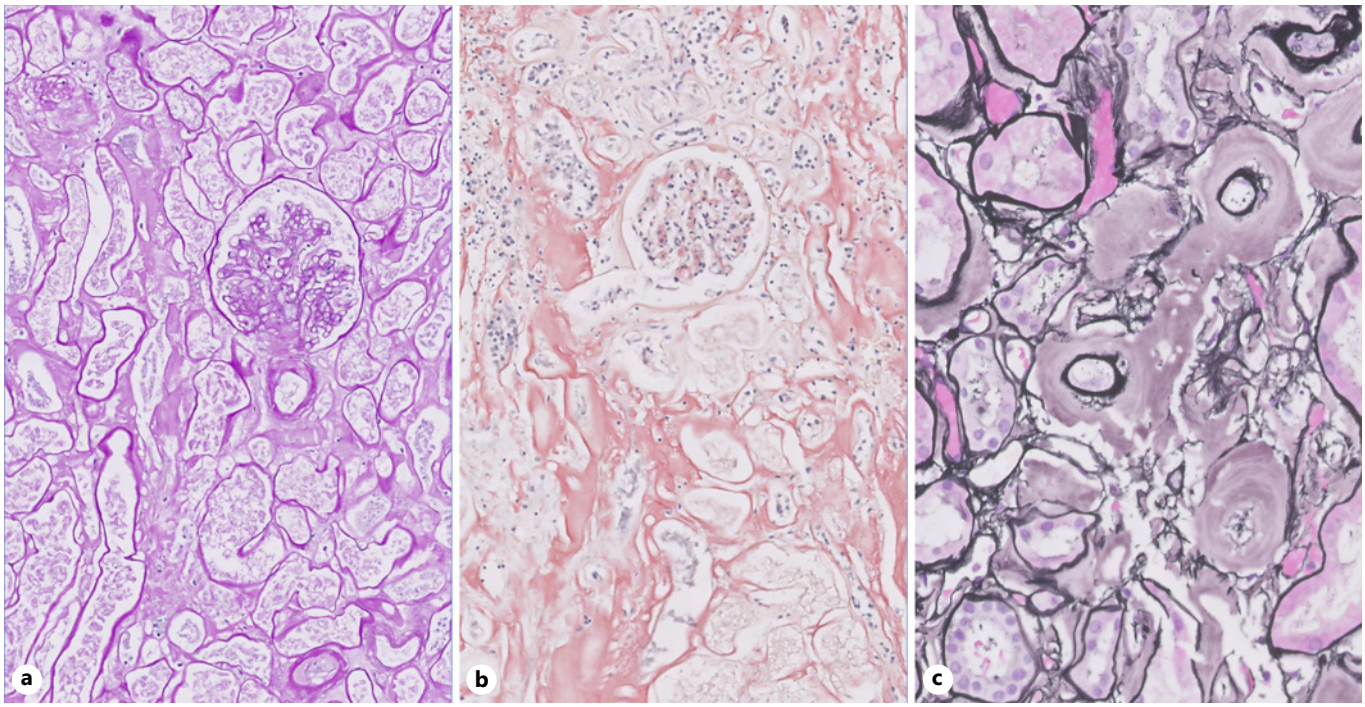


**Fig. 7.** LECT2 amyloidosis (ALECT2). **a** PAS-pale material predominantly in the interstitium (PAS stain, ×10). **b** Congo red-positive material predominantly involving the mesangium with minimal glomerular involvement (×10). **c** Silver-pale amyloid material in vessels (silver stain, ×40).

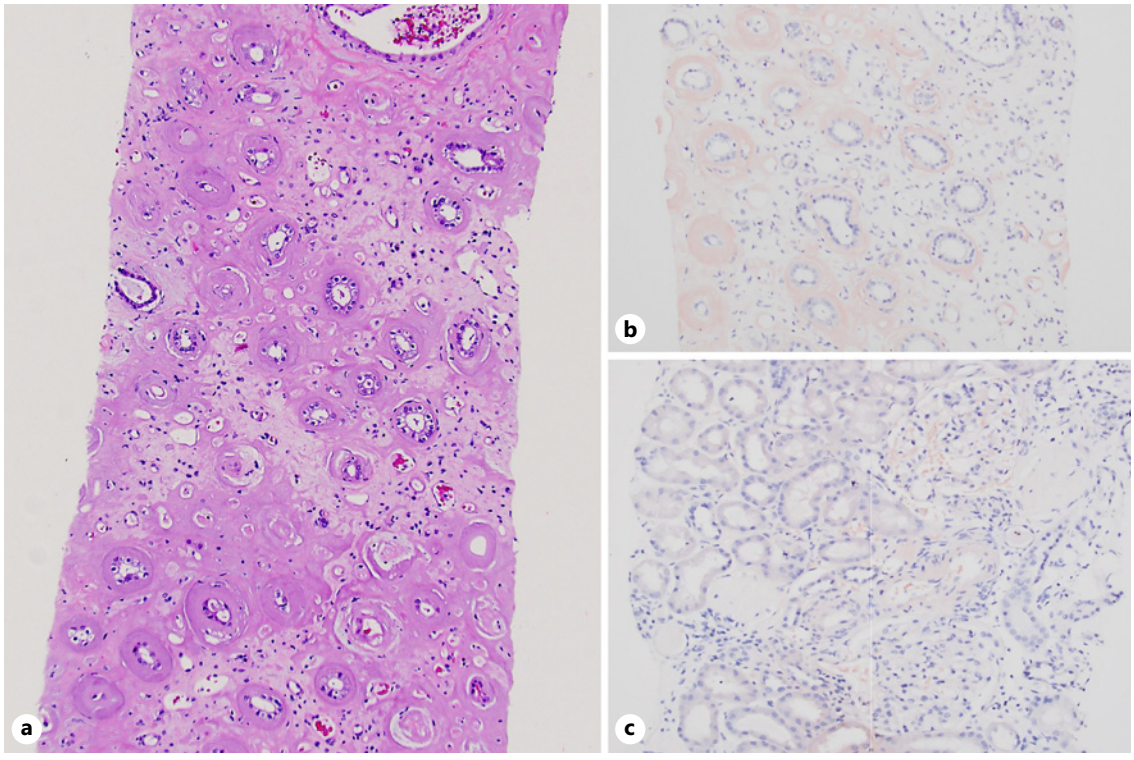


**Fig. 8.** Transthyretin amyloidosis (ATTR). **a** Amorphous amyloid material involving vessels only (H&E, ×20). **b** Congo red-positive material in vessel walls (×20). **c** Congo red amyloid in vessel walls with glomerular sparing (×20).

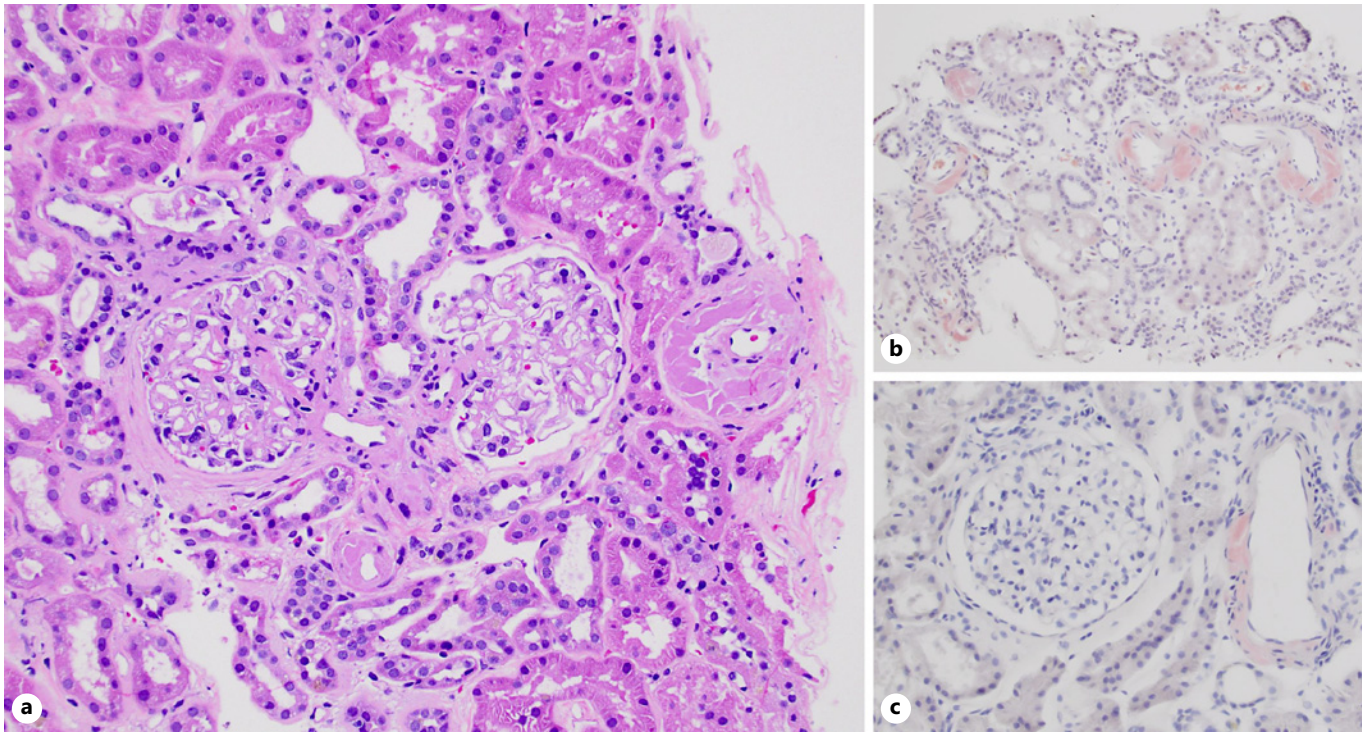


**Fig. 9.** Apolipoprotein AIV amyloidosis (AApoAIV). **a** Amyloid material in the deep medulla interstitium and tubular basement membranes (H&E, ×10). **b** Congo red highlighting amyloid along the tubular basement membranes and interstitium (×10). **c** Cortex with no evidence of amyloid deposition (Congo red, ×20).

immunohistochemistry, or LC-MS must be performed, certain histologic and clinical features can guide the differential diagnosis. The specific features of different amyloidosis are discussed in more detail below, and the distribution and salient histologic features are summarized in Table 1.

AA amyloidosis is a deposition of serum amyloid protein A which is an apolipoprotein that is synthesized in the liver as an acute-phase reactant [14]. Historically, it is the most common type of amyloidosis and was usually attributed to chronic infections including tuberculosis, but the advent and accessibility of effective antimicrobial therapy have resulted in shifting demographics, especially in developed countries [15, 16]. In the USA, autoimmune diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease are the most common causes of those with known etiologies, though other causes including hereditary cases such as Familial Mediterranean fever can also be seen [16–19]. As in this index case, there are a growing number of amyloidosis cases among younger patients with a history of intravenous drug use [20, 21]. Herein we describe a 24-year-old patient, who, to the best of our knowledge, is the youngest described in the literature. AA amyloid can involve any compartment of the kidney but nearly always involves the glomeruli [22]. Vascular involvement is common, and AA amyloidosis can sometimes involve predominantly the vasculature [23]. Because of the glomerular involvement, most patients present with proteinuria, and an immunohistochemical stain for protein A can be performed to confirm the diagnosis, which should be suspected in patients without a paraprotein and with a history of a chronic inflammatory condition. AA amyloid can be misdiagnosed as AL amyloid, and immunohistochemistry can be unreliable, so confirmatory testing by LC-MS should be performed if there is any discrepancy [24, 25].

Amyloidosis related to a paraprotein is the most common form of renal amyloidosis in developed countries and occurs in the setting of plasma cell dyscrasias or lymphoproliferative disorders [22, 26]. This type of amyloid can deposit as either heavy chain (AH), light chain (AL), or both (ALH). AL/AH/ALH amyloid can involve all compartments of the kidney and deposit in other organs as well (Fig. 4a). It usually involves the glomeruli to some extent, but up to 8% may not show glomerular involvement, and rare cases may involve the vasculature only [22, 26, 27]. Conversely,

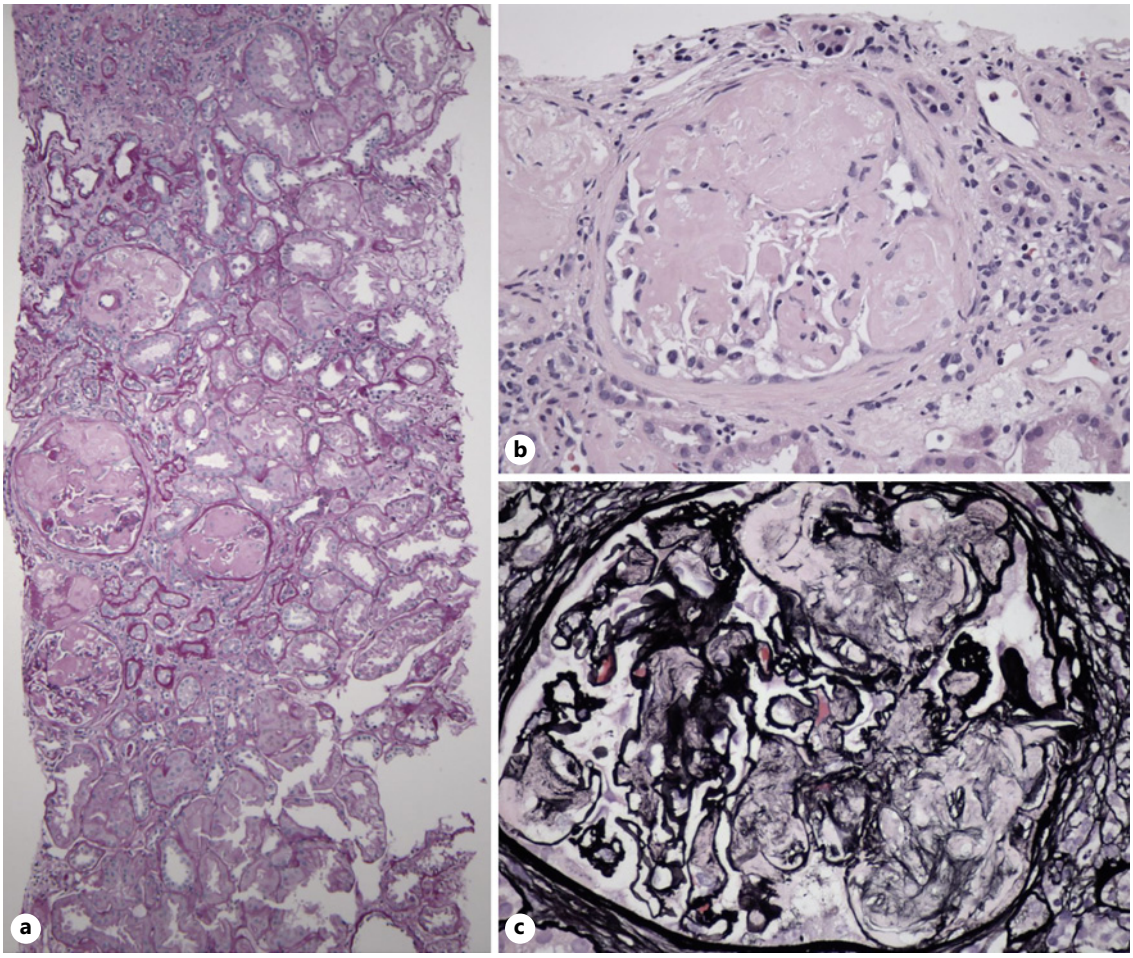


**Fig. 10.** Apolipoprotein CII amyloidosis (AApoCII). **a** Amorphous amyloid material involving the glomeruli (H&E, ×10). **b** Amyloid material involving a glomerulus; Congo red stain was negative (H&E, ×40). **c** Silver-negative amyloid material in the mesangium.

rare cases may show extensive glomerular deposits without significant involvement of the other compartments of the kidney [28]. The characteristic subepithelial spikes are seen more often with this amyloid type, though this feature is not specific for a given type of amyloid (Fig. 4b) [22]. Unsurprisingly, given the glomerular involvement, AL, AH, and ALH amyloidosis more commonly present with nephrotic syndrome and have the highest levels of proteinuria [22]. These paraprotein-related amyloidosis are generally best diagnosed by immunofluorescence (Fig. 4d). However, approximately 9% will show no staining on immunofluorescence including after antigen retrieval [22, 29]. This is likely because the epitope to which the antibody binds is not present in the abnormal amyloid protein. Alternative methods of identification including immunohistochemistry or immunogold labeling on electron microscopy may be useful in such cases, provided the epitope specificity is different. Occasionally these patients will not have a detectable clone in the serum at the time of diagnosis [30]. This is likely because the majority of the abnormal protein is deposited in tissues. In addition to depositing in the glomeruli, interstitium, and vessels, amyloidogenic cast nephropathy can be seen in rare cases [31]. Similarly, intratubular cytoplasmic AL amyloidosis is associated with extrarenal amyloidosis [32].

Fibrinogen amyloidosis (AFib) is seen in patients with mutations in fibrinogen A α-chain. It is a rare form of amyloidosis with a strikingly glomerular distribution showing almost complete replacement of the glomeruli with little to no vascular or interstitial deposition (Fig. 5a, b) [33, 34]. Despite this intense glomerular involvement, the classic "spikes" on silver stain are not

commonly seen in this form of amyloidosis (Fig. 5c) [22]. Immunofluorescence may show positivity for fibrinogen (Fig. 5d), but, if negative or weak, immunohistochemical staining for fibrinogen will usually confirm the diagnosis and should be performed in cases with strikingly glomerular dominant deposition [35]. Immunohistochemistry is not definitive in approximately 10% of cases, in which case either genetic testing or LC-MS should be performed [36]. Mutations of the offending gene are inherited in an autosomal dominant fashion and have variable penetrance, so patients may not have a family history of renal disease [36, 37] Due to the involvement of other organs, these patients may have other symptoms including peripheral neuropathy [38]. They also often have a personal or family history of coronary artery disease and systemic atheromas which, on histologic examination, also contain amyloid protein and often precede renal disease [39]. Because the protein is formed in the liver, these patients should be treated with a liver alone or combined liver and kidney transplant [39].

Gelosin amyloidosis is also known as Hereditary Amyloidosis, Finish type, and is caused by mutations in the eponymous gelosin gene. This amyloid type clinically presents with progressive ophthalmologic, neurologic, and dermatologic signs in most patients [40]. Particularly with certain mutations, renal involvement may be underestimated, but proteinuria is rare in these patients and described predominantly in homozygotes [40–42]. Similar to AFib, gelosin amyloidosis is usually restricted to the glomeruli but can also show involvement of vessels (Fig. 6a, b). By contrast though, it usually does not replace the glomeruli in the distinctive fashion of AFib but rather conforms to a more traditional glomerular involvement pattern with fibrils involving the mesangium and extending along the glomerular capillary loops (Fig. 6c) [43, 44]. Some cases may show only weak staining for Congo red [43]. Immunofluorescence will be negative in these cases, but an immunohistochemical stain for gelsolin will be positive. If renal disease is present, patients usually present with nephrotic syndrome [44].

Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a form of amyloidosis that predominantly affects older patients of Mexican ancestry and is not associated with a mutation in the LECT2 gene [45–47]. This amyloid type deposits primarily in the cortical interstitium with or without tubular basement membrane involvement, with relative sparing of the medulla; the glomeruli and vessels are also commonly involved, although to a much lesser degree than the interstitium (Fig. 7) [46, 47]. Although ALECT2 deposits outside the kidney, it does not cause any extrarenal symptoms [46, 47]. Immunofluorescence will be negative in this amyloid type. An immunohistochemical stain for LECT2 will be positive and should be performed in Mexican and non-Caucasian patients with cortical interstitial dominant amyloid deposition [48, 49]. Patients usually present with slowly progressive renal failure and may have proteinuria, but nephrotic syndrome is rare [50].

Transthyretin amyloidosis (ATTR) is the most common hereditary form of amyloidosis and, although more broadly described in the heart and peripheral nervous system, also affects the kidney [51]. ATTR may present with proteinuria, but deposits can also be seen in patients without proteinuria; notably, the degree of proteinuria correlates to the severity of renal involvement [52–54]. As compared to AL or AA amyloidosis, it more frequently involves the tubulointerstitium, often in the medulla, but can also be seen in the glomeruli [55]. The ATTR S52P variant shows amyloid deposition predominantly in the vessels (Fig. 8) and tubular basement membranes, and the ATTR V30M variant shows deposition in the glomeruli; other variants do not have a specific affinity for deposition described [51, 55]. An immunohistochemical stain for transthyretin (prealbumin) is available in cases where this form of amyloidosis is suspected. However, it should be noted that transthyretin immunohistochemical stain has been reported to show false positivity in heart biopsies [24]. Accordingly, a low threshold for additional confirmatory tests including genetic testing and LC-MS may be prudent.

Lysozyme amyloid is a very rare form of hereditary amyloidosis that is clinically characterized by sicca syndrome, diarrhea, and renal dysfunction due to deposition in the salivary tract, GI tract, and kidney [56]. In the kidney, a specific pattern of amyloid deposition has not been described [56, 57]. An immunohistochemical stain for lysozyme is available.

By far the most common and only sporadic form of apoliprotein-derived amyloid is amyloid A, but several other apolipoproteins have also been shown to cause amyloidosis. Apolipoprotein AI amyloidosis (AApoAI) is a hereditary amyloidosis that involves the kidney in cases with N-terminus mutations [22, 58]. Reports about the distribution of deposition in the kidney vary, with some showing a distinct prediction for the interstitium with or without involvement of the larger arteries and others showing predominantly glomerular involvement [22, 59, 60]. However, the largest cohort of patients studied showed dominant

deposition in the interstitium of the inner medulla without significant glomerular involvement [61]. Accordingly, these patients may present with renal dysfunction in the absence of proteinuria [61]. Notably, all of the patients in that study had Leu75Pro mutations. However, there seems to be some variability in distribution with different mutations. For example, in a report of Leu64Pro mutation, striking glomerular involvement was seen [58, 61]. Immunohistochemical staining for ApoAI can be performed.

Apolipoprotein AII (AApoAII) is another form of apoliprotein-associated familial amyloidosis. Unlike the other forms of apolipoprotein, this amyloid type consistently shows striking glomerular involvement [62–64]. Specifically, this form of amyloid may enter the differential with AFib since it also can completely replace glomeruli. Some cases of AApoAII amyloidosis show multinucleated giant cells in the glomeruli, which may serve as a trigger to perform additional testing including immunohistochemistry for ApoAII [63].

Apolipoprotein AIV (AApoAIV) shows a medullary-restricted pattern with large interstitial deposits with cortical sparing (Fig. 9). Amyloid is absent in the glomeruli, interstitium, and vessels of the cortex in these patients [65, 66]. Patients clinically usually have progressive renal dysfunction, often with little to no proteinuria [66].

The final forms of apolioprotein-associated amyloidosis described in the kidney are derived from apolipoprotein CII (AApoCII) and CIII (AApoCIII). Both are very rare. AApoCII shows predominantly glomerular involvement with nodular expansion of the mesangium (Fig. 10). Tubulointerstitial involvement is rare, and vessels are not involved in AApoCII amyloidosis. Like gelosin, these AApoCII amyloids may show only weak or negative Congo red staining. Because of the glomerular involvement, patients with AApoCII usually have nephrotic-range proteinuria [5, 67]. In AApoCIII, abundant vascular deposition is seen, but there is also moderate involvement of the glomeruli and tubulointerstitium. Unlike AApoCII, AApoCIII is positive for Congo red [68].

## Treatment and Follow-Up

Unfortunately, this patient was lost to follow-up. In general, the treatment of amyloidosis is challenging. In cases of AL amyloidosis, treatment centers around clone-directed therapy. Similarly, for AA amyloidosis, treatment focuses on controlling the underlying inflammatory process with the goal of reducing the amount of circulating SSA protein by reducing its production in the liver. Some hereditary amyloidosis may require transplantation including transplantation of the liver. Recently, there has been increased focus on inflammatory cascade blockers including interleukin-1, interleukin-6, and tumor necrosis factor-α inhibitors, which have been shown to be effective even in cases where the underlying etiology cannot be identified [69, 70]. Additionally, RNA-targeted gene-editing therapies have recently been used in the treatment of ATTR [71].

## Conclusion

Amyloidosis is a relatively common finding in renal biopsies, and the correct diagnosis and typing of the amyloid are essential for prognosis and treatment. Although definitive diagnosis often relies on ancillary studies including immunofluorescence, immunohistochemistry, and LC-MS, the histologic pattern of the amyloid and clinical scenario can provide important clues to narrow the differential diagnosis and guide further workup. In this case, although the age of onset is surprising, the clinical history of extensive drug use and chronic wounds on this patient's arms are important clues to the diagnosis of AA amyloid.

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## Statement of Ethics

Written informed consent was obtained from participants for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

## Conflict of Interest Statement

The authors have no conflicts of interest.

## Funding Sources

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## Author Contributions

Dr. Biederman drafted the manuscript, Dr. Dreyfus contributed the clinical information, and Drs. Dasgupta, Satoskar, Nadasdy, and Brodsky edited and substantially contributed to the content.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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